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SOLID-PHASE ORGANIC SYNTHESIS

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Edited by

KEVIN BURGESS
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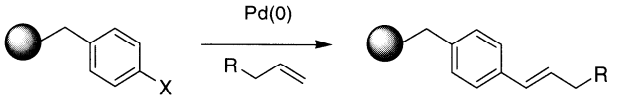

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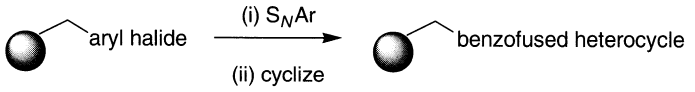

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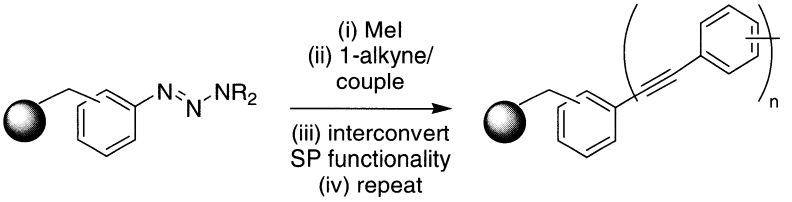

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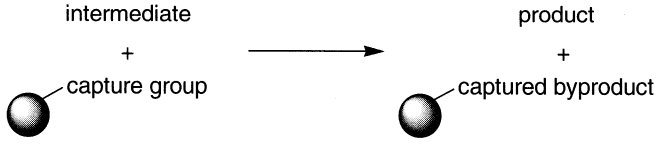

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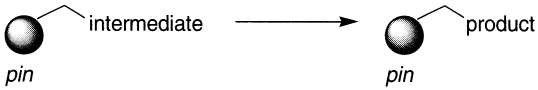

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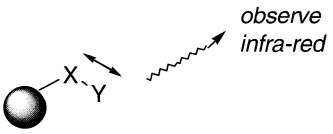

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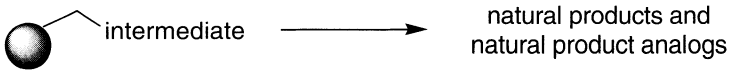

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PREFACE

Method development in combinatorial chemistry has, to all intents and purposes, happened. The insights of people like Geysen, Furka, Houghton, Lam, Lebl, Hruby, Gallop, Pirrung, and Schultz led the rest of us to realize that we could, and should, be doing what we were doing much faster and more efficiently. The pharmaceutical industry has changed dramatically because of this, and others, like the oil and polymer industries, are beginning to appreciate the value of these approaches.

Conversely, development of methods for solid-phase synthesis is happening. Supported methods pioneered by Leznoff and others attracted little interest until the right person, at the right place, at the right time, Jon Ellman, reinstated them to a prominent position. Many other groups were working on solid-phase methods to support combinatorial efforts, but Jon's papers were certainly the first to attract widespread attention in the 1990s. Most of the combinatorial and high-throughput methods that are finding practical application today use solid-phase chemistry in some form, and these methods would be used even more extensively if supported organic chemistry were refined further. It seems inevitable that the literature on solid-phase organic synthesis will continue to expand rapidly over the next decade as researchers explore the scope of this technique.

This book is a compilation of reviews from some leaders in various aspects of solid-phase syntheses. I undertook to compile them because of a conviction that a collection of specialized reports in this area would be useful. In fact, I believe that, if the demand exists, it might be useful to

publish similar compilations annually or biannually. Certainly, not all the important aspects of solid-phase syntheses are covered in this book; there is room for a sequel.

To encourage top people to contribute to this book, I tried to keep the style close to something familiar and chose that of *The Journal of Organic Chemistry*. In some cases the format is not quite the same, however. Most of those deviations are my mistakes or a compromise with Wiley's standard format, but inclusion of titles in the reference section was a deliberate transgression designed to make the work more reader-friendly. The abbreviations used throughout this book are the same as those listed in *The Journal of Organic Chemistry*. The preferred format of each chapter was a reasonably comprehensive review of a narrowly defined area. Jiong Chen and I wrote Chapter 1 to illustrate the type of format that might be useful to a large number of readers. Some authors preferred to concentrate on work from their own laboratories, though, and I encouraged this when authors had a coherent and well-rounded story to tell from their own research. A single chapter in this book includes some illustrative experimental procedures because, in that particular case, the methods have not been widely used in the pharmaceutical industry, and a few protocols seemed especially valuable. In general, constructive criticism and suggestions regarding the format of this book would be welcome (burgess@mail.chem.tamu.edu).

I want to thank Barbara Goldman and her associates at Wiley for their guidance, all the contributors for coming through in the end, Armin Burghart and Jiong Chen (two postdoctoral associates at A&M) for proofreading some chapters that I changed a lot, and my research group for tolerating this distraction.

Kevin Burgess

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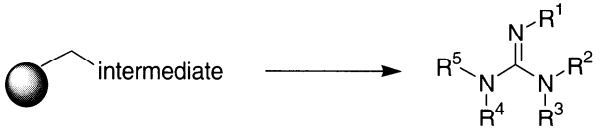
CHAPTER 1

SOLID-PHASE SYNTHESES OF GUANIDINES



KEVIN BURGESS and JIONG CHEN
Texas A & M University

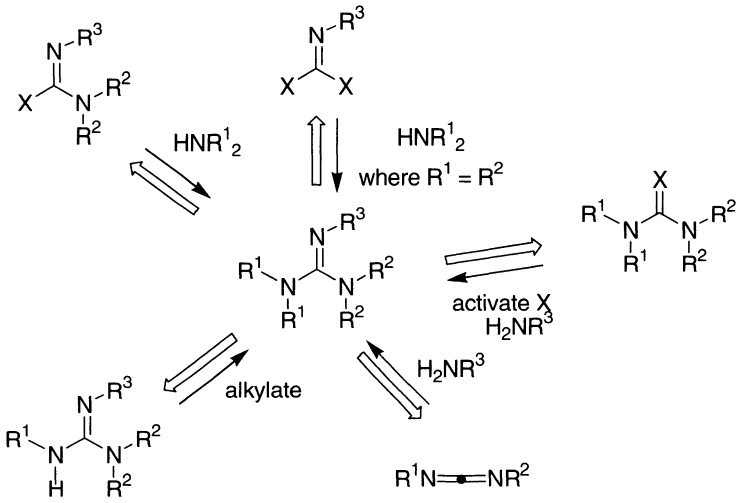
1.1. INTRODUCTION

Guanidines are basic molecules (pK_a of guanidine = 12.5) with a capacity to form intermolecular contacts mediated by H-bonding interactions. Consequently, they are potentially useful pharmacophores in medicinal chemistry,[1] have proven applications as artificial sweeteners,[2,3] and are useful as probes in academic studies of intermolecular associations, including "supramolecular complexes." Expedited access to these molecules via solid-phase synthesis is therefore a worthy goal. This chapter outlines various

solution-phase syntheses of guanidines, then gives a more detailed description of work that has been done to adapt these methods to supported syntheses.

1.2. OUTLINE OF SOME SOLUTION-PHASE APPROACHES TO GUANIDINES

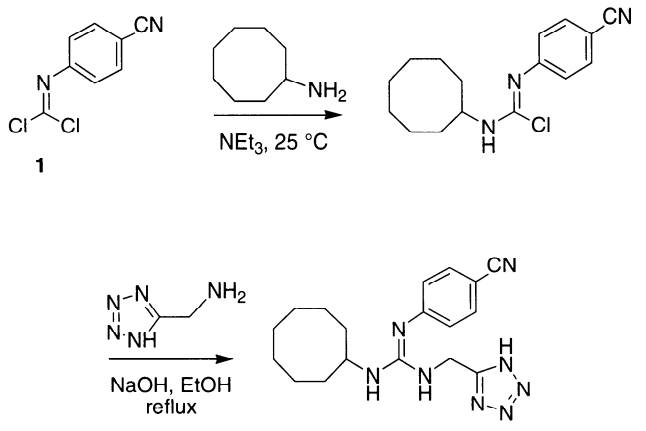
It is difficult to formulate retrosynthetic analyses of guanidines because their substitution patterns determine the most efficient routes to these materials. Some generalities are outlined in Scheme 1. These syntheses are discussed more fully in the following subsections, although the coverage is intended to be an outline of the approaches most relevant to solid-phase syntheses, not a comprehensive summary.



Scheme 1.

1.2.1. From Electrophiles Containing One Nitrogen Atom

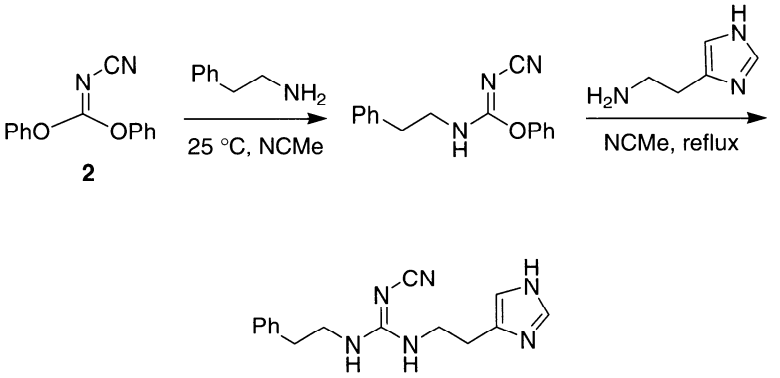
Imidocarbonyl dichlorides that are functionalized with an electron-withdrawing group (e.g., **1**) react with amines at room temperature or below, affording symmetrical guanidines.[4] It was originally suggested that guanidines with less symmetrical substitution patterns could not be formed



Scheme 2.

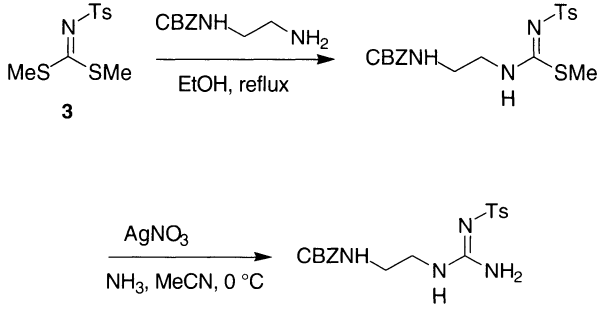
by stepwise displacement of leaving groups from imidocarbonyl dichlorides,[4] but that suggestion has been shown to be incorrect, as illustrated in Scheme 2.[5]

Stepwise displacement of phenoxide from diphenyl carbonimidates (e.g., **2**) is also possible, as in Scheme 3.[6]



Scheme 3.

Imidoyl dichlorides are formed by chlorination of the corresponding *S,S*-dialkylimidodithiocarbonimidates, but the latter compounds can also be used as starting materials for syntheses of guanidines. In this type of synthesis, an amine is generally heated with the *S,S*-dialkylimidodithiocar-



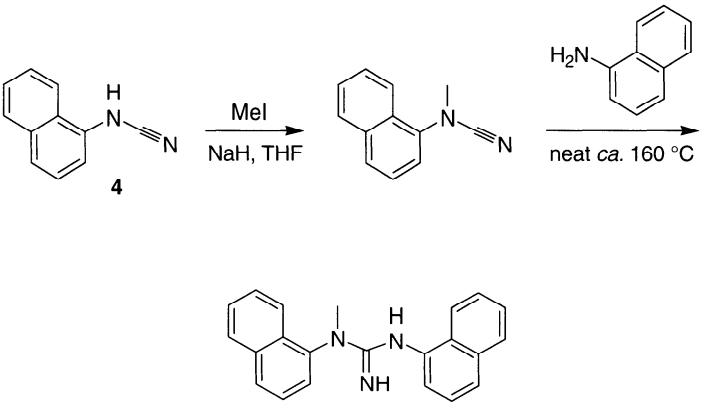
Scheme 4.

bonimidate (e.g., **3**) to cause the first displacement; then the product is treated with the second amine and a metal salt with high affinity for sulfur to give the guanidine (Scheme 4).[7,8]

1.2.2. From Electrophiles Containing Two or More Nitrogen Atoms

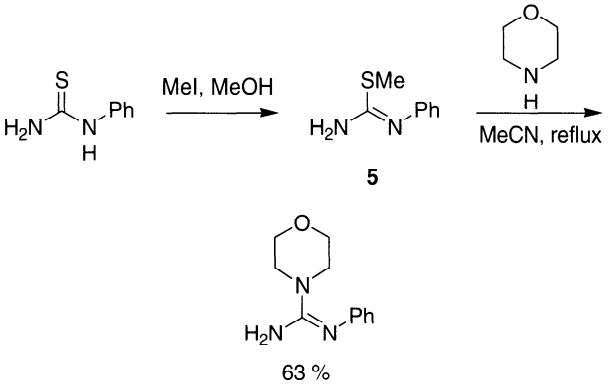
Cyanamides like **4** (from amines and cyanogen bromide) provide access to guanidines. This approach allows for introduction of different substituents, and alkylating intermediates can further increase the diversity of products produced. However, high temperatures are required, especially with aromatic amines, for the final addition to give the guanidine products (Scheme 5).[9]

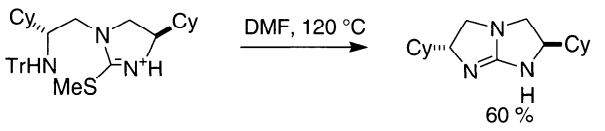
A comparatively large selection of thioureas can be formed from the reaction of amines with isothiocyanates, hence they are attractive starting materials for formation of guanidines. A common solution-phase approach to this reaction involves abstraction of the sulfur via a thiophillic metal salt, like mercuric chloride.[10] For solid-phase syntheses, however, formation of insoluble heavy-metal sulfides can have undesirable effects on resin properties and on biological assays that may be performed on the product. A more relevant strategy, with respect to this chapter, is *S*-alkylation of thioureas and then reaction of the methyl carbamimidothioates formed (e.g., **5**, Scheme 6) with amines. This type of process has been used extensively in solution-phase syntheses.[11–14] Two examples are shown in Scheme 6;[11] the second is an intramolecular variant, which involves concomitant detritylation.[15]



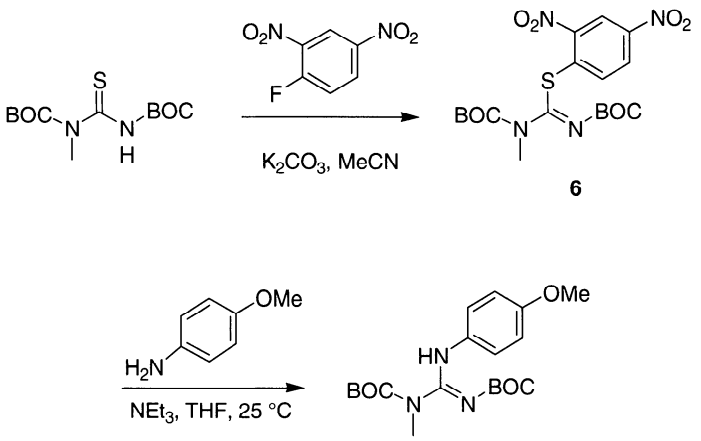
Scheme 5.

Methanethiol is a by-product of reactions of the type illustrated in Scheme 6. This is unlikely to be produced in amounts that would cause problems in solid-phase syntheses, but alternatives are available that avoid this noxious by-product. For instance, an S_NAr displacement of fluoride





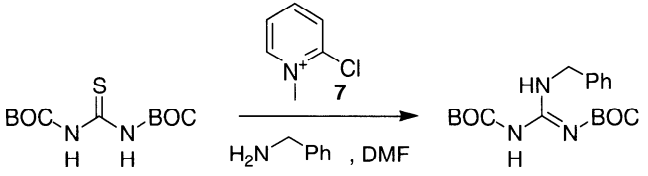
Scheme 6.



Scheme 7.

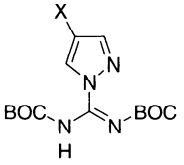
from 2,4-dinitrofluorobenzene gives the activated system **6**.[16] The latter can be reacted with amines to give guanidines (Scheme 7), though complications occur for deactivated aromatic amines.

Other electrophiles have been used to activate thioureas in one-pot processes to give guanidines directly. These include water-soluble carbodiimides[17,18] and the Mukaiyama reagent **7**, as illustrated in Scheme 8.[19] The thioureas shown in Schemes 7 and 8 have two electron-withdrawing substituents. Issues relating to the generality of these reactions are not well documented for thioureas having less electron-withdrawing *N*-substituents.

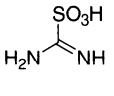


Scheme 8.

Shown below are some other electrophiles that have been used to form guanidines from amines. The pyrazole derivatives **8**[20] have been used extensively in peptide syntheses.[21] The aminoiminomethanesulfonic acid derivative **9**[22] might be the intermediate formed when thioureas are oxidized and then reacted with amines to form guanidines; certainly **9** is a useful



8 X = H or NO_2



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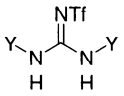
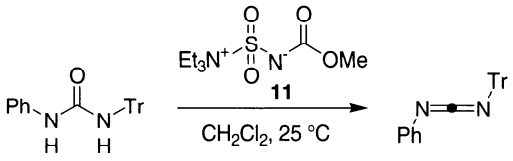
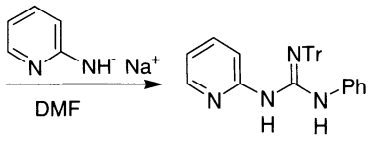


10 Y = BOC or CBZ

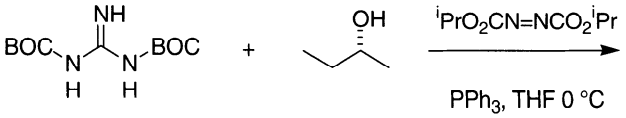
guanylating agent. Triflylguanidines **10** as guanidinylating agents are a relatively new innovation.[23] This is a potentially useful discovery because the triflylguanidines can be formed in two steps from guanidine hydrochloride.

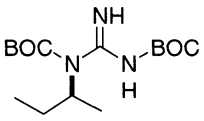
Guanidines may also be formed by reaction of amines with carbodiimides. This reaction is limited by the availability of carbodiimides, which are usually formed by several methods,[24] including dehydration of ureas with the Edward Burgess reagent **11** (Scheme 9).[25–27]





Scheme 9.





Scheme 10.

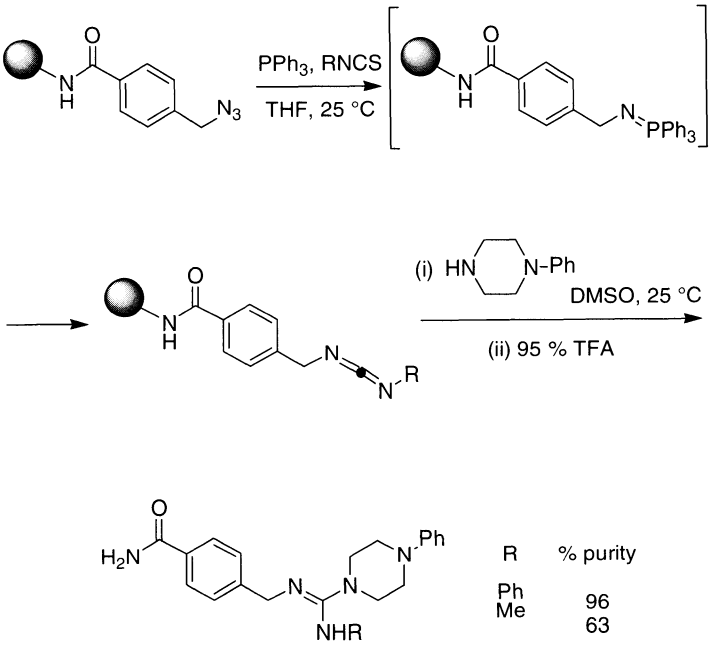
Finally, alkylation reactions can be used to add substituents to guanidines. These may be performed under quite basic conditions (e.g., NaH/alkyl halide)[28,29] or via the Mitsunobu process, as illustrated in Scheme 10.[30]

1.3. SOLID-PHASE SYNTHESES INVOLVING RESIN-BOUND ELECTROPHILES

1.3.1. Supported Carbodiimides

Supported carbodiimides can be produced via aza-Wittig reactions. The example in Scheme 11 shows the reaction of a benzylic azide with triphenylphosphine to give an aminophosphorane.[31] This was then coupled with phenylisothiocyanate to give the corresponding carbodiimide.

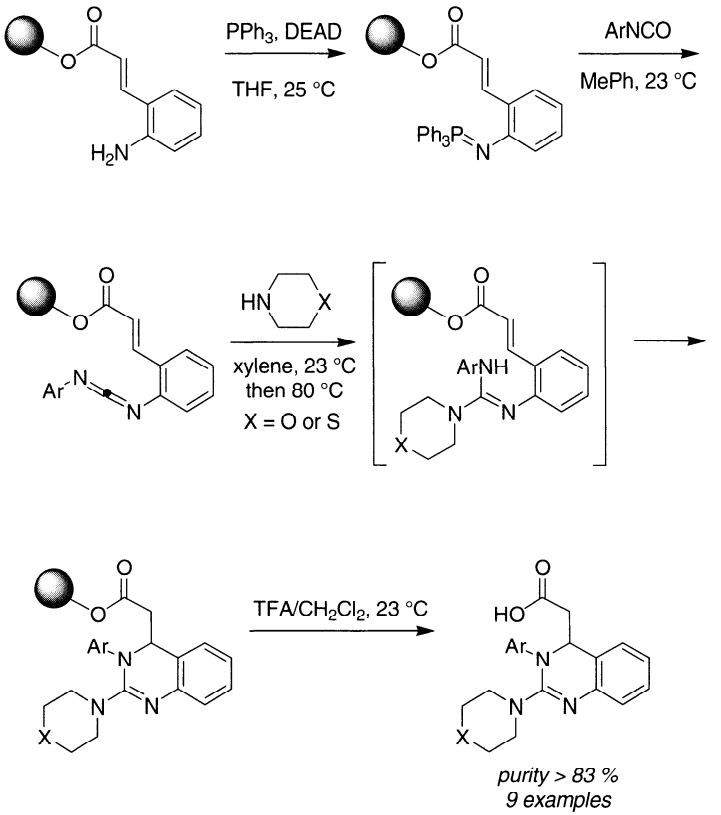
The sequence shown in Scheme 11 was more effective if the isothiocyanate was premixed with the azide, rather than added after the phosphine. Aza-Wittig reagents can undergo exchange reactions with carbodiimides;



Scheme 11.

in the absence of isothiocyanate, this occurs between supported aza-Wittig and supported carbodiimide, giving undesirable symmetric guanidines. This illustrates an important feature in solid-phase syntheses; that is, *reactive centers on a support are close enough to perform intermolecular reactions unless the resin loading is kept low*. Our group has found that intermolecular reactions are effectively suppressed in one particular reaction when resin loadings of 0.3 mmol/g or less were used. The support used in Scheme 11 was a Rink functionalized pin (Chiron) with an unspecified loading level.

The presence of the aryl spacer groups, derived from the benzylic azide, in Scheme 11 was critical; the reaction failed when short-chain aliphatic linkers were used. We suspect this may be due to unwanted cyclization

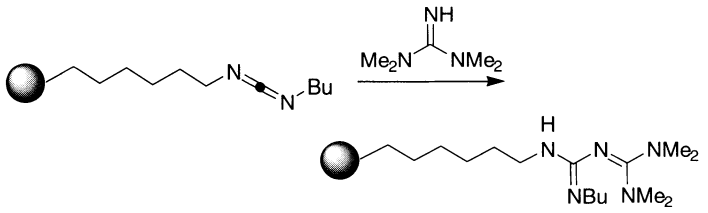


Scheme 12.

reactions. Moreover, sterically encumbered isothiocyanates and acyl isothiocyanates did not react well in the sequence. Overall, the scope of this process is relatively limited.

Scheme 12 features a similar approach to that shown in Scheme 11, except that the guanidines were designed to undergo Michael addition to give a bicyclic system.[32] Mitsunobu reaction of the corresponding nitro cinnamic acid with Wang resin followed by reduction of the NO_2 functionality ($SnCl_2$) formed the required amino cinnamic acid ester starting material. Formation of the carbodiimide and conversion to the guanidines were monitored by IR (N=C=N, 2135 cm^{-1}). Formation of the guanidines was slower than the Michael addition step, hence the temperature had to be raised in the penultimate step of the sequence.

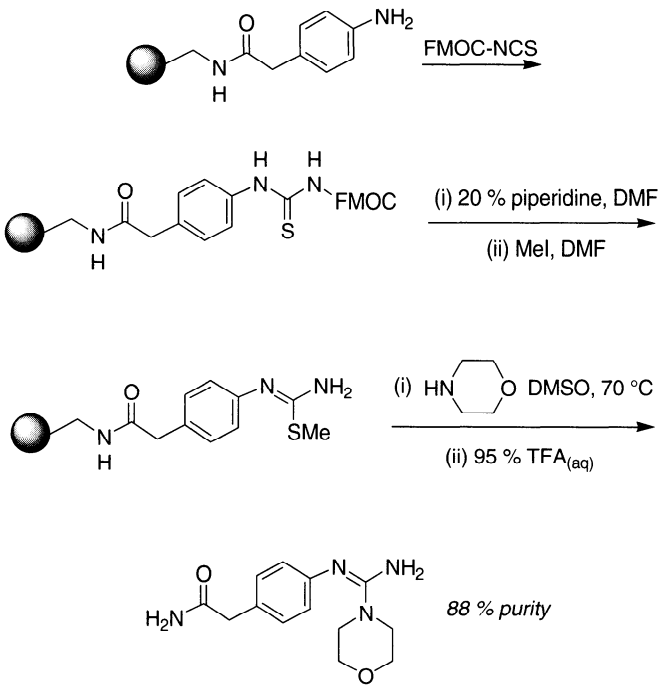
A carbodiimide-grafted polystyrene resin was reacted with tetramethylguanidine to give an interesting biguanide structure (Scheme 13). This was assayed as a catalyst for a transesterification reaction.[33] Incidentally, resin-bound guanidines are useful bases for processes involving resin capture.[34]



Scheme 13.

1.3.2. Supported Thioureas

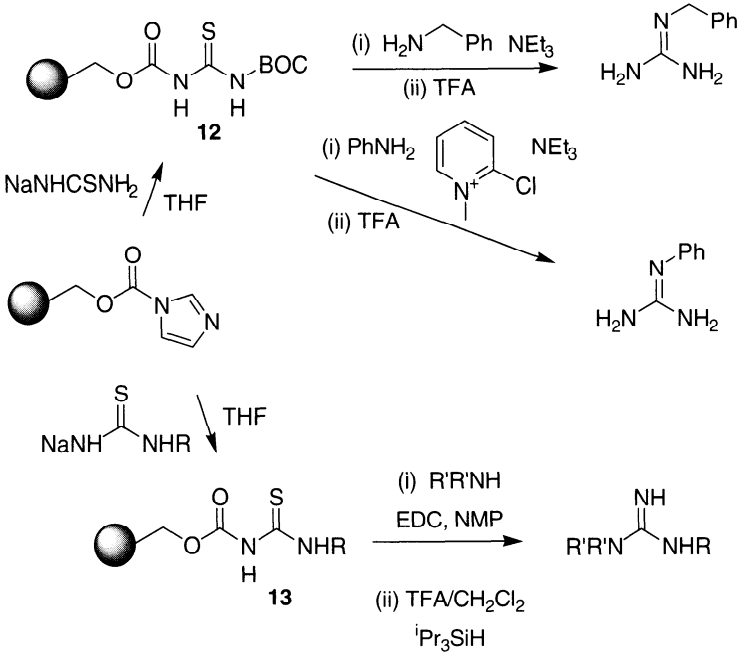
Scheme 14 shows a typical example in a series of reactions in which a supported amino acid reacted with fluorenylmethoxycarbonyl isothiocyanate to give a supported (on Rink's amide)[35] thiourea.[36] Removal of the *N*-protection followed by *S*-alkylation gave supported isothioureas. Reaction of these with amines, then cleavage from the resin, afforded substituted guanidines. For 10 examples the purities were between 40 and 92%. An aryl group separates the resin from the guanidine, just as in the sequences shown in Schemes 11 and 12.



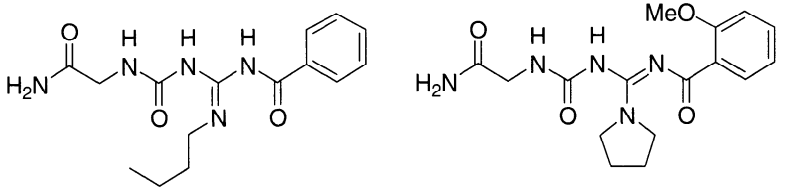
Scheme 14.

Another strategy in which thioureas were *N*-linked to a carboxyimidazole resin and then converted to guanidine products is shown in Scheme 15.[37] Thus the supported BOC-protected thiourea **12** reacted with aliphatic amines without any activating agent. Aromatic amines, however, required activation, and the Mukaiyama pyridinium **7** was used for this. Conversely, acyl-, aryl-, allyl-, and alkyl-substituted thioureas **13** were linked to the resin as a precursor to other guanidines, many lacking the activating effect of electron-withdrawing groups. The intermediate thioureas were treated with EDC, then with amine, to give the products. The authors of this work state that the method was used extensively to form many different products (>45), but lists of the specific compounds produced were not given.

A very similar method has been used by Lin and Ganesan to produce *N*-acyl-*N'*-carbamoylguanidines.[38] The activating agent used by them was mercuric chloride, and the waste heavy metal was removed by filtration at the end of the synthesis. Scheme 16 shows two compounds prepared by this method.

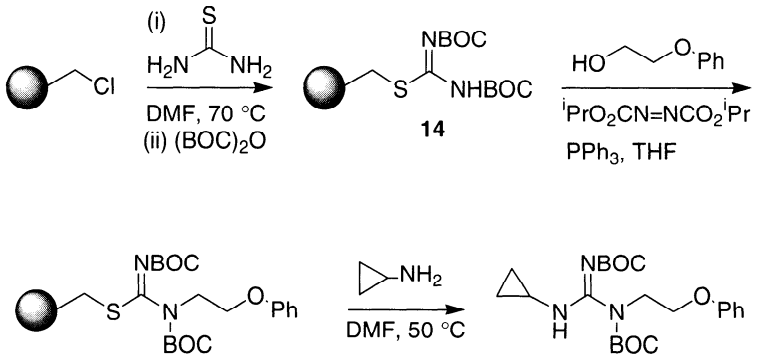


Scheme 15.



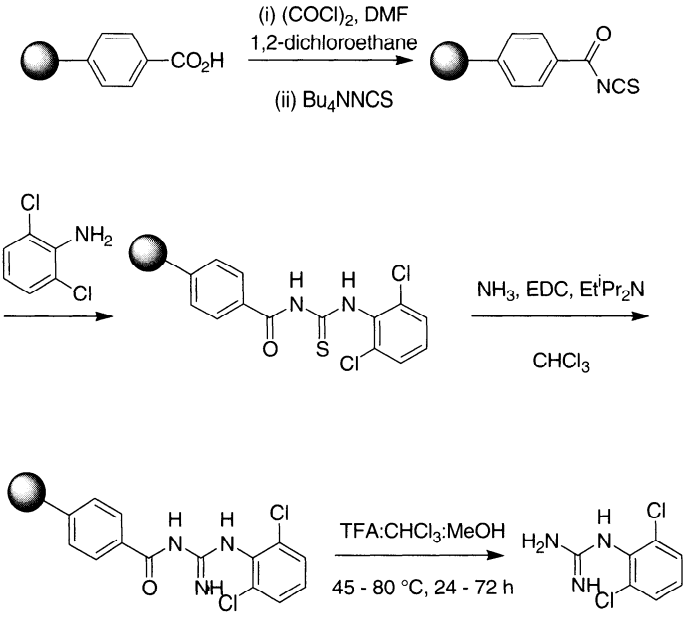
Scheme 16.

Work by Dodd and Wallace on solid-phase guanidine syntheses is unique insofar as an *S*-linked thiourea **14** was used.[39] Their approach exploits the previous findings of one of these researchers regarding the efficacy of *bis*-BOC-protected guanidines in Mitsunobu reactions (Scheme 10).[30] They treated Merrifield resin with excess thiourea to give a supported thiouronium salt, as illustrated in Scheme 17. Both nitrogen atoms of this material were masked on the solid phase by reactions with $(BOC)_2O$ and Hünig's base. Mitsunobu reactions of the supported *bis*-BOC-protected isothiourea gave a monoalkylated product. This was then reacted with



Scheme 17.

ammonia or primary alkylamines to give guanidines with concomitant cleavage from the resin. This paper featured 13 examples and a typical experimental procedure was given; it describes what appears to be an excellent solid-phase synthesis of many guanidines.



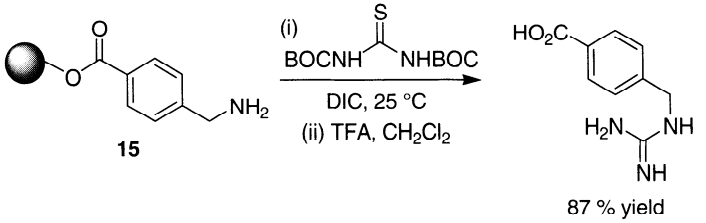
Scheme 18.

Wilson and Li have recently used supported acylisothiocyanates to capture amines as thioureas.[40] The latter were then activated using a carbodiimide reagent, then reacted with a second amine to form guanidine products. An appealing feature of this approach is that hindered and relatively unreactive anilines can be used in the first step due to the electrophilicity of the acylisothiocyanates (Scheme 18).

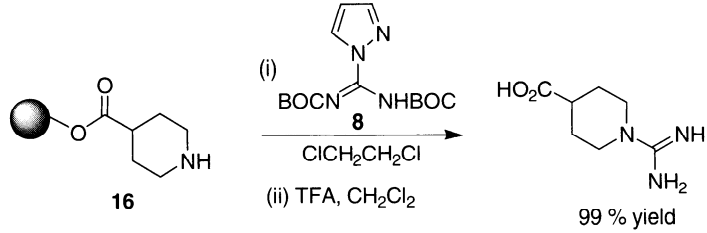
1.4. SOLID-PHASE SYNTHESES INVOLVING ELECTROPHILES IN SOLUTION

In general, solid-phase syntheses tend to work better when an excess of a reactive intermediate in solution is allowed to react with a less reactive entity on a solid phase. This approach is not always used, often due to the cost and/or availability of one of the reagents; indeed, all the reactions highlighted in the previous section adopted the opposite strategy. Consequently, it is interesting to compare those reports with one described in this section wherein the reactive reagent was used in solution.

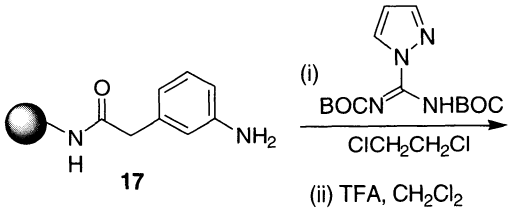
Four supported amines, one primary, one secondary, and two arylamines, were reacted with guanylating agents in solution and on a solid phase in a set of comparative experiments (Scheme 19).[41] The supported primary and secondary amines **15** and **16** gave high yields of product (>85%) when



(1)



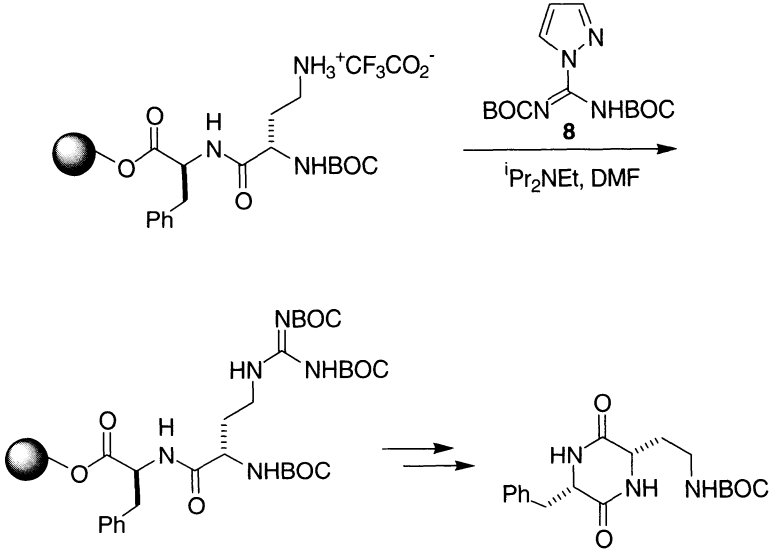
(2)



(3)

reacted with a carbodiimide-activated thiourea, or an *N,N'*-bis(*tert*-butoxycarbonyl)-1-guanylpyrazole **8**. The aromatic amines gave less product, or none at all (Scheme 17), on the solid phase but were guanylated in solution.

Shey and Sun reported syntheses of guanidines that almost exactly parallel those shown in reactions 1–3, except that polyethylene glycol was used for the support.[42] All the reaction steps were therefore carried out in solution, but some of the purifications relied on precipitation.

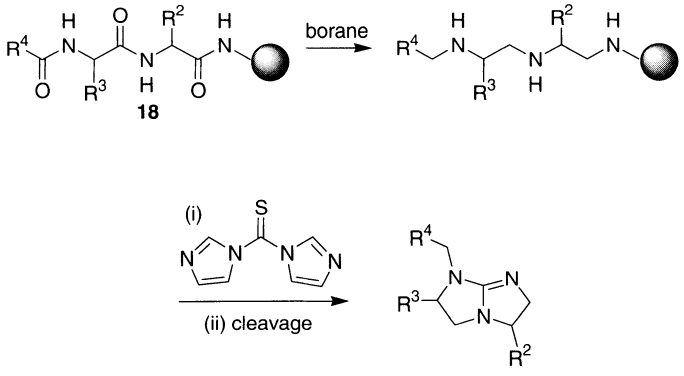


Scheme 19.

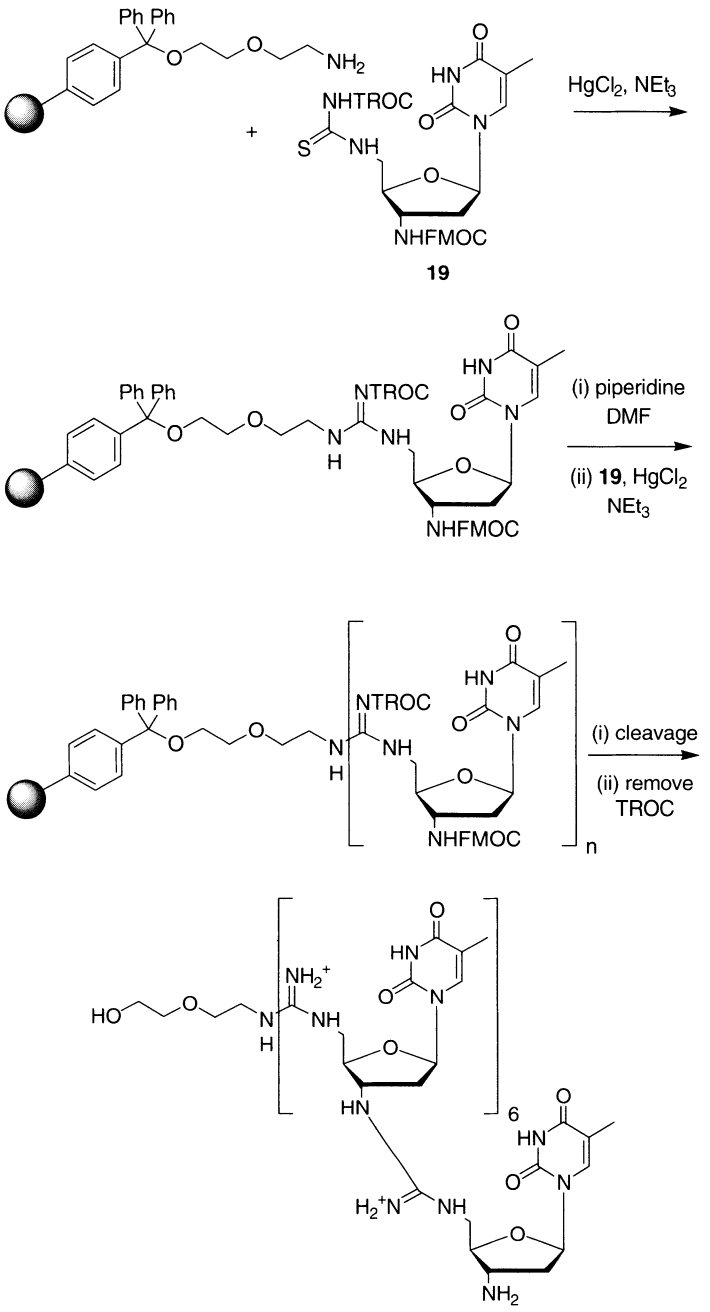
Reagent **8** has also been used to add guanidine groups to a supported dipeptide intermediate to a diketopiperazine[43] that is reported to be a catalyst for enantioselective Strecker reactions.[44] The key step is shown in Scheme 19.

An impressive solid-phase synthesis of bicyclic guanidines has been communicated, and the approach is outlined in Scheme 20.[45,46] *N*-acylated dipeptides **18** were reduced to triamines by exhaustive borane reduction, then reacted with thiocarbonyldiimidazole. An intermediate thiocarbonyl was cyclized to the guanidine product in this process.

Antisense oligonucleotides with guanidine groups substituted for phosphates bind to natural DNA with particularly high melting temperatures. This is because the positive charge of an oligoguanidine strand complements that of a natural oligophosphate. Solid-phase syntheses of antisense DNA strands wherein guanidine replaces phosphate has been achieved via reactions of a nucleoside–carbodiimide with a resin-bound strand with a free 3′-amino group (Scheme 21).[47,48] The 5′-thiourea **19** starting material was prepared from a 3′-protected 5′,3′-diaminothymidine and trichloroethoxycarbonylisothiocyanate (TROC-NCS). Mercuric chloride was then used to convert this to the corresponding carbodiimide in situ. Thus a trityl-based resin with an amino terminus was coupled with **19**; then further cycles of FMOC removal and coupling were used to build the antisense strand. Finally, cleavage from the resin and removal of the TROC groups gave the desired heptamer product.



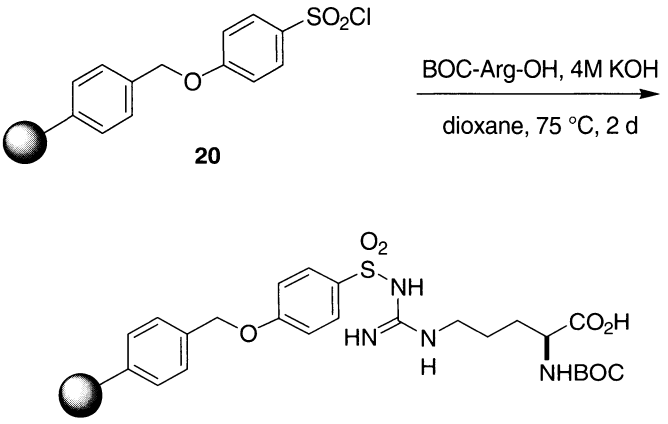
Scheme 20.


Ph Ph
NH2
NHTROC
S
NH
HN
O
N
HgCl2, NEt3
NHFMOC
19
NTROC
(i) piperidine
DMF
(ii) 19, HgCl2
NEt3
(i) cleavage
(ii) remove
TROC
n
HO
NH2+
6
H2+N

Scheme 21.

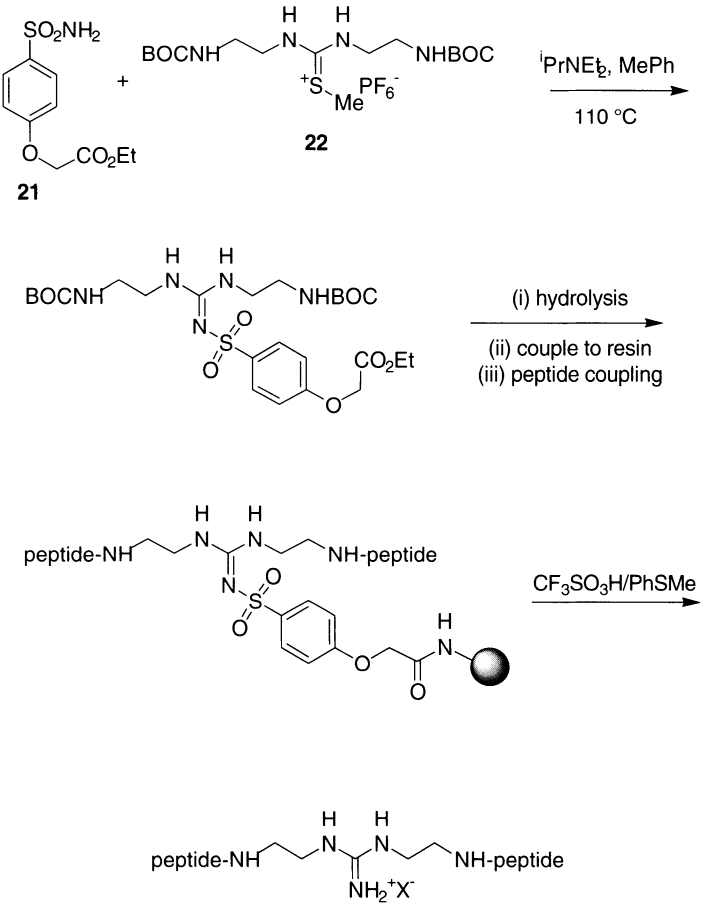
1.5. OTHER SUPPORTED GUANIDINES

Guanidines have been used as a point of attachment for solid-phase syntheses in transformations that do not involve construction of a guanidine. In one case (Scheme 22) the modified Merrifield resin **20** was reacted with N_{α}-BOC-Arg to give a side-chain-anchored amino acid.[49] This was then used in peptide syntheses. The resin–linker system was shown to be compatible with both BOC and FMOC coupling strategies. Several cleavage conditions were investigated, but only anhydrous HF gave clean formation of the desired products; other conditions resulted in unwanted fission of the resin–linker bond.



Scheme 22.

Another approach to coupling guanidines to solid supports was key to solid-phase syntheses of parallel peptide strands, "tweezer receptors" (Scheme 23).[50] Combination of the sulfonamide **21** with the thiouronium salt **22** followed by hydrolysis of the ester group gave the linker required for this work. It was then coupled to aminomethylpolystyrene resin and used as a foundation for syntheses of two symmetrical peptide strands. Cleavage from the resin was achieved using triflic acid in the presence of a peptide scavenger. The resin–linker system is not benzylic and hence is more stable to acids than the linkage shown in Scheme 21 and less vulnerable to unwanted fission at the linker position.



Scheme 23.

1.6. CONCLUSION

No single approach will be universally the best for preparations of guanidines of all types. Of the methods that involve supported guanylating reagents, those of Dodd and Wallace and of Josey et al. (Schemes 16 and 15, respectively) seem to be particularly useful. Solid-phase syntheses of guanidines in which the guanylating reagent is in solution have been explored less than the alternative strategy and appear to have some merit. Indeed, a very recent paper has compared solid-phase syntheses of oligomeric guanidines by various routes and concludes that the best method

is via reaction of resin bound amines with thioureas activated with EDC {1(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride}.[51]

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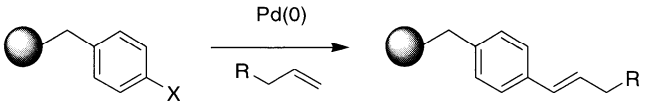
CHAPTER 2

PALLADIUM-CATALYZED CARBON–CARBON BOND FORMATION ON SOLID SUPPORT



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2.1. INTRODUCTION

Palladium-catalyzed carbon–carbon bond formation has emerged as one of the most powerful methods in organic synthesis. Consequently, it is unsurprising that adaptation of such methods to the solid phase is an important initiative. Many pharmacophores and scaffolds are directly accessible with simple palladium-catalyzed chemistry, for example, the biaryl subunit,[1] which has also been used as the template for a "universal library."[2]

Several features of palladium-catalyzed carbon–carbon bond formation reactions are attractive in high-throughput chemistry. These reactions tend to be

- possible at ambient temperature and pressure, under nonanhydrous conditions, and with exposure to the atmosphere, hence amenable to automation;
- high yielding for a range of substrate types;
- tolerant of a range of solvents. Solvent is a major consideration for any solid-phase reaction as the choice can be compromised by the solid phase. Usually the solvent of choice is one which swells the support well, allowing access to internal sites. It is interesting to note that since much solid-phase chemistry is conducted on hydrophobic polystyrene-type supports, there are few examples to date of purely aqueous solid-phase palladium-catalyzed reactions. These have been shown to proceed extremely well in solution, often with accelerated rates and lower catalyst levels than the related reactions in organic solvents;[3]
- flexible with respect to which component is used in solution and which is anchored to the solid phase.

This review is divided into four main sections, covering the Heck, Stille, and Suzuki reactions, with miscellaneous reactions being included at the end. Processes featuring alkynes in copper co-catalyzed Sonogashira-type couplings have been included in the section on Heck reactions.[4] This review does not cover carbon–carbon bond formation processes using immobilized catalysts.[5–7] Similarly, fluorous-phase syntheses[8–11] and those on polyethylene glycol[12–14] are excluded.

2.1.1. Practical Considerations

Some special considerations apply when palladium complexes are to be used in solid-phase chemistry. Two obvious concerns are penetration of relatively large palladium complexes into resins and the effects of the resin microenvironment on dissociation of ligands from fully coordinated palladium complexes to give active species. The success of the chemistry reported to date has been an empirical test of these questions, but such factors may explain instances in which, for example, the ligandless

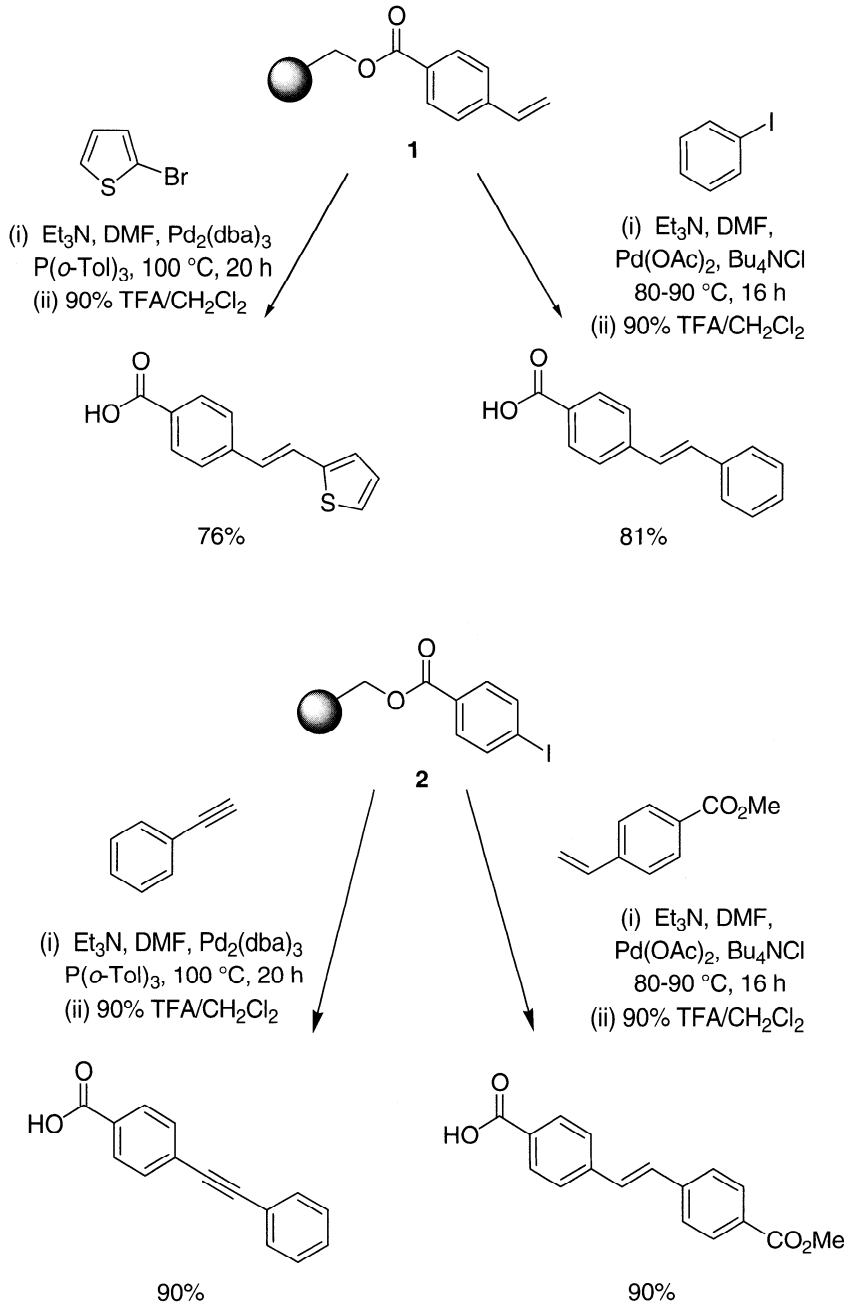
$Pd_2(dba)_3$ catalyst is preferred over the more congested $Pd(PPh_3)_4$. Moreover, some reaction protocols allow for diffusion of the palladium catalyst into the resin prior to addition of other reagents.

Removal of palladium at the end of solid-phase reactions has been achieved in different ways. Palladium can be washed away from the support with the other excess reagents and by-products, but complications can arise as a result of palladium appearing in cleaved products even after washing (which has necessitated brief chromatography for purification), or palladium black deposition during the course of the chemistry. For example, we have observed that palladium-catalyzed processes on chloromethyl resin that still contains unsubstituted sites leads to palladium black deposition [possibly due to insertion of palladium (0) into the CH_2Cl bond], whereas the same resin lacking redundant chloromethyl sites presented no such difficulties.[15] Ellman introduced a KCN/DMSO wash to remove deposited palladium, a strategy that has been adopted by others (see below). In general, while inexpensive reagents may be used in excess for solid-phase reactions to drive them to completion, the levels of palladium *catalyst* need not be increased proportionally. Often the level of catalyst may be slightly increased from, say, 5 to 20 mol %, but the palladium is always still substoichiometric. This reduces the expense and problems of disposal.

2.2. HECK REACTION[16]

2.2.1. Early Work

In one of the earliest papers with a specific intent to demonstrate the feasibility of palladium-catalyzed reactions on solid supports, Yu et al. showed the production of simple coupled products by the Heck reaction (Scheme 1).[17] It was noted that the Heck reaction conditions are usually mild, do not require anhydrous or inert atmospheric conditions, and that the reaction is therefore suited to automation. By attaching to Wang[18] resin either 4-vinylbenzoic acid or 4-iodobenzoic acid and then subjecting these functionalized supports (**1** and **2**) to the appropriate coupling partner (either aryl halides/triflates or olefins/phenylacetylene), the reaction was successfully demonstrated in good to excellent yield. The catalyst system varied according to the reagents, but was based around either $Pd(OAc)_2$ with no added phosphine or $Pd_2(dba)_3$, and required heating overnight. It had been previously shown that the presence of a phase transfer agent (PTA) allowed

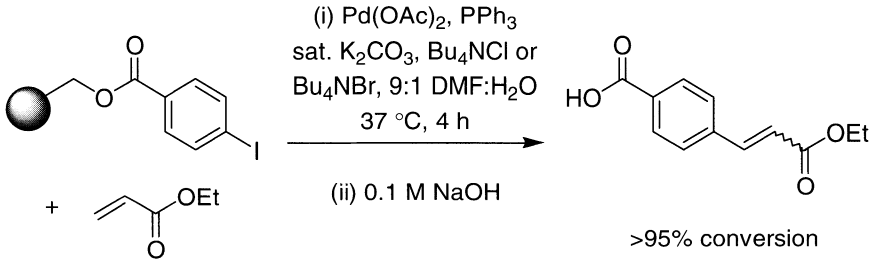

1
(i) Et3N, DMF, Pd2(dba)3
P(o-Tol)3, 100 °C, 20 h
(ii) 90% TFA/CH2Cl2
(i) Et3N, DMF,
Pd(OAc)2, Bu4NCl
80-90 °C, 16 h
(ii) 90% TFA/CH2Cl2
76%
81%
2
(i) Et3N, DMF, Pd2(dba)3
P(o-Tol)3, 100 °C, 20 h
(ii) 90% TFA/CH2Cl2
(i) Et3N, DMF,
Pd(OAc)2, Bu4NCl
80-90 °C, 16 h
(ii) 90% TFA/CH2Cl2
90%
90%

Scheme 1.

the solution-phase Heck reaction to proceed at mild temperatures,[19,20] but in these solid-phase cases the reaction appeared to require heating despite the presence of tetrabutylammonium chloride.

Unsuccessful couplings arose when resin-bound olefin was reacted with aryl triflates (presumably reflecting the lower reactivity observed in solution) and also when resin-bound iodide was reacted with ethyl propionate, where polymerized products were observed. Interestingly, attempts at transesterification as a means to release the products were unsuccessful. The stereochemistry (i.e., cis/trans) of the products was not addressed.

A later report demonstrated similar chemistry under milder conditions.[21] The apparently reduced effectiveness of the PTA in the previous work was noted, as was a further report where Pd/M_2CO_3/PTA had been demonstrated to catalyze the Heck reaction in water in excellent yield under mild conditions.[22] This chemistry was therefore adapted to the solid phase. After tethering 4-iodobenzoic acid to TentaGel resin, the reaction with ethyl acrylate was examined and found to be successful with the conditions shown in Scheme 2. Initial attempts to run the reaction in neat water failed to convert starting material to product in much more than about 50% yield, but introduction of a DMF–water solvent mixture solved this problem. The chemistry was adapted for the coupling of a number of olefins (generally those with attached electron-withdrawing groups). In contrast to the previous report, where these reactions were shown with reversal of polarity (i.e., the reaction of solution-phase iodides and bromides with resin-bound 4-vinylbenzoic acid), no products were obtained in these reversed cases.



Scheme 2.

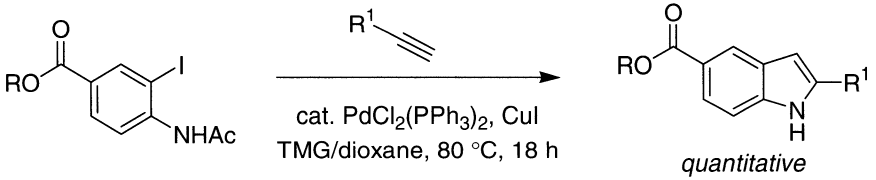
2.2.2. Indole and Benzofuran Formation

The most widely applied method for indole formation, the Fischer indole synthesis, has been shown on solid support.[23] Following a report of the ability of tetramethylguanidine (TMG) to promote palladium-catalyzed coupling and cyclization in the solution-phase one-pot synthesis of 2-unsubstituted benzofurans,[24] this methodology was used in the synthesis of a number of indoles on solid support with high yields and under mild reaction conditions.[25] A pilot solution-phase study to identify effective conditions found a solvent system of TMG–dioxane at 80°C promoted the coupling *and cyclization* with a mixed catalyst system of $PdCl_2(PPh_3)_2$ and CuI in 18 h (Scheme 3).

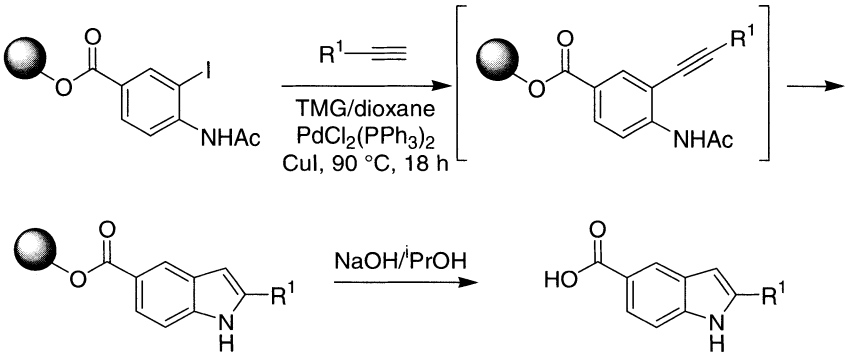
Transfer of these reaction conditions to TentaGel was possible, albeit the conditions involved a slight increase in temperature (Scheme 4). Yields varied from 48 to 95%, with the only observed by-product resulting from incomplete cyclization, implying almost quantitative conversion for the palladium-catalyzed step. The sequence appears to be robust and rapid.

In a follow-up communication,[26] similar chemistry was used for the production of 2-substituted benzofurans beginning not with an anthranilic acid derivative, but with a resin-bound *ortho*-hydroxy aryl iodide **3**. In the solid-phase work, depicted in Scheme 5, the relevant carboxylic acid was linked to TentaGel via a Mitsunobu reaction, and after deprotection was seen to undergo smooth Heck coupling and cyclization, giving essentially pure compounds in 40–70% overall yield after cleavage.

In a simple extension of this indole work, Collini and Ellingboe[27] introduced an extra element of diversity by using a method originally exemplified in solution.[28] This allowed for the synthesis of trisubstituted indoles. The method, shown in Scheme 6, involves the Sonogashira palladium/copper co-catalyzed step to introduce the initial alkyne diversity. After conversion of the aniline group to the trifluoroacetamide, a second palla-

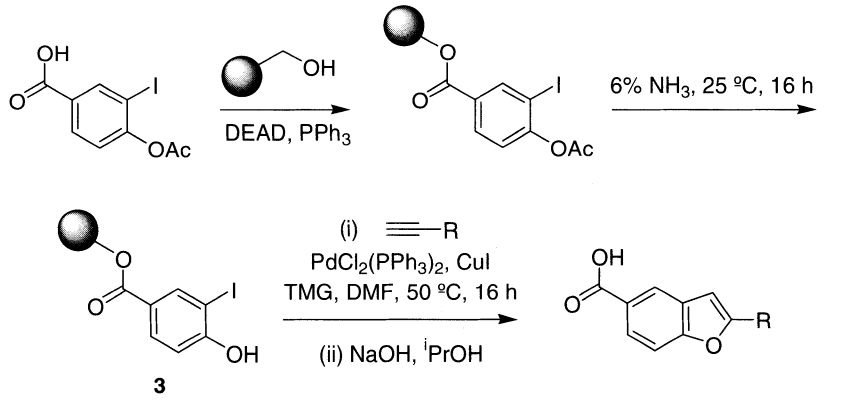


Scheme 3.

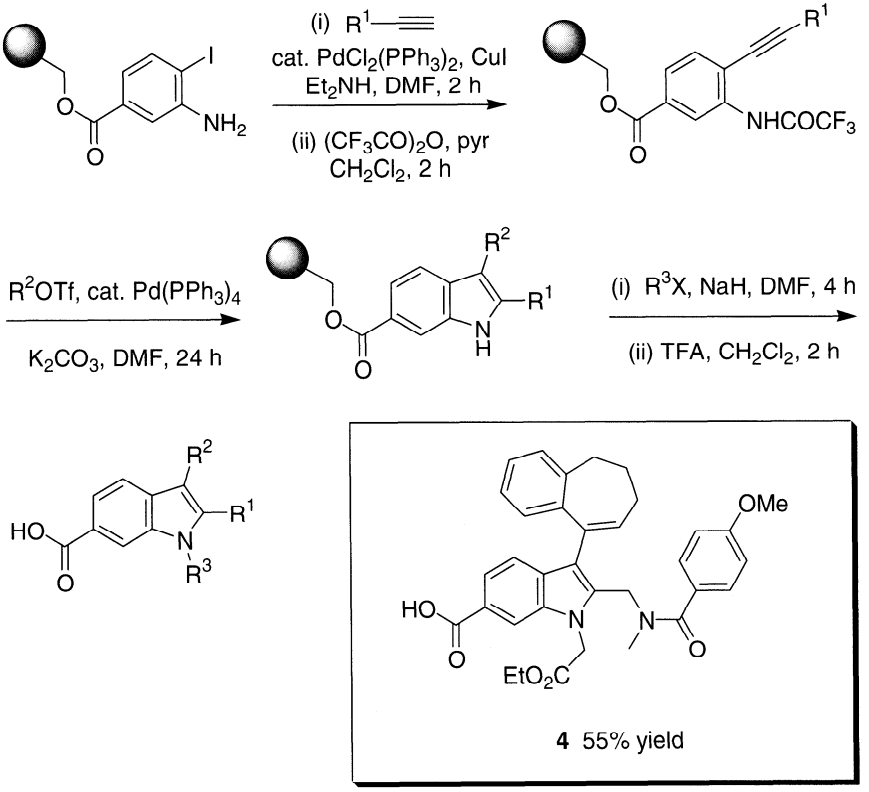


Scheme 4.

dium-catalyzed step, in which there is included the vinyl triflate of a second element of diversity, allows for limited functionality at the 3-position also. The nitrogen may be alkylated using NaH and the appropriate organohalide. The method allows for the production of complex indoles such as **4**, with a



Scheme 5.

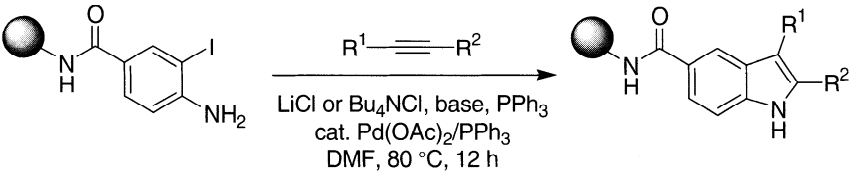


Scheme 6.

number of other examples being given of successful syntheses in low to good overall yields.

The indole pharmacophore has attracted further attention in the work of Zhang et al. (see also below, Scheme 10), who used the route developed by Larock[29] for the heteroannulation of internal alkynes with *o*-iodoanilines (Scheme 7).[30] The cyclization proceeded well on the solid phase. In the case of unsymmetrical alkynes, the predominant species was the expected one with the more sterically demanding group in the 2-position.

In a useful extension to this chemistry, the coupling of the starting iodoaniline with trimethylsilylalkynes was found to give the silylated species **5**, which can be a useful precursor to either 2-unsubstituted indoles or 2-halogenated derivatives as shown in Scheme 8. These could then be taken on further with standard organometallic coupling reactions.

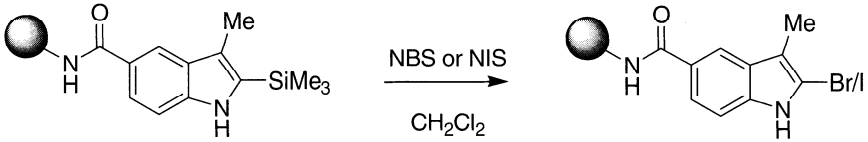


Scheme 7.

In another investigation featuring the indole nucleus, the related 2-oxindole pharmacophore was shown to be easily derived using the synthesis shown in Scheme 9, involving an *intra*molecular Heck reaction to close the second ring.[31] The resin-bound iodoaniline **6** was derivatized first with a reductive alkylation, followed by coupling with an α,β-unsaturated acyl chloride. This established a substrate for the pivotal Heck reaction, using 30 mol % $Pd(OAc)_2$ at 100°C in DMF. Cleavage (TFA) and product analysis showed that, save for acryloyl chloride cases (R^2 = H), yields and purities were good. In all cases more (*E*) double bond isomer was produced than (*Z*). No special washing conditions were needed after the palladium coupling step, and no problems with palladium black deposition were observed.

