Carbon–Carbon Bond Forming Solid-Phase Reactions

Beth A. Lorsbach and Mark J. Kurth*

Department of Chemistry, University of California, Davis, California 95616

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Contents

Beth A. Lorsbach was born in Missouri in 1971. She received her B.A. in chemistry from Boston University in 1993. She began her doctoral research at University of California, Davis, in 1995, joining the research groups of Professor Mark J. Kurth and Professor R. Bryan Miller. Her doctoral research has focused on developing solid-phase organic reactions to deliver heterocyclic compounds. She is currently a fourth-year graduate student whose research effort focuses on the synthesis and use of cross-linked polymers in asymmetric reactions.

Mark J. Kurth was born in Iowa in 1953. He received his B.A. degree in 1976 from the University of Northern Iowa, where he worked with Professor James G. MacMillan. He earned his Ph.D. degree at the University of Minnesota (1980), where he worked with Professor Thomas R. Hoye on the total synthesis of brominated marine natural products such as aplysistatin. After a postdoctoral study with Professor Wolfgang Oppolzer at the University of Geneva (1980–81) developing chiral auxiliaries for the Diels–Alder reaction, he joined the chemistry faculty at the University of California, Davis. His current research activities span natural products total synthesis, synthetic methods development, solid-phase organic synthesis and combinatoral chemistry, and polymer synthesis and characterization.

I. Introduction

Merrifield's pioneering work in solid-phase peptide synthesis in the 1960s has had a dramatic impact on synthetic organic chemistry in the 1990s.[1] While organic chemists such as Leznoff and Frechet established the validity of small-molecule solid-phase synthesis in the 1970s,[2,3] the focus today is on applying solid-phase synthesis in combinatorial discovery efforts. In this regard, the majority of small molecules synthesized on solid phase have been heterocyclic in nature.[4]

The solid-phase organic synthesis of small organic molecules depends greatly on the adaptation of solution reactions to solid phase. In contrast to the plethora of solid-phase organic syntheses employing heteroatom bond forming reactions, there are fewer

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examples of solid-phase carbon−carbon bond forming reactions. Driven by the important role of carbon−carbon bond formation in organic synthesis, this is now changing.[5] Furthermore, carbon−carbon bond manipulations allow for greater diversity in biological and medicinal targets. This review summarizes the literature for the period 1990−1997 as it relates to carbon−carbon bond forming solid-phase reactions resulting in small organic molecules.

II. Metal-Catalyzed Coupling Reactions

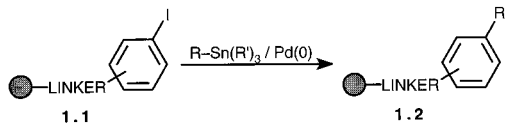
Perhaps the most prevalent method for solid-phase carbon−carbon bond formation is metal-catalyzed coupling reactions. The Stille[6] reaction was the first palladium-catalyzed reaction to be performed on solid support; Heck[7] and Suzuki[8] coupling reactions soon followed. Solid-phase variants of the Stille, Heck, and Suzuki coupling reactions are now very reliable and often efficient reactions.

While these reactions have been used primarily to make biaryl compounds, solid-phase metal-catalyzed coupling reactions have also been used to synthesize indole analogues, 2-aminoaryl ketone derivatives, and 1,4-benzodiazepine-2,5-dione derivatives, and for intramolecular macrocyclization.[9]

2.1. Stille Coupling Reactions

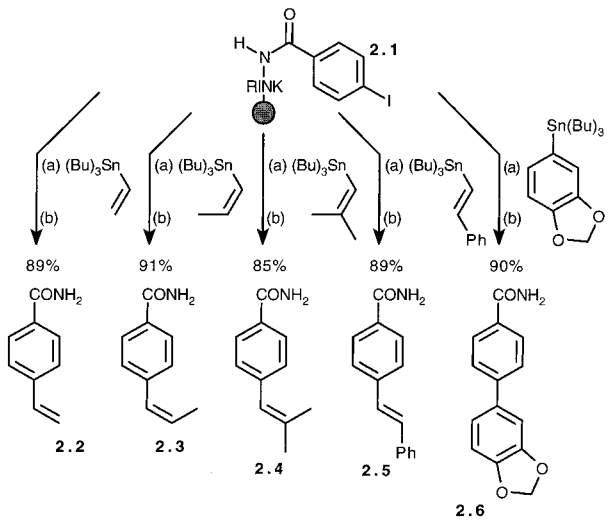
Deshpande was the first to adapt the Stille coupling reaction to solid support in the synthesis of biaryls.[10] Commercially available FMOC-Ala-Wang resin[11] and FMOC-Rink resin[12] were both chosen as the polymer backbone (Scheme 1) in the synthesis of

Scheme 1



vinyl and biaryl derivatives. In this report, polymer-bound aryl iodides were coupled with vinyl or aryl stannanes. Scheme 2 depicts the seven compounds

Scheme 2[a]

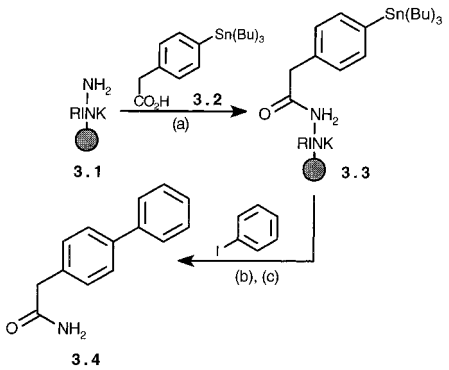


[a] Reagents: (b) Pd_2dba_3 (5 mol %), $AsPh_3$ (20 mol %).

synthesized, along with the yields for each derivative. Interestingly, respectable yields were obtained even for couplings with hindered stannanes (**2.4**) [$(CH_3)_2$-CH=CHSnBu_3] and aryl stannanes (**2.6**) [Ar−SnBu_3].

Sucholeiki used the Stille coupling reaction in the synthesis of biaryl derivatives;[13] he examined polymer-bound aryl stannanes as well as polymer-bound aryl iodides and triflates. Scheme 3 illustrates the solid-

Scheme 3[a]



[a] Reagents: (a) DIC, CH_2Cl_2; (b) biaryl coupling; (c) 5% TFA−CH_2Cl_2.

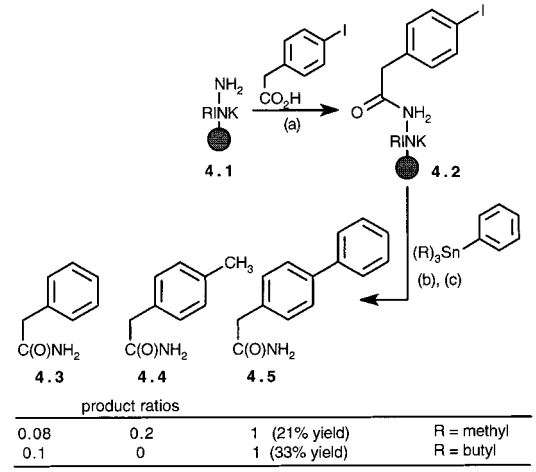
phase Stille coupling of polymer-bound aryl stannanes with aryl triflates and iodides. The aryl stannane (**3.2**) was attached to the Rink[12] amide resin using diisopropylcarbodiimide (DIC). Aryl stannane loading was measured both by tin elemental analysis (0.3 mmol of tin/g) and by a quantitative ninhydrin test for the free amines remaining after amide formation.

Variation of the palladium catalyst showed that tris(dibenzylideneacetone)dipalladium (Pd_2dba_3) was most effective for performing solid-phase Stille coupling reactions between polymer-bound aryl stannanes and organic electrophiles. In this study, the commonly used Stille conditions of triphenylphosphine and $PdCl_2(PPh_3)_2$ did not give the biaryl product. Instead, these conditions produced phenylacetamide and tri-*n*-butyltin byproducts. However, the use of Farina conditions[14] (tri-2-furylphosphine (TFP) and Pd_2dba_3) gave the desired biaryl product.

Switching solid- and solution-phase reagents by having a polymer-bound aryl iodide (**4.2**) rather than a polymer-bound aryl stannane had considerable influence on reaction efficiency. For example, 4-iodophenylacetic acid was attached to the Rink amide resin using DIC in CH_2Cl_2 to yield the polymer-bound aryl iodide; a loading at 0.3 mmol of iodine/g was determined by iodine elemental analysis. Employing the coupling conditions of TFP and Pd_2dba_3 with trimethylphenyltin, only 21% of the biaryl product was obtained after cleavage (Scheme 4). However, this was more effective than the Stille coupling of a polymer-bound aryl iodide with an aryl stannane, which gave only 15% of the biaryl product.

The use of tributylphenyltin rather than trimethylphenyltin afforded 33% of the biaryl product. The authors attribute this to alkyl transfer from tributylphenyltin being 10 times slower than from trimethylphenyltin. Thus, $(C_6H_5)CH_2CONH_2$ and *p*-$(CH_3C_6H_4)CH_2CONH_2$ byproducts are formed more slowly when using tributylphenyltin.

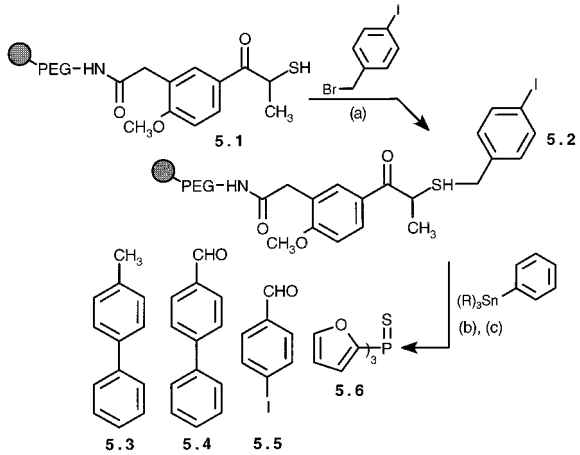
Scheme 4[a]



[a] Reagents and conditions: (a) DIC, CH_2Cl_2; (b) Pd_2dba_3, LiCl, TFP, NMP, 25 °C; (c) 5% TFA−CH_2Cl_2.

Another approach developed by Sucholeiki was to employ a resin which, upon cleavage, would deliver substrates not having an amide moiety.[15] The resin selected for this purpose was NpSSMpact resin (**5.1**), a photoactive support. The NpSSMpact resin was photochemically cleaved after Stille coupling to afford a biaryl compound (see compounds **5.3** and **5.4**) without amide or carboxylic acid appendages. Treating the resin-bound thiol (**5.1**) with DIEA and 4-iodobenzyl bromide in DMF gave the polymer-bound benzyl thioether (**5.2**) (Scheme 5). Loading of the

Scheme 5[a]



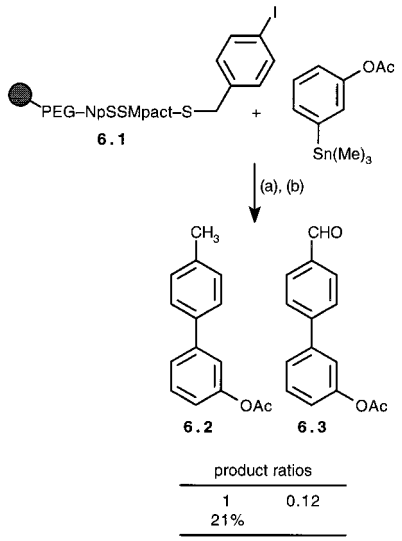
[a] Reagents and conditions: (a) DIEA, DMF; (b) Pd_2dba_3, LiCl, TFP, NMP, 25 °C; (c) *hν* (350 nm), CH_3CN.

polymer was determined by iodine elemental analysis (0.2 mmol of iodine/g). The resin-bound aryl iodide was treated with TFP, Pd_2dba_3, and a trialkylphenylstannane, and subsequent irradiation at 350 nm cleaved the biaryl products from the resin.

Unfortunately, biaryl yields were low, and side products of unreacted aryl iodide and trifurylphosphine sulfide were formed. The formation of trifurylphosphine sulfide was avoided by reducing the amount of TFP used, but the amounts of palladium catalyst and trialkylphenylstannane required were higher than those used in the Rink amide coupling experiments. Indeed, 4 times as much catalyst and nearly 4 times the amount of trialkylstannane were needed to achieve coupling. Interestingly, tributylphenyltin gave much lower yields than trimethylphenyltin when using the NpSSMpact resin (R = CH_3, 10% yield of biaryl; R = butyl, 3% yield of biaryl), opposite of the results observed with tributylphenyltin when using the Rink amide resin.

The NpSSMpact resin-bound aryl iodide (**6.1**) was also coupled with functionalized aryl stannanes (see compounds **6.2** and **6.3**). As illustrated in Scheme 6,

Scheme 6[a]

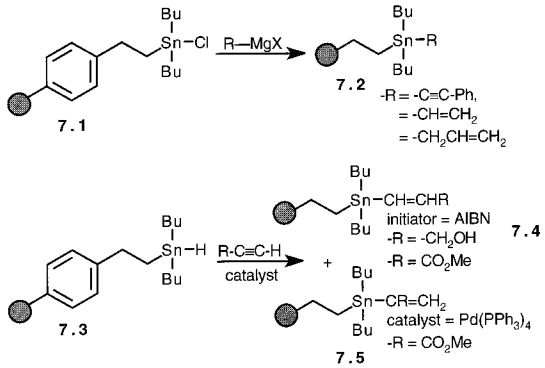


[a] Reagents and conditions: (a) Pd_2dba_3, LiCl, TFP, NMP, 25 °C; (b) *hν* (350 nm), CH_3CN.

treating polymer-bound aryl iodide with 15 equiv of (3-acetoxyphenyl)trimethyltin, TFP, and Pd_2dba_3 afforded the desired biaryl in 21% yield after photocleavage.

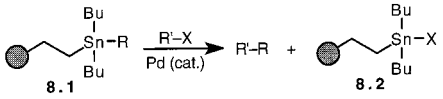
Development of an efficient resin-bound organotin reagent is important in the Stille coupling reaction because it avoids the operational difficulties of removing residual organotin compounds. Furthermore, the resin-bound stannane can be regenerated and recycled for repeated use in the coupling reaction. With these advantages in mind, Kuhn and coworkers used commercially available cross-linked polystyrene to develop a resin-bound organotin reagent.[16] The resin-bound stannane (**7.2**) was prepared via hydrostannation or Grignard reaction (Scheme 7).

Scheme 7



These polymer-bound stannanes (**8.1**) were coupled with organic electrophiles via the Stille reaction [2% $Pd(PPh_3)_4$, toluene, 80 °C, 24−60 h] to give various alkynyl or alkenyl coupled products in moderate yields (Scheme 8).

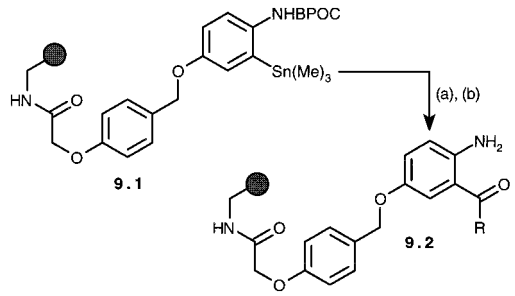
Scheme 8



Ellman has incorporated a solid-phase Stille coupling reaction into his synthesis of 1,4-benzodiazepine derivatives.[17] The lack of commercially available 2-aminoaryl ketones, one of the building blocks needed for the synthesis of 1,4-benzodiazepine derivatives, prompted development of a solid-phase synthesis of 2-aminoaryl ketone derivatives. This solid-phase synthesis implemented a Stille coupling reaction between an acid chloride and a polymer-bound aryl stannane.

The *N*-BPOC-protected (2-aminoaryl)stannane ester was attached to aminomethylated polystyrene resin (Wang resin) with DIPEA and a catalytic amount of DMAP in NMP. The 2-(4-biphenyl)isopropyloxycarbonyl (BPOC) protecting group was chosen because it is unaffected by Stille conditions and can be removed under mildly acidic conditions to which the linker is stable. The polymer-bound aryl stannane (**9.1**) was coupled with aromatic and aliphatic acid chlorides via Stille coupling using $Pd_2dba_3{\cdot}CHCl_3$. Acid scavengers (K_2CO_3 and *i*-Pr_2EtN) were used in the Stille coupling reactions to prevent protodestannylation and carbamate deprotection (Scheme 9). The

Scheme 9[a]

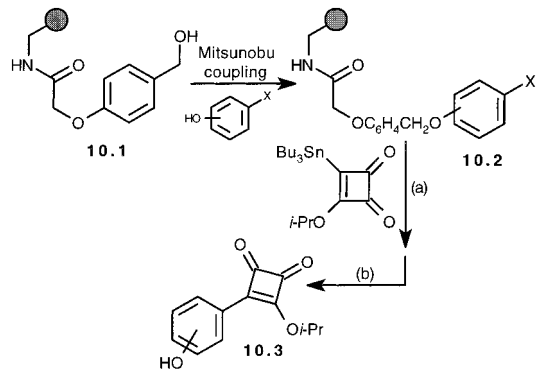


[a] Reagents: (a) THF, K_2CO_3, DIEA, Pd_2dba_3, ArC(=O)Cl or RC(=O)Cl; (b) 97:3 CH_2Cl_2/TFA.

use of $Pd(PPh_3)_4$ required high temperatures to afford coupling products, which resulted in some cleavage of the BPOC protecting group. After the solid-phase Stille coupling reaction, the resin was treated with dilute KCN in DMSO to remove the palladium residue deposited in the coupling reaction. The BPOC group was deprotected with 3% TFA in CH_2Cl_2 to afford the polymer-bound 2-aminoaryl ketone (**9.2**).

A solid-phase Stille coupling reaction was also used in the synthesis of cyclobutenedione derivatives.[18] Wang resin was functionalized via a Mitsunobu reaction with an iodophenyl ether (both ortho and para ether linkages were observed). The polymer-bound iodoaryl ether (**10.2**) was coupled with tributlytin isopropyl squarate using the Stille reaction (Scheme 10).[19] After TFA cleavage, the desired

Scheme 10[a]

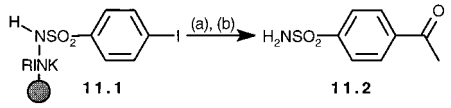


[a] Reagents: (a) Pd^{II}, CuI, DMF; (b) TFA, CH_2Cl_2.

squaric acid derivative was obtained in 95% yield (**10.3**). While good yields of the cyclobutenedione derivatives can be achieved, a logistical drawback to this methodology is the need to synthesize stannylated squarates.

Sulfonyl chlorides react readily in solution with amines to give sulfonamides. Spear and co-workers adapted this methodology to solid support and explored reactions with a resin-bound sulfonamide.[20] The Stille coupling was performed on the resin-bound sulfonamide-linked aryl iodide (**11.1**) (Scheme 11) by

Scheme 11[a]

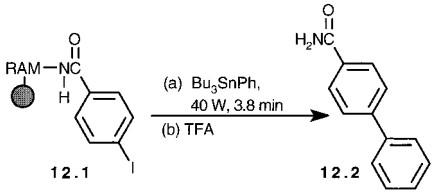


[a] Reagents: (a) Pd_2dba_3, Ph_3As, $CH_2{=}C(OEt)SnBu_3$, NMP; (b) TFA, CH_2Cl_2.

reacting with Pd_2dba_3, triphenylarsine, and 1-(ethoxyvinyl)tributyltin in NMP. This gave the desired 4-acetyl sulfonamide (**11.2**) in 79% yield upon cleavage from the resin.

A final example of a solid-phase Stille coupling reaction incorporated an interesting twist—microwave irradiation to reduce reaction times.[21] Aryl halides were attached to TentaGel S RAM resin, and a microwave-assisted Stille reaction was performed (Scheme 12). The aryl iodide (**12.1**) was treated with

Scheme 12



Bu_3SnPh under microwave irradiation (3.8 min at 40 W) to give the polymer-bound biaryl product. The biaryl product was cleaved from the polymer by treatment with TFA (**12.2**). This technique has also been extended to other palladium-catalyzed coupling reactions.

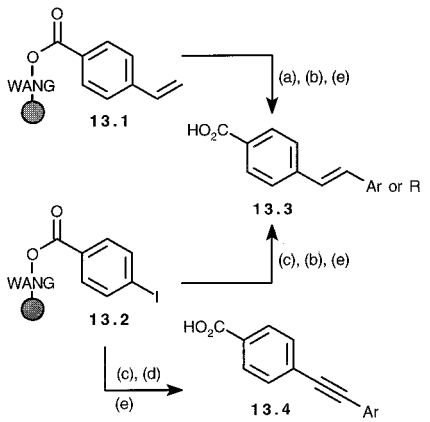
2.2. Heck Reactions

The Heck reaction[7] has been used extensively in solution to prepare substituted olefins. A typical Heck

reaction proceeds by palladium-catalyzed carbon–carbon bond formation between an alkyl/aryl halide and a vinyl component.[7] Adaptation of the Heck reaction to solid-phase organic synthesis has been largely successful due to the mild conditions employed to achieve coupling.

Yu and co-workers coupled polymer-bound aryl iodides with styrene and coupled polymer-bound olefins with aryl halides to give disubstituted olefins.[22] They treated Wang resin with either 4-vinylbenzoic acid or 4-iodobenzoic acid, DIC, and a catalytic amount of DMAP in DMF at 60 °C to give either the polymer-bound aryl styrene or the polymer-bound aryl iodide, respectively (Scheme 13). These resins

Scheme 13[a]



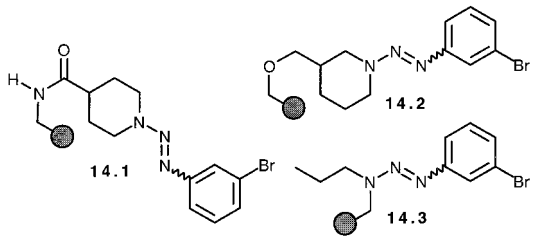
[a] Reagents and conditions: (a) resin (200 mg), aryl halide (100 mg), Et_3N (50 μL) in DMF (3 mL); (b) A: $Pd(OAc)_2$ (20 mg), *n*-Bu_4NCl (20 mg), 80–90 °C, 16 h; or B: Pd_2dba_3 (30 mg), P(2-Tol)$_3$ (20 mg), 100 °C, 20 h; (c) resin (200 mg), olefins or phenylacetylenes (100 mg), Et_3N (50 μL) in DMF (3 mL); (d) A: $Pd(OAc)_2$ (20 mg), *n*-Bu_4NCl (20 mg), 80–90 °C, 16 h; or B: Pd_2dba_3 (30 mg), P(2-Tol)$_3$ (20 mg), 100 °C, 20 h; (e) 90% TFA/CH_2Cl_2.

were treated with aryl halides/triflates or olefins/phenylacetylenes, respectively, to give disubstituted products or acetylenes upon cleavage.

Polymer-bound (styryl) moieties coupled more readily with aryl iodides than with aryl bromides. In fact, the more reactive P(2-Tol)$_3$ ligated palladium was required to couple aryl bromides. Similar results were obtained in coupling the resin-bound halide with olefins. However, no Heck reaction could be observed when reacting solution ArX with polymer-bound olefin, even though a variety of catalysts were examined [$Pd(OAc)_2$, $Pd(PPh_3)_2Cl_2$, Pd_2dba_3, or PdP(2-Tol)$_3$].

