JOURNAL OF combinatorial CHEMISTRY

Volume 9, Number 4 July/August 2007

Reviews

Advances in Solid-Phase Cycloadditions for Heterocyclic Synthesis

Lidia Feliu,[†] Patricia Vera-Luque,[‡,§] Fernando Albericio,[‡,||] and Mercedes Álvarez*[,‡,⊥]

LIPPSO, Department of Chemistry, University of Girona, 17071-Girona, Spain, and Institute of Research in Biomedicine, Barcelona Science Park, University of Barcelona, 08028-Barcelona, Spain

Received January 24, 2007

1. Introduction

Solid-phase synthesis (SPS) of non-peptidic small molecule libraries has become a mainstream activity within the pharmaceutical industry to identify novel biologically active molecules and to accelerate structure−activity relationship (SAR) studies.[1] Cycloadditions are highly versatile in heterocyclic synthesis; [2+2] cycloadditions, the Diels−Alder reaction, and 1,3-dipolar cycloadditions are preferred routes to four-, six-, and five- membered heterocycles, respectively.

In drug discovery, cycloadditions are used to generate diversity in compound libraries by variation of the structure of both reactive components (e.g., diene/dienophile or 1,3-dipole/dipolarophile). Because libraries for biological screening encompass myriad heterocyclic structures and are commonly synthesized on solid-phase, there has been a surge of interest in solid-phase cycloadditions, some of which have been covered in recent reviews (e.g., dipolar cycloadditions of nitrile oxides and azomethine ylides (Kantorowski and Kurth),[2] dipolar cycloadditions (Harju and Yli-Kauhaluoma),[3] the Diels−Alder reaction (Yli-Kauhaluoma),[4] and enantioselective cycloadditions (Lessmann and Waldmann)).[5] The present article is the first review focused on the preparation of heterocyclic small molecules assembled via solid-phase [2+2], [4+2], and [3+2] cycloadditions. Only solid-phase cycloadditions involving the formation of new heterocyclic rings are considered here. On the basis of this criterion, cycloadditions using a previously constructed heterocycle (e.g., [4+2] cycloadditions with maleimides as dienophiles) are excluded. Although the majority of the chemistry presented here is for use on polystyrene -based solid supports, there are also examples of reactions using non-cross-linked polyethyleneglycol (PEG) supports. The latter are soluble in the reaction solvent, and upon reaction completion, are precipitated out in ether, thus making them amenable to solution and solid-phase chemistry. Thus, reactions are carried out with all reactants in solution, but the excess of some of reagents are simply removed by filtration.[6] Reactions carried out with this kind of support are denoted by the use of

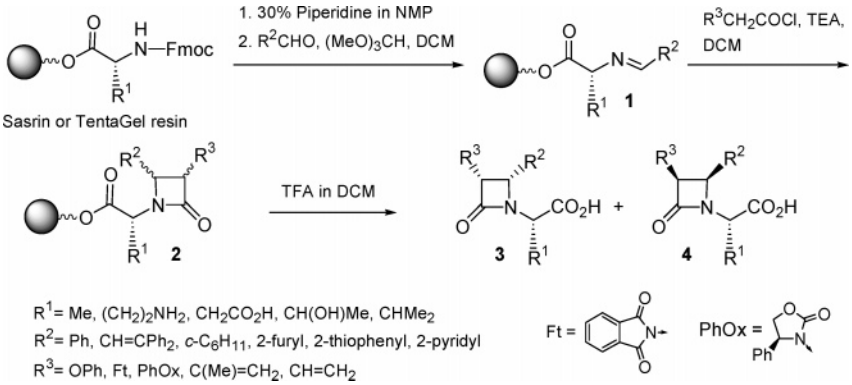
instead of

which is used for the fully insoluble solid support. This review covers literature up to December 2006.

* To whom correspondence should be addressed. E-mail: malvarez@pcb.ub.es.
[†] LIPPSO, Department of Chemistry, University of Girona.
[‡] Institute of Research in Biomedicine, Barcelona Science Park, University of Barcelona.
[§] Current address: Department of Organic Chemistry, University of Alcalá, Spain.
[||] Department of Organic Chemistry, University of Barcelona.
[⊥] Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona.

10.1021/cc070019z CCC: $37.00
Published on Web 05/12/2007

Scheme 1



2. [2+2] Cycloadditions

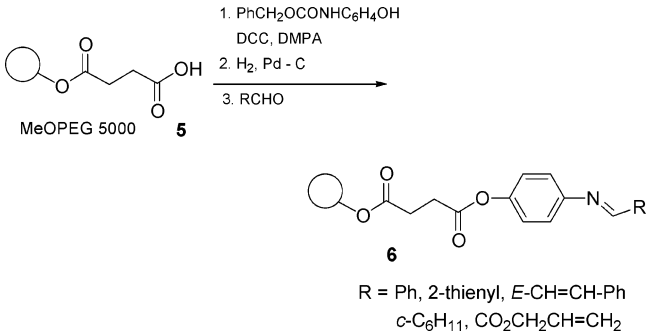
Heterocycles prepared by solid-phase [2+2] cycloaddition comprise diversely substituted β-lactams, new heterocyclic systems (section 2.1.1), and intermediates for the synthesis of polycyclic compounds (section 2.1.2).

Moreover, γ-lactams and γ-lactones have been obtained using a [2+2] cycloaddition (section 2.2) to generate a cyclobutanone, followed by a Baeyer−Villiger or Beckmann transposition to give the oxygen- or nitrogen-containing heterocycle, respectively. These reactions are the only examples included herein in which the heterocycle is not constructed during cycloaddition and have been included because of their relative scarcity in the literature.

2.1. Formation of β-Lactams. Monocyclic β-lactams are versatile intermediates in organic synthesis. The high-strain energy of the 4-membered ring makes its amide bond relatively labile toward nucleophilic attack. Through this mechanism, β-lactams have been used as intermediates in the synthesis of heterocycles, amino acids, and their derivatives.[7] From a combinatorial perspective, the β-lactam template is a highly modular scaffold from which numerous building blocks can be obtained. In addition, the reaction conditions reported by Staudinger[8] for the synthesis of β-lactams in solution are mild enough to tolerate a large variety of functional groups. Therefore, various substituents can be incorporated into the final products through β-lactam intermediates. In fact, the Staudinger reaction has been adapted to the solid-phase by different authors for the preparation of β-lactams via a [2+2] cycloaddition reaction of ketenes with resin-bound imines derived from amino acids.

Gallop et al.[9] employed the Staudinger reaction to efficiently construct libraries of densely functionalized heterocycles. Imines were prepared by anchoring the carboxylic acid residue of an amino acid to a Sasrin resin (with a low content of TFA-cleavable linker) or a TentaGel resin (a PEG and polystyrene graft resin) derivatized with a photolabile linker. After removal of the Fmoc protecting group by treatment with piperidine in *N*-methyl-2-pyrrolidinone (NMP), the resulting amines were condensed with an alkyl, aromatic, or α,β-unsaturated aldehyde to yield the resin-bound imines **1**. The addition of acid chlorides to a dichloromethane (DCM) suspension of the imine resins in the presence of triethylamine (TEA) led to the in situ generation of a ketene and to the subsequent [2+2] cycloaddition. Products were cleaved from the support by treatment of **2** with a solution of TFA in DCM. Cycloadditions of achiral ketenes with resin-bound imines derived from homochiral amino acids and either aromatic or α,β-unsaturated aldehydes were highly cis selective but proceeded with only modest levels of stereoinduction from the asymmetric center of the amino acid (Scheme 1). Thus, the two cis diastereomeric β-lactams **3** and **4** were formed in ratios from 1:1 to 3:1 (based on ^{1}H NMR and HPLC).

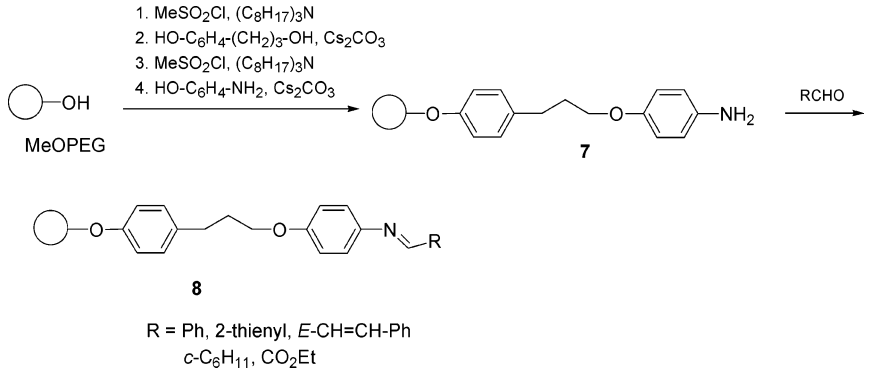
Scheme 2



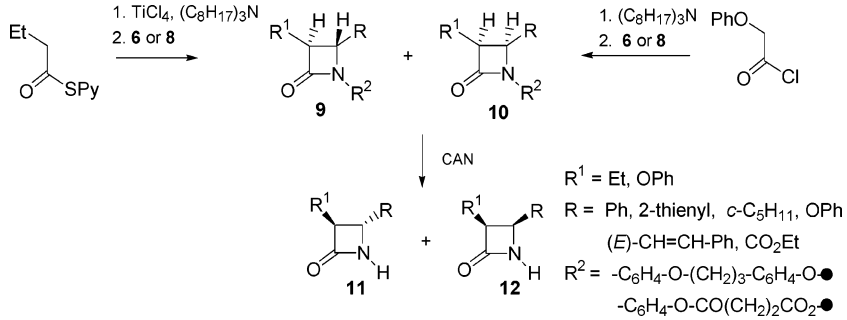
Cozzi et al.[10] reported the synthesis of imines immobilized on polyethylene glycol monomethylether (MeOPEG) of molecular weight 5000 and their transformation into β-lactams by two different procedures. In their communication,[10a] the authors used succinic acid as linker by formation of mono-MeOPEG succinate **5** which was then condensed with *N*-(4-hydroxyphenyl)-*O*-benzylcarbamate in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) (Scheme 2). The resulting resin-bound benzyloxycarbonyl-protected aniline was then subjected to catalytic hydrogenation to yield the corresponding free amine. The representative imines **6** were prepared by the addition of the aldehyde to the melted amine, followed by stirring of the thick oily mixture and removal of the unreacted aldehyde and the released water under vacuum.

The second procedure described by Cozzi et al.[10b] was based on the use of a 4-(3-propyl)phenyl residue as a spacer. The reaction of MeOPEG mesylate with the cesium salt of the commercially available 3-(4-hydroxyphenyl)-1-propanol in DMF, followed by mesylation of the resulting alcohol and then reaction with the cesium salt of *p*-aminophenol, afforded the resin **7** in 91% overall yield (Scheme 3). Imines **8** were obtained by reaction of the anchored amine **7** with the appropriate aldehyde in DCM using magnesium sulfate or trimethylorthoformate as dehydrating agent.

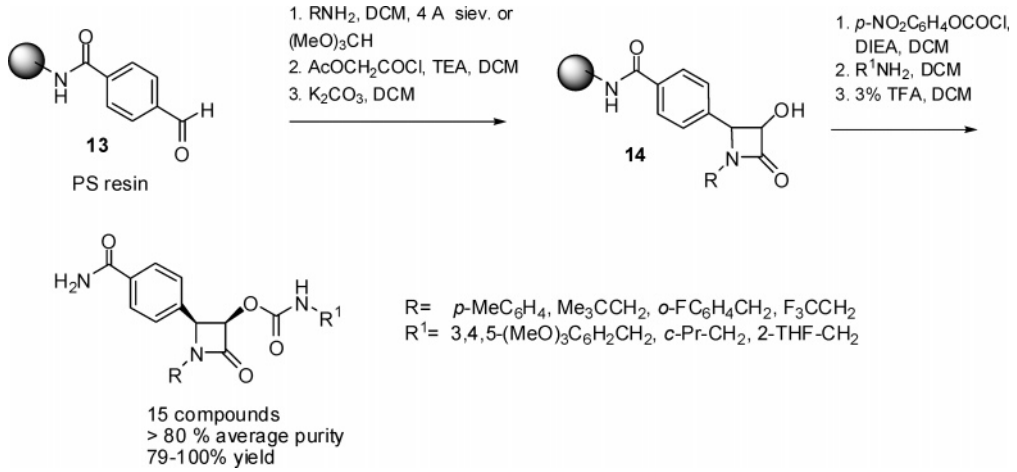
Scheme 3



Scheme 4



Scheme 5

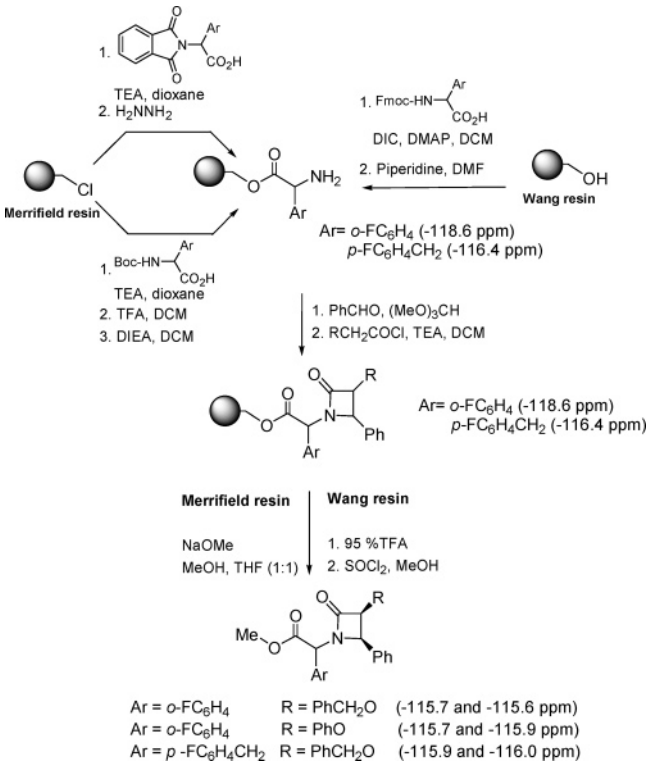


Imines **6** and **8** were used in the synthesis of β-lactams via the enolate/imine condensation and the [2+2] cycloaddition, respectively, which are the two most popular methods for β-lactam synthesis. The β-lactams **9** and **10** were cleaved from the resin by treatment with ceric ammonium nitrate (CAN) to directly yield *N*-unsubstituted azetidinones. Under these conditions, β-lactams **11** and **12** were obtained in yields ranging from 40 to 57% (Scheme 4).

Sing and Nuss[11] developed a methodology for the rapid SPS of combinatorial libraries of β-lactams via the Staudinger reaction. A set of imines was synthesized by reaction of *p*-carboxybenzaldehyde **13** with various primary amines in anhydrous DCM in the presence of molecular sieves or trimethylorthoformate (Scheme 5). The desired azetidinones **14** were formed by treatment of the imines with acetoxyacetyl chloride in DCM in the presence of TEA at room temperature or 0 °C. The hydroxyl group of **14** was derivatized using *p*-nitrophenyl chloroformate as activating agent.

The solid-phase Staudinger synthesis of β-lactams from commercially available fluorinated α-amino-acids has been monitored by ^{19}F NMR spectroscopy.[12] The substrate was anchored through its carboxylate group onto a Merrifield or Wang resin, both of which are polystyrene resins that can cleaved by strong acids. The former can also be cleaved by nucleophiles and the latter by TFA. The amine was transformed into the corresponding imine by condensation with an aldehyde. The fluorine atom was used as an analytical probe for recording NMR spectra. Each of the chemical products linked to the resin was characterized by a single ^{19}F NMR signal, whereby the respective chemical shift was related to each chemical step according to the adjacent group modifications. ^{19}F NMR spectroscopy, which is highly

Scheme 6



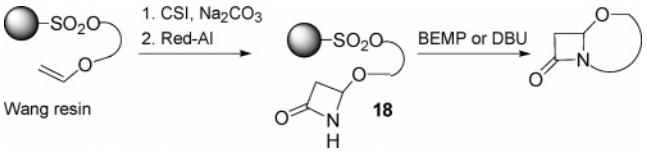
sensitive because of the natural abundance of ^{19}F and which offers broad dispersion of chemical shifts because of the strong polarizability of the fluorine atom, is very convenient for monitoring reactions on the solid phase.[13] The simplicity of qualitative and quantitative analysis by ^{19}F NMR allows rapid development of new synthetic steps (Scheme 6).

The β-lactams obtained by [2+2] solid-phase cycloaddition were transformed into other heterocyclic systems as indicated in the following sections.

2.1.1. Solid-Phase Transformation of β-Lactams into Dihydro-2(1*H*)-quinolones. The SPS of 4-amino-3,4-dihydro-2(1*H*)-quinolones from amino acids, aldehydes, and acid chlorides through the rearrangement of β-lactam intermediates has been described (Scheme 7).[14] Resin-bound amines **15** were condensed with *o*-nitrobenzaldehydes in DCM in the presence of anhydrous Na_2SO_4 as a drying agent to furnish imines **16**. After the products were washed with DCM and dried under high vacuum over P_2O_5, [2+2] cycloaddition of **16** with ketenes, generated in situ from the corresponding acetylacetyl or phenoxyacetyl chloride in the presence of TEA, was carried out in DCM at −78 °C. To monitor the reaction, β-lactam intermediates **17** were cleaved from the resin using HF/anisole and analyzed by ^1H NMR. Reduction of the nitro group of **17** with $SnCl_2$ produced the rearrangement to give the quinolones. Polystyrene-based methylbenzhydrylamine (MBHA) resin was chosen as the solid support because of its stability in the conditions used (i.e., stable to TFA, but labile to anhydrous HF to provide the desired amines).

2.1.2. Synthesis of Azeto[2,1-*b*]oxazol-5-one and Azeto-[2,1-*b*][1,3]oxazin-6-one. Solid-phase [2+2] cycloadditions of chlorosulphonyl isocyanate (CSI) to chiral vinyl ethers were studied by Chmielewski et al. for different solid supports.[15] The authors chose 5-*O*-vinyl and (*Z*)-5-*O*-propenyl ethers of 1,2-*O*-isopropylidene-α-D-glucofuranose and (*Z*)-3-*O*-propenyl ethers of 1,2-*O*-isopropylidene-α-D-xylofuranose. The reported strategy consisted of binding of the vinyl ether to the polymer support through a sulfonyl linker, followed by the cycloaddition (Scheme 8). The

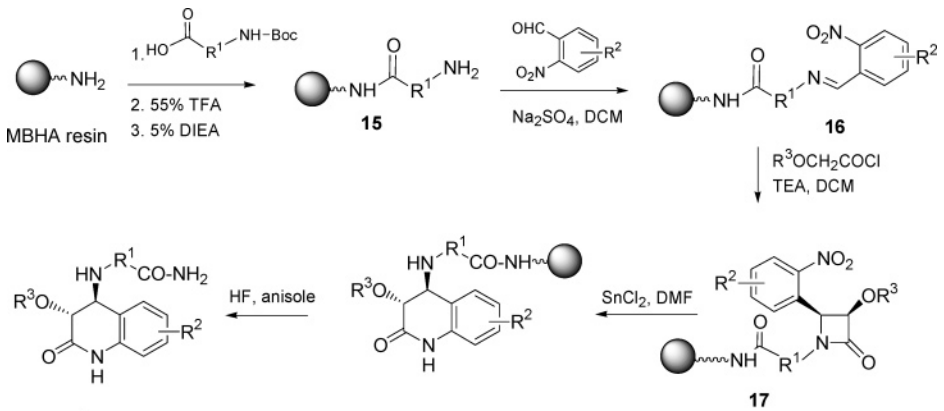
Scheme 8



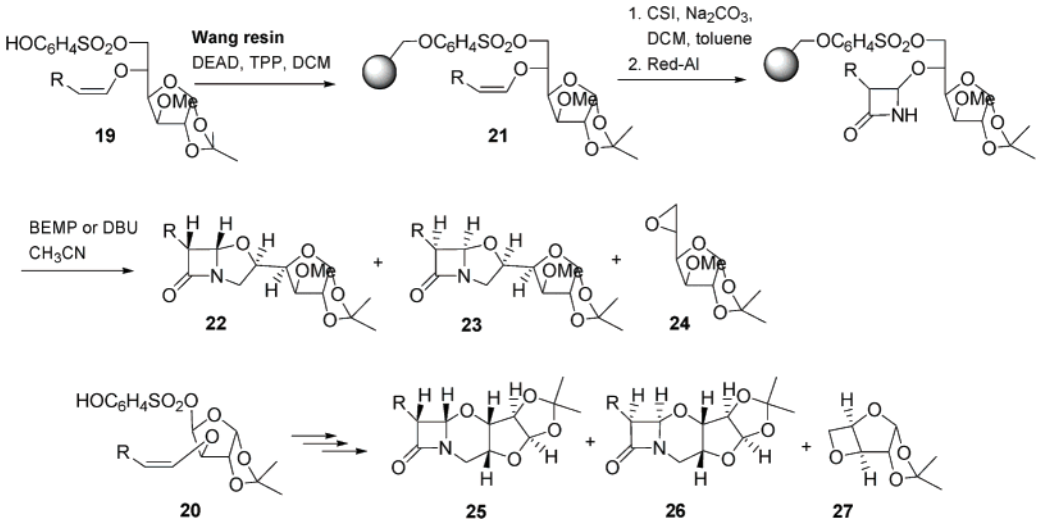
bicyclic compounds were obtained through a cyclization/cleavage step by treatment of the cycloaddition product **18** with a strong organic base such as 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) or 1,8-diazabiciclo[5.4.0] undec-7-ene (DBU).

Vinyl ethers **19** and **20** were anchored to Wang resin through the *p*-oxyphenylsulphonyl linker (Scheme 9). The polymer-bound vinyl ethers **21** gave mixtures of the corresponding diastereomeric clavams **22** and **23** accompanied by the oxirane **24**. Similarly, the oxacephams **25** and **26** and the oxetane **27** were obtained by using **20** for anchoring to

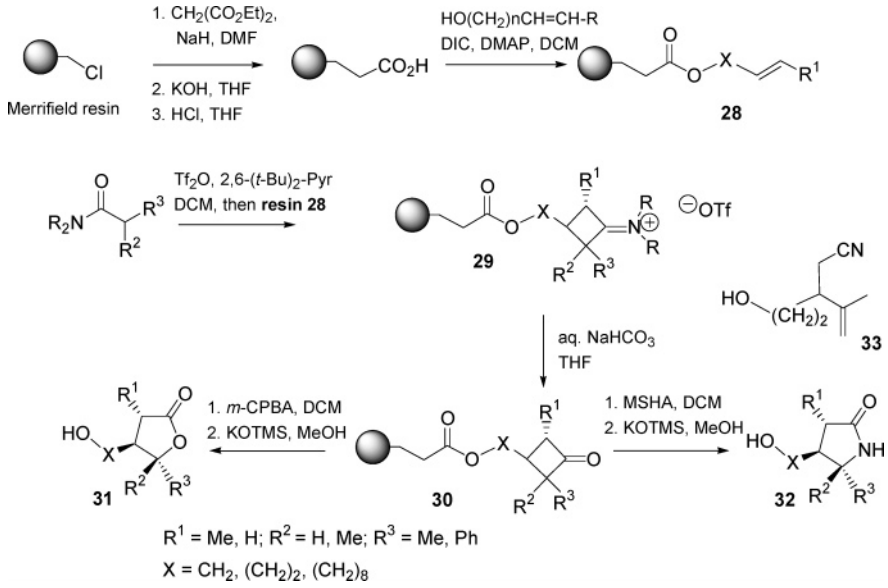
Scheme 7



Scheme 9



Scheme 10



the Wang resin. This cyclization/cleavage step was performed in the presence of BEMP or DBU.[15a]

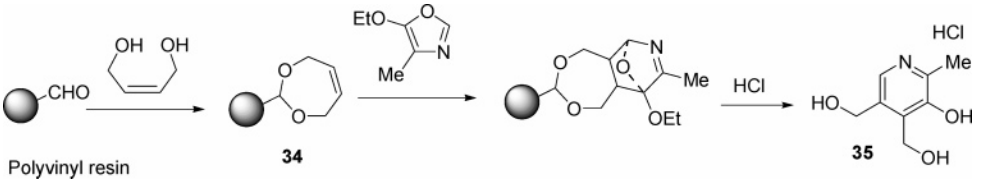
In a later work, the authors attached the same substrates to {5-[4-(methyl)phenyl]pentyl}polystyrene (MPP) resin, which is based on a Merrifield resin containing a longer benzyl type linker, and on/to non-cross-linked chloromethylated polystyrene (NCPS), which is a soluble polymer.[15b] [2+2] Cycloaddition followed by intramolecular alkylation of the β-lactam nitrogen led to mixtures of the diastereomeric oxacephams or clavams with low stereoselectivity and the corresponding oxetanes or oxiranes as byproducts, respectively. Reactions performed using a soluble polymer had similar results to those of reactions carried out in solution.

2.2. Formation of γ-Lactams and γ-Lactones. [2+2] Cycloaddition has been used to synthesize cyclobutanone iminium salts that were subsequently transformed into numerous structural classes, including γ-lactams and γ-lactones.[16] Commercially available alkenols were immobilized onto a carboxylated polystyrene resin, which was prepared from Merrifield resin in three simple steps (Scheme 10). The ester-linked alkene resins **28** were added to a 5-fold excess of the keteneiminium salts generated in situ from *N*,*N*-dialkylamide according to Ghosez's method,[17] leading to the formation of resin-bound cyclobutanone iminium salts **29**. Although the iminium species were sufficiently stable to be isolated, they were readily hydrolyzed to the corresponding cyclobutanone resins **30** without any significant cleavage of the ester, using aqueous $NaHCO_3$ in tetrahydrofuran (THF). Baeyer−Villiger ring expansion of ketones **30** using *m*-CPBA provided γ-lactones **31**, which were cleaved from the resin by transesterification. Similarly, Beckmann rearrangement of **30** (R^2 = H, R^3 = Ph), followed by transesterification, also proceeded cleanly to provide γ-lactams **32**. However, subjecting resin **30** (R^2, R^3 = Me) to the same conditions led to the Beckmann fragmentation product **33**.

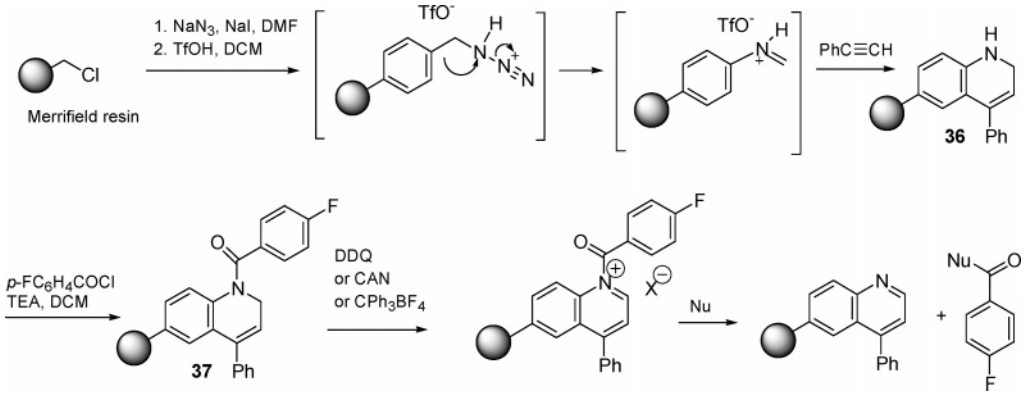
3. [4+2] Cycloaddition

The Diels−Alder reaction is one of the most powerful reactions in synthetic chemistry. Although it was first conceived for the construction of six-membered carbocycles, the use of heteroatomic dienes or dienophiles has broadened the scope and utility of the reaction. In fact, these hetero-

Scheme 11



Scheme 12



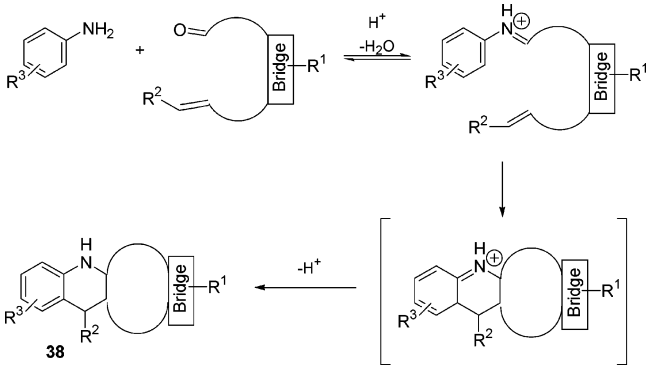
Diels−Alder reactions are invaluable for the preparation of six-membered heterocycles. Since a broad gamut of heterodienes and heterodienophiles can be used in either normal or inverse electron-demand hetero-Diels−Alder reactions, myriad heterocycles can be obtained. Extension of this reaction onto a solid support considerably increased its potential for generating molecular diversity. Therefore, it is not surprising that solid-phase hetero-Diels−Alder reactions have recently been used to prepare combinatorial libraries. Several examples of this chemistry have been reported in the literature, in which either the diene or the dienophile is bound to the resin.

3.1. Nitrogen-Containing Heterocycles. Nitrogen-containing heterocycles can be prepared through two types of solid-phase [4+2] cycloaddition reaction. The first uses azadienes for introduction of nitrogen into the six-membered ring, while the second utilizes an imine or an azo-compound dienophile as the source of nitrogen.

3.1.1. Azadienes. Synthesis of Pyridines, Pyridones, and Polycyclic Systems. Pyridoxine (Vitamin B) has been synthesized from a 2-butene-1,4-diol ketal that undergoes Diels−Alder addition with an oxazole derivative. The key step was covalent attachment of the dienophile to a polymeric backbone (Scheme 11). Cyclic acetal resin **34** was thus prepared by condensation of *cis*-2-butene-1,4-diol and polyvinyl resin with formyl functionalization.[18] Diels−Alder addition of 5-ethoxy-4-methyloxazole as diene to the polymeric dienophile **34** gave the intermediate adduct, which was then converted into pyridoxine **35** under acidic conditions.

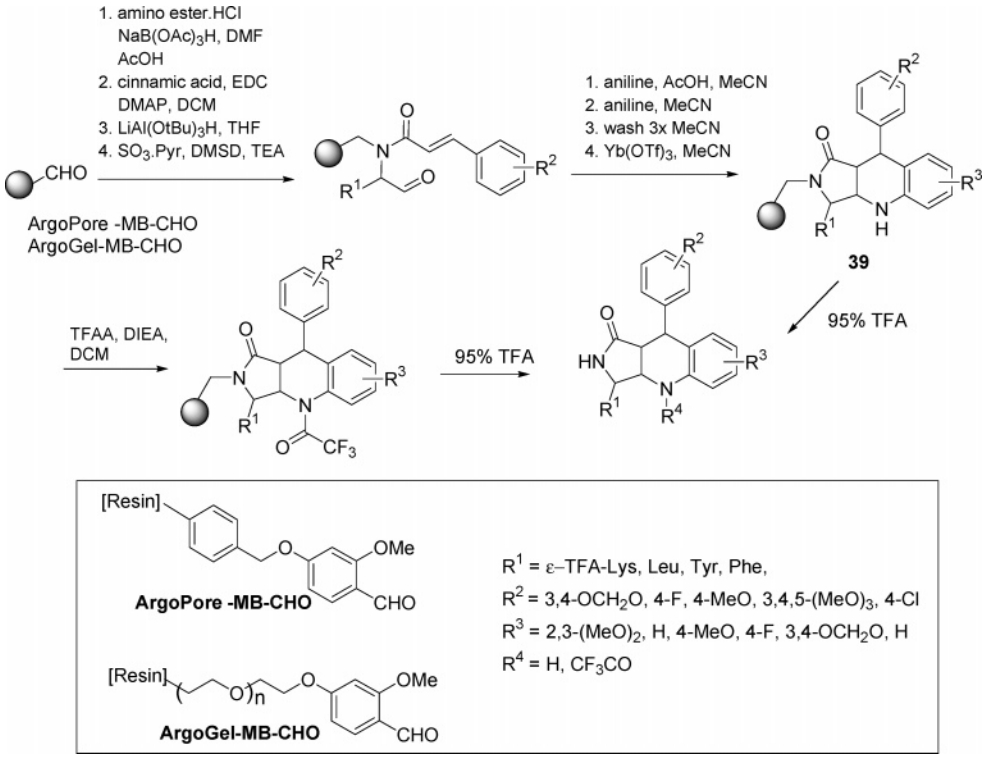
An azidomethyl-polystyrene has been developed for combinatorial solid-phase chemistry as safety-catch linker,[19] which is a linker that can be converted from a relatively stable form to a labile, isolatable, and cleavable form.[20] The linker was obtained by nucleophilic substitution of a Merrifield resin with sodium azide followed by an acid-promoted Schmidt rearrangement. The resulting polymer-bound iminium intermediate then underwent aza Diels−Alder cycloaddition with PhC≡CH as a dienophile, leading to the resin-supported dihydroquinoline **36**. The use of resin **36** as a new safety-catch linker for solid-phase organic synthesis was then investigated. Treatment of **36** with 4-fluorobenzoyl chloride and TEA afforded resin **37** (Scheme 12). The resulting amide bond was shown to be stable under conditions of acidic or basic hydrolysis, Boc/Fmoc removal, or reductive conditions (e.g., $NaBH_4$ in MeOH). The resin−substrate bond was activated by various oxidizing reagents such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), CAN, and triphenylcarbenium tetra-fluoroborate to give the acyl quinolinium resin. The amide bond of the acylquinolinium salt was then cleaved using a nucleophile such as benzylamine or, for CAN, water.

