Synthesis of Diverse and Complex Molecules on the Solid Phase

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ABSTRACT

In this paper we summarize our efforts toward optimizing key reactions on the solid phase which tolerate a variety of functional groups. These groups were sequentially modified, allowing the production of novel and diverse compound libraries on the solid phase.

Introduction

An important application of organic chemistry is the design and synthesis of new molecules for potential use in medicine, crop protection, or material sciences, among others. Drug discovery requires the iterative synthesis of numerous individual analogues of a biologically active compound in order to improve on activity, bioavailability, or selectivity, a process generally called "lead optimization". It has been estimated that for each new drug approved this process requires the synthesis of approximately 10 000 compounds, a very laborious, time-consuming, and expensive effort. Today, combinatorial chemistry and automated multiparallel synthesis enable chemists to produce analogues of a particular organic molecule much more efficiently and rapidly than by nonautomated, so-called classical methods. For these reasons, each pharmaceutical and agrochemical company invests a substantial portion of its research budget in combinatorial approaches to small-molecule synthesis, either in-house or in collaboration with one of the numerous start-up companies active in this field.[1]

Combinatorial chemistry finds its origin in the field of peptide synthesis with the pioneering work of Merrifield in 1963, who developed chloromethylated polystyrene as a useful functionalized solid phase for convenient preparation of peptides.[2] Since then, Geysen and Houghten have developed various methods for multiple parallel synthesis of peptides (respectively multipin and tea-bag methods).[3,4] Later, Furka and co-workers[5] developed the "split and mix" method, allowing the synthesis of large peptide libraries as equimolar mixtures. Solid-phase synthetic chemistry has been successfully employed for the synthesis of peptides,[6] peptidomimetics,[7] oligonucleotides,[8] and oligosaccharides.[9] Application of solid-phase chemistry to the synthesis of nonoligomeric, small organic molecules was first described by Leznoff and co-workers[10] in a study describing the resin-bound synthesis of unsymmetrical carotenoides and by Crowley and Rapoport,[11] who reported Dieckman cyclization on solid support. In 1992, Bunin and Ellman demonstrated the solid-phase synthesis of pharmaceutically relevant compounds (benzodiazepine).[12] Since then, research directed toward developing reactions on the solid phase has increased at an enormous pace: several academic groups are committed to improving solid-phase chemistry, numerous companies are involved developing more and more sophisticated tools aiding the chemist both in design and synthesis of compound libraries, and there are frequent conferences and several journals committed to combinatorial sciences.[1]

With a few exceptions,[13] so far only relatively simple nonoligomeric structures have been synthesized on the solid phase. In this article we summarize our systematic efforts toward optimizing a number of reactions for polystyrene-linked substrates. In a further effort, these reactions were then successfully applied for the production of rather complex and diverse substances libraries.

Sebastian Wendeborn was born in Berlin, Germany, in 1965. After receiving his "Vordiplom" from the University of Freiburg/Germany in 1986 he moved to Philadelphia, where he continued his studies in chemistry at the University of Pennsylvania under the guidance of Prof. K. C. Nicolaou, with whom he moved to the Scripps Research Institute in 1989. Upon receiving his Ph.D. in 1992, he joined Prof. A. Eschenmoser's group at the ETH-Zürich, Switzerland, for postdoctoral studies and joined the Ciba Central Research Laboratories in 1994. Currently, he is a Senior Scientist in Novartis Crop Protection. His research interests include total synthesis of natural products, nucleic acid chemistry, combinatorial chemistry, and synthesis and design of biologically active molecules.

Alain De Mesmaeker was born in 1955 in Brussels, Belgium. He studied chemistry at the University of Louvain, where he obtained his Ph.D. in 1983 (Prof. H. G. Viehe). After a postdoctoral stay at the Weizmann Institute (Prof. M. D. Bachi), he joined the Central Research Laboratories of Ciba (CRL) in Basle, Switzerland, where he acted as group leader until 1997. Within Novartis, he moved to the "Chemistry Research" group of Crop Protection. His research interests include radical chemistry, total synthesis of natural products, reaction mechanisms, carbohydrate and nucleic acid chemistry, and the design and synthesis of biologically active molecules.

Wolfgang Brill was born in 1959 in Frankfurt am Main, Germany. He obtained his Diplom at the Johann Wolfgang von Goethe University, Frankfurt, Germany, in 1985. In 1989 he obtained his Ph.D. at the University of Colorado, Boulder, with Prof. Marvin H. Caruthers on the synthesis of novel internucleotide linkages. After postdoctoral research with Prof. Horst Kunz at the Johannes Gutenberg University, Mainz, Germany, he joined the Central Research Laboratories of Ciba-Geigy AG in 1991. There, he was involved in antisense research, synthesis of heterocyclic tyrosine kinase inhibitors, and combinatorial chemistry. Since 1997, he has been part of the combinatorial chemistry unit of Novartis Pharma AG, in Basle.

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Sabine Berteina received her Ph.D. degree in organic chemistry from the University of Paris XI in 1994 with Prof. A. Lubineau. After a year of research in the Analytical Research and Development Department of Bristol-Myers Squibb (Paris) and 2.5 years of postdoctoral work in the field of combinatorial chemistry in the group of Dr. Alain De Mesmaeker, first in the Central Research Laboratories of Ciba, then in the Novartis Crop Protection division in Basle, Switzerland, she joined the Institute of Organic and Analytical Chemistry of the University of Orléans (France) in 1998 as Assistant Professor. Her research interests include heterocyclic chemistry and solid-phase synthesis of pharmacologically interesting molecules.

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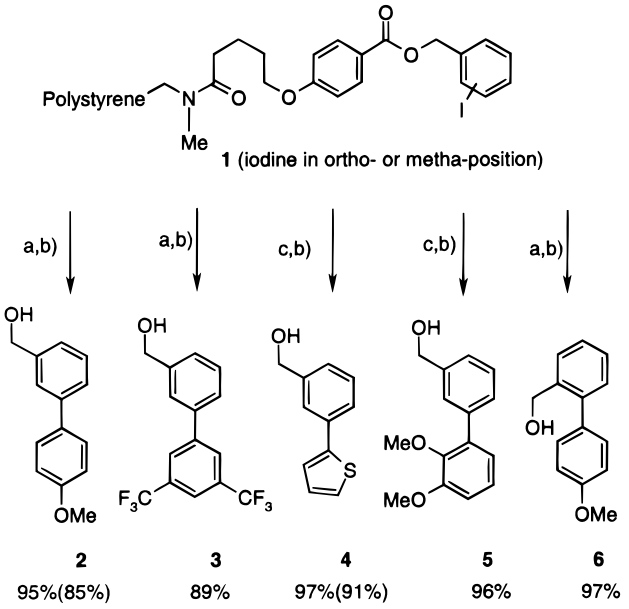
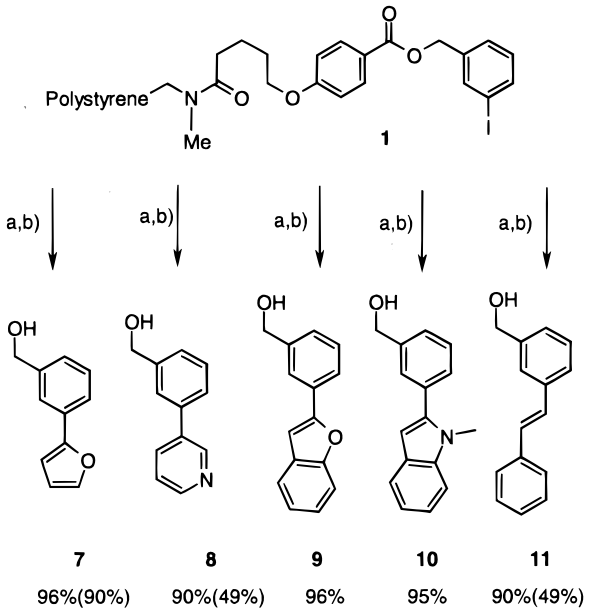
Scheme 1[a]