A solid-phase synthesis of phenylacetylene oligomers employed the Heck reaction between a polymer-bound aryl iodide and a terminal acetylene. A 1-aryl-3,3-dialkyltriazene linker was used to link the aryl iodide to the solid support.[23] Three different reagents have been attached to polystyrene beads via the 1-aryl-3,3-dialkyltriazene group (Scheme 14). Resin **14.1** was formed by the peptide coupling of a triazene-acid to aminomethylated polystyrene. Resin **14.2** was formed by reaction of a chloromethylated polystyrene with an excess of an alcohol-triazene. Resin **14.3** is unique because it has the triazene moiety directly linked to the polystyrene, as opposed to having a

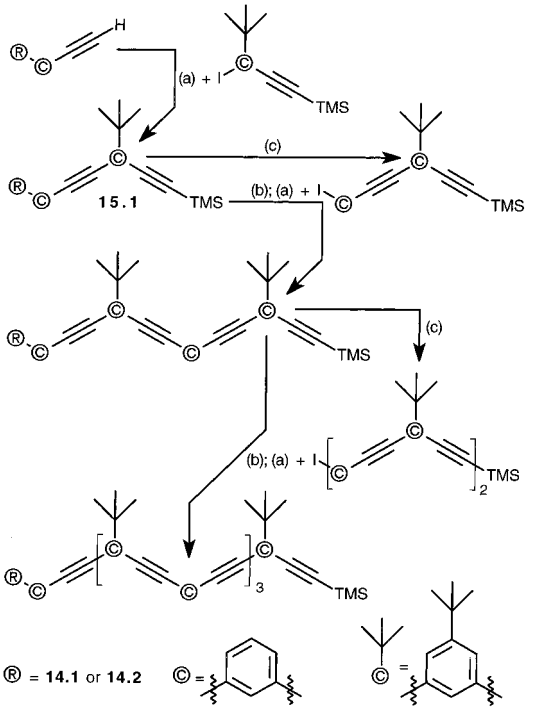
Scheme 14



spacer functionality between the polystyrene backbone and the triazene.

The polymer-bound aryl bromide of **14.1** underwent a Heck reaction with (trimethylsilyl)acetylene, giving a protected phenylacetylene (Scheme 15), while depro-

Scheme 15[a]



[a] Reagents and conditions: (a) Pd_2dba_3, CuI, Ph_3P, TEA, DMF, 65 °C, 24 h; (b) KOH, THF, MeOH, 75 °C, 1 h; (c) MeI, 110 °C, 6 h.

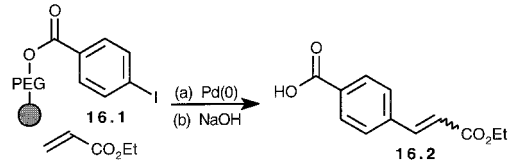
tection of the trimethylsilyl group to give the terminal alkyne allowed for a second Pd(0)-catalyzed coupling. This strategy accommodates an iterative synthesis of phenylacetylene oligomers, as illustrated by obtaining a hexamer in 61% overall yield. However, one serious drawback with resin **14.1** was that the amide spacer made IR analysis ineffective for monitoring the solid-phase reactions because the terminal acetylenic C–H stretch at 3311 cm^{-1} was obscured by the N–H stretch. Thus, cleavage of the oligomer from the resin was required to determine the extent of reaction progress.

Switching to resin **14.2**, which employs an ether spacer group between the polystyrene backbone and the triazene functionality facilitated reaction monitoring using IR. The same iterative process illustrated in Scheme 15 was utilized for resin **14.2**. Here, IR analysis was more useful in determining reaction completeness; the appearance of absorptions at 3311 and 2109 cm^{-1} were assigned to the terminal

alkyne, while the presence of the (trimethylsilyl)-acetylene was indicated by a band at 2156 cm^{-1}. The disappearance/appearance of these absorptions proved to be a reliable method for monitoring these reactions. Finally, use of resin **14.3** in this process allowed for a direct link between the polystyrene backbone and the triazene. The major advantage of using this resin was that synthesis of the trifunctional triazenes in resins **14.1** and **14.2** was avoided. Efforts to produce longer oligomers were unsuccessful.

A solid-phase Heck reaction for vinylation of aryl halides has also been demonstrated.[24] Beginning with commercially available TentaGel hydroxy resin,[25] 4-iodobenzoic acid was attached to the polymer using DCC/DMAP in CH_2Cl_2 at 37 °C for 12 h. Palladium-catalyzed coupling of the polymer-bound 4-iodobenzoate (**16.1**) with ethyl acrylate (Scheme 16) was

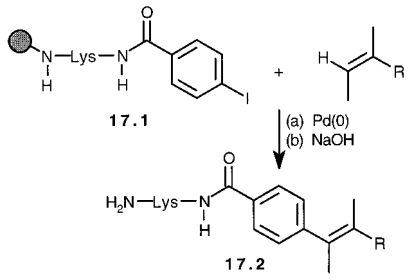
Scheme 16



achieved with the following reaction conditions: 0.3 M ethyl acrylate, 0.05 M $Pd(OAc)_2$, 0.1 M PPh_3, Bu_4NCl, and either 0.3 M K_2CO_3 or saturated K_2CO_3. The polymer was washed (DMF and CH_3OH), and subsequent treatment with 0.1 M NaOH cleaved the coupled product (**16.2**) from the resin. The yield of the coupled product was 43%, with the remainder being unreacted starting material. Increasing the solvent ratio of DMF to H_2O improved yields; a 0.3 M solution of ethyl acrylate in DMF/H_2O (90:10) gave 95% yield of the Heck coupled product when reacted with the polymer-bound 4-iodobenzoate.

In an attempt to further explore the solid-phase vinylation of aryl halides, 4-iodobenzoic acid was attached to Millipore PS-PEG-PAL resin through a BOC-protected lysine residue. The polymer-bound aryl iodide (**17.1**) was subjected to Pd-catalyzed vinylation conditions similar to those used with the TentaGel resin (Scheme 17). After a solid-phase Heck

Scheme 17

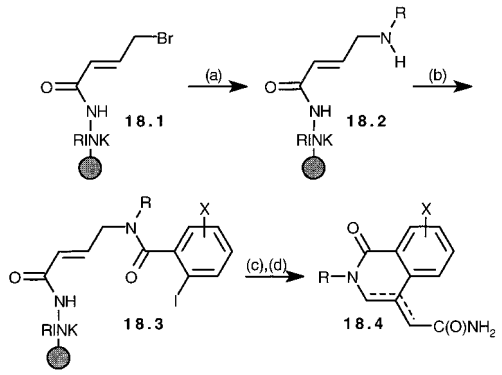


reaction, the resin was washed (DMF, CH_3OH) and dried under vacuum. Treating the resin with TFA (TFA/CH_2Cl_2/anisole = 47/50/3, room temperature, 30 min) cleaved the coupled product (**17.2**) from the resin.

Various vinylic reagents were used, including substrates with electron-withdrawing groups (R = $-CONH_2$, $-CONMe_2$, $-CN$, $-CHO$). Nevertheless, the solid-phase Heck coupling of a polymer-bound alkene with a 4-vinylbenzoic acid and an aryl halide resulted in the recovery of unreacted starting material.

Thus far, we have discussed only intermolecular solid-phase Heck reactions. A solid-phase intramolecular version of the Heck reaction, however, has been employed to synthesize substituted 1-(2*H*)-isoquinolinones.[26] This synthesis began by acylating Rink amide resin with *trans*-4-bromo-2-butenoic acid (**18.1**) (Scheme 18). The bromide underwent S_N2

Scheme 18[a]

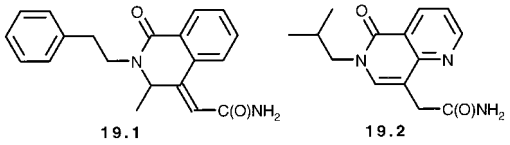


[a] Reagents and conditions: (a) 2.0 M RNH_2 in DMSO, rt, 2 h; (b) 0.5 M acid chloride, 0.5 M TEA, rt, 2 × 30 min; (c) $Pd(PPh_3)_4$, NaOAc, PPh_3, DMA, 85 °C, 5 h; (d) 95/5 TFA/H_2O, rt, 20 min.

displacement to give the secondary amine (**18.2**). A second acylation step with *o*-iodobenzoic acid, which was prepared from anthranilic acid, gave the intermediate iodide (**18.3**) to be used in the intramolecular Heck reaction. The resin (**18.3**) was treated with $Pd(PPh_3)_4$ in DMA, NaOAc, and PPh_3, and heated to 85 °C for 5 h.

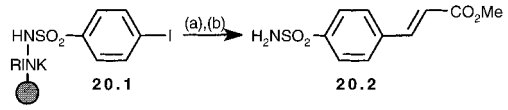
Several monopeptoids were made via this route, with variations at the amine-based side chains as well as with different aryl substitution (R = *i*-Bu, CH_2CH_2Ph, Ph; X = H, 5-CH_3, 8-F, 7-Cl, 6,7-di-OCH_3, 5-OCH_3). This process can be extended to 2-bromopyridine-3-carboxylic acid (**19.1**) and *o*-haloheteroarenecarboxylic acids (**19.2**), which allows for enhanced diversity (Scheme 19).

Scheme 19



Similar to their studies of the stability of sulfonamide-linked resins with respect to the Stille coupling, Spear and co-workers also performed a Heck reaction with these sulfonamide resins.[20] The sulfonamide resin was prepared by treating Rink amide resin with 4-iodophenylsulfonyl chloride and pyridine in CH_2Cl_2 at room temperature. The polymer-bound aryl iodide (**20.1**) coupled with methyl acrylate via the Heck reaction in the presence of $Pd(OAc)_2$ (Scheme 20). Cleavage from the resin with TFA in CH_2Cl_2 afforded the α,β-unsaturated methyl ester phenylsulfonamide (**20.2**) in 95% yield.

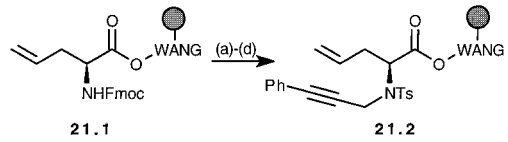
Scheme 20[a]



[a] Reagents: (a) $Pd(OAc)_2$, TEA, $(n\text{-}Bu)_4NCl$, methyl acrylate, DMF; (b) TFA/CH_2Cl_2.

The solid-phase synthesis of fused bicyclic amino acid derivatives incorporated a Heck reaction for increased diversification.[27] The work began with the allyl FMOC-protected glycine attached to Wang resin (Scheme 21). The secondary amine was deprotected

Scheme 21[a]

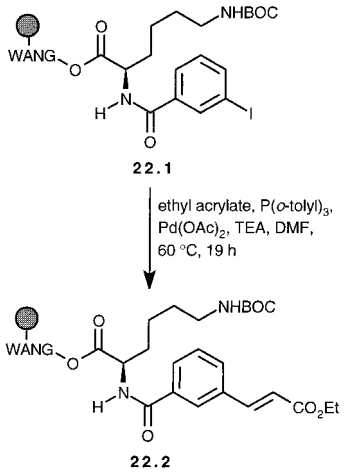


[a] Reagents: (c) 20% piperidine, CH_2Cl_2; (b) TsCl, TEA, CH_2Cl_2; (c) propargyl bromide, Cs_2CO_3, DMF; (d) $(PPh_3)_2PdCl_2$, CuI, iodobenzene, TEA, CH_2Cl_2.

(20% piperidine, CH_2Cl_2) and subsequently tosylated (TsCl, Et_3N, CH_2Cl_2). The sulfonamide was N-alkylated with propargyl bromide (Cs_2CO_3, DMF), and this newly formed polymer-bound alkyne underwent palladium-catalyzed coupling with iodobenzene [$(Ph_3P)_2PdCl_2$, CuI, Et_3N, CH_2Cl_2] to give **21.2**. This eneyne intermediate serves as precursor to interesting bicyclic amino acid derivatives.

Monitoring of the Heck coupling reaction by magic angle spinning (MAS) NMR spectroscopy was reported.[28] The MAS NMR technique, which minimizes line broadening by spinning the sample at an angle of 54.7°,[29] was used to monitor the intermediates of a three-step solid-phase synthesis of substituted olefins (Scheme 22).

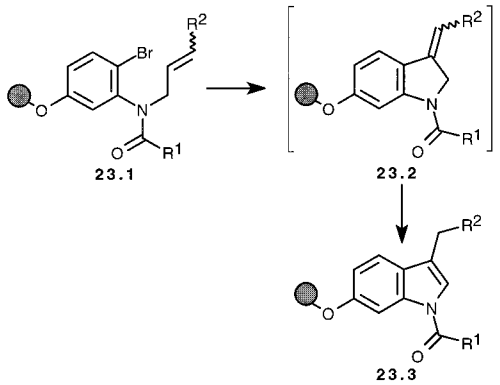
Scheme 22



A second example of a solid-phase intramolecular Heck reaction of aryl halides can be seen via the synthesis of indole derivates.[30] This intramolecular Heck reaction proceeds through a 5-exo-trig transition state to give the exo olefin intermediate, which isomerizes to give the indole product (Scheme 23).

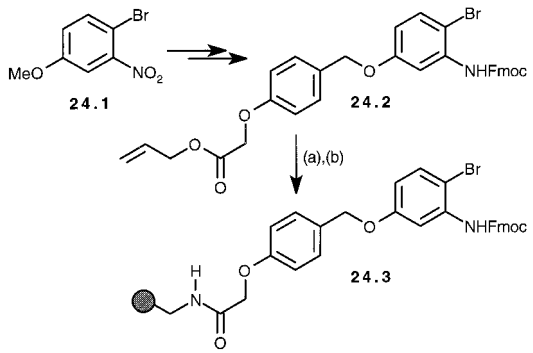
The synthesis of the starting resin-bound aryl halide began with 4-bromo-3-nitroanisole (**24.1**), which

Scheme 23



was demethylated (BBr_3, CH_2Cl_2) to give the phenol. This intermediate was coupled with allyl 2-(4-bromomethyl)-phenoxyacetate (in 91% yield). Reduction of the nitro group with $Na_2S_2O_4$ gave the primary amine, which was protected with FMOCCl (**24.2**) (Scheme 24). The resulting allyl ester was converted

Scheme 24[a]

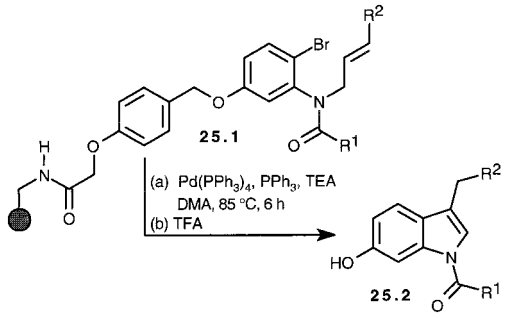


[a] Reagents and conditions: (a) $Pd(PPh_3)$, Bu_3SnH, CH_2Cl_2, 22 °C, 40 min; (b) TentaGel S−NH_2, DIC, HOBT, DMF, 22 °C, 2 d.

to the carboxylic acid and coupled with TentaGel S−NH_2[31] resin to give the polymer-bound aryl bromide (**24.3**). This intermediate was then converted into the Heck precursor by removal of the FMOC, acylation of the amine with acid chloride, and alkylation with allyl bromide.

The Heck precursor **25.1** underwent a 5-exo-trig cyclization when treated with $Pd(PPh_3)_4$, PPh_3, and Et_3N in DMA (dimethylacetamide) at 85 °C for 6 h (Scheme 25). An inert atmosphere is critical because

Scheme 25

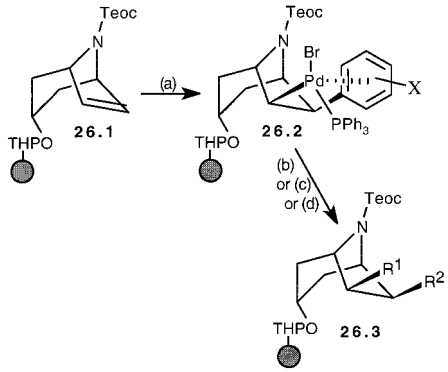


the palladium is oxidized at higher temperatures, which results in debromination of **25.1**. The indole derivatives **25.2** were released from the polymer after

treating the resin with TFA. Several indole analogues were synthesized in yields ranging from 65 to 94%.

One example of a multicomponent coupling process is Ellman's palladium-mediated three-component coupling process giving tropane derivatives.[32] The first step in this three-component process involved a Heck reaction. Typically, a Heck reaction pathway proceeds via oxidative addition of Pd(0) to the aryl halide with subsequent insertion of an alkene into the σ-aryl C−Pd bond.[7] The olefin insertion step gives the syn product in which the organic ligand from the palladium is attached to the least hindered carbon of the olefin.[7] A β-hydride elimination follows, delivering the disubstituted alkene. However, in Ellman's case, the organopalladium intermediate obtained from the olefin insertion process was stable toward β-hydride elimination. The process began with the coupling of a dihydropyran-functionality bound to a polystyrene resin and an ethyl 3-α-hydroxy-8-azabicyclo[3.2.1]oct-6-ene-8-[[(trimethylsily)ethyl]oxy]-carbonyl to give the polymer-bound olefin intermediate needed for Heck reaction (**26.1**) (Scheme 26). This

Scheme 26[a]



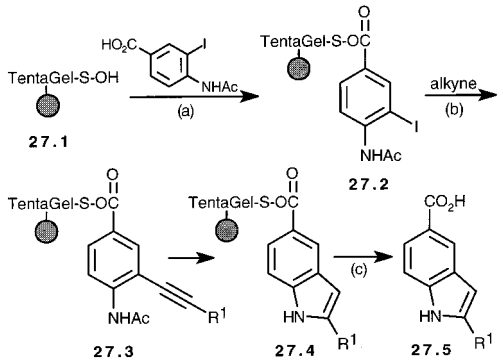
[a] Reagents and conditions: (a) aryl bromide (X = H, 4-methoxy, 4-methyl, $Pd(PPh_3)_4$, THF, 66 °C; (b) arylboronic acid, 2 N Na_2CO_3, PPh_3, THF or anisole, 66 °C; (c) HCO_2H, TEA, PPh_3, DMF, 60 °C; (d) $C_6H_5C{\equiv}CH$, CuI, Bu_4NCl, DMF, 66 °C.

olefin underwent oxidative addition in the Heck reaction [aryl bromide (X = H, 4-methoxy, 4-methyl), $Pd(PPh_3)_4$, THF, 66 °C], giving the stable organopalladium(II) complex (**26.2**). Electron-rich aryl bromides were found to react more rapidly than electron-poor aryl bromides in this system compared to analogous norborene and norboradiene systems. This resin-bound organopalladium intermediate could be washed (degassed THF) and stored under inert atmosphere at room temperature.

The fact that the resin-bound organopalladium intermediate can be isolated allows for library synthesis, using a split synthesis strategy. Reactions of the organopalladium intermediate with various nucleophiles gives two sites of diversity at R^1 and R^2 (**26.3**) (Scheme 26). One example was the coupling of the polymer-bound palladium species with arylboronic acids via Suzuki reaction.[33] The Suzuki coupling of this organopalladium species, with both electron-rich and electron-deficient boronic acids, was very effective. Alternatively, the resin-bound palladium intermediate, **26.2**, can be treated with formic acid to exchange the palladium substituent for a hydrogen or into the *cis*,*exo*-5-aryl-6-alkynyl compound by treatment with Bu_4NCl, Et_2NH, CuI, and phenylacetylene.

A solid-phase approach to the synthesis of indoles involved the palladium/copper-catalyzed coupling of alkynes with resin-bound iodoaniline derivatives.[34] The coupling reaction produced an alkyne intermediate which presumably cyclizes to give the indole derivative (Scheme 27). The solid-phase variant of

Scheme 27[a]



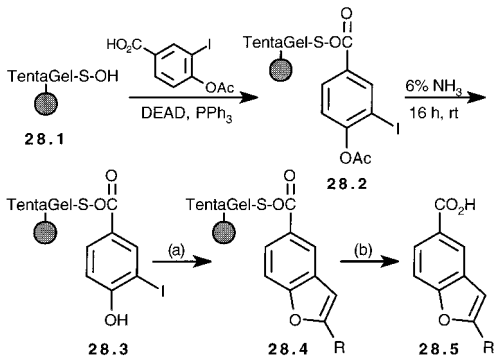
[a] Reagents and conditions: (a) PPh_3, DEAD, THF, rt; (b) $Pd(PPh_3)_2Cl_2$, CuI, TMG, dioxane, 90 °C; (c) aq NaOH, *i*-PrOH.

this coupling reaction was performed on commercially available TentaGel S resin (**27.1**) in which the free hydroxyl of the resin underwent a Mitsunobu reaction to give the polymer-bound iodoaniline derivative. The resin-bound iodoaniline moiety **27.2** was coupled with a monosubstituted alkyne and rapidly cyclized in situ to give the indole product. The indole (**27.4**) was cleaved from the resin with NaOH 1 M/*i*-PrOH, giving the indole carboxylic acid heterocycles in 50−80% overall yield (overall yields were based on the loading of the polymer-bound iodide 0.2 mmol/g resin). Although several alkynes were considered, aryl-substituted alkynes were most commonly used.

The same authors extended their studies to the solid-phase synthesis of 2-substituted benzofuran carboxylic acids, which were prepared via a solid-phase Heck coupling of a resin-bound hydroxy iodide and an acetylene.[35] Several acetylenes were employed: R = $(CH_2)_5CH_3$, *t*-Bu, Ph, $(CH_2)_3Cl$, $(CH_2)_3$-OH, $C(OH)(CH_3)_2$, CH_2NH_2, and CH_2NEt_2. First, TentaGel S−OH (**28.1**) was coupled with 4-hydroxy-3-iodobenzoic acid via the Mitsunobu reaction (the 4-hydroxyl was protected as the acetate to avoid self-condensations and was removed prior to the palladium-catalyzed coupling with alkynes). The resulting resin-bound *o*-hydroxy iodide (**28.3**) underwent palladium-catalyzed cyclization with an acetylene to give the polymer-bound benzofuran (Scheme 28). This benzofuran carboxylic acid (**28.5**) was cleaved from the polymer with 1 N NaOH/*i*-PrOH.

While there are numerous examples of palladium-catalyzed macrocyclizations in solution, Hauske and co-workers have demonstrated the first solid-phase palladium-mediated macrocyclization.[36] Using a modified Heck reaction, several macrocyclic compounds were synthesized. TentaGel PHB resin (**29.1**) was reacted with carbonyldiimidazole (CDI) to give the

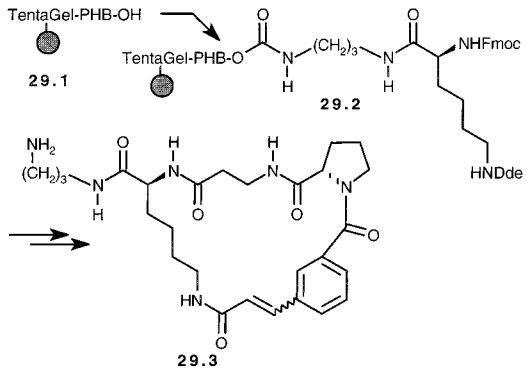
Scheme 28[a]



[a] Reagents and conditions: (a) HC≡CR, $Pd(PPh_3)_2Cl_2$, CuI, TMG, DMF, 50 °C; (b) aq NaOH, *i*-PrOH.

imidazolide resin, which was treated with 1,3-diaminopropane to give a functionalized amino resin and an acid-labile carbamate linker (Scheme 29). The

Scheme 29

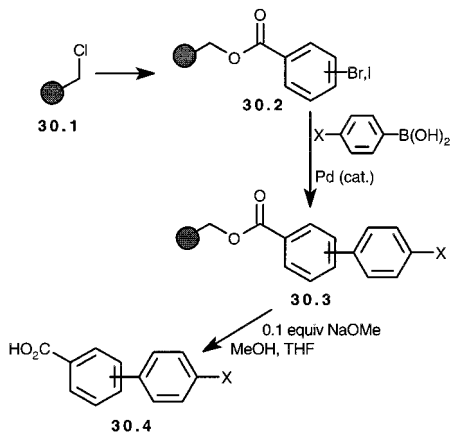


modified Heck reaction effected macrocyclization [$Pd(OAc)_2$, PPh_3, Bu_4NCl, $DMF/H_2O/Et_3N$, room temperature] to give the macrocycle in 78% yield.

