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Purification Principles in High-Speed Solution-Phase Synthesis*Steffen Weinbrenner and C. Christoph Tzschucke*

1.1

Introduction

The benefits of solution-phase synthesis over solid-phase synthesis are the following: A great many more solution-phase reactions have been optimized and documented in the literature compared to currently available solid-phase reactions. A large number of protecting group reagents is commercially available whereas the number of solid-phase synthesis resins, often used as solid-phase protecting reagents, is still limited. In solution-phase chemistry, the range of organic reactions is in principle very large, whereas on solid phases there are limitations, for example, if one of the reagents or solvents is incompatible with the support material. Reaction progress as well as product identity and purity may be checked by well-established chromatographic and spectroscopic methods and the time needed for chemistry development in the preparation of libraries in solution phase is much less than for solid-phase approaches.

In contrast to the large number of advantages of solution-phase parallel synthesis, there is one major disadvantage, namely the “purification problem”. Given that solution- and solid-phase sample manipulation are both convenient and easily automated, the limitation to solution-phase parallel synthesis is the isolation of the desired compounds. Thus, the throughput attainable in automated solution-phase synthesis is directly related to the work-up procedures and to the purification process. Therefore, easy and efficient purification methodologies are required for high-speed solution-phase synthesis.

In this chapter, an overview is given of various purification strategies for automated solution-phase chemistry that have appeared in the recent literature.

1.2

Liquid-Liquid Extraction

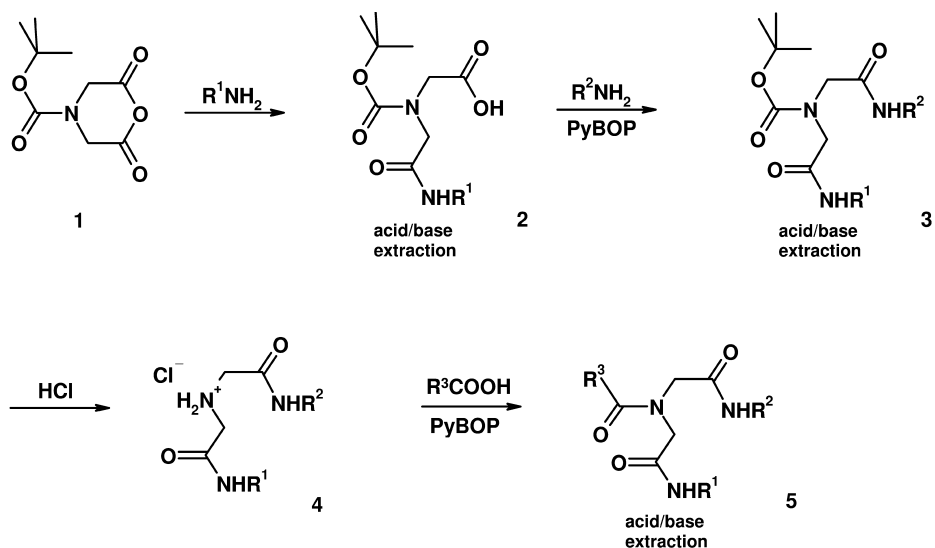
1.2.1

Aqueous Work-Up

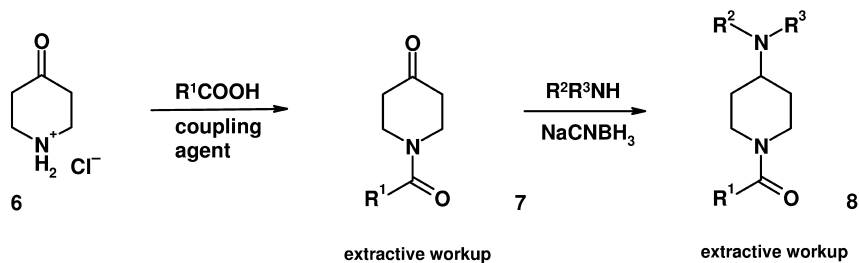
Aqueous work-up is a well-known purification method and is used extensively in traditional organic chemistry. The principle of this method is to use an aqueous and an organic liquid phase, which are immiscible. Each particular substance exhibits specific partitioning between the two phases and, thus, it is possible to separate substances. In the context of the generation of combinatorial libraries of individual compounds, this purification principle was first used by Boger et al. [1, 2].