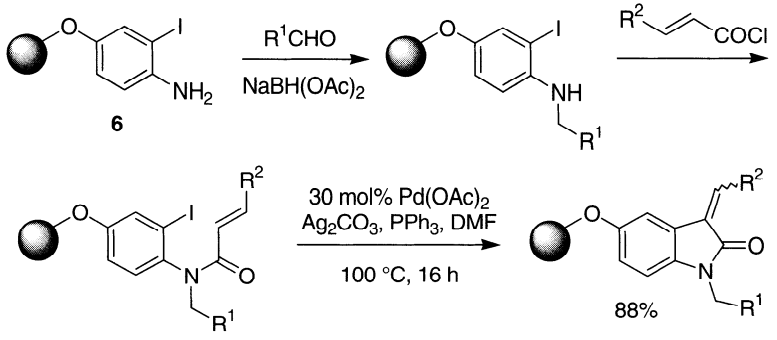
Zhang et al.[32] constructed compounds with either an indole or benzofuran nucleus in a similar way using the support-bound intramolecular Heck reaction. Their strategy was based on cyclization of *N*-allyl-substituted *ortho*-haloanilines to indoles in solution.[33,34] Having found that *ortho*-iodides underwent the solution-phase coupling with greater ease than the corresponding *ortho*-bromides, they set about applying their chosen reaction conditions to the solid phase (Scheme 10). It was noted that the presence of tetrabutylammonium chloride and water appeared to help the solution-phase reactions.

If the allyl nitrogen were unalkylated, the reaction went in lower yield (60%) than its solution-phase counterpart (80%), and a variety of unidenti-



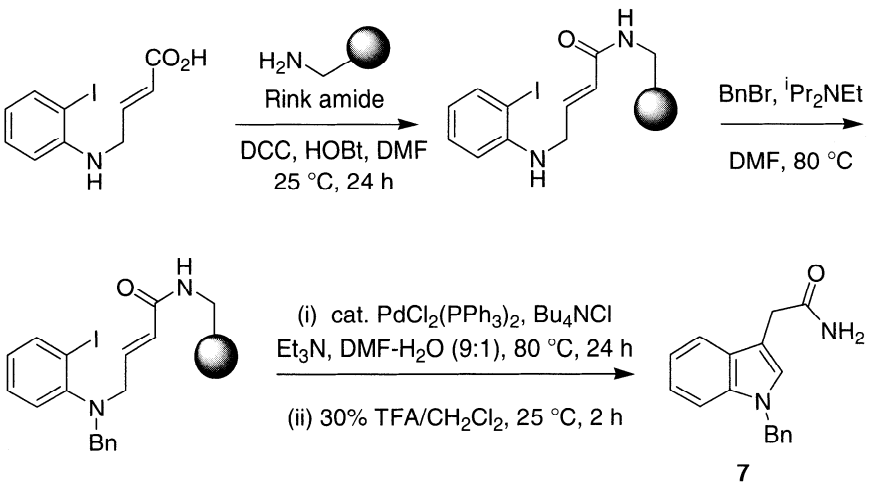
5

Scheme 8.



Scheme 9.

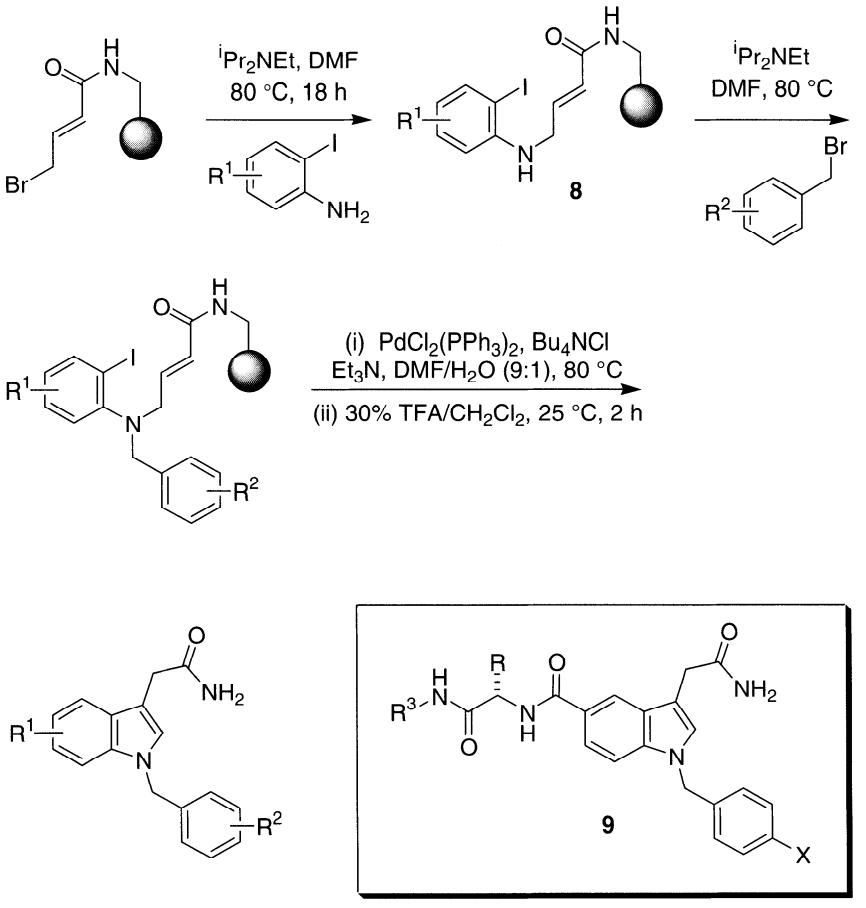
fied products were formed. It has been shown that TFA can induce the dimerization of indole 3-acetic acid and its methyl ester.[35] To avoid this possible complication, the same reaction was attempted but with an allyl *N*-alkylated material (the alkylation was performed on resin), with the desired indole **7** being formed in 88% yield after 24 h at 80°C, using $PdCl_2(PPh_3)_2$ as the catalyst. No exocyclic double bonds were observed. This implies that the initial β-hydrido elimination product was subject to a further addition (by PdH) to give a new σ-adduct which could effect double



Scheme 10.

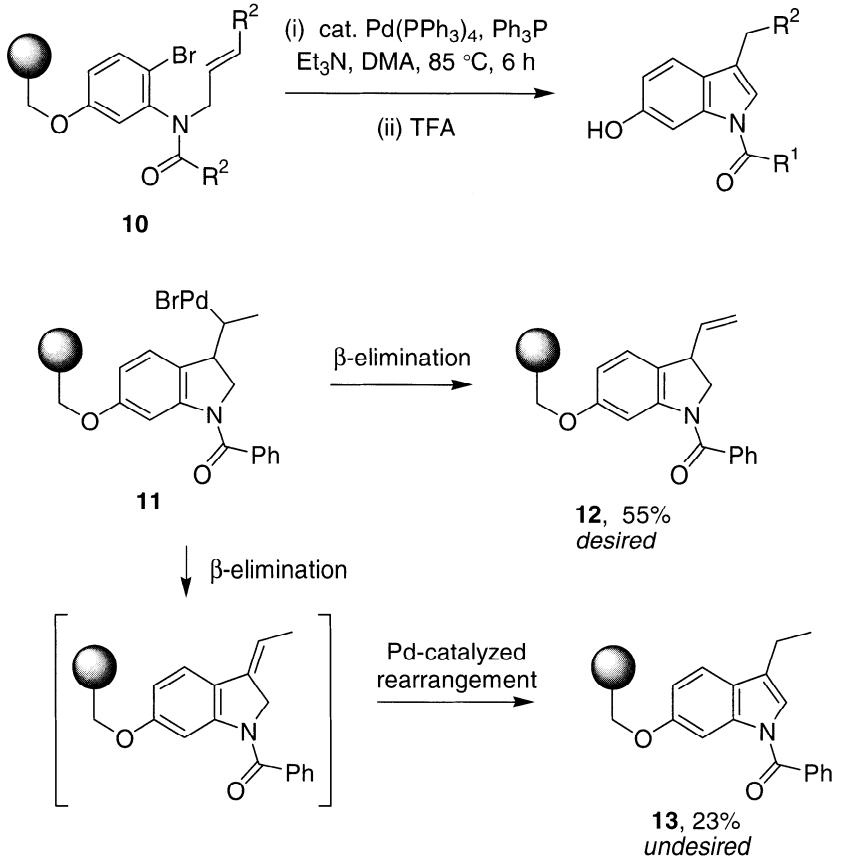
bond migration to allow formation of the more thermodynamically stable endocyclic indole.

A common goal of library synthesis is to maximize diversity around a core, so the synthetic route described above was extended to accommodate a variety of substituted aryl groups. The modified route is shown in Scheme 11. The solid-phase starting material was Rink amide resin,[36] which had been loaded with γ-bromocrotonic acid (attempts to load with other suitable fragments, such as fumaraldehydic acid, or the pentafluorophenol-activated ester, failed). Substituted *ortho*-iodoanilines could then be used to alkylate



Scheme 11.

this resin to give the support-bound precursor **8**. As before, the nitrogen could then be alkylated, providing additional diversity, before the cyclization step was performed to give the desired indoles after cleavage in high purity and 67–88% yields overall based on the loading of the initial resin. Both electron-withdrawing and electron-donating substituents were tolerated as R^1. A small (18-member) library was prepared where the methyl ester functionality incorporated as R^1 was cleaved (with potassium trimethylsilanolate)[37] and then coupled to a peptide fragment to give compounds of type **9**. Adaptation of this work to the benzofuran nucleus, that is, the replacement of the NH with O, was also shown for two cases, with similar yields and purities; this followed from the solution-phase studies by

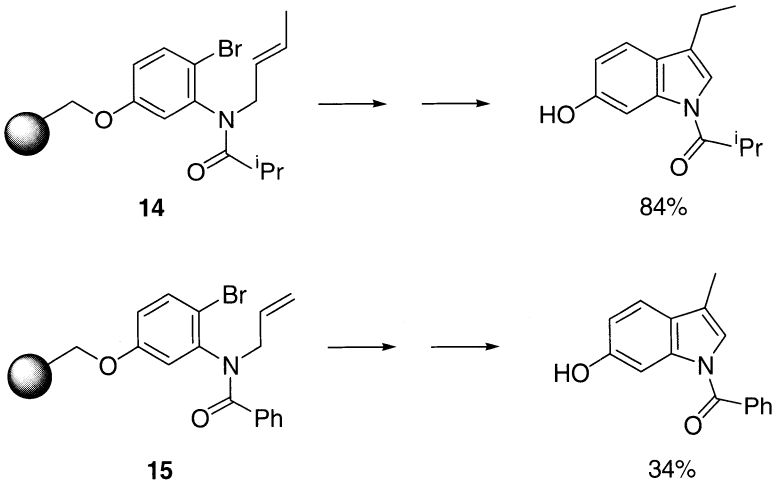


Scheme 12.

Larock.[38] The method allows for variation in the aromatic ring component. An interesting feature of this work, probably influenced by the ease of cleavage of the Rink linker, is that all characterization and yield calculations were done off-bead.

The same exo to endo bond migration shown above was postulated earlier by Yun and Mohan in their studies on the synthesis of indole analogues.[39] The precursor species **10**, assembled principally in solution, then derivatized on resin, was subjected to Heck conditions at elevated temperature, as shown in Scheme 12. The progress of the reaction was monitored by HPLC of cleaved product. It was claimed that an inert atmosphere was essential to the reaction owing to the oxidation of Pd(0) at elevated temperatures; this catalyst oxidation was associated with unwanted reductive debromination of the starting material, though the mechanism for this is unclear. Eight different indoles were produced, using 50 mol % palladium catalyst for the cyclization, in good to excellent yields based on the initial loading of the polymer; poor purities were obtained in some cases, however. An interesting by-product was formed in the case of the indole shown in Scheme 12. At the stage of β-elimination from **11**, the sterically less hindered path appears to have been taken to generate the terminal alkene **12** rather than that to give the desired indole **13**.

Steric influences were proposed to account for the result shown above, but other observations suggest that it is the phenyl group that is important



14 84%

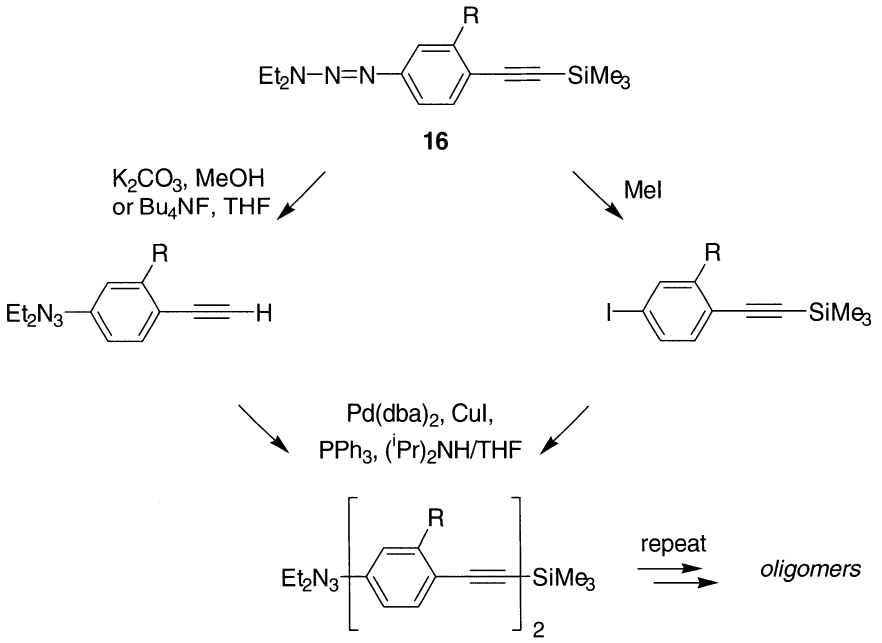
15 34%

Scheme 13.

and that it somehow disfavors endo elimination. Thus Scheme 13 indicates the case of amide **14** wherein an *iso*-propyl group (rather than a phenyl) is present. This cyclization proceeds well. Conversely, the yield for the cyclization is low when there is no alternative elimination possible, but again a phenyl group is attached to the amide, that is, for substrate **15**.

2.2.3. Polymer Construction on Solid Support

In a study of syntheses of polymers on solid support, Tour et al. found they could rapidly produce oligo(1,4-phenyleneethynylene)s of defined lengths.[40] This area will not be discussed in detail, but since a report by Moore in 1994, much elegant and efficient solid-phase chemistry has been developed (see Chapter 4).[41,42] Solution-phase chemistry used for the present example is shown in Scheme 14. Central to this are a palladium/copper co-catalyzed coupling reaction and a doubly protected monomer unit **16** having a silylated alkyne and a diethyltriazene group. The former may be protodesilylated to generate a terminal alkyne for the coupling, and the



Scheme 14.

latter, simply by treatment with methyl iodide, gives the aryl iodide. These may then be coupled and the sequence begun again.

Adaptation of this protocol to the solid phase required development of a diethyltriazene derivative facilitating linkage to chloromethyl polystyrene. The solution developed is shown in Scheme 15. The palladium/copper co-catalyzed steps appeared to proceed well, such that when two-thirds of the cross-coupled resin **17** was cleaved with methyl iodide, the liberated dimer was recovered in 86% yield for the two-step process. This dimer was added to the remaining third of the resin (after desilylation with TBAF) under the same conditions to produce the tetramer. Thus progressively larger polymers of defined length can be constructed via this iterative sequence of reactions. Yields for the three-step deprotection, coupling, and cleavage cycle were typically 92–93%. During this process the resin increases greatly in size, and its properties, once an 8-mer or 16-mer are attached, presumably differ from the starting resin. There is no indication that such changes affect the success of the organometallic coupling reaction.

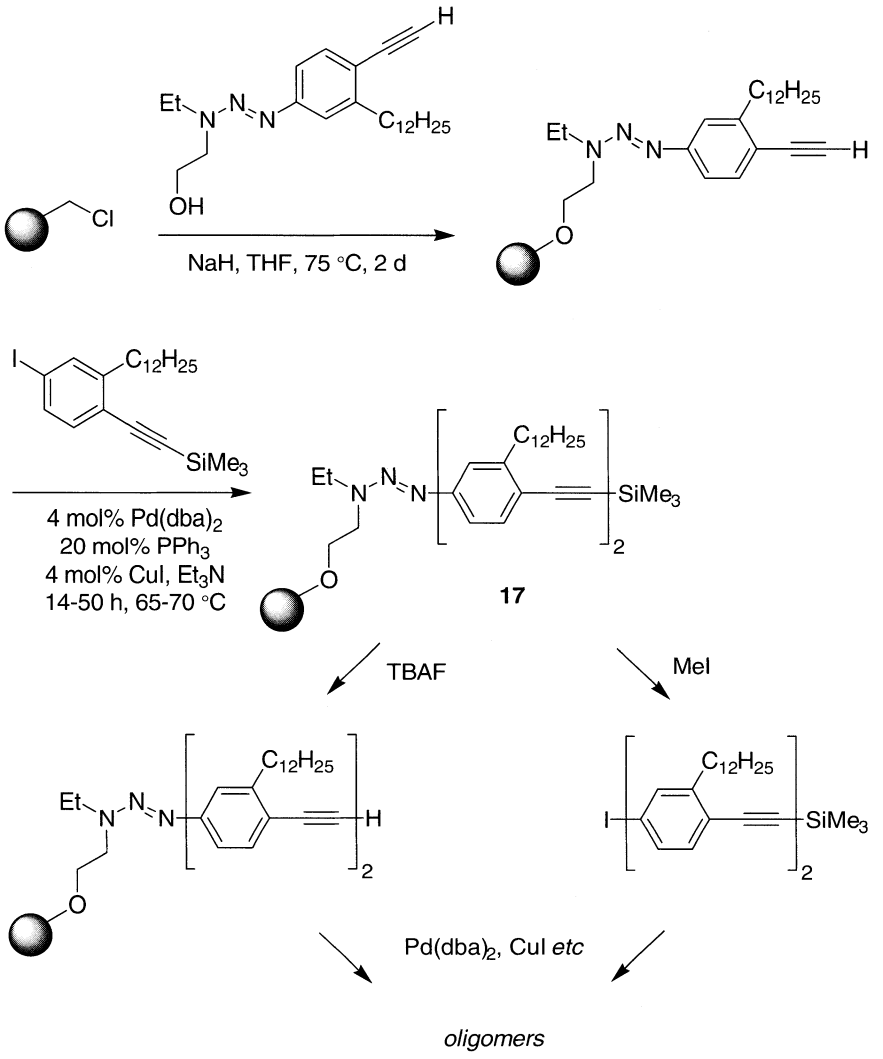
The triazene linker featured above is a "traceless" one that efficiently yields an aryl iodide upon treatment with methyl iodide. It is perhaps not well known to the combinatorial chemistry community.

2.2.4. Other Uses of Solid-Phase Heck Reactions

Spear et al. chose the Heck reaction to elaborate 4-iodophenylsulfonyl chloride attached to Rink amide resin, that is, sulfonamide **18**.[43] The reaction (Scheme 16) was reported to be quantitative, as was a simple Stille coupling on the same molecule. Raju and Kogan used a Suzuki coupling on solid support (see below)[44] to illustrate use of a new carbamate linker for the generation of more diverse sulfonamides than those above.

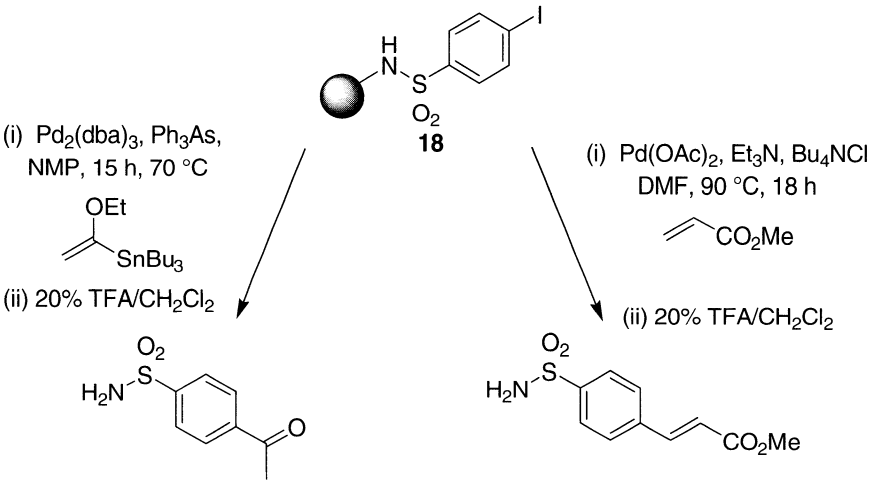
Ruhland et al. used $PdCl_2$(dppf)-NEt_3 Heck conditions to add to a resin-bound aryl iodide, thereby generating supported 4-styryl β-lactams, as shown in Scheme 17.[45] This catalyst system, also found to be effective for the Suzuki reaction (see Section 2.4), is unusual for the Heck reaction and had only previously been used for an intramolecular cyclization.[46] The more usual conditions of $Pd(OAc)_2$/phosphine/NEt_3 or K_2CO_3 were found to be ineffective.

Palladium-mediated Heck carbon–carbon bond formation has been used to introduce diversity via a scheme based on Pauson–Khand cyclizations, to generate fused bicyclic amino acid derivatives.[47,48] The sequence of



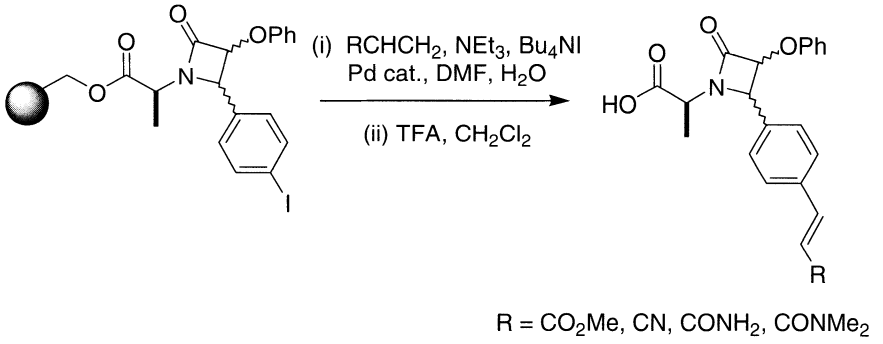
Scheme 15.

reactions shown in Scheme 18 was also exemplified in solution, but it was found that the solid-phase version, on Wang resin, provided improved yields with easier work-up and isolation. Copper(I) co-catalysis was used in this Sonogashira-type coupling. The polarity of the reaction, in which a solid-supported alkyne is coupled to an added halide, is unusual. Flash column chromatography was used to separate a minor diastereoisomer in each case.

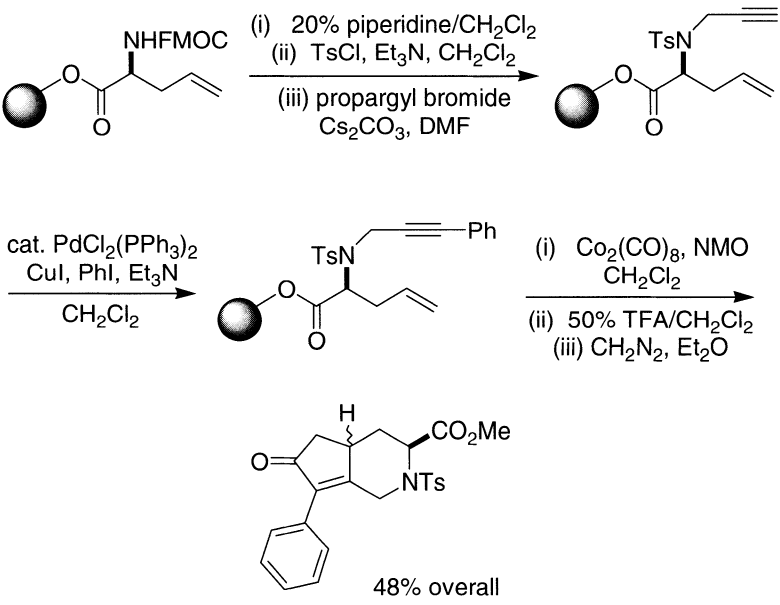


Scheme 16.

The chemistry described above was adapted to a library format. For example, instead of beginning with protected (*S*)-allyl glycine methyl ester, and introducing a propargylic group by alkylation, a support-bound propargylic glycine derivative was used and the allylic unit was introduced later by *N*-alkylation. This allowed the sense of the bicycle to be reversed. The palladium step allowed both electron-withdrawing and electron-donating groups to be introduced. Overall isolated yields of the cyclized material were impressive, as high as 86%.



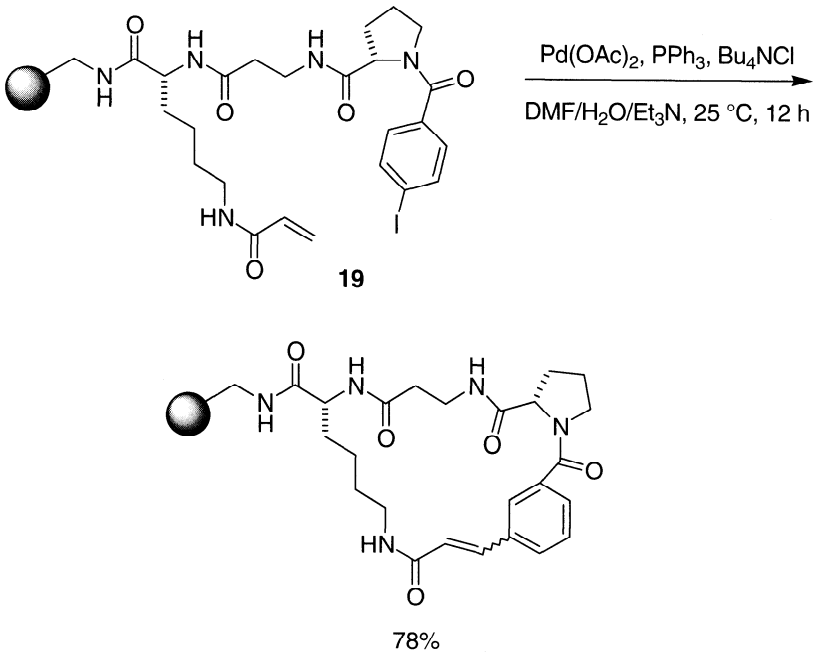
Scheme 17.



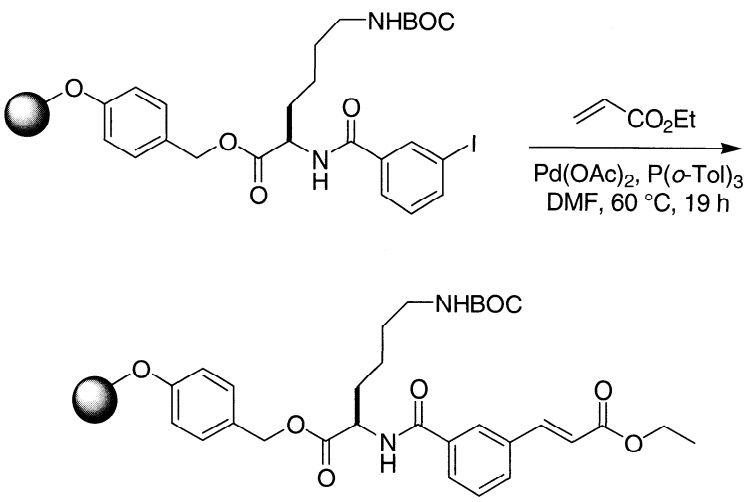
Scheme 18.

One of the most striking demonstrations of the Heck reaction on solid phase was an efficient macrocyclization reaction by Hauske et al. They cyclized the resin-bound species **19** under mild conditions and obtained products with high post-cleavage purity (Scheme 19).[49] The efficiency of these reactions for a variety of structural modifications in the ring seems to suggest that the pseudodilution effects of site isolation on resin are important.

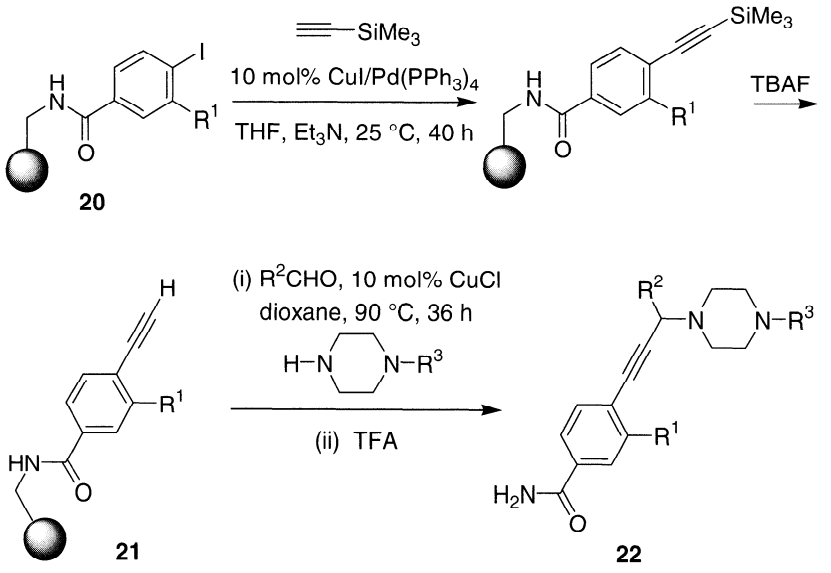
Magic angle spinning (MAS) NMR spectroscopy has been used to monitor reactions on solid support,[50,51] as demonstrated for a three-step process involving a Heck transformation.[52] The key step involves the simple coupling of ethyl acrylate to an aryl iodide bound to a Wang Lys(Boc) resin (Scheme 20). Examining the resin with TOCSY NMR spectroscopy facilitated observation of the appearance of ethyl acrylate peaks on resin; it was also possible to deduce the trans nature of the resultant double bond. Cleavage of the resin with 90% TFA in DCM resulted in a single peak on HPLC analysis, and from this the authors concluded that the reactions in the sequence had proceeded quantitatively.



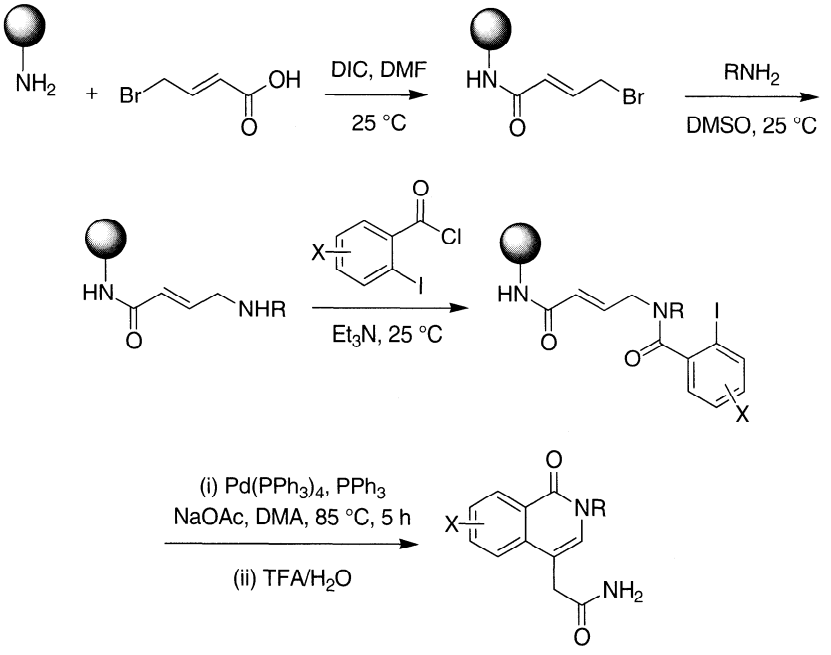
Scheme 19.



Scheme 20.



Scheme 21.



Scheme 22.

A more recent use of the palladium/copper co-catalyzed Sonogashira reaction is the solid-phase synthesis of propargylamines (Scheme 21).[53] The coupling was used at the outset of a library synthesis to convert the resin-bound aryl iodide **20** to terminal acetylene **21**. The product was substrate for a Mannich reaction with an aldehyde and substituted piperazine in solution to yield, after cleavage, propargylamines **22** in good yields and purities. Various secondary amines were shown to be successful in the Mannich step, but ortho- and meta-substituted iodobenzoic acids initially could not be substituted for the para-isomer. The reactions were successfully performed by changing from a polystyrene- to a PEG-based support (with the same linker); no details were given, however.

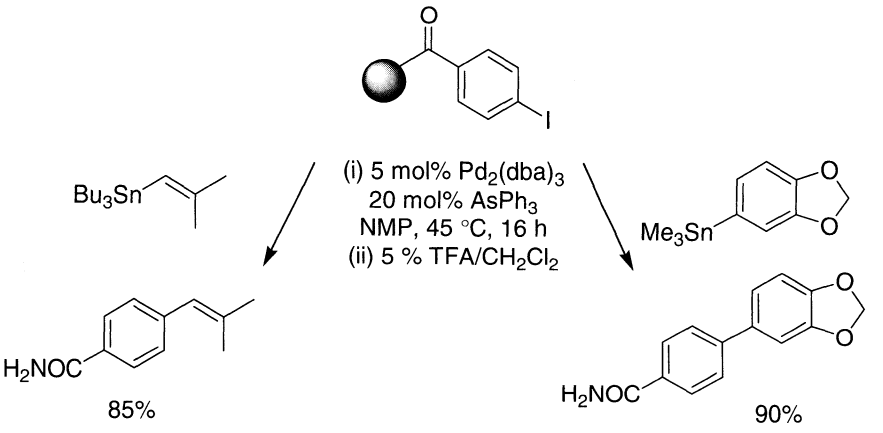
In the final example of the Heck reaction on solid support, a Chiron group[54,55] used a palladium-catalyzed cyclization step to prepare heterocycles. An example of their work, the production of 1-(2H)-isoquinolinones, is shown in Scheme 22.

2.3. STILLE REACTION[56]

An early attempt to use the Stille reaction on solid support is detailed in a paper from 1994 by Deshpande.[57] In this, an aryl iodide linked to Rink amide or Wang resin is coupled to a number of vinyl and one arylstannanes (Scheme 23). The protocol used only 5 mol % $Pd_2(dba)_3$ and proceeded in typically 90% yield at 45°C. Interestingly, the reactions were simply left to stand (rather than being shaken) overnight.

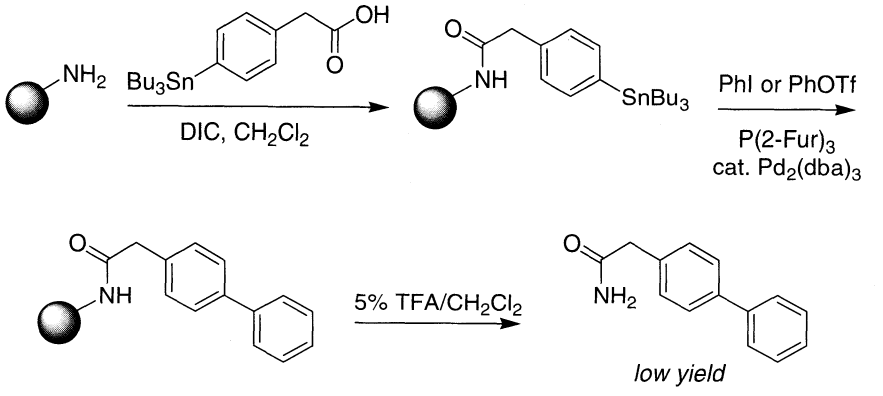
In a subsequent paper on the use of the Stille reaction to form biaryls,[58] the reaction was carried out under ambient conditions to allow robotic automation of the process. Attachment of the tin species to resin was very straightforward, in that 4-tri-*n*-butylstannylphenylacetic acid was linked to Rink amide resin simply using a DIC coupling. Loading of this species was determined by tin elemental analysis and correlated with a quantitative ninhydrin test of free amines remaining on the support (Scheme 24).

One of the earliest examples of gel phase carbon NMR spectroscopy facilitated detection of support-bound tin species. When the Stille couplings were attempted using triphenylphosphine and $PdCl_2(PPh_3)_2$, no products were observed on cleavage from the resin. However, when the conditions developed by Farina[59] were used [tri-2-furylphosphine and $Pd_2(dba)_3$], biphenyl was produced in low yield, with iodobenzene giving a higher yield of product (15%) than benzene triflate (3%). Having shown partial conver-

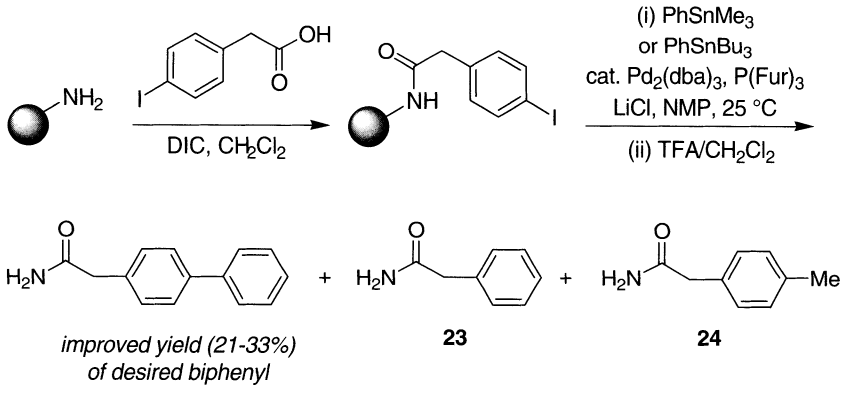


Scheme 23.

sion at room temperature in 12 h, the polarity of the reaction was switched using 4-iodophenylacetic acid bound to the resin (Scheme 25). This reacted with trimethylphenyl tin under Farina conditions and formed the biphenyl product in 21% yield. Using tributylphenyl tin, the yield increased to 33%. However, other products were also formed, such as **23** and **24**, the latter arising from alkyl transfer from the tin species. It was suggested that the polymer-bound tin species might adversely affect the swelling properties of the resin. However, the differences in the yields are really quite small in



Scheme 24.



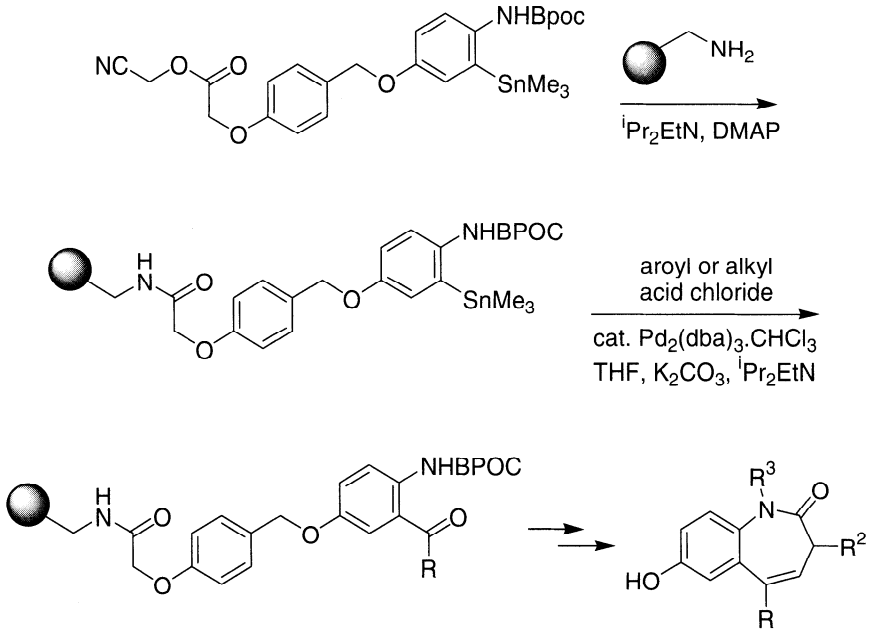
Scheme 25.

these cases, and a more thorough study of these reactions would be needed to formulate definite conclusions.

This chemistry was repeated with a traceless photolabile linker.[60] The desired biphenyl was formed, but the couplings gave side products, and all yields of the desired biphenyl were lower than 30%.

The Stille reaction was central to Ellman's synthesis of 1,4-benzodiazepines from support-bound stannanes.[61] The method features solid-phase syntheses of 2-aminoaryl intermediates; these are not as widely available as the other building blocks for the desired product, so the Stille step increases the diversity of accessible products (Scheme 26). The catalyst of choice was "ligandless" $Pd_2(dba)_3 \cdot CHCl_3$. Elevated temperatures were required for this reaction to proceed with $Pd(PPh_3)_4$ as catalyst. To avoid any acid formed in the reaction initiating either carbamate deprotection or protodesilylation, potassium carbonate and Hunig's base were added as scavengers. It is in this study that Ellman introduced a dilute KCN–DMSO wash to rid the resin of palladium black deposited during the coupling. The final, unpurified benzodiazepines were isolated in typically greater than 80% purity at the end of the sequence.

Chemistry similar to this was used in Ellman's paper to promote application of a silicon-based traceless linker.[62] The full report on this work[63] shows that both aliphatic and aromatic acid chlorides may be used in the coupling step. The same approach is also shown to be successful with a germanium-based linker in place of the silicon. The couplings were typically performed for 1 h only, with equilibration time of a few minutes



Scheme 26.

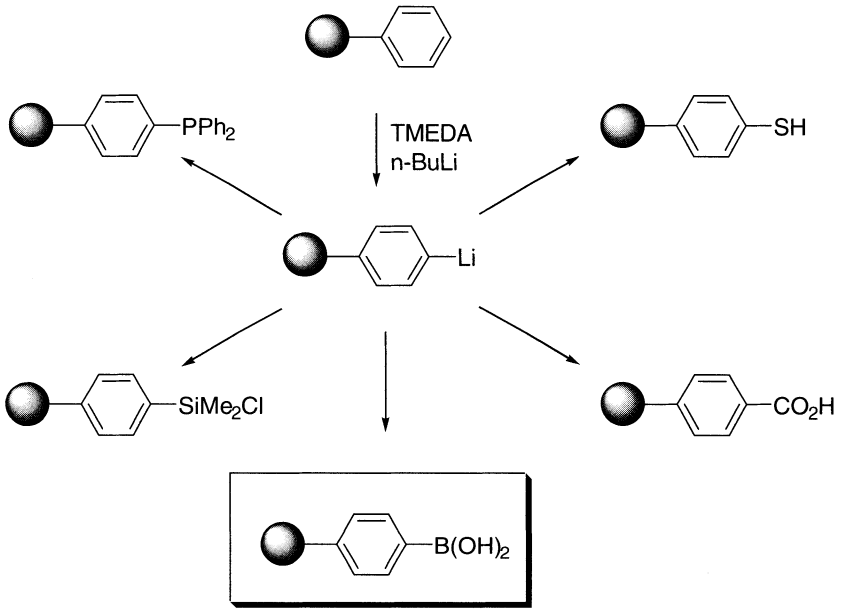
allowed for the reagents to diffuse into the resin prior to the addition of the acid chloride. A KCN–DMSO wash was used as standard throughout.

The copper-catalyzed coupling of polymer-bound aryl iodides with stannanes has also been demonstrated.[64]

2.4. SUZUKI REACTION[65]

2.4.1. Early Work

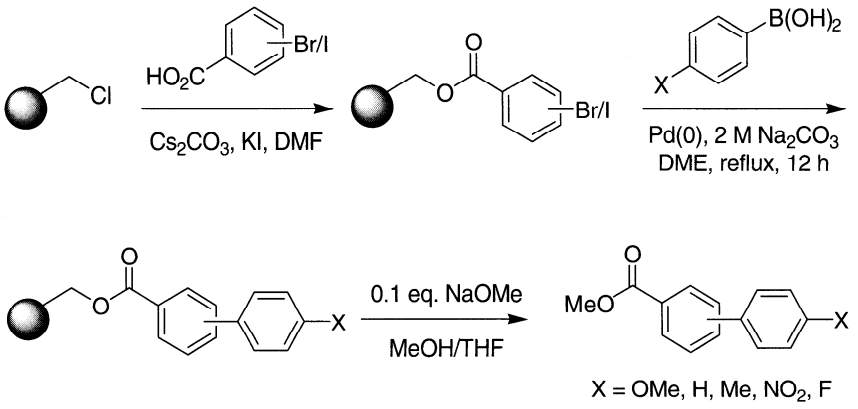
Farrall and Frechet recognized the possibility of forming polymer-bound boronic acids in 1976.[66] Supported *para*-benzeneboronic acid groups were generated by direct lithiation of polystyrene, giving a *para*-lithio intermediate that could be used to generate a host of other resins also (Scheme 27). Conversion to the boronic acid was one of the more successful transformations. The purpose of this transformation was to allow the attachment of sugars to the solid phase via the boronate.



Scheme 27.

The Suzuki reaction was used in liquid crystal syntheses[67] to modify the properties of a polymer by the introduction of aromatic groups to a boronic acid functionalized backbone. Palladium-catalyzed couplings have found wide use in this field.[68,69]

One of the earliest investigations into the utility of the Suzuki reaction on solid support for combinatorial chemistry was that carried out by Frenette and Friesen[70] to form the biaryl subunit, which is an important pharmacophore in its own right. A number of polymer-supported aryl halides were generated by the cesium carbonate-mediated loading of *o*-, *m*-, and *p*-substituted haloaromatic carboxylic acids onto Merrifield resin, and these were then coupled with a small number of commercially available boronic acids bearing both electron-withdrawing and donating groups (Scheme 28). Cleavage of such products from the resin was achieved by a facile transesterification reaction with methoxide. A number of catalysts were tested for the couplings, with all except $Pd_2allyl_2Cl_2$ giving good results. Eventually $Pd(PPh_3)_4$ was used and gave excellent yields of products in >90% purities, more or less devoid of any unreacted starting materials or by-products. Interestingly, the coupling reactions were performed using

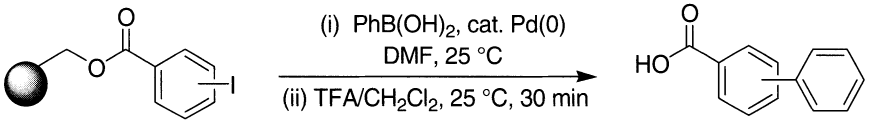


Scheme 28.

degassed DME, which is a common solvent for Suzuki reactions but is not frequently used in solid-phase chemistry. DME was identified as a solvent of choice for the Suzuki protocol in 1984.[71]

Chemistry outlined earlier for construction of supported benzodiazepines by Ellman[72] involved the use of the Stille reaction (see above); a synthesis of 1,4-benzodiazepine-2,5-diones was then reported by the same group,[73] wherein Suzuki couplings were used as a late step to introduce extra diversity. They favored this reaction because it gives high yields. Moreover, numerous aromatic and heteroaromatic boronic acids are available, and alkylboranes can be readily formed in situ by hydroboration methods (see below). Two couplings were shown to exemplify the strategy. A team from Chiron synthesized the same pharmacophore on solid support,[74] incorporating similar Suzuki chemistry to that of the other group, as part of a different overall approach to this pharmacophore.

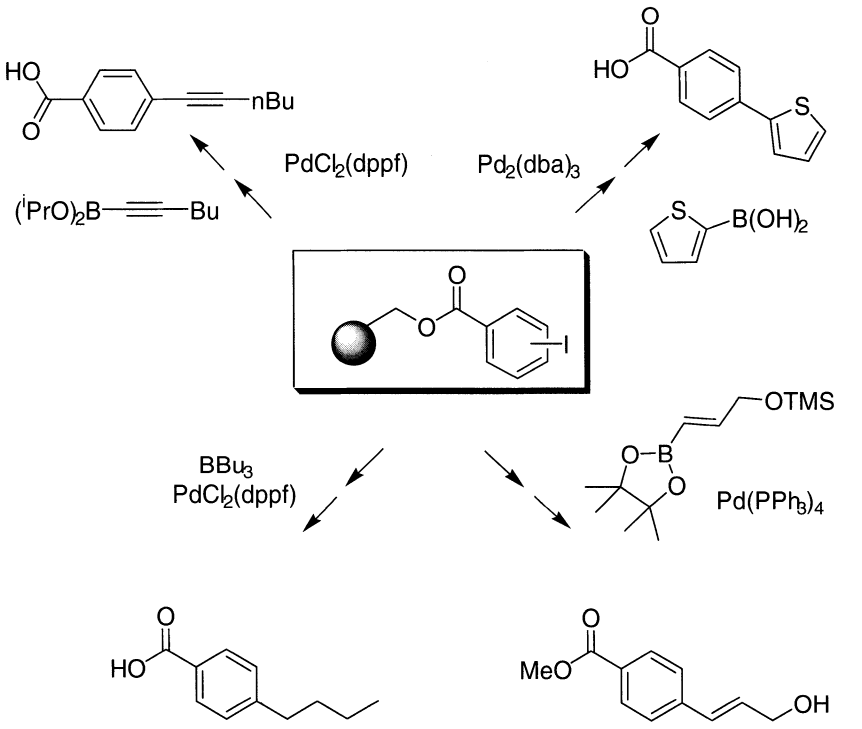
Guiles et al.[75] utilized *o*-, *m*-, and *p*-iodobenzoic acid attached to a solid support in couplings with phenylboronic acid at room temperature (Scheme 29). A pilot investigation into effective catalyst systems in DMF revealed, unsurprisingly, that $Pd_2(dba)_3$ and $Pd(PPh_3)_4$ were effective catalysts but Pd(II) and Ni(II) complexes were ineffective. Optimization of the base used, solvent selected, and catalyst levels was not reported. The couplings were quite slow (18 h at room temperature) and were affected by steric crowding in the case of the ortho-benzoate. The less reactive bromo-substituted analogues of these reactions were found not to proceed at all. Product purities after cleavage were routinely found to be greater than 95% by HPLC



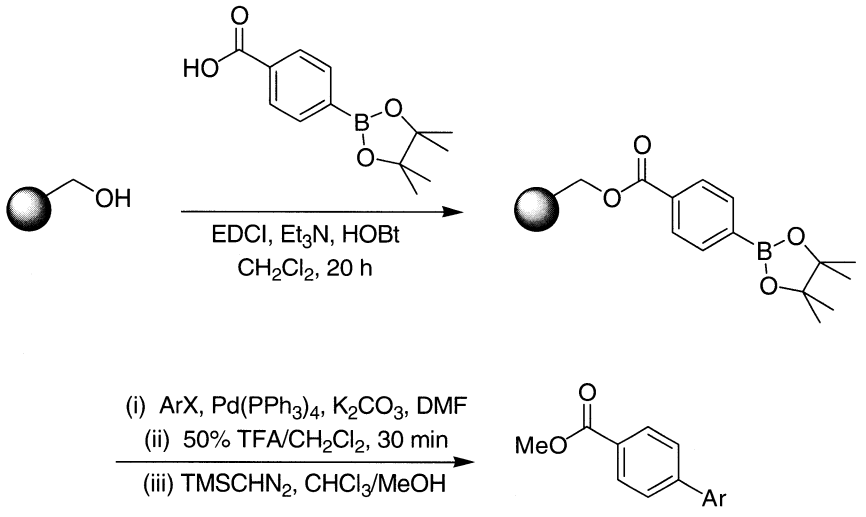
Scheme 29.

and proton NMR spectroscopy, and reaction yields varied from moderate to excellent.

The results of these studies were then used to demonstrate the versatility of the reaction by coupling a variety of boronic species with the same resin-bound iodobenzoate (Scheme 30). Catalyst suitability was found to depend upon the specific reaction performed, and the yields were again moderate to excellent. Of particular note is the success of the Pd(II) catalyst [presumably generating Pd(0) in situ], in contrast to the studies outlined in



Scheme 30.



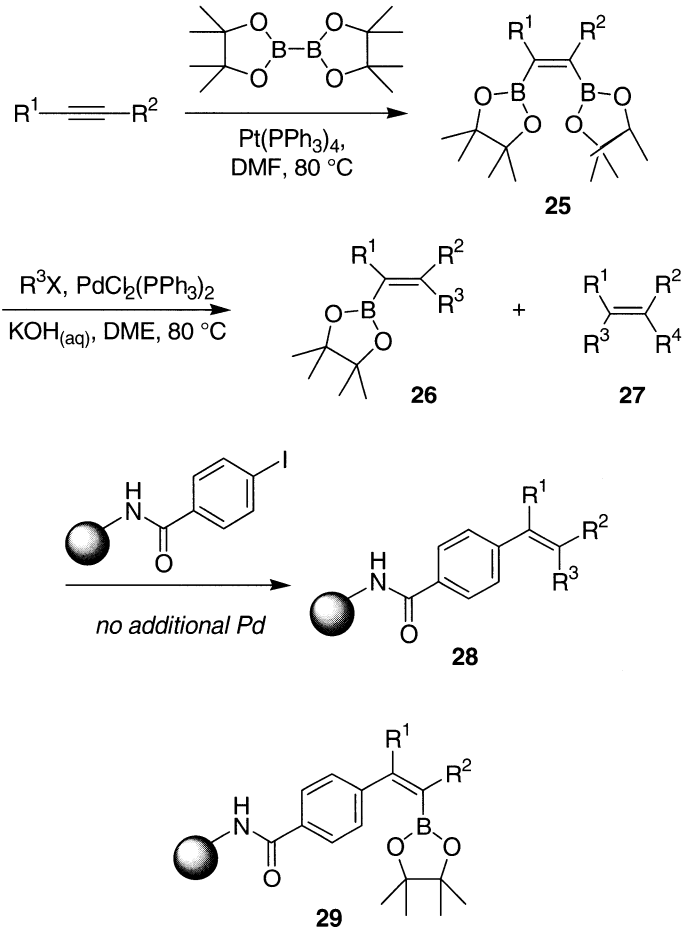
Scheme 31.

Scheme 29, in the coupling of a tributylborane to yield *p*-butylbenzoic acid upon cleavage.

In a similar way, Guiles and co-workers immobilized an aryl pinacol boronate on resin via an ester linkage, and then a small number of aryl halides were coupled to this (Scheme 31). The products were cleaved and immediately transformed into their methyl esters, presumably for ease of analysis and separation from unreacted boronate. The reaction was found to be slower than that of the opposite polarity (i.e., with the resin-bound iodide), and only moderate yields were obtained after as much as 48 h. Yields could be considerably improved upon a second round of coupling, but only one example was given of this. The aryl bromides were found to react only upon heating.

2.4.2. Resin Capture

Resin capture was demonstrated by Armstrong in 1996[76] and used elegantly in the solution-then-solid phase generation of a range of Tamoxifen analogues. Suzuki chemistry and a support-bound boronate were used.[77] The strategy is shown in Scheme 32. It features a recent addition to organoborane chemistry, Suzuki and Miyaura's platinum-catalyzed conversion of alkynes to *cis-bis*(boryl)alkenes.[78] This chemistry was used by Armstrong to gener-



formed in good yield if order of addition is adjusted, but unstable

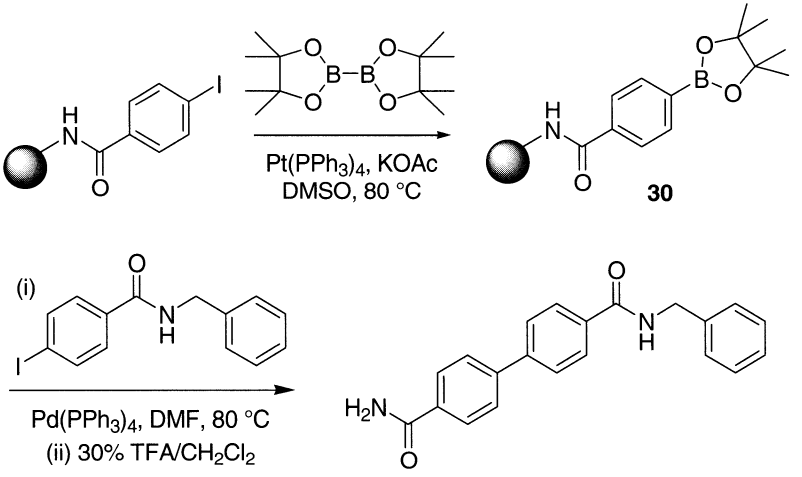
Scheme 32.

ate such alkenes **25** in solution; these were used in the next step without isolation or purification. Thus the crude product was reacted with 1.5 equivalents of an organohalide to give a mixture of mono- and disubstituted compounds **26** and **27**. The first coupling is faster than the second, so **26** dominated **27** in this intermediate product mixture. Control over regiochemistry was not possible if $R_1 \neq R_2$. This product, again crude, is reacted *without*

the addition of further palladium, with a supported aryl iodide to generate the final resin-bound species **28**. The obvious advantage of this method is that only **26** is captured by the solid phase, and therefore the final step in the library synthesis is also a purification step.

A variety of conditions were tried for the coupling, and aqueous KOH in DME were found to be optimal. Although $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ worked equally well as catalysts, the latter was easier to handle, and this becomes an important issue when many reactions must be run to make a library. The resin-bound vinyl boronates **29**, which would be produced if the order of addition of halides were different, were not stable with respect to deboration, and subsequent yields using this strategy were low.

In addition to the synthetic route shown in Scheme 32, Armstrong approached the synthesis from the other direction, by converting the initial resin-bound iodide to a supported pinacolatoboronate **30** under platinum catalysis (Scheme 33). This was then coupled in the usual way with a solution-phase aryl iodide in high yield, and with much more satisfactory results than were obtained with the vinylboronates **29**. This chemistry was later shown to be useful in solution for one-pot biaryl synthesis by genera-



Scheme 33.

tion of the boronate in situ, where the competition of boronate formation and aryl cross-coupling is finely controlled by the base.[79]

The work by Armstrong was extended to include the room temperature resin capture of trisubstituted ethenes with a pendant boronate group.[80] Modification of the amide linker above to a novel silyl-based one allowed for the traceless cleavage of superior analogues.

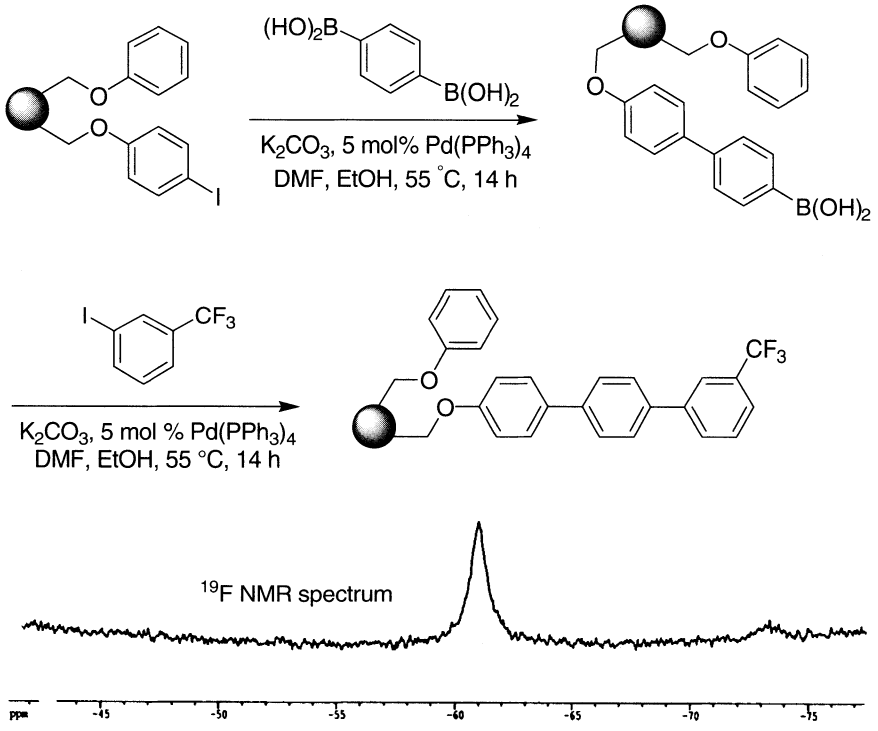
A similar sequence was performed later by others,[81] in which the formation of the boronate was performed using palladium ($PdCl_2$(dppf)), rather than platinum, catalysis,[82] and ortho-, meta-, and para-boronates were formed. These were then coupled with a variety of aryl iodides and bromides under almost identical conditions to those used by Armstrong to generate, after cleavage, the biaryls in good yield. The reaction was markedly slower when support-bound ortho-substituted boronates were used in the coupling reaction. Both the initial formation of the boronate and the subsequent coupling reaction were allowed 20 h each to run to completion.

Using related chemistry, we have found these repetitive couplings to be facile and have used aromatic diboronic acids[83] to generate simple terphenyl structures on solid support.[84] We used gel-phase fluorine NMR spectroscopy[85] to observe the incorporation of the appropriate groups (Scheme 34) in repeated palladium-catalyzed reactions at slightly elevated temperature (55°C). This unoptimized two-step process was complete in essentially 24 h.

2.4.3. Tropane Synthesis

Ellman reported two palladium-catalyzed reactions as part of a process to generate tropane derivatives on solid support.[86] The first step (Scheme 35) was a Heck-type addition of an arylpalladium species, generated in situ, across the double bond present in the starting material. What is striking is that the reactive η^2 organopalladium intermediate **31** is treated as a discrete, isolated species, seemingly stable to β-elimination (some related intramolecular complexes have been isolated in solution).[87] Here the β-hydrogens are not periplanar with the palladium, giving the observed stability. The first stage of the reaction, the oxidative addition across the double bond, is favored by the use of electron-rich aryl bromides. Formal split-and-mix approaches feature isolation of this intermediate; the palladium is consequently not used catalytically.

A Suzuki reaction is then performed on **31** in THF with carbonate as base and also with added triphenylphosphine, which complexes to the Pd(0) and

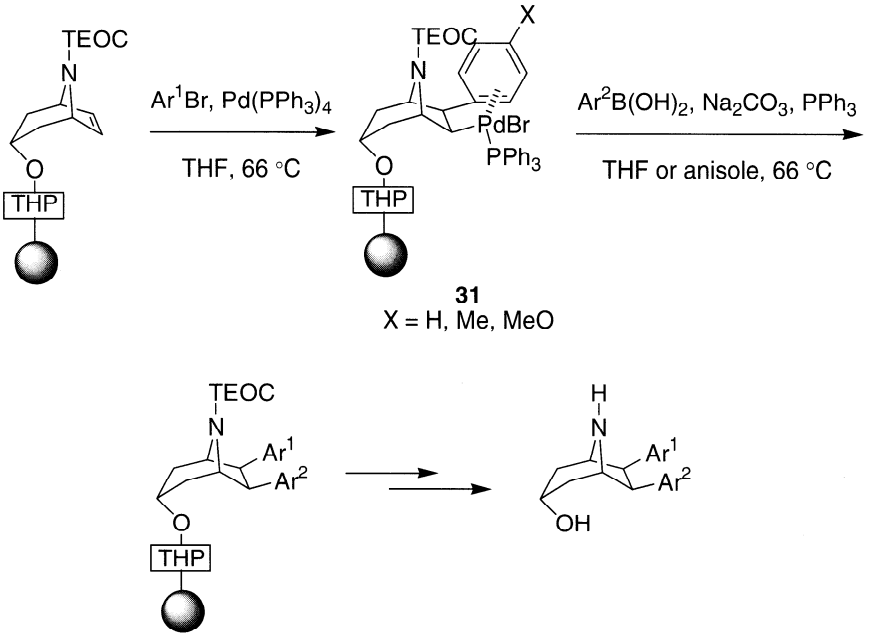


Scheme 34.

prevents formation of palladium black. The suspension is refluxed for 48 h. Complete conversion at this stage was observed using either electron-poor or electron-rich boronic acids. Alternatively, formic acid treatment gave replacement with hydrogen. Another option that was also shown to proceed well was to carry out a coupling to an alkyne using Cu(I) as a co-catalyst.

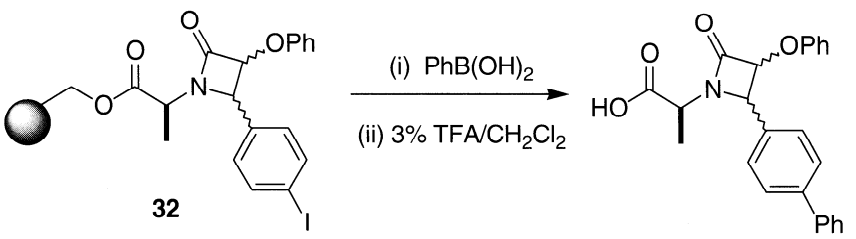
2.4.4. β-Lactam Synthesis

Ruhland et al. used both the Suzuki and Heck (see above) reactions on solid support in their generation of libraries of biaryl- and styryl-substituted β-lactams.[45] A preliminary investigation was performed into the most generally suitable catalytic system for preparation of their libraries. This featured coupling of phenylboronic acid with a resin-bound iodophenyl β-lactam **32** (Scheme 36); the latter compound had been formed from a



Scheme 35.

[2+2] cycloaddition of a phenoxy ketene with a resin-bound aldimine ester. Ambient temperature coupling reactions with these systems would be attractive, but attempts to perform the trial coupling at room temperature with a variety of catalysts failed to reproduce the successful results obtained by Guiles et al. for similar reactions.[75] Successful couplings were achieved with the more usual conditions of heating in DMF with $Pd(PPh_3)_4$, but a tetraarylphosphonium β-lactam resulting from quaternization by the iodo-

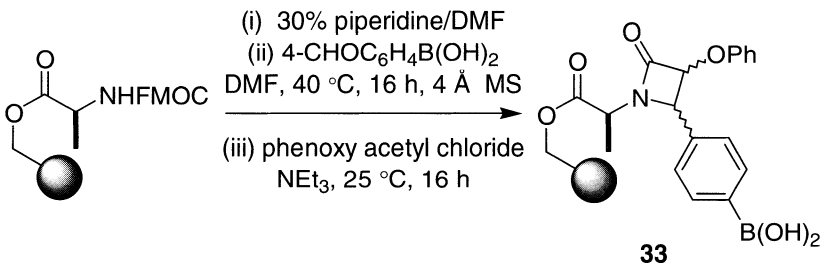


Scheme 36.

phenyl β-lactam of triphenylphosphine was a major by-product. Indeed, this was isolated quantitatively when boronic acid was excluded from the reaction mixture. Use of 20 mol % $PdCl_2(dppf)$ in the presence of excess triethylamine circumvented this problem, and provided an effective system for the coupling of the resin-bound bromide analogue of **32**. Subsequently, six different boronic acids were coupled with the same resin-bound aryl iodide to show tolerance to several functional groups; electron-rich (methoxy-) and electron-poor (nitro-) aryl boronic acids both gave good yields. Different boronic acid regiochemistries were also well tolerated since all three isomers (*o*-, *m*-, and *p*-) of methoxyphenyl boronic acid gave product yields within the range 65–80%. 3-Acetamidophenyl- and 2-thienyl boronic acids were also shown to couple with similar efficacy. Preparative HPLC was used to purify all compounds after cleavage in this study.