Scheme 13



A flexible combinatorial synthetic strategy has been developed in which an aldehyde-bridge-alkene motif is the key component in several intramolecular reactions.[21] The strategy has been most extensively explored with the formal aza Diels−Alder cyclization, which afforded a series of configurationally and functionally diverse heterocyclic compounds. The substrates, which included substituted salicylaldehydes, glyoxylic esters and amides, and *N*-acyl-*R*-aminoaldehydes, all reacted with a variety of anilines to yield the set of tetrahydroquinoline derivatives **38** (Scheme 13).

Scheme 14

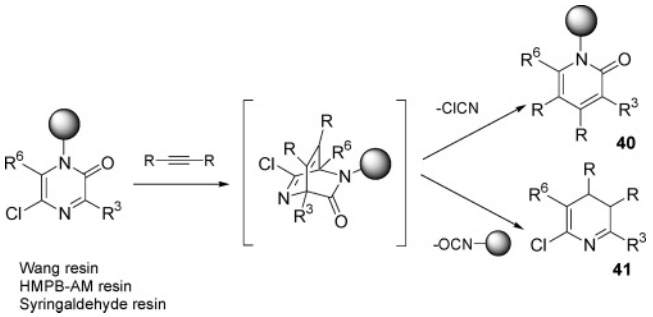


The resins ArgoPore and ArgoGel, which are polystyrene-based resins possessing acid-labile linkers, and PEG-polystyrene grafted, respectively, have been evaluated for loading efficiency and acetylation, using an amino acid ester, as well as for cleavage, using trifluoroacetic acid (Scheme 14). The resins were efficiently loaded with leucine methyl ester and then acetylated. Functional group transformations provided the formyl group, which subsequently reacted with a substituted aniline. The resulting adduct was then subject to Diels−Alder cycloaddition to give **39**. After cleavage with 95% aqueous TFA, ArgoGel provided final products in higher yield and purity than did ArgoPore.[22] Cleavage of the basic tetrahydroquinoline from the resin using TFA proved to be difficult because of the cationic charge of the molecule under acidic conditions but proceeded smoothly upon acylation of the basic nitrogen with trifluoroacetic anhydride (TFAA).

A library of many biologically interesting structures has been synthesized on solid-phase using 2(1*H*)-pyrazinone.[23] It was based on the microwave-assisted solid-phase Diels−Alder cycloadditions of 2(1*H*)-pyrazinones with dienophiles, whereby a traceless linker was used to separate the resulting pyridines from the pyridinone byproducts. The pyridinones **40** remained on the solid support with concomitant release of the pyridine products **41** into solution (Scheme 15). On the basis of this chemistry, the same group later prepared libraries of 2(1*H*)-pyrazinone analogues, which very often exhibit interesting biological activity.[24]

Cycloadditions have also been evaluated on acid-labile polystyrene supports, including Wang resin (which has an alkoxy group para to the anchoring point), HMPB-AM resin (a kind of Sasrin linker-based resin with an alkoxy group para and a methoxy group ortho to the anchoring point), and syringaldehyde-based resin (with an alkoxy group para and

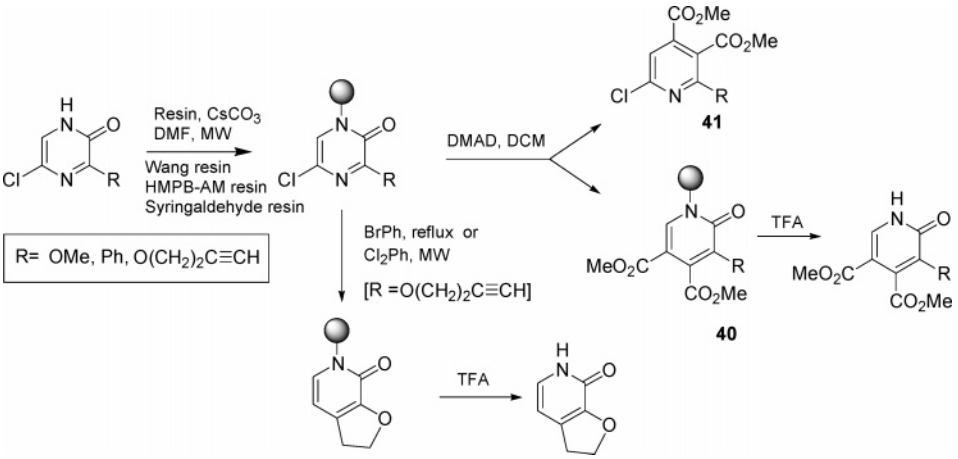
Scheme 15



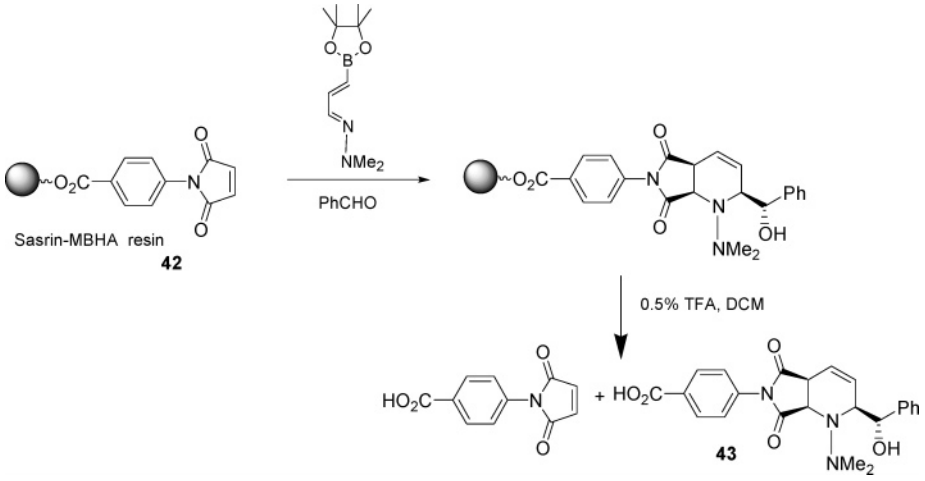
two alkoxy groups meta to the anchoring point). All solid-phase steps (i.e., linking, cycloaddition, and cleavage) were carried out under both thermal and controlled microwave irradiation conditions. In general, significant rate enhancements were found for reactions run under high-temperature microwave conditions; reaction times decreased from hours or days to minutes. The same conditions were then applied to intermolecular cycloadditions using dimethyl acetylenedicarboxylate (DMAD) and intramolecular Diels−Alder reactions, as shown in Scheme 16.

The three-component aza[4+2]/allylboration reaction for highly diastereocontrolled access to polysubstituted-hydroxyalkyl piperidines from maleimides, 4-boronohydrazonodienes, and aldehydes has been tested in the solid phase.[25] The solid-supported aza[4+2]/allylboration was carried out using Sasrin-MBHA resin **42**, a diene, and benzaldehyde (Scheme 17). After the normal resin washes, the supported product was cleaved from the resin using 0.5% TFA in DCM to give **43**. The reaction was followed by HPLC (UV) and MS (ES), whereby reaction completion was confirmed by the absence of maleimide cleaved from the resin. The

Scheme 16



Scheme 17



analytical data indicated that the solid-phase tandem reaction proceeds faster than its solution-phase counterpart.

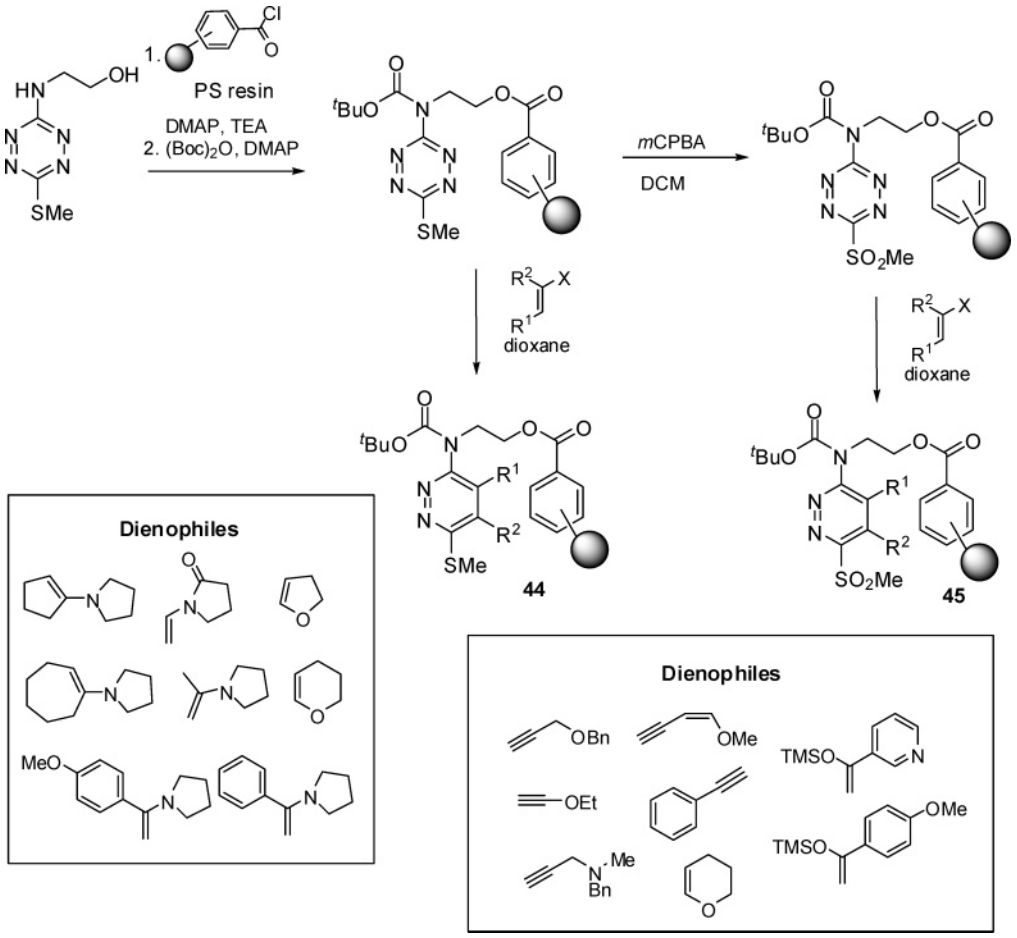
3.1.2. Diazadienes. Synthesis of Pyridazines. Thermally promoted, inverse electron-demand Diels−Alder reactions of resin-bound asymmetrically substituted 1,2,4,5-tetrazines have been explored with diverse electron-rich dienophiles (Scheme 18). The reactions afforded functionalized 1,2-pyridazines **44** and **45** bearing sulfur-based leaving groups (−SR or $-SO_2R$) at the C-6 position.[26]

3.1.3. Imines as Dienophiles. Synthesis of Tetrahydropyridines and Pyridones. Hydroxymethylpolystyrene has been transformed into the polymer-supported *o*-quinodimethane **46** and subsequently used as a diene for hetero-Diels−Alder reactions.[27] Dihydrobenzopyrans and tetrahydroisoquinolines were then obtained in moderate to good yields by treatment of **46** with the proper aldehydes (section 3.2.1.2) or imines followed by Brönsted or Lewis acid nucleophilic cleavage (Scheme 19).

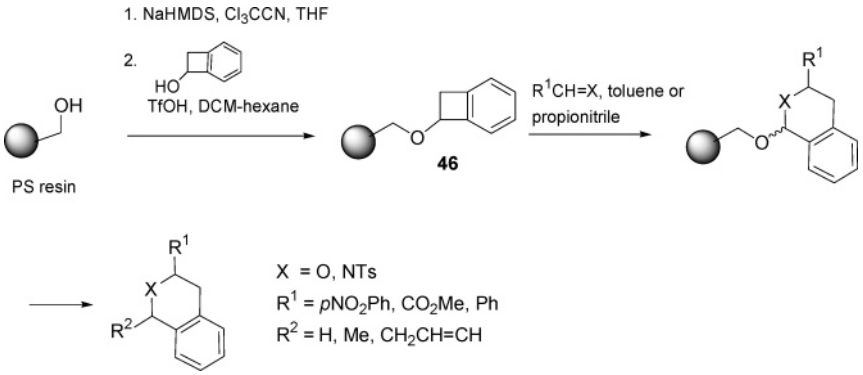
Aminomethylated polystyrene resin has been directly used (i.e., without any modification) as the immobilized amine component of a solid-phase aza Diels−Alder reaction (Scheme 20). Direct combination of the resin, a diene, an aldehyde, and lanthanide(III) triflate smoothly provided a tetrahydropyridine ring. The catalytic efficiency of four lanthanide triflates [hydrated or anhydrous as $La(OTf)_3$, $Nd(OTf)_3$, $Dy(OTf)_3$, and $Yb(OTf)_3$] was tested, and the catalyzed reactions were also compared to a reaction without any Lewis acid. There was no major difference among the yields obtained with the four lanthanide triflates, although that of $Yb(OTf)_3$ was slightly higher. The reaction without Lewis acid did not yield any product. The [4+2] adducts were efficiently cleaved from the solid support using a traceless release method involving *N*-dealkylation of the tertiary amine via treatment of the resin-bound product with 1-chloroethyl chloroformate and subsequent methanolic decomposition of the resulting carbamate. The piperidine derivatives **47** were thus obtained in reasonable to excellent yields with purity.[28]

Barluenga et al. reported a similar methodology using more sophisticated dienes, in which 2-amino-1,3-butadienes underwent solid-phase imino-Diels−Alder reaction to provide a highly diverse series of substituted piperidines (Scheme 21).[29] Solid-supported imines were prepared by condensation of Kobayashi's BOBA (*p*-benzyloxybenzylamine) resin[30] with different aromatic aldehydes, employing trimethyl orthoformate for dehydratation or, alternatively, from a *p*-hydroxybenzaldehyde-modified Wang resin. The cycloaddition reaction furnished 4-piperidones **48** and 4-aminopiperidines **49** with high diastereoselectivity and very good yields and purity after cleavage of the products from the solid support.

Scheme 18



Scheme 19



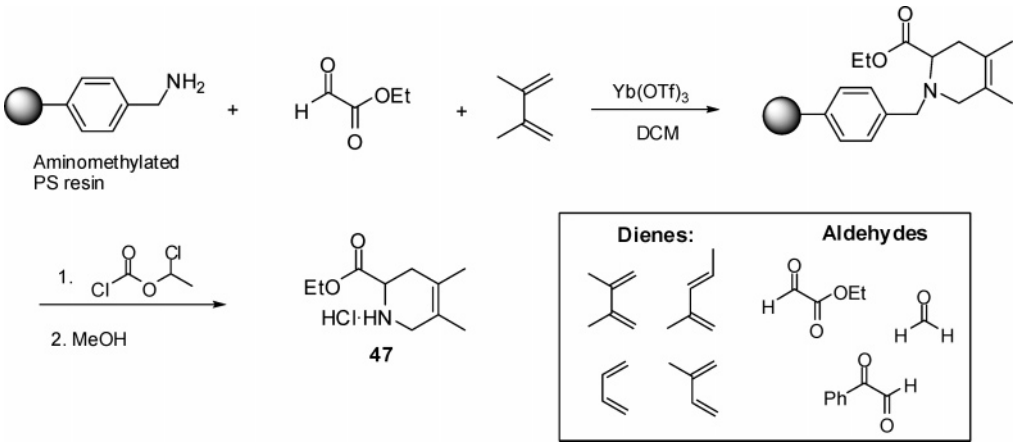
An efficient method for the construction of 2,3-dihydro-4-pyridones on solid support has been developed using a Lewis acid-catalyzed Diels−Alder reaction of Danishefsky's diene with polymer-bound aldimines (Scheme 22).[31] The Wang resin-bound imines **50** were treated with Danishefsky's diene **51** in dry THF in the presence of a Lewis acid to form the 2,3-dihydro-4-pyridones **52** on the resin. Various Lewis acids were tested, including $ZnCl_2$, $AlCl_3$, Et_3AlCl, $TiCl_4$, $BF_3{\cdot}OEt_2$, and $Yb(OTf)_3$, of which the water tolerant Lewis acid $Yb(OTf)_3$ gave the highest yield. $Yb(OTf)_3$ is among the lanthanide Lewis acid catalysts that have been used in studies of solution phase aza Diels−Alder and other organic reactions.

The aforementioned procedure was performed using imines linked through the nitrogen atom to a Rink amide resin, an aminomethyl polystyrene-based resin. The product is cleavable from the Rink linker by TFA (Scheme 23). Even ketones were transformed into 2,2-disubstituted dihydropyridones **53**[32] using this method.

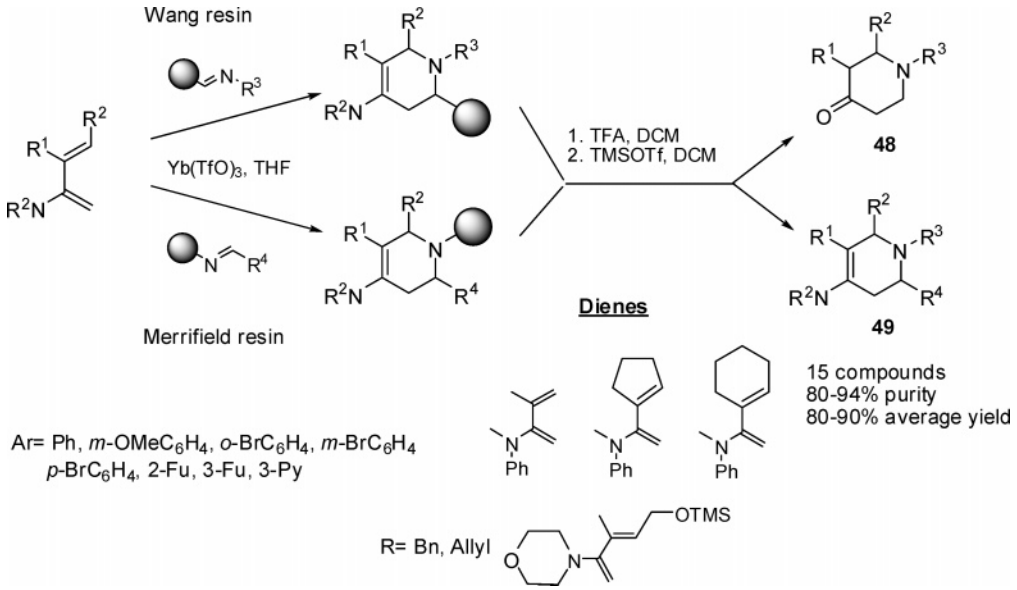
A diverse set of 2,3-dihydro-4-pyridones has also been prepared on a soluble polymer support, where PEG-supported amine or aldehyde was used to generate the imine component (Scheme 24).[33]

The same methodology was used with Danishefsky's diene to synthesize the peptidomimetic opioids **54** and **55**, which are derived from *N*-alkyl-2-alkyl-2,3-dihydro-4-pyridone (Scheme 25). The central reaction with readily available building blocks under mild conditions, illustrating the utility of the [4+2] cyclocondensation in the synthesis of novel, complex heterocycles.[34]

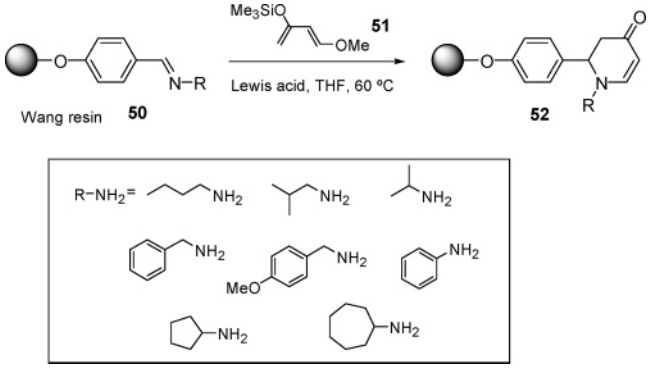
Scheme 20



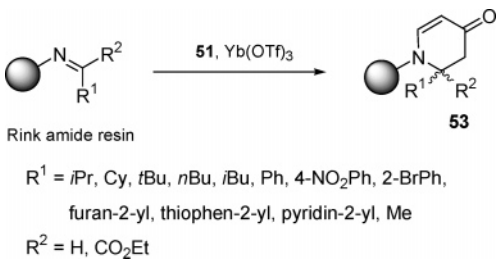
Scheme 21



Scheme 22



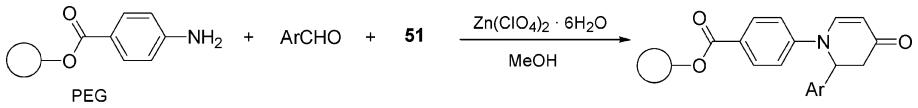
Scheme 23



3.1.4. Azo Compounds as Dienophiles. Synthesis of Pyridazines. In the late 1970s, Gaviña et al. developed the first example of a solid-phase aza Diels−Alder reaction with their preparation of a perhydropyridazine for a mechanistic study of the pericyclic reactions of diimines.[35] The diimine dienophile was obtained in situ by oxidation of hydrazine hydrochloride, and then it was reacted with a solid-supported diene.

N-Acyl-2-substituted-dihydro-4-pyridones, dihydro-4-pyridones, 3,4-ketopiperidines, 2,4-disubstituted pyridines and tetrahydropyridines have also been efficiently synthesized on a solid support, using a resin activation/capture (REACAP) approach (Scheme 26). REACAP is centered about the on-resin formation of a reactive intermediate that is subsequently transformed into a stable, covalently supported molecule.[36] For example, in the synthesis of the *N*-acyl-2-substituted-dihydro-4-pyridone **56**, the requisite acyl-pyridinium complex was obtained from reaction of the precursor, ether-bound 4-hydroxypyridine **57**, with an acid chloride. Treatment of the complex with a Grignard reagent led to the resin-bound enol ether **58**, as well as unreacted starting material **57**. A stereospecific Diels−Alder addition afforded a series of highly substituted 5-oxo-2-azabicyclo[2.2.2]octane **59** (Y = C) and triaza analogues **59** (Y = N). The scope of the

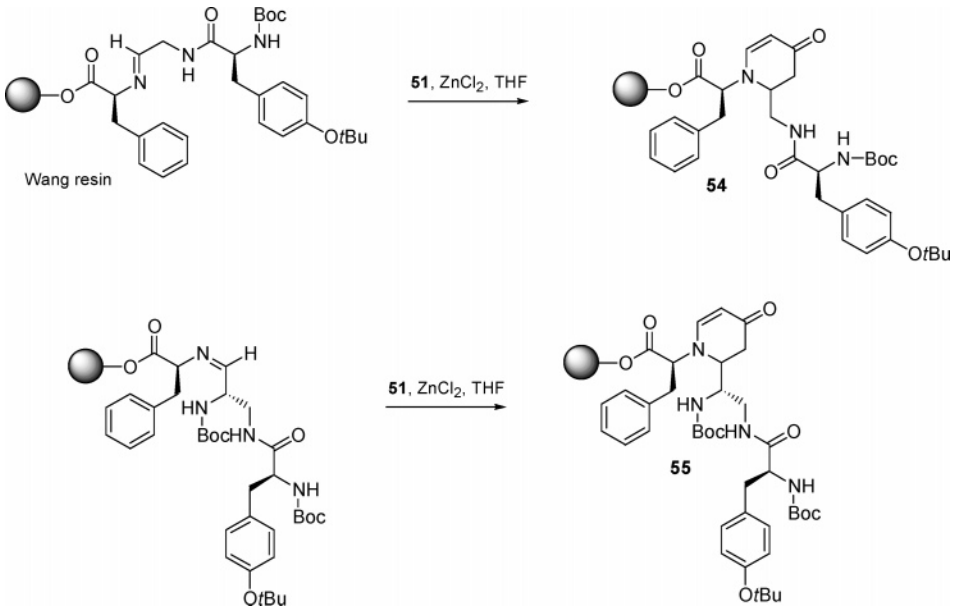
Scheme 24



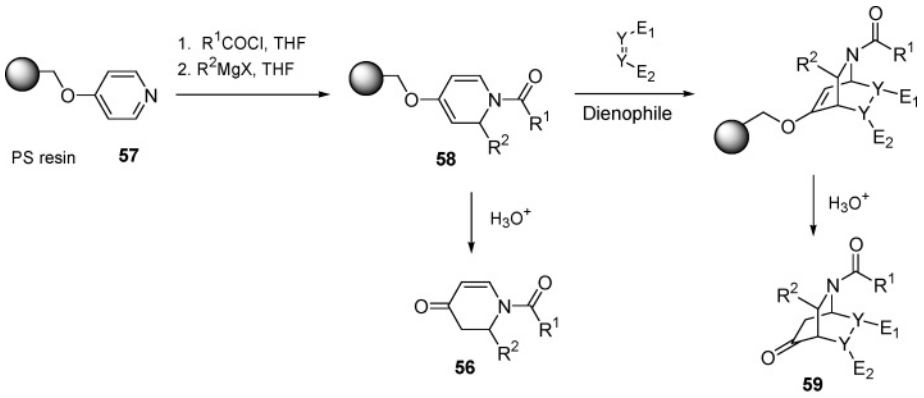
ArCHO

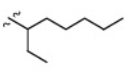
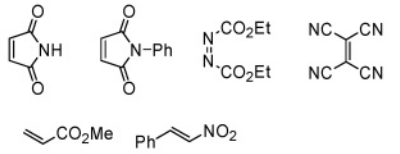
PhCHO, 4-MeC_6H_4CHO, 3-MeC_6H_4CHO, 4-$MeOC_6H_4CHO$, 3-$MeOC_6H_4CHO$, 3-FC_6H_4CHO, 4-ClC_6H_4CHO, 3-ClC_6H_4CHO, 4-BrC_6H_4CHO, 3-BrC_6H_4CHO, 4-NCC_6H_4CHO, 3,5-$F_2C_6H_3CHO$, 3,5-$Cl_2C_6H_3CHO$, 2-Naphthaldehyde, Furfural

Scheme 25



Scheme 26

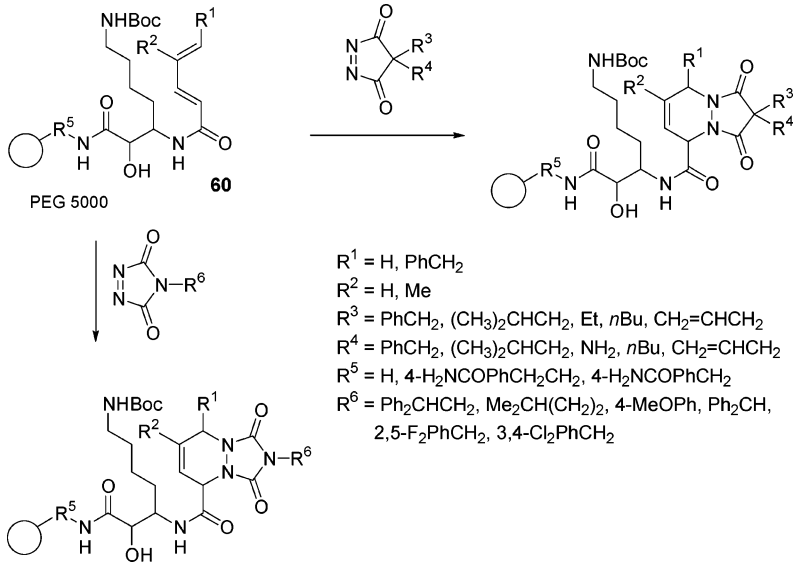


R^1 = Ph, *p*-Me-Ph, *m*-OMe-Ph, 	**Dienophile:** 
R^2 = Ph, Cy, TMS, Me	

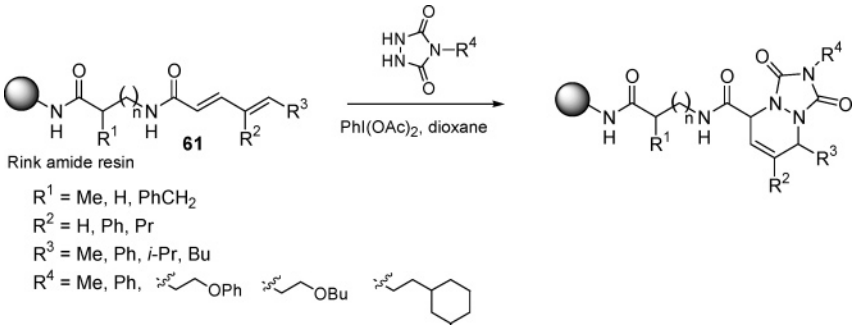
reaction is quite broad because excellent purity and stereospecificity were obtained for a variety of dienophiles and dienes. The approach is readily amenable to automation and has been used to prepare libraries based on the highly rigid bicyclo[2.2.2]octane and triaza analogues.

Solid-phase Diels−Alder cycloadditions have been shown to be highly efficient for the synthesis of libraries of compounds that mimic the secondary structures of certain proteins. PEG-5000 poly(ethylene glycol) monomethyl ether resin was used to prepare the anchored dienes **60**.[37] A typical synthetic sequence, involving attachment of the linker, coupling of the dienoic acid, Diels−Alder cycloaddition, and cleavage, affords products of greater than 90% purity and in high yield. The dienophiles used for the reaction comprised several

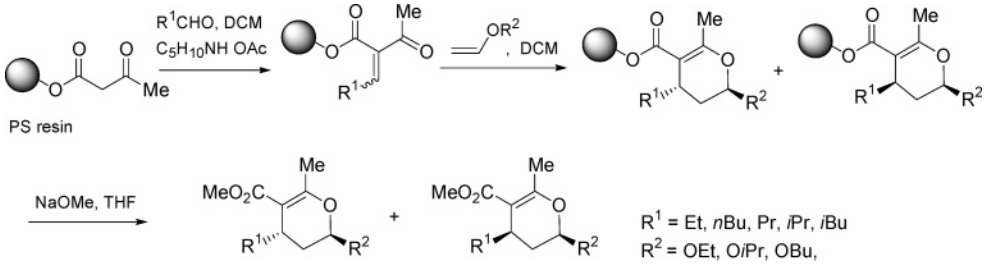
Scheme 27



Scheme 28



Scheme 29



pyrazolinediones and 1,2,4-triazolinediones (Scheme 27). The methodology developed was then used for the preparation of libraries of analogues, from which several potent and selective inhibitors of proteases have been discovered.[38]

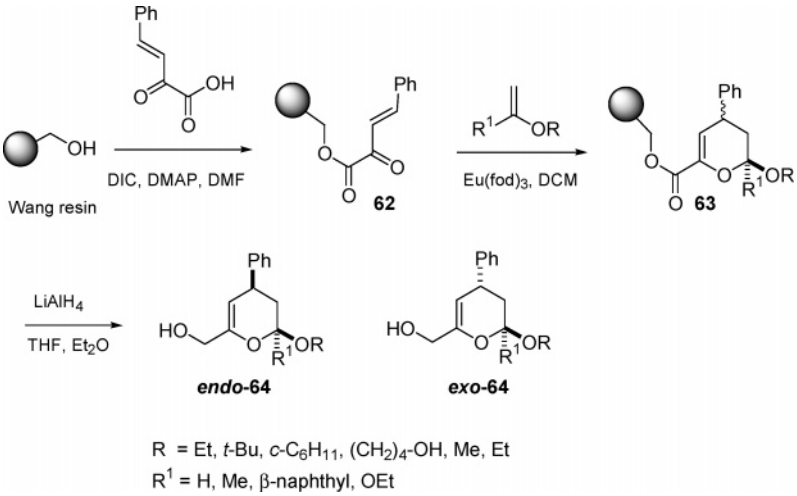
A similar strategy was used for the SPS of a library of triazolopyridazines by in situ generation of the azo compounds via oxidation of a pyrazolidindione. The Homer−Wadsworth−Emmons (HWE) reagent diethylphosphonoacetic acid was attached to the *N*-terminus of an amino acids on Rink amide resin (Scheme 28). HWE reaction with a variety of α,*β*-unsaturated aldehydes gave high conversion to the diene amides **61**. Subsequent [4+2] cycloaddition with 4-substituted urazines, followed by cleavage of the product from the resin, gave triazolopyridazines.[39]

3.2. Oxygen-Containing Heterocycles. 3.2.1. Synthesis of Pyrans. Chemoinformatic analysis of natural product structures[40] has revealed that the tetrahydropyran motif is among the most common of natural scaffolds, present as a core element in myriad antibiotics, marine toxins, and pheromones.[41] Tetrahydropyranes can be synthesized on solid-phase supports via Diels−Alder chemistry, either by reaction of an α,*β*-unsaturated ketone, as oxadiene, with a dienophile or by reaction of a carbodiene with a ketone as dienophile.

