Carbon–Carbon Bond-Forming Solid-Phase Reactions. Part II

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Received June 26, 2000

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I. Introduction

There has been a plethora of polymer-supported syntheses since Merrifield[1] began peptide synthesis on the solid phase. Solid-phase organic synthesis (SPOS) has become a very efficient method for production of combinatorial libraries,[2] and with the implementation of high-throughput screening for biological evaluation for hits and leads, combinatorial libraries have become very important for pharmaceutical and agricultural chemistry. There have been several recent reviews on solid-phase chemistry.[3] In addition to traditional cross-linked resins, soluble polymer-supported reactions are increasing in popularity as well.[4] Heteroatom−carbon bond formation has been a mainstay not only for solid-phase peptide synthesis (SPPS), but also SPOS of heterocycles.[5] The formation of carbon−carbon bonds in solid-phase reactions is just as important but has been later in coming to age. A recent review from our group focused on carbon−carbon connections on the solid phase.[6] In the past two years there have been even more examples of SPOS in general as well as syntheses containing carbon−carbon bond-forming reactions. There are also more than a handful of recent papers that combined several different carbon−carbon bond-forming reactions in sequence or in divergent syntheses. This review is intended to update that previous publication for the period of January 1998 to December 1999.

II. Metal-Catalyzed Coupling Reactions

This area of research has been well adapted to organic reactions on polymer supports. Metal-catalyzed coupling methodologies are useful for the design of combinatorial libraries and have also been exploited to provide examples of SPOS on novel supports and/or linkers. Pd-catalyzed coupling reactions are the most prevalent method for creating carbon−carbon bonds in polymer-supported reactions.

1. Stille Coupling

The Stille coupling[7] has been used extensively for the palladium coupling of alkenyl or aryl stannanes with aryl or alkenyl bromides, iodides, or triflates. A key benefit of solid-phase Stille reactions is purification, as separation of the tin from the product can be tedious in solution phase. The reaction conditions in this review include examples of either the halide or the stannane being attached to the polymer support. Janda and co-workers[8] studied Stille coupling reactions of polymer-bound aryl iodides with both aryl and alkenyl tributylstannanes. First, several reaction parameters were tested to optimize the conditions of the cross-coupling on a soluble PEG (poly(ethylene glycol)) support (Scheme 1). The optimized conditions called for $PdCl_2(PPh_3)_2$ in DMF

10.1021/cr000086e CCC: $36.00
Published on Web 12/14/2000

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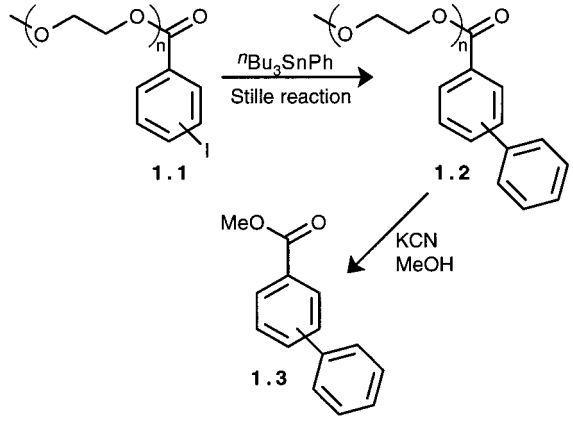
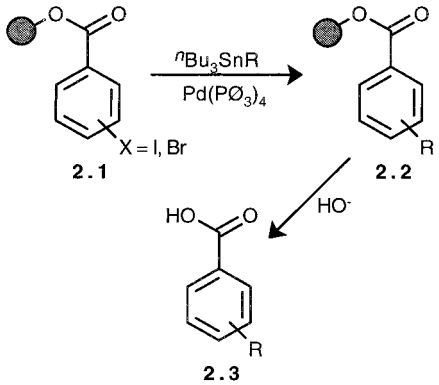
with addition of LiCl. A reaction time of 48 h was required for reaction concentration of 20 mM, but dilution to 10 mM allowed for reaction to be completed in 24 h. These conditions were utilized for the coupling of polymer-bound *o*- or *p*-iodobenzoic esters (**1.1**) with eight different stannanes to produce biaryl **1.2**. Cleavage from the polymer support with KCN in MeOH furnished **1.3** where yields for the *para* and *ortho* coupling were 71−99% and 69−90%, respectively, with all purities >95%.

Another example of the Stille coupling, this time on a polystyrene resin, was shown by Chamoin et al.[9] In this letter there were eight different polymer-bound aryl bromides or iodides (Scheme 2), including

Scheme 1



Scheme 2

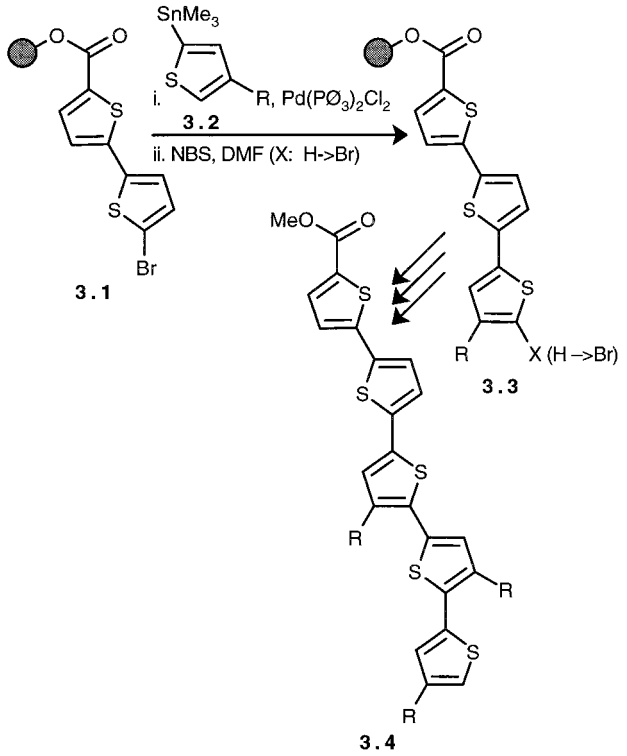


o-, *m*-, and *p*-bromo and -iodo benzoic esters **2.1** as well as a bromofuran and bromopyridine (not shown). The tributyl stannanes employed included the following: phenyl, vinyl, 2-furyl, 2-thienyl, *o*-*N*,*N*-diethylamidophenyl, and *o*-*N*,*N*-diethylcarbamic-phenyl. Stille coupling occurred with the addition of $Pd(PPh_3)_4$ to furnish **2.2**. A total of 22 Stille coupling products (**2.3**) were cleaved from the support with hydroxide, and the isolated yields ranged from 71% to 95%. Similar results were obtained for *meta*-substituted iodobenzoates using six different aryl, alkenyl, or alkynyl stannanes.[10] In this case, cuprous iodide catalyst (10 mol %) was added in the presence of NaCl to achieve yields ranging from 55% to 94%.

The general advantageous characteristics of SPOS allowed Malenfant and Fréchet to produce oligothiophenes via Stille coupling with high efficiency.[11] The resin selected was a macroporous highly cross-linked ArgoPore polystyrene (Scheme 3). The starting bithienyl compound was coupled to the solid support with a pendant carboxylic acid to produce the ester. The unsubstituted 5 position of the second thiophene ring was brominated with NBS to furnish aryl bromide **3.1**. Addition of 2-(trimethylstannyl)-4-octyl-thiophene (**3.2**) with $Pd(PPh_3)_2Cl_2$ in DMF produced **3.3**. This iterative process (bromination, Stille coupling) was repeated three times before final cleavage gave pentamer **3.4** in 90% yield and 89% purity (reverse-phase HPLC). Purities were also reported for the dimer, trimer, and tetramer and their corresponding bromides.

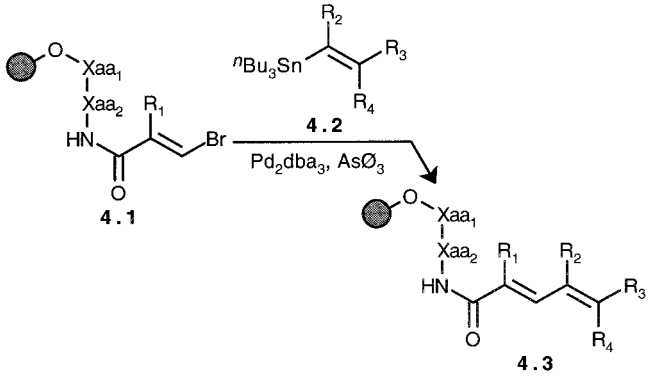
Blaskovich and Kahn reported the coupling of an alkenyl bromide with an alkenyl stannane to produce

Scheme 3



dienes.[12] Both PEG and Wang resins were used in these syntheses (Scheme 4). DIC-mediated coupling

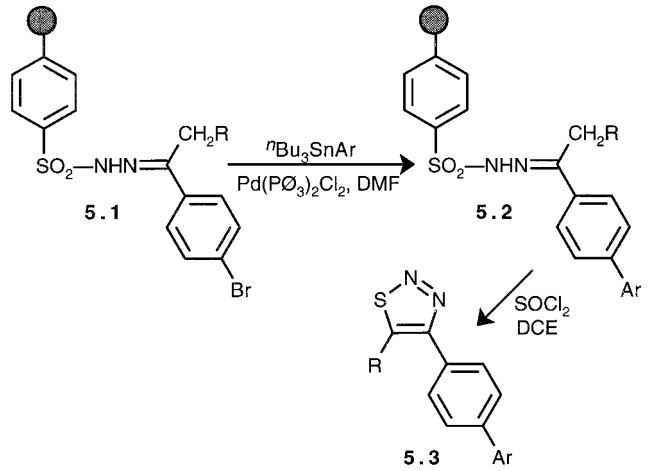
Scheme 4



of β-bromoacrylic acids to the N-terminus of an amino acid attached to the resin afforded alkenyl bromide **4.1**. Next, a dozen different alkenyl stannanes (**4.2**) were coupled to the bromide catalyzed by $Pd_2(dba)_3$ and $AsPh_3$ catalysis to furnish diene **4.3**. Cleavage of the ester linker with TFA or DBU in MeOH afforded the corresponding acid and methyl ester, respectively. The use of a polymer-bound alkenyl stannane for the Stille coupling to alkenyl bromides was also examined but found to be unsuccessful.

4-Biaryl-1,2,3-thiadiazoles were synthesized on polystyrene resin employing a catch and release sulfonylhyrazone linker.[13] Two different polymer-bound aryl bromides were realized, and two different aryl stannanes were employed in the coupling (Scheme 5). The coupling of aryl bromide **5.1** with the stannane was brought about with $Pd(PPh_3)_2Cl_2$ in DMF to generate **5.2**. The final thiadiazoles were cleaved and cyclized by addition of thionyl chloride in DCE,

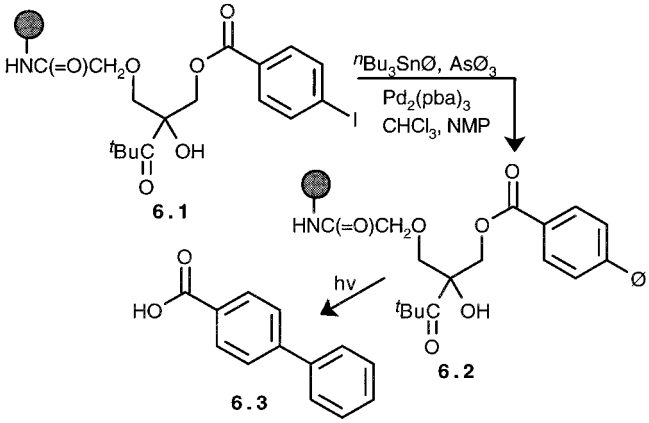
Scheme 5



giving thiadiazole **5.3** with overall yields of 71−80% and purities ranging from 85% to 93%.

The Stille coupling has been demonstrated utilizing TentaGel S resin with a photolabile linker (Scheme 6).[14] DIC coupling of 4-iodobenzoic acid to the polymer-

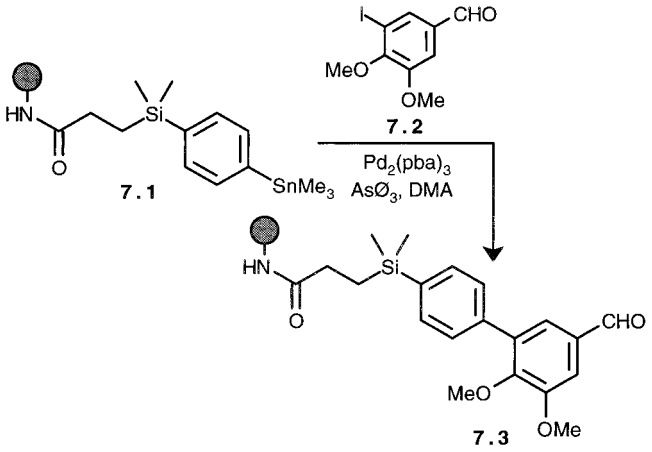
Scheme 6



bound hydroxy-functionalized linker gave aryl iodide **6.1**, which was subsequently coupled with tributylphenyltin via $Pd_2(dba)_3$ and $AsPh_3$−$CHCl_3$ in NMP to provide biaryl **6.2**. After cleavage from the resin by photolysis, biphenyl carboxylic acid **6.3** was obtained in 50% yield and 93% purity for the five-step synthesis. This novel photolabile linker was also utilized in the Suzuki coupling. Polymer-bound aryl iodide **6.1** was coupled with phenylboronic acid employing $PdCl_2(dppf)$ with TEA in DMF. The overall yield of the biaryl acid was 72%, and the purity was 93%.

There are also examples of Stille couplings where the aryl stannane was attached to the polystyrene resin.[15] In this example, a β-silylamide traceless linker was utilized in the solid-phase synthesis (Scheme 7). The Stille coupling was done with *O*-methyl-5-iodovanillin (**7.2**) employing normal Stille conditions to produce **7.3**. Further solid-phase reactions were done on the aldehyde to produce a library of compounds that were cleaved under acidic conditions. In another paper, the aryl stannane was attached to gel-phase polystyrene and a palladium catalyst was put to use to do similar chemistry.[16] In

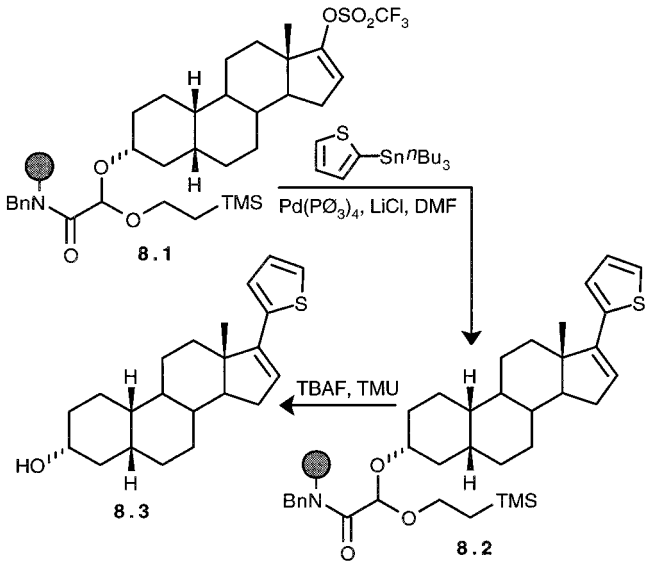
Scheme 7



this case, there were nine aryl bromide examples shown, which delivered biaryls in isolated yields of 80−95%. One aryl bromide containing a 1,2-amino alcohol was reported not to couple under these conditions.

The Stille coupling has also proven effective when utilizing polymer-bound vinyl triflates.[17] In this research, a SEM (trimethylsilylethoxy)methyl linker was utilized on Wang or TentaGel resins as well as pins (Scheme 8). In the example illustrated, the vinyl

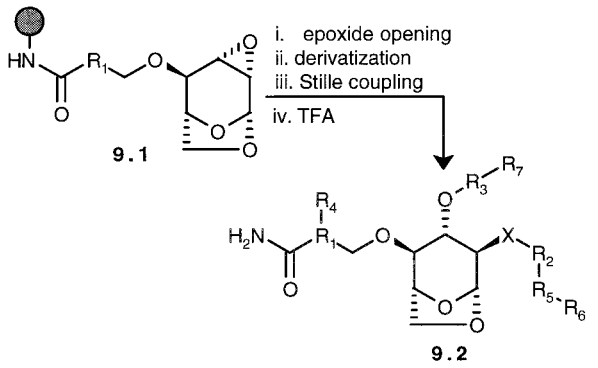
Scheme 8



triflate was part of a steroidal compound and attached to the solid phase to give **8.1**. Coupling of 2-(tributylstannyl)thiophene to this triflate occurred with $Pd(PPh_3)_4$ and LiCl in DMF to furnish **8.2**. The 17-(2′-thiophenyl)-5β-estra-16-ene was cleaved from the solid support with TBAF in tetramethylurea to afford **8.3** (38% yield with an HPLC-determined purity of 90%).

Solid-phase synthesis of levoglucosan derivatives has been accomplished employing the Stille coupling.[18] Polystyrene- or RAM-based resins with a Rink amide linker were selected for this synthesis (Scheme 9). There was a tremendous amount of derivatization beginning from polymer-supported epoxide **9.1**. The aryl iodide was located at various positions in the

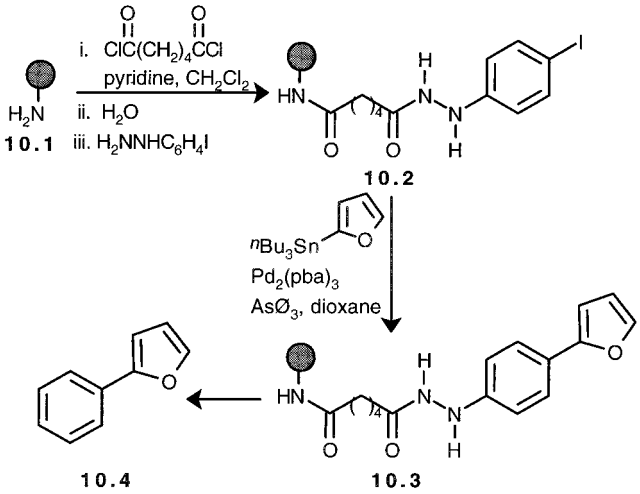
Scheme 9



compound, and aryl or alkenyl tributylstannanes were coupled with $Pd_2(dba)_3$ and $AsPh_3$ in dioxane. These compounds were cleaved from the resin with TFA in 1,2-dichloroethane to afford **9.2**.

Another example of a traceless linker used in solid-phase Stille couplings was reported by Stieber et al.[19] Polystyrene, TentaGel, and ArgoPore amino resins were used in these syntheses (Scheme 10). First,

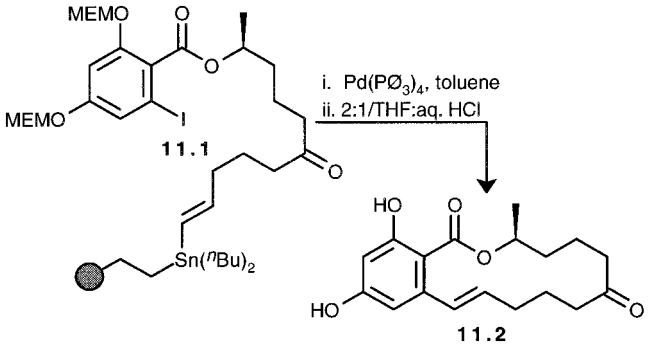
Scheme 10



addition of adipic dichloride to the amine and subsequent DIC coupling of the resultant acid with 4-iodophenylhydrazine gave polymer-supported aryl iodide **10.2**. The Stille coupling of 2-furyl-tributylstannane that followed employed $AsPh_3$ and $Pd_2(dba)_3$ in dioxane at 60 °C for 1 day to yield **10.3**. The novel hydrazide linker was cleaved by oxidation and subsequent nucleophilic attack. The purified products (**10.4**) were obtained in 50−90% overall yield for the three-step sequence.

One last example of the Stille coupling on the solid phase utilized a novel cyclo-release strategy. Nicolaou et al. developed this strategy and applied it to the synthesis of (*S*)-zearalenone.[20] This special case of an intramolecular Stille coupling is, to the best of our knowledge, the first example in SPOS. The stannane and the aryl iodide were both attached to the polystyrene resin (Scheme 11). Polymer-bound tin reagent **11.1** also played the role of the linker which was cleaved by the Stille coupling via $Pd(PPh_3)_4$ in toluene at 100 °C for 2 days. The macrocycle was produced in 53% yield, which was converted to (*S*)-

Scheme 11

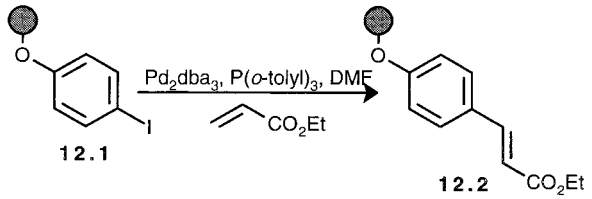


zearalenone (**11.2**) by acid deprotection of the MEM (methoxyethoxymethyl) ethers.

2. Heck Coupling

The addition of alkyl or aryl moieties to unactivated alkenes or alkynes via palladium catalysts is an excellent way to diversify combinatorial libraries, and thus the Heck reaction[21] has become common in both solution phase[22] as well as solid phase. An example of the Heck reaction with an aryl iodide attached to the polymer support (Wang or PEG-HMP) was shown by Hanessian (Scheme 12).[23] Aryl iodide **12.1** was

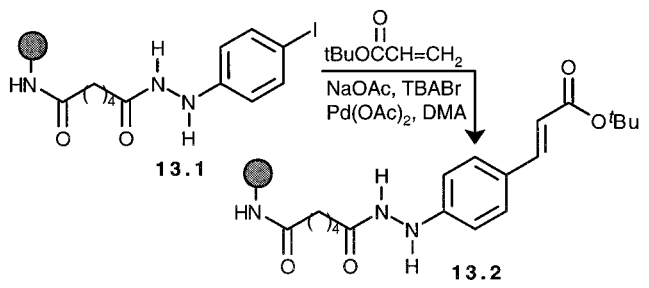
Scheme 12



coupled with ethyl acrylate in the presence of $Pd_2(dba)_3$ and P(*o*-tolyl)$_3$ to produce **12.2**. Cleavage of the *p*-alkoxybenzyl ether with TFA afforded ethyl 4-hydroxycinnamate in over 90% yield. It should be noted here that substituting $Pd(OAc)_2$ for $Pd_2(dba)_3$ was detrimental to the Heck coupling, but no explanation was given.

Another case employed aryl iodide attached to the solid support (polystyrene, TentaGel, or ArgoPore resins) using the hydrazide traceless linker as previously shown in Scheme 10 (Scheme 13).[19] In the

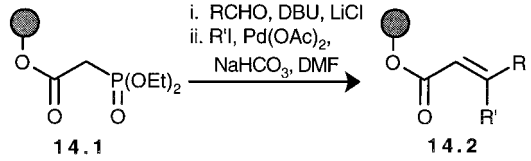
Scheme 13



coupling of polymer-supported aryl iodide **13.1** to *tert*-butyl acrylate, $Pd(OAc)_2$ was the catalyst accompanied by NaOAc and TBABr in DMA to give **13.2**. Cleavage from the resin with cupric acetate in methanol containing pyridine or with *n*-propylamine as solvent or with NBS and pyridine in DCM produced the *tert*-butyl cinnamate in yields of 83−96% with ArgoPore resin performing best.

An example of an alkene being attached to the resin, in this case mPEG 5000, has also been shown.[24] The disubstituted *E*-alkenes used in these Heck couplings were synthesized via a Horner−Emmons reaction of polymer-bound phosphonate and various aldehydes (Scheme 14). These supported alkenes

Scheme 14



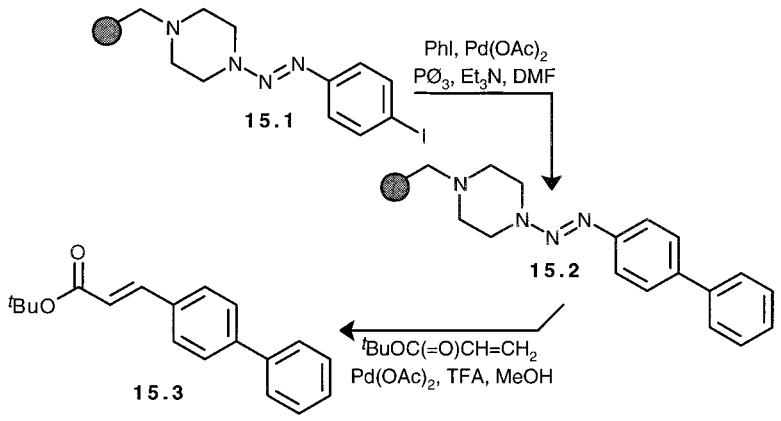
were coupled to aryl iodides stereoselectivly with $NaHCO_3$ and $Pd(OAc)_2$ in DMF to furnish **14.2**. Yields varied from 82% to 95%, while the *Z*/*E* ranged from >99/1 to 26/74. A good example of enhanced SPOS selectivity stated that a *Z*/*E* ratio of 90/10 for one solution-phase synthesis increased to 98/2 when accomplished on a polymer support.

Two examples of the Stille coupling reactions mentioned earlier diversified their combinatorial libraries by also employing Heck reactions on the same polymer-bound substrates. One example, similar to Scheme 8, utilized the same vinyl triflate to couple phenylacetylene utilizing PPh_3 and $Pd(OAc)_2$ in DMF with tributylamine.[17] The overall yield for the Heck coupling and attachment and cleavage of the steroidal moiety from the support was 46%. Brill et al. developed levoglucosan derivatives by Heck coupling similar to that shown in Scheme 9.[18] In this case, reactions occurred at a number of positions on the core structure, and Suzuki and Sonogashira coupling reactions were also used to expand diversification.

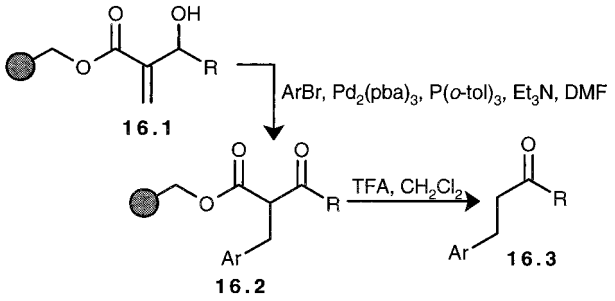
There are many new linker technologies being developed for SPOS, and some have been demonstrated in Heck coupling reactions. One such example showed the efficient use of a novel triazene traceless linker.[25] Another paper[26] where this triazene linker was originally disclosed used the Heck reaction on aryl iodides and cleaved the traceless linker under acidic conditions. The triazene was first produced by reaction of polymer-bound piperazine with aryl diazonium salts (Scheme 15). Polymer-bound aryl iodide **15.1** was coupled with iodobenzene employing $Pd(OAc)_2$, PPh_3, and TEA in DMF to produce polymer-supported biaryl **15.2**. A one-pot cleavage with TFA and Heck coupling with *tert*-butyl acrylate employing $Pd(OAc)_2$ in MeOH occurred in 12 h at 40 °C and gave ester **15.3**. The other 19 examples produce a broad range of compounds with yields of 29−97%.

Kulkarni and Ganesan describe the synthesis of *β*-keto esters by Heck coupling of polymer-bound allyl alcohols.[27] Acrylate attached to Wang resin underwent a Baylis−Hillman reaction and carbon−carbon bond formation (Scheme 16). The substituted acrylates produced (**16.1**) were subject to aryl bromides with $Pd_2(dba)_3$, P(*o*-tolyl)$_3$, and TEA in DMF at 100 °C for 24 h to generate **16.2**. Subsequent cleavage of

Scheme 15



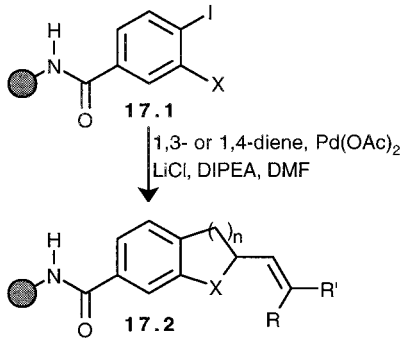
Scheme 16



the β-keto ester with TFA in DCM also brought about decarboxylation to afford the corresponding ketone (**16.3**) in overall yields of up to 49% with six different aryl bromides.

Another Heck-type coupling reaction, this time on a Rink resin, has been utilized to produce indolines, tetrahydroquinolones, dihydrobenzofurans, and chromanes (dihydrobenzopyrans).[28] In each case, the aryl iodide attached to the support possessed the iodo moiety *ortho* to a phenol or protected aniline (Scheme 17). The coupling reaction of iodide **17.1** was carried

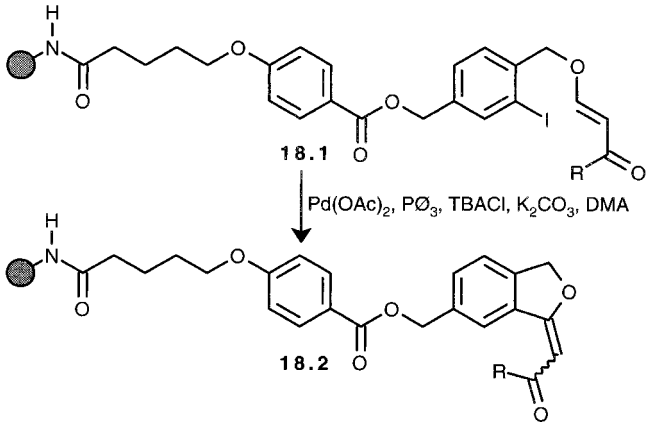
Scheme 17



out with a 1,3- or 1,4-diene prescribing $Pd(OAc)_2$, LiCl, and DIPEA in DMF at 100 °C to afford the desired bicyclic compound **17.2**. Yields of the TFA-cleaved amides varied from 69% to 93% and purities ranged from 49% to 90% for the 18 examples.

There are also examples of intramolecular Heck reactions being carried out on solid supports. Examples were carried out on both polystyrene and Rink resin attached through a base-labile linker.[29] This paper reports the syntheses of isoquinolones and benzofurans; the latter is shown here (Scheme 18).

Scheme 18

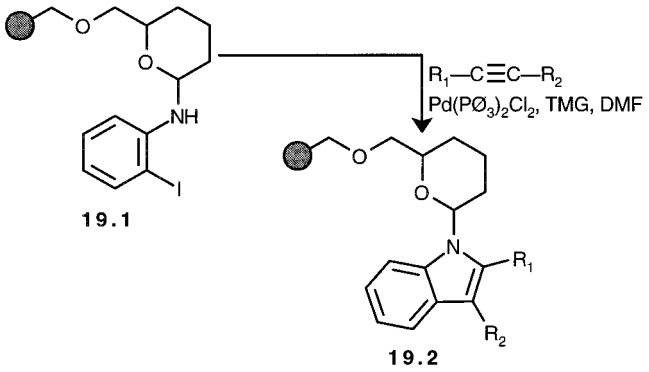


The aryl iodide was first attached to the polymer support, and the *o*-methylhydroxy moiety was reacted with a propiolate or ethynyl ketone to furnish **18.1**. The intramolecular Heck coupling was achieved with $Pd(OAc)_2$, PPh_3, TBACl, and K_2CO_3 in DMA at 100 °C to provide benzofuran **18.2**. Cleavage of the Rink amide with TFA afforded yields of 80% for the methyl ester ($R = OCH_3$) and 70% for the methyl ketone ($R = CH_3$). It should be noted that the combination of the Rink and base-labile linkers allows for cleavage with NaOMe or TFA to produce different products. In the benzofuran case, it was shown that the basic route lead to decomposition of the products and recovered yields were only 30−50%.

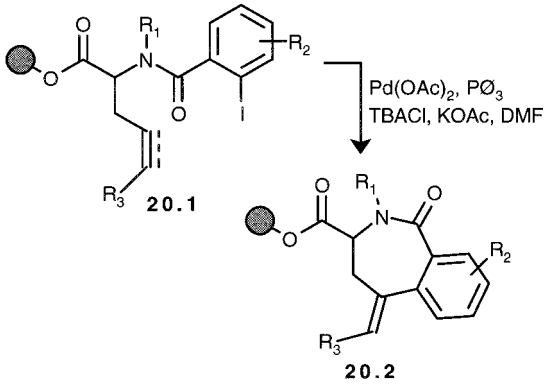
Another intramolecular Heck reaction was utilized in the synthesis of substituted indoles.[30] Ellman's THP resin[31] was selected as the starting point for this synthesis (Scheme 19). After attaching 2-iodoaniline to form polymer-bound aminal **19.1**, coupling of disubstituted alkynes was performed via $Pd(PPh_3)_2Cl_2$ with TMG in DMF at 110 °C for 5 h and repeated a second time for 16 h to produce polymer-supported indole **19.2**. Four of the six alkynes were unsymmetrical, and three of these showed complete regioselectivity. The one other unsymmetrical alkyne afforded an isomeric ratio of 84:15 as determined by HPLC. Yields of the isolated indoles, after cleavage of the aminal with 10% TFA, varied from 53% to 97%.

One final example of the intramolecular Heck reaction involved Wang resin as the solid support.[32] This resin was substituted with derivatives containing an alkene/alkyne and an amine moiety (Scheme

Scheme 19



Scheme 20



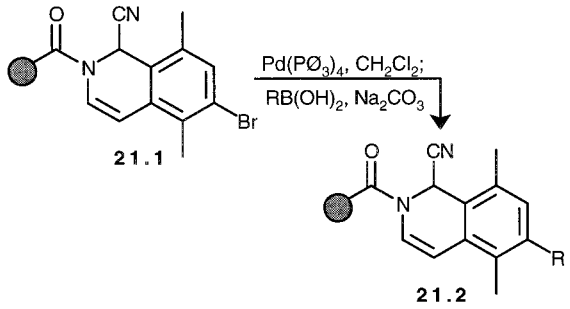
20). The polymer-supported secondary amine was acylated with 2-iodobenzoyl chlorides to deliver **20.1**. With both aryl iodide and alkene/alkyne attached, intramolecular cyclization occurred with $Pd(OAc)_2$, PPh_3, and KOAc in DMF at 70 °C to give a ϵ-caprolactam-like moiety bound to the resin. Cleavage from the resin followed by esterification with diazomethane produced the desired bicyclic lactam **20.2** in 60% yield from the starting alkene. Internal alkynes were applied in place of the alkene to give products in yields of 39−73%.

3. Suzuki Coupling

The Suzuki or Suzuki−Miyaura coupling[33] of aryl halides with boronic acids or boronates is well documented in solution as well as on the solid phase. As with the previous coupling reactions, the Suzuki coupling also occurs under very mild conditions and can tolerate the wide variety of functional groups present in a combinatorial library. The use of boronic acids or other boranes has also allowed the coupling to be conducted in water and biphasic solutions. The reliability of the Suzuki reaction makes it very popular for SPOS of small molecule combinatorial libraries. Its reliability has also been exploited in displaying the usefulness of novel supports and linkers in example syntheses.

Solid-phase Suzuki reactions have been studied by Kurth and co-workers.[34] The bromoisoquinolines were attached to the polystyrene resin through a Reissert[35] complex (Scheme 21). Polymer-supported aryl bromide **21.1** was reacted by Suzuki coupling with either phenylboronic acid or 3-thienylboronic acid. The reaction proceeded with addition of Pd-

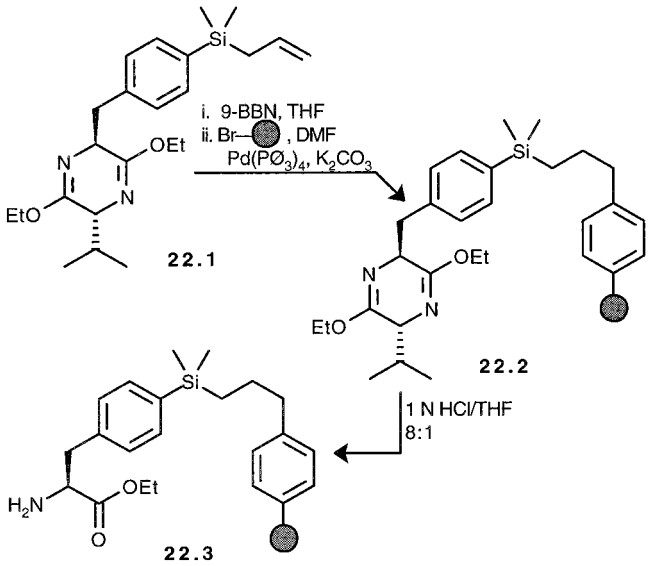
Scheme 21



$(PPh_3)_4$ in DCM with the bromide followed by the boronic acid and 2 M aqueous Na_2CO_3 to deliver substituted Reissert complex **21.2**. It should be noted that although Suzuki couplings were successful for 6-bromoisoquinoline Reissert complexes, the 4-bromo derivative was not conducive to coupling. Further derivatization including alkylation and 1,3-dipolar cycloadditions followed, and subsequent hydrolysis of the Reissert compound delivered the target isoxazolinoisoquinolines.

Another reference utilized the Suzuki coupling reaction to synthesize their traceless linker on the solid support (Scheme 22).[36] Hydroboration of allyl-

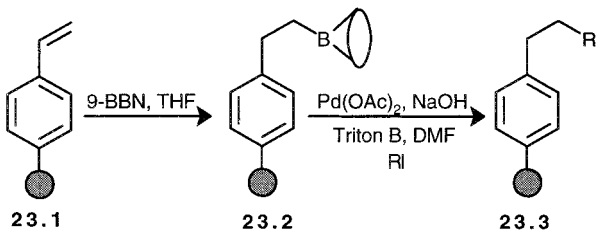
Scheme 22



silane **22.1** with 9-BBN formed the corresponding borane, which was coupled to bromopolystyrene resin with $Pd(PPh_3)_4$ and K_2CO_3 in DMF to give **22.2**. Acid hydrolysis of the bislactim afforded chiral amino ester **22.3**, which could be further modified (*N*-acylation, saponification, amide formation). It was noted that the Boc-protected amino acids could be generated first, followed by hydroboration and Suzuki coupling of the allyl silane.

Another use of the Suzuki coupling to attach linkers to the resin has also been reported.[37] This method also employed hydroboration of a polymer-bound alkene to form the borane (Scheme 23). Vinyl polystyrene **23.1** was treated with 9-BBN in THF to provide polymer-supported borane **23.2**. This borane was coupled to five different aryl, vinyl, or alkyl iodides [$Pd(OAc)_2$ employed as the catalyst for aryl

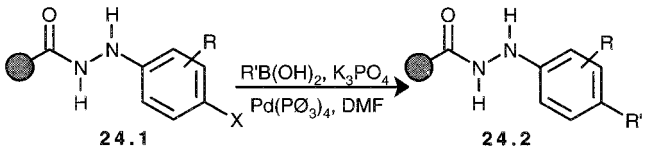
Scheme 23



iodides and $PdCl_2$(dppf) in the other cases]. Yields of **23.2** varied from 55% to 85% based on the mass of product cleaved or by comparison of IR integration to standards.

A novel oxidation-labile traceless linker for the Suzuki coupling was shown to be effective for SPOS.[19] In these syntheses polystyrene, TentaGel, and Argo-Pore resin were implemented (Scheme 24). Aryl

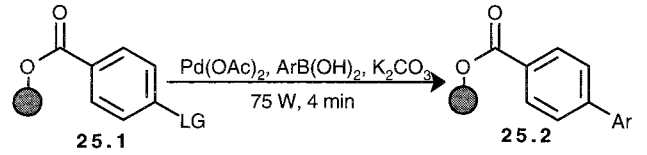
Scheme 24



bromides and iodides were bound to the solid support (**24.1**) and subsequently coupled with several aryl boronic acids to provide biaryl **24.2**. These boronic acids included *p*-methoxy, *p*-carbaldehyde, and 2-thienyl systems. The conditions for the coupling varied but included $Pd_2(dba)_3$ or $Pd(PPh_3)_4$ plus either K_2CO_3 or K_3PO_4 in DMF or DMF/H_2O (6:1). In one case, no inorganic base was applied but, in this case, the solvent was DMF/TEA (1:1). This new aryl hydrazide linker, first shown in Scheme 10 of this review, was cleaved in two steps (step 1 oxidation, step 2 addition of nucleophiles).

A very interesting approach to the SPOS Suzuki coupling is to apply microwave technology to reduce solid-phase reaction times to 4 min or less.[38] Esterification of PEG resin with aryl acids containing bromo, iodo, triflate, or nonaflate substituents at the *para* position delivered the precursor for the coupling reaction (Scheme 25). Thermal methods were first

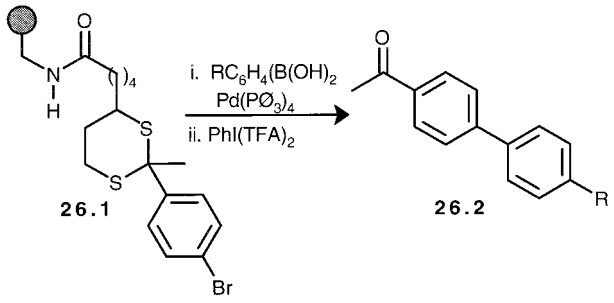
Scheme 25



reported in this reference using $Pd(OAc)_2$, K_2CO_3, and five different aryl boronic acids in water. The thermal method was modified to microwave conditions to furnish polymer-bound biaryl **25.2** in 4 min. The ideal microwave power was determined to be 75 W, although it was noted that the resin and linker were determined to be stable up to 900 W. In addition to the advantage of decreased reaction time, it was also determined that undesired cleavage of the ester linker was greatly reduced compared with normal Suzuki conditions.

A novel polystyrene-bound thioacetal linker developed by the Huwe group has proven its utility in part by Suzuki coupling.[39] The aryl bromide was bound to the polymer by thioacetal formation of 4-bromoacetophenone with polymer-bound lipoic acid (Scheme 26). Aryl bromide **26.1** was coupled with four differ-

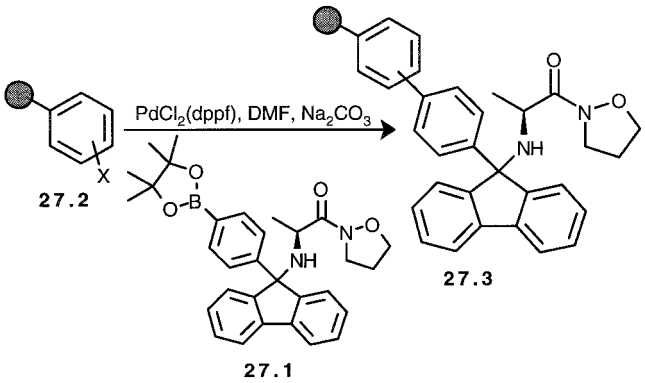
Scheme 26



ent arylboronic acids to supply the polymer-supported biaryl. The conditions of $Pd(PPh_3)_4$ and Na_2CO_3 in a solution of DMF, DME, and H_2O at 80 °C brought about the coupling overnight. The boronic acids included phenyl, *p*-chlorophenyl, *p*-methoxyphenyl, and *m*-nitrophenyl. Deprotection of the thioacetal (cleavage from resin) was achieved using [bis-trifluoroacetoxy)iodo]benzene in DCM, EtOH, and H_2O (4.5:4.5:1) for 30 min at ambient temperature to afford **26.2**. The overall yields of purified biaryl methyl ketones ranged from 28% to 34%.

Another report used the Suzuki coupling to attach a novel linker system, 9-phenylfluoren-9-yl, to the support.[40] The polymers employed were PEG-5000 and NCPS (non-cross-linked polystyrene) as well as Merrifield and Wang resins (Scheme 27). The first

Scheme 27

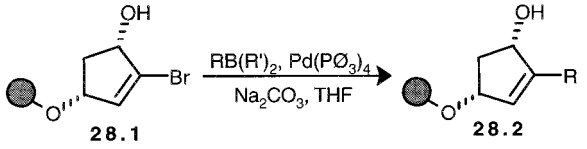


step was to produce arylboronate **27.1** for the linker in solution. This was done from the corresponding bromide applying diboron pinacol ester in the presence of $PdCl_2$(dppf). The boronate produced was coupled to polymer-bound aryl bromides or iodides (**27.2**) in the presence of $PdCl_2$(dppf) and 2 M Na_2CO_3 in DMF at 80 °C. One of these new resin linkers was utilized for the solid-phase synthesis of enantiopure norephedrines, which included a carbon−carbon bond-forming Grignard reaction seen later in this review (Scheme 191).

Ellman's group employed the use of Suzuki couplings in the efficient synthesis of prostaglandins.[41] The polymer-bound cyclopentenyl bromides were

utilized and coupled with different alkyl boranes (Scheme 28). The boranes were formed by hydro-

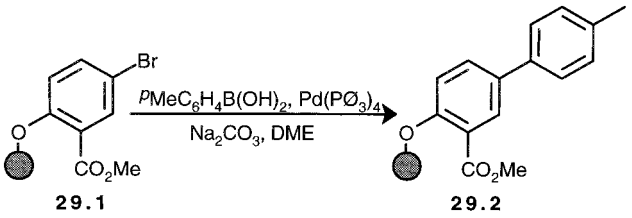
Scheme 28



boration of alkenes with 9-BBN and followed by a subsequent coupling to bromide **28.1** with $Pd(PPh_3)_4$ and 2 M Na_2CO_3 in THF at 65 °C. One unique example of a borane applied in the Suzuki coupling was the sodium salt of an acyl sulfonamide. These 11 E_1-, E_2-, F_1- and F_2-prostaglandins were obtained in 49−60% isolated yield.[41a] Twenty-six other E_1 derivatives were also synthesized in 18−56% yield.[41b]

A different type of solid support used in the Suzuki coupling is the polymer disc.[42] Styrene and vinylbenzyl chloride were copolymerized with divinylbenzene, PEG400 diacrylate, or PEG1000 diacrylate. The resulting cross-linked polymer rods were sliced into discs 1−2.5 mm thick and used in place of the traditional resin beads. The synthesis carried out to validate this support incorporated the Suzuki coupling reaction (Scheme 29). Methyl 5-bromosalicylate

Scheme 29

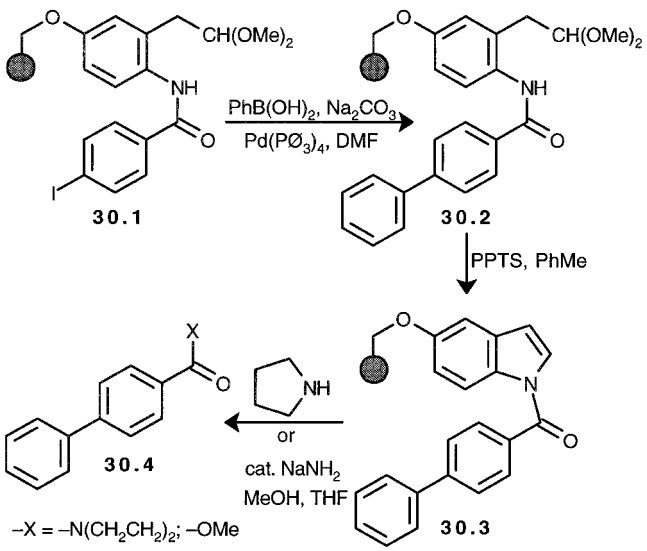


was first attached to the support to yield **29.1**. *p*-Tolylboronic acid was coupled to the disc-bound aryl bromide with $Pd(PPh_3)_4$, and Na_2CO_3 in DME at 90 °C to produce **29.2**, and the benzylphenyl ether was cleaved with TMSBr and TFA (1:1) in DCM to afford the free phenol. The attachment, coupling, and cleavage were completed in an overall conversion of 4−11%.

The Suzuki coupling reaction was also employed to validate a novel safety-catch linker.[43] The safety-catch linker was first attached to the solid support by employing 4-amino-3-(2′,2′-dimethoxyethyl)phenol (Scheme 30). The polymer-supported aniline was reacted with 4-iodobenzoyl chloride with pyridine in DCM to furnish aryl iodide **30.1**. Biaryl production by coupling of phenylboronic acid with the polymer-bound iodide was brought about under normal Suzuki conditions to give **30.2**. Deprotection of the acetal with PPTS provided acylindole **30.3** by cyclization of the aldehyde with the amide moiety. With the safety-catch linker now activated, the product was cleaved with pyrrolidine or methanol (cat. sodium amide) to afford **30.4**. Yields were 84% and 92%, respectfully, while the purities were >95% and >98%.

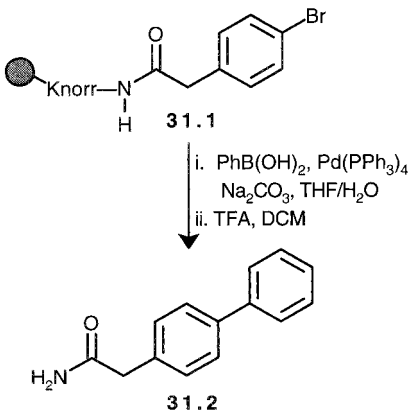
Polystyrene Microtube reactors[44] have also been utilized in SPOS Suzuki couplings.[45] The aryl bromide (4-bromophenylacetic acid) was coupled to the

Scheme 30



Merrifield Microtubes through a Knorr linker (Scheme 31). Implementing $Pd(PPh_3)_4$ and Na_2CO_3 in a solu-

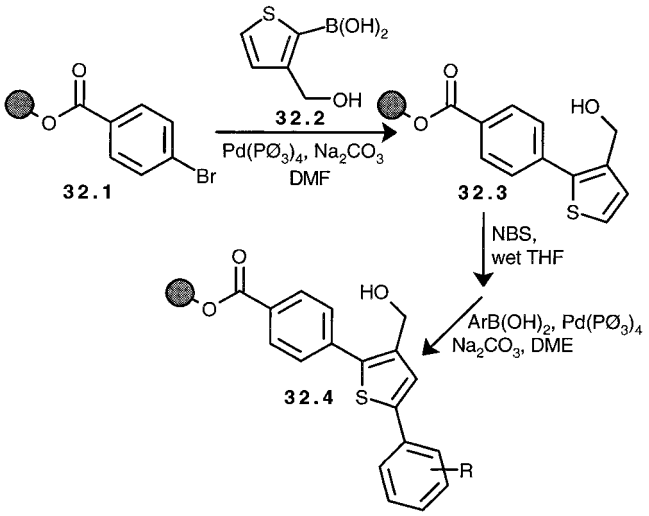
Scheme 31



tion of THF/H_2O (4:1) at 60 °C for 2 days allowed for phenylboronic acid to be coupled to polymer-bound bromide **31.1** quantitatively. Cleavage from the support with TFA/DCM (1:1) delivered biaryl amide **31.2** in 79% overall yield and >95% purity as determined by HPLC.