Starting with a protected anhydride scaffold **1** and adding amine, he obtained the first sublibrary, which was purified by acid/base extraction. The monoamides **2** were partitioned and the portions were treated with amine and coupling agent to afford diamides **3**. This second sub-library was also purified by acid/base extraction and, after cleavage of Boc and partition, the last step of library synthesis involved coupling to various acids. To remove unreacted starting materials, reagents, and the reaction by-products, further aqueous acid and base extractions were applied (Scheme 1).

Employing this methodology, the authors prepared a library of 125 ($5 \times 5 \times 5$) amides of type **5** in high purity ($> 90\%$ HPLC) and overall yields ranging from 32 to 85% (30–100 mg). A further 960-member amide library was synthesized using this scaffold with overall yields in the range 10–71%, but no purity data were given.



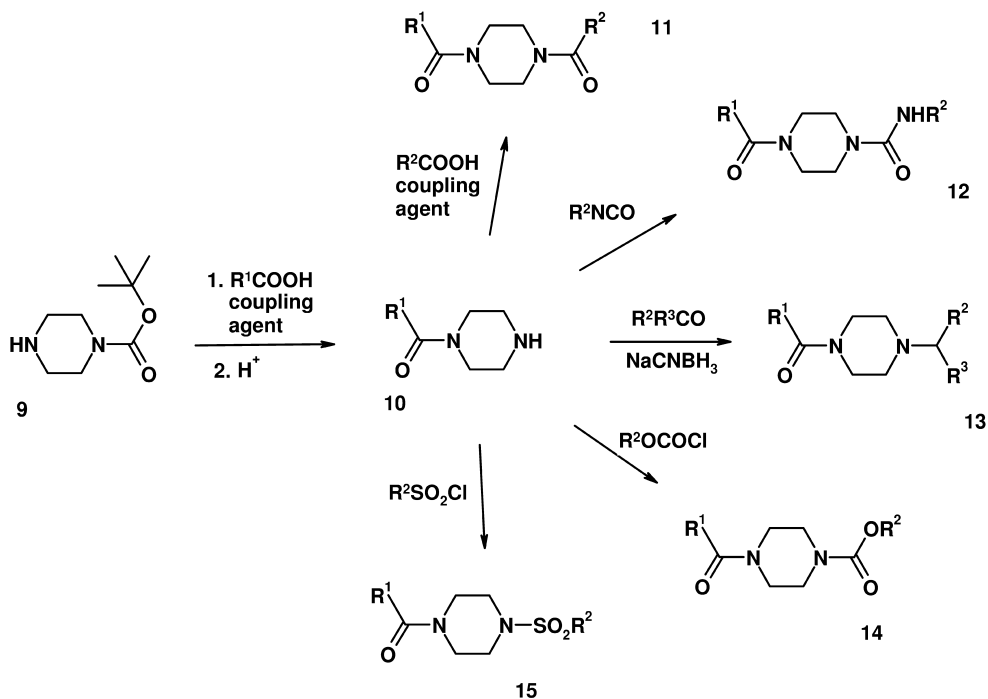
Scheme 1



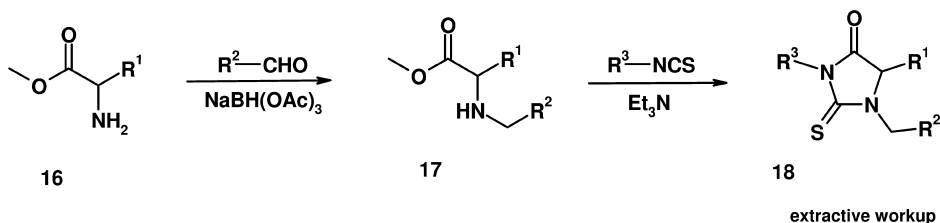
Scheme 2

This method has also been extended to other anhydride scaffolds [2, 3] and to combinations of such scaffolds [4–7].