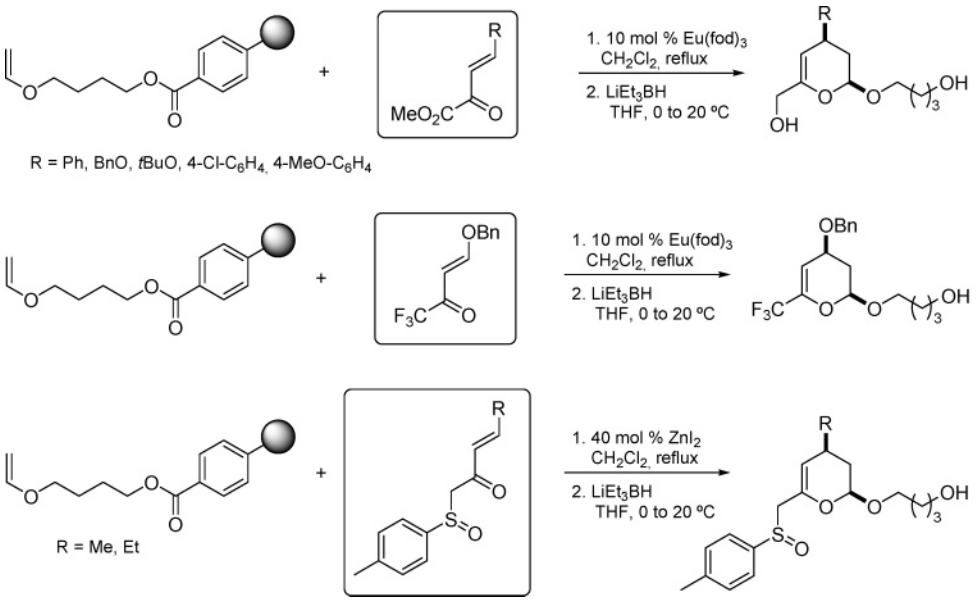
3.2.1.1. α,*β*-Unsaturated Ketones as Dienes. Tietze et al. reported the first SPS of a 3,4-dihydropyran, which involved the Knoevenagel transformation of a polystyrene resin-linked acetoacetate into an α,*β*-unsaturated ketone (an oxabutadiene) that then underwent inverse electron-demand Diels−Alder cycloaddition (Scheme 29).[42] The authors evaluated several aldehyde enol−ethers for the latter step.

The resin-bound heterodiene **62**, obtained by esterification of the free OH groups of a Wang resin with benzylidenepyru-

Scheme 30



Scheme 31



vic acid in the presence of diisopropylcarbodiimide (DIC), has been reacted with various soluble electron-rich dienophiles in [4+2] heterocycloadditions catalyzed by Eu(fod)$_3$ (Scheme 30). Reductive cleavage of the heterocycloadducts **63** using $LiAlH_4$ in ether/THF at 20 °C, followed by mild hydrolysis with aq Na_2SO_4, proceeded smoothly to afford epimeric mixtures of the primary allylic alcoholsproducts *endo*-**64** (major epimer) and *exo*-**64** in high overall yields.[43,44]

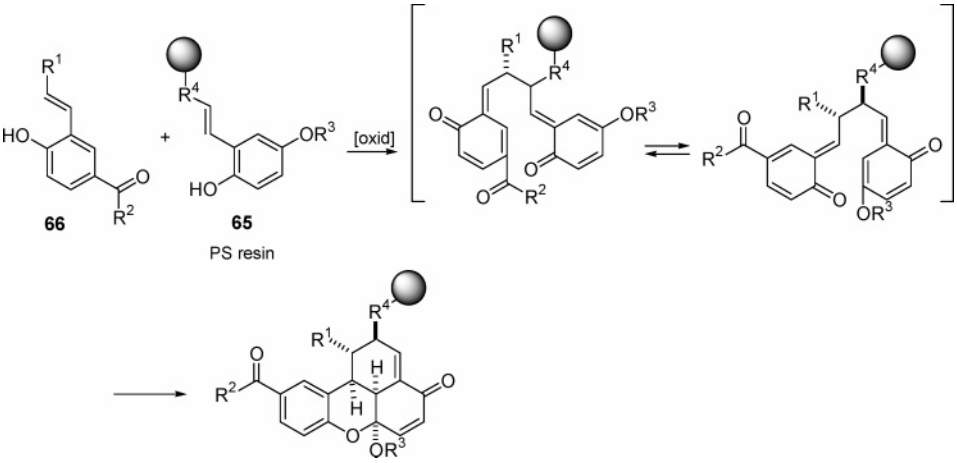
Resin-bound dienophiles, including the carboxypolystyrene-bound vinyl ether of 1,4-butanediol, have been used in efficient, endo-selective hetero-Diels−Alder reactions under Lewis-acid conditions with heterodienes bearing methyl ester, trifluoromethyl, and *p*-tolylsulphinylmethyl groups at the C-2 position. Reductive cleavage of the supported adducts afforded functionalized dihydropyrans, which are particularly interesting for combinatorial synthesis (Scheme 31).[45]

The biomimetic synthesis of carpanone, first accomplished by Chapman, involves diastereoselective oxidative homocoupling of an electron-rich *o*-hydroxystyrene followed by rapid, endo-selective, inverse electron-demand Diels−Alder cycloaddition.[46] To construct a library of carpanone analogues, Lindsley et al. expanded on the original chemistry to include intermolecular oxidative heterodimerization of *o*-hydroxystyrenes.[47] The use of electronically distinct *o*-hydroxystyrenes under the influence of a suitable oxidant, the oxidatively more-reactive electron-rich phenol **65**, immobilized in the solid-phase to reduce its propensity for homodimerisation, reacted preferentially with the oxidatively less-reactive electron-deficient phenol **66** (Scheme 32).

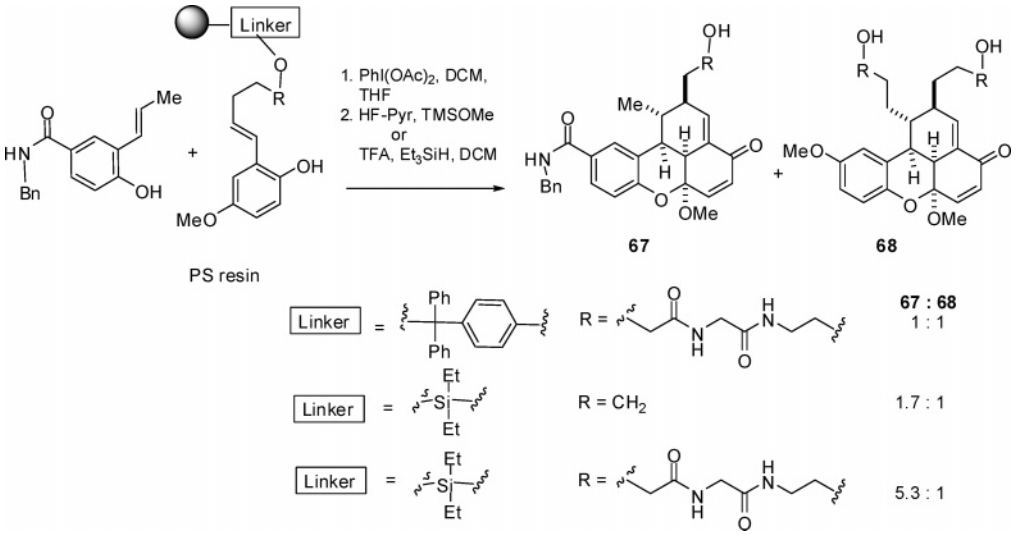
A silicon-based linker combined with an amide-based spacer provided the highest ratio of heterocoupled to homocoupled product, whereas the silicon linker and a hydrocarbon spacer afforded only a slight preference for heterocoupling (Scheme 33). A trityl-based linker and an amide spacer afforded a 1:1 ratio of **67** and **68**.

The use of an amide-based linker attached to the resin through a silyl linkage diminished competitive intrabead coupling. In the six experiments reported, the reaction tolerated diverse functional groups, making it amenable to diversity-oriented synthesis (Scheme 34). The procedure was recently used for the synthesis of a 10 000-member library of carpanone analogues (see section 4.1.5.1, Scheme 72).[48]

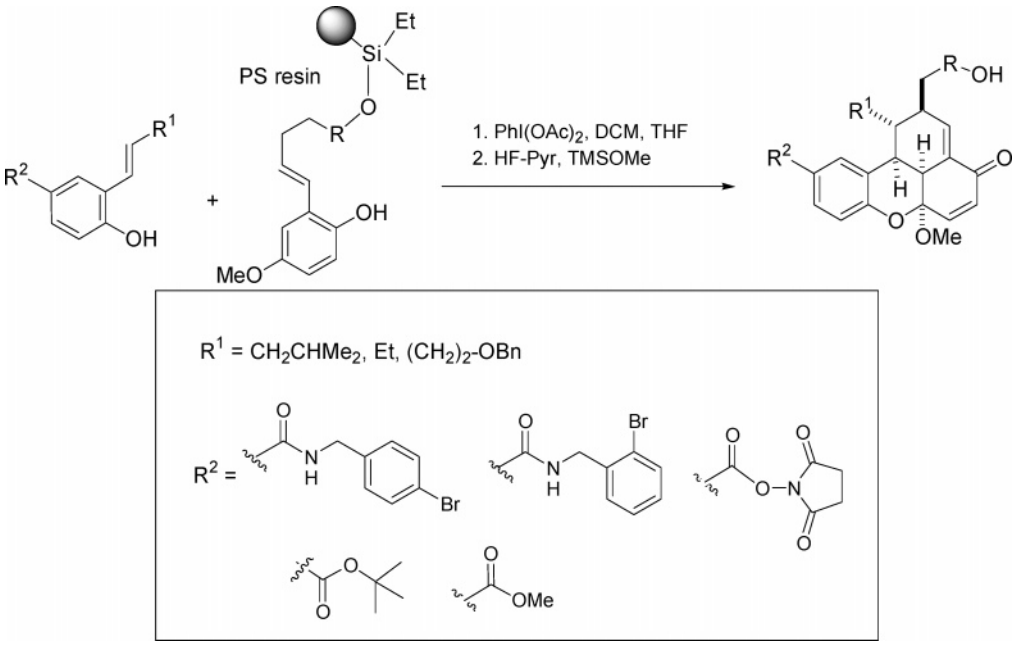
Scheme 32



Scheme 33



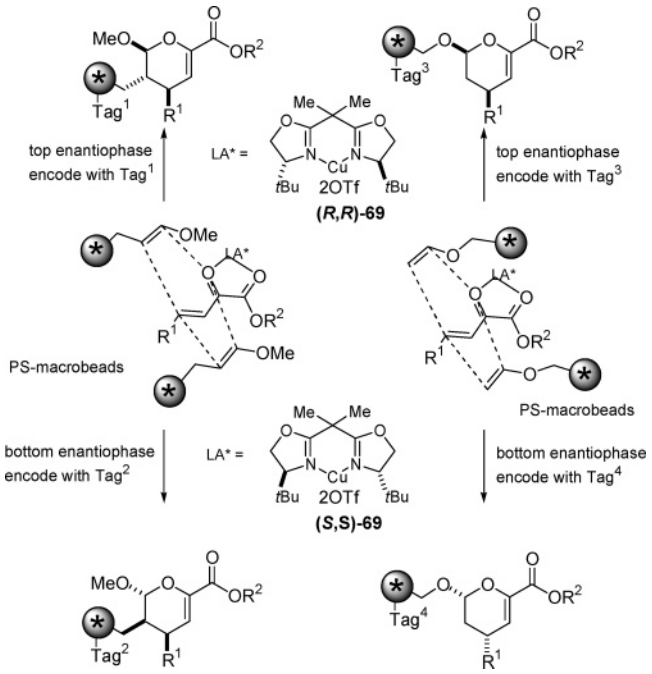
Scheme 34



Whole-cell fluorescence imaging revealed a series of molecules from the library that were able to inhibit exocytosis from the Golgi apparatus.

Evans et al. demonstrated that [Cu(*S*,*S*)-*t*-Bu-Box](OTf)$_2$-catalyzed asymmetric hetero-Diels−Alder reactions (i.e., inverse electron-demand heterocycloadditions of vinyl ethers

Scheme 35



and unsaturated ketoesters) generate a dihydropyran core with up to three chiral centers in a single step.[49] However, the reaction has not been widely explored for diversity-oriented synthesis, which is generally performed on polymer support.[50] The asymmetric cycloaddition was used to synthesize a set of dihydropyrancarboxamides on high-capacity, 500−600 nm polystyrene macrobeads, providing 4320 encoded[51] compounds with high diastereo- and enantioselectivity (Scheme 35).[52] Each bead contained predominantly a single dihydropyrancarboxamide.[53]

Each of the vinyl ethers **BB70** was loaded onto pools of macrobeads using silyl triflate. The support-bound vinyl ethers were then treated with heterodienes **BB71** in THF in the presence of 20 mol % of the [(*t*BuBOX)Cu(OTf)$_2$] complex [(*S*,*S*)- or (*R*,*R*)-**69**], and finally, **BB72** were introduced to provide the support-bound cycloadducts **73**−**75** (Scheme 36). The polystyrene macrobead serves as a microreactor: an important element of the one-bead, one-stock-solution technology platform. Both enantiomers of the ligand were used in separate reactions to obtain a duplicate result and to detect potential matched/mismatched pairs resulting from the use of chiral starting materials (Scheme 36). After the washing and drying steps were completed, each of the cycloadducts was cleaved from the silyl ether linker with hydrogen fluoride/pyridine.

This library synthesis succeeded in using stereochemistry as a diversity element and extended the asymmetric hetero-cycloaddition reaction to the solid-phase, but only one of two potential diastereomers (for the unsubstituted vinyl ethers) was accessed. Catalyst systems with complete external control over enantio- and diastereoselectivity are required to fully realize the potential of stereoselective catalysis in diversity-oriented organic synthesis.

Kurosu et al. used a Cu(OTf)$_2$ complex of Inda-Box (**76**) to catalyze hetero-Diels−Alder reactions of polymer-supported vinyl ethers, obtaining dihydropyrancarboxylic acid derivatives with excellent diastereo- and enantioselectivities.[54] The authors used SynPhase Lanterns (Mimotopes), which feature a non cross-linked surface polymer grafted to an inert base (Scheme 37), as solid supports.

3.2.1.2. Aldehydes and Ketones as Dienophiles. An example of a hetero-Diels−Alder reaction using aldehydes as dienophiles is described in section 3.1.3. Polymer-supported electron-rich dienes were prepared by Mann et al. using Merrifield resin and propanol as spacer (Scheme 38).[55] Preparation of functionalized resin **77** was performed following a literature procedure.[56] Resin **77** has key advantages over the native Brassard diene (e.g., unlike the unanchored reagent, it remains inert in storage at −18 °C for several months). The reactivity of resin **77** in the hetero-Diels−Alder reaction was examined using various aldehydes and ketones and several Lewis acids (e.g., $BF_3{\cdot}Et_2O$, $ZnCl_2$, $MgBr_2$, and Me_2AlCl). Of the Lewis acids tested, Me_2AlCl was the best activator. Cycloaddition and cleavage were achieved in a single step.

Waldmann et al.[57] carried out an enantioselective oxa-Diels−Alder reaction between a polymer-bound aldehyde and Danishefsky diene to assemble the core structure of several natural products (Scheme 39). Catalysts **78** and **79**, developed by Katsuki et al.[58] and Jacobsen et al.,[59] respectively, were tested in the reaction (Figure 1).

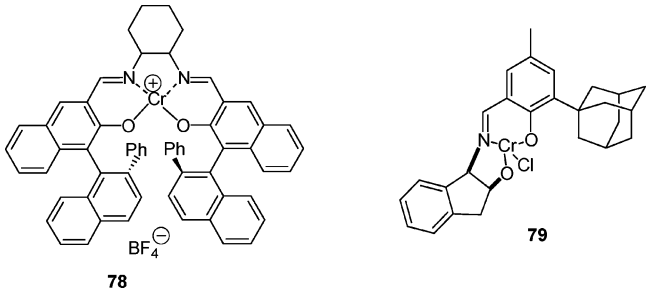


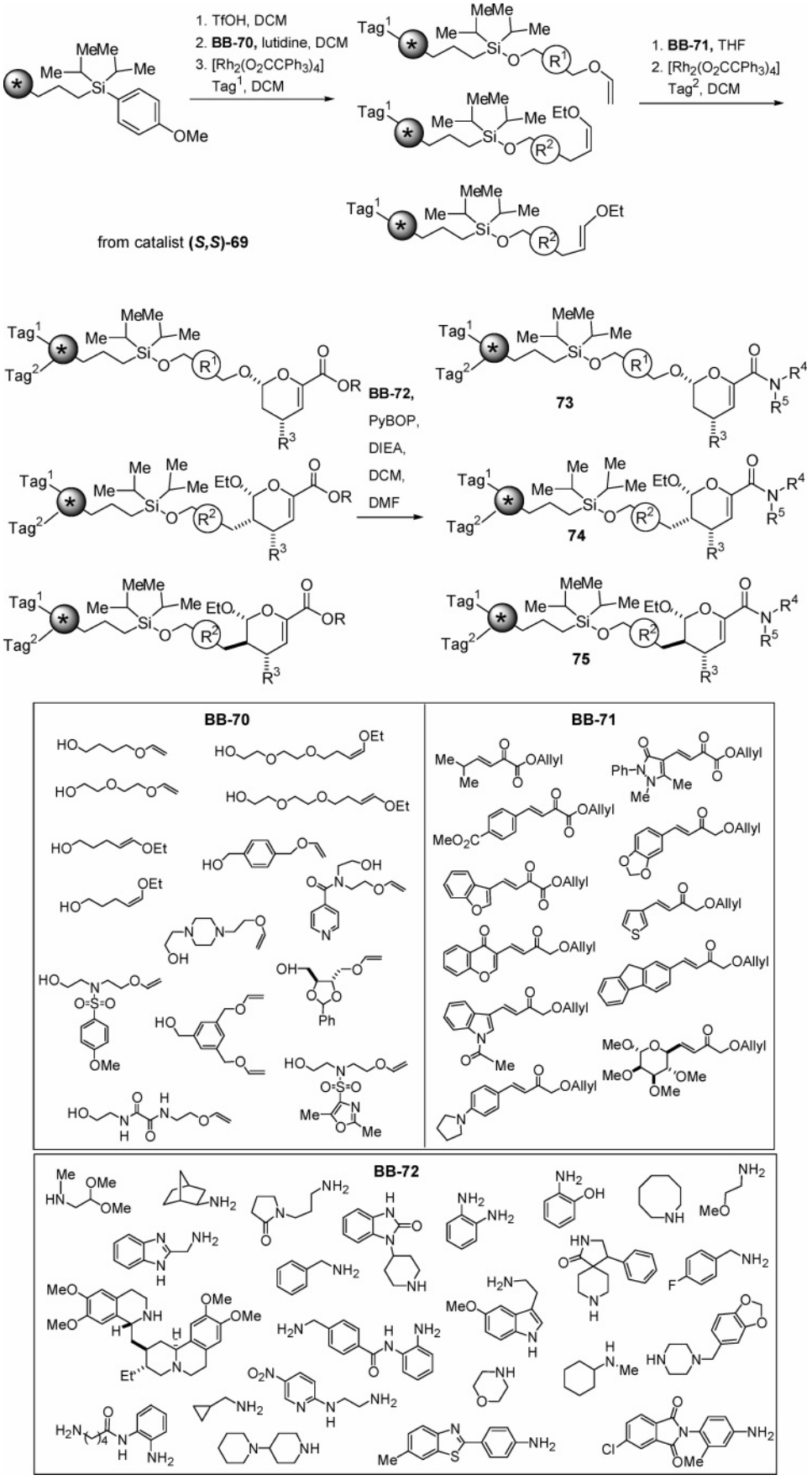
Figure 1.

Although both compounds catalyzed the cycloaddition, the reaction did not proceed to completion with **79**. The best results were obtained with Danishefsky's diene **(51)** and the catalyst **78** at room temperature. After acidic cleavage of the product from the resin, the desired dihydropyrones **80** were obtained in 10−40% overall yield (five steps) and with enantiomeric ratios up to >99% (Scheme 39).

3.2.2. Nitrosoketones as Dienophiles. The 1,2,4-oxadiazole-4-oxide ring has been attached to a Wang resin through position 3 and through position 5 of the heterocycle (see section 4.2.1.3), thereby providing a versatile starting point for diverse synthons.[60] This class of heterocycles is thermally stable up to 130 °C and can be stored indefinitely in the dark, but they easily undergo photochemical cycloreversion to nitriles and nitrosocarbonyls. Photolysis generates the nitrosocarbonyl intermediates **81**, which are released into solution and, in the case of hetero-Diels−Alder cycloadditions, trapped by suitable dienes and, in the case of ene reactions, by olefins. The resin collected after the last step allows for recycling of the starting material (Scheme 40).

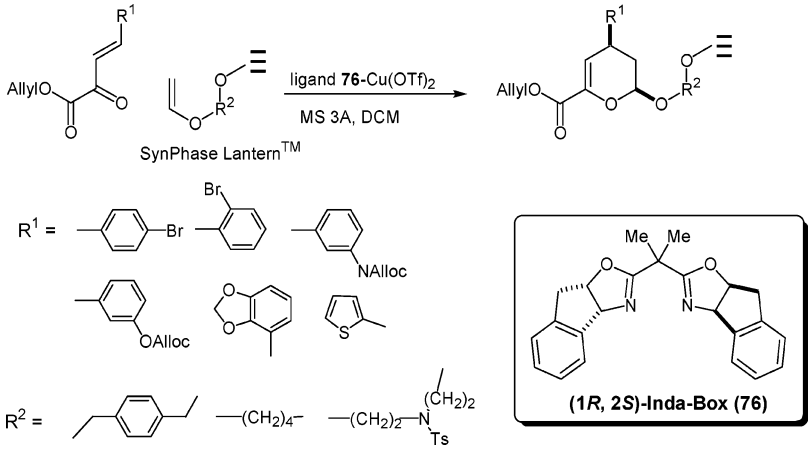
3.2.3. α,α′-Dioxothiones as Dienes. Synthesis of Thiapyranes. Menichetti et al. have studied α,α′-dioxothiones

Scheme 36

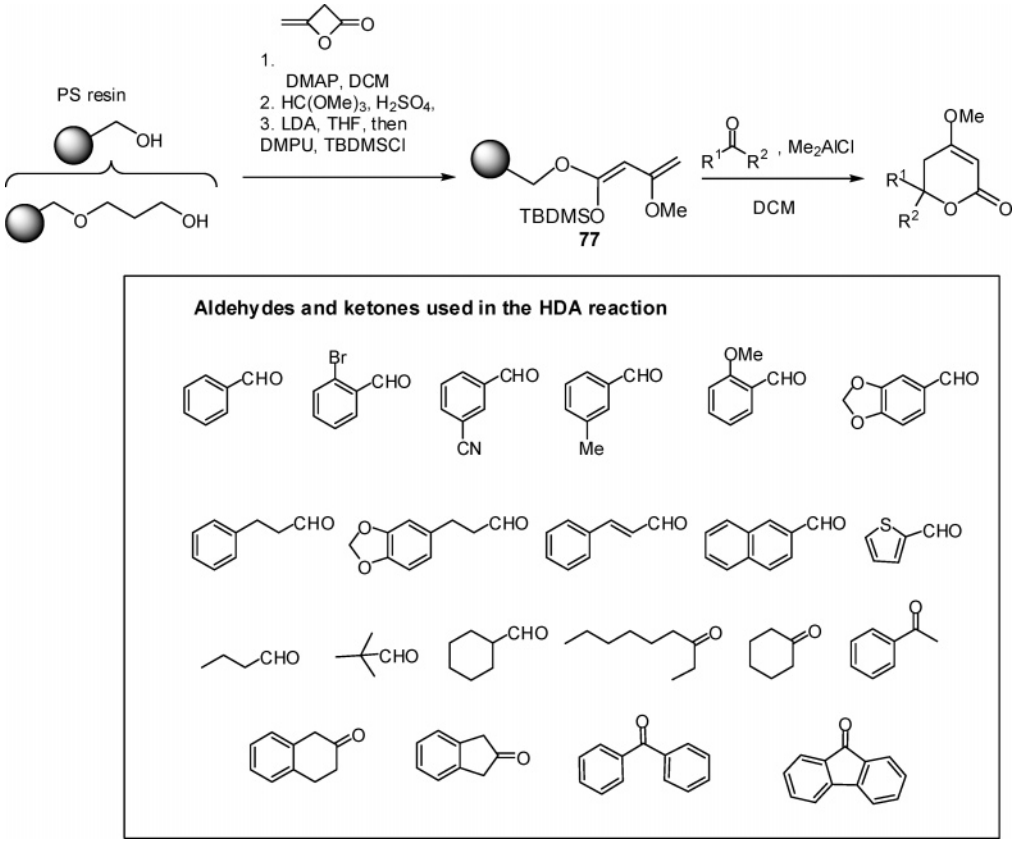


as electron-poor heterodienes in inverse electron-demand hetero-Diels−Alder reactions using various electron-rich alkenes (Scheme 41).[61] The authors developed a practical procedure for the formation of solid-supported α,α′-dioxothiones, starting from β-ketoester-modified Wang and hydroxymethylated polystyrene (PS) resins. The hetero-

Scheme 37



Scheme 38



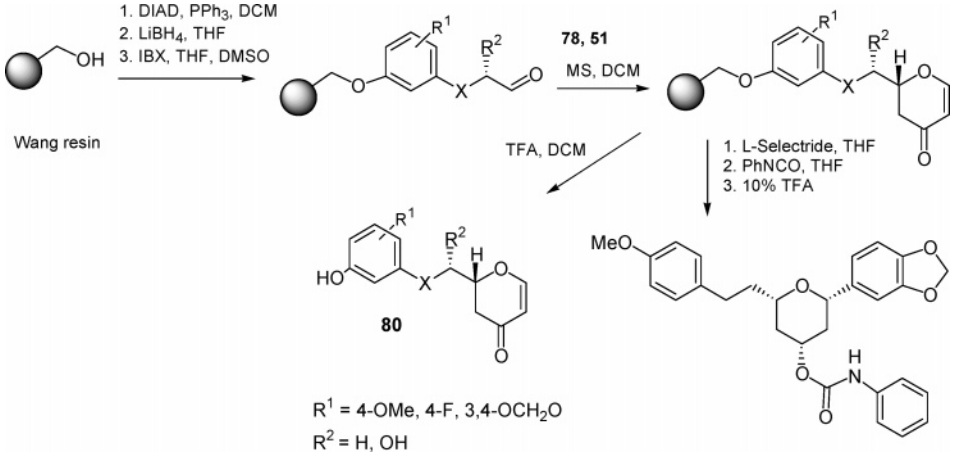
Diels−Alder reactions of these species, used either as electron-poor dienes or dienophiles, followed by simple cleavage of the products from the resin by transesterification with sodium methoxide, provided the desired cycloadducts in overall yields up to 90%.

3.3. Polycyclic Nitrogen- and Oxygen-Containing Heterocycles. 3.3.1. Furane as a Diene. Synthesis of Polyheterocyclic Compounds. Tricyclic compounds have been prepared by solid-phase intramolecular Diels−Alder reaction of vinylfurans.[62] The synthesis began with treatment of a phosphonoacetyl-Wang resin with an Fmoc-protected amino aldehyde in the presence of Et_3N and LiBr, followed by Fmoc group removal with piperidine to give primary amines (Scheme 42). The resin-bound trienes **82** were conveniently constructed using commercially available substituted furan derivatives. The epoxyhydroisoindoline carboxylic acids **83** were then obtained in only a few steps. Endo-selectivity was observed in all the cases.

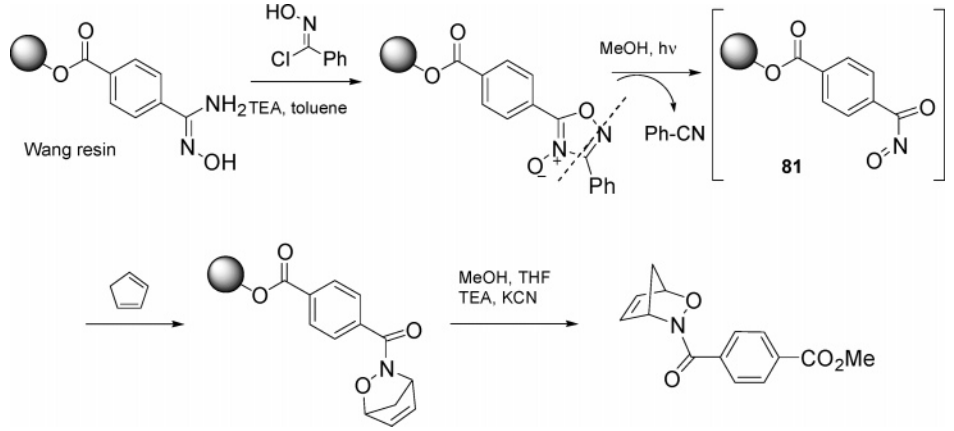
Rigid, highly substituted nitrogen- and oxygen-containing tricycles have been synthesized on ArgoGel. The resin-bound furans **84**, obtained by reductive amination of the appropriate furfural,[63] were subject to intramolecular Diels Alder reaction with several activated dienophiles. Standard TFA cleavage of the resulting products from the resin afforded the tricyclic compounds **85** (Scheme 43).

The same method was used by Paulvannan[64] via tandem four-component condensation/intramolecular Diel-Alder reaction for the preparation of a small library of compounds similar to **85** (Scheme 44). Oikawa also constructed a structurally related library using a tandem Ugi/Diels−Alder

Scheme 39



Scheme 40



reaction of 5-hydroxymethylfurfural anchored to a PEG monomethyl ether solid support.[65]

The furan-based scaffold 5-hydroxymethylfurfural has also been used by Kundu[66] to prepare highly diverse libraries via solid-phase cycloaddition, multicomponent, and cyclization reactions.

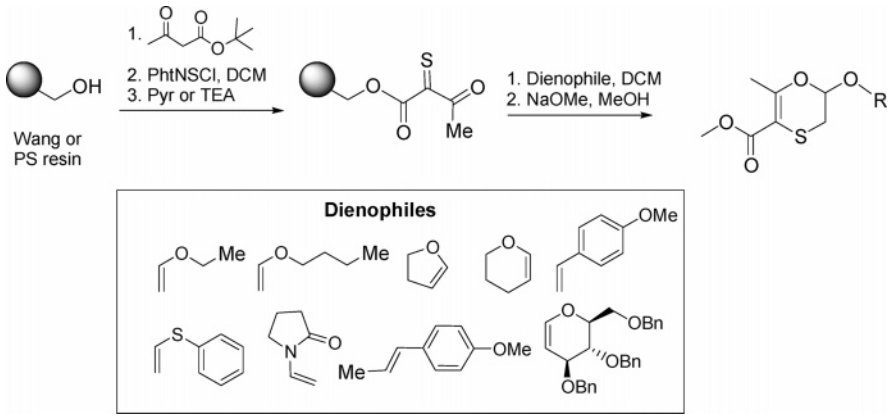
"Tandem reactions" are powerful tools for the synthesis of structurally complex five-, six-, and seven-membered rings. Tandem Ugi-4 component coupling and intramolecular Diels−Alder reaction[67] was first achieved in solution to obtain a polycyclic compound with high stereoselectivity. The same strategy was later applied to the efficient solid-phase synthesis of structurally complex compounds such as **88**, using the triisopropylsilyl protecting group to mimic a silicon-based linker.[68] The functionalized resin **86** was obtained from polystyrene (PS) beads containing a carbon and silicon linker that allows attachment and release of small molecules via silicon−oxygen. The immobilized amine **86** was treated with excess furfural, benzyl isocyanide, and fumaric acid (3-bromobenzyl)monocarboxamide to give the intramolecular Diels−Alder adduct **87** as a single stereoisomer which was subsequently transformed to the 7−5−5−7 polycyclic compound **88** (Scheme 45).