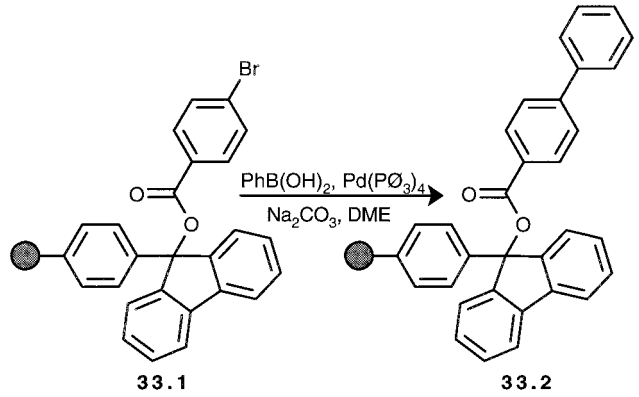
The solid-phase synthesis of 2,5-diarylthiophene derivatives also incorporated the Suzuki coupling in this case to form two carbon−carbon bonds.[46] First, the bromo and iodo aryl acids were coupled to Wang resin (Scheme 32). The aryl bromide **32.1** and 3-hydroxymethylthiophene-2-boronic acid (**32.2)** were coupled employing $Pd(PPh_3)_4$ and Na_2CO_3 in DME to furnish **32.3**. After NBS was used to brominate the polymer-bound thiophene (at the 5 position), an arylboronic acid was coupled applying the same conditions in a second Suzuki reaction to give triaryl **32.4**. Twenty different polymer-bound aryl and heteroaryl halides were incorporated along with six separate aryl or heterarylboronic acids. It should be noted that a lithium borate was also employed as a nucleophile under Suzuki conditions to perform an alkylation with a polymer-bound alkyl bromide (generated from the alcohol shown). These thiophenes were found to be novel phosphodiesterase-4 inhibitors.

Scheme 32



A new support developed from polystyrene utilizes a 9-phenylfluoren-9-yl moiety as the linker.[47] It was determined that the acid stability of this linker is 6000 times that of the trityl linker; a cleavage protocol of 20% TFA in DCM/MeOH (9:1) was found effective. The linker was attached to the resin by lithiation of the polystyrene and (carbon−carbon) condensation with 9-fluorenone (Scheme 33), and

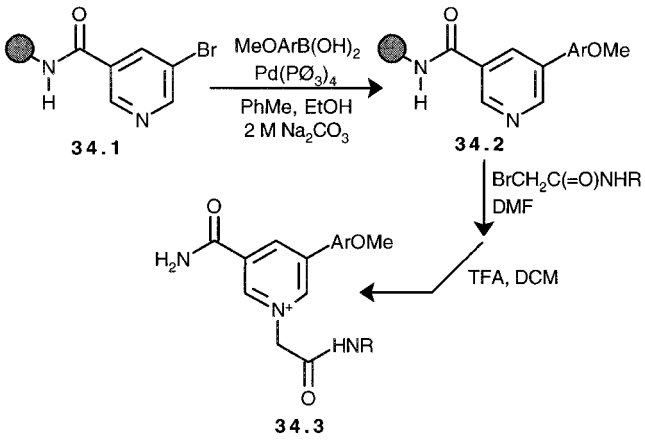
Scheme 33



4-bromobenzoic acid was coupled to the resulting alcohol to give ester **33.1**. Suzuki cross-coupling of phenylboronic acid with the supported aryl bromide was brought about with $Pd(PPh_3)_4$ and Na_2CO_3 in DME to provide **33.2**. Instead of 4-bromobenzoic acid, 4-bromophenol could also be employed to produce the ether. Yields of the corresponding acid and phenol, following cleavage and purification, were 88% and 32%, respectively. The crude purities of cleaved products were both determined to be >95%.

The synthesis of a 1,3,5-trisubstituted pyridinium salt library incorporated the solid-phase Suzuki coupling.[48] 5-Bromonicotinic acid was first attached to the resin through a Rink amide linker (Scheme 34). This polymer-bound aryl bromide (**34.1**) was coupled with *p*- or *o*-methoxyphenylboronic acid using $Pd(PPh_3)_4$ and 2 M Na_2CO_3 in toluene/EtOH (9:1) at 90 °C for 1 day to produce **34.2**. Several of these bromomethylcarbamoyl species were *N*-alkylated to deliver the corresponding pyridinium salts. Cleavage with TFA in DCM afforded 11 representative com-

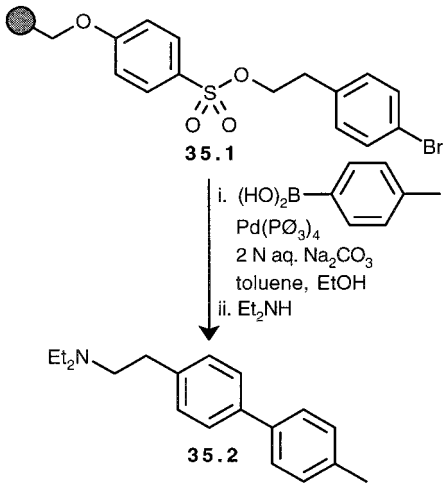
Scheme 34



pounds of **34.3** in 25−80% yield and purities of 80−98%. Utilizing additional boronic acids with this chemistry delivered a library of 40 pyridinium salts.

Arylsulfonate ester SPOS linkers have demonstrated their compatibility with the Suzuki coupling reaction.[49] 4-Bromophenethyl alcohol was immobilized on the polystyrene resin by forming its sulfonate ester (Scheme 35). In one example, 4-methylphenyl-

Scheme 35



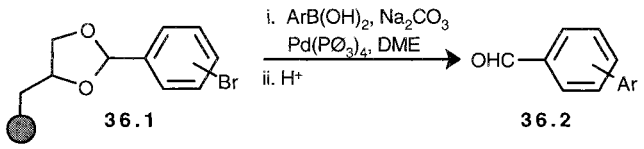
boronic acid was coupled to polymer-bound aryl bromide **35.1** with $Pd(PPh_3)_4$, in 2 M aqueous Na_2CO_3, toluene, and EtOH at 90 °C for 20 h to produce the biaryl. The products could be cleaved from the sulfonate ester by displacement with nucleophiles. In this case, heating in neat diethylamine produced amine **35.2** in 23% overall yield with purity of 90% (determined by NMR).

The silicon linker shown in Scheme 7 was also demonstrated to be effective for Suzuki couplings.[15] This acid-labile, traceless linker was first attached to aminomethyl polystyrene resin. 1-Naphthaleneboronic acid, *p*-tolylboronic acid, and four formylarylboronic acids were coupled using $Pd(PPh_3)_4$ and aqueous Na_2CO_3 in DME. Subsequent cleavage from the resin was achieved with TFA/DCM (1:1). A 101-member biaryl library was developed combining the Suzuki and Stille coupling reactions.

One last example of the Suzuki coupling in SPOS described the syntheses of biaryl and heterobiaryl

aldehydes employing the Leznoff acetal linker.[50] The 1,2-diol bound to Merrifield resin was produced from solketal, and subsequently 2-, 3-, or 4-bromobenzaldehydes were attached as the acetal using PTSA and Na_2SO_4 in toluene (Scheme 36). Polymer-support

Scheme 36



bromide **36.1** was coupled with eight different boronic acids and one boronate under standard Suzuki conditions to provide the biaryl. Cleavage of the acetal was brought about with 3 M HCl/dioxane (1:1) to afford aldehyde **36.2**. Yields, of the 15-member library produced, ranged from 45% to 95%. It is interesting to note that applying alkyl boronate 2-Boc-aminophenyl and simultaneous cleavage of the acetal and aniline deprotection afforded phenanthridine, via 2-amino-2′-formylbiphenyl, in 90% yield.

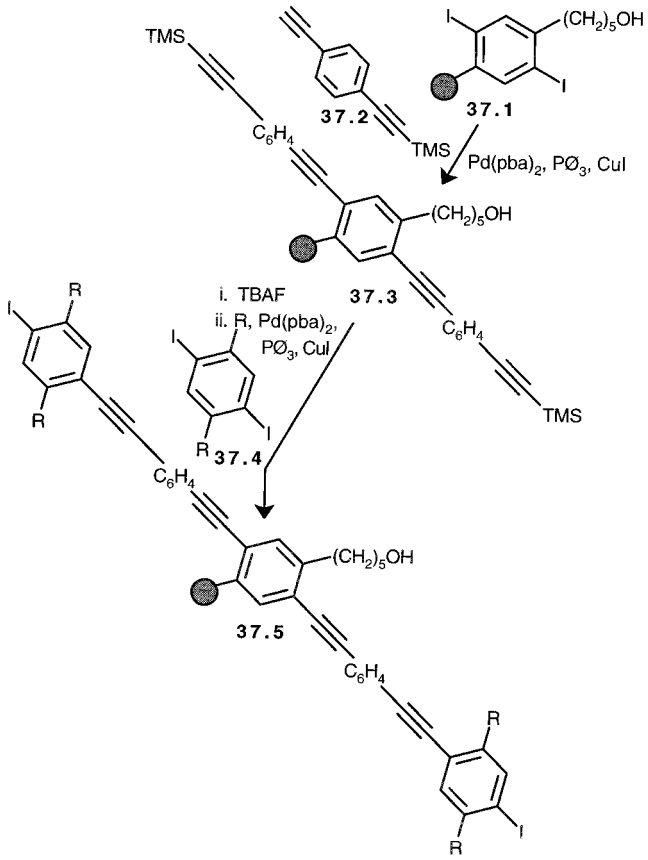
4. Sonogashira Coupling

The last palladium-catalyzed cross-coupling described in this review is the Sonogashira reaction.[51] This reaction couples aryl bromides or iodides with unactivated terminal alkynes. The one major requirement is a Cu(I) cocatalyst usually delivered in the form of CuI. These reactions are conducted under very mild conditions and can be performed in the presence of many other functional groups, thus making this reaction ideal for combinatorial library design. The first example of Sonogashira coupling was extensive application in the synthesis of 1,4-phenylacetylene oligomers.[52] The diiodoaryl diol was attached to Merrifield resin through Ellman's THP linker (Scheme 37). Polymer-bound aryl diiodide **37.1** was subject to cross-coupling with alkyne **37.2** utilizing $Pd(dba)_2$, PPh_3, and CuI in Et_2NH/THF (1:4) to furnish **37.3**. Deprotection of the polymer-bound protected alkyne with TBAF in THF afforded a terminal alkyne for the second coupling (same conditions), this time with aryl diiodide **37.4**, to produce diaryliodide **37.5**. The third coupling utilized **37.2** and was followed by deprotection to again produce terminal alkynes on these growing chains. Coupling with a diaryliodide produced the target oligomer after cleavage of the acetal with PPTS in *n*-BuOH and EDC. It should be pointed out that the diaryliodide employed in the fourth and final coupling was obtained from cleaving **37.5** from the solid support.

The overall yield of the final oligomer was 20% for the seven-step synthesis. The length of this linear oligomeric chain of 17 phenyl rings and 16 triple bonds was determined to be 121 Å. In another reference using similar chemistry, there was an alternating block co-oligomer with both phenyl and thienyl rings alternating with the alkynes.[53] In this case, the final compound (21% yield in nine steps with 15 phenyl, 8 thienyl, and 22 alkyne groups) had a precise length of 161 Å.

Cross-coupling reactions have also been employed as a step in the derivitization of oligonucleotides.[54]

Scheme 37

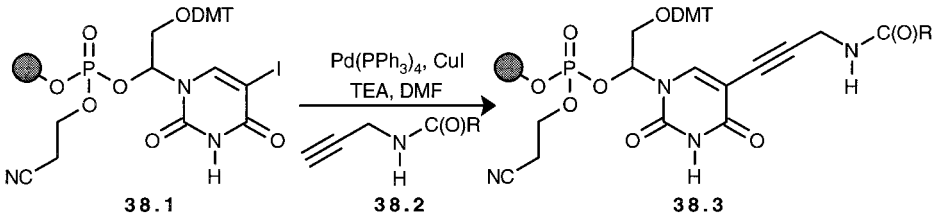


Solid-phase synthesis of DNA molecules that incorporate the 5-iodouridine moiety were automated (Scheme 38). Off-synthesizer modification consisted of Sonogashira coupling of bound iodide **38.1** with four amidoalkynes (**38.2**). Conditions for this coupling were $Pd(PPh_3)_4$, CuI, and TEA in DMF. Yields of **38.3** for the cross-coupling reaction were 85−92% for six examples. After this Sonogashira modification, the automated DNA synthesis was continued to produce the library of oligonucleotides.

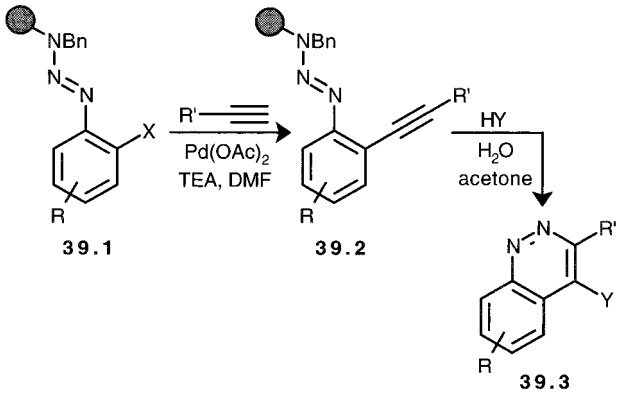
The next example of the Sonogashira reaction coupled an aryl bromide or iodide with an alkyne as part of a cinnolines synthesis.[55] Here a triazene linker was used to attach the aryl halide to the polystyrene support (Scheme 39). Terminal alkynes were coupled to polymer-bound halide **39.1** employing $Pd(OAc)_2$ and TEA in DMF at 80 °C to provide **39.2**. CuI could not be applied because it coordinates to the triazene linker. Utilizing the Richter reaction, which is novel to SPOS, the products were cleaved and cyclized with HCl or HBr in aqueous acetone to afford cinnoline **39.3**. Yields for the five cinnolines produced were 47−95%, and purities reported were 60−95%.

Solid-phase synthesis of diverse propargylamines incorporated both the Sonogashira coupling and the Mannich reaction.[56] The Rink amide linker was employed to attach the aryl iodide to the polystyrene solid support (Scheme 40). The cross-coupling of iodide **40.1** with TMS−acetylene proceeded with CuI and $Pd(PPh_3)_4$ in THF/TEA (1:1). Removal of the TMS group with TBAF in THF afforded terminal alkyne **40.2**. The three-component, carbon−carbon bond-forming Mannich reaction utilizing the polymer-

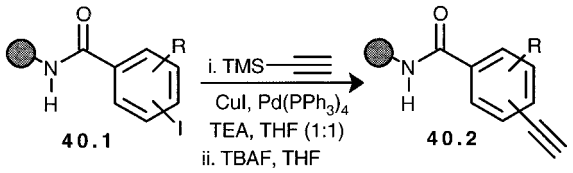
Scheme 38



Scheme 39



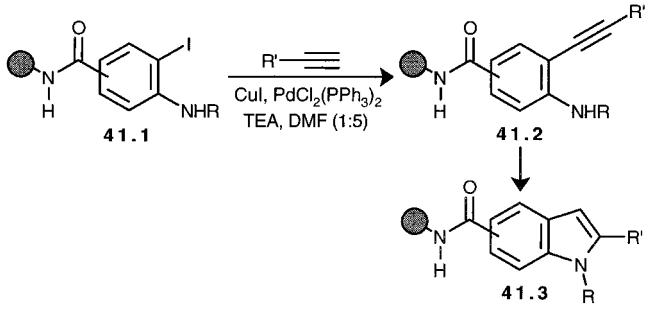
Scheme 40



bound alkyne with an aldehyde and amine that followed is shown later in this review (Scheme 76).

Another application of the Sonogashira coupling was in the SPOS of substituted indoles.[57] Two different *o*-iodoanilines (−NH_2 and −NHMs) were first bound to the polystyrene resin with a Rink amide linker (Scheme 41). The polymer-bound aryl iodides

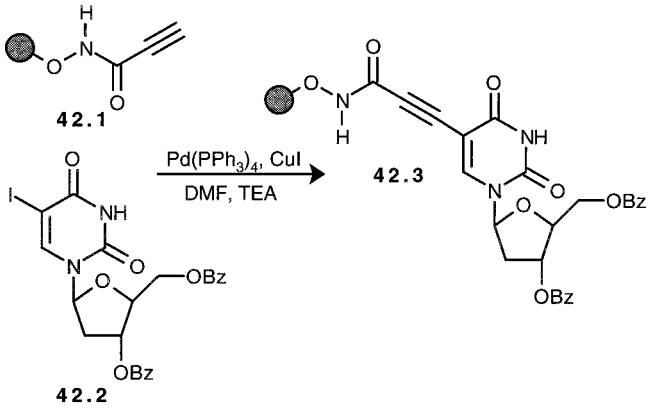
Scheme 41



(**41.1**) were cross-coupled with alkynes. Conditions for the coupling were CuI and $Pd(PPh_3)_4$ in DMF/TEA (5:1) at 80 °C and provided **41.2**. When the unsubstituted aniline (R = H) was employed, cleavage with 30% TFA in DCM afforded the free amide of **41.1** in 96% yield and 95% purity with no cyclized indole detected. When the mesylate derivative (R = Ms) was employed, indole **41.3** was formed exclusively in the coupling reaction. Yields of isolated indoles were 86−96%, and their purities were 79−98% for the four examples.

Another coupling of nucleosides with 5-iodouridine moieties to alkynes has also been shown under Sonogashira conditions.[58] Hydroxylamine was bound to the 2-chlorotrityl resin support through the oxygen (Scheme 42), and DCC coupling of the amine with

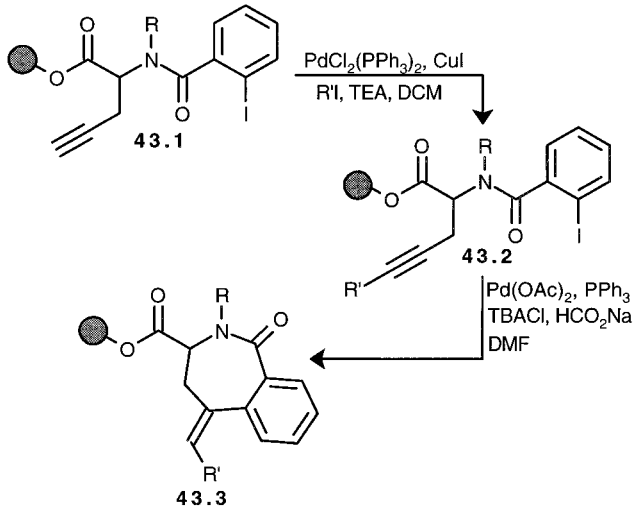
Scheme 42



propiolic acid afforded polymer-bound alkyne **42.1**. The cross-coupling of the terminal alkyne with iodouridine **42.2** employed CuI and $Pd(PPh_3)_4$ in DMF/TEA and yielded internal alkyne **42.3**. Cleavage from the resin with 5% TFA in DCM afforded the desired hydroxamic acid in a yield of 89%.

Bolton and Hodges SPOS Heck coupling (Scheme 20) has also employed Sonogashira coupling conditions in the synthesis of benzazepines.[32] Wang resin-bound alkynamines were coupled with 2-iodobenzoic acid (Scheme 43). Terminal alkyne **43.1** was sub-

Scheme 43

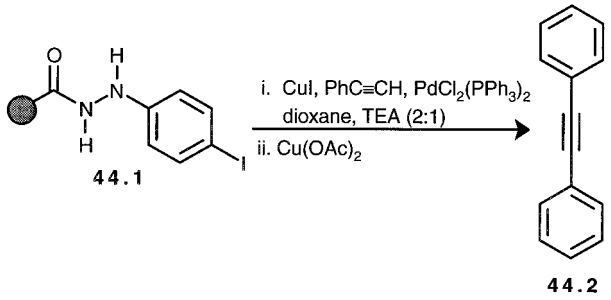


jected to intermolecular coupling with aryl iodides under standard Sonogahira coupling conditions to

produce internal alkyne **43.2**. This aryl iodide was next subjected to Heck-type intramolecular coupling conditions as shown previously to provide cyclized product **43.3**. These products were cleaved from the solid phase with TFA/DCM (1:1) and subsequently esterified with diazomethane.

One last example of the Sonogashira coupling shows the utility of this reaction along with an oxidation-labile hydrazide traceless linker.[59] Polystyrene, TentaGel, and ArgoPore resins were all effective in this solid-phase synthesis (Scheme 44).

Scheme 44

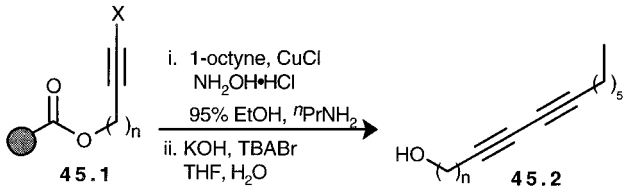


Aryl iodide was attached to the resin to provide **44.1** and subsequently coupled with phenylacetylene to furnish the internal alkyne. The coupling conditions here included CuI and $PdCl_2(PPh_3)_2$ in dioxane/TEA (2:1). Oxidation of the hydrazide with Cu(II) or NBS generated the corresponding acyl diazene, which was easily cleaved with the addition of nucleophiles and afforded diphenylacetylene (**44.2**). Overall yields varied from 50% to 93% depending on cleavage protocol and resin implemented.

5. Cadiot–Chodkiewicz Coupling

Recently the polymer-supported Cadiot−Chodkiewicz[60] coupling reaction has also been adapted to the solid phase.[61] This reaction couples a terminal alkyne with a 1-haloalkyne in the presence of a Cu(I) catalyst. In the synthesis of unsymmetrical diynes, there is a problem with symmetrical coupling as a side reaction in the solution phase. Incorporating the haloalkyne onto a polystyrene support through an ester linker greatly reduces symmetrical coupling (Scheme 45). The coupling of several polymer-bound

Scheme 45



1-chloro- and 1-bromoalkynes **45.1** with 1-octyne was accomplished using CuCl as a catalyst with hydroxylamine hydrochloride in a solution of 95% ethanol and *n*-propylamine. Subsequent cleavage of the six coupled products from the resin with KOH and TBABr in THF and H_2O afforded cross-coupled diynes **45.2** in yields from 34% to 84% with only one example giving a trace of homocoupled product.

III. Condensation Reactions

1. Aldol Condensation

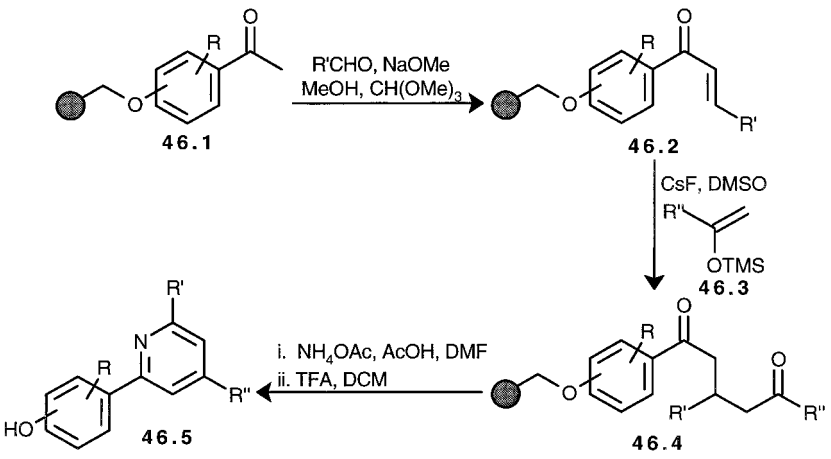
Utilization of the aldol condensation has become an important part in carbon−carbon bond-forming SPOS reactions. Enolates are employed as nucleophiles and condensed with aldehydes or ketones. Depending on reaction conditions, subsequent elimination of the β-hydroxyl moiety to form the conjugated alkene is possible. These aldol products were subsequently utilized to form such molecules as phenols, heterocycles, and polyketides. One example developed the Claisen−Schmidt-type of aldol condensation to the solid phase in the preparation of pyridine derivatives (Scheme 46).[62] Hydroxyacetophenones were attached to Wang resin to provide polymer-supported methyl ketone **46.1**. The corresponding enolate was condensed with several alkyl or aryl aldehydes to furnish **46.2**. Trimethyl orthoformate and sodium methoxide in methanol were prescribed to generate the enolate. When aryl aldehydes were utilized the sodium methoxide needed to be added last. In cases where alkyl aldehydes were applied, they were added last. Silyl enol ether **46.3** underwent Michael addition to unsaturated ketones in another carbon−carbon bond-forming reaction to provide 1,5-diketone **46.4**. The diketone produced was cyclized with ammonium acetate and acetic acid in DMF to afford the pyridine ring. Cleavage from the resin with TFA produced phenolic-containing pyridine **46.5**. The 10 examples reported showed overall isolated yields of 19−62% and HPLC purities of 21−81%.

An asymmetric aldol condensation was performed employing a polymer-bound aldehyde (polystyrene, Merrifield, or trityl which are denoted as L in the scheme).[63] The nucleophile in this condensation was the boron enolate of a thioester (Scheme 47). In this asymmetric case, either the ligands (from methone) attached to boron were chiral (**47.2**, route A) or the thioester itself was chiral (**47.3**, route B). The six examples for route A (**47.4**) showed yields of 18−77% and ee's of 80−94%. Route B, producing **47.5**, showed diastereoselectivities of >95% and >96% with yields of 86% and 50% for two examples.

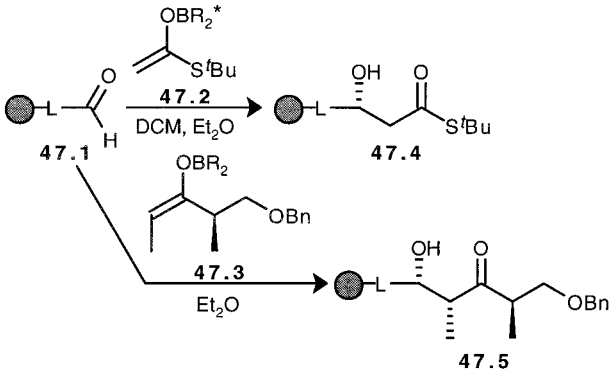
A solid-phase nitro aldol or Henry condensation has been developed for the modification of peptides.[64] The preparation of a new polyoxyethylene-polyoxypropylene copolymer, given the acronym POEPOP, was followed by attachment of HMBA linker and peptide synthesis (Scheme 48). The peptide sequence was terminated with the serine residue, which was oxidized with sodium periodate to afford aldehyde **48.1**. The aldol condensation was carried out on the polymer-supported aldehyde with nitromethane and triethylamine without dehydration to produce the corresponding alcohol. The product was cleaved from the resin with NaOH to afford **48.2** (as an equal mixture of two diastereomers) in 60% yield.

Katritzky's group has reported an example of the Robinson annulation in the synthesis of substituted phenols (Scheme 49).[65] Hydroxypyridine was attached to Merrifield resin and alkylated with bromoacetone to give pyridinium salt **49.1**. The enolate, formed with NaOH, underwent Michael addition to

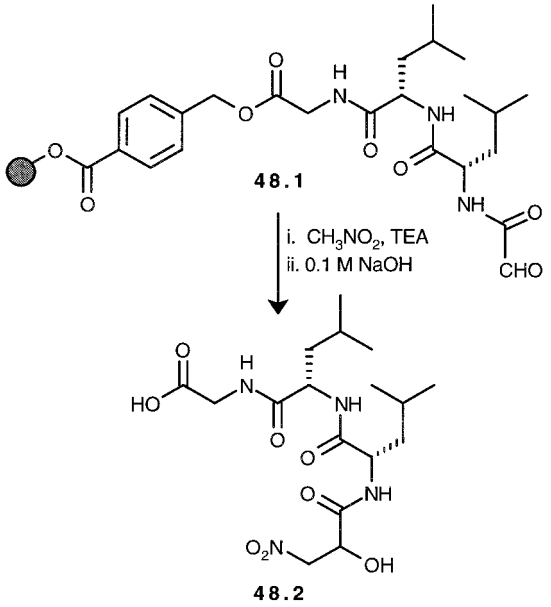
Scheme 46



Scheme 47



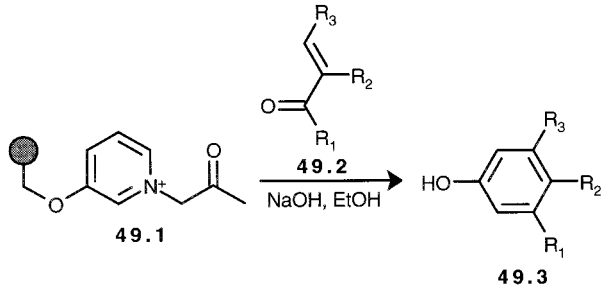
Scheme 48



α,β-unsaturated ketone **49.2**. Subsequent intramolecular aldol condensation followed by elimination of the pyridine linker afforded the phenoxide of **49.3**. Filtration from the resin followed by acidification produced the appropriate phenols. Twelve examples were given, and isolated yields ranged from 52% to 85%, and purities, analyzed by GC/MS, varied from 72% to 100%.

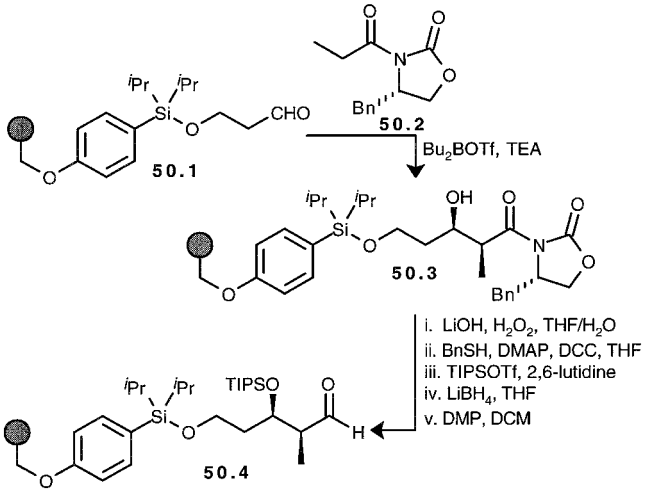
Another asymmetric aldol condensation was applied in developing the SPOS of polyketides.[66] Mer-

Scheme 49



rifield resin was selected and aldehydes attached through a silyl ether linker (Scheme 50). The boron

Scheme 50

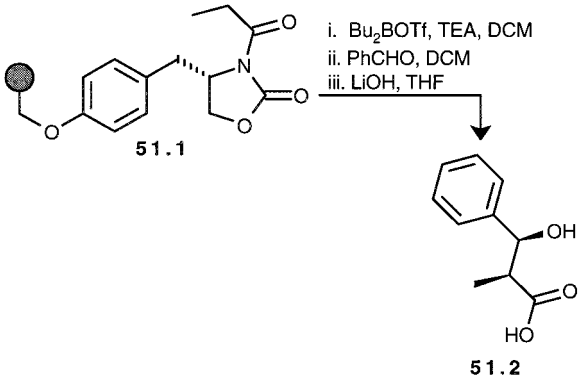


enolate of Evans chiral *N*-acyloxazolidinone (**50.2**) was condensed with the polymer-bound aldehyde (**50.1**) to give **50.3**. The reaction diastereoselectivity was determined to be ≥99% by capillary GC. Cleavage of the chiral auxiliary was followed by functional group transformations affording aldehyde **50.4,** which was utilized in additional asymmetric Aldol reactions. After the synthesis, cleavage of the silyl linker was induced by TBAF. Two triketides were produced with this chemistry in overall yields of 7% and 12%.

Examples of polymer-bound chiral auxiliaries being utilized in aldol condensations have also been shown.[67] Tyrosine was reduced to the amino alcohol and

converted to the corresponding oxazolidinone (Scheme 51). The phenol was attached to Merrifield resin,

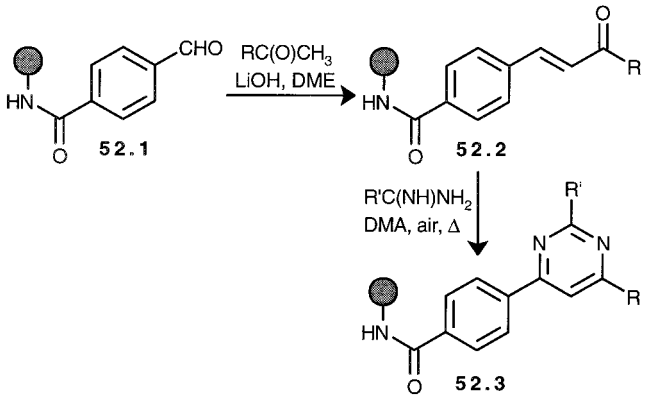
Scheme 51



which provided **51.1** after *N*-acylation. The polymer-supported boron enolate, formed with dibutylboron triflate, was condensed with benzaldehyde. Excess reagents in SPOS usually attributes to increased yields, but in this case excess boron reagent hurt diastereoselectivity by reversing the desired syn product. The best results were obtained by using excess dibutylboron triflate but draining excess reagent before addition of the aldehyde. The product was cleaved from the *N*-acyloxazolidinone linker with LiOH to afford **51.2** in 63% overall yield. The purity of crude product was 94%, and its diastereoselectivity was >98% as determined by HPLC.

The use of α,β-unsaturated ketones, produced by aldol condensation, has been applied to the solid-phase synthesis of a combinatorial library of pyrimidines.[68] 4-Formylbenzoic acid was attached to Rink amide resin (Scheme 52). This aryl aldehyde (**52.1**)

Scheme 52

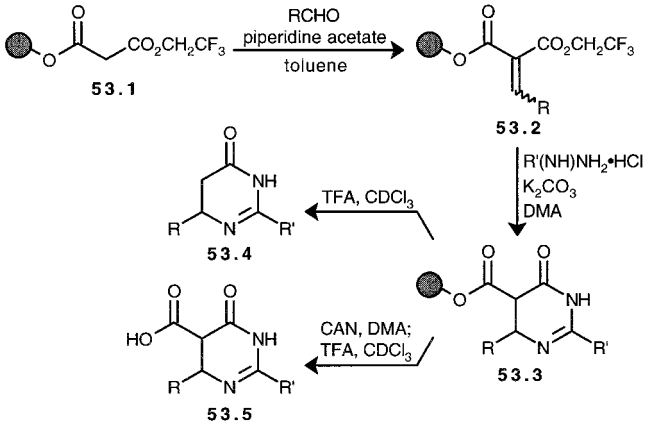


was condensed with enolates from acetone or aryl methyl ketones in a Claisen-Schmidt reaction. Four examples of this aldol reaction produced α,β-unsaturated ketone **52.2** with crude purities of 93−95% and isolated yields by preparative HPLC of 64−98%. Various amidines were applied to the unsaturated ketone to create cyclized product **52.3**. TFA (20%) in DCM was employed to cleave products from the Rink resin. There were eight pyrimidines synthesized in overall yields of 52−98%. It was also shown that the Wittig reaction similarly produced α,β-unsaturated ketone **52.2** upon reaction of phosphorus ylides with this initial polymer-bound aldehyde.

2. Knoevenagel Condensation

The Knoevenagel condensation[69] is usually differentiated from the aldol condensation in that the nucleophilic carbanion has two electron-withdrawing groups instead of one. The electrophile is typically an aldehyde (ketones are possible) and in most cases should not contain any α protons. The subsequent dehydration is also much more likely than in aldol reactions. Solid-phase synthesis of pyrimidinones via the Knoevenagel reaction[70] was accomplished by first attaching Meldrum's acid to Wang resin. Esterification delivered the malonate, which was utilized in the Knoevenagel reaction (Scheme 53). Condensation

Scheme 53

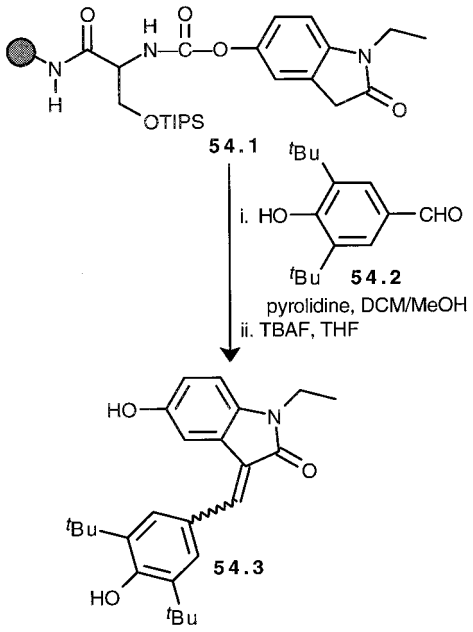


of **53.1** with three different aryl aldehydes was accomplished with piperidine acetate in toluene to furnish **53.2**. Yields of isolated products for this condensation were 79−89%. Reaction of these products with amidine hydrochlorides and K_2CO_3 in DMA produced cyclized product **53.3**. Cleavage from the resin with TFA in $CDCl_3$ produced dihydropyrimidinone **53.4**, while treatment with CAN before cleavage produced pyrimidinone **53.5**. It is worth mentioning that since the cleavage for this synthesis was carried out in dueterated chloroform, the cleaved product was able to be directly analyzed by ^{1}H NMR.

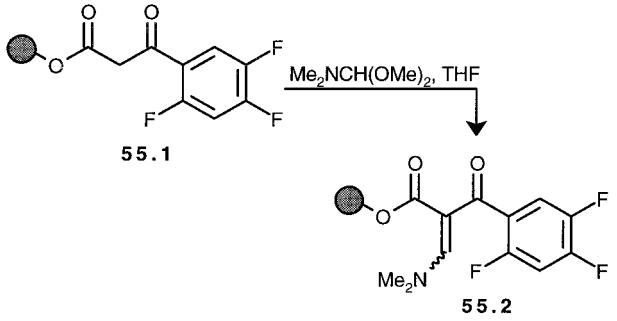
A Knoevenagel-type reaction was selected to help show the effectiveness of a novel serine-based linker.[71] The oxindole was first attached to the solid support with the silyl linker (Scheme 54). The enolate of oxindole **54.1**, formed by pyrolidine, was condensed with aryl aldehyde **54.2**. Cleavage of the product from the resin occurred with TBAF in THF to afford **54.3**. This fluoride treatment initially deprotected the serine alcohol, which formed an oxazolidinone and released the phenolic product. The isolated yield was 78% and its purity 92%.

Synthesis of Ciprofloxacin was carried out in a solid/solution-phase synthesis.[72] The unique "resin" was the soluble tetrabenzo[*a*,*c*,*g*,*i*]fluorene with a *p*-decyloxybenzyl alcohol (Wang-like) linker (Scheme 55). The soluble support could be absorbed onto charcoal, using polar solvents, for facile purification of intermediates by filtration of impurities as in resin supports. Desorption from the charcoal was achieved

Scheme 54



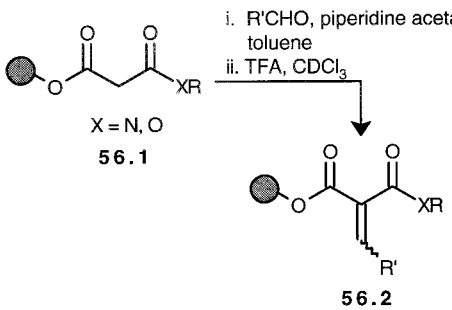
Scheme 55



by employing a nonpolar solvent. Attachment of β-ketoester to the soluble support gave **55.1**, which was followed by Knoevenagel condensation with *N*,*N*-dimethylformamide dimethylacetal in THF to give **55.2**. The tetrabenzo[*a*,*c*,*g*,*i*]fluorene (Tbf) linker could be cleaved after completion of the synthesis by treatment with 90% TFA in DCM.

Knoevenagel condensations of not only malonates but also malonamic esters have been shown on Wang resin.[73] This SPOS chemistry was utilized in the preparation of a 96-member library of methylene malonamic acids (Scheme 56).[74] The polymer-bound

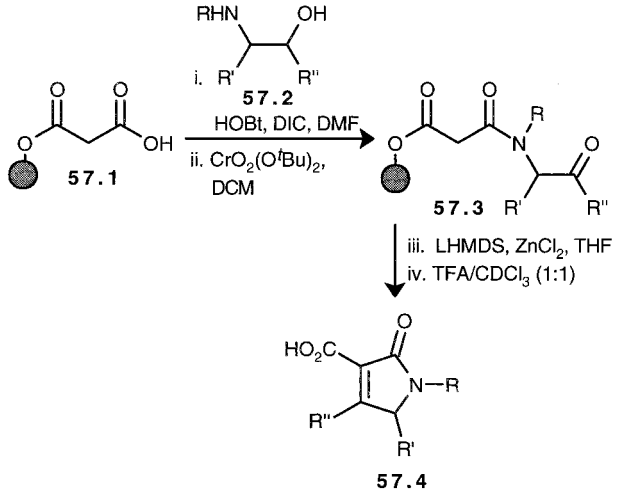
Scheme 56



malonates or malonamides (**56.1**) were condensed with aldehydes applying piperidine acetate in toluene to give the conjugate alkene, which was cleaved to afford **56.2**. There were eight "XR" groups and 12 aldehydes in the combinatorial project. Cleavage, as in Scheme 53, was accomplished with TFA in $CDCl_3$ and allowed not only HPLC but also ^{1}H NMR characterization directly.

Carboxypyrrolinones have been synthesized efficiently on the solid phase.[75] The synthesis began with malonic acid bound to Wang resin (Scheme 57).

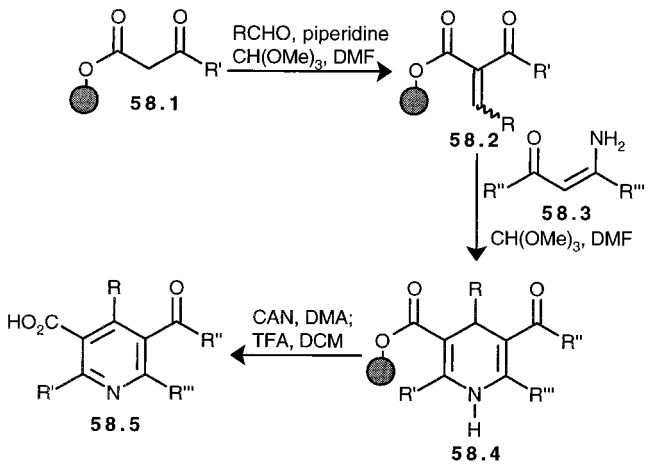
Scheme 57



A wide variety of amino alcohols were coupled to acid **57.1** with DIC and HOBT in DMF. Several commercially available primary amino alcohols were coupled with aldehydes via reductive amination, while aryl amino alcohols were prepared by epoxide opening with anilines to furnish **57.2**. After amide formation, the alcohol was oxidized to corresponding ketone or aldehyde **57.3** with $CrO_2(Ot\text{-}Bu)_2$. Cyclization by an intramolecular Knoevenagel condensation was found to be more effective with LiHMDS than with LDA; both employed with $ZnCl_2$. The reported yields for this reaction step were 69−94%. Cleavage from Wang resin with TFA/$CDCl_3$ (1:1) provided carboxypyrrolinones **57.4** in overall yields of 43−80%.

Knoevenagel condensation and subsequent Hantzsch condensation produced highly substituted 2,2′-bipyridyls and tripyridyls.[76] Sasrin resin was employed in this SPOS, and β-ketoacids were coupled to the support (Scheme 58). Polymer-bound β-keto-

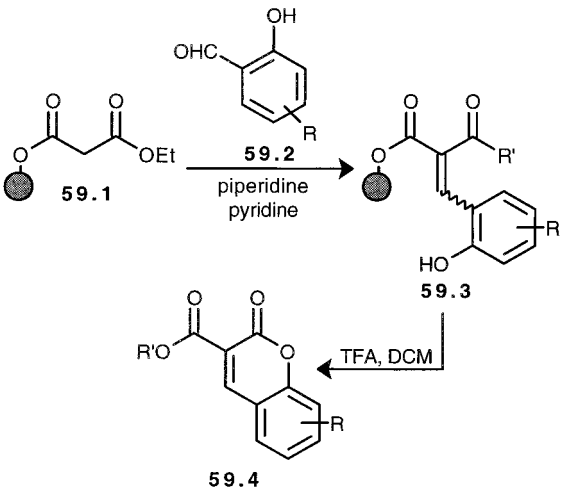
Scheme 58



ester **58.1** was condensed with aldehydes with piperidine and trimethyl orthoformate in DMF at 65 °C to produce **58.2**. Hantzsch condensation with acyl enamine **58.3** applying trimethyl orthoformate in DMF at 80 °C followed to provide dihydropyridine **58.4**. Oxidation to the respective pyridine employing CAN was followed by cleavage with 10% TFA in DCM to afford **58.5**. A library of 11 dipyridines and one tripyridine was created in overall isolated yields of 28−33%, while HPLC-estimated crude yields were 47−84%.

Products from the solid-phase Knoevenagel condensation have been extended to produce substituted coumarins (Scheme 59).[77] Wang-bound malonates

Scheme 59

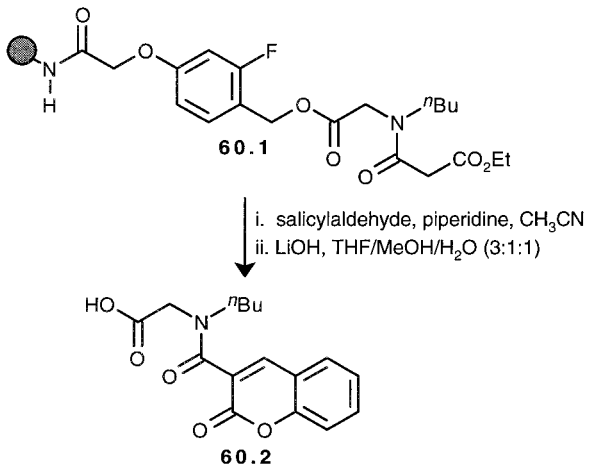


(**59.1**) were prepared and subsequently condensed with several salicylaldehydes (**59.2**) applying piperidine in pyridine to yield **59.3** as a mixture of stereoisomers. Transesterification and cleavage from the resin was accomplished with TFA/DCM (1:2) to afford **59.4**. Overall yields for the coumarin-3-carboxylic acids were 16−40%. Depending on which isomer was produced in the Knoevenagel reaction, either the desired acid or its ethyl ester (R′ = H or Et) was produced since the malonate has two nonequivalent esters with which the phenol could be cyclized.

Another example of the Knoevenagel condensation producing coumarins has also been demonstrated.[78] The synthesis was monitored by gel-phase ^{19}F NMR because a fluorinated linker was used as an attachment to the TentaGel resin (Scheme 60). In this case, ethyl malonyl chloride was reacted with polymer-bound amine to furnish **60.1**. This supported β-amidoester was condensed with salicylaldehyde using piperidine in refluxing acetonitrile. Under the Knoevenagel conditions, concomitant cyclization also occurred to produce the desired coumarin. Cleavage with 1 M LiOH in THF/MeOH/H_2O (3:1:1) afforded coumarin **60.2** in 55% overall yield. It was observed that acidic cleavage (TFA) of the Wang-like ester gave much lower yields. Fluorine NMR not only allowed for reaction monitoring but also indicated that some product was cleaved from the resin during the Knoevenagel condensation.

Lee and co-workers utilized the Knoevenagel reaction in the solid-phase asymmetric synthesis of

Scheme 60



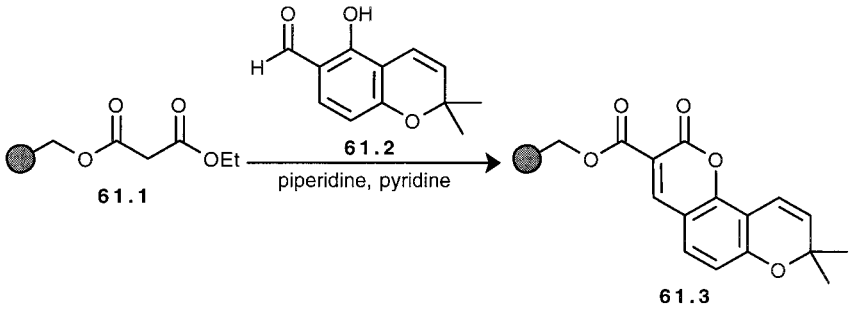
khellactones.[79] Ethyl malonate was attached to Wang resin to provide the polymer-bound β-diester (Scheme 61). Knoevenagel reaction of polymer-supported diactivated methylene **61.1** with substituted *o*-hydroxybenzaldehyde **61.2** (prepared in solution phase) employed piperidine in pyridine to produce polymer-bound khellactone **61.3**. Sharpless asymmetric dihydroxylation of the nonaromatic alkene was followed by diesterification. Cleavage from the Wang resin with TFA in DCM provided these substituted khellactones in >90% purity and yields of 24−44% after purification (six examples).

A final example of the Knoevenagel condensation was performed along with the Hantzsch reaction for the synthesis of pyrrolo[3,4-*b*]pyridines.[80] ArgoGel or TentaGel resins containing a β-ketoester moiety and a protected amine allowed for the cycloelimination (some have referred to this as cyclative release) of the product from the resin (Scheme 62). The condensation reaction of β-ketoester **62.1** was carried out with several aldehydes employing trimethyl orthoformate and piperidine in DMF at 65 °C to supply **62.2**. This was condensed with enamino esters, enamino ketones, or enamino nitriles (**62.3**) using trimethyl orthoformate in DMF at 80 °C for 12 h to provide the dihydropyridine. This dihydropyridine intermediate was oxidized with CAN to produce the corresponding pyridine **62.4**. Cleavage with 70% TFA in DCM produced the pyridinium salts that were neutralized to afford **62.5**. Yields for eight examples were reported to have crude purities of 90−98%, and overall isolated yields were 20−41%. Implementation of an extra methylene spacer on the tethered amine allowed for 7,8-dihydro[1,6]naphthyridin-5(6*H*)-ones to be synthesized. In this case, enamino amides were also proven effective for the Hantzsch reaction.