2.3. Suzuki Coupling Reactions

The first solid-phase Suzuki coupling reaction was demonstrated by Friesen en route to biaryls,[37] which are present in several biologically active compounds.[38] The synthesis began by treating commercially available Merrifield's resin (**30.1**) with bromo- or iodobenzoic acids (Cs_2CO_3, KI, DMF, 80 °C) to give the resin-bound aryl halides needed for Suzuki coupling (Scheme 30). These polymer-bound aryl halides (**30.2**)

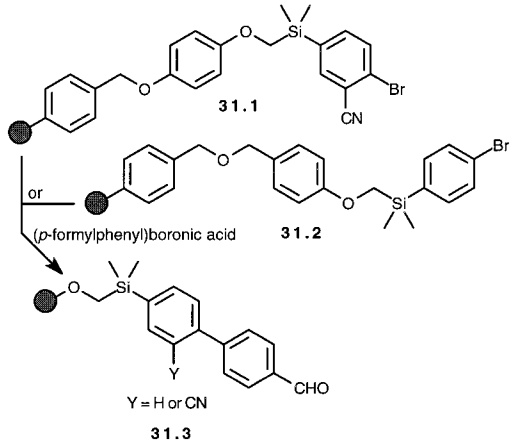
Scheme 30



underwent the Suzuki coupling reaction with appropriate aryl boronic acids. Initial efforts focused on the effects different palladium catalysts had on the biaryl coupling; all but one of the catalysts examined [$Pd_2(C_3H_5)_2Cl_2$] proved effective in the Suzuki coupling reaction. As in other palladium-catalyzed reactions, aryl bromides were found to be less reactive than aryl iodides. (A variety of substituted aryl bromides [ortho, para, meta] are commercially available, and various boronic acids [electron-rich or electron-poor] are accessible.)

A solid-phase Suzuki coupling reaction was used in the study of protodetachable arylsilane polymer linkages.[39] Beginning with Merrifield's resin, two silane-linked phenyl bromides were synthesized. These two silane-linked phenyl bromides (**31.1** or **31.2**) underwent Suzuki coupling with (*p*-formylphenyl)boronic acid to give polymer-bound biphenyl aldehydes (**31.3**) (Scheme 31). IR analysis was used

Scheme 31

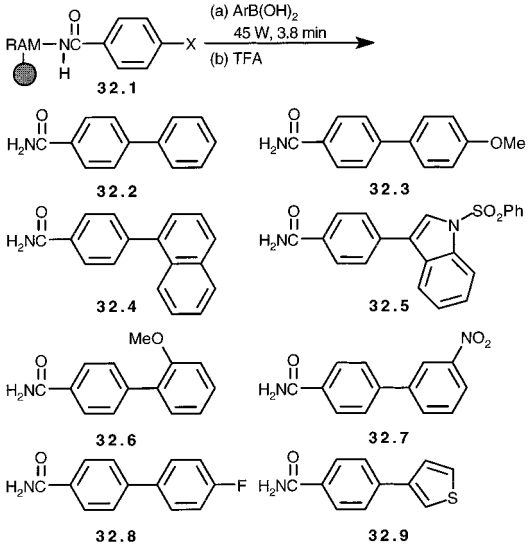


to monitor the reaction, and ^1H NMR spectroscopy, using MAS,[40] provided further evidence for the biaryl aldehyde.

In an attempt to reduce reaction times, the solid-phase microwave-assisted palladium-catalyzed coupling of aryl and heteroaryl boronic acids with iodo- or bromobenzoic acids was investigated. While solid-phase Suzuki coupling reactions have been used to synthesize biaryls, this is the first example of a microwave-assisted solid-phase Suzuki coupling reaction (a microwave-assisted Stille coupling was discussed in Scheme 12).[21] Eight boronic acids were coupled with either 4-bromo or 4-iodobenzoic acid linked to TentaGel S RAM (Rink amide) resin (**32.1**) (Scheme 32). These polymer-bound aryl halides were subjected to 45 W microwave irradiation (3.8 min) in the presence of an arylboronic acid. The coupled biaryl products were cleaved from the resin with TFA.

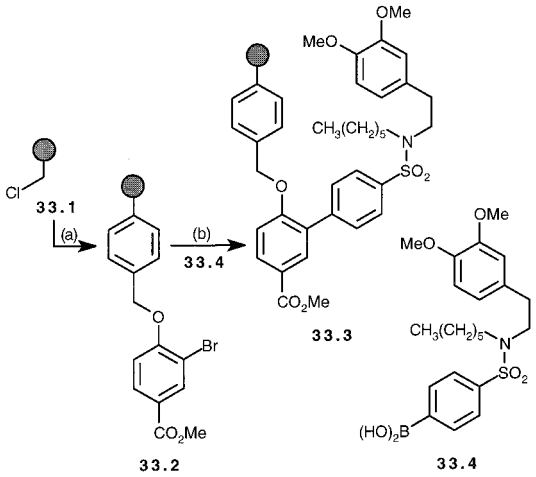
The use of MAS ^1H NMR in combination with a spin−echo was used to monitor $LiAlH_4$ reduction of a polymer-bound methyl benzoate to the corresponding alcohol.[41] While NMR spectroscopy studies are beyond the scope of this review, the synthesis of the resin-bound methyl benzoate did include a Suzuki coupling reaction. Methyl 3-bromo-4-hydroxy-benzoate was attached to Merrifield's resin (**33.1**) with NaOMe in dimethyl acetamide at 80 °C. The result-

Scheme 32



ing aryl bromide (**33.2**) underwent a Suzuki coupling with the aryl boronic acid, as shown in Scheme 33.

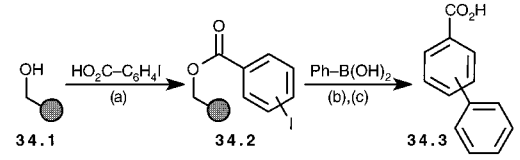
Scheme 33[a]



[a] Reagents and conditions: (a) methyl 3-bromo-4-hydroxybenzoate, NaOMe/DMA, 80 °C; (b) $Pd(PPh_3)_4$, K_2CO_3/toluene, EtOH, 80 °C, **33.4**.

In an attempt to develop a set of general conditions for performing solid-phase Suzuki coupling reactions, Guiles and co-workers coupled SASRIN[42] and Wang resins with an iodobenzoic acid, using standard conditions.[43] Several catalysts were examined for use in the Suzuki coupling reaction of phenylboronic acid at room temperature (Scheme 34). The catalysts Pd-

Scheme 34[a]

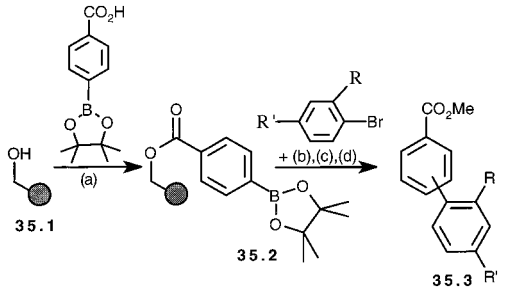


[a] Reagents and conditions: (a) EDCI, TEA, HOBT, CH_2Cl_2, rt; (b) Pd(0) (cat.), DMF, rt; (c) TFA, CH_2Cl_2, rt.

$(PPh_3)_4$ and Pd_2dba_3, both Pd(0), were found to be effective, whereas $PdCl_2$(dppf) failed to deliver the biaryl. Most of the solid-phase Suzuki coupling reactions were complete in 18 h at room temperature. However, *o*-iodobenzoate was somewhat slower due to increased steric interactions. Furthermore, the polymer-bound bromobenzoate derivatives were found to be unreactive when subjected to similar Suzuki coupling conditions. Aryl, alkyl, alkenyl, and heteroaromatic boronic acids were all effective in producing the coupled product. Cleavage of the benzoate was achieved with TFA at room temperature for 30 min, and typical yields were found to be >56% (based on the loading of the iodobenzene resin). Interestingly, certain catalysts were more efficient depending on the boron reagent selected for coupling. For example, Pd_2dba_3 was more efficient at aryl and heteroatom couplings, and $PdCl_2$(dppf) was more effective at coupling alkenylboronic ester.

Also examined were the coupling of boronic esters with various aryl halides (Scheme 35). Both bromo-

Scheme 35[a]

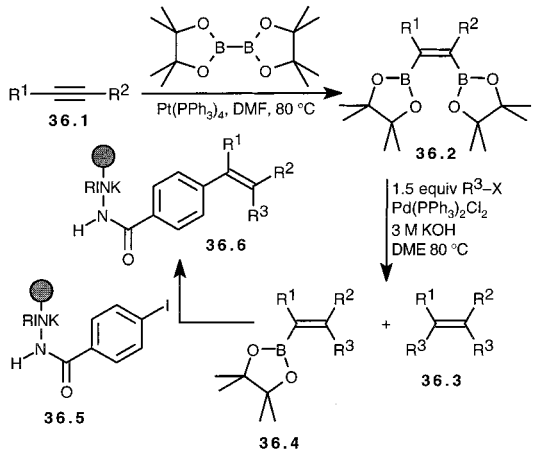


[a] Reagents and conditions: (a) EDCI, TEA, HOBT, CH_2Cl_2; (b) $Pd(PPh_3)_4$ (cat.), K_2CO_3, DMF; (c) TFA, CH_2Cl_2; (d) $TMSCHN_2$, $CHCl_3$, MeOH.

and iodobenzenes with electron-donating and electron-withdrawing substituents produced the biaryl product. The rate of the coupling reaction was slower for the polymer-bound boronic ester than for the polymer-bound aryl halide. Moreover, the coupling reactions with aryl bromides required heat to drive the reaction to completion.

Most solid-phase Suzuki coupling reactions have focused on coupling a resin-bound aryl halide with a solution-phase boronic acid. However, due to the limited number of boronic acids available commercially, developing new methods of attaching the boron species to the resin has generated interest. A clever Suzuki coupling method combined a solution-phase variant of the Suzuki coupling with a subsequent solid-phase Suzuki coupling reaction.[44] Tetrasubstituted ethylenes were synthesized in this "resin capture" strategy. First, using the method developed by Miyaura and Suzuki,[45] alkynes were transformed into the bis(boryl)alkenes via a platinum-catalyzed diboration process. The bis(boryl)alkene (**36.2**) underwent a solution-phase Suzuki coupling reaction to give a diaddition (**36.3**) (a tetrasubstituted ethylene) and a monoaddition (a boronate ester) product (**36.4**), which was then captured by a resin-bound aryl iodide (**36.5**) in a solid-phase Suzuki coupling reaction (Scheme 36). The crude reaction mixture, containing the boronate ester and the diaddition product, was reacted directly with a Rink polymer-bound aryl iodide. Only the boronate ester reacted with the resin-bound aryl iodide via a solid-phase Suzuki coupling reaction.

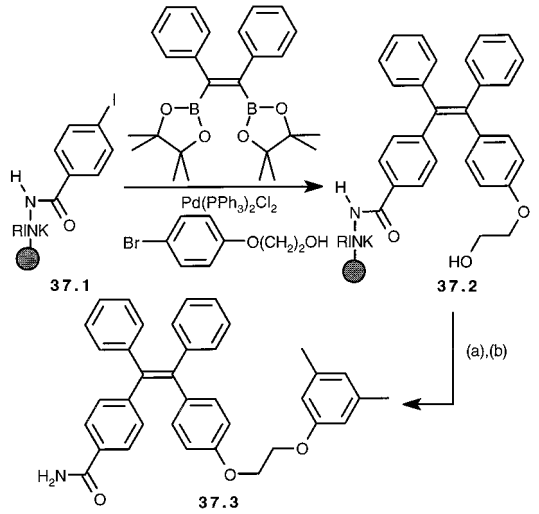
Scheme 36



Many bases and catalysts were studied, such as KOH in DME, and $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$ catalysts were found to be the most effective in the coupling processes. The second Suzuki coupling reaction (performed on the solid phase) did not require additional palladium catalyst. Moreover, the bis-boronate derivative was used in the solution-phase Suzuki coupling reaction without purification because the starting alkyne was unreactive toward the Suzuki coupling conditions. Along these lines, the crude mixture of the monoboronate ester and the diaddition product was also used without purification in the solid-phase Suzuki coupling reaction.

Other synthetic transformations were performed after the resin capture of the monoboronate ester. For example, the bis-boronate shown in Scheme 37 was

Scheme 37[a]

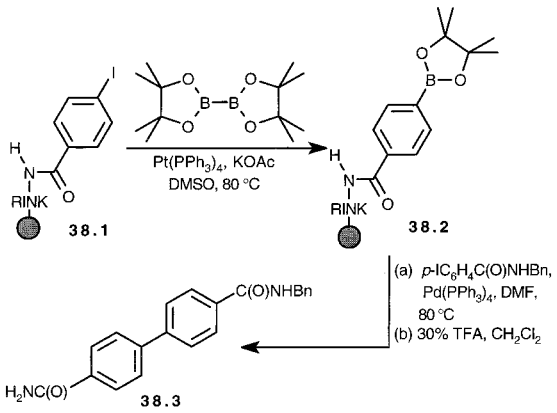


[a] Reagents and conditions: (a) 3,5-dimethylphenol, diisopropylazodicarboxylate, triphenylphosphine, *N*-ethylmorpholine, 16 h; (b) 30% TFA in CH_2Cl_2.

reacted with the resin-bound aryl iodide (**37.1**) and 2-(4-bromophenoxy)ethanol to give the polymer-bound tetrasubstituted alkenol. The free-hydroxy moiety was condensed with 3,5-dimethylphenol (Mitsunobu conditions) and, upon cleavage with TFA, gave the highly functionalized tetrasubstituted olefin compound (**37.3**) in >95% yield.

A final example of the scope of the resin capture technique involves the platinum-catalyzed reaction of a resin-bound aryl iodide (**38.1**) with the bis(boryl)-alkene (Scheme 38). This solid-phase Suzuki coupling

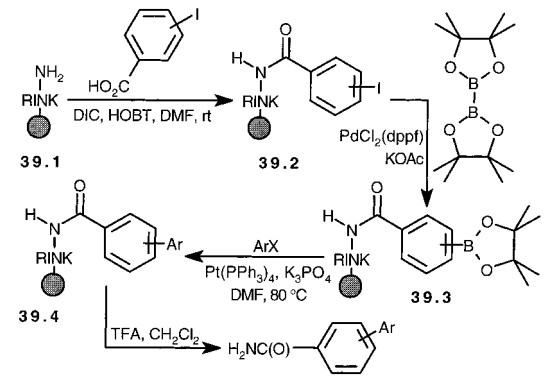
Scheme 38



reaction gave a polymer-bound aryl boronic ester (**38.2**) that was coupled with *N*-benzyl-4-iodobenzamide via a second solid-phase Suzuki coupling reaction.

Similar to the previous example, polymer-bound boronates have been synthesized via a palladium-catalyzed reaction between resin-bound aryl halides and the pinacol ester of diboron.[46] The resulting polymer-bound boronate was used further in Suzuki coupling reactions. Following conditions established by Miyaura, the polymer-bound *p*-iodobenzamide (**39.2**) was converted to the resin-bound boronate (**39.3**), which was then used to optimize the Suzuki coupling reaction. Optimized reaction conditions were $Pt(PPh_3)_4$, K_3PO_4, DMF, 80 °C, and 4−6 h (Scheme 39). Several solid-phase Suzuki coupling reactions

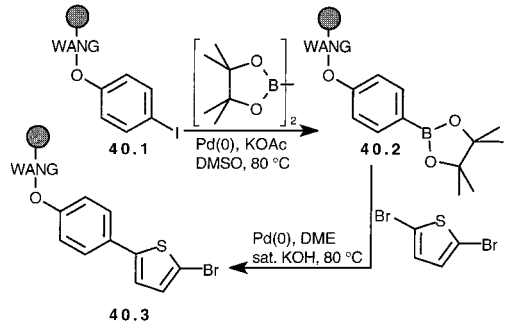
Scheme 39



were performed with the polymer-bound boronate and variously functionalized aryl halides. The meta- and ortho-substituted polymer-bound boronates were also synthesized and used in Suzuki coupling reactions.

As mentioned previously, Armstrong used a solid-phase Stille coupling reaction en route to cyclobutenedione derivatives (see Scheme 10). In the same paper, a solid-phase Suzuki coupling to a polymer-bound boronate with 2,5-dibromothiophene was performed to incorporate a second site of diversity in his squaric acid derivative.[18] As illustrated in Scheme 40, the iodophenol attached to Wang resin was converted to the polymer-bound boronate (**40.2**), followed by pal-

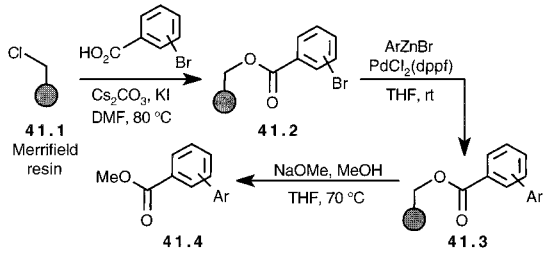
Scheme 40



ladium-catalyzed Suzuki coupling with 2,5-dibromothiophene.

An alternative palladium-catalyzed cross-coupling reaction, which avoids the need for boronic acids, coupled aryl zinc bromides with aryl bromides to form biaryl derivatives.[47] The polymer-bound aryl bromo carboxylic acids (**41.2**) were treated with phenyl zinc bromide and $PdCl_2$(dppf) in THF at room temperature for 18 h to afford the coupled biaryl product in 76% yield (Scheme 41). The preferred catalysts for

Scheme 41



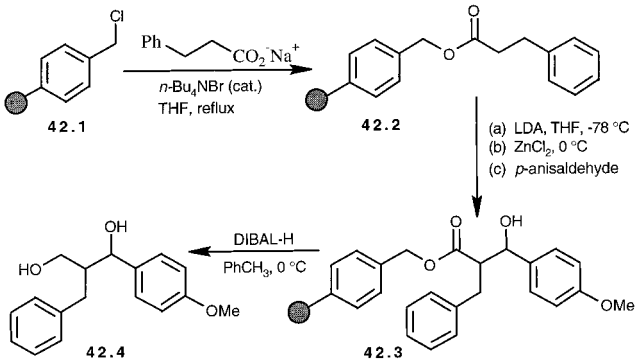
this coupling reaction were found to be $PdCl_2[P(o\text{-}Tol)_3]_2$ and $PdCl_2$(dppf). These optimized conditions were extended to several different aryl zinc bromides (p-OCH_3−C_6H_4ZnBr, m-OCH_3−C_6H_4ZnBr, o-OCH_3−C_6H_4ZnBr, m-F−C_6H_4ZnBr, p-F−C_6H_4ZnBr, thiophene-2-zinc bromide, p-benzonitrile zinc bromide) and polymer-bound arylcarboxylic acids. The effectiveness and versatility of this method offers an alternative to traditional solid-phase Suzuki coupling reactions.

III. Condensation Reactions

3.1. Aldol Condensation

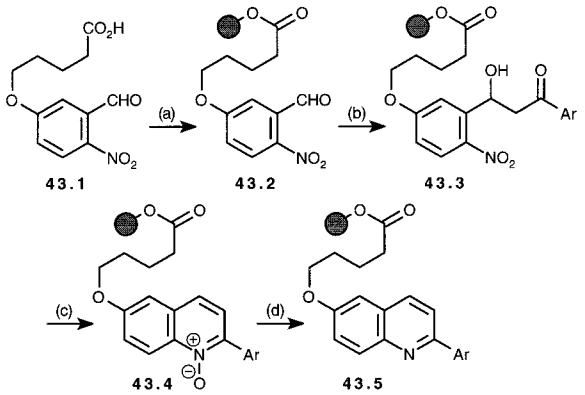
Solid-phase aldol condensations have been conducted by Kurth and co-workers.[48] In the process of developing an antioxidant library, Merrifield's resin was esterified with sodium dihydrocinnamate in refluxing THF (Scheme 42). The newly formed resin-bound ester was treated with LDA at −78 °C in THF, and after 90 min a solution of $ZnCl_2$ was added ($ZnCl_2$ reduces retro-aldolization). The resulting mixture was warmed to 0 °C, and p-anisaldehyde was added. Workup afforded the polymer-bound hydroxyester, and subsequent reduction with DIBAL-H gave the diol in 26% overall yield based on the chloride loading of Merrifield's resin. Seven aryl aldehydes and two aryl ketones were used in this work to synthesize a 27-compound library of propanediol derivatives.

Scheme 42



A solid-phase synthesis of disubstituted quinolines was conducted using an aldol condensation.[49] A carboxylic acid (**43.1**) was esterified with commercially available hydroxyethyl polystyrene resin to give a polymer-bound aldehyde (**43.2**) (Scheme 43). The

Scheme 43[a]

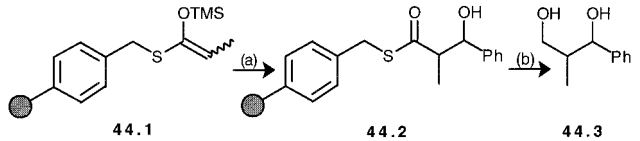


[a] Reagents and conditions: (a) hydroxyethyl polystyrene, DIPC, DMAP, CH_2Cl_2; (b) $CH_3C(O)Ar$, K_2CO_3, THF, Δ; (c) CH_2Cl_2, C_2H_5OH, $SnCl_2{-}2H_2O$, reflux, 4 h; (d) CH_2Cl_2, toluene, $TiCl_3$, 22 °C overnight.

resin-bound aldehyde was treated with K_2CO_3 and an aryl methyl ketone to give the aldol addition product (**43.3**), which was further cyclized with ethanolic tin(II) chloride to deliver the pyridine ring. Six aryl ketones were used in the aldol condensation step, and the reaction was monitored by IR analysis.

The Mukaiyama aldol reaction,[50] an aldol condensation between silyl enol ethers and aldehydes, has been adapted to solid phase.[51] In a reaction catalyzed by scandium triflate ($Sc(OTf)_3$), polymer-bound silyl enol ethers were reacted with various aldehydes to give β-hydroxy thioesters. Reaction conditions for this solid-phase Mukaiyama aldol reaction were optimized for the model reaction of benzaldehyde with the resin-bound silyl enol ether (**44.1**) (Scheme 44).