4. [3+2] Cycloadditions

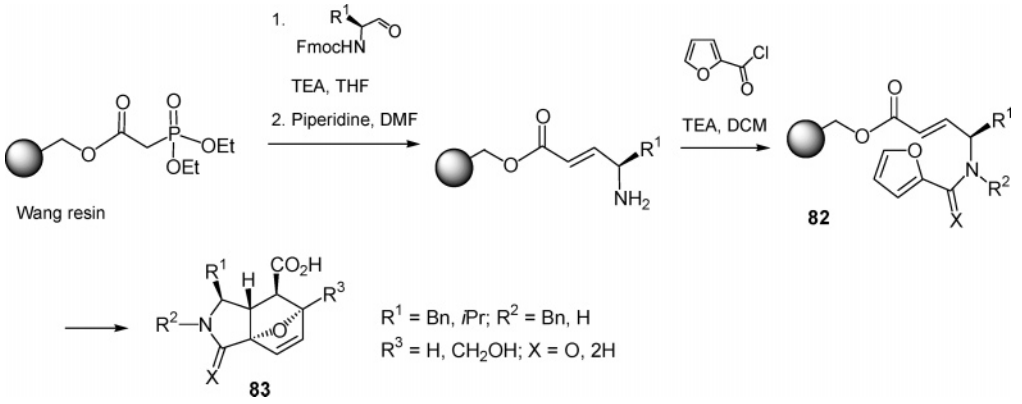
1,3-Dipolar cycloadditions are among the most important and versatile synthetic methods for the preparation of five-membered heterocycles.[69] They proceed through the addition of 1,3-dipoles to dipolarophiles. Numerous 1,3-dipoles, containing various combinations of carbon and heteroatoms, are available. Dipolarophiles include alkenes and alkynes, as well as double and triple bond-bearing heteroatoms. Because of the possible combinations of 1,3-dipoles and dipolarophiles, many types of 1,3-dipolar cycloadditions have been reported. Although the bulk of the chemistry has been performed in solution, several solid-phase 1,3-dipolar cycloadditions have recently been performed, whereby either the 1,3-dipole or the dipolarophile is immobilized onto the solid support. Solid-phase 1,3-dipolar cycloadditions have been used to prepare libraries of monocyclic five-membered heterocycles and fused derivatives. Because early work in this area has already been reviewed,[2,3] herein we focus on the relevant literature published from 2003 to 2006.

4.1. Nitrogen-Containing Heterocycles. 4.1.1. Azomethine Ylides. 4.1.1.1. Acyclic Azomethine Ylides. Synthesis of Pyrrolidines, Pyrroles, and Pyrrolo[3,4-*c*]pyrroles. Pyrrolidines and pyrroles can be formed by [3+2] cycloaddition reaction of azomethine ylides to alkenes and to alkynes, respectively. Komatsu et al. developed a synthesis of pyrrolidine and pyrrole derivatives from polymer-supported *N*-silylated azomethine ylides (Scheme 46).[70] The 1,3-dipoles were generated from resin-bound α-silylimines **89** by treatment with trifluorophenylsilane in toluene at 40 or 60 °C for 48 h. The reaction was performed in the presence of different cyclic and acyclic dipolarophiles to yield diverse cycloadducts, which were cleaved from the resin with TFA.

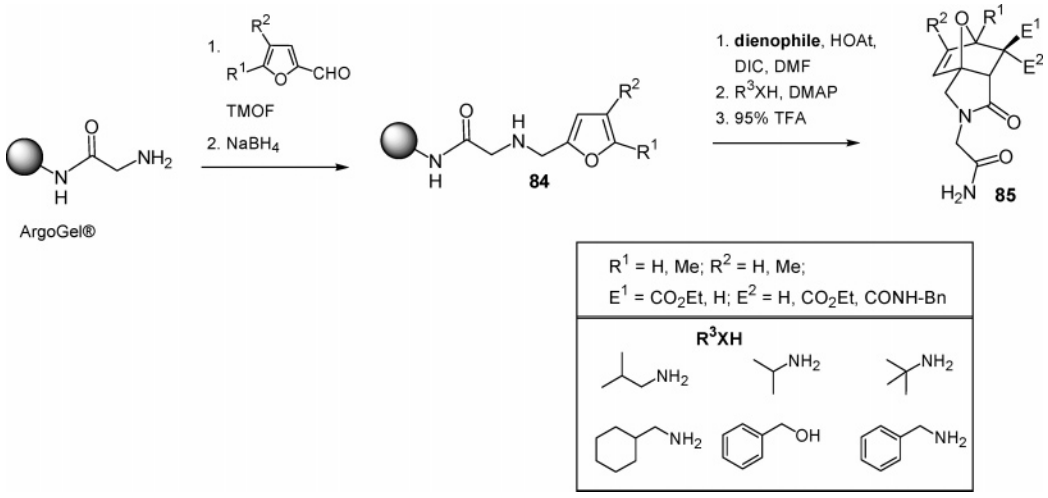
Scheme 41



Scheme 42



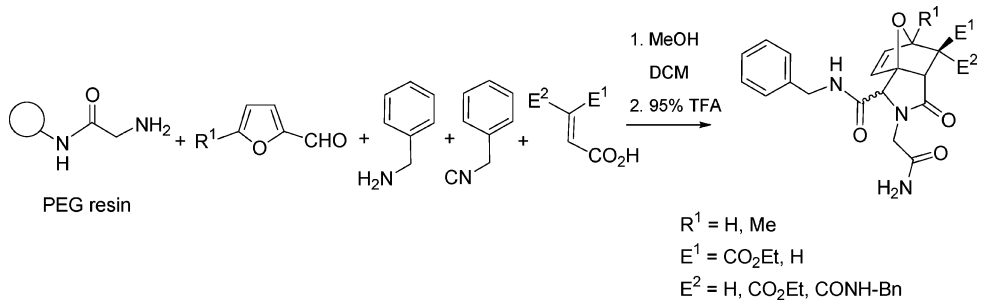
Scheme 43



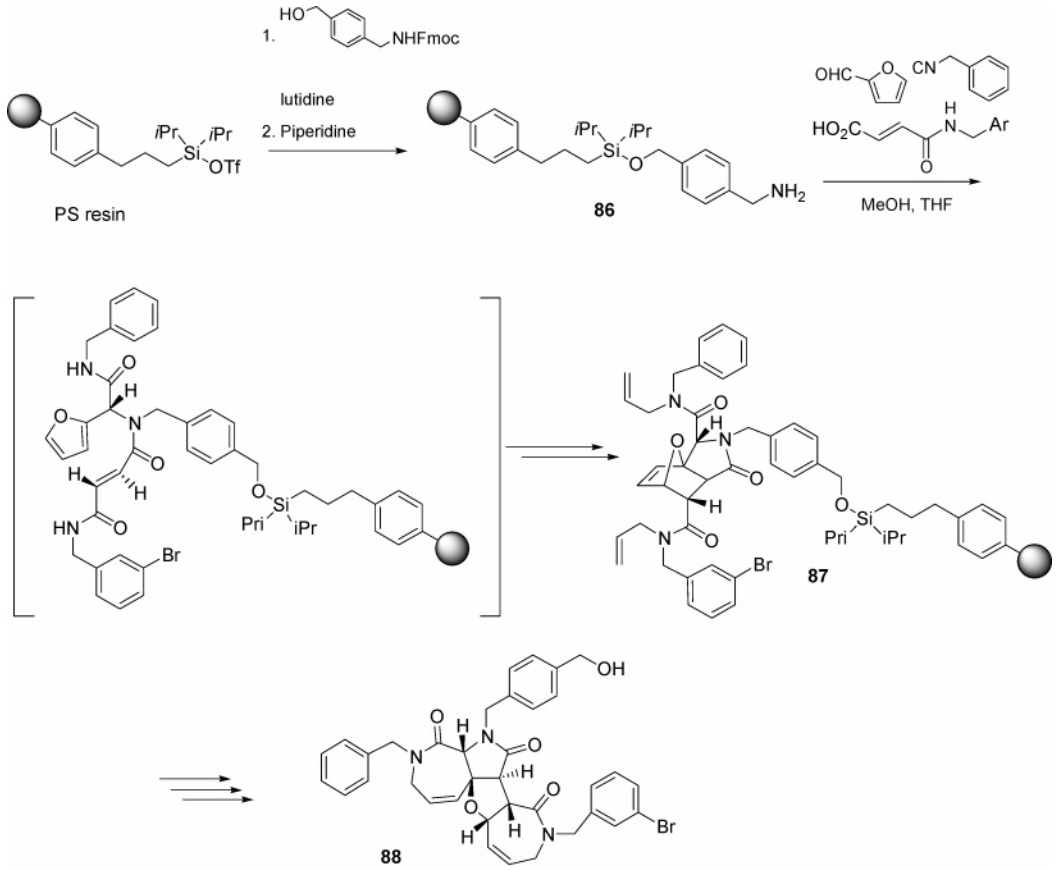
Thus, *N*-phenylmaleimide was reacted with polymer-bound α-silylimines **89a**−**d** to afford the bicyclic pyrrolidine derivatives **90** and **91** in 61−81% yields. Notably, compounds **90a** and **91a** were obtained in the highest yields and with high stereoselectivity. In fact, lower yields and stereoselectivity were obtained when **90a** and **91a** were prepared in solution following a similar approach. Other dipolarophiles, such as dimethyl fumarate and dimethyl maleate, were reacted with **89a** to give the tetrasubstituted pyrrolidines **92**−**93** (53% yield) and **94**−**95** (43% yield), respectively. Although the stereoselectivities of these reactions were not satisfactory, the stereochemistry of the two carbon centers derived from the dipolarophiles was retained. Finally, reaction of DMAD with **89a**, followed by oxidation with DDQ, yielded the expected pyrrole **96** (31% yield) and the byproduct **97** (12% yield). The authors also described a traceless variant of the strategy, in which dimethylsilylated polystyrene **98** is used as starting resin (Scheme 47).

Schreiber et al. described a catalytic asymmetric [3+2] cycloaddition of olefins to resin-bound azomethine ylides for the solid-phase preparation of substituted pyrrolidines (Scheme 48).[71] The synthesis started from alkylsilyl-derivatized PS macrobeads (500−600 μm), which were reacted with 4-hydroxybenzaldehyde and methyl glycinate. The

Scheme 44



Scheme 45



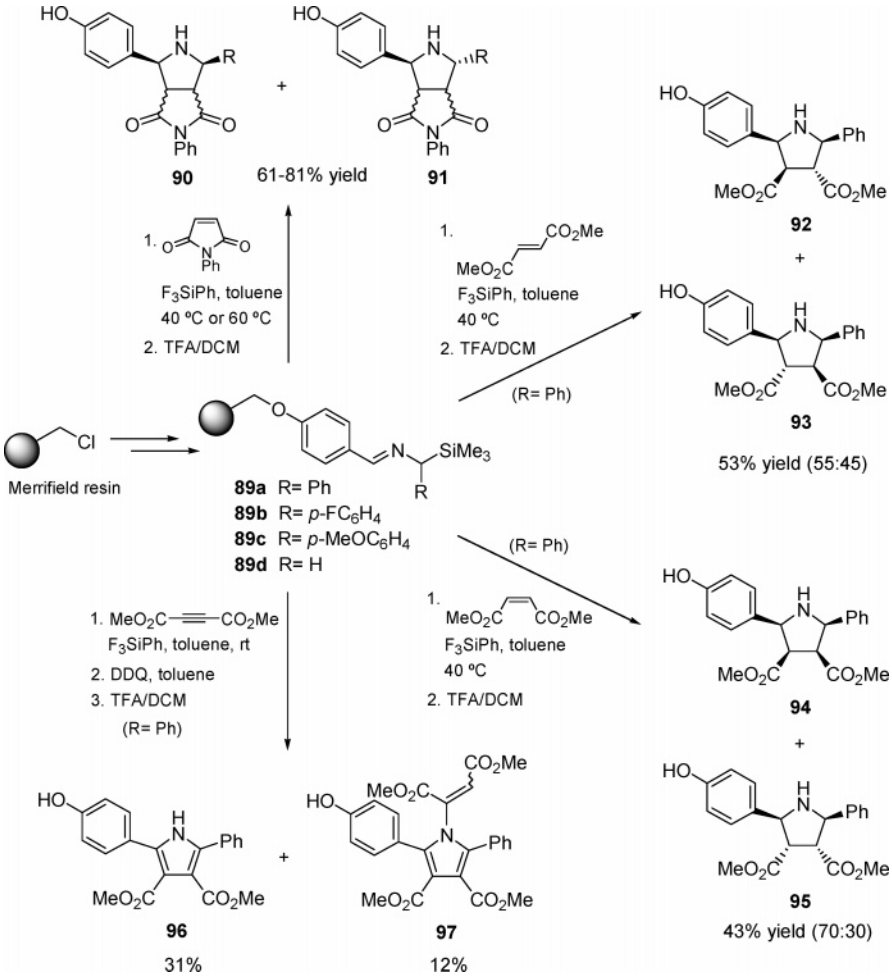
resulting macrobead-bound iminoester **99** was treated with *tert*-butyl acrylate, DIEA, and silver(I) acetate/(*S*)-1-(2-diphenylphosphino-1-naphthyl)isoquinoline (QUINAP) as catalyst in THF at −45 °C for 40 h. Cleavage of the product from the resin with HF/pyridine, followed by a TMSOEt quench, provided the pyrrolidine **100**, having three stereogenic centers, in 79% yield and 90% ee over three steps.

A similar procedure has been used to synthesize fulleropyrrolidines (Scheme 49).[72] Treatment of PEG-polystyrene-bound iminoesters **101** with an excess of C_{60} fullerene in *o*-dichlorobenzene at 100 °C for 6 h, followed by an acidic cleavage step, afforded fulleropyrrolidine derivatives **102** in 76−85% yield. The solid-phase method proved to be more efficient than an analogous method in solution with respect to reaction time, total amount of solvent needed, and yields.

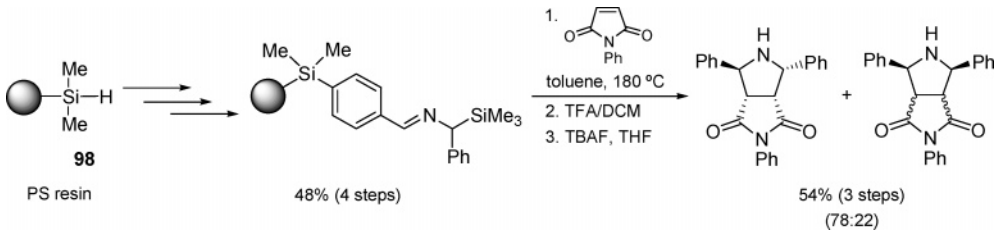
On the basis of this type of cycloaddition, Portnoy et al. described a SPS of pyrrolidines through a three-component 1,3-dipolar cycloaddition involving a resin-bound aldehyde, sarcosine (*N*-methylglycine), and an acyclic alkene (Scheme 50).[73] When these compounds were heated in DMF, a nonstabilized azomethine ylide was generated by decarboxylation of the imine that is formed by reaction of the aldehyde and sarcosine. Cycloaddition of the 1,3-dipole with methyl acrylate provided diastereomers **103** and **104** in a 6:1 ratio. The regioselectivity of the cycloaddition decreased when acrylonitrile was used as dipolarophile. The reaction produced two major compounds, **105** and **106**, along with traces of **107** and **108**. After TFA cleavage from the resin, the final products were obtained in high yield and purity.

Pyrrolo[3,4-*c*]pyrroles have likewise been synthesized, except *N*-phenylmaleimide was used as the dipolarophile, whereby either the aldehyde or the amino acid is immobilized on *p*-alkoxy aldehyde resin (Scheme 51).[73] In the former, resin-bound aldehyde, *N*-phenylmaleimide, and an amino acid (sarcosine, *N*-methylated alanine, or *N*-methylated valine) were heated in DMF at 90 °C for 24 h. In the latter,

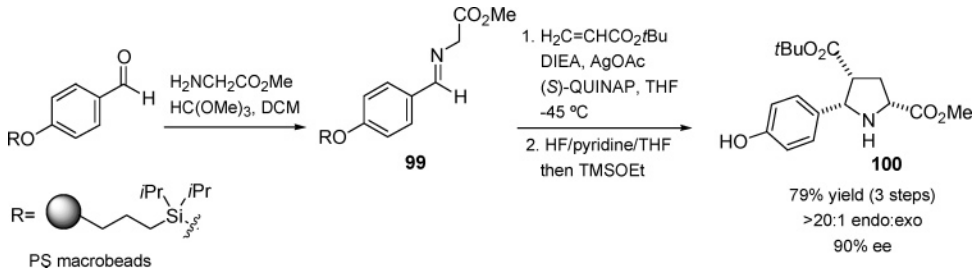
Scheme 46



Scheme 47



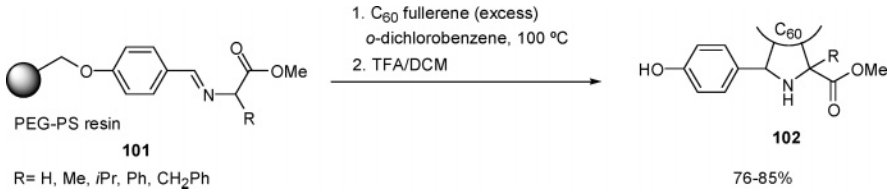
Scheme 48



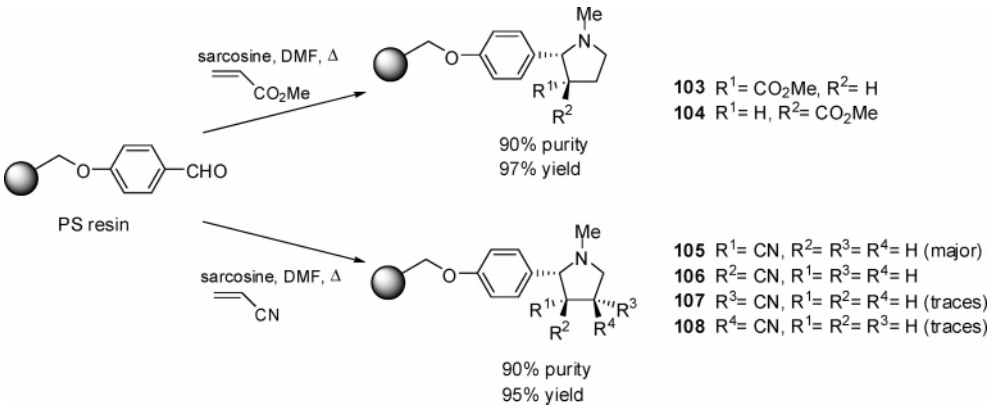
resin-bound *N*-benzylglycine **109**, benzaldehyde, and *N*-phenylmaleimide were heated in DMF. In both cases, bicyclic, diastereomeric pyrrolidines were obtained in high yields and purities and were analyzed on-resin and in solution after TFA cleavage.

4.1.1.2. Pyridinium Ylides. Synthesis of Indolizines. Heterocyclic azomethine ylides have been reported to afford polycyclic derivatives via [3+2] cycloadditions with alkenes and alkynes. Chen et al. prepared 1,2,3-trisubstituted indolizines on soluble polymer from in situ-generated PEG-bound pyridinium ylides (Scheme 52).[74] In this study, PEG-supported pyridinium salt **110** was used as precursor to the pyridinium ylide. Exposure of **110** to alkenes in a solution of DIEA and tetrakis(pyridine)cobalt(II) dichromate (TPCD) in DMF at 80−90 °C for 2−3 h led to formation of the pyridinium ylide, followed by cycloaddition with the alkenes

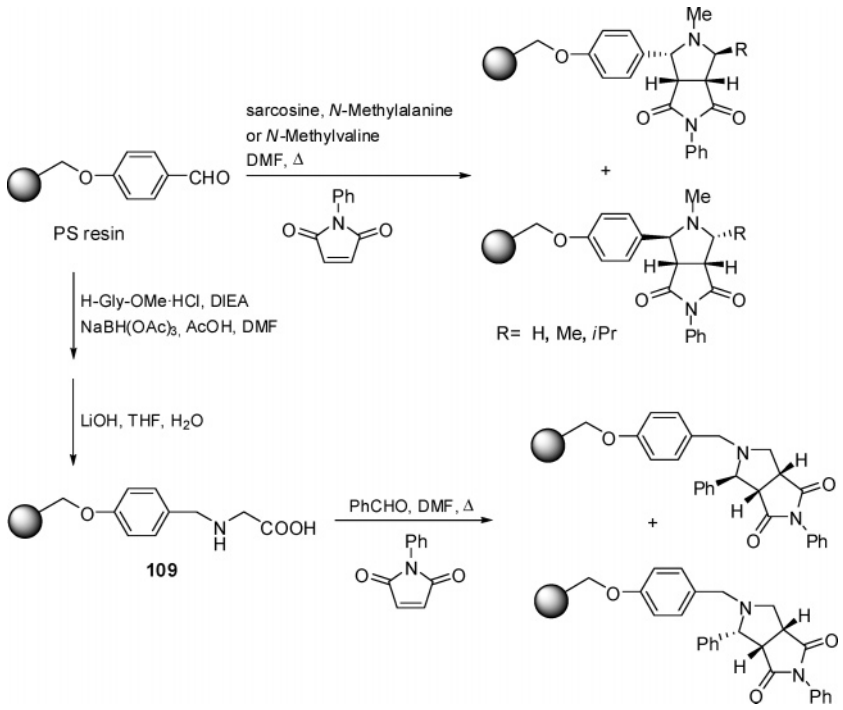
Scheme 49



Scheme 50



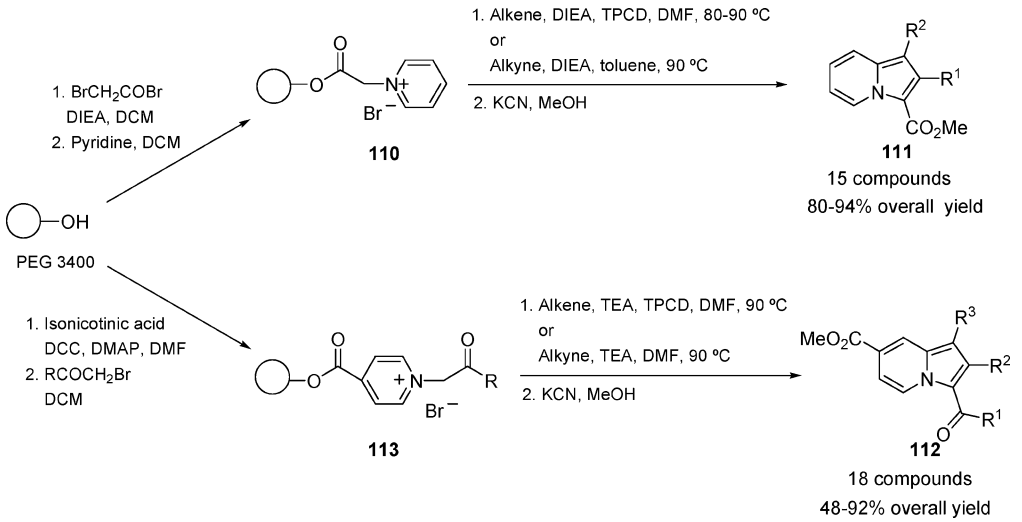
Scheme 51



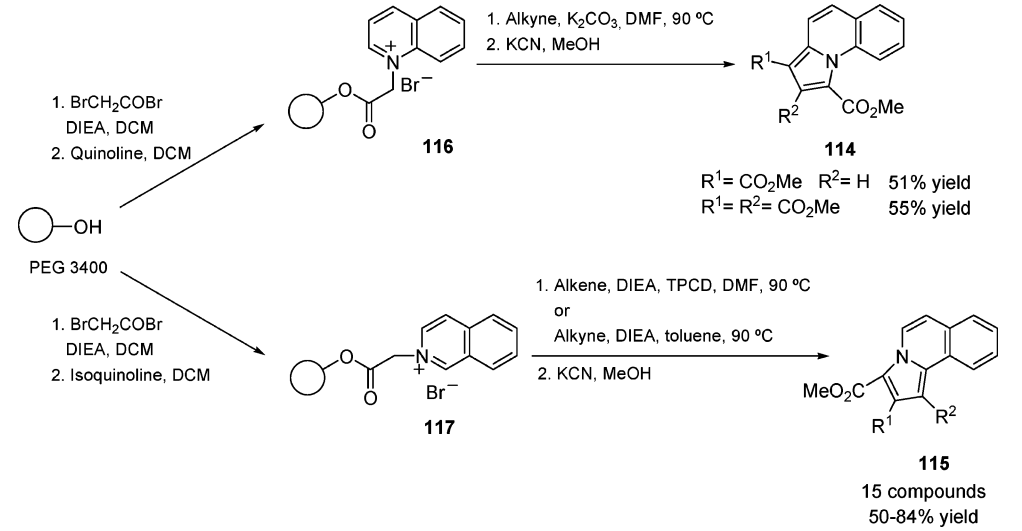
and, finally, oxidation of the resulting dihydroindolizine cycloadducts to the corresponding PEG-bound indolizines. Alternatively, PEG-bound indolizines were synthesized from **110** by reaction with alkynes in the presence of DIEA. The target compounds **111** were released from the support using KCN in methanol and then purified by column chromatography. The final trisubstituted indolizines were isolated in 80−94% overall yield. Later, the authors applied the same strategy to prepare 1,2,3,7-tetrasubstituted indolizines **112** (Scheme 52).[75] In this case, PEG-bound compound **113** was the pyridinium salt involved in the 1,3-dipolar reaction. Unlike **110**, the pyridine ring of **113** was attached to the polymer support through position 4.

4.1.1.3. Quinolinium and Isoquinolinium Ylides. Synthesis of Pyrrolo[1,5-*a*]quinolines, Pyrrolo[1,5-*a*]isoquinolines, and Polycyclic Compounds. PEG-supported quinolinium and isoquinolinium ylides were employed as 1,3-dipoles in the synthesis of pyrrolo[1,5-*a*]quinolines **114** and pyrrolo[5,1-*a*]isoquinolines **115** (Scheme 53).[76] The former were prepared from PEG-supported quinolinium salt **116** on reaction with alkynes and K_2CO_3 as base in DMF at 90 °C overnight. In these conditions, the corresponding quinolinium

Scheme 52



Scheme 53



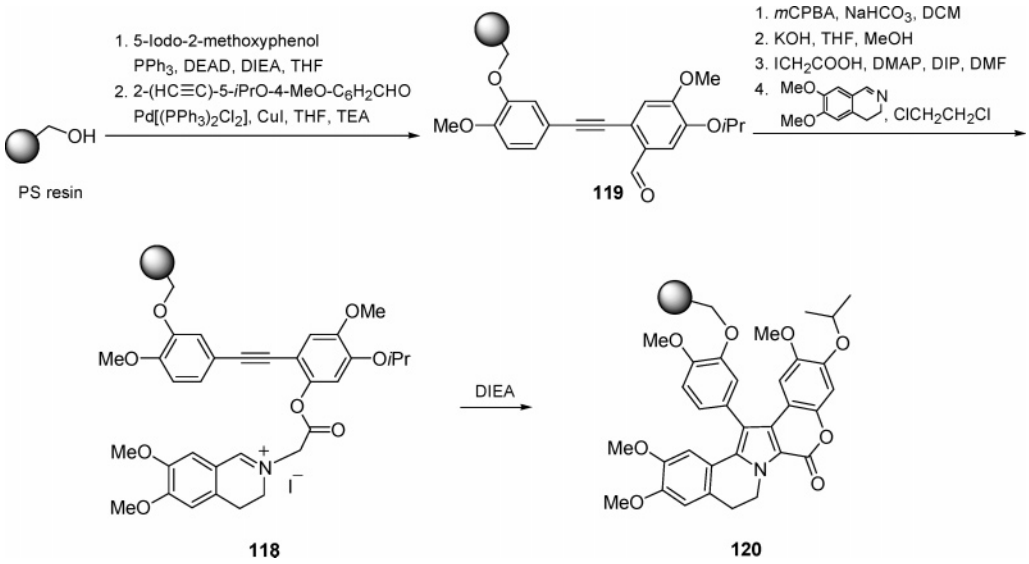
ylide was formed and underwent cycloaddition with the alkynes. A similar 1,3-dipolar reaction occurred by treating isoquinolinium salt **117** with either alkenes or alkynes. The resulting PEG-bound pyrroloquinolines and pyrroloisoquinolines were subsequently cleaved from the solid support by treatment with 1% KCN in methanol. Upon purification by column chromatography, pyrroloquinolines **114** and pyrroloisoquinolines **115** were isolated in moderate to high yields (50−84%).

An intramolecular [3+2] cycloaddition of a 3,4-dihydroisoquinolinium salt to a triple bond, with simultaneous formation of two heterocyclic rings, was the key step in the total SPS of the pentacyclic compounds lamellarins U and L (Scheme 54).[77] Quinolinium salt **118**, constructed on a hydroxymethyl functionalized polystyrene resin, provided the backbone of the lamellarins. Anchoring of the 5-iodo-2-methoxyphenol to the resin by a Mitsunobu reaction, followed by a $PdCl_2(PPh_3)_2$ and CuI-catalyzed Sonogashira cross-coupling reaction between the iodophenoxy resin and 2-ethynyl-5-isopropoxy-4-methoxybenzaldehyde, gave the bisarylacetylene resin **119**. An important step in this approach was the solid-phase Baeyer−Villiger conversion of the aldehyde into the formate. Hydrolysis of the formate gave a phenol resin used for reaction with iodoacetic acid, employing the standard conditions for ester bond formation (i.e., a polar solvent such as DMF, DIP/DMAP as coupling reagent). *N*-Alkylation of 3,4-dihydro-6,7-dimethoxyisoquinoline with the resin iodide afforded the quinolinium salt **118**. [3+2] Cycloaddition using DIEA as base provided the anchored and protected skeleton of the lamellarins **120**.

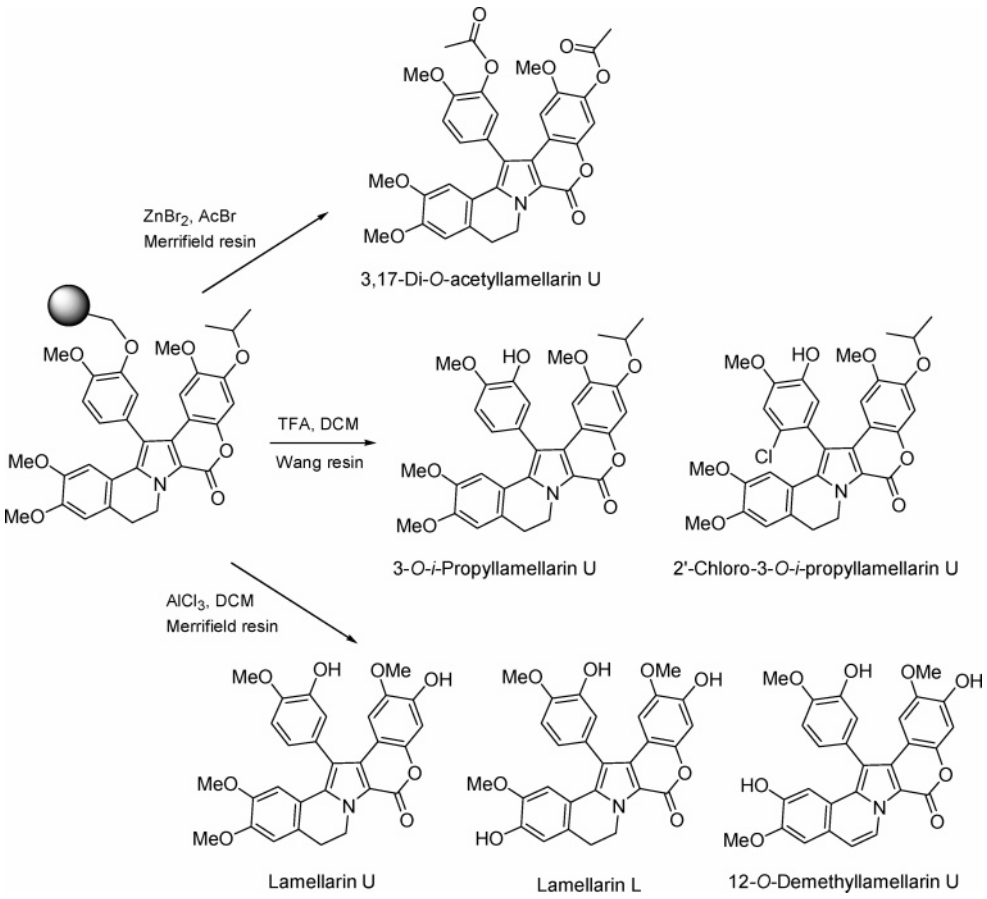
Lewis acids, such as $AlCl_3$ or $ZnCl_2$ in dry DCM, were used to cleave the products from the resin. The same group later demonstrated how the cleavage conditions and the resin employed could be used to introduce diversity for pharmacological screening, ultimately providing more druglike compounds. (Scheme 55).[78]

4.1.2. Nitrilimines. 4.1.2.1. Alkenes/Alkynes as Dipolarophiles. Synthesis of Pyrazoles and Pyrazolines. Cycloadditions of nitrilimines with alkynes and alkenes have been used to prepare pyrazoles and pyrazolines, respectively. Takahashi et al. applied this method to prepare a library of 25 pyrazoles from polymer-supported vinylsulfones (Scheme 56).[79] The resin-bound sulfones **121** were prepared from Rink amide resin and then reacted with hydrazonyl chlorides and TEA in DCM at room temperature. In this reaction step, cycloaddition of **121** with the in situ-generated nitrilimines

Scheme 54



Scheme 55

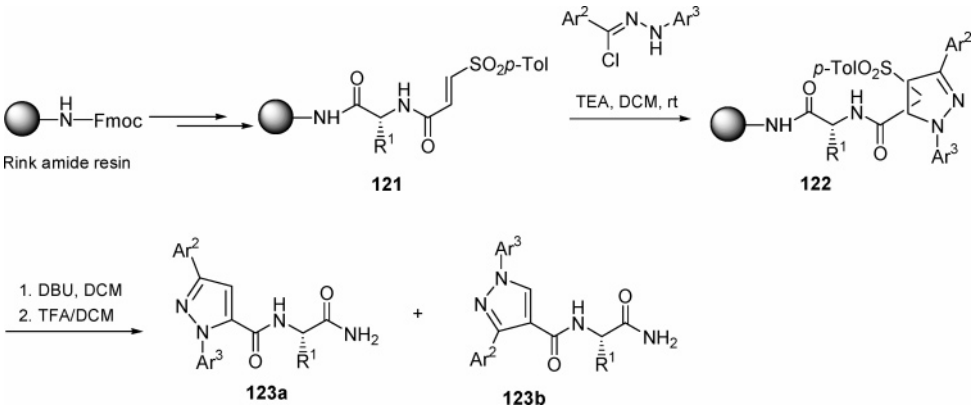


led to the resin-bound pyrazolines **122**. β-Elimination of the *p*-toluenesulphonyl group of **122** with DBU and final acidic cleavage afforded pyrazoles **123** in high purity, with **123a** as the major isomer. The authors attributed the regioselectivity of the reaction to the presence of the *p*-toluenesulphonyl group.