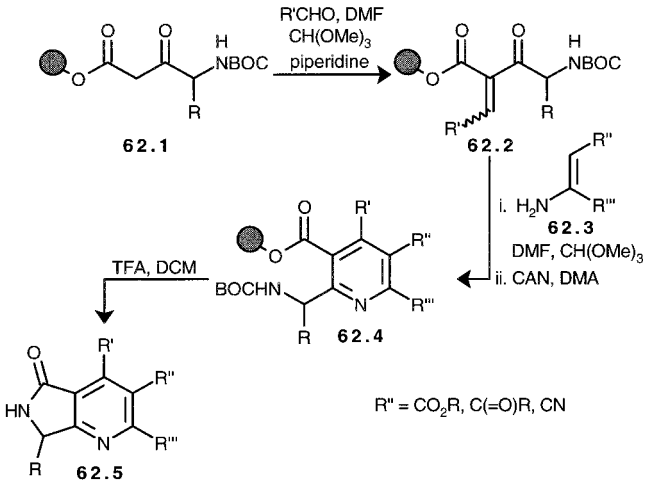
3. Claisen Condensation

The Claisen condensation is a very useful solid-phase reaction for carbon−carbon bond formations. Dieckmann (intramolecular Claisen) condensations are also important in carbon−carbon connections, especially solid-phase cycloeliminations. One example of the Claisen condensation shows the utility of a novel 9-phenylfluoren-9-yl linker as seen in Scheme 33.[47] *p*-Aminoacetophenone was attached to this

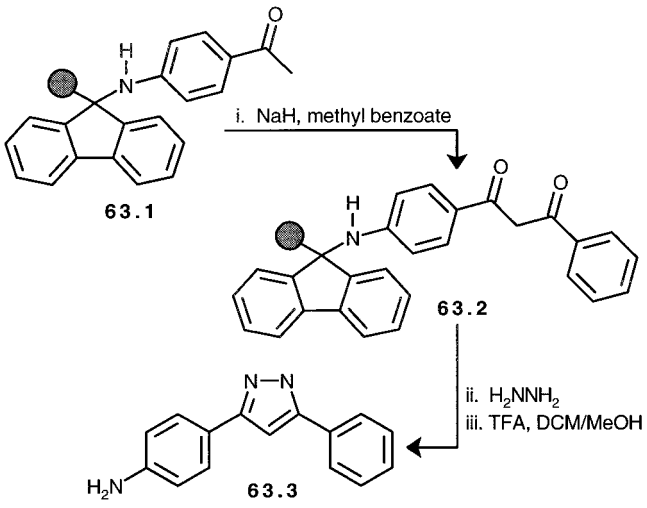
Scheme 61



Scheme 62



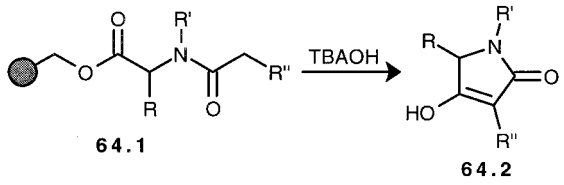
Scheme 63



polystyrene-bound linker (Scheme 63), and sodium hydride was added to form the enolate of **63.1**, which subsequently condensed with methyl benzoate to produce β-diketone **63.2**. Treatment with hydrazine produced the pyrazole, which was cleaved with 20% TFA in DCM/MeOH (9:1) to afford **63.3**. The crude product was obtained in >95% yield, and after chromatography, the overall isolated yield was 78%.

The synthesis of tetramic acids on the solid phase was accomplished via the Dieckmann condensation.[81] Wang resin was selected for this work and esterified with protected amino acids (Scheme 64). Deprotection followed by amide formation provided a diversified library of intermediates **64.1**. Treatment with base

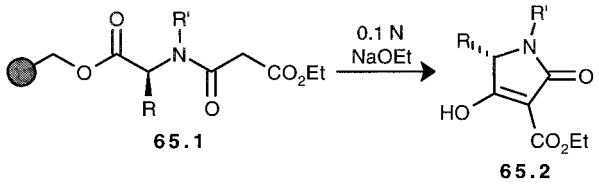
Scheme 64



caused the intramolecular condensation, which also served as a method for cycloelimination from the resin to deliver **64.2**. Potassium *tert*-butoxide or LiHMDS worked well, but the most facile method in terms of purification was to employ TBAOH, which was removed with Amberlyst A-15 scavenger resin. There were 11 tetramic acids reported with yields of 68−91% and purities of 63−96% determined by reverse-phase HPLC.

Another solid-phase synthesis of tetramic acids utilized the Dieckmann condensation.[82] Here Wang resin was selected and the ester linkage utilized for cleavage in a cycloelimination step (Scheme 65). A

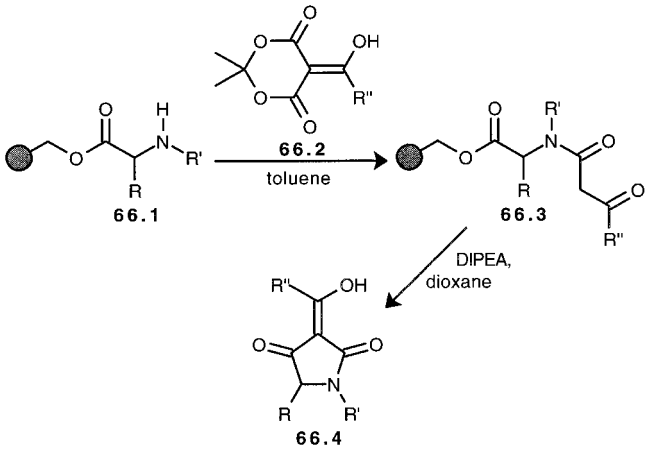
Scheme 65



significant difference in this study, relative to other SPOS reports of tetramic acids, was ethyl malonic acid being coupled to the polymer-supported amino acid to give β-amidoester **65.1**. The base selected to produce the enolate was 0.1 M sodium ethoxide, and subsequent cyclization afforded tetramic acid **65.2**. The crude yields were 67−100%, while the purities were 90−100% as determined by HPLC.

The Dieckmann condensation is efficient at producing tetramic acids, and in another report, 3-acyl derivatives were synthesized on the solid phase (Scheme 66).[83] Hydroxymethyl polystyrene resin was coupled with amino acids and the free amine reductively aminated to give templates **66.1**. This resin-bound secondary amine was acylated with *C*-acyl Meldrum's acids **66.2** in refluxing toluene to give β-ketoamide **66.3**. The use of 30% DIPEA in dioxane brought about the Dieckmann cycloelimination and produce tetramic acid **66.4** in the best purities. There were 11 3-acyl tetramic acids reported in overall yields ranging between 11% and 61% with purities of 80−100%. Another report employing this chemis-

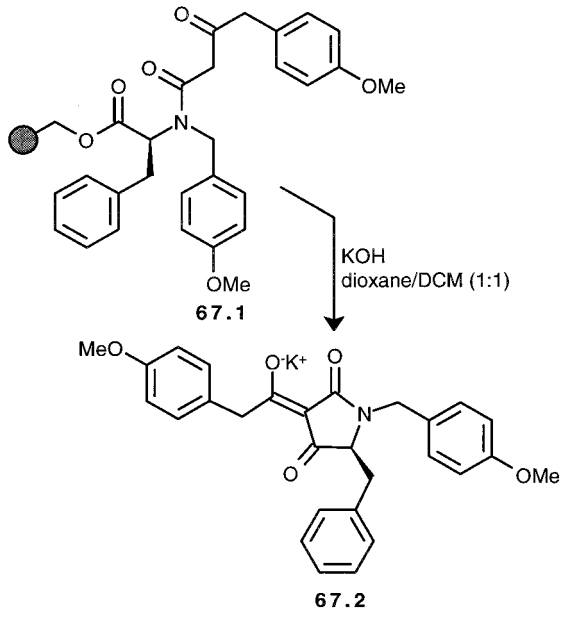
Scheme 66



try also shows the synthesis of 3-acyl tetramic acids.[84] In this case, KOH in MeOH was chosen as the conditions for the base-catalyzed Dieckmann condensation and there were 21 enantiomeric examples which afforded yields of 43−92%.

High-loading Merrifield resin was employed for the fast scale-up and synthesis of large quantities of a 3-acyl tetramic acid on the solid phase.[85] Affordable Merrifield resin was converted to Wang resin (Scheme 67), and amino acid coupling (Fmoc-Phe), deprotec-

Scheme 67



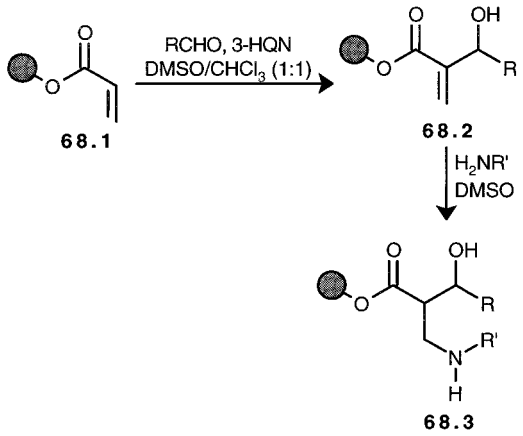
tion (piperidine), reductive amination (*p*-anisaldehyde) and subsequent acylation by a substituted Meldrum's acid produced *β*-ketoamide **67.1**. Acylation of the secondary amine with the acyl Meldrum's acid was repeated in a double coupling to provide improved yields. Base (KOH) induced cycloelimination via Dieckmann condensation in dioxane/DCM (1:1) produced 52 g of **67.2** in an overall yield of 40%, while the crude purity was 95%.

4. Baylis–Hillman Reaction

The Baylis−Hillman reaction[86] is another carbon−carbon bond-forming reaction that has recently been transferred from solution-phase to solid-phase synthesis. This reaction couples activated alkenes (mostly acrylates), as nucleophiles (after Michael addition of catalyst), with electrophilic moieties of which aldehydes are the most common. The catalyst for this reaction is most often a tertiary amine (DABCO is most common), but phosphines have also been employed effectively, particularly in SPOS where removal of the phosphine does not create an issue.

One example of the Baylis−Hillman reaction was used in the solid-phase synthesis of amino alcohols.[87] In this SPOS, the starting polymer-bound acrylate was created on 2-chlorotrityl chloride resin (Scheme 68). Optimization of the Baylis−Hillman reaction

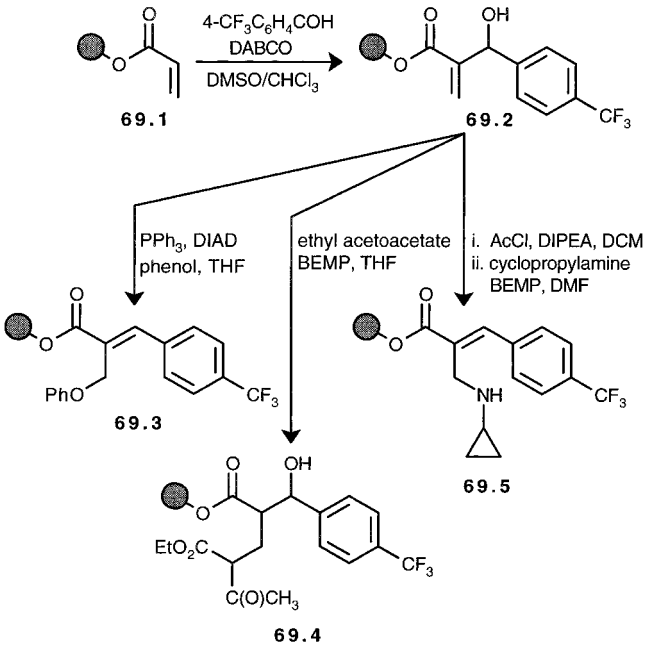
Scheme 68



established that 3-hydroxyquinuclidine (3-HQN) performed better overall on a variety of aldehydes than 1,4-diazabicyclo[2.2.2]-octane (DABCO). Preliminary studies also showed that 16 equiv of aldehyde and 10 equiv of amine in DMSO/$CHCl_3$ (1:1) for 2 days gave optimal results. Higher yields were obtained when the Baylis−Hillman procedure was repeated 2−5 times. Employing 26 different aldehydes produced a library of compounds (**68.2**). The very electron-rich 2,4-dimethoxybenzaldehyde was the only example that did not react. Products could be cleaved from the resin with TFA in DCM, and purities (15, 57−97%) were determined by HPLC. The second step was the Michael addition of 2-phenylethylamine to produce desired 1,3-amino alcohols **68.3** in 12−95% purity.

Another example from the Jung group shows the versatility of the polymer-bound Baylis−Hillman adduct in SPOS (Scheme 69).[88] The 2-chlorotrityl resin was implemented as the support, and the acrylate was attached to provide **69.1**. The Baylis−Hillman reaction was carried out with 16 equiv of 4-trifluoromethylbenzaldehyde and 10 equiv of DABCO in DMSO/$CHCl_3$ (1:1) for 2 days and the process repeated (double coupling) to furnish **69.2**. The cleaved adduct showed a purity of 97% and an isolated yield of 85% for the Baylis−Hillman reaction. This intermediate was shown to be useful in different nucleophilic additions. The standard Mitsunobu reaction conditions employing phenol as the nucleophile selectively gave the S_N2' product, and only stereoisomer **69.3** was isolated. The enolate of ethyl acetoacetate was shown to Michael add to the unsatur-

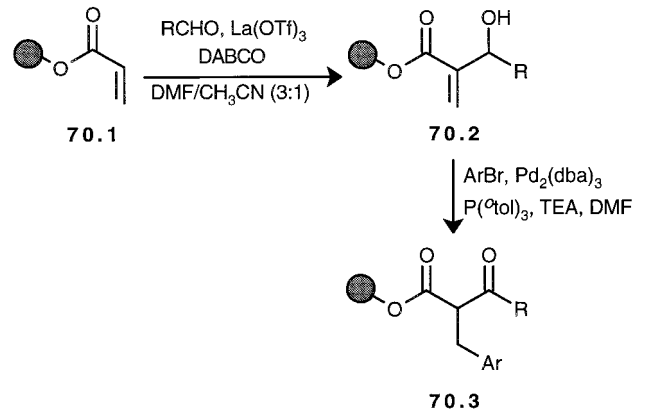
Scheme 69



ated ester in the presence of BEMP in THF to provide **69.4** in a second carbon−carbon bond-forming reaction. The resin-bound ketoester produced in this reaction was treated with hydrazines to afford the corresponding pyrazolones. One last application of **69.2** was esterification of the alcohol which would subsequently eliminate upon Michael addition of cyclopropylamine with BEMP in DMF to afford **69.5** as a single stereoisomer.

The synthesis of polymer-bound β-ketoesters also applied the Baylis−Hillman reaction in combination with the Heck reaction shown earlier in Scheme 16.[89] Acrylic acid was loaded onto Wang resin with acryloyl chloride and TEA in DCM (Scheme 70). The Baylis−

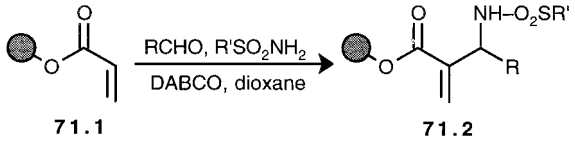
Scheme 70



Hillman reaction of polymer-bound acrylate **70.1** with aldehydes was achieved with DABCO in DMF/acetonitrile (3:1) at room temperature with lanthanum(III) trifluoromethanesulfonate as a secondary catalyst. The Heck coupling with aryl bromides produced β-ketoester **70.3**, which could be further derivatized before being cleaved from the support with TFA.

One last example of the Baylis−Hillman reaction here employs a three-component condensation.[90] Again, 2-chlorotrityl resin was utilized as the solid support for the attached acrylate (Scheme 71). Not

Scheme 71



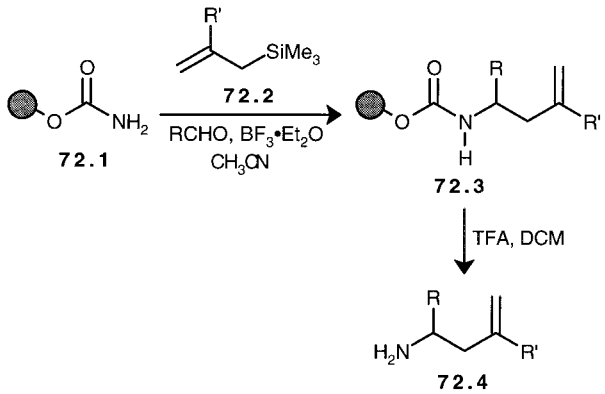
only aldehydes but also sulfonamides were added along with the DABCO to acrylate **71.1**. The reaction was heated at 70 °C for 20 h in dioxane to afford sulfonamide **71.2**. In this reference, two separate libraries were produced: one with toluenesulfonamide and eight aldehydes and the other with 4-trifluoromethylbenzaldehyde and eight various sulfonamides. Purities for 16 examples ranged from 53% to 90% as determined by HPLC after cleavage from the resin with TFA.

5. Mannich Reaction

The Mannich reaction[91] is a very effective carbon−carbon bond-forming reaction that has been adapted to SPOS. Condensation of aldehydes with amines, amides, or carbamates gives the corresponding imines or iminium species which are condensed with various nucleophiles. In these examples, the nucleophiles are carbons with active hydrogens (for C−C connections). As can be seen in the following examples, any of these reactants could be bound to the polymer support.

One example of the Mannich reaction involved SPOS preparation of homoallylic amines.[92] The solid-phase synthesis on Wang resin commenced by treatment of the resin with *p*-nitrophenyl chloroformate to provide the carbonate (Scheme 72). Ammonia was

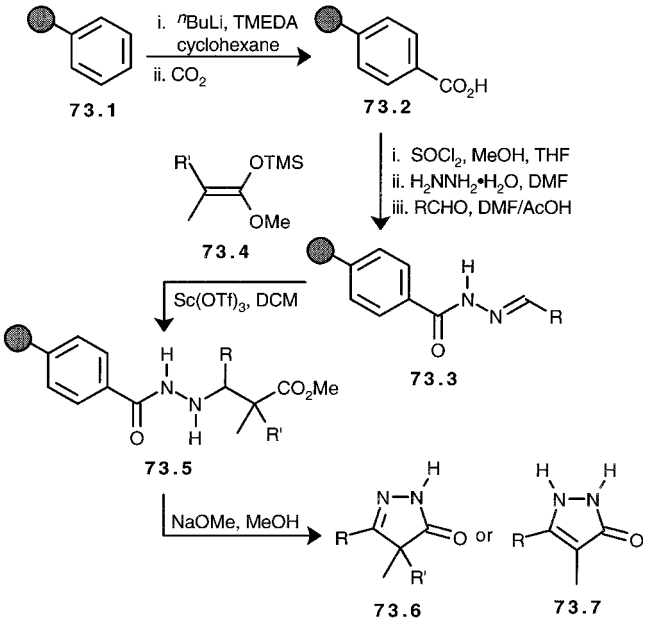
Scheme 72



added to afford polymer-bound carbamate **72.1**, which was reacted with aldehydes and silane **72.2** in the presence of $BF_3 \cdot Et_2O$ in acetonitrile to produce **72.3**. These products could be cleaved from the resin with 50% TFA in DCM to give the desired homoallylic amine **72.4**. Employing 29 different aldehydes with two or three different silanes produced a combinatorial library. The overall yields varied greatly from a high of 60%; however, eight aldehydes did not afford any product with the certain silane employed.

The Mannich reaction was also put to use in the SPOS of pyrazolones from an acylhydrazone linker.[93] The synthesis began from polystyrene resin or 5-(4′-chloromethylphenyl)pentylpolystyrene (CMPP) resin (Scheme 73). The resin was lithiated and treated with

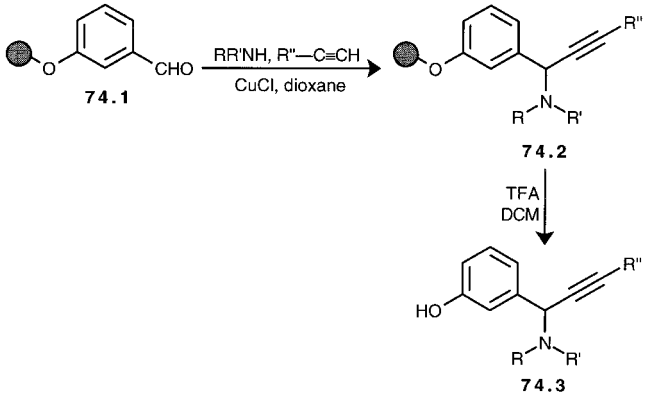
Scheme 73



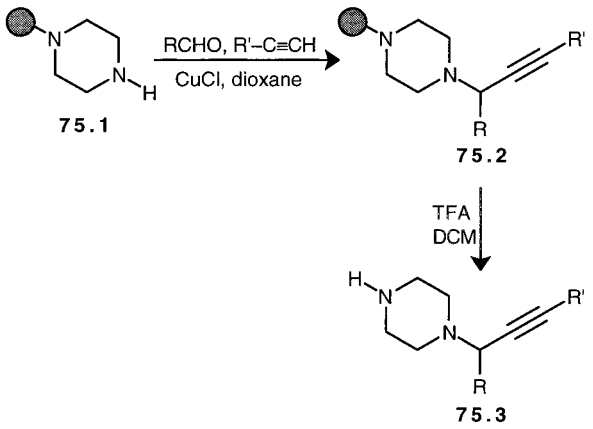
carbon dioxide (forming a C−C bond) to afford carboxylic acid **73.2** upon acidification. Esterification was followed by addition of hydrazine to give the supported hydrazide, and condensation with aldehydes provided the titled acylhydrazone **73.3**. Condensation of ketene silyl acetal **73.4** with the hydrazone employing scandium(III) triflate in DCM produced Mannich base **73.5** in 12 h at room temperature. Cleavage and cyclization to afford pyrazolone derivative **73.6** or **73.7** was accomplished with sodium methoxide in methanol at 60 °C. The yields were 38−88% on polystyrene for the four examples, while the CMPP resin yields were 56−88% for 12 examples. Addition of a carbon spacer on the CMPP resin did improve yields in two cases where polystyrene afforded unfavorable yields.

McNally and co-workers report the SPOS Mannich reaction where either the aldehyde (Scheme 74) or the amine (Scheme 75) could be attached to the solid support.[94] 3-Hydroxybenzaldehyde was attached to

Scheme 74



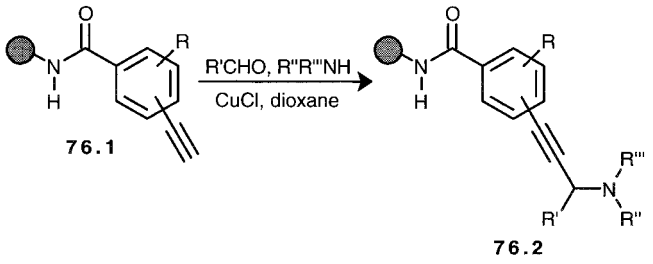
Scheme 75



the Wang resin to furnish polymer-bound aldehyde **74.1**, and the Mannich reaction of a secondary amine and terminal alkyne with the supported aldehyde occurred by applying CuCl in dioxane at 70−75 °C and produced **74.2**. The substituted propargylamines could be cleaved from the resin with TFA in DCM to give **74.3**. The HPLC purities for the three examples given varied from 27% to 74%. In the second example, piperazine was attached to 2-chlorotrityl chloride resin to provide polymer-bound amine **75.1**. The same Mannich conditions with various aldehydes and terminal alkynes provided a different class of propargylamines (**75.2**). Cleavage from the resin was again achieved with TFA in DCM to afford **75.3**, and the purities were 52−95% for the 21 examples reported.

The SPOS of propargylamines shown earlier (Scheme 40) for the Sonogashira reaction were also employed in the Mannich reaction.[56] As opposed to the previous two examples, this strategy proceeded with the alkyne bound to the polystyrene or PEG-based Rink resin (Scheme 76). Polymer-supported

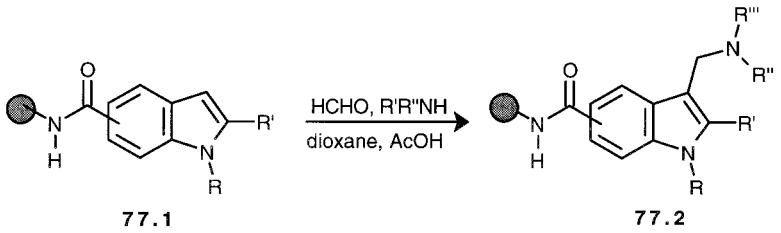
Scheme 76



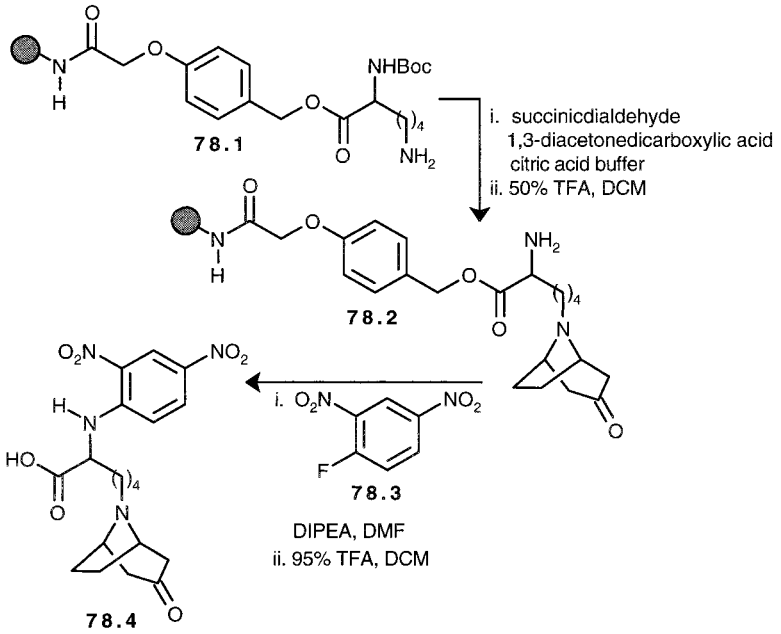
terminal alkyne **76.1** was condensed with aldehydes and secondary amines in the presence of CuCl in dioxane at 90 °C to produce **76.2**. The products were cleaved from the resin with TFA/H_2O (9:1) to afford the corresponding carboxylic acid. Several complex propargylamines were isolated in overall yields of 70−89% with purities of 80−95%.

The Mannich reaction has also been applied to the synthesis of substituted indoles on the solid phase.[57] The polymer-bound indoles, synthesized by the Sonogashira reaction in Scheme 41, were subsequently utilized in a Mannich reaction (Scheme 77). Polymer-supported indole **77.1** was reacted with formaldehyde

Scheme 77



Scheme 78



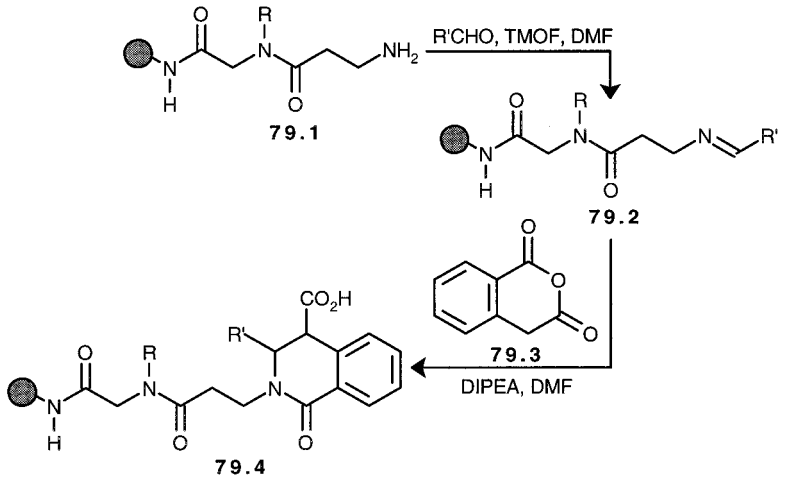
and secondary amines to give 3-aminomethylindoles **77.2**. This Mannich reaction took place in the presence of acetic acid with dioxane as solvent. Overall isolated yields after cleavage with 30% TFA in DCM were 71−100%, while purities were 80−100% (20 examples). The Rink resin was attached to either the 5- or 6-position of the indole moiety in these investigations.

The synthesis of tropanes, first reported by Robinson,[95] has also been utilized in the SPOS of similar alkaloids.[96] The tropane synthesis can be thought of as double Mannich reaction where a three-component condensation is followed by a intramolecular Mannich condensation. TentaGel resin was selected for this synthesis and a Wang-like linker attached (Scheme 78). Coupling with lysine, in which both amino groups were protected (α = Boc, ϵ = Fmoc), provided polymer-bound amine **78.1** after Fmoc deprotection. The amine, succinicdialdehyde, and 1,3-diacetonedicarboxylic acid were condensed in a citric acid buffer (pH = 4.4). The Boc group was deprotected with TFA/DCM (1:1) in 20 min to produce **78.2** with only a small amount of cleavage taking place. This amine was coupled with 1-fluoro-2,4-dinitrobenzene (**78.3**) and DIPEA in DMF. Cleavage of the tropane derivative with 95% TFA in DCM for 2 h afforded **78.4** with a purity of 93% (HPLC).

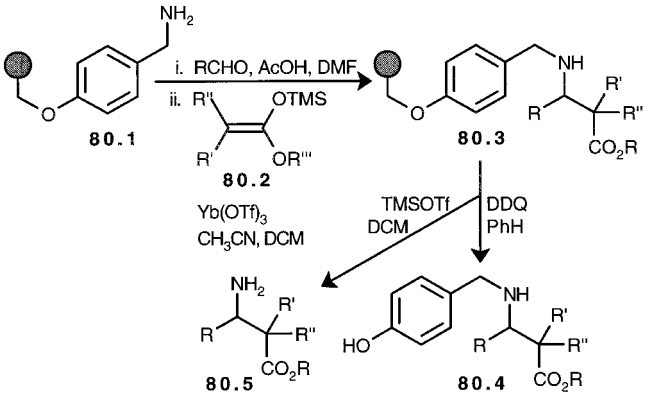
The Mannich reaction has been exploited in the solid-phase synthesis of a combinatorial library of tetrahydroisoquinolinones.[97] MBHA resin was employed and initially coupled with bromoacetic acid to provide the amide linker, and the bromide was subsequently displaced with a primary amine (Scheme 79). The resultant secondary amine was coupled with Fmoc-protected β-alanine, which gave amine **79.1** after deprotection. Imine formation with aldehydes utilizing TMOF in DMF followed to produce **79.2**, which was then reacted with homophthalic anhydride (**79.3**) and DIPEA in DMF to provide tetrahydroisoquinolinone **79.4**. Coupling of the acid with amines provided further derivatization prior to cleavage from the resin with HF.

Lastly, the Mannich reaction has also been shown to be effective with a novel polymer-supported amine resin.[98] This *p*-benzyloxybenzylamine or BOBA resin is unique in that it can be cleaved at two different, condition-dependent, locations as shown in Scheme 80. The polymer-bound amine (**80.1**) was first condensed with aldehydes to form the corresponding imine. Subsequent condensation with silyl enolate **80.2** and $Yb(OTf)_3$ in DCM or DCM/acetonitrile (1:1) provided polymer-bound Mannich base **80.3**. Under acidic conditions, trimethylsilyl triflate was utilized to cleave the benzyl phenyl ether and afforded phenol **80.4** in yields of 59−98%. Conversely, **80.3** could also be cleaved at the benzylamine under oxidative conditions by employing DDQ. This produced amine **80.5** in isolated yields of 50−84%. An array of monosaccharides has also been realized on the solid phase with a similar Mannich-type reaction.[99]

Scheme 79



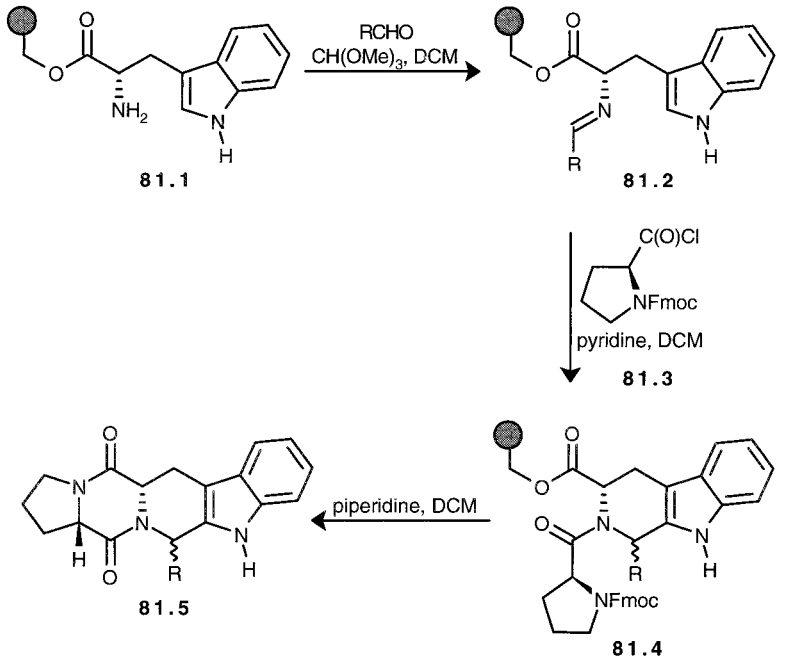
Scheme 80



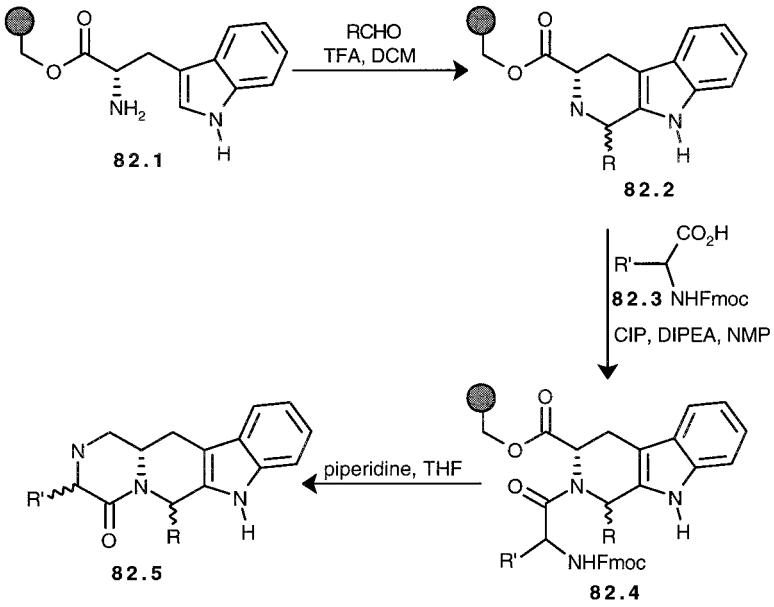
6. Pictet–Spengler Reaction

The Pictect−Spengler reaction[100] is another carbon−carbon bond-forming condensation reaction utilized in SPOS. The reaction is efficient for the synthesis of alkaloids, especially tetrahydro-β-carboline derivatives. Normally the condensation of an imine and nucleophile is preformed under protic conditions, but the first example mentioned here proceeds through a unique *N*-acyliminium intermediate.[101] The solid-phase synthesis of demethoxyfumitremorgin C analogues began with L-tryptophan bound to Wang resin (Scheme 81). Addition of aldehydes to amine **81.1** in the presence of TMOF in DCM provided polymer-bound imine **81.2** for the upcoming Pictet−Spengler reaction. Fmoc-L-proline acid chloride (**81.3**) was added to obtain the titled *N*-acyliminium intermediate in situ, which with pyridine in DCM underwent an intramolecular condensation to afford tetrahydro-β-carboline **81.4**. Deprotection of the Fmoc group allowed for cycloelimination from the resin by formation of the diketopiperazine and afforded **81.5**. The overall isolated yields were reported to range from 49% to 76% for seven entries, and their cis−trans ratios were reported. Ten other examples were also given using other amino acid chlorides, and their yields were 36−88%.

Scheme 81



Scheme 82

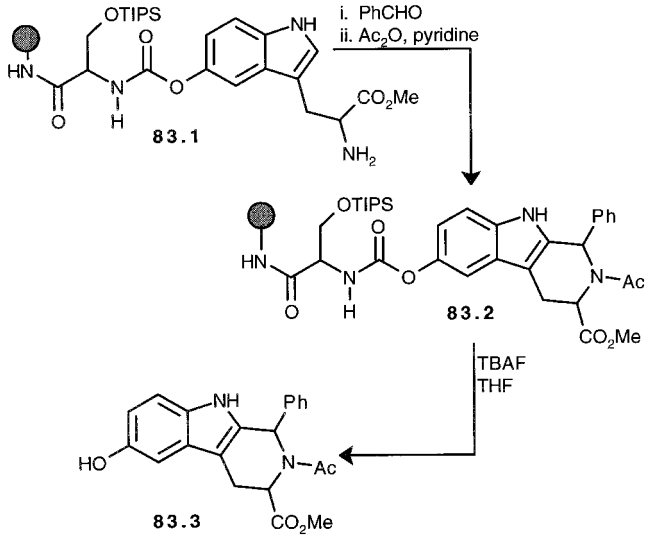


The synthesis of fumitrmorgin, verruculogen, and tryprotstatin derivatives have also been reported by employing solid-phase Pictet−Spengler reactions.[102] Hydroxyethylpolystyrene resin was esterified with L-tryptophan via normal coupling procedures (Scheme 82). Subsequent condensation with aldehydes utilizing TFA in DCM for 16 h provided tetrahydro-β-carboline **82.2**. Double coupling of the resultant secondary amine with Fmoc-protected amino acids (**82.3**) occurred with CIP and DIPEA in NMP for 16 h to furnish **82.4**. It was noted that generating the acid chloride in situ with CIP was more efficient than preparation and isolation with thionyl chloride. This method was also found to be more successful than coupling with reagents such as PyBroP. Fmoc deprotection with piperidine in THF led to formation of the diketopiperazine via cycloelimination and produced **82.5**. A table with 42 examples showed yields ranging between 50% and 99%, and purities were between 58% and 91%.

A novel serine-based linker that exhibited its effectiveness in the Knoevenagel reaction in Scheme 54 was also tested with the Pictet−Spengler reaction.[71] The Boc-protected 5-hydroxytryptophan methyl ester was attached to amino-functionalized TentaGel resin through the silyl-protected, serine-based, carbamate linker (Scheme 83). TFA deprotection of the Boc group provided polymer-bound tryptophan **83.1**. Imine formation of the primary amine with benzaldehyde allowed for the Pictet−Spengler condensation to follow with the addition of acetic anhydride and pyridine. The tetrahydro-β-carboline derivative (**83.2**) was cleaved from the linker with TBAF in THF. The yield of **83.3** was 95% and the purity reported to be 83%.

The SPOS of several tetrahydro-β-carboline-3-carboxamides was reported utilizing a 4-hydroxythiophenol linker.[103] The synthesis proceeded with tryptophan tethered to the support as the hydrochloride salt after Boc deprotection (Scheme 84). Heating polymer-bound salt **84.1** with aldehydes in toluene at 80 °C produced condensation product **84.2** as the

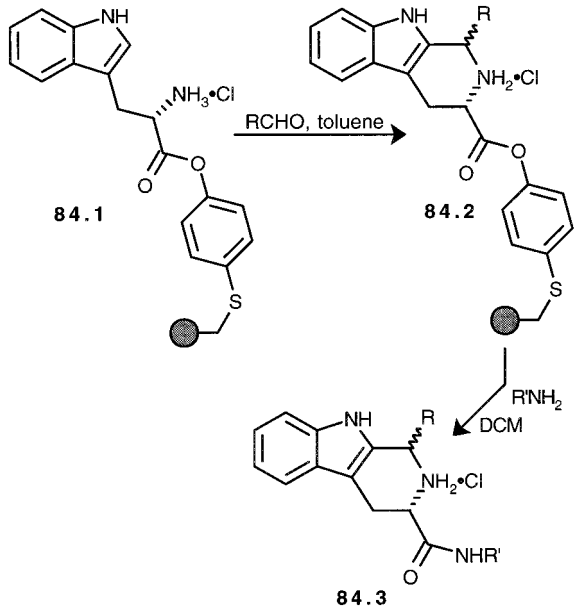
Scheme 83



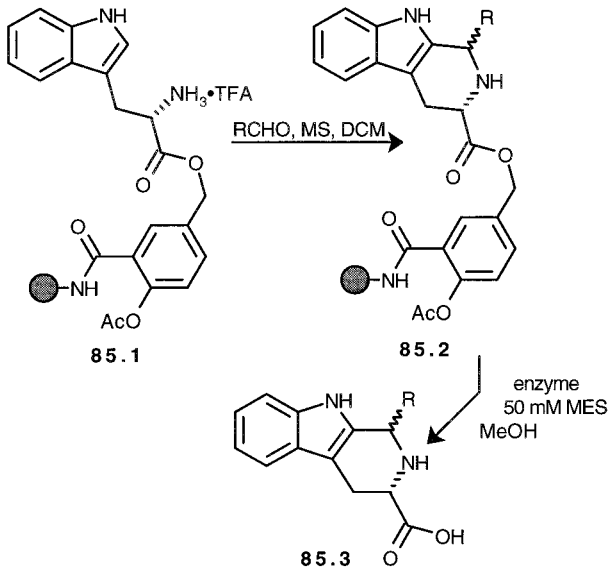
ammonium chloride salt. Cleavage of the 4-hydroxythiophenol linker was achieved by addition of amines in DCM to produce tetrahydro-β-carboline-3-carboxamide **84.3**. A mixture of cis and trans isomers (~1:2) was reported for the 345-compound library where the average purity was >95%. It was also shown that acylation of Pictet−Spengler adduct **84.2** with Boc-protected glycine or β-alanine allowed for cycloelimination upon deprotection and produced diketopiperazines or the corresponding seven-membered bis-lactams.

Utilization of an enzyme cleavable linker has also been shown to be effective in the Pictet−Spengler reaction.[104] The enzyme-labile linker in this case was a derivative of 5-hydroxymethylsalicylic acid (Scheme 85). Attachment of Boc-tryptophan produced salt **85.1** after deprotection with TFA. The aldehyde was added in DCM with molecular sieves at 50 °C to bring about the condensation and generated **85.2**. Reported yields including attachment of tryptophan, deprotection of amine, and condensation with aldehyde were 55−85%. The tetrahydro-β-carboline could be cleaved

Scheme 84



Scheme 85



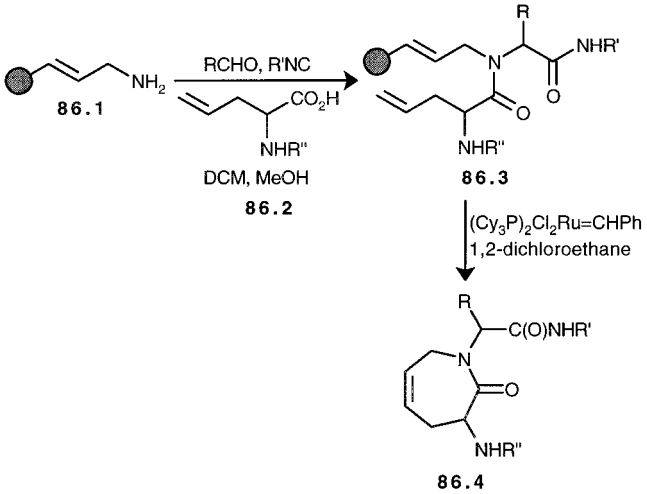
from the resin by employing lipase RB 001−05 in 50 mM MES buffer/MeOH (3:2) at a pH of 5.8 at 30 °C to deliver the desired products (**85.3**) in 70−80% yield.

7. Ugi Reaction

Multiple-component condensation (MCC) reactions such as the Ugi reaction[105] are outstanding for the solid-phase synthesis of combinatorial libraries. The coupling of an aldehyde, amine, carboxylic acid, and isonitrile can lead to a very diverse library of compounds in a single step. The isonitriles are the most limited of these functionalities but can be prepared from the corresponding primary amine. In the SPOS examples to date, all these species except the carboxylic acid have been bound to the polymer support. The least commercially available isonitriles make good candidates for resin attachment since, in SPOS, only the three components not bound to the resin are varied in combinatorial library production. However, the amine is usually supported as more commercially available supports contain this functionality.

The synthesis of β-turn mimetics was accomplished on the solid phase via Ugi reaction followed by ring-closing metathesis.[106] This synthesis commenced with the construction of the cinnamylamine resin, where the amine undergoes the Ugi condensation and the alkene the subsequent metathesis (Scheme 86). The

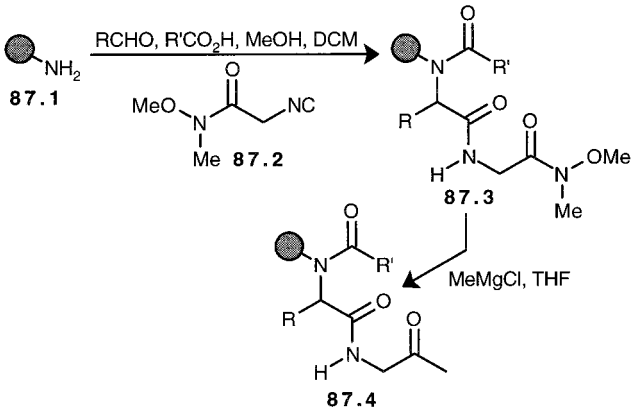
Scheme 86



multiple-component condensation reaction of polymer-bound amine **86.1** with an aldehyde, isonitrile, and amino acid containing a terminal alkene (**86.2**) occurred in DCM/MeOH and gave **86.3**. Cycloelimination of the dialkene from the resin via ring-closing metathesis with Grubbs ruthenium catalyst afforded lactam **86.4**. Yields for the Ugi condensation and the RCM cleavage were 21−62% as a mixture of diastereomers.

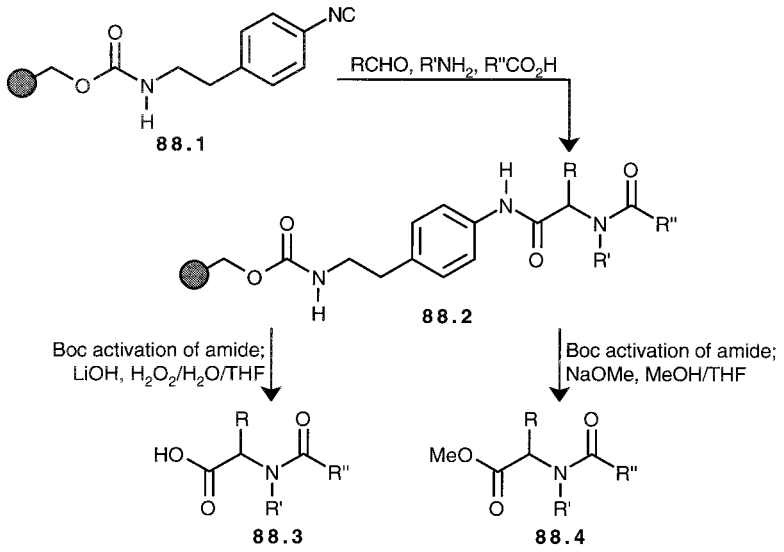
Armstrong and co-workers utilized the Ugi four-component condensation to produce a library of acylated dipeptides to be tested for anticonvulsant activity (Scheme 87).[107] Amino-functionalized Rink

Scheme 87



resin **87.1** was condensed with an aldehyde, isonitrile **87.2**, and a carboxylic acid in DCM/MeOH (4:1) to furnish **87.3**. In this solid-phase synthesis the isonitrile contained a Weinreb amide moiety, and subsequent methyl Grignard addition to this polymer-bound amide afforded methyl ketone **87.4**. Eight different aldehydes and 12 carboxylic acids were

Scheme 88

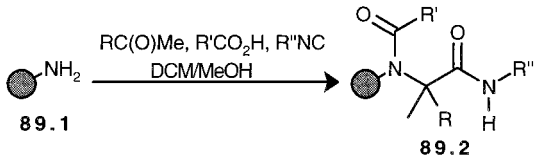


combined to produce the 96-member library of targets that were cleaved with TFA in DCM with most overall yields being >50%. Five examples were synthesized on a larger scale with yields of 55−80% and purites of >90%.

The Ugi condensation was used with a novel safety-catch carbamate linker (Scheme 88).[108] The isonitrile was attached to Wang resin through the carbamate linker to give resin **88.1**. Condensation with a primary amine, aldehyde, and carboxylic acid produce polymer-bound dipeptide **88.2**. The reaction was driven to completion by addition of excess of reagents. The disappearance of the IR stretch for the isonitrile at 2132 cm^{-1} was monitored to determine reaction progress. Release of the safety-catch (activation) in this linker was achieved by Boc addition to the secondary benzamide. Subsequent cleavage with hydroxide or methoxide provided acid **88.3** or methyl ester **88.4**. The ester moiety was used further to synthesize heterocycles such as 1,4-benzodiazepines, diketopiperazines, ketopiperazines, or dihydroquinoxalinones.

The use of methyl ketones instead of the aldehydes in SPOS Ugi condensation reactions has also been demonstrated. α-Methylated amino acids are produced from the Ugi condensation.[109] Amino-functionalized Rink resin served as the amine of the four components for the condensation (Scheme 89). The

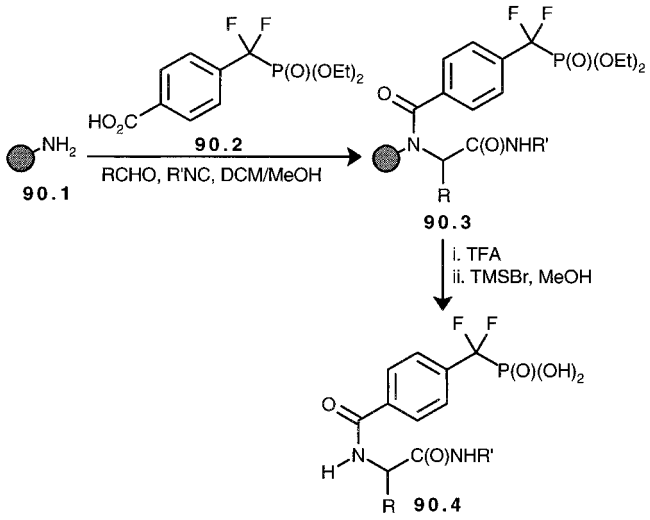
Scheme 89



methyl ketone was added to amine **89.1** along with a carboxylic acid and an isonitrile in DCM/MeOH (4:1), and **89.2** was obtained after 24 h at room temperature. Cleavage from the resin with 10% TFA in DCM afforded desired product in 31−43% yield (nine examples).