Scheme 44[a]

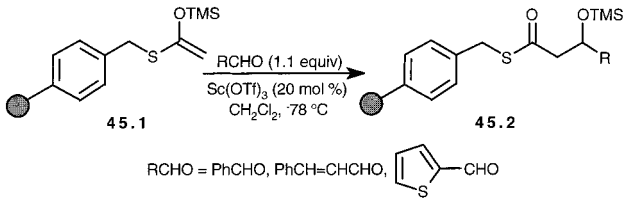


[a] Reagents and conditions: (a) PhCHO, $Sc(OTf)_3$, CH_2Cl_2; (b) $LiBH_4$, Et_2O, rt.

The amount of catalyst and temperature were varied, with 20 mol % of $Sc(OTf)_3$ and −78 °C giving the best yield (82% based on the loading of the enol ether) of aldol product. Reduction of the β-hydroxy thioester cleaved the 1,3-diol from the resin.

Several aldehydes were examined, including aromatic, aliphatic, α,β-unsaturated, and heterocyclic aldehydes, producing the aldol products in moderate yield. However, when an α-unsubstituted silyl enol ether was used, the aldol condensation proceeded in poor yield, with the exception of *tert*-butyldimethylsilyl enol ether (Scheme 45). The solid-phase aldol

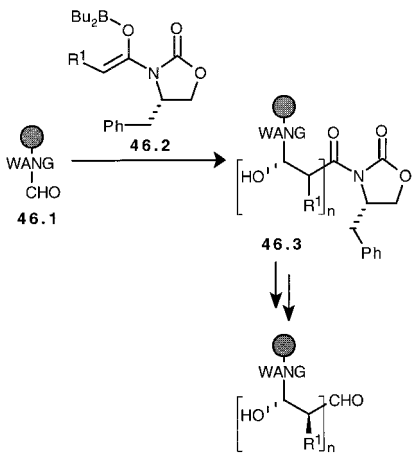
Scheme 45



reaction of silyl enol ethers with aldehydes, catalyzed by $Sc(OTf)_3$, gave better yields than similar solid-phase aldol condensations with zinc enolates under basic conditions.

An asymmetric solid-phase aldol reaction has been used to synthesize polyketides.[52] Here, a solid-phase asymmetric aldol mimicked the well-known stereocontrolled solution methods previously developed.[53] Wang resin was oxidized with the sulfur trioxide pyridine complex to give the resin-bound aromatic aldehyde (**46.1**) (a strong absorption was observed in the IR spectrum at 1696 cm^{-1}). Addition of boron enolate (**46.2**) to the polymer-supported aldehyde ($R^1 = CH_3$) delivered **46.3**, with two new carbonyl bands in the IR spectrum (1780 cm^{-1} attributed to the urethane carbonyl and 1700 cm^{-1} due to the amide functionality) (Scheme 46). The hydroxy group re-

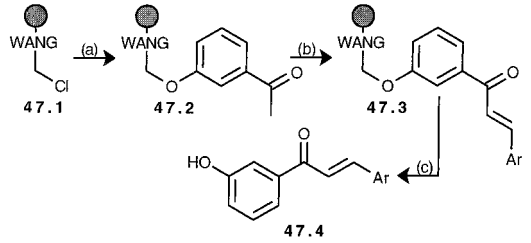
Scheme 46



sulting from the aldol condensation was observed in the IR spectrum as a broad band at 3530 cm^{-1}. Treating the benzyl ether of the Wang resin with boron trichloride cleaved the *syn*- and *anti*-aldol adducts in an 87:13 ratio. The decreased stereocontrol was attributed to syn−anti epimerization upon treatment with boron trichloride (a solution analogue of this reaction was performed, giving a syn-to-anti ratio of 90:10).

Another solid-phase aldol condensation reaction was reported between polymer-supported 3-hydroxyacetophenone and aryl aldehydes to give α,β-unsaturated ketones upon resin cleavage.[54] Chlorinated Wang resin (**47.1**) (resin loading was 0.49 mmol/g) was coupled with 3-hydroxyacetophenone, using Cs_2CO_3 and NaI to give the polymer-bound ketone. Solid-phase aldol reaction of this polymer-bound ketone (**47.2**) was achieved by treatment with NaOMe in MeOH/THF (Scheme 47). Five different aryl alde-

Scheme 47[a]

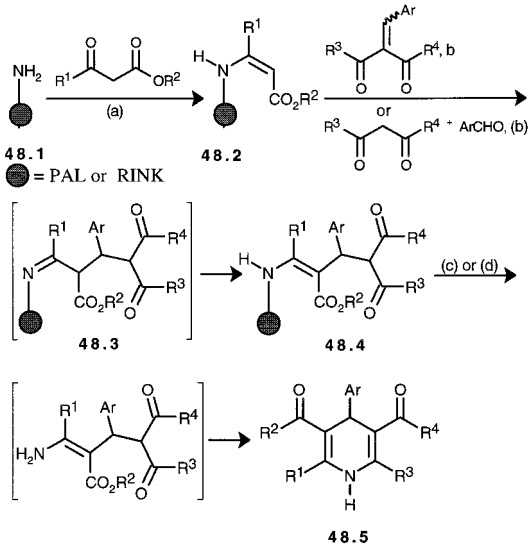


[a] Reagents: (a) 3-hydroxyacetophenone, Cs_2CO_3, NaI, DMF; (b) ArCHO (12 equiv), NaOMe, MeOH, THF; (c) TFA, CH_2Cl_2.

hydes were employed (p-$C_6H_4OCH_3$, p-C_6H_4Br, o,p-$Cl_2C_6H_3$, 1-naphthyl, p-PhC_6H_4), giving satisfactory yields of the respective enones. Resin cleavage of these phenoxy enones was mediated by TFA (**47.4**).

Targeting biologically important 1,4-dihydropyridine (DHP) compounds,[55] Gordeev and co-workers developed a solid-phase synthesis of 1,4-dihydropyridines.[56] Their solid-phase approach utilized a two- or three-component cyclocondensation of enamino esters with 2-arylidene β-keto esters or β-keto esters and aldehydes. The solid-phase synthesis of Nifedipine[57] was selected as a case study (Scheme 48) and began with PAL[58] or Rink amine

Scheme 48[a]



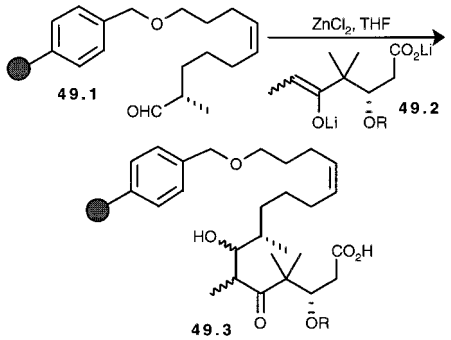
[a] Reagents and conditions: (a) 4 Å molecular sieves, CH_2Cl_2; (b) 4 Å molecular sieves, pyridine, 45 °C; (c) 95% TFA/THF; (d) 3% TFA/CH_2Cl_2.

resins, which were treated with methyl acetoacetate to give the resin-bound methyl aminocrotonate (**48.2**) ($R^1 = R^2 = CH_3$). The *N*-tethered enamino ester was treated with either 2-nitrobenzaldehyde and methyl

acetoacetate or methyl 2-(2-nitrobenzylidene). The final dihydropyridine was cleaved from the polymer with 95% TFA/THF. Eight dihydropyridine derivatives were synthesized using this solid-phase strategy [$R^1 = CH_3$, $^{13}CH_3$, CH_2CH_3; $R^2 = CH_3$, CH_2CH_3, $CH(CH_3)_2$; $R^3 = CH_3$, C_6H_5; $R^4 = OCH_3$, OCH_2CH_3, $O(CH_2)_2OCH_3$, *O*-Allyl].

A nice application of the solid-phase aldol reaction was demonstrated by Nicolaou[59] in his solid-phase synthesis of epothilones A and B precursors.[60] Merrifield's resin was converted via several synthetic steps to a resin-bound aldehyde (**49.1**) (Scheme 49).

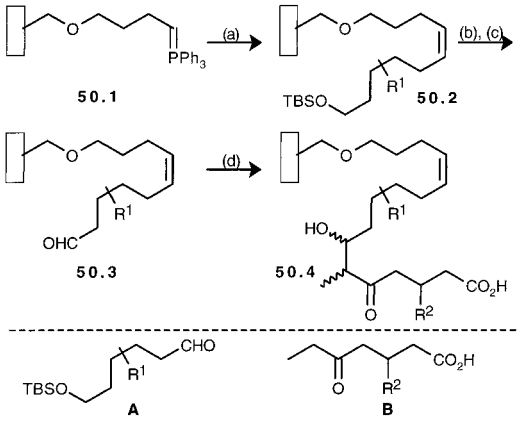
Scheme 49



This aldehyde was treated with the dianion of a keto acid (**49.2**) together with $ZnCl_2$ in THF, affording a mixture of aldol diastereomers (90% yield, 1:1 ratio). This mixture was subjected to additional synthetic transformations leading ultimately to epothilone A. Epothilone B was synthesized in a similar manner.

Nicolaou continued his solid-phase epothilone studies by developing a library of epothilone derivatives.[61] The solid-phase synthesis of the epothilone analogues again utilized an aldol condensation reaction (Scheme 50), which was achieved by treating these resin-

Scheme 50[a]



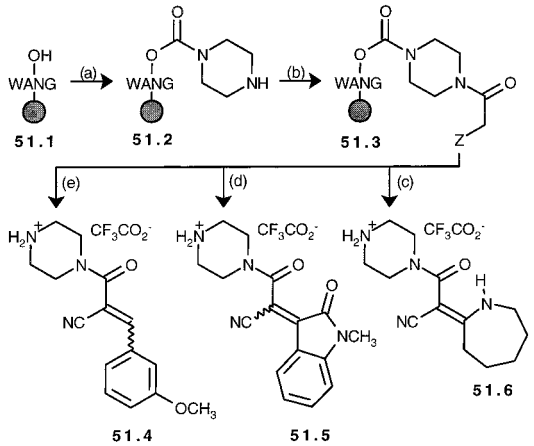
[a] Reagents and conditions: (a) A + NaHMDS (3.0 equiv), THF/DMSO (1:1), 25 °C, 12 h; (b) 0.2 M HCl in THF; (c) $(COCl)_2$, DMSO, TEA; (d) $ZnCl_2$ in THF; B + LDA in THF.

bound aldehydes with β-ketoacid dianions to give a mixture of diasteromeric carboxylic acids in ≥90% yield. Three β-ketoacids were effectively coupled to three resin-bound aldehydes (Scheme 50).

3.2. Knoevenagel Condensations

Another classical carbon−carbon bond forming reaction that has been adapted to solid-phase is the Knoevenagel condensation. Instances of solid-phase Knoevenagel condensations have been reported in the patent literature;[62] a solid-phase Knoevenagel condensation, for example, was used in the formation of monoacyl piperazines.[63] In this study, Wang resin (**51.1**) was coupled with piperazine and monoacylated with cyanoacetic acid and 3-oxobutyric acid (Scheme 51). The cyanoacetamide (**51.3**) was reacted

Scheme 51[a]

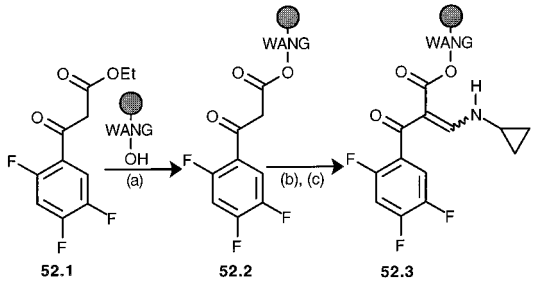


[a] Reagents and conditions: (a) (i) 4-nitrophenyl chloroformate, CH_2Cl_2/pyridine (1:1), (ii) piperazine, DMF; (b) Z = CN; cyanoacetic acid anhydride; Z = $C(O)CH_3$; 4-nitrophenyl 3-oxobutyrate, toluene/DIPEA (3:1); (c) 1-aza-2-methoxy-1-cycloheptene, DMF/DIPEA (8:1), then TFA/CH_2Cl_2 (1:1); (d) 1-methylisatin, DMF/piperidine (6:1), then TFA/CH_2Cl_2 (1:1); (e) 3-methoxybenzaldehyde, DMF/piperidine (6:1), then TFA/CH_2Cl_2 (1:1).

with 3-methoxybenzaldehyde, 1-methylisatin, and 1-aza-2-methoxy-1-cycloheptene to give the condensation products. Treatment with TFA cleaved the piperazines from the resin. The amides, resulting from 3-methoxybenzaldehyde and 1-methylisatin, were obtained as diastereomeric mixtures. The condensation product from 1-aza-2-methoxy-1-cycloheptene gave only one diastereomer as evidenced by NMR spectroscopy. Unfortunately, reaction of the 3-oxobutyramide with the same two carbonyl compounds and the iminoether did not yield the respective condensation products after cleavage from the resin.

Quinolones[64] were prepared by solid-phase synthesis employing a Knoevenagel condensation[65] that began with esterification of commercially available Wang resin by 2,4,5-trifluorobenzoylacetic acid ethyl ester (**52.1**) (Scheme 52). Solid-phase Knoevenagel

Scheme 52[a]

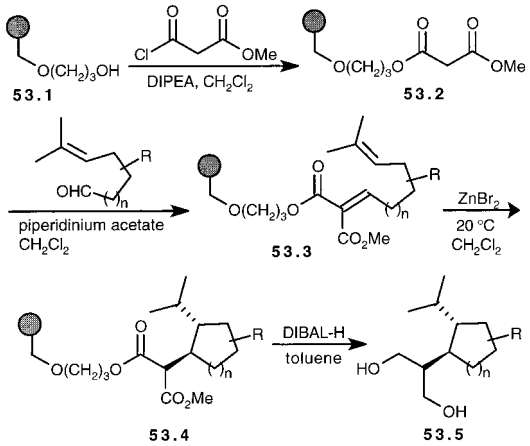


[a] Reagents and conditions: (a) DMAP, toluene, 110 °C; (b) $(MeO)_2CHNMe_2$, THF, 25 °C; (c) $NH_2C_3H_5$, THF, 25 °C.

condensation of the resin-bound β-keto ester (**52.2**) with dimethylformamide dimethyl acetal and cyclopropylamine afforded the condensation product (**52.3**), as confirmed by gel-phase ^{13}C NMR. Cyclization of the condensation product gave the desired quinolone (Ciprofloxacin).

Examples of stereoselective solid-phase syntheses are rare. Tietze, however, has demonstrated a stereoselective solid-phase synthesis of cyclopentane and cyclohexane derivatives in which a unique tandem Knoevenagel−ene reaction was employed.[66] Resin (**53.1**) was reacted with diiso-1,3-propanediolate, and subsequent workup with water gave the spacer-functionalized resin with a free-hydroxyl group (Scheme 53). The spacer-functionalized resin was

Scheme 53

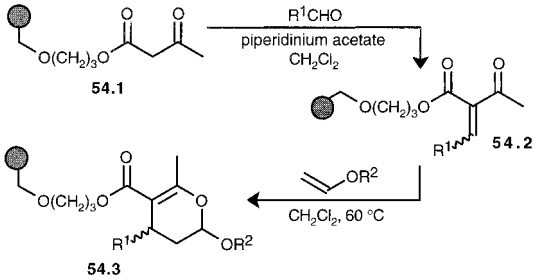


treated with methyl malonyl chloride to give a malonate resin for use in the Knoevenagel condensation. Condensation of the polymer-bound malonate (**53.2**) was achieved by adding the appropriate aldehyde (five different aldehydes were used), piperidium acetate, and $ZnBr_2$. These solid-phase Knoevenagel condensations proceeded without external drying agents, with the exception of α-substituted aldehydes which required Na_2SO_4 and heat. The subsequent ene reaction gave either the polymer-bound cyclopentane or cyclohexane derivative (**53.4**). Reduction of the Knoevenagel product with DIBAL-H cleaved the diol (**53.5**) from the resin.

Another solid-phase domino reaction combined the Knoevenagel condensation with a Diels−Alder cycloaddition. Resin-bound acetoacetate (**54.1**) was reacted with five aliphatic aldehydes to give oxabutadienes.[67] The Knoevenagel products underwent an inverse electron-demand hetero-Diels−Alder cycloaddition with enol ethers to give polymer-bound cycloadducts (**54.3**) (Scheme 54). The cycloaddition products were cleaved from the resin by basic transesterification with NaOMe. An array of nine substituted methyl 3,4-dihydro-2*H*-pyran-5-carboxylates were synthesized in overall yields ranging from 12 to 37%. The diastereoselectivity of the solid-phase reactions was moderate, ranging from 1:1 to 5:1 for the endo (2,4-*cis*) and exo (2,4-*trans*) products (Scheme 54).

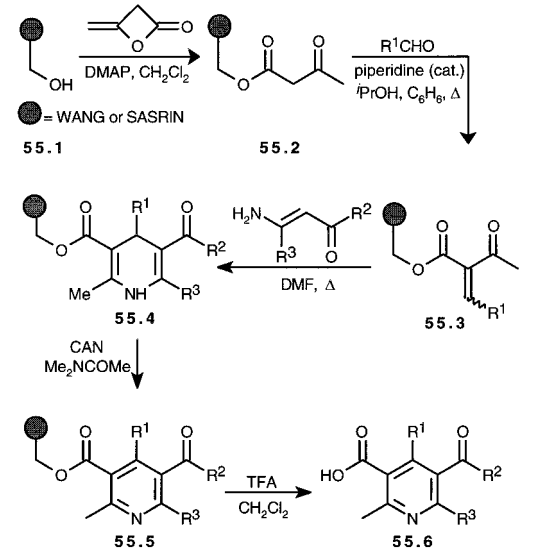
A solid-phase Knoevenagel condensation was also employed in the synthesis of pyridine and pyrido[2,3-*d*]pyrimidines.[68] Wang or SASRIN resins were con-

Scheme 54



verted to β-keto esters (**55.2**) via acetoacetylation with diketene. Condensation with aldehydes gave resin-bound Knoevenagel products (**55.3**) that underwent a Hantzsch heterocyclization with methyl aminocrotonate to give 1,4-dihydropyridine derivatives (Scheme 55). Oxidation with ceric ammonium

Scheme 55

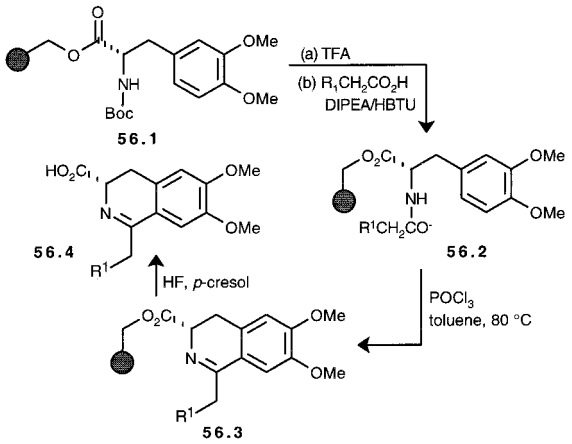


nitrate (CAN) gave resin-bound pyridines (**55.5**) (R^1 = Ph, *p*-$HOOCC_6H_4$, *o*-FC_6H_4, 2-naphthyl, 4-Py, *m*-$O_2NC_6H_4$, *p*-$MeOC_6H_4$, *n*-hexyl, H; R^2 = *i*-PrO, Me, $CH_2CMe_2CH_2$, Et, H; R^3 = Me, H, Et, allyl), which were cleaved with 95% TFA or 3% TFA in CH_2Cl_2.

3.3. Bischler–Napieralski Reaction

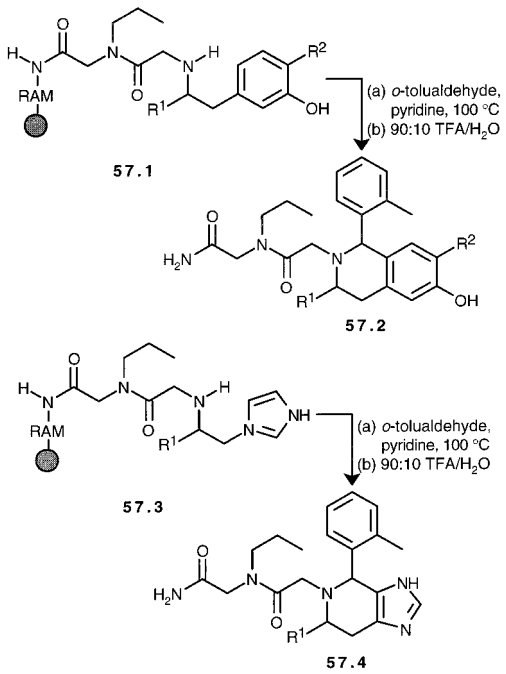
Efficient solid-phase syntheses of dihydro- and tetrahydroisoquinoline[69] derivatives have been reported.[70] These isoquinoline derivatives were synthesized via a solid-phase Bischler−Napieralski reaction.[71] Merrifield's resin was selected because the ester linkage proved stable to reaction conditions throughout the synthesis, whereas Wang and PAM resins were unstable to $POCl_3$. The solid-phase synthesis began with attachment of BOC-protected (L)-3,4-dimethoxyphenylalanine to Merrifield's resin (Scheme 56). The BOC group was removed, and the free amine was acylated with acetic acid derivatives (R^1 = H, C_6H_5) and HBTU. Several variations of the Bischler−Napieralski reaction were attempted in which heating the resin with $POCl_3$ in toluene at 80 °C gave the best yields. The dihydroisoquinoline (**56.4**) was isolated after treatment with HF and *p*-cresol and purified using HPLC.

Scheme 56



Another example of a solid-phase Bischler−Napieralski reaction used in the process of forming isoquinoline derivatives has been reported by Hutchins and co-workers.[72] Their solid-phase synthesis of 1,2,3,4-tetrahydroisoquinolines and 4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridines began with TentaGel S RAM resin, which was converted to **57.1** (Scheme 57). Cyclocondensation of **57.1** was achieved by

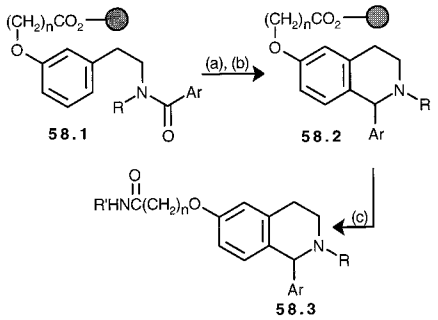
Scheme 57



heating the resin with an aldehyde to afford a resin-bound tetrahydroisoquinoline. A study of solid-phase cyclization solvent and temperature led to 100 °C in pyridine as optimal conditions. Typical cleavage methods (90% TFA/H_2O) gave the tetrahydroisoquinolines, and several substituents were incorporated into this solid-phase synthesis strategy (R^1 = CH_3, CO_2CH_3, H). Similarly, the presence of ortho aryl substituents (R^2 = OH, OCH_3) on resin **57.1** did not affect the cyclocondensation. Moreover, aromatic, aliphatic, and heteroaromatic aldehydes were used to give C_1-substituted tetrahydroisoquinolines (R^3 = C_6H_5, *o*-CH_3−C_6H_4, *o*-OCH_3−C_6H_4, *p*-NO_2−C_6H_4, *o*-Cl_2−C_6H_4, *p*-C_5H_4N, 2-furyl, −$CH_2C_6H_5$, *i*-Bu). Resin **57.3** was heated with various aldehydes to give 4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridines.