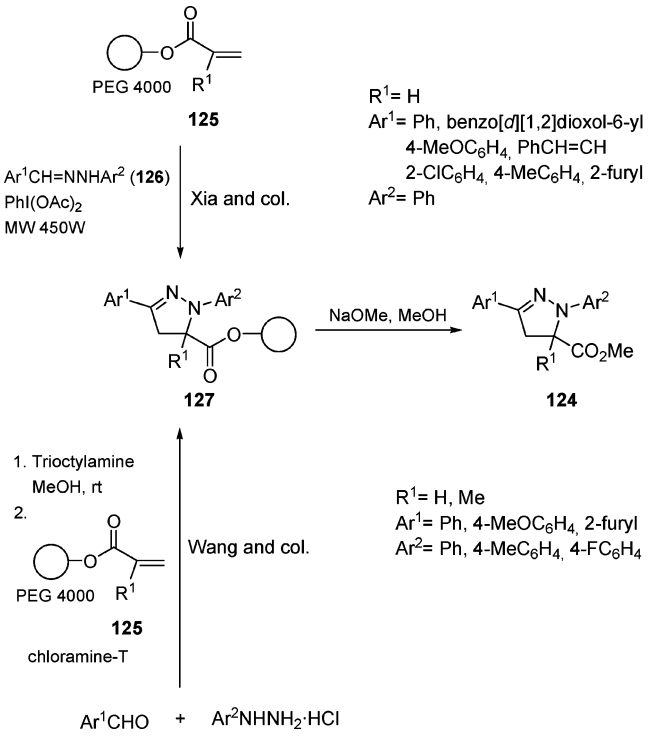
Xia et al. used a similar 1,3-dipolar cycloaddition for the regioselective synthesis of the pyrazoline derivatives **124** on soluble polymer (Scheme 57).[80] The authors employed the PEG-bound acrylate **125** as dipolarophile and nitrilimines, generated in situ by oxidation of the aldehyde phenylhydrazones **126** with (diacetoxy)iodobenzene, as 1,3-dipoles. Microwave-assisted cycloaddition of the components afforded PEG-bound pyrazolines **127** in 4 min. Upon treatment of **127** with NaOMe in methanol, the 1-phenyl-3-substituted-2-pyrazolinyl-5-carboxylates **124** were isolated in good to excellent yields (61−94%) and with total regioselectivity.

An alternative synthesis of pyrazolines on soluble polymer support was developed by Wang et al. (Scheme 57).[81] In this case, the PEG-bound pyrazolines **127** were prepared in

Scheme 56



Scheme 57



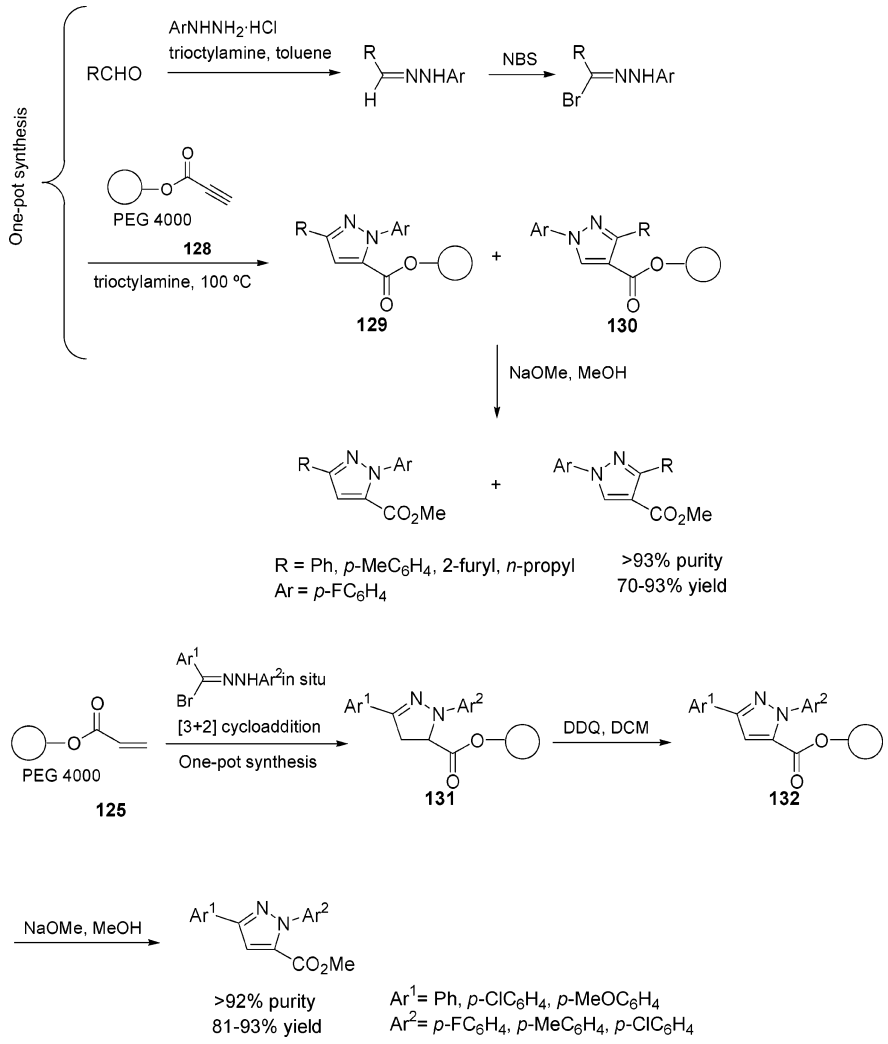
parallel by a one-pot condensation of aryl aldehydes and hydrazines in the presence of trioctylamine in methanol at room temperature, followed by addition to the reaction mixture of chloramine-T and PEG-supported acryloyl esters **125**. The nitrilimines were thus formed from the aldehydes and hydrazines, and then they underwent cycloaddition with the acrylate derivative. Cleavage of the target pyrazolines was achieved by treatment of **127** with NaOMe in MeOH. NMR, GC-MS, and HRMS analysis revealed that **124** was the only isomer present. Following this procedure, 18 pyrazolines were prepared in good yield (69−91%) and high purity (>89%).

The same group later reported a similar one-pot synthesis of pyrazoles on soluble polymer (Scheme 58).[82] They used the PEG-bound propiolate **128** as dipolarophile to form the PEG-bound regioisomeric pyrazoles **129** and **130**. When the PEG-bound acrylate **125** was employed as dipolarophile, the PEG-bound regiospecific 5-substituted pyrazolines **131** were obtained, and then they were converted to the corresponding PEG-bound pyrazoles **132** by oxidative aromatization with DDQ. The target compounds were cleaved from the support under basic conditions in good yields and purities.

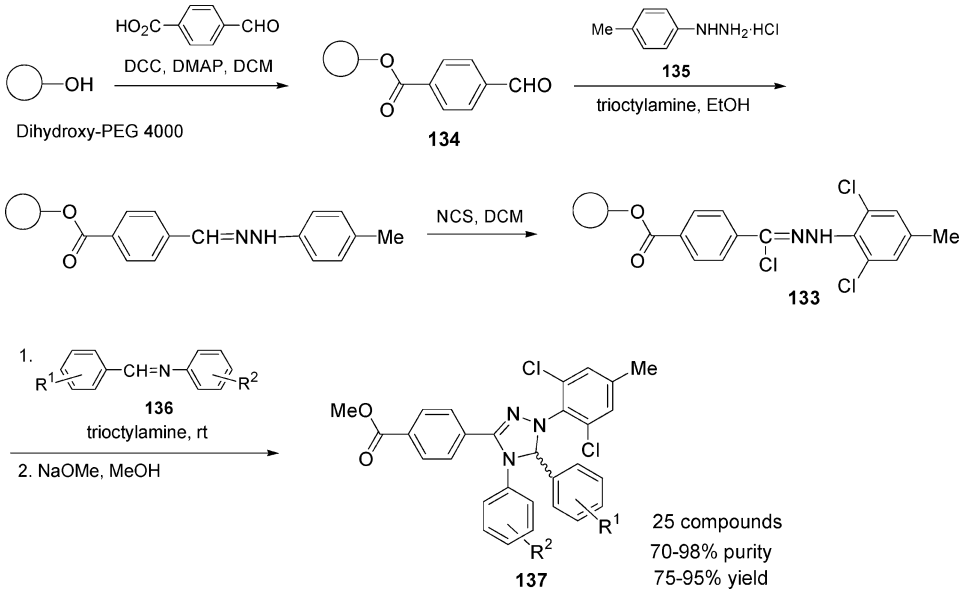
4.1.2.2. Imines as Dipolarophiles. Synthesis of 4,5-Dihydro-1,2,4-triazoles. Wang et al. described the first polymer supported synthesis in solution of tetraaryl-4,5-dihydro-1,2,4-triazoles via [3+2] cycloaddition of a PEG-bound nitrilimine with imines (Scheme 59).[83] The precursor to the nitrilimine derivative was the hydrazonyl chloride **133**, which was synthesized from PEG 4000 in three steps by attachment of 4-formylbenzoic acid onto the support, reaction of PEG-supported aldehyde **134** with hydrazine hydrochloride **135**, and α-chlorination of the resulting hydrazone. Treatment of **133** with imines **136** in the presence of trioctylamine at room temperature afforded the corresponding nitrilimine and led to construction of the triazole ring through 1,3-dipolar cycloaddition. The resulting PEG-bound tetraaryl-1,2,4-triazoles were cleaved from the resin with NaOMe. This method was successfully applied in the parallel synthesis of a library of 25 1,2,4-triazoles **137**, which were obtained in good to excellent yields (75−95%) and purities (70−98%). The library was screened for optical properties, leading to the identification of six compounds with high fluorescent quantum yields.

4.1.3. Münchnones. Synthesis of 1,2,4-Triazoles. A traceless SPS of 3,5-disubstituted 1,2,4-triazoles through 1,3-dipolar cycloaddition of polymer-bound 1,3-oxazolium-5-olates (münchnones) and diazodicarbonyl compounds was developed by Yli-Kauhaluoma et al. (Scheme 60).[84] Ameba resin-supported carboxylic acids **138** were prepared via a three-step sequence inolving reductive amination with phenylglycine methyl esters, *N*-acylation with a variety of carboxylic acid chlorides, and hydrolysis with KOH. Treatment of carboxylic acids **138** with either diethyl diazodicarboxylate (DEAD) or 4-phenyl-4*H*-1,2,4-triazoline-3,5-dione provided resin-bound 1,2,4-triazoles **139**. This involved in situ formation of münchnones **140**, their subsequent 1,3-dipolar cycloadditions with the diazodicarbonyl compound, and finally, elimination of carbon dioxide from the resulting cycloadducts. TFA cleavage of the products from the resin, followed by column chromatography afforded compounds **141** in high yields and purities. It was observed that the cycloaddition using 4-phenyl-4*H*-1,2,4-triazoline-3,5-dione required less time than that using DEAD and also led to slightly better yields. This strategy was also reported by

Scheme 58



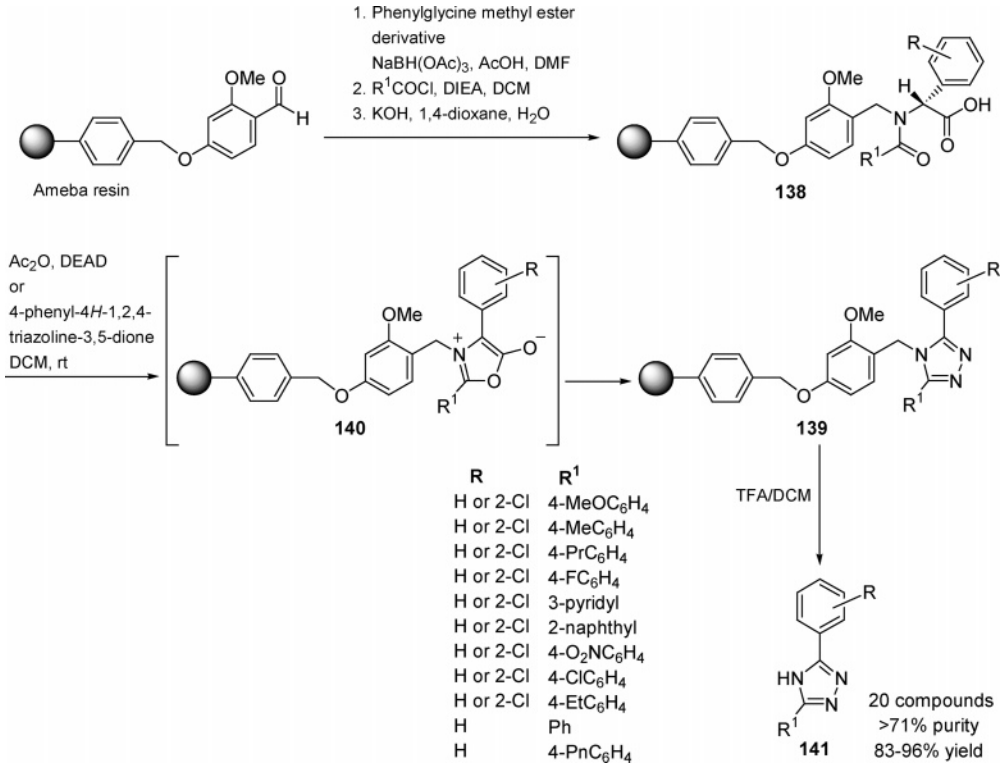
Scheme 59



Wang et al., except with PEG 6000 as solid support.[85] The authors prepared 11 PEG-bound 3,5-disubstituted 1,2,4-triazoles in good to excellent yields (87−94%) and ≥92% purity upon isolation by ether precipitation and subsequent TFA cleavage from the solid support.

4.1.4. Pyridinium *N*-Imines. Synthesis of Pyrazolo[2,3-*a*]pyridines. Pyridinium *N*-imines have been employed as 1,3-dipoles for the SPS of pyrazolopyridines (Scheme 61).[86] The resin-bound alkynes **142** were prepared by attachment of alkynoic acids to the bromo-Wang resin **143** and then

Scheme 60



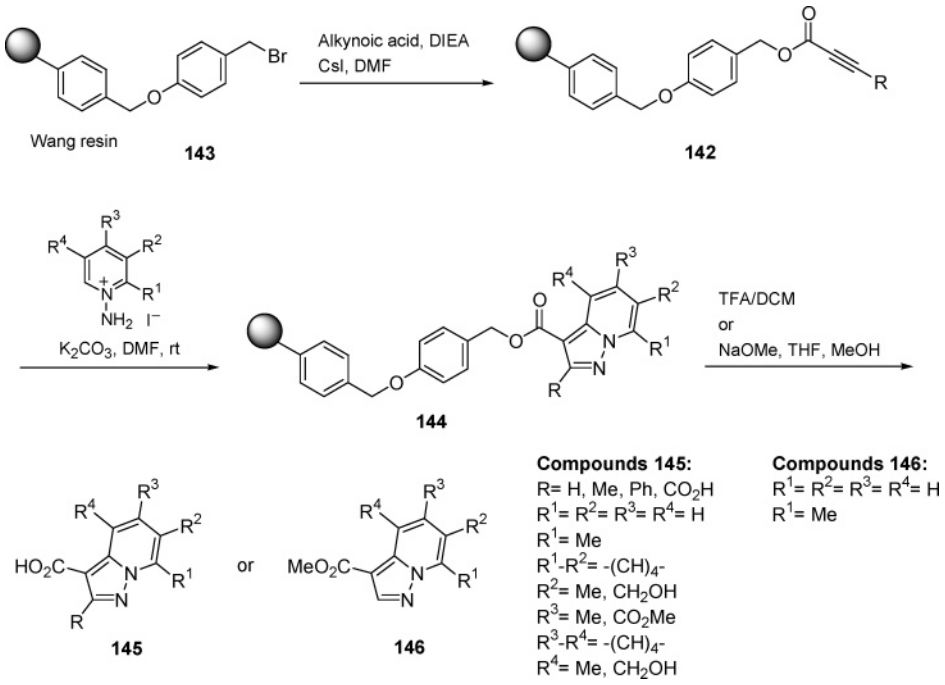
reacted with various *N*-aminopyridine iodides and K_2CO_3 in DMF. 1,3-Dipolar cycloaddition of **142** with the in situ-generated pyridinium imines, followed by aromatization of the resulting cycloadduct led to resin-bound bicyclic compounds **144**. TFA treatment of **144** provided the pyrazolopyridinecarboxylic acids **145**, and exposure to sodium methoxide afforded the methyl ester derivatives **146**. The majority of final compounds were obtained in moderate to high yields and in high purities. The authors explored the side reactions and regiochemistry of the cycloaddition extensively.

4.1.5. Azides. 4.1.5.1. Alkynes and Alkenes as Dipolarophiles. Synthesis of 1,2,3-Triazoles. 1,2,3-Triazoles have myriad applications in synthetic and medicinal chemistry. The most versatile method for the synthesis of 1,2,3-triazoles is the Huisgen 1,3-dipolar cycloaddition reaction between an azide and an alkyne. This process is considered to be the best "click" reaction to date, benefiting from the low reactivity of azides and alkynes, as well as from their stability under common synthetic conditions.[87] Click chemistry, introduced by K. Barry Sharpless in 2001,[87a] is an approach inspired by biosynthetic pathways, whereby small units are joined together. Cu(I) catalysis of this reaction has allowed the synthesis of substituted 1,2,3-triazoles in mild conditions with total regioselective control and high yields. These syntheses have been performed in solution and, more recently, on solid-phase supports. A recent review by Maarseveen et al. covers solution-phase results with some representative solid-phase examples and describes a mechanistic approach of the Cu(I)-catalyzed azide−alkyne coupling.[88] Additional examples of solid-phase Huisgen 1,3-dipolar cycloaddition chemistry are summarized in this section.

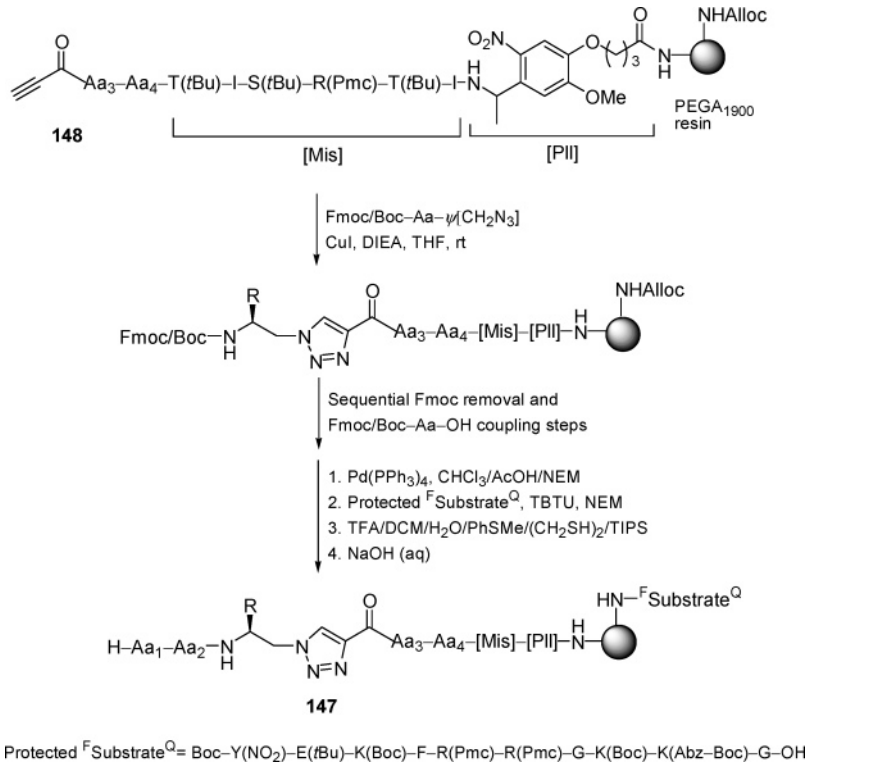
1,2,3-Triazoles have been shown to be excellent scaffolds for peptidomimetics. In addition to their rigid aromatic structure and resistance to hydrolytic cleavage, they can mimic a peptide bond because of their topological and hydrogen-bonding similarities to amines.[87e,89] In fact, incorporation of 1,2,3-triazoles into peptides constitutes an useful approach for lead discovery and optimization in biomedical research. Meldal et al. recently synthesized a library of peptidotriazoles through azide−alkyne 1,3-dipolar cycloaddition to identify inhibitors against a recombinant *Leishmania mexicana* cysteine protease (Scheme 62).[90] The one-bead two-compounds split and mix library was prepared on $PEGA_{1900}$ resin, which is a hydrophilic polyamide/polyethylene glycol copolymer, and was encoded by ladder synthesis. The final resin-attached peptidotriazoles had the structure **147**. Twenty residues were coupled at each amino acid position and the resin **148**, derivatized with propargylic acid, was treated with 5-protected β-amino azides in the presence of catalytic amounts of CuI at 25 °C to produce 1,4-disubstituted triazoles. After Alloc group removal, a substrate for *L. mexicana* CPB2.8ΔCTE was coupled, and finally, all side-chain protecting groups were cleaved using TFA. About one-half of the 800 000 possible peptidotriazoles were obtained. The biological activity of the library was evaluated on solid-phase supports, and 23 compounds were resynthesised and evaluated in solution. The K_i values of the most active compounds ranged from 76 to 240 nM.

Eichler et al. prepared a set of peptides based on a 1,4-disubstituted triazole motif (Scheme 63).[91] The authors coupled the thirteen resin-bound tetrapeptides **149**, acylated at their *N*-terminal amino group with propiolic acid, to the protected azido-peptide N_3Ac-T(*t*Bu)S(*t*Bu)K(Boc)Y(*t*Bu)R-

Scheme 61



Scheme 62

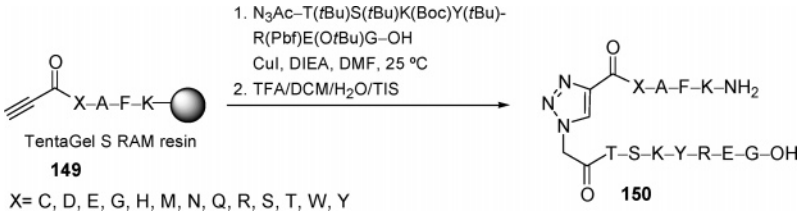


Protected $^{F}Substrate^{Q}$= Boc–Y(NO_2)–E(*t*Bu)–K(Boc)–F–R(Pmc)–R(Pmc)–G–K(Boc)–K(Abz–Boc)–G–OH

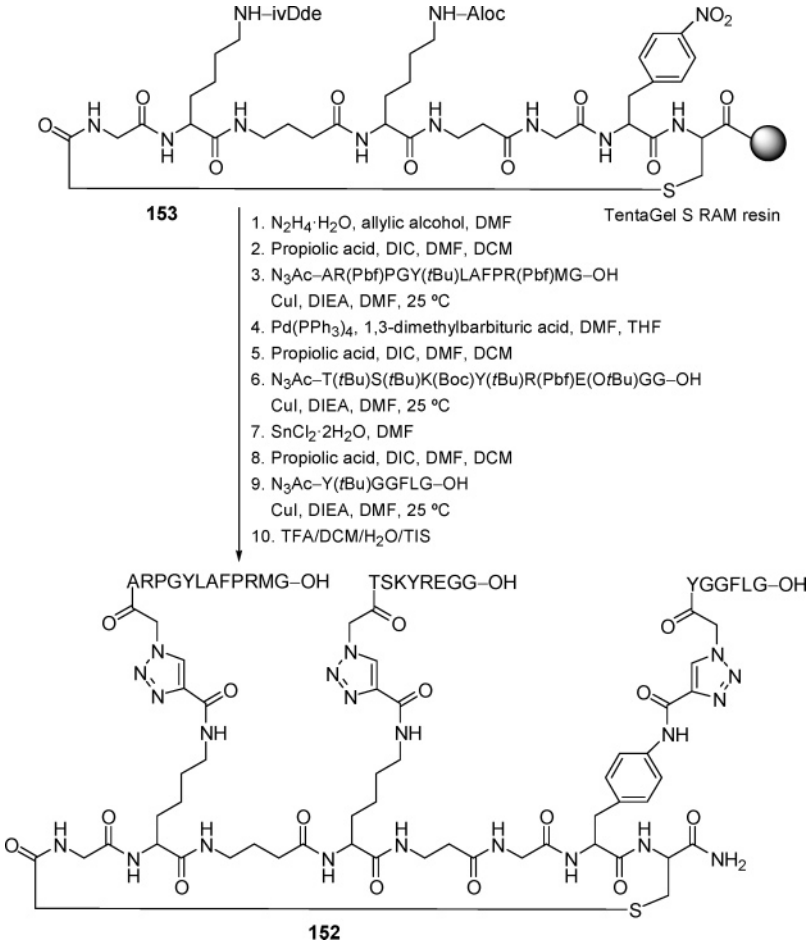
(Pbf)E(O*t*Bu)G-OH using Cu(I) catalysis. Subsequent TFA cleavage of the products from the resin afforded the peptides **150** in high purity. The regioselectivity of the triazole formation was analyzed by ^{1}H NMR spectroscopy of compound **151** (Figure 2). On the basis of this procedure, the same authors described the solid-phase preparation of the peptide **152**, which bears two triazole rings attached to the side-chain amino group of two lysine residues and one triazole linked to a 4-aminophenylalanine residue (Scheme 64). Each triazole was selectively constructed from the resin-bound cyclic scaffold **153**. The corresponding free amino group was obtained, either by selective removal of the protecting group of a lysine or by reduction of the nitro group of 4-nitrophenylalanine, acylated with propiolic acid, and coupled to the corresponding azido-peptide using Cu(I) catalysis. After formation of the third triazole, peptide **152** was cleaved from the resin with TFA and then purified by HPLC.

Zhang and Fan described the SPS of the peptidotriazoles **154** and **155** with alternating triazole and amide backbone linkages (Scheme 65 and Figure 3).[92] Both peptidotriazoles were prepared from Rink amide resin via multiple cycles of

Scheme 63



Scheme 64



1,3-dipolar cycloaddition of a 4-pentynoyl group and the corresponding Fmoc-protected amino azide using soluble Cu-(I) catalyst. Compound **154** was prepared from the Fmoc-proline-azide **156** and was obtained in 62% yield after TFA cleavage from the resin and HPLC purification. Compound **155** was synthesized from side-chain protected Fmoc-Lys, Tyr, Asp, and Leu amino azides and was obtained in 56% yield after TFA cleavage from the resin and HPLC purification.

In a study by Finn et al., Cu(I)-catalyzed azide−alkyne [3+2] cycloaddition promoted solid-phase head-to-tail peptide cyclodimerization of the Arg-Gly-Asp (RGD)-containing

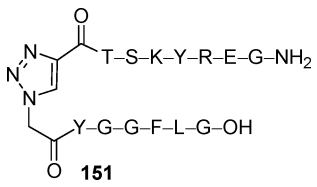
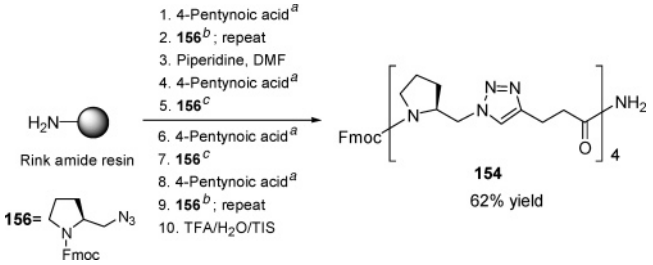


Figure 2.

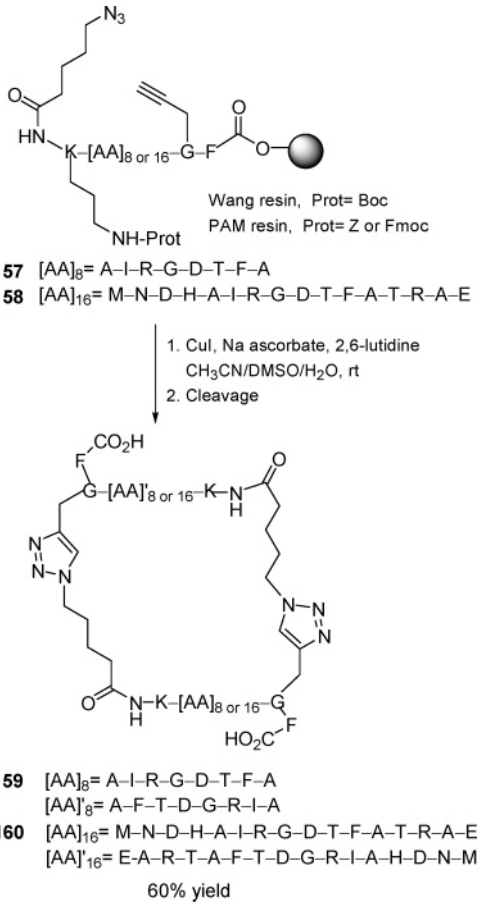
Scheme 65



[a] PyBop, HOBt, DIEA, DMF. [b] CuI, ascorbic acid, DIEA, 2,6-lutidine, DMF. [c] CuI, ascorbic acid, piperidine, DMF.

peptides **157** and **158**, leading to the cyclic peptides **159** and **160**, respectively, each of which contains two 1,2,3-triazole rings (Scheme 66).[93] The two key structural features of the starting peptide sequences were an L-propargylglycine located in the second amino acid position and a 5-azidopentanoyl group at the *N*-terminus. Cyclodimerization was achieved through triazole formation by exposure of the linear sequences to CuI, Na ascorbate, and 2,6-lutidine for 16 h at

Scheme 66



157 $[AA]_8$= A–I–R–G–D–T–F–A
158 $[AA]_{16}$= M–N–D–H–A–I–R–G–D–T–F–A–T–R–A–E

159 $[AA]_8$= A–I–R–G–D–T–F–A
$[AA]'_8$= A–F–T–D–G–R–I–A
160 $[AA]_{16}$= M–N–D–H–A–I–R–G–D–T–F–A–T–R–A–E
$[AA]'_{16}$= E-A–R–T–A–F–T–D–G–R–I–A–H–D–N–M

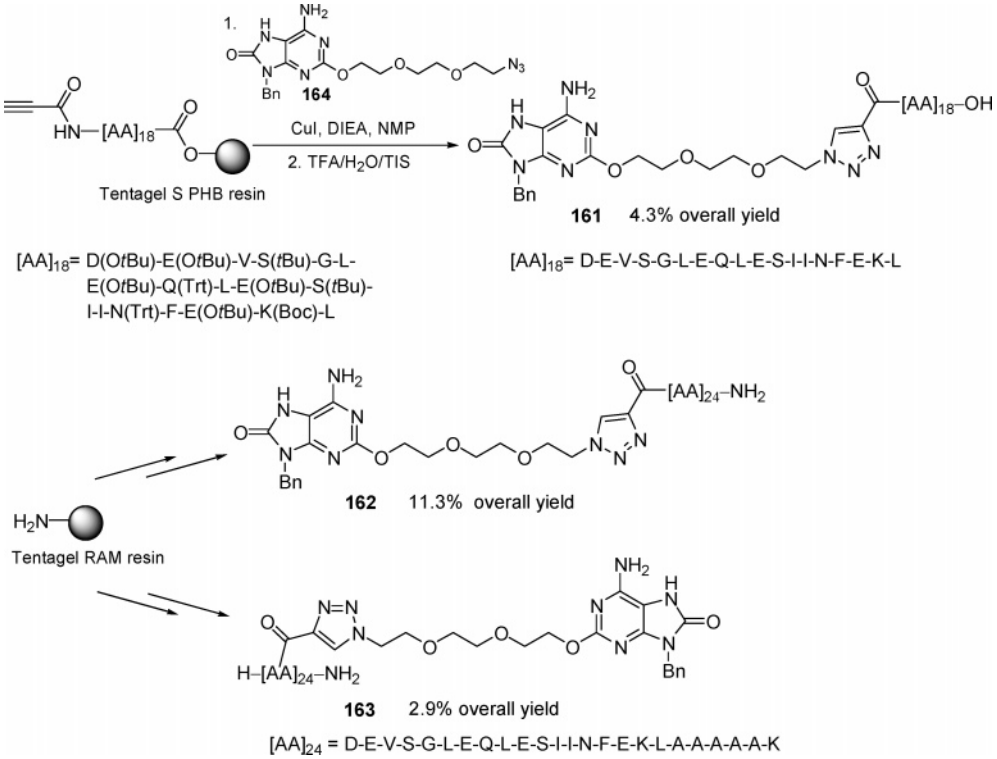
60% yield

room temperature. Subsequent acid cleavage and HPLC purification revealed that **159** and **160** were obtained in an approximately 60% yield for cyclodimerization. Although monocyclization was achieved by switching the positions of the azide and alkyne groups, the monocycle was obtained along with the cyclic dimer in a 1:2 mixture. In this case, the linear peptide included a side-chain-derivatized glutamic azide as second residue and propargyl glycine at its *N*-terminus.