The solid-phase synthesis of protein tyrosine phosphatase inhibitors was also achieved via the Ugi condensation.[110] Again, amino-functionalized Rink resin **90.1** was selected for the condensation (Scheme 90) with various aldehydes and isonitriles along with

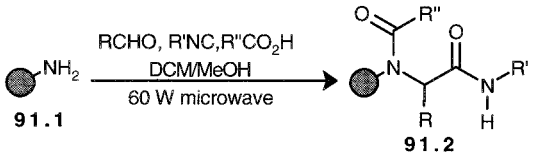
Scheme 90



4-[(diethoxyphosphinyl)difluoromethyl]benzoic acid **90.2** (in DCM/MeOH) and afforded **90.3**. TFA cleavage of the Rink amide, followed by solution-phase phosphonate ester hydrolysis with TMSBr in MeOH, afforded the desired phosphonic acid **90.4**. It was noted that solid-phase hydrolysis of the phoshonate ester prior to cleavage was not efficient, most likely due to the acid sensitivity of the Rink resin. Eighteen aldehydes along with six isonitriles produced a 109-compound library of these potential inhibitors. Yields and purities for 25 of the derivatives were 10−95% and 48−97%, respectively.

A final example of the SPOS Ugi condensation reaction employed microwave irradiation to accelerate reaction rates.[111] This is the first known use of microwave conditions in the solid-phase Ugi condensation. Normally the solid-phase reaction occurs in 1−2 days, but the use of microwave irradiation cut this time to about 5 min (Scheme 91). TentaGel resin was selected because of its compatibility with micro-

Scheme 91

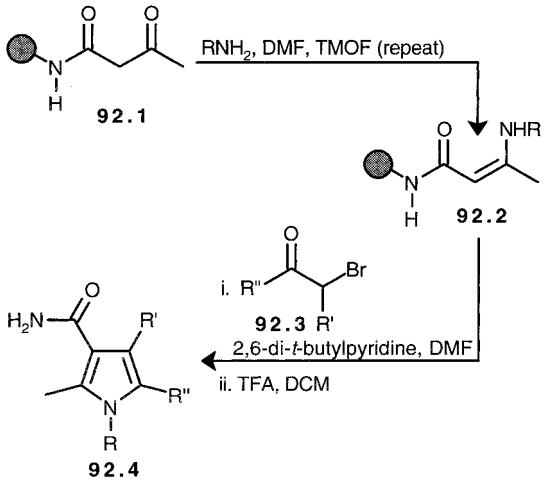


wave conditions, and an amino-functionalized Rink linker was subsequently attached to give **91.1**. Condensation with an aldehyde, isonitrile, and carboxylic acid occurred in DCM/MeOH (2:1) at 60 W to provide **91.2**. Two isonitriles, three carboxylic acids, and three aldehydes were selected to establish the small library (18 components). The overall yields of products cleaved from the resin with TFA were 24−96%.

8. Miscellaneous Condensations

There are numerous examples of other miscellaneous condensation reactions that have been report in solid-phase syntheses. One example is the Hantzsch condensation which was described in Schemes 58 and 63 for the synthesis of 2,2′-bipyridines and pryrrolo[3,4-*b*]pyridines. The Hantzsch pyrrole synthesis[112] has also been adapted to SPOS (Scheme 92).[113] Polymer-supported acetoacetamide **92.1** was

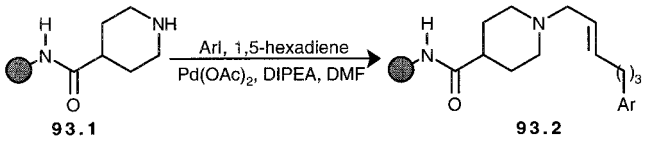
Scheme 92



prepared from amino-functionalized Rink resin (three successful routes were devised), and addition of primary amines with TMOF in DMF provided enamine **92.2** after double coupling. The addition of α-bromoketone **92.3** with 2,6-di-*tert*-butylpyridine (DIPEA and pyridine were found to be less efficient bases) in DMF produced the polymer-bound pyrrole. Cleavage from the resin with 20% TFA in DCM afforded product **92.4** in 85−98% purity for 17 examples. When histamine was applied as the amine, no desired product could be isolated.

There have also been other types of multiple-component condensations similar to the Ugi reaction. Wang and Huang developed a palladium-catalyzed three-component condensation on the solid phase.[114] 4-Carboxypiperidine was tethered to Rink resin, and this polymer-bound amine was coupled with aryl iodides and 1,5-hexadiene in the presence of $Pd(OAc)_2$ and DIPEA in DMF (Scheme 93). Eleven examples

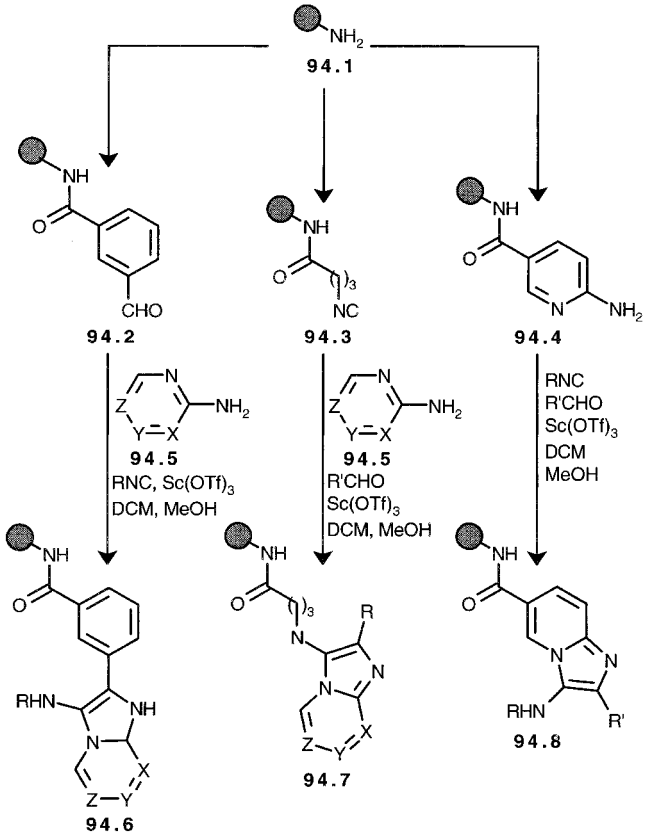
Scheme 93



afforded products, after TFA cleavage, in yields of 70−95% and purities of 53−86%. Polymer-bound piperidine **93.1** was also condensed with iodobenzene and six other dienes under similar conditions to deliver **93.2** (75−91% yield, 68−92% purity). Other supported amines were also examined with 1,5-hexadiene and aryl iodides. Three bound secondary amines worked well (75−87% yield, 52−69% purity), while the one primary amine tested did not produce the desired condensation product.

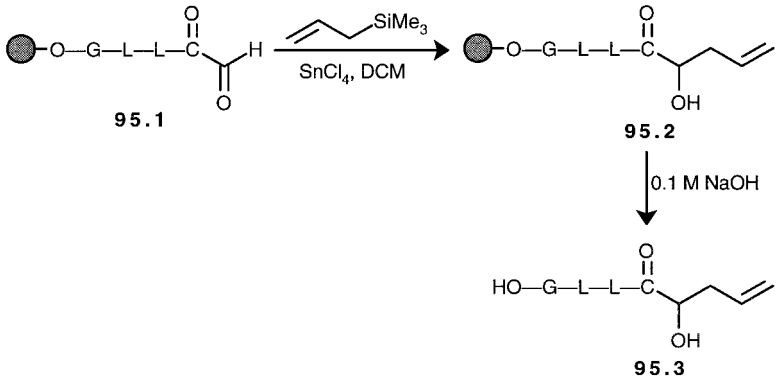
Blackburn utilized multiple-component condensation reactions to synthesize 3-aminoimidazo[1,2-*a*]-azines on the solid phase.[115] In this work, it was shown that the aldehyde, amine, or isonitrile could be attached to the resin (Scheme 94). Rink resin **94.1**

Scheme 94



was coupled with various carboxylic acids to give polymer-bound aldehyde **94.2**, isonitrile **94.3**, and aminopyridine **94.4**. For the isonitrile Fmoc-GABA was first attached to the resin and deprotected. Reaction of the amine with 2,3,5-trichlorophenylformate supplied the corresponding formamide, which was dehydrated to the isonitrile with CCl_4, PPh_3, and TEA in DCM. Polymer-supported aldehyde and isonitrile were subsequently reacted with arylamine **94.5** along with the other component (isonitrile or aldehyde) employing $Sc(OTf)_3$ in DCM/MeOH to provide

Scheme 95

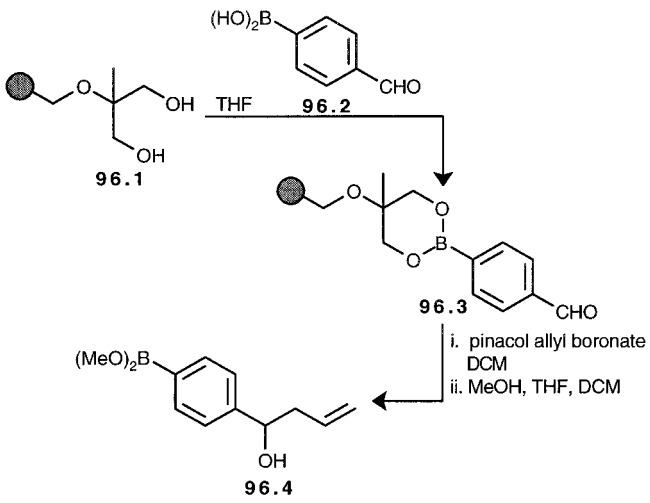


94.6 and **94.7**. The 2-aminopyridine was reacted with isonitriles and aldehydes under the same conditions to give **94.8**. Cleavage of all these examples from the resin with TFA in DCM afforded products in 0−80% for 21 entries. The HPLC purities for the crude products ranged from 10% to 100%.

Rademann et al. showed that modification of the N-terminal of a SPPS oligopeptide afforded a polymer-support aldehyde which could be further derivatized.[64] One option for the derivatization was the Henry reaction shown in Scheme 48; another shown here is the Sakurai reaction (Scheme 95). Allyltrimethylsilane was condensed with the solid-supported aldehyde by treatment with tin(IV) chloride in DCM to produce **95.2**. Titanium(IV) chloride and trimethylsilyl triflate were also investigated but found to be less effective than the tin reagent. The HMBA linker was cleaved with 0.1 M sodium hydroxide to afford tripeptide **95.3** in 69% yield as a 2:1 mixture of diastereomers.

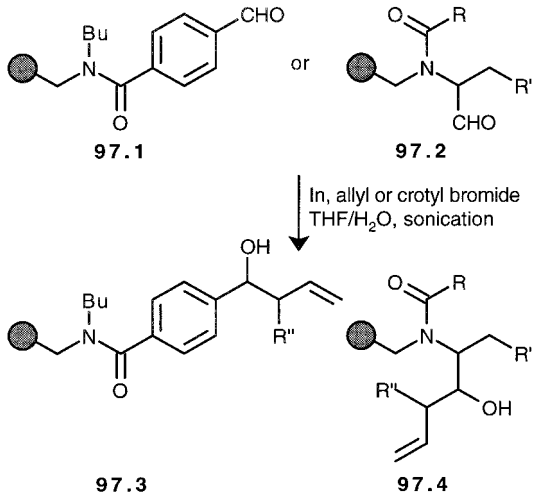
The condensation of a boronate with an aldehyde utilizing a novel boronic ester linker has been reported (Scheme 96).[116] After synthesizing diol-containing resin **96.1**, addition of 4-formylphenylboronic acid (**96.2**) afforded polymer-bound aldehyde **96.3**. Pinacol allyl boronate was condensed with the aldehyde in DCM to give the homoallylic alcohol. Cleavage of this boronic ester linker occurred with MeOH/THF/DCM (5:5:2) to afford free boronate **96.4** in an overall yield of 67%.

Scheme 96



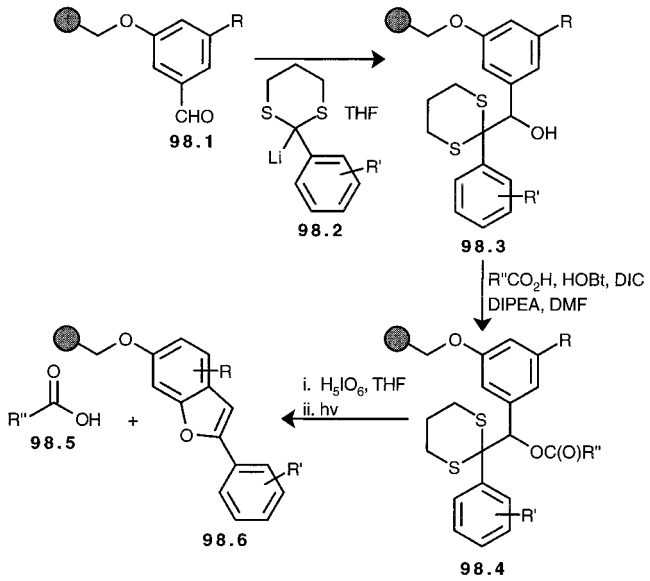
Dolle and co-workers also reacted pinacol allyl boronate with polymer-bound aldehydes and found that allylindiums were also successfully condensed with these same aldehydes (Scheme 97).[117] The polymer-supported aldehydes could be aromatic **97.1** or aliphatic **97.2**. Indium-mediated allyl bromide or crotyl bromide reaction with the aldehydes produced the corresponding homoallylic alcohols **97.3** and **97.4**. The reaction was brought about with sonication for 5 h in THF/H_2O (1:1). Yields for three examples using boronates were 70−100%, while nine examples with indium afforded products in 65−99% yields. The *N*-*o*-nitrobenzamide linker employed allowed for products to be cleaved by photolysis.

Scheme 97



The condensation of a dithiane anion with an aldehyde was demonstrated in the solid-phase synthesis of a dithiane-protected benzoin photolabile linker.[118] Preparation of this novel linker system began with the synthesis of several resin-bound aldehydes (Scheme 98). Addition of **98.2**, produced by *n*-BuLi treatment of the corresponding 2-aryl-1,3-dithiane, to resin-bound aldehydes (**98.1**) in THF produced photolabile safety-catch linker **98.3**. These derivatives were applied in the syntheses to optimize the substituents and the type of support. Coupling of carboxylic acids to the secondary alcohol (produced from the dithiane condensation) gave **98.4** by employing HOBt, DIC, and DIPEA in DMF. Deprotection of the dithiane (removal of the safety-catch) was accomplished with periodic acid in THF, which was

Scheme 98

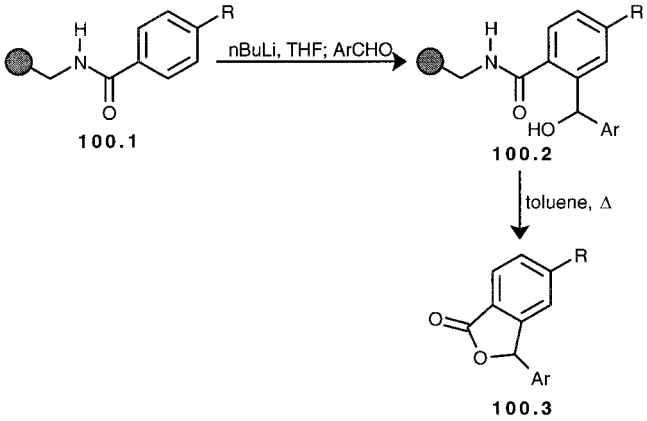


found to be superior to methyl triflate in DCM. Irradiation of the resin at 350 nm in THF/MeOH (3:1) afforded the liberated acid (**98.5**) and resin byproduct benzofuran **98.6**.

The solid-phase acylation of activated methylene compounds has also been reported by Sim et al. (Scheme 99).[119] Several carboxylic acids were coupled to Wang resin (**99.1**) with DIC and HOBt in DMF to give **99.2**. These activated methylene compounds were coupled to benzoic acid with DEPC (diethyl phosphorocyanidate) and TEA in DMF. When β-cyanoester was bound to the resin (**99.3**), several carboxylic acids were condensed using DEPC and TEA in THF. In all cases, the cyano or keto esters produced were cleaved and decarboxylated with TFA/triethylsilane/DCM (70:10:20) to afford ketone **99.4** (5 examples 0−45% yield) or **99.5** (14 examples 0−80% yield). Another report from this lab showed the acylation of polymer-bound active methylenes (cyanoacetate) with anhydrides and isotoic anhydrides. Here, β-ketonitriles and 4-hydroxyquinolin-2(1*H*)-ones were produced, respectively.[120]

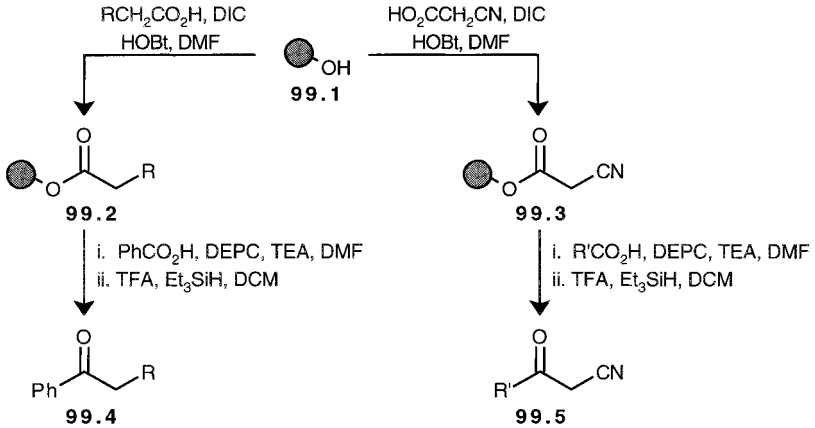
Janda and co-workers utilized their new polytetrahydrofuran (PTHF) cross-linked polystyrene resin for the synthesis of a phthalide library.[121] Three novel aminomethylated resins were prepared by suspension polymerization of *N*-(4-vinylbenzyl)phthalimide with styrene and different oligotetrahydrofuran cross-linkers followed by phthalimide hydrazinolysis. It was found that the longest cross-linker was optimal, so this resin was selected to carry out the library synthesis (Scheme 100). Acylation of the polymer-bound amine with benzoic acids gave amide **100.1**. Excess *n*-BuLi in THF allowed for ortholithiation, which subsequently underwent condensation with aromatic aldehydes to furnish **100.2**. The titled phthalide derivatives **100.3** were produced via cycloelimination in refluxing toluene. Eight selected aldehydes were used along with polymer-bound benzamide (41−64%), 4-methoxybenzamide (50−59%), and 4-trifluoromethylbenzamide (66−81%) to provide 24 compounds.

Scheme 100

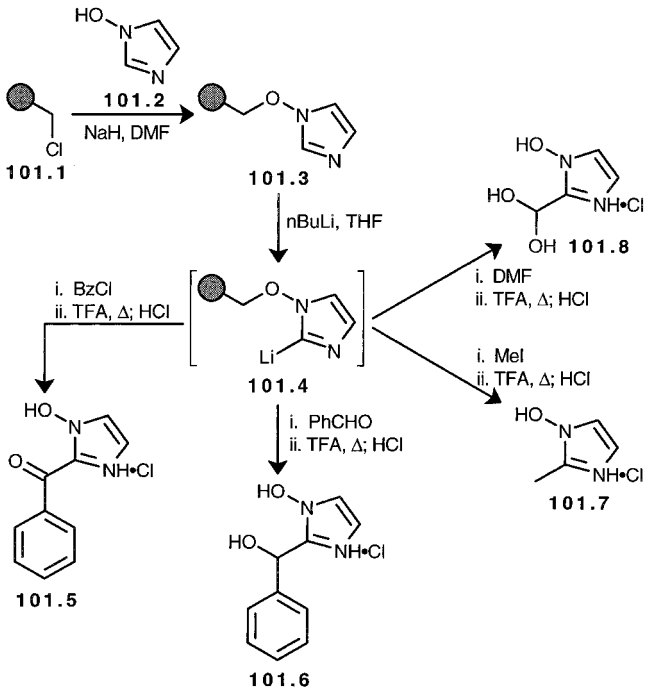


Ortholithiation and its subsequent condensation with carbon electrophiles has been demonstrated for carbon−carbon bond formation of polymer-supported *N*-hydroxyimidazole (Scheme 101).[122] Merrifield resin **101.1** was *O*-alkylated with the sodium alkoxide of 1-hydroxyimidazole **101.2** to give **101.3**. Orthometalation with *n*-BuLi (LDA was substituted when benzoyl chloride was the electrophile) in THF provided intermediate **101.4**, which reacted with several electrophiles (including several carbon electrophiles used to create carbon−carbon bonds). The substituted alkoxyimidazoles were cleaved from the resin with TFA and treated with concentrated hydrochloric acid to produce HCl salts. The conversions and isolated

Scheme 99



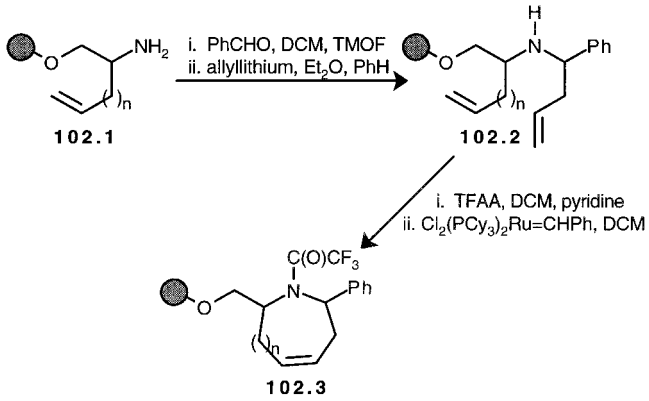
Scheme 101



yields were reported for benzoyl chloride (**101.5**, 102%, 58%), benzaldehyde (**101.6**, 96%, 52%), methyl iodide (**101.7**, 93%, 92%), and DMF (**101.8**, 97%, 81%).

The SPOS of unsaturated six-, seven-, and eight-membered azacycles produced carbon−carbon connections via ring-closing metathesis as well as condensation of an alkyllithium with an imine.[123] The synthesis began with the attachment of unsaturated trichloroacetamides to chlorotrityl resin (Scheme 102). Hydrolysis of the amide gave polymer-bound

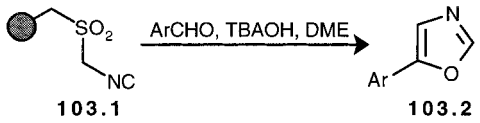
Scheme 102



amine **102.1**, which was condensed with aldehydes employing TMOF in DCM to produce the corresponding imine. Polymer-supported dialkenylamine **102.2** was formed by condensation of the imine with allyllithium and subsequently acylated with TFAA to give the analogous amide. Ring-closing olefin metathesis using Grubbs ruthenium catalyst gave the unsaturated azacycle **102.3**. Product yields after cleavage from the trityl resin with TFA were 85%, 89%, and 87% when $n = 1$, 2, and 3, respectively. The alkene was also carried further in the solid-phase synthesis (for example, epoxidation) before cleavage.

Kulkarni and Ganesan adapted van Leusen's TosMIC reagent to the solid phase for synthesis of oxazoles.[124] The solid-support equivalent of *p*-tolylsulfonylmethyl isocyanide (PS-TosMIC) followed a route similar to solution-phase protocols,[125] starting from polystyrene-based thiol (Scheme 103). Conden-

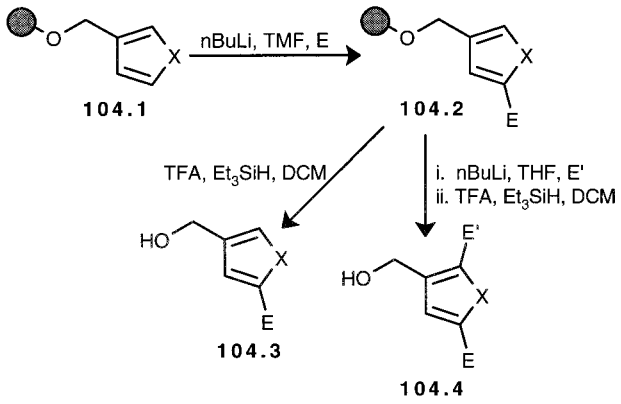
Scheme 103



sation of PS-TosMIC **103.1** with aromatic aldehydes in the presence of TBAOH in DME afforded 5-aryloxazole **103.2**. Isolated yields after purification by chromatography for 10 examples were 25−50%. Other bases (potassium carbonate, TBAF, and sodium ethoxide) were less satisfactory than TBAOH, and TentaGel resin was not stable under these reaction conditions.

Ganesan also demonstrated the solid-phase synthesis of functionalized furans and thiophenes via lithiation followed by either alkylation or condensation.[126] First, 3-hydroxymethyl-substituted heterocycles were attached to trityl resin (Scheme 104).

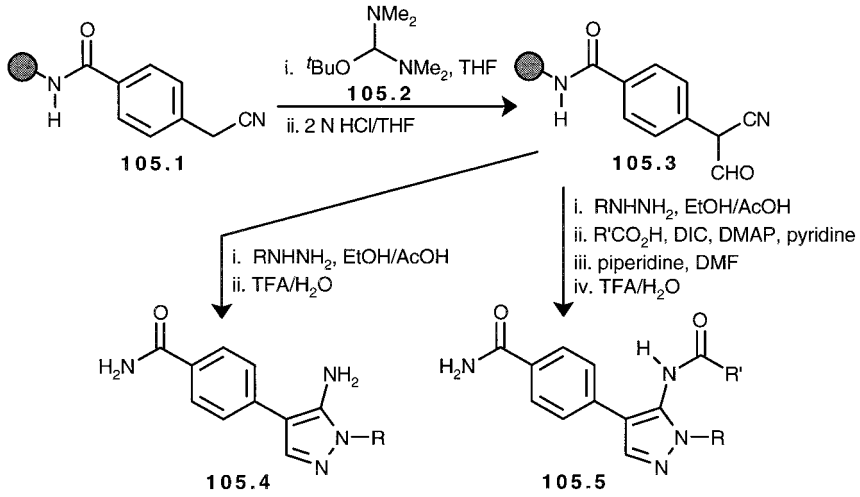
Scheme 104



Addition of *n*-BuLi to heterocycle **104.1** caused lithiation selectively at the C-5 position of the heterocycle due to steric hindrance (at C-2). Quenching these lithiated heterocycles with electrophiles produced polymer-supported 2,4-substituted heterocycle **104.2**, which was cleaved from the resin with TFA/triethylsilane/DCM to give **104.3**. Alternatively, a second lithiation−electrophile addition sequence (at the original C-2 position) could proceed cleavage, affording **104.4**. Isolated yields for 10 examples of 2,4-disubstituted heterocycles were 51−84%, while two examples of 2,3,5-trisubstituted thiophenes had yields of 57−64%.

The SPOS of 5-aminopyrazole derivatives using Bredereck's reagent[127] for C−C bond formation has been reported (Scheme 105).[128] Polymer-bound (TentaGel resin with a Rink amide linker) benzyl nitrile **105.1** was condensed with Bredereck's reagent (**105.2**) in THF to produce the desired enamine, which was hydrolyzed with 2 N HCl/THF to give aldehyde **105.3** as the key intermediate. Condensation with hydrazines in a mixture of EtOH/AcOH at

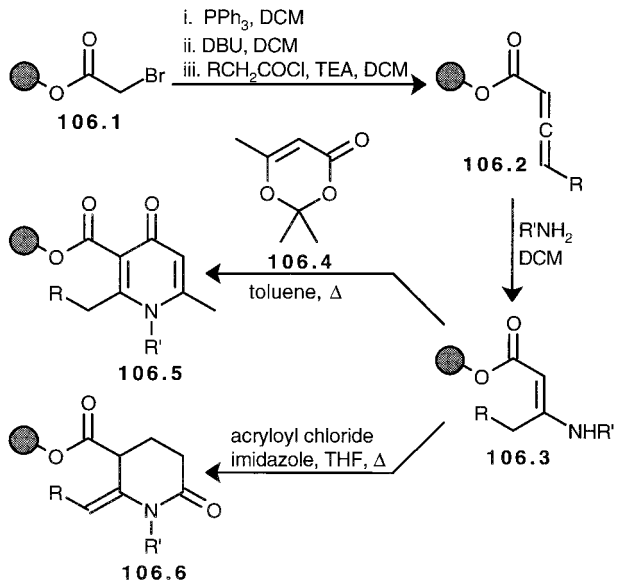
Scheme 105



70 °C afforded polymer-bound 5-aminopyrazole, and cleavage with TFA/H_2O (19:1) could follow to afford **105.4**. Alternatively, acylation of the amine with a carboxylic acid (DIC and DMAP in pyridine) could precede the cleavage and give **105.5**. Reported purities of four examples each were 83−97% and 96−100%, respectively.

The soluble poly(ethylene glycol) monomethyl ether (MPEG) was employed in the synthesis of polymer-bound allenecarboxylates.[129] Bromoacetyl bromide was first attached to the MPEG support (Scheme 106). Addition of triphenylphosphine to **106.1** gave

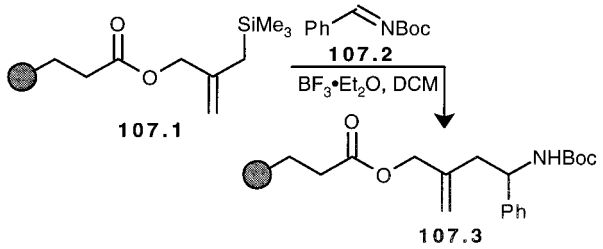
Scheme 106



the analogous phosphonium salt, which underwent ylide formation with DBU. The ylide was condensed with acid chlorides in the presence of TEA to furnish allene **106.2** and subsequently reacted with amines in DCM to provide enamine **106.3**. The enamine was cyclized with 2,2,6-trimethyl-1,3-dioxin-4-one (**106.4**) in refluxing toluene or with acryloyl chloride employing imidazole in refluxing THF to afford 4-pyridone **106.5** or δ-lactam **106.6**, respectively. The yields of the 4-pyridones were 50−81%, and purities were 85−96% for six examples. The δ-lactams showed yields of 29−54% for six examples.

Brown and Fisher employed the condensation of an allylsilane with an imine as a key step in the solid-phase synthesis of pyrrolidines.[130] Carboxyethylated polystyrene was prepared from cross-linked polystyrene resin and diethyl malonate in the first carbon−carbon bond-forming reaction (Scheme 107).

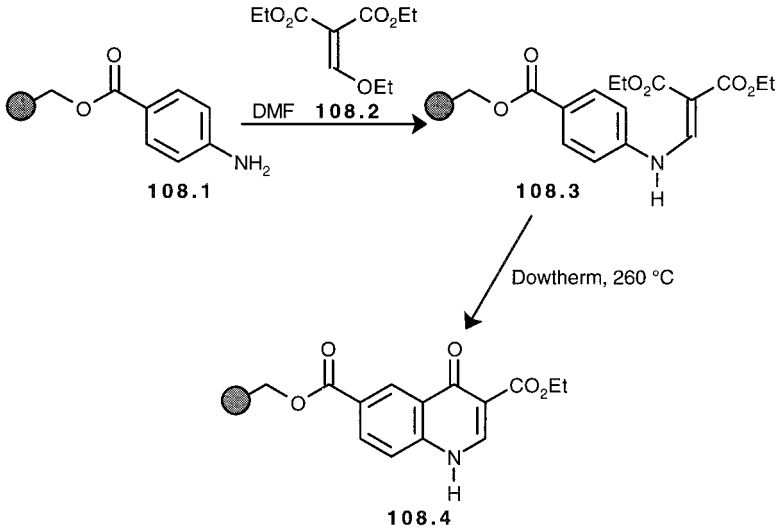
Scheme 107



2-Hydroxymethyl-3-trimethylsilylpropene was coupled to the resin with DIC and DMAP to provide polymer-supported silane **107.1**. The condensation of the allylic silane with imine **107.2** (imino−Sakurai reaction) was brought about using BF_3·Et_2O in DCM and produced Boc-protected amine **107.3**. Boc deprotection was followed by reductive amination with benzaldehyde to produce the corresponding benzylamine. Cleavage of the allylic ester with $Pd(acac)_2$ and dppe generated the *p*-allyl palladium complex, which underwent cyclization with the amine and afforded the desired pyrrolidine.

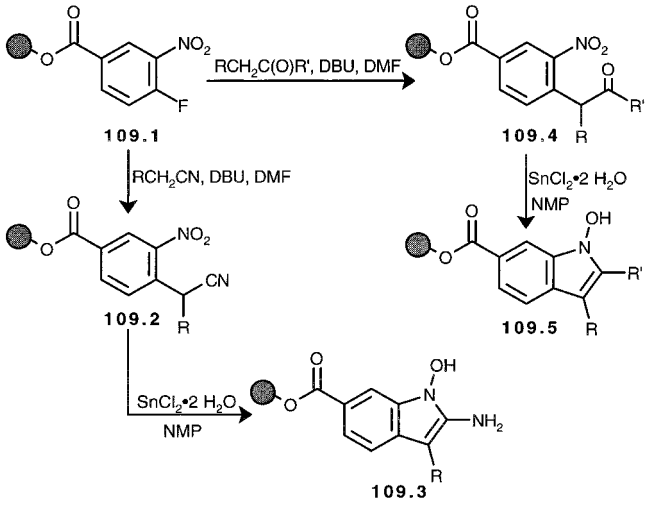
Another example of a solid-phase carbon−carbon condensation was in the synthesis of quinolones.[131] Cesium 4-aminobenzoate was first coupled to Merrifield resin by formation of the ester linker (Scheme 108). Reaction of polymer-bound aniline **108.1** with diethyl ethoxymethylenemalonate (**108.2**) in DMF provided unsaturated malonate **108.3**. Heating this intermediate in Dowtherm at 260 °C allowed for cyclization to 4-quinolone derivative **108.4**. The product was cleaved from the resin with TFA or the ethyl ester was converted to the amide with primary amines prior to cleavage. Isolated yields, after preparative TLC, of 68−98% were reported for four examples.

Scheme 108



Nucleophilic aromatic substitution has been grouped into this category of miscellaneous reactions. The synthesis of *N*-hydroxydindoles was shown to be produced from polymer-bound aryl fluorides.[132] 4-Fluoro-3-nitrobenzoic acid was first attached to Wang resin (Scheme 109). The carbanion of acetonitrile

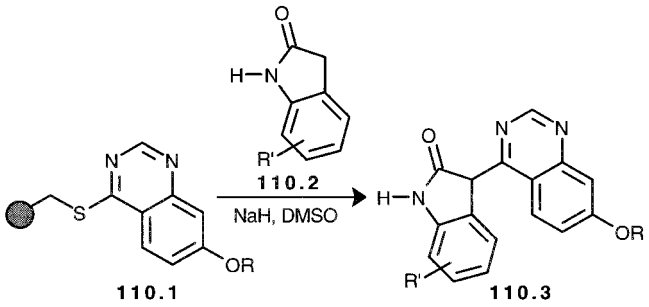
Scheme 109



produced in the presence of DBU in DMF added to aryl fluoride **109.1** to generate nitrile **109.2**. Partial reduction of the nitro group with $SnCl_2$ in NMP proceeded with concomitant cyclization to produce *N*-hydroxy-2-aminoindole **109.3**. A second pathway replaced the nitrile with a ketone and, upon reaction with polymer-bound aryl fluoride **109.1** in the presence of DBU, provided ketone **109.4**. Reduction with $SnCl_2$ in NMP and cyclization furnished *N*-hydroxyindole **109.5**. Cleavage from the Wang resin with TFA afforded the corresponding *N*-hydroxydindoles in yields of 39−74%. This same type of C−C connecting reaction was also applied to the synthesis of benzo[*c*]isoxazoles.

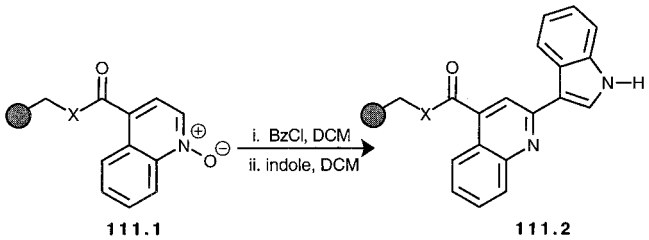
Hennequin et al. described the solid-phase synthesis of oxindole quinazolines by employing nucleophilic aromatic substitution in the cleavage protocol.[133] Quinazolines were first converted to the corresponding thioquinazolones with phosphorus pentasulfide in pyridine (Scheme 110). The thioquinazolone was attached to Merrifield resin with DBU in DMF to give sulfide **110.1**. The carbanion of oxindole **110.2** was generated with NaH in DMSO at 100 °C and displaced the sulfide to give oxindole quinazoline **110.3**. Anionic oxindole polymerization occurred readily under these conditions, and a 10-fold excess was employed to bring about complete cleavage of the quinazoline. Solid-phase extraction of the quinazoline onto acidic SCX sulfonic silica allowed for facile removal of impurities. The purified product was released from the resin with dilute ammonia and afforded pure derivatives in 35−72% yield.

Scheme 110



The solid-phase condensation of heterocycles has been reported by utilizing *N*-oxide chemistry.[134] Quinoline-4-carboxylic acid was coupled to Wang resin or a Wang resin with diamine linker (Scheme 111). Oxidation of the polymer-supported quinoline

Scheme 111



with *m*-CPBA provided quinoline-*N*-oxide **111.1**. Activation of the *N*-oxide with benzoyl chloride in

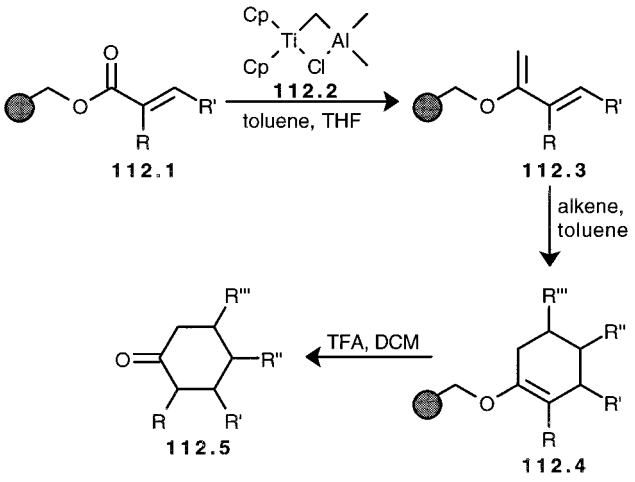
DCM was followed by alkylation with indole to give diheterocycle **111.2**. Cleavage with TFA provided the corresponding acid (38−100% yield, 78−100% purity, seven examples) or amide (84−100% yield, 100% purity, two examples) if the amine linker was employed. In this quinoline example *N*-methylpyrrole or enamines was successfully substituted in place of the indoles. The utilization of polymer-bound isoquinoline-*N*-oxide was also shown to be effective in the condensation with indole.

IV. Cycloaddition Reactions

1. Diels–Alder Reaction

The Diels−Alder[135] reaction was first applied to the solid phase some 20 years ago.[136] Since then, there have been a large number of examples including inter- and intramolecular variants, supported diene or dienophile (for intermolecular), normal or inverse electron demand, and ordinary or hetero-Diels−Alder. The solid-phase synthesis of substituted cyclohexanones employed the Tebbe olefination as well as the Diels−Alder reaction (Scheme 112).[137] In this

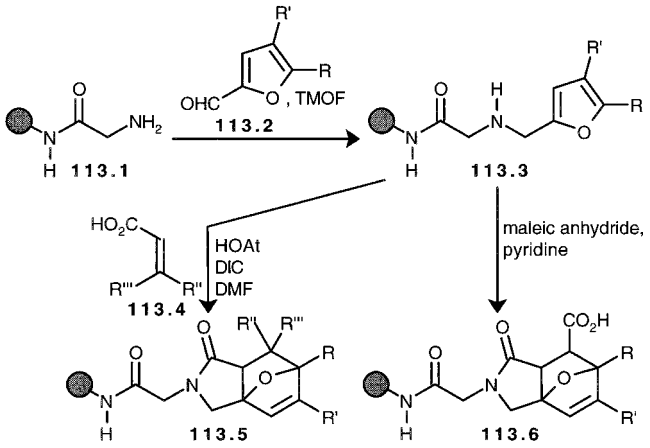
Scheme 112



example, polymer-bound acrylate **112.1** was converted to the electron-rich diene with the commercially available Tebbe reagent (**112.2**). It was determined that this solid-phase Tebbe methylenation was less efficient if the reagent was generated in situ or if Petasis reagent was employed. The cycloaddition of diene **112.3** with dienophiles in toluene produced a library of cyclohexanones (**112.5**) after TFA hydrolysis of the enol ether cycloadduct **112.4**. Temperatures reported for the solid-phase Diels−Alder reaction were 80−100 °C, except for maleimides where 25 °C was sufficient.

A solid-phase intramolecular Diels−Alder (IMDA) reaction was used in the synthesis of tricyclic nitrogen heterocycles with potential biological activities.[138] ArgoGel resin with a Rink amide linker was aminofunctionalized and glycine was attached (Scheme 113). Reductive amination of amine **113.1** with substituted furfurals (**113.2**) produced secondary amine **113.3** containing the supported diene. The dieneophiles, α,β-unsaturated carboxylic acids **113.4** in this case, were coupled to the amine with HOAt

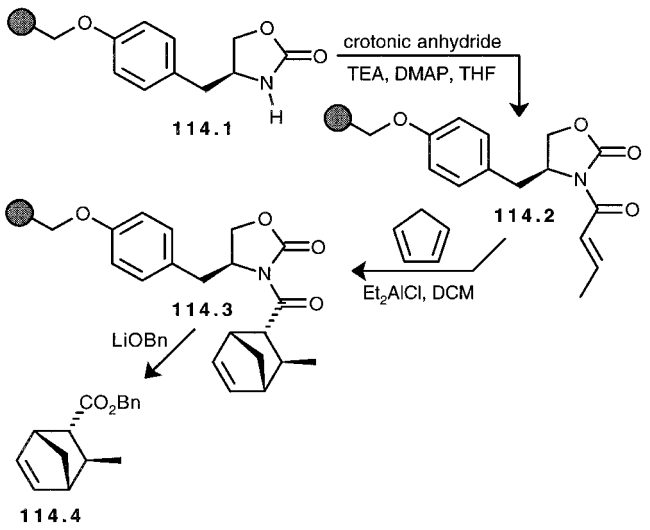
Scheme 113



and DIC in DMF. With both the diene and dienophile attached to the support (a supported triene), the intramolecular cycloaddition proceeded to furnish **113.5**. Maleic anhydride could also be applied in the coupling to amine **113.3** which provided **113.6** after concomitant cycloaddition.

Chiral auxiliaries such as Evans oxazolidinone[139] have also been utilized for stereoselective Diels−Alder cycloadditions on the solid support.[140] The synthesis commenced with construction of the solid-supported oxazolidinone (Scheme 114). *N*-Acylation

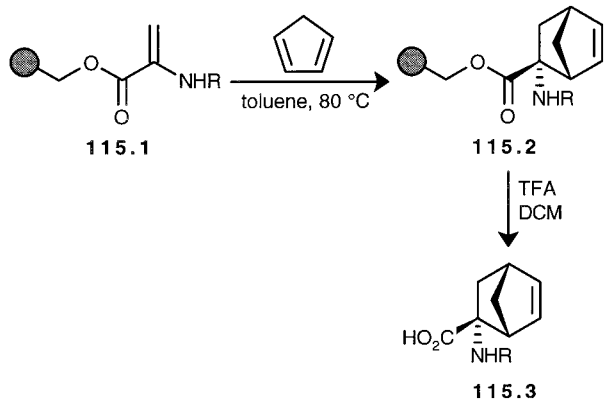
Scheme 114



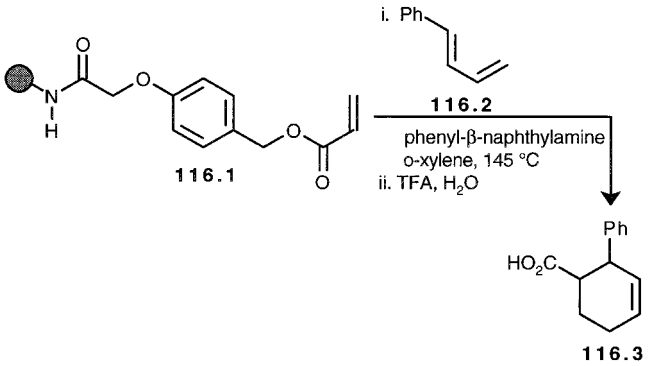
of oxazolidinone **114.1** with crotonic anhydride provided polymer-bound chiral dienophile **114.2**. Cycloaddition with cyclopentadiene was catalyzed with diethylaluminum chloride in DCM and provided **114.3**. Wang resin was not compatible with the diethylaluminum chloride, while Merrifield resin was stable to this Lewis acid. The cycloadduct was cleaved from the resin with lithium benzyloxide, and **114.4** was isolated in a yield of 26% for five steps. The endo:exo ratio of 21:1 and an ee of 86% were reported by analyzing the 500 MHz ^{1}H NMR spectra [Eu(hfc)$_3$ was used to determine % ee].

The synthesis of carbocyclic containing amino acids was reported via the Diels−Alder cycloaddition of solid-supported dehydroalanines.[141] The first aspect

Scheme 115



Scheme 116



of this synthesis was to obtain the desired polymer-bound dehydroalanine dienophile (Scheme 115), and several synthetic pathways to give **115.1** were described. The cycloaddition with cyclopentadiene in toluene at 80 °C provided **115.2**, and the carbocyclic amino acid **115.3** was obtained by cleavage from Wang resin with 20% TFA in DCM. The exo to endo ratios of the cycloadducts were from 2:1 to 4:1 and the isolated yields were 51−81%.

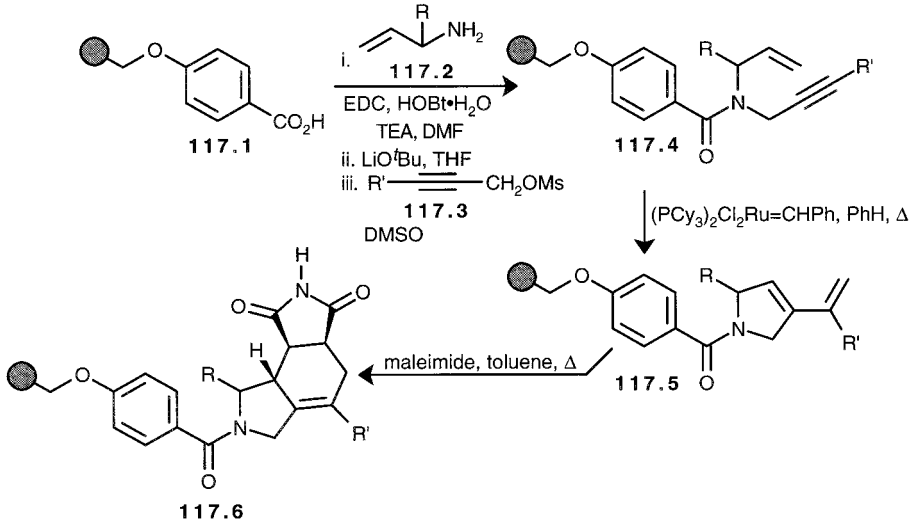
Diels−Alder and 1,3-dipolar cycloaddition reactions were examined to demonstrate the utility of novel polystyrene-grafted fluoropolymer MicroTubes.[142] The Diels−Alder example shown here begins with an amino-functionalized MicroTube with a Wang linker (Scheme 116). Polymer-bound acrylate **116.1** was prepared and utilized in the cycloaddition with 1-phenyl-1,3-butadiene (**116.2**) with phenyl-*β*-naphthylamine as an additive in refluxing *o*-xylene (145 °C). Cleavage with TFA in H_2O produced 2-phenyl-3-cyclohexenecarboxylic acid (**116.3**) as a mixture of cis and trans isomers in an overall yield of 45%.

The ene−yne metathesis was used to prepare polymer-supported dienes for use in the Diels−Alder cycloaddition (Scheme 117).[143] Amide formation between allylamine **117.2** and *p*-hydroxybenzoic acid bound to Wang resin (**117.1**) was followed by *N*-alkylation of the amide with propargyl mesylate **117.3** to give ene−yne **117.4**. Grubbs ruthenium catalyst was exploited for the ene−yne metathesis to provide the expected diene **117.5**. Reaction of the polymer-bound diene with maleimide in toluene at 105 °C afforded hexahydroisoindole **117.6**. Many other dieneophiles were utilized to provide a combinatorial library of 10 × 4 × 5 × 16. In another report, the synthesis of octahydrobenzazepinones also utilized tandem ene−yne cross metathesis and Diels−Alder cycloaddition reactions.[144]

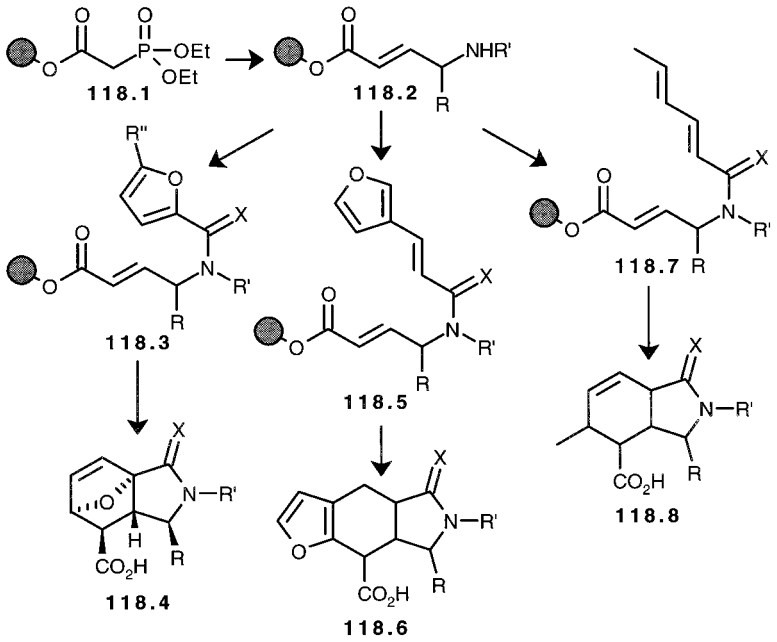
Another example of the intramolecular Diels−Alder reaction employs several different dienes.[145] The first carbon−carbon bond-forming reaction came from a Horner−Emmons reaction between Fmoc-protected amino aldehydes and phosphonoacetyl−Wang resin **118.1** (Scheme 118). Deprotection was followed by reductive amination to deliver the corresponding secondary amine **118.2**. *N*-Acylation or reductive amination with three different dienes provided **118.3**, **118.5**, and **118.7**, where X = O or H_2. Now, with both diene and dienophile attached to the solid support, the cycloaddition was allowed to proceed in DCM for 16 h to 7 days and afforded cycloadducts **118.4**, **118.6**, and **118.8** after cleavage from the resin.