A drawback with the strategy depicted in Scheme 36 is the limited commercial availability of boronic acids and esters compared to the corresponding availability of iodides. The synthetic strategy was easily reversed, however, by generating the resin-bound boronic acid **33** by the method shown in Scheme 37. This reaction was observed to proceed with higher yield on ArgoGel-MB-OH, a poly(ethylene glycol)-grafted resin, than on polystyrene-based supports. Polyethylene graft resins presumably facilitate penetration of the polar phenoxyacetyl-chloride-derived ketene intermediate into the resin.

Application of the conditions previously used for the Suzuki coupling of **32** [20 mol % $PdCl_2(dppf)/NEt_3$] gave poor results, while addition of water drove the reaction to completion. Catalyst systems based upon $PdCl_2(dppf)$-NEt_3-DMF-H_2O were found to give good to excellent yields of coupled products when both electron-deficient and electron-rich aryl iodides were used. This reaction could even be performed in the air, a distinct advantage



33

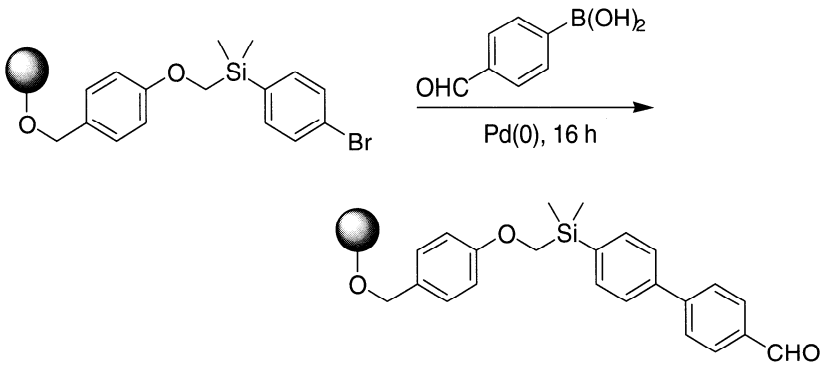
Scheme 37.

for automated synthesis. Perhaps unsurprisingly for a solvent system that includes water, the yields were somewhat dependent upon the choice of solid support. The usual polystyrene supports suffered presumably due to the shrinking effect caused by aqueous mixtures. The overall findings support the intuitive idea that a reversal of polarity in the Suzuki coupling (and indeed any of the organometallic coupling processes) does not necessarily mean a decrease in yield of the reaction. The further use of these same catalyst systems for the Heck reaction has been described above.

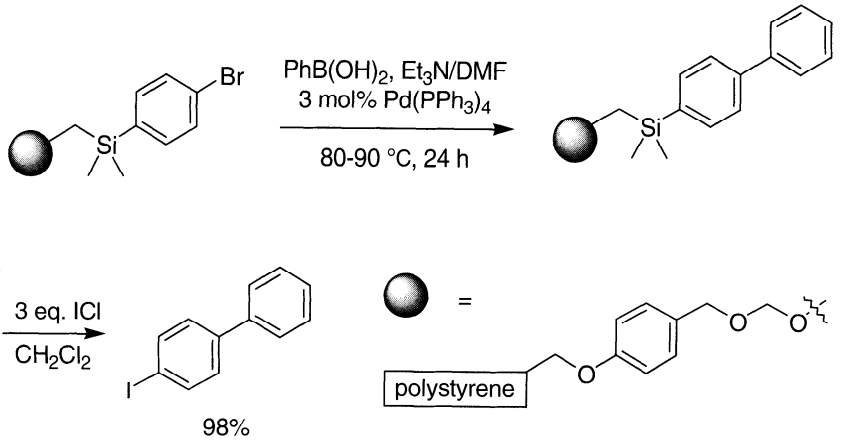
2.4.5. Silyl-Based Synthesis

Veber et al.[88] used Suzuki couplings on a solid support to generate simple biphenyls (Scheme 38), in the presence of a silyl linker, which was cleaved to release these structures without trace of the linkage position.

In a simple strategy to biaryl formation, Han et al.[89] showed that silicon-directed ipso-substitution and concomitant cleavage from supports could be used for formation of functionalized biphenyls. For this they used a tethered silyl aryl bromide in a Suzuki cross-coupling reaction, followed by the ipso-substitution/cleavage step (Scheme 39). A variety of boronic acids were coupled in this manner. The only difficulty occurred with electron-deficient nitrophenylboronic acid where the desired product was formed under anhydrous conditions in only 33% yield (the remainder being starting material). Reversion to the more usual conditions of aqueous base–DME (i.e., those used by Frenette and Friesen)[70] improved the yield to 82%.

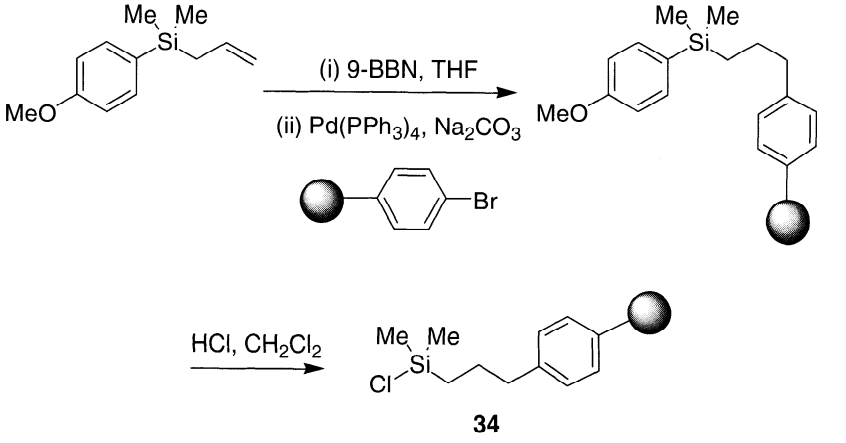


Scheme 38.



Scheme 39.

Ellman used silyl chemistry for the direct linkage of aromatics onto the solid support by converting an aryl bromide to aryl lithium and reacting this with a silyl resin.[90] It is the production of the silyl resin that is of interest in the context of this review, since an in situ Suzuki coupling was used to link the allyl silane to bromomethyl polystyrene resin (Scheme 40). 9-BBN is used to carry out the regioselective hydroboration, and this is linked to the resin with palladium catalysis in the usual way. After brief exposure of this



34

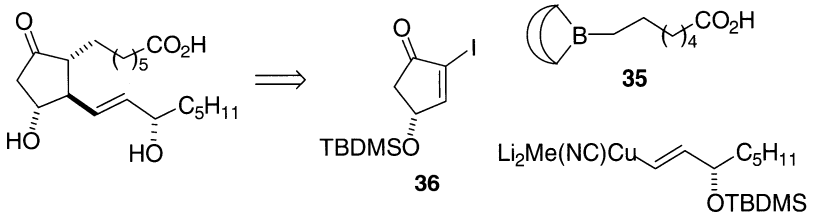
Scheme 40.

resin to an HCl solution in dichloromethane, the resin **34** is activated and ready for loading with lithiated aryls. This chemistry is far simpler than that used by the same group in an earlier paper[62] wherein a similar alkene is hydroxylated using 9-BBN, and then linked to the resin via cyanomethyl 4-hydroxyphenoxyacetate. This direct in situ Suzuki coupling provides a more direct strategy for the attachment process.

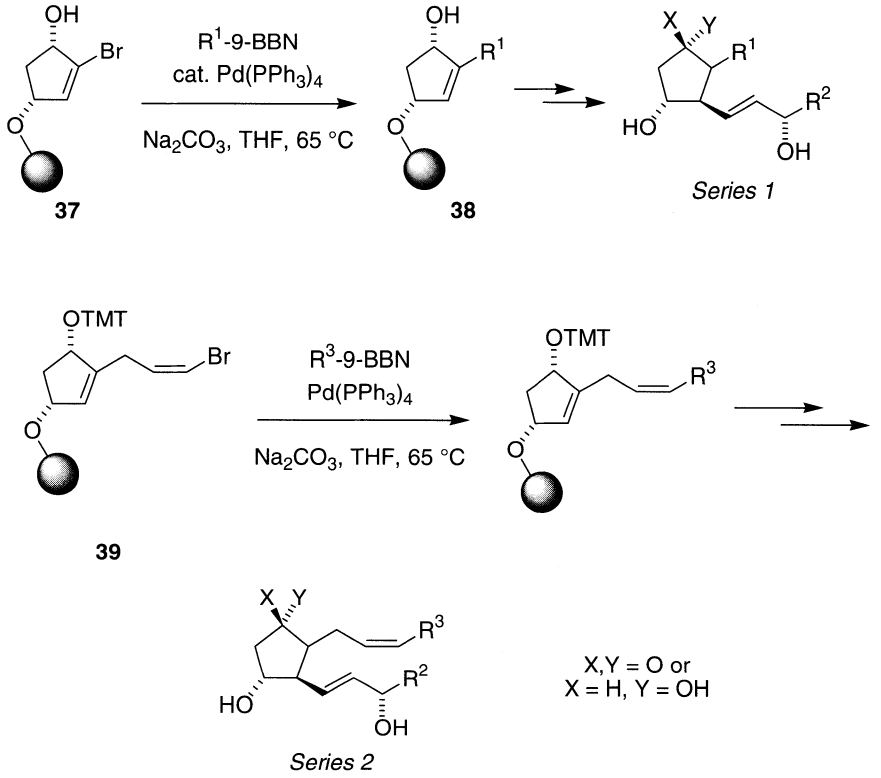
2.4.6. Prostaglandin Synthesis

Ellman utilized the Suzuki coupling twice between a support-bound vinyl bromide and an alkyl 9-BBN derivative in a solid-phase synthesis of E- and F-series prostaglandins.[91] The Suzuki reaction was performed in situ, with the hydroboration of a terminal olefin being followed by the palladium-mediated step. This sequence is attractive in library synthesis because of the wide range of suitable commercially available alkenes. The inspiration behind this chemistry was the solution-phase work of Johnson and Braun,[92] where the couplings of **35** with 2-iodo-4-(silyloxy)cyclopent-2-enone **36** went well at room temperature with $PdCl_2(dppf)$–$AsPh_3$ as catalyst (Scheme 41). The modular chemistry demonstrated in this paper was clearly amenable to adaptation to a solid-phase strategy.

When this approach was used on solid support (Scheme 42), the β-alkoxy ketones resulting from the coupling did not stand up well to the basic, and forcing, conditions required for complete Suzuki coupling. Hence an alternative was investigated in which the supported bromocyclopentenol **37** was coupled with the borane to generate the alkylated derivative **38**, which was then functionalized at the other alkene carbon en route to the series 1 prostaglandins (i.e., with one double bond in the side chain). In a similar way, another core structure **39** was used to generate series 2 prostaglandins. In this route, one cis double bond was introduced at an early stage, and this



Scheme 41.

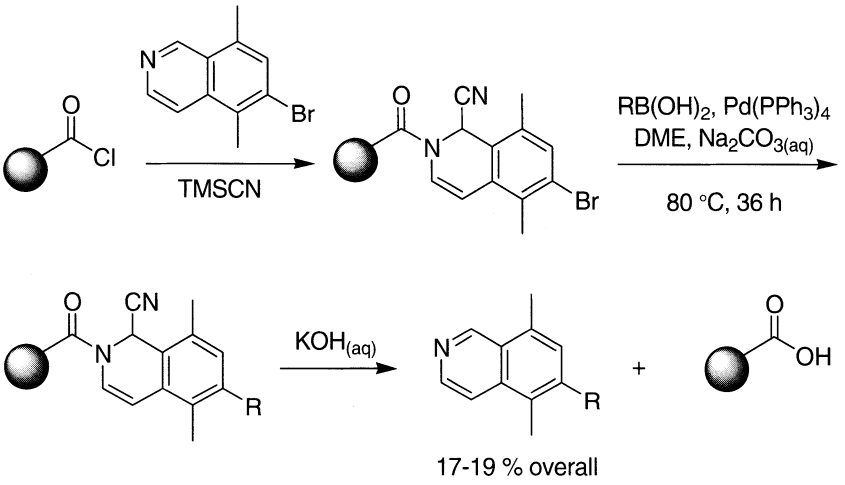


Scheme 42.

was then coupled with alkyl 9-BBN derivatives. Refluxing THF was used for both couplings. No yields are given for the coupling steps, but overall yields for the prostaglandin syntheses range from 49 to 60%, implying that every step was quite efficient. This synthetic scheme illustrated that relatively complex synthetic strategies can be performed reliably on solid supports.

2.4.7. Reissert-Based Synthesis

A solid-phase Suzuki reaction has been described by Kurth et al. in their syntheses of novel isoxazolinoisoquinoline heterocycles via a traceless strategy (Scheme 43).[93] The Suzuki coupling was used as an efficient means to introduce extra diversity into the pharmacophore, and a Reissert-based



Scheme 43.

strategy was used as a resin-capture method for the immobilization of the isoquinoline in the first step of this synthesis. Surprisingly, solution-based Suzuki chemistry was ineffective for coupling boronic acids to 4-bromoisoquinoline (perhaps due to the electron-rich nature of this bromoenamide), but the sequence shown in Scheme 43 produced the desired product in an average yield of 66% per step. The overall yield for the sequence was reported to be significantly lower than from a direct solution-phase Suzuki reaction of 6-bromo-5,8-dimethylisoquinoline. However, the compounds released after the Reissert hydrolysis did not seem to require further purification. In solid-phase syntheses, purity is often more important than yield, especially if the objective is to prepare libraries for biological screens, so the latter result is satisfying in this respect.

2.4.8. Microwave Chemistry

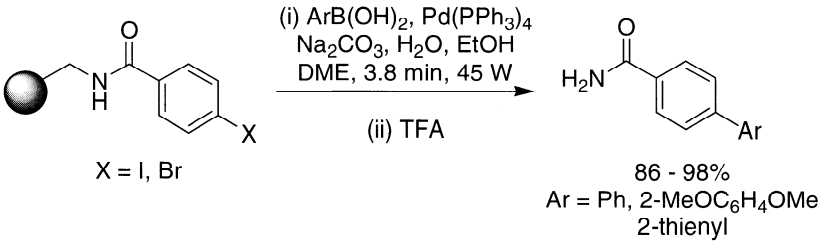
Fluorous phase modifications of the Stille reaction were shown by Curran et al. to be accelerated by microwave irradiation.[10] Similarly, Hallberg et al. demonstrated that such irradiation gives remarkably fast solid-phase Suzuki reactions, in the generation of biaryl units.[9] Their reaction involved the coupling of a tethered (Rink amide TentaGel) aryl iodide or bromide with several boronic acids under 45 W of irradiation at 2450 MHz in sealed

vessels (Scheme 44). The reactions typically gave excellent yields (~95%) in 3.8 min. Little reactivity difference was observed between the aryl iodides and bromides, in contrast to the solution-phase reactions where the rate differences for these two substrates are significant. A simple Stille coupling with tributylphenyl tin was also reported to give 85% yield of product, with no apparent butyl transfer. Minimal decomposition of the resin polyethylene glycol was observed as a result of the microwave irradiation. The reactions could conveniently be performed on a very small scale in sealed Pyrex tubes, and a KCN–DMSO wash was used to remove precipitated palladium black.

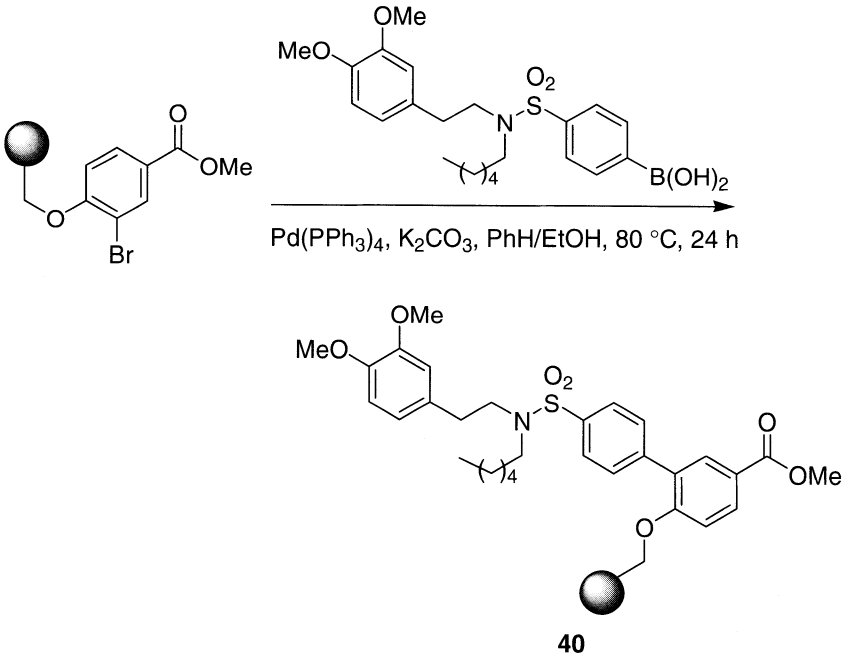
2.4.9. Miscellaneous Uses of the Suzuki Reaction

Sarkar et al.[94] constructed the relatively complicated structure **40** (Scheme 45) on a solid support by using a Suzuki coupling. The objective of this work was to demonstrate the efficacy of spin echo MAS ^{1}H NMR spectroscopy for gauging reactions on solid supports. The coupling was performed successfully under standard conditions, and a KCN in DMSO wash was used to remove adsorbed palladium after the reaction.

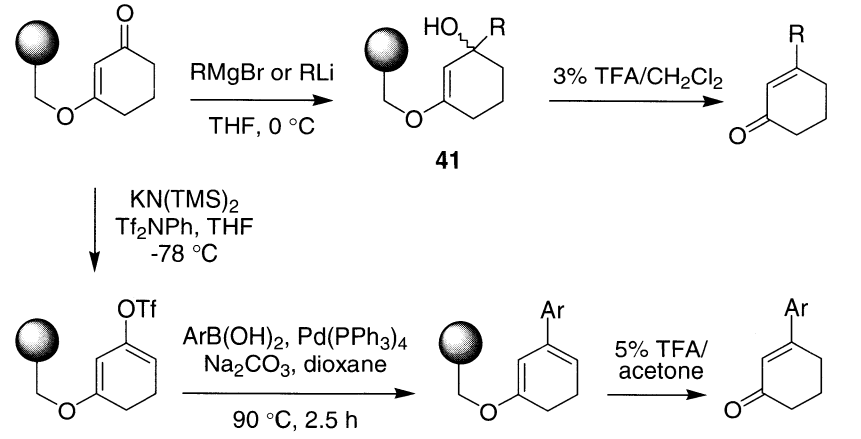
Grignard reactions of a resin-bound 1,3-cyclohexanedione have been shown to proceed in good to moderate yields (Scheme 46).[95] Moreover, the purity of the TFA-cleaved product was excellent, possibly because the addition product **41** is more sensitive to acid than the starting dione. Lower yields were produced from secondary organometallic reagents, however. This led to the investigation of the effectiveness of Suzuki couplings of the resin-bound vinyl triflate with a range of commercially available boronic acids to produce similar products. The Suzuki reaction is therefore used here as an alternative to Grignard-type processes for carbon–carbon bond formation. This work included an early example of the use of vinyl triflates



Scheme 44.



Scheme 45.



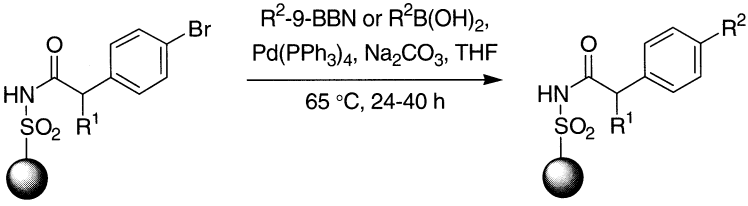
Scheme 46.

in solid-phase Suzuki reactions. Deoxygenated dioxane was used with $Pd(PPh_3)_4$, and the boronic acids were used in sevenfold excess under an inert atmosphere at 90°C for only 2.5 h. While the yields of these processes were only good to poor, the purities of the cleaved material was greater than 95% as judged by HPLC. Thus both methods can be used, but their applicability with respect to different coupling partners (e.g., alkyl vs. aryl/vinyl) varies.

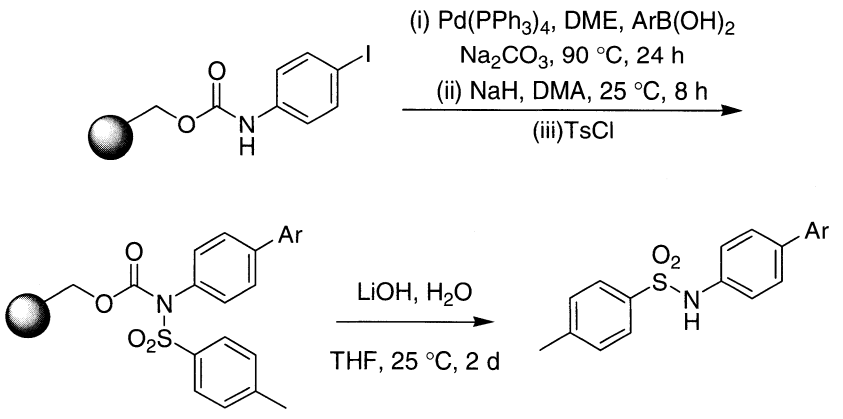
The Suzuki reaction was used in Ellman's report of a safety-catch linker based around Kenner's acylsulfonamide,[96] to introduce an aromatic site of diversity in a library based on the phenylacetic acid skeleton. The products were used for the generation of compounds useful in the inhibition of cyclooxygenase (Scheme 47). Mildly basic reaction conditions in the Suzuki reaction are well suited to this transformation since this prevents the protonation of the safety-catch linker. Good yields were seen in all cases using both arylboronic acids and also alkyl 9-BBN derivatives. Interestingly, whereas THF gave good results, DME enhanced the precipitation of palladium black in the resin. This was a significant concern because Pd(0) catalytically decomposes diazomethane, and this was the reagent used for activation of the linker prior to cleavage.

Raju and Kogan demonstrated the synthesis of simple, diverse sulfonamides using a new carbamate linker.[44] They also showed that the Suzuki reaction could be used for convenient introduction of diversity in their solid-phase synthesis. The three-step sequence is shown in Scheme 48. The purities of the cleaved compounds are good, but the sequence yields are low (32–33%).

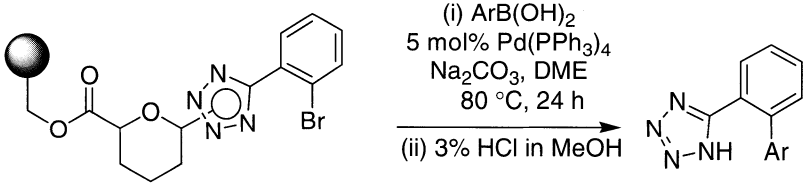
Yoo et al.[97] used the solid support not only as a tether for the synthesis of biphenyltetrazole derivatives, but also as a protecting group for the acidic tetrazole moiety. The latter functionality was prevented from interfering with subsequent chemistry. Specifically, a support-bound dihydropyran was



Scheme 47.



Scheme 48.

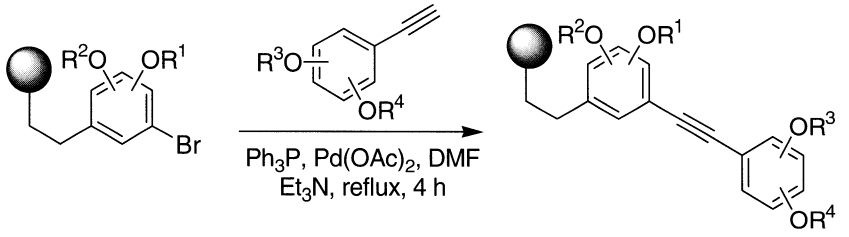


Scheme 49.

used which is carboxylate reminiscent of Ellman's THP linker for the immobilization of alcohols.[98] The palladium-catalyzed reaction (Scheme 49) coupled a tethered *ortho*-bromo tetrazole and phenyl or tolyl boronic acid. After cleavage, the yield was 53–57% for the two steps. Biphenyltetrazole is a pharmacophore of interest in the field of angiotensin II receptor antagonists.[99,100]

2.5. MISCELLANEOUS REACTIONS

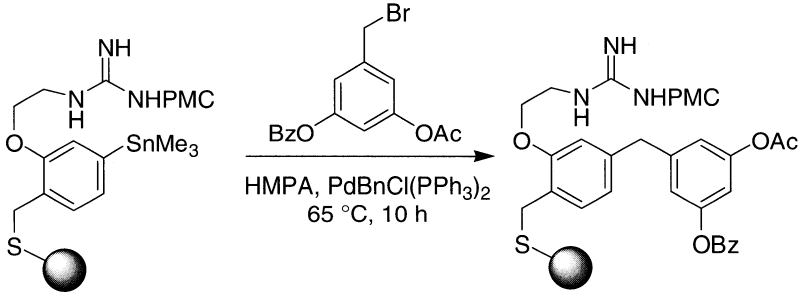
Sphinx Pharmaceuticals[101] patented successful Stille (with a resin-bound organostannane) and Suzuki (with a supported boronic acid) cross-couplings. In the same patent, they also reported a coupling of a phenylacetylene with a resin-bound bromide wherein $Pd(OAc)_2$ was the catalyst (Scheme 50).



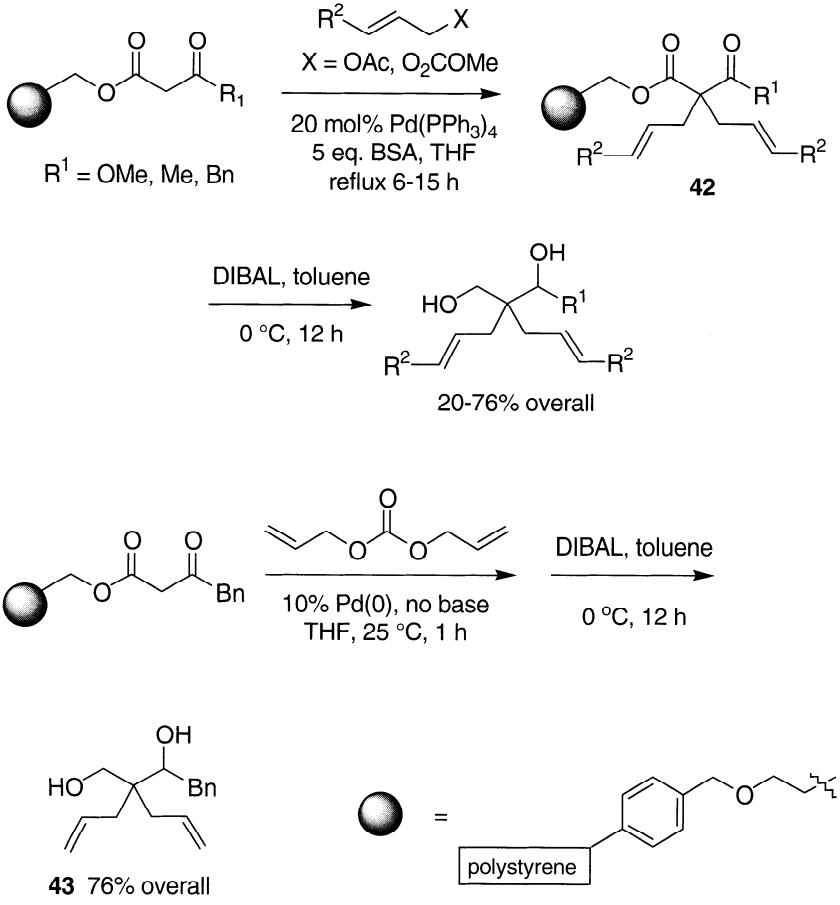
Scheme 50.

Coupling of a benzyl bromide and a resin-bound stannane in the presence of a protected guanidine (Scheme 51), en route to solid-phase synthesis of bradykinin antagonists, is also reported in this patent.[101]

Palladium-catalyzed allylic substitution has been demonstrated recently.[102] Polymer-bound malonates and acetoacetates were alkylated with allylic acetates using $Pd(PPh_3)_4$ as catalyst (Scheme 52). Palladium-catalyzed carbon–nitrogen bond formation between a support-bound secondary amine and two bis-allylic templates had been shown previously.[103] The products **42** were cleaved from the resin with DIBAL to give the diols in low to moderate yield. The polymer-bound β-keto esters displayed high reactivity, with dialkylation being observed under these conditions. Monoalkylation was only seen with more sterically hindered acetates (such as cyclic allylic acetates), and allylic chlorides (using one equivalent of BuLi as base). When an allylic carbonate, diallyl carbonate, was used, no addition of base was necessary since the leaving group carbonate decarboxylates to generate an alkoxide which may itself act as a base. The yield from this reaction (76% of **43**) was the highest obtained in the study. The



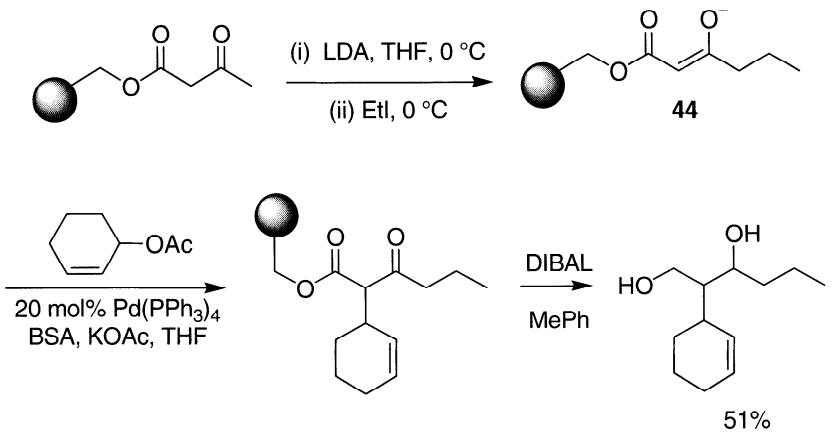
Scheme 51.



Scheme 52.

reaction was performed with less palladium (10 mol %) and at room temperature for only 1 h.

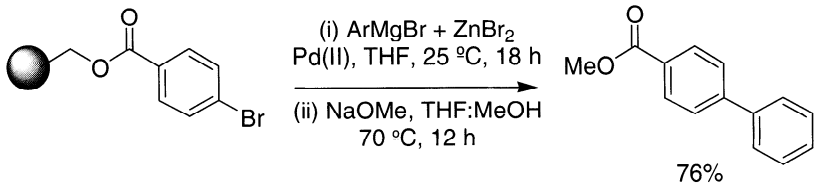
Combination of the work described above with prior studies by the same group on γ-alkylation of polymer-bound acetoacetate (with LDA and an alkylating agent such as iodoethane) enabled the monoanion **44** (Scheme 53) to be used for allylic alkylation under palladium catalysis. This allows the one-pot regioselective dialkylation of acetoacetate in 51% yield for the four-step process, including reductive cleavage. This method does suffer from the slight disadvantage inherent in such a dianion strategy that, unlike



Scheme 53.

most solid-phase reactions, excess reagents may not be used for the first alkylation.

Another solution to the limited availability of boronic acids is derivatization of a halide before the palladium-catalyzed coupling with another, support-bound halide. For example, palladium-catalyzed coupling of support-bound aryl bromides with zinc organometallics to form a number of biaryls was reported (Scheme 54).[104] The protocol is simplified by the in situ preparation of the organozinc, followed by the immediate addition of the resin. Catalytic $PdCl_2(dppf)$, $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, and $PdCl_2(P(o\text{-}tol)_3)_2$ were all found to be highly effective, with the Pd(II) catalysts presumably generating the required Pd(0) in situ. Moderate to good yields were obtained when the reaction was performed at ambient temperature over 18 h. Meta- and ortho-substituted aryl bromides gave similar results. Transesterification was successfully used to cleave product from the resin.



Scheme 54.

After completion of this chapter, Snieckus et al. published examples of the solid-phase Stille[105] and Suzuki[106] reactions in which were included stannanes and boronic acids synthesized in solution via a directed ortho metalation procedure,[107] ultimately allowing for the construction of a range of tricyclic structures.

2.6. CONCLUDING REMARKS

Palladium-catalyzed transformations greatly enhance the scope of solid-phase synthetic chemistry. A number of fundamental pharmacophores are accessible through a variety of reliable manipulations that may be performed in high yield under mild conditions. This area continues to grow, as solution-phase chemistry is adapted to provide better methods for carbon–carbon bond formation in combinatorial chemistry. We view these advances as central to the field and look forward to future developments.

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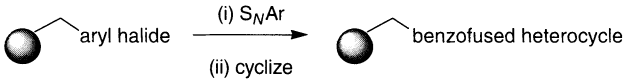
CHAPTER 3

BENZOFUSED HETEROCYCLES VIA SOLID-PHASE S_NAR REACTIONS



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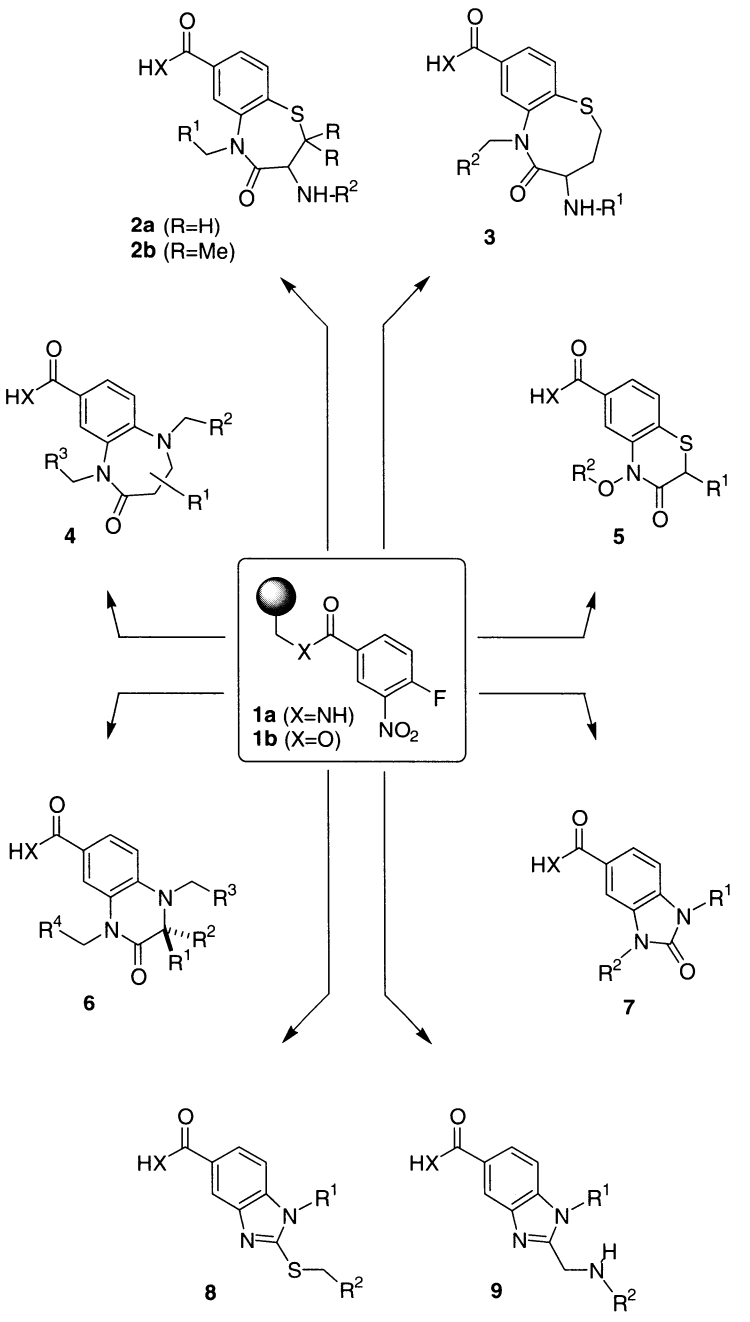
3.1. INTRODUCTION

Future historians of organic chemistry may ultimately chronicle the 1990s as the decade in which shaded spheres (symbolizing polymeric resins) graced the pages of virtually every synthetic journal as reagents *de rigeur*. This sudden interest in solid-phase organic synthesis has mainly been fueled by the widespread application of combinatorial technologies in pharmaceutical discovery and is reflected in an almost exponential growth in the number of publications cataloging reaction types compatible with substrates immobilized on insoluble polymeric supports.[1–3]

In drug discovery there are principally two useful library formats. The first may be called "primary libraries" for use in high-throughput screening, where a priori no specific structure or substructure is obligatory as a starting point. Conversely, "focused (or biased) libraries" are purposefully constructed around a known starting structure having biological activity, to be used in optimizing the activity (or other properties) of the lead compound.

Our group has recently been particularly interested in primary libraries from which pharmaceutically attractive lead molecules might hopefully be found. One goal has been to assemble a portfolio of small-molecule libraries to be used in initial lead discovery against a broad panel of emerging and proven pharmaceutical targets. Relying exclusively on solid-phase methods, we have tried to achieve a blend between generating (i) scaffolds with proven pedigree in medicinal chemistry (e.g., β-lactams, benzodiazepines); (ii) other templates densely packed with functional groups that have received less systematic investigation; and (iii) "novel," unexplored chemotypes. Among questions of significant interest are the relative merits of screening numerous libraries of moderate size (say 10,000–50,000 members) comprising many different template structures, versus screening numerically larger libraries (>>100,000 members) of a limited selection of chemotypes.

Experience has shown that the most time-consuming steps in library synthesis typically involve demonstrating the feasibility of generating a particular central core structure on solid support as well as rehearsing the compatibility of variously functionalized monomers with the synthetic scheme. The assembly of a highly diverse library portfolio based on different central scaffolds is, therefore, bound to involve a significant investment in terms of time and manpower. With this in mind, it is attractive to consider synthetic strategies that provide access to multiple, structurally diverse core structures starting from common, fundamental intermediates and to use similar sequences of synthetic transformations in conjunction with the appropriate monomer inputs. One such intermediate is the imine, and we have previously described its exploitation in a variety of solid-phase cycloaddition and condensation reactions.[3] Another example of a versatile synthon is 4-fluoro-3-nitrobenzoic acid **1**. We and other groups have now shown that a variety of benzofused heterocycles can be derived from resin-bound 4-fluoro-3-nitrobenzoic acids **1a**,**b** via solid-phase nucleophilic aromatic substitution (viz. S_NAr) reactions with either sulfur or nitrogen nucleophiles (Scheme 1).



Scheme 1.

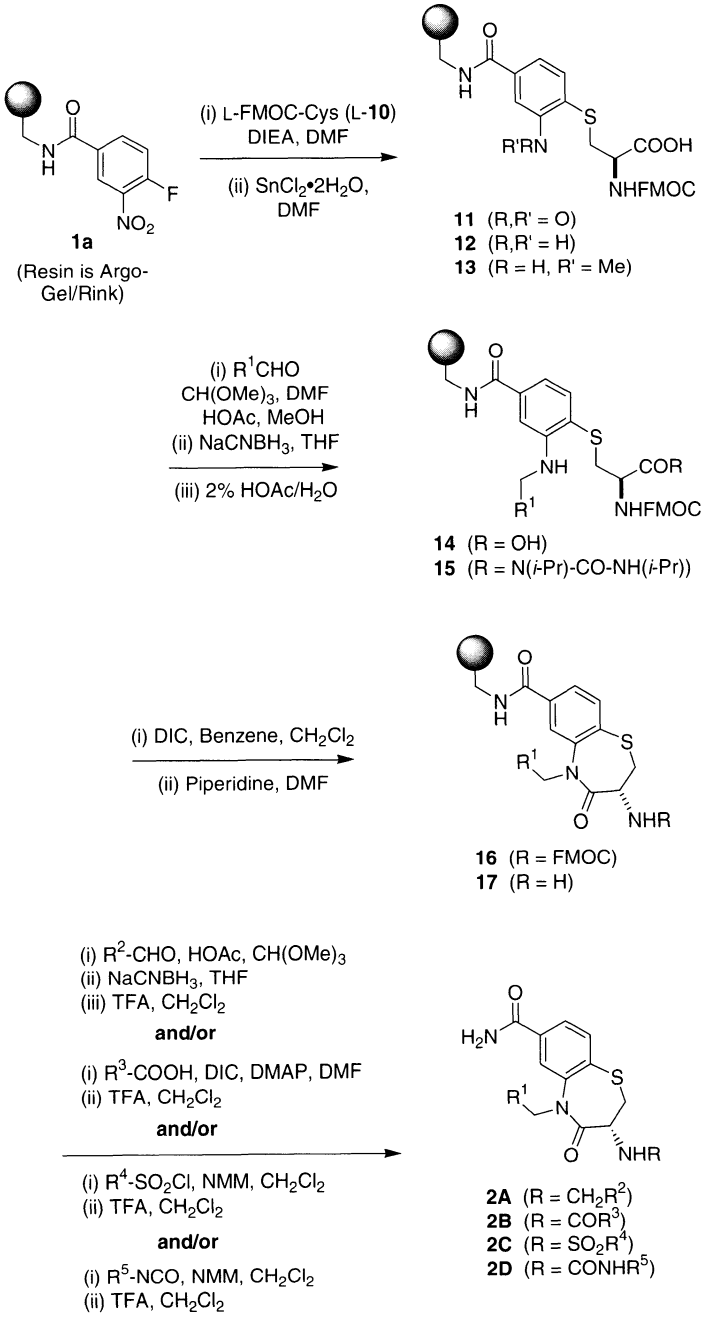
This chapter will give an account of work performed to date in this area, covering solid-phase syntheses of 1,5-benzothiazepin-4-ones **2a**,**b**,[4] 1,6-benzothiazocin-5-ones **3**,[5] 1,5-benzodiazepin-2-ones **4**,[6,7] 4-alkoxy-1,4-thiazin-3-ones **5**,[5] quinoxalin-2-ones **6**,[5,8,9] benzimidazolones **7**,[10] 2-alkylthiobenzimidazoles **8**,[11] and 2-alkylaminomethylbenzimidazoles **9**.[12]

3.2. FORMATION OF [6,7]- AND [6,8]-FUSED SYSTEMS

3.2.1. 1,5-Benzothiazepin-4-ones (2) and 1,6-Benzothiazocin-5-ones (3)

Along with the dihydropyridines (e.g., nifedipine) and phenylalkylamines (e.g., verapamil), 1,5-benzothiazepin-4-ones (e.g., diltiazem) are among the most widely used drugs in the treatment of cardiovascular disorders. They are calcium antagonists interacting with the L-type voltage-gated Ca^{2+} channel.[13,14] Many solution-phase protocols for synthesis of 1,5-benzothiazepin-4-ones can be found in the literature,[15] but no solid-phase synthesis has been reported to date. We envisaged a synthetic approach to 1,5-benzothiazepinones **2a** that involved nucleophilic aromatic substitution reactions on solid support, in which the basic benzothiazepine skeleton was to be assembled from a resin-bound 4-fluoro-3-nitrobenzoic acid **1** and a suitably protected form of cysteine (Scheme 2).[4]

Exposure of **1a** to a solution containing 1.5 equivalents of Fmoc-L-cysteine **10** and DIEA in DMF[16] resulted in smooth conversion to the 2-nitro-thioether **11**, which was subsequently reduced to the corresponding primary aniline **12** using $SnCl_2 \cdot 2H_2O$ in DMF.[17] In accordance with literature data,[18] the subsequent reductive alkylation of **12** proved to be problematic due to the poor nucleophilicity of the aniline nitrogen as compared with that of aliphatic amino groups. Particularly low yields were obtained for aromatic aldehydes bearing electron-donating and/or ortho substituents, as well as for aliphatic aldehydes. After extensive optimization, conditions were identified where resin **12** was reacted with a large molar excess of aldehyde in a mixture of trimethylorthoformate,[19,20] DMF, MeOH, and acetic acid at 50°C. Using this protocol, a variety of aromatic aldehydes cleanly afforded the corresponding secondary anilines **14** (Figure 3.1). The only significant side product occasionally present in minor amounts (5–10%) was the *N*-methyl-aniline **13**, arising from incorporation of the


(i) L-FMOC-Cys (L-10)
DIEA, DMF
(ii) $SnCl_2 \cdot 2H_2O$,
DMF
1a
(Resin is Argo-Gel/Rink)
11 (R,R' = O)
12 (R,R' = H)
13 (R = H, R' = Me)
(i) R^1CHO
$CH(OMe)_3$, DMF
HOAc, MeOH
(ii) $NaCNBH_3$, THF
(iii) 2% $HOAc/H_2O$
14 (R = OH)
15 (R = N(i-Pr)-CO-NH(i-Pr))
(i) DIC, Benzene, CH_2Cl_2
(ii) Piperidine, DMF
16 (R = FMOC)
17 (R = H)
(i) R^2-CHO, HOAc, $CH(OMe)_3$
(ii) $NaCNBH_3$, THF
(iii) TFA, CH_2Cl_2
and/or
(i) R^3-COOH, DIC, DMAP, DMF
(ii) TFA, CH_2Cl_2
and/or
(i) R^4-SO_2Cl, NMM, CH_2Cl_2
(ii) TFA, CH_2Cl_2
and/or
(i) R^5-NCO, NMM, CH_2Cl_2
(ii) TFA, CH_2Cl_2
2A (R = CH_2R^2)
2B (R = COR^3)
2C (R = SO_2R^4)
2D (R = $CONHR^5$)

Scheme 2.

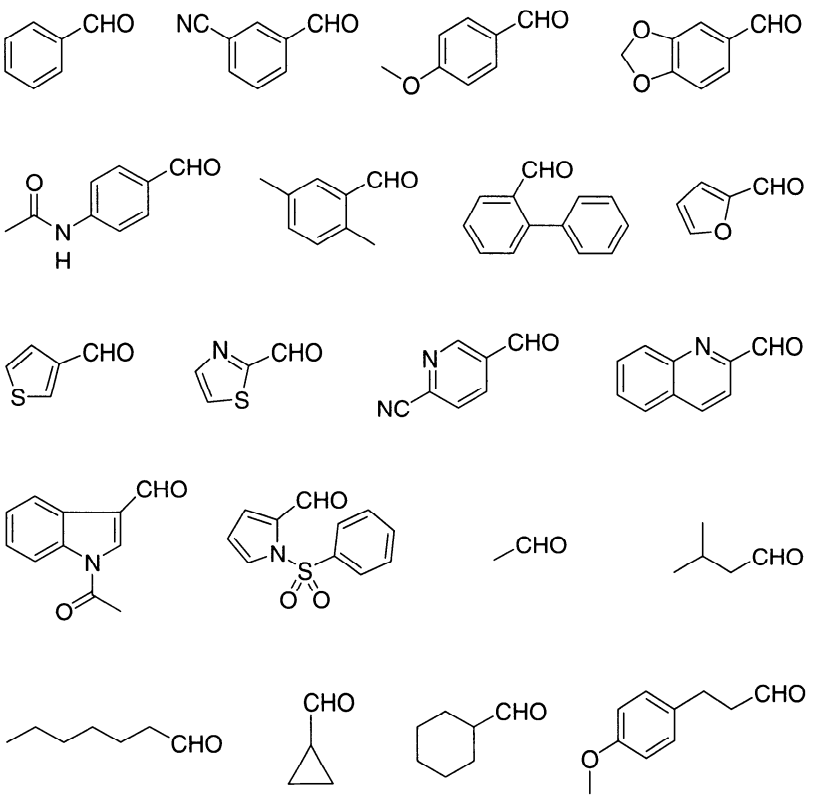
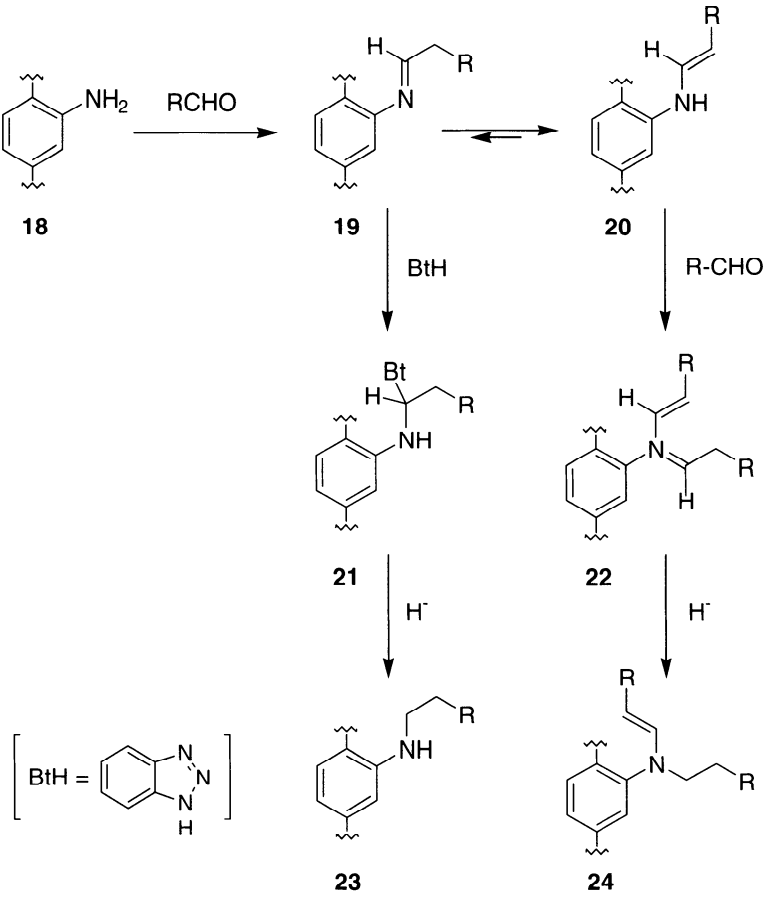


Figure 3.1. Selection of aldehydes R^1CHO successfully used in the reductive alkylation of primary aniline **12**.

methine-carbon of the orthoformate.[21,22] Electron-rich aldehydes, such as *N*-alkylamino-benzaldehydes and *N*-methylated indole- and pyrrole-carboxaldehydes, however, failed to afford any of the desired secondary anilines.

In contrast to aromatic aldehydes, aliphatic aldehydes invariably afforded complex mixtures of products when submitted to the above conditions. Based on their molecular weights, a few products could tentatively be identified as dialkylated, as well as dehydrodialkylated, compounds, such as **24**. These perhaps were derived from tautomerization of the initially formed imine **19** to the thermodynamically more stable enamine **20** followed by reaction with a second aldehyde molecule and subsequent reduction (Scheme 3).



Scheme 3.

To suppress enamine-derived side products, we explored addition of benzotriazole (BtH) to the reaction mixture. The premise behind these experiments was the ability of BtH to form stable adducts with imines,[23,24] thereby blocking tautomerization of **19** to **20** through in situ formation of the benzotriazolyl derivative **21**. It was hoped that subsequent hydride displacement of the Bt moiety would afford the desired mono alkylated products **23**. Indeed, analytical high-performance liquid chromatography (HPLC) revealed a remarkable improvement in terms of product purity, especially for reactions carried out at room temperature, with the desired secondary anilines **23** being essentially the only products detected. In

further studies, the benzotriazole-mediated suppression of enamine-derived side-product formation was shown to be of broad scope. However, enamine-derived side products were still observed for reactions with phenylacetaldehyde or, more markedly, with diphenylacetyldehyde, where the driving force for tautomerization is particularly strong. Figure 3.1 displays a representative selection of aldehydes that were successfully employed in the reductive alkylation step using the optimized conditions outlined above.

With a variety of secondary anilines **14** in hand, formation of the seven-membered thiazepine ring was attempted using a selection of common coupling reagents, including HATU/DIEA, DIC/HOBt, DIC/DMAP, and EDC, as well as some non-carbodiimide-type reagents, such as DECP and Mukaiyama's reagent. It was found that only DIC solutions in solvents of low polarity, such as benzene and/or CH_2Cl_2, and devoid of additives like HOBt or DMAP were able to furnish the desired *N*(5)-alkylated benzothiazepinones **16** (Scheme 2). Use of polar solvents like DMF or NMP resulted in formation of considerable amounts (20–50%) of the corresponding *N*-acylureas **15** as side products.[25,26] Moreover, it was imperative that the resin **14** resulting from reductive alkylation be subjected to a wash with aqueous acetic acid (2% v/v) prior to cyclization. Omitting this washing step completely inhibited cyclization of the secondary anilines **14**; under the reductive alkylation conditions, the carboxyl function in **14** had been converted into its sodium salt, which was unreactive toward carbodiimide-type reagents. Gratifyingly, the newly established cyclization conditions proved to be of wide generality, allowing essentially all secondary anilines **14** to be smoothly converted to the corresponding *N*(5)-substituted 1,5-benzothiazepinones **16**.

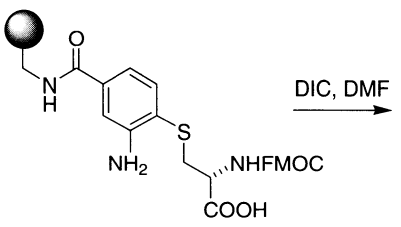
The remaining steps completing the synthetic sequence featured manipulation of the exocyclic amino group of the 1,5-benzothiazepinone template. This included Fmoc removal from **16** and treatment of the resulting primary amines **17** with aldehydes, carboxylic acids, sulfonyl chlorides, and/or isocyanates to generate, upon cleavage from resin, the corresponding secondary amines **2A**, amides **2B**, sulfonamides **2C**, and/or ureas **2D**, respectively (Scheme 2). These four transformations reliably afforded the desired 3,5-disubstituted 1,5-benzothiazepin-4-ones in high purities and yields, showing full compatibility with all types of functional groups examined. In subsequent studies, we demonstrated that the solid-phase assembly of benzothiazepinones according to Scheme 2 proceeded without racemization at the α-carbon atom.[4]

We have previously described how chemical-encoding strategies can facilitate identification of bioactive compounds from large combinatorial libraries.[27,28] Compatibility of our dialkylamine encoding method with the 1,5-benzothiazepinone synthesis has been established through model studies. The extra steps devoted to the introduction of the chemical codes were shown not to adversely affect the purity of the 1,5-benzothiazepinone compounds.[4] We have used this chemistry to generate a number of large encoded 1,5-benzothiazepinone libraries for high-throughput screening.

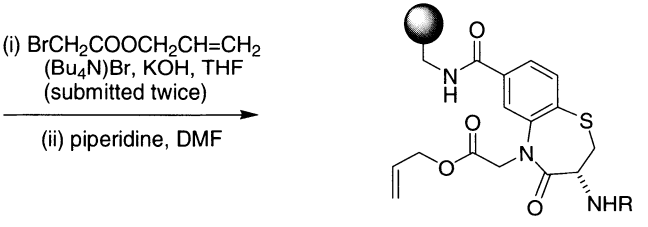
In an attempt to extend the scope and the diversity of the benzothiazepinone chemistry on solid support, we explored the possibility of alkylating *N*(5) *after* formation of the seven-membered ring (Scheme 4). This sequence is known in solution-phase chemistry, albeit with a different protecting group strategy for the α-amino group.[29] In contrast to the secondary anilines **14** derived from reductive alkylation of **12**, the cyclization of the primary aniline **12** was found to proceed smoothly under a variety of common amide-bond-forming conditions. After cyclization of the primary aniline **12** using DIC in DMF, the resulting *N*(5)-unsubstituted benzothiazepinone **25** was subjected twice to phase-transfer alkylation conditions using allyl-bromoacetate, Bu_4NBr, and KOH powder in THF, to afford the orthogonally protected intermediate **26** (Scheme 4). We were surprised to find that the Fmoc-protecting group was stable under the phase-transfer alkylation conditions. Fmoc deprotection, followed by acylation of the primary amino group and Pd(0)-catalyzed cleavage of the allyl ester function furnished acids **29**, which were reacted with primary and/or secondary amines in the presence of DECP in DMF to afford the corresponding amides **30** upon cleavage from the resin. Again, the high optical purity of these compounds was established by HPLC analysis.

Having thus demonstrated the feasibility of two solid-phase routes affording 3,5-disubstituted 1,5-benzothiazepin-4-ones **2A-D** (Scheme 2) or of the molecular type **30** (Scheme 4), we now attempted to further generalize the scope of the synthetic strategy. Interchanging Fmoc-cysteine **10** for Fmoc-penicillamine **31** and Fmoc-homocysteine **32** should potentially provide access to 2,2-dimethyl-1,5-benzothiazepin-4-ones **2b** and 1,6-benzothiazocin-5-ones (**3**), respectively. Gratifyingly, both routes could be enabled almost without any additional chemistry optimization work (see Scheme 5).

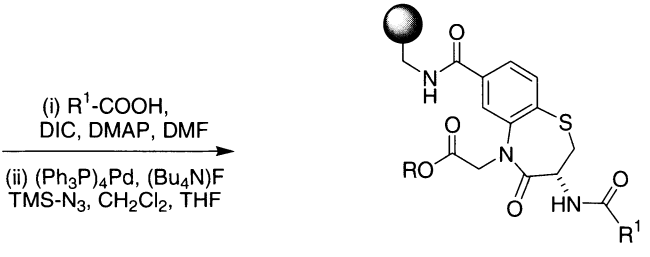
In the case of **31**, slightly harsher conditions were required to drive the nucleophilic aromatic substitution to completion, so the reaction was car-



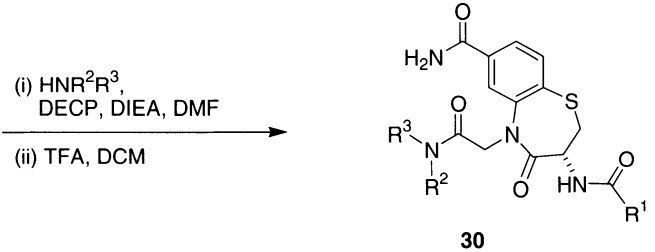
12 25



26 (R = FMOC)
27 (R = H)

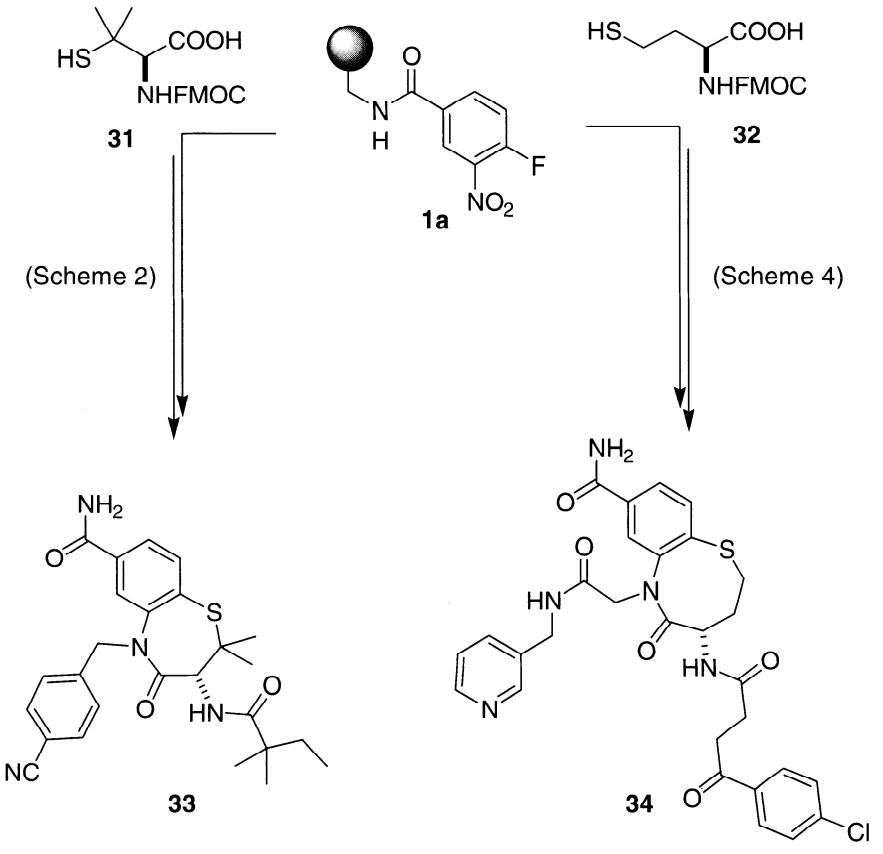


28 (R = $CH_2CH{=}CH_2$)
29 (R = H)



30

Scheme 4.



Scheme 5.

ried out at 40–45°C instead of 25°C. All remaining steps of the synthetic route summarized in Scheme 2 (reductive alkylation route) proceeded smoothly under the conditions previously optimized for Fmoc-cysteine. The same held true when **31** was employed in the alternative synthetic sequence depicted in Scheme 4 (amide alkylation route). Compound **33** is a representative 2,2-dimethyl-1,5-benzothiazepin-4-one synthesized via the reductive alkylation route (Scheme 5).

In the case of the series derived from homocysteine **32**, the critical transformation proved to be formation of the eight-membered ring. This was successful only if the aniline nitrogen was present in its nonalkylated form. Thus the synthetic efforts were restricted to the amide alkylation

route, which furnished novel 1,6-benzothiazocin-5-ones such as **34**, though in somewhat lower purity than typically observed for the benzothiazepine series.

In summarizing this section, two efficient, high-yielding solid-phase routes to 3,5-disubstituted 1,5-benzothiazepin-4(5*H*)-ones (**2a**) from resin-bound 4-fluoro-3-nitrobenzoic acid **1a** and Fmoc-cysteine **10** were developed, amenable to both the synthesis of discrete, optically pure compounds and the generation of large encoded libraries. In one scenario, alkylation of *N*(5) was effected prior to cyclization, using aldehydes under highly optimized reductive alkylation conditions, and involved use of benzotriazole in cases of enolizable aliphatic aldehydes. In the second approach, the *N*(5) substituents were introduced after formation of the seven-membered ring using phase-transfer amide alkylation conditions. In subsequent experiments, the underlying synthetic strategy was extended to the synthesis of related structures, such as 2,2-dimethyl-1,5-benzothiazepin-4-ones **2b** and 1,6-benzothiazocin-5-ones **3**.

3.2.2. 1,5-Benzodiazepin-2-ones (4)

Given their impressive therapeutic activities, it is not surprising that benzodiazepines were among the first small molecules to be synthesized on solid support.[30] The main synthetic interest, however, has so far focused on 1,4-benzodiazepin-2-ones[31–33] and 1,4-benzodiazepin-2,5-diones,[34–38] with 1,5-benzodiazepin-2-ones having received little attention.[39] It was therefore opportune to explore the possibility of extending the strategy outlined in Section 3.2.1 to include synthesis of benzodiazepinones **4**. We envisaged that this could be done by substituting the β-mercapto acid nucleophiles (cysteine, penicillamine) with β-amino acids. Information in the literature suggested that solid-phase S_NAr reactions with nitrogen nucleophiles were possible.[40–42] These reactions typically use DMF or NMP as solvents and, occasionally, DIEA as an auxiliary base.[42]

Preliminary experiments using β-amino acids as S_NAr nucleophiles showed that they either completely failed to react or afforded product mixtures, due to their poor solubility in nonaqueous solvents. β-Amino acid esters, on the other hand, are readily soluble in DMF, but only a few are commercially available. In this section, two different approaches are described that have successfully circumvented these problems. The key features are (i) a novel aqueous solvent system allowing the use of free α- and

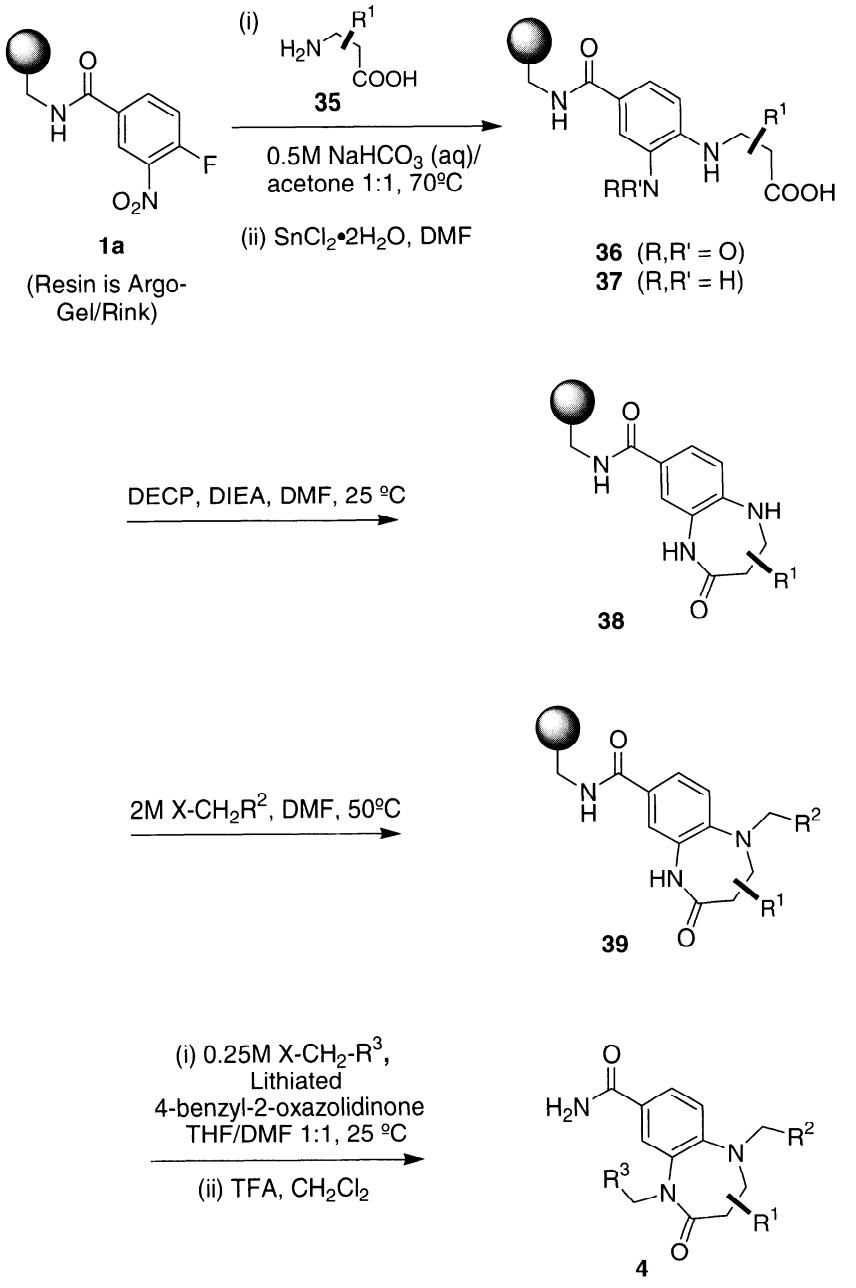
β-amino acids for solid-phase S_NAr reactions[5,6] and (ii) an efficient solution-phase synthesis to augment the number of β-amino acid esters available.[7]

Our approach was based on the observation that it is possible to perform S_NAr reactions on solid support with amino acids using a solvent system comprised, in equal parts, of acetone and an aqueous 0.5 M $NaHCO_3$ solution at temperatures around 70–75°C. Application of this solvent system to the synthesis of quinoxalin-2-ones **6** from **1a** and α-amino acids is described in Section 3.3.2. With respect to the synthesis of 1,5-benzodiazepin-2-ones **4**, more than 40 examples of aliphatic and aromatic β-amino acids **35** were found to furnish the desired *o*-nitro anilines **36**, about 80% of which were successfully carried on to eventually afford the benzodiazepinone products **4** (Scheme 6). In general, the anthranilic acids required slightly harsher conditions to drive the fluorine displacement to completion (75–80°C, 72 h vs. 70–75°C, 24 h for aliphatic β-amino acids).