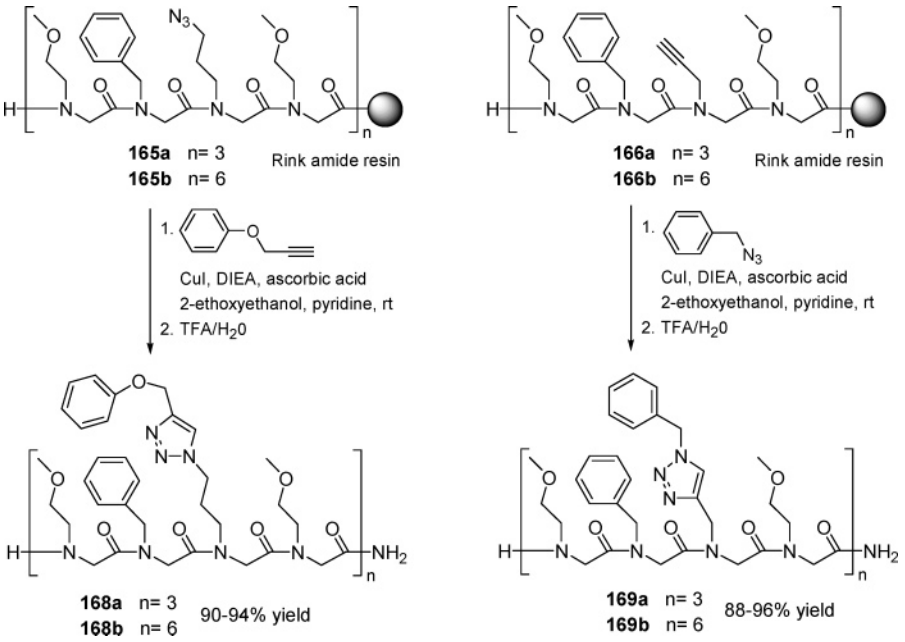
1,2,3-Triazole formation through Cu(I)-catalyzed Huisgen cycloaddition has been used to link peptides to an 2-alkoxy-8-hydroxyadenine derivative. This approach led to the synthesis of the hydroxyadenylpeptide conjugates **161**, **162**, and **163**, which contain the major histocompatibility complex class I epitope SIINFEKL (Scheme 67).[94] As exemplified for **161**, alkyne-derivatized peptide Tentagel resins were coupled to the azidoadenine derivative **164** under Cu(I) catalysis in the presence of DIEA. The conjugates **161**, **162**, and **163** were released from the resin with TFA and were obtained in 4.3, 11.3, and 2.9% overall yields, respectively, after purification. These conjugates abolished the production of the T helper cell (Th1)-activating cytokine IL-12p40. In comparison with a mixture of their individual components, they led to improved antigen presentation in vitro, but they did not induce dendritic cell activation.

Kirshenbaum et al. developed two solid-phase azide−alkyne procedures for the synthesis of peptoids that bear multiple triazolyl side chains. Using the first, the authors formed triazole rings at the resin-bound 8mer, 12mer, and 24mer peptoid scaffolds **165**−**167** as a postoligomerization step (Scheme 68 and Figure 4).[95] This occurred via multisite conjugation of peptoid azido- or alkynyl-functionalized side-chains to an alkyne or azide, respectively, in the presence of CuI, DIEA, and ascorbic acid for 15 or 72 h at room temperature. Triazoles were formed at three positions of **165a** and **166a** and at six positions of **165b** and of **166b**, affording oligomers **168a**−**b** and **169a**−**b** in high overall yields (88−96%) after acidic cleavage. Notably, this procedure allowed

Scheme 67

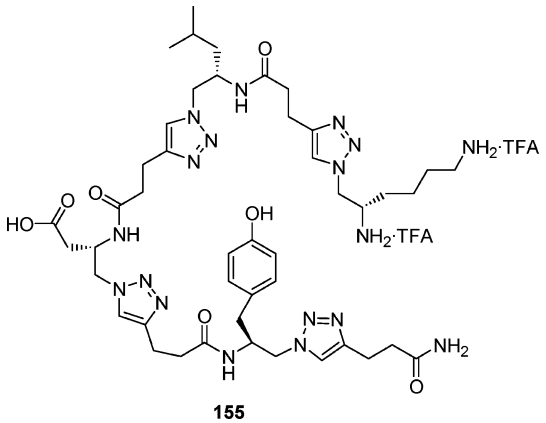


Scheme 68



multiple conjugation of the peptoids **166a** or **167** to ligands with biologically relevant structures, such as the fluorophore **170**, the nucleoside **171**, and the peptoid trimer **172** (Figure 4).

In the second of the aforementioned procedures, the triazoles are formed between oligomerization cycles.[96] The authors thus prepared the peptoid dodecamer **173**, which bears four distinct triazolyl side-chains, by sequential cycles of peptoid chain elongation and azide−alkyne coupling (Scheme 69). After TFA cleavage of the products from the resin, the triazole formation was determined to be highly efficient (>95% conversion), and the crude final product was obtained with >75% overall purity. A preliminary study of the applicability of this procedure to the development of peptoids as biosensor platforms was also performed. The authors thus prepared a peptoid hexamer with two side chains substituted with a triazolylferrocene unit and a 17α-triazolylestradiol moiety, respectively, using the above procedure. The effect of the estradiol and triazole units on the redox properties of the ferrocene was studied. Whereas cyclic voltammetry experiments indicated that the 1,2,3-triazole motif significantly decreased the redox potential of the ferrocene unit, it was observed that the estradiol moiety did not affect it.



155

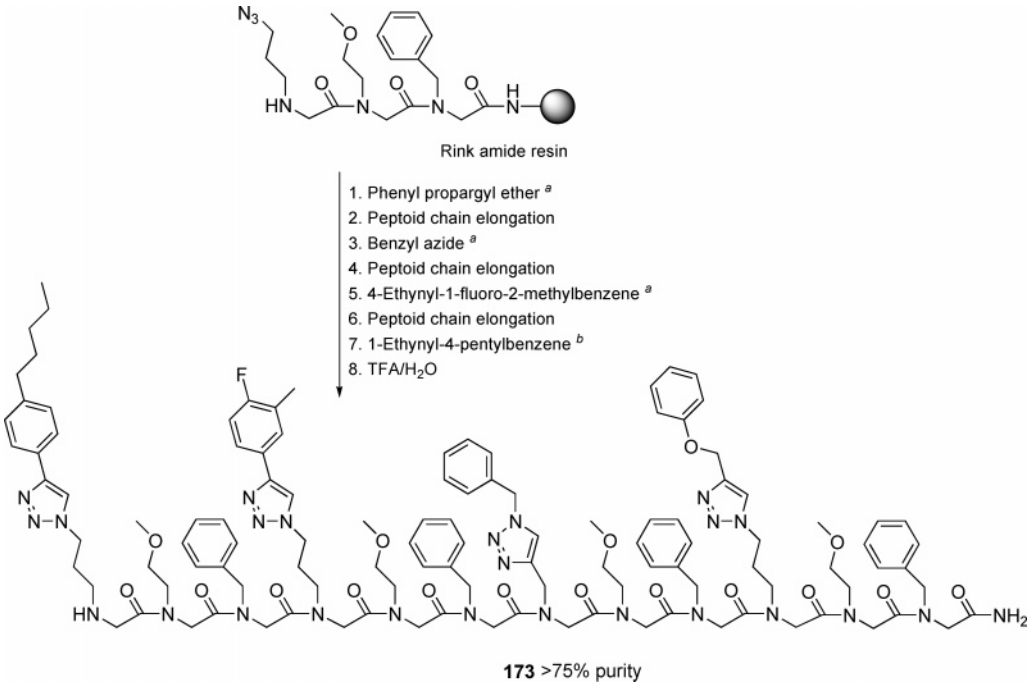
Figure 3.

Non-peptidic structures containing the 1,2,3-triazole motif have also been prepared using click chemistry. Yli-Kauhaluoma et al. described the SPS of the *N*-hydroxybenzyltriazoles **174** from the commercially available bromo-Wang resin **143** (Scheme 70).[97] The reaction sequence included treatment of the resin with sodium azide and subsequent conjugation of the resulting resin-bound azide **175** with various alkynes. After TFA cleavage of the products from the resin, the authors observed that the triazoles **174** had been obtained, together with the corresponding *N*-unsubstituted triazoles **176**. Following a similar route, the authors prepared unsubstituted triazoles **176** tracelessly from the 2-methoxy-substituted resin **177** (Scheme 70). The resin was synthesized by chlorination of commercially available polymer-bound 4-hydroxy-2-methoxybenzyl alcohol. Purification of crude products by column chromatography afforded compounds **174** and **176** in 17−58% yield. The regiochemistry of the cycloaddition was determined by ^{1}H NMR of the products and confirmed by X-ray analysis.

As part of a library of 1,2-diheterocyclic-substituted (*E*)-olefins, Huang et al. prepared the 1,2,3-triazolyl and isoxazolinyl derivatives **178** from the selenenyl bromide resin **179**, which is a PS-functionalyzed solid support cleavable through a selenoxide syn elimination to introduce a new E double bond (Schemes 71 and 86).[98] The resin **179** was treated with $NaBH_4$ and propargyl bromide to give the corresponding propargyl-functionalized resin **180**. 1,2,3-Triazoles were formed through a one-pot 1,3-dipolar cycloaddition of the resin **180** with NaN_3 and aryl halides in the presence of CuI, proline, and TEA at 65 °C for 12 h in dimethyl sulfoxide (DMSO).

A set of 78 triazole derivatives with the general structure **181** were synthesized as part of a 10.102 compound library based on the natural product carpanone and directed to

Scheme 69



[a] CuI, ascorbic acid, DIEA, 2-butanol, DMF, pyridine, room temp. [b]CuI, ascorbic acid, DIEA, DMF, pyridine, room temp.

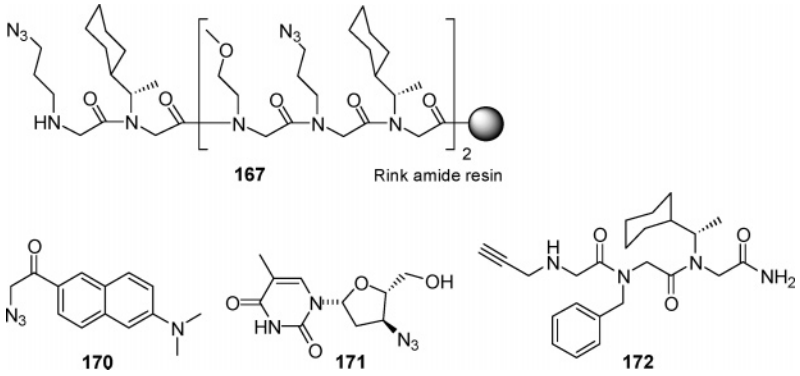
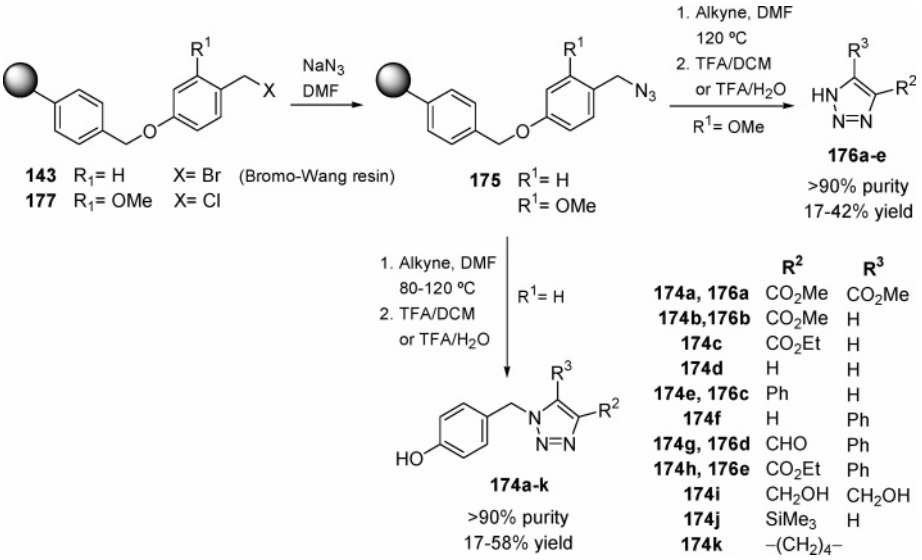


Figure 4.

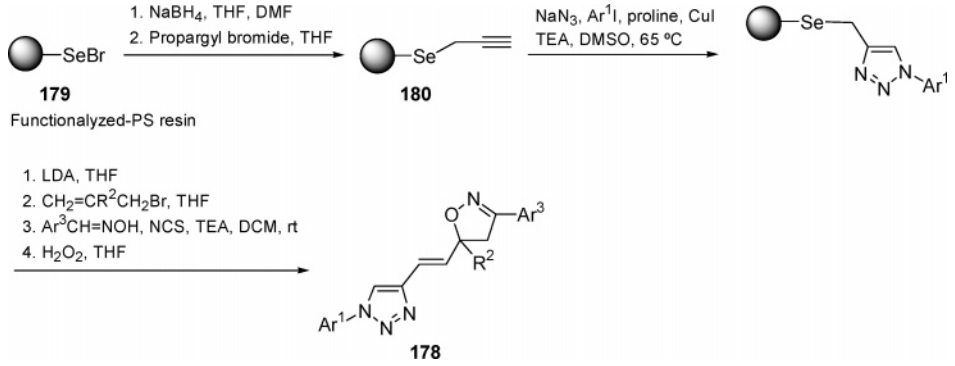
Scheme 70



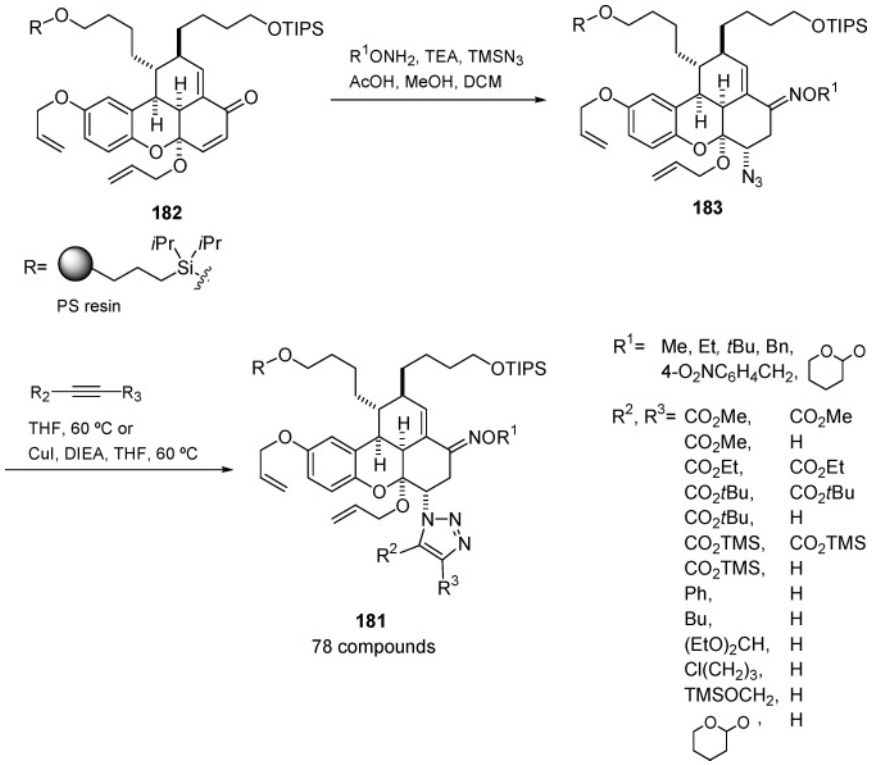
	R2	R3
174a, 176a	CO_2Me	CO_2Me
174b,176b	CO_2Me	H
174c	CO_2Et	H
174d	H	H
174e, 176c	Ph	H
174f	H	Ph
174g, 176d	CHO	Ph
174h, 176e	CO_2Et	Ph
174i	CH_2OH	CH_2OH
174j	$SiMe_3$	H
174k	$-(CH_2)_4-$	

discover inhibitors of exocytosis from the Golgi apparatus (Scheme 72).[48] The library was prepared from high-capacity (500 μm) PS beads by the split-pool method, using a "one-bead−one-stock solution" strategy. Multicomponent reaction of on-resin tetracycle **182** with $TMSN_3$ and six hydroxylamines afforded resin-bound azides **183**, which were then

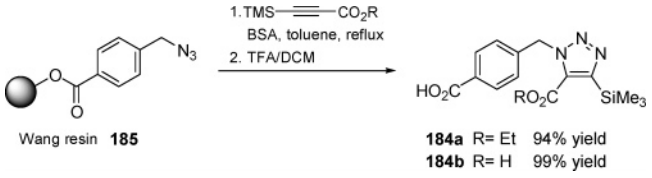
Scheme 71



Scheme 72



Scheme 73



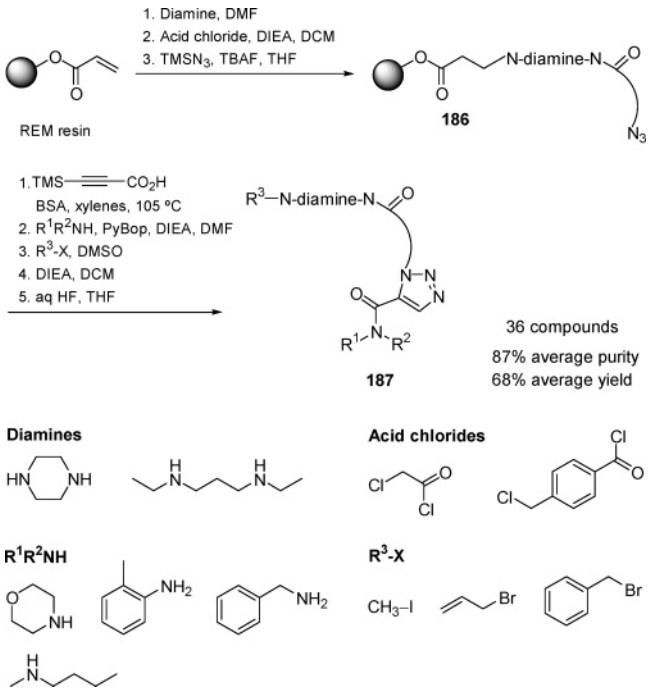
crossed with thirteen alkynes in a [3+2] cycloaddition to afford triazoles **181**.

Hlasta et al. reported the SPS of 1*H*-1,2,3-triazoles via trimethylsilyl-directed 1,3-dipolar cycloaddition (Scheme 73).[99] The triazoles **184a** and **b** were produced regioselectively and in high yield by treatment of the Wang resin-bound azide **185** with ethyl trimethylsilylpropynoate and trimethylsilylpropynoic acid, respectively, in the presence of bis(trimethylsilyl)acetamide (BSA) in toluene at reflux for 18 h, followed by TFA cleavage of the product from the resin. The procedure was used for the cycloaddition of the acryloyl resin (REM)-bound azides **186** with trimethylsilylpropynoic acid to prepare a library of the 1,5-disubstituted 1*H*-1,2,3-triazoles **187** (Scheme 74). Of the 48 compounds prepared, 36 were obtained in excellent yields and purities.

Sulfones have been used to direct 1,3-dipolar cycloaddition, allowing the regioselective preparation of the 1,2,3-triazoles **188**−**190** (Scheme 75).[100] The resin-bound vinylsulfones **191** and **192** were synthesized from PS sodium sulfinate resin **193**, and then they were exposed to NaN_3 in DMF with microwave irradiation to afford the 4,5-disubstituted- and 4-monosubstituted-2*H*-1,2,3-triazoles **188** and **190**, respectively. The vinylsulfone **191** was also reacted with alkylhalides and NaN_3 in a one-pot 1,3-dipolar cycloaddition to yield the 2,4,5-trisubstituted-2*H*-1,2,3-triazoles **189**. In these reactions, the sulfone group not only controlled the regiochemistry of the cycloaddition but also served as traceless linker; upon in situ elimination of the sulfone, the triazoles were released. A total of 23 triazoles were prepared with overall yields ranging from 37 to 78%.

Azide−alkyne [3+2] cycloadditions have also been performed on soluble polymers, such as the MeOPEG. Molteni et al. prepared 4- and 5-monosubstituted triazoles by heating

Scheme 74



the MeOPEG-supported azide **194** with the monosubstituted acetylenes **195** in toluene (Scheme 76).[101] After diethyl ether precipitation, a regioisomeric mixture of MeOPEG-linked triazoles **196** and **197** was obtained in near quantitative yields and was subsequently analyzed by ^{1}H NMR spectroscopy. The 1,2,3-triazoles **198** and **199** were released from the polymer by treatment with formic acid and then purified by silica gel chromatography (71−85% overall yield).

Morvan et al. used microwave-assisted click chemistry to attach carbohydrates to oligonucleotides bound to a thymidine succinyl-controlled pore glass (CPG) solid support (Scheme 77).[102] The three galactosyl azide derivatives **200** were trapped by the solid-supported trivalent alkyne oligonucleotide **201** in MeOH/H_2O in the presence of $CuSO_4$ and sodium ascorbate with microwave irradiation at 60 °C for 20 min. The resulting beads were treated with concentrated aqueous NH_4OH to afford the deprotected trigalactosylated compound **202**. Complete conversion of the three alkyne residues into triazoles was confirmed by HPLC and MALDI-TOF MS analyses.

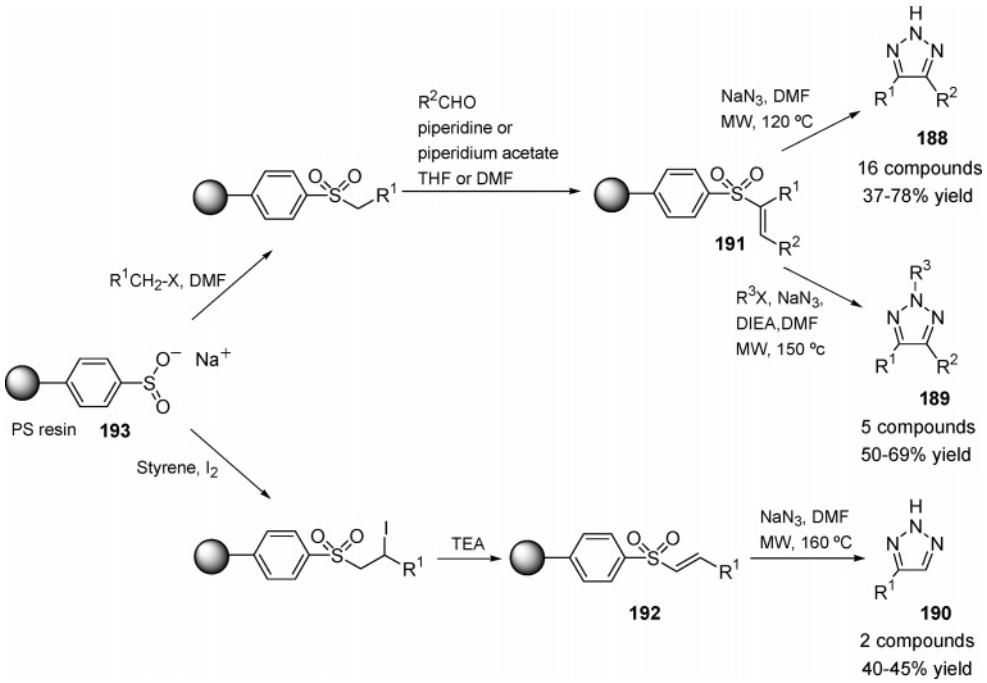
Taking advantage of the click chemistry strategy, the 1,2,3-triazole formation via azide−alkyne coupling has been employed to construct linkers for solid-phase organic synthesis. In this context, Gmeiner and co-workers developed the REM-based resin **203** as well as the amide backbone-based resins **204** and **205** (Schemes 78−81). The triazolylmethyl acrylate resin **203** was obtained by cycloaddition of the azidomethyl polystyrene resin **206** and propargyl acrylate in the presence of CuI catalyst and DIEA at 35 °C (Scheme 78).[103] The resin was evaluated by preparation of the tertiary amines **207**−**209**. The synthetic sequence involved Michael addition of aliphatic and cyclic secondary amines to resin **203**, alkylation of the resulting resin-bound amines, and subsequent basic cleavage of the products from the resin via Hofmann elimination. The final amines were obtained in high yields (53 to 82%) and purities (>91%).

The formylindolylmethyltriazole resin **204** was prepared by Cu(I)-promoted coupling of the azidomethyl polystyrene resin **206** and *N*-propargylindole-3-carbaldehyde (Scheme 79),[104] and it was then used for the parallel synthesis of 42 *N*-arylpiperazinoalkyl-substituted arylcarboxamides following a backbone-amide linker (BAL) strategy (Scheme 80).[105] The building blocks were incorporated by reductive amination of **204** in the presence of $NaBH(OAc)_3$, HOAt/DIC-mediated acylation, removal of the Boc group by TMSOTf, and finally, arylation of the piperazine according to Buchwald and Hartwig's method, using $Pd_2(dba)_3$ and (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphtyl (BINAP) as catalyst. The reagents were two *N*-aminoalkyl-*N*′-*tert*-butyloxycarbonylpiperazines, seven arylcarboxylic acids, and three bromoaryl derivatives. TFA cleavage of the products from the resin afforded arylcarboxamides **210** in yields ranging from 9 to 37% with an average purity of >85%. The compounds were evaluated for binding affinities toward the dopaminergic G-protein-coupled receptors D1, $D2_{long}$, $D2_{short}$, D3, and D4, as well as the adrenergic α_1 subtype. Five hits were identified as high binders to the receptor D3 subtype. The best K_i value was of 0.28 nM and corresponded to a biphenylcarboxamide bearing a 2-chlorophenyl substituent and with a chain length of 4 carbons between the carboxamide group and the piperazine ring.

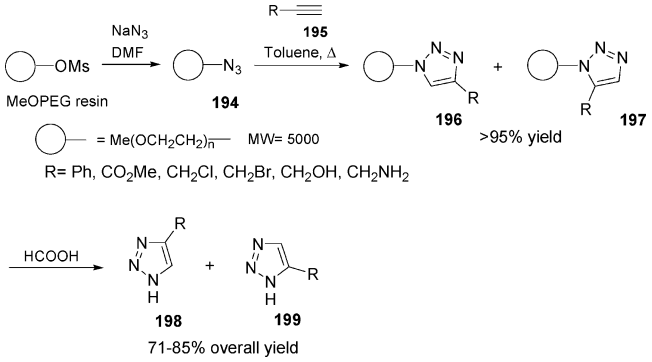
The same group reported the parallel synthesis of a library of sixty 1,2,3-triazole-4-carboxamides from the formylaryloxymethyltriazole resin **205** (Scheme 81).[106] In this case, alkyne−azide 1,3-dipolar cycloaddition was used for both the functionalization of the resin and the synthesis of the compounds. The BAL-based resin **205**, which was prepared in a manner similar to that of **204**,[104] was subjected to reductive amination using $NaBH(OAc)_3$ with ten primary amines, including *N*-phenylpiperazinyl- and 4-phenyl-3,6-dihidro-2*H*-pyridinyl-substituted alkylamines and 4-amino-1-benzylpiperidine. The resulting amino-bound resins **211** were then *N*-acylated with two alkynoic acids using DIC. Triazoles were generated by cycloaddition of the acylated resins **212** with three benzylazides at 150 °C for 48 h. After TFA cleavage of the products from the resin, the carboxamides **213** were obtained with an average purity of 90%. The compounds were screened for binding to D1, $D2_{long}$, $D2_{short}$, D3, D4, α_1, 5-HT_1, and 5-HT_{2A} receptors. High-affinity binders at the D3, α_1, and 5-HT_1 receptors were found. In particular, compounds with K_i values in the medium picomolar range for the α_1 receptor were determined.

On the basis of the aforementioned 1,2,3-triazolyl-derived linkers, Dolle et al. developed solid/solution-phase annulation (SPAn) resins for the one-step preparation of five-, six-, and seven-membered heterocyclic lactams from primary amines.[107] As shown for the isoindolinones **214** in Scheme 82, Cu(I)-catalyzed alkyne−azide coupling allowed loading of azide resin **206** with the solution-prepared propargyl 2-bromomethylbenzoate **215** through triazole formation. Subsequent annulation by tandem *N*-alkylation with a primary amine, followed by intramolecular acylation in DMSO with excess MP-carbonate and microwave irradiation, afforded the final isoindolinones **214** with an average yield of 35% and >90% purity after purification. This approach was successfully

Scheme 75



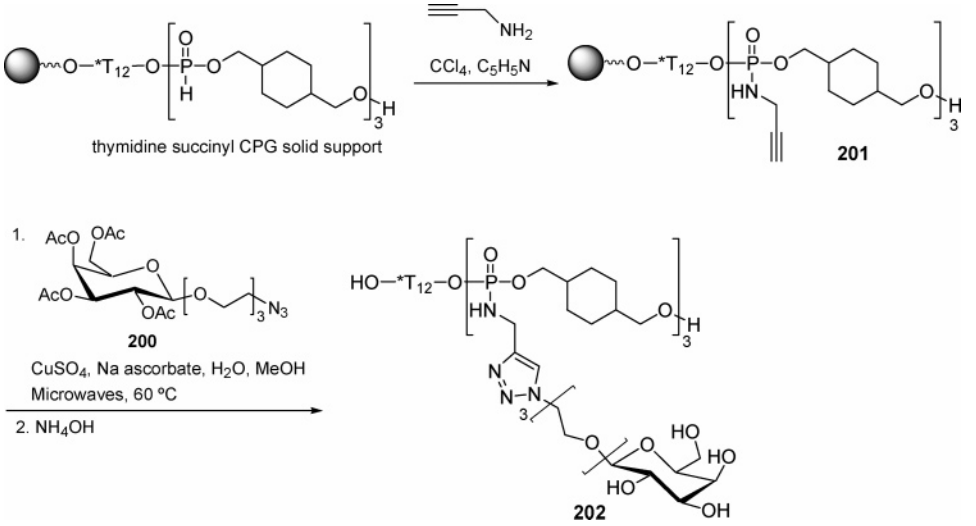
Scheme 76



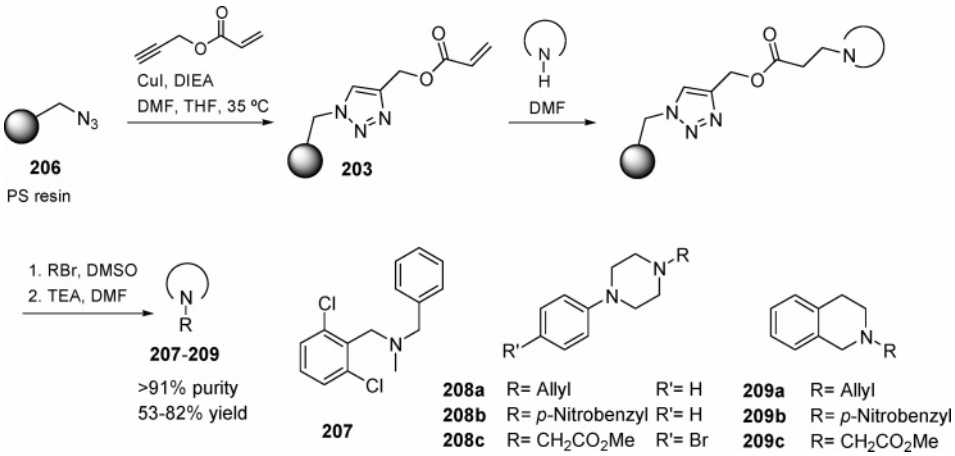
applied to the preparation of pyrrolidinone, piperidinone, morpholinone, piperazinone, and quinazolinedione derivatives, as well as to the formation of seven-membered rings, to yield bicyclic and tricyclic compounds (Figure 5).