Combinatorial libraries from 3,5-cyclohexadiene-1,2-diols were produced by employing the SPOS Diels−Alder cycloaddition reaction.[146] Here, 3-bromo-3,5-cyclohexadiene-1,2-diols were coupled to the resin through acetal formation (Scheme 119). Epoxidation of the nonsubstituted alkene, amine-opening of the

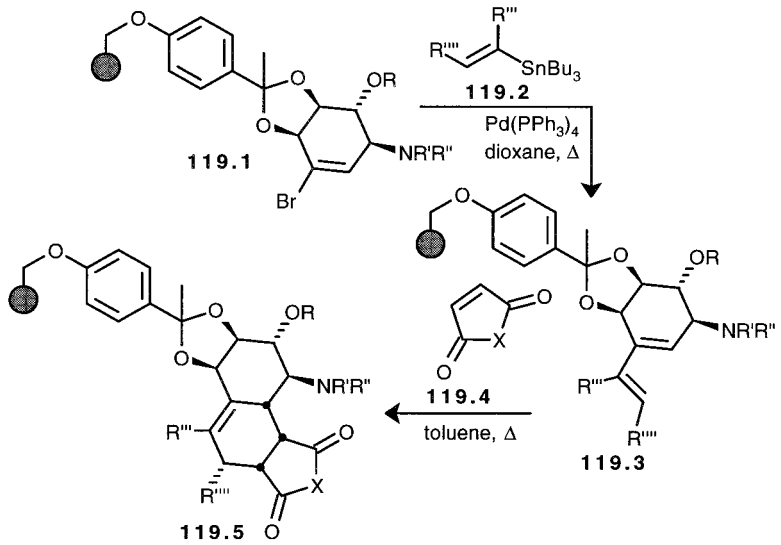
Scheme 117



Scheme 118



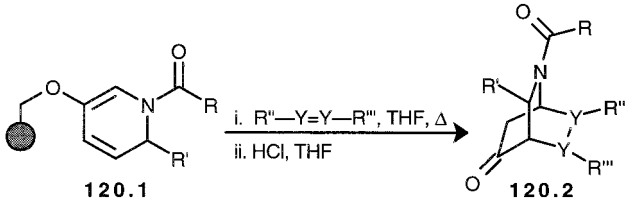
Scheme 119



epoxide, and alcohol substitution afforded alkenyl bromide **119.1**. Utilization of Stille coupling (other examples shown previously in this review) with vinyl stannanes (**119.2**) produced polymer-supported diene **119.3** for the subsequent Diels–Alder reaction. Dienophiles **119.4** such as maleimides and naphthoquinones allowed for cyclization in toluene at 50 and 80 °C, respectively, and afforded cycloadducts **119.5**. Cleavage from the resin with TFA in DCM provided 10 examples with yields of 61–96% and purities of 70–95%.

Chen and Munoz showed the solid-phase synthesis of 2-acyl-5-oxo-2-azabicyclo[2.2.2]octane derivatives.[147] Resin-bound enol ether diene was produced via a resin activation/capture approach also known as REACAP technology (Scheme 120). Diene **120.1** was reacted with dienophiles in THF to generate cycloadducts attached to the resin as the enol ether. Cleavage from the resin by hydrolysis of the enol ether was accomplished by employing HCl in THF and afforded

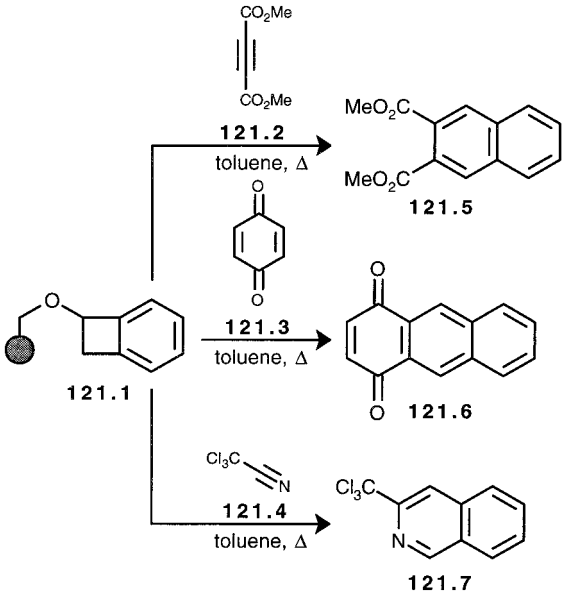
Scheme 120



ketone **120.2**. Substitution of azo compounds (Y = N) for the alkene resulted in hetero-Diels–Alder cycloadditions and thus afforded the triaza derivatives of the titled compound.

Normal and hetero-Diels–Alder cycloadditions have also been studied with polymer-bound *o*-quinodimethanes.[148] Polymer-bound benzocyclobutenol (novel traceless linker) was attached to the resin as the precursor to the *o*-quinodimethane (Scheme 121). Heating **121.1** in toluene at 105 °C produced the reactive diene. Dimethyl acetylenedicarboxylate

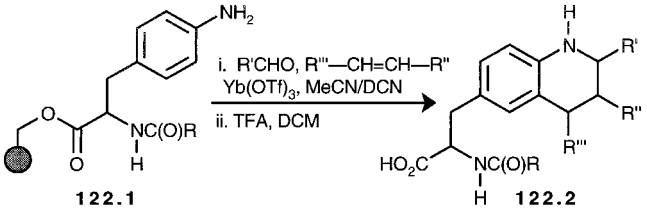
Scheme 121



(**121.2**) and benzoquinone (**121.3**) were applied as dienophiles to afford **121.5** and **121.6**, while trichloroacetonitrile (**121.4**) was utilized as dienophile for the hetero-Diels−Alder cycloaddition to give **121.7**. Additional examples of tandem Diels−Alder Lewis acid-mediated reactions were also reported in the formation of carbon−carbon bonds.

Hetero-Diels−Alder reactions have been utilized for the solid-phase synthesis of tetrahydroquinolines.[149] This SPOS began with 4-aminophenylalanine derivatives attached to Wang resin (Scheme 122). The aniline (**122.1**) was reacted with aldehydes

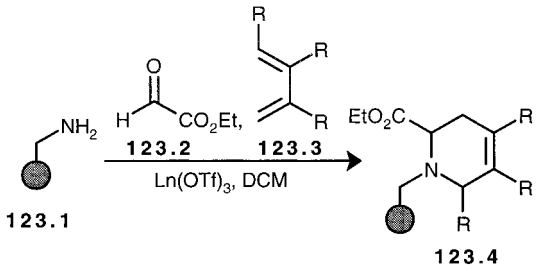
Scheme 122



to produce the corresponding imine in situ, which cyclized with dienophiles in the presence of $Yb(OTf)_3$ in acetonitrile/DCM. Several other catalysts (TFA, $BF_3 \cdot Et_2O$, etc.) were also tested, but the results were less gratifying. Cleavage from the resin with TFA in DCM afforded **122.2**. There was also a unique example that employed citronellal as both the aldehyde and dienophile in a rare intramolecular hetero-Diels−Alder. There was another report that examined similar chemistry where either the aldehyde or the dienophile was attached to the solid support.[150]

Wang and co-workers also utilized the hetero- or aza-Diels−Alder reaction with different lanthanide(III) triflates to produce tetrahydropyridines.[151] The reaction began with commercially available aminomethylated polystyrene resin (Scheme 123). The amine (**123.1**) was reacted with aldehydes, such as ethyl glyoxylate **123.2**, and the corresponding imine generated in situ was cyclized with butadienes **123.3** in the presence of lanthanide(III) triflates to provide

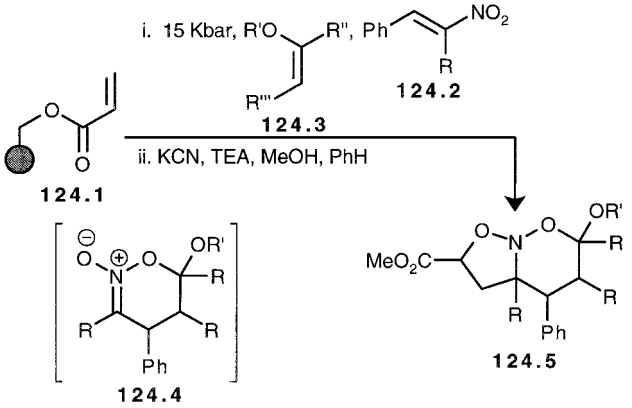
Scheme 123



123.4. In this research La, Nd, Dy, and Yb triflates were investigated. The benzylamine was cleaved from the resin with 1-chloroethyl chloroformate to afford products.

Scheeren and Kuster examined tandem hetero-Diels−Alder/1,3-dipolar cycloadditions at high pressures.[152] After careful testing, it was found that Wang resin and its ester linker were stable to the high pressures required for this methodology (Scheme 124). Resin-bound acrylate **124.1** was prepared as the

Scheme 124

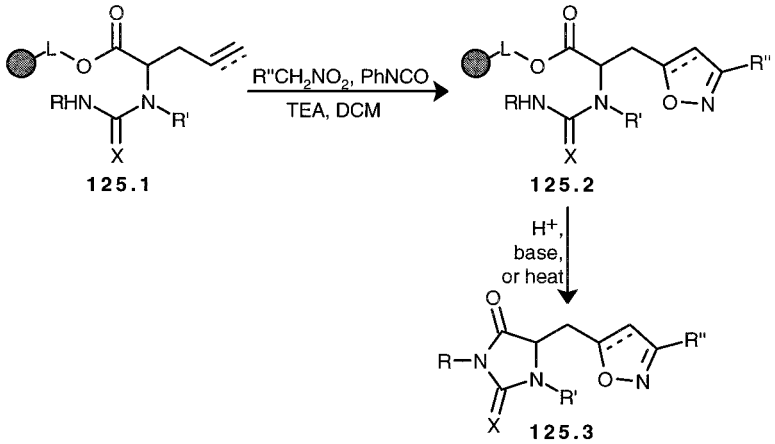


electron-deficient alkene for the cycloadditions. *β*-Nitrostyrene **124.2** and electron-rich enol ether **124.3** reacted in a solution-phase inverse electron demand hetero-Diels−Alder reaction to form nitronate **124.4** in situ without any catalyst at 15 Kbar. This nitronate acts as the 1,3-dipole in the subsequent [3+2] cycloaddition with the polymer-supported acrylate. Cleavage from the resin by transesterification with KCN, TEA, and MeOH in benzene afforded six examples of nitroso-acetal **124.5** in overall isolated yields of 33−52%.

2. 1,3-Dipolar Cycloaddition

The 1,3-dipolar cycloaddition reaction has also been well adapted to SPOS as seen in a recent review by Kurth and Kantorowski.[153] These reactions have been shown to accommodate a range of dipoles (nitrile oxide, azomethine ylide, nitrone, etc.) and dipolarophiles (alkene and alkyne). Kurth and co-workers illustrate the use of nitrile oxides for the formation of isoxazoles and isoxazolines in the synthesis of novel hydantoin[154] and thiohydantoin compounds.[155] Polymer-supported ureas and thioureas containing a pendant alkene or alkyne were first generated from reaction of the amine with isocyanates or thioisocyantes (Scheme 125). The nitrile oxides were gener-

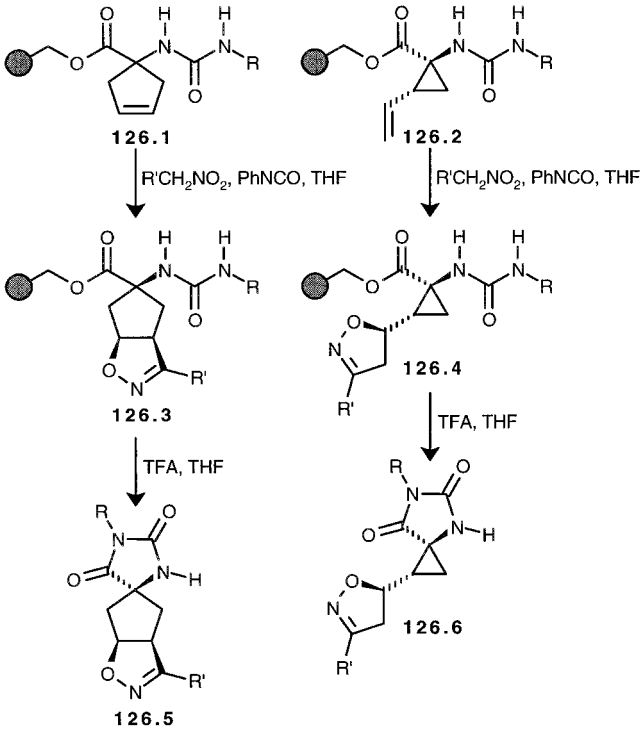
Scheme 125



ated in situ by dehydration of the primary nitro compound with phenyl isocyanate (Mukaiyama method).[156] 1,3-Dipolar cycloaddition of the nitrile oxide with the alkene/alkyne produced the corresponding isoxazol(in)e **125.2**. Cleavage of the ester linker via cycloelimination with the urea/thiourea afforded diheterocyclic compound **125.3**. Average overall yields for 18 examples of the isoxazolothiohydantoins were 30−40%. It is also noted that the cyclization of the hydantions was also achieved with gentle warming without acid or base catalyst if R′ was an alkyl group.[157]

Park et al. also described diastereoselective 1,3-dipolar cycloadditions in the synthesis of novel isoxazoline-containing spirocyclic hydantoins.[158] The synthesis began with attachment of vinylcyclopropane or cyclopentene moieties to the resin (Scheme 126).

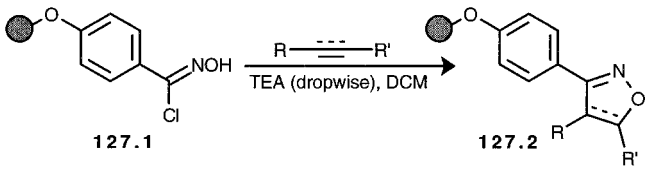
Scheme 126



The nitrile oxide was selected as the 1,3-dipole and produced in situ again by Mukaiyama's method. 1,3-Dipolar cycloaddition of the nitrile oxide with alkene **126.1** and **126.2** produced isoxazolines **126.3** and **126.4**, respectively. The diastereoselectivity arose from hydrogen bonding between the nitrile oxide oxygen and the urea NH which directed face selectivity of the nitrile oxide addition to alkene. Cycloelimination was accomplished with TEA in THF to afford six cyclopentanoids **126.5** in 21−30% overall yield and four cyclopropanoids **126.6** in 15−22%.

Isoxazol(in)es have also been produced in SPOS with the nitrile oxide being attached to the polymer support. The nitrile oxide in this case was generated in situ by dehydrohalogenation of the supported hydroximoyl chloride (Scheme 127). Hydroximoyl

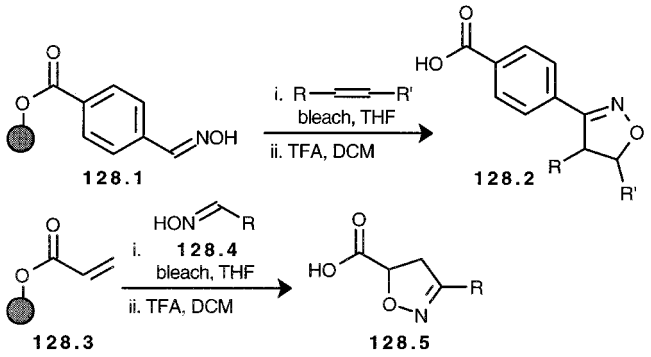
Scheme 127



chloride **127.1** was produced from the initial polymer-bound 4-hydroxybenzaldehyde in two steps preceding through the aldoxime. Ten-fold excess dipolarophile (alkene or alkyne) in DCM was followed by slow addition of TEA to furnish the nitrile oxide. The 1,3-dipolar cycloaddition produced a small library of isoxazoles and isoxazolines **127.2**. This chemistry was shown to be efficient for a solid-phase one-pot synthesis, and 10 heterocycles were produced in 60−80% yield and all examples possessed >90% purity.

Polymer-bound nitrile oxides have also been prepared and reacted directly from the aldoxime by addition of bleach.[159] 4-Formylbenzoic acid was attached to Wang resin and hydroxylamine added to produce the aldoxime (Scheme 128). Alkenes and polymer-supported aldoxime **128.1** were reacted with bleach in THF to produce the isoxazoline and afford **128.2** after cleavage with TFA in DCM (60−94% for six examples). Conversely, polymer-bound acrylate **128.3** was employed as the dipolarophile for reaction with nitrile oxides generated from aldoxime **128.4** and bleach. The solution-phase nitrile oxide produced excellent yields (90−98% for four examples) of isox-

Scheme 128

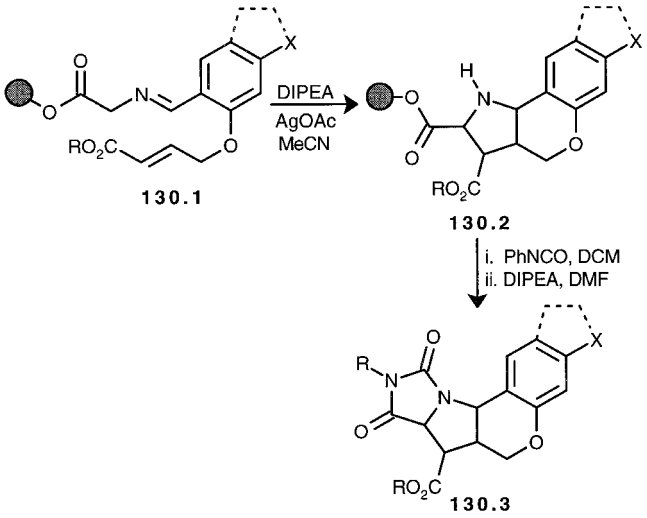


azoline **128.5** after cleavage from the resin with TFA. The high yield could have more to do with the dipolarophile (methyl acrylate yielded 94% of **128.2**), as opposed to which species (nitrile oxide vs alkene) is attached to the solid support.

The synthesis of isoxazolinoisoquinolines by Lorsbach et al. (shown previously in Scheme 21 for Suzuki coupling) also utilized a 1,3-dipolar cycloaddition reaction (Scheme 129).[34] Polymer-supported benzoyl chloride **129.1** was prepared and subjected to isoquinolines (**129.2**) and trimethylsilyl cyanide to provide Reissert complex **129.3** (carbon−carbon connection) as the linker in this synthesis. Carbon−carbon bond-forming alkylation of the Reissert complex with allyl bromides provided the pendant dipolarophile (**129.4**) and nitrile oxides, generated in situ using the Mukaiyama method, underwent cycloaddition to provide isoxazoline **129.5**. Hydrolysis of the Reissert complex followed with KOH in THF to provide a small library of isoxazolinoisoquinolines **129.6**.

Kurth and co-workers utilized a solid-supported azomethine ylide in a intramolecular 1,3-dipolar cycloaddition.[160] This report began with the synthesis of *O*-alkenyl salicylaldehydes and 2-hydroxy-1-naphthaldehyde (Scheme 130). The aldehyde was reacted

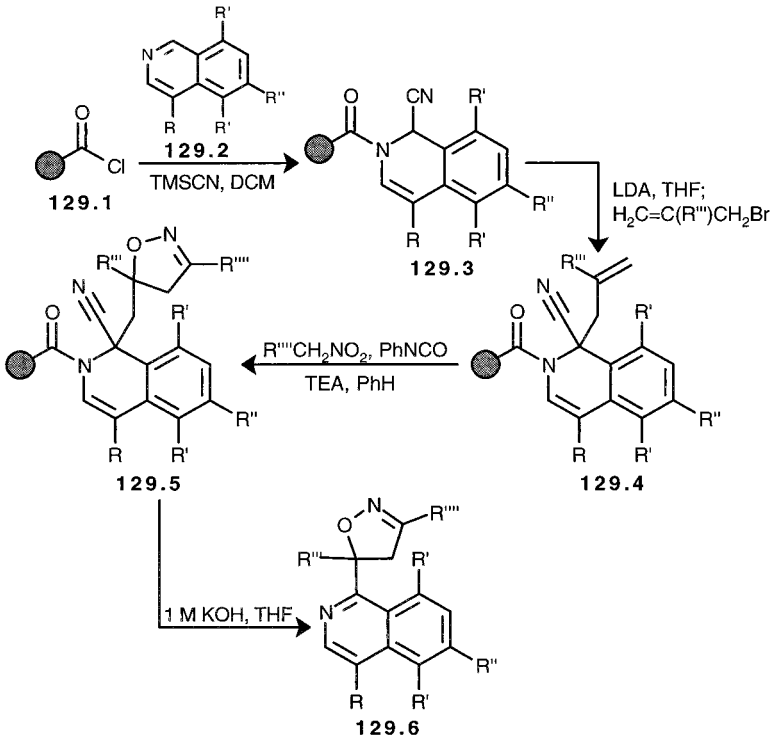
Scheme 130



with polymer-bound amine in the presence of TMOF to provide imine **130.1** as the azomethine ylide precursor. The 1,3-dipole was produced with DIPEA and silver(I) acetate in acetonitrile, and subsequent intramolecular 1,3-dipolar cycloaddition occurred directly to give proline moiety **130.2**. Addition of phenylisocyanate to the proline derivative gave the corresponding urea, which underwent cycloelimination from the resin with DIPEA in DMF to afford **130.3**. More recently, Gallop has also shown the usefulness of intramolecular 1,3-dipolar cycloaddition with azomethine ylides in the solid-phase synthesis of triaza tricyclic systems.[161]

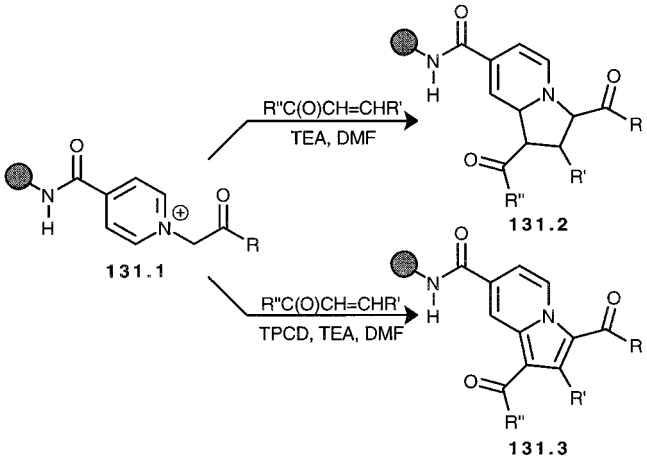
Goff described the use of the pyridinium ylide as a 1,3-dipole in the SPOS of indolizines.[162] Isonicotinic

Scheme 129



acid was bound to Rink resin and the pyridine nitrogen quaternized with α-bromomethyl ketones (Scheme 131). Polymer-bound α-pyridinium ketone

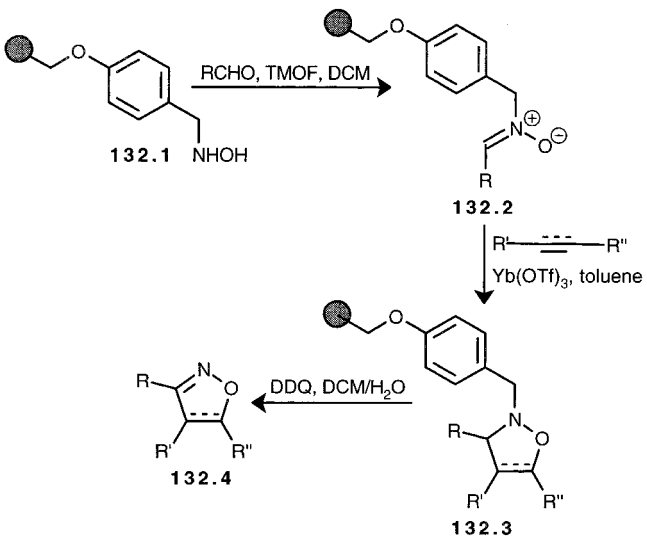
Scheme 131



131.1 was transformed into the corresponding pyridinium ylide with TEA in DMF and subsequently cyclized with α,*β*-unsaturated ketones to provide tetrahydroindolizine **131.2**. Cleaving the Rink linker with TFA also caused the undesired opening of the tetrahydroindolizine and yielded the N-substituted pyridinium salt. When the cycloaddition reaction was repeated in the presence of TPCD [Co(pyridine)$_4$-(HCrO$_4$)$_2$], polymer-bound aromatic indolizine **131.3** was obtained, which was cleaved from the resin with TFA without any decomposition.

Kobayashi used polymer-supported nitrones to produce a library of isoxazol(in)es.[163] The synthesis of polymer-bound hydroxylamine occurred in three steps from Merrifield resin (Scheme 132). Condensa-

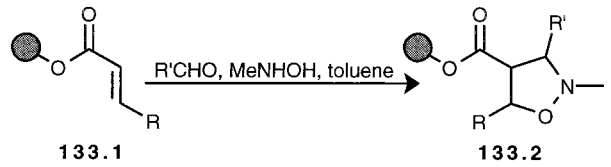
Scheme 132



tion of aldehydes with hydroxylamine **132.1** in the presence of TMOF in DCM produced nitrone **132.2**. This nitrone reacted with the dipolarophile (alkene or alkyne) in toluene with Yb(OTf)$_3$ as the catalyst for the cycloaddition and provided isoxazol(id)ine **132.3**. This heterocycle was cleaved from the resin with DDQ in DCM/H$_2$O (10:1) to provide corresponding isoxazol(in)e **132.4**. The use of six different dipolarophiles provided a library of 13 derivatives with overall yields of 47−89%.

Solid-supported dienophiles were also used in the synthesis of isoxazolidines (Scheme 133).[164] Nitrones,

Scheme 133



employed as the dipole, were produced in situ by the reaction of aldehydes with *N*-methylhydroxylamine. This nitrone reacted with polymer-supported alkene **133.1** to produce isoxazolidine **133.2**. Cleavage from the 2-chlorotrityl resin with TFA in DCM provided the corresponding carboxylic acids in 24−45% yield.

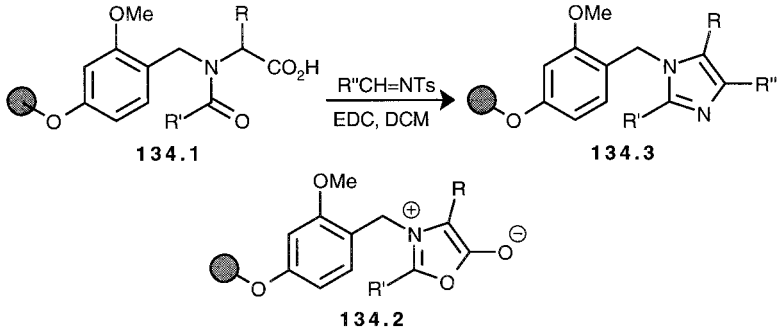
Bilodeau and Cunningham described the solid-phase 1,3-dipolar cycloaddition of munchnones with tosylimines.[165] SPOS commenced with 4-hydroxy-2-methoxybenzaldehyde being bound to ArgoGel resin (Scheme 134). The aldehyde was reductively aminated with amino esters, and the resulting secondary amine was acylated with acid chlorides to give amide **134.1** after saponification of the ester. In the presence of EDC and tosylimines in DCM, the amido acid was converted to munchnone **134.2** in situ and underwent regioselective 1,3-dipolar cycloaddition with the tosylimine. Subsequent elimination of toluenesulfinic acid and CO_2 produced imidazole **134.3**. Twelve examples were reported to produce yields of 49−99% and purities of 94−98%.

Consecutive pyridinium ylide 1,3-dipolar and nitrile oxide 1,3-dipolar cycloadditions, often described as the Tsuge reaction,[166] have been reported in SPOS.[167] The pyridinium salt bound to Wang resin served as precursor to the first cycloaddition (Scheme 135). The pyridinium ylide of **135.1** was generated in situ with TEA in THF and underwent 1,3-dipolar cycloaddition with maleimides to produce intermediate heterocycle **135.2**. Addition of hydroximoyl chloride **135.3** followed by dropwise addition of TEA produced the nitrile oxide in situ, which underwent 1,3-dipolar cycloaddition to produce polymer-bound alkaloid **135.4**. Cleavage from the Wang resin with TFA also caused hydrolysis of the isoxazoline moiety and rearomatization to the pyridinium salt. Employing amines for cleavage allowed for conversion of the polymer-bound ester to the corresponding amide without disruption of the isoxazoline heterocycle.

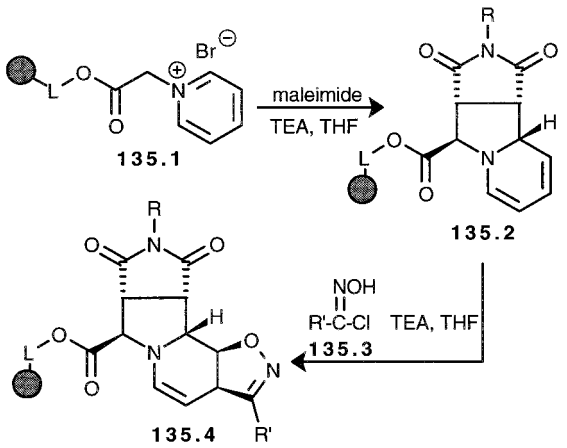
3. Staudinger Reaction

The Staudinger reaction is a [2+2] cycloaddition to produce *β*-lactams from imines and ketenes generated from treatment of acid chlorides with TEA. This carbon−carbon bond-forming reaction is important due to the known biological activity of *β*-lactams. Singh and Nuss recently prepared a library of *β*-lactams utilizing the Staudinger cycloaddition reaction (Scheme 136)[168] where the solid-supported aldehyde (from coupling of 4-formylbenzoic acid to amino-functionalized resin) reacted with primary amines in

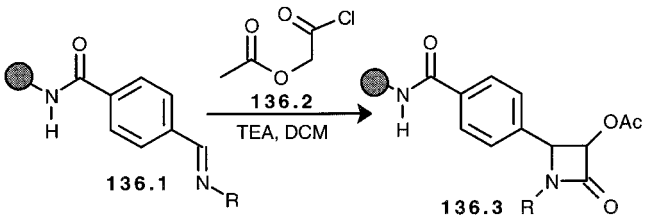
Scheme 134



Scheme 135



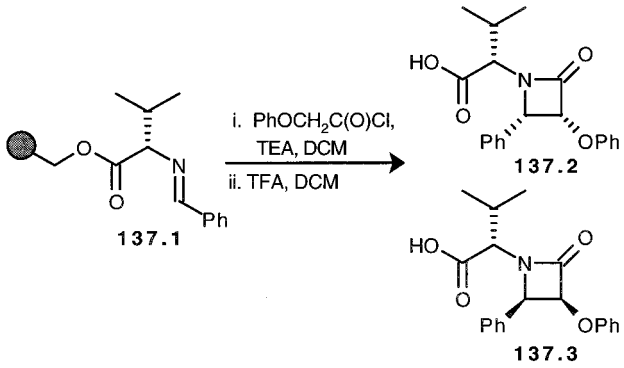
Scheme 136



the presence of molecular sieves or TMOF to supply the corresponding imine **136.1**. Reaction of acetoxyacetyl chloride (**136.2**) with TEA in DCM formed the desired ketene in situ, which cyclized with the imine to provide 3-acetoxy-substituted β-lactam **136.3**. After cleavage from the resin with 3% TFA in DCM, the isolated yields were 89−96% and HPLC purities ranged from 98% to 100% for four examples. Further derivatization was also described to produce a small library of β-lactams prior to cleavage from the resin (yields and purites given).

The Staudinger reaction was also shown to be effective in the scale-up synthesis (100 g) of chiral β-lactams.[85] This synthesis began with the preparation of Sasrin resin from Merrifield resin (Scheme 137). Attachment of Fmoc-valine to the resin was followed by deprotection and imine formation to produce **137.1**. Phenoxyacetyl chloride and TEA in DCM produced the ketene, which cyclized with the polymer-bound imine to produce β-lactams **137.2** and **137.3** after cleavage with TFA in an overall yield of 60% from the Sasrin resin. The purity was >99%, and the diastereomer ratio was 2:1. Another example of the Staudinger reaction employed poly(ethylene glycol) as the soluble support, and it showed that

Scheme 137

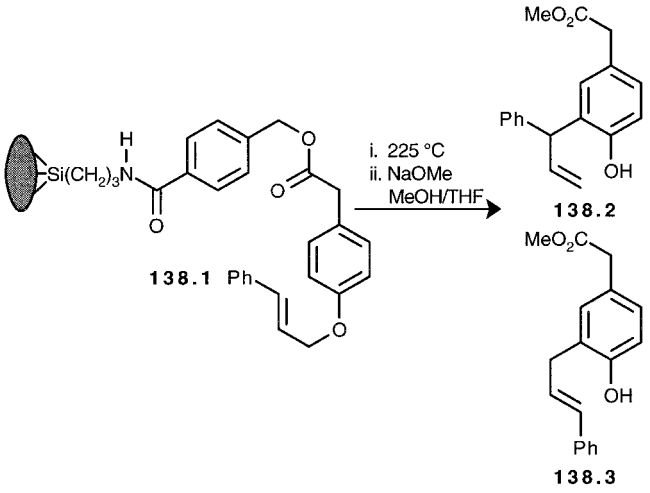


substituting trioctylamine in place of TEA for the reaction improved purification when precipitating the polymer with diethyl ether.[169]

4. Rearrangements

Sigmatropic rearrangements are another example where new carbon−carbon bonds may be formed. One solid-phase example is a Claisen rearrangement which takes place on silica gel or mesoporous molecular sieve support.[170] Either silica support was functionalized with (aminopropyl)triethoxysilane and coupled with 4-hydroxymethylbenzoic acid (Scheme 138). DIC coupling of 4-cinnamyloxybenzoic acid to

Scheme 138

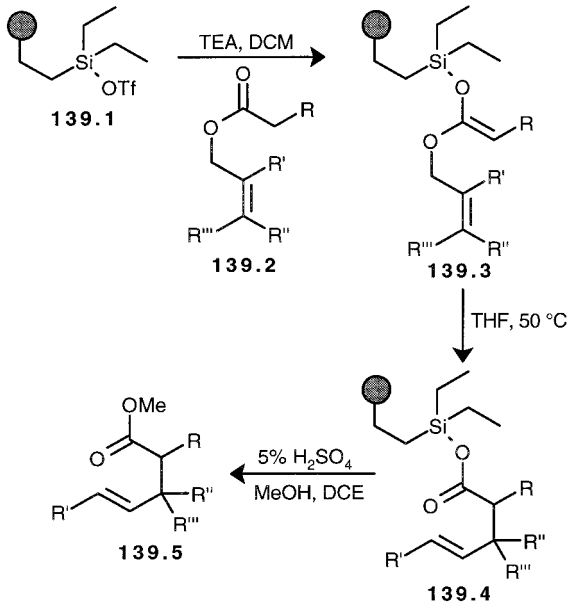


the alcohol in DCM/DMF provided **138.1** as the rearrangement precursor. Heating to 225 °C brought about the solid-phase Claisen rearrangement and furnished the supported phenol. Cleavage from the

solid support was accomplished with sodium methoxide in MeOH/THF. Use of the mesoporous molecular sieve support afforded only **138.2** in 27% and 35% yields. When silica gel was used as the support, a 1.6:1 mixture of **138.2** and **138.3** was obtained. It was concluded that this difference was due to the greater distance between bound molecules in the mesoporous molecular sieves.

The Ireland–Claisen rearrangement of silyl ketene acetals has also been demonstrated on a polystyrene support.[171] The precursor for the rearrangement was prepared by reaction of a supported silyl triflate (**139.1**; Scheme 139) with unsaturated ester **139.2**

Scheme 139



and TEA in DCM. Rearrangement of **139.3** took place by heating this resin in THF to 50 °C and gave silyl ester **139.4**. The silyl ester was cleaved from the resin with H_2SO_4 in MeOH/EDC (1:1) to afford unsaturated methyl ester **139.5**. Six different examples were reported with five giving yields of 52–60% and purities of 86–100%, while one gave no desired product.

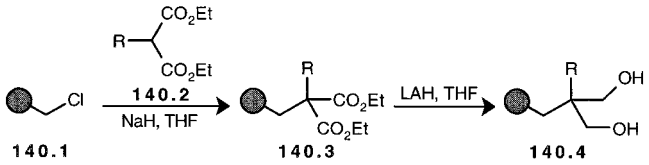
V. C-Alkylation Reactions

Alkylations are also a common method for carbon–carbon bond formation in organic chemistry, and numerous solid-phase examples have been reported. Examples with either the carbon nucleophile or electrophile attached to the solid support are given. Here, the reactions have been classified according to the type of nucleophile. Enolates are the most common and make up one class while all other nucleophiles are grouped into a second class.

1. Enolate Alkylations

The chemistry of enolates is very rich and has been well adapted to SPOS. Several different types of enolates are successfully employed as the bound or solution reagent while carbon electrophiles include alkyl halides and triflates. One example was applied to the construction of a novel TentaGellike resin that would effectively double the resin loading (Scheme 140).[172] Merrifield resin (**140.1**) was selected as the

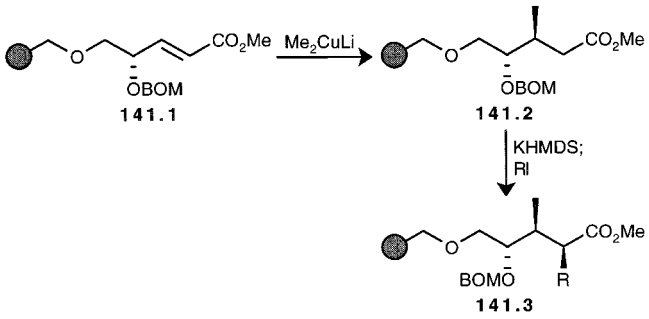
Scheme 140



polymer-supported electrophile and reacted with enolates of diethyl malonate or diethyl methylmalonate **140.2**. These β-diester enolates were produced in situ with NaH in THF and afforded **140.3**. After alkylation, the polymer-bound diester was reduced with LAH in THF to give the desired diol **140.4**. PEG-grafted copolymers were generated on both diols with ethylene oxide and potassium *tert*-butoxide in THF to produce higher loading hydroxy resins. Chloro-, amino-, Wang-, and HMBP-functionalized resins were constructed from these hydroxy resins.

Michael addition of a cuprate and alkylation of the resulting enolate provided two carbon–carbon forming reactions in the synthesis of contiguous stereogenic molecules (Scheme 141).[173] This stereoselective

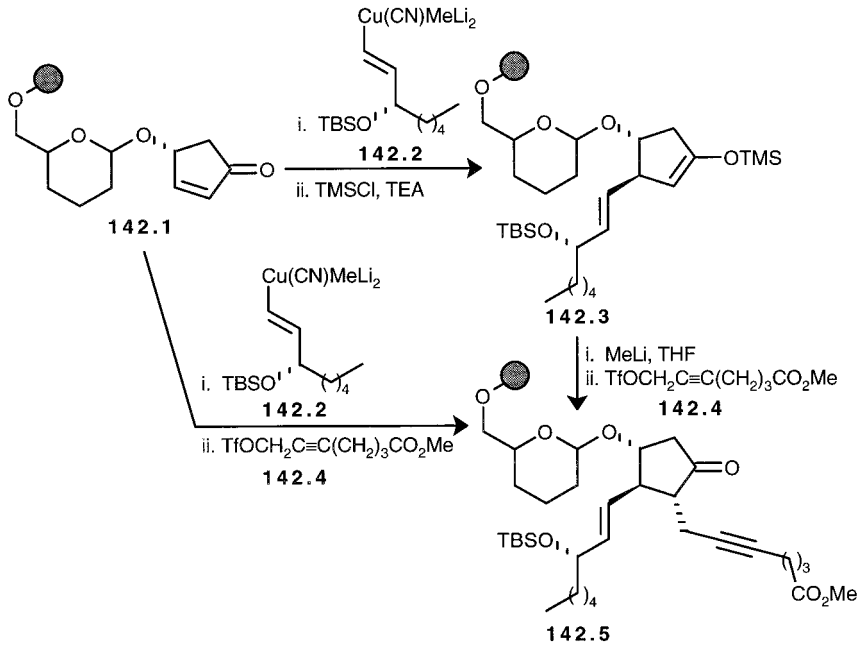
Scheme 141



synthesis began with attachment of chiral α,β-unsaturated ester **141.1** to Wang resin. Treatment of the acrylate with methyl cuprate resulted in stereoselective Michael addition and produced saturated ester **141.2**, which was converted to its enolate with KHMDS. Stereoselective alkylation followed by addition of an alkyl iodide to generate **141.3**. Cleavage from the Wang resin with 3% TFA also caused cyclization to the δ-lactone. The % de was not reported for either of these two carbon–carbon bond-forming reactions.

Janda and Chen employed non-cross-linked polystyrene as a soluble support in the synthesis of prostaglandin $F_{2\alpha}$.[174] The total synthesis of this natural product utilized an enolate alkylation and the Michael addition of a cuprate (Scheme 142). Ellman's dihydropyran linker was employed, and chiral 4-hydroxy-2-cyclopenten-1-one was attached to give **142.1**, which provided the cyclopentane core of $PGF_{2\alpha}$ with high stereoselectively. Stereospecific and regioselective addition of cuprate **142.2** to the polymer-bound α,β-unsaturated ketone produced the corresponding copper enolate, which was directly alkylated with triflate **142.4** to afford cyclopentanone **142.5**. Alternatively, the copper enolate could be trapped and

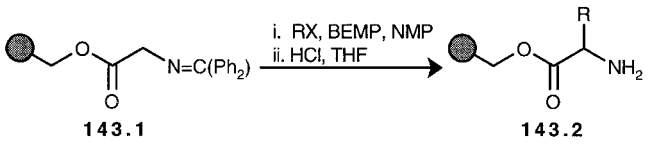
Scheme 142



isolated as its silyl enol ether **142.3** and the enolate regenerated with methyllithium. Hydrogenation of the alkyne to the *cis*-alkene with Lindlar's catalyst, stereospecific reduction of the ketone with L-selectride, and saponification with LiOH was followed by silyl deprotection and cleavage (HF) to complete the total synthesis. The overall isolated yield for the 10-step synthesis was reported as ~30%.

A solid-phase synthesis of α-amino acids by the alkylation of polymer-bound ester enolates has been reported.[175] Glycine bound to Wang resin was converted to the benzophenone imine (Scheme 143), and

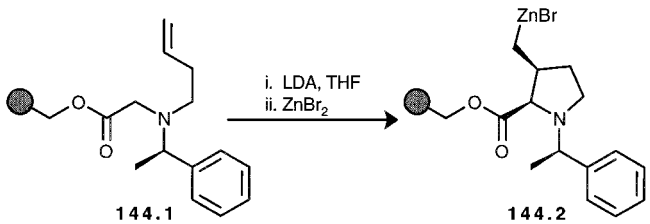
Scheme 143



Schwesinger bases (BEMP when activated halides were present and BTPP for nonactivated halides) in NMP were used to generate the enolate of **143.1** in situ. Subsequent alkylation of the alkyl halide and hydrolysis of the resultant imine with hydroxylamine or 1 N HCl produced polymer-supported amino acid **143.2**. Enantioselective alkylations (44−89% ee) were studied by employing a cinchona-based quaternary ammonium salt as an additive.

Karoyan et al. reported the solid-phase synthesis of 3-substituted prolines.[176] Transesterification of Wang resin with an ester containing a homoallylic amine provided the precursor for the enolate cyclization (Scheme 144). Application of LDA in THF to amino ester **144.1** produced the ester enolate that, upon addition of zinc bromide, furnished chiral proline core **144.2**. This organozinc was protonated to give the methyl substituent or reacted with iodine to produce the corresponding methyl iodide. Cleavage from the Wang resin was accomplished with TFA and afforded the carboxylic acid. The use of triphosgene

Scheme 144

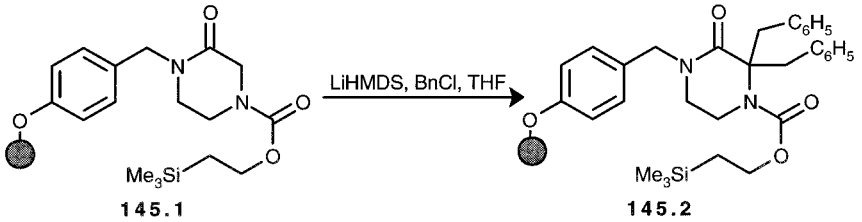


cleaved the benzylamine as well as the resin linker to give 3-methylproline or the iodomethyl derivative.

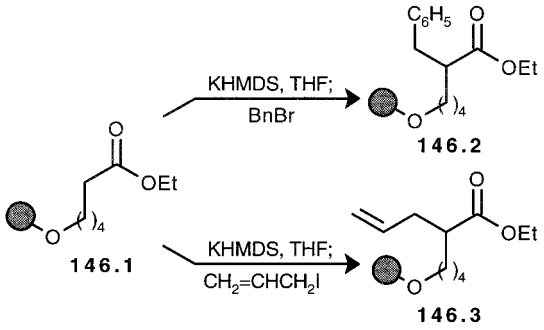
The enolate of polymer-bound 2-ketopiperazine was proven useful in carbon−carbon bond-forming solid-phase alkylations.[177] A 2-ketopiperazine, with a 4-hydroxybenzyl substituent at N1 and 2′-trimethylsilylethyl carbamate (TEOC protecting group) at N4, was prepared and subsequently attached to the 2-chlorotrityl chloride resin (Scheme 145). The enolate of **145.1** was formed in situ with 5 equiv of LiHMDS at room temperature in the presence of 5 equivof benzyl chloride. Only dialkylated product **145.2** was observed in this case (cleavage with TFA in DCM/MeOH showed 92% yield). In attempts to produce monoalkylated 2-ketopiperazines, mixtures of di-, mono-, and unalkylated amides were obtained. The TEOC group could be deprotected with TBAF to give the amine, which could be acylated before cleavage.

One other solid-phase example of *C*-alkylation with enolate nucleophiles also employed the Heck reaction (as seen in Scheme 12**)**. Ethyl 6-hydroxyhexanoate was bound to Wang or PEG-HMP resin (Scheme 146),[23] and the ester enolate of **146.1** was formed with KHMDS in THF at −78 °C. Addition of activated electrophiles (benzyl bromide and allyl iodide) was followed by warming to 0 °C and provided monoalkylated products **146.2** and **146.3**. Ozonolysis of **146.3** produced the corresponding aldehyde, which was reduced with $NaBH_4$ under sonication to furnish the γ-lactone.

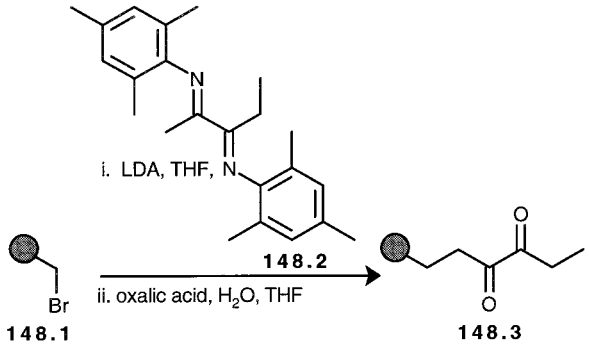
Scheme 145



Scheme 146



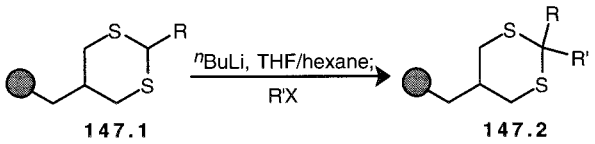
Scheme 148



2. Miscellaneous Alkylations

The synthesis and use of polymer-supported 1,3-dithianes have been employed in SPOS (Scheme 147).[178] 4-Vinylbenzyl chloride was alkylated with

Scheme 147

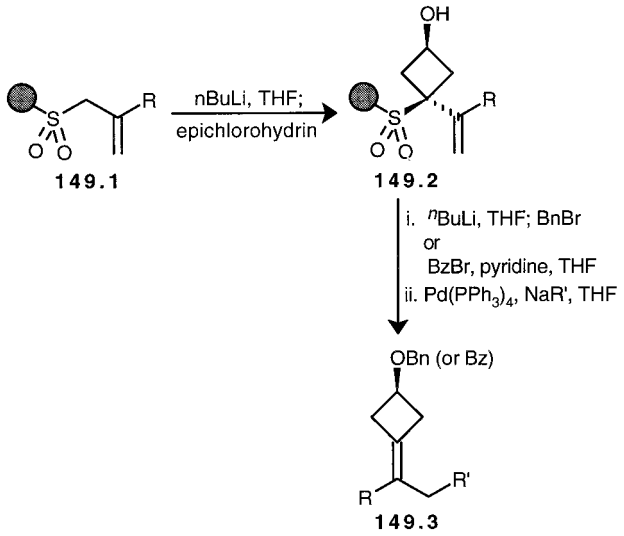


diethyl malonate and reduced with LAH to provide the corresponding 1,3-diol. After tosylation, the monomer was copolymerized with styrene in dioxane employing AIBN. Conversion to the starting 1,3-dithiol was accomplished in two steps (potassium thioacetate, LAH). Condensation of this dithiol with aldehydes in the presence of $BF_3 \cdot Et_2O$ gave thioacetal **147.1**. The dithiane carbanion was formed with *n*-BuLi and alkylated to give thioketal **147.2**. Cleavage of the 1,3-dithiane and liberation of the ketone was achieved with periodic acid. Interestingly, methyl ketones gave iodomethyl ketones when cleaving with H_5IO_6, while cleavage with $Hg(ClO_4)_2 \cdot 3H_2O$ afforded the methyl ketones.

Regioselective formation of the α-carbanion of 1,2-diimines and subsequent alkylation with polymer-bound electrophiles has been reported (Scheme 148).[179] The kinetic anion of unsymmetrical diimine **148.2,** produced in situ with LDA, was alkylated with bromomethyl polystyrene (**148.1**). The polymer-bound diimine produced was tested for its chelation to metals. The imines were also hydrolyzed with oxalic acid to produce α-diketone **148.3**, and the resultant diketone lead to an entire library of solid-phase diimines. The polymer-supported diimines produced could form Ni(II) or Pd(II) complexes, and these were tested as potential olefin-polymerization catalysts.