A similar use of the solid-phase Bischler−Napieralski reaction has been reported[73] wherein 1,2,6-trisubstituted 1,2,3,4-tetrahydroisoquinoline derivatives were prepared by a multiple-step synthesis. In this study, 2-hydroxylethylpolystyrene was used to tether resin-bound amides (Scheme 58) prepared

Scheme 58[a]



[a] Reagents and conditions: (a) $POCl_3$, toluene, 85 °C; (b) $NaBH_4$, CH_2Cl_2, CH_3OH; (c) $R'NH_2$, Me_3Al, CH_2Cl_2, toluene.

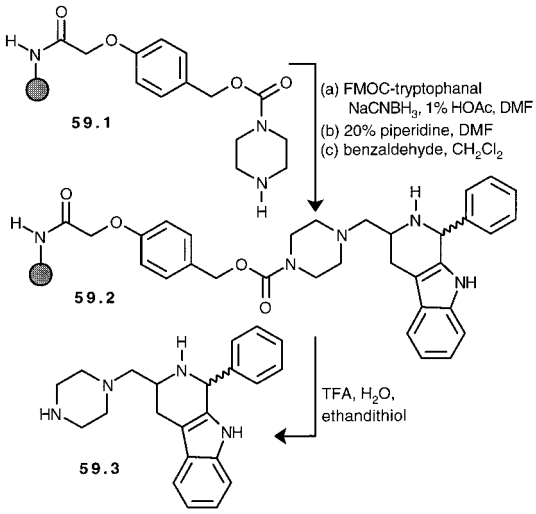
from two amines (R = *i*-Bu, *n*-pentyl) and two acyl chlorides (Ar = C_6H_5, 3-thiophenyl). The resin-bound amide (**58.1**) was treated with $POCl_3$ to achieve Bischler−Napieralski ring closure, providing an imidium ion which was reduced and cleaved from the resin to give (**58.3**).

3.4. Pictet–Spengler Reaction

The Pictet−Spengler reaction is an intramolecular reaction between iminium ions and aromatic C-nucleophiles[74] and has been used extensively to synthesize both tetrahydroisoquinolines and tetrahydro-*β*-carboline alkaloids. A general solid-phase synthesis of tetrahydro-*β*-carbolines has been reported,[75] mimicking literature solution-phase precedents. The solid-phase synthesis of tetrahydro-*β*-carbolines began with the coupling of piperazine to 4-nitrophenyl-4-oxycarbonylmethylphenoxyacetyl carbonate resin. This coupling reaction yielded an amino alkyl urethane resin (**59.1**). The secondary amino groups were either protected as the FMOC-Trp hydroxybenzotriazole ester or reductively alkylated by FMOC-tryptophanal (Scheme 59). Deprotection of the primary amino groups was followed by condensation of the tryptophan residues with aldehydes to give tetrahydro-*β*-carbolines (**59.2**), and standard TFA cleavage conditions afford the resin-free tetrahydro-*β*-carbolines (**59.3**) (overall yields ranged from 55 to 85%). Several aldehydes were used in this solid-phase strategy, including benzaldehyde, 3,4,5-trimethoxybenzaldehyde, 2-bromobenzaldehyde, 2,4-dichlorobenzaldehyde, isobutanal, cyclohexylcarboxyaldehyde, BOC-phenylalaninal, and 3-methoxybenzaldehyde.

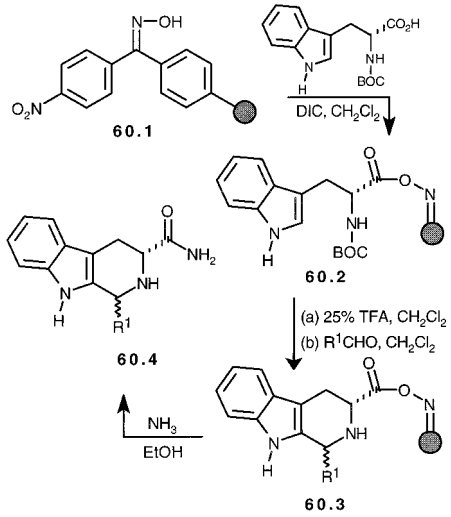
A similar solid-phase Pictet−Spengler reaction has been used to synthesize tetrahydro-*β*-carboline derivatives in which the Kaiser oxime (**60.1**) was used.[76] This resin is stable to acidic reaction conditions,[77] a requisite for performing the acid-catalyzed Pictet−

Scheme 59



Spengler reaction. DIC coupling was used to attach BOC-L-tryptophan to the oxime resin to deliver **60.2**. The BOC group was removed, the appropriate aldehyde (R^1 = 2-methylpropyl, phenyl, 4-chlorophenyl, ethyl, 4-benzyloxyphenyl, 4-methoxyphenyl) was added, and a subsequent Pictet–Spengler cyclization ensued to give the resin-bound tetrahydro-β-carboline (**60.3**) (Scheme 60). These derivatives were cleaved

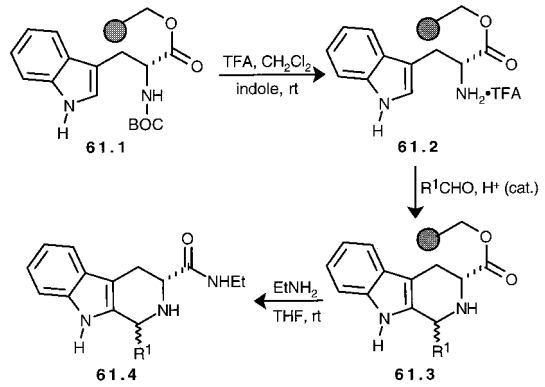
Scheme 60



from the resin as a diastereomeric mixture by reaction with NH_3 in ethanol (overall yields determined by HPLC ranged from 84 to 94%).

The previously mentioned solid-phase Pictet–Spengler studies used resins that were stable to acidic reaction conditions. Typically, solution-phase Pictet–Spengler reactions are carried out in protic solvents with acid catalysts, conditions not generally amenable to solid-phase reactions since most resins do not swell in protic solvents and acidic conditions exclude the use of acid-cleavable linker strategies. In the face of these solid-phase limitations, a solid-phase Pictet–Spengler reaction in benzene or toluene with FMOC-Trp-Wang resin was attempted.[78] While plagued by slow reaction times at room temperature, the cyclization did occur in moderate yield upon heating at 80 °C. The Wang resin was abandoned in favor of commercially available BOC-Trp-Merrifield's resin which was *N*-deprotected. Subsequent addition of various aldehydes in excess afforded the cyclized product (Scheme 61).

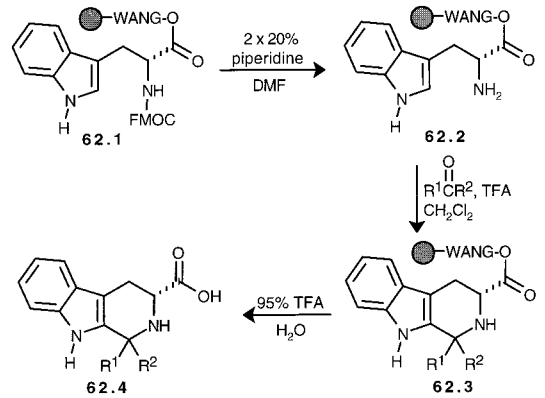
Scheme 61



Traditionally, acid-catalyzed Pictet–Spengler reactions employ $POCl_3$ as catalyst. However, the milder catalyst, TFA, was selected for the solid-phase cyclization. A series of different concentrations of TFA in CH_2Cl_2 (0, 1, 5, 10, 20, 50%) were examined, and all were effective in promoting the cyclization, although rates were slower with low concentrations of TFA. The majority of aldehydes employed were successful in delivering the tetrahydro-β-carboline in average yields, with the exception of 4-nitro-substituted aromatic aldehydes which gave little or no product. Aliphatic aldehydes afforded the cyclization products in lower purity than aromatic aldehydes. The use of halogen-substituted aryl aldehydes as well as 4-formylphenylboronic acid set the stage for further diversification by incorporating a Suzuki coupling reaction.

In parallel with this study, Mayer and co-workers also reported a solid-phase synthesis of 1,2,3,4-tetrahydro-β-carbolines via the Pictet–Spengler reaction.[79] Commercially available FMOC-L-tryptophan-Wang resin was deprotected with 20% piperidine in DMF to give the resin-bound amine (**62.2**) (Scheme 62). Treatment of an aldehyde or ketone with 1% TFA

Scheme 62



in CH_2Cl_2 afforded the resin-bound tetrahydro-β-carboline (**62.3**). Suspending the resin in neat TFA

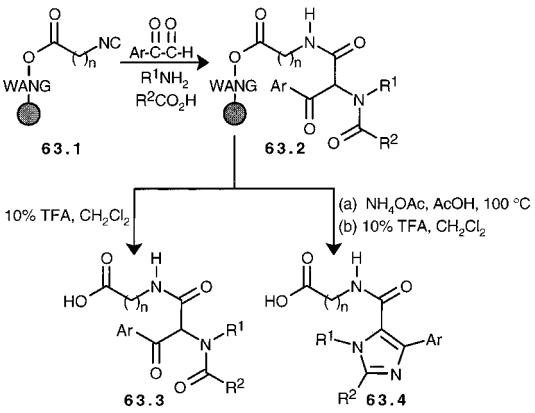
gave the tetrahydro-β-carboline in moderate to excellent overall yield (60−97%).

3.5. Ugi Reaction

Multiple-component condensation reactions,[80] in which three or more components are joined in one step, are extremely advantageous for adaptation to the solid-phase.[81] The Ugi reaction[82] is a four-component condensation reaction in which three components are commerically available. The Ugi reaction is limited by the isocyanide derivative since few isocyanides are commercially available. One approach to this limitation is to prepare a resin-bound isocyanide moiety which can then serve as a common building block for use in solid-phase Ugi reactions.

The first reported solid-phase Ugi reaction involved the synthesis of α-(*N*-acyl-*N*-alkylamino)-β-ketoamides on Wang resin, selected because it is stable to heating in AcOH.[83] The polymer-bound isocyanides (**63.1**) ($n = 10$ or 2) were reacted with phenylglyoxal, isobutylamine, and benzoic acid (1:1:1) to give the α-(*N*-acyl-*N*-alkylamino)-β-ketoamides (**63.2**) in one step (Scheme 63). Treatment with TFA gave the

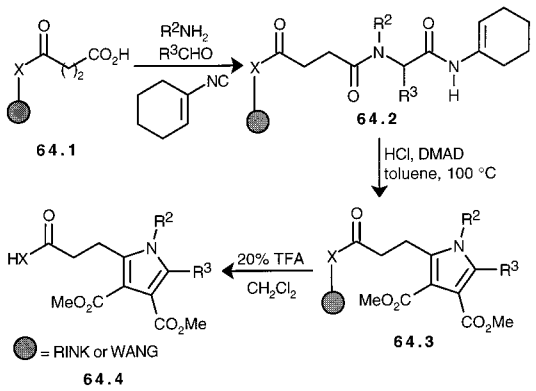
Scheme 63



appropriate amides in average yield (45−50%, with $R^1 = i\text{-}C_4H_9$, C_6H_5, 4-$MeOC_6H_4$ and $R^2 = C_6H_5$, 4-F−C_6H_4, *n*-C_6H_4, $C_6H_5CH_2$). Interestingly, the isocyanide linker length had no effect on the Ugi condensation yield. Furthermore, aliphatic and aromatic carboxylic acids were amenable to the solid-phase Ugi condensation. The only primary amine attempted was aniline, and it was not useful for the solid-phase Ugi reaction. Similarly, the arylglyoxals used can be varied without affecting the yield of the condensation reaction.

Another solid-phase four-component Ugi reaction continued with the theme of a general isocyanide, but here the isocyanide 1-isocyanocyclohexene was not attached to the polymer.[84] More importantly, the α-acylaminoamide produced in the Ugi reaction was further converted to pyrrole derivatives by reaction with dimethyl acetylenedicarboxylate (DMAD). Rink or Wang resins were converted into resin-bound carboxylic acids (**64.1**), which were treated with a primary amine, an aldehyde, and 1-isocyanocyclohexene in a 1:1 mixture of CH_2Cl_2/CH_3OH (Scheme 64). The polymer-bound α-acylaminoamide (**64.2**) was

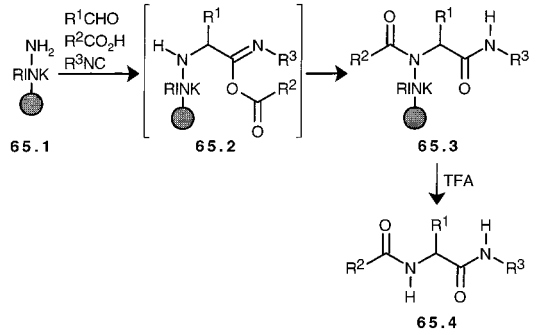
Scheme 64



treated with DMAD in toluene to afford the resin-bound pyrrole. The pyrrole moieties were cleaved under standard conditions (TFA, CH_2Cl_2) and isolated in 5−20% overall yield.

Armstrong continued his efforts in the solid-phase Ugi reaction with the attachment of the amine to the resin.[85] A 96-compound library of α-acylamino amides was prepared using 12 carboxylic acids, 8 aldehydes, and 1 isonitrile with the polymer-bound amine. In this study, a 96-well microtiter plate was used in which each well contained an individual reaction (Scheme 65). This study showed that the solid-phase

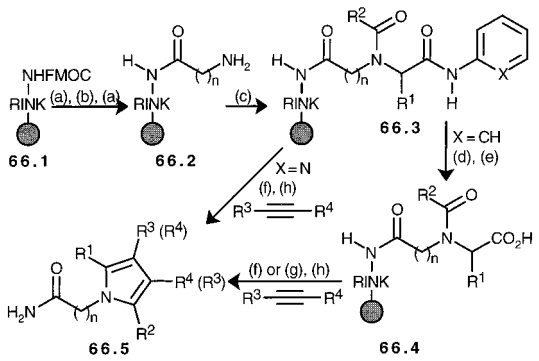
Scheme 65



Ugi reaction was sensitive to substituents on the aldehyde. Aliphatic aldehydes and aldehydes containing electron-donating groups worked quite well (excellent overall yields); however, aldehydes containing electron-withdrawing groups resulted in lower overall yields. Carboxylic acid derivatives containing a phenolic motif also resulted in lower product yield. In a side venture to address the lack of commercially available isocyanides, three isocyanides were prepared by reacting α-lithiated benzylisocyanide with methyl iodide, cyclohexyl bromide, and benzyl bromide to give the respective isocyanides, which were used without purification in the solid-phase Ugi reaction.

Shortly after Armstrong's report of a solid-phase Ugi route to pyrroles, Mjalli followed with a similar synthesis of tetra- and pentasubstituted pyrroles.[86] As with Armstrong's protocol, the intermediate en route to the desired pyrroles was a münchnone. Mjalli's münchnone, formed in a single step from the Ugi condensation product, underwent a 1,3-dipolar cycloaddition with alkynes to afford the pyrrole (Scheme 66). Treatment of the condensation product,

Scheme 66[a]

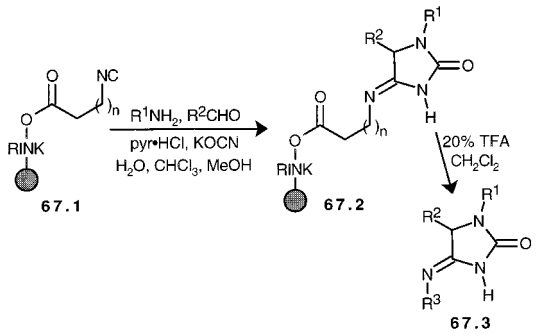


[a] Reagents and conditions: (a) 20% piperidine, DMF; (b) HBTU, HOBT, *N*-FMOC-amino acid (n = 1 or 2), DIPEA, DMF; (c) R^1CHO, PhNC, or 2-pyrNC, R^2CO_2H, 1:1:1 $CHCl_3$/pyr/MeOH, 65 °C; (d) TEA, DMAP, BOC_2O, CH_2Cl_2; (e) 4:1 (1 N LiOH−5% H_2O_2)/THF; (f) alkyne, Ac_2O, 65−100 °C. (g) alkyne, isobutyl chloroformate, TEA, toluene, 100 °C; (h) 20% TFA, CH_2Cl_2; azeotrope toluene.

a phenyl amide, with an alkyne and cleavage with TFA gave the pyrrole derivative. Ten different pyrroles were prepared in overall yields ranging from 24 to 72% (R^1 = Et, *i*-Pr, *n*-Pr, *n*-Bu, *i*-Bu; R^2 = 4-Br−C_6H_4, 4-MeO−C_6H_4, Ph, $C_6H_5CH_2$, 4-Me−C_6H_4, 4-CF_3−C_6H_4; R^3 = CO_2Me, CO_2H, Et, H; R^4 = CO_2Me, CO_2H, CO_2Et).

The solid-phase Ugi condensation was extended to the synthesis of hydantoin 4-imides.[87] Ugi discovered earlier that reacting aldehydes, amines, and isocyanides in the presence of HOCN gave hydantoins through incorporation of the acid counterion.[88] This solution-phase synthetic strategy was adapted to solid-phase (Scheme 67) in which the isocyanide

Scheme 67

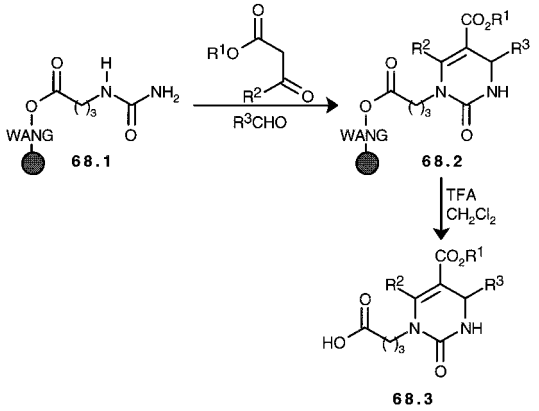


moiety was attached (n = 5, 10) to Wang resin and stirred with aldehydes [R^2 = *n*-C_3H_7, *trans*-$(CH_2)_2$-CH=CH$(CH_2)_4CH_3$, *n*-C_7H_{15}, *sec*-C_4H_9, −CH_2CH-$(CH_3)CH_2C(CH_3)_3$, −CH$(CH_2CH_3)(CH_2)_3CH_3$, *c*-C_6H_{11}], amines [R^1 = *n*-C_8H_{17}, *sec*-C_4H_9, *i*-C_3H_7, *p*-BrPhCH_2, *n*-C_4H_9, *p*-ClPhCH_2, *m*-F-*o*-MePh, *i*-C_5H_{11}, −CH-$(CH_3)CH_2CH(CH_3)_2$], and HOCN (generated in situ). The hydantoin 4-imides were cleaved with 20% TFA/CH_2Cl_2 in 36−81% overall yield.

3.6. Miscellaneous Condensation Reactions

The Biginelli dihydropyrimidine synthesis,[89] another multiple-component condensation, was adapted to solid phase.[90] The Biginelli dihydropyrimidine synthesis combines β-ketoesters, aldehydes, and ureas to give dihydropyrimidines. Wang resin was modified to give the polymer-bound ester (**68.1**) (Scheme 68), and the solid-phase Biginelli dihydropyrimidine

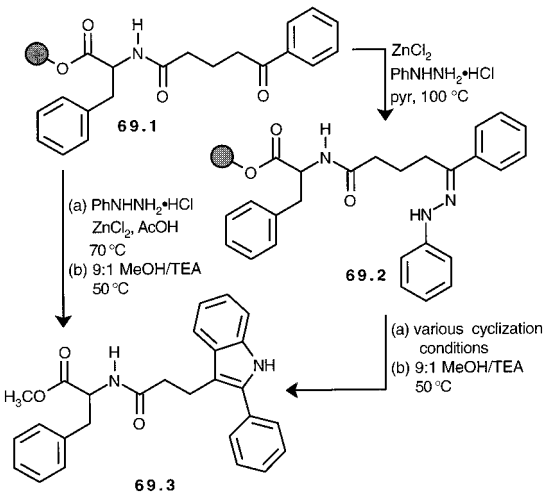
Scheme 68



synthesis was performed using an excess of both β-ketoester and aldehyde. The dihydropyrimidines (R^1 = −CH_3, −CH_2CH_3, −$CH_2C_6H_5$; R^2 = −CH_3, −$C_6H_5(CH_2)_2$, −CH_2CH_3; R^3 = −C_6H_5, 4-OCH_3−C_6H_4, 4-OH−C_6H_4, 2-Cl−C_6H_4, 3-NO_2−C_6H_4, 2-naphthyl) were cleaved by treatment with TFA in 10−20% yield.

The Fischer indole synthesis[91] has also been adapted to the solid phase.[92] In this study, hydrazone intermediate **69.2** could be prepared by heating polymer-bound ketone **69.1** with phenylhydrazine hydrochlorides and $ZnCl_2$ (Scheme 69). This polymer-bound

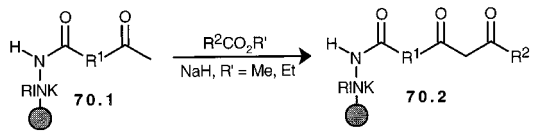
Scheme 69



hydrazone (**69.2**) was then subjected to several cyclization variants. The optimized cyclization conditions of AcOH in $ZnCl_2$ gave the desired indole in 65% yield. The initial polymer-bound ketone (**69.1**) could be directly converted to the indole by heating with phenylhydrazine hydrochloride and $ZnCl_2$ in glacial AcOH. Moreover, due to the necessity of heating the cyclization reactions, the polystyrene served as a more effective polymer support than did PEG-PS.

A solid-phase Claisen condensation has also been reported.[93] En route to pyrazole and isoxazole heterocycles, a solid-phase Claisen condensation was performed to give the requisite β-diketone (Scheme

Scheme 70



70). The polymer-bound amide (**70.1**) (R^1 represents spacers used) was treated with NaH and R^2COOR' [$R^2 = C_6H_5$, 4-$CH_3OC_6H_4$, 4-ClC_6H_3(2-NO_2), 4-ClC_6H_3-(2-Cl), 4-$CH_3OOCC_6H_4$, 4-NCC_6H_4, CH_3; $R' =$ Me or Et]. Carboxylic esters with α-hydrogens, weakly acidic heteroaromatic compounds, and nitro compounds all failed to give condensation products.

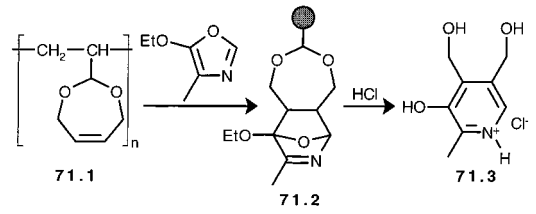
IV. Cycloaddition Reactions

4.1. Diels–Alder Reaction

The Diels–Alder cycloaddition is the most synthetically efficient method for the preparation of six-membered rings,[94] and yet only a limited number of solid-phase Diels–Alder reactions have been reported to date. In addition to the hetero-Diels–Alder reaction mentioned previously in this review (section 3.2),[67] only five other solid-phase Diels–Alder reactions have been reported during the 1990–97 period.