[a] Conditions: (a) 4 equiv of Ar-B(OH)$_2$, 9 equiv of K_2CO_3, 0.1 equiv of Pd(OAc)$_2$, dioxane:H_2O, (6:1), 100 °C, 24 h. (b) 6 equiv of NaOMe, MeOH:dioxane (1:4), rt, 24 h. (c) 4 equiv of Ar-B(OH)$_2$, 9 equiv of K_2CO_3, 0.1 equiv of Pd(OAc)$_2$, dioxane:H_2O, (6:1), 100 °C, 24 h; double coupling. Yields in parentheses refer to isolated yields.

Scheme 2[a]



[a] Conditions: (a) 3 equiv of R-SnBu$_3$, 0.1 equiv of Pd$_2$(dba)$_3$, 0.4 equiv of AsPh$_3$, dioxane, 50 °C, 24 h. (b) 6 equiv of NaOMe, MeOH:dioxane (1:4), rt, 24 h. Yields in parentheses refer to isolated yields.

1. Intermolecular Palladium-Mediated Cross Couplings

Among the versatile reactions already investigated on solid support, the Pd-mediated C−C bond formation received much attention due to its enormous potential for the derivatization of functionalized structures.[14] Although several recent reports encouraged the use of Pd-mediated C−C bond-forming reactions on solid support, generally applicable procedures leading to single products of defined structures in high purity and high overall yield were not yet available.[15] We therefore decided to systematically investigate palladium-mediated cross coupling reactions on the solid phase.[16]

Suzuki Coupling. The first Pd-mediated C−C bond-forming reaction we optimized on the solid phase was the coupling between a polystyrene-bound aryl iodide with boronic acids (Suzuki coupling). During our investigations it became evident that the catalyst Pd(OAc)$_2$ (ligand-free conditions) gave superior results compared to Pd(Ph$_3$P)$_4$. However, even with this catalyst, double couplings were sometimes necessary to ensure complete conversion of starting material.[17] Nonactivated aryl bromides (bearing no electron-withdrawing substituents) were much less reactive compared to the corresponding aryl iodides, leading to unsatisfactory overall yields. Consistent high conversion of polystyrene-bound aryl bromide into the coupled products could not be obtained although various reaction conditions were investigated. Although certain functionalities are not well tolerated in the Suzuki coupling reaction, most substrates gave very satisfactory results. Selected examples are shown in Scheme 1.[16a] It is noteworthy that the stabilized benzoate ester attaching the substrate to the solid phase is stable under the rather basic Suzuki coupling conditions but liberates the desired alcohol upon treatment with NaOMe in a mixture of MeOH:dioxane (1:4) at room temperature.

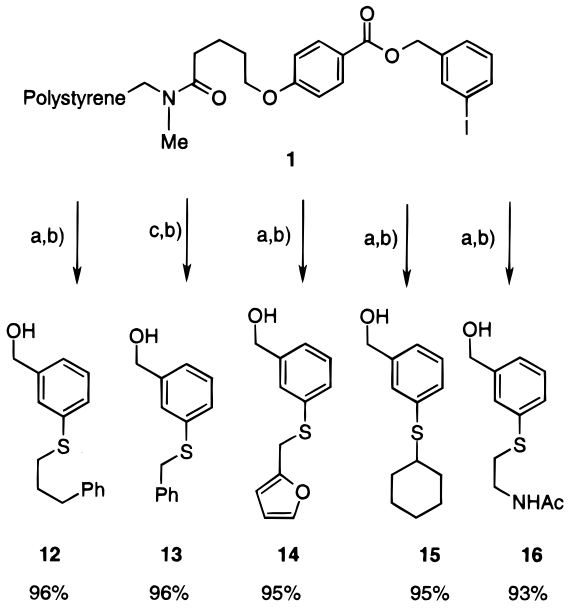
Stille Couplings.[18,19] Upon screening of various reaction conditions typically applied in solution chemistry, two protocols were found to work best for Stille coupling on the solid phase. While the use of Pd(Ph$_3$P)$_4$ in dioxane at 100 °C gave satisfactory results in many cases, the procedure involving Pd$_2$dba$_3$ and triphenyl arsine gave superior results in most cases.[19a] Selected coupling reactions are shown in Scheme 2.

Coupling with Terminal Thiols. While the coupling of amines with aryl halides has been the focus of recent publications, the coupling of thiols with aromatic halides has received relatively little attention.[20] We decided to investigate this reaction for the elaboration of combinatorial libraries, realizing the large number of commercially available thiols and the rich chemistry of sulfur-containing compounds. Scheme 3 summarizes some of our results. Primary as well as secondary thiols coupled in excellent yields under our optimized reaction conditions.

Coupling with Terminal Acetylenes. A powerful reaction for combinatorial chemistry is the coupling of aromatic iodides with terminal acetylenes (Scheme 4).[21] We found reaction conditions involving the use of the catalyst PdCl$_2$(Ph$_3$P)$_2$ most favorable. Noteworthy are the mild reaction conditions, requiring temperatures of only 25−50 °C. Propargylic alcohols are compatible with these reactions. In contrast, the corresponding amines had to be protected as NH-Boc groups.

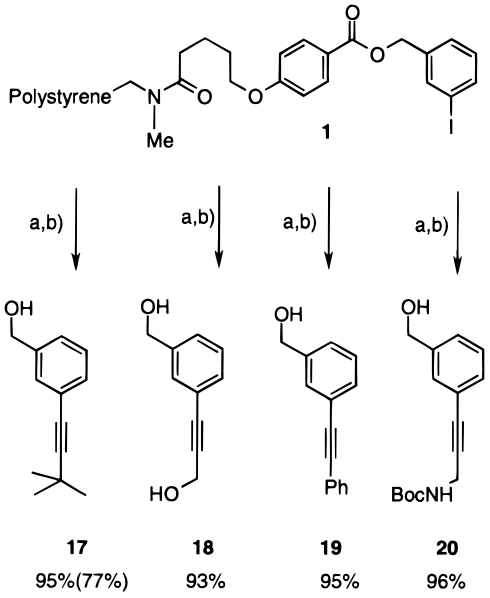
Heck Reactions. Conditions had to be carefully optimized in order to achieve complete conversion in the Heck reaction between a solid-phase bound aryl iodide and electron-deficient olefins.[22,23] Pd(OAc)$_2$ was by far the best catalyst for this reaction, and *n*-Bu$_4$NCl as an additive was essential. The best results were obtained with NaOAc

Scheme 3[a]



[a] Conditions: (a) 4 equiv of RSH, 0.2 equiv of Pd_2dba_3, 0.8 equiv of dppf, 8 equiv of *i*-Pr_2NEt, DMA, 60 °C, 24 h. (b) 6 equiv of NaOMe, MeOH: dioxane (1:4), rt, 24 h. (c) 8 equiv of RSH, 0.4 equiv of Pd_2dba_3, 1.6 equiv of dppf, 16 equiv of *i*-Pr_2NEt, DMA, 60 °C, 24 h.