Kurth and co-workers showed that sulfone carbanions can be utilized for alkylations in the SPOS of cyclobutylidenes.[180] The allylic sulfone in this synthesis was prepared by addition of SO_2 to lithiated polystyrene (to produce the lithium sulfinate) and followed by alkylation with the appropriate allylic bromide (Scheme 149). Addition of excess *n*-BuLi in

Scheme 149

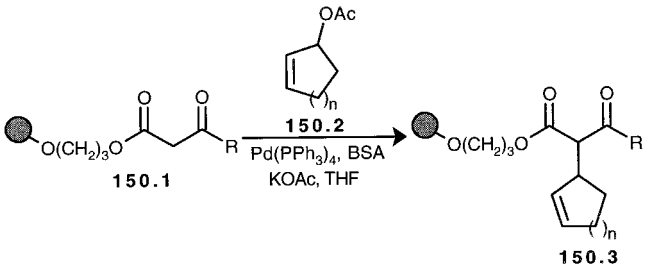


THF produced the dianion of **149.1**, which, upon addition of excess epichlorohydrin, underwent intermolecular alkylation followed by intramolecular alkylation (two carbon−carbon bonds formed) to produce cyclobutanol **149.2**. Alkylation or acylation of the alcohol was followed by S_N2' displacement of the sulfone linker with carbon nucleophiles (the sodium salts of 2-acetylcyclopentanone, diethyl methylmalonate, and ethyl cyanoacetate) catalyzed with $Pd(PPh_3)_4$. The traceless linker provided cyclobutylidene **149.3** in overall isolated yields of 30−38%. Solution-phase reactions using $Mo(CO)_6$ were also employed in the S_N2' displacement alkylation, but

yields were inferior to the Pd-mediated displacement and were not applied in the solid-phase synthesis.

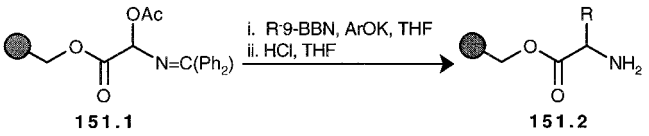
Tietze et al. also reported Pd-mediated displacement alkylations on the solid phase.[181] Hydroxymethyl polystyrene resin with a 1,3-propanediol tether was functionalized with 1,3-dicarbonyl compounds (Scheme 150), either as β-keto esters (R = alkyl) or β-diesters (R = *O*-alkyl). Treatment of 1,3-dicarbonyl **150.1** with allylic acetate **150.2** employing BSA, potassium acetate, and $Pd(PPh_3)_4$ in THF provided monoalkylated product **150.3**. Employing less hindered electrophiles such as allyl acetate provided only the respective dialkylated products. Allylic chlorides could be used in place of allylic acetates, and when allylic carbonates were used, the reaction proceeded without the use of base (BSA). DIBAL-H reduction cleaved the corresponding 1,3-diols in yields of 20−76%. In another carbon−carbon bond-forming reaction, the dianion of polymer-bound acetoacetate was also reported to be mono-*C*-alkylated with ethyl iodide.

Scheme 150



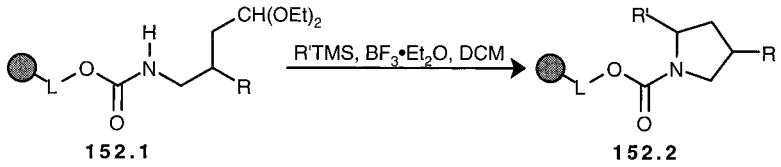
The resin-bound glycine anion shown earlier in Scheme 143 is also accompanied by its corresponding polymer-supported glycine cation.[182] Glycine bound to Wang resin (at the C terminus) was converted to the corresponding benzophenone imine, which was reacted with lead tetraacetate in DCM to give acetate **151.1** (Scheme 151). Alkylation with organoboranes (triethyl borane, 9-alkyl-9-BBN, or 9-aryl-9-BBN) was accomplished with potassium 2,6-di-*tert*-butyl-4-methylphenoxide (ArOK) in THF. Hydrolysis of the imine provides polymer-bound amino acid **151.2**, which could be further derivatized or cleaved from the resin.

Scheme 151



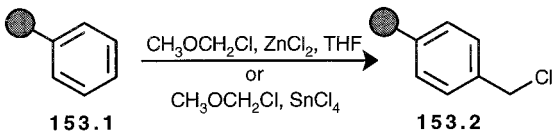
In the development of a novel carbamate linker for SPOS, the alkylation of its *N*-acyliminium ion has been described.[183] Various tethers were employed to connect this carbamate linker to the polystyrene resin and the linker that proved to be cleaved cleanly under basic condition was the 2-hydroxyethyl sulfone. The carbonate of this hydroxy-functionalized resin was generated with *p*-nitrophenyl chloroformate, and addition of 4,4-diethoxybutylamines produced the corresponding polymer-bound carbamates (Scheme 152). Cyclization of **152.1** was brought about with $BF_3{\cdot}Et_2O$ in DCM to provide the *N*-acyliminium ion in situ, and subsequent alkylation of the acyliminium ion proceeded in the presence of several trimethylsilyl nucleophiles (allyl, acetophenone silyl enol ether, and 2-(chloromethyl)allyl) to produce **152.2** (allenyltributyltin was also employed to introduce propargyl group).

Scheme 152



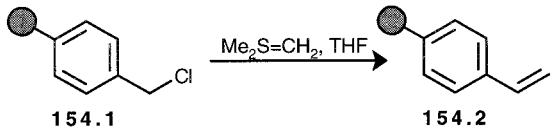
Chloromethylation of phenyl rings is important to the functionalization of resins and an alternative to employing functionalized monomer in the polymerization step. This alkylation is effective with chloromethyl methyl ether and either $ZnCl_2$[184] or $SnCl_4$ (Scheme 153).[185] These alkylations were both performed on novel solid-phase resins (polystyrene−tetraethyleneglycol diacrylate copolymer resin by Kumar and Pillai; macroporous resin by Janda group). Either Lewis acid converted unfunctionalized resin **153.1** to the corresponding Merrifield type resin **153.2**.

Scheme 153



One last example of alkylation is found in the synthesis of vinylpolystyrene resin from Merrifield resin.[186] Dimethylsulfonium methylide, produced from trimethylsulfonium iodide and *n*-BuLi, was reacted with Merrifield resin and LiI in THF (Scheme 154).

Scheme 154

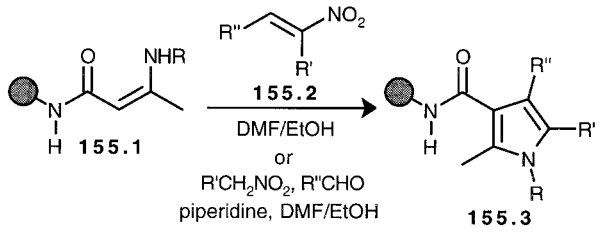


The alkylation and concomitant elimination effectively produced vinylpolystyrene (**154.2**). Subsequent hydroboration with 9-BBN followed by oxidative workup produced the homobenzylic alcohol. Esterification with 4-bromobenzoyl chloride gave the corresponding ester with a loading of 1.1 meq/g (Br elemental analysis) which compared well to 1.2 meq/g for the initial Merrifield resin.

VI. Michael Additions

The Michael addition of nucleophiles is very common in the solution phase—especially with nucleophilic amines. Carbon nucleophiles are not as common in the solution phase or the solid phase, but many examples are now being seen in SPOS. Vinylogous amides are one example of nucleophiles, and nitroalkenes are good Michael acceptors as shown in the synthesis of pyrroles.[187] Acetoacetylation of Rink resin provided a β-keto amide which was converted to the corresponding vinylogous amide with amines and TMOF (Scheme 155). Vinylogous amide **155.1**

Scheme 155

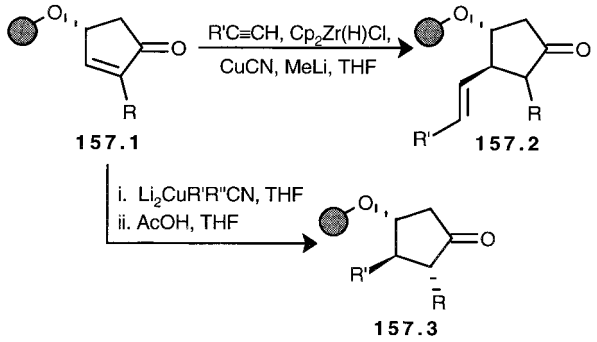


underwent Michael addition to nitroalkene **155.2** in DMF/EtOH (1:1) at 60 °C. A concomitant intramolecular Nef reaction formed pyrrole **155.3**. Alternatively, primary nitroalkanes and aldehydes could be successfully substituted for the nitroalkene in this reaction with the addition of piperidine and a temperature increase to 70 °C. Although the overall yields and purities were slightly better employing nitroalkenes vs the two components (46−90% and 86−96% vs 50−89% and 70−94%), the versatility of the two components provides an edge from a combinatorial perspective.

The synthesis of a Prostanoid libriary utilized the Michael addition on a soluble support.[188] The use of Ellman's linker was to attach the cyclopentenone through a chiral 4-hydroxy group via acetal formation (Scheme 156), and Michael addition to polymer-supported α,β-unsaturated ketone **156.1** was achieved by addition of alkenylcuprates, in turn produced from their alkynes (steps i−iv). The enolate formed from this addition was isolated as silyl enol ether **156.2** by addition of TMSCl. These enol ethers were converted back to enolates with methyllithium addition and alkylated with propargyl triflates which gave prostanoid libraries after cleavage with HF.

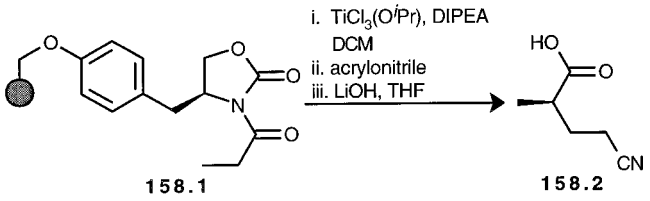
Thompson et al. also showed the utility of Michael additions in the SPOS of E and F series prostaglandins as displayed in Scheme 28 (Suzuki coupling).[41a] The hydroxycyclopentane core was attached to polystyrene by utilizing a diethyl or dibutyl silyl linker (Scheme 157). Next, the α position of the ring was substituted via the Suzuki coupling which produced cyclopentenone **157.1** after alcohol oxidation. Michael addition of vinyl cuprates (produced from alkynes with Cp_2ZrHCl, CuCN, and MeLi) gave **157.2**. Addition of higher order alkyl cuprates also effected conjugated addition to produce **157.3**. The silyl linker was cleaved with dilute HF in pyridine to give the alcohol.

Scheme 157



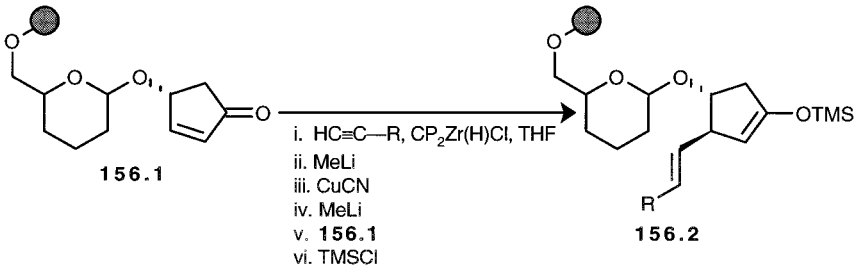
The enantioselective Michael addition of polymer-bound Evans oxazolidinone enolates has been demonstrated (enantiomeric aldol shown in Scheme 51).[67] The chiral oxazolidinone was synthesized from L-tyrosine and then, utilizing the phenol, attached to Merrifield resin (Scheme 158). Propionylation of the

Scheme 158

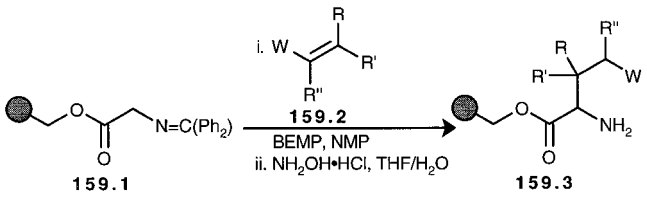


resin-bound oxazolidinone produced **158.1**, and the *N*-acyloxazolidinone was enolized with $TiCl_3(OiPr)$ and DIPEA in DCM; after removing excess reagents, the desired Michael addition took place with acrylonitrile. The product was cleaved from the resin with LiOH in THF to afford acid **158.2** in 52% crude yield. Amide formation of the acid with (*S*)-1-phenethylamine established a diastereomeric ratio of 89:11 as determined by ^1H NMR.

Scheme 156



Scheme 159

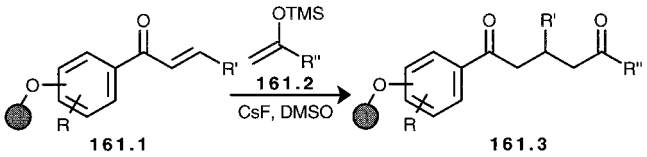


Domínguez and co-workers demonstrated the solid-phase synthesis of glutamic acid derivatives applying the Michael addition.[189] Fmoc-glycine was attached to Wang resin, deprotected, and the imine formed with benzophenone (Scheme 159). The enolate of iminoester **159.1** was obtained using BEMP in NMP, and this subsequently underwent conjugated addition with **159.2**. The imine was hydrolyzed with hydroxylamine hydrochloride to produce free amine **159.3**, which was acylated with quinaldic acid and cleaved from the resin with TFA. A total of 13 different Michael acceptors were utilized (61−88% yield and 70−97% purity). However, two Michael acceptors (3-phenylacrylonitrile and diethyl isopropylidenemalonate) were not effective in this solid-phase synthesis.

The chemistry of polymer-bound organozincates and cuprates has been examined, and reactions involving conjugated additions have been established.[190] 4-Iodobenzoic acid was attached to Merrifield resin with cesium carbonate in DMF (Scheme 160). Metal−halogen exchange of **160.1** with Li_2R_2-CuCN (R = methyl or trimethylsilylmethyl) or *t*-Bu_3-ZnLi proceeded to give the cuprate and zincate, respectively. The zincate was converted to the cuprate with lithium cyanothienylcuprate. Michael addition of these cuprates to 2-cyclohexenone occurred to give **160.2**, which was cleaved from the resin with sodium methoxide. Reported yields were 61% for the cuprate when generated from the zincate and 39% (R = trimethylsilylmethyl) and 10% (R = methyl) from the cuprate directly. It was also mentioned that aromatic zincates were employed for palladium cross-coupling reactions with iodobenzene, while aromatic and alkyl zincates were utilized in condensation and alkylation reactions.

The synthesis of 2,4,6-trisubstituted pyridines on the solid phase (Scheme 46) incorporated a carbon−carbon bond-forming Michael addition (Scheme 161).[62] The aldol reaction of acetophenones attached to Wang resin with aldehydes produced conjugated ketone **161.1**. This polymer-bound Michael acceptor was condensed with silyl enol ether **161.2** in the presence of CsF in DMSO to produce **161.3** and this δ-diketone was converted to the pyridine derivative with ammonium acetate in a solution of acetic acid and DMF, open to the air, at 100 °C.

Scheme 161



Another Michael addition from the adduct of the Baylis−Hillman reaction in Scheme 69 also underwent a similar Michael addition (Scheme 162).[88] The enolate of ethyl acetoacetate (**162.2**), produced with BEMP in THF, successfully underwent a conjugate addition with **162.1** to produce **162.3**. TFA-mediated cleavage afforded the corresponding acid in 80% purity and isolated yield of 75%.

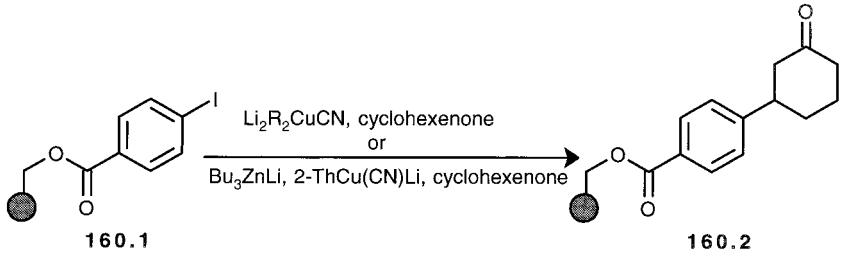
The domino reaction[191] shown by Gutke and Spitzner contains two sequential Michael additions in the SPOS of tricylco[3.2.1.0]octanes.[192] 1,3-Cyclohexanedione was attached to hydroxymethyl polystyrene to give the polymer-bound β-keto enol ether (Scheme 163). LDA was utilized to generate the kinetic enolate (**163.1** was obtained), and excess base was removed before addition of methyl 2-chloro-2-cyclopropylidenacetate. Michael addition of the enolate to **163.2** provided the first carbon−carbon connection and produces a new enolate as well as a β-alkoxy-α,β-unsaturated ketone. The second conjugated addition (an intramolecular solid-phase Michael) proceeded to give a third enolate, which underwent an intramolecular alkylation with the α-chloroester and formed the third carbon−carbon bond and produced **163.3**. Wittig reaction on the resulting ketone, utilizing the ylide produced from methyl triphenyl phosphonium bromide and *tert*-butoxide in THF, provided the fourth carbon−carbon bond and furnished alkene **163.4**.

VII. Olefination Reactions

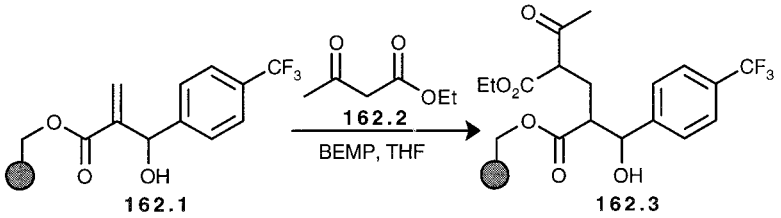
1. Wittig Reaction

The tetrahydroquinoxalin-2-ones synthesized on the solid phase were derivatized employing the Wittig olefination.[193] Coupling of 4-fluoro-3-nitrobenzoic acid to Wang resin was followed by nucleophilic aromatic substitution of the fluoride with an amine (Scheme 164). Reduction of the nitro group gave the polymer-bound diaminobenzoate, which was subsequently diacylated with chloroacetic anhydride to produce **164.2**. The addition of aldehydes with DIPEA and PBu_3 in NMP mediated the cyclization of the second-

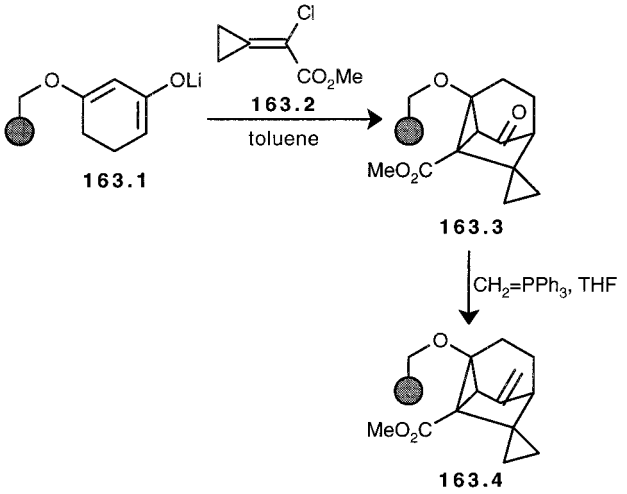
Scheme 160



Scheme 162



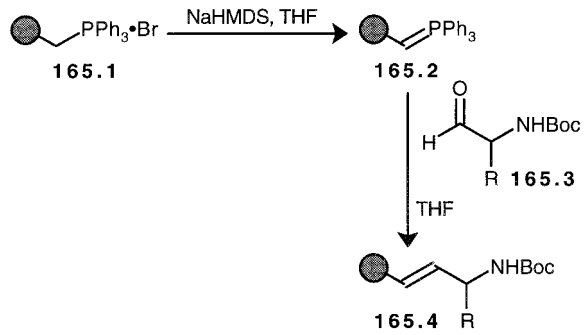
Scheme 163



ary amide with the alkyl chloride to form the tetrahydroquinoxalin-2-one. Phosphonium salt formation of the second (unreacted) alkyl chloride led to the phoshorous ylide, and subsequent Wittig reaction with the aldehyde produced **164.3**. There were four examples of **164.3** which were cleaved with TFA to give the free acid in 80−90% purity and isolated yields of 26−43% after recrystallization.

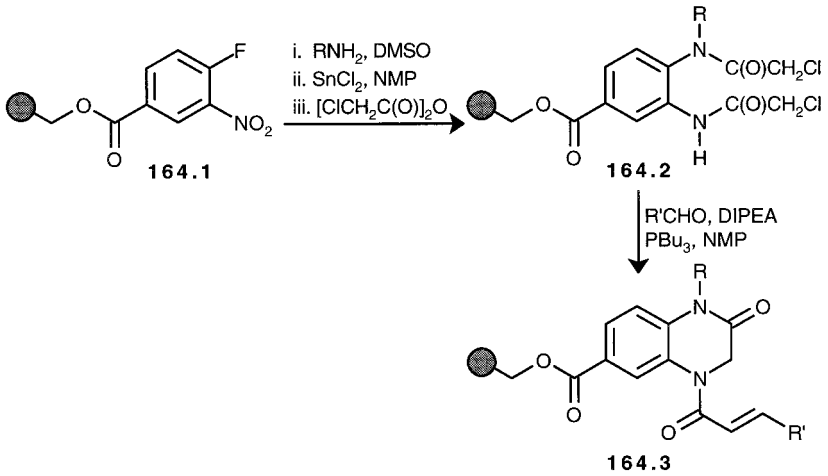
Application of an alkene linker produced via a Wittig reaction was used in the solid-phase synthesis of peptide aldehydes.[194] Hydroxymethyl polystyrene resin was converted to the bromomethyl derivative, which was transformed to the triphenylphosphonium bromide with triphenylphosphine in toluene (Scheme 165). Phosphonium salt **165.1** was converted to ylide **165.2** with NaHMDS in THF and condensed with N-protected amino aldehydes **165.3** to produce **165.4**. The Boc group was removed and the amine subsequently coupled with benzoic acid. Polymer-bound ozonolysis and reductive workup with DMS cleaved the alkene linker and produced the peptide bearing the desired aldehyde. The first example afforded the aldehyde monopeptide in 45% yield, and from this chemistry, a small library of 27 tripeptide aldehydes was prepared incorporating SPOS and SPPS.

Scheme 165

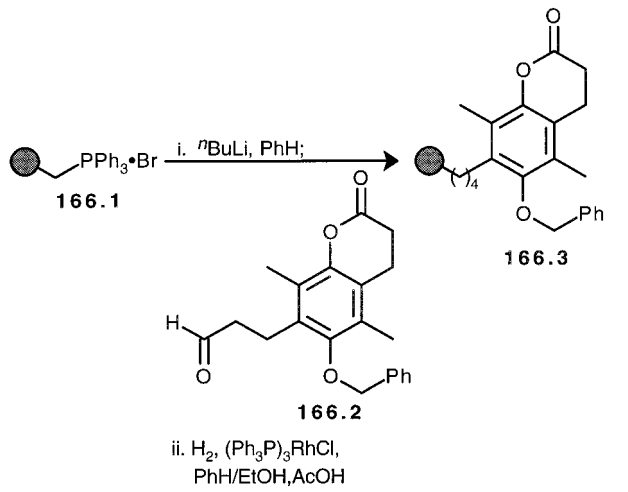


The synthesis of a novel linker for SPPS was prepared employing a similar Wittig olefination reaction.[195] The reaction began with the polystyrene-bound phosphonium salt of Merrifield resin (Scheme 166). In this case the ylide of **166.1** was formed with *n*-BuLi in benzene and subsequently condensed with aldehyde **166.2**, which was prepared in a multistep solution-phase synthesis. Hydrogenation of the resultant polymer-supported olefin was brought about with Wilkinson's catalyst to create saturated equivalent **166.3**, which was successfully converted to the corresponding quinone system with an ester attachment to the first amino acid. Two-step cleavage conditions of this novel linker called for reduction with $NaBH_4$ to give the dihydroquinone followed by treatment with TBAF to provide the free peptide.

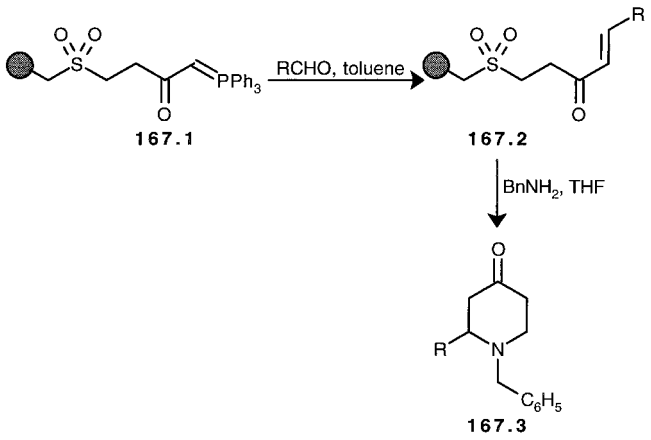
Scheme 164



Scheme 166



Scheme 167

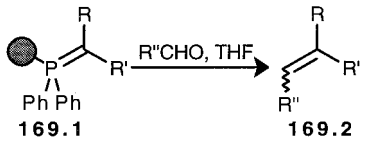


The solid-phase synthesis of piperidin-4-ones was accomplished by employing resin-bound 4-benzylsulfonyl-1-triphenylphosphoranyliene-2-butanone as the Wittig reagent.[196] Merrifield's resin was converted to the thiol (step 1 potassium thioacetate, step 2 $LiBH_4$), which underwent Michael addition to methyl vinyl ketone (Scheme 167). The sulfide was oxidized (MCPBA), and the methyl ketone was brominated (pyridinium bromide perbromide). Addition of triphenylphosphine produced the phosphonium salt, which was converted to ylide **167.1** with NaOH. This phosphorus ylide was reacted with various aldehydes in toluene to attain α,β-unsaturated ketone **167.2**. Michael addition of benzylamine was followed by elimination of the sulfone (traceless linker) to give a second α,β-unsaturated ketone. The ketone underwent an intramolecular Michael addition with the amine and generated **167.3**. The reaction occurred in 3 days at room temperature, and the product was isolated in 50−76% overall yield (5 examples).

Lew and Chamberlin reported the solid-phase synthesis of a library of potassium channel blockers for the human T cell Kv1.3.[197] Solution-phase synthesized 2-bromo-5-methyl(triphenylphosphonium bromide)benzoic acid was attached to polystyrene-based Kenner's acylsulfonamide safety-catch linker as modified by Ellman (Scheme 168). Polymer-bound phosphonium salt **168.1** was converted to the ylide with potassium *tert*-butoxide and subsequently reacted with aldehydes to provide **168.2**. Suzuki coupling provided another carbon−carbon bond-forming reaction and further diversified the library by combining polymer-bound aryl bromide **168.2** with aryl boronic acids employing Na_2CO_3 and $Pd(PPh_3)_4$ in DMF to give **168.3**. The safety-catch was activated by alkylation of the acylsulfonamide with bromoacetonitrile and subsequently cleaved with the addition of amines. A library of 400 compounds was prepared, and of these, 12 lead compounds had IC_{50} values less than 10 μM.

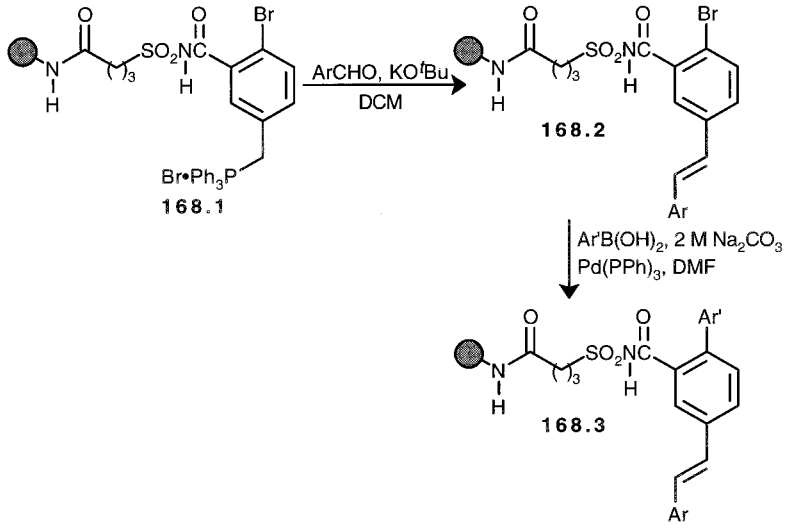
The synthesis of β-hydroxyamines employed a solid-phase Wittig reaction to provide the intermediate alkenes.[198] Polystyrene-bound triphenylphosphine was transformed to the polymer-supported phosphonium salt (Scheme 169). Treatment with NaHMDS

Scheme 169



created polymer-bound phosphorus ylide **169.1**. Wittig reaction with aldehydes proceeded to afford free

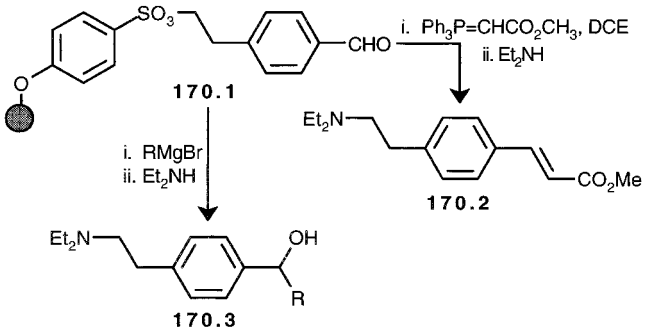
Scheme 168



trisubstituted alkene **169.2**. Reaction of the alkene with dimethyldioxirane provided the epoxide, which was subsequently opened with amines to afford β-hydroxyamines.

Arylsulfonate esters shown in Scheme 35 have also been used as linkers in the SPOS Wittig reaction (Scheme 170).[49] 2-(4-Formylphenyl)ethanol was re-

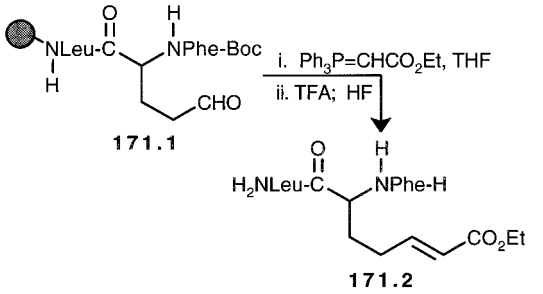
Scheme 170



acted with polymer-bound sulfonyl chloride to produce sulfonate ester **170.1**. This aldehyde was reacted with the phosphorus ylide ($Ph_3P{=}CHCO_2CH_3$) to provide the cinnamate and cleaved from the resin with diethylamine to afford **170.2**. The isolated yield was 60%, while the purity, by NMR, was 80%. Polymer-bound aldehyde **170.1** was reacted with Grignard reagents as an alternative way to form carbon−carbon bonds. Addition of phenyl- or methylmagnesium bromide to the aldehyde produced **170.3** after cleavage with diethylamine (42−50% yield and 90% purity).

Paris et al. showed the post-SPPS modification by SPOS of aspartyl or glutamyl groups on a MBHA resin.[199] The peptide synthesis was carried out employing Boc-protected amines where the acid side chains of the aspartic or glutamic acids were in Weinreb amide form (Scheme 171). After tripeptide

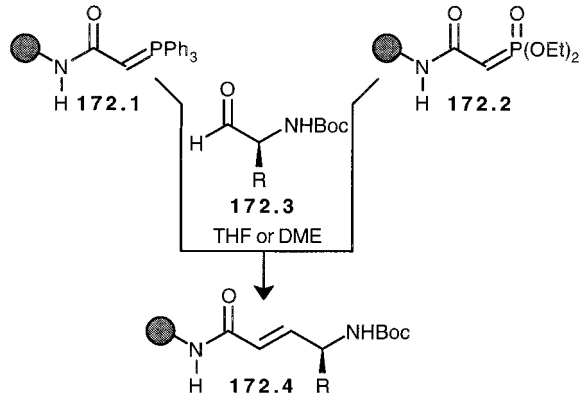
Scheme 171



synthesis, the Weinreb amide was reduced to aldehyde **171.1** with LAH or $LiAlH(Ot\text{-}Bu)_3$. This aldehyde was converted to α,β-unsaturated ester **171.2** with $Ph_3P{=}CHCO_2CH_3$. The final peptide was cleaved from the resin with TFA. Four other solid-phase tripeptides were carried through this same post-modification sequence with overall yields for the five examples being 57−90%.

Wittig and Horner−Emmons reactions were both employed in the solid-phase synthesis of peptide aldehydes.[200] The Wittig route began with the coupling of chloroacetic acid to amino-functionalized MBHA resin (Scheme 172). Reaction with triphenyl-

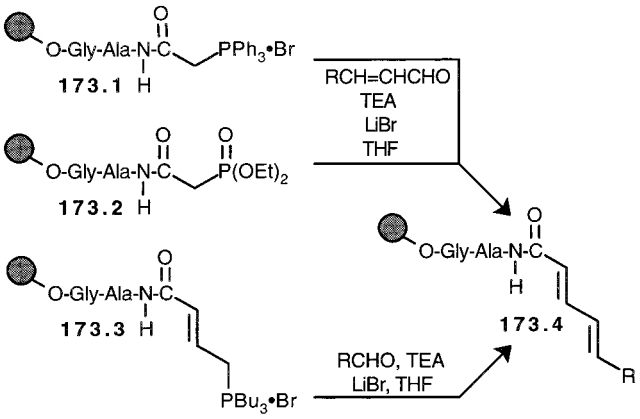
Scheme 172



phosphine followed by treatment with *n*-BuLi provided ylide **172.1**. Alternatively, diethyl phosphonoacetic acid coupled to the amine resin was converted to stabilized ylide **172.2** with DBU and $MgBr_2$. Olefination reactions of either of these ylides with Boc-protected amino aldehyde **172.3** in THF or DMF provided acrylamide **172.4**. SPPS was subsequently carried out to provide tripeptides which were cleaved by ozonolysis of the alkene. Yields and purities were reported along with amount of epimerization induced in the first amino acid residue by the olefination reaction.

The solid-phase synthesis of dienes shown in Scheme 4 employing Stille couplings have alternatively been prepared by Wittig and Horner−Wadsworth−Emmons reactions.[12] All methods tried were effective in the generation of the polymer-bound dienes (Scheme 173). Coupling of bromoacetic acid

Scheme 173

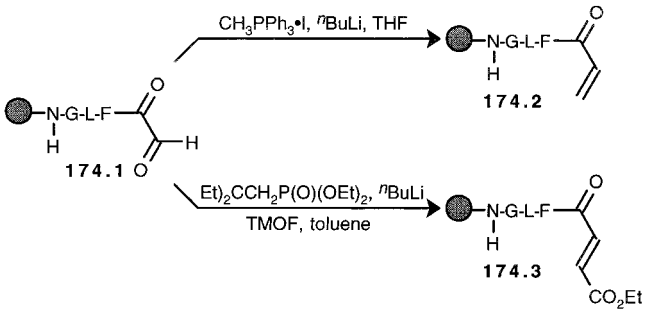


to MPEG-bound peptides followed by addition of triphenylphosphine provided **173.1**. Diethyl phosphonoacetic acid was coupled to the polymer-bound peptide to give **173.2**. Reaction of either of these ylide precursors with α,β-unsaturated aldehydes in the presence of TEA and LiBr in THF provided diene **173.4**. Alternatively, coupling of 4-bromocrotonic acid to the polymer-bound peptide followed by reaction with tributylphosphine produced **173.3**. Diene **173.4** was produced from the phosphonium salt employing aldehydes with TEA and LiBr.

A SPOCC (superpermeable organic combinatorial chemistry) resin was prepared and utilized with a Rink linker in a peptide synthesis.[201] SPPS produced

a tetrapeptide that was terminated with a serine residue (Scheme 174), which was converted to poly-

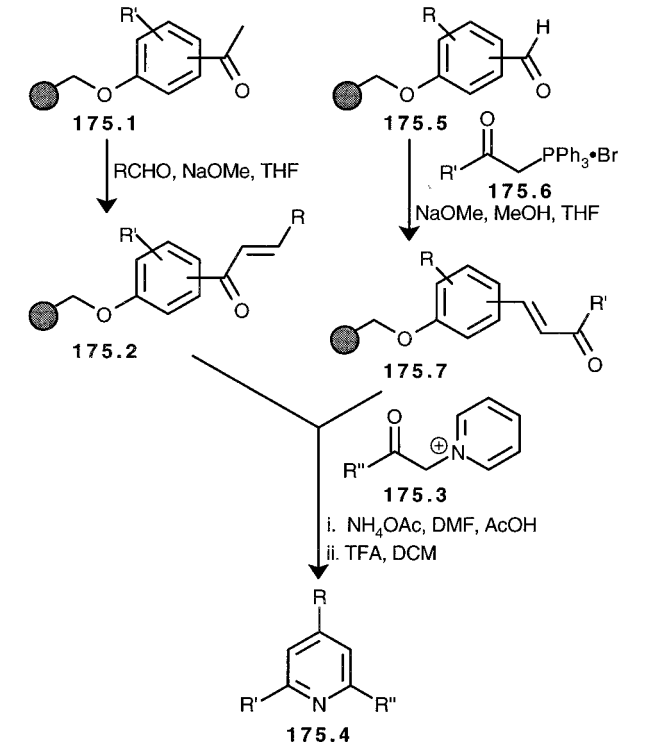
Scheme 174



mer-supported aldehyde **174.1** with periodate. Wittig reaction of the polymer-bound aldehyde with methyltriphenylphosphonium iodide and *n*-BuLi gave acrylamide **174.2**. Triethyl phosphonoacetate was reacted with *n*-BuLi and added to the polymer-bound aldehyde in a Horner−Wadsworth−Emmons reaction to provide **174.3**. These products were cleaved from the SPOCC−Rink resin with TFA.

The solid-phase synthesis of nitrogen-containing heterocycles embraces several pathways, one of which included the Wittig reaction and a second the aldol reaction.[202] In the aldol reaction, hydroxyacetophenones were attached to Wang resin, while in the Wittig reaction hydroxybenzaldehydes were coupled to the resin (Scheme 175). Aldol reaction of polymer-

Scheme 175

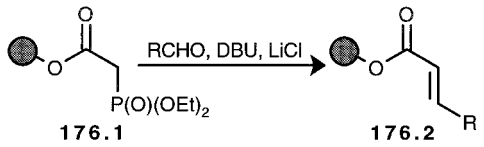


bound methyl ketone **175.1** with aldehydes employing NaOMe in THF provided α,β-unsaturated ketone **175.2**. Addition of β-keto pyridinium salt **175.3** to the enone with NH_4OAc in DMF/AcOH allowed for cyclization to the pyridine system. TFA-mediated cleavage from the Wang resin afforded pyridine **175.4**. Wittig reaction between polymer-bound aldehyde **175.5** and the ylide of phosphonium bromide **175.6** (generated with NaOMe in MeOH/THF) initiated the second pyridine pathway. This olefination reaction produced α,β-unsaturated ketone **175.7**, which was similarly reacted with the β-keto pyridinium salt (**175.3**) to furnish pyridine **175.4**. The Knoevenagel reaction was also employed in this study for the solid-phase synthesis of pyrazole derivatives.

2. Horner–Emmons Reaction

The Horner−Emmons reaction is also a valuable option for producing olefins on the solid phase. The stereoselective SPOS of 3,3-disubstituted acrylates shown previously in Scheme 14 were prepared by Heck coupling reaction of 3-substituted acrylates[24] and in turn generated from the Horner−Wadsworth-Emmons reaction. Diethylphosphonoacetic acid was coupled to mPEG 5000 support (Scheme 176), and

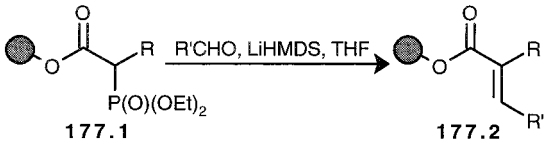
Scheme 176



olefination of diethylphosphonoacetate **176.1** with aldehydes was brought about with DBU and LiCl to provide acrylate **176.2** stereoselectively.

Salvino and co-workers also reported a solid-phase Horner−Emmons olefination reaction.[203] Three different diethylphosphonoacetic acids [R = −H, $-CH_2-CH_3$, and $-(CH_2)_3Ph$] were attached to Wang resin (Scheme 177), and olefination reaction of phospho-

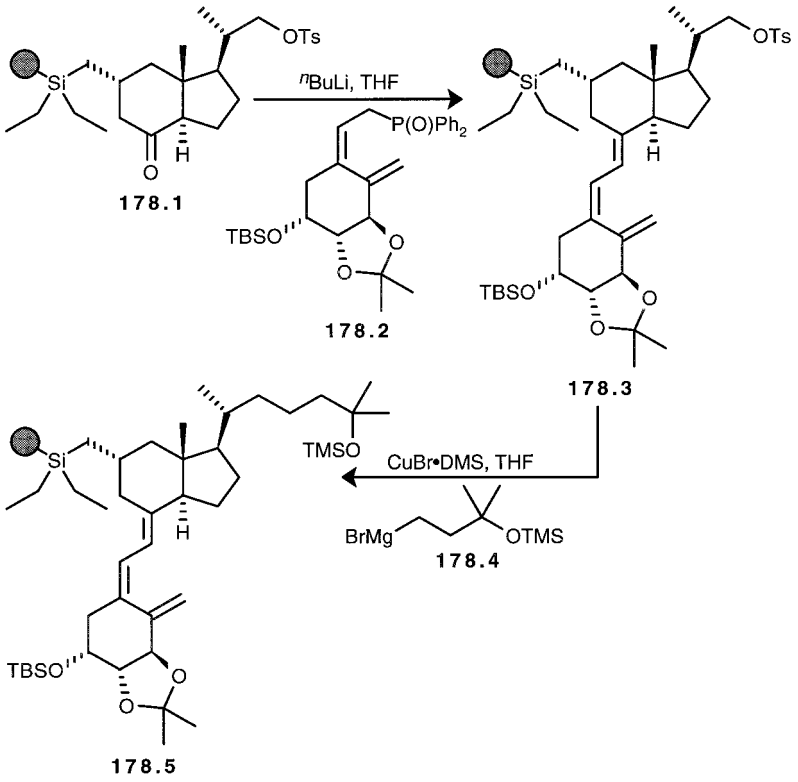
Scheme 177



nate **177.1** with aldehydes was achieved by applying LiHMDS in THF and furnished acrylate **177.2**. Cleavage of the Wang ester with TFA produced the acrylic acids in 67−95% yield as determined by gravimetric analysis and 48−97% purity for 48 examples. Crude aldehydes generated from a novel solid-phase Weinreb amide were also employed directly in this same type of Horner−Emmons reaction.[204] Six examples were reported with 31−82% yield and 89−99% HPLC purity.

The solid-phase synthesis of vitamin D_3 analogues utilized sequential olefination and cuprate addition.[205] The CD-ring system of vitamin D_3 was first attached to polystyrene resin (via β-hydroxy group) through a diethylsilyl linker (Scheme 178). The CD-ring system in **178.1** contains the ketone required for a Horner−Wittig reaction and also a pendant tosylate group for the alkylation reaction. After solution-phase synthesis of diene-containing phosphine oxide **178.2**, treatment with *n*-BuLi generated the ylide, which subsequently reacted with polymer-bound ketone **178.1** and provided triene **178.3**. Grignard reagent

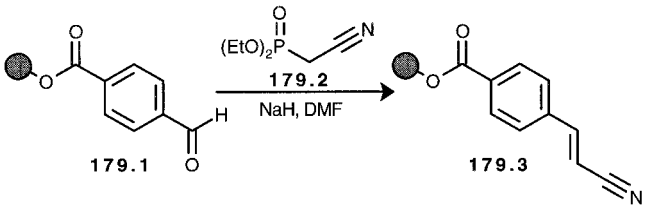
Scheme 178



178.4 was added to the polymer-supported tosylate with CuBr·DMS complex in THF and gave alkylated product **178.5**. Treatment with HF·Py deprotected the ketal and silyl groups as well as the silyl linker to afford the vitamin D_3 system in 62% overall yield from the initially loaded ketone.

The Horner−Emmons reaction on the solid phase has also been employed to generate α,β-unsaturated nitriles as intermediates in the synthesis of 3-amino-2-pyrazolines.[206] The polymer-bound aldehyde for the olefination reaction was obtained by coupling (HBTU and DIPEA in DMF) of 4-formylbenzoic acid to amino-functionalized Rink resin (Scheme 179). The

Scheme 179

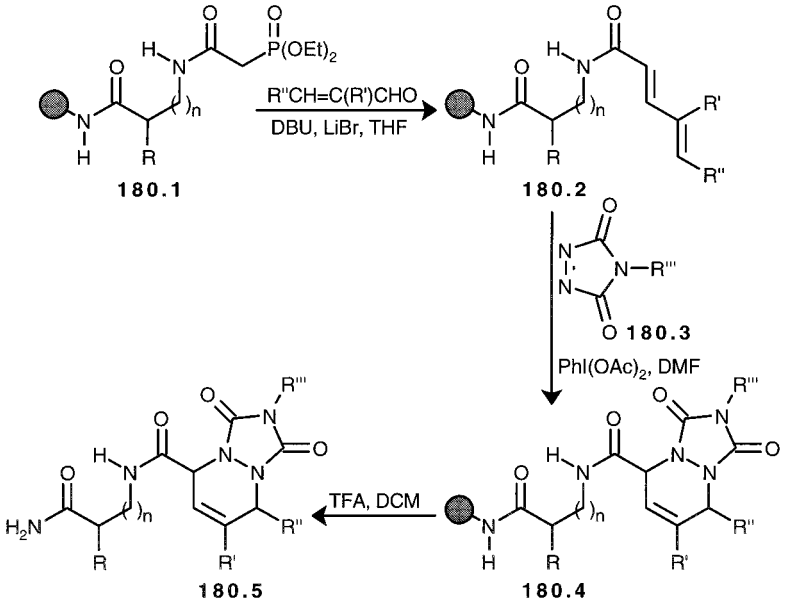


aldehyde (**179.1**) was reacted with the stabilized ylide generated from diethyl cyanomethylphosphonate (**179.2**) and NaH in DMF to produce polymer-bound α,β-unsaturated nitrile **179.3**. Reaction of the unsaturated nitrile with various hydrazines produced 3-amino-2-pyrazolines, which were cleaved from the resin with TFA. The 3-amino group was also acylated or sulfonated prior to cleavage to provide a more diverse library of pyrazolines. The solid-phase synthesis of 24 potential antiinflammatories possessed yields of 27−95%.

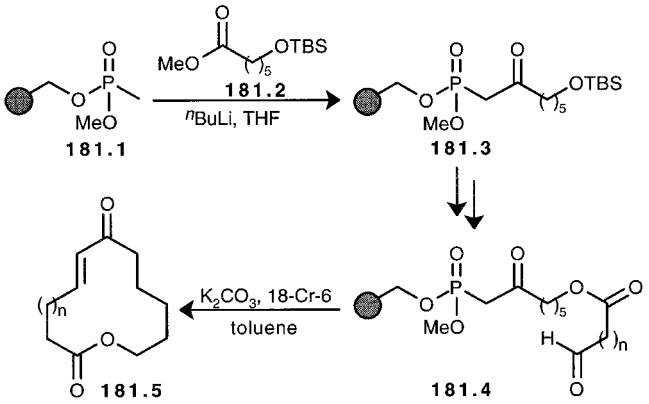
α,β-Unsaturated aldehydes have been employed in the Horner−Emmons olefination reaction to generate polymer-supported dienes, which were further utilized in solid-phase hetero-Diels−Alder reactions.[207] Boldi and co-workers implemented this chemistry for the solid-phase synthesis of triazolopyridazines. Amino-functionalized Rink resin was coupled with Fmoc-protected α- and β-amino acids (Scheme 180). Deprotection followed by coupling of the amine with diethylphosphonoacetic acid gave **180.1**. α,β-Unsaturated aldehydes were added to the phosphonate with DBU and LiBr in THF to give diene **180.2**, which was reacted with urazines (generated from oxidation of urazole **180.3** with iodobenzene diacetate) in a [4+2] cycloaddition to give polymer-bound triazolopyridazine **180.4**. Cleavage from the resin with TFA in DCM afforded **180.5**. Unsubstituted urazines (R‴ = H) were also employed but required replacing DMF with dioxane. There were 10 derivatives reported with 24−82% yield and 40−93% purity.

Nicolaou et al. successfully applied the phosphonate group as a traceless linker in SPOS.[208] The Horner−Emmons reaction in this case occurred with concomitant cycloelimination (Scheme 181). Merrifield resin was alkylated with 1,4-butandiol, and the resulting alcohol was phosphonated to provide **181.1**. The phosphorus ylide, produced with addition of *n*-BuLi, underwent alkylation with methyl ester **181.2** to form a carbon−carbon bond and yielding **181.3**. Several steps in the polymer-supported synthesis followed (deprotection, acylation, deprotection, and oxidation) to provide aldehyde-containing β-ketophosphonate **181.4**. The addition of potassium carbonate and 18-crown-6 to the resin in toluene effected the olefination and furnished macrocyclic lactone **181.5** containing an endocyclic α,β-unsaturated ketone. The 18- (n = 7) and 20-membered (n =

Scheme 180



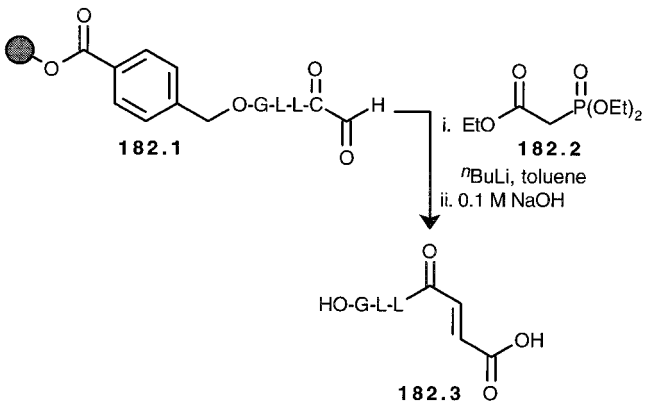
Scheme 181



9) macrocylces were obtained in 58% and 62% yield, and both were ≥90% pure by ^{1}H NMR.