Ritter and co-workers[95] have used the Diels–Alder reaction to synthesize pyridoxine (vitamin B_6).[96] Their synthetic approach began with a poly(vinyl formal) polymer that was prepared by radical polymerization of acrolein (Scheme 71).[97] The poly(vinyl

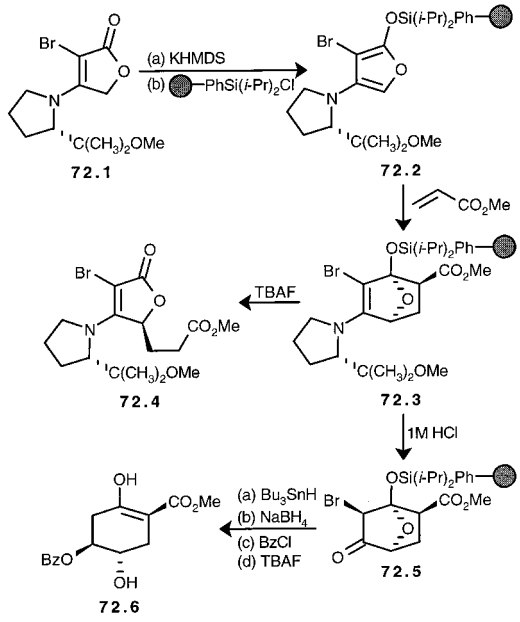
Scheme 71



formal) polymer was condensed with *cis*-2-butene-1,4-diol to give solid-phase cyclic acetal (**71.1**). The condensation reaction was monitored by IR analysis to follow the disappearance of the carbonyl band (1710 cm^{-1}). The resulting polymer-bound alkene served as the dienophile in the ensuing solid-phase Diels–Alder reaction. The diene, 5-ethoxy-4-methyloxazole, was heated in a sealed tube with the resin-bound dienophile for 5 h, and the polymer-bound cycloadduct intermediate (**71.2**) was treated with acid to afford pyridoxine (**71.3**).

A more conventional solid-phase Diels–Alder reaction involved resin-bound nonracemic 3- or 4-aminofurans attached through a silyoxy polymer linker.[98] These furans served as dienes in the cycloaddition reaction with methyl acrylate in a model study of the Diels–Alder reaction. The silyl-functionalized polymer was prepared according to literature procedures[99] and reacted with the enolate of nonracemic 4-aminofuranone (**72.2**). The amount of enolate incorporated into the polymer (84%) was determined by recovery of the unreacted aminofuranone. The resin-bound nonracemic 4-aminofuran was reacted with methyl acrylate to give the resin-bound oxabicycloheptene (**72.3**) (Scheme 72). The facial selectivity

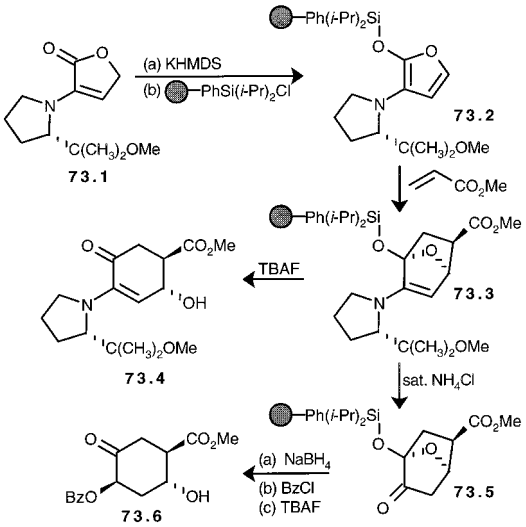
Scheme 72



of the cycloaddition reaction was determined by hydrolytic cleavage of the cycloadduct with 1 M HCl. Debromination (Bu_3SnH), reduction of the polymer-bound oxabicycloketone ($NaBH_4$), protection of the resulting alcohol (BzCl), and cleavage from the resin (TBAF) gave the enol form of the β-keto ester (**72.6**) in 49% overall yield. Chiral HPLC analysis of the enolic β-keto ester, compared to a racemic standard, determined the enantiomeric purity to be >99%. A parallel solution synthesis afforded the enolic β-keto ester in 52% yield over five steps. Other dienophiles were examined, including dimethyl fumarate, dimethyl maleate, acrylonitrile, and phenyl vinyl sulfone.

The resin-bound nonracemic 3-aminofuran (**73.2**) also underwent Diels–Alder cycloaddition with methyl acrylate to give a resin-bound oxabicycloheptene product (**73.3**) (Scheme 73). Again, the facial selectiv-

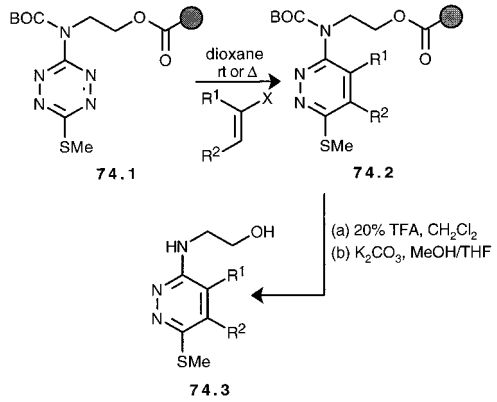
Scheme 73



ity was determined by chiral HPLC. The resin-bound enamine (**73.3**) was hydrolyzed to the ketone, followed by stereoselective reduction with $NaBH_4$ and protection of the alcohol (BzCl). The cyclohexanone product (**73.6**) was cleaved with TBAF and obtained in 2% overall yield. This chemistry was extended to the same dienophiles used with the 4-aminofuran.

An inverse electron demand solid-phase Diels–Alder reaction involving resin-bound 1,2,3,4-tetrazines has been reported.[100] The unsymmetric tetrazine was reacted with polymer-bound benzoyl chloride (DMAP, Et_3N, CH_2Cl_2, room temperature, 48 h) to afford a polymer-bound amino tetrazine (**74.1**) that was protected with $(BOC)_2O$. In addition, the methyl sulfide substituent was oxidized to the sulfone. These resin-bound azadienes (R = SO_2Me or SMe_2) behaved as electron-deficient dienes in the inverse electron-demand Diels–Alder reaction with dienophiles (Scheme 74), and the cyclo-

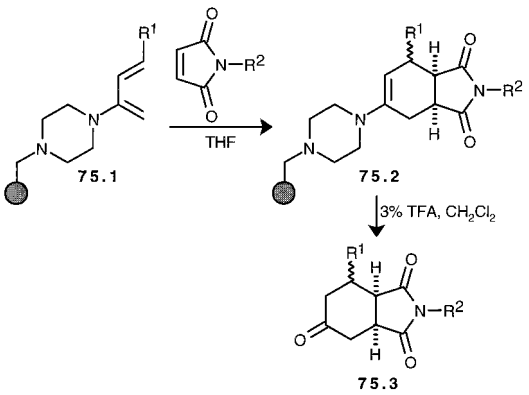
Scheme 74



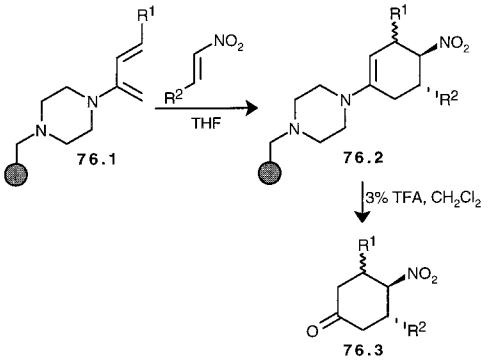
adducts (**74.2**) were cleaved with TFA. Several 3-amino-6-thiomethyl-1,2-pyridazines and 3-amino-6-sulfonylmethyl-1,2-pyridazines were prepared by this method. In general, azadienes with the sulfone group were more reactive than azadienes with the methyl sulfide. Both of these azadienes underwent regioselective Diels–Alder reactions, with the more electron-rich end of the dienophile combining with the more electron-poor end of the tetrazine.

A solid-phase Diels–Alder reaction has been used to synthesize 3,4,5-trisubstituted cyclohexanones.[101] In this work, resin-bound 2-aminobutadienes (**75.1**) underwent cycloaddition with maleimides and nitrostyrenes. The 2-aminobutadienes (R^1 = C_6H_5, 4-F–C_6H_4, 4-OCH_3–C_6H_4, *t*-Bu) were reacted with N-substituted maleimides [R^2 = CH_3, 4-Br–C_6H_4, 4-OCH_3–C_6H_4, (4-$CH_3O_2CC_6H_4$)CH_2, 4-CH_3-CH_2–C_6H_4], which afforded azabicyclo[3,6]nonanes (**75.3**) in moderate yields upon cleavage with TFA (Scheme 75). The azabutadienes (**76.1**) (R^1 = 4-OCH_3–C_6H_4, 4-Br–C_6H_4, 4-F–C_6H_4, 3-pyr, 4-Br–C_6H_4) also underwent [4 + 2] cycloaddition with nitrostyrenes (R^2 = C_6H_5, 4-NO_2–C_6H_4, 4-Br–C_6H_4, 4-OCH_3–C_6H_4, 3-CF_3–C_6H_4) to give 4-nitrocyclohexanones (**76.3**) in average yield upon cleavage from the resin (Scheme 76).

Scheme 75



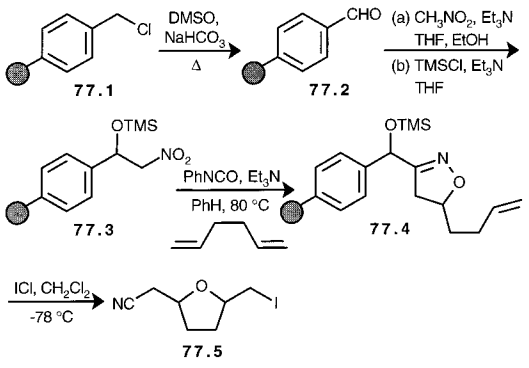
Scheme 76



4.2. 1,3-Dipolar Cycloadditions

Solid-phase 1,3-dipolar cycloaddition reactions have recently been reviewed.[102] Kurth and co-workers reported the use of a solid-phase 1,3-dipolar cycloaddition in the synthesis of 2,5-disubstituted tetrahydrofurans.[103] Merrifield's resin (**77.1**) was oxidized to the appropriate resin-bound aldehyde (**77.2**) and condensed with nitromethane to afford the resin-bound 2-nitro-1-phenylethan-1-ol (**77.3**)[104,105] The hydroxyl was protected (TMSCl, Et_3N) to suppress dehydration. The requisite resin-bound nitrile oxide was generated in situ by reacting the resin-bound nitroalkane (**77.3**) with PhNCO (Scheme 77). Subsequent 1,3-dipolar cyclization with

Scheme 77

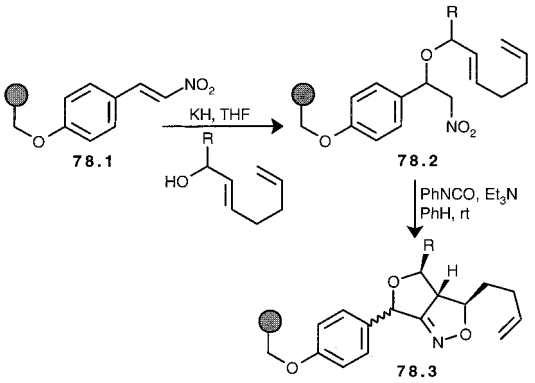


1,5-hexadiene (present in 3-fold excess) gave the polymer-bound isoxazoline (**77.4**), which was treated with ICl to promote electrophilic cyclization, affording the 2,5-disubstituted tetrahydrofuran (**77.5**)

as a mixture of diastereomers (1:1.92) in 18% overall yield.

Kurth and co-workers have also examined the solid-phase intramolecular version of the 1,3-dipolar cycloaddition followed by electrophilic cyclization.[106] Merrifield's resin was treated with anisaldehyde (with NaOH in DMSO, forming the phenoxide in situ) to give the polymer-bound (benzyloxy)benzaldehyde, which was then converted to the resin-bound nitrostyrene (**78.1**) (CH_3NO_2, NH_4OAc, HOAC, reflux, 15 h). Michael addition of dienol alkoxides to the resin-bound nitrostyrene afforded polymer-bound nitro ethers (**78.2**) (Scheme 78), which, in turn, under-

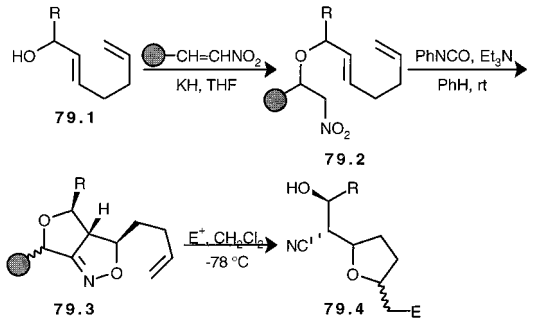
Scheme 78



went a 1,3-dipolar cycloaddition reaction upon PhNCO dehydration to give polymer-bound tetrahydrofuroisoxazolines (**78.3**). Electrophilic cyclization with concomitant resin release afforded cyclic ethers in moderate overall yields.

These cyclic ethers were also prepared via the polymer-bound nitroolefin (**79.2**) (Scheme 79). The

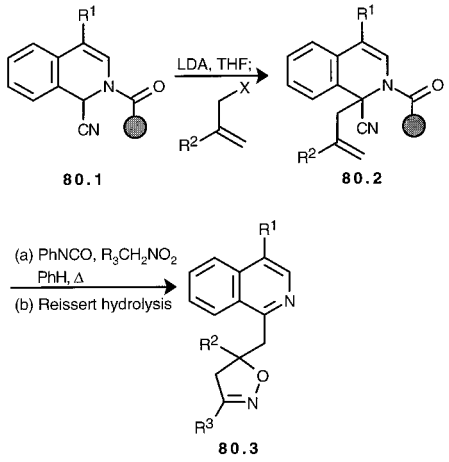
Scheme 79



resin-bound nitroolefin (**79.2**) was converted to the nitroalkane via a Michael addition, and an intramolecular 1,3-dipolar cycloaddition was achieved by PhNCO treatment to give the tetrahydrofuroisoxazolines (**79.3**). Yields and stereoselectivities were no different from those observed for the resin-bound aldehyde route (Scheme 77).

A solid-phase 1,3-dipolar cycloaddition reaction was utilized in the synthesis of various isoxazolinoisoquinoline derivatives.[107] In this study, isoquinoline derivatives were reacted with a polymer-bound benzoyl chloride[108] and TMSCN to give the polymer-bound Reissert[109] compound (**80.1**). This Reissert compound was alkylated at C-1 to give a resin-bound olefin (**80.2**), which underwent a 1,3-dipolar cycloaddition upon treatment with PhNCO and a nitroalkane (Scheme 80). Interestingly, despite the large

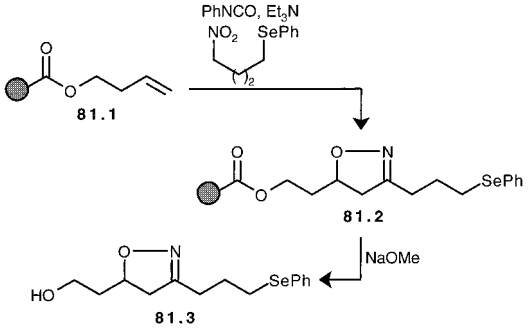
Scheme 80



excess of the nitrile oxide present (5 equiv) only the exocyclic olefin underwent 1,3-dipolar cycloaddition; the enamide olefin was unaffected. Even sterically hindered exocyclic olefins were more reactive in the 1,3-dipolar cycloaddition reaction than the less hindered enamide. Reissert hydrolysis cleaved the isoxazolinoisoquinoline heterocycles (**80.3**) from the resin.

Kurth and co-workers have also demonstrated a solid-phase combinatorial synthesis of polyisoxazolines involving the iterative[103] application of nitrile oxide 1,3-dipolar cycloadditions.[110] Polystyrene (styrene/2% divinylbenzene copolymer) was converted to the resin-bound 3-butenyl benzoate (**81.1**) via lithiation/CO_2 quench, treatment with $SOCl_2$, and esterification. The polymer-bound 3-butenyl benzoate underwent a 1,3-dipolar cycloaddition with 1-nitro-4-(phenylseleno)butane in the presence of PhNCO and Et_3N (Scheme 81). Transesterification with NaOMe

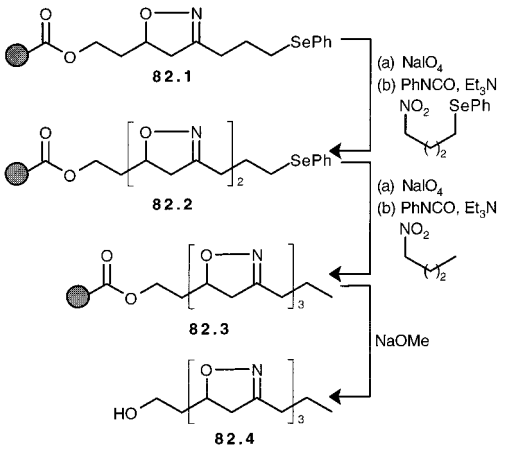
Scheme 81



cleaved the isoxazoline from the polymer (44% overall yield), validating that the 1,3-dipolar cycloaddition step was successful.

Employing a selenide oxidation−elimination step immediately after the 1,3-dipolar cycloaddition reaction regenerated a polymer-bound olefin, which was subjected to a second 1,3-dipolar cycloaddition

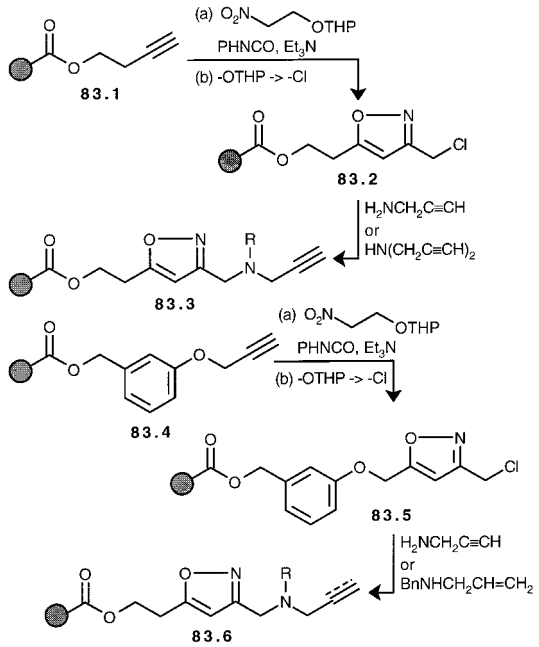
Scheme 82



(Scheme 82). Another selenide oxidation−elimination step was performed, followed by a third 1,3-dipolar cycloaddition. Finally, NaOMe transesterification gave the triisoxazoline in 18% overall yield (eight steps). This methodology was used to create a 64-compound library of triisoxazolines using four different nitroseleno ethers and four different nitroalkanes.

Continuing with iterative protocols, an iterative solid-phase synthesis of isoxazole/isoxazoline polyheterocycles with a spacer group separating the repeating isoxazolines has been reported.[111] The solid-phase approach began with a polymer-bound benzoyl chloride moiety which was reacted with appropriated alkynols to give polymer-bound benzoyl esters (**83.1**). These esters were reacted with THP-protected 2-nitroethanol, PhNCO, and Et_3N (nitrile oxide generated in situ), and a 1,3-dipolar cycloaddition ensued (Scheme 83). Deprotection of the

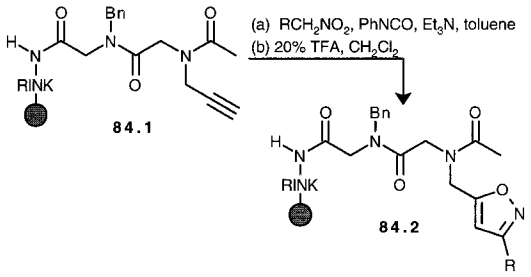
Scheme 83



THP moiety allowed for the incorporation of isoxazole spacers, which was accomplished by *N*-alkylating with benzylallylamine to give a tertiary amine (**83.3**).The resulting resin-bound olefin was subjected to 1,3-dipolar cycloaddition conditions to give an isoxazoline moiety. The benzoyl ester was transesterified to give the heterocycle derivative in 35% overall yield. Several different polyheterocycle derivatives were prepared via this solid-phase protocol.

Pei and Moos have also reported a solid-phase synthesis of isoxazole and isoxazoline derivatives via a 1,3-dipolar cycloaddition reaction of nitrile oxides with alkynes and alkenes.[112] Rink amide resin was converted to various polymer-bound peptoid moieties according to literature procedures.[113] Two different protocols effected the solid-phase 1,3-dipolar cycloaddition reactions. One method employed toluene at 100 °C, while the other method used CH_2Cl_2/H_2O at room temperature. The nature of the nitrile oxide precursor dictated method selection. The nitrile oxides were generated either from the nitroalkane, PhNCO, and Et_3N or from oxidation of oximes with NaOCl and Et_3N (Scheme 84). The in situ generation of nitrile

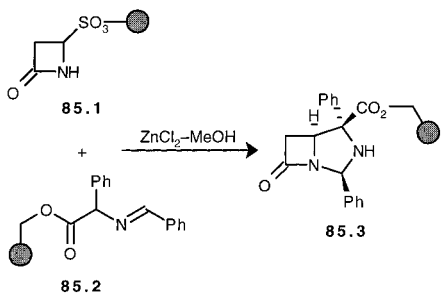
Scheme 84



oxides was followed by an immediate cycloaddition with the resin-bound alkyne or alkene. Single regioisomers of the isoxazoles and isoxazolines were formed and then cleaved from the resin with 20% TFA. Nine isoxazole peptoid derivatives and two isoxazoline derivatives were prepared via this method.

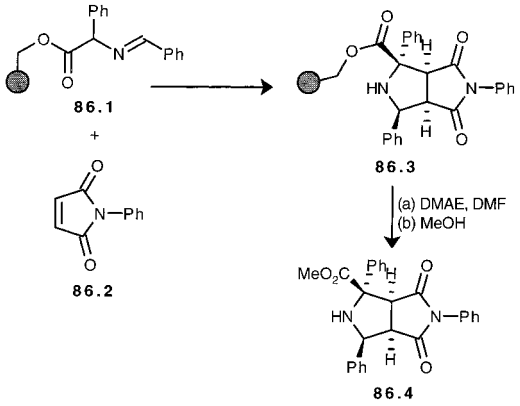
A solid-phase 1,3-dipolar cycloaddition reaction was used to synthesize structurally similar β-lactam derivatives.[114] A solution-phase model study showed that cyclic imines reacted with nitrile imides through a [3 + 2] cycloaddition reaction to afford the β-lactam derivative. The key intermediate in this cycloaddition was the azet-2(3*H*)-one, and verification of this species behaving as the dipolarophile was accomplished via a three-phase test.[115] The polymer-bound 4-oxoazetidin-2-yl toluene *p*-sulfonate (**85.1**) was reacted with a polymer-bound imine (**85.2**) (a trapping agent) to give the resin-bound β-lactam derivative (**85.3**) (Scheme 85). IR analysis of this resin displayed an

Scheme 85



absorption at 1740 cm^{-1}, which was attributed to the β-lactam carbonyl functionality. The β-lactam moiety was cleaved from the resin by treatment with 2-dimethylaminoethanol in DMF and MeOH. It is interesting to note that the polymer-supported imine (**86.1**) underwent a separate 1,3-dipolar cycloaddition with *N*-phenylmaleimide (**86.2**) to give the bicyclic heterocycle (Scheme 86). The bicyclic heterocycle

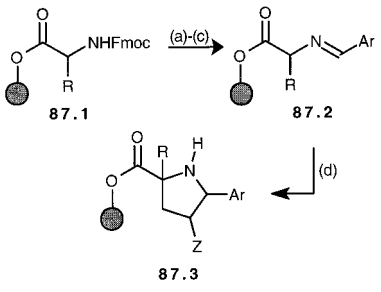
Scheme 86



(**86.3**) was then cleaved from the resin by treatment with 2-dimethylaminoethanol in DMF and MeOH.