Triazole formation through azide−alkyne cycloaddition has been used for applications other than organic synthesis, such as the functionalization of surfaces or polymers.[108] As an example, the group of Collman and Chidsey described the first report of the use of the Huisgen 1,3-dipolar cycloaddition to modify electrode surfaces.[108c] The authors formed 1,2,3-triazole rings on self-assembled monolayers incorporating azidoundecanethiol chains at the surface by reaction of the chains with ethynyl or propynone ferrocene at room temperature in aqueous solvents. The two ferrocenes required different catalytic conditions, which the authors studied. A study by Emrick et al. exemplifies the use of solid-phase click chemistry to search for polymer-based biomaterials.[108l] The group prepared the PEG- and peptide-grafted aliphatic polyesters **216** and **217** as depicted in Scheme 83. α,ω-PEG-1100-monomethyl ether azide **218** was grafted to acetylene-functionalized polyester through triazole-ring formation in the presence of sodium ascorbate and $CuSO_4$ at 80 °C for 10−12 h. The amphiphilic nature of the resulting PEG-grafted polyester **216** was studied, and its biocompatibility

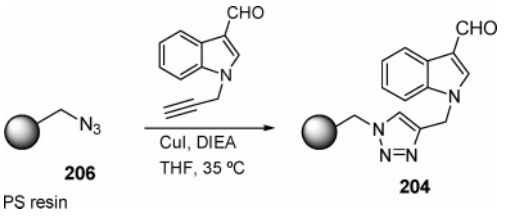
Scheme 77



Scheme 78



Scheme 79



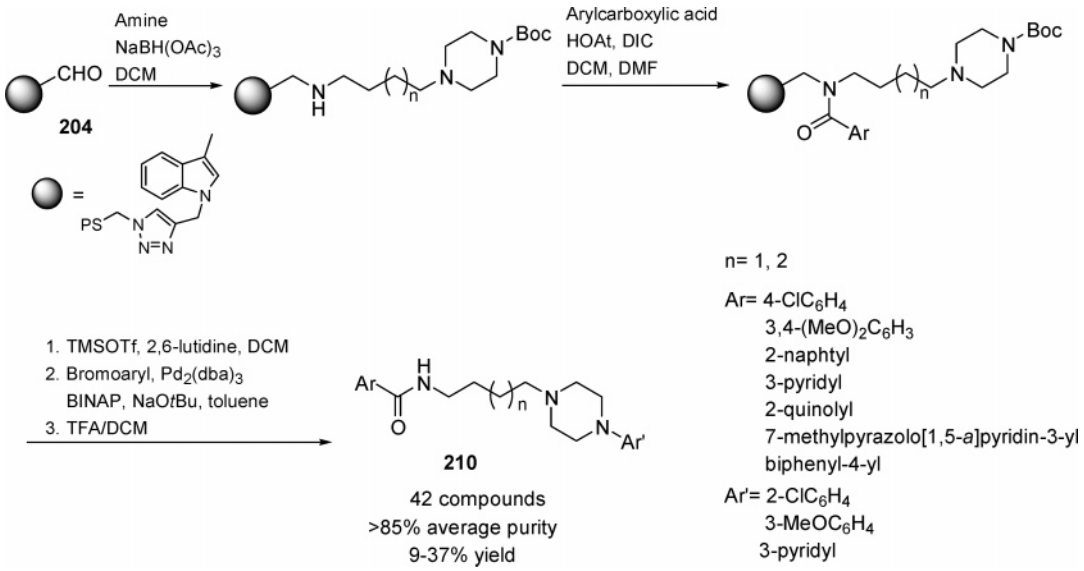
was shown by minimal essential medium and hemolysis experiments. The aliphatic polyester-graft oligopeptide **217** was similarly synthesized, but a higher temperature was required for the alkyne−azide coupling. Notably, no degradation of the polyester was detected in the 1,2,4-triazole step formation of either synthesis. Another example of related chemistry is the recently reported synthesis of biohybrid amphiphiles from a polymer and a protein.[108i]

^{18}F-radiolabeled peptides have also been prepared using click chemistry. Conjugation of ^{18}F-fluoroalkynes to various peptides functionalized with 3-azidopropionic acid via CuI-mediated 1,3-dipolar cycloaddition yielded the desired ^{18}F-labeled products in 10 min with good to excellent yields and excellent radiochemical purity.[109]

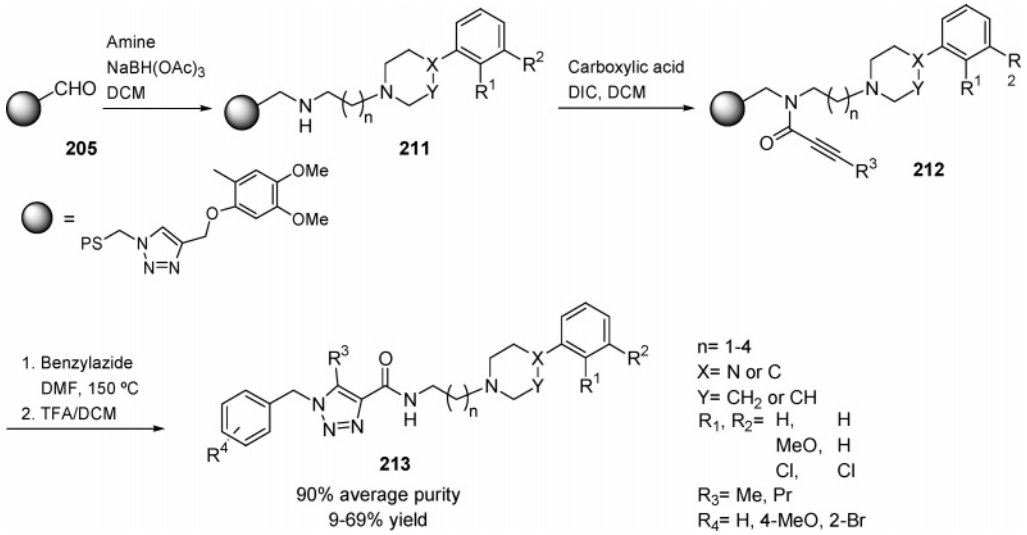
4.1.5.2. Nitriles as Dipolarophiles. Synthesis of 1,2,3,4-Tetrazoles. Griebenow et al. have prepared 1,2,3,4-tetrazoles on solid-phase supports through azide−nitrile cycloaddition.[110] The authors synthesized a library of 20 biphenyl tetrazoles that have points of diversity at both biphenyl rings (Scheme 84). Starting from the resin-bound 2-allyloxy-5-cyano-4-iodobenzene derivative **219**, the biphenyl system was constructed by Suzuki cross-coupling with phenylboronic acids. These conditions also led to the deallylation of the phenolic group, which was then derivatized via a Mitsunobu reaction. A set of five boronic acids and four alcohols were crossed in the two steps to provide the resin-bound alkoxy biphenyl nitriles **220**. The tetrazole ring was then formed by reaction of the nitrile group of **220** with Me_3SiN_3 and catalytic *n*-Bu_2SnO in *o*-xylene for 50 h at 90 °C. Biphenyl tetrazoles **221** were isolated in moderate yields (14−44%) and good to excellent purities (59−93%) after TFA cleavage from the resin and purification by HPLC.

Molteni et al. extended their previously reported protocol for the synthesis of MeOPEG-1,2,3-triazoles to the preparation of 1,2,3,4-tetrazoles (Scheme 85).[101] The electron-poor nitriles **222** were used as dipolarophiles and reacted with the MeOPEG-supported azide **194** in toluene at 90 °C. Upon addition of diethyl ether to the crude reactions, the MeOPEG-supported 1,2,3,4-tetrazoles **223** were obtained in near quantitative yields.

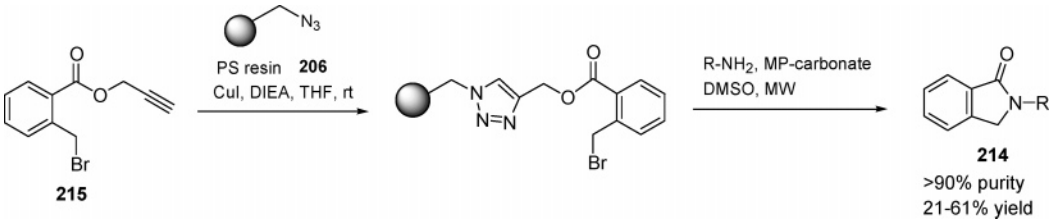
Scheme 80



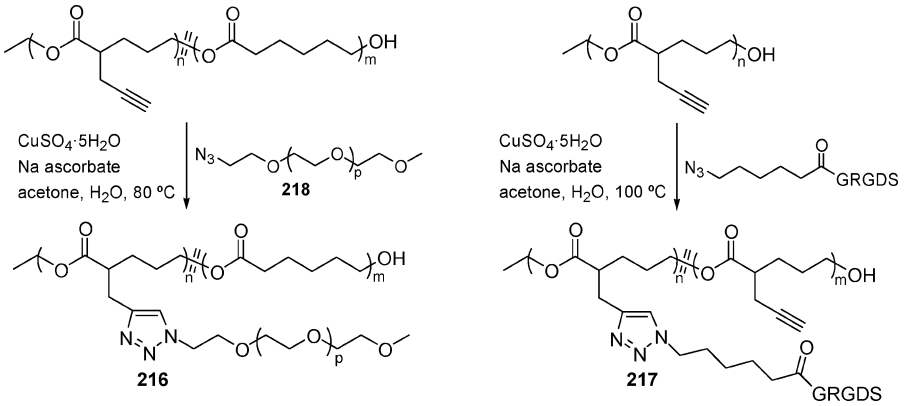
Scheme 81



Scheme 82



Scheme 83



The reaction between a nitrile and an azide to yield a tetrazole was recently applied in the synthesis of polymeric materials containing 5-vinyltetrazole units.[111] The tetrazole ring formation was performed post-polymerization, starting from homopolymers of acrylonitrile and random and block copolymers of acrylonitrile and styrene.

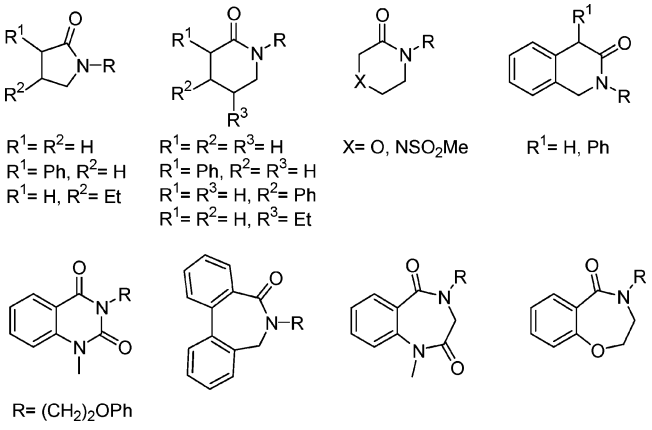
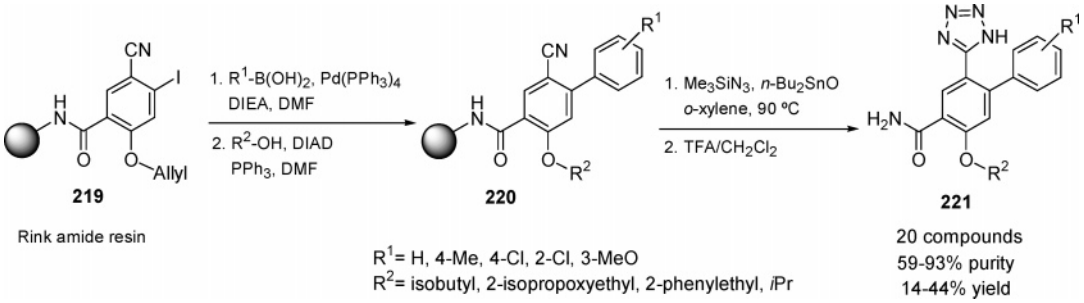


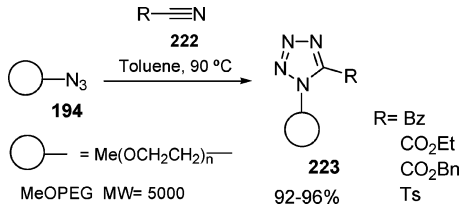
Figure 5.

4.2. Nitrogen- and Oxygen-Containing Heterocycles. 4.2.1. Nitrile Oxides. 4.2.1.1. Alkynes and Alkenes as Dipolarophiles. Synthesis of Isoxazoles and 2-Isoxazolines. The 1,3-dipolar cycloaddition of nitrile oxides with alkynes and with alkenes is a powerful method for the preparation of isoxazoles and isoxazolines, respectively. Following this approach, Huang et al. synthesized a library of the 1,2-diheterocyclic-substituted (*E*)-olefins **178**, **224**, and **225** from the polystyrene selenenyl bromide resin **179** (Schemes 71 and 86).[98] Key steps included on-resin preparation of the 1,2,3-triazole, isoxazole, or 1,2,4-oxadiazole ring, followed by α-alkylation with substituted allyl bromide and, finally, formation of the isoxazoline ring. A one-pot 1,3-dipolar cycloaddition of the propargyl resin **180** with NaN_3 and aryl

Scheme 84



Scheme 85

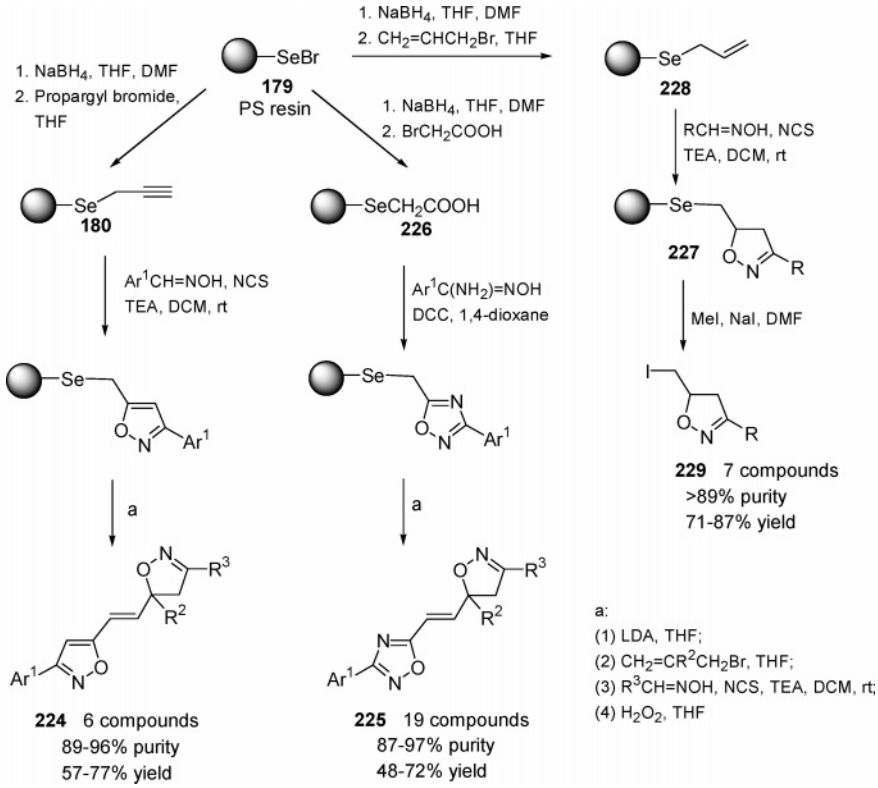


halides, catalyzed by CuI and proline, produced 1,2,3-triazoles. Isoxazoles and isoxazolines were obtained using nitrile oxides as 1,3-dipoles based on previous work by the same group.[112] A Porco's two-step one-pot condensation of the resin **226** with amidoximes furnished 1,2,4-oxadiazoles. Final treatment with H_2O_2 prompted selenoxide syn elimination of the resin, releasing the expected compounds in moderate to good yield and with good purity. Similarly, the same group prepared resin-bound isoxazolines **227** from allyl-selenium resin **228**.[113] In this case, cleavage was performed by treatment with MeI−NaI to yield the 3-substituted 5-(iodomethyl)isoxazolines **229** in 71−87% yield and >89% purity. The isoxazoline ring was further derivatized at the iodine group.

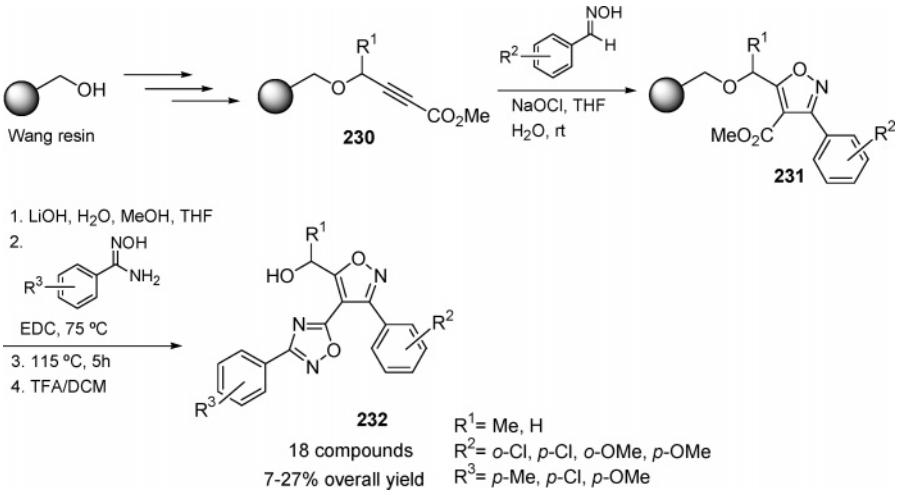
A similar approach was employed by Kurth and Quan in the preparation of an 18-member library of isoxazol-4-yl-[1,2,4]oxadiazoles (Scheme 87).[114] The resin-bound alkynes **230** were synthesized from Wang resin in a three-step sequence and then were reacted with benzaldehyde oximes in the presence of excess bleach for 3 days. The corresponding nitrile oxides were generated in situ, leading to the 3,4,5-trisubstituted isoxazoles **231** through a [3+2] cycloaddition. Subsequent formation of the 1,2,4-oxadiazole ring was achieved by hydrolysis of the methyl esters **231**, followed by a Porco's two-step, one-pot condensation with diverse benzamidoxime derivatives. After TFA cleavage of the products from the resin and purification by column chromatography, the final compounds **232** were obtained in 7−27% overall yield.

The nitrile oxide 1,3-dipolar cycloaddition with alkynes was also reported by Fukazawa et al., who used it to prepare a library of liquid crystalline isoxazoles (Scheme 88).[115] Immobilization of the alkynes **233** on Rink amide resin was followed by cycloaddition with nitrile oxides generated in situ from chlorooximes **234** upon reaction with TEA. Tf_2O treatment yielded the expected isoxazoles **235** or **236**

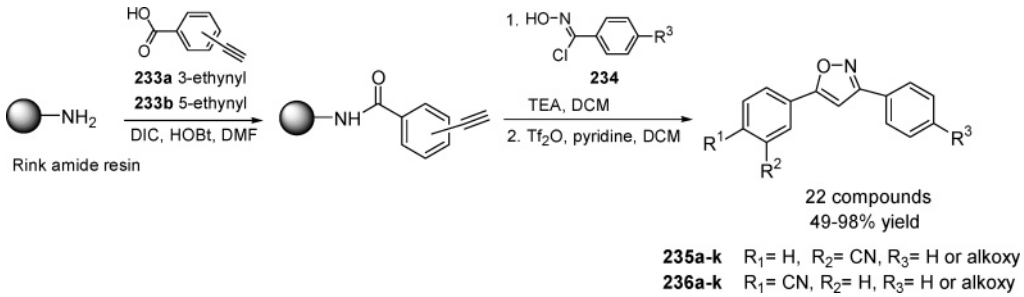
Scheme 86



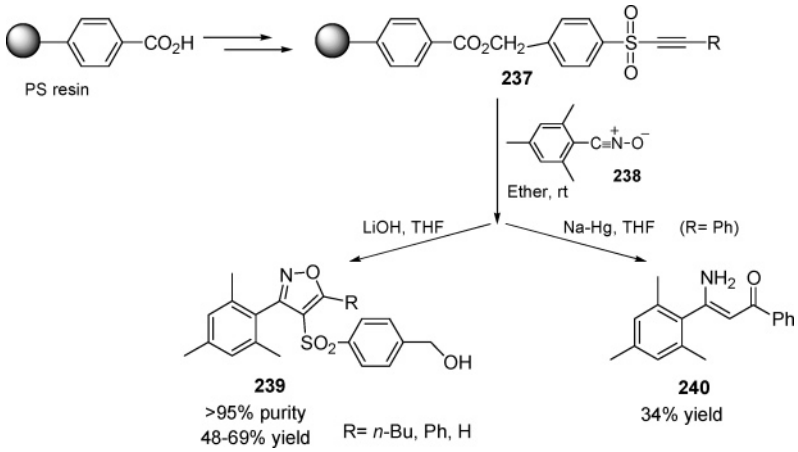
Scheme 87



Scheme 88



Scheme 89

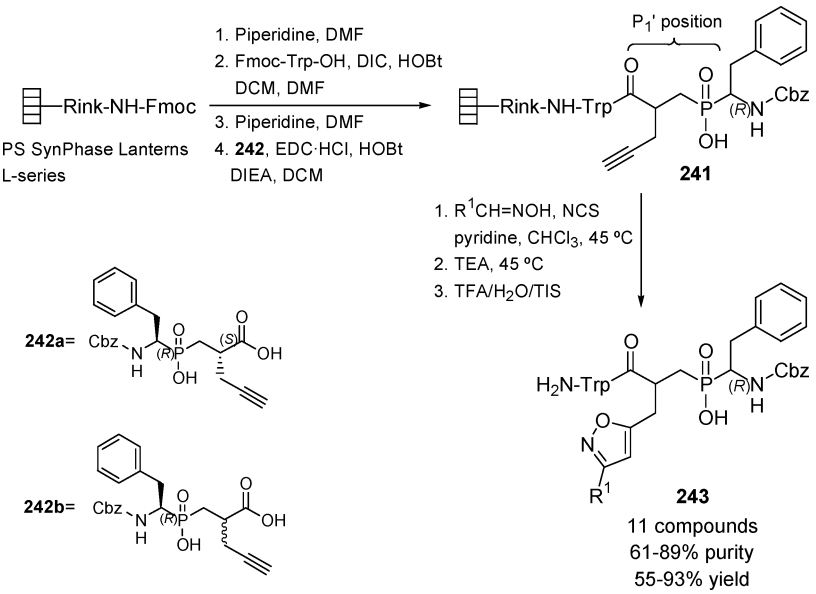


which were purified by column chromatography and isolated in yields ranging from 49 to 98% and in >95% purity. The mesomorphic properties of the products were then studied.

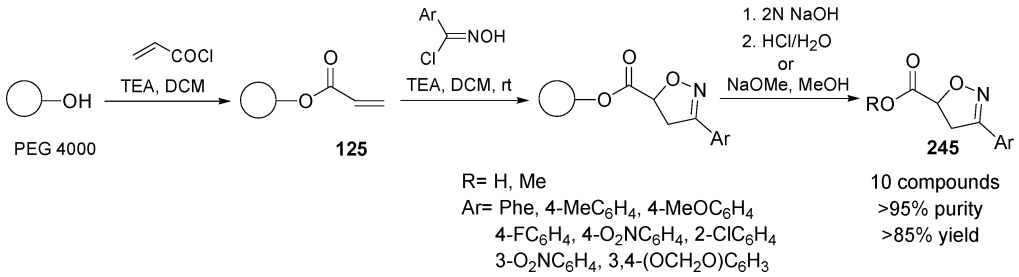
Back and Zhai synthesized isoxazolyl sulfones from the resin-bound acetylenic sulfones **237** and nitrile oxide **238** (Scheme 89).[116] Upon completion of the cycloaddition, the resulting adducts were released from the resin with LiOH to afford the sulfones **239** in yields ranging from 48 to 69% and with a crude purity of >95%. However, the 5-phenyl-substituted cycloadduct was instead treated with 5% sodium amalgam, leading to reductive desulfonylation and N−O cleavage to produce compound **240**, obtained in 34% yield after purification by flash chromatography.

Isoxazole-containing phosphinic tripeptides, designed as potential matrix metalloprotease inhibitors, were prepared on SynPhase Lanterns through an alkyne−nitrile oxide cycloaddition (Scheme 90).[117] The alkynyl-functionalized phosphinic tripeptide **241** linked to Rink amide lanterns was synthesized as both optically pure and a mixture of epimers at the P_1' position from **242a** and **242b**, respectively. The cycloaddition of **241** to nitrile oxides was optimized by Multipin technology. The best results were obtained by treating **241** with a 0.56 M chloroform solution of in situ-generated nitrile oxide at 45 °C for 24 h. The reaction required three to four repetitions of the treatment to proceed to completion. TFA cleavage of the products from the lantern afforded the phosphinic peptides **243** in good yields (65−

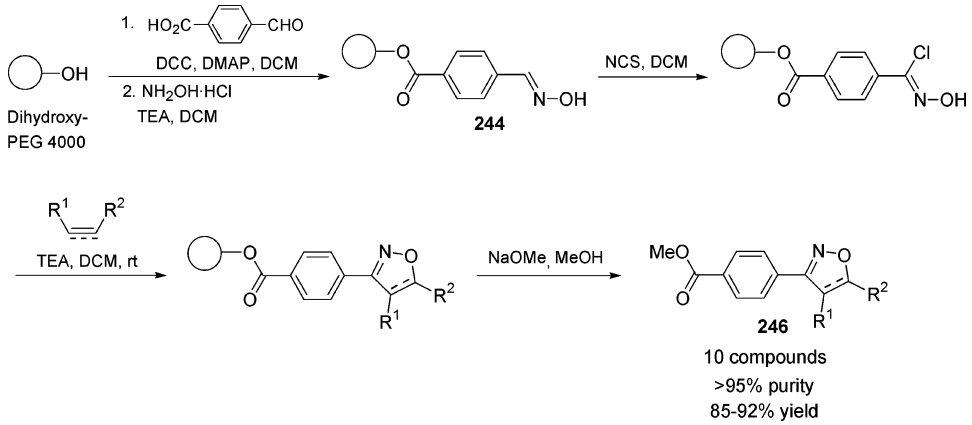
Scheme 90



Scheme 91



Scheme 92

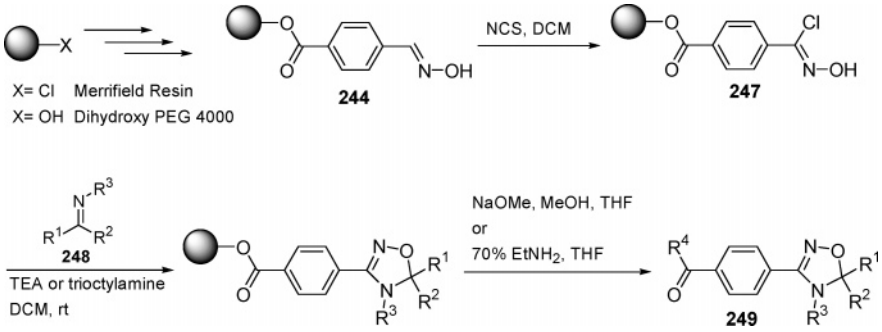


93%) and purities (70−89%). Only the cycloaddition involving a nitrile oxide that bears a *p*-cyanophenyl substituent did not go to completion; hence the corresponding peptide was obtained in lower yield (55%) and purity (61%). Interestingly, no racemization was observed when optically pure tripeptides were used in the cycloaddition reaction.

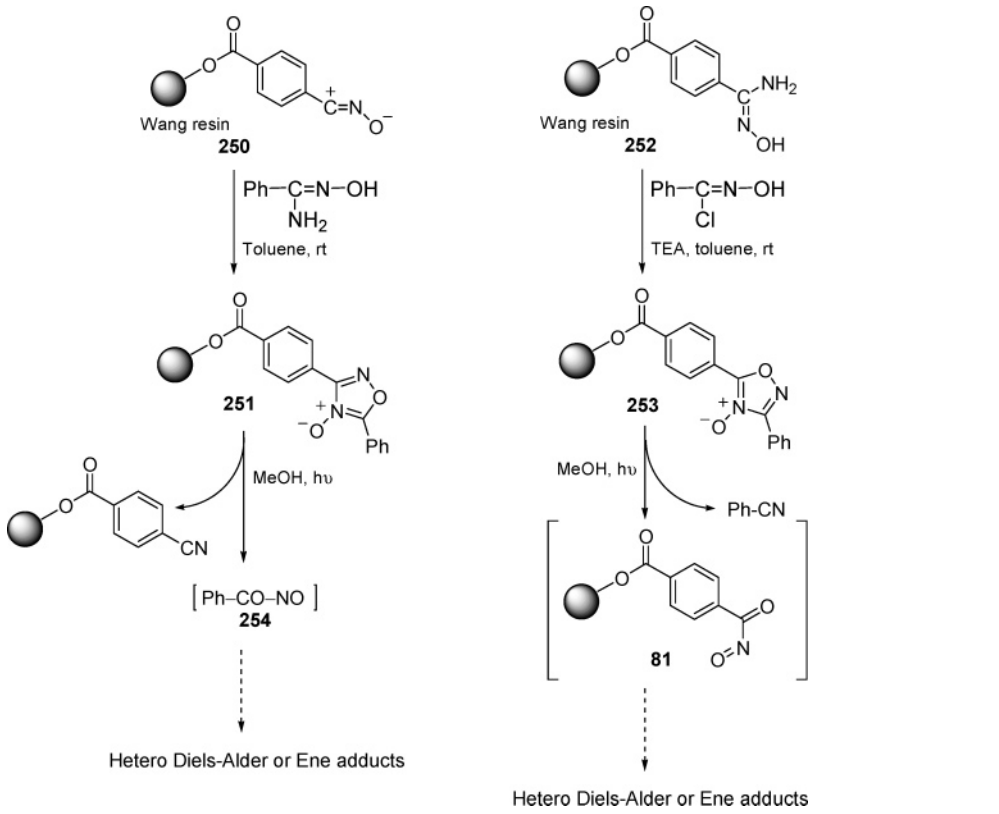
Wang et al. described a one-pot synthesis of isoxazoles and isoxazolines on soluble polymer support (PEG 4000), in which the nitrile oxide is trapped with an alkene or alkyne.[118] The authors developed two procedures according to polymer-bound component involved in the cycloaddition. In the first, the PEG-bound acrylate **125** was reacted with nitrile oxides generated in situ (Scheme 91), whereas in the second, the PEG-supported oxime **244** provided the corresponding nitrile oxide, which then underwent cycloadditions with alkenes or alkynes (Scheme 92). In both procedures, the one-pot isoxazoline and isoxazole syntheses were performed by stirring the oxime with *N*-chlorosuccinimide in DCM at 25−30 °C, followed by addition of the dipolarophile and TEA and, finally, stirring of the reaction mixture at room temperature. Cleavage of the products from the support using NaOMe in methanol or aqueous 2N NaOH afforded the target isoxazolines and isoxazoles **245** and **246**. A total of 20 compounds were prepared in high yields (85−92%) and purities (>95%).