Scheme 4[a]



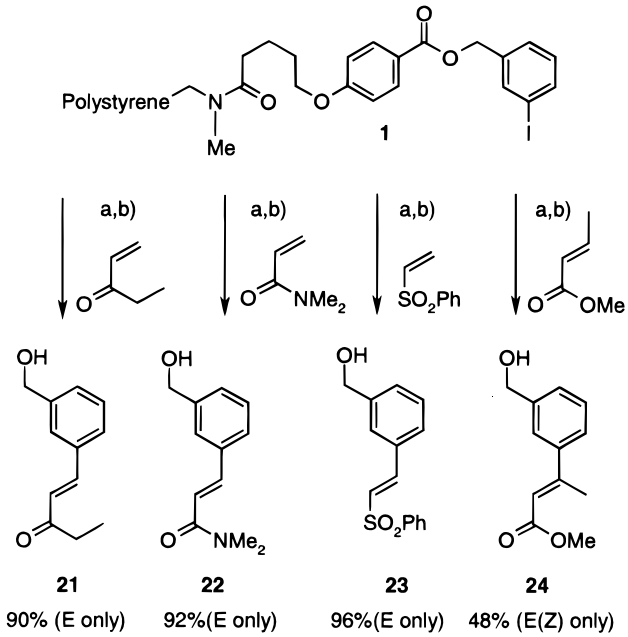
[a] Conditions: (a) 4 equiv of R−C≡C−H, 0.1 equiv of $PdCl_2(Ph_3P)_2$, 0.2 equiv of CuI, Et_3N:dioxane (1:2), rt, 24 h. (b) 6 equiv of NaOMe, MeOH: dioxane (1:4), rt, 24 h. Yields in parentheses refer to isolated yields.

as the base and *N*,*N*-dimethylacetamide as solvent. Selected results are summarized in Scheme 5.

2. Palladium-Mediated and Radical Cyclization Reactions

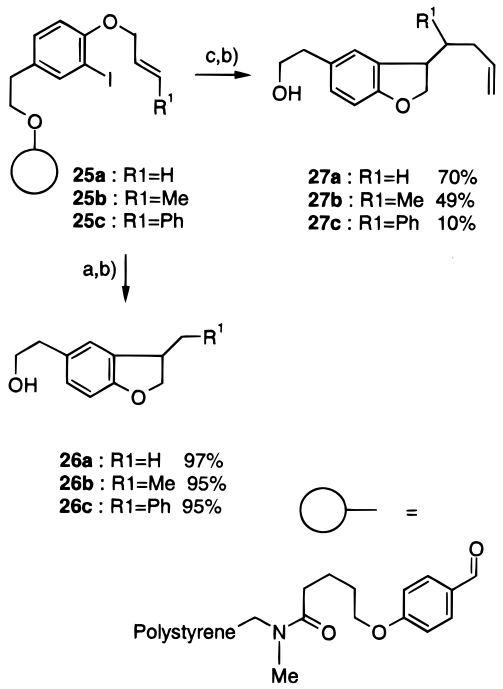
We have demonstrated in several cases the successful application of radical chemistry and Heck reactions to the formation of cyclic systems on the solid phase.[24,25] The derivatives **25a**−**c** (Scheme 6) smoothly cyclize to the dihydrobenzofuran when treated with *n*-Bu_3SnH and AIBN in refluxing benzene. Moreover, the intermediate

Scheme 5[a]



[a] Conditions: (a) 8 equiv of olefin, 3 equiv of NaOAc, 2 equiv of Bu_4NCl, 0.25 equiv of $Pd(OAc)_2$, DMA, 100 °C, 24 h. (b) 6 equiv of NaOMe, MeOH: dioxane (1:4), rt, 24 h.

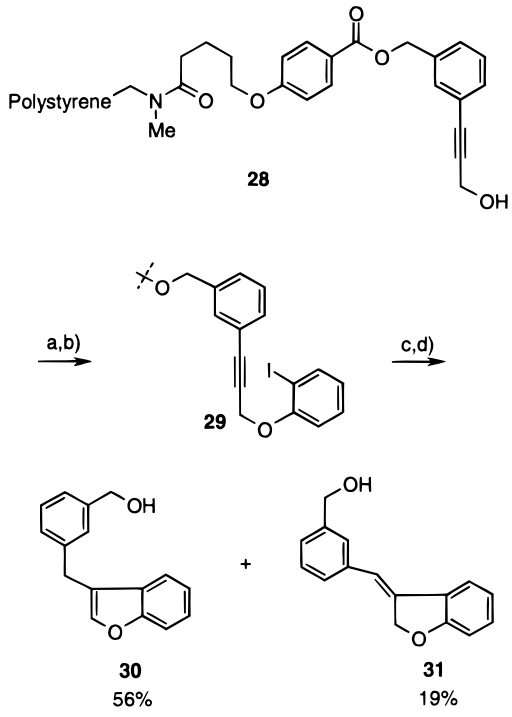
Scheme 6[a]



[a] Conditions: (a) 3 equiv of *n*-Bu_3SnH, 0.6 equiv of AIBN, benzene, reflux, 46 h. (b) 6 equiv of MeONa, MeOH:dioxane (1:4), rt, 24 h. (c) 15 equiv of allyltributyltin, 1.5 equiv of AIBN, benzene, reflux, 46 h.

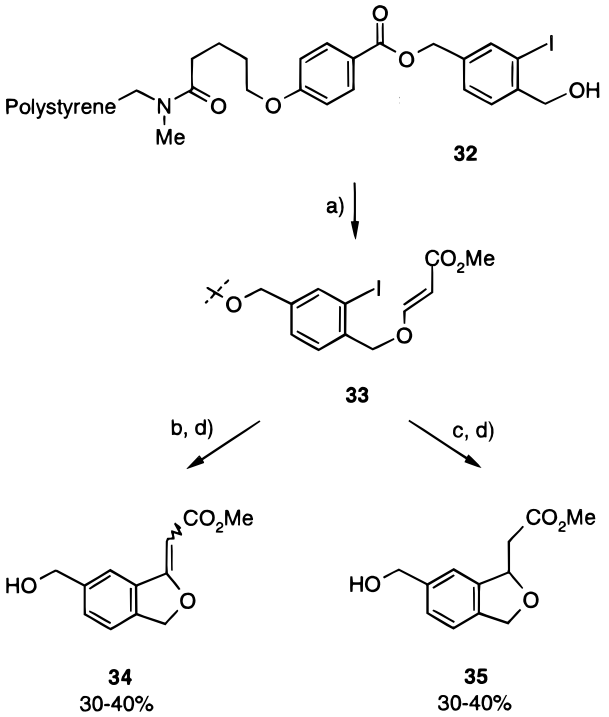
cyclized radical can be trapped by allytributyltin, resulting in compounds **27a**−**c**. It is noteworthy that the cyclized radical was trapped by allyltributyltin without interference of the benzylic hydrogen atoms from polystyrene. We combined several of our methods optimized on the solid phase for the elaboration of structures **30** and **31** (Scheme 7). After Pd-mediated coupling of proparylic alcohol with solid-phase bound phenyl iodide, followed by chlorination

Scheme 7[a]



[a] Conditions: (a) 3 equiv of $Me_2C{=}C(NMe_2)Cl$, CH_2Cl_2, rt, 5 h. (b) 10 equiv of *o*-iodophenol, 10 equiv of Schwesinger base,[26] 2 equiv of Bu_4NBr, dioxane, 60 °C, 24 h. (c) 3 equiv of *n*-Bu_3SnH, 0.6 equiv of AIBN, benzene , reflux, 46 h. (d) 6 equiv of MeONa, MeOH:dioxane (1:4), rt, 24 h.