Gallop and co-workers have developed a solid-phase synthesis of functionalized pyrrolidines utilizing a 1,3-dipolar cycloaddition of polymer-bound azomethine ylides.[116] Either TentaGel AC or SASRIN FMOC-protected amino acid resins (**87.1**) were deprotected with 20% piperidine in DMF to give the α-amino esters, which underwent condensation with various aldehydes (aromatic and heteroaromatic) in $CH(OMe)_3$ to give polymer-supported aryl imines (**87.2**). The conditions empolyed to achieve solid-phase cycloaddition of metalloazomethine ylides to electron-poor olefins were developed previously for solution-phase reactions (Scheme 87).[117] Gel-

Scheme 87[a]

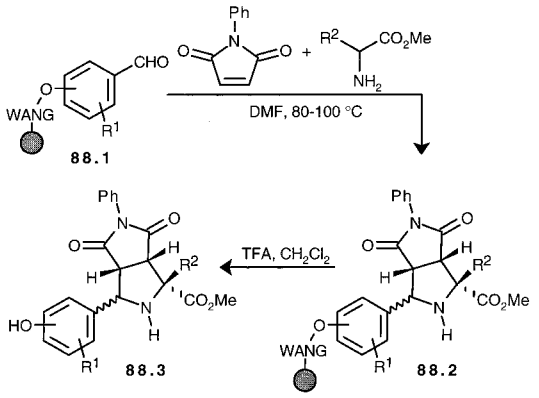


[a] Reagents and conditions: (a) 20% piperidine, DMF; (b) 1 M ArCHO, $CH(OMe)_3$; (c) Ac_2O, DIPEA; (d) 1 M olefin, 1 M $AgNO_3$, 1 M Et_3N, CH_3CN.

phase ^{13}C NMR techniques were used to characterize the resin-bound intermediates. This solid-phase synthetic protocol was extended to the synthesis of combinatorial libraries of functionalized pyrrolidines.

Another example of a solid-phase 1,3-dipolar cycloaddition of a resin-bound azomethine ylide to synthesize proline analogues has been reported by Hamper.[118] Here, a multicomponent reaction protocol was used for the preparation of the bicyclic proline derivatives. A resin-bound aryl aldehyde (**88.1**), an α-amino ester, and a maleimide were combined in one step to give bicyclic proline heterocycles (**88.2**) (Scheme 88). Nine benzaldehydes were used in this

Scheme 88

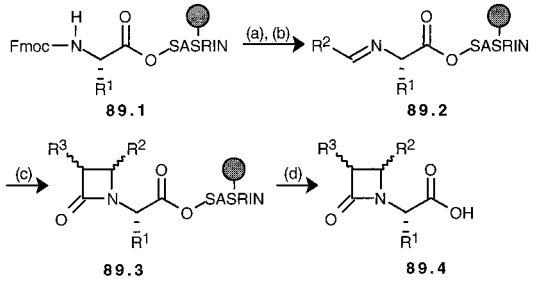


three-component synthesis. The bicyclic cycloaddition products were cleaved from the resin with TFA and obtained as a diastereomeric mixture.

4.3. Staudinger Reaction

Solid-phase application of the Staudinger reaction to give β-lactams has been reported.[119] Commercially available FMOC-protected amino acid SASRIN resin (**89.1**) was deprotected (piperidine in NMP) and condensed with alkyl, aromatic, or α,β-unsaturated aldehydes in $(MeO)_3CH/CH_2Cl_2$ to deliver the polymer-bound imines (**89.2**) (Scheme 89). The [2 + 2] cy-

Scheme 89[a]

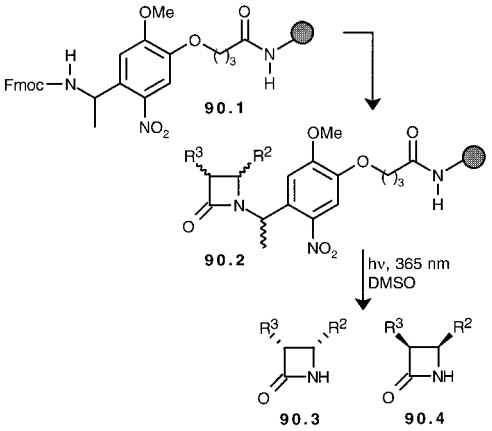


[a] Reagents and conditions: (a) 30% piperidine, NMP; (b) 0.8 M R^2CHO, $(MeO)_3CH$, CH_2Cl_2; (c) 0.8 M R^3CH_2COCl, Et_3N, CH_2Cl_2; (d) 3% TFA, CH_2Cl_2.

cloaddition reaction was performed by slowly treating resin-bound imines with acid chlorides and Et_3N in CH_2Cl_2. The acid chloride was converted in situ to a ketene. The β-lactam derivatives (**89.4**) were cleaved from the resin with TFA in 55−97% yields.

TentaGel resin functionalized with the photolabile linker α-methyl-6-nitrovaleratrylamine[120] was also subjected to [2 + 2] cycloaddition reactions. This linker was stable to both acidic and basic conditions, and the β-lactam products were photolyzed (365 nm) from the resin. The amino group of the linker participated in Schiff base formation and subsequent [2 + 2] cycloaddition (Scheme 90).

Scheme 90



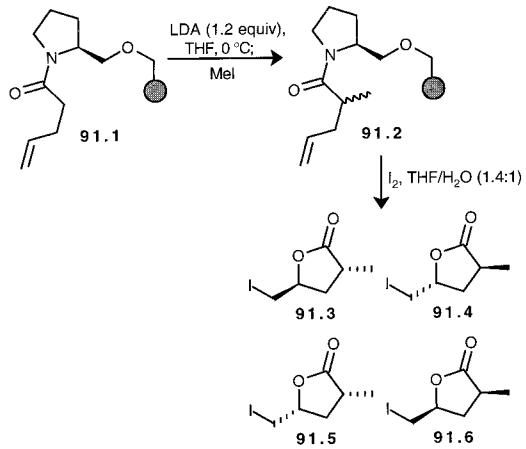
V. C-Alkylation Reactions

5.1. Via Enolates

There are numerous examples of solution-phase C-alkylation steps being incorporated into solid-phase synthetic strategies. However, studies involving solid-phase carbon−carbon bond forming alkylation reactions are scarce. Kurth and co-workers have reported a three-step solid-phase synthesis of γ-butyrolactones that involved a C_α-alkylation step.[121] Their solid-phase synthetic strategy began with attachment of a chiral auxiliary to Merrifield's resin through an ether linkage. Previous solution-phase experiments by Evans demonstrated that chiral amide C_α-alkylation gave highest stereoselectivities with (*L*)-prolinol;[122] thus, (*L*)-prolinol (N-acylated) was attached to Merrifield's resin. An amide absorption (1646 cm^{-1}) was observed in the IR spectrum, confirming chiral auxiliary attachment to the resin. Prior to investigating the C_α-alkylation step, the iodolactonization of the polymer-bound pentenamide was performed to afford the γ-butolactone as a 65:35 mixture of enantiomers in 40% overall yield.

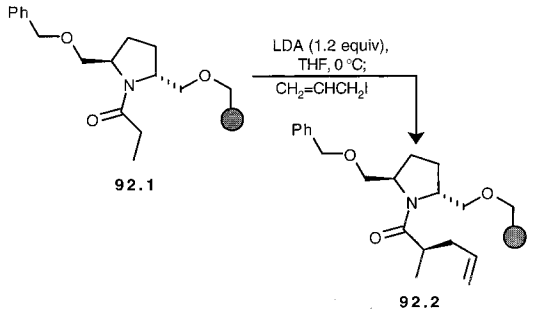
The solid-phase C_α-amide alkylation step was achieved by treating the polymer-bound pentenamide (**91.1**) with LDA and MeI. Upon iodocyclization, 5-(iodomethyl)-3-methyl-γ-butyrolactones (63:4:31:2 mixture of isomers) were obtained in 33% overall yield (Scheme 91). This study demonstrated that (1) solid-phase C_α-alkylation was an effective method and (2) the diastereoselectivities of the solid-phase alkylation process were similar to those found for the solution-phase alkylations of prolinol-derived amides.

Scheme 91



This work was continued by developing a "C_2-symmetric" pyrrolidine-base chiral auxiliary and applying the same three-step process (N-acylation, C_α-alkylation, and iodolactonization).[123] The C_2-symmetric pyrrolidine-based auxiliary *trans*-(2*R*,5*R*)-(*N*-propionyl)-2,5-bis(hydroxymethyl)pyrrolidine[124] was attached to Merrifield's resin to give the polymer-bound free hydroxyl and amide moieties (3440 and 1647 cm^{-1}, respectively) (Scheme 92). To prevent

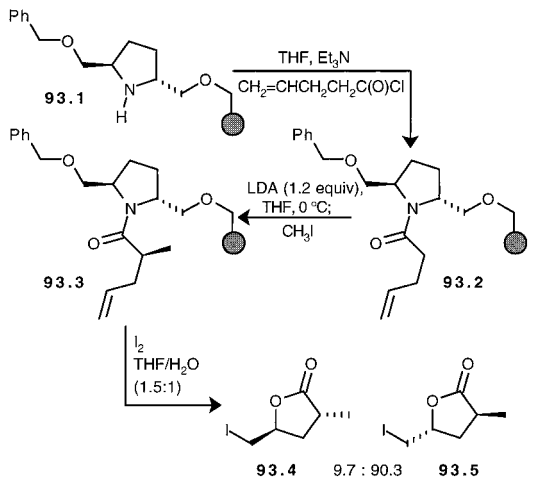
Scheme 92



competing O-alkylation, the remaining hydroxyl moiety was protected as the benzyl ether (disappearance of the 3440 cm^{-1} absorption was observed in the IR spectrum) to give the polymer-bound C_2-symmetric pyrrolidine (**92.1**). This resin was treated with LDA (it was assumed that this proceeded via the *Z*-enolate, based on literature precedent)[125] and allyl iodide to deliver the C_α-alkylated resin (**92.2**). Subsequent iodolactonization afforded the γ-butyrolactones (93.5:6.5 mixture of isomers) in 34% overall yield from *trans*-(2*R*,5*R*)-(*N*-propionyl)-2,5-bis(hydroxymethyl)pyrrolidine. The lactone ratios established that the solid-phase C_α-alkylation selectivity was >14:1, thus making this C_2-symmetric chiral auxiliary (pyrrolidine auxiliary) more selective than the chiral auxiliary derived from (*L*)-prolinol.

The resin-bound C_2-symmetric chiral auxiliary could be recovered and reused in an *N*-acylation process, followed by both C_α-alkylation and iodolactonization (Scheme 93). The resin-bound 4-pentenoy-

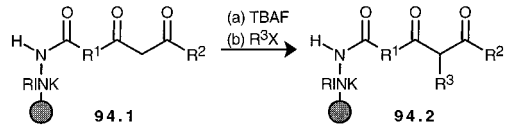
Scheme 93



lamide (**93.2**) (1639 cm^{-1}) was treated with LDA and MeI to afford the C_α-alkylated resin, and iodolactonization delivered the γ-butolactones as a mixture of isomers (9.7:90.3).

As previously discussed (Scheme 70), a solid-phase Claisen condensation was reported for the functionalization of pyrazoles and isoxazoles.[93] The same authors performed an α-alkylation on the diketone formed from the Claisen condensation. The α-alkylation was most effective when TBAF was present both to prevent O-alkylation and to increase the nucleophilicity of the enolate (Scheme 94). Simple

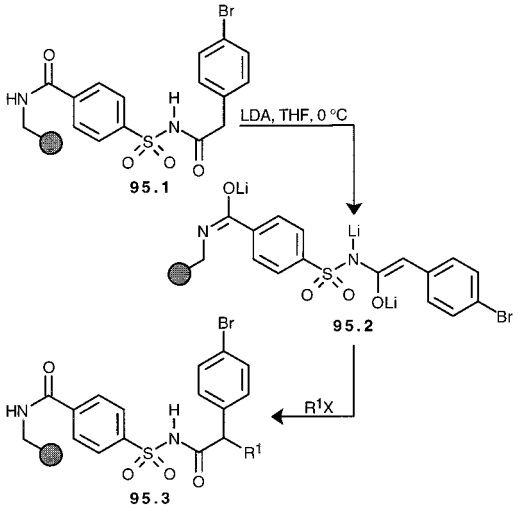
Scheme 94



alkyl iodides, ethyl bromoacetate, and allyl bromides were successful in the α-alkylation. However, iodoacetonitrile and bromoacetophenone failed to alkylate the resin-bound diketone completely. This solid-phase alkylation process failed when acidic or basic heteroatom substituents were used.

Ellman has also examined a solid-phase enolate alkylation of a sulfonamide resin en route to arylacetic acid derivatives.[9c] The resin-bound sulfonamide resin was treated with pentafluorophenyl 4-bromophenylacetate in DMAP to give the resin-bound acylsulfonamide (**95.1**) (Scheme 95). This polymer-

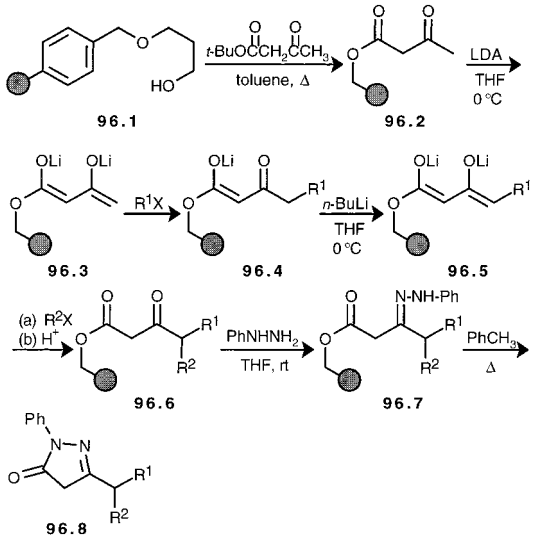
Scheme 95



bound acylsulfonamide underwent deprotonation with LDA (15 equiv) to give the trianion, which was subsequently monoalkylated by addition of an alkyl halide. It is worth noting that, after treatment with LDA, the polymer beads were blue in color, and the blue color dissipated upon addition of the alkyl halide. Activated and unhindered alkyl halides (methyl iodide, benzyl bromide), as well as hindered halides (isopropyl iodides), gave rapid and complete alkylation of the sulfonamide trianion. Interestingly, very little dialkylation product was observed (<4% for methyl iodide). In addition, the alkylated acylsulfonamide could either be cleaved under basic conditions to give the alkylated product or be subjected to a Suzuki coupling reaction to diversify the aryl acetic acid derivatives (R^1 = H, Me, Br, Et, *i*-Pr).

Tietze reported a solid-phase alkylation of a polymer-bound acetoacetate to give γ-alkylated β-ketoesters that were cyclized with phenylhydrazine to give 1-phenylpyrazolone derivatives.[127] The polymer-bound β-ketoester was prepared by transacetoacetylation of a *tert*-butylacetoacetate polystyrene-based hydroxyl group (**96.1**) (Scheme 96).[128] The resin-

Scheme 96



bound β-ketoester (**96.2**) derivative was then treated with LDA to give a dianion (**96.3**),[129] which was trapped with different alkyl halides to give the γ-alkylated β-ketoester monoanion. It is worth noting that the resin became red in color upon formation of the dianion and faded after addition of the alkyl halide. The monoanion was subjected to a second addition of base (*n*-BuLi) and a second alkyl halide to afford the resin-bound γ,γ-dialkylated β-ketoester (**96.6**). Subsequent one-step cyclization and cleavage gave the desired 1-phenylpyrazolone derivative and was achieved by treatment of the resin-bound γ,γ-dialkylate β-ketoester with phenylhydrazine (20 equiv) and heating the polymer-bound hydrazone intermediate (**96.7**).

5.2. Miscellaneous Alkylations

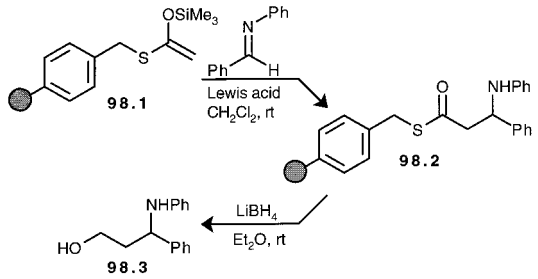
Silyl enol ethers have been used in solution-phase reactions as isolable enolate equivalents.[130] Developing polymer-bound silyl enol ethers is desirable for use in combinatorial synthesis as they are versatile reagents for use in many C−C bond forming reactions. Solid-phase synthesis of silyl enol ethers and subsequent reactions with imines to produce amino alcohols have been reported.[131] Merrifield's resin was treated with potassium thioacetate to deliver the polymer-bound thioester (IR 1693 cm^{-1}), which was treated with TMSOTf and Et_3N[132] to give the polymer-bound silyl enol ether (**97.1**). Four other polymer-bound silyl enol ethers were prepared in a similar fashion (Scheme 97).

Reaction of the polymer-bound silyl enol ethers with imines was examined using resin (**98.1**), *N*-benzylideneaniline, and several Lewis acids. Traditional Lewis acids ($TiCl_4$, $SnCl_4$, $BF_3{\cdot}OEt_2$) gave

Scheme 97

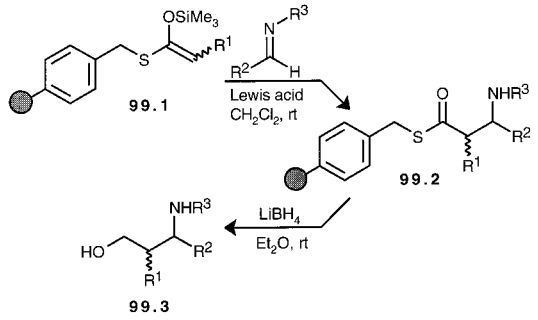
moderate yields, but Lewis acids such as $Sc(OTf)_3$ or $Hf(OTf)_4$ gave better yields. Cleavage of the amino alcohol was accomplished with $LiBH_4$ in Et_2O (Scheme 98). Resin **99.1** (R^1 = H, OBn, Me) was reacted with

Scheme 98



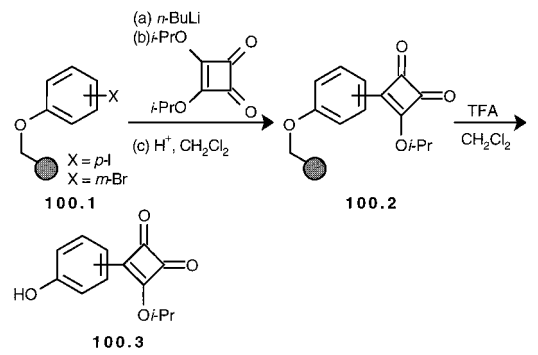
several imines (R^2 = Ph, 2-furyl, 2-thiophene, *c*-C_6H_{11}, *p*-ClPh, *p*-OMePh; R^3 = Ph, $PhCH_2$, *p*-OMePh) and $Sc(OTf)_3$, followed by treatment with $LiBH_4$ to give the desired amino alcohols in yields ranging from 42 to 79% (Scheme 99).

Scheme 99



As previously mentioned in this review, Armstrong developed a solid-phase synthesis of squaric acid derivatives (Scheme 10).[18] One solid-phase route was based on the solution-phase synthesis of squaric acid derivatives via a 1,2-addition reaction.[133] Halogenated phenols were coupled to Wang resin and treated with BuLi to effect lithium–halogen exchange[134] and generate the polymer-bound anion, which was quenched with diisopropyl squarate and cleaved with TFA to deliver the desired squaric acid derivative (**100.3**) (Scheme 100).

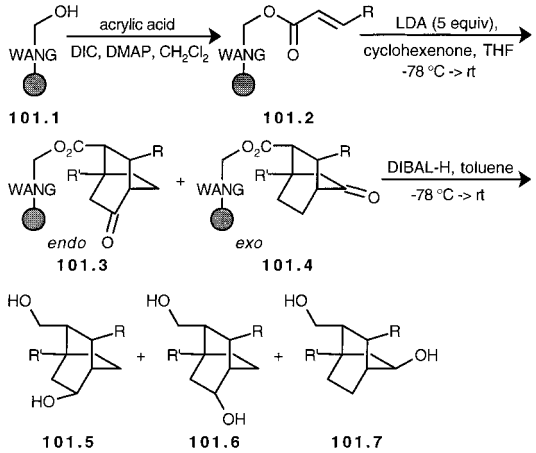
Scheme 100



VI. Michael Additions

Although there have been reports of heteroatom solid-phase Michael addition reactions, use of Michael addition reactions in carbon–carbon bond forming processes has been limited.[135] In one study, Ley and co-workers used a carbon–carbon bond forming process to synthesize bicyclo[2.2.2]octane derivatives.[136] Resin-bound acrylates[137] were reacted with cyclohexenones, followed by reductive amination and cleavage to afford bicyclo[2.2.2]octanes (see compounds **101.5**, **101.6**, and **101.7**). Commercially available Wang resin was converted to the polymer-bound acrylates (DIC, various acrylic acids, DMAP, CH_2Cl_2), which were then treated with dienolate bases obtained from 3-methyl-2-cyclohexenone and 3-ethoxy-2-cyclohenenone to give resin-bound bicyclo[2.2.2]-octanones (Scheme 101). The stereoselectivities of

Scheme 101



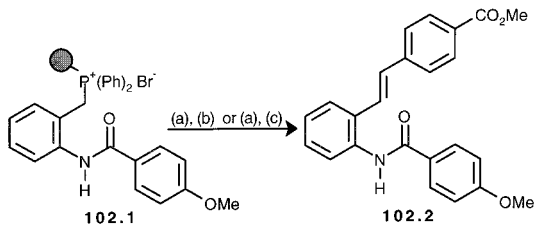
these tandem Michael additions were determined after the bicyclo[2.2.2]octanones were cleaved from the resin with DIBAL-H to give the appropriate diols. GC analysis was used to determine the endo–exo ratios.

VII. Olefination Reactions

7.1. Wittig Reaction

Polymer-bound phosphonium salts have been previously reported[138] for use in solid-phase Wittig reactions[139] with the advantage that the usual byproduct of phosphine oxide remains attached to the resin. For example, Hughes has reported the use of a polymer-supported phosphonium moiety in a solid-phase Wittig reaction.[140] The phosphonium salt was prepared by treating commercially available resin-bound triphenylphosphine[141] with 2-nitrobenzyl bromide (DMF, 70 °C, 48 h).[142] Gravimetric analysis was used to determine the loading of the polymer-bound phosphonium salt. The nitro group on the resin-bound phosphonium salt (**102.1**) was transformed to an amide (reduction of the nitro group followed by acylation of the amine), which underwent a Wittig reaction with methyl 4-formylbenzoate with concomitant cleavage from the resin to furnish stilbenes (**102.2**) (Scheme 102).