Subsequent reduction of the nitro group with $SnCl_2 \cdot 2H_2O$ in DMF afforded the corresponding di-anilines **37**, along with varying amounts of the cyclic intermediates **38**, depending on the nature of the substituents derived from the β-amino acids (R^1). The partial formation of the seven-membered ring was then driven to completion using DECP and DIEA in DMF. Notably, all other cyclization conditions examined failed, including heating **37** in the absence of reducing agent or treatment with the carbodiimide-type reagents previously found successful in the benzothiazepine series (see Section 3.2.1).

Alkylation at *N*(5) of the cyclic intermediates **38** was accomplished using concentrated solutions of alkyl halides in DMF at 50°C. Addition of a base proved not only unnecessary but even counterproductive in terms of the purity of the resulting *N*(5)-substituted benzodiazepinones **39**. Alkyl halides producing good results in this reaction include more than 40 benzyl bromides, allyl bromide, various esters of bromoacetic acid, as well as methyl and ethyl iodide. Other alkyl iodides, along with benzyl chlorides and α-bromo acetophenones, however, did not give satisfactory results.

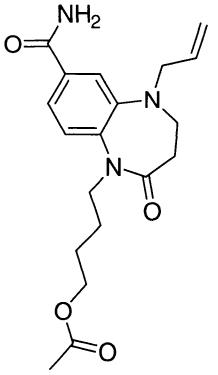
The final alkylation at *N*(1) of **39** was accomplished using alkyl halides and lithiated 4-benzyl-2-oxazolidinone as a base.[30,31] The halides used for *N*(5)-alkylation were also found suitable for *N*(1)-alkylation, with the notable expansion to include other alkyl iodides beyond methyl and ethyl iodide. From the spectroscopic data of the final products **4**, and in agreement with literature data in similar systems,[30,31] no evidence was found for *C*-


(i)
35
0.5M NaHCO3 (aq)/
acetone 1:1, 70ºC
(ii) SnCl2•2H2O, DMF
1a
(Resin is Argo-
Gel/Rink)
36 (R,R' = O)
37 (R,R' = H)
DECP, DIEA, DMF, 25 ºC
38
2M X-CH2R2, DMF, 50ºC
39
(i) 0.25M X-CH2-R3,
Lithiated
4-benzyl-2-oxazolidinone
THF/DMF 1:1, 25 ºC
(ii) TFA, CH2Cl2
4

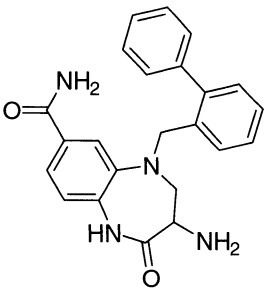
Scheme 6.

and/or *O*-alkylation. Full compatibility of this 1,5-benzodiazepinone synthesis with our dialkylamine encoding method has been established through model studies analogous to those performed with the benzothiazepine compounds.[4] Figure 3.2 displays a selection of structures, compounds **40–45**, accessible from this first synthetic approach.

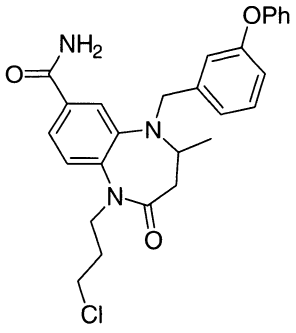
Lee and co-workers have developed a complementary approach to 1,5-benzodiazepinones in which **1a** was reacted with a variety of α- and/or β-substituted β-amino acid esters **46** (Scheme 7).[7] Many of these building



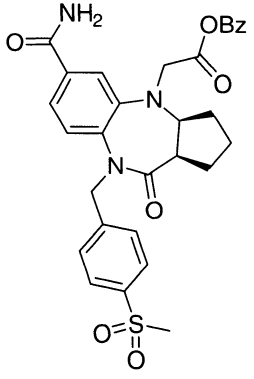
40



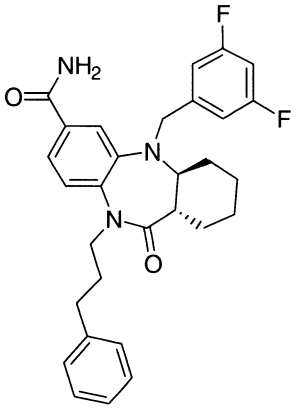
41 (±)



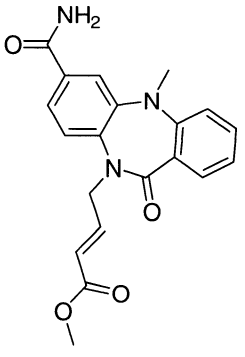
42 (±)



43 (±)

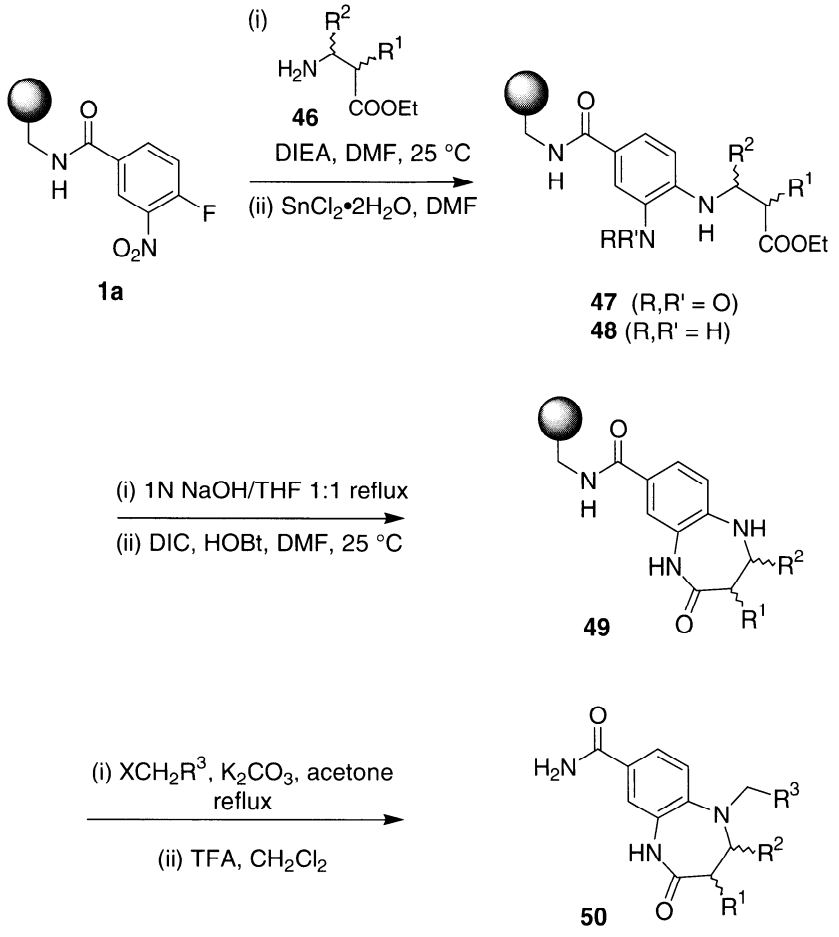


44 (±)



45

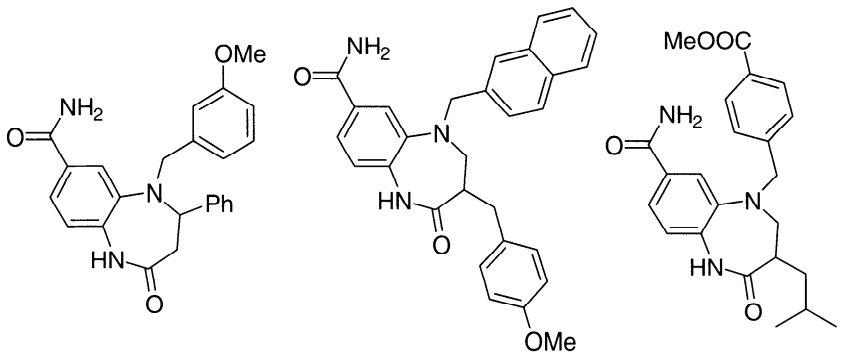
Figure 3.2. Selection of 1,5-benzodiazepin-2-ones synthesized from **1a** and commercially available β-amino acids **35**.



Scheme 7.

blocks were prepared in advance by an expedient solution-phase synthesis involving a Knoevenagel condensation of ethyl cyanoacetate with aldehydes, followed by reduction of the resulting acrylic nitriles.

The S_NAr reaction was performed in DMF using DIEA as an auxiliary base and allowed to proceed for three days at room temperature. Subsequent reduction of the aromatic nitro group of **47** with $SnCl_2 \cdot 2H_2O$ in DMF was followed by hydrolysis of the ester moiety using a heterogeneous mixture of 1 N NaOH and THF at reflux for 24 h. Closure of the seven-membered ring using DIC and HOBt afforded the benzodiazepin-2-ones **49** in good



51 (±) **52** (±) **53** (±)

Figure 3.3. Selection of 1,5-benzodiazepin-2-ones synthesized from **1a** and β-amino acid esters **46**.

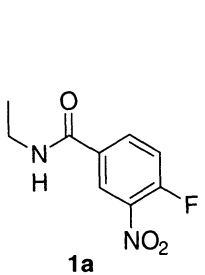
overall yields. Additional diversity was introduced at the penultimate step by alkylating the *N*(5)-position with five different benzyl bromides using K_2CO_3 as a base in refluxing acetone (see also Section 3.3.2).[8] Figure 3.3 shows a selection of benzodiazepinone structures (**51**–**53**) shown to be accessible from this second synthetic approach.

3.3. FORMATION OF [6,6]-FUSED SYSTEMS

3.3.1 4-Alkoxy-1,4-thiazin-3-ones (5)

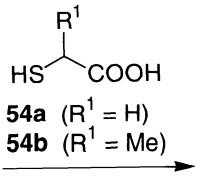
A logical extension of the synthetic strategy underlying our solid-phase approach toward 1,5-benzothiazepinones was to replace the β-mercapto acids (cysteine, penicillamine) by α-mercapto acids, such as mercaptoacetic acid **54a** or thiolactic acid **54b**. This change would facilitate access to the corresponding [6,6]-fused systems, i.e. 1,4-benzothiazin-3-ones **57**. As with the benzothiazepines, no solid-phase synthesis of benzothiazines has been reported to date.

To test our proposed synthesis of [6,6]-fused systems, 4-fluoro-3-nitrobenzamide **1a** was reacted with solutions of **54a** or **54b** in DMF, with DIEA as base (Scheme 8). The solid-phase S_NAr reaction again proved reliable and afforded the corresponding *o*-nitrothioethers **55a** or **55b**, re-



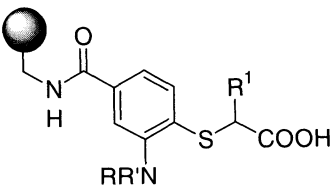
1a

(Resin is Argo-Gel/Rink)



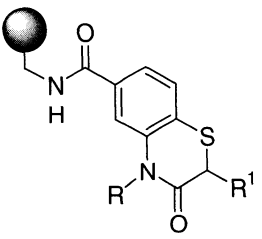
54a (R^1 = H)
54b (R^1 = Me)

DIEA, DMF, 25 °C



55a (R^1 = H; R,R' = O)
55b (R^1 = Me; R,R' = O)
56a (R^1 = H; R,R' = H)
56b (R^1 = Me; R,R' = H)

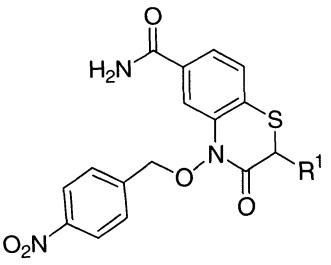
$SnCl_2 \bullet 2H_2O$, DMF



57a (R^1 = H; R = H)
57b (R^1 = Me; R = H)
58a (R^1 = H; R = OH)
58b (R^1 = Me; R = OH)

(i) 4-NO_2-benzylbromide
DIEA, DMF, 25 °C

(ii) TFA, CH_2Cl_2



59a (R^1 = H)
59b (R^1 = Me)

Scheme 8.

spectively, in high purities and yields. Exposure of **55** to standard nitro-group reduction conditions ($SnCl_2 \cdot 2H_2O$ in DMF), however, did not furnish the expected *o*-alkylthio-anilines **56a** and **56b** or the corresponding 1,4-benzothiazin-3-ones **57a** and **57b**. Another set of products was obtained in purities exceeding 90%. These were the corresponding cyclic hydroxamic acids **58a** and **58b**, respectively, based on mass spectrometry (MS), nuclear magnetic resonance (NMR), and infrared (IR) data, as well as on their reactivity toward alkylating agents. Thus, treatment of **58a** and **58b** with *p*-nitrobenzyl bromide at room temperature resulted in smooth conversion to the corresponding 4-(*p*-nitrobenzyloxy)-1,4-benzothiazin-3-ones **59a** and **59b**, respectively.

The literature contains several references to reductive cyclizations producing cyclic hydroxamic acids like those described above, though not in solid-phase chemistry.[43–47] We showed that this reaction competes well with lactam formation. The relative extent of these two reaction pathways is highly dependent on the presence and the nature of other heteroatoms and substituents around the ring system as well as on the conditions used to effect the reduction.

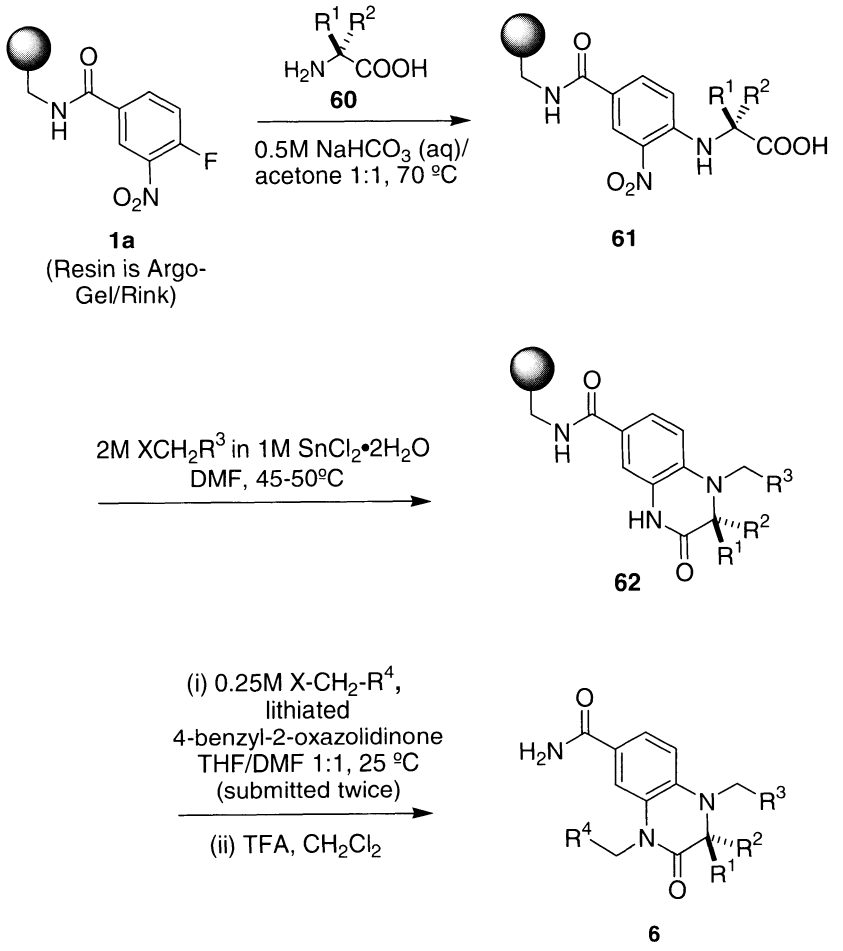
From a pharmaceutical discovery perspective, it could be fruitful to embark on a library synthesis using cyclic hydroxamic acid templates. There are several reports describing interesting bioactivities for such compounds, particularly as inhibitors of metal-dependent enzymes.[48–52] However, only three α-mercapto acid monomers are currently available from commercial sources; hence the structural diversity of products that could be easily prepared is limited. Several approaches to introducing additional points of diversity into the benzothiazinone scaffold are currently under investigation.

3.3.2. Quinoxalin-2-ones (6)

Quinoxalin-2-ones **6**, the [6,6]-fused ring homologues of the 1,5-benzodiazepinones **4**, are accessible through an analogous set of solid-phase transformations using α-amino acids in place of β-amino acids in nucleophilic aromatic substitution reactions of **1a**. A solution-phase version of this reaction sequence has previously been reported by TenBrink and co-workers in studies of quinoxalinones as γ-aminobutyric acid (GABA)/benzodiazepine receptor partial agonists.[53,54] Although less extensively investigated than the benzodiazepinones, quinoxalinones have been applied

as ligands for excitatory amino acid receptors,[55,56] as analgesics,[57] and as inhibitors of aldose reductase.[58]

Three groups have independently developed solid-phase synthetic approaches toward the quinoxalinones.[5,8,9] In our approach, the central intermediate **1a** was reacted with a variety of α-amino acids **60** using the aqueous solvent system [0.5 M $NaHCO_3$(aq)/acetone 1 : 1] described above for the synthesis of 1,5-benzodiazepinones (Scheme 9).[6]



Scheme 9.

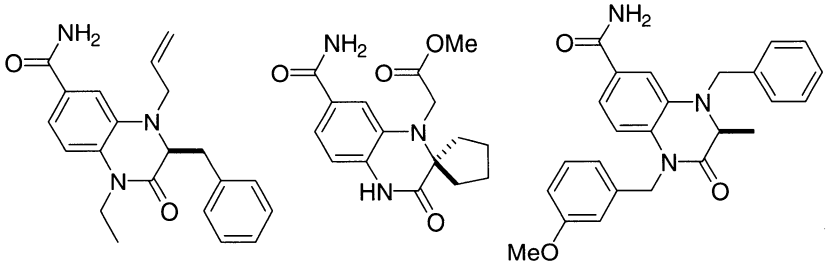
The conditions required for complete fluorine displacement were milder for α-amino acids compared to those typically needed for β-amino acids (60°C vs. 75°C). A wide range of α-amino acids were shown to afford the desired *o*-nitro-anilines **61** with purities exceeding 85%. These included all the proteinogenic amino acids, and representative *N*-methyl amino acids, spirocyclic amino acids (e.g., 1-amino-1-cyclopentanecarboxylic acid), and other nonnatural amino acids. As in the benzodiazepinone case, all attempts to alkylate or acylate the secondary aniline nitrogen of **61** prior to reduction of the nitro group proved unfruitful and afforded essentially unchanged starting material. From our previous experience in the benzothiazine series (Section 3.3.1), we expected that exposure of **61** to the standard nitro-group reduction conditions (2 M $SnCl_2 \cdot 2H_2O$, DMF) would exclusively afford cyclic products (i.e., either lactams or hydroxamates). Indeed, the single product isolated from the reduction of **61** was identified in all cases as the corresponding lactam, with no detectable amounts of either acyclic material or cyclic hydroxamic acid being present. The driving force for spontaneous cyclization was found to be so strong that even in cases where the carboxyl function was protected in the form of a primary carboxamide or a *tert*-butyl ester, no traces of acyclic products could be detected. In the latter case, solid-phase, magic-angle-spinning NMR experiments demonstrated that cyclization does not occur during the TFA cleavage of the products from the resin but rather on the solid support during the reduction step. This was inferred from the solid-state NMR spectrum of the resin derived from the reduction step, which no longer showed the characteristic signal for the *tert*-butyl ester function, clearly evident in the starting material. In an ambitious attempt to subvert the spontaneous cyclization by capturing the intermediate primary aniline function with alkylating agents, we submitted resin **61** to a 1 M solution of $SnCl_2 \cdot 2H_2O$ in DMF containing, in addition, benzyl bromide at high concentration (2 M). To our surprise and delight, we were able to isolate a single product from the reaction. This was not, however, the anticipated *N*(1)-alkylated quinoxalinone, but rather the *N*(4)-alkylated compound **62**, as shown by ^1H NMR. Subsequently, this same product was also obtained, albeit in somewhat lower purity, by subjecting **61** to the same reagents in a stepwise manner. Rather fortuitously, we had thus discovered an expedient two-step procedure for the solid-phase synthesis of 3,4-disubstituted quinoxalin-2-ones from **1a**. In further experiments, this protocol was shown to be of broad scope in terms of functional groups derived from both amino acids (R^1/R^2) and alkylating agents (R^3).

Some 30 benzyl bromides, allyl bromide, and different esters of bromoacetic acid were found to work well in the *N*(4)-alkylation reaction. Benzyl chlorides, α-bromo acetophenones, as well as unactivated alkyl bromides, however, did not give satisfactory results.

For the final step involving functionalization at *N*(1) of **62**, anilide deprotonation with lithiated 4-benzyl-2-oxazolidinone as a base and alkylation with benzyl bromides again proved effective. Compared to the results obtained in the benzodiazepine series, the *N*(1)-alkylation reaction was generally found to proceed less smoothly with the 3,4-disubstituted quinoxalinones **62**. Good results were obtained only if the resin batches were submitted twice to the alkylation conditions. Figure 3.4 displays a selection of structures (**63–65**) accessible from this first synthetic approach. In no case was there any evidence for racemization at the α-carbon atom of the amino acid.

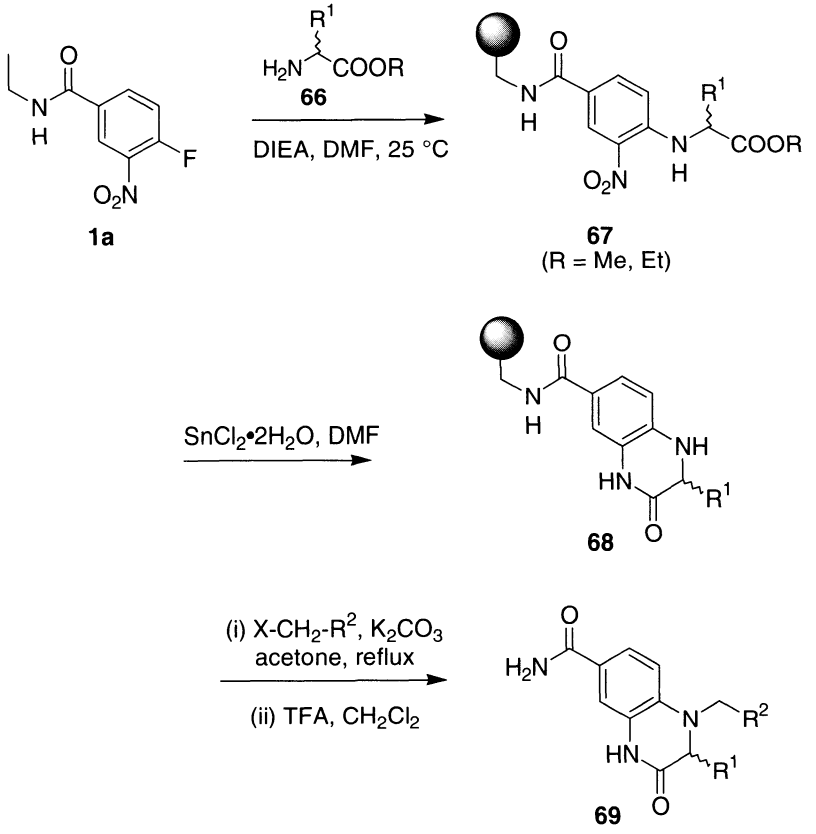
In the synthetic approach reported by Lee and colleagues,[8] resin-bound 4-fluoro-3-nitrobenzoic acid **1a** was treated with methyl and/or ethyl esters of α-amino acids **66** in DMF using DIEA as a base (Scheme 10). The resulting *o*-nitro anilines **67** were then subjected to nitro-group reduction with the intermediate di-anilines undergoing spontaneous cyclization to quinoxalinones **68**. Subsequent alkylation at *N*(4) using benzyl bromides in refluxing acetone with K_2CO_3 as base followed by cleavage from the resin ultimately afforded the 3,4-disubstituted quinoxalinones **69** in good purities and yields.

An interesting side reaction was observed upon cleavage of the *N*(4)-underivatized quinoxalinones **68** (Scheme 11). A significant fraction of the

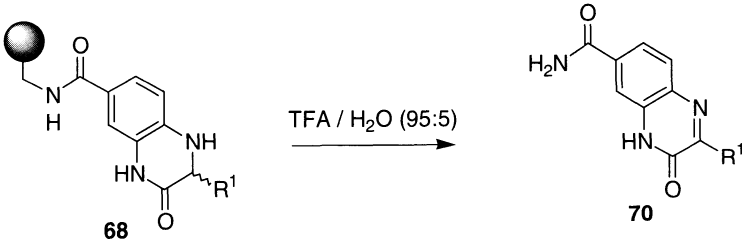


63 **64** **65**

Figure 3.4. Selection of quinoxalin-2-ones synthesized from **1a** and α-amino acids **60**.



Scheme 10.

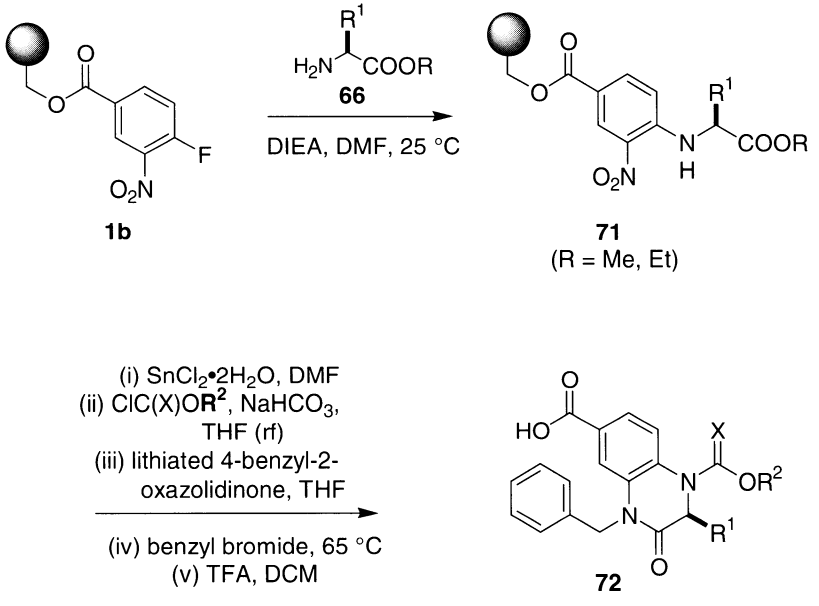


Scheme 11.

cleaved material had undergone oxidation to the 3,4-dehydroquinoxalinones **70**. This oxidation could be suppressed by prior functionalization at *N*(4), as in the preparation of **69** above.

A second side reaction suffered by *N*(4)-unfunctionalized quinoxalinones leading to racemization at the α-carbon was revealed in the closely related studies of Morales and co-workers, who assembled the [6,6] ring system from 4-fluoro-3-nitrobenzoic acid coupled as an ester to Wang resin (**1b**) (Scheme 12).[9] This undesirable side reaction could also be prevented by functionalization of *N*(4) prior to cleavage, which in this instance was accomplished by acylation with chloroformates and thiochloroformates. Derivatization at *N*(1) was again effected using the Ellman alkylation protocol and provided optically pure samples of the quinoxalinones (**72**).

To summarize this section, several research groups have effectively exploited parallels between S_NAr strategies leading to [6,7]- and [6,6]-benzofused heterocycles and have described complementary reaction protocols suitable for generating diverse combinatorial libraries of benzothiazin-3-ones and quinoxalin-2-ones.



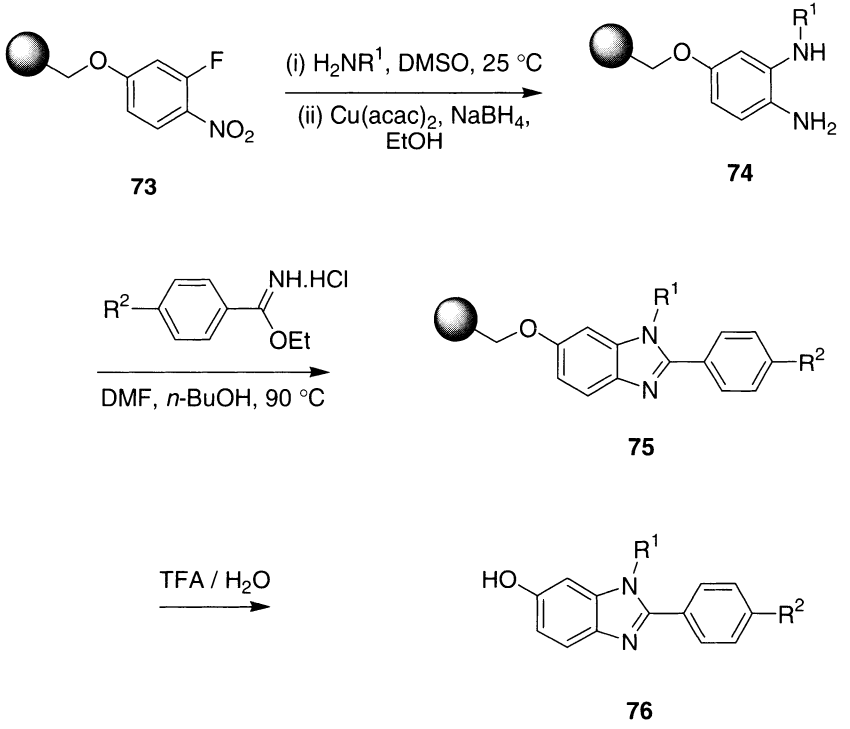
Scheme 12.

3.4. FORMATION OF [6,5]-FUSED SYSTEMS

3.4.1. Benzimidazoles

Benzimidazoles and their derivatives possess varied pharmacological activities[59,60] and have therefore been targets of intense synthetic efforts using both solution- and solid-phase methods. In one of the pioneering studies on the assembly of benzofused heterocycles via S_NAr reactions of *o*-fluoro-nitroarenes, Phillips and Wei reported a solid-phase synthesis of benzimidazoles from 3-fluoro-4-nitrophenol, amines, and ethyl benzimidates (Scheme 13).[61]

The *o*-fluoro-nitroarene was attached to TentaGel resin as a phenolic ether **73** via a modified Wang-type linker. Following aminolysis of **73**, reduction of the intermediate nitroaniline to di-aniline **74** proceeded poorly



73 **74** **75** **76**

Scheme 13.

under the standard $SnCl_2$ conditions, but satisfactory results were obtained with $Cu(acac)_2$–$NaBH_4$. Treatment of **74** with a substituted benzimidate at elevated temperatures afforded benzimidazole **75**, which upon cleavage provided the phenol product **76** in isolated yields of ~50–90%.

3.4.2. Benzimidazolones (7)

The same authors have also reported on the solid-phase synthesis of benzimidazolones **7** from resin-bound 4-fluoro-3-nitrobenzoic acid **1b**, amines, disuccinimidocarbonate (DSC), and alkyl halides (Scheme 14).[10]

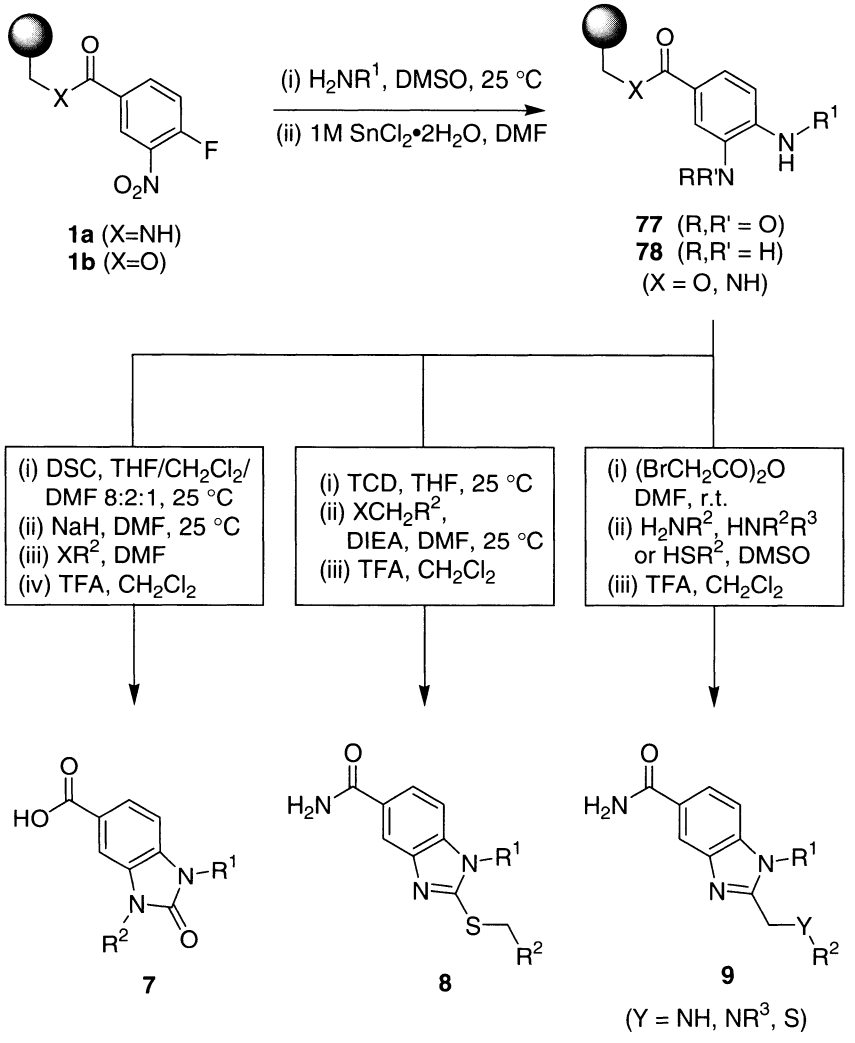
Treatment of **1b** with different amines at ambient temperature, followed by Sn(II)-mediated reduction of the nitro group under standard conditions afforded the corresponding di-anilines **78** in good yields and purities. Among a variety of phosgene-type reagents evaluated (e.g., phosgene, triphosgene, CDI, DSC), only DSC was found to give reliably high yields of monosubstituted benzimidazolones. Alkylation of the second nitrogen was effected with alkyl halides and NaH as a base, to afford, upon cleavage from the resin, the desired 1,3-disubstituted benzimidazolones (**7**) in excellent isolated yields.

3.4.3. 2-Alkylthio-benzimidazoles (8)

Lee et al. explored another variant of the benzimidazole theme (Scheme 14) by showing that it is possible to generate 1-substituted 2-alkylthiobenzimidazoles **8** from **1a**, amines, 1,1′-thiocarbonyldiimidazole (TCD), and benzylic halides.[11] The title compounds and their corresponding sulfoxides have been reported to have a variety of potentially valuable pharmacological properties.[62–64] The di-anilines **78** (X = NH) were prepared following standard methods and treated with TCD to yield the corresponding benzimidazole-2-thiones. Subsequent *S*-alkylation using benzylic halides in the presence of DIEA in DMF at ambient temperature followed by TFA cleavage furnished the title compounds **8** in high purities and yields.

3.4.4. 2-Alkylaminomethyl- and 2-Thiomethyl-benzimidazoles (9)

Tumelty in our group pursued yet another benzimidazole idea, whereby substituted 1-aryl-2-aminomethyl-benzimidazoles **9** were assembled from



Scheme 14.

1a, anilines, bromoacetic anhydride, and amines (Scheme 14).[12] The use of thiols in place of amines provided the corresponding substituted 1-aryl-2-thiomethyl-benzimidazoles. Both compound classes have proven to be important as leads in several drug discovery programs and have utility as anti-arrhythmic and antiviral agents.[65–67] As in the two prior examples, di-anilines **78** (R = NH) constitute key intermediates. However, in contrast

to the two previous reports, R^1 was exclusively derived from anilines rather than alkyl- or aralkyl primary amines, thereby generating benzimidazoles containing the pharmacologically important diphenylamine motif. Elevated temperatures and the use of an auxiliary base (DIEA) were required for the S_NAr reaction to go to completion, particularly for anilines with deactivating electron-withdrawing substituents. Reaction of **78** with bromoacetic anhydride furnished exclusively monobromoacetylated intermediates. It is assumed that the acylation occurs on the primary aniline rather than on the deactivated secondary diphenylamine nitrogen. This issue is academic with respect to the structures of the final benzimidazoles, since both bromoacetylated intermediates would afford the same products upon cyclodehydration. Displacement of bromide by primary and/or secondary amines and by thiols is then possible, as illustrated in Scheme 14. The final step involved treatment of the resin-bound intermediates with TFA for 16 h to release the products with concomitant cyclodehydration forming the benzimidazoles **9**.

3.5. CONCLUSIONS AND OUTLOOK

The goal of this review was to present a highly versatile synthetic strategy enabling solid-phase syntheses of a variety of pharmacologically relevant, "privileged" templates, such as benzodiazepines, benzothiazepines, and benzimidazoles. Starting from a common intermediate, resin-bound 4-fluoro-3-nitrobenzoic acid **1a**,**b**, eight different benzofused heterocyclic core structures were assembled using the same basic series of synthetic transformations in conjunction with the appropriate core building blocks (Scheme 1). The general synthetic sequence consisted of nucleophilic aromatic displacement of fluorine by sulfur and/or nitrogen nucleophiles, subsequent reduction of the *o*-nitro group, and cyclization, followed (and/or preceded) by introduction of further functionality at suitable positions.

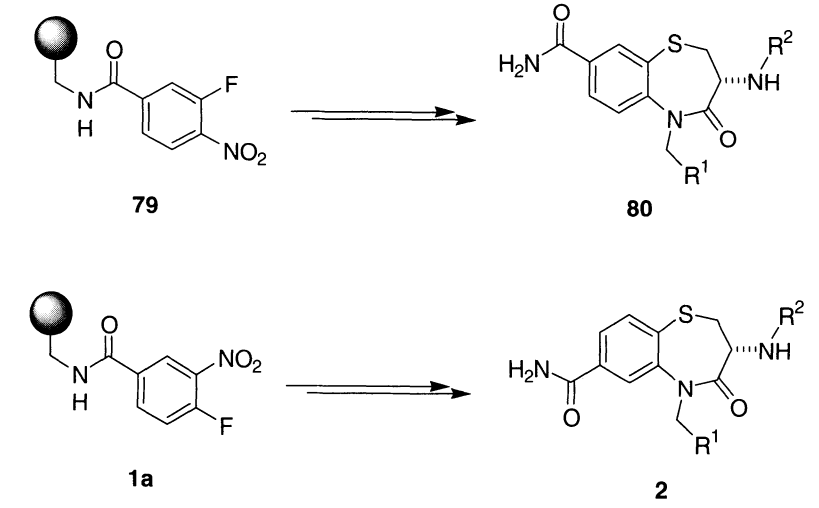
As mentioned in the introduction, typically one of the most time-consuming steps in the synthesis of a combinatorial library by solid-phase methods is demonstrating the feasibility and generality of the synthesis of a particular core structure on resin. Hence a strategy wherein the synthetic transformations, once developed and optimized, can subsequently be reused in different contexts to produce an array of different compound classes has considerable merit. Having initially invested a considerable amount of time in establishing the practicability of the first scaffold chemistry (the ben-

zothiazepine nucleus), we found that the requisite time periods for subsequent chemistry development were shorter every time a new core structure synthesis was attempted. A clear appreciation of this inherent synthetic efficiency is also evident in the work of the R. W. Johnson and Berlex groups, who have exploited similar concepts in pursuit of attractive molecules for biological evaluation.

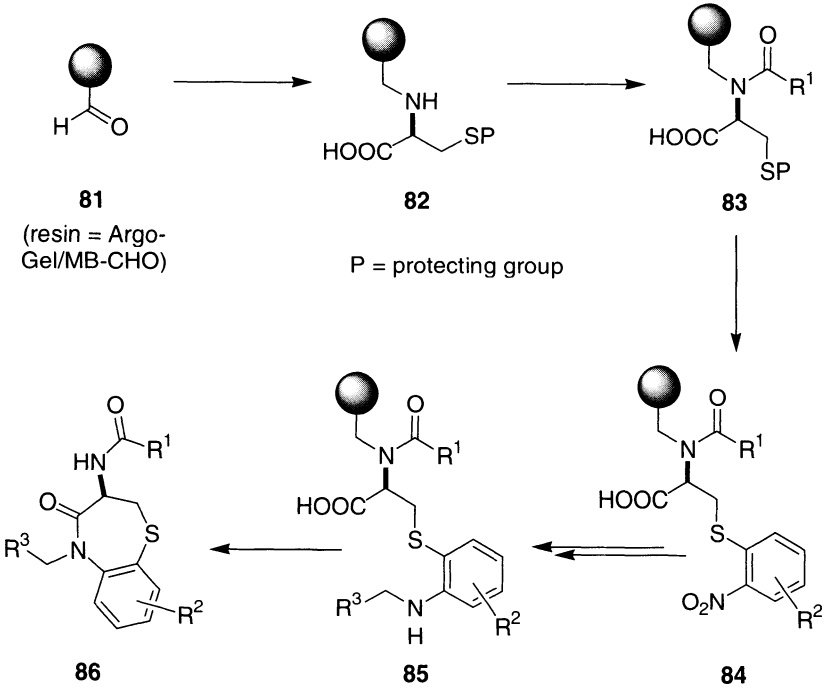
While considerable progress has been made in using solid-phase S_NAr chemistry for library synthesis, there is certainly room for further development. One area that, in our opinion, deserves particular attention in the future relates to the way in which the compounds are tethered to the solid support. In spite of the impressive diversity of ring systems attainable from resin **1**, all compounds bear a common carboxamide and/or carboxyl function at the former attachment point of the aromatic ring to the solid support. Given the potential impact of this obligatory tethering "scar" on the biological activity of these compounds, it seems imperative to consider ways of altering the nature and/or the position of the linkage to the solid support. A few efforts have already been made with regard to different tethering strategies. As noted in Section 3.4.1, Phillips and Wei achieved a benzimidazole synthesis from an *o*-fluoro-nitroaryl template tethered to the solid support via an ether linkage **73**, affording, upon TFA cleavage, 6-hydroxy-benzimidazoles **76** (Scheme 13).[61]

In a model study on the effect of changing the position of the attachment point, we carried out the benzothiazepinone synthesis starting from resin-bound 3-fluoro-4-nitrobenzoic acid **79** instead of 4-fluoro-3-nitrobenzoic acid **1a** (Scheme 15).[5] Gratifyingly, we were able to obtain 8-carbamoyl-1,5-benzothiazepin-4-ones **80** in purities and yields that were comparable to those reported previously for 7-carbamoyl-1,5-benzothiazepin-4-ones **2**.

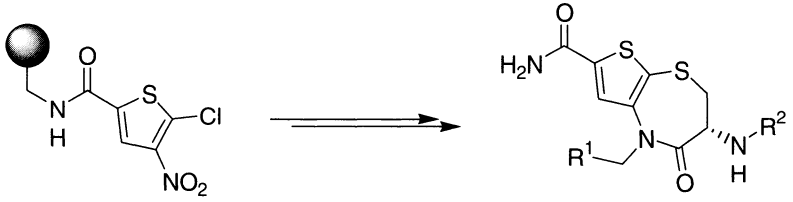
A "traceless" strategy for solid-phase syntheses of the benzofused heterocycles would be highly desirable. Silicon- and/or germanium-linking strategies as reported by Ellman (among others)[32] could be one way of achieving this, pending proof of compatibility between the ligand and the linker chemistry. In a modification and extension of the entire synthetic concept, we have recently shown that it is also possible to assemble 1,5-benzothiazepin-4-ones via the route shown in Scheme 16, attaching the ligand to the solid support through its aliphatic portion, rather than through the aromatic nucleus.[68] Thus, a suitably protected form of cysteine was reacted with a resin **81** equipped with an aldehyde–linker under reductive amination conditions, followed by acylation of the resulting secondary



Scheme 15.



Scheme 16.



87 88

Scheme 17.

amine. S_NAr reaction with different *o*-fluoro-nitroarenes, followed by reduction of the nitro group, reductive alkylation of the primary aniline function, and cyclization afforded, upon TFA cleavage from the resin, the desired 1,5-benzothiazepinones **86** in good purities and yields. It is envisaged that certain other benzofused heterocycles, such as 3-amido-1,5-benzodiazepin-2-ones, could also be assembled using this new synthetic approach.

Another potential avenue for future development is extrapolation of these chemistries from benzofused to heteroanellated heterocycles. We have recently been able to show that thieno[2,3-*b*][1,4]thiazepine-5-ones (**88**)[69] can be synthesized on solid support from resin-bound 5-chloro-4-nitrothiophene-2-carboxylic acid (**87**) using essentially the same synthetic protocols developed in the carbocyclic series (Scheme 17 and Section 3.2.1).[5] The starting material, 5-chloro-4-nitrothiophene-2-carboxylic acid, was synthesized in solution from commercially available 5-chlorothiophene-2-carboxylic acid.

In conclusion, it is clear that the S_NAr approach to benzofused heterocycles can provide pharmaceutically attractive compounds for high-throughput screening. We anticipate that useful lead molecules will emerge from these studies and look forward to reporting new correlations between bioactivities and molecular structure.

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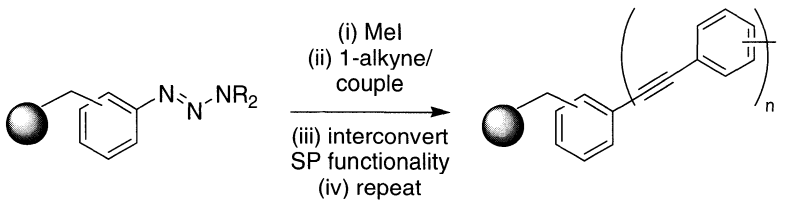
CHAPTER 4

SOLID-PHASE SYNTHESIS OF SEQUENCE-SPECIFIC PHENYLACETYLENE OLIGOMERS



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4.1. INTRODUCTION

Solid-phase organic synthesis (SPOS) is an established technique for generation of peptides,[1,2] nucleotides,[3] and more recently, carbohydrates (oligosaccharides).[4,5] Supported syntheses of nonbiological oligomers[6–16] and other small molecules[17–21] have also been reported, reflecting the method's

intrinsic practicality. Concerns over the true value of solid-phase syntheses[22] have been swept aside by advances in combinatorial chemistry and automatic synthesizer technology for the generation of biomolecules and substances for biological assays.[23]

Solid-phase organic syntheses of nonbiological oligomers have advantages over solution-phase methods with respect to sequence control, ease of purification, and speed. The products can be well-defined oligomers that are unlike the mixtures usually obtained in classical polymer syntheses. This chapter explores some recent developments in this area, with an emphasis on our own work at the University of Illinois.

4.2. STRATEGIES

4.2.1. Stepwise Addition

Stepwise addition involves growing an oligomer by coupling a single monomer to a "free" terminus, as seen in Figure 4.1 (shaded and unshaded attachments correspond to protected and deprotected moieties, respectively). This method is useful for preparing smaller products, aperiodic sequences, and short oligomers for fragment condensation (see Section 4.2.2). Aperiodic oligomers result when the monomers coupled in each

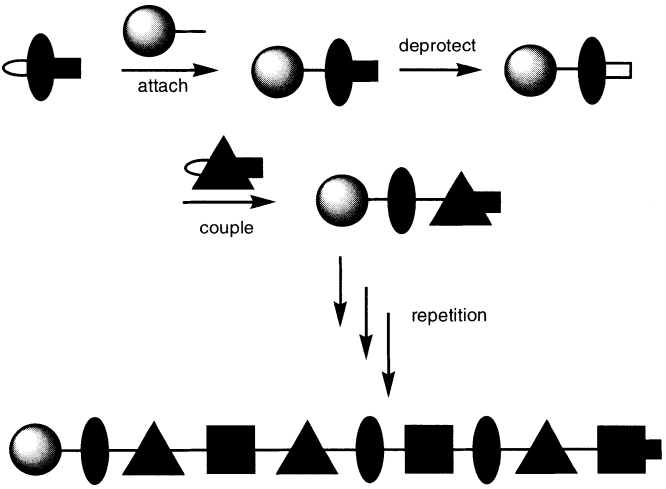


Figure 4.1. Stepwise construction of an aperiodic oligomer sequence.

iterative cycle are different. This is the basis for solid-phase synthesis of peptides[1,2] and some combinatorial libraries.[17,18,21]

A drawback of the strategy shown above is that oligomer growth is relatively inefficient. It is this reason that makes stepwise addition strategies most suitable for smaller oligomers. Another problem arises from the difficulties associated with separation of defective products, for example, octamer from nonamer.

4.2.2. Fragment Condensation

Fragment condensation methods involve coupling of oligomer moieties to longer, higher molecular weight components (Figure 4.2).[24] In this strategy, purification of the final product is often easier since the oligomers usually have a greater difference in molecular weight. Moreover, the efficiency of synthesis is potentially much greater than for stepwise syntheses.

There are many ways to implement the fragment method. For instance, it is possible to prepare a dimer or trimer, then grow the desired oligomer using these fragments as the "effective" monomer for each step. However, a better method, known as the divergent–convergent approach,[25] involves splitting the bead pool at each iteration of the synthetic cycle. The first half of the bead pool is deprotected while the second half is cleaved from the bead in a way that leaves a reactive terminal group. The free second

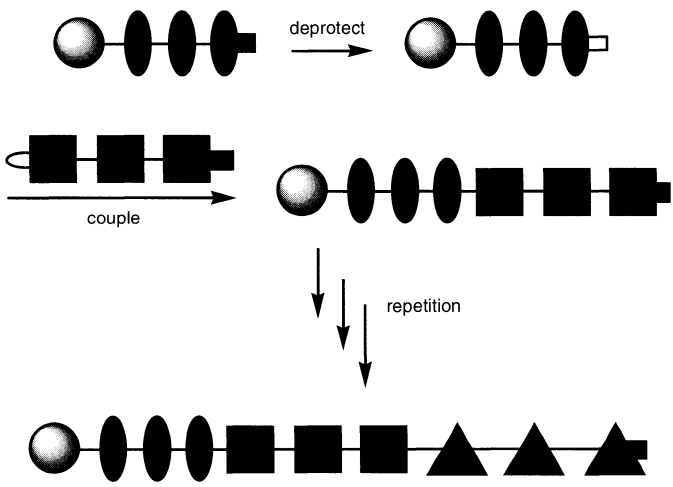


Figure 4.2. Stepwise construction of a periodic oligomer sequence.

fragment is now the "effective" monomer and can be added to the bound oligomer. This method doubles the oligomer length during each iteration of the synthetic cycle.

4.2.3. Polymerization

A third strategy in the solid-phase syntheses of oligomers involves AB_n polymerization of monomer from the support. In this approach the polymer bead acts as the chain initiator or focal point in the polymerization. Like solution-phase polymerization reactions, this approach will give polydisperse structures. However, polymerization from solid support can be used to control molecular weight and may also lead to narrower polydispersities.[26] Furthermore, the resin-bound tether becomes an end group of the polymer once cleaved, facilitating control of end-group chemistry. To obtain higher yields, it is imperative that polymerization occurs mostly from the "bound" terminus and minimally in solution. Monomer addition rate and concentration can be varied to achieve this.

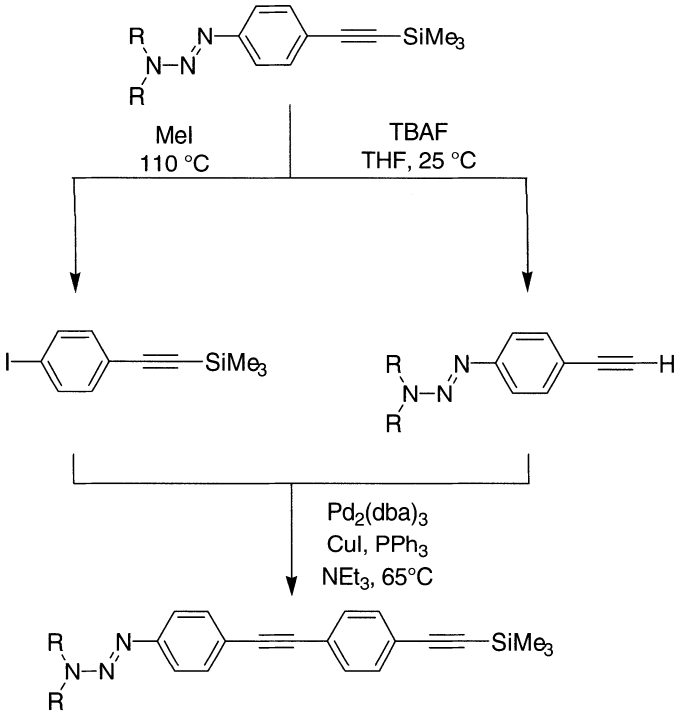
4.3. SYNTHETIC TACTICS

Phenylacetylene chemistry allows construction of shape-persistent molecular architectures through structural control and monomer diversity.[27] Combination of this method with solid-phase techniques enhances the rate at which compounds can be made, especially because automation is possible. Oligomer libraries may also be accessible using this type of chemistry.

4.3.1. Coupling–Deprotection–Coupling Triads

Efficiency of the deprotection and coupling reactions are critical to the success of any iterative solid-phase synthesis. Shown in Scheme 1 is a triad of reactions for phenylacetylene oligomer synthesis: trimethylsilyl deprotection,[28,29] triazene unmasking of an iodobenzene,[30] and the Sonogashira coupling of a terminal acetylene with an aryl iodide.[31–33] Representative procedures for each step in this sequence are included at the end of this chapter.

The triad illustrated in Scheme 1 is a combination of three efficient reactions. Trimethylsilyl (TMS) deprotection is accomplished by the addition of tetrabutylammonium fluoride (TBAF) and the reaction proceeds



Scheme 1.

within 5 min. Triazene unmasking involves placing the support in neat methyl iodide in a sealed tube and heating to 110°C for 12 h. Yields of this reaction are generally high, although a few instances have been encountered when by-products were formed. The mechanism of this reaction has not been carefully studied, but the following is known: The reaction rate is increased by electron-donating substituents on the aromatic ring.[30] In the cleavage of a hexamer from solid support, a side product was formed and determined to be the 1-iodo-olefinic hexamer derivative (Figure 4.3).[15] Further characterization indicated that the by-product was a result of the trimethylsilyl acetylene moiety reacting with HI produced under cleavage conditions. Attempts to quench HI in situ (by the addition of propylene oxide or potassium carbonate) resulted in slow or no reaction. This observation suggests an acid-catalyzed mechanism for the decomposition of aryl triazenes and iodomethane. The reaction may also involve radical interme-

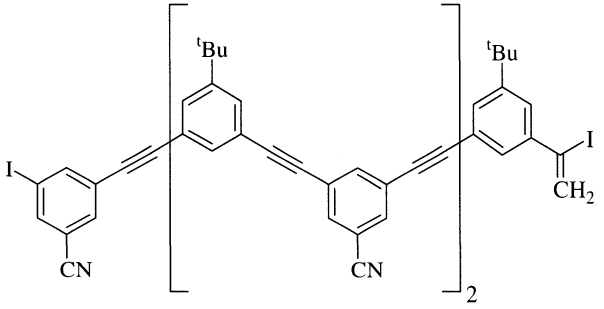
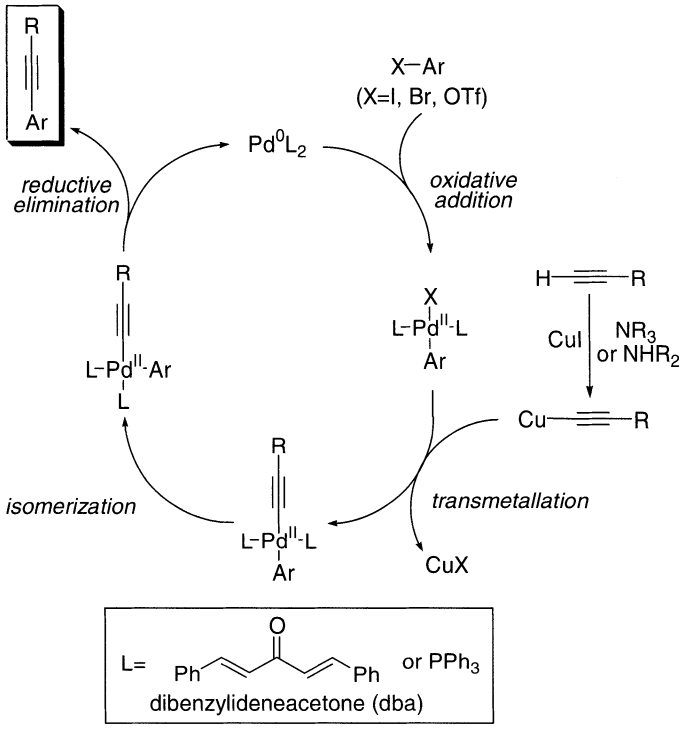


Figure 4.3. 1-Iodoarylalkyne impurity produced during the cleavage of the corresponding hexamer.

diates; hence, functional groups that are sensitive to radicals may need to be avoided.

The final reaction in the triad, a palladium-catalyzed cross-coupling, features a catalyst "cocktail" solution. This is stable for up to one month and hence is particularly convenient for repeated use in solid-phase syntheses; the supernatant is added via cannula in the cross-coupling of aryl halides and terminal alkynes. The procedure for cocktail generation is also included at the end of this chapter. The generally accepted mechanism of palladium-catalyzed cross-coupling of aryl halides to terminal alkynes is shown in Scheme 2.[31] Palladium starts out in the zero oxidation state. Triphenylphosphine is added to replace the highly labile dibenzylideneacetone (dba) ligands on palladium. The catalyst converts to the more robust Pd(II) state upon oxidative addition into the aryl halide bond. A slight excess of aryl halide (1.1 equiv) is used to maintain palladium in this more durable state. This also helps to prevent diacetylenes formed by oxidative dimerization. In the next step of the catalytic cycle, triethylamine removes the acidic terminal acetylene proton, producing copper acetylide and triethylammonium iodide. Transmetallation then occurs between this species and the Pd(II) complex, regenerating copper halide. Finally, the palladium complex rearranges to accommodate reductive elimination of the aryl acetylene, palladium returns to its zero oxidation state, and the cycle continues.

Catalyst levels necessary for the reactions outlined above usually do not exceed 5 mol %. Bromoiodoaryl monomers can also be used for selective displacements: The iodide functionality reacts much faster than bromides.[34]



Scheme 2.

The reaction also can be used to synthesize TMS-acetylated monomers from aryl halides (the terminal acetylene is simply trimethylsilylacetylene) and to mono-TMS-acetylate meta-di-halides. Work-up involves filtration to remove inorganic salts followed by separation via column chromatography. With the use of triphenylphosphine in this reaction, the opportunity for phenyl-aryl interchange in the palladium complex does exist, as seen in Scheme 3.[35] Coupling yields are typically high for smaller oligomers, suggesting that ligand–monomer interchange is not a significant side reaction. As the oligomer length increases, yields tend to decrease, which is an indication that the rate of this side reaction may become competitive.

Scheme 3.

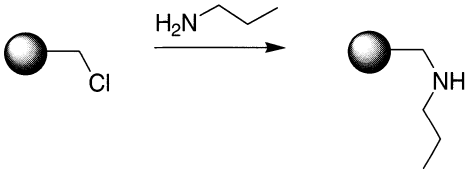
4.3.2. Tethers

Triazene linkers facilitate removal of oligomers from solid supports in one step.[14,15] Triazene masking groups have been tested in solution-phase synthesis of phenylacetylene oligomers.[30] Triazenes are stable to many of the reagents commonly encountered in monomer synthesis, as seen in Table 4.1, though the stability of triazenes is lowered by electron-releasing groups or sterically bulky ortho substitutes.[30] Electron-deficient aromatic systems lend stability by making the lone pair on the amino nitrogen less nucleophilic and, therefore, less reactive. On the other hand, electron-rich rings tend to increase the reactivity of the triazene. At the bench, triazenes must be handled with care due to their suspected carcinogenicity.[36] Most triazenes are stable to air and can be stored for months at a time. Triazene monomers are thermally stable and can be distilled under vacuum below 140°C.

Several triazene tethers for solid-phase synthesis have been investigated to optimize preparation and cleavage steps. Initially, a Merrifield resin with a piperdinemethyl ether triazene tether was made, but under rather inconvenient conditions (NaH at 70°C in a sealed tube for 96 h). In a similar fashion, a monomer attached to a (2-hydroxyethyl)-3-ethyl-triazene linkage was also prepared.[16] A tether featuring an amide linkage was also synthesized by coupling the triazene monomer to the tether under mild conditions (25°C for 1.5 h) via dicyclohexylcarbodiimide (DCC) activation. These tethers proved to be problematic for several reasons. First, they had to be synthesized separately, and activating agents were required for the coupling. Second, they produce oligomer sequences that are end capped with an iodobenzene lacking a side chain, which is unfortunate if homooligomers are the desired targets. A more versatile tether, and one that could be made directly from the monomer, was prepared by converting Merrifield resin

TABLE 4.1. Reactivity of Triazenes

Triazene Stability	Triazene Lability
Aqueous NaOH	MeI (110°C)
Methoxide	Acids (e.g., acetic acid, TFA)
Pd cross-coupling reactions	Lewis acids (e.g., $AlCl_3$, BCl_3, TfOH)
Butyllithium	Br_2
Grignard reagents	Me_3SiI
Catechol borane	Strong alkylating reagents



Scheme 4.

end groups into a *n*-propylaminomethylated functionality, then reacting with a diazonium salt to create the triazene tether (Scheme 4).

Procedures for the preparation of propylaminomethylated resin and the corresponding tethered monomers are found at the end of this chapter.

The *n*-propylaminomethylated tether is the best identified to date because of its versatility and ease of synthesis. Although yields tend to vary depending on the side chain, the advantage of this route is that the tether is created directly from the desired monomer; thus the oligomer does not have an unsubstituted capping monomer. A protocol was developed to test that all the amino sites on the bead are converted to triazenes.[15] The diazonium salt was added portionwise to the DMF–resin suspension and an aliquot was removed and quenched with diethylamine to form the 3,3-diethyltriazene. If any excess of the diazonium remained, the corresponding triazene was formed and detected by gas chromatography (GC). The reaction was complete

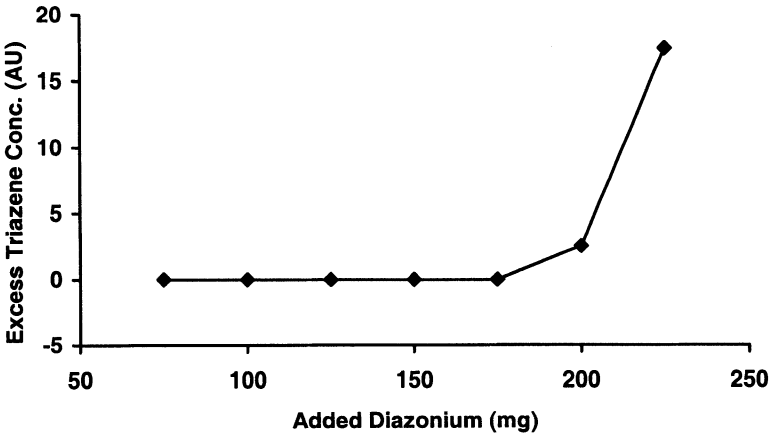


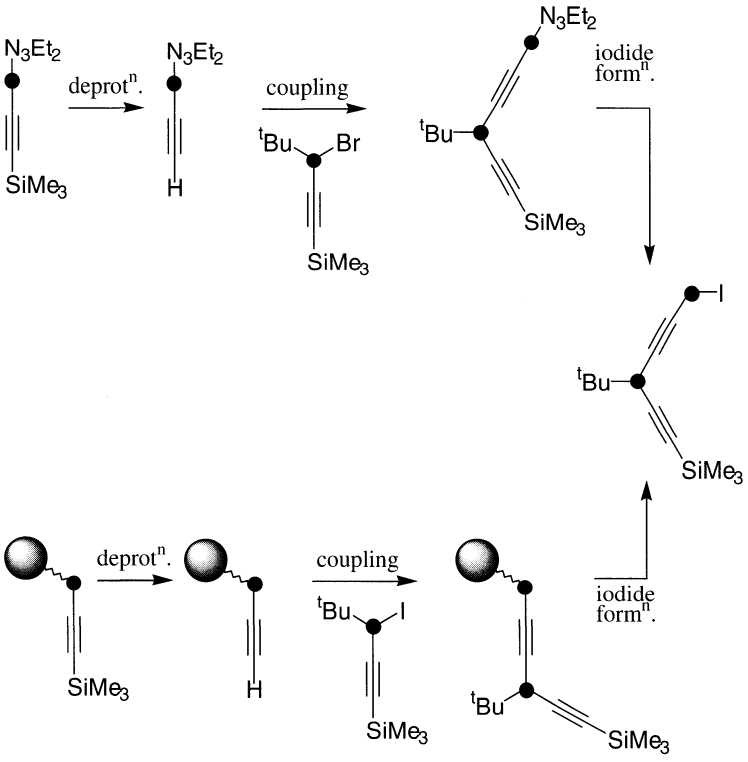
Figure 4.4. Attachment of benzenediazonium salts to *n*-propylaminated Merrifield's resin monitored by gas chromatography. Completion of the reaction corresponds to increased concentration of triazene.

when a significant amount of triazene had been observed (Figure 4.4). Altogether, the *n*-propylaminomethylated linkage is the tether of choice and can be extended beyond phenylacetylene oligomers.

4.4. ILLUSTRATIVE APPLICATIONS

4.4.1. Oligomers

A comparative study of phenylacetylene oligomer synthesis on a solid support[14] with solution-phase approaches has been undertaken.[37] Results from syntheses featuring a "free" and "bound" terminal acetylene are shown in Scheme 5. (For clarity, substituted arene units are symbolized as a filled circle throughout the rest of this chapter.)



Scheme 5.

In both cases, a similar *t*-butyl aryl halide was coupled to a terminal acetylene. Oligomer growth in solution can occur from either end of the oligomer, whereas the bound oligomer can only grow from one end. The solution yield for the reaction triad of the free dimer was 80% whereas the yield of the "supported" dimer was 89%. Figure 4.5 shows the yields for the reaction triad of higher oligomers from the dimer using the fragment condensation method.