Scheme 8[a]



[a] Conditions: (a) 6 equiv of methyl propiolate, 6 equiv of *N*-methylmorpholine, dioxane, rt, 48 h. (b) 0.3 equiv of $Pd(OAc)_2$, 0.6 equiv of Ph_3P, 2 equiv of *n*-Bu_4NCl, 4 equiv of K_2CO_3, DMA, 100 °C, 27 h, 30−40%. (c) 3 equiv of *n*-Bu_3SnH, 0.6 equiv of AIBN, benzene, reflux, 48 h, 30−40%. (c) 6 equiv of MeONa, MeOH:dioxane (1:4), rt, 24 h.

with Ghosez's reagent ((1-chloro-2-methylpropenyl)dimethylamine) and substitution with 2-iodophenol, 5-*exo*-dig cyclization affords compounds **30** and **31** in good combined yield.

When substrate **33** is cyclized under Heck reaction conditions, unsaturated compound **34** is obtained in 30−40% yield, while the radical-mediated cyclization results in the saturated analogue **35** in comparable yields (Scheme 8). The relatively modest overall yields arise partially from decomposition of the products under the basic conditions required for the cleavage from the resin.

Scheme 9 summarizes our strategies for the synthesis of quinoline derivatives on the solid phase.[27] The resin-bound secondary amine **36** reacts smoothly with electron-deficient acetylenes to give enamines **37a**−**c** in high yields (ca. 90%, as determined through cleavage from the solid phase). Intramolecular Heck reaction followed by methanolysis produces dihydroisoquinolines **38a**−**c**, which oxidize when exposed to air to the corresponding isoquinolinones **39a**−**c**. Crude and isolated yields are modest to excellent. Alternatively, secondary amine **36** can be alkylated with allyl bromides in the presence of Schwesinger base[26] to give allylamines **40a**−**c**, which can be cyclized to the corresponding substituted methylene tetrahydroisoquinolines **41a**,**b** in high overall yields.

Radical cyclization on the solid phase could even be performed between a phenyl iodide and an aniline. Intermediate **43** (Scheme 10), obtained from nucleophilic substitution of solid-phase bound benzyl chloride **42** with aniline, can be cyclized in a radical reaction to give phenanthridine **45** after oxidation. Multiple additions of small amounts of reagents (*n*-Bu_3SnH, AIBN) to the reaction mixture were necessary for complete conversion, making automation a necessity for a library synthesis involving this reaction.

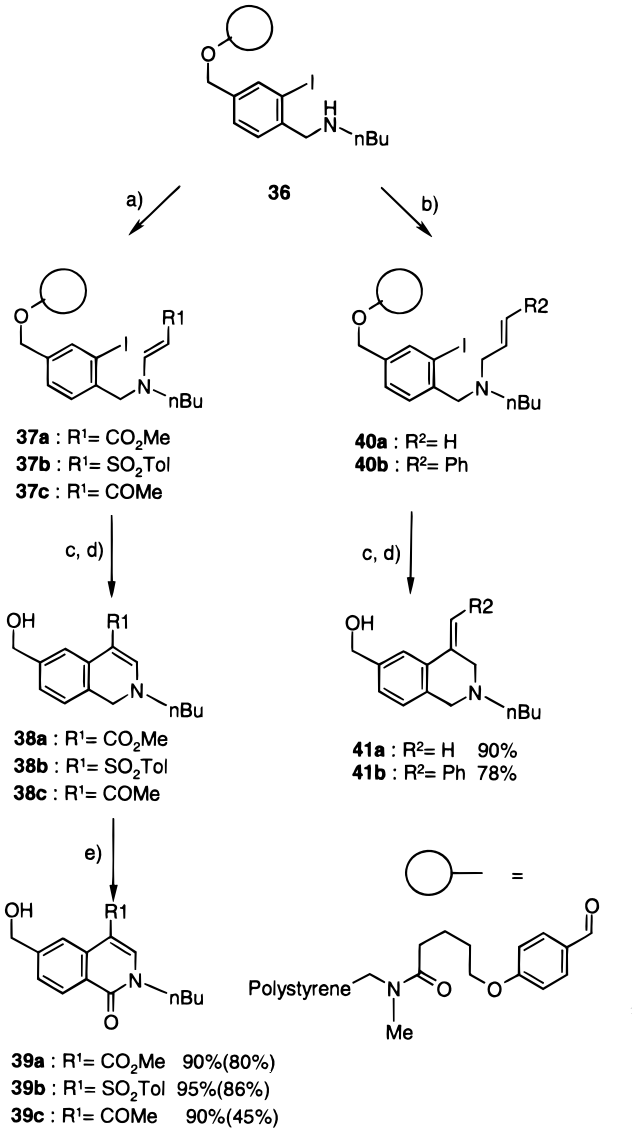
3. Derivatization of Highly Functionalized Core Structures

The above-mentioned reaction types were applied to more complex core structures in order to challenge their utility in library production. The solid-phase derivatization of two different types of highly functionalized core structures are presented in the following paragraphs. We have demonstrated that our reaction conditions optimized in model systems were applicable without major modifications.

Derivatization of Solid-Phase Bound Cyclohexadiene-*cis*-diol. Even though the variety of reactions known[28] for cyclohexadiene diols makes them highly desirable candidates for library core structures, so far no other studies reporting their derivatization on the solid phase besides our own have been reported in the field of combinatorial chemistry.[29] The synthetic strategy for derivatization is outlined in Figure 1. The diol functionality is utilized as the point of attachment to the solid phase through a ketal. Selective epoxidation and epoxide opening lead to a first derivatization. Further modification of the core structure can be achieved through palladium-mediated cross couplings of the C(6) vinyl bromide.

Scheme 11 summarizes the attachment of the rather acid sensitive cyclohexadiene diols to the solid phase. For

Scheme 9[a]



[a] Conditions: (a) 4 equiv of R−C≡C−H, CH_2Cl_2, rt, 24 h. (b) 4 equiv of Br−CH_2−CH=CH−R^2, 2 equiv of Schwesinger base,[26] dioxane, rt, 70 h. (c) 0.2 equiv of $Pd(OAc)_2$, 0.4 equiv of Ph_3P, 2 equiv of *n*-Bu_4NCl, 4 equiv of K_2CO_3, DMA, 100 °C, 24 h. (d) 6 equiv of MeONa, MeOH:dioxane (1:4), rt, 24 h. (e) O_2, dichloroethane, rt, 24 h. Yields in parentheses refer to isolated yields.