A similar approach has been used for the synthesis of 7900 products derived from reactions of piperidone **6** (Scheme 2), of 7500 compounds derived from a piperazine template **9** (Scheme 3), and of 6000 products derived from 4-aminobenzylamine [8]. Thus, over 20000 compounds have been synthesized by using solution-phase chemistry and liquid-liquid extraction work-up procedures. For acylations, the authors used a work-up procedure that typically involved robotic addition of an aqueous solution of NaHCO_3 to the reaction vials, agitation, and robotic removal of the organic layer. Reductive aminations required a work-up that con-



Scheme 3



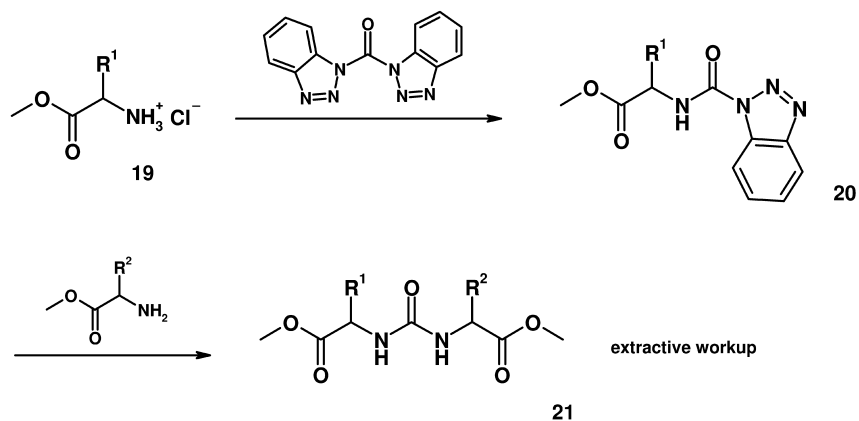
Scheme 4

sisted of the robotic addition of dilute aqueous hydrochloric acid (to destroy excess NaCNBH_3), neutralization with aqueous NaOH , extracting into dichloromethane, and removal of the organic layer.

The purity of the intermediates was assessed by TLC, MS, and ^1H NMR, and intermediates that were less than 90% pure were not used in subsequent reactions. Unfortunately, only a randomly chosen fraction (~5%) of the final products was analyzed by MS and only a few products were analyzed by HPLC. Thus, there are no reliable data about the identities and purities of the final products. Nevertheless, this work is an impressive example of solution-phase synthesis of a large combinatorial library and an automated liquid-liquid extraction purification strategy.

A similar acid/base washing strategy has been employed for the synthesis of an aryl piperazine library [9]. The synthesis was based on a nucleophilic aromatic substitution of nitro-fluoro aromatic compounds with Boc-piperazine and subsequent Schotten-Baumann acylation with acid chlorides. The products were purified by extractive work-up after each step.

An efficient one-pot protocol has been developed for the solution-phase synthesis of thiohydantoin (Scheme 4) [10]. After reductive alkylation of amino acid esters **16**, the isothiocyanate was added together with triethylamine, leading to thiohydantoin products **18**. The work-up procedure was performed by adding gly-



Scheme 5

cine as a quenching reagent (scavenger) followed by aqueous extraction to remove the borate salts, triethylamine, and the water-soluble “scavenger products”.

Using this procedure, a library of over 600 discrete compounds was generated on a 0.1 mmol scale. Some 10% of the compounds of the library were checked by HPLC analysis and showed purities of 52–98%.

For the parallel synthesis of ureas based on amino acids, a solid-phase synthesis as well as a solution-phase synthesis were used (Scheme 5) [11]. Solution-phase synthesis gave the desired compounds **21** in yields ranging from 80–100% and purities in the range 71–97%. The work-up involved extraction of the benzotriazole formed in the coupling steps. An aqueous borax buffer (pH 9.2) was used and the separation of the CH₂Cl₂ layer from the aqueous phase was performed in cartridges equipped with a PTFE frit.