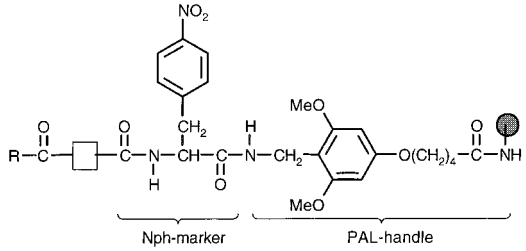
Scheme 102[a]



[a] Reagents and conditions: (a) methyl 4-formylbenzoate, NaOMe, MeOH, Δ; (b) Grignard's reagent T, AcOH; (c) aminomethyl resin, AcOH, MeOH/dioxane.

Vágner and co-workers have reported solid-phase synthesis of carbon−carbon double bonds via Wittig reactions in which a resin-bound aldehyde or ketone reacts with a solution-phase phosphorane ylide or phosphanate anion.[143] Commercially availabile TentaGel S resin was modified, and the pendant amino groups were treated with linkers [tris(alkoxy)benzylamide (PAL) and *N*-FMOC-*p*-nitrophenylalanine (Nph)]. Cleavage of the PAL linkage delivered alkene products with a terminal Nph−NH_2 moiety. The terminal Nph−NH_2 group was important as a chromophore to aid in HPLC analysis of the products. A generic structure of the resin-bound substrate used in this solid-phase Wittig reaction is illustrated in Scheme 103 (the square represents the various

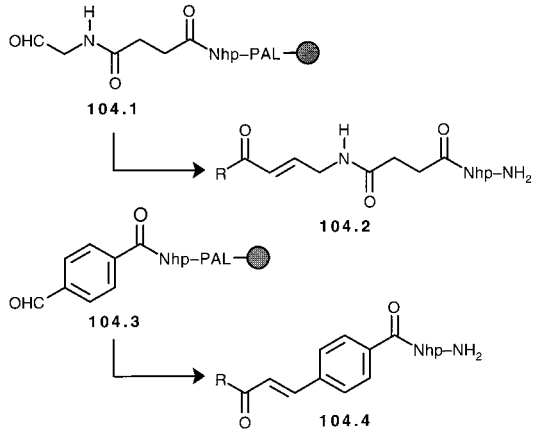
Scheme 103



aldehydes or ketones utilized).

The resin-bound aromatic or aliphatic aldehydes (**104.1**) were converted quantitatively to the appropriate *E*-olefins (as determined by HPLC and ^{1}H NMR analysis) upon treatment with stabilized phosphoranes (Scheme 104). Unfortunately, resin-bound

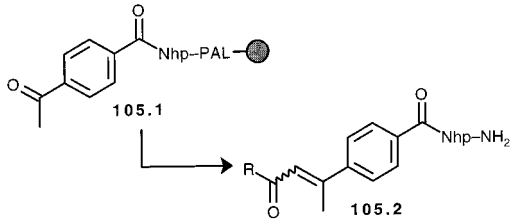
Scheme 104



ketones were slow to react and afforded very little of the desired olefinic products.

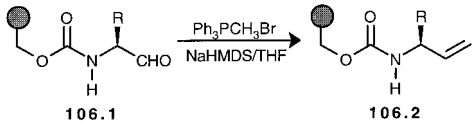
The resin-bound aldehydes also reacted with phosphonate ester anions (generated from the phosphonate ester, a teritary amine, and LiBr) to give the desired alkenes. The stereochemistry of the olefin was dependent on the phosphonate ester anion used. For example, triethyl phosphonoacetate gave only *E*-alkenes, while bis(2,2,2-trifluoroethyl) (methyoxycarbonyl)phosphonate gave the *Z*-olefin.[144] Polymer-bound ketones (**105.1**) were unreactive under standard conditions; however, addition of a strong base (DBU with LiBr or KHMDS)[145] afforded the desired olefin (**105.2**) (Scheme 105).

Scheme 105



A solid-phase Wittig reaction has also been used in the synthesis of olefin and hydroxyethylene peptidomimetics.[146] The solid-phase synthetic approach began with an acyl imidazole-modified Wang resin, which was converted to polymer-bound aldehydes via reaction with amino alcohols followed by oxidation. These resin-bound aldehydes (**106.1**) were subjected to a solid-phase Wittig reaction by treatment with NaHMDS and Ph_3PCH_3Br to give allylic amines (**106.2**) (Scheme 106). The solid-phase Wittig reaction

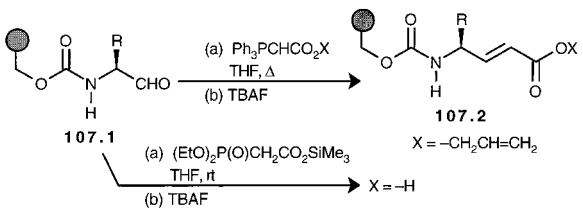
Scheme 106



was monitored by IR analysis, which revealed that the aldehyde absorption at 1732 cm^{-1} disappeared. A few allylic amines were cleaved with TFA/CH_2Cl_2 and subsequently protected as the *N*-BOC derivatives; these amines were then isolated in 21% yield (based on Wang resin loading).

The resin-bound aldehydes (**107.1**) could also be used in solid-phase Horner−Emmons olefinations. A commercially available Horner−Emmons reagent (Scheme 107) reacted with the polymer-supported

Scheme 107

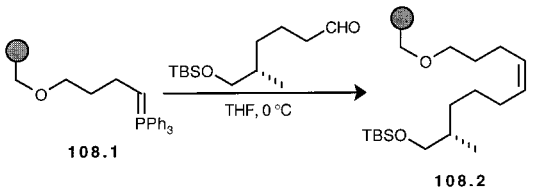


aldehyde to afford the α,β-unsaturated acids after cleavage of the silyl protecting group (TBAF).

Nicolaou has used a solid-phase aldol reaction (section 3.1) en route to epothilones A and B.[59] In the same study, a solid-phase Wittig reaction was per-

formed to convert Merrifield's resin to the desired polymer-bound olefinic intermediate. Merrifield's resin was treated with 1,4-butanediol, Ph_3P-I_2-imidazole, and Ph_3P to give the polymer-bound phosphonium salt (Scheme 108), which was converted to

Scheme 108

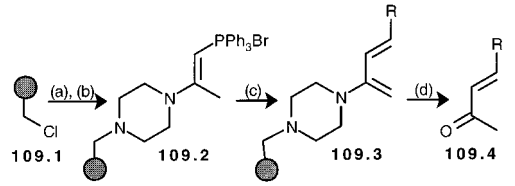


the resin-bound ylide (**108.1**) by treatment with NaHMDS. Subsequent addition of an aldehyde afforded the polymer-supported olefin moiety (**108.2**) (>70% yield). The olefin derivative was assigned as *Z*; however, the geometry was not absolutely confirmed.

Nicolaou continued his solid-phase study of epothilone derivatives by developing a combinatorial synthetic approach, including another solid-phase Wittig olefination reaction.[61] Merrifield's resin was converted to the polymer-bound ylide and treated with an aldehyde to give the desired olefin (see section 3.1 and Scheme 50 of this review).

Finally, a solid-phase Wittig reaction has been used in the synthesis of 2-aminobutadienes,[147] which were desirable for use in solid-phase Diels–Alder reactions. The solid-phase synthesis began with Merrifield's resin, which was converted to the resin-bound 2-(*N*-piperazino)prop-1-enyl-1-triphenylphosphonium bromide (**109.2**) (Scheme 109). The polymer-

Scheme 109[a]



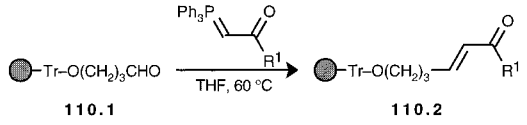
[a] Reagents and conditions: (a) piperazine, dioxane, Δ; (b) propargyl triphenylphosphonium bromide, CH_2Cl_2; (c) (i) KO *t*-Bu, THF, (ii) RCHO, Δ; (d) 3% TFA, CH_2Cl_2.

supported 2-(*N*-piperazino)prop-1-enyl-1-triphenylphosphonium bromide was treated with KOtBu (resin turned red–orange, indicating ylide formation) and RCHO to give the olefination product, a resin-bound butadiene (**109.3**). The butadiene was cleaved from the resin with 3% TFA to give the α,*β*-unsaturated methyl ketone (Scheme 109). Prior to performing the solid-phase olefination, the resin needed to be meticulously dried. While drying in a vacuum oven proved inadequate, resin azeotroped with benzene prior to being used in the olefination was effective.

Several aldehydes were examined (R = Ph, 4-MeO–Ph, 4-NO_2–Ph, 4-CN–Ph, 3-CN–Ph, 4-F–Ph, 4-*t*-Bu–Ph, 3-pyridyl, 2-furyl, cyclohexyl, *n*-nonyl); benzaldehydes with electron-withdrawing groups did not give the expected α,*β*-unsaturated methyl ketone. The stereochemistry in the resin-bound butadienes (3,4 carbon–carbon double bond) was not assigned directly. However, only the *E* α,*β*-unsaturated methyl ketones were isolated, implying that the resin-bound 2-amionbutadiene also had *E* geometry.

Kurth and co-workers reported a solid-phase Wittig olefination en route to *β*-mercapto ketones.[135] The polymer-bound aldehyde (**110.1**) was treated with 2-triphenylphosphoranylidene-2-propanone and heated to 60 °C (Scheme 110). Several ylides were selected

Scheme 110

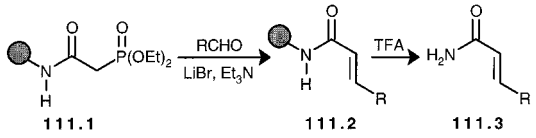


for use in the solid-phase Wittig reaction (R^1 = Me, *t*-Bu, Ph), and all gave the polymer-bound olefin.

7.2. Horner–Emmons Reactions

Not surprisingly, solid-phase Horner–Emmons reactions have also been reported. For example, a solid-phase Horner–Emmons reaction proved to be very effective for synthesizing peptides.[148] Thus, polymer-bound diethylphophonoacetamide (**111.1**)[149] was reacted with an aldehyde, LiBr, and Et_3N to achieve the Horner–Emmons olefination reaction (Scheme 111). This gave the resin-bound unsaturated

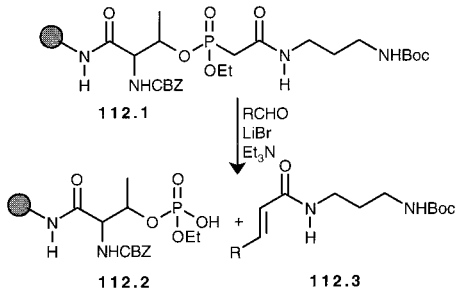
Scheme 111



amide (**111.2**), which was cleaved from the polymer with TFA. Several aldehydes gave excellent yields of α,*β*-unsaturated amides, including bulky aliphatic aldehydes (isopropylaldehyde, >95% conversion to olefination product) and aromatic aldehydes (benzaldehyde, >95% conversion).

A second approach to the solid-phase synthesis of α,*β*-unsaturated amides was to incorporate the phosphonoacetamide moiety through the phosphoester bond. This was desirable because performing the solid-phase Horner–Emmons reaction would not only give the alkene but also cleave the desired olefin product from the resin (Scheme 112). The geometry

Scheme 112



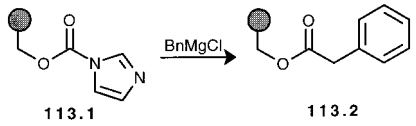
of the α,*β*-unsaturated amide was found to be *E*, as observed by ^{1}H NMR. Gel-phase ^{31}P was also used to characterize intermediates still attached to the resin.

VIII. Organometallic Reactions

8.1. Grignard Reaction

Solid-phase Grignard reactions have been used effectively in the synthesis of methylphosphonate dimers.[150] However, an early example of a solid-phase Grignard reaction was reported by Hauske and Dorff.[151] Wang resin was converted to the corresponding imidazolide carbamate by treatment with carbonyl diimidazolide, which was converted to enolizable esters by reaction with an organometallic. Thus, the polymer-bound imidazolide (**113.1**) was treated with benzylmagnesium chloride to give the resin-bound phenacetic ester in good yield (Scheme 113). This established a route to a diverse number

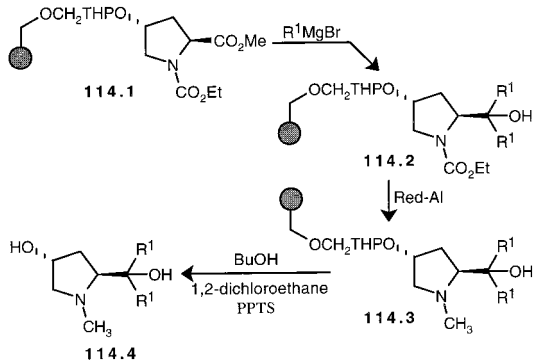
Scheme 113



of enolizable esters with potential for further diversification.

Ellman also examined the utility of a solid-phase Grignard reaction in the synthesis of 2-pyrrolidinemethanol ligands.[152] First, Merrifield's resin (functionalized as the DHP ether) was treated with *N*-[(ethyloxy)carbonyl]-4-hydroxyproline methyl ester to give the resin-bound 2-pyrrolididinemethanol precursor (**114.1**). This resin-bound methyl ester, when treated with a large excess of Grignard reagent (Scheme 114), afforded the resin-bound trisubstituted

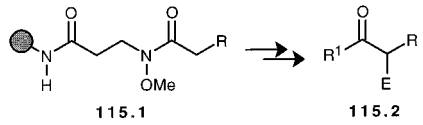
Scheme 114



alcohol (**114.2**) in good yield. Treatment with PPTS cleaved these diols from the resin ($R^1 = C_6H_5$; $R^2 = CH_3$, CH_2CH_3).

Ketones and aldehydes were prepared in modest yields via a solid-phase Grignard reaction.[153] Weinreb amides are known to selectively give ketones when reacted with organometallic reagents (both Grignard and lithium species).[154] The solid-phase strategy involved attachment of the methoxyamine to Rink resin, followed by the coupling of a carboxylic acid. The polymer-bound methoxamine underwent enolate alkylation to give the Weinreb-type amide resin, which was treated with various Grignard reagents (R = Me, $-CH_2CH_2CH{=}CH_2$, $PhCH_2-$, Ph) (Scheme 115).

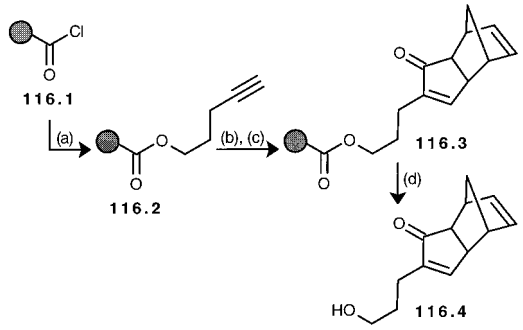
Scheme 115



8.2. Pauson–Khand Cycloaddition

The first solid-phase Pauson−Khand reactions were performed by Schore.[155] Merrifield's resin was converted to the acid chloride according to Leznoff's procedure[2] and esterified with 4-pentyn-1-ol. The resulting polymer-bound alkyne was treated with $Co_2(CO)_8$ in benzene to afford the polymer-supported alkyne−$Co_2(CO)_6$ complex (IR analysis: 2016, 2052, 2093 cm^{-1}; Scheme 116). Subsequent heating of this

Scheme 116[a]

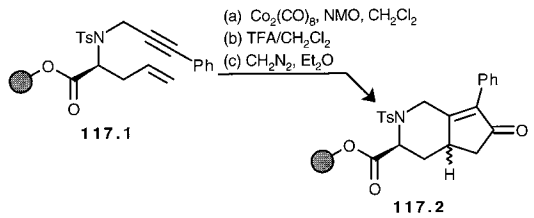


[a] Reagents and conditions: (a) $HC{\equiv}C(CH_2)_3OH$, pyridine, Δ; (b) $Co_2(CO)_8$, PhH, rt; (c) norbornadiene, PhH, Δ; (d) Bu_4NCl, KOH, H_2O/THF.

polymer-bound complex, with an appropriate olefin, gave the Pauson−Khand product (IR analysis: 1603, 1710, 3026 cm^{-1}). Cleavage of the ester linkage with TBACl, KOH, and H_2O (80 °C, THF, 48 h) delivered the desired cycloadducts (R = OAc, CO_2Me, CH_2OAc, CH_2OH) in moderate overall yield.

Previously in this review, a solid-phase synthesis of azabicyclo[4.3.0]nonen-8-one was reported that employed a Heck reaction (Scheme 21).[27] In this same paper, a solid-phase Pauson−Khand cycloaddition was performed en route to azabicyclo[4.3.0]-8-one derivatives. The polymer-bound alkyne (**117.1**) (Wang resin) was treated with $Co_2(CO)_8$ and NMO to promote the Pauson−Khand cyclization. Cleavage and esterification gave the desired cycloadduct (Scheme 117) as a mixture of diastereomers in 48% overall

Scheme 117

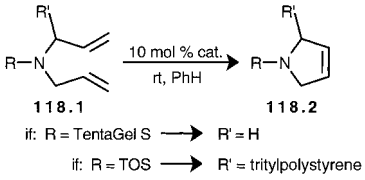


yield (based on the resin loading, which was determined as 0.57 mmol/g). Bolton followed up his initial studies with additional solid-phase intramolecular Pauson−Khand reactions en route to bicyclic amino acid derivatives with several additional compounds prepared.[156]

8.3. Miscellaneous Organometallic Reactions

Olefin metathesis of polymer-bound olefins has been reported with the use of a ruthenium catalyst.[157] Several polymers were examined (TentaGel S, tritylpolystyrene), as were various points of attachment of the resin to the olefin substrate (Scheme 118). Two

Scheme 118



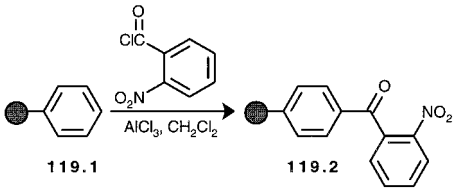
different catalysts were examined [$Cl_2(PCy_3)_2Ru{=}CH{-}CH{=}CPh_2$ and $Cl_2(PCy_3)_2Ru{=}ChPh$], both of which proved effective in mediating olefin metathesis. The yields of the heterocyclic products were excellent (70−95% overall based on the resin loadings; all resin loadings were determined to be between 0.4 and 0.6 mmol/g).

IX. Friedel–Crafts Acylation

Solid-phase Friedel−Crafts acylation reactions have primarily been used to functionalize commercially available polystyrene (2% divinyl benzene copolymer). In one instance, polystyrene was treated with $AlCl_3$ in CH_2Cl_2 and *o*-NO_2-benzoyl chloride (Scheme 119). This solid-phase Friedel−Crafts acylation gave the keto resin, which was subjected to further synthetic transformations.[158]

Aminomethyl resins have previously been prepared from Merrifield's resin and potassium phthalimide to give a phthalimidomethyl resin intermediate, which upon hydrolysis gives the amine.[159] Other methods of preparing aminomethyl resins have included direct amidomethylation.[160] Aminomethyl resins have also been prepared via a solid-phase Friedel−Crafts reaction in which $FeCl_3$ was used as the Lewis acid catalyst.[161] Polystyrene (2% divinyl benzene) was treated with *N*-(chloromethyl)phthalimide and $FeCl_3$ to give the aminomethyl resin (Scheme 119). The

Scheme 119

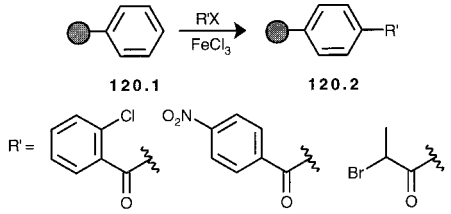


solid-phase Friedel−Crafts acylation was determined to be quantitative up to 2 mmol N/g (determined by nitrogen elemental analysis).

The catalyst $FeCl_3$ has also been used to catalyze other solid-phase Friedel−Crafts acylation reactions en route to functionalizing polystyrene. Polystyrene, in turn, was found to react with 2-bromopropionyl chloride, *p*-nitrobenzoyl chloride, and *o*-chlorobenzoyl chloride to afford the respective resins (Scheme 120).

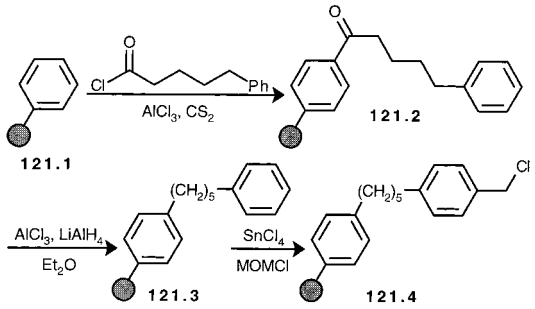
Another polystyrene linker resin was prepared utilizing two solid-phase Friedel−Crafts acylations.[162]

Scheme 120



Polystyrene was acylated with 5-phenylvaleryl chloride and $AlCl_3$ in CS_2 (Scheme 121). The acylated

Scheme 121



resin was then reduced with $AlCl_3{-}LiAlH_4$[163] to give the 5-phenylpentyl resin. This resin was treated with $SnCl_4$ and MOMCl to give the chloromethylated resin, 5-(4′-chloromethylphenyl)pentylpolystyrene, which was used further in solid-phase imino aldol reactions of silyl enol ethers.

X. Summary and Outlook

In the past several years, the chemical community has enthusiastically embraced small-molecule synthesis on solid phase, and there has been an accompanying explosion in reports of solid-phase carbon−carbon bond forming reactions. As evidenced by this review of the literature (1990−97), some carbon−carbon bond forming reactions can now be considered "routine" (for example, metal-mediated coupling reactions). Others, such as stereoselective carbon−carbon bond forming reactions, have been demonstrated, but their full potential has not yet been realized.

Carbon−carbon bond formation is at the core of organic chemistry. This fact, coupled with ever-unfolding advances in resins, linkers, cleavage strategies, analytical techniques, etc., suggests that further exciting developments in solid-phase carbon−carbon bond forming reactions and strategies can be anticipated.

XI. Acknowledgments

The authors thank Mrs. Kara Ishii for editorial assistance.

XII. Glossary

BOC	*tert*-butoxycarbonyl
BPOC	[[2-(4-biphenyl)isopropyl]oxy]carbonyl
DBU	1,8-diazabicyclo[5.4.0]undecane
DIC	diisopropylcarbodiimide
DIPEA	*N*,*N*-diisopropylethylamine

DMA	*N*,*N*-dimethylacetamide
DMAE	2-dimethylaminoethanol
FMOC	9-fluorenylmethoxycarbonyl
HBTU	*N*-{1*H*-benzotriazol-1-yl)(dimethylamino)methylene}-*N*-methylmethanaminium hexafluorophosphate *N*-oxide
NMO	4-methylmorpholine *N*-oxide
NMP	1-methyl-2-pyrrolidinone
$PdCl_2$-(dppf)	bis[(2-diphenylphosphino)ferrocene]dichloro-palladium(II) complex
Pd_2dba_3	tris(dibenzylideneacetone)dipalladium
TBAF	tetrabutylammonium fluoride
TBACl	tetrabutylammonium chloride
Teoc	[[(trimethylsilyl)ethyl]oxy]carbonyl
TMG	tetramethylguanidine

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