Several comparisons can be made between the solution- and solid-phase approaches. Yields of oligomers formed on the solid phase fluctuate more than solution methods, though both are similar. Solution yield calculations were compiled from isolated yields for each of the three transformations,

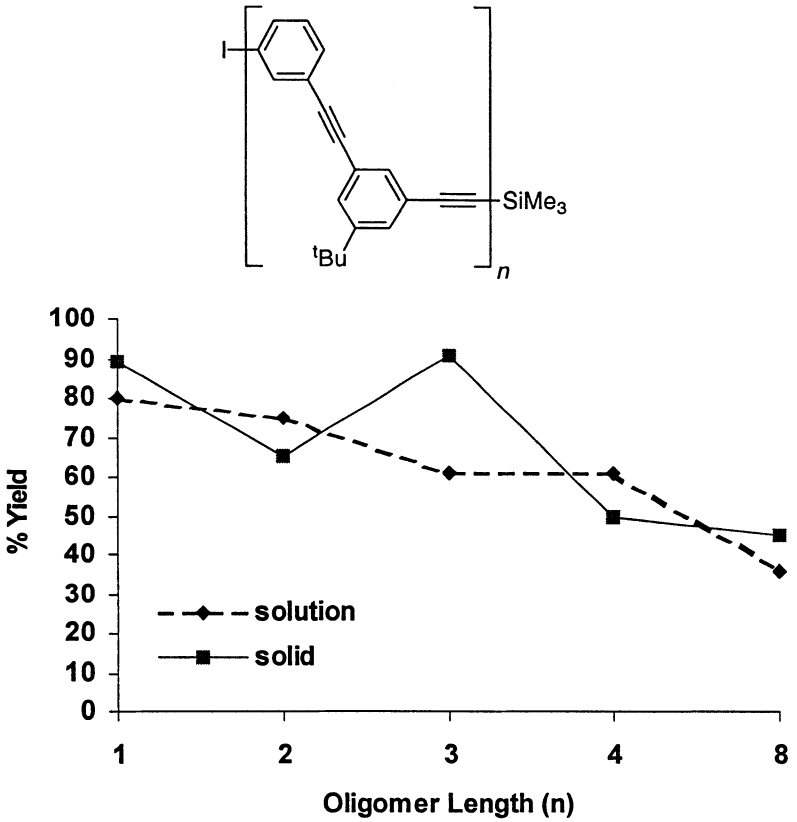
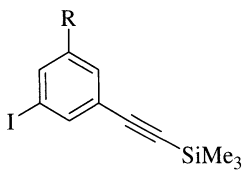


Figure 4.5. Solution- and solid-phase oligomer yields versus length for the indicated oligomer series.

and solid-phase yields were determined by the amount of isolated material obtained after deprotection, coupling, and cleavage. Ease of purification is the main advantage of the solid-phase approach. In solution methods, difficulties with purification increase with oligomer lengths. For instance, when making the dodecamer, it is necessary to separate unreacted hexamer and the catalyst from the product. For supported methods, however, the unreacted hexamer is washed away with the catalyst. Once the oligomer has been cleaved from the bead, chromatography allows for facile separation of the dodecamer from higher molecular weight oligomers (e.g., those occurring from intramolecular reactions on the bead). The bound hexadecamer was further reacted via the fragment condensation approach to make the 32-mer in 95% yield and 5% unreacted hexadecamer. At this point, it was increasingly difficult to separate the higher oligomers from the cleaved 32-mer. Furthermore, solubility problems arose. The bound 32-mer could be further reacted to obtain the 64-mer along with the lower analogues present. Although this sequence-doubling strategy has its limitations, it is evident that free oligomers up to the hexadecamer can be obtained readily using this method.

Solid-phase methods have also been used to generate similar para-substituted phenylacetylene oligomers.[13] In these syntheses, complete generation of the target hexadecamer was shown to be viable for both solution- and solid-phase methods. However, the solid-phase method generated the target in higher yield (79% vs. 24% overall by solution phase), and the purification involved only one chromatographic step.

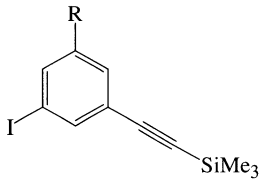
The potential of solid-phase methods for meta-substituted phenylacetylene oligomers was further investigated utilizing monomers with four different side chains (Figure 4.6).[15] Monomers **A** and **B** were synthesized on and cleaved from the support. As seen in Table 4.2, data for the brominated and trimethylsilylacetylated versions of the monomers demonstrate that the coupling and cleavage reactions proceed in high yield and



	R
A	O-(n-C_6H_{13})
B	CO_2-(n-C_6H_{13})
C	^{t}Bu
D	CN

Figure 4.6. Side-chain variations for phenylacetylene monomers.

TABLE 4.2. Yields and Purities of Monomers A and B and Heterooligomers A–D Formed on a Solid Phase



R

A O-(n-C_6H_{13})
B CO_2-(n-C_6H_{13})
C ^{t}Bu
D CN

Monomer	Yield (%)	Purity[a] (%)
I–**A**–Br	98	98
I–**A**–TMS	94	97
I–**B**–Br	90	95
I–**B**–TMS	98	94

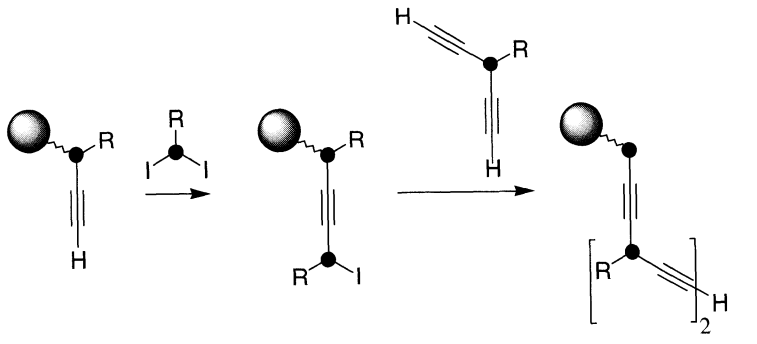
[a]Monitored by HPLC analyses.

purity. Heterooligomers were also synthesized via a stepwise addition to the solid support giving dimers and hexamers in moderate yield and high purity by high-performance liquid chromatography (HPLC; Table 4.3).

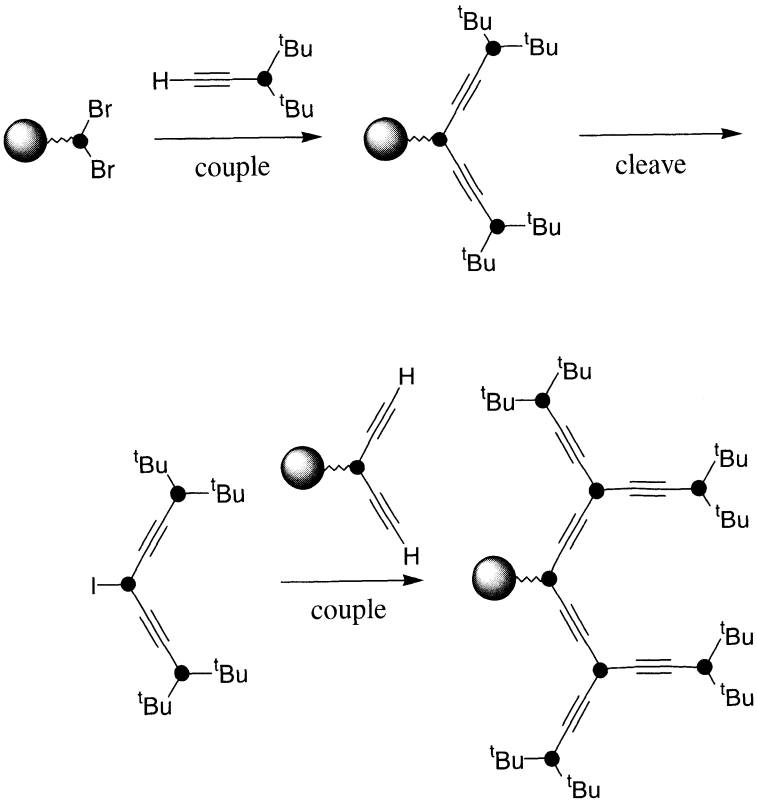
Another method for preparation of higher oligomers takes advantage of site isolation on a solid phase.[6] It proceeds via alternate addition of a pair of symmetrical difunctional monomers in a stepwise addition obviating the need for deprotection steps (Scheme 6). The sequence is extended one unit at a time, unlike solution approaches that tend to involve growth from both ends. This method has not yet been fully investigated, so it is difficult to speculate about its effectiveness or to foresee potential problems.

TABLE 4.3. Oligomers of Monomers A–C

Oligomer	Yield (%)	Purity (%)
I–**A**–**A**–TMS	84	95
I–**A**–**B**–TMS	88	94
I–**B**–**A**–TMS	76	91
I–**B**–**B**–TMS	75	96
I–$\mathbf{B}_3$–$\mathbf{A}_3$–TMS	48	92
I–(**D**–**C**)$_3$–TMS	58	98



Scheme 6.



Scheme 7.

TABLE 4.4. Solution- and Solid-Phase Synthesis of Dendrimers

Generation	Dendrimer	Solution-Phase Yield (%)	Solid-Phase Yield (%)
0	I–$\mathbf{M}_3$–(^{t}Bu)$_4$	88	85
1	I–$\mathbf{M}_7$–(^{t}Bu)$_8$	82	80
2	I–$\mathbf{M}_{15}$–(^{t}Bu)$_{16}$	84	78
3	I–$\mathbf{M}_{31}$–(^{t}Bu)$_{32}$	81	77
4	I–$\mathbf{M}_{63}$–(^{t}Bu)$_{64}$	85	68

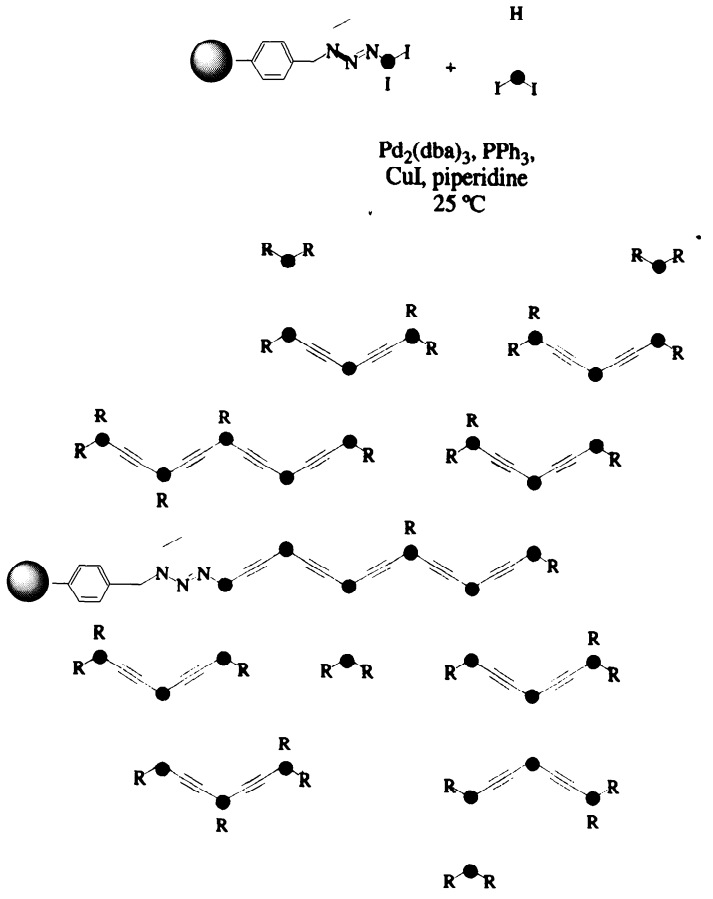
4.4.2. Dendrimers

Branched phenylacetylene monomers can be used to construct dendrimers on supports. This was accomplished using a triazene tether as a focal point, the reaction triad outlined above, and an AB_2 monomer, as seen in Scheme 7.[16] As in similar solution-phase convergent dendrimer syntheses, the first step was to prime the periphery of the dendrimer with *t*-butyl groups by di-coupling of a triazene-tethered dibromoaryl monomer with (di-*t*-butylphenyl)acetylene. In this and all subsequent coupling steps, an excess amount of the monodendron acetylene was used to drive the reaction to completion. The reagents and catalysts were washed away and the excess monodendron was recovered. At the end of the first step, the tri-aryl dendron I–M_3–(*t*-Bu)$_4$ was cleaved from the support (M represents the dendritic monomer unit). Two equivalents of this product were then coupled with the triazene-tethered di-acetylene aryl monomer to produce the heptaaryl dendron I–M_7–(*t*-Bu)$_8$.

The process shown above was repeated for up to four cycles and the data obtained for these syntheses are shown in Table 4.4. A significant amount of monocoupling occurred during the fourth generation, and all attempts to drive this reaction to completion failed. This was likely due to congestion of the growing dendrimer within the resin cavities. Consistent with this, the fourth-generation dendrimer was obtained when a lower resin loading was used. Overall, dendrons up to the third generation can be made in gram quantities. Yields were slightly lower than for comparable solution-phase approaches, but purification was much easier.

4.4.3. Hyperbranched Polymers

A hyperbranched polymerization from solid support was developed as a one-pot synthesis for branched polymers that mimic dendrimers (Scheme


H
Pd2(dba)3, PPh3,
CuI, piperidine
25 °C
R = I
H
Pd2(dba)3, PPh3,
CuI, piperidine
25 °C
tBu tBu
R =
tBu tBu

Scheme 8.

8).[26] The polymerization was carried out beginning with triazene-tethered 3,5-diiodobenzene as a focal point of an AB_2 polymerization with 3,5-diiodophenylacetylene. The degree of branching is limited by steric factors due to the size limitations within the bead or adjacent dendrimers. To ensure that the polymer was soluble after being cleaved, the iodo ends were capped with (3,5-di-*tert*-butylphenyl)ethyne. Polydispersity in the product of this synthesis was less than for comparable solution-phase routes (1.3 vs. >2.5). Furthermore, size exclusion chromatography traces showed only monomodal distributions for support-grown products while a bimodal elution profile was seen for those made in solution. Moreover, the molecular weight of the product could be controlled by the monomer to the focal point ratio used in the supported route. Purification in the solid-phase route was also relatively convenient.

Polymer resins with different loadings and cross-linking were investigated. Lower loadings and cross-linking gave better yields and narrower polydispersities (Table 4.5). Examination of the dry solid support by polar-

TABLE 4.5. Data for Solid-Phase Synthesis of a Hyperbranched Polymer

	By Focal Point–Monomer Ratio					
Physical Parameter[a]	17:5	35:1	70:1	140:1	280:1	560:1
Mass increase of solid support, %						
I	200	250	470	760	1025	1245
II	100	190	550	900	1230	1350
III	26	120	55	190	235	305
Yield of polymer, %						
I	53	35	35	19	20	12
II	7	21	18	17	14	6
III	19	9	7	8	4	3
Polydispersity of polymer						
I	1.37	1.33	1.28	1.34	1.29	1.47
II	1.46	1.57	1.38	1.42	1.44	1.73
III	1.56	1.41	1.51	1.49	1.89	1.74

[a]I, II, and III correspond to resin degree of functionality (in mmol/g) 0.7, 1.7, and 1.7, respectively. In addition, they correspond to the degree of cross-linking of the polystyrene beads with divinylbenzene: 1, 1, and 2%, respectively.

ized optical microscopy revealed that the beads became birefringent and grew in size as they took up more monomer. The birefringence was most likely due to internal stress within the expanded polymer beads. Furthermore, at high monomer to focal point monomer ratios, the spherical beads shattered into a fine powder.

There are a number of potential advantages to solid-supported hyperbranched polymerizations. First, since the focal point functional group is bound to the solid support, intramolecular cyclization between the focal point and a peripheral group is impossible. This problem has been implicated as limiting solution-grown hyperbranched polymers.[38] Second, the terminal ends can easily be modified with different monomers providing different periphery with a common internal structure. This type of modification can be extended to other monomers to make layered hyperbranched copolymers. Third, cleavage from the support after terminal group capping ensures one unique focal point functional group per molecule. This site could be used to construct multidendron architectures or hybrid structures.

4.4.4. Monitoring and Characterization

Monitoring reaction progress throughout a multistep synthesis is a relatively difficult task.[22] Typical methods used for solution-phase synthesis, including thin-layer chromatography (TLC), GC, and most types of mass spectrometry (MS), are less informative for solid-phase methods. However, Fourier transform infrared (FTIR) spectroscopy and nuclear magnetic resonance (NMR) are particularly useful in solid-phase strategies.

"Null-to-null" IR monitoring has been used to track the reaction sequence of growing oligomers bound to a polymer resin. This method is simple and nondestructive. FTIR spectroscopy has been used for the specific case of phenylacetylene oligomers.[14,15] Infrared analyses are conveniently performed by placing approximately 1 mg of the resin between two NaCl plates, swelling the beads with one drop of carbon tetrachloride, and immediately recording an FTIR spectrum. Attempts to record the spectrum without swelling the beads results in a poor signal. The convergent synthesis of the oligomers, detailed previously, involves a trimethylsilyl-protected acetylene group as the "exposed" reactive site off the polymer bead. TMS-protected oligomers have a characteristic band at 2156 cm^{-1} (strong) corresponding to a carbon–carbon bond stretch of the TMS–acetylene (Figure 4.7). After deprotection using TBAF in THF for 5 min, the newly

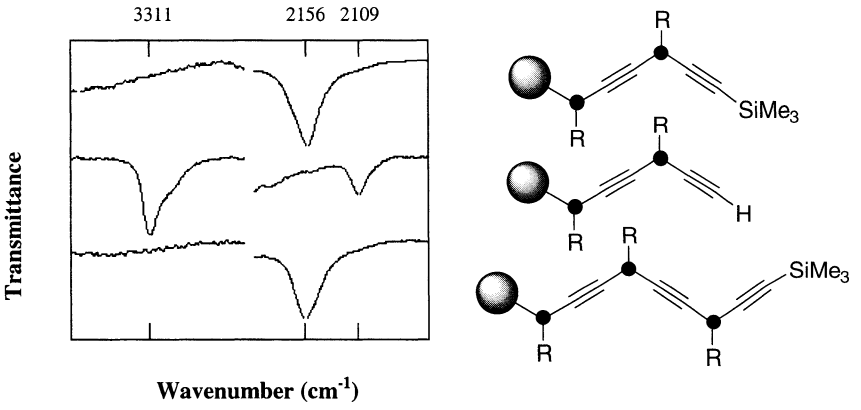


Figure 4.7. Infrared spectra used to monitor cross-coupling and deprotection reactions on resin-bound phenylacetylene oligomers. Observation of a null at 3311 and 2156 cm^{-1} corresponds to complete acetylene coupling and trimethylsilylacetylene deprotection, respectively.

formed terminal acetylene is easily identified in a similar manner; bands at 3311 cm^{-1} (strong) and 2109 cm^{-1} (weak) correspond to carbon–hydrogen and carbon–carbon bond stretches, respectively. The deprotection step is therefore accompanied by complete disappearance (null signal) of the TMS–acetylene stretch. The reliability of this method was corroborated by the liberation and characterization of oligomers and is approximately sensitive to a detection level of 5% unreacted material. This method was also used to evaluate cleavage of sequences from the solid support by checking for the presence of IR bands attributed to the oligomers themselves.

Other laboratories have used FTIR spectroscopy to determine the kinetics of reactions on different polymer supports[39] and to enumerate factors regulating site interactions in different types of supports (see Chapter 7, p. 219).[40] A major weak point of the procedure is the need for IR diagnostic functions or changes in hybridization to be involved in the transformation to be investigated. For phenylacetylene oligomers, however, the TMS and terminal acetylene absorptions are ideal.

Both ^{13}C NMR and ^{1}H NMR have also been used to monitor solid-phase syntheses. For ^{13}C NMR methodologies, the main concern lies in the thousands of transients needed to properly visualize bead-attached moieties. Recently, a rapid technique has been developed.[41] The method takes advan-

tage of commercially available NMR tube inserts that position resin within the observation coils of an NMR instrument. Spectra are clear and easily deconvoluted, attributed mainly to the highly characteristic and ^{13}C-enriched functions involved. As little as 20 mg of support containing less than 1 mg of compound yielded meaningful spectra in as few as 64 transients. For phenylacetylene systems, ^{13}C NMR was used to track the preparation of the *n*-propylamination of Merrifield's resin, a transformation detailed previously. A comparison of the spectra of the chloromethyl polymer and *n*-propylaminomethyl polymer indicates complete substitution of the benzyl chloride for the benzyl-*n*-propylamino group. These results were verified by a null chlorine percentage in elemental analysis.

^1H NMR has also been a valuable monitoring method for SPOS. Reported first in 1994, several uses of magic angle spinning (MAS) to enhance the spectra of suspensions of polymer-supported compounds are now documented.[42] More recently, a spin echo twist was added to the MAS technique.[43] Selective quenching of the polystyrene signal (often a problem with its broad peaks in the aromatic region) could be achieved by a judicious choice of τ values in a spin echo pulse sequence. Polymer-supported ^1H NMR two-dimensional spectra have also been obtained; the results from COSY and TOCSY analyses can be highly informative.

4.5. SCOPE AND LIMITATIONS

The final part of this chapter deals with the scope and limitations of solid-phase phenylacetylene-oligomer syntheses. Solution-phase methods have several advantages making it the method of choice in some cases. Larger scales can be realized more easily and rapidly because cumbersomely large amounts of resin are needed to prepare gram quantities of product on a solid phase. Even if the resin is affordable, small mechanical losses in long synthetic procedures can accumulate to be significant. All the common monitoring techniques (TLC, GC, MS) that are used routinely in solution-phase syntheses can only be performed after cleavage of intermediates/product in solid-phase routes. Moreover, yields from solution-phase methods are more reliable because the product is isolated in larger amounts.

Numerous difficulties can arise when calculating yields in solid-phase syntheses.[13] Errors in resin weight, molar concentration of products on the resin, and elemental analysis can be relatively large. Three distinct cases were identified, and these required different methods of yield determination

TABLE 4.6. Three Possible Yield Calculations for Solid-Phase Syntheses

Case Number	Tracking Method	Equation[a]	Estimated Error
1	Gain of N in product	$Y = 1/[(N_c/N_p)\,(M_c N_{si}/E) - N_{si}\,\Delta M]$	±0.13
2	Loss of Cl in product	$Y = [\Delta M(N_p/N_e)E/M_e N_e] + 1$	±0.29
3	Triazene N in reactant and product	$Y = \{[1/(1 + \Delta E/E_i)] - 1\}/N_{si}\,\Delta M$	±0.92

[a] Y is yield, N_e is the number of moles of tag element, N_p is the moles of product, M_e is the molecular weight of the tag element (g/mol), N_{si} is the moles of starting functionality in 1 g of the initial resin, E is the weight fraction of the tag element (from elemental analysis), ΔM is the change in molecular weight upon reaction, and ΔE is the change in the tag element's weight fraction.

(Table 4.6). Specifically, the methods used were to (1) add a tag (type of atom or physical change tracked in these calculations); (2) remove a tag element from the resin during reaction; or (3) use a tag element unique to the resin before and after reaction. Error was estimated by accessing limitations of elemental analyses and known resin functionalization error. While the third case listed could not be applied to the phenylacetylene

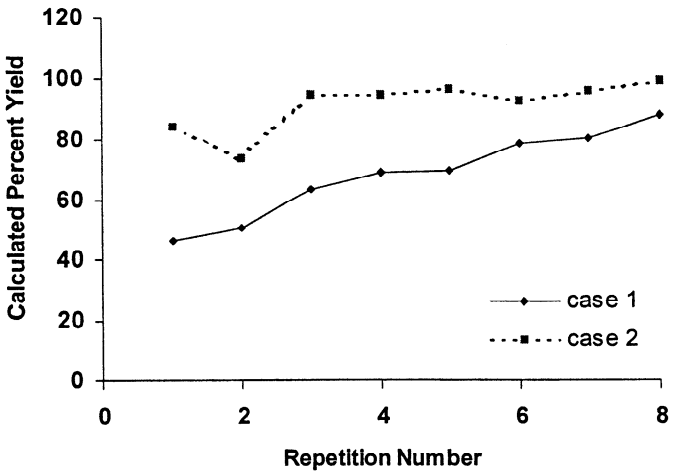


Figure 4.8. Cases 1 and 2 (Table 4.6) calculated yields for *n*-propylamination of Merrifield's resin versus chronological reaction attempt.

oligomer system, cases (1) and (2) were applicable to transformation of Merrifield's resin to the *n*-propylaminomethyl-substituted resin. Figure 4.8 shows calculated yields using both cases 1 and 2 for this transformation. Yields were variable for even this simple starting transformation. Taking error into consideration, as well as low detection limits for nitrogen and chlorine in elemental analyses, the stated yields are quite liberal. In addition, their irregularity over eight reaction attempts (given in chronological order) highlights the unreliability. Since it is extremely difficult to estimate a dependable degree of substitution because the resin comprises a vast majority of the mass, yield calculations are inherently variable.

Despite the obstacles discussed above, solid-phase syntheses of oligomers do have two significant advantages over solution techniques. First, purifications in solid-phase techniques are easier and faster than in solution and are more likely to be amenable to automation. Second, hetero-oligomerizations are relatively easy to arrange if one component is anchored to a solid phase. Overall, the advantages of solid-phase syntheses of oligomers, as well as other products, can be appreciable for reproducible, reliable, and easily monitored reaction schemes.

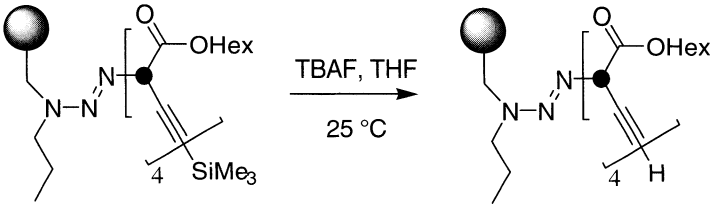
4.6. CONCLUSION

Solid-phase methods are applicable to syntheses of sequence-specific oligomers and dendritic structures. The triazene chemistry developed for this specific purpose may also be useful in other types of syntheses. Further development of solid-phase syntheses of this type into combinatorial synthesis of oligomers is the next logical step. Solid-phase methods will never completely replace solution-phase approaches to oligomers, but either technique should be considered with respect to the special characteristics and requirements for the system under investigation.

4.7. REPRESENTATIVE PROCEDURES[44]

4.7.1. Trimethylsilyl Deprotection

To a suspension of the polymer-supported trimethylsilyl (TMS) protected acetylene tetramer (241 mg, 0.0757 mol) in THF (2 mL) was added a solution of tetrabutylammonium fluoride (TBAF) in wet THF (0.15 mL, 1.0

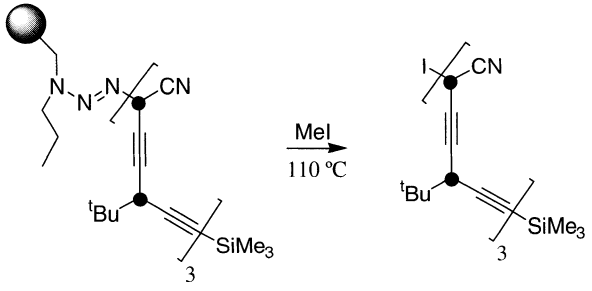


Scheme 9.

M) (Scheme 9). The suspension was agitated periodically for 5 min. The polymer beads were transferred to a fritted filter using THF and washed sequentially (7.2 mL) with THF and then methanol. The polymer beads were dried in vacuo to a constant mass to give polymer-supported terminal acetylene as light yellow beads.

4.7.2. Cleavage of Oligomers from the Polymer Support

A suspension of the polymer-supported TMS-protected acetylene hexamer (2.71 g, 0.279 mequiv/g) and iodomethane (27.0 mL) were degassed and heated at 110°C in a sealed tube for 12 h (Scheme 10). After the iodomethane was removed in vacuo, the product was extracted from the resin using hot CH_2Cl_2. The resulting solution was cooled and filtered through a plug of silica gel, and the CH_2Cl_2 was removed in vacuo to give an oily brown residue. The residue was purified by filtration through a plug of silica gel in CH_2Cl_2 to give 459.8 mg (0.44 mmol, 58%) of iodo-terminated hexamer as a white powder.



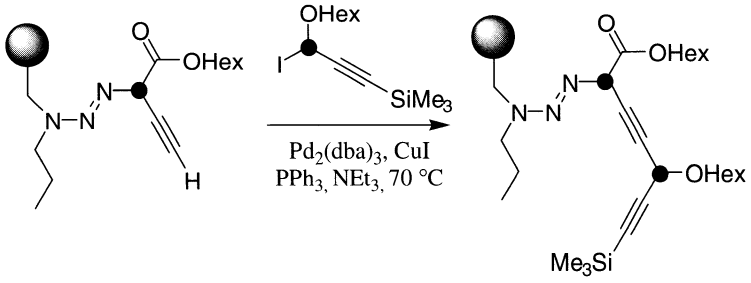
Scheme 10.

4.7.3. Preparation of a Soluble Pd(0) Coupling Solution

Under a nitrogen atmosphere, a mixture is prepared consisting of tris(dibenzylideneacetone)-dipalladium(0) (34.5 mg, 60 μmol), Cu(I) iodide (11.4 mg, 60 μmol), triphenylphosphine (78.7 mg, 0.30 mmol), and dry, degassed triethylamine (15 mL) as solvent. The mixture is degassed and filled with nitrogen two more times, then stirred at 70°C for 2 h. After standing overnight, the supernatant from this solution can be transferred via cannula in the amount of 6 mL/g (0.7 mequiv/g) resin to another flask for use in the palladium-catalyzed cross-coupling reaction of an aryl halide and a terminal acetylene.

4.7.4. Palladium-Catalyzed Coupling

To a heavy-walled flask equipped with a nitrogen inlet side arm was added resin-bound terminal acetylene (684.4 mg resin, 0.274 mmol, 0.448 mequiv/g resin) and aryl iodide (120.6 mg, 0.3011 mmol) (Scheme 11). The flask was evacuated and back-filled with nitrogen a minimum of three times. The supernatant of a separate 0.2 M catalyst cocktail solution (previously prepared) was added via cannula (5 mL, 3.0 mmol) to the reaction flask. The flask was kept sealed at 65°C for 12 h and agitated periodically to remix polymer beads stuck on flask walls. The beads were then transferred to a fritted filter using methylene chloride and washed with methylene chloride (21 mL). Excess aryl iodide can be recovered from the first methylene chloride wash. All further washes were carried out in the ratio of 30 mL/g resin. The resin was washed sequentially with DMF, 0.05 M solution of sodium diethyl dithiocarbamate in 99 : 1 DMF–diisopropylethylamine,



Scheme 11.

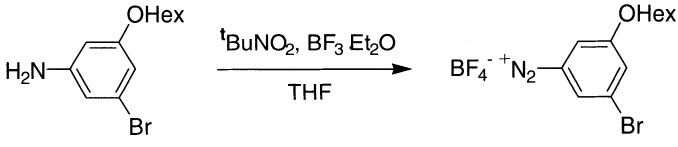
DMF, methylene chloride, and MeOH and then dried in vacuo to a constant mass giving resin-bound oligomer as light yellow to brown polymer beads.

4.7.5. Preparation of Propylaminomethylated Resin

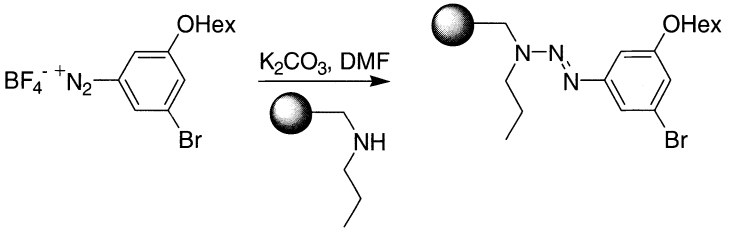
See Scheme 4. A suspension of chloromethyl polystyrene–1% divinyl benzene copolymer beads (66.0 g, 0.700 mequiv Cl, 200–400 mesh) and *n*-propylamine (300 mL) was degassed and heated at 70°C for 86 h in a sealed tube. The polymer was transferred to a coarse sintered glass filter using methylene chloride and washed with methylene chloride (400 mL). The resin was then thoroughly washed according to the following protocol to remove non–covalently bound material. Resin was placed in a 1-L flask, fitted with a magnetic stirrer at 70°C and stirred slowly with dioxane–2 N NaOH (1 : 1, v/v, 400 mL) for 30 min. Solvent was removed by aspiration through a coarse sintered glass filter. This was repeated once with dioxane–2 N NaOH (1 : 1, v/v, 400 mL), twice with dioxane–water (1 : 1, v/v, 400 mL), followed by hot DMF (1 L), methanol (1 L), and benzene (1 L). The resin was then rinsed with hot methanol (1 L) and dried in vacuo to a constant mass to give white propylaminomethyl poly(styrene)–1% divinylbenzene copolymer beads.

4.7.6. Generation of a Diazonium Salt

To a dry three-neck 250-mL round-bottom flask equipped with a 100-mL addition funnel and nitrogen inlet is added boron trifluoride etherate (8.14 mL, 66.2 mmol) (Scheme 12). The flask is then chilled to −15°C in an ice–acetone bath. The aryl amine (4.5 g, 16.54 mmol) is dissolved in THF and added slowly over 20 min. *tert*-Butyl nitrite (6.9 mL, 57.9 mmol) in THF is then added to the mixture over 30 min. The reaction is stirred another 10 min at −15°C and then warmed to 5°C over 20 min. Hexane is added (300 mL) to the mixture upon which a solid precipitates. The solid is removed by filtration and washed with cold ether and dried in vacuo to give



Scheme 12.



Scheme 13.

3-bromo-5-hexyloxybenzenediazonium tetrafluoroborate (5.62 g, 15.22 mmol, 92%) as a yellow powder.

4.7.7. Preparation of Triazene-Tethered Monomer

To a chilled (0°C) suspension of *n*-propylaminomethyl poly(styrene)–1% divinylbenzene copolymer beads (4.32 g, 0.522 mequiv N/ g resin, 2.25 mmol, 200–400 mesh), finely ground potassium carbonate (590 mg, 4.5 mmol), and DMF (50 mL) was added 3-bromo-5-hexyloxybenzenediazonium tetrafluoroborate (1.0 g, 2.69 mmol) in portions over 1 h (Scheme 13). After each addition, an aliquot of the DMF supernatant was diluted in diethylamine and analyzed by GC. Once diethyltriazene was detected, the additions were ceased and the suspension was transferred to a fritted filter using DMF and washed sequentially with 120 mL of the following solvents: MeOH, water, MeOH, THF, and MeOH. The beads were then dried in vacuo to a constant mass to give 1-(3-bromo-5-hexyloxyphenyl)-3-propyl-3-(benzyl supported) triazene as light yellow material.

ACKNOWLEDGMENT

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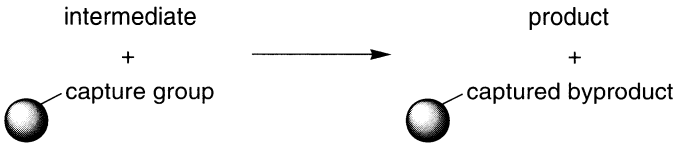
CHAPTER 5

POLYMER-ASSISTED SOLUTION-PHASE METHODS FOR CHEMICAL LIBRARY SYNTHESIS



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5.1. INTRODUCTION

The requirement for life sciences disciplines to discover and optimize small molecules with a heightened sense of capacity and timeliness has led to an explosion in methodologies to synthesize organic compounds in greater

numbers and with increased efficiency. A major impetus for this requirement arose from the advent of ultra-high throughput biological screening technologies. Genomics will soon make it possible to screen compounds for activities against a myriad of potential targets of pharmaceutical and agricultural importance, thus accentuating the need for large numbers of synthetic small molecules. This triad of genomics, robust high-throughput screening, and responsive high-throughput chemical synthesis looks to become a powerful paradigm for life sciences discovery research.

During the early part of this decade, most efforts in high-throughput synthesis utilized solid phase organic synthesis (SPOS) techniques.[1–3] SPOS was a natural outgrowth of earlier methods used to synthesize peptides and oligonucleotides.[4] This method has several advantages over traditional solution-phase synthesis:

- Excesses of solution-phase reactants and reagents can be used to drive reactions to completion; these reagents can then be washed away from polymer-bound intermediates.
- The split-mix synthesis technique can allow geometric numbers of compounds to be prepared using an arithmetic number of reaction chambers.[5]
- Chemical[6–8] or radio frequency [9,10] tagging methods can be used for compound identification.

However, there are also some serious practical and theoretical constraints, including the following:

- Tethering of library intermediates to polymer supports requires a functionality devoted to this role; hence all library members are typically endowed with the same functional group.
- Attachment of library substrates to the support and final release of library products introduce two additional steps in a synthesis.
- Heterogeneous reactions must conform to high specifications (conversions ~98% for each step) if multiple steps are to provide reasonably pure products.
- Materials released from the polymer support tend to be contaminated with truncated intermediates.

- Specialized analytical tools are required to monitor reactions and purities of polymer-supported intermediates.
- With the exception of one-step multicomponent reactions, solid-phase organic syntheses are linear, because convergent sequences would require removal of intermediates from the polymer support.[11]

Many laboratories have investigated alternative solution-phase strategies for preparing combinatorial libraries to overcome these limitations of solid-phase organic synthesis.[12–15] This chapter reviews advances that have been made over the last two years in "polymer-assisted syntheses."[16–18] This approach is in many ways complementary to solid-phase organic synthesis. In polymer-assisted solution-phase strategies, the polymer supports are used to tether reactants, reagents, or catalysts rather than to tether library members. Functionalized supports are also often used to chemoselectively sequester solution-phase reaction species (e.g., excess reactants) during purification. Additionally, soluble bifunctional (chemically tagged) reagents can be used to mediate solution-phase reactions, with the bifunctional tag serving a post-reaction trafficking role to mediate purification. In summary, polymer-assisted solution-phase methods:

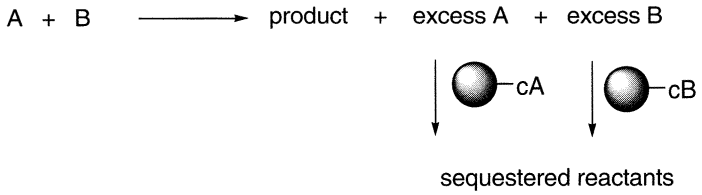
- do not require attachment of library members to a support;
- do not compromise diversity introduced by obligatory linking functionality;
- need no additional steps for attachment and release from a polymer support;
- often involve reaction incubation in a homogeneous medium with predictable and reliable reaction kinetics;
- provide a strategy for purification after reactions that do not proceed to completion, reducing the need for high stringency validation;
- allow use of conventional analytical tools for assessing reaction progress and chemical purities; and
- accommodate convergent as well as linear synthetic strategies.

This chapter categorizes major approaches to polymer-assisted solution-phase syntheses. It highlights recent reports describing multistep chemical library synthesis using only polymer-assisted purifications, so disproving the assertion that solution-phase syntheses of libraries is limited only to

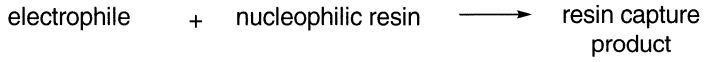
one- or two-step campaigns. Examples are provided wherein both solid-phase organic synthesis and polymer-assisted solution-phase strategies are used in the same library synthesis campaign. Indeed, polymer-assisted technologies are increasingly applied by practitioners of solid-phase organic synthesis during "resin-release" reactions, and solid-phase organic syntheses are being used in polymer-assisted schemes, especially for "resin-capture" of solution-phase intermediates or products.

5.2. REACTANT SEQUESTRATION

Reactant sequestration provides a rapid method for removing an excess of solution-phase reactants, as shown below. Excess **A** or **B** is used to drive a bimolecular reaction to completion and, after the transformation is complete or has reached equilibrium, a resin bearing an organic functionality (cA) complementary to that of **A** is added to sequester excess **A**. Conversely, a resin expressing cB functionality could also be used to sequester remaining **B**. Filtration and concentration affords purified product. Reactant-sequestering resins were independently reported by various research groups and have been called "solid-phase scavenging agents,"[19] "complementary molecular reactivity sequestrants,"[20] and "polymer-supported quenching reagents."[21]

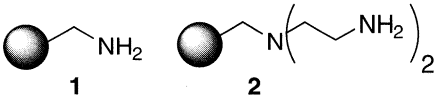


Several resins have been used frequently in reactant sequestration. Aminomethylpolystyrene **1** and the more highly functionalized polyamine resins **2** and **3** have been reported to sequester excesses of solution-phase electrophiles, including isocyanates, isothiocyanates, sulfonyl chlorides, acid chlorides, anhydrides, aldehydes, and imines. Cross-site reactivity is not an issue with the more densely functionalized sequestering resins so their use in an automated laboratory environment offers a significant resin and volume economy compared to less densely functionalized resins.

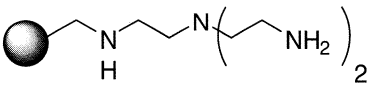


electrophiles = RNCO, RNCS, RSO_2Cl, RCOCl, RCHO, RCH=NR

nucleophilic resin =

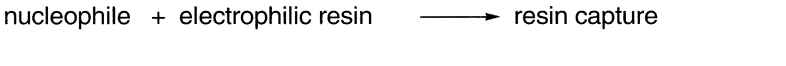


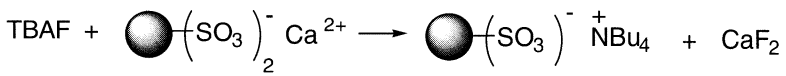
1 **2**



3

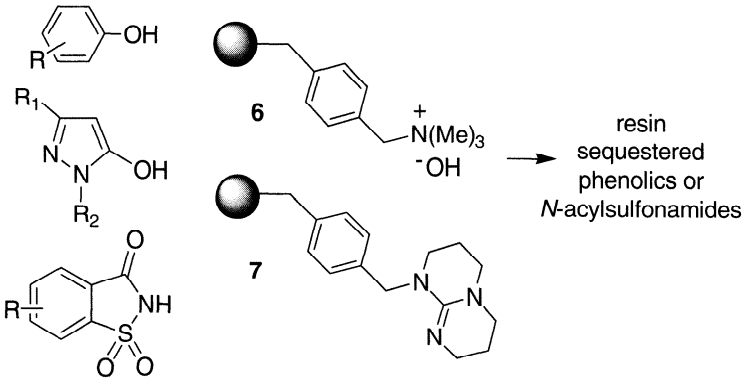
Appropriately functionalized resins can sequester excess nucleophiles from solution-phase reactions. Thus the calcium sulfonate resin **4** captures tetra-*n*-butylammonium fluoride (TBAF) from a variety of desilylation reactions.[22,24] Polymer-bound tetra-*n*-butylammonium sulfonate and insoluble calcium fluoride are formed. The applicability of this strategy was illustrated for deprotection of β-trimethylsilylethyl esters as well as silyl ethers.





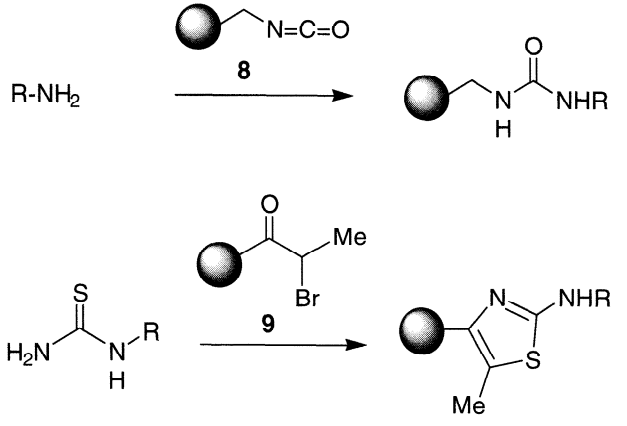
4 **5**

A quaternary ammonium hydroxide ion exchange resin **6** was shown to sequester phenols, hydroxypyrazoles, and other weakly acidic heterocycles.[25] The sequestered nucleophiles could also be used as polymer-supported reactants. Similarly, the guanidine-functionalized resin **7** was also shown to be a useful capture agent for weakly acidic nucleophiles, including phenols and cyclic *N*-acyl sulfonamides.[26]



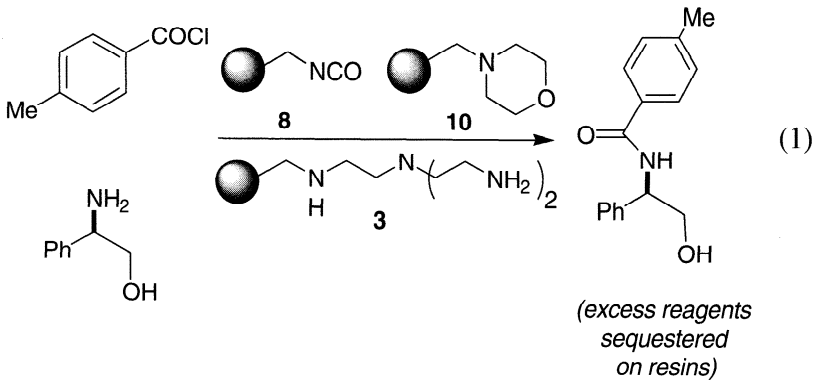
A methyl isocyanate–functionalized resin **8** has been used to sequester excesses of amines or hydrazines from solution phase when these reactants were used in urea-forming reactions or pyrazole-forming reactions.[19,21] Finally, the α-bromoketone resin **9** was shown to efficiently sequester thioureas from solution in Hantzsch aminothiazole-forming reactions.[27]

nucleophile + electrophilic resin ⟶ resin capture product



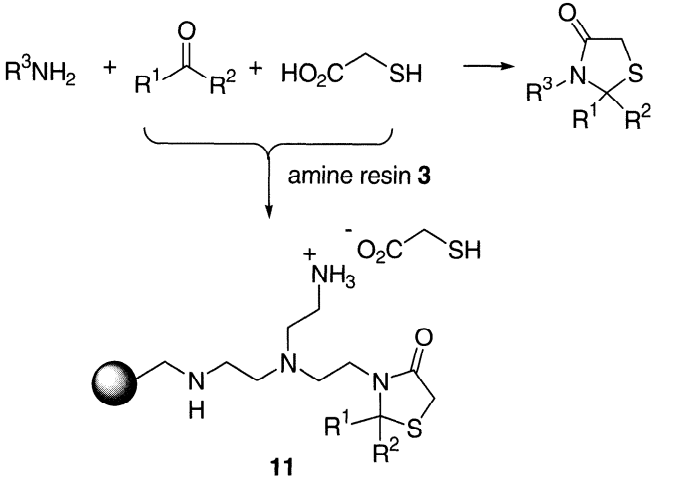
Resin capture can be faster and more efficient than classical methods of purification (e.g., chromatography). Chemoselective sequestration requires minimal amounts of solvent for separating reactants from solution-phase products. Gradient elution techniques, common in chromatographic separations, are avoided, saving time and solvent. Additionally, concurrent use

of resins containing otherwise incompatible functionality is possible, allowing two different reagents to be captured simultaneously. Equation 1 illustrates this concept for the amine-functionalized support **3** and the isocyanate-functionalized resin **8**.[21] Cross-resin reactions do not occur because of site isolation on the supports.



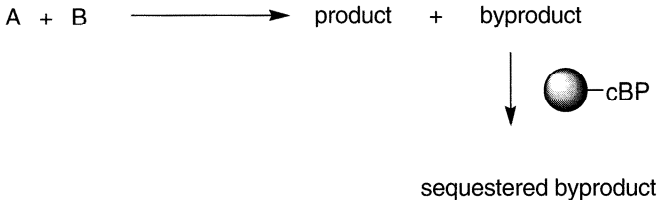
(1)

A single, functionalized resin can be designed to capture more than one reactant. For instance, resin **3** has been used to sequester excess aldehydes/ketones and thioacetic acids.[28] Specifically, the polyamine resin **3** did this by forming the resin-bound thiazolidinones **11** and salts from the excess reagents, leaving the desired thiazolidinones in solution.

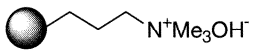


5.3. BYPRODUCT SEQUESTRATION

Byproduct sequestration using a supported functional group (cBp in the diagram below) complementary to that of byproduct is a logical extension of reactant sequestration. There are fundamental differences between the two methods, however. Reactant-sequestering resins are exclusively used *after* solution-phase reactions to remove excess substrates, whereas byproduct-sequestering resins can be present during or after the transformation. One advantage of adding a capture agent to a reaction in progress is that byproduct-sequestering resins can drive equilibrium reactions to completion. A second distinction is that reactant sequestration usually involves covalent bond formation with a functionalized resin, whereas byproduct sequestration typically relies on ion-pairing (acid–base) interactions.



Carboxylic acids generated in acylation reactions have been effectively sequestered by ion pair formation with Amberlite IRA-68 ion exchange resin.[29,3] Similarly, 4-nitrophenoxide formed in acylations of 4-nitrophenyl esters has been captured by anion exchange with the quaternary ammonium hydroxide resin **12**.[31] An exception to ion pair–mediated sequestration of byproducts is the polyamine functionalized resin **3** that was shown to covalently sequester the β-methoxy enone hydrolysis byproduct from Danishefsky's diene via imine formation.[23]



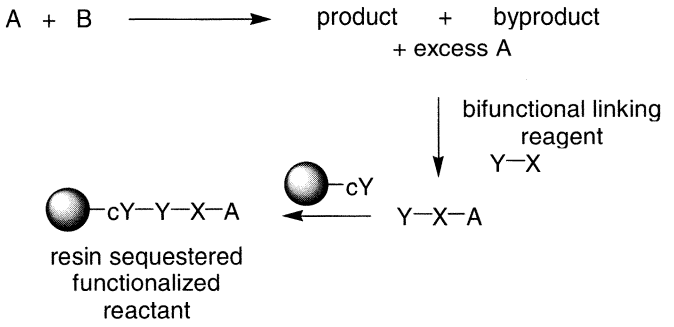
12

It is anticipated that additional byproduct-sequestering resins will be reported in the near future, highlighting novel ionic and covalent sequestration strategies. In particular, the application of byproduct-sequestering resins (other than acid scavengers) to help drive reactions to completion would demonstrate a significant advance in this area.[32]

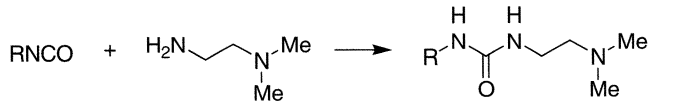
5.4. SOLUTION-PHASE DERIVATIZATION TO FACILITATE POLYMER-ASSISTED SEQUESTRATION

5.4.1. Reactant Solution-Phase Linking Reagents

Direct sequestration of a reactant by an insoluble resin is impractical if the kinetics is sluggish and impossible if the solution-phase reactant does not contain a functionality to enable direct sequestration. These limitations led several research groups to use "bifunctional solution-phase linking reagents," also referred to as "sequestration-enabling-reagents."[33]

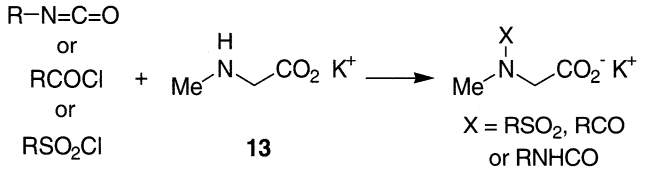


In a typical process N,N-dimethyl-ethylenediamine has been used to transform excess isocyanate reactants into amine-tagged ureas that can be sequestered from solution phase.[34,35] Glycine has been used as a carboxy-tagged solution-phase linking reagent to convert aldehydes or isothiocyanates to the carboxy-tagged imines or thioureas, respectively.[36] Similarly, the more nucleophilic sarcosine salt **13** has been used to derivatize isocyanates, acid chlorides, or sulfonyl chlorides as carboxy-tagged derivatives (equation 3). [37] Finally, the carboxy-tagged thiourea **14** was utilized to convert excess α-bromoketones to carboxy-tagged aminothiazoles for capture by ion exchange resins. [34]



(2)

can be sequestered on acidic ion-exchange resin



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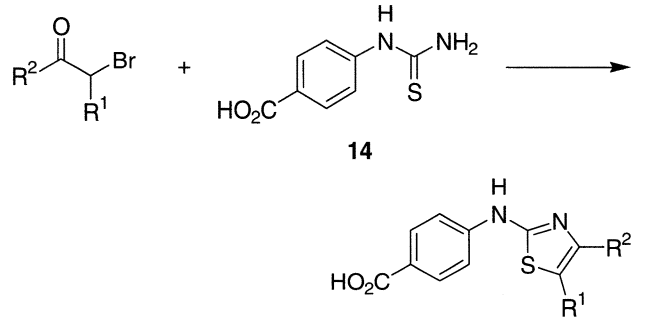
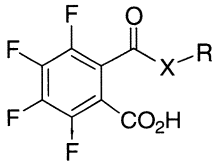


(4)

A few solution-phase linking reagents facilitate sequestration of modestly reactive nucleophiles. Tetrafluorophthalic anhydride was shown to be sufficiently reactive to derivatize electron-deficient and sterically hindered anilines, amines, and alcohols as the carboxy-derivatized species **15**.[32,33] Benzenesulfonyl isocyanate was also shown to efficiently derivatize anilines, amines, or alcohols, forming acidic sulfonylureas or sulfonylcarbamates **16**, which can be sequestered on a polyamine-functionalized resin. Use of these highly reactive soluble linking reagents facilitated purification of products even from low-yielding, incomplete reactions. Finally, hexafluoro-*iso*-propyl oxalate was used to convert poorly reactive anilines to their sequestrable half-esters **17**.[38] These anilines did not further react to form bis-amides, so preserving a hexafluoro-*iso*-propyl ester for covalent sequestration by a polyamine-functionalized resin.



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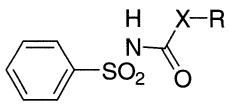
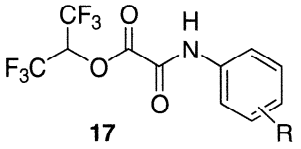


16 X = NH or O

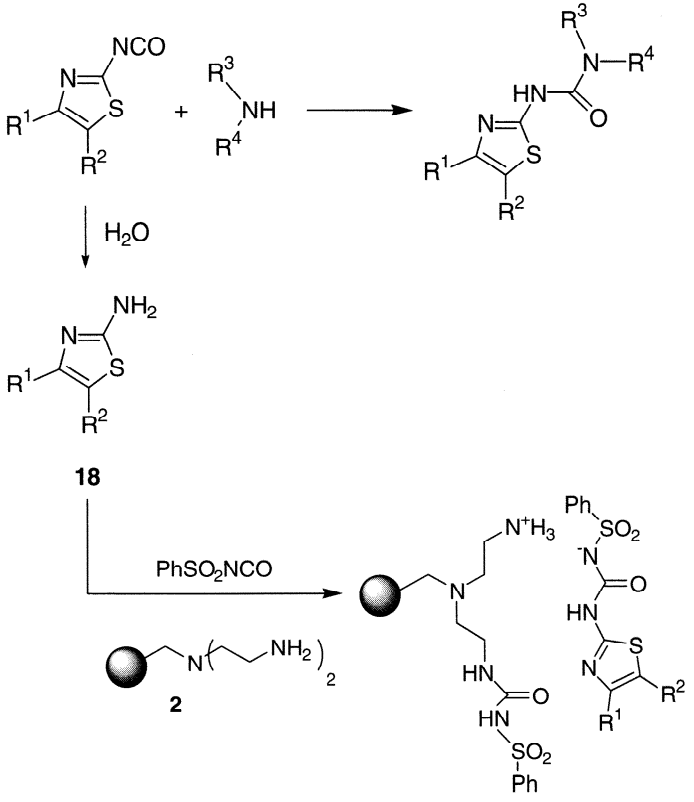


17

Solution-phase syntheses employing linking reagents provide an alternative to solid-phase organic synthesis when poor conversions and incomplete reactions yield "deletion intermediates" upon release from resin. Applications are highlighted in various multistep syntheses covered at the end of this chapter.

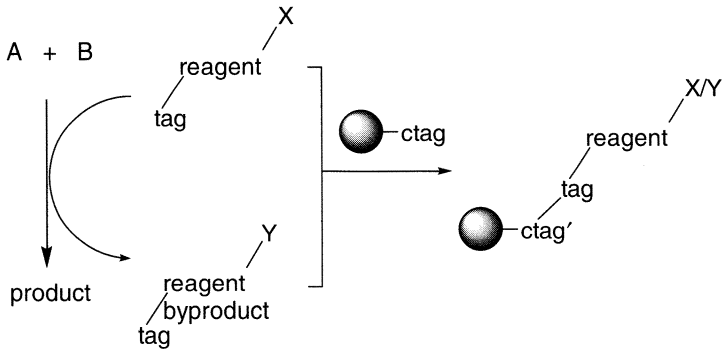
5.4.2. Byproduct Solution-Phase Linking Reagents

Poorly reactive (poorly sequestrable) byproducts are more frequently encountered than poorly sequestrable reactants. A few reports have appeared describing the use of soluble bifunctional linking reagents to chemically tag



byproducts to affect their removal. One application featured benzenesulfonyl isocyanate to sequester an aminothiazole side product **18**, formed on hydrolysis of the thioazolyl isocyanate reactant by adventious water. These electron-deficient amines were transformed into acidic acylsulfonimides and then sequestered as ionic adducts.[32]

5.5. SOLUBLE BIFUNCTIONAL REAGENTS

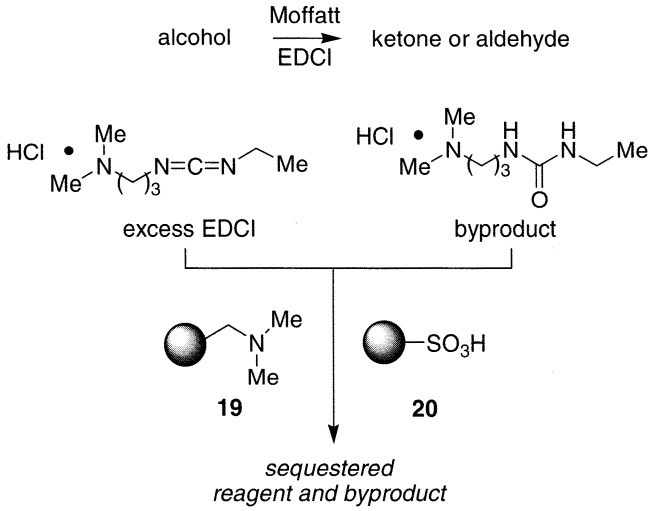


Classical reagents possess inherently reactive functionality; however, the spent reagent byproducts typically exhibit low reactivity and often lack sufficient functionality to enable their sequestration. Bifunctional reagents offer a technique for sequestration of reagents and byproducts. A bifunctional reagent contains a conventional reagent functionality 'X' and also contains a remote chemical functional group 'tag.' The 'tag' functionality does not interfere with the performance of the reagent, but does offer a molecular recognition handle to affect the post-reaction sequestration of excess reagent and byproduct.

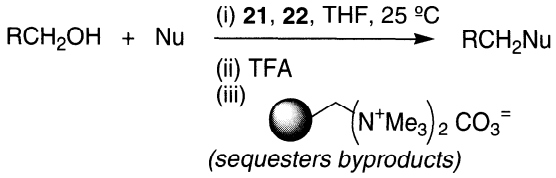
5.5.1. Bifunctional Reagents for Condensation Reactions

1-Ethyl-3(3-dimethylaminopropyl)carbodiimide (EDCI) is a commercially available, tertiary-amine-tagged, condensation reagent that has been used in parallel reactions to mediate amide bond formation between carboxylic acids and amines.[34] Excess EDCI and the urea byproduct formed from it were removed after the reaction via ion exchange capture. EDCI was also used in a parallel-array format to mediate dichloroacetic acid–catalyzed Moffatt

oxidations of hydroxyethylamines.[20] A mixed-resin bed containing A-21 tertiary amine resin **19** and Amberlyst A-15 sulfonic acid resin **20** was used to sequester HCl and the free-base forms of reagent and reagent byproduct. The mixed resin bed of amine and acid functionalities could be used without interfering with each other because the two functional groups were site isolated from each other. Simultaneous acid and base extractions were thereby possible.



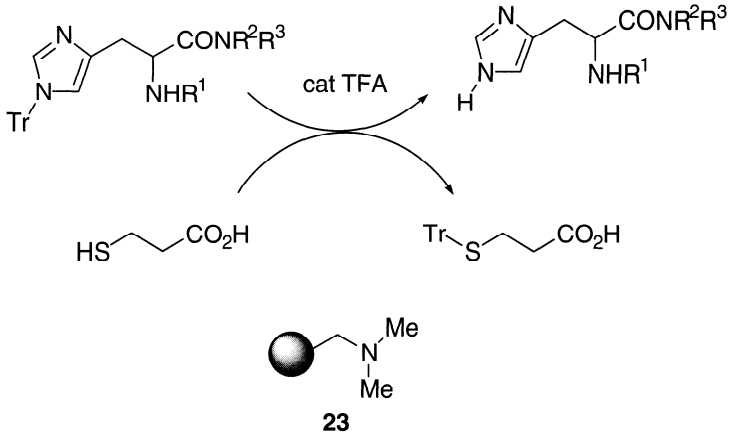
Bifunctional reagents have recently been used to facilitate separations in the Mitsunobu reaction.[39] Mitsunobu products are often hard to separate from excess reagents and byproducts, including phosphines and phosphine oxides. The "tagged" phosphine **21** and azodicarboxylate **22** and the byproducts formed from these are converted to the carboxylic acid forms by treatment with trifluoroacetic acid (TFA) at the end of the reaction. The excess reagents and byproducts could then be captured on an ion exchange resin for convenient removal.



(5)

5.5.2. Bifunctional Reagents for Removal of Trityl Groups

3-Mercaptopropionic acid has been used as a scavenger in detritylation of protected imidazoles. In the purification, A-21 tertiary amine–functionalized resin **23** sequestered excess of this acidic reagent, the tritylated byproduct formed from it, and TFA (reaction 6).[32]

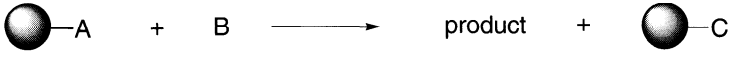


(6)

23

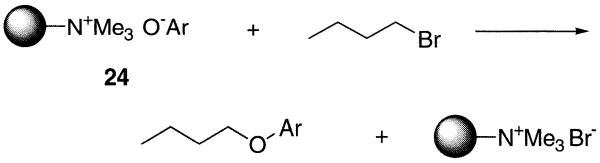
The role of bifunctional (tagged) reagents in the transformations described above is similar to that of polymer-immobilized reagents. However, they exhibit more reliable reaction kinetics because they react in the solution phase. Moreover, manipulation of these reagents is more easily automated since transfer of solutions is much easier than transfer of solids.

5.6. POLYMER-SUPPORTED SUBSTRATES



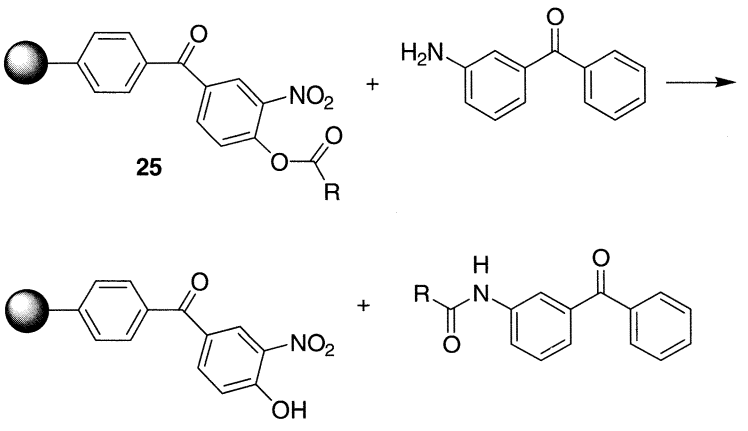
Polymer-supported reactants are most useful for cases where reactant byproducts would otherwise be difficult to sequester. Recycling of the

support is possible in the frequently encountered case where the byproduct is a polymer-supported leaving group. A recent example illustrates a process in which a mixture of 10 phenolic compounds was immobilized on Amberlite IRA-900, giving reagent **24** (reaction 7). This polymer-supported mixture was reacted with butyl bromide to give the product aryl ethers and a supported quaternary ammonium bromide as an easily removed byproduct.[25]



24 (7)

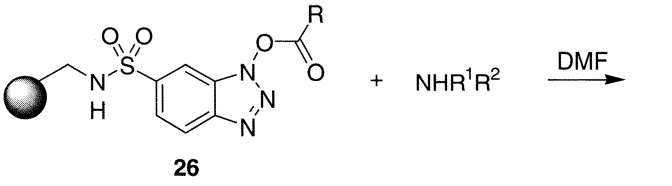
Several polymeric acyl-transfer reactants have been used to give amide/ester products in the solution phase. The excess polymer-bound acyl-transfer reactants and polymer-bound nucleofuge byproducts are easily removed after completion of the reactions. One such application involved the activated nitrophenyl esters **25** (reaction 8).[40] A mixture of 10 acid chlorides was converted to an equimolar mixture of 10 amide products; a potent preemergent herbicide was discovered using this parallel synthetic approach.[41]



25 (8)

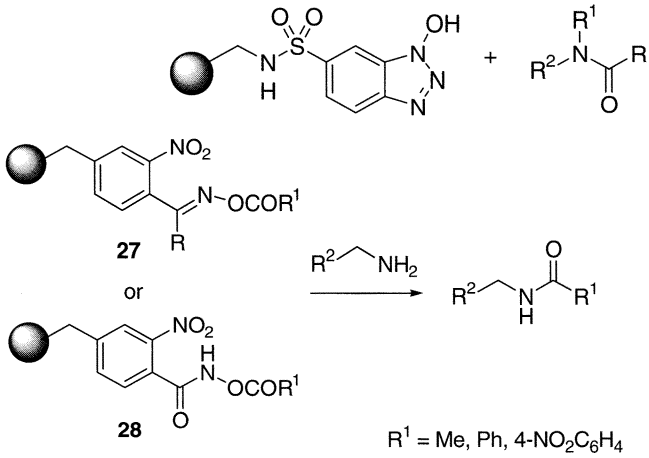
Polymer-bound active esters **26** were prepared from a 1-hydroxybenzotriazole (HOBt) functionalized polymer and carboxylic acids in the presence of tripyrrolidinyl-bromophosphonium hexafluorophosphate (Py-

BrOP). These active esters react smoothly with amines at room temperature (reaction 9).[42] Similarly, supported oximino esters **27**[43] and hydroxamic esters **28**[44] undergo facile acyl transfer reactions with amines at room temperature (reaction 10). The spent activating agent can be regenerated many times (by acylation with the appropriate acid chloride) without appreciable loss in activity.