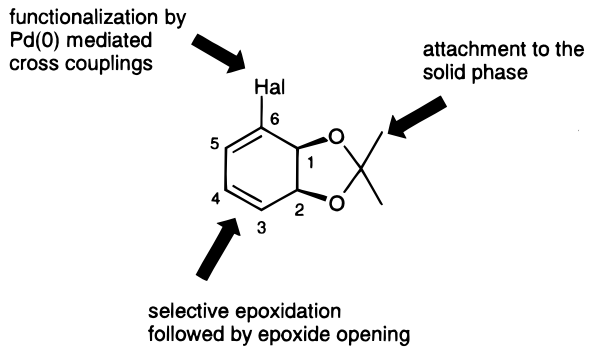
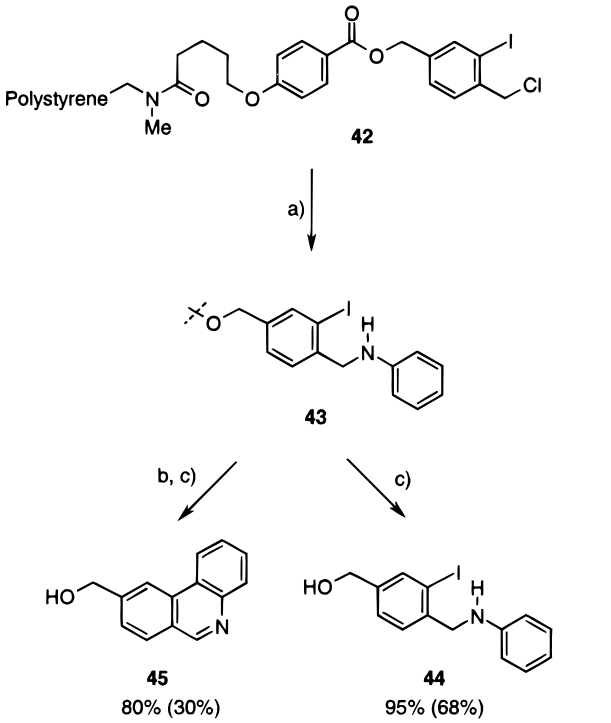


FIGURE 1. 3,5-Cyclohexadiene-I-1,2-diols as core structures for combinatorial chemistry.

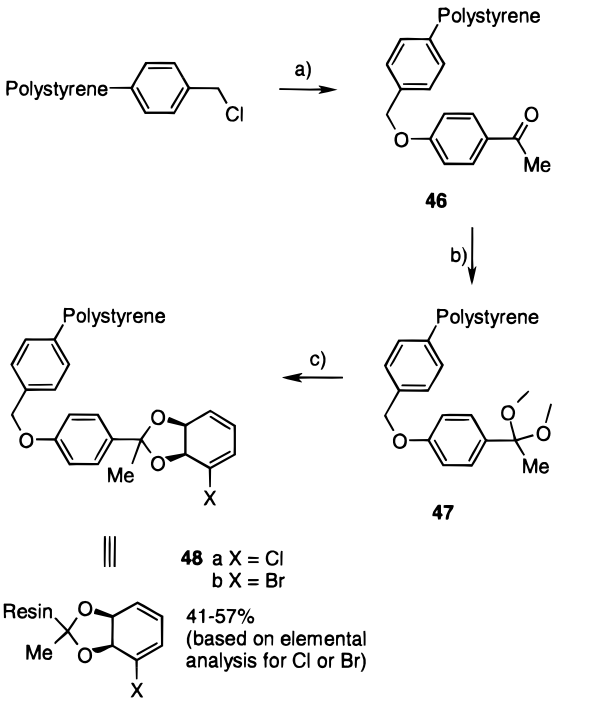
optimum ketalization of the cyclohexadiene diols, it was crucial to use the solid-phase bound dimethylacetal of the

Scheme 10[a]



[a] Conditions: (a) 10 equiv of aniline, 3 equiv of diisopropylethylamine, 2 equiv of *n*-Bu_4NI, dioxane, 100 °C, 36 h. (b) *n*-Bu_3SnH, AIBN, benzene, reflux. (c) 6 equiv of MeONa, MeOH:dioxane (1:4), rt, 24 h. Yields in parentheses refer to isolated yields.

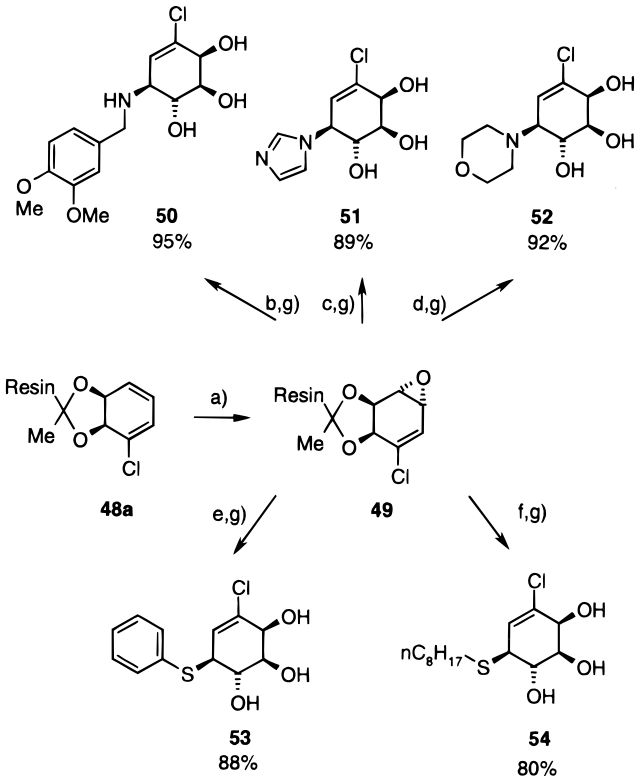
Scheme 11[a]



[a] Conditions: (a) 5 equiv of 4-hydroxyacetophenone, 5 equiv of NaH, THF, DMA, 80 °C, 16 h. (b) 14 equiv of $HC(OMe)_3$, 6 equiv of MeOH, 0.05 equiv of (±)-champhor-10-sulfonic acid. (c) 4 equiv of (1-(S)-*cis*-3-chloro (or bromo)-3,5-cyclohexadiene-1,2-diol, 0.1 equiv of pyridinium *p*-toluonesulfonate, CH_2Cl_2, rt, 2 h.