4.2.1.2. Imines as Dipolarophiles. Synthesis of 1,2,4-Oxadiazolines. Wang et al. reported the first one-pot SPS of 1,2,4-oxadiazolines through a [3+2] cycloaddition of

Scheme 93



Scheme 94

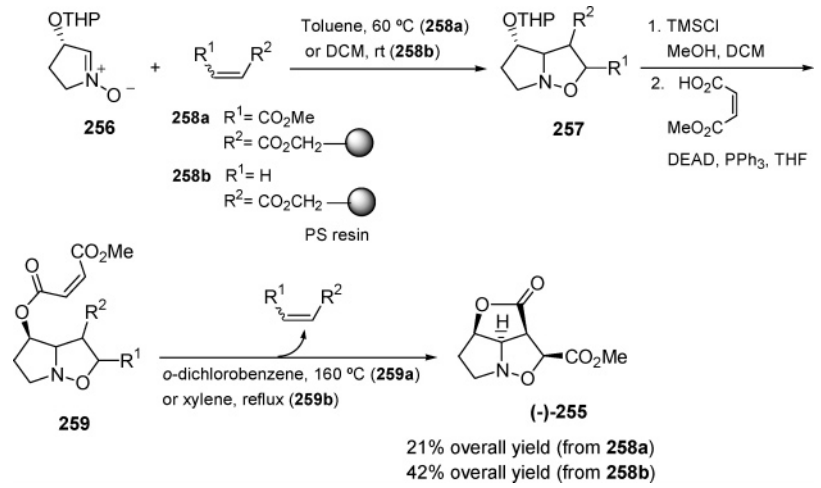


imines with resin-bound nitrile oxides (Scheme 93).[119] Conversion of the resin-supported oxime **244** to the chloro-oxime **247** and subsequent cycloaddition between the corresponding nitrile oxide and the imines **248** were performed in a parallel one-pot fashion. The resulting cycloadducts were cleaved from the resin by treatment with either NaOMe in methanol and THF or 70% ethylamine in THF. The authors thus prepared a 20-member library of the 1,2,4-oxadiazolines **249**, which were obtained in good yields (64−96%) and purities (77−97%). The same group later applied the aforementioned chemistry using PEG 4000 as soluble polymer support to prepare a variety of 1,2,4-oxadiazolines in good yields and purities.[120] In a separate work, they described an alternative approach for the synthesis of 1,2,4-oxadiazolines, based on the cycloaddition of PEG-bound imines to in situ-generated nitrile oxides.[121]

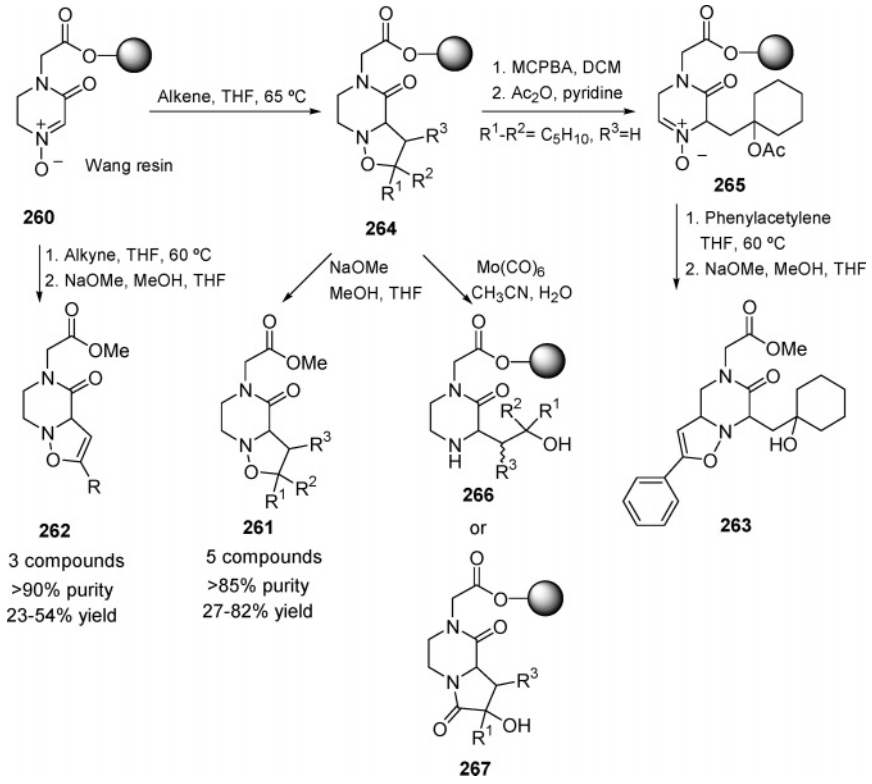
4.2.1.3. Amidoximes as Dipolarophiles. Synthesis of 1,2,4-Oxadiazole-4-oxides. 1,2,4-Oxadiazole-4-oxides have been prepared on Wang resin by 1,3-dipolar cycloaddition of nitrile oxides to amidoximes and were then used for photochemical generation of nitrosocarbonyl derivatives (Scheme 94).[60] The change of the resin-bound component of the cycloaddition altered the reaction outcome. Hence, reaction of the resin-bound nitrile oxide **250** with excess benzamidoxime in toluene at room temperature for 48 h led to the 1,2,4-oxadiazole-4-oxides **251**, which are linked to the Wang resin through position 3. In contrast, reaction of a resin-bound amidoxime such as **252** with an excess of benzhydroximoyl chloride in the presence of TEA led to the 1,2,4-oxadiazole-4-oxides **253**, which are linked to the resin through position 5. Photolysis of **251** and **253** led to the on-solution and resin-bound nitrosocarbonyls **254** and **81**, respectively, which were then trapped in situ by dienes in hetero-Diels−Alder reactions or by olefins in ene reactions (see section 3.2.2).

4.2.2. Nitrones. Synthesis of Isoxazolidines, 4-Isoxazolines, Pyrrolo[1,2-*b*]isoxazoles, and Isoxazolo[2,3-*a*]pyrazinones. Isoxazolidines and 4-isoxazolines can be syn-

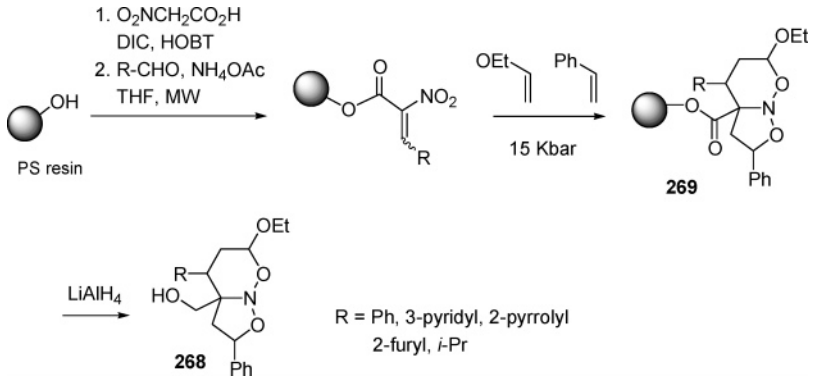
Scheme 95



Scheme 96



Scheme 97



thesized via [3+2] cycloaddition of a nitrone with an alkene and with an alkyne, respectively. Although this reaction has been widely used in solution, there are few examples of its use on solid-phase supports. However, a variety of structures have been obtained using the procedure by employing either solid-supported alkenes or nitrones. This chemistry has been

extensively reviewed by Rück-Braun et al.[122] Preparation of the tricyclic compound **255** from the pyrroline *N*-oxide **256** exemplifies the utility of cyclic nitrones as 1,3-dipoles in SPS (Scheme 95).[123] The nitrone was key to the [3+2] cycloaddition reaction between the chiral pyrroline *N*-oxide **256** and a solid-supported dipolarophile, leading to the formation of the isoxazolidine ring of the pyrrolo[1,2-*b*]-isoxazole **257**. This step served to link **256** to the solid-phase, as well as to mask the nitrone functionality to avoid later racemization of the C-3 stereocentre of the pyrroline ring. The authors used two solid-supported dipolarophiles containing a maleate or acrylate moiety. Reaction with the polystyrene maleate resin **258a** was carried out in toluene at 60 °C for 2.5 h, and reaction with the REM resin **258b** was performed in toluene at room temperature in 24 h. After THP group removal and esterification of the free hydroxyl group with monomethyl maleate, **259** was transformed to the final compound (−)-**255** through a 1,3-dipolar cycloreversion/intramolecular cycloaddition domino process for which the nitrone group was again crucial. This step was completed in 7 h by the heating of **259a** in *o*-dichlorobenzene at 160 °C or **259b** in xylenes at 140 °C, affording (−)-**255** in 21 and 42% overall yields, respectively.

Rück-Braun and Wiershem recently synthesized isoxazolo-[2,3-*a*]pyrazinones from the polymer-supported cyclic nitrone **260** (Scheme 96).[124] Using alkenes as dipolarophiles, the authors obtained the isoxazolidines **261** in >85% purity after basic cleavage from the resin and 27−82% yields after HPLC purification. [3+2] Cycloaddition of **260** with alkynes, followed by sodium methoxide cleavage from the resin, provided the isoxazoline derivatives **262** in >90% purity, which were then purified by HPLC and isolated in 23−54% yields. Finally, isoxazoline **263** was prepared from the resin-bound tricyclic isoxazolidine **264** ($R_1 = R_2 = C_5H_{10}$) by oxidative N−O bond cleavage with MCPBA, *O*-acylation, [3+2] cycloaddition reaction of the resulting nitrone **265** with phenylacetylene, and finally, treatment with sodium methoxide. Interestingly, oxidative N−O bond cleavage of the resin-bound isoxazolidines **264** led to the 1,3-aminoalcohols **266** or the lactams **267**, which were further derivatized by *N*-acylation or Mitsunobu reactions, respectively.

5. Tandem [4+2]/[3+2] Cycloadditions

High-pressure-promoted tandem [4+2]/[3+2] cycloadditions of ethyl vinyl ether, styrene, and resin-bound nitroalkenes have been described.[125] A wide array of the bicyclic nitroso acetals **268** were thus obtained as mixtures of diastereomers. Various resin-bound nitroalkenes were prepared in one step from resin-bound nitroacetic acid and a wide variety of aldehydes via a microwave-assisted Knoevenagel reaction (Scheme 97). Ethyl vinyl ether (as dienophile) and styrene (as dipolarophile) were added to the resin-bound nitroalkene (as heterodiene). A pressure of 15 kbar was applied to the reaction mixture, yielding the tandem adducts **269**. Subsequent reduction of the ester linker with $LiAlH_4$ gave the 3-hydroxymethyl substituted nitroso acetals **268**.

Acknowledgment. Dedicated to Professor Miguel Yus in commemoration of his 60th birthday.

References and Notes

(1) (a) Lam, K. S.; Lebl, M.; Krchnak, V. *Chem. Rev.* **1997**, *97*, 411−448. (b) Shuttleworth, S. J.; Connors, R. V.; Fu, J.; Liu, J.; Lizarzaburu, M. E.; Qiu, W.; Sharma, R.; Wanska, M.; Zhang, A. J. *Curr. Med. Chem.* **2005**, *12*, 1239−1281. (c) Edwards, P. J.; Morrell, A. I. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 594−605. (d) Breinbauer, R.; Manger, M.; Scheck, M.; Waldmann, H. *Curr. Med. Chem.* **2002**, *9*, 2129−2145.

(2) Kantorowski, E. J.; Kurth, M. J. *Mol. Diversity* **1996**, *2*, 207−216.

(3) Harju, K.; Yli-Kauhaluoma, J. *Mol. Diversity* **2005**, *9*, 187−207.

(4) Yli-Kauhaluoma, J. *Tetrahedron* **2001**, *57*, 7053−7071.

(5) Lebmann, T.; Waldmann, H. *Chem. Commun.* **2006**, 3380−3389.

(6) (a) Mutter, M.; Uhmann, R.; Bayer, E. *Justus Liebigs Ann. Chem.* **1975**, 901−15. (b) Spanka, C.; Wentworth, P. J.; Janda, K. D. *Comb. Chem. High Throughput Screening* **2002**, *5*, 233−240.

(7) (a) Manhas, M. S.; Amin, S. G.; Bose, A. K. *Heterocycles* **1976**, *5*, 669−699. (b) Kano, S.; Ebata, T.; Shibuya, *S. Chem. Pharm. Bull.* **1979**, *27*, 2450−2455. (c) Kano, S.; Ebata, T.; Denta, Y.; Hibino, Shibuya, S. S. *Heterocycles* **1977**, *8*, 411−416. (d) Ojima, I.; Pei, Y. *Tetrahedron Lett.* **1992**, *33*, 887−890. (e) Ojima, I.; Pei, Y. *Tetrahedron Lett.* **1990**, *31*, 977−982.

(8) For a review, see: Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; Verlag Chemie: New York, 1993; pp 295−368.

(9) Ruhland, B.; Bhandari, A.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 253−254.

(10) (a) Molteni, V.; Annunziata, R.; Cinquini, M.; Cozzi, F.; Benaglia, M. *Tetrahedron Lett.* **1998**, *39*, 1257−1260. (b) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F. *Chem.—Eur. J.* **2000**, *6*, 133−138.

(11) Singh. R.; Nuss, J. M. *Tetrahedron Lett.* **1999**, *40*, 1249−1252.

(12) Le Roy, I.; Mouysset, D.; Mignani, S.; Vuilhorgne, M.; Stella, L. *Tetrahedron* **2003**, *59*, 3719−3727.

(13) Albericio, F.; Pons, M.; Pedroso, E.; Giralt, E. *J. Org. Chem.* **1989**, *54*, 360−366.

(14) Pei, Y.; Houghten, R. A.; Kiely, J. S. *Tetrahedron Lett.* **1997**, *38*, 3349−3352.

(15) (a) Łysek, R.; Furman, B.; Cierpucha, M.; Grzeszczyk, B.; Matyjasek, Ł.; Chmielewski, M. *Eur. J. Org. Chem.* **2002**, 2377−2384. (b) Łysek, R.; Grzeszczyk, B.; Furman, B.; Chmielewski, M. *Eur. J. Org. Chem.* **2004**, 4177−4187.

(16) Brown, R. C. D.; Keily, J.; Karim, R. *Tetrahedron Lett.* **2000**, *41*, 3247−3251.

(17) Falmagne, J. B.; Schmit, C.; Escudero, J.; Vanlierde, H.; Ghosez, L. *Org. Synth.* **1990**, *69*, 199−204.

(18) Ritter, H.; Sperber, R. *Macromolecules* **1994**, *27*, 5919−5920.

(19) Arseniyadis, S.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* **2004**, *45*, 2251−2253.

(20) (a) Lloyd-Williams, P.; Albericio, F.; Giralt, E. *Tetrahedron* **1993**, *49*, 11065−11133. (b) Patek, M.; Lebl, M. *Biopolymers* **1998**, *47*, 353−363. (c) James, I. W. *Tetrahedron* **1999**, *55*, 4855−4946.

(21) Spaller, M. R.; Thielemann, W. T.; Brennan, P. E.; Bartlett, P. A. *J. Comb. Chem.* **2002**, *4*, 516−522.

(22) The presence of PEG facilitates the swelling of the resin in polar solvents (Zalipsky, S.; Chang, J. L.; Albericio, F.; Barany, G. *React. Polym.* **1994**, *22*, 243−258), which are the most common for the cycloadditions

(23) Kaval, N.; Van der Eycken, J.; Caroen, J.; Dehaen, W.; Strohmeier, G. A.; Kappe, C. O.; Van der Eycken, E. *J. Comb. Chem.* **2003**, *5*, 560−568.

(24) Kaval, N.; Dehaen, W.; Van der Eyken, E. *J. Comb. Chem.* **2005**, *7*, 90−95.
(25) Toure, B. B.; Hamid Hoveyda, R. H. R.; Tailor, J.; Ulaczyk-Lesanko, A.; Hall, D. G. *Chem.—Eur. J.* **2003**, *9*, 466−474.
(26) Panek, J. S.; Zhu, B. *Tetrahedron Lett.* **1996**, *37*, 8151−8154.
(27) Craig, D.; Robson, M. J.; Shaw, S. J. *Synlett*, **1988**, 1381−1383.
(28) Zhang, W.; Xie, W.; Fang, J.; Wang, P. G. *Tetrahedron Lett.* **1999**, *40*, 7929−7933.
(29) Barluenga, J.; Mateos, C.; Aznar, F.; Valdés, C. *Org. Lett.* **2002**, *4*, 3667−3670.
(30) Kobayashi, S.; Auki, Y. *Tetrahedron Lett.* **1998**, *39*, 7345−7348.
(31) Wang, Y.; Wilson, S. R. *Tetrahedron Lett.* **1997**, *38*, 4021−4024.
(32) Sax, M.; Berning, S.; Wünsch, B. *Tetrahedron* **2005**, *61*, 205−211.
(33) Guo, H.; Wang, Z.; Ding, K. *Synthesis* **2005**, 1061−1068.
(34) Creighton, C. J.; Zapf, C. W.; Bu, J. H.; Goodman, M. *Org. Lett.* **1999**, *1*, 1407−1409.
(35) Gaviña, F.; Gil, P.; Palazón, B. *Tetrahedron Lett.* **1979**, *20*, 1333−1336.
(36) Chen, C.; Munoz, B. *Tetrahedron Lett.* **1999**, *40*, 3491−3494.
(37) Blaskovich, M.; Kahn, M. *J. Org. Chem.* **1998**, *63*, 1119−1125.
(38) Ogbu, C. O.; Qabar, M. N.; Boatman, P. D.; Urban, J.; Meara, J. P.; Ferguson, M. D.; Tulinsky, J.; Lum, C.; Babu, S.; Blaskovich, M. A.; Nakanishi, H.; Ruan, F.; Cao, B.; Minarik, R.; Little, T.; Nelson, S.; Nguyen, M.; GalP, A.; Kahn, M. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2321−2326.
(39) Boldi, A. M.; Charles Johnson, R. C. R.; Eissa, H. O. *Tetrahedron Lett.* **1999**, *40*, 619−622.
(40) Koch, M. A.; Schuffenhauer, A.; Scheck, M.; Wetzel, S.; Casaulta, V; Odermatt, A.; Ertl, P.; Waldmann, H. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 17272−17277.
(41) For reviews, see: (a) Elliott, M. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2301−2323. (b) Álvarez, E.; Candenas, M. L.; Pérez, R.; Ravelo, J. L.; Martín, J. D. *Chem. Rev.* **1995**, *95*, 1953−1980. (c) Shimizu, Y. M. *Chem. Rev.* **1993**, *93*, 1685−1698. (d) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897−1909.
(42) Tietze, L. F.; Hippe, T.; Steinmetz, A. *SynLett* **1996**, 1043−1044.
(43) Leconte, S.; Dujardin, G.; Brown, E. *Eur. J. Org. Chem.* **2000**, 639−643.
(44) Dujardin, G.; Leconte, S.; Coutable, L.; Brown, E. *Tetrahedron Lett.* **2001**, *42*, 8849−8852.
(45) Arboré, A.; Dujardin, G.; Maignan, C. *Eur. J. Org. Chem.* **2003**, 4118−4120.
(46) Chapman, O. L.; Engel, M. R.; Springer, J. P.; Clardy, J. C. *J. Am. Chem. Soc.* **1971**, *93*, 6696−6698.
(47) Lindsley, C. W.; Chan, L. C.; Goess, B. C.; Joseph, R.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 422−423.
(48) Goess, B. C.; Hannoush, R. N.; Chan, L. K.; Kirchhausen, T.; Shair, M. D. *J. Am. Chem. Soc.* **2006**, *128*, 5391−5403.
(49) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635−1649.
(50) Schreiber, S. L. *Science* **2000**, *287*, 1964−1969.
(51) Ohlmeyer, M. H. J.; Swanson, R. N.; Dillard, L. W.; Reader, J. C.; Asouline, G.; Kobayashi, R.; Wigler, M.; Still, W. C. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 10922−10926. (b) Nestler, H. P.; Bartlett, P. A.; Still, W. C. *J. Org. Chem.* **1994**, *59*, 4723−4724.
(52) Blackwell, H. E.; Pérez, R.; Schreiber, S. L. *Angew. Chem., Int. Ed*. **2001**, *40*, 3421−3425.
(53) Stavenger, R. A.; Stuart L.; Schreiber, S. L. *Angew. Chem., Int. Ed*. **2001**, *40*, 3417-3421.
(54) Kurosu, M.; Porter, J. R.; Foley, M. A. *Tetrahedron Lett.* **2004**, *45*, 145−148.
(55) Pierres, C.; George, P.; van Hijfte, L.; Ducep, J.-B.; Hibert, M.; Mann, A. *Tetrahedron Lett.* **2003**, *44*, 3645−3647.
(56) Tietze, L. F.; Steinmetz, A. *Angew. Chem.* **1996**, *35*, 651−652.
(57) Sanz, M. A.; Voigt, T.; Waldmann, H. *Adv. Synth. Catal.* **2006**, *348*, 1511−1515.
(58) Aikawa, K.; Irie, R.; Katsuki, T. *Tetrahedron* **2001**, *57*, 845−851.
(59) (a) Joly, G. D.; Jacobsen, E. N. *Org. Lett.* **2002**, *4*, 1795−1798. (b) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398−2400.
(60) Quadrelli, P.; Scrocchi, R.; Piccanello, A.; Caramella, P. *J. Comb. Chem.* **2005**, *7*, 887−892.
(61) Menichetti, S.; Mori, M.; Nativi, C. *Tetrahedron* **2005**, *61*, 5005−5010.
(62) Sun, S.; Murray, W. V. *J. Org. Chem.* **1999**, *64*, 5941−5945.
(63) Paulvannan, K.; Chen, T.; Jacobs, W. *SynLett* **1999**, 1609−1611.
(64) Paulvannan, K. *Tetrahedron Lett.* **1999**, *40*, 1851−1854.
(65) Oikawa, M.; Ikoma, M.; Makoto Sasaki, M. *Tetrahedron Lett.* **2005**, *46*, 415−418.
(66) Gupta, P.; Singh, S. K.; Pathak, A.; Kundu, B. *Tetrahedron* **2002**, *58*, 10469−10474.
(67) Paulvannan, K. *Tetrahedron Lett.* **1999**, *40*, 1851−1854.
(68) Lee, D.; Sello, J. K.; Schreiber, S. L. *Org. Lett.* **2000**, *2*, 709−712.
(69) (a) Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*; Wiley: New York, 1984. (b) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley-VCH: Weinheim, Germany, 2002. (c) Kobayashi, S.; Jørgensen, K. A. *Cycloaddition Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2002.
(70) Okada, H.; Akaki, T.; Oderaotoshi, Y.; Minakata, S.; Komatsu, M. *Tetrahedron* **2003**, *59*, 197−205.
(71) (a) Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174−10175. (b) Pittman, C. U., Jr. *Polym. News* **2005**, *30*, 85−92.
(72) Kawamura, Y.; Akai, Y.; Tsukayama, M. *Int. J. Mod. Phys. B* **2003**, *17*, 1910−1915.
(73) Ben-Aroya Bar-Nir, B.; Portnoy, M. *Heterocycles* **2006**, *67*, 511−518.
(74) Chen, Z.; Yue, G.; Lu, C.; Yang, G. *Synlett* **2004**, 1231−1234.
(75) Yue, G.; Chen, Z.; Yang, G. *J. Heterocycl. Chem.* **2006**, *43*, 781−786.
(76) Yue, G.; Wan, Y.; Song, S.; Yang, G.; Chen, Z. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 453−458.
(77) Cironi, P.; Manzanares, I.; Albericio, F.; Álvarez, M. *Org. Lett.* **2003**, *5*, 2959−2962.
(78) Cironi, P.; Cuevas, C.; Albericio, F.; Álvarez, M. *Tetrahedron* **2004**, *60*, 8669−8675.
(79) Fuchi, N.; Doi, T.; Takahashi, T. *Chem. Lett.* **2005**, *34*, 438−439.
(80) Xia, M.; Pan, X. *Synth. Commun.* **2004**, *34*, 3521−3528.
(81) Wang, Y.-G.; Zhang, J.; Lin, X.-F.; Ding, H.-F. *Synlett* **2003**, 1467−1468.
(82) Lin, X.-F.; Wang, Y.-G.; Ding, H.-F. *Chin. J. Chem.* **2004**, *22*, 415−418.
(83) Shou, W.-G.; Yang, Y.-Y.; Wang, Y.-G. *Synthesis* **2005**, 3535−3540.
(84) Samanta, S. K.; Yli-Kauhaluoma, J. *J. Comb. Chem.* **2005**, *7*, 142−146.
(85) Wang, J.-K.; Zong, Y.-X.; Yue, G.-R. *Synlett* **2005**, 1135−1136.
(86) Harju, K.; Kylänlahti, I.; Paananen, T.; Polamo, M.; Nielsen, J.; Yli-Kauhaluoma, J. *J. Comb. Chem.* **2006**, *8*, 344−349.
(87) (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004−2021. (b) Kiick, K. L.; Saxon, E.; Tirrel, D. A.; Bertozzi, C. R. *Proc. Natl. Acad. Sci. U.S.A.*

2002, *99*, 19−24. (c) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599. (d) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057−3064. (e) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128−1137. (f) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188−5240.

(88) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51−68.

(89) (a) Horne, W. S.; Stout, C. D.; Ghadiri, M. R. *J. Am. Chem. Soc.* **2003**, *125*, 9372−9376. (b) Horne, W. S.; Yadav, M. K.; Stout, C. D.; Ghadiri, M. R. *J. Am. Chem. Soc.* **2004**, *126*, 15366−15367.

(90) Tornøe, C. W.; Sanderson, S. J.; Mottram, J. C.; Coombs, G. H.; Meldal, M. *J. Comb. Chem.* **2004**, *6*, 312−324.

(91) Franke, R.; Doll, C.; Eichler, J. *Tetrahedron Lett.* **2005**, *46*, 4479−4482.

(92) Zhang, Z.; Fan, E. *Tetrahedron Lett.* **2006**, *47*, 665−669.

(93) Punna, S.; Kuzelka, J.; Wang, Q.; Finn, M. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 2215−2220.

(94) Weterings, J. J.; Khan, S.; van der Heden, G. J.; Drijfhout, J. W.; Melief, C. J. M.; Overkleeft, H. S.; van der Burg, S. H.; Ossendorp, F.; van der Marel, G. A.; Filippov, D. V. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3258−3261.

(95) Jang, H.; Fafarman, A.; Holub, J. M.; Kirshenbaum, K. *Org. Lett.* **2005**, *7*, 1951−1954.

(96) Holub, J. M.; Jang, H.; Kirshenbaum, K. *Org. Biomol. Chem.* **2006**, *4*, 1497−1502.

(97) Harju, K.; Vahermo, M.; Mutikainen, I.; Yli-Kauhaluoma, J. *J. Comb. Chem.* **2003**, *5*, 826−833.

(98) Xu, W.-M.; Huang, X.; Tang, E. *J. Comb. Chem.* **2005**, *7*, 726−733.

(99) Coats, S. J.; Link, J. S.; Gauthier, D.; Hlasta, D. J. *Org. Lett.* **2005**, *7*, 1469−1472.

(100) Gao, Y.; Lam, Y. *Org. Lett.* **2006**, *8*, 3283−3285.

(101) (a) Garanti, L.; Molteni, G. *Tetrahedron Lett.* **2003**, *44*, 1133−1135. (b) Molteni, G.; Del Buttero, P. *Tetrahedron* **2005**, *61*, 4983−4987.

(102) Bouillon, C.; Meyer, A.; Vidal, S.; Jochum, A.; Chevolot, Y.; Cloarec, J.-P.; Praly, J.-P.; Vasseur, J.-J.; Morvan, F. *J. Org. Chem.* **2006**, *71*, 4700−4702.

(103) Löber, S.; Gmeiner, P. *Tetrahedron* **2004**, *60*, 8699−8702.

(104) Löber, S.; Rodriguez-Loaiza, P.; Gmeiner, P. *Org. Lett.* **2003**, *5*, 1753−1755.

(105) Bettinetti, L.; Löber, S.; Hübner, H.; Gmeiner, P. *J. Comb. Chem.* **2005**, *7*, 309−316.

(106) Rodriguez Loaiza, P.; Löber, S.; Hübner, H.; Gmeiner, P. *J. Comb. Chem.* **2006**, *8*, 252−261.

(107) Dolle, R. E.; MacLeod, C.; Martinez-Teipel, B.; Barker, W.; Seida, P. R.; Herbertz, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 5830−5833.

(108) (a) Binder, W. H.; Kluger, C. *Macromolecules* **2004**, *37*, 9321−9330. (b) Bryan, M. C.; Fazio, F.; Lee, H.-K.; Huang, C.-Y.; Chang, A.; Best, M. D.; Calarese, D. A.; Blixt, O.; Paulson, J. C.; Burton, D.; Wilson, I. A.; Wong, C.-H. *J. Am. Chem. Soc.* **2004**, *126*, 8640−8641. (c) Collman, J. P.; Devaraj, N. K.; Chidsey, C. E. D. *Langmuir* **2004**, *20*, 1051−1053. (d) Díaz, D. D.; Punna, S.; Holzer, P.; Mcpherson, A. K.; Sharpless, K. B.; Fokin, V. V.; Finn, M. G. *J. Polym. Sci., Part A: Pol. Chem.* **2004**, *42*, 4392−4403. (e) Lee, J. K.; Chi, Y. S.; Choi, I. S. *Langmuir* **2004**, *20*, 3844−3847. (f) Lummerstorfer, T.; Hoffmann, H. *J. Phys. Chem. B* **2004**, *108*, 3963−3966. (g) Meng, J.-C.; Averbuj, C.; Lewis, W. G.; Siuzdak, G.; Finn, M. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 1255−1260. (h) Seo, T. S.; Bai, X.; Ruparel, H.; Li, Z.; Turro, N. J.; Ju, J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5488−5493. (i) Cornelissen, J. J. L. M.; Dirks, A. J.; Opsteen, J. A.; Reynhout, I. C.; Hatzakis, N.; Sly, J.; Rowan, A. E.; van Hest, J. C. M.; Nolte, R. J. M. *Polym. Prepr.* **2005**, *46*, 41−42. (j) Devaraj, N. K.; Miller, G. P.; Ebina, W.; Kakaradov, B.; Collman, J. P.; Kool, E. T.; Chidsey, C. E. D. *J. Am. Chem. Soc.* **2005**, *127*, 8600−8601. (k) Opsteen, J. A.; van Hest, J. C. M. *Chem. Commun.* **2005**, 57−59. (l) Parrish, B.; Breitenkamp, R. B.; Emrick, T. *J. Am. Chem. Soc.* **2005**, *127*, 7404−7410.

(109) Marik, J.; Sutcliffe, J. L. *Tetrahedron Lett.* **2006**, *47*, 6681−6684.

(110) Kivrakidou, O.; Bräse, S.; Hülshorst, F.; Griebenow, N. *Org. Lett.* **2004**, *6*, 1143−1146.

(111) Tsarevsky, N. V.; Bernaerts, K. V.; Dufour, B.; Du Prez, F. E.; Matyjaszewski, K. *Macromolecules* **2004**, *37*, 9308−9313.

(112) Huang, X.; Xu, W.-M. *Org. Lett.* **2003**, *5*, 4649−4652.

(113) Xu, W.-M.; Wang, Y.-G.; Miao, M.-Z.; Huang, X. *Synthesis* **2005**, 2143−2146.

(114) Quan, C.; Kurth, M. *J. Org. Chem.* **2004**, *69*, 1470−1474.

(115) Haino, T.; Tanaka, M.; Ideta, K.; Kubo, K.; Mori, A.; Fukazawa, Y. *Tetrahedron Lett.* **2004**, *45*, 2277−2279.

(116) Back, T. G.; Zhai, H. *Chem. Commun.* **2006**, 326−328.

(117) Makaritis, A.; Georgiadis, D.; Dive, V.; Yiotakis, A. *Chem.—Eur. J.* **2003**, *9*, 2079−2094.

(118) (a) Shang, Y.-J.; Wang, Y.-G. *Chin. J. Chem.* **2003**, *21*, 7−8. (b) Shang, Y.-J.; Yuan, L.; Wang, Y.-G. *J. Chem. Res.* **2004**, *5*, 336−338.

(119) Lin, X.-F.; Cui, S.-L.; Wang, Y.-G. *Chem. Lett.* **2003**, *32*, 842−843.

(120) (a) Lin, X.-F.; Zhang, J.; Cui, S.-L.; Wang, Y.-G. *Synthesis* **2003**, 1569−1573. (b) Lin, X.-F.; Zhang, J.; Wang, Y.-G. *Tetrahedron Lett.* **2003**, *44*, 4113−4115.

(121) Shang, Y.-J.; Shou, W.-G.; Wang, Y.-G. *Synlett* **2003**, 1064−1066.

(122) Rück-Braun, K.; Freysoldt, T. H. E.; Wierschem, F. *Chem. Soc. Rev.* **2005**, *34*, 507−516.

(123) Pisaneschi, F.; Cordero, F. M.; Brandi, A. *Synlett* **2003**, 1889−1891.

(124) Wierschem, F.; Rück-Braun, K. *Eur. J. Org. Chem.* **2004**, 2321−2324.

(125) Kuster, G. J.; Scheeren, H. W. *Tetrahedron Lett.* **2000**, *41*, 515−519.

CC070019Z