26

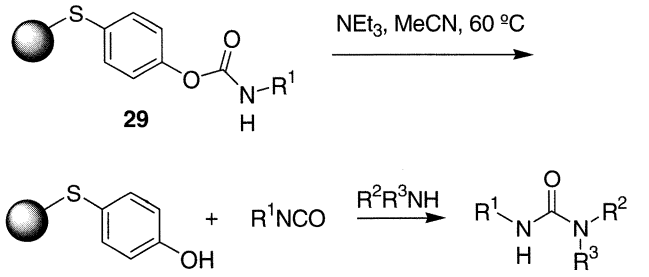
(9)



(10)

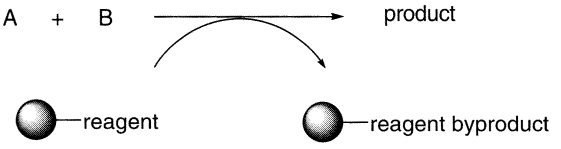
R^1 = Me, Ph, 4-$NO_2C_6H_4$

A novel thiophenoxy 4-nitrophenylcarbonate–linked resin has been used to generate isocyanates in solution phase through the intermediacy of a resin-bound carbamate **29**. The released isocyanates could be trapped with amines to form substituted ureas.[45]



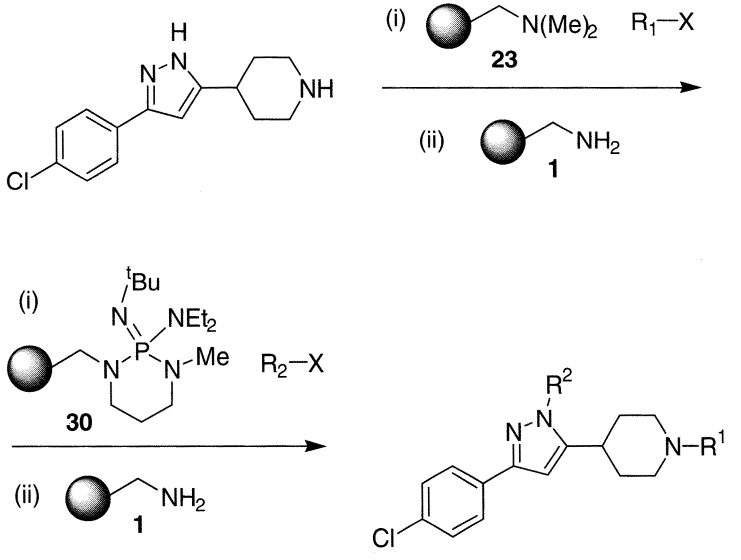
5.7. POLYMER-SUPPORTED REAGENTS

Polymer-supported reagents differ from polymer-supported substrates in that the former mediate a reaction rather than becoming an integral part of the product. A major attribute of tethered reagents is that both the reagent and the reagent byproduct can be directly filtered away from solution-phase products.

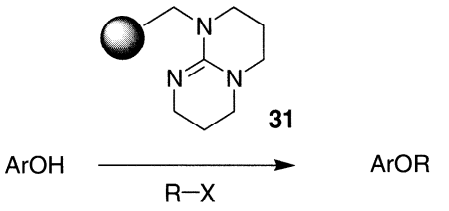


5.7.1. New Polymeric Bases

The polymer-supported superbase **30** was developed and used for the deprotonation and alkylation of weakly acidic nitrogen heterocycles such as indoles, phthalazinones, and pyrazoles.[46] The diagram below illustrates the use of superbase **30** to alkylate a weakly basic pyrazole NH after acylation or alkylation of the more nucleophilic piperidine NH. Aminomethyl resin **1** was added after each step to sequester excess alkyl and/or acyl halide from the solution phase.



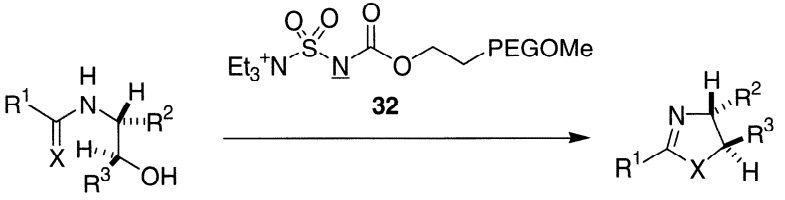
A polymer-bound guanidine base **31** has been used for the formation of aryl ethers from suitable phenols and alkyl halides. In addition to serving as a base to affect deprotonation, reagent **31** also acts as a sequestering agent for excess starting phenol (reaction 11). [26]



(11)

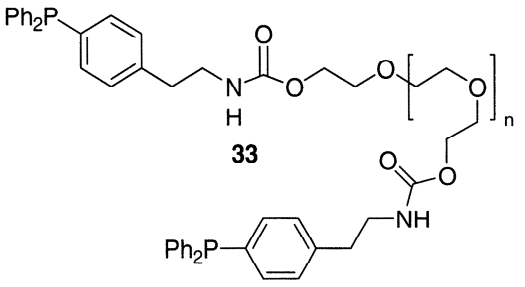
5.7.2. Polymeric Reagents that Mediate Condensation Reactions

A polyethylene glycol (PEG 2000) linked Burgess reagent **32** was prepared and used to mediate cyclodehydration of β-hydroxy amides and thioamides (equation 12).[47] Filtration through a silica gel plug afforded the desired oxazolines and thiazolines in high yields and purities. Interestingly, in some cases the yields of products were superior to yields obtained using the classical Burgess reagent.

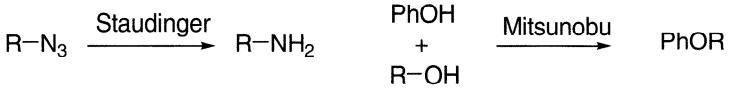


(12)

The PEG3400-linked triarylphosphine **33** was developed as a liquid-phase polymeric reagent for use in Staudinger and Mitsunobu reactions.[48] Precipitation of the PEG polymer with cold diethyl ether, filtration, and evaporation afforded the purified products.

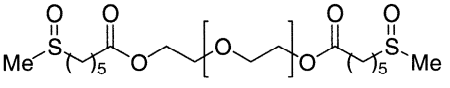


33



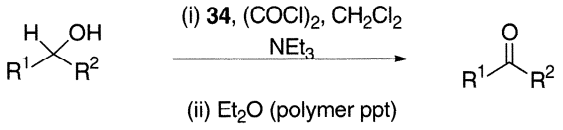
5.7.3. Polymeric Oxidizing Reagents

Swern oxidations have been performed using the PEG2000 bound sulfoxide **34** as a dimethylsulfoxide (DMSO) substitute (reaction 13).[49,50] Several alcohols were efficiently oxidized to their aldehydes or ketones using this reagent, oxalyl chloride, and triethylamine. Precipitation of the polymer with cold diethyl ether and filtration through a pad of silica afforded the desired oxidized products in very good yields and purities. The reduced sulfide polymer could be reoxidized to sulfoxide **34** with sodium metaperiodate and used again in reactions with no appreciable loss in oxidation capacity.



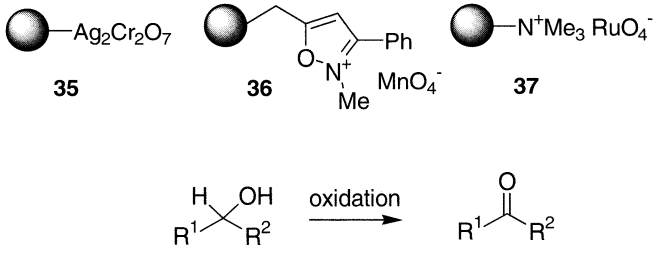
34

(13)



Several other polymer-bound oxidizing reagents have recently been reported in the literature (reaction 14). A polyethyleneimine-supported silver dichromate **35** has been shown to be a stable, mild, and efficient oxidizing agent for the conversion of alcohols to carbonyl compounds.[51] A

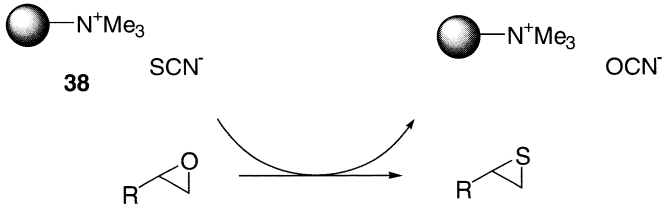
polymer-supported isoxazolinium permanganate **36** was shown to oxidize alcohols to carbonyl compounds in nearly quantitative yields.[52] It was also reported that the polymer **36** could be regenerated and reused several times. Similarly, pyrazolinium permanganate and pyrazolinium chromium (VI) reagents have also been reported as efficient oxidizing agents.[53,54] A polymer-supported perruthenate **37** has also been recently reported for the oxidation of alcohols to their aldehydes or ketones.[55] Polymer **37** can be used either in stoichiometric amounts or as a catalyst in combination with a co-oxidant (*N*-methylmorpholine oxide or trimethylamine oxide). The desired oxidized products were obtained in high yields and purities after filtration and evaporation. It was also shown that the catalyst could be reactivated and reused in further oxidation reactions.



(14)

5.7.4. Polymeric Reagents for Oxirane to Thiirane Conversion

A series of epoxides has been efficiently converted to the corresponding thiiranes using a polymer-bound quaternary ammonium thiocyanate **38**. The polymeric byproduct of this transformation is the supported cyanate.[56]

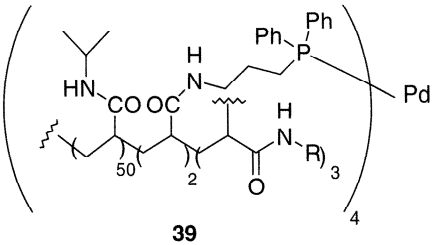


5.8. POLYMER-SUPPORTED CATALYSTS

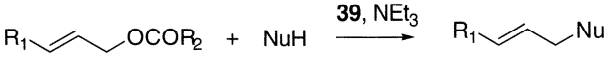
5.8.1. Polymer-Supported Palladium Catalysts

A polymer-bound Pd(0)–phosphine catalyst **39** has been reported that is soluble in water or mixed aqueous/organic media.[57] This catalyst was used

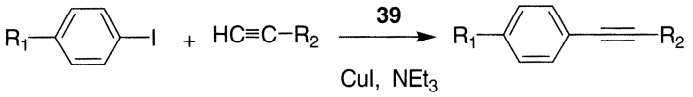
to mediate allylic substitutions and cross-coupling reactions of aryl iodides with terminal alkynes. The catalyst was removed by ether-induced precipitation or thermal-induced precipitation. The latter operation takes advantage of the inverse temperature solubility dependence of the polymer, that is, increased temperature results in a *decreased* solubility of **39**.



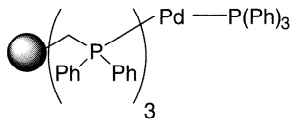
39



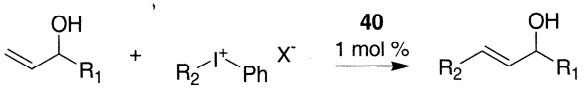
(Nu is benzenesulfinate or secondary amine)



A polyethylene glycol–polystyrene graft copolymer palladium catalyst has been used in allylic substitution reactions of allyl acetates with various nucleophiles in aqueous media.[58] Another polymer-bound palladium catalyst **40** was developed and used in a Heck coupling of allylic alcohols with hypervalent iodonium salts to afford the substituted allylic alcohols as the sole products under mild conditions with high catalytic efficiency.[59] The same polymer-bound palladium catalyst has also been used for Suzuki cross-coupling reactions.[60]



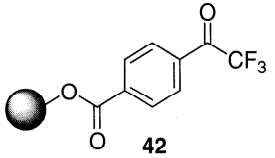
40



5.8.2. Polymer-Supported Catalysts for Epoxidation and Dihydroxylation

Polyaniline-supported Co(II) catalyst **41** was used to catalyze the epoxidation of various alkenes under oxygen atmosphere at ambient temperature.[61–63] One report [61] described a synthesis of α-hydroxy-β-aminopyrrolidinc amides as potential HIV protease inhibitors (Scheme 1). In this synthesis, catalyst **41** also mediated epoxide ring opening of the epoxide intermediate by an aniline to afford the desired product.

Polymer-bound trifluoromethyl aryl ketone **42** was prepared by attaching 4-(trifluoroacetyl)benzoic acid to a suitably functionalized resin and used as a catalyst in Oxone-mediated epoxidations.[64] The reactions proceed by in situ generation of the polymer-supported (trifluoromethyl)-dioxirane. A series of epoxides was formed in good to excellent yield.



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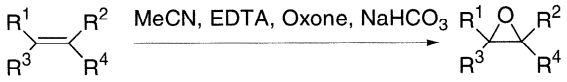
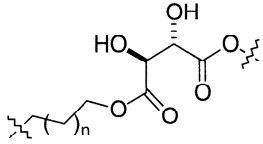
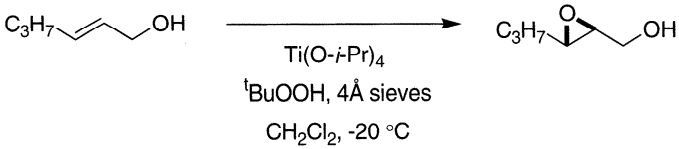


(15)

A polymer-supported Sharpless epoxidation catalyst was prepared using linear poly(tartrate ester) catalyst ligands **43**.[65] This catalyst system was used in the reaction of *trans*-hex-2-en-1-ol with titanium *tetra*-isopropoxide and *tert*-butyl hydroperoxide to afford the desired epoxide in high chemical yield and moderate enantiomeric excess.



43



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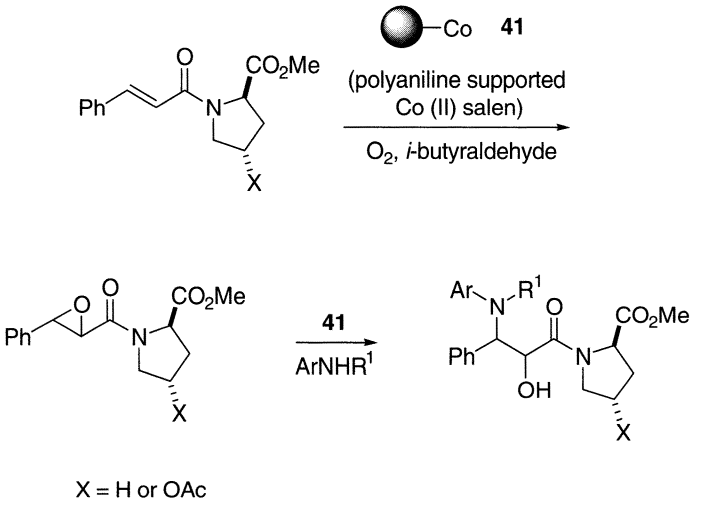
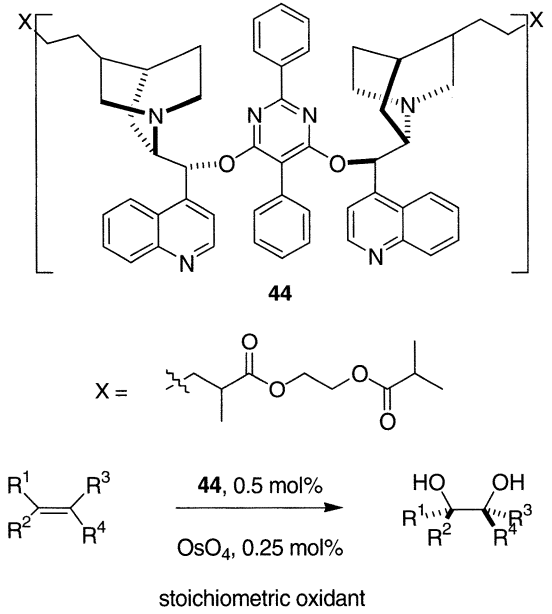


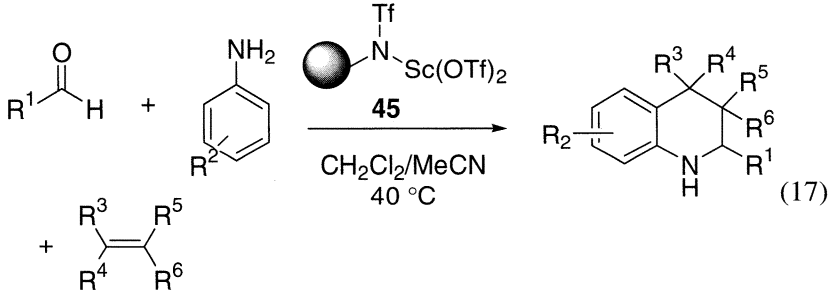
Scheme 1.

A polymeric cinchona alkaloid–derived ligand **44** was prepared and used to catalyze the asymmetric dihydroxylation of olefins (see the diagram below).[66] Both aliphatic and aromatic olefins afforded diols with good enantioselectivities.

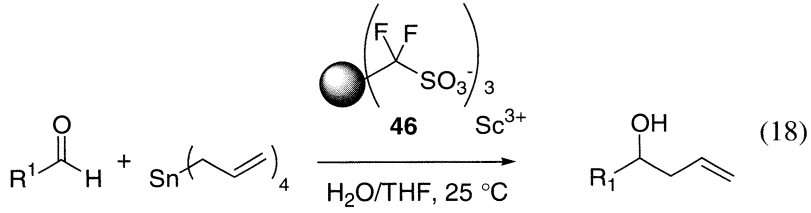


5.8.3. Polymer-Supported Catalysts in Carbon–Carbon Bond-Forming Reactions

A partially soluble polyallylscandium triflamide ditriflate **45** was prepared and used to catalyze a three-component coupling reaction.[67] An aldehyde, an aromatic amine, and an alkene were mixed in the presence of the catalyst to afford tetrahydroquinolines (equation 17). The catalyst was recovered from the reaction mixtures by precipitation with hexane and could be recycled without loss of activity. Another polymer-supported scandium catalyst was prepared by treating Nafion with scandium chloride to afford the Nafion–scandium catalyst **46**.[68] This catalyst was used in allylation reactions of carbonyl compounds by tetraallyltin (equation 18). It could be easily recovered by filtration and reused without appreciable loss of activity.

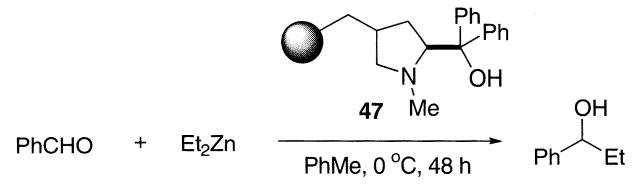


(17)



(18)

A polymer-bound 2-pyrrolidinemethanol **47** was prepared and used as a chiral ligand in the reaction of diethylzinc with benzaldehyde. The alcohols were formed with 100% conversion and 89% enantiomeric excess (equation 19).[69] The same results were obtained using 2 or 5 mol % of the catalyst.

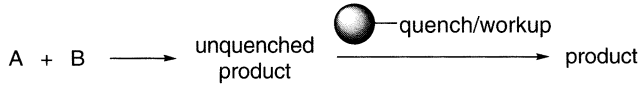


(19)

A naphthalene supported polymer was prepared by radical copolymerization of 2-vinylnaphthalene, styrene, and divinylbenzene.[70] This catalyst was used to mediate metallation of alkyl chlorides by lithium. The reaction was done in the presence of electrophiles to afford, after quenching, the desired addition products.

5.9. POLYMERS FOR REACTION QUENCHING/WORKUP

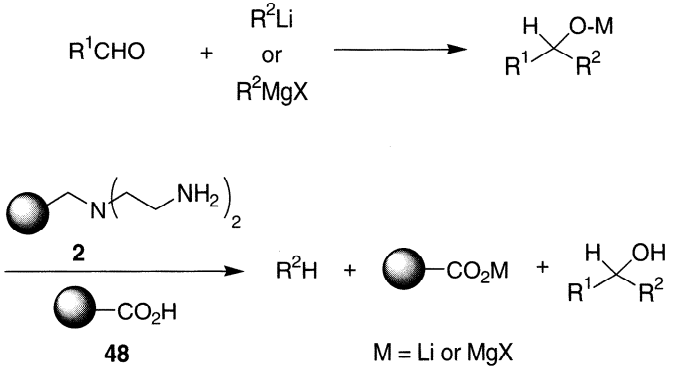
Chemically functionalized polymers have also been used in polymer-assisted solution-phase synthesis to perform reaction-quenching functions. These polymers often are used in operations that substitute for traditional liquid-phase extractions in classical synthesis.



Resin quenching is often preferable to traditional liquid-phase extractions in automated processes. The advantages of this technique in robotic syntheses are

- avoidance of emulsions;
- circumvention of unreliable meniscus-reading or volume transfer robotic-software commands; and
- simultaneous extractions by use of multiple-quenching resins (mixed-resin beds).[20]

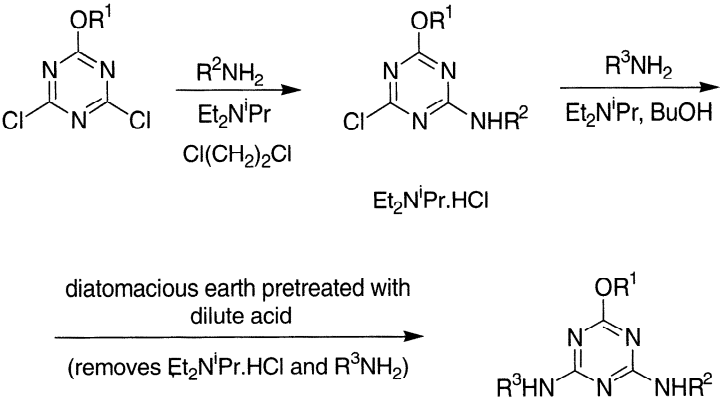
Scheme 2 depicts an application of the carboxyl-functionalized IRC-50S resin **48** to quench parallel-array organometallic reactions.[20] Nonisolable alkoxide salts formed from the reaction of aldehydes with organolithiums



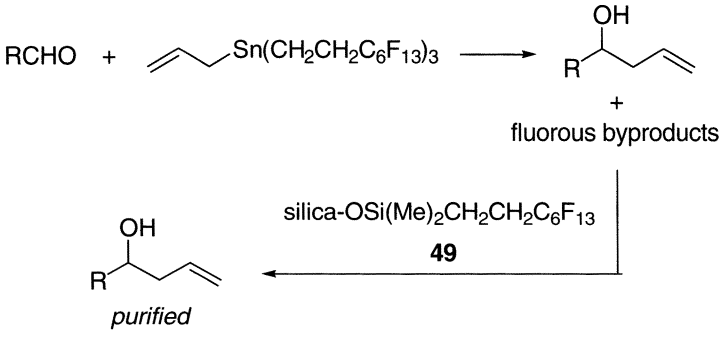
Scheme 2.

or Grignard reagents were quenched by resin **48** to give the corresponding alcohol products after simple filtration. Excess organometallic reactants were simultaneously quenched to give volatile hydrocarbon byproducts. Mixed-resin beds were also highlighted in this report: The polyamine-functionalized resin **2** was simultaneously used to sequester unreacted aldehydes from the solution phase.

Diatomacious earth has recently been reported as an insoluble polymer support for accomplishing the equivalent of liquid-phase extraction. Preadsorption of water, aqueous base, or aqueous acid onto diatomacious earth provided an insoluble, flow-through material for parallel, high-throughput purification of solution-phase reactions.[71] Scheme 3 illustrates this tech-



Scheme 3.



Scheme 4.

nique in a synthesis of diamine-functionalized triazines. Filtration of the crude mixtures from sequential S_NAr reactions through columns of acid-treated diatomacious earth led to sequestration of excess amine R^3–NH_2 and the amine hydrochloride byproducts. The end products were isolated in excellent yields and purities.

Fluorous-tagged reagents, coupled with post-reaction fluorous liquid-phase extraction, has been reported as a synthetic strategy for solution-phase chemical library synthesis.[14,15] A polymer-supported fluorous-phase has recently been developed as an extension of this methodology.[72] Scheme 4 illustrates how the fluorous chromatographic support **49** was used to separate homo-allylic alcohols from fluorous-tagged allyl stannanes and their byproducts. Filtration of crude reaction mixtures through the fluorous-phase bonded silica gel support led to efficient sequestration of the fluorous-tagged stannane reagents and byproducts. This polymer-fluorous-phase quench technique should widely expand the scope of reactions that can be handled efficiently in a robotic laboratory environment when avoidance of liquid-phase extraction is desired.

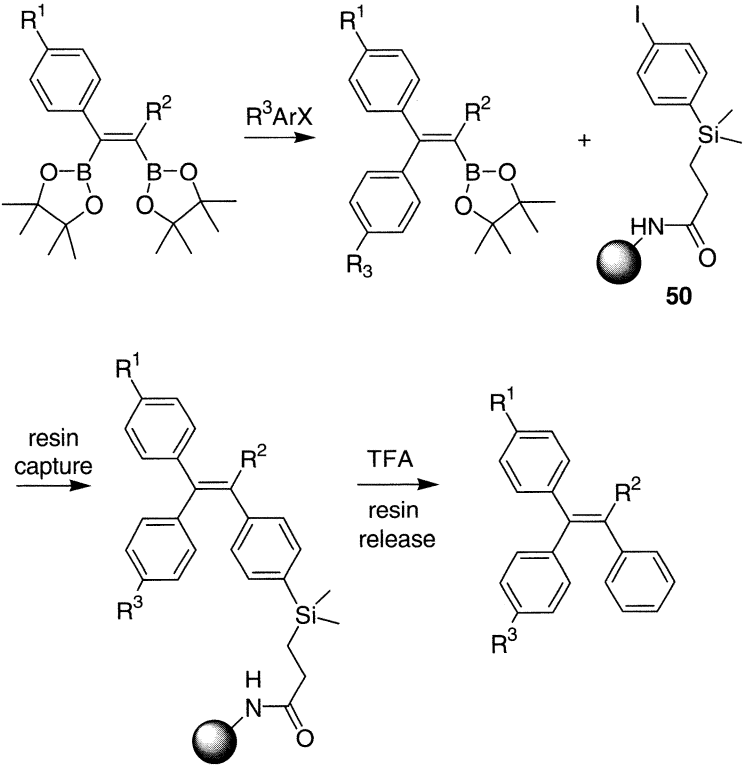
5.10. COMBINATIONS OF SOLID- AND SOLUTION-PHASE TECHNIQUES IN ORGANIC SYNTHESIS

5.10.1. Resin Capture of Products from Solution-Phase Syntheses

Solid- and solution-phase organic syntheses are no longer distinct branches of chemistry, and several reports of combined technology applications have

emerged. One such application is now referred to as "resin capture" of solution-phase library products.

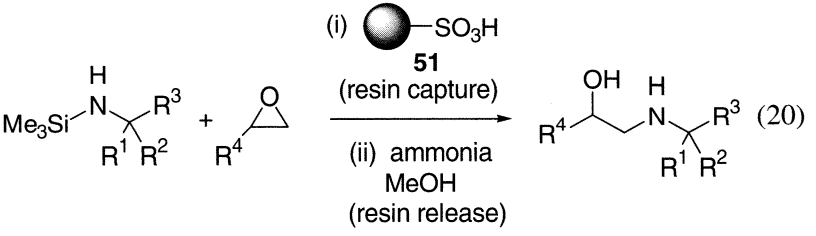
The first report of resin capture in solution-phase chemical library synthesis involved the covalent capture of solution-phase Ugi reaction products onto a functionalized polystyrene resin.[73] Excess reactants, reagents, and reagent byproducts were washed away from the resin-captured intermediates. Further manipulation and release afforded purified solution-phase products for screening. More recently the same group reported on resin capture as a technique for the preparation of tetrasubstituted olefin libraries.[74,75] As illustrated in Scheme 5, *cis*-vinyl di-boryl esters were reacted with aryl halides (R^3ArX) in parallel Suzuki reactions, leading to solution-phase intermediates. Another Suzuki reaction, this time with the

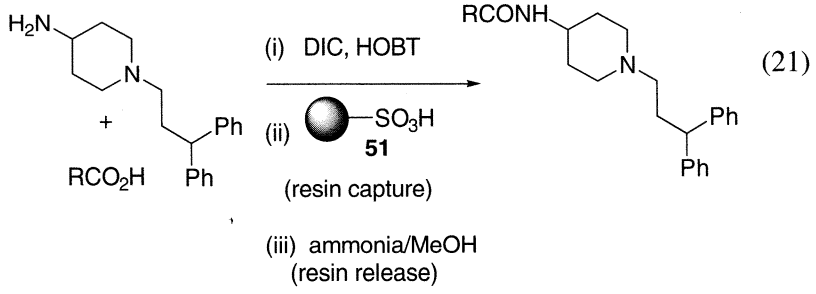


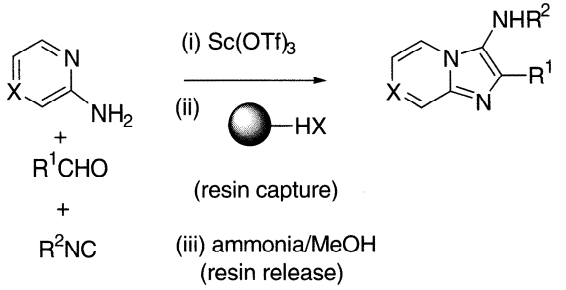
Scheme 5.

polymer-supported aryl iodide **50**, led to resin-captured intermediates. Excess of solution-phase reactants, reagents, palladium catalyst and any undesired bis-Suzuki side products (from solution-phase reaction of excess R^3ArX at the second boryl ester site) were rinsed away from the captured intermediates. Finally, trifluoroacetic acid–mediated release (protodesilylation) led to the isolation of purified tetrasubstituted alkenes.

In addition to these reports of covalent resin capture, several groups have used reversible ion pairing as a resin-capture/resin-release technique. In one report, the parallel-array reactions of excess epoxides with trimethylsilyl-protected primary amines gave crude ethanolamines (reaction 20).[76] Cationic resin capture of the ethanolamines was mediated by the strongly acidic sulfonic acid ion exchange resin **51**. Rinsing and subsequent release by ammonia/methanol cationic exchange afforded purified ethanolamines. A similar report described the resin capture of tertiary amine products by a strongly acidic sulfonic acid cation exchange resin (reaction 21).[31] A solution-phase synthesis of amino-imidazopyridines, formed in a multicomponent reaction involving aminopyridines, aldehydes, and isocyanides, was described. A similar cationic resin-capture/ammonia-release strategy was employed (reaction 22).[77]

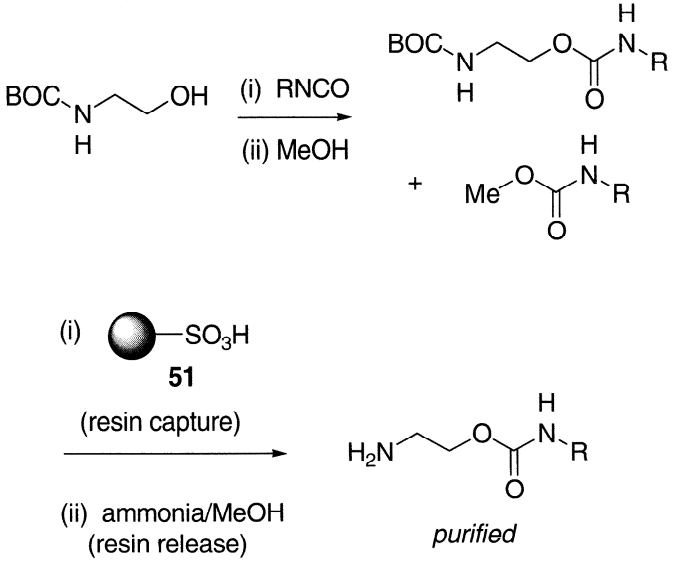




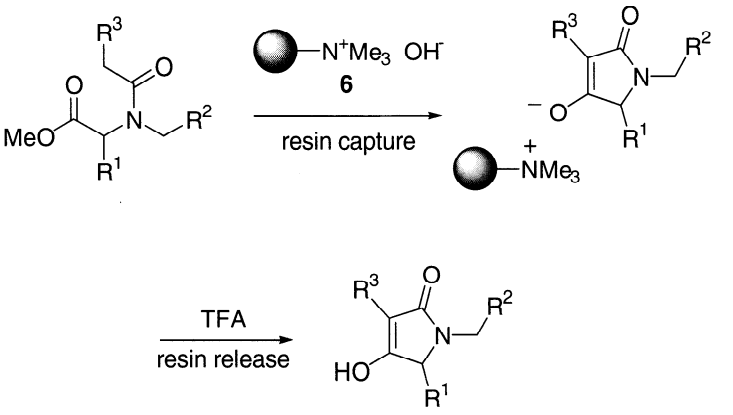


(22)

An interesting variant of cationic-resin capture has recently been reported wherein a strongly acidic cation exchange resin mediated sequential amine deprotection and resin capture (Scheme 6). [78] Protected aminoalcohols were reacted with an excess of isocyanates to form *N*-BOC-amine carbamates in solution phase. Methanol was subsequently added to quench excess isocyanates as the neutral methyl carbamate byproducts. Sulfonic acid resin **51** was then used to affect amine-BOC group deprotection and resin capture of the deprotected amines. Washing of the resin bed and release (ammonia/methanol) afforded purified amine carbamate products.

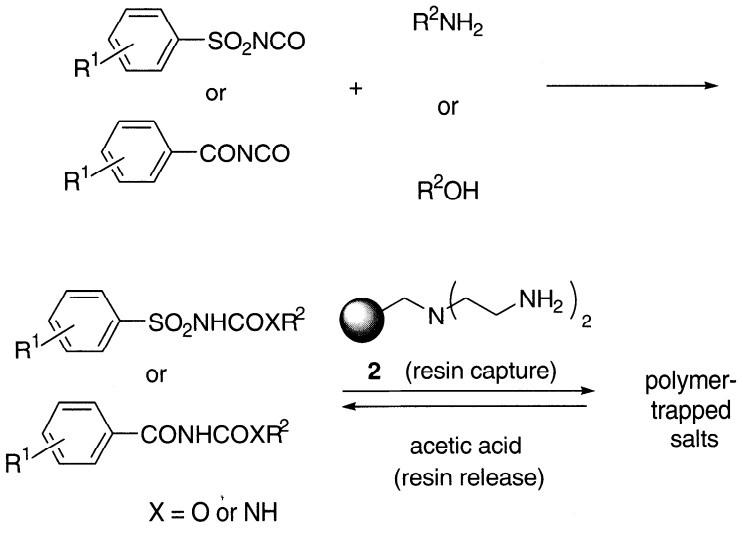


Scheme 6.



Scheme 7.

Anionic resin capture of solution-phase library products has also been reported. The anion exchange resin A-26 hydroxide **6** was used in a dual capacity to mediate Dieckmann condensations of solution-phase library intermediates and also to affect resin capture of the formed tetramic acids as polymer-bound intermediates (Scheme 7).[79] Rinsing, followed by tri-

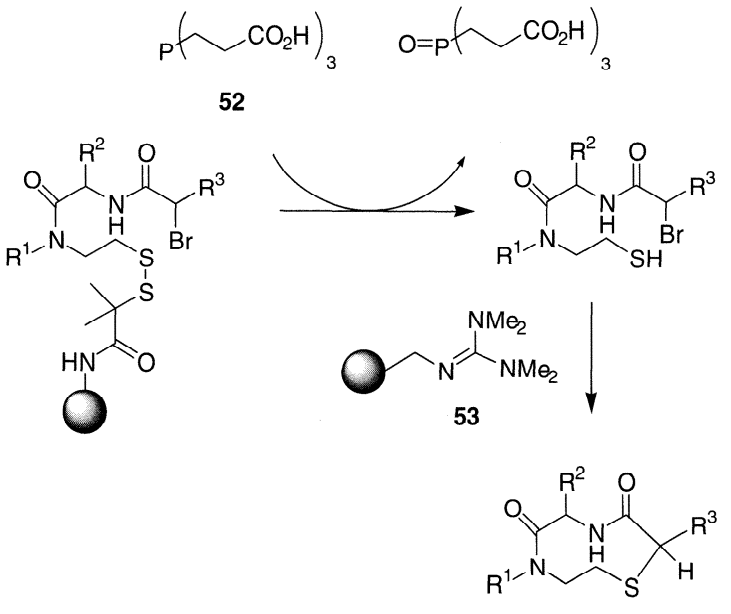


Scheme 8.

fluoroacetic acid–mediated resin release, afforded purified tetramic acids. Anionic resin capture has also been reported to purify a series of acidic *N*-sulfonylureas, *N*-sulfonylcarbamates, *N*-acylureas, and *N*-acyl carbamates (Scheme 8). The basic polyamine resin **2** affected ionic resin capture of these intermediates. Rinsing, followed by acetic acid–mediated release, afforded purified products.[32]

5.10.2. Use of Solution-Phase Technologies to Expand the Scope of Solid-Phase Organic Synthesis

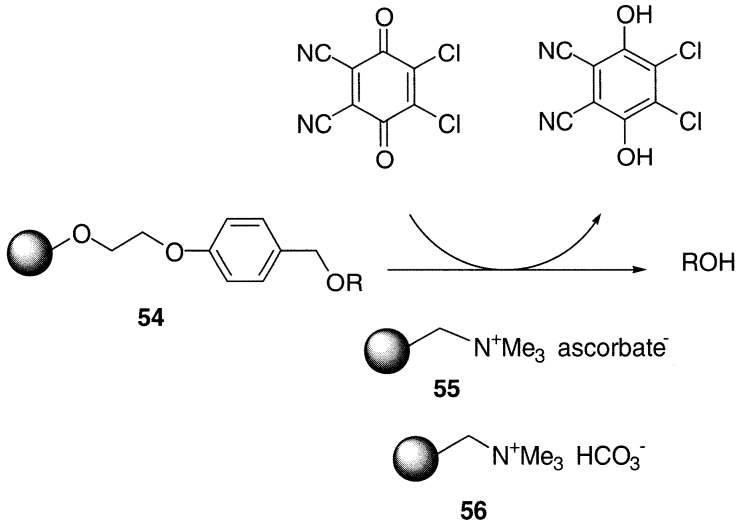
Polymer-assisted solution-phase technology has expanded the range of reactions that can efficiently be used to release products from polymer supports. Prior to this "combined technology" approach, only volatile reagents (e.g., HF, TFA) were typically used in release steps; however, polymer-assisted solution-phase techniques are now enabling the use of nonvolatile reagents. Scheme 9 illustrates how the carboxy-tagged phosphine **52** was used to mediate the release of sulfides from solid-phase supported disulfides.[80] The tetramethylguanidine-functionalized resin **53**



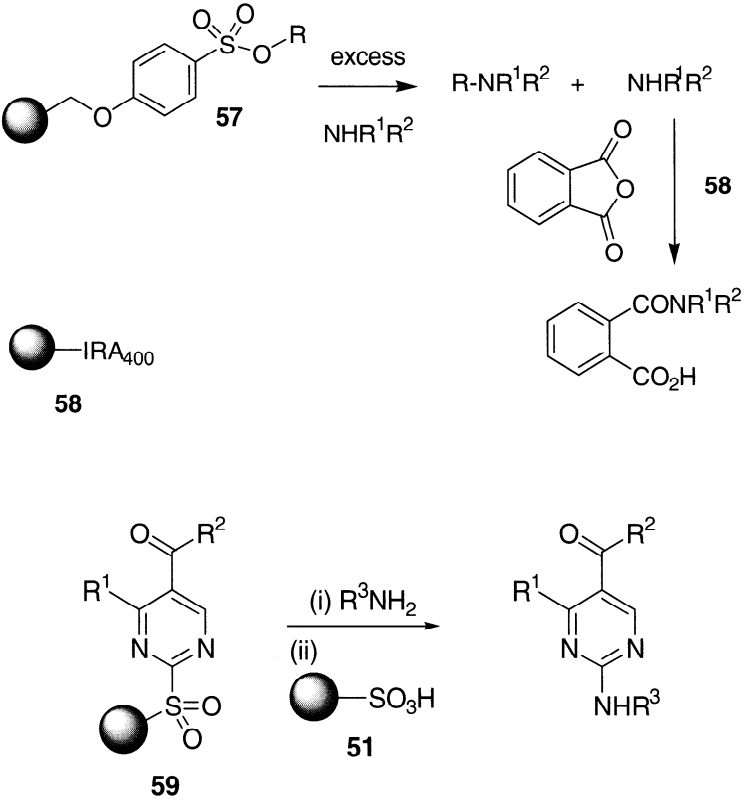
Scheme 9.

was then added to the reaction mixtures to sequester carboxy-tagged phosphine and the corresponding phosphine oxide and also to mediate the solution-phase cyclization to the desired β-turn mimetics.

The nonvolatile oxidant (DDQ) was used to mediate the release of alcohols from solid-phase Wang-type ethers **54**.[81] Purification of the released alcohols was affected by the use of a mixed-resin bed containing Amberlyst A-26 ascorbate **55** (to reduce excess DDQ to its hydroquinone byproduct) and also Amberlyst A-26 bicarbonate **56** (to sequester the acidic hydroquinone byproducts). Filtration afforded purified alcohols in excellent yields and purities.



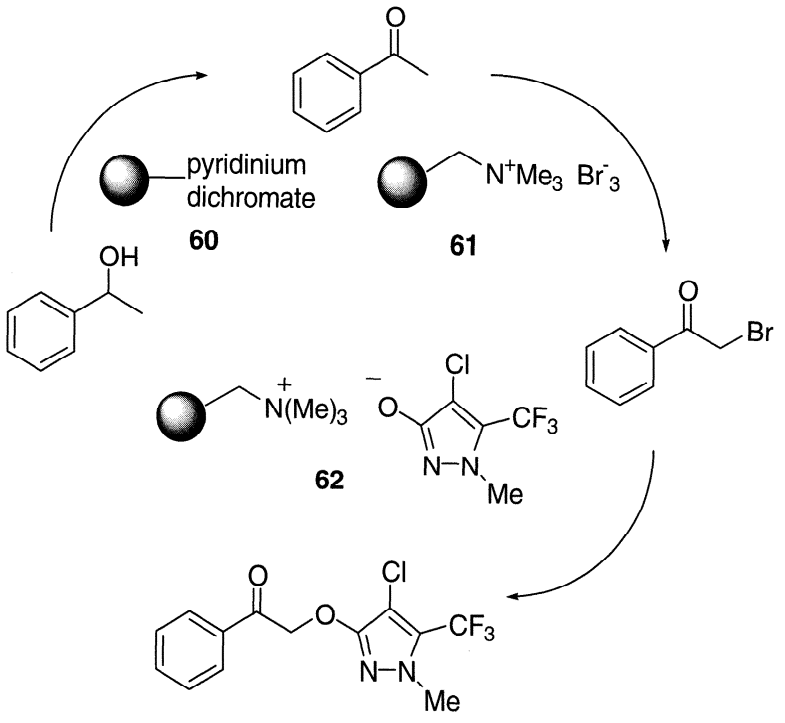
Release of substrates from polymer supports can sometimes provide an opportunity to increase diversity. For instance, excess secondary amines were used to release tertiary amines from a series of polymer-bound alkyl sulfonates **57** (see the diagram below).[82] Phthalic anhydride was then used as a solution-phase linking reagent to transform the excess secondary amines into their phthalate half acids, which in turn were sequestered by the amine-functionalized ion exchange resin IRA-400 **58**. Similarly, excess amines were used to mediate diversifying release from polymer-bound pyrimidin-2-yl sulfones **59**, forming the desired 2-aminopyrimidines (reaction 23).[83] The strongly acidic sulfonic acid ion exchange resin **51** was then added to sequester excess amines from the solution phase.



(23)

5.11. MULTISTEP/ONE-CHAMBER SOLUTION-PHASE SYNTHESIS

One research group has exploited the concept of polymer "site-isolation" in a multistep/one-chamber solution-phase synthesis in which all the reagents, catalysts, and downstream reactants required for a multistep synthesis were combined in one reaction chamber. For instance, a one-chamber/three-step synthesis of substituted acetophenones has been reported (Scheme 10).[84] An α-phenethyl alcohol was introduced into a reaction chamber containing the polymer-supported reagents and reactants necessary to accomplish oxidation by polymer-supported pyridinium dichromate **60**; bromination by the A-26 perbromide resin **61**; and nucleophilic displacement by the A-26 phenoxide resin **62**. Filtration afforded the

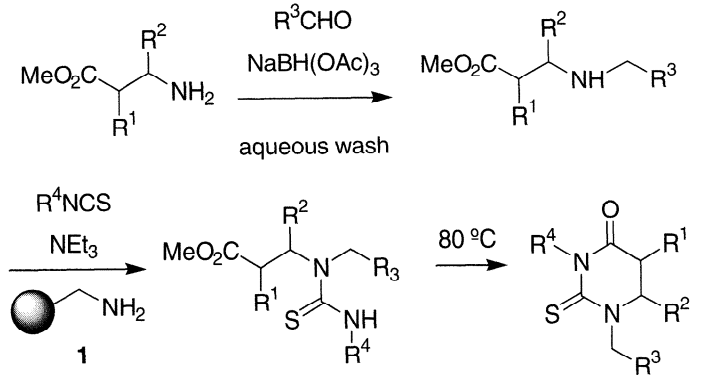


Scheme 10.

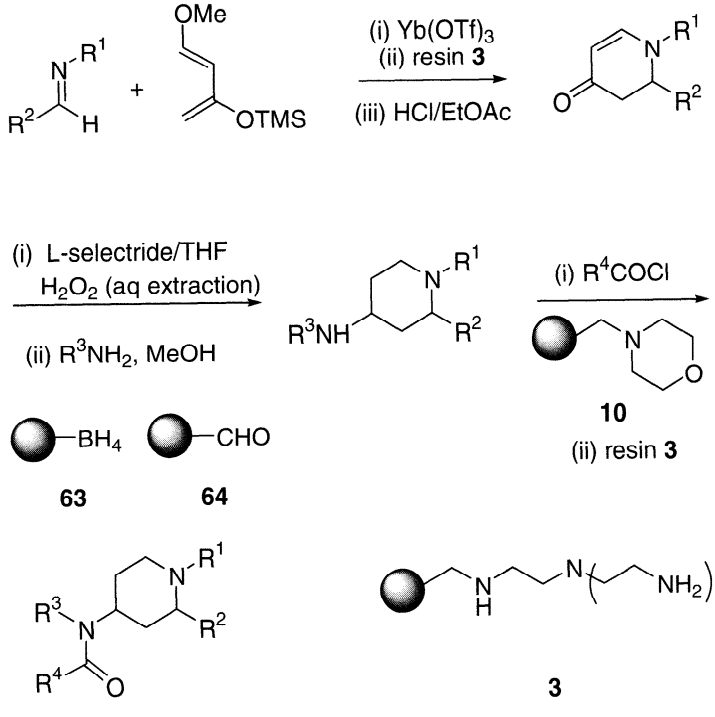
product in 48% yield, compared with a 42% overall yield when each of the three steps was performed separately.

5.12. POLYMER-ASSISTED TECHNOLOGIES IN MULTISTEP SOLUTION-PHASE SYNTHESES

Polymer-assisted methodology has been used several times for parallel-array synthesis of libraries involving three to five synthetic steps. Scheme 11 shows a three-step solution-phase synthesis of 2-thioxo-4-dihydro-pyrimidinones wherein the key purification step involved amine resin **1** to sequester excess aldehydes and isothiocyanates from upstream transformations. Thermal cyclization of the purified intermediates gave the desired 2-thioxo-4-dihydropyrimidinones in excellent yields and purities.[85]



Scheme 11.

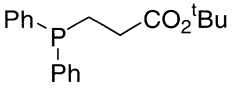


Scheme 12.

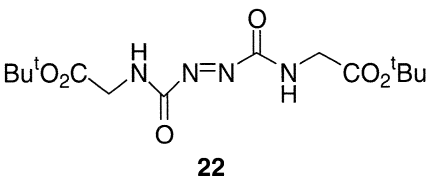
A four-step solution-phase synthesis of 4-aminopiperidines containing four sites of diversity is shown in Scheme 12.[23] Polymer-assisted steps involved

- polyamine resin **3** to sequester residual imine reactant and unwanted enone byproduct generated from Danishefsky's diene;
- supported borohydride reagent **63**;
- aldehyde resin **64** to sequester excess amine reactants;
- polymer-supported tertiary amine base **10** to mediate amine acylations; and,
- polyamine resin **3** to sequester excess acylating reactants.

Bifunctionally tagged Mitsunobu reagents **21** and **22**, quaternary ammonium carbonate resin **65**, tetrafluorophthalic anhydride (as a solution-phase linking reagent), and amine-functionalized resin **2** were used in a three-step solution-phase synthesis of a series of substituted hydroxypiperidines.[39] No further purification (e.g., liquid-phase extraction or chromatography) was required, and products were isolated in good yields and purities.



21



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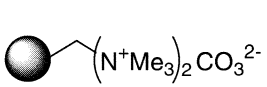

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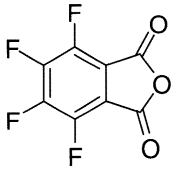
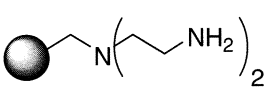
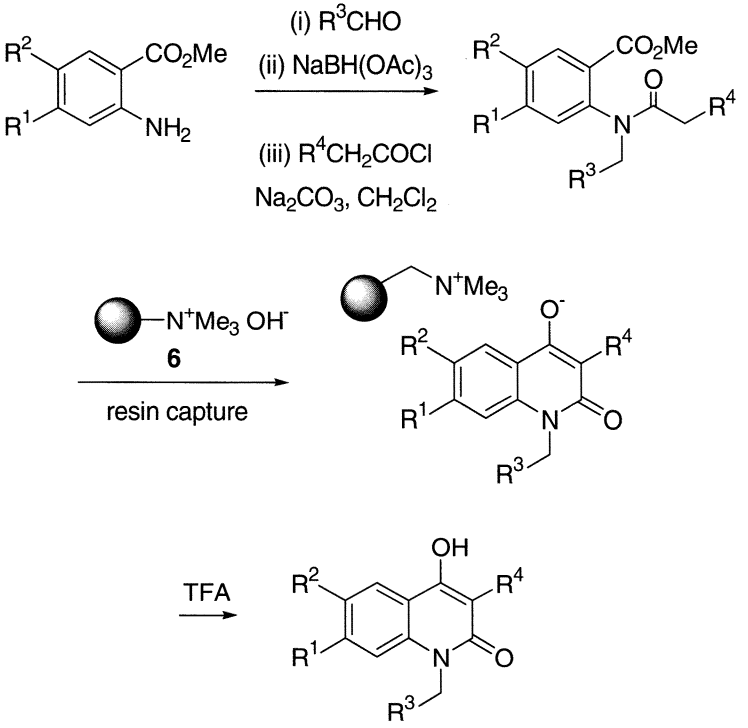




2

A four-step synthesis of a series of 4-hydroxyquinolinones starting from anthranilates is shown in Scheme 13.[86] Resin capture of the Dieckmann cyclization intermediates was used as the main purification technique for this synthesis. Rinsing of the resin-captured adducts removed neutral and

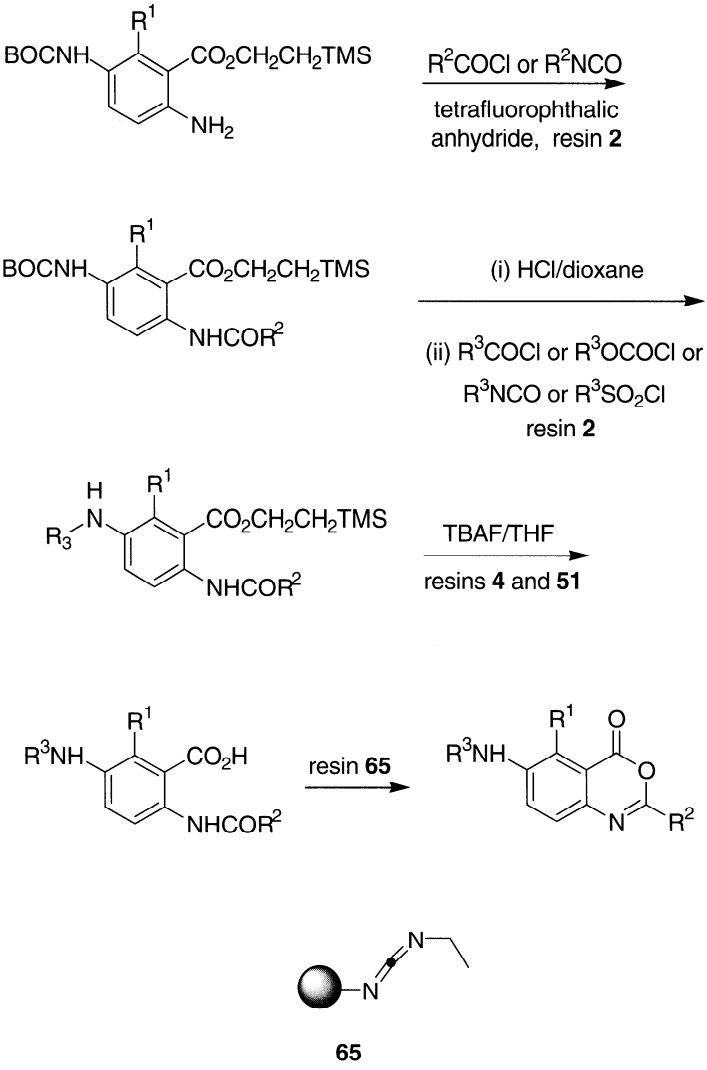


Scheme 13.

basic impurities from the first three steps. The TFA-mediated resin release led to the isolation of the desired 4-hydroxyquinolinones in excellent purities and good overall yields.

Finally, a five-step solution phase synthesis of benzoxazinones used a combination of reactant-sequestering resins, a bifunctional linking reagent, a polymer-supported reagent, and solid-phase quench for synthesis and purification (Scheme 14)[22]: This features

- tetrafluorophthalic anhydride and electrophile-sequestering resin **2** in the first step;
- electrophile-sequestering resin **2** for purification in step 3;
- TBAF-quenching calcium sulfonate resin **4** and acidic-quench resin **51** in step 4; and
- polymeric EDCI reagent **65** in step 5 to mediate the cyclodehydration.



65

Scheme 14.

5.13. CONCLUSION

Polymer-assisted solution-phase synthesis offers strategies for chemical library construction that complement solid-phase methods. Tools now available include chemoselective sequestering resins, bifunctional solution-phase linking reagents, bifunctional chemically tagged reagents, and an

expanded range of available polymer-supported reactants, reagents, and catalysts. Applications such as resin capture/resin release and polymer-assisted use of nonvolatile reagents for SPOS release protocols are now blurring the boundary between polymer-assisted solution-phase and solid-phase synthesis. Finally, polymer-assisted solution-phase technologies are now sufficiently mature to enable multistep library synthesis.

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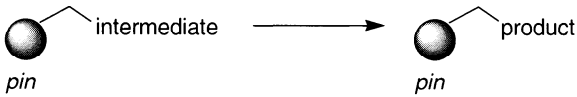
CHAPTER 6

SOLID-PHASE ORGANIC SYNTHESIS ON RADIATION-GRAFTED POLYMER SURFACES: APPLICATION OF SYNPHASE CROWNS TO MULTIPLE PARALLEL SYNTHESES



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6.1. MULTIPLE PARALLEL SYNTHESES OF INDIVIDUAL COMPOUNDS

6.1.1. Introduction

After a few frenzied years of development in combinatorial chemistry, there is now a clearly identifiable trend away from the synthesis of complex

mixtures/pools of compounds toward multiple parallel syntheses of individual compounds. This trend has been established largely to circumvent the time-consuming process of "deconvoluting" compound mixtures to identify biologically active components and, also, to avoid the problem of "false positives." Using high-throughput chromatographic and structural analyses, for example, HPLC, electrospray mass spectrometry (ESMS), and even NMR spectroscopy, it is now possible to analyze libraries of hundreds to thousands of individual compounds to establish the purity and structural integrity of the libraries' constituents. This information is essential for determining which reaction products are suitable for biological screening. Solid-phase organic synthesis continues to be a popular method for preparation of libraries,[1] although solution-phase methods are also used.[2] Syntheses of compounds on discrete units of solid-phase material, such as SynPhase crowns,[1,3] simplify handling issues associated with multiple parallel syntheses. These units of solid support can be "tagged" electronically for identification purposes or placed in particular spatial patterns, for example, 8×12-array formats, as in the case of the Multipin method (Figure 6.1). An important advantage of both of these parallel synthesis techniques

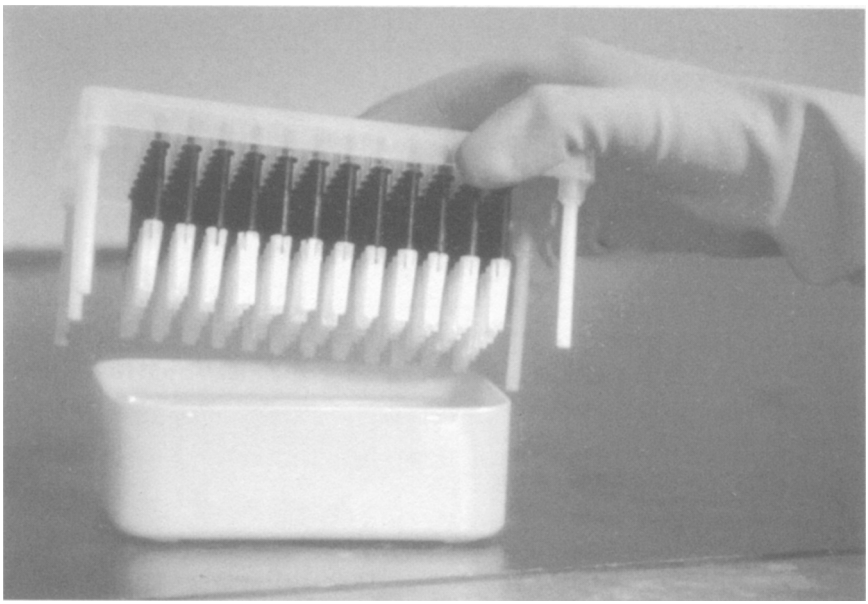


Figure 6.1. Block of 96 I–series crowns being washed in a polypropylene bath containing organic solvent.

is the ability to track individual reactions facilitating identification of expected structures on each SynPhase crown.

6.1.2. Radiation-Grafted Polymer Surfaces

Most solid-phase organic syntheses described in the literature have been performed on beaded cross-linked polystyrene resin.[4] A small, though growing volume of published work has been performed on radiation-grafted polymer surfaces, such as SynPhase crowns. Radiation-grafted polymers were first used for peptide synthesis in the early 1980s.[1,5,6] Following many years of development, the graft polymers now available on SynPhase crowns include polystyrene[3] and a hydrophilic copolymer of methacrylic acid and dimethylacrylamide,[3] both of which can be used for solid-phase organic synthesis. Although dissimilar in appearance, radiation-grafted polymer surfaces have a number of physical properties that are similar to resins from a synthetic perspective. In both cases, synthesis takes place within a solvated cross-linked polymer gel. Unlike cross-linked resins, the graft polymer is anchored to a rigid base polymer unit (Figure 6.2), which could be presented in a number of formats: for example, as films or injection-molded items. In the case of the SynPhase crowns, the base polymer is injection molded as a small rigid finned device with a moderately large surface-to-volume ratio.[7,8] The shape and size of the base polymer can be varied to control loading. For example, at the time of writing, the polystyrene-grafted, I-series SynPhase crown could be produced with loadings up to 35 μmol on a device that is 20 mm long and up to 6 mm in diameter.

The advantages of SynPhase crowns over conventional solid-phase syntheses on resin beads are as follows:

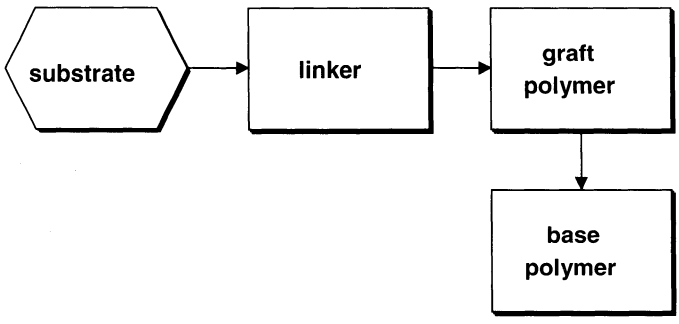


Figure 6.2. Schematic of crown surface.

- It is not necessary to weigh the solid support when setting up reactions because the scale of the reaction is determined by the crown loading.
- Unlike resins, polymer solvation is limited to the graft polymer, so there is little increase in overall crown dimensions.
- The graft polymers are well solvated in a variety of solvents.
- Crowns can be locked into an array format for multiple parallel handling and ready identification (i.e., the Multipin method, as shown in Figure 6.1).
- Alternatively, individual crowns can be uniquely tagged for multiple parallel handling (TranStem/TranSort method).
- Removal of excess reagents and solvent can be achieved without any risk of blockage; either by rapid filtration through a coarse mesh or simply lifting a "block" of crowns (Figure 6.1) out of a solvent bath, and shaking off excess reagent/solvent.
- No loss of solid support occurs, which could lower compound yield, during washing or transfer steps in a multistep synthesis.

The handling advantages of this type of solid support for carrying out multiple parallel syntheses mean that libraries involving tens to hundreds of compounds are conveniently prepared. The use of tagging techniques expands the potential library size into the thousands (see Section 6.4).

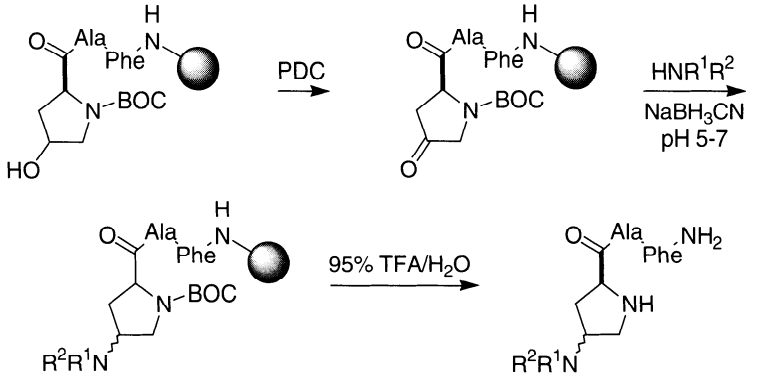
6.1.3. Optimization of Solid-Phase Chemistry

A large proportion of the time spent in library production involves optimizing the chemistry. This optimization process usually entails translating chemistry from the solution phase to the solid phase and achieving satisfactory yield and purity. Another form of optimization may involve the translation of chemistry developed on one solid phase (e.g., TentaGel) to another type of solid phase (e.g., 2% cross-linked polystyrene beads). Either way, the process typically involves investigation of general conditions to see if the chemistry will proceed on the chosen solid phase and then the fine tuning to obtain satisfactory purities and yields. Conditions that may be varied to improve yield include time, temperature, concentration of reagent(s), ratio of reagents, selection of reagents and/or catalysts, choice of solvent and/or co-solvents, and the selection of the graft polymer type. Hundreds of experiments may be required to achieve an optimal set of conditions.

SynPhase crowns may be used to perform large numbers of optimization reactions in parallel. This "library of reaction conditions" may be analyzed by assaying product purities after cleavage from the solid phase using high-throughput techniques such as HPLC and ESMS. Overall, this approach can greatly reduce the time required for this critical step of compound library development.

The reaction screening approach described above is used routinely in our laboratories and has been illustrated using reductive amination of 4-oxoproline on methacrylic acid/dimethyl acrylamide (MD) grafted SynPhase crowns.[9] In this example, the concentrations of the amine and sodium cyanoborohydride as well as the solvent and the pH of the reaction solution were varied. Product analysis revealed that high amine concentration and moderately low reductant concentration were beneficial to the reaction and that methanol gave slightly improved results over ethanol. More importantly, it was observed that pH had a major influence on the reaction, with pH 5–6 giving superior results to pH 7 for primary amines. When the optimization studies were expanded to include anilines, high amine concentration was again found to be beneficial, as was very low reductant concentration, although pH 7 was preferable to pH 5–6 (Scheme 1).

Consideration of reaction mechanisms helps reduce the number of reaction variables, but trial and error still plays a large part in optimization processes. Large numbers of reactions therefore are required to fully optimize chemistries. In our experience, one variable for which the optimal



Scheme 1.

condition is not readily predictable is solvent. The solvent in a solid-phase reaction has many roles to play, not only as a solvating agent for the reactants, intermediates, and transition states, but also to solvate the polymer well, and must aid in the transport of the solution-phase reactants into the polymer network. We have frequently found that the optimal solvent for a solid-phase reaction is not the same as that routinely used for the same solution-phase reaction. For example, whereas tetrahydrofuran would be used for a solution-phase Mitsunobu ether formation or a Suzuki aryl alkylation, we have found dimethylacetamide to be beneficial for ether formation[10] and ethoxyethanol to be the solvent of choice for the Suzuki reaction.[11]

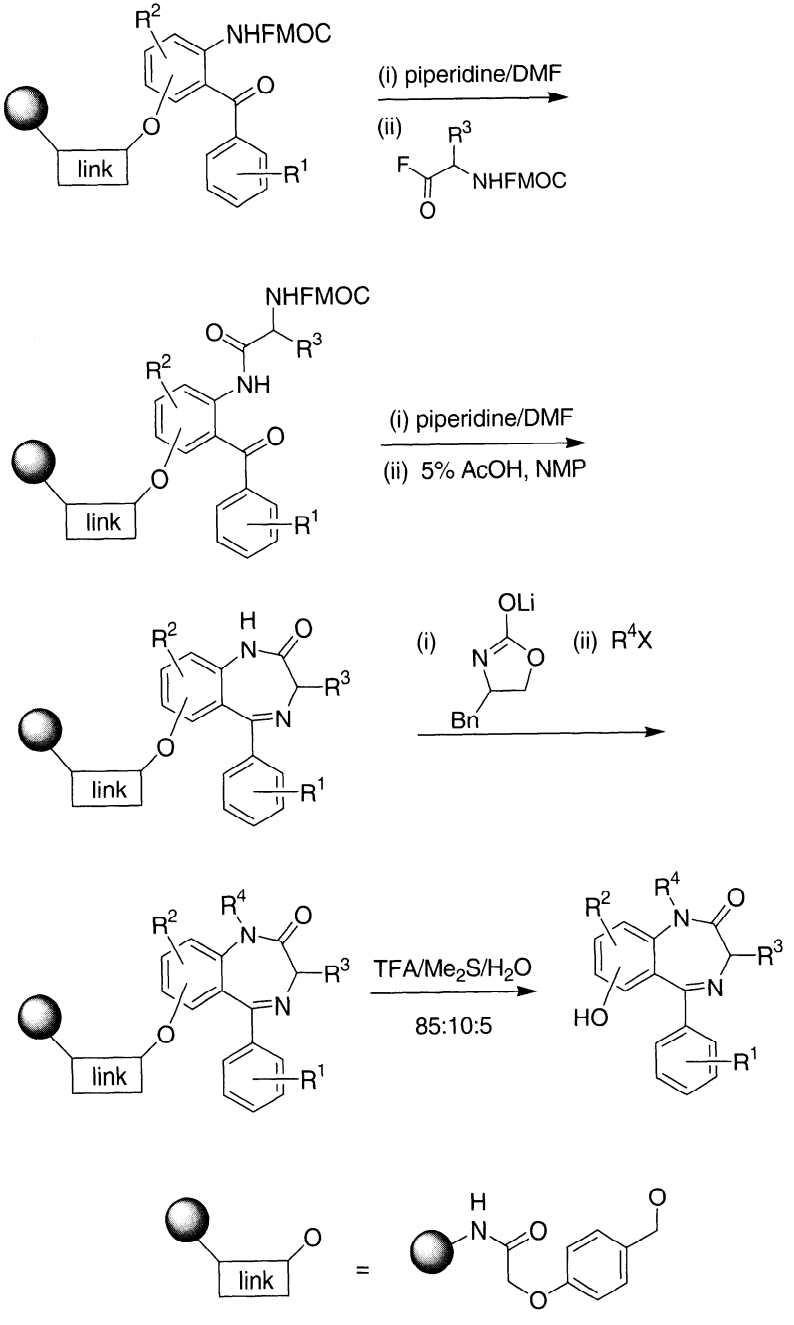
6.2. SYNTHETIC APPLICATIONS OF SYNPHASE CROWNS

6.2.1. Benzodiazepines

A variety of multistep syntheses that feature SynPhase crowns as the solid support have been published. The first reported example of nonpeptide synthesis on crowns was described by Ellman in 1994. In that work a 192-member benzodiazepine library was prepared and evaluated for binding against the cholecystokinin A receptor.[12] Ellman et al.[13] have also prepared a library of 1680 benzodiazepines (Scheme 2) using the Wang linker for attachment of a phenol to the crown. The linker was attached to the aminobenzophenone moiety in solution; the assembled unit was then coupled to the crowns in bulk in a round-bottomed flask. The fluoren-9-ylmethoxycarbonyl (FMOC) group was removed and coupling to the poorly nucleophilic aniline nitrogen was achieved using the amino acid fluoride. Deprotection and subsequent treatment with 5% acetic acid in *N*-methylpyrrolidone (NMP) achieved cyclization. The resulting anilide was alkylated with an alkyl halide using lithiated 5-phenylmethyl-2-oxoazolidinone as the base. This unusual base was selected to closely match the pK_a of the anilide group. Cleavage was performed using trifluoroacetic acid with water and dimethyl sulfide as volatile scavengers.