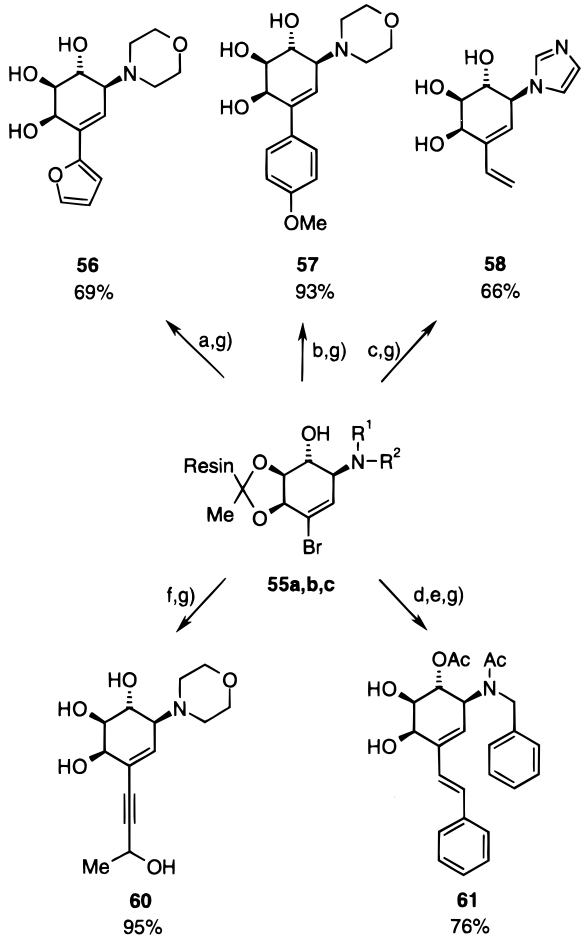
para-alkoxy benzoacetonide. Starting from Merrifield resin with a loading of 1.7 mmol/g, **48** could be obtained with a loading of approximately 0.5 mmol/g.

Scheme 12[a]



[a] Conditions: (a) 3 equiv of dimethyldioxirane, 0.1 M in acetone. (b) 8 equiv of 3,4-dimethoxybenzylamine, dioxane, 80 °C. (c) 8 equiv of imidazole, dioxane, 80 °C. (d) 8 equiv of morpholine, dioxane, 80 °C. (e) 4 equiv of thiophenol, 4.3 equiv of $LiN(SiMe_3)_2$, dioxane, 80 °C, 72 h. (f) 4 equiv of 1-octanethiol, 4 equiv of $LiN(SiMe_3)_2$, dioxane, 80 °C, 50 h. (g) 5% CF_3COOH, CH_2Cl_2, rt, 1.5 h.

Scheme 13[a]



[a] Conditions: (a) 3 equiv of 2-(tributylstannyl)furan, 0.2 equiv of $Pd(Ph_3P)_4$, dioxane, 100 °C, 24 h. (b) 8 equiv of 4-methoxybenzeneboronic acid, 18 equiv of K_2CO_3, 0.2 equiv of $Pd(AcO)_2$, dioxane:H_2O (6:1), 100 °C, 24 h, double-coupling. (c) 3 equiv of vinyltributyltin, 0.2 equiv of $Pd(Ph_3P)_4$, dioxane, 100 °C, 24 h. (d) Ac_2O, pyridine, DMAP, rt, 16 h. (e) 3 equiv of tributylstyrylstannane, 0.2 equiv of $Pd(Ph_3P)_4$, dioxane, 100 °C, 24 h. (f) 8 equiv of 3-butyn-2-ol, 0.4 equiv of CuI, 0.2 equiv of $PdCl_2(Ph_3P)_2$, dioxane: *i*-Pr_2NEt (2:1), 100 °C, 24 h, double coupling. (g) 5% CF_3COOH, CH_2Cl_2, rt, 1.5 h.

Monoepoxidation of **48** was achieved using a freshly prepared acetone solution of dimethyldioxirane (Scheme 12).[30] The reactivity of the resulting allylic epoxide **49** is suited perfectly for solid-phase chemistry. It can be handled easily and stored extensively (at 0 °C) without loss due to degradation, while it is quite reactive toward nucleophiles.

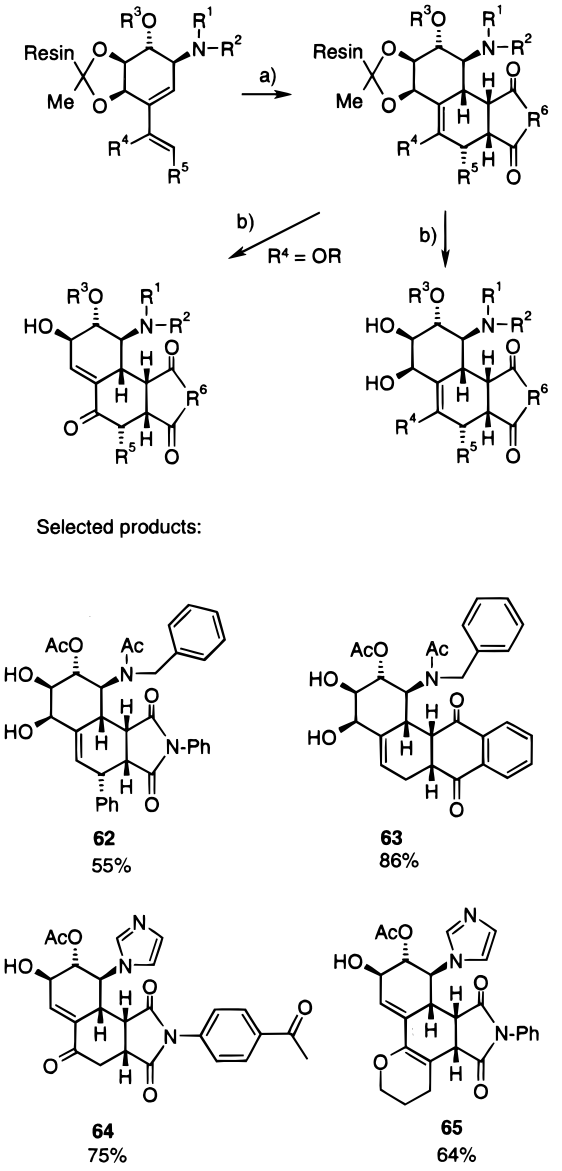
Epoxide opening with amines proceeded smoothly at room temperature and gave, upon cleavage from the resin, the resulting triols in almost quantitative yields (Scheme 12: **50**, **51**, and **52**). Anilines gave less satisfactory results due to their lower nucleophilicity. Epoxide opening with thiols was also possible under optimized conditions utilizing $LiN(TMS)_2$. When lithium thiolates were too insoluble, $LiN(TMS)_2$ and TMSOTf were used to generate the trimethylsilylated mercaptans (as more soluble nucleophiles) and LiOTf as a powerful catalyst in the epoxide-opening reaction. Thus, products could be obtained in 70−80% yield upon cleavage from the solid phase.

Stille couplings proceeded very well with vinyl bromides **55a**−**c** (Scheme 13). In contrast to our model studies with aryl iodides, $Pd(Ph_3P)_4$, rather than $Pd(Ph_3As)_4$, was the preferred catalyst in this case.[16a] Coupling with acetylenes proceeded to completion only when double couplings were performed.[16b] Vinylic tin reagents allowed for the efficient synthesis of solid-phase bound dienes starting from vinylic bromides **55a**−**c**. We were pleased to observe that Diels−Alder reactions with numerous maleimides and naphthoquinone proceeded to give the resulting polycyclic structures in high yields and purities as single diastereomers, as shown in Scheme 14. In certain cases (**64** and **65**), acid-catalyzed cleavage from the resin was accompanied by water loss to give the corresponding unsaturated compounds as single products.

Epoxide **49** was also reacted with deprotonated 2-iodophenol to give **66** (Scheme 15).[31] Radical cleavage of the I−C bond with *n*-Bu_3SnH/AIBN resulted in 5-*exo*-dig cyclization of the resulting radical onto the vinylic chloride. The cyclized products **67a**,**b** were obtained in 71% yield along with reduced noncyclized **68**. In analogy, **69** underwent a radical cyclization reaction to give, upon cleavage from the solid phase and acylation of the crude product, **70** in 52% yield, along with reduced **71** (40%).