Procedure

Preparation of 5 [1]: A solution of *N*-(*tert*-butyloxy)carbonyliminodiacetic acid (**1**) (0.349 g, 1.50 mmol) in dimethyl formamide (DMF) (15 mL) was treated with *N*'-(3-dimethylaminopropyl)-*N*-ethyl-carbodiimide hydrochloride (EDC) (0.294 g, 1.54 mmol) at 25 °C. The mixture was stirred at 25 °C for 1 h, and then the amine (1 equiv.) was added and the reaction mixture was stirred for 20 h. It was then poured into 10% aqueous HCl (60 mL) and extracted with ethyl acetate (100 mL). The organic phase was washed with 10% HCl (40 mL) and saturated aqueous NaCl (2 × 50 mL), dried (Na₂SO₄), filtered, and concentrated in vacuo to yield the diacid monoamides **2**. Each of the diacid monoamides **2** was dissolved in anhydrous DMF (20 mL/mmol) and the solutions obtained were divided into three equal portions in three separate vials. Each solution was then treated with one of the three amines (1 equiv.), diisopropylethylamine (2 equiv.), and (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) (1 equiv.). Each solution was stirred at 25 °C for 20 h. The respective mixture was then poured into 10% HCl and extracted with ethyl acetate. The organic phase was washed sequentially with 10% HCl, saturated aqueous NaCl, 5% aqueous NaHCO₃, and further saturated aqueous NaCl, then dried (Na₂SO₄), filtered, and concentrated to yield the diamides **3**. Each of the diamides **3** was dissolved in 4 N HCl/dioxane (32 mL/mmol) and the respective mixture was stirred at 25 °C for 45 min. The solvent was then removed in vacuo, the residue was dissolved in anhydrous DMF (28 mL/mmol), and the solution obtained was divided into three equal portions, which were placed in three separate vials. Each solution was treated with one of three carboxylic acids (1 equiv.) followed by diisopropylamine (3 equiv.) and PyBOP (1 equiv.) and the mixtures were stirred for 20 h. Each mixture was then poured into 10% HCl and extracted with ethyl acetate. The organic phase was washed sequentially with 10% HCl, saturated aqueous NaCl, 5% aqueous NaHCO₃, and further saturated aqueous NaCl, then dried (Na₂SO₄), filtered, and concentrated in vacuo to yield the final products **5**.

Procedure

Preparation of 21 [11]: A solution of amino acid methyl ester hydrochloride **19** (0.2 mmol, 1 equiv.) and diisopropylethylamine (1.1 equiv.) in DMF (1 mL) was added to 1,1'-carbonylbisbenzotriazole (1 equiv.) in dichloromethane (1 mL) and the resulting mixture was shaken overnight at rt. Then, a solution of the second amino acid methyl ester (1 equiv.) and diisopropylethylamine (1.1 equiv.) in DMF (1 mL) was added and the resulting mixture was shaken overnight at rt. The samples were concentrated in vacuo, the residue was dissolved in dichloromethane, and the resulting solutions were transferred to syringes equipped with a PTFE frit, mounted on a VacMaster. The organic layer was washed with 0.1 M borax buffer (2 × 2 mL; pH 9.2) and 0.2 M HCl (2 × 2 mL). The organic phase was collected in pre-weighed tubes and concentrated in vacuo to yield the urea **21**.

1.2.2

Phase-Separation Techniques

The traditional separation of two phases (in most cases, organic/aqueous) can be performed in a parallel manner by several methods. One possibility is to use a robotic system with phase detection and liquid-level detection (see Section 8.3). Another method is the use of adsorbent packing cartridges to adsorb the aqueous phase (Na_2SO_4 , MgSO_4 , alumina, EXTrelut[®]). Furthermore, a hydrophobic membrane or frit (PTFE) in a polypropylene cartridge can be used to separate a dichloromethane or chloroform phase from an aqueous phase (Fig. 1). The dichloromethane or chloroform phase can pass through the frit, while the aqueous phase remains on top of the filter.