N-Terminal peptide aldehydes, used previously as reactants for carbon−carbon bond-forming reactions (Schemes 48 and 95), have also been employed in the Horner−Wadsworth−Emmons reaction.[64] SPPS was utilized to synthesize a tetramer in which the last residue was serine (Scheme 182). Oxidative cleavage of the serine with $NaIO_4$ produced polymer-supported aldehyde **182.1**, which was treated with the phosphorus ylide generated by the reaction of triethylphosphonoacetate (**182.2**) with *n*-BuLi in toluene. Cleavage from the POEPOP resin was accomplished by ester saponification with 0.1 M NaOH to afford diacid **182.3** in 64% yield.

Scheme 182

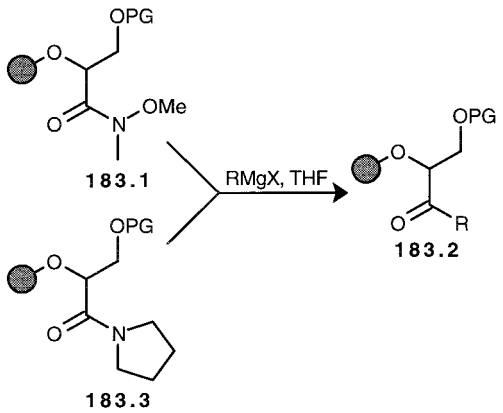


VIII. Organometallic Reactions

1. Grignard Reactions

Grignard addition to carbon electrophiles (esters, amides, aldehydes, etc.) is one of the most utilized types of solid-phase organometallic reactions. Either the carbon nucleophile or the carbon electrophile have been attached to the polymer support. Ellman and co-workers employed a Grignard reaction in the solid-phase synthesis of aspartyl protease inhibitors.[209] The first task was to examine the well-known Weinreb amide as the Wang resin-bound electrophile (Scheme 183). Addition of Grignard reagents in THF

Scheme 183

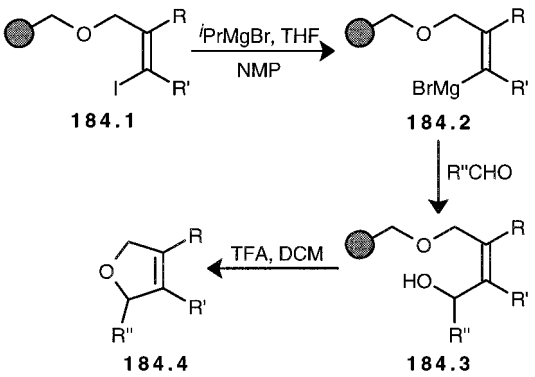


to Weinreb amide **183.1** did bring about the desired transformation and provided **183.2**. However, one minor side reaction was N−O bond cleavage with the corresponding *N*-methyl amide being formed (7−18%). Replacement of Weinreb amide with pyrroli-

dine amide **183.3** solved this problem. It was noted that racemization of the chiral α-alkoxy carbon was <2% under these conditions. Excess Grignard reagent was found to be easily quenched by the addition of acetone, and the desired aspartyl protease inhibitor was obtained in 68% overall yield (eight steps). Grignard addition to polymer-bound Weinreb amides was also shown in combination with the Ugi multiple-component condensation depicted in Scheme 87.

There are far fewer examples of polymer-bound Grignard reagents, but Rottländer and Knochel explored this area in the synthesis of 2,5-dihydrofurans and 1,3-dihydroisobenzofurans.[210] Starting with trichloroacetimidate Wang resin, aryl or alkenyl iodides were attached through tethered hydroxyl functionalities (Scheme 184). Iodine−magnesium

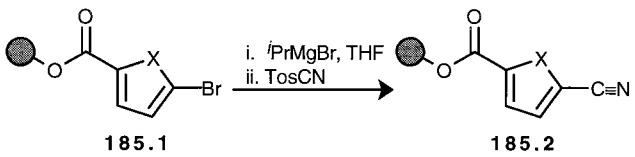
Scheme 184



exchange of iodide **184.1** with *i*-PrMgBr in THF/NMP (40:1) delivered **184.2**. Reaction of the polymer-supported Grignard reagent with aldehydes produced alcohol **184.3**. Cleavage from Wang resin with TFA also caused cyclization and produced desired dihydrofurans **184.4** (20 examples, crude yield = 55−95%, HPLC purity = 81−99%) and isobenzofurans (10 examples, crude yield = 69−98%, HPLC purity = 92−99%).

This chemistry was compatible with heteroaryl halides as precursors to the Grignard reagents.[211] These aryl bromides and iodides (3- or 4-iodobenzoic acid or 5-bromofuroic or thienoic acid) were attached to Wang resin through an ester linkage (Scheme 185).

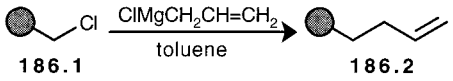
Scheme 185



Halogen−magnesium exchange reaction of **185.1** followed employing *i*-PrMgBr in THF. The polymer-supported Grignard reagent was reacted with different electrophiles such as tosyl cyanide to give **185.2**. Cuprates were generated from the polymer-bound magnesium bromides and reacted with allylic bromides.

The Grignard reaction was used in the synthesis of polymer-bound alkylsilanes for use as novel linkers.[212] Merrifield resin was selected for this synthesis, and the benzyl chloride moiety present in this resin was the electrophile for the Grignard reagent (Scheme 186) (allylmagnesium chloride in toluene at 60 °C)

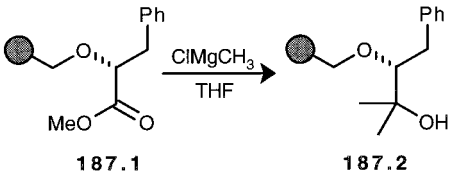
Scheme 186



to give polymer-supported alkene **186.2**. This alkene was subsequently hydrosilylated with dialkylsilanes, and the resulting trialkylsilane was chlorinated with 1,2-dichloro-5,5-dimethylhydantoin. The polymer-supported trialkylsilyl chloride could be linked to alcohols, aromatics, heteroaromatics, allyls, or alkynes. This novel silyl linker is cleaved with TFA, TBAF, or HF.

p-Alkoxybenzyl ethers linkers (Wang or PEG-HMP), which have been used in the Heck reaction (Scheme 12) and enolate alkylation (Scheme 146), have also been employed to make carbon−carbon bonds with Grignard reactions.[23] In this case, methyl 2-(*R*)-hydroxy-3-phenylbutyrate was attached to the resin through the hydroxy group (Scheme 187). This

Scheme 187

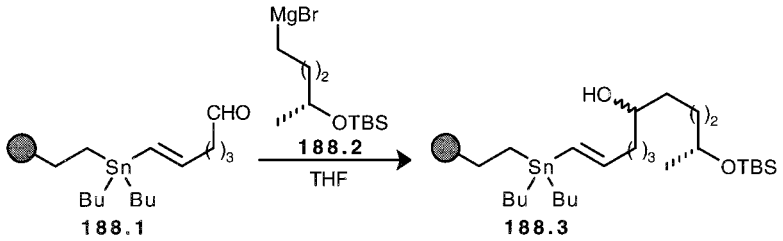


polymer-bound methyl ester **187.1** was reacted with methylmagnesium chloride to produce alcohol **187.2** after Grignard additions. Cleavage with 10% TFA in DCM provided the chiral diol in 70% overall yield. No racemization was detected under these conditions.

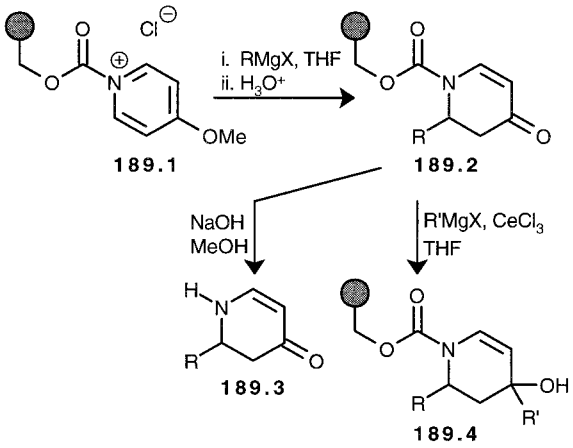
Nicolaou et al. applied a solid-phase Grignard reaction in the synthesis of (*S*)-zearalenone.[20] Polymer-supported tin chloride was prepared and reacted with an alkenyllithium containing a tethered TBS-protected alcohol (Scheme 188). The resulting alkenyl stannane was TBS deprotected and subsequently oxidized to give polymer-bound aldehyde **188.1**. Chiral TBS-protected Grignard reagent **188.2** was added to the aldehyde to give both diastereomers of **188.3**, which were oxidized to give the corresponding ketone. TBS deprotection gave the alcohol, which was subsequently coupled with 2,4-di(methoxyethoxymethyoxy)-6-iodobenzoic acid to provide the precursor to the Stille cycloelimination step shown in Scheme 11.

Resin activation/capture approach (REACAP) technology (Munoz and co-workers) allows for the first reactant to form a reactive intermediate with the linker (activation), which will only remain attached if the second reagent subsequently reacts (capture).[213] In this work hydroxymethyl polystyrene was converted to the chloroformate and reacted with 4-methoxypyridine (Scheme 189). Reactive intermediate **189.1** was reacted with Grignard reagents in THF to form a carbon bond with C2 of the pyridine system. Acid hydrolysis of the enol ether gave polymer-bound dihydropyridone **189.2**. Any intermediate not reacted with the Grignard reagent was hydrolyzed to the

Scheme 188



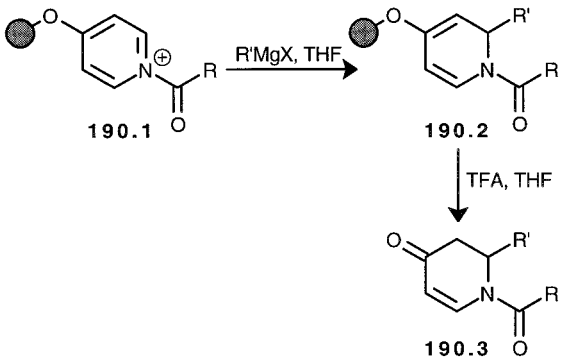
Scheme 189



starting hydroxymethyl polystyrene resin. Cleavage from the resin with NaOH afforded the desired dihydropyridone **189.3**. This same REACAP technology was used in the synthesis of 2,4-disubstituted pyridines and tetrahydropyridines.[214] Reaction of **189.2** with a second Grignard reagent in the presence of $CeCl_3$ provided **189.4**, and cleavage of this product with TFA produced the corresponding 2,4-disubstituted pyridines under oxidative conditions (O_2 or air) or the 2,4-disubstituted tetrahydropyridines under reductive conditions (triethylsilane).

The Grignard reaction was also applied in the SPOS of *N*-acyl-2-substituted-dihydro-4-pyridones with REACAP technology.[215] 4-Hydroxypyridine was coupled to hydroxymethyl polystyrene under Mitsunobu conditions (Scheme 190), and the resultant

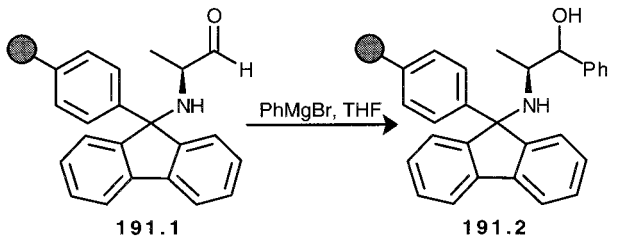
Scheme 190



supported pyridine was reacted with acid chlorides to provide reactive intermediate **190.1**. Subsequent reaction with Grignard reagents provided **190.2**, which were cleaved with TFA to give 18 examples of **190.3** in 19−62% yield and purity levels of 75−99%. Any reactive intermediate (**190.1**) that did not undergo Grignard addition was cleaved to the corresponding acid and polymer-bound pyridine precursor. The synthesis of 2-azabicyclo[2.2.2]octane and triaza derivatives also applied this chemistry to **190.2** and utilized it in the Diels−Alder reaction as shown in Scheme 125.

The solid-phase reaction of Grignard reagent with aldehydes was examined in the study of α-[*N*-(phenylfluorenyl)]amino carbonyl compounds.[40] This polymer-supported synthesis of norephedrines included the use of Suzuki coupling (Scheme 27). Reduction of the polymer-bound isoxazolidide (produced from the Suzuki coupling) with LAH provided the aldehyde (**191.1**; Scheme 191), and subsequent addition of

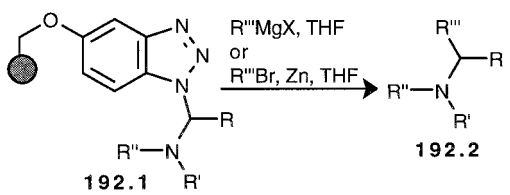
Scheme 191



phenylmagnesium bromide furnished polymer-bound amino alcohol **191.2**. Cleavage of the 9-phenylfluoren-9-yl linker with TFA/DCM/anisole (1:2:2) afforded Boc-protected norephedrine after treatment with di-*tert*-butyl dicarbonate. It was noted that an isolated yield of 60% of the Boc-protected norephedrine contained a 3:1 ratio of diastereomers. Solution-phase results reported a yield of 66% but a 1:1 mixture of diastereomers.

Katritzky et al. reported the use of polymer-supported benzotriazoles as useful scaffolds in SPOS.[216] 3,4-Diaminophenol was attached to Merrifield resin directly or 4-amino-3-nitrophenol was attached and reduced with $SnCl_2$. Reaction of the diamine with isoamyl nitrite in the presence of AcOH and HCl in dioxane delivered the polymer-bound benzotriazole (Scheme 192), and subsequent Mannich

Scheme 192

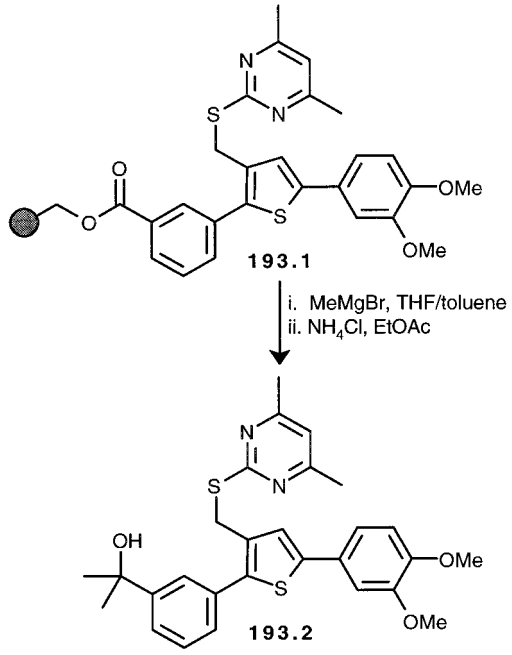


reaction with aldehydes and amines produced Mannich base **192.1**. Application of Grignard reagents resulted in displacement of the triazole and cleavage

from the resin to afford amine **192.2**. Furthermore, organozinc reagents, formed from alkyl bromides and zinc, reacted similarly. Combinatorial libraries of complex amines have been synthesized applying similar solid-phase benzotriazole chemistry where the carbon−carbon bond formation occurred with Grignard-mediated cleavage.[217] In this case, hydride was also used as the nucleophile.

Grignard reagents have been employed in other cleavage reactions-such as in the SPOS of the substituted thiophenes previously shown in a Suzuki coupling reaction (Scheme 32).[46] After several synthetic steps (including Suzuki couplings), the desired PDE-4 inhibitor was obtained on the resin (Scheme 193). The ester linker of benzoate **193.1** was cleaved

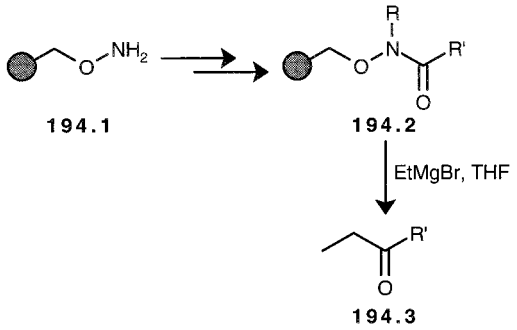
Scheme 193



with methylmagnesium bromide to afford tertiary alcohol **193.2** after workup with ammonium chloride in ethyl acetate.

In the solid-phase synthesis of ketones, the products were cleaved from the support via Grignard addition to the Weinreb amide linker.[203] Wang *O*-hydroxylamine resin was prepared by coupling of *N*-hydroxyphthalimide to the polymer followed by hydrolysis of the phthalimide with methylamine (Scheme 194). Polymer-bound hydroxylamine **194.1** was converted to the Weinreb amide by acylation.

Scheme 194

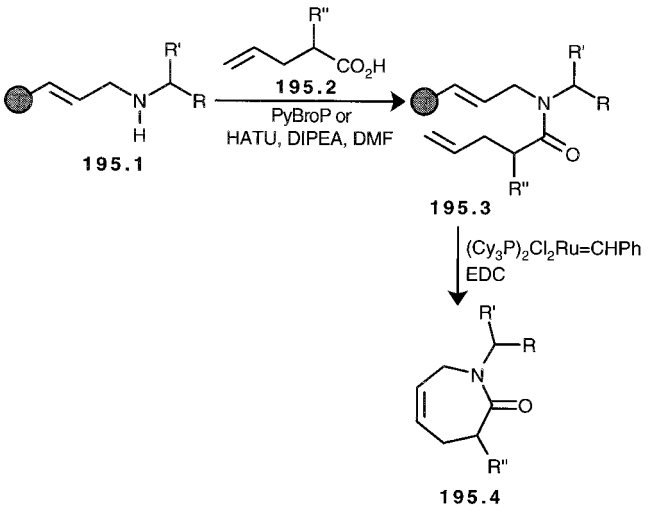


Alkylation of the amide with an alkyl halide was brought about with DBU to give amide **194.2**, and cleavage of this amide with ethylmagnesium bromide provided ethyl ketone **194.3** (23% and 68% yield, 97% and 78% purity).

2. Metathesis Reaction

Olefin metathesis reactions such as ring-closing metathesis[218] (RCM) and ring-opening metathesis (ROM) have been shown in SPOS. The solid-phase synthesis of Freidinger lactams employed RCM for the cycloelimination step.[219] Polymer-bound cinnamyl alcohol was obtained from polymer-supported benzaldehyde (Scheme 195).[220] Alkylation of 2,4-dinitro-

Scheme 195

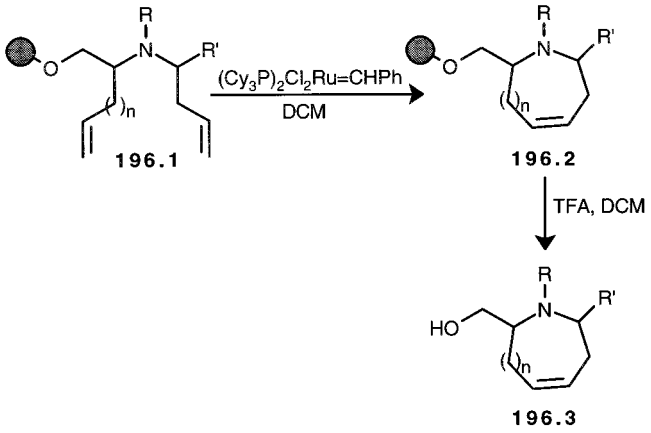


benzenesulfonamide under Mitsunobu conditions was followed by Fukuyama−Mitsunobu reaction with primary or secondary alcohols to deliver allylic amine **195.1** after cleaving of the arylsulfonamide. Coupling of this amine with substituted 4-pentenoic acids (**195.2**) and DIPEA in DMF occurred equally well with PyBroP or HATU. This gave polymer-bound diene **195.3**, which was cleaved from the resin with $(Cy_3P)_2Cl_2Ru{=}CHPh$ in EDC. This cycloelimination afforded Freidinger lactam **195.4** in 15−36% overall yield for 10 entries. Similar Freidinger lactams were synthesized employing RCM cycloelimination on intermediates prepared via the Ugi multiple-component condensation reaction (Scheme 86).[106]

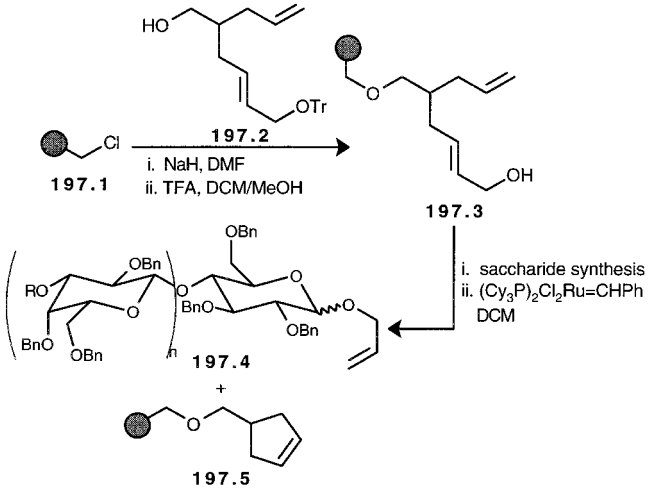
Solid-phase synthesis of various azacycles have also employed a RCM reaction without the cycloelimination strategy.[123] Preparation of the chlorotrityl-bound diene involved carbon−carbon bond formation between alkyllithiums and imines, already shown in Scheme 102. The dialkenylamine (**196.1**) shown in Scheme 196 was cyclized with Grubbs ruthenium catalyst $[(Cy_3P)_2Cl_2Ru{=}CHPh]$ in DCM to provide six- to eight-member azacycle **196.2** (n = 0−2). Utilizing 8−15% ruthenium catalyst provided 85−89% yield for the ring-closing metathesis step. These final azacycles were cleaved from the solid support with TFA in DCM to yield amino alcohol **196.3**.

The solid-phase synthesis of oligosaccharides utilized a novel diene linker that allowed for cleavage from the support employing RCM.[221] The solid-phase

Scheme 196



Scheme 197

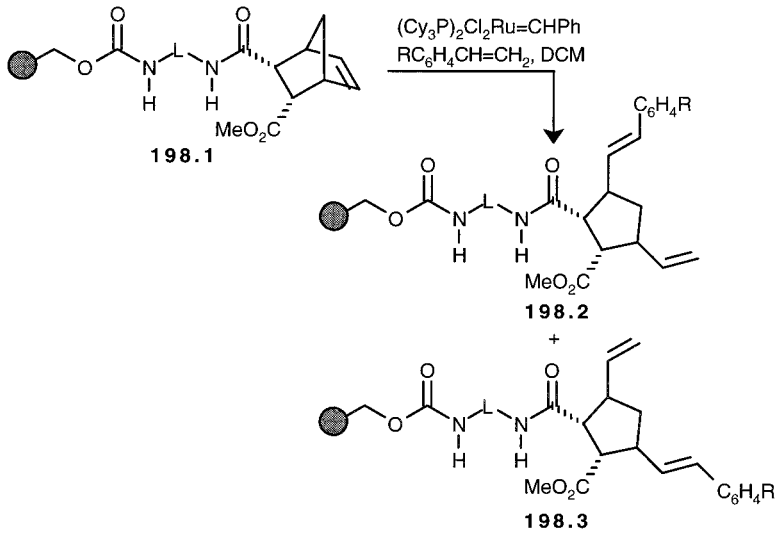


synthesis commenced with the incorporation of the linker to the support (Scheme 197). Alkylation of Merrifield resin with dienol **197.2** followed by deprotection (TFA) of the trityl alcohol provided **197.3**. The latent hydroxy moiety was the attachment point for the saccharides, and synthesis (solid-phase saccharide synthesis) could be carried out to form oligosaccharides. Completion of the solid-phase synthesis was followed by cleavage of the product from the resin with Grubbs catalyst in DCM. The ring-closing metathesis reaction produced allyl-protected oligosaccharide **197.4** and polymer-bound cyclopentene **197.5**. One disaccharide was attached and cleaved in 82% yield, while attachment of a disaccharide followed by coupling a second disaccharide produced a tetrasaccharide upon RCM cleavage in 51% overall yield.

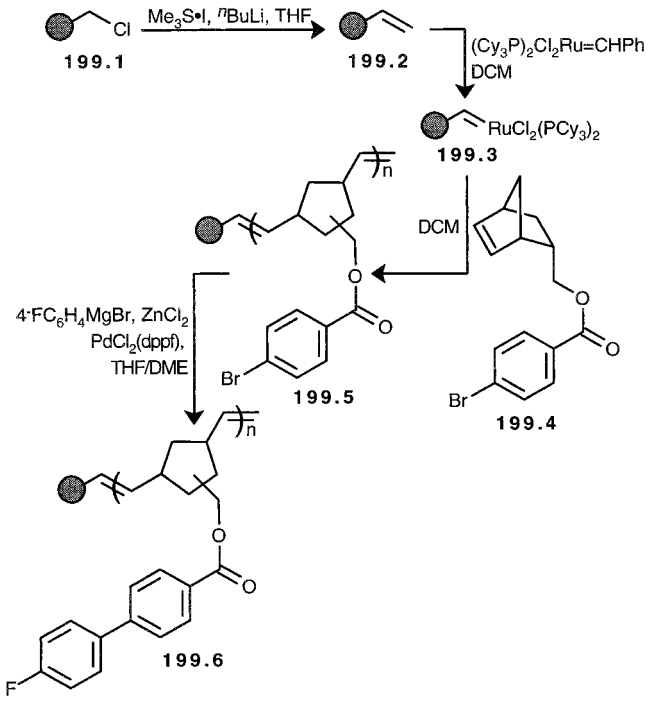
Ring-opening metathesis (ROM) in SPOS has been applied to the synthesis of tetrasubstituted cyclopentanes from polymer-bound bicyclic alkenes.[222] Wang resin was converted to the carbamate with 1,1′-carbonyldiimidazole followed by addition of diamines with different aliphatic and aromatic spacers "L" (Scheme 198). The terminal amine was coupled with *mono*-methyl *cis*-5-norbornene-*endo*-2,3-dicarboxylate employing PyBOP in NMM to give **198.1**. ROM with Grubbs catalyst in the presence of substituted styrenes produced a mixture of both cyclopentane regioisomers **198.2** and **198.3**. It was noted that the methyl ester could be hydrolyzed and subsequently coupled with the amide to provide the succinimide and eliminate the regioisomers. A library of 4608 compounds was prepared after the ester was converted to an amide and the carbamate was cleaved with TFA.

High-loading ROMP-spheres were produced by Barrett and co-workers employing ROM.[223] The first carbon−carbon bond formation prepared the requisite vinyl polystyrene from Merrifield resin (Scheme 199). Reaction of vinyl polystyrene **199.2** with Grubbs catalyst [$(Cy_3P)_2Cl_2Ru{=}CHPh$] in DCM lead to polymer-supported Grubbs catalyst **199.3**. The immobilized ruthenium catalyst was reacted with 5-norbornen-2-ylmethyl 4-bromobenzoate (**199.4**) in a living polymerization to give solid-supported polymer **199.5** after quenching the reaction with ethyl vinyl ether. Loading of these novel ROMP-spheres ranged from 2.5 to 3 mmol g^{-1} (by weight increase) compared with initial loading of vinyl polystyrene of 0.8 mmol g^{-1}. The swelling properties of these beads were examined in several solvents, and a graph was given indicating volume changes. One carbon−carbon bond-forming reaction on these novel polymers was the zinc- and palladium-catalyzed coupling of 4-fluorophenylmag-

Scheme 198



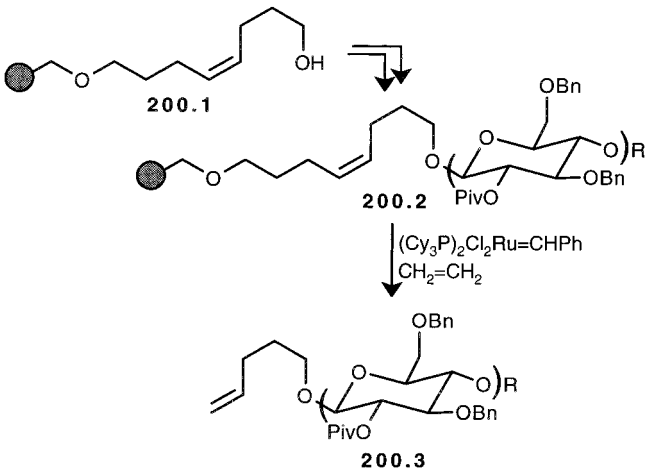
Scheme 199



nesium bromide to the polymer-support aryl bromide to give **199.6**. ROM with Grubbs catalyst was extended to make block copolymers by addition of 5-norbornen-2-ylmethyl 4-nitrobenzoate after the initial polymerization but before termination with ethyl vinyl ether. Polymer-supported Grubbs catalyst **199.3** was also prepared for use in solution-phase RCM.[224]

Another synthesis of oligosaccharides on the solid phase employed an alkene linker in an olefin cross-metathesis cleavage strategy.[225] Mono-DMT-protected 4-octene-1,8-diol was attached to Merrifield resin (Scheme 200). Deprotection with dichloroacetic acid

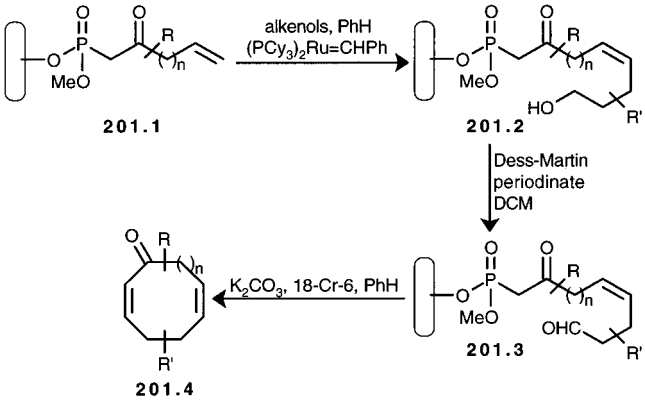
Scheme 200



gave polymer-bound alkenol **200.1** and allowed for loading determination via release of the DMT moiety. Attachment of the monosaccharide preceded the SPSS to furnish **200.2**. Solid-phase glycosation reactions were examined with glycosyl phosphates, thioglycosides, and glycosyl trichloroacetimidates. The alkene linker was cleaved employing Grubbs catalyst under an ethylene atmosphere to afford alkene **200.3**.

SMART microreactors were utilized in the synthesis of a combinatorial muscone library.[208] The Mikrokans were functionalized with methyl phosphonate, which was deprotonated with *n*-BuLi and alkylated with esters as in Scheme 181. However, in this case, the ester contained a terminal alkene (Scheme 201).

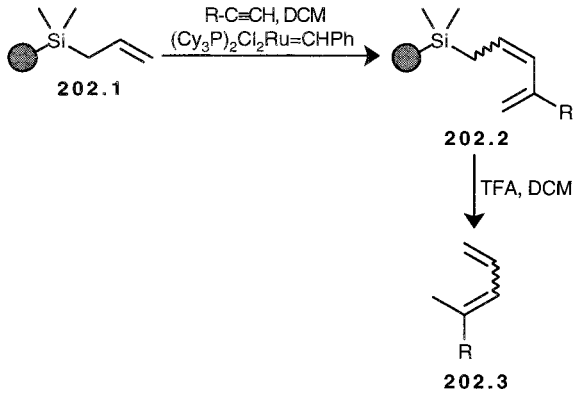
Scheme 201



Polymer-supported alkene **201.1** was coupled with alkenols in an olefin cross-metathesis utilizing Grubbs catalyst in benzene to generate **201.2**. The resulting polymer-bound primary alcohol was oxidized (Dess–Martin) to aldehyde **201.3**, and Horner–Emmons reaction (K_2CO_3 and 18-crown-6 in benzene) provided cycloelimination and gave α,β-unsaturated ketone **201.4**. Conjugate addition of cuprates in solution phase converted **201.4** to the saturated ketone and was followed by hydrogenation to remove the other carbon–carbon double bond.

Schuster and Blechert described the solid-phase cross-metathesis of alkynes with alkenes (ene–yne metathesis).[226] Allyldimethylsilyl polystyrene was chosen as the linker, providing a terminal alkene for the metathesis reaction (Scheme 202). Reaction of

Scheme 202

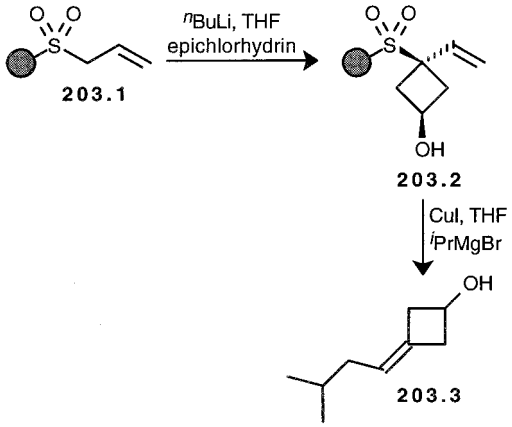


this alkene with terminal alkynes applying Grubbs catalyst [$(Cy_3P)_2Cl_2Ru$=CHPh] supplied polymer-supported diene **202.2**. The silyl linker could be cleaved with 1.5% TFA in DCM to afford 1,3-diene **202.3** with cleavage yields ranging from 0.35 mmol/g to 0.55 mmol/g for six examples.

3. Miscellaneous Organometallic Reactions

Miscellaneous organometallic reactions cover all other solid-phase carbon−carbon bond-forming metal-containing reactions. The large majority of these are based on cuprate additions. Novel metalating reagents such as organocuprates and organozincates shown by Kondo et al. (Scheme 160) possess good chemoselectivity.[190] Kurth and co-workers employed a cuprate addition in the synthesis of cyclobutylidenes.[180] In this work, lithiated polystyrene was converted to the polymer-bound sulfinate (via addition of SO_2), which was alkylated (allyl bromide) to provide the allyl sulfone (**203.1**; Scheme 203). Dian-

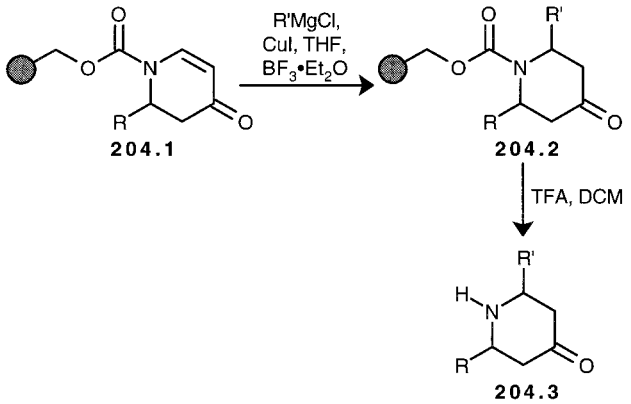
Scheme 203



ion formation with *n*-BuLi was followed by dialkylation (Scheme 149) with epichlorohydrin to deliver **203.2**. Orgaoncuprate, preformed by the combination of isopropylmagnesium bromide and CuI, was added to the allyl sulfone in a S_N2' displacement of the sulfinate. This traceless linker strategy provided cyclobutylidene **203.3** in a low yield (10%); use of palladium-catalyzed S_N2' displacement was preferred as shown previously. Chen and Janda employed the Michael addition of organocuprates in a polymer-supported synthesis of prostaglandin $F_2\alpha$ (Scheme 142).[174]

The 1,4-addition of cuprates were also applied in the solid-phase synthesis of piperidin-4-ones employing REACAP technology (Scheme 204).[213] The addi-

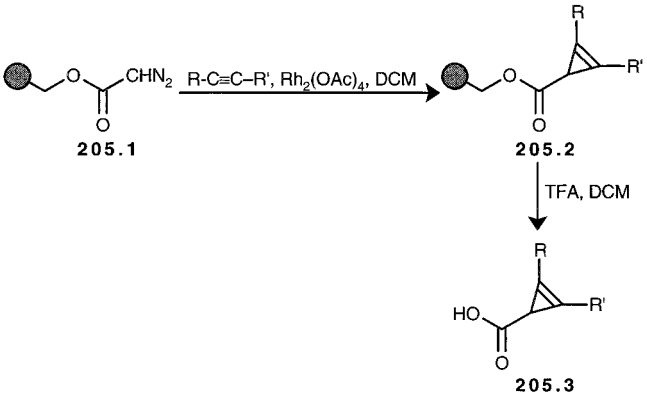
Scheme 204



tion of Grignard reagents in the first carbon−carbon bond-forming reaction provided polymer-supported dihydropyridone **204.1**. Cuprates produced from alkylmagnesium chlorides and CuI were added to the dihydropyridone in the presence of $BF_3{\cdot}Et_2O$ to accomplish the second carbon−carbon bond-forming reaction and furnished **204.2** in 51−65% de. Cleavage from the resin with TFA in DCM afforded piperidin-4-one **204.3** in 27−32% overall yield and 86−95% purity by GCMS. Hanessian and co-workers also described the conjugated addition of cuprates in the presence of TMSCl as shown in Scheme 141.[173]

A solid-phase cyclopropenation reaction was achieved with a Rh(II) catalyst.[227] The precursor for the cyclopropene was the polymer-bound diazo moiety, which was first prepared (Scheme 205) by

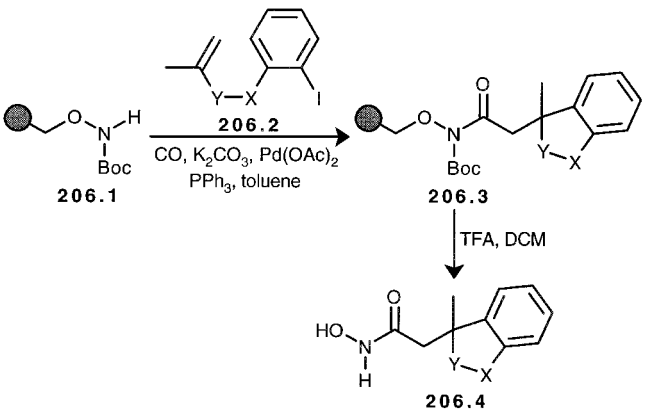
Scheme 205



coupling of Fmoc-protected glycine to Wang resin followed by deprotection (piperidine) and diazotization of the amine (HCl, $NaNO_2$) to give diazoester **205.1**. A second synthesis called for coupling of acetoacetic acid to Wang resin followed by diazo transfer ($TosN_3$, DIPEA) and subsequent deacetylation to provide **205.1**. With the polymer-bound diazoester in hand, acetylenes were added by the action of rhodium acetate in DCM to provide cyclopropene **205.2**. In this cyclopropenation reaction, two carbon−carbon bonds were formed. Cleavage of cyclopropenic acid **205.3** from the resin with TFA provided yields >30%.

Grigg et al. reported a palladium-catalyzed cascade reaction in the synthesis of hydroxamic acids on the solid phase.[228] Wang resin was functionalized with Boc-protected hydroxylamine (**206.1**; Scheme 206) and then reacted with carbon monoxide (1 atm) and

Scheme 206

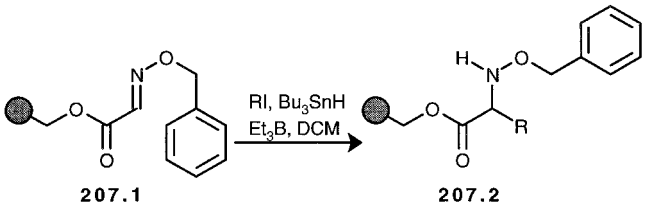


alkene **206.2** (containing an aryl iodide) prescribing $Pd(OAc)_2$ and PPh_3 in toluene. This palladium-catalyzed cascade reaction constructs two carbon−carbon bonds to provide **206.3** (X = O, OCH_2, or NR and Y = CH_2 or CO). Synchronous cleavage from the Wang resin and deprotection of the Boc group with TFA provided hydroxamic acids **206.4**. Isolated yields for 17 examples were 21−96%.

IX. Radical Reactions

Radical reactions are just now beginning to develop as a useful method for carbon−carbon bond formation in SPOS. One example reports the solid-phase synthesis of amino acid derivatives via a radical reaction.[229] Glyoxylic oxime benzyl ether was coupled to Wang or TentaGel OH resins with DCC and DMAP in DCM or 2,6-dichlorobenzoyl chloride and pyridine in DMF, respectively (Scheme 207). Alkyl radicals

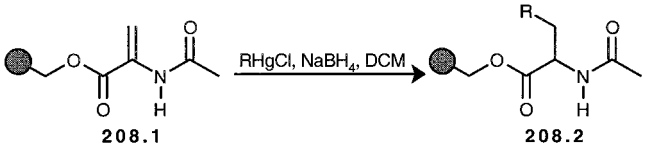
Scheme 207



could be generated from the corresponding alkyl iodide employing Bu_3SnH and Et_3B in DCM and subsequently reacted with polymer-bound oxime benzyl ether **207.1**. Primary, secondary, and tertiary radicals were employed; primary examples, however, were not very efficient. Primary ethyl radicals could also be generated from triethylborane (with O_2), which also reacted with oxime ether **207.1**. Cleavage of product **207.2** from the resin with TFA afforded *N*-benzyloxy amino acids in yields of 24−83%.

The solid-phase radical reaction of *N*-acetyl dehydroalanine provided another route to amino acid derivatives.[230] The *N*-acetyl dehydroalanine was bound to Wang resin employing Mitsunobu chemistry (Scheme 208), and **208.1** was then subjected to alkyl

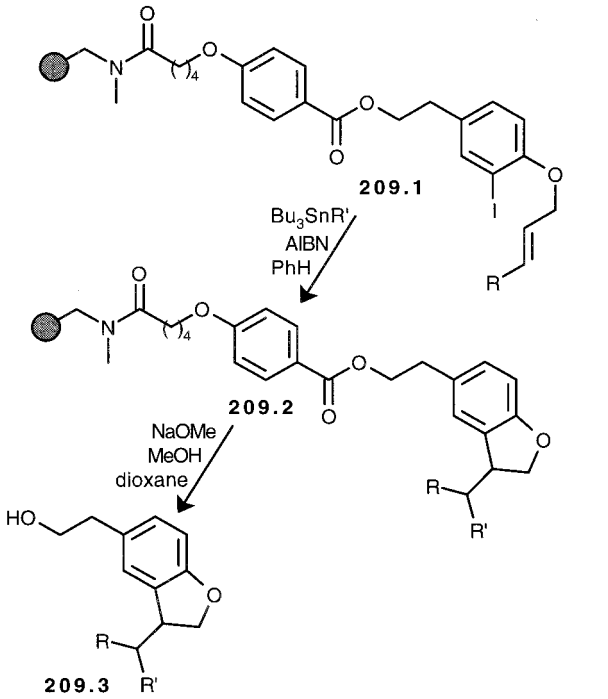
Scheme 208



radicals generated in situ by the addition of sodium borohydride to the alkylmercury choride in DCM. Conjugate addition of the radical provided polymer-supported *N*-acetyl amino ester **208.2**. Cleavage from the Wang resin was achieved with TFA in DCM to afford the free acid in 49−60% yield.

Berteina and De Mesmaeker applied tandem radical addition/cyclization chemistry to SPOS.[231] *N*-Methyl aminomethyl polystyrene was coupled with a carboxylic acid containing an *o*-iodophenol synthesized in the solution phase (Scheme 209). Alkylation of the polymer-bound phenol with allylic bromides was brought about with BEMP in dioxane to give

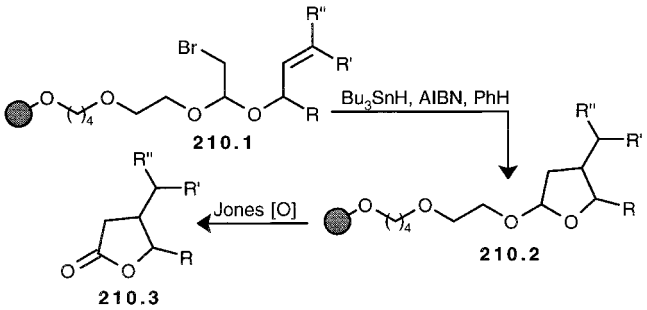
Scheme 209



209.1. The polymer-supported radical addition/cyclizations followed with Bu_3SnH and AIBN in refluxing benzene. Allyltributylstannane was also applied with AIBN to provide **209.2**, where R′ = H or CH_2-CH=CH_2. Implementation of allyltributylstannane allowed for two consecutive carbon−carbon bond-forming radical additions on the solid phase. Products were cleaved from the benzoate linker with NaOMe to provide dihydrobenzofuran **209.3**.

The solid-phase synthesis of γ-butyrolactones by Watanabe et al. incorporated a radical cyclization reaction.[232] 2-Chloroethyl vinyl ether was first alkylated with 1,4-butandiol, and the resulting 4-alkoxybutanol was bound to Merrifield resin (Scheme 210).

Scheme 210

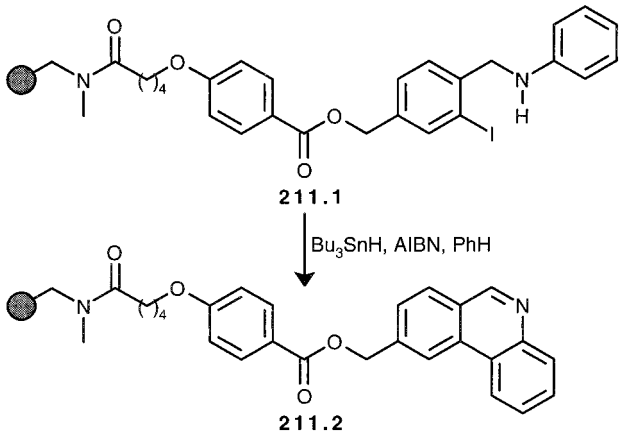


The polymer-bound vinyl ether was reacted with NBS in the presence of allylic alcohols to give acetal **210.1**. Radical cyclization reaction with Bu_3SnH and catalytic AIBN in refluxing benzene provided supported-acetal **210.2**. Subsequent Jones oxidation of this acetal resulted in cleavage from the resin and afforded γ-butyrolactone **210.3**. Seven examples proceeded in 47−93% yield for the radical cyclization and oxidative cleavage steps (23−43% overall based on initial chloride loading of Merrifield resin).

Radical cyclizations have been employed to make benzoquinolines.[29] *N*-Methylaminomethylpolystyrene

was coupled with a carboxylic acid containing a *p*-alkoxybenzoate linker (Scheme 211). The pendant

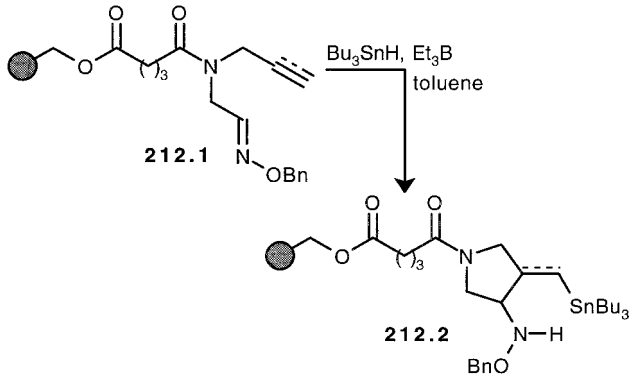
Scheme 211



o-iodo benzyl alcohol was convert to the benzyl chloride and subsequently reacted with aniline, TBAI, and DIPEA to give iodoamine **211.1**. Radical cyclization was performed with Bu_3SnH and AIBN in benzene to furnish polymer-bound benzoquinoline **211.2**, which was cleaved with NaOMe in MeOH/dioxane (1:4) to produce the desired product in 80% yield.

Radical cyclization reactions employing polymer-supported oxime benzyl ethers were employed in the synthesis of pyrrolidines.[233] The solution-phase synthesis commenced with α-chloroacetaldoxime benzyl ether, which was subsequently reacted with allyl or propargylamine (Scheme 212). The resulting second-

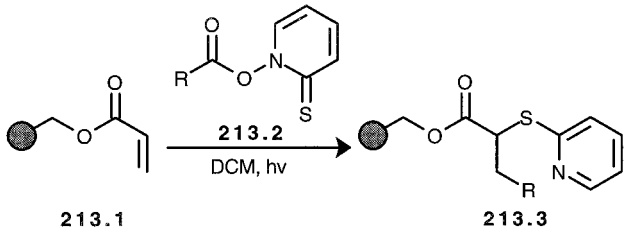
Scheme 212



ary amine was reacted with glutaric anhydride to generate an amide which contained the pendant carboxylic acid. This was coupled to Wang resin to provide **212.1**. Radical cyclization proceeded between the oxime and alkene/alkyne employing Bu_3SnH plus AIBN or Et_3B (radical initiators) to yield **212.2**. TFA-mediated cleavage of the Wang ester provided the corresponding acid (four examples) in 47−77% isolated yield. 9-BBN was also attempted as a radical initiator, but only a trace amount of product was obtained.

Zhu and Ganesan established the conjugate addition of radicals using Barton esters.[234] Acryloyl chloride was coupled (DIPEA and DCM) to Wang resin or to a TentaGel resin possessing a Wang-type

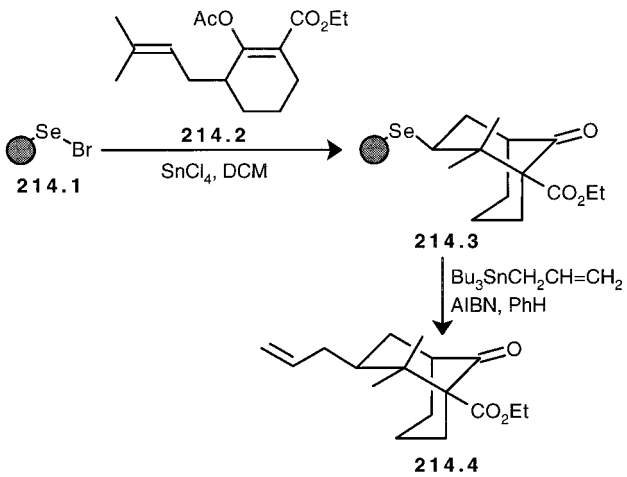
Scheme 213



linker (Scheme 213). Radicals were then generated in situ from Barton ester **213.2** by irradiation with a tungsten lamp, and subsequent conjugated addition to supported acrylate **213.1** was followed by termination with 2-thiopyridine to provide **213.3**. The isolated yields (after purification) for five examples were 32−94% on polystyrene and 17−78% on TentaGel. In both cases, it was noted that the example employing the benzyl radical resulted in the lowest yields. It was also noted that acrylamide attached to polystyrene- or TentaGel-based Rink resin proceeded but in lower yields compared to the acrylates.