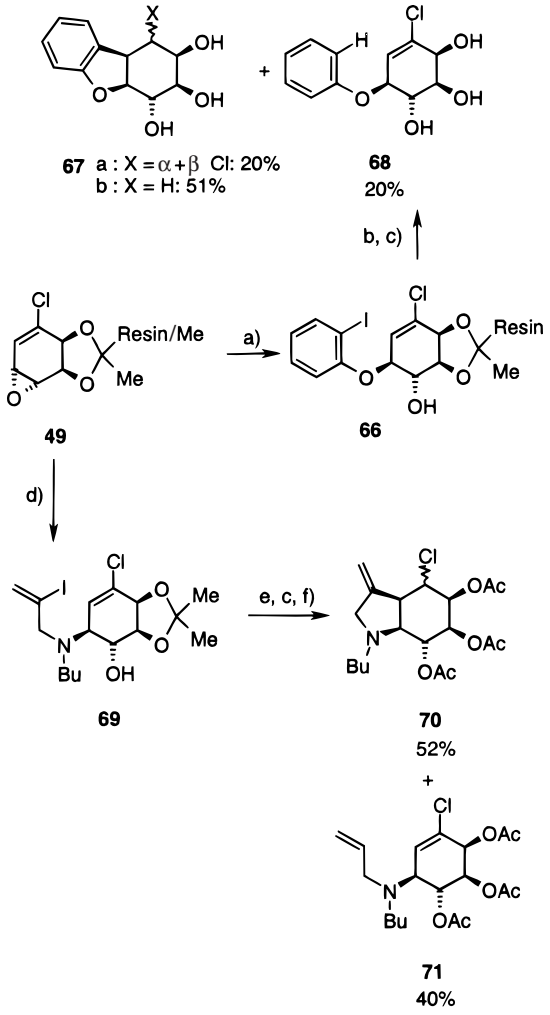
Solid-Phase Bound Levoglucosan as a Core Structure. In another study, we investigated reactions of solid-phase linked levoglucosan epoxide **75**, a very attractive core structure which can be functionalized to polysubstituted

Scheme 14[a]



[a] Conditions: (a) 8 equiv of maleimide, toluene, 50 °C, 50 h or 8 equiv of naphthoquinone, 80 °C, 50 h. (b) 5% CF_3COOH, CH_2Cl_2, rt, 1.5 h.

Scheme 15[a]



[a] Conditions: (a) 6 equiv of 2-iodophenol, 6 equiv of Schwesinger base,[26] dioxane, 100 °C, 90 h. (b) 15 equiv of *n*-Bu_3SnH, 1.9 equiv of AIBN, benzene, reflux, 80 h. (c) CF_3CO_2H:H_2O:CH_2Cl_2 (5:1:94), rt, 1 h. (d) 5 equiv of butyl(2-iodoallyl)amine, 50 mM $LiClO_4$, 2,6-lutidine, 50 °C, 21 h. (e) 3 equiv of *n*-Bu_3SnH, 0.6 equiv of AIBN, benzene, reflux, 48 h. (f) 20 equiv of Ac_2O, 10 equiv of Et_3N, pyridine, rt, 16 h.

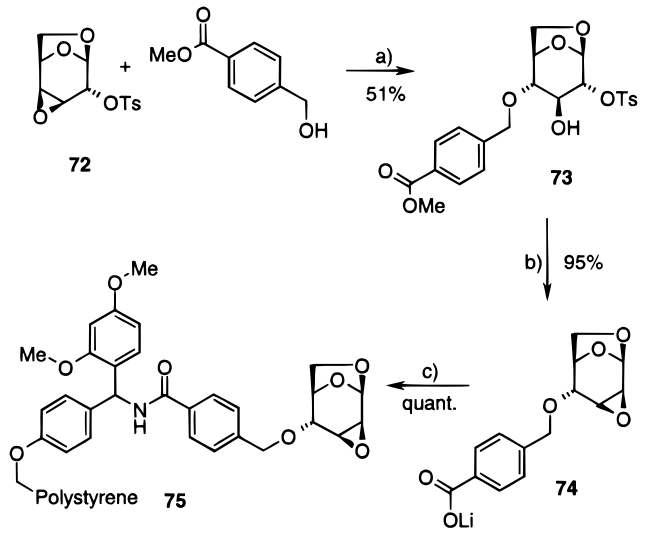
carbohydrate derivatives.[32] In contrast to the previously discussed oxirane, levoglucosan epoxide **75** is very stable and requires Lewis acid activation for successful nucleophilic attacks. It turned out to be most practical to synthesize epoxide **74** in solution, as shown in Scheme 16. Therefore, epoxide **72** was opened with 4-hydroxymethylbenzoic acid methyl ester in the presence of BF_3•EtO_2. **73** was then hydrolyzed to the corresponding lithium carboxylate with concomitant epoxide formation. The resulting intermediate **74** was attached to polystyrene Rink resin.

The 2,3-epoxide **75** could be opened with amines, alcohols, and thiols. Some selected examples are shown in Scheme 17. Schwesinger base was the preferred reagent for generation of alcoholates, which then reacted with epoxide **75** at 100 °C to give **76** and **77** upon trifluoromethylacetic acid-mediated cleavage from the polymer.[26] Amines, such as 3-iodo-benzylamine, reacted with the epoxide in the presence of $LiBPh_4$ in 2,6-lutidine to give **78** in high yield. Thiophenol also served as an excellent nucleophile when deprotonated with DBU. The corresponding product **79** was obtained as a single isomer and in high yield upon acidic cleavage from the solid phase. Deprotonation with KOtBu of the axial 3′-OH generated in the epoxide ring-opening allowed for clean alkylation at room temperature with electrophiles such as 1-iodododecane to give **80** in excellent yield. This transformation is remarkable due to the rather high steric hindrance around the axial 3′-OH.

Palladium-mediated cross couplings, previously established in model systems, were successfully applied to this highly functionalized core structure. Aryl iodide **81** reacted in both acetylene and Suzuki couplings to give **82** and **83** in excellent yields (Scheme 18).