6.2.2. Purines

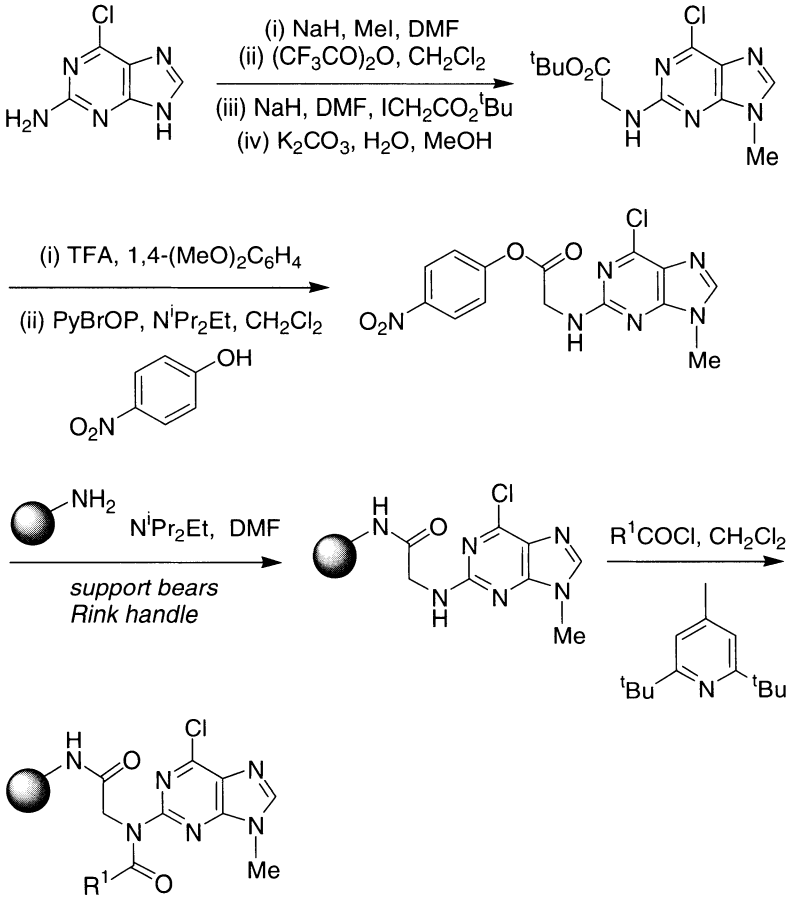
Schultz and co-workers have described a crown-based synthesis of 406 purines varying at the C-2 and C-6 positions.[14] This library was targeted for


R2
NHFMOC
O
O
link
R1
(i) piperidine/DMF
(ii)
R3
F
NHFMOC
O
NHFMOC
O
R3
R2
NH
O
O
link
R1
(i) piperidine/DMF
(ii) 5% AcOH, NMP
H
R2
N
O
R3
N
O
link
R1
OLi
(i)
N
O
Bn
(ii) R4X
R4
R2
N
O
R3
N
O
link
R1
TFA/Me2S/H2O
85:10:5
R4
R2
N
O
R3
N
HO
R1
link
O
=
H
N
O
O
O

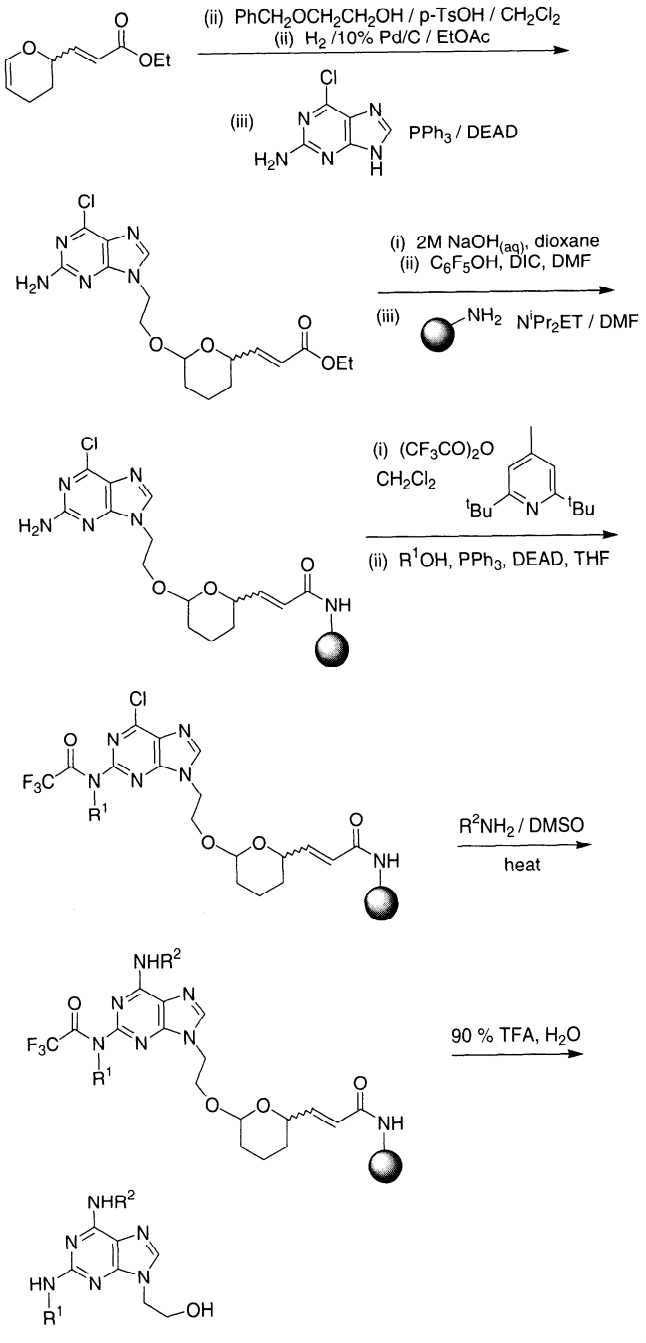
Scheme 2.

cyclin-dependent kinases. Following the incorporation of a common 2-chloropurine derivative onto the Rink amide-forming linker, diversity was introduced into the 6-position via an S_NAr reaction (Scheme 3). The 2-amino function was then acylated with acyl chlorides in the presence of 4-methyl-2,6-di-*tert*-butylpyridine, and the products cleaved using trifluoroacetic acid in dichloromethane with dimethyl sulfide as scavenger. Overall yields of 30–75% were reported.

Scheme 4 outlines an alternative synthesis of a library of disubstituted purines by a strategy similar to that shown in Scheme 3[15] except that



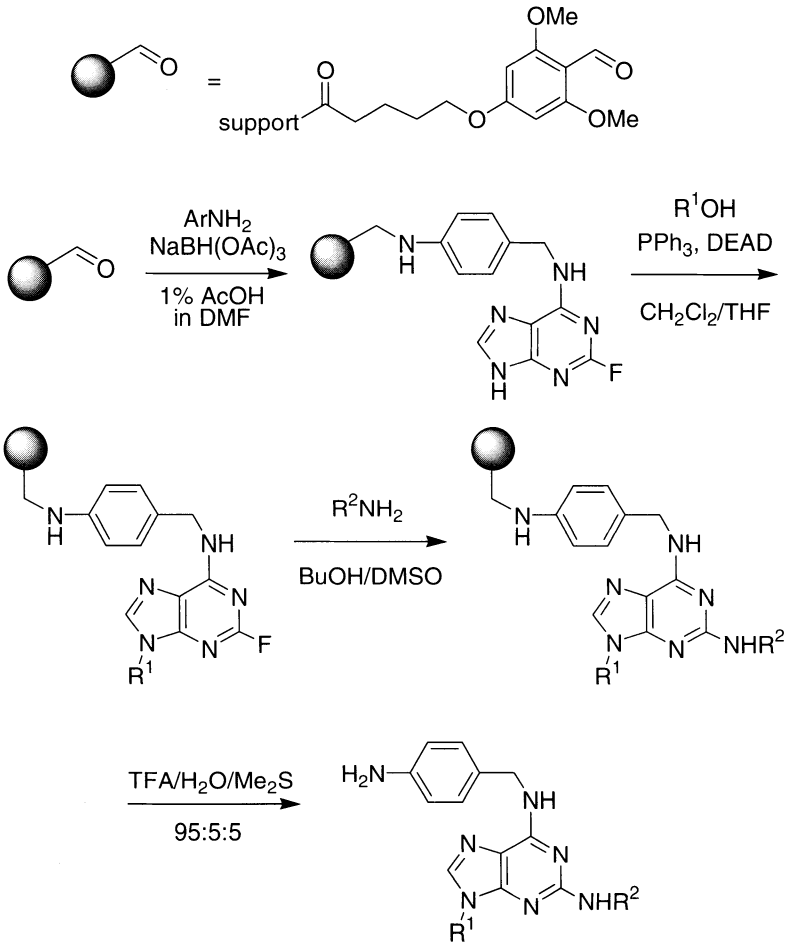
Scheme 3.


(ii) PhCH2OCH2CH2OH / p-TsOH / CH2Cl2
(ii) H2 /10% Pd/C / EtOAc
(iii)
PPh3 / DEAD
(i) 2M NaOH(aq), dioxane
(ii) C6F5OH, DIC, DMF
(iii)
NiPr2ET / DMF
(i) (CF3CO)2O
CH2Cl2
(ii) R1OH, PPh3, DEAD, THF
R2NH2 / DMSO
heat
90 % TFA, H2O

Scheme 4.

Ellman's tetrahydropyranyl linker[16] was used to attach the purine through the 9-position.

In another purine library synthesis, Schultz and co-workers attached a 6-aminomethylaniline side chain to the PAL linker[17,18] via reductive amination (Scheme 5). Alkylation at the 9-position was achieved using Mitsunobu conditions and an S_NAr reaction was used to functionalize the 2-position with amines. The final cleavage of the aniline was achieved using 90%

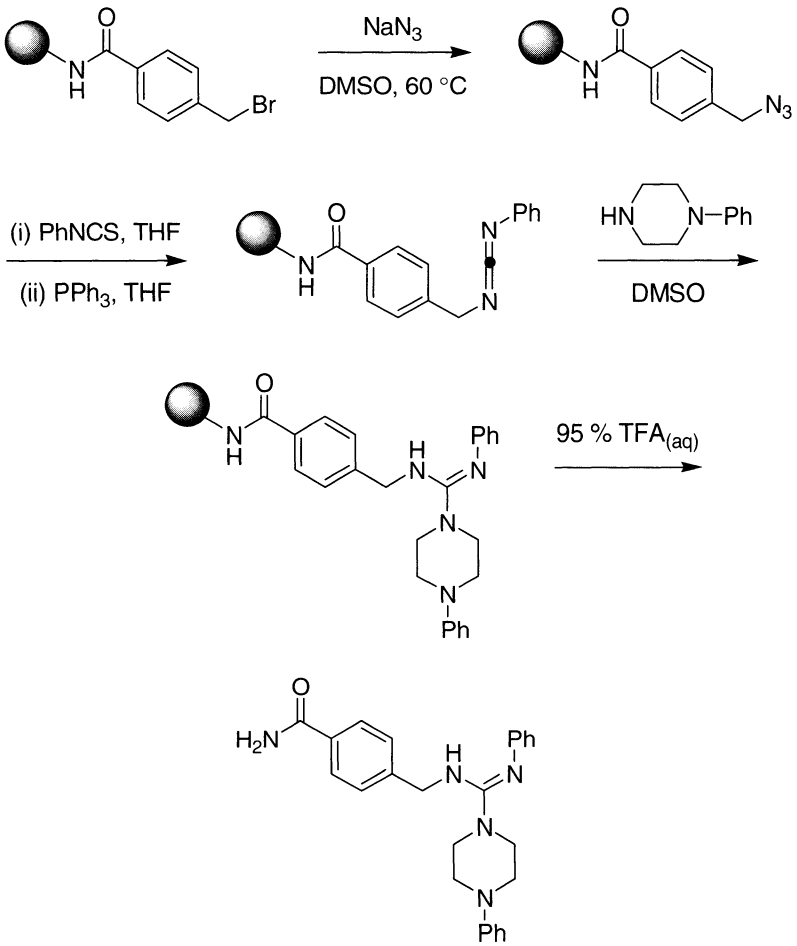


Scheme 5.

trifluoroacetic acid/10% water. Reported HPLC purities ranged between 51 and 85%, with an average value of 70%.

6.2.3. Guanidines

A series of trisubstituted guanidines has been prepared by Drewry et al.[19] α-Bromo-*p*-toluamide was converted to the azide by reaction with sodium



Scheme 6.

azide (Scheme 6). Treatment with an isothiocyanate followed by triphenylphosphine furnished the carbodiimide, most likely via a Staudinger/aza-Wittig reaction sequence. The order of addition was important to minimize side products from this step. Treatment of the intermediate carbodiimide with an amine provided the guanidine. Cleavage of the Rink linker was achieved using 95% TFA–H_2O. The reported model system had a purity of 96% by HPLC.

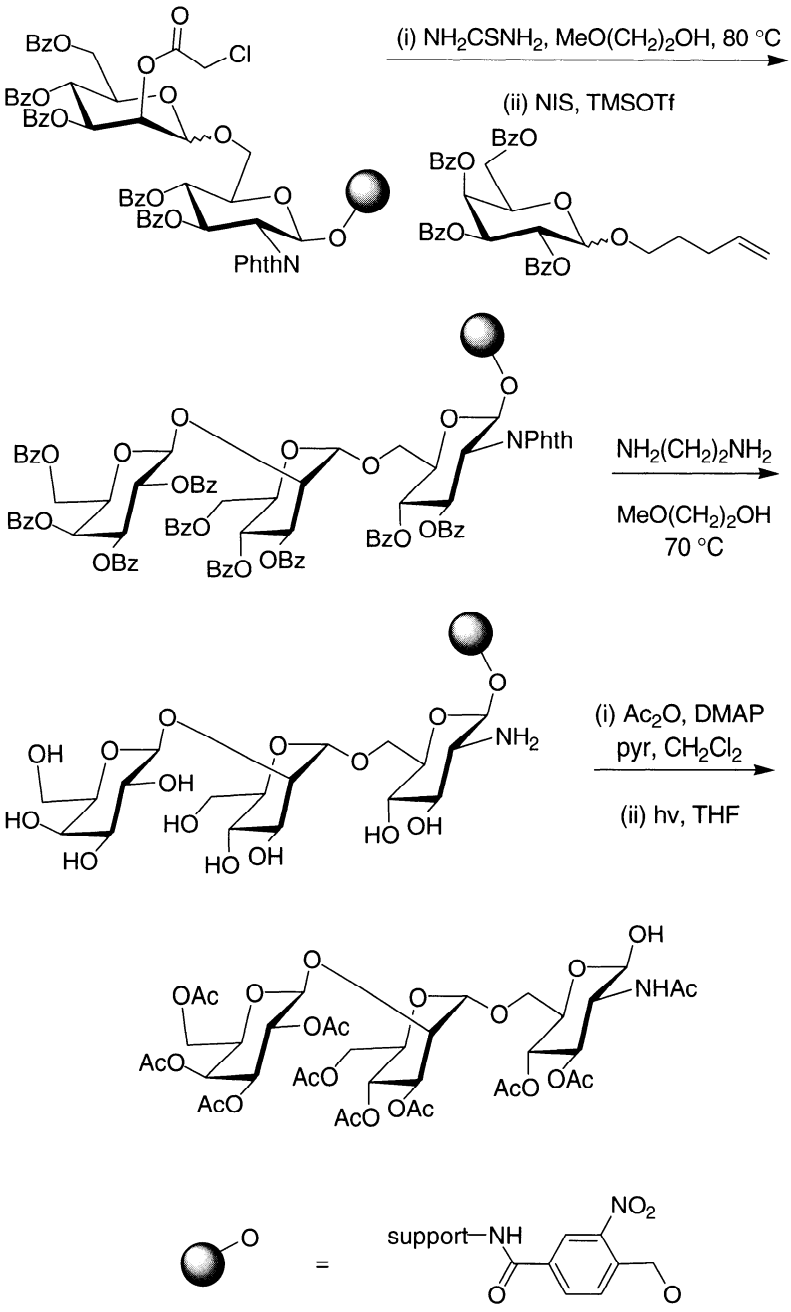
6.2.4. Polysaccharide Synthesis

Scheme 7 shows how trisaccharides were prepared on a radiation-grafted polymer surface.[20] The photolabile 4-hydroxymethyl-3-nitrobenzamido handle[21] and *N*-iodosuccinimide–triethylsilyltriflate coupling chemistry were used. Product purities were similar to those obtained using Tentagel macrobeads.

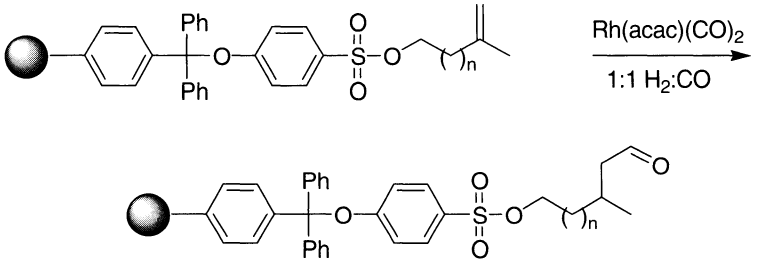
6.2.5. Hydroformylation and Hydrogenation

In an interesting application of a gaseous reagent to solid-phase synthesis, Takahashi and co-workers demonstrated hydroformylation of an unactivated alkene using synthetic gas (1 : 1 H_2–CO) and a Rh(I) catalyst (Scheme 8).[22] The reaction was typically performed at 40°C in toluene at a pressure of 75 atm. Conversions of 99% were obtained following careful reaction optimization. Variation in the concentration of catalyst could be used to alter the regioselectivity of the reaction.

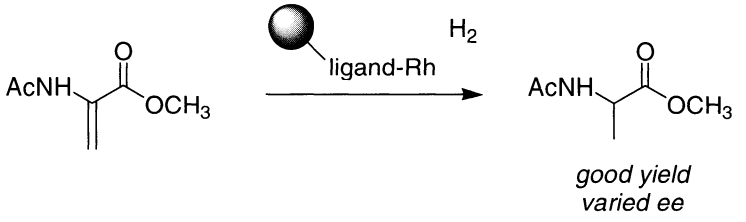
SynPhase crowns can also be used as the polymer support for solid-supported reagents in solution-phase combinatorial chemistry. Gilbertson and co-workers used crowns to prepare a bank of 63 solid-supported peptide-based chiral phosphine ligands to investigate a rhodium-catalyzed hydrogenation (Scheme 9).[23] The pentapeptide ligands each had two phosphine-containing residues, but the positions of these residues and the peripheral sequences were varied. Rhodium complexes of these ligands were formed in situ, and this library of catalysts was then used for asymmetric hydrogenation of dehydroalanine. Screening revealed that some conditions gave very high conversions. Although the enantioselectivity was low, it was dependent on the ligand used. Recycling of ligands attached to the crowns was possible.


(i) NH_2CSNH_2, $MeO(CH_2)_2OH$, 80 °C
(ii) NIS, TMSOTf
$NH_2(CH_2)_2NH_2$
$MeO(CH_2)_2OH$
70 °C
(i) Ac_2O, DMAP
pyr, CH_2Cl_2
(ii) hv, THF
support—NH
NO_2

Scheme 7.



Scheme 8.



Scheme 9.

6.3. LINKER DEVELOPMENT USING SYNPHASE CROWNS

Expanding the variety and properties of linker groups increases the scope of practical applications of radiation-grafted polymer surfaces for the parallel synthesis of organic compounds. Linker molecules have a bearing on the types of reactions that can be performed and the ease of isolation of products after cleavage.

A wide range of linker groups are currently used with SynPhase crowns. They accommodate formation of the following functional groups upon cleavage: carboxylic acids, primary and secondary amides, sulfonamides, alcohols, phenols, amines, anilines, anilides, hydroxymates, aldehydes, ketones, and thiols.

An important criteria in solid-phase synthesis is product purities immediately after cleavage from the support. Ideally, the target compound should be cleaved into a solvent–reagent system that can be easily removed, usually by evaporation. Solvents/cleavage reagents that are difficult to remove may compromise subsequent biological screening of the libraries. Consequently,

cleavage strategies featuring volatile acids (e.g., TFA) and scavengers are common.

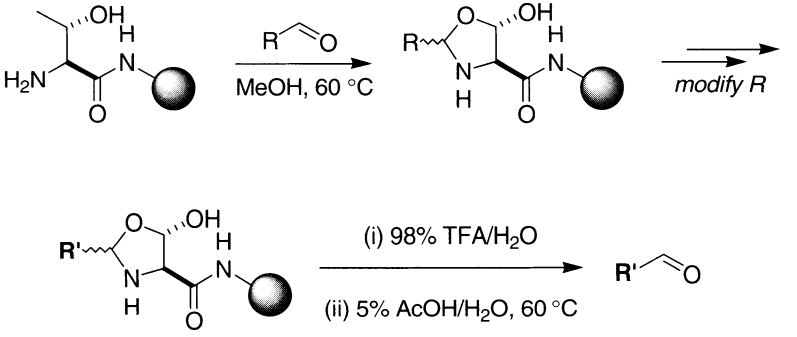
This section outlines useful strategies for preparing aldehydes and hydroxamic acids that were developed on SynPhase crowns.

6.3.1. Linkers to Generate Aldehydes

Recently, we developed a simple and efficient aldehyde linker using crowns as the solid support.[24] It consists of the amino acid threonine coupled to the crown via the carboxyl group, leaving the nucleophilic amino and alcohol functional groups free for oxazolidine formation with an aldehyde (Scheme 10). To investigate this attachment method, threonine was added to the Sasrin linker[25] and a range of condensation conditions were then investigated. Benzaldehyde was used for the initial studies. The product formed was treated with 1% TFA–DCM, conditions that cleaved the Sasrin linker, but not the oxazolidine aldehyde linker. Variables included solvent (MeOH or DMF), additive (1% EtN^iPr_2 or 1% AcOH), temperature (25 or 60°C), time (2 or 18 h), and aldehyde concentration (0.1 M or 2 M). Product purities were assessed using analytical reverse-phase HPLC and ESMS.

Superior attachment conditions were identified as 0.1 M aldehyde in methanol with 1% N^iPr_2Et for 2 h at 60°C; these gave >90% incorporation. Additional experiments showed that the N^iPr_2Et additive was not required.

The first conditions investigated for cleavage of the oxazolidine ring were 95% TFA–H_2O. These gave, at best, only 10% cleavage. Consideration of the cleavage mechanism suggested that increasing the water concentration and temperature might assist the reaction. Efficient cleavage was ultimately

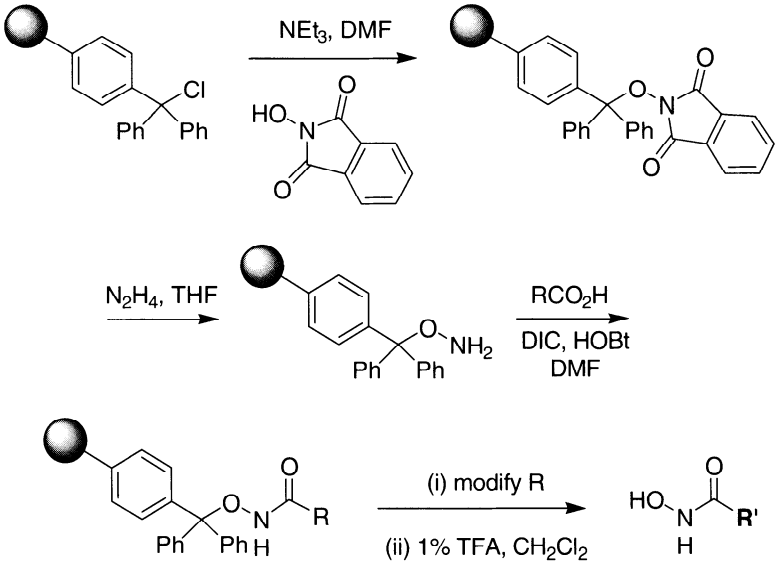


Scheme 10.

achieved using 5% AcOH–H_2O at 60°C for 30 min. Other mild aqueous acids, such as 0.1% TFA in 60% acetonitrile–water, also proved effective; this cleavage solution is more suitable when hydrophobic target compounds are being cleaved. Dependence on water concentration has proven advantageous because TFA labile protecting groups can be removed using 100% TFA prior to cleavage with mild aqueous acids at 60°C. The linker is now routinely used for the synthesis of aldehydes, specifically libraries of potential protease inhibitors.

6.3.2. Linkers to Generate Hydroxamic Acids

Hydroxamic acids are key functional groups in some matrix metalloproteinase (MMP) inhibitors. This observation has motivated several groups to develop linkers that give hydroxamic acids on cleavage.[26–29] Prior to these publications, we had developed a route to hydroxamic acids based on the trityl linker.[30] *N*-hydroxyphthalamide was attached to the trityl linker on SynPhase crowns (Scheme 11). The phthalamide-protecting group was cleaved using hydrazine hydrate in DMSO and a carboxylic acid coupled to the hydroxylamine on the solid phase using DIC/HOBt to form the



Scheme 11.

hydroxamate. On completion of the synthesis, cleavage was performed using 1% TFA–DCM for 30 min. Exclusion of water from the cleavage mixture is critical; use of 95%TFA–H_2O causes significant hydrolysis of the hydroxamic acid to the corresponding carboxylic acid. We have found this linker to be very clean and efficient, with the steric bulk of the trityl group hindering unwanted side reactions by the nucleophilic hydroxamate nitrogen.

6.4. TAGGING METHODS FOR IDENTIFYING INDIVIDUAL CROWNS

One-compound-per-well strategies for parallel syntheses require multiple additions. A library of 500 compounds prepared in 500 wells in three steps and using $5 \times 10 \times 10$ reagents requires 1500 additions. Conversely, strategies featuring only one vial per reagent require far fewer additions. In that case, when, for example, 10 reagents are used in a particular step, only 10 vials per addition would be required. For 500 compounds made in three steps from $5 \times 10 \times 10$ reagents, only 25 additions would be necessary.

Tagging the individual SynPhase crowns facilitates dramatic reduction in workload as outlined above. Unique tags identify the reaction history of the crown, instead of the grid position in the 8×12 array (Multipin) method. Coloring (in the stems and on attached tags) has been used in our laboratory as a tagging method for preparation of libraries of 800 compounds. This approach, however, does have limitations. Colors that can be used and easily distinguished are limited in number, and this form of coding is unsuitable when there is a need to unambiguously identify individual crowns in a mixed batch.

Radiofrequency tags[31,32] (i.e., transponders) facilitate manipulation of much larger and/or more complex libraries than color coding does. In this approach, read-only transponders are encapsulated in the removable polypropylene stem (called a TranStem; Figure 6.3) that clips into the crown. The transponders used in our system are manufactured by Baumer, who claim to be able to produce 2^{64} unique codes. Consequently, TranStems uniquely identify each crown used in the synthesis. In practice, the TranStem with crown attached is passed in front of a radiofrequency reader (viz. antenna) to computer register the transponder code. A software package called TranSort manages the entire synthesis. For example, TranSort, which has a multimedia function, instructs the chemist both visually and verbally

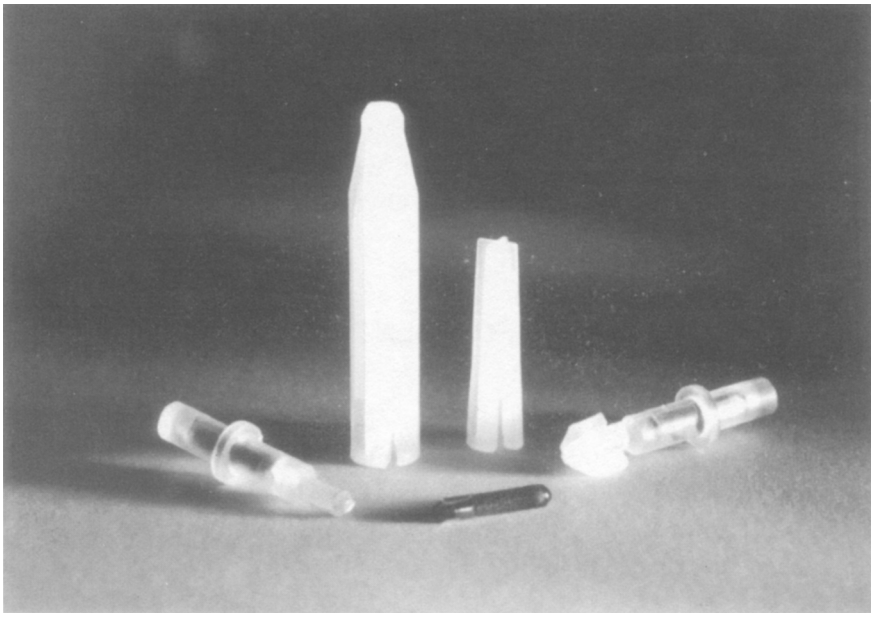


Figure 6.3. Back (left to right): P-series SynPhase crown; I-series SynPhase crown. Front (left to right): polypropylene stem with transponder encapsulated (TranStem); transponder; O-series crown attached to TranStem.

to place a given crown (and stem) into a particular reaction flask. The reading step is repeated for each crown and the reaction carried out. When the reaction is complete, all the crowns can be combined for the washing step to reduce handling time. The sort–reaction–combine–wash–resort cycle (Figure 6.4) is repeated for each reaction step in the combinatorial synthesis, except when all crowns are to be treated with the same reagent. Steps that involve treating all crowns with the same reagent can be carried out in a single large flask. TranSort tracks the reaction history of each crown and at the completion of the synthesis may be used to place the crowns in a predefined pattern in the 96-well format for cleavage, hence greatly simplifying the final cleavage step. The program also provides an output file defining the reaction history (i.e., the predicted product) for each position in the 96-well plates, which can be imported into a variety of chemical structure compatible data-handling programs. Furthermore, the program has the capability to interface with other commonly used chemical library software. The synthesis tagging method has also been fully auto-

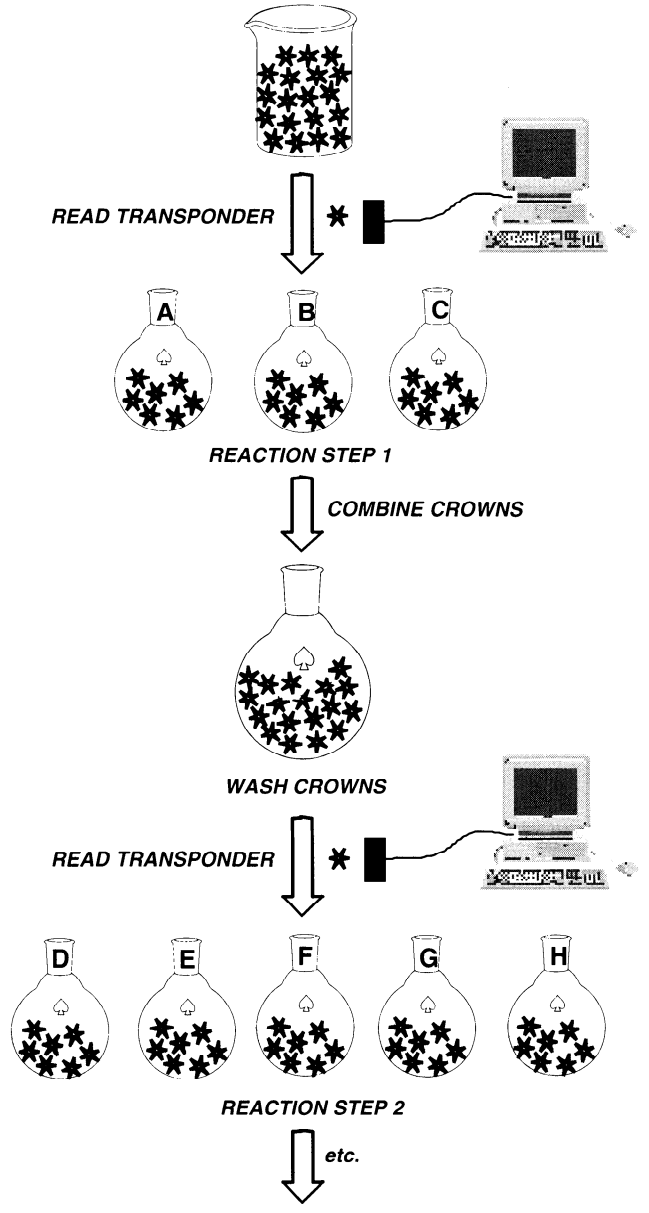


Figure 6.4. The sort–reaction–combine–wash–resort cycle for library synthesis using radiofrequency tagging of individual SynPhase crowns.

mated and is currently being used for the production of libraries of thousands of compounds.[32]

6.5. FUTURE DEVELOPMENTS

SynPhase crowns have been used routinely in our laboratory for the synthesis of small-molecule libraries for the last six years and for peptide and peptide mimetic synthesis since the late 1980s. This has been possible due to improvements in the graft polymers and an expansion of the range of linker systems available on crowns. The method has recently been extended to allow for the synthesis of thousands of compounds using TranStem to tag and TranSort to track syntheses. Both crowns and their applications are being constantly assessed and improved. The compound loading on crowns has been significantly increased and the void volume decreased, thus allowing more final product while using less solvent and reagents. New base polymers are being developed to allow high-temperature stability, permitting the use of reaction temperatures in excess of 200°C. The TranSort program is being upgraded to provide greater synthetic flexibility. The most exciting advances, however, have been in automation. An automated version of the TranSort system is already in existence and in regular use to prepare libraries of thousands of compounds. This robotic system is being continuously refined. All of these improvements indicate that SynPhase crowns will continue to be a useful tool to the combinatorial chemist both in the development of novel chemistries and linkers and in the synthesis of multi-milligram quantities of tens to thousands of individual compounds on solid support.

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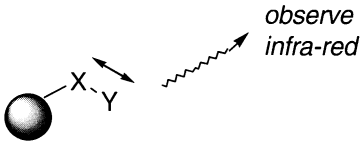
CHAPTER 7

VIBRATIONAL SPECTROSCOPY FOR OPTIMIZATION OF SOLID-PHASE ORGANIC SYNTHESES



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7.1. INTRODUCTION

This chapter describes how Fourier transform infrared (FTIR) spectroscopy can be used to monitor solid-phase organic reactions directly on solid supports. Examples encompassing a range of reaction conditions are discussed to demonstrate the value of this method for optimization of solid-phase organic syntheses.

7.1.1. Optimization of Solid-Phase Organic Synthesis

Solid-phase organic syntheses[1] typically use large excesses of reagents to drive reactions to completion so that, ideally, products liberated from resins should not require purification. Optimization of conditions is a critical part of solid-phase syntheses. Transfer of organic reactions in solution to a solid matrix is not a trivial undertaking, and lack of analytical methods accentuates this problem. Libraries prepared without adequate refinement of conditions tend to be of poor quality. For libraries so large that all the constituents cannot be fully characterized, well-optimized reaction conditions are absolutely essential. Techniques like "split and pool,"[2] for instance, can only be applied successfully after thorough optimization.

7.1.2. Monitoring Solid-Phase Organic Synthesis by FTIR Spectroscopy

Organic reactions selected to synthesize a combinatorial library should be reproducible and well behaved; hence the resin-bound products are rarely unknowns. Consequently, the major analytical task in solid-phase organic synthesis is to confirm the presence of the desired products rather than a full structural elucidation. For several reasons, FTIR spectroscopy is particularly suited for this task. First, functional group interconversions are easily monitored by IR spectroscopy. The functional group monitored need not be directly involved in the reaction; the building blocks used in reaction optimization can be selected to contain an IR detectable group at a remote site. Second, direct observation of compounds on a solid phase is generally quicker and more convenient than methods based on cleavage and then analysis of intermediates. Third, some synthetic intermediates are unstable to the necessary cleavage conditions. Conversely, on-support analytical methods indicate the success of the reaction prior to the cleavage step; this is the most relevant information. Finally, FTIR spectroscopy is a sensitive technique that requires only small amounts of sample. Moreover, it can be performed without destruction of even the small amount of material that is required.

7.1.3. Typical Characteristics of Solid Supports

Typical solid supports used in organic syntheses are resin beads formed from cross-linked polystyrene (PS; 40–150 μm diameter), polystyrene–

polyethyleneglycol (PS-PEG) polymer grafts, or surface-functionalized polypropylenes such as in the multipin method (see Chapter 6).

Low cross-linked polystyrene resins (1% divinylbenzene) is probably the most popular solid support. These resins swell to 2–6 times their original volume depending on the solvent used. Swollen resin, after removal of solvent and without excessive drying, remains in a rubbery state and can be easily flattened for FTIR study in the transmission mode. The support-bound compound should be washed free of reagent and solvent.

7.2. SPECTROSCOPIC METHODS APPLICABLE TO DIFFERENT SAMPLE SIZES

Ten milligrams of resin contains approximately 50,000–70,000 beads (~50 μm diameter). Sample sizes used in analyses via vibrational spectroscopy range from single beads to 10-mg aliquots.

7.2.1. Single-Bead Analyses

FTIR Microspectroscopy.[3] A microscope accessory coupled to a liquid-nitrogen-cooled mercury–cadmium–telluride (MCT) detector can be used to obtain an IR spectrum. This is possible in both the transmission and reflectance modes. Several beads are spread on an IR-transparent window (NaCl, KBr, diamond) and possibly flattened via a hand-press or a compression cell. The IR beam is focused on a single bead using the view mode of the microscope. The blank area surrounding the bead is isolated using an adjustable aperture, and a spectrum is recorded using 32 scans (<1 min). A nearby blank area of the same size on the IR transparent window is recorded as the background.

Single-Bead FT Raman Spectroscopy.[4] Microscope accessories are also available that facilitate collection of FT Raman spectra on single-bead samples. Fourier transform FT Raman spectroscopy is a technique based on inelastic light scattering, in which scattered photons exchange energy with the sample. Most commonly, the scattered photon loses energy to a vibrational mode of the sample molecule, leading to a downward frequency shift. This Raman shift is equal in energy to the light absorbed by the same

molecule in an IR absorption experiment if the vibrational mode is observable in both techniques.

Intensities of Raman absorptions are governed by polarizability changes during vibrations. Strong FT Raman signals can be obtained for functional groups with low polarity and high polarizability such as S–S and symmetric vibrations of groups with high degree of symmetry such as NO_2. The FT Raman spectra are free of the fluorescence interference because the excitation light used is in the near-IR region.

7.2.2. Microscale Analyses (~100 beads)

Analyses of sample sizes of approximately 100 beads are convenient at the reaction optimization stage in solid-phase organic syntheses. As in single-bead analyses, reactions in progress can be followed continually using microscale analysis methods. Several readily available spectroscopic accessories that facilitate such analyses are described below.

Beam Condensers.[4c] Beam condensers are used to focus the IR radiation from a beam that is typically 8 mm in diameter to one that is around 2 mm at the sample plane. This allows the analysis of 50–100 resin beads without KBr dilution. A diamond compression cell is used to flatten beads and to support the sample throughout the measurement. The same diamond cell without beads is then used to record a background spectrum.

Attenuated Total Reflection (ATR).[4c] A sample brought in contact with the totally reflecting surface of a high-refractive-index material (the ATR crystal), will, on IR irradiation, give an evanescent wave in the less dense medium that extends beyond the reflecting interface. This wave will be attenuated in regions of the IR spectrum where the sample absorbs energy. Observation of such waves constitute ATR measurements. Only the small amounts of beads necessary to cover the area of the ATR crystal are required.

Macro–FT Raman Spectroscopy.[4c] The FT Raman spectra can be acquired in macromode on a small amount of beads. The advantages compared to single-bead Raman measurement are reduced acquisition time and the excitation energy.

7.2.3. Macroscale Analyses (5–10 mg of beads)

KBr Pellet Methods.[5] Finely ground (ideally 0.5 μm average particle size) sample and pure, dry, spectroscopic grade KBr powder are featured. Usually concentrations of about 1% sample in KBr are used. These samples are pressed in dies until the KBr particles coalesce into a clear disk. The disks can be analyzed in regular FTIR instruments generating standard 8-mm-diameter IR beams. Resin beads generally cannot be ground, so the sample particle size in a KBr pellet remains to be 50–100 μm; this is appreciably larger than the 0.5 μm ideal. Light scattering and interference from stray light are two consequences of this imperfect sample preparation. Another drawback of this method is that it is difficult to prepare moisture-free KBr powder. Conversely, a compelling advantage of this approach is that the required apparatus can often be found "in house" in nonspecialized laboratories.

Diffuse Reflectance Infrared Fourier Transform Spectroscopy (DRIFT).[6] When IR radiation is directed onto the surface of a solid sample, two types of energy reflectance can occur: specular and diffuse. The specular component is the radiation that reflects directly off the sample surface (i.e., not absorbed by the sample). Diffuse reflectance is the radiation that penetrates into the sample and then emerges. Diffuse reflectance accessories are designed to optimize the diffuse reflected energy and suppress the specular component. The optics therefore selectively directs the scattered radiation to the IR detector.

Photoacoustic Spectroscopy.[7] When modulated IR radiation is absorbed by a sample, the substance heats and cools in response to modulated IR energy impinging on it. This thermal hysteresis is converted into pressure waves that can be communicated to surrounding gases and detected by acoustic detectors (essentially a sensitive microphone in the enclosed sample chamber). In such measurements, the acoustic detector replaces the IR detector of the spectrometer.

7.2.4. Analyses of Surface-Functionalized Polymers

Attenuated Total Reflectance (Micro-ATR and ATR[8]). The ATR method discussed above is designed to record spectra from the surface of a solid

sample. Therefore, ATR is ideally suited to analyses of surface-functionalized polymers. The ATR waves decay exponentially with distance from the surface of the crystal interface. This decay is such that the signal is difficult to detect beyond a few micrometers; hence ATR is effectively insensitive to sample thickness. Attenuated total reflectance is the best IR technique, for instance, for analyses of Multipin crowns and Microtubes.

7.2.5. Quantitative Methods

Spectrophotometric and fluorimetric methods can be used to quantitate organic compounds bound to solid supports. Conversely, methods based on cleavage, purification, and weighing are rarely practical because the amounts of cleaved compounds to be weighed are too small.

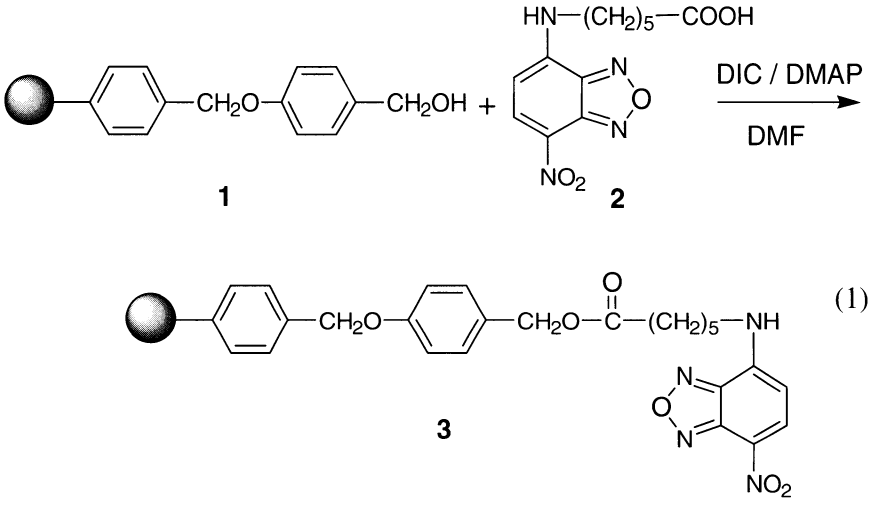
A general principle for the quantitation of the absolute amount of organic functional groups on polymer supports using spectrophotometric or fluorimetric methods has been developed.[9] This features chromophoric reagents that can react specifically with an organic functional group. Observed decrease in reagent concentration in the supernatant can then be used to deduce the absolute amount of organic functional groups on solid support.

7.3. OPTIMIZATION IN SOLID-PHASE ORGANIC SYNTHESES

7.3.1. Reaction Kinetics

Organic reactions carried out on polymer support have generally been assumed to be slower than the corresponding homogeneous solution reactions. The experimental data to test this speculation have not been obtained until recently when single-bead FTIR is used in the study of reaction kinetics.[3a,c,d,4c,9,10,11]

One approach to following reaction kinetics on a solid phase is as follows. A trace amount of resin beads is taken out of a reaction vessel, rinsed briefly with solvent, and subjected to single-bead FTIR analysis or analysis by FTIR with a beam condenser. As an example, the kinetics of the reaction shown in reaction 1 was studied,[4c] that is, a combination of Wang resin **1** with succinimidyl 6-(*N*-(7-nitrobenz-2-oxa-1,3-diazo-4-yl)amino)hexanoate **2** to produce compound **3**. The IR spectra for this transformation are



(1)

shown in Figure 7.1. The disappearance of the starting material IR bands at 3577 and 3458 cm^{-1} coincided with emergence of product bands at 1732, 1580, and 3352 cm^{-1}. Completion of the reaction can be inferred from disappearance of the hydroxyl bands at 3577 and 3458 cm^{-1}. Area integration of the emerging band at 1732 cm^{-1} plotted against time (Figure 7.2) gave a time course that was fitted to a pseudo-first-order rate equation yielding a rate constant of 3.8×10^{-4} s^{-1}.

A variety of solid-phase organic reactions have been studied using approaches that are similar to the one outlined above. Figure 7.3 summarizes kinetic data for the reactions depicted in reactions 1–16, representing 16 solid-phase organic reactions with pseudo-first-order reaction rates ranging from 1.1×10^{-4} to 5.0×10^{-3}. These data demonstrate that solid-phase organic reactions proceed faster than most have presumed previously. As seen in Figure 7.3, many of these solid-phase organic reactions were complete in 2–3 h. In some cases extended reaction times (e.g., 24 or 48 h) are unnecessary and may even allow more side products to form.

7.3.2. Selection of Optimal Solid Supports

Optimal reaction conditions and reaction rates in solid-phase syntheses vary greatly among solid supports. This is due to the chemical/physical environ-

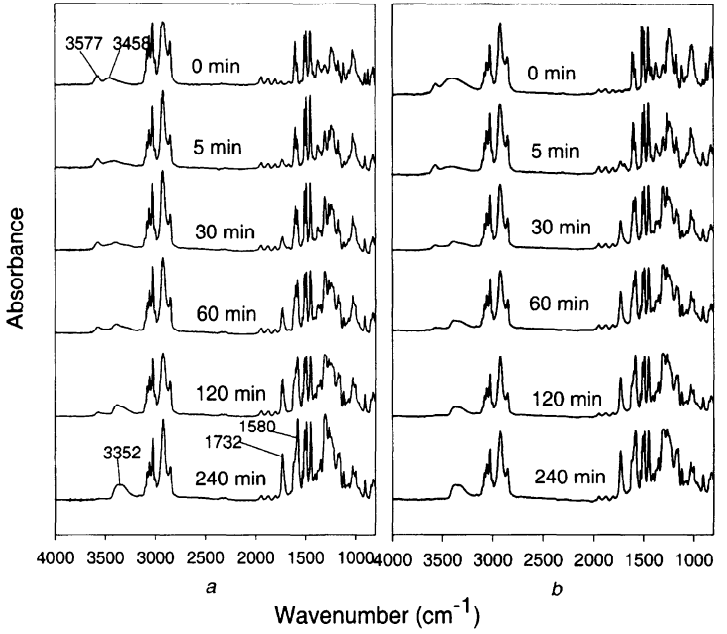


Figure 7.1. IR spectra of the reaction product at various times during reaction 1 obtained by (*a*) the single-bead FTIR and (*b*) the beam condenser FTIR.

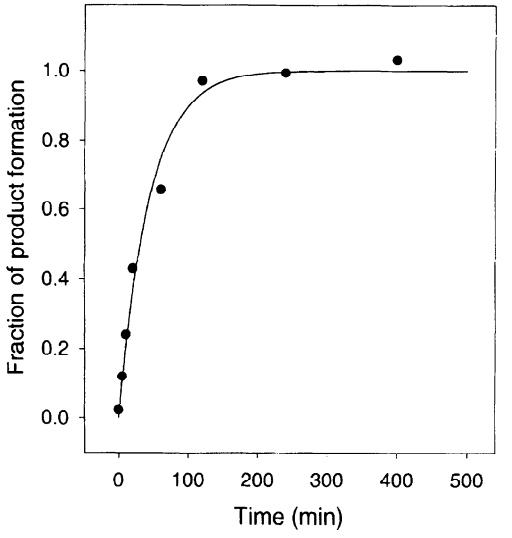


Figure 7.2. Time course of reaction 1 followed by integration of the IR band of the product at 1732 cm^{-1} from single bead FTIR experiments.

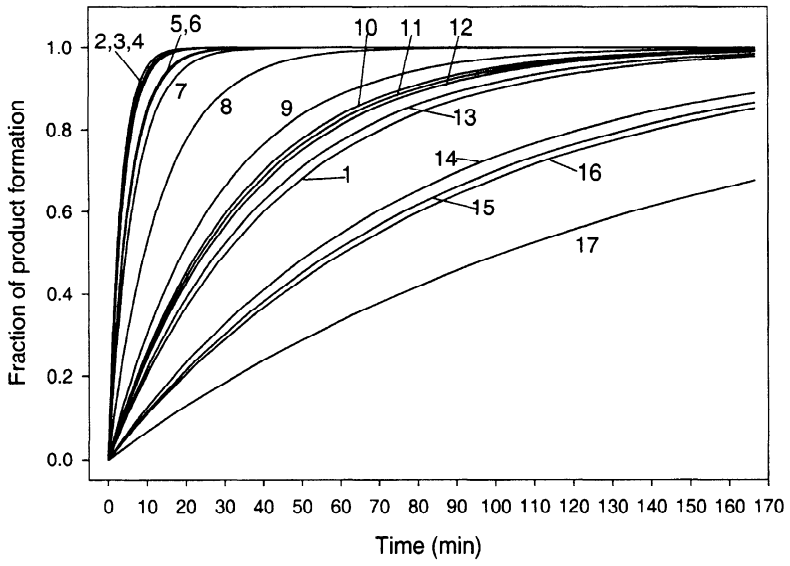
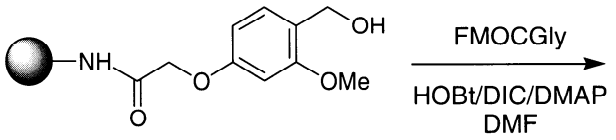


Figure 7.3. Time courses of reactions 1–17. The kinetics of product formation was analyzed as in Figures 7.1 and 7.2. The rate constants obtained from the best fit are displayed for each reaction. *Pseudo*-first-order rate constants (s^{-1}) determined for the reactions were: (1) 3.8×10^{-4}; (2) 5.0×10^{-3}; (3) 4.6×10^{-3}; (4) 4.3×10^{-3}; (5) 3.1×10^{-3}; (6) 3.0×10^{-3}; (7) 2.5×10^{-3}; (8) 1.23×10^{-3}; (9) 6.0×10^{-4}; (10) 5.0×10^{-4}; (3b*) 4.8×10^{-4}; (11) 4.6×10^{-4}; (12) 4.1×10^{-4}; (13) 2.2×10^{-4}; (14) 2.0×10^{-4}; (15) 1.9×10^{-4}; (16) 1.1×10^{-4}. Here *3b represents the same as reaction 3 carried out using 100-fold less starting resin and 50% of the resin loading as compared to the original reaction 3.



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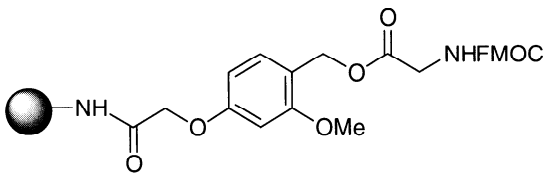

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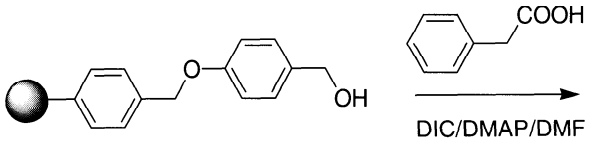

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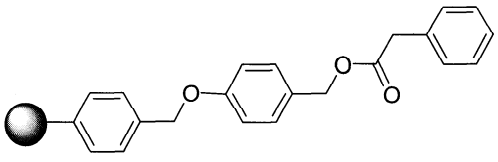

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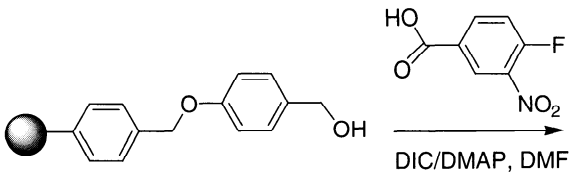

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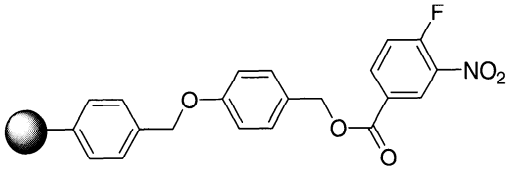

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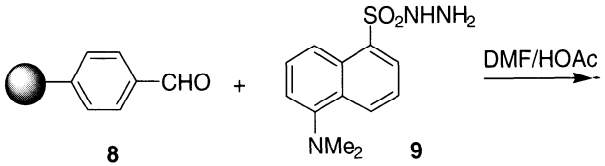

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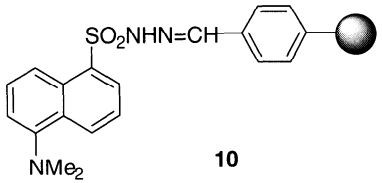

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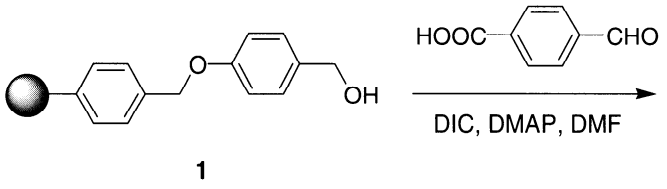

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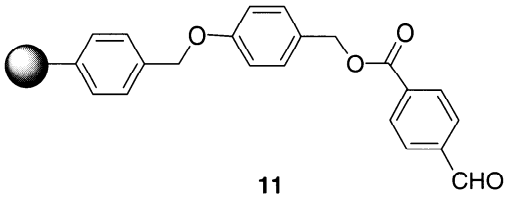
(6)



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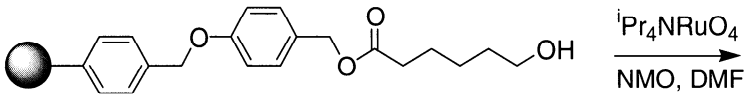

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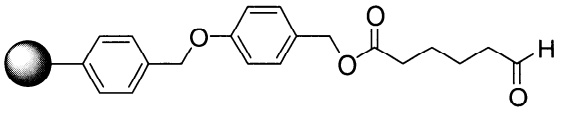
(7)



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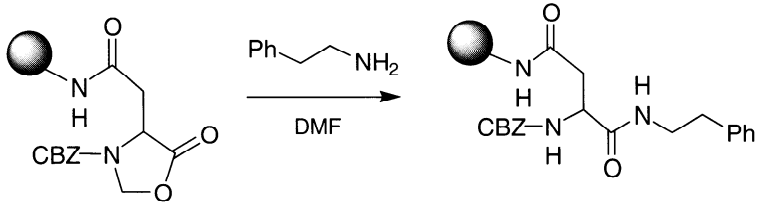
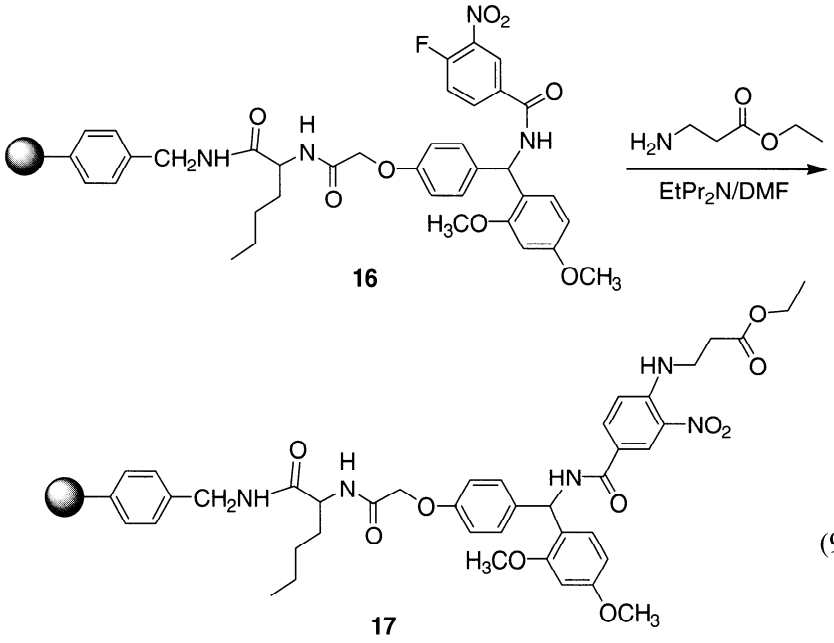
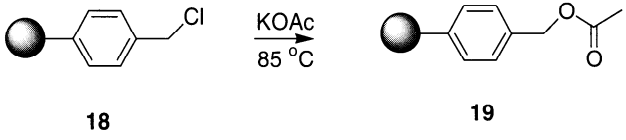


14 15

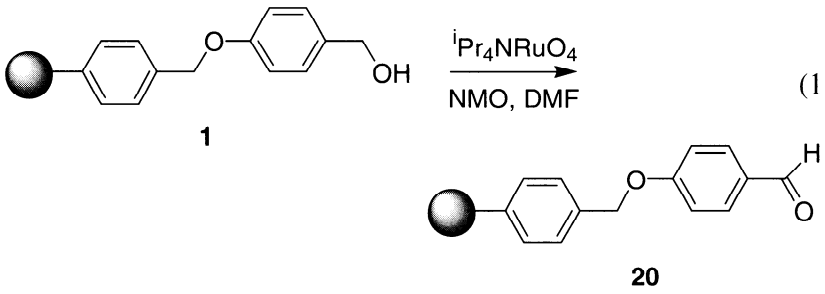
(8)


NO2
F
O
NH
H
N
O
CH2NH
O
H3CO
OCH3
H2N
O
O
EtPr2N/DMF
HN
O
NO2
HN
O
16
17

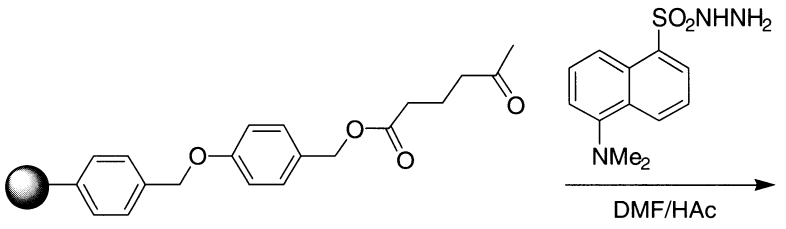
(9)


Cl
KOAc
85 °C
O
O
18
19

(10)


O
OH
iPr4NRuO4
NMO, DMF
H
O
1
20

(11)



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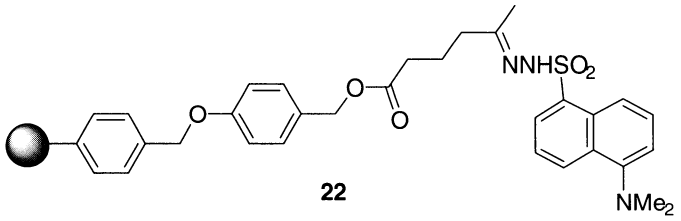
(12)



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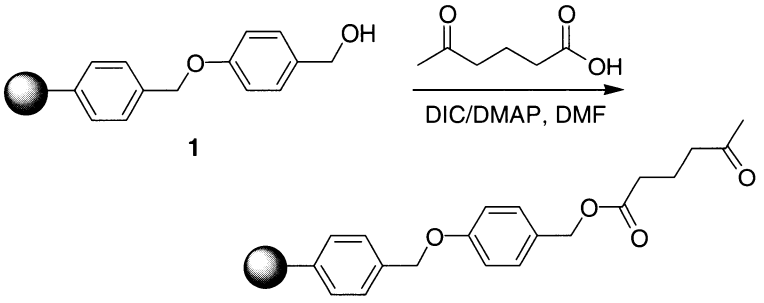

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(13)

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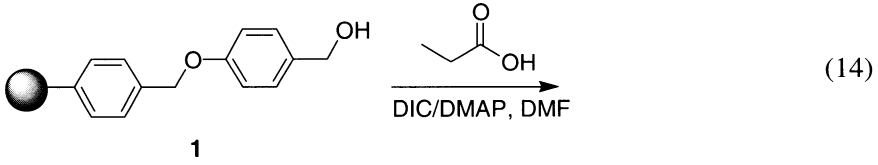

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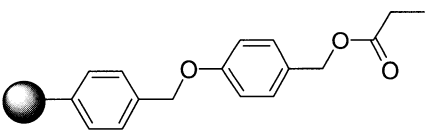

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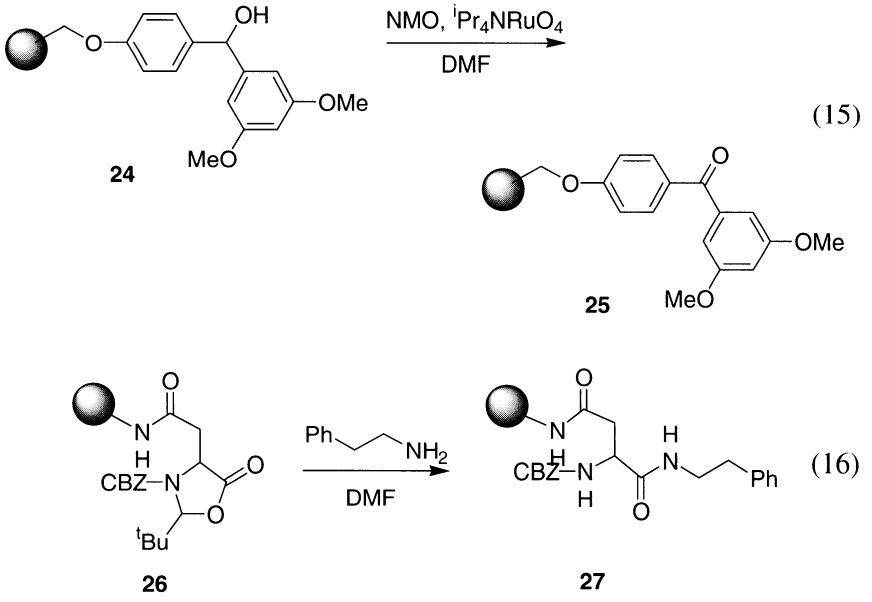


24 25 (15)

26 27 (16)

ment created by the resins. Polystyrene, for instance, is highly hydrophobic. In the absence of linkers, reactions on polystyrene resin tend to be dominated by this consideration. However, polystyrene–PEG resin is based on a very small portion of cross-linked 1% divinylbenzene–polystyrene backbones extensively grafted with PEG linkers having about 40–60 ethylene oxide units. The PEG content is therefore up to 70% of the resin weight. It is the PEG chains that largely govern the mechanical and physical/chemical behavior of the resin. Moreover, reactive sites in some polystyrene–PEG resins are separated from the hydrophobic polystyrene core by the long flexible PEG spacers. Consequently, such resins are characterized by good miscibility with most solvents, including water. Indeed, polystyrene–PEG has been described as a quasi-homogeneous and "solution-like" reaction support. It is commonly assumed that reactions carried out on polystyrene–PEG resins proceed faster than those carried out on polystyrene resins.

Several reactions (3, 5, 11–14, and 16) were carried out on these resins under identical conditions to compare reaction rates on polystyrene and polystyrene–PEG resins.[11] The results are collected in Table 7.1. These data show that reactions on polystyrene–PEG resin are not always faster than on polystyrene resins. For example, reaction 16 is much slower on polystyrene–PEG resin than on polystyrene resin.

TABLE 1. Comparison of Reaction Rates on PS- and TG-Based Resins

Reaction	k_{PS} (s^{-1})	k_{TG} (s^{-1})	k_{TG}/k_{PS}
12	4.6×10^{-4}	1.8×10^{-3}	3.9
14	2.2×10^{-4}	2.3×10^{-4}	1.0
3	4.8×10^{-4}	4.2×10^{-4}	0.9
15	2.0×10^{-4}	2.2×10^{-4}	1.1
5	3.1×10^{-3}	1.8×10^{-3}	0.6
13	4.1×10^{-4}	1.9×10^{-4}	0.5
16	1.13×10^{-4}	6.26×10^{-6}	0.055

Another kind of solid support that has gained more popularity is the surface-modified polypropylene, such as the Multipin crown and Microtubes. Reaction 3 was carried out on lightly and highly cross-linked polystyrene resins (1% and >20% divinylbenzene, respectively), polystyrene–PEG resin, and a surface-functionalized Microtube reactor.[12] The reaction kinetics on these supports is compared in Figures 7.4 and 7.5. The reaction on the highly cross-linked polystyrene resin was shown to be slower than on other supports and the reaction on Microtube was faster than on polystyrene resins.