Nicolaou et al. showed the solid-phase synthesis of [3.3.1]bicycles with radical additions to a selenium linker.[235] Polystyrene selenium bromide **214.1**, which had been previously reported,[236] was used as the starting resin (Scheme 214). Enol acetate **214.2** was

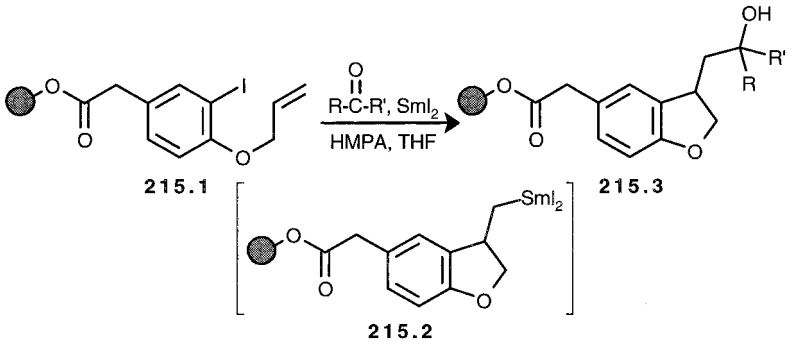
Scheme 214



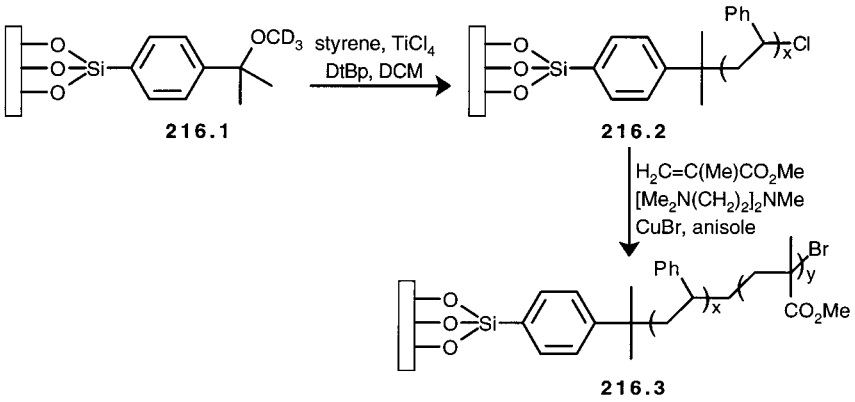
attached to the resin with $SnCl_4$ in DCM and underwent carbon−carbon bond-forming cyclization to give polymer-supported [3.3.1] bicycle **214.3**. Polystyrene selenium phthalimide did not produce any loaded bicycle, even though it was expected from the solution-phase results. With the polymer-bound bicyclic moiety in hand, cleavage of the selenium linker was accomplished with oxidation−elimination or radical addition. Radical addition with allyltributyltin and AIBN initiator in benzene at reflux provided a second carbon−carbon bond-forming reaction and afforded free bicyclic moiety **214.4** in 37% yield.

Polymer-supported radical cyclization and anionic capture have been demonstrated with samarium(II) iodide.[237] The solution-phase synthesis of 4-(3-propenoxy)-3-iodophenylacetic acid was carried out in three steps (Scheme 215). This acid was coupled (DIC, DMAP, DMF) to TentaGel S PHB resin to provide supported allyl *o*-iodophenyl ether **215.1**.

Scheme 215



Scheme 216



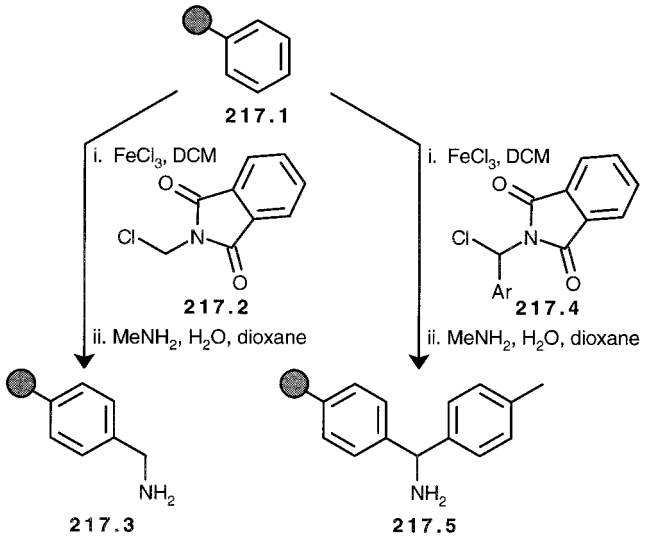
Radical cyclization with SmI_2 in HMPA/THF provided the intermediate benzofuran/samarium iodide system **215.2**, which underwent anionic capture with aldehydes or ketones to furnish **215.3**. The ester linker was cleaved with TFA to provide the corresponding acids in 7−45% yield in four ketone examples and 5% for an aldehyde example.

One last example of radical reaction is the radical polymerization of methyl methacrylate on a silicate-support.[238] The synthesis of aryltrichlorosilane was carried out from 4-bromoacetophenone (Scheme 216). This trichlorosilane was attached to silicone wafers or silicon crystals to provide trideuteriomethyl ether **216.1**. Solid-supported carbocation polymerization of styrene with $TiCl_4$ and DtBP in DCM provided **216.2**, and radical polymerization of methyl methacrylate followed with CuBr and pentamethyldiethylenetriamine in anisole at 90 °C to provide block copolymer **216.3**. Some properties of these novel "polymer brushes" were examined (thickness and water contact angle).

X. Friedel–Crafts Reactions

Friedel−Crafts alkylation and acylation reactions have been known for some time in SPOS. Introduction of this chemistry was crucial as it allowed for substitution to the polystyrene or polystyrene resin (styrene-*co*-divinylbenzene) after polymerization as opposed to requiring functionalized monomers for the polymerization. An example of Friedel−Crafts alkylation was utilized in the preparation of aminomethyl and 4-methylbenzhydrylamine polystyrene resins.[239] The preparation of *N*-(chloromethyl)phthalimide and *N*-(α-chloro-4-methylbenzyl)phthalimide as the desired alkylating agents was first discussed (Scheme 217). Cross-linked polystyrene beads **217.1** were alkylated with *N*-(chloromethyl)phthalimide (**217.2**) by employing $FeCl_3$ in DCM. Dephthaloylation of the resulting resin with methylamine in H_2O/dioxane produced aminomethyl polystyrene (AMPS) resin **217.3**. Friedel−Crafts alkylation of polystyrene with *N*-(α-chloro-4-methylbenzyl)phthalimide (**217.4**) required the use of $TiCl_4$ as Lewis acid catalyst to prepare 4-methylbenzhydrylamine polystyrene (MBHA) resin **217.5** after methylaminolysis of the phthalimide. It should also be noted here that the AMPS resin was used in a trial synthesis that

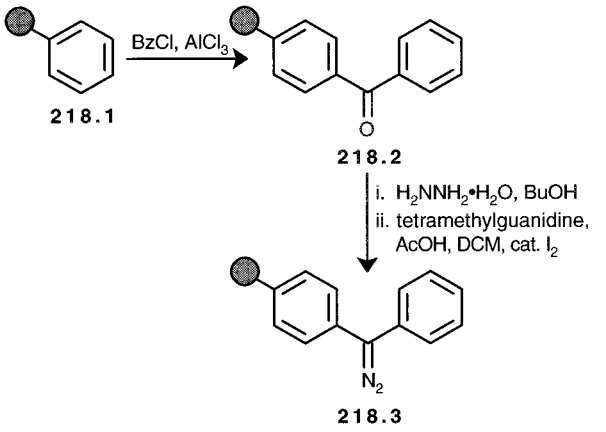
Scheme 217



included the carbon−carbon bond-forming Horner−Emmons reaction of a polymer-bound aldehyde.

A diphenyldiazomethane resin, which was employed in the solid-phase synthesis of protected peptide alcohols, was prepared by Friedel−Crafts acylation (Scheme 218).[240] Cross-linked polystyrene

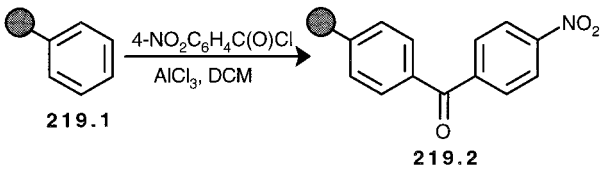
Scheme 218



resin **218.1** was subjected to benzoyl chloride in the presence of $AlCl_3$ to furnish polymer-supported diphenyl ketone **218.2**, which was reacted with hydrazine in BuOH to provide the corresponding hydrazone. Oxidation of the hydrazone with peracetic acid and TMG in the presence of catalytic iodine in DCM provided diphenyldiazomethane **218.3**. Alcohols could be attached to the solid support in the presence of BF_3•Et_2O. This development lead to the SPPS of *t*-Bu-protected peptide alcohols.

Friedel−Crafts acylation was employed in the development of a novel oxime resin for the solid-phase synthesis of substituted ureas (Scheme 219).[241]

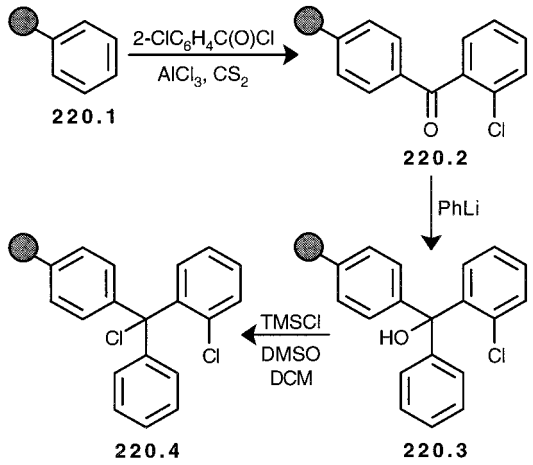
Scheme 219



The synthesis began with cross-linked polystyrene resin **219.1**, which was acylated with *p*-nitrobenzoyl chloride and $AlCl_3$ in DCM to give diaryl ketone **219.2**. This polymer-bound ketone was reacted with hydroxylamine hydrochloride and pyridine in EtOH to give the corresponding ketoxime. The oxime could be reacted with phosgene or triphosgene and subsequently converted to the carbamate with an amine. The oxime−carbamate was reacted with additional amines at elevated temperatures to cleave the desired urea from the ketoxime resin.

The efficient synthesis of 2-chlorotrityl chloride resin shown by Orosz and Kiss also employed a Friedel−Crafts acylation (Scheme 220).[242] Cross-linked polystyrene was acylated with 2-chlorobenzoyl chloride in the presence of $AlCl_3$ in CS_2 to give ketone **220.2**. A second carbon−carbon bond was formed by the addition of phenyllithium to the polymer-bound ketone to provide tertiary alcohol **220.3**. This alcohol was converted to 2-chlorotrityl chloride resin (**220.4**)

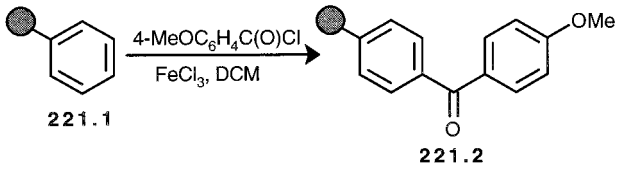
Scheme 220



with TMSCl and DMSO in DCM. This resin was determined to be satisfactorial for the SPPS of 5−12 residue peptides.

The synthesis of a novel α-(4-methoxyphenyl)-benzyl chloride provides one last example of the Friedel−Crafts acylation. This novel second-generation Merrifield resin was coined MAMP, which is the acronym for Merrifield alpha-methoxyphenyl (Scheme 221). Polystyrene resin **221.1** was acylated with

Scheme 221



4-methoxybenzoyl chloride employing $FeCl_3$ in DCM to furnish ketone **221.2**. Reduction of this ketone with $LiBH_4$ provided the polymer-bound alcohol, which was converted to the novel chloride resin with acetyl chloride in toluene. Primary amines were attached to the resin via displacement of the secondary chloride and the resultant amine acylated. After the synthesis, cleavage of the amide from this new resin was demonstrated by treatment with TFA/H_2O/DCM (9:1:90).

XI. Summary and Outlook

A broad range of polymer-supported carbon−carbon bond-forming reactions have been shown to be useful—indeed, more advantageous in many cases—than their solution-phase counterparts. Of the 224 papers reporting solid-phase carbon−carbon bond-forming reactions between January 1998 and December 1999, there was an almost equal distribution between the two years (1998 = 114, 1999 = 110). The majority of these papers focused on at least one of three major areas: (1) development of new synthetic methodology for polymer-supported synthesis; (2) development of novel linkers for attaching the scaffold to the support; and (3) application of solid-phase carbon−carbon bond-forming reactions to the synthesis of a targeted library of compounds. Again, it should be pointed out that many references report

multiple carbon−carbon bond-forming reactions, either in a synthetic sequence or in parallel syntheses. Some of these papers included up to four different carbon−carbon bond-forming reactions (Lorsbach et al., ref 34; Stieber et al., ref 19; and Brill et al., ref 18).[243,244] On the other hand, many have used syntheses that generate more than one carbon−carbon bond in a single reaction. The Diels−Alder reaction is the most common of the multiple carbon−carbon bond-forming reactions, but the domino reaction reported by Gutke and Spitzner (Scheme 163) forms three different carbon−carbon bonds. Much still remains to be done in this area of research—be it new synthetic method development or novel reaction sequence development.

The implementation of novel linkers for SPOS has also been an area of much interest, and the use of carbon−carbon bond-forming reactions has been applied to show the utility of these linkers. A large selection of new linkers, many of which have different cleavage protocols, are now available for future utilization. While the application of SPOS to the generation of combinatorial libraries is increasing, the measure of research in this area has not been accurately depicted because it is often more production oriented than research oriented. In light of the broad range of reactions, reaction sequences, linkers, and cleavage strategies utilized in carbon−carbon bond-forming solid-phase chemistry reviewed here, it is our belief that this remains a fruitful area of chemical research.

XII. Acknowledgments

We thank the National Science Foundation for their generous support of our work in this area. We also thank Dr. Beth Lorsbach and the referees for their advice and editing.

XIII. Glossary

acac	acetylacetonate
AIBN	2,2′-azobisisobutyronitrile
9-BBN	9-borabicyclo[3.3.1]nonane
BEMP	2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
Boc	*tert*-butoxycarbonyl
BSA	bis(trimethylsilyl)acetamide
BTPP	*tert*-butylimino-tri(pyrrolidino)phosphorane
CAN	cerric ammonium nitrate
CIP	2-chloro-1,3-dimethylimidazolidium hexfluorophosphate
DABCO	diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPC	diethyl phosphorocyanidate
DIC	diisopropyl carbodiimide
DIPEA	*N*,*N*-diisopropylethylamine
DMA	*N*,*N*-dimethylacetamide
DMAP	*N*,*N*-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DMT	4,4′-dimethoxytrityl
dppf	diphenylphosphinoethane
dppf	(2-diphenylphosphino)ferrocene
DtBP	di-*tert*-butylpyridine
EDC	1,2-dichloroethane (ethylene dichloride)
Fmoc	9-fluorenylmethoxycarbonyl
HATU	*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate
HOBt	1-hydroxybenzotriazole
KHMDS	potassium hexamethyldisilylamide
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilylamide
MCPBA	*m*-chloroperbenzoic acid
NBS	*N*-bromosuccinimide
NCS	*N*-bromosuccinimide
NMM	*N*-methylmorpholine
NMP	1-methyl-2-pyrrolidinone
PPTS	pyridinium *p*-toluenesulfonate
PTSA	*p*-toluenesulfonic acid
PyBroP	bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
PyBOP	benzotiazole-1-yl-oxy-trispyrrolidinophosphonium hexfluorophosphate
RCM	ring-closing metathesis
ROM	ring-opening metathesis
SPOS	solid-phase organic synthesis
SPPS	solid-phase peptide synthesis
SPSS	solid-phase saccharide synthesis
TBABr	tetrabutylammonium bromide
TBACl	tetrabutylammonium chloride
TBAF	tetrabutylammonium fluoride
TBAOH	tetrabutylammonium hydroxide
TEA	triethylamine
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyranyl
TMG	1,1,3,3-tetramethylguanidine
TMOF	trimethylorthoformate
TMS	trimethylsilyl
W	watt

XIV. References

(1) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149−54.
(2) For survey on synthesis of combinatorial libraries, see: (a) Hermkens, P. H. H.; Hamersma, H. *J. Comb. Chem.* **1999**, *1*, 307−16. (b) Dolle, R. E.; Nelson, K. H., Jr. *J. Comb. Chem.* **1999**, *1*, 235−82. (c) Lebl, M.; Leblova, Z. *Dynamic Database of References in Molecular Diversity*. Internet http://www.5z.com/.
(3) (a) Brown, R. C. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3293−320. (b) Hall, S. E. *Mol. Diversity* **1999**, *4*, 131−142. (c) James, I. W. *Mol. Diversity* **1998**, *3*, 181−90. (d). Brown, A. R.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Synlett* **1998**, 817−27.
(4) (a) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489−510. (b) Wentworth, P., Jr.; Janda, K. D. *Chem. Commun.* **1999**, 1917−24.
(5) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449−472.
(6) Lorsbach, B. A.; Kurth, M. J. *Chem. Rev.* **1999**, *99*, 1549−81.
(7) Labadie, J. W.; Tueting, J.; Stille, J. K. *J. Org. Chem.* **1983**, *48*, 4634−42.
(8) Sieber, F.; Wentworth, P., Jr.; Janda, K. D. *J. Comb. Chem.* **1999**, *1*, 540−6.
(9) Chamoin, S.; Huldsworh, S.; Snieckus, S. *Tetrahedron Lett.* **1998**, *39*, 4175−8.
(10) Kang, S.-K.; Kim, J. S.; Yoon, S.-K.; Lim, K.-H.; Yoon, S. S. *Tetrahedron Lett.* **1998**, *39*, 3011−2.
(11) Malenfat, P. R. L.; Fréchet, J. M. J. *Chem. Commun.* **1998**, 2657−8.
(12) Blaskovich, M. A.; Kahn, M. *J. Org. Chem.* **1998**, *63*, 1119−25.
(13) Hu, Y.; Baudart, S.; Porco, J. A., Jr. *J. Org. Chem.* **1999**, *64*, 1049−51.
(14) Peukert, S.; Giese, B. *J. Org. Chem.* **1998**, *63*, 9045−51.

(15) Hone, N. D.; Davies, S. G.; Devereux. N. J.; Taylor, S. L.; Baxter, A. D. *Tetraherdron Lett.* **1998**, *39*, 897−900.
(16) Broody, M. S.; Finn, M. G. *Tetrahedron Lett* **1999**, *40*, 415−8.
(17) Koot, W.-J. *J. Comb. Chem.* **1999**, *1*, 467−73.
(18) Brill, W. K.-D.; Mesmaeeker, A. D.; Wendeborn, S. *Synlett* **1998**, 1085−90.
(19) Stieber, F.; Grether, U.; Waldmann, H. Angew. *Chem.* **1999**, *111*, 1142−5; Angew. *Chem., Int. Ed. Engl.* **1999**, *38*, 1073−7.
(20) Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Murphy, F. Angew. *Chem.* **1998**, *110*, 2677−80; *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2534−7.
(21) Plevyak, J. E.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2454−6.
(22) de Meijere, A.; Meyer, F. E. *Angew. Chem.* **1994**, *106*, 2473; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379−411.
(23) Hanessian, S.; Xie, F. *Tetrahedron Lett.* **1998**, *39*, 737−40.
(24) Blettner, C. G.; König, W. A.; Stenzel, W.; Schotten, T. *Tetrahedron Lett.* **1999**, *40*, 2101−2.
(25) Bräse, S.; Schroen, M. Angew. *Chem.* **1999**, *111*, 1139−42; *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1071−3.
(26) Bräse, S.; Enders, D.; Köbberling, J.; Avemaria, F. *Angew. Chem.* **1998**, *110*, 3614−6; *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3413−5.
(27) Kulkarni, B. A.; Ganesan, A. *J. Comb. Chem.* **1999**, *1*, 373−8.
(28) Wang, Y.; Huang, T.-N. *Tetrahedron Lett.* **1998**, *39*, 9605−8.
(29) Berteina, S.; Wendeorn, S.; De Mesmaeker, A. *Synlett* **1998**, 1231−3.
(30) Smith, A. L.; Stevenson, G. I.; Swain, C. J.; Castro, J. L. *Tetrahedron Lett.* **1998**, *39*, 8317−20.
(31) Thompson, L. A.; Ellman, J. A. *Tetrahedron Lett.* **1994**, *35*, 9333−6.
(32) Bolton, G. L.; Hodges, J. C. *J. Comb. Chem.* **1999**, *1*, 130−3.
(33) (a) Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437−40. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−83.
(34) Lorsbach, B. A.; Bagdanoff, J. T.; Miller, R. B.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 2244−50.
(35) Reissert, A. *Chem. Ber.* **1905**, *38*, 1603−14.
(36) Lee, Y.; Silverman, R. B. *J. Am. Chem. Soc.* **1999**, *121*, 8407−8.
(37) Vanier, C.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* **1999**, *40*, 4335−8.
(38) Blettner, C. G.; König, W. A.; Stenzel, W.; Schotten, T. *J. Org. Chem.* **1999**, *64*, 3885−90.
(39) Huwe, C. M.; Künzer, H. *Tetrahedron Lett.* **1999**, *40*, 683−6.
(40) Gosselin, F.; Van Betsbrugge, J.; Hatam, M.; Lubell, W. D. *J. Org. Chem.* **1999**, *64*, 2486-93.
(41) (a) Thompson, L. A.; Moore, F. L.; Moon, Y.-C.; Ellman, J. A. *J. Org. Chem.* **1998**, *63*, 2066−7. (b) Dragoli, D. R.; Thompson, L. A.; O'Brien, J.; Ellman, J. A. *J. Comb. Chem.* **1999**, *1*, 534−9.
(42) Hird, N.; Hughes, I.; Hunter, D.; Morrison, M. G. J. T.; Sherrington, D. C.; Stevenson, L. *Tetrahedron* **1999**, *55*, 9575−84.
(43) (a) Todd, M. H.; Oliver, S. F.; Abell, C. *Org. Lett.* **1999**, *1*, 1149−51. (b) Todd, M. H.; Oliver, S. F.; Abell, C. *Org. Lett.* **1999**, *1*, 1687.
(44) Dimensions for these reactors were 25 × 5 mm (L × OD), and loadings were 25−35 umol/reactor as determined by chloride ion-selective electrode.
(45) Li, R.; Xiao, X.-Y.; Czarnik, A. W. *Tetrahedron Lett.* **1998**, *39*, 8581−4.
(46) Han, Y.; Giroux, A.; Lépine, C.; Laliberté, F.; Huang, Z.; Perrier, H.; Bayly, C. I.; Young, R. N. *Tetrahedron* **1999**, *55*, 11669−85.
(47) Bleicher, K. H.; Wareing, J. R. *Tetrahedron Lett.* **1998**, *39*, 4587−90.
(48) Lago, M. A.; Nguyen, T. T.; Bhatnagar, P. *Tetrahedron Lett.* **1998**, *39*, 3885−88.
(49) Baxter, E. W.; Rueter, J. K.; Nortey, S. O.; Reitz, A. B. *Tetrahedron Lett.* **1998**, *39*, 979−82.
(50) Chamoin, S.; Houldsworth, S.; Kruse, C. G.; Bakker, I.; Snieckus, V. *Tetrahedron Lett.* **1998**, *39*, 4179−82.
(51) Sonogashira, K.; Tohda, Y.; Nagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467−70.
(52) Huang, S.; Tour, J. M. *J. Am. Chem. Soc.* **1999**, *121*, 4908−9.
(53) Huang, S.; Tour, J. M. *J. Org. Chem.* **1999**, *64*, 8898−906.
(54) Khan, S. I.; Grinstaff, M. W. *J. Am. Chem. Soc.* **1999**, *121*, 4704−5.
(55) Bräse, S.; Dahmen, S.; Heuts, J. *Tetrahedron Lett.* **1999**, *40*, 6201−3.
(56) Dyatkin, A. B.; Rivero, R. A. *Tetrahedron Lett.* **1998**, *39*, 3647−50.
(57) Zhang, H.-C.; Brumfield, K. K.; Jaroskova, L.; Maryanoff, B. E. *Tetrahedron Lett.* **1998**, *39*, 4449−52.
(58) Khan, S. I.; Grinstaff, M. W. *Tetrahedron Lett.* **1998**, *39*, 8031−4.
(59) Stieber, F.; Grether, U.; Waldmann, H. Angew. *Chem., Int. Ed.* **1999**, *38*, 1073−7.
(60) Cadiot, P.; Chodkiewicz, W. Couplings of Acetylenes. In *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, 1969.
(61) Montierth, J. M.; DeMario, D. R.; Kurth, M. J.; Schore, N. E. *Tetrahedron* **1998**, *54*, 11741−8.
(62) Chiu, C.; Tang, Z.; Ellingboe, J. W. *J. Comb. Chem.* **1999**, *1*, 73−7.
(63) Gennari, C.; Ceccarelli, S.; Piarulli, U.; Aboutayab, K.; Donghi, M.; Paterson, I. *Tetrahedron* **1998**, *54*, 14999-5016.
(64) Rademann, J.; Meldal, M.; Back, K. *Chem. Eur. J.* **1999**, *5*, 1218−25.
(65) Katritzky, A. R.; Belyakov, S. A.; Fang, Y.; Kiely, J. S. *Tetrahedron Lett.* **1998**, *39*, 8051−4.
(66) Reggelin, M.; Brenig, V.; Welcker, R. *Tetrahedron Lett.* **1998**, *39*, 4801−4.
(67) Phoon, C. W.; Abell, C. *Tetrahedron Lett.* **1998**, *39*, 2655−8.
(68) Marzinzik, A. L.; Felder, E. R. *J. Org. Chem.* **1998**, *63*, 723−7.
(69) Jones, G. In *Organic Reactions*; Adams, R., Ed.; John Wiley & Sons: New York, 1967; Vol. 15, pp 204−599.
(70) Hamper, B. C.; Gan, K. Z.; Owen, T. J. *Tetrahedron Lett.* **1999**, *40*, 4973−6.
(71) Chou, Y.-L.; Morrissey, M. M.; Mohan, R. *Tetrahedron Lett.* **1998**, *39*, 757−60.
(72) (a) Hay, A. M.; Hobbs-Dewitt, S.; MacDonald, A. A.; Ramage, R. *Tetrahedron Lett.* **1998**, *39*, 8721−4. (b) Hay, A. M.; Hobbs-Dewitt, S.; MacDonald, A. A.; Ramage, R. *Synthesis* **1999**, 1979−85.
(73) Hamper, B. C.; Kolodziej, S. A.; Scates, A. M. *Tetrahedron Lett.* **1998**, *39*, 2047−50.
(74) Hamper, B. C.; Snyderman, D. M.; Owen, T. J.; Scates, A. M.; Owsley, D. C.; Kesselring, A. S.; Chott, R. C. *J. Comb. Chem.* **1999**, *1*, 140−50.
(75) Miller, P. C.; Owen, T. J.; Molyneaux, J. M.; Curtis, J. M.; Jones, C. R. *J. Comb. Chem.* **1999**, *1*, 223−34.
(76) Tadesse. S.; Bhandari, A.; Gallop, M. A. *J. Comb. Chem.* **1999**, *1*, 184−7.
(77) Watson, B. T.; Christiansen, G. E. *Tetrahedron Lett.* **1998**, *39*, 6087−90.
(78) Svensson, A.; Bergquist, K.-E.; Fex, T.; Kihlberg, J. *Tetrahedron Lett.* **1998**, *39*, 7193−6.
(79) Xia, Y.; Yang, Z.-Y.; Brossi, A.; Lee, K.-H. *Org. Lett.* **1999**, *1*, 2113−5.
(80) Bhandari, A.; Li, B.; Gallop, M. A. *Synthesis* **1999**, 1951−60.
(81) Kulkarni, B. A.; Ganesan, A. *Tetrahedron Lett.* **1998**, *39*, 4369−72.
(82) Matthews, J.; Rivero, R. A. *J. Org. Chem.* **1998**, *63*, 4808−10.
(83) Weber, L.; Iaiza, P.; Biringer, G.; Barbier, P. *Synlett* **1998**, 1156−8.
(84) Romoff, T. T.; Ma, L.; Wang, Y.; Campbell, D. A. *Synlett* **1998**, 1341−2.
(85) Raillard, S. P.; Ji, G.; Mann, A. D.; Baer, T. A. *Org. Process Res.Dev.* **1999**, *3*, 177−83.
(86) (a) Baylis, A. B.; Hillman, M. E. D. German Patent 2155113, 1972. (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001−62.
(87) Richter, H.; Jung, G. *Mol. Diversity* **1998**, *3*, 191−4.
(88) Richter, H.; Walk, T.; Höltzel, A.; Jung, G. *J. Org. Chem.* **1999**, *64*, 1362−5.
(89) Kulkarni, B. A.; Ganesan, A. *J. Comb. Chem.* **1999**, *1*, 373−8.
(90) Richter, H.; Jung, G. *Tetrahedron Lett.* **1998**, *39*, 2729−30.
(91) Tramontini, M.; Angiolini, L. *Tetrahedron* **1990**, *46*, 1791−837.
(92) Meester, W. J. N.; Rutjes, F. P. J. T.; Hermkens, P. H. H.; Hiemstra, H. *Tetrahedron Lett.* **1999**, *40*, 1601−4.
(93) Kobayashi, S.; Furuta, T.; Sugita, K.; Okitsu, O.; Oyamada, H. *Tetrahedron Lett.* **1999**, *40*, 1341−4.
(94) McNally, J. J.; Youngman, M. A.; Dax, S. L. *Tetrahedron Lett.* **1998**, *39*, 967−70.
(95) Robinson, R. *J. Chem. Soc.* **1917**, *111*, 762−8.
(96) Jönsson, D.; Molin, H.; Undén, A. *Tetrahedron Lett.* **1998**, *39*, 1059−62.
(97) Lebl, M.; Krchňák, V.; Ibrahim, G.; Pires, J.; Burger, C.; Ni, Y.; Chen, Y.; Podue, D.; Mudra, P.; Pokorny, V.; Poncar, P.; Zenisek, K. *Synthesis* **1999**, 1971−8.
(98) Kobayashi, S.; Aoki, Y. *Tetrahedron Lett.* **1998**, *39*, 7345−8.
(99) Kobayashi, S.; Wakabayashi, T.; Yasuda, M. *J. Org. Chem.* **1998**, *63*, 4868−9.
(100) (a) Pictet. A.; Spengler, T. *Chem. Ber.* **1911**, *44*, 2030−6. (b) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797−894.
(101) Wang, H.; Ganesan, A. *Org. Lett.* **1999**, *1*, 1647−9.
(102) van Loevezijn, A.; van Maarseveen, J. H.; Stegman, K.; Visser, G. M.; Koomen, G.-J. *Tetrahedron Lett.* **1998**, *39*, 4737−40.
(103) Fantauzzi, P. P.; Yager, K. M. *Tetrahedron Lett.* **1998**, *39*, 1291−94.
(104) Sauerbrei, B.; Jungmann, V.; Waldmann, H. *Angew. Chem.* **1998**, *110*, 1187−90; *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1143−6.
(105) Ugi, I.; Lohberger, S.; Karl, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Peramon: New York, 1991; Vol. 2, pp 1083−109.
(106) Piscopio, A. D.; Miller, J. F.; Koch, K. *Tetrahedron* **1999**, *55*, 8189−98.
(107) Kim, S. W.; Bauer, S. M.; Armstrong, R. W. *Tetrahedron Lett.* **1998**, *39*, 6993−6.
(108) Hulme, C.; Peng, J.; Morton, G.; Salvino, J. M.; Herpin, T.; Labaudiniere, R. *Tetrahedron Lett.* **1998**, *39*, 7227−30.

(109) Kim, S. W.; Shin, Y. S.; Ro, S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1665−8.
(110) Li, Z.; Yeo, S. L.; Pallen, C. J.; Ganesan, A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2443−6.
(111) Hoel, A. M. L.; Nielsen, J. *Tetrahedron Lett.* **1999**, *40*, 3941−4.
(112) Hantzsch, A. *Chem. Ber.* **1890**, *23*, 1474−6.
(113) Trautwein, A. W.; Sübmuth, R. D.; Jung, G. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2381−4.
(114) Wang, Y.; Huang, T.-N. *Tetrahedron Lett.* **1999**, *40*, 5837−40.
(115) Blackburn, C. *Tetrahedron Lett.* **1998**, *39*, 5469−72.
(116) Carboni, B.; Pourbaix, C.; Carreaux, F.; Deleuze, H.; Maillard, B. *Tetrahedron Lett.* **1999**, *40*, 7979−83.
(117) Cavallaro, C. L.; Herpin, T.; MuGuinness, B. F.; Shimshock, Y. C.; Dolle, R. E. *Tetrahedron Lett.* **1999**, *40*, 2711−4.
(118) Lee, H. B.; Balasubramanian, S. *J. Org. Chem.* **1999**, *64*, 3454−60.
(119) Sim, M. M.; Lee, C. L.; Ganesan, A. *Tetrahedron Lett.* **1998**, *39*, 2195−8.
(120) Sim, M. M.; Lee, C. L.; Ganesan, A. *Tetrahedron Lett.* **1998**, *39*, 6399−402.
(121) Garibay, P.; Toy, P. H.; Hoeg-Jensen, T.; Janda, K. D. *Synlett* **1999**, 1438−40.
(122) Havez, S.; Begtrup, M.; Vedso, P. *J. Org. Chem.* **1998**, *63*, 7418−20.
(123) Pernerstorfer, J.; Schuster, M.; Blechert, S. *Synthesis* **1999**, 138−44.
(124) Kulkarni, B. A.; Ganesan, A. *Tetrahedron Lett.* **1999**, *40*, 5633−6.
(125) Hoogenboom, B. E.; Oldenziel, O. H.; van Leusen, A. M. *Org. Synth.* **1977**, *57*, 102−6.
(126) Li, Z.; Ganesan, A. *Synlett* **1998**, 405−6.
(127) Bredereck, H.; Effenberger, F.; Botsch, H. *Chem. Ber.* **1964**, *97*, 3397−406.
(128) Wilson, R. D.; Watson, S. P.; Richards, S. A. *Tetrahedron Lett.* **1998**, *39*, 2827−30.
(129) Far, A. R.; Tidwell, T. T. *J. Comb. Chem.* **1999**, *1*, 458−60.
(130) Brown, R. C. D.; Fisher, M. *Chem. Commun.* **1999**, 1547−8.
(131) Srivastava, S. K.; Haq, W.; Murthy, P. K.; Chauhan, P. M. S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1885−8.
(132) Stephensen, H.; Zaragoza, F. *Tetrahedron Lett.* **1999**, *40*, 5799−802.
(133) Hennequin, L. F.; Piva-Le Blanc, S. *Tetrahedron Lett.* **1999**, *40*, 3881−4.
(134) Hoemann, M. Z.; Melikian-Badalian, A.; Kumaravel, G.; Hauske, J. R. *Tetrahedron Lett.* **1998**, *39*, 4749−52.
(135) Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1928**, *460*, 98−122.
(136) Yedidia, V.; Leznoff, C. C. *Can. J. Chem.* **1980**, *58*, 1144−50.
(137) Ball, C. P.; Barrett, A. G. M.; Commercon, A.; Compere, D.; Kuhn, C.; Roberts, R. S.; Smith, M. L.; Venier, O. *Chem. Commun.* **1998**, 2019−20.
(138) Paulvannan, K.; Chen, T.; Jacobs, J. W. *Synlett* **1999**, 1609−11.
(139) Evans, D.; Chapman, K.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238−56.
(140) Winkler, J. D.; McCoull, W. *Tetrahedron Lett.* **1998**, *39*, 4935−6.
(141) Burkett, B. A.; Chai, C. L. L. *Tetrahedron Lett.* **1999**, *40*, 7035−8.
(142) Zhao, C.; Shi, S.; Mir, D.; Hurst, D.; Li, R.; Xiao, X.-Y.; Lillig, J.; Czarnik, A. W. *J. Comb. Chem.* **1999**, *1*, 91−95.
(143) Heerding, D. A.; Takata, D. T.; Kwon, C.; Huffman, W. F.; Samanen, J. *Tetrahedron Lett.* **1998**, *39*, 6815−8.
(144) Schürer, S. C.; Blechert, S. *Synlett* **1999**, 1879−82.
(145) Sun, S.; Murray, W. V. *J. Org. Chem.* **1999**, *64*, 5941−5.
(146) Wendeborn, S.; De Mesmaeker, A.; Brill, W. K.-D. *Synlett* **1998**, 865−8.
(147) Chen, C.; Munoz, B. *Tetrahedron Lett.* **1999**, *40*, 3491−4.
(148) Craig, D.; Robson, M. J.; Shaw, S. J. *Synlett* **1998**, 1381−3.
(149) Kiselyov, A. S.; Smith, L., II; Armstrong, R. W. *Tetrahedron* **1998**, *54*, 5089−96.
(150) Kiselyov, A. S.; Smith, L., II; Virgilio, A.; Armstrong, R. W. *Tetrahedron* **1998**, *54*, 7987−96.
(151) Zhang, W.; Xie, W.; Fang, J.; Wang, P. G. *Tetrahedron Lett.* **1999**, *40*, 7929−33.
(152) Kuster, G. J.; Scheeren, H. W. *Tetrahedron Lett.* **1998**, *39*, 3613−6.
(153) Kantorowski, E. J.; Kurth, M. J. *Mol. Diversity* **1996**, *2*, 207−16.
(154) Park, K.-H.; Abbate, E.; Najdi, S.; Olmstead, M. M.; Kurth, M. J. *Chem Commun.* **1998**, 1679−80.
(155) Park, K.-H.; Kurth, M. J. *J. Org. Chem.* **1999**, *64*, 9297−300.
(156) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *62*, 5339−42.
(157) Park, K.-H.; Kurth, M. J. *Tetrahedron Lett.* **1999**, *40*, 5841−4.
(158) Park, K.-H.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 6579−85.
(159) Cheng, J.-F.; Mjalli, A. M. M. *Tetrahedron Lett.* **1998**, *39*, 939−42.
(160) Gong, Y.-D.; Najdi, S.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 3081−86.
(161) Peng, G.; Sohn, A.; Gallop, M. A. *J. Org. Chem.* **1999**, *64*, 8342−9.
(162) Goff, D. A. *Tetrahedron Lett.* **1999**, *40*, 8741−5.
(163) Kobayashi, S.; Akiyama, R. *Tetrahedron Lett.* **1998**, *39*, 9211−14.
(164) Haap, W. J.; Kaiser, D.; Walk, T. B.; Jung, G. *Tetrahedron* **1998**, *54*, 3705−24.
(165) Biladeau, M. T.; Cunningham, A. M. *J. Org. Chem.* **1998**, *63*, 2800−01.
(166) Tsuge, O.; Kanemasa, S.; Takenaka, S. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3631−35.
(167) (a) Bicknell, A. J.; Hird, N. W.; Readshaw, S. A. *Tetrahedron Lett.* **1998**, *39*, 5869−72. (b) Brooking, P.; Crawshaw, M.; Hird, N. W.; Jones, C.; MacLachlan, W. S.; Readshaw, S. A.; Wilding S. *Synthesis* **1999**, 1986−92.
(168) Singh, R.; Nuss, J. M. *Tetrahedron Lett.* **1999**, *40*, 1249−52.
(169) Benaglia, M.; Cinquini, M.; Cozzi, F. *Tetrahedron Lett.* **1999**, *40*, 2019−20.
(170) Sucholeiki, I.; Pavia, M. R.; kresge, C. T.; McCullen, S. B.; Malek, A.; Schramm, S. *Mol. Diversity* **1998**, *3*, 161−71.
(171) Hu, Y.; Porco, J. A., Jr. *Tetrahedron Lett.* **1999**, *40*, 3289−92.
(172) Gooding, O. W.; Baudart, S.; Deegan, T. L.; Heisler, K.; Labadie, J. W.; Newcomb, W. S.; Porco, J. A., Jr.; van Eikeren, P. *J. Comb. Chem.* **1999**, *1*, 113−22.
(173) Hanessian, S.; Ma, J.; Wang, W. *Tetrahedron Lett.* **1999**, *40*, 4631−4.
(174) Chen, S.; Janda, K. D. *Tetrahedron Lett.* **1998**, *39*, 3943−6.
(175) O'Donnell, M. J.; Delgado, F.; Pottorf, R. S. *Tetrahedron* **1999**, *55*, 6347−62.
(176) Karoyan, P.; triolo, A.; Nannicini, R.; Giannotti, D.; Altamura, M.; Chassaing, G.; Perrotta, E. *Tetrahedron Lett.* **1999**, *40*, 71−4.
(177) Zhu, Z.; Mckittrick, B. *Tetrahedron Lett.* **1998**, *39*, 7479−82.
(178) Bertini, V.; Lucchesini, F.; Pocci, M.; De Munno, A. *Tetrahedron Lett.* **1998**, *39*, 9263−6.
(179) (a) Boussie, T. R.; Coutard, C.; Turner, H.; Murphy, V.; Powers, T. S. *Angew. Chem.* **1998**, *110*, 3472−5; *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3272−5. (b) Boussie, T. R.; Murphy, V.; Hall, K. A.; Coutard, C.; Dales, C.; Petro, M.; Carlson, E.; Turner, H. W.; Powers, T. S. *Tetrahedron* **1999**, *55*, 11699−710.
(180) Cheng, W.-C.; Halm, C.; Evarts, J. B.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1999**, *64*, 8557−62.
(181) Tietze, L. F.; Hippe, T.; Steinmetz, A. *Chem. Commun.* **1998**, 793−4.
(182) O'Donnell, M. J.; Delgado, F.; Drew, M. D.; Pottorf, R. S.; Zhou, C.; Scott, W. L. *Tetrahedron Lett.* **1999**, *40*, 5831−5.
(183) Veerman, J. J. N.; Rutjes, F. P. J. T.; van Maarseveen, J. H.; Hiemstra, H. *Tetrahedron Lett.* **1999**, *40*, 6079−82.
(184) Kumar, K. S.; Pillai, V. N. R. *Tetrahedron* **1999**, *55*, 10437−46.
(185) Hori, M.; Gravert, D. J.; Wentworth, P., Jr.; Janda, K. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2363−8.
(186) Sylvain, C.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* **1998**, *39*, 9679−80.
(187) Trautwein, A. W.; Jung, G. *Tetrahedron Lett.* **1998**, *39*, 8263−6.
(188) Lee, K. J.; Angulo, A.; Ghazal, P.; Janda, K. D. *Org. Lett.* **1999**, *1*, 1859−62.
(189) Domínguez, E.; O'Donnell, M. J.; Scott, W. L. *Tetrahedron Lett.* **1998**, *39*, 2167−70.
(190) Kondo, Y.; Komine, T.; Fujinami, M.; Uchiyama, M.; Sakamoto, T. *J. Comb. Chem.* **1999**, *1*, 123−6.
(191) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136.
(192) Gutke, H.-J.; Spitzner, D. *Tetrahedron* **1999**, *55*, 3931−6.
(193) Zaragoza, F.; Stephensen, H. *J. Org. Chem.* **1999**, *64*, 2555−7.
(194) Hall, B. J.; Sutherland, J. D. *Tetrahedron Lett.* **1998**, *39*, 6593−6.
(195) Zheng, A.; Shan, D.; Shi, X.; Wang, B. *J. Org. Chem.* **1999**, *64*, 7459−66.
(196) Barco, A.; Benetti, S.; De Risi, C.; Marchetti, P.; Pollini, G. P.; Zanirato, V. *Tetrahedron Lett.* **1998**, *39*, 7591−4.
(197) Lew, A.; Chamberlin, A. R. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3267−72.
(198) Bolli, M. H.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2243−6.
(199) Paris, M.; Douat, C.; Heitz, A.; Gibbons, W.; Martinez, J.; Fehrentz, J.-A. *Tetrahedron Lett.* **1999**, *40*, 6079−82.
(200) Paris, M.; Heitz, A.; Guerlavais, V.; Cristau, M.; Fehrentz, J.-A.; Martinez, J. *Tetrahedron Lett.* **1998**, *39*, 7287−90.
(201) Rademann, J.; Grotli, M.; Meldal, M.; Bock, K. *J. Am. Chem. Soc.* **1999**, *121*, 5459−66.
(202) Grosche, P.; Höltzel, A.; Walk, T. B.; Trautwein, A. W.; Jung, G. *Synthesis* **1999**, 1961−70.
(203) Salvino, J. M.; Kiesow, T. J.; Darnbrough, S.; Labaudiniere, R. *J. Comb. Chem.* **1999**, *1*, 134−9.
(204) Salvino, J. M.; Mervic, M.; Mason, H. J.; Kiesow, T.; Teager, D.; Airey, J.; Labaudiniere, R. *J. Org. Chem.* **1999**, *64*, 1823−30.

(205) Doi, T.; Hijikuro, I.; Takahashi, T. *J. Am. Chem. Soc.* **1999**, *121*, 6749−50.
(206) Lyngso, L. O.; Nielsen, J. *Tetrahedron Lett.* **1998**, *39*, 5845−8.
(207) Boldi, A. M.; Johnson, C. R.; Eissa, H. O. *Tetrahedron Lett.* **1999**, *40*, 619−22.
(208) Nicolaou, K. C.; Pastor, J. Winssinger, N.; Murphy, F. *J. Am. Chem. Soc.* **1998**, *120*, 5132−3.
(209) Lee, C. E.; Kick, E. K.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 9735−7.
(210) Rottländer, M.; Knochel, P. *J. Comb. Chem.* **1999**, *1*, 181−3.
(211) Boymond, L.; Rottländer, M. Cahiez, G.; Knochel, P. *Angew. Chem.* **1998**, *110*, 1801−4; *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1701−3.
(212) Hu, Y.; Porco, J. A., Jr.; Labadie, J. W.; Gooding, O. W.; Trost, B. M. *J. Org. Chem.* **1998**, *63*, 4518−21.
(213) Chen, C.; McDonald, I. A.; Munoz, B. *Tetrahedron Lett.* **1998**, *39*, 217−20.
(214) Chen, C.; Munoz, B. *Tetrahedron Lett.* **1998**, *39*, 3401−4.
(215) Chen, C.; Munoz, B. *Tetrahedron Lett.* **1998**, *39*, 6781−4.
(216) Katritzky, A. R.; Belyakov, S. A.; Tymoshenko, D. O. *J. Comb. Chem.* **1999**, *1*, 173−6.
(217) Paio, A.; Zaramella, A.; Ferritto, R.; Conti, N.; Marchioro, C.; Seneci, P. *J. Comb. Chem.* **1999**, *1*, 317−25.
(218) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426−7.
(219) Piscopio, A. D.; Miller, J. F.; Koch, K. *Tetrahedron Lett.* **1998**, *39*, 2667−70.
(220) Frechet, J. M.; Schuerch, C. J. *J. Am. Chem. Soc.* **1971**, *93*, 492−6.
(221) Knerr, L.; Schmidt, R. R. *Synlett* **1999**, 1802−4.
(222) Cao, J.; Cuny, G. D.; Hauske, J. R. *Mol. Diversity* **1998**, *3*, 173−9. (b). Cuny, G. D.; Cao, J.; Sidhu, A.; Hauske, J. R. *Tetrahedron* **1999**, *55*, 8169−78.
(223) Barrett, A. G.; Cramp, S. M.; Roberts, R. S. *Org. Lett.* **1999**, *1*, 1083−6.
(224) Ahmed, M.; Barrett, A. G. M.; Braddock, D. C.; Cramp, S. M. Procopiou, P. A. *Tetrahedron Lett.* **1999**, *40*, 8657−62.
(225) Andrade, R. B.; Plante, O. J.; Melean, L. G.; Seeberger, P. H. *Org. Lett.* **1999**, *1*, 1811−4.
(226) Schuster, M.; Blechert, S. *Tetrahedron Lett.* **1998**, *39*, 2295−8.
(227) Cano, M.; Camps, F.; Joglar, J. *Tetrahedron Lett.* **1998**, *39*, 9819−22.
(228) Grigg, R.; Major, J. P.; Martin, F. M.; Whittaker, M. *Tetrahedron Lett.* **1999**, *40*, 7709−11.
(229) Miyabe, H.; Fujishima, Y.; Naito, T. *J. Org. Chem.* **1999**, *64*, 2174−5.
(230) Yim, A.-M.; Vidal, Y.; Viallefont, P.; Martinez, J. *Tetrahedron Lett.* **1999**, *40*, 4535−8.
(231) Berteina, S.; De Mesmaeker, A. *Tetrahedron Lett.* **1998**, *39*, 5759−62.
(232) Watanabe, Y.; Ishikawa, S.; Takao, G.; Toru, T. *Tetrahedron Lett.* **1999**, *40*, 3411−4.
(233) Miyabe, H.; Tanaka, H.; Naito, T. *Tetrahedron Lett.* **1999**, *40*, 8387−90.
(234) Zhu, X.; Ganesan, A.; *J. Comb. Chem.* **1999**, *1*, 157−62.
(235) Nicolaou, K. C.; Pfefferkorn, J. A.; Cao, G.-Q.; Kim, S.; Kessabi, J. *Org. Lett.* **1999**, *1*, 807−10.
(236) Nicolaou, K. C.; Pastor, J.; Barluenga, S.; Winssinger, N. *Chem. Commun.* **1998**, 1947−8.
(237) Du, X.; Armstrong, R. W. *Tetrahedron Lett.* **1998**, *39*, 2281−4.
(238) Zhao, B.; Brittain, W. J. *J. Am. Chem. Soc.* **1999**, *121*, 3557−8.
(239) Adams, J. H.; Cook, R. M.; Hudson, D.; Jammalamadaka, V.; Lyttle, M. H.; Songster, M. F. *J. Org. Chem.* **1998**, *63*, 3706−16.
(240) Mergler, M.; Dick, F.; Gosteli, J.; Nyfeler, R. *Tetrahedron Lett.* **1999**, *40*, 4663−4.
(241) Scialdone, M. A.; Shuey, S. W.; Soper, P.; Hamuro, Y.; Burns, D. M. *J. Org. Chem.* **1998**, *63*, 4802−7.
(242) Orosz, G.; Kiss, L. P. *Tetrahedron Lett.* **1998**, *39*, 3241−2.
(243) Lorsbach et al. included the following: (1) Reissert complex formation, (2) C-alkylation, (3) 1,3-dipolar cycloaddition, (4) Suzuki coupling.
(244) Stieber et al. and Brill et al. included the following: (1) Stille coupling, (2) Heck coupling, (3) Suzuki coupling, (4) Sonogashira coupling.

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