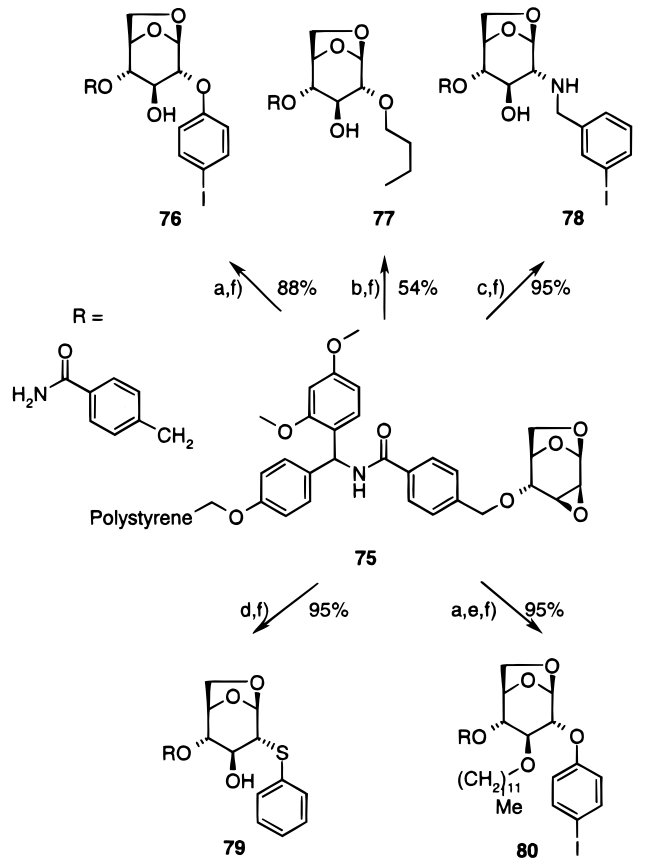
Scheme 19 demonstrates the superiority of ligand-free Suzuki coupling conditions over those previously published in the literature as well as the importance of double couplings in certain cases.[17] A single coupling reaction

Scheme 16[a]



[a] Conditions: (a) 0.2 equiv of $BF_3{\cdot}OEt_2$, PhMe, 100 °C. (b) 0.77 M LiOH, MeOH:H_2O (3:1), 17 h, rt. (c) 1 equiv of Polystyrene Rink resin, 3 equiv of *N*,*N*′-diisopropylcarbodiimide, 3 equiv of 1-hydroxybenzotriazole, DMA, 60 °C, rt.

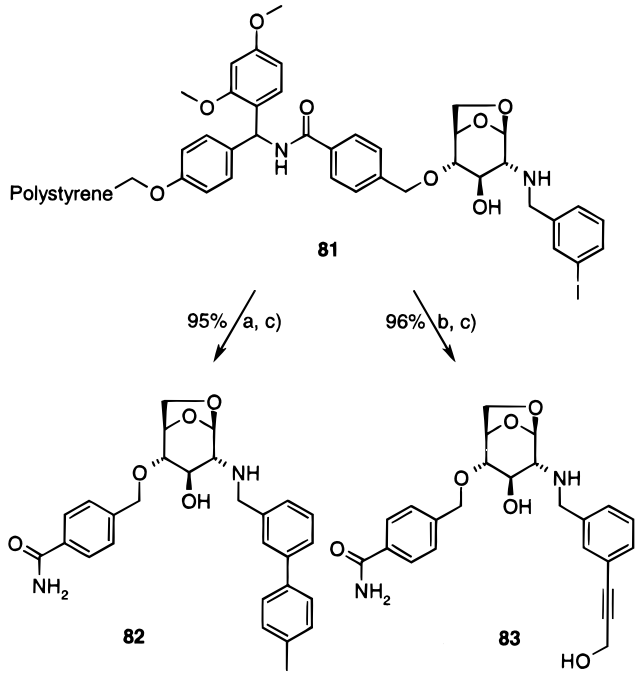
Scheme 17[a]



[a] Conditions: (a) 8 equiv of 4-iodophenol, 26 equiv of Schwesinger base,[26] dioxane:hexane (2:1), reflux, 1.5 h. (b) 8 equiv of *n*-butanol, 26 equiv of Schwesinger base, dioxane:hexane (2:1), reflux, 14 h. (c) 20 equiv of 3-iodobenzylamine, 2 equiv of $LiBPh_4$, 2,6-lutidine, 100 °C, 24 h. (d) 10 equiv of thiophenol, 10 equiv of DBU, THF:dioxane (1:4), 80 °C, 16 h. (e) 50 equiv of KO^{t}Bu, 25 equiv of $CH_3(CH_2)_{11}I$, THF, rt, 16 h. (f) 20% TFA in $ClCH_2CH_2Cl$.

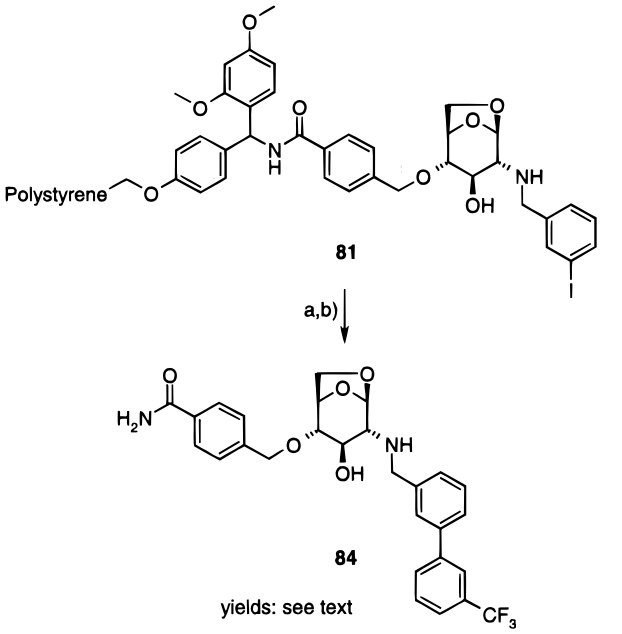
between solid-phase bound aryl iodide and 3-trifluoromethylphenyl boronic acid gave product **84** in 70% yield,

Scheme 18[a]



[a] Conditions: (a) 8 equiv of 4-methylbenzeneboronic acid, 18 equiv of K_2CO_3, 0.1 equiv of $Pd(OAc)_2$, dioxane:H_2O (6:1), 100 °C, 24 h. (b) 8 equiv of propargyl alcohol, 0.4 equiv of CuI, 0.2 equiv of $PdCl_2(Ph_3P)_2$, dioxane:Et_3N (2:1), rt, 24 h. (c) 20% TFA in $ClCH_2CH_2Cl$.

Scheme 19[a]



[a] Conditions: (a) 4 equiv of 3-trifluoromethylphenyl boronic acid, 9 equiv of K_2CO_3, 0.1 equiv of $Pd(OAc)_2$, dioxane:H_2O, (6:1), 100 °C, 24 h. (b) 20%TFA, CH_2Cl_2.

together with unreacted starting material. A second addition of more reagents and catalyst improved the yield to 82%. However, a third addition resulted in no further improvement. The accumulation of catalyst poison during the reaction could account for these observations. Consequently, the yields could be optimized dramatically when the resin was washed extensively prior to the second coupling in order to remove all catalyst poison. The

desired product was then obtained in 95% yield. These results compare favorably to those obtained when the reaction was performed under more commonly used conditions ($ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, DME−H_2O, 90 °C);[33] single couplings delivered the product in 55% yield along with 24% starting material and two additional, unidentified side products.

4. Conclusions

Solid-phase chemistry has great potential for library production in multiparallel synthesis. To obtain high-quality libraries, high-yielding reactions are required for each step in the synthetic sequence. Careful optimization of each reaction step is required. We have summarized our efforts toward optimizing several types of Pd(0)-mediated cross couplings and radical chemistry, as well as the elaboration of two highly functionalized core structures. We have demonstrated that radical- and Pd(0)-mediated reactions, among others, are particularly appropriate for the derivatization of highly functionalized core structures due to the compatibility of these reactions with numerous unprotected groups, such as alcohols, amines, ketones, aldehydes, etc.

Frequently, satisfactory results could be achieved only through double couplings or, as in the radical reactions, multiple additions of reagents. It is obvious that such procedures require sophisticated automation equipment.

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