Perhaps, unsurprisingly, the effects of polymer matrix on the reaction rate are probably at least as complex as solvent effects in solution-phase reactions, and broad generalizations about the characteristics of any given support in a series of different reactions are inappropriate. Reaction rates on supports depend on solvent swelling, selective adsorption, hydrogen bonding, hydrophobicity, and polarity. No single polymer support is best for all reactions.

7.3.3. Optimization of Reaction Conditions

Solvents. Solvents have a multiple role in solid-phase organic syntheses, that is, stabilizing the transition state, swelling of polymer support, and solubilizing the reagents/substrates. Nonuniform solvation of resins gives rise to complex and poorly reproducible reactions. Therefore, solvent selection is often critical for solid-phase organic syntheses on polystyrene resins. An example is shown in Figure 7.6. These data concern reaction 17, which was carried out on polystyrene resin in different solvents. Although

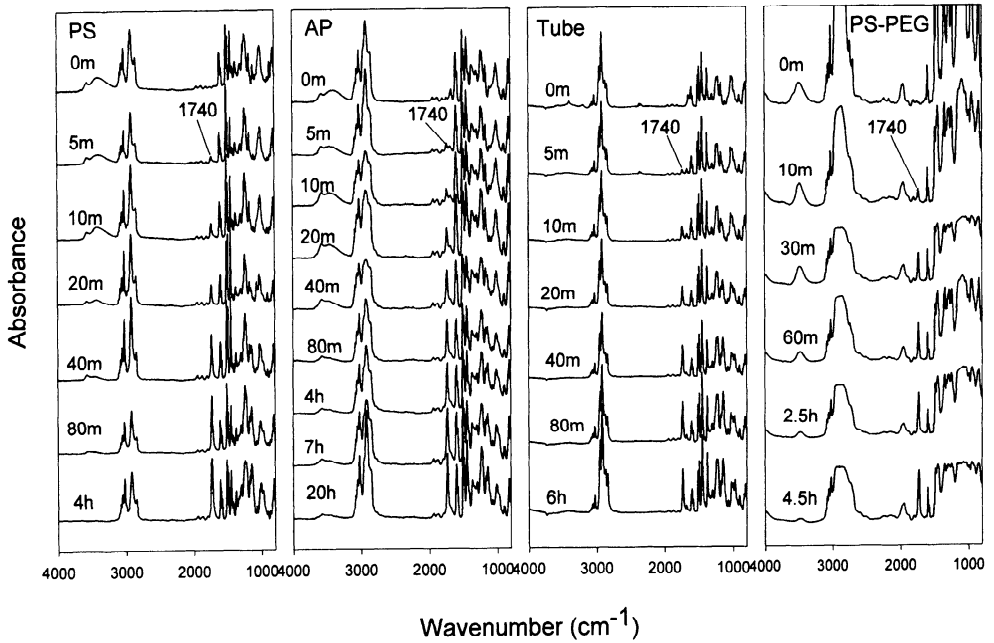


Figure 7.4. Single-bead IR spectra of the product for the reaction 3 at various times on PS = polystyrene, AP = ArgoPore, Tube = Microtube reactor, and PS-PEG = polystyrene–polyethyleneglycol resin.

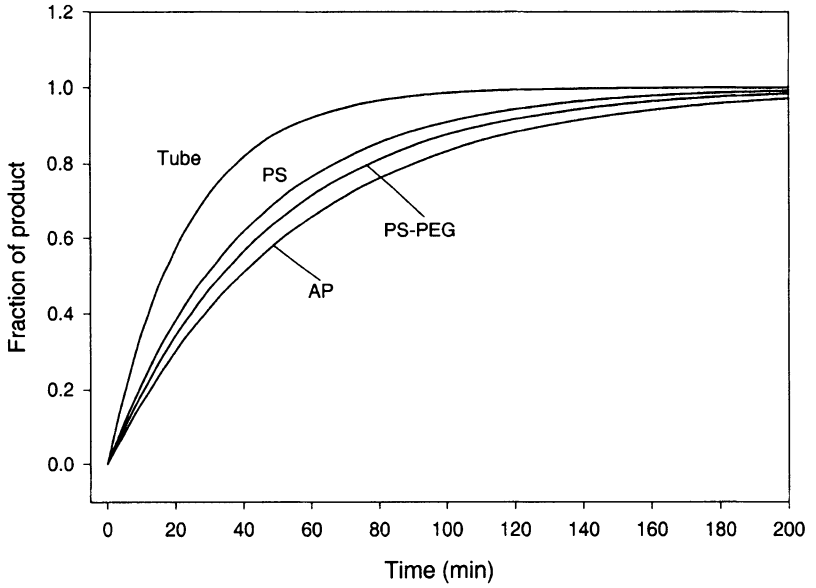


Figure 7.5. Time courses for reactions as in Figure 7.4 wherein IR peak areas at 1740 cm^{-1} for various time points were fitted to a *pseudo*-first-order rate equation. Rate constants were obtained by the best fit as in Figure 7.2.

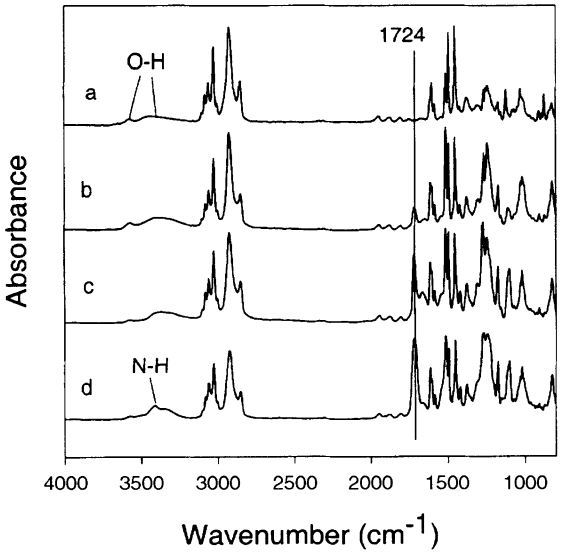
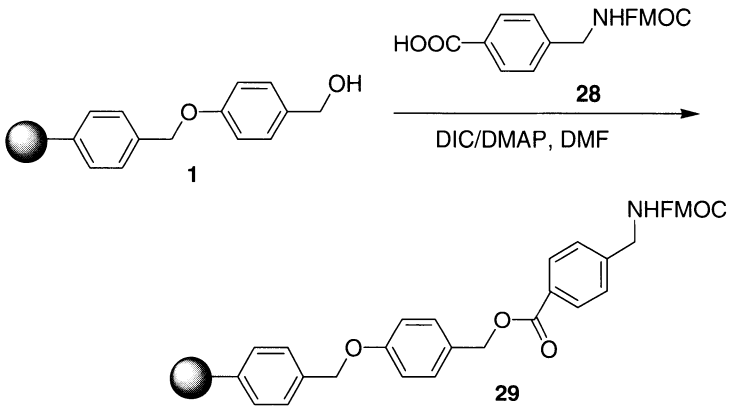


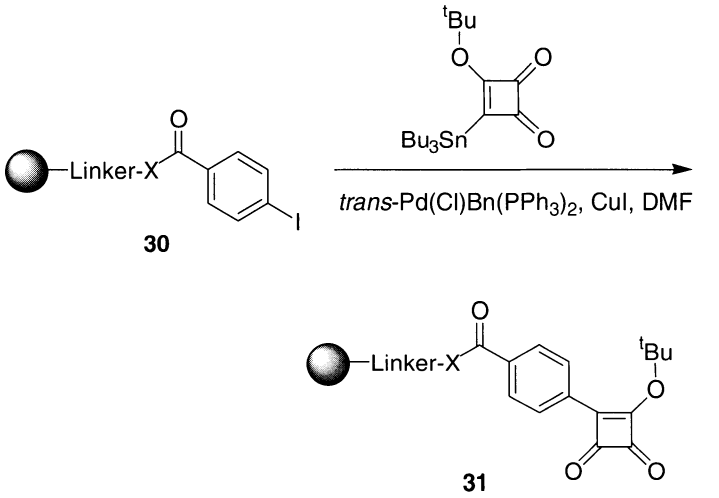
Figure 7.6. Single-bead IR spectra of the product for reaction 17 in different solvents as shown.



(17)

DMF is a good swelling solvent, the reaction does not proceed to completion due to the poor solubility of the reagents in that medium. The reagents have better solubility in DMSO, but use of 2 : 1 DMF–DMSO did not improve the reaction yield. Pyridine, which is a better solvent for the reagent and a good swelling solvent for polystyrene resin, was ultimately shown to be the best solvent tested.

Linkers. Linkers mainly affect the attachment and detachment steps. Figure 7.7 gives data for the Stille reaction 18 with various chemical linkers. The characteristic carbonyl bands of the squarate moiety at 1780 and 1750 cm^{-1}, and those of the ester or amide linkage bonds, allow facile monitoring



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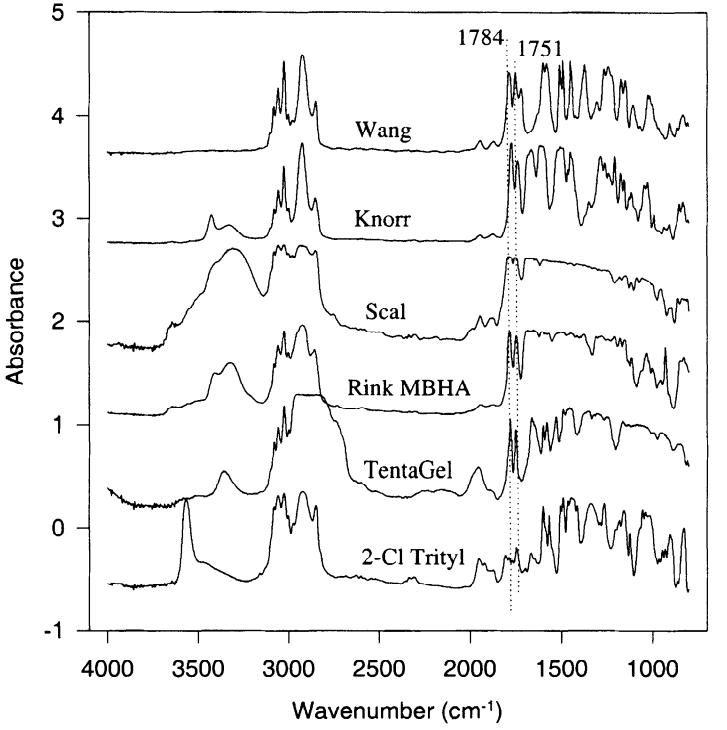

Figure 7.7. Single-bead IR spectra of reaction 18 product on resins with different linkers.

of this attachment reaction. These data show that the trityl linker is not suitable for this attachment reaction although it is a linker, which is easy to cleave.

Mixing/Agitation. Typically, bead suspensions are agitated by shaking in reaction tubes mounted in orbit shakers (~ 45°), by angular shaking (20°–30°) on a wrist shaker, by rotating tubes at an angle of 180° or 360° (whole turn), by bubbling N_2 gas, or by the conventional magnetic stirring.

Reaction 5 was studied as a test case to compare the mixing efficiency in six different mixing methods.[13] Single-bead IR and fluorescence quantitation methods[9] were used to monitor the reaction. Figure 7.8 shows IR spectra from 40 and 30 individual beads after a 30-min reaction interval (in a twofold excess dansylhydrazine in DMF) shaking with a wrist shaker or an orbit shaker. In this experiment, the wrist shaking was more efficient than the orbit shaking. However, the 360° rotation and nitrogen-bubbling meth-

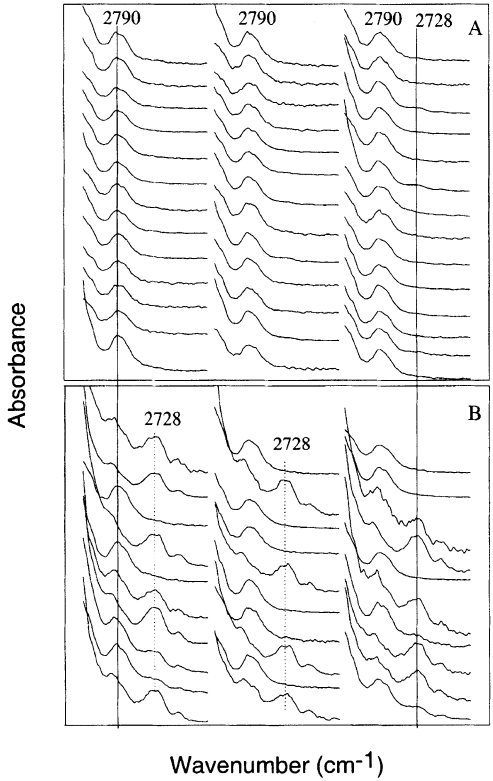

Figure 7.8. IR spectra taken from individual formylpolystyrene beads after 30 min with a two-fold excess of dansylhydrazine in DMF mixed using (A) a wrist shaker and (B) an orbit shaker with the reaction tube fixed at a 45° angle. The starting material has a band at 2728 cm^{-1} and the product at 2790 cm^{-1}.

ods provided the highest mixing efficiencies under mild conditions. Magnetic stirring also gave high mixing efficiencies but also caused fragmentation of the beads. The 180° rotation mixing experiment required longer reaction times and may not be suitable for slow reactions. Mixing with an orbit shaker did not give satisfactory reaction yields compared with the other techniques. A larger excess of reagent (10-fold) and a doubled reaction time, however, can drive this reaction to completion with orbit shaking.

Catalyst. More catalyst is usually required in solid-phase reactions compared with solution-phase methods. This is because it is necessary to

maintain an effective concentration inside the bead. Reaction 11 is a catalytic oxidation of the benzylic alcohol **1** to a resin-bound aldehyde **20**. This was monitored by single-bead IR (Figure 7.9)[10c] and by aldehyde quantitation.[9] The yield of this reaction was shown to be 94% when 0.2 equivalents of *tetra-n*-propylammonium perruthenate (TPAP) were used.[9] The areas of IR bands that undergo changes were integrated, fitted to a *pseudo*-first-order rate equation, and plotted against time (Figure 7.10). The rate was shown to depend on the amount of TPAP used.

7.3.4. Loading and Yield Determination

Solid-phase organic reactions are hard to quantitate; spectrophotometric or fluorimetric methods are probably the best approach. A general method for

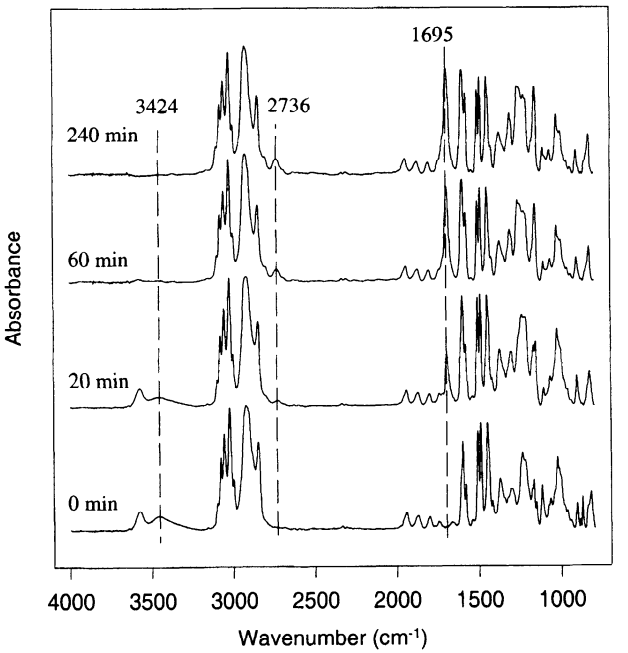

Figure 7.9. IR spectra taken from a single bead at various times in reaction 11. Spectra were taken from a single flattened bead at 0, 20, 60, and 240 min after the initiation of the oxidation reaction. The hydrogen-bonded and unbonded hydroxyl stretch near 3400–3600 cm^{-1} disappears as the intensities of the bands for the aldehyde C–H (2736 cm^{-1}) and the aldehyde carbonyl (1695 cm^{-1}) increase.

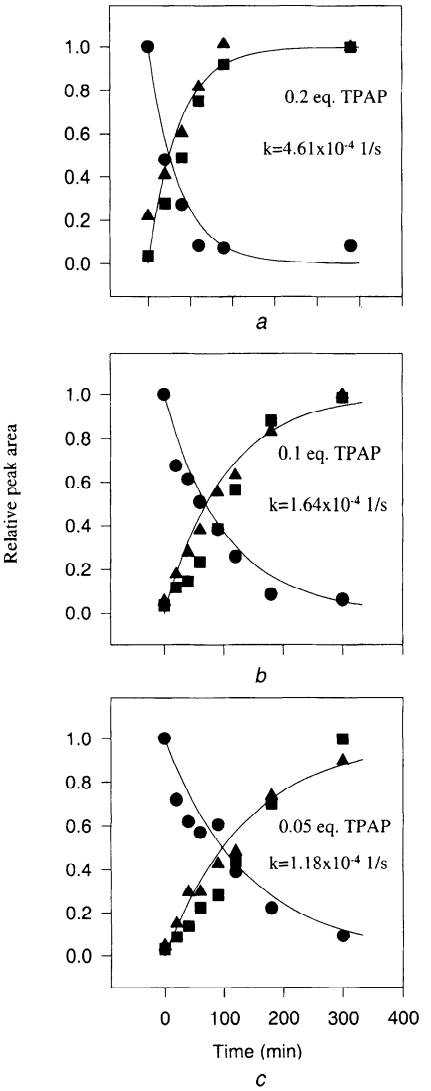

Figure 7.10. Time course for reaction 11. All spectra were normalized by making the intensity of the polystyrene band at 1945 cm^{-1} equal. The area integration for the hydroxyl band from 3181 to 3637 cm^{-1} (circles), aldehyde C–H band from 2664 to 2766 cm^{-1} (squares), and aldehyde carbonyl band from 1641 to 1765 cm^{-1} (triangles) for spectra at various times are plotted against time. Lines were calculated from the best fit to a first-order reaction equation with the rate constant shown. The amount of catalyst TPAP was 0.2 eq in A, 0.1 eq in B and 0.05 eq in C.

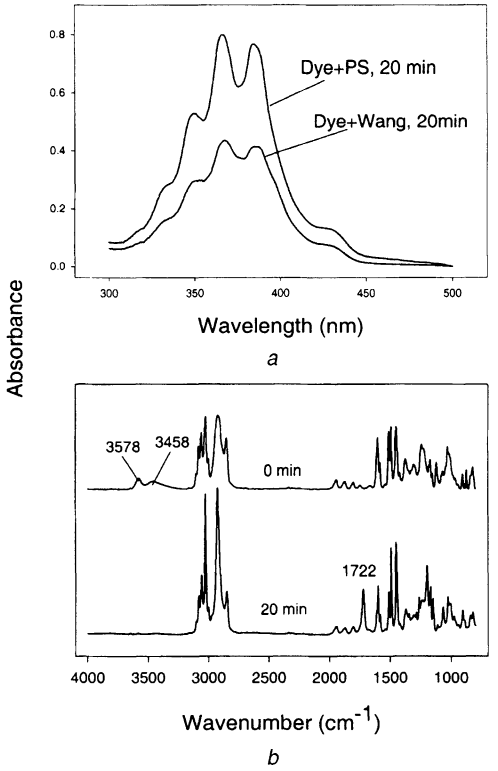

Figure 7.11. UV–Visible absorption of 9-anthroylnitrile in the supernatant (A) and single-bead FTIR spectra taken from the resin (B) before and after a 20-min reaction.

aldehydes and ketones has been developed.[9] Hydroxyl groups are routinely quantitated by reaction with 9-anthroylnitrile for 20 min in DMF[14]; Figure 7.11 shows the UV–visible spectra of 9-anthroylnitrile in the supernatant and the single-bead IR spectra of the solid sample before and after a 20-min reaction. Similarly, carboxyl groups are routinely quantitated by reaction with 1-pyrenyldiazomethane for 50 min in ethyl acetate. In general, these methods take about 1 h or less and require 2–10-mg resin samples.

7.4. CONCLUSION

"Cleave-and-analyze" methods can be used in solid-phase organic syntheses, but direct spectroscopic analyses are convenient and sometimes provide

information that would be hard to obtain in any other way. The IR spectral shifts and peak-area changes can be used to observe intermediates in solid-phase syntheses. Single-bead FTIR spectroscopy, for instance, is a simple, sensitive, fast, and convenient method for following reactions on a solid support without stopping them or cleaving product from the resin. Single-bead FTIR can also provide kinetic information. Fourier transform FTIR internal reflection spectroscopy in the micro- and macro-formats is now the primary analytical method for monitoring of reactions directly on surface-functionalized polymers.

Dye-coupling/consumption techniques enable quantitation of functional groups on resin. However, this area is at an early stage of refinement; more quantitative analytical methods for quantifying a diverse set of organic functional groups are required.

ACKNOWLEDGMENTS

The author is very grateful to co-workers at Novartis for participating in the projects described and to the co-authors in references 3a, 3b, 4c, 9, 10a–c, and 11–14. In particular, the author thanks Lina Liu, Robert Dunn, Qing Tang, Qun Sun, Wenbao Li, and Roger E. Marti for their contributions.

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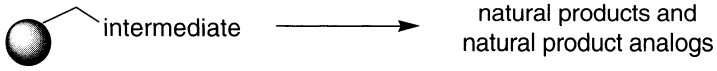
CHAPTER 8

RECENT ADVANCES IN SOLID-PHASE SYNTHESIS OF NATURAL PRODUCTS



LAWRENCE J. WILSON
Procter & Gamble Pharmaceuticals

8.1. INTRODUCTION

Solid-phase synthetic methods[1,2] feature convenient purification procedures coupled with opportunities for automation.[3–5] These attributes have been widely exploited to prepare libraries of small molecules via parallel and combinatorial approaches. A logical extrapolation of these efforts is the supported syntheses of larger, more complex natural products and natural product analogs. Such efforts are consistent with the pharmaceutical industry objectives behind most high-throughput syntheses since, historically, the unique properties of natural products have provided a fertile ground for

breakthrough discoveries in biological and medicinal chemistry. [6,7] This chapter highlights some beautiful syntheses of nonoligomeric natural products on solid phases.

There are several ways to prepare libraries of natural product derivatives on a solid phase. These include (a) total synthesis on the resin; (b) derivation of supported natural products; and (c) syntheses of analogs based on a natural product scaffold. This review will provide examples of all these approaches.

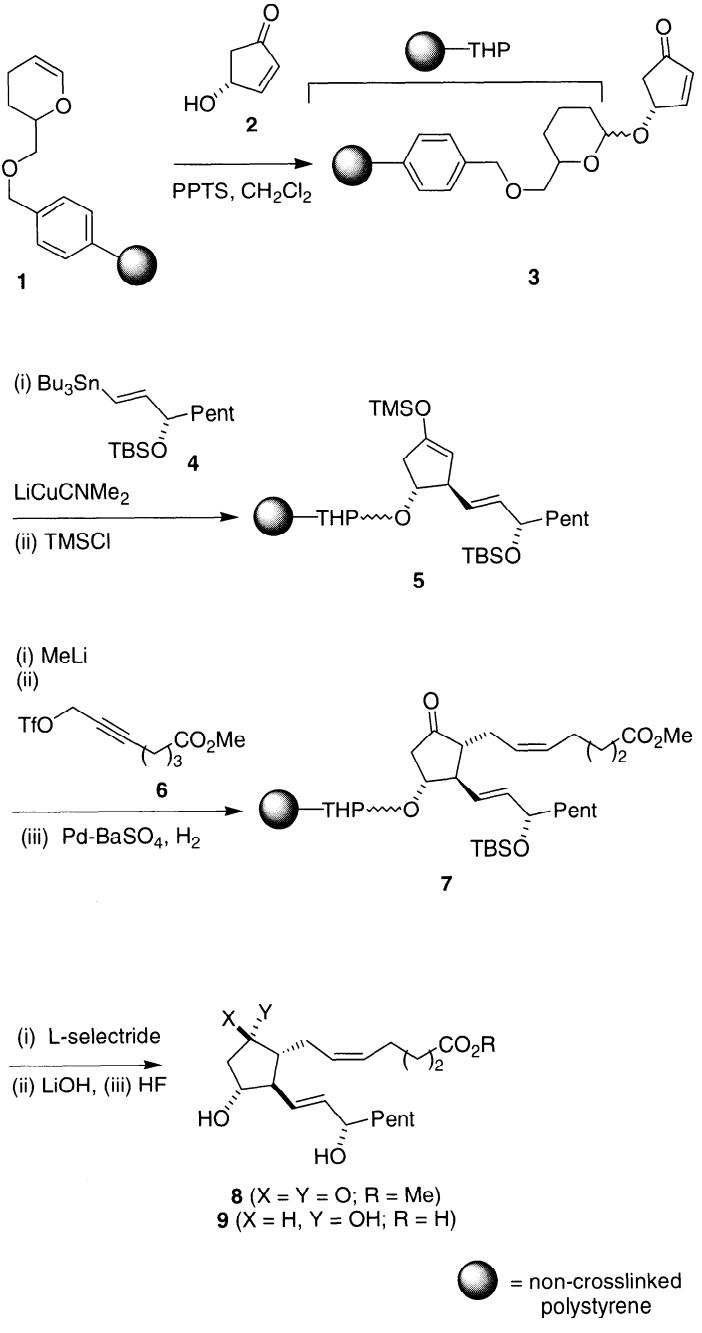
8.2. PROSTAGLANDINS

Prostaglandins are complex structures that have a wide range of biological activities. Syntheses of these molecules are challenging because their biological activities are highly dependent upon stereochemistry (and stereochemical impurities) and because the products/intermediates tend to be unstable to many reaction conditions.[8] Two main strategies have appeared for solid-phase synthesis of both the E- and F-series prostaglandins. They both are based on solution-phase approaches, and they both feature cyclopentene synthons generated in solution and then attached to a resin.

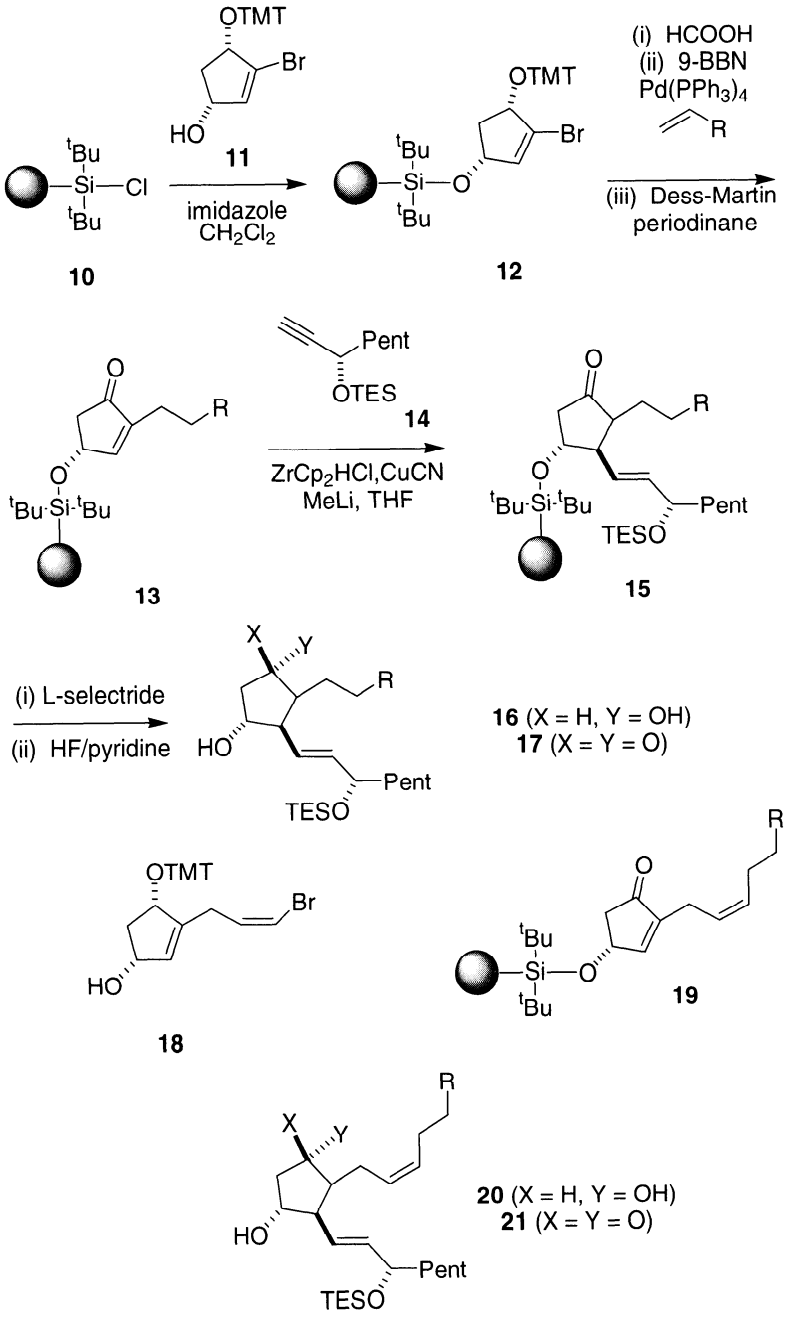
8.2.1. PGE_2 Methyl Ester and $PGF_{2\alpha}$

Janda and Chen's approach to the E- and F-series prostaglandins (Scheme 1)[9,10] takes advantage of Noyori's convergent three-component coupling strategy.[11] It features non-cross-linked polystyrene (NCPS) as a support. This soluble support facilitates synthetic operations in solution, extraction into organic phase during work-up procedures, and the direct measurement of nuclear magnetic resonance (NMR) spectra by conventional means.[12]

Details of the Janda–Chen synthesis were as follows. A tetrahydropyran (THP) linker was attached to the NCPS support enabling attachment of alcohols via THP ether formation.[13] The THP-NCPS resin **1** is derivatized with *R*-(+)-4-hydroxy-2-cyclopentanone **2**, giving the THP ether-based resin **3**, followed by coupling of the C_{13-20} fragment by enone–cuprate addition. The cuprate required was generated from the corresponding *E*-vinyl stannane **4**. The resulting enolate was trapped as the silyl enol ether **5**. Then regeneration of the enolate with methyl lithium was followed by alkylation with the C_{1-7} fragment via the corresponding propargyl triflate **6**. Lindlar hydrogenation provides compound **7** having the cis double bond


1
2
PPTS, CH_2Cl_2
THP
3
(i) Bu_3Sn
Pent
TBSO
4
$LiCuCNMe_2$
(ii) TMSCl
TMSO
THP
Pent
TBSO
5
(i) MeLi
(ii)
TfO
CO_2Me
6
(iii) Pd-$BaSO_4$, H_2
7
(i) L-selectride
(ii) LiOH, (iii) HF
X
Y
CO_2R
HO
Pent
HO
8 (X = Y = O; R = Me)
9 (X = H, Y = OH; R = H)
= non-crosslinked polystyrene

Scheme 1.


OTMT
Br
HO
11
imidazole
CH2Cl2
tBu
Si
Cl
tBu
10
OTMT
Br
O
12
(i) HCOOH
(ii) 9-BBN
Pd(PPh3)4
R
(iii) Dess-Martin
periodinane
Pent
OTES
14
ZrCp2HCl,CuCN
MeLi, THF
13
15
TESO
(i) L-selectride
(ii) HF/pyridine
X
Y
16 (X = H, Y = OH)
17 (X = Y = O)
18
19
20 (X = H, Y = OH)
21 (X = Y = O)

Scheme 2.

at C_{5-6}. Cleavage from the resin at this juncture provided the PGE_2 methyl ester **8** in 37% overall yield from NCPS chloride resin.[9] Alternatively, L-selectride reduction followed by saponification of the methyl ester and cleavage from the resin gave $PGF_{2\alpha}$ **9** in 30% overall yield.[10] Only the naturally occurring stereoisomers were observed.

8.2.2. PGE and PGF Analogs

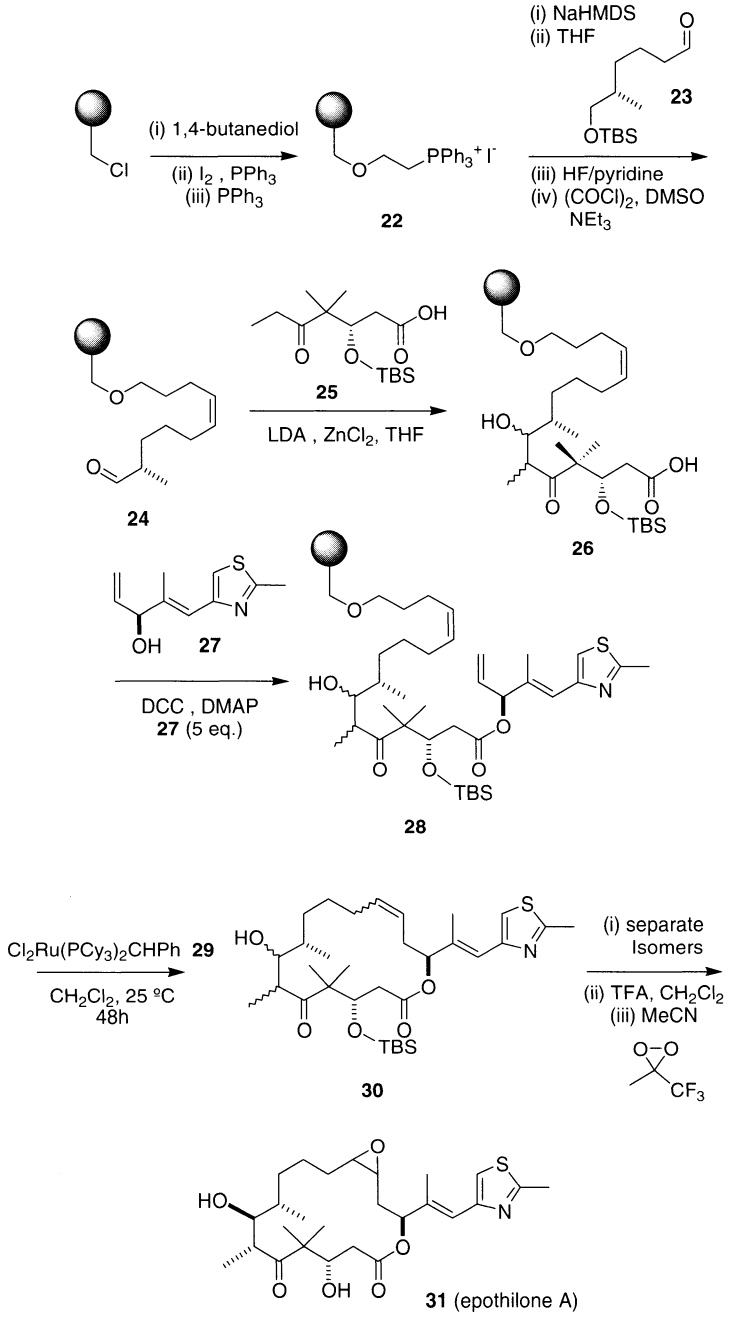
The prostaglandin synthesis developed by Ellman and co-workers (Scheme 2) differs from Janda's in several respects. Analogs of both E and F series (differing in the C_{1-7} side chain) were prepared.[14] In their approach, 2-bromocyclopentene derivatives were synthesized in solution prior to resin attachment. In the first example, the 2-bromocyclopentene **11** was linked to the chlorodibutylsilyl polystyrene resin **10** as the silyl ether **12**.[15] Deprotection of the trimethoxytrityl alcohol-protecting group (TMT), Suzuki coupling with an alkylborane generated in situ from a monosubstituted alkene, and oxidation[16] provided the resin-bound cyclopentenone **13** with the C_{1-7} side chain in place.[17]

Hydrozirconation of alkyne **14**, followed by cuprate addition, was then used to install the C_{13-20} side chain of **15**. Reduction of the ketone (L-selectride) followed by hydrogen fluoride cleavage provides the F-series derivatives **16**, while direct cleavage of **15** gave the E-series compounds **17**.

Other derivatives were prepared by modifications of the original Ellman route. Thus, a second cyclopentene precursor **18** containing the C_{5-6} cis double bond was carried through to give the resin-bound intermediate **19** via a Stille coupling and an oxidation. Subsequent cuprate addition, reduction, and cleavage give **20** and **21** (the F and E series) with the C_{5-6} double bond intact. This type of approach was used to synthesize 11 more compounds in this series.

8.3. EPOTHILONE A

This total synthesis is the first of three preparations of macrocycles that will be described (epothilone A, zearalenone, and muscone). All feature cyclization/release strategies that involve carbon–carbon bond formation.[18] These efforts illustrate how the research on supported syntheses of highly complex structures has inspired the use of creative linker strategies for attachment to a solid phase.


(i) NaHMDS
(ii) THF
23
OTBS
(i) 1,4-butanediol
(ii) I2 , PPh3
(iii) PPh3
PPh3+ I-
22
(iii) HF/pyridine
(iv) (COCl)2, DMSO
NEt3
25
LDA , ZnCl2, THF
24
26
27
DCC , DMAP
27 (5 eq.)
28
Cl2Ru(PCy3)2CHPh 29
CH2Cl2, 25 ºC
48h
30
(i) separate
Isomers
(ii) TFA, CH2Cl2
(iii) MeCN
31 (epothilone A)

Scheme 3.

The specific strategy used by Nicolaou and co-workers in their synthesis of the anticancer agent epothilone A[19] was alkene metathesis[20] (Scheme 3). This gave cyclization to 16-membered ring compounds while simultaneously cleaving the product from the resin. The alkene functionality formed in this key step was ultimately transformed into the epoxide group of the natural product.

The linker synthesis began by etherification of chloromethyl polystyrene with 1,4-butanediol (Scheme 3). Iodide formation and displacement with triphenylphosphine provided the resin-bound phosphonium salt **22**. Wittig olefination of this support with aldehyde **23** gave a supported *Z*-alkene. Desilylation and Swern oxidation give resin-bound aldehyde **24**, ready for introduction of the second sizable organic fragment by aldol condensation of the zinc di-enolate of **25** [formed by treatment with lithium diisopropylamide (LDA) and $ZnCl_2$]. The resulting resin-bound alcohol **26** was generated with modest stereoselectivty, and the isomers were not separated until later in the synthesis.

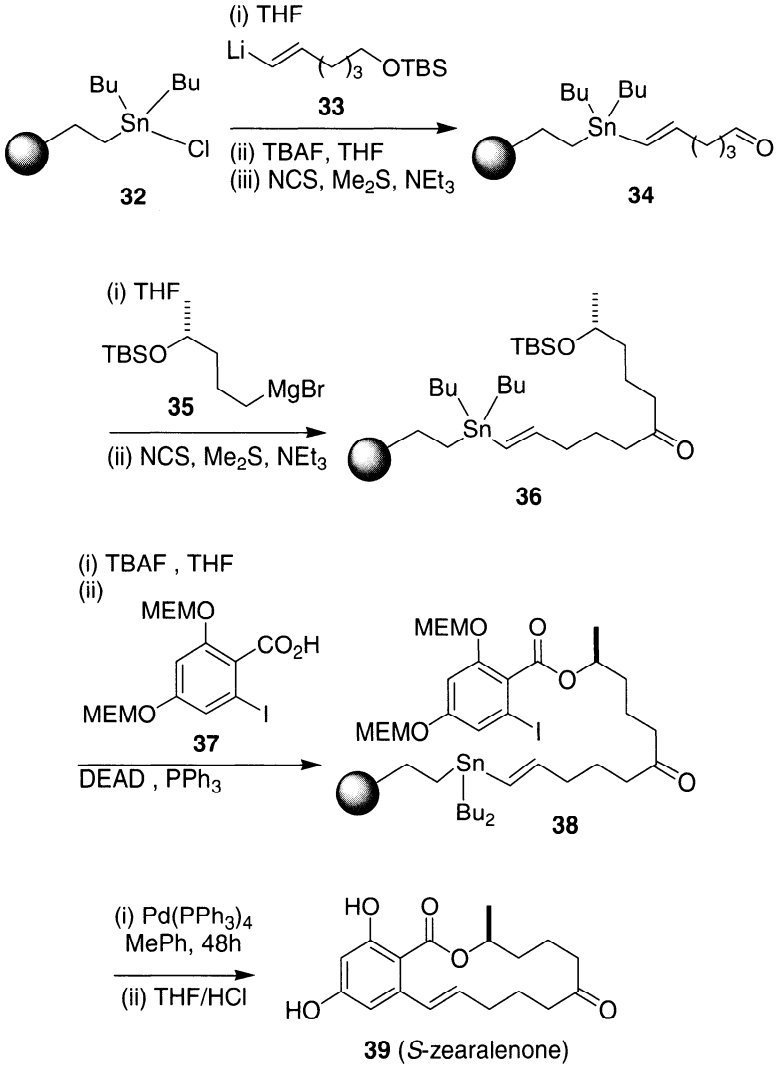
Nicolaou's group attached the final fragment in their synthesis by esterification of the resin acid **26** with the heterocycle containing alcohol **27**. The product ester **28** set the stage for the key step of the synthesis: metathesis mediated by Grubbs catalyst **29**. This proceeded smoothly causing cyclization to the desired 16-membered ring compounds **30** with concomitant liberation of the products into solution. Four isomers of **30** were produced from each of these reactions, that is, both *E*- and *Z*-alkenes (*E*–*Z* ratio = 6 : 4) from the metathesis, and three isomer configurations (ratio 3 : 1 : 6) from the aldol condensation of **24** with **25**. The isomers were separated and the appropriate compound (isolated in 16% yield from the mixture) was desilylated, then epoxidized with methyl(trifluoromethyl) dioxirane to yield epothilone A **31** contaminated with a small amount of the α-epoxide isomer. This methodology was used by the same group to create a library of over 100 epothilone analogs for study in the effectiveness of inhibition of tubulin assembly and cytotoxic effects in taxol-resistant tumor cells.[21]

8.4. (*S*)-ZEARALENONE

Coupling of aryl halides with alkenyl stannanes promoted through palladium metal catalysis, otherwise known as the Stille coupling, has many applications,[22] including solid-phase variants (see Chapter 2).[3–5] One of these is featured in Nicolaou and co-workers' solid-phase synthesis of (*S*)-zearalenone wherein a resin-bound alkenylstannane undergoes a Stille cycli-

zation/cleavage process (Scheme 4).[23] This was adopted from an earlier solution phase strategy but required development of a novel tin-based linker.[24]

The synthesis of (*S*)-zearalenone began with creation of the chlorodibutylstannyl polystyrene resin **32**, which ultimately would serve as a Stille coupling partner. Oxidation of chloromethyl polystyrene resin fol-



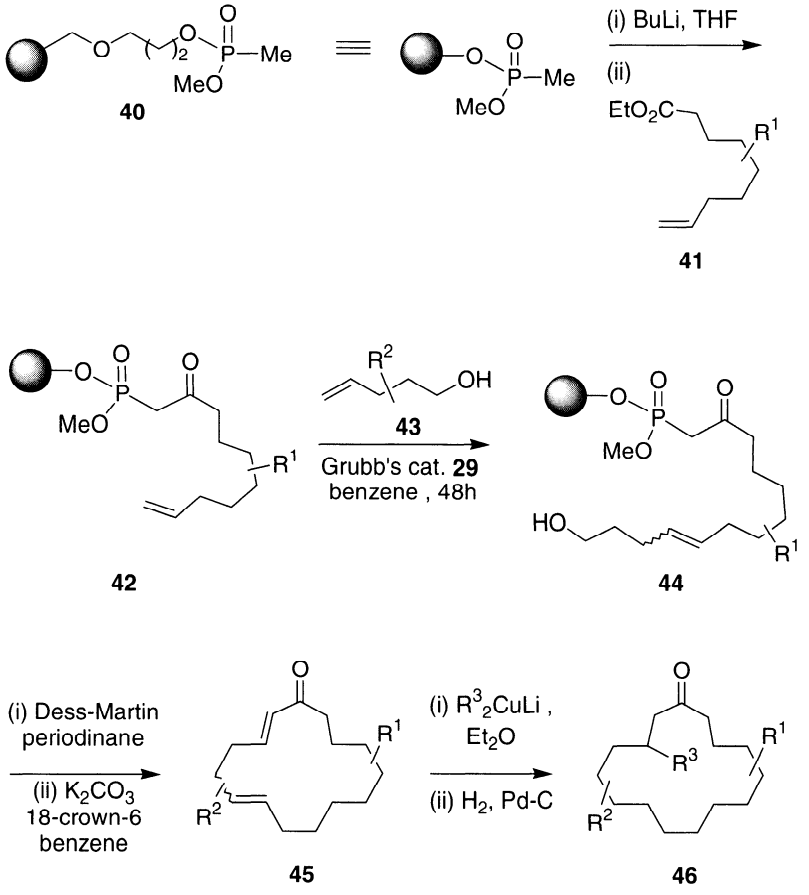
Scheme 4.

lowed by reaction of the resulting aldehyde with methyltriphenylphosphorane gave vinyl polystyrene. Reaction of this with dibutyldichlorostannane (Bu_2SnCl_2) in the presence of a radical initiator gave the required resin **32** in 90% yield for the three steps (Scheme 4). Coupling of the vinyl lithium species **33** to the tin polymer **32** occurred upon direct treatment to form the *E*-vinylstannane-functionalized polymer exclusively. Desilylation and Corey–Kim oxidation then gave the corresponding *E*-stannyl aldehyde **34**. Attachment of the second key fragment occurred by treatment with Grignard reagent **35** followed by Corey–Kim oxidation to give the *E*-stannylketone **36**. The final piece **37** was connected through Mitsunobu coupling of the alcohol obtained by desilylation of **36**. In the featured cleavage step, treatment of the resin-bound stannyl/aryl-iodide **38** with palladium catalyst induced cyclization/release (54% yield for the cyclization) and formed (*S*)-zearalenone **39** upon acid-induced deprotection of the methoxyethoxymethyl (MEM) protecting groups.

8.5. DL-MUSCONE

Intramolecular ketophosphonate-aldehyde condensation[25] has been used by Nicolaou and co-workers as a cyclization release strategy to form macrocycles in the muscone series of natural products (Scheme 5).[26] A highlight of this work was development of a unique phosphonate resin.

Details of the muscone synthesis were as follows. The resin precursor **40** was prepared by reaction of the low-load chloromethyl polystyrene with 1,4-butanediol followed by capping with $CH_3P(O)(OCH_3)Cl$ (97% yield overall). This resin is loaded into SMART microreactors for directed-sorting-based library synthesis.[27] The resins were then treated with *n*-BuLi and a series of long-chain alkenyl esters **41** to give the corresponding ketophosphonates **42**. Chain extension of these alkenes was affected via alkene metathesis with alkene substrates **43** (using Grubb's catalyst **29**), thereby affording a collection of olefinic alcohols **44**. These alcohols **44** were oxidized under Dess–Martin conditions,[16] then treated with potassium carbonate to promote condensation with the resulting aldehyde. Ketomacrocycles **45** were thus released from the resin. No dimeric product was obtained, even though it was in analogous solution-based chemistry. Cuprate addition to the product enones **45** followed by hydrogenation gave the muscone-based products **46**, including racemic muscone (**46**, $R^1 = R^2 = H$; $R^3 = CH_3$).



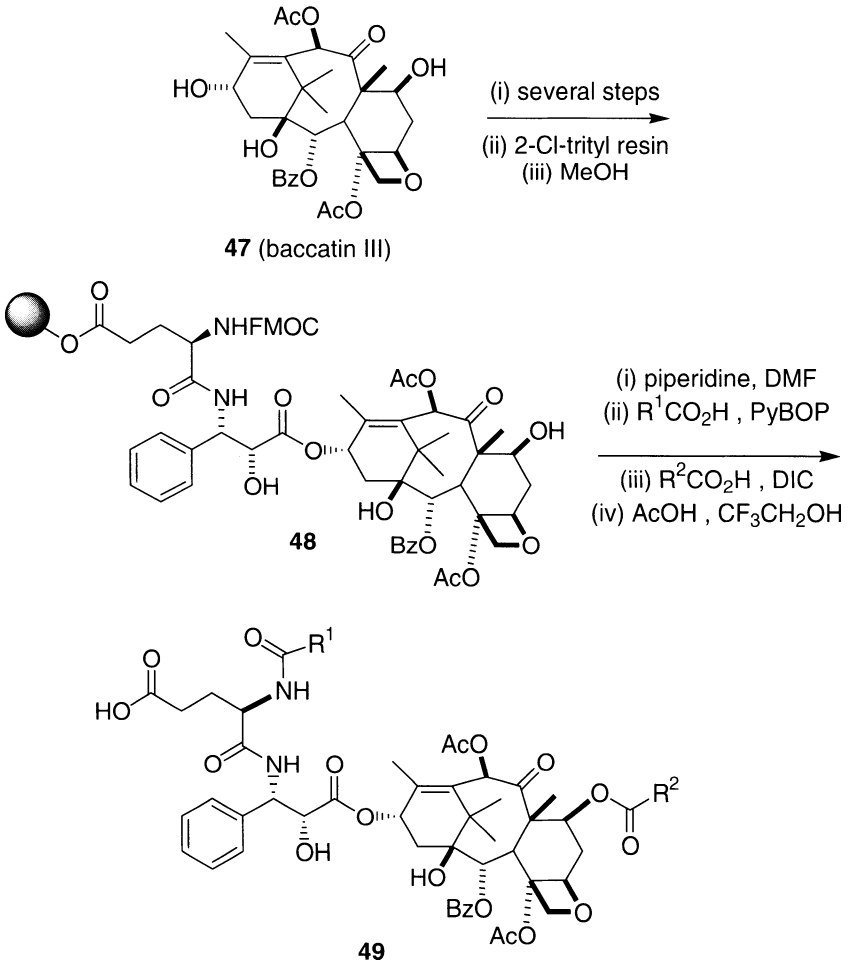
40 41 42 44 45 46

Scheme 5.

8.6. TAXOID LIBRARIES FROM BACCATIN III

This is the first of two syntheses included in this chapter to highlight how natural product-based scaffolds can be attached to a resin for convenient derivatization into libraries. The other example is the synthesis of sarcodictyin libraries described in the next section. In both cases, interesting libraries were made with minimal development time by performing scaffold construction in solution or obtaining it from a natural source.

Scheme 6 describes the taxoid library synthesis.[28] The supported and highly functionalized intermediate **48** was produced from baccatin III **47** in several steps. These involved elaboration of baccatin III in solution by



Scheme 6.

connecting the taxol β-amino acid side chain, then adding an FMOC-protected glutamic acid derivative onto this. That same glutamic acid served as a point of attachment to 2-chlorotrityl resin to give **48**. An excess of resin was used to trap this precious intermediate, then the unreacted functional groups were capped with methanol. At this point the resin was loaded into radiofrequency-encoded microcans for efficient construction of the library.[27] Removal of the FMOC groups gave a primary alcohol that was acylated in the presence of the secondary alcohol on the Eastern cyclohexyl

ring. The latter alcohol was then acylated using another batch of carboxylic acids (R^2CO_2H). Resin cleavage gave a library of 400 taxoid analogs **49**. Isolated yields varied from 27 to 72% with purities ranging from 55 to 100%.

8.7. SARCODICTYIN LIBRARIES

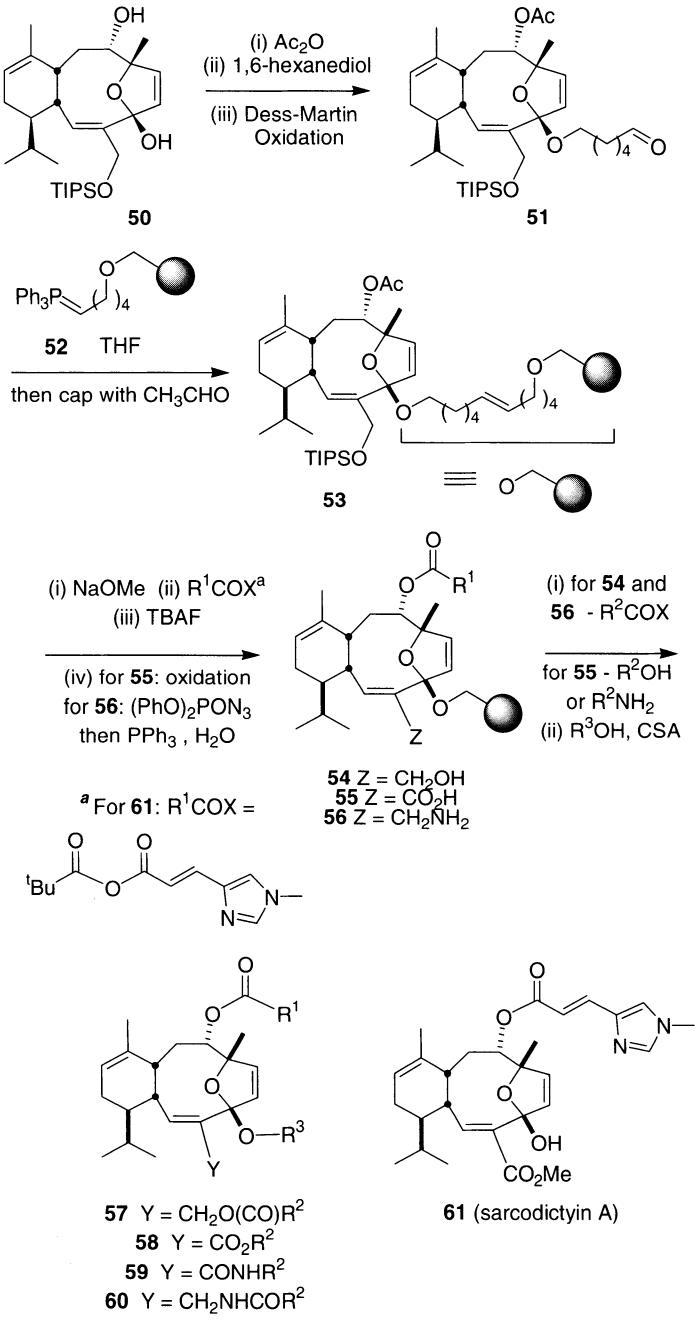
Sarcodictyin libraries have been prepared from the supported scaffold **50** (Scheme 7). This scaffold was made via an approach developed in a solution-phase synthesis of sarcodictyin A.[29] Again, this synthesis is from Nicolaou and co-workers.[30] Scaffold **50** was modified for resin attachment by acylation of the secondary alcohol, creation of an aldehyde linker via ketal formation from the tertiary alcohol, then oxidation.[16] This sequence gave the aldehyde **51** that was then attached to the resin by reaction with an excess of the phosphorane resin **52** followed by capping with acetaldehyde. The result was the pivotal anchored intermediate **53**. This was then derivatized via the following steps: (a) deacetylation by methanolysis was followed by coupling of the imidazole acrylate side chain found in the natural product; (b) desilylation and oxidation of alcohol **54** with Dess–Martin periodinane–$NaClO_2$ to give the corresponding carboxylic acid **55**[16]; and (c) various operations on the acid formed, including esterification with methanol. The resulting compounds were cleaved from the resin by ketal hydrolysis to yield the desired library. Sarcodictyin A **61** was formed in 51% yield from resin **53**.

About 100 analogs were synthesized by the route outlined in Scheme 7. These were assayed for their ability to inhibit tubulin polymerization, and several compounds more active than the natural product were discovered.

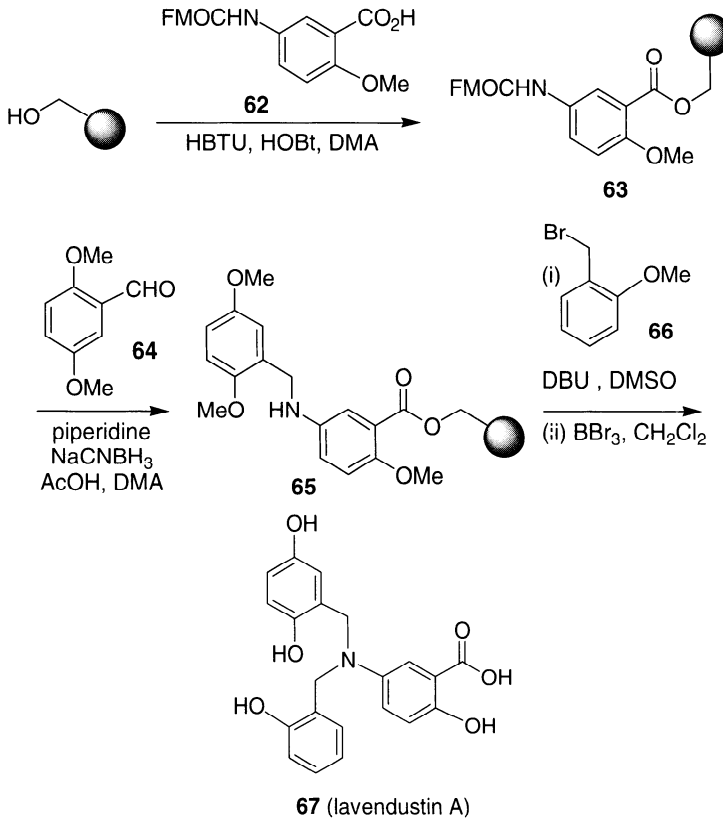
8.8. LAVENDUSTIN A

One of the first reported solid-phase syntheses of a nonoligomeric natural product was that of lavendustin A.[31] This compound is a potent tyrosine kinase inhibitor. Fortunately, the structure of this material is highly amenable to synthesis and elaboration on a solid phase. In fact, the synthesis was reported by a researcher working alone on this project (Green).[31]

Scheme 8 shows how this synthesis was performed. FMOCprotected methoxy-3-amino-benzoic acid **62** was attached to hydroxymethyl polystyrene resin. The resulting ester **63** was deprotected and then reductively


OH
OH
TIPSO
50
(i) Ac_2O
(ii) 1,6-hexanediol
(iii) Dess-Martin Oxidation
OAc
TIPSO
51
Ph_3P
52 THF
then cap with CH_3CHO
OAc
TIPSO
53
(i) NaOMe (ii) R^1COX^a
(iii) TBAF
(iv) for 55: oxidation
for 56: $(PhO)_2PON_3$
then PPh_3, H_2O
54 Z = CH_2OH
55 Z = CO_2H
56 Z = CH_2NH_2
(i) for 54 and 56 - R^2COX
for 55 - R^2OH
or R^2NH_2
(ii) R^3OH, CSA
[a] For 61: R^1COX =
tBu
57 Y = $CH_2O(CO)R^2$
58 Y = CO_2R^2
59 Y = $CONHR^2$
60 Y = CH_2NHCOR^2
61 (sarcodictyin A)
OH
CO_2Me

Scheme 7.



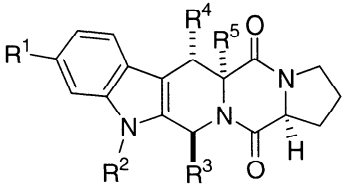
Scheme 8.

aminated with 2,5-dimethoxy-benzaldehyde **64** to give the resin-bound secondary aniline **65**. The synthesis was completed by amine alkylation with 2-methoxy-benzyl bromide **66**, simultaneous resin cleavage, and demethylation to yield the natural product **67** in 90% yield from **63**. A series of 60 lavendustin analogs were synthesized from three benzoic acids, five benzaldehydes, four benzyl bromides, and three starting resins. Yields varied from 10-83% with purities in the 30–97% range.

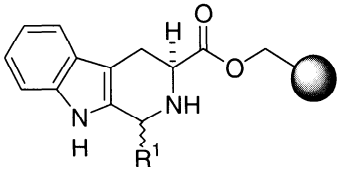
8.9. INDOLYL DIKETOPIPERAZINES

The indolyl diketopieprazine family of natural products includes the fumitremorgins, verruculogens, and cyclotryprostatins **68**. A solid-phase syn-

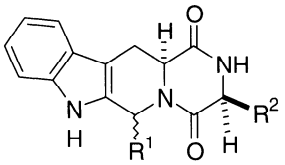
thesis of analogs of this group of compounds was reported recently.[32] It featured Pictet–Spangler cyclizations onto resin-bound (Wang) L-tyrosine derivatives. Several aldehydes (R^1CHO) were used to give the compounds **69**. Acylation with FMOC-protected amino acids and cyclization/cleavage from the resin formed the diketopiperazine products **70**. Forty-two examples were reported, with yields and purities reported in the 50–99% range.



68



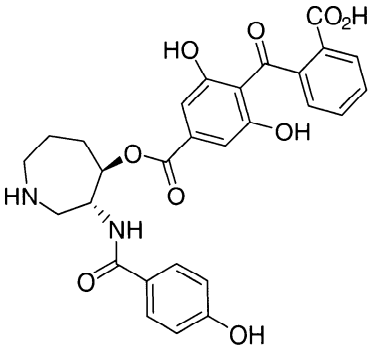
69



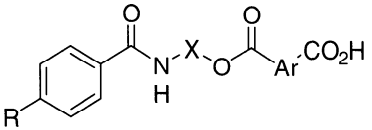
70

8.10. BALANOL ANALOGS

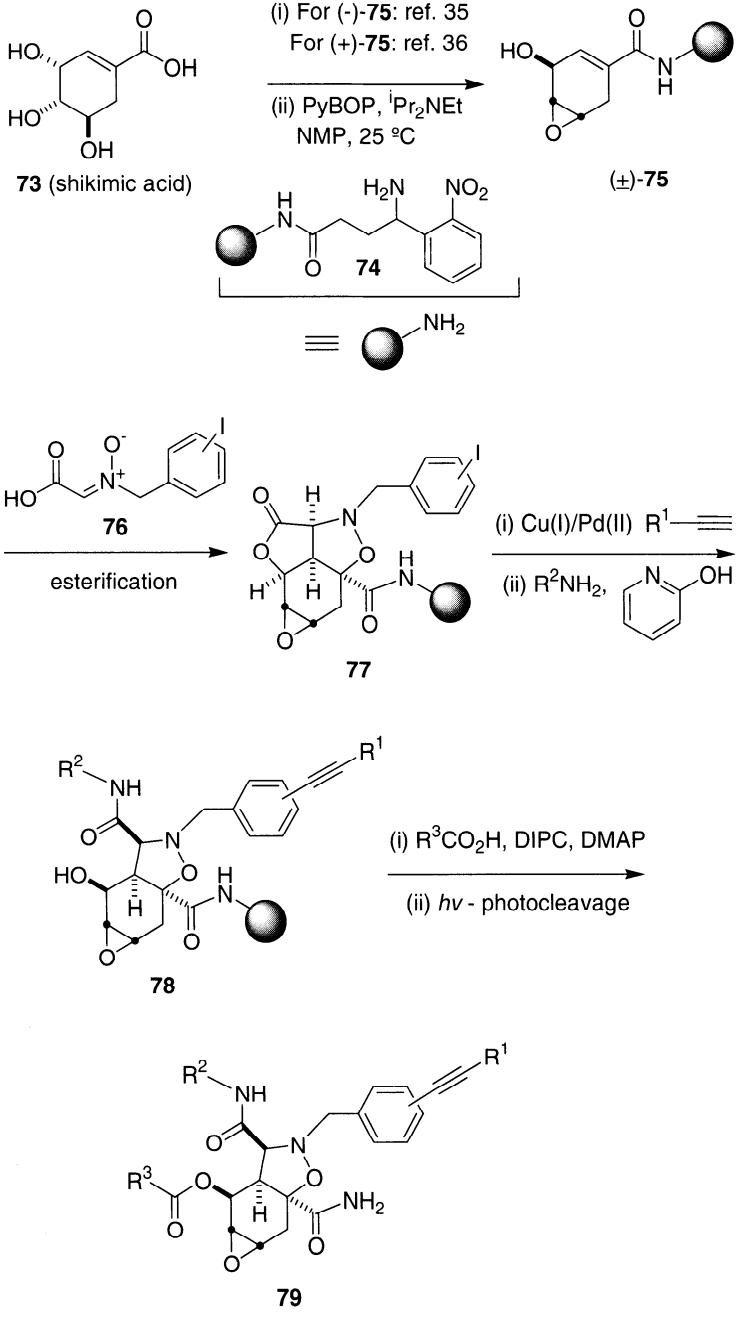
Several truncated analogs of the natural product balanol **71** were prepared on a solid phase by Nielsen and Lynso.[33] Thus, symmetrical di-acids were linked to Wang resin, followed by coupling a number of FMOCprotected



71 (balanol)



72


(i) For (-)-75: ref. 35
For (+)-75: ref. 36
(ii) PyBOP, iPr2NEt
NMP, 25 ºC
73 (shikimic acid)
(±)-75
74
76
esterification
77
(i) Cu(I)/Pd(II) R1
(ii) R2NH2,
(i) R3CO2H, DIPC, DMAP
(ii) hv - photocleavage
78
79

Scheme 9.

amino alcohols via O-acylation (FMOC–NH–X–OH). Deprotection and *N*-acylation with aromatic acids gave the compounds **72** after cleavage from the resin. Thirty-two analogs were produced in a split-mix format as four pools of eight compounds.

8.11. PSEUDOALKALOIDS FROM SHIKIMIC ACID

The final example described in this chapter is that done by Schrieber and co-workers. They used a scaffold with multivariant sites derived from shikimic acid. However, the end products of their synthesis were compact, highly functionalized structures reminiscent of alkaloids.[34] An objective of this study was to produce a very large number of compounds for miniaturized cell-based assays. In fact, about 2 million compounds were made.

The synthetic approach used in this work is shown in Scheme 9. Two known solution pathways were used to convert shikimic acid to an epoxide intermediate. In fact, both the (–)[35] and the (+)[36] enantiomers were formed. After minor synthetic transformations, these epoxides were linked to Tentagel S aminomethyl resin with an *o*-nitrophenyl-derived photocleavable linker **74**[37] via amide bond formation to give intermediate **75**. The first point of variation was added via various iodo-benzyl nitrone carboxylic acids **76** via 1,3-dipolar addition/esterification reactions. Highly constrained resin-bound tetracyclic hydrooxazoles **77** were thereby produced.

Manipulations of compound **77** facilitated incorporation of three additional points of diversity (to **78** and **79**). These were (i) Sonogashira coupling of terminal alkynes to the aryl iodide functionality; (ii) addition of primary amines to selectively open the lactone; and (iii) use of carboxylic acids to esterify the resulting alcohol. The chemistry was cleverly designed to avoid protecting-group manipulations. Photochemical cleavage of the products from the solid support gave the primary amides **79**. This reaction sequence was adapted to split-pool methods giving a 2.18-million-member library. Analysis of this library via nanodroplet assay techniques gave compounds showing selectivity toward TNF activation.

8.12. CONCLUSIONS

The solid-phase syntheses of natural products and natural product derivatives that have been reported to date illustrate several different approaches to the challenge of preparing libraries of bioactive products. Total syntheses

of complex materials are possible. Derivatization of highly functionalized intermediates is another approach. It is even possible to derivatize a natural product, giving a supported scaffold that can be used to prepare totally different materials that look as if they are natural products that have not yet been discovered.

Arguments that are frequently made to justify natural product synthesis (e.g., leads to methodological developments) can certainly be made in this field. Several interesting methods, some of which feature the resin as an integral part, have been developed in the course of these syntheses. Moreover, and perhaps unlike some solution-phase syntheses, these works have well-defined practical applications. Products of significant numbers of compounds having likely looking structures tend to lead to biological hits. This field will undoubtedly undergo significant expansion in the next decade.

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