Another separation method involves cooling of the organic/aqueous phase to $-20\text{ }^\circ\text{C}$ in deep-well plates in the presence of pins. After the freezing process, the aqueous phase can be removed as ice attached to the array of pins while the organic phase remains in the deep-well plate. By this so-called “lollipop” method, 96 aqueous/organic mixtures can be easily separated [12].

1.2.3

Fluorous Biphasic Systems

A different extractive work-up is based on fluorous biphasic systems. This concept was first introduced for the recovery of rhodium complexes from hydroformylation processes [13] and was soon extended to separation procedures in combinatorial chemistry [14]. It has been the subject of several reviews [15–21].

Perfluoroalkanes exhibit a temperature-dependent immiscibility with many common organic solvents. Concomitantly, their solvating power is very low, i.e., organic molecules are virtually insoluble in fluorous solvents. The solubility of a substance can be increased by the attachment of perfluoroalkyl chains, so-called fluorous tags, to the molecule (Fig. 2).

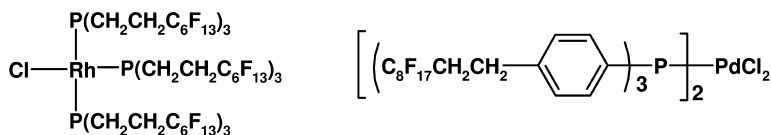


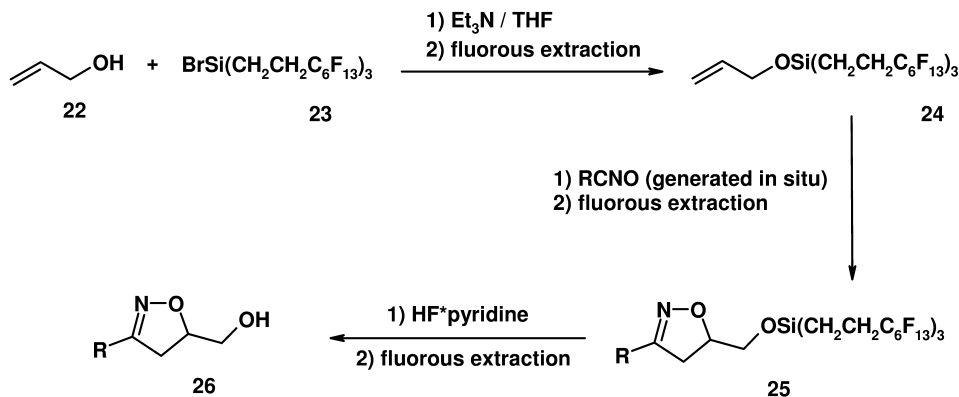
Fig. 3

room temperature. Only at low temperatures do they separate into biphasic systems.

The fluororous tag can be attached to catalysts, reagents, or the substrate itself. Several fluororous-tagged transition metal complexes have been developed, which can be recovered from reaction mixtures by fluororous extraction and then reused. Examples of fluororous transition metal complexes are shown in Fig. 3.

Fluororous-tagged reagents are very attractive for reactions in which a stoichiometric by-product is formed that is difficult to separate. An example is perfluoroalkylated triphenylphosphane for use in Wittig and aza-Wittig reactions, where the corresponding phosphane oxide is removed by fluororous extraction [22, 23]. Similarly, fluororous sulfoxide has been employed in Swern oxidations, and fluororous carbodiimide has been used as a coupling reagent [24, 25].

The attachment of fluororous tags to substrates is usually accomplished with modified protecting groups. After a reaction, the product is easily purified by fluororous-phase extraction, provided that complete conversion has been achieved. Upon completion of the reaction sequence, the fluororous protecting group is cleaved and again separated by fluororous-phase extraction. Examples include fluororous silyl groups and fluororous benzyloxycarbonyl groups or *tert*-butyloxycarbonyl groups (Fig. 2). An early example of a synthesis that employed the fluororous extraction strategy is the preparation of isoxazolines shown in Scheme 6 [14]. Nowadays, work-up with perfluorinated solvents is increasingly being replaced by fluororous solid-phase extraction (Section 1.3.2).



Scheme 6

Procedure

Preparation of 26 [14]: Allyl alcohol **22** (0.91 mmol) and triethylamine (1 equiv.) were dissolved in dry tetrahydrofuran (THF) (2 mL) under argon. A solution of bromo tris(2-perfluorohexylethyl)silane **23** (0.25 equiv.) in THF (2 mL) was slowly added to the reaction mixture at 25 °C. The resulting mixture was stirred at 25 °C for 3 h. After removal of the solvent, the residue was purified by three-phase extraction with FC-72 (10 mL), dichloromethane (10 mL), and water (10 mL). The organic/aqueous biphasic mixture was extracted twice more with FC-72 (10 mL). After concentration of the combined fluororous extracts, the residue was purified by flash chromatography (hexane/diethyl ether, 50:1) to yield a colorless oil.

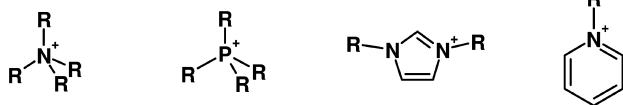
To a solution of this silyl ether **24** (0.1 mmol) in benzotrifluoride (BTF) (4 mL) were added a nitroalkane (0.99 mmol), phenyl isocyanate (1.98 mmol), and two drops of triethylamine. The reaction mixture was stirred at 25 °C for 3 days. After removal of the solvent, the residue was purified by three-phase extraction with FC-72 (20 mL), benzene (20 mL), and water (20 mL). The combined fluororous extracts were concentrated to yield the isoxazolines **25**, which were dissolved in diethyl ether (3 mL) at 25 °C. HF pyridine (0.1 mL) was added and the solution was stirred for 1 h at 25 °C. After removal of the solvent, the residue was redissolved in dichloromethane (20 mL). Saturated aqueous NH_4Cl (10 mL) was added and the organic/aqueous biphasic mixture was washed twice with FC-72 (10 mL). After separation of the layers, the aqueous phase was extracted twice with dichloromethane and the combined organic phases were dried (MgSO_4) and concentrated to yield the deprotected isoxazoline **26**.

1.2.4

Ionic Liquids

Room temperature ionic liquids are organic salts with low melting points. Because of their ionic nature, their vapor pressure is negligible. Some ionic liquids can be employed over a wide temperature range. The typical classes of ionic liquids are shown in Fig. 4.

Typical Cations



Typical Anions

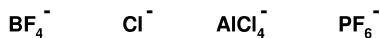


Fig. 4

Most widely used are *N,N'*-dialkylimidazolium salts, since they are easily prepared. Ionic liquids have been used as solvents for numerous reactions. Their physical and chemical properties vary with the combination of cation and anion. This allows a degree of tuning of their properties. Since they are highly polar solvents, ionic liquids can dissolve many inorganic salts and transition metal complexes, and often form biphasic mixtures with non-polar organic solvents. Thus, organic products can be extracted from ionic liquids, while ionic transition metal catalysts are immobilized. Volatile products can be easily distilled off from ionic liquids, since the latter show no volatility [17].

A growing number of reactions has been carried out in ionic liquids. Examples include Ru-catalyzed hydrogenations of alkenes and Pd-mediated C–C couplings.

In principle, it is conceivable that ionic liquids may be used for the immobilization of catalysts in a parallel set-up, but so far this has not been employed in combinatorial chemistry. This is probably due to the high costs of ionic liquids, the general problems associated with liquid-liquid separations in parallel work-up, and the fact that this is a relatively new technology.

1.3

Solid-Phase Extraction

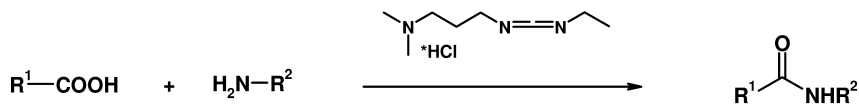
The principles of solid-phase extraction (SPE) or liquid-solid extraction (LSE) are similar to that of liquid-liquid extraction, involving a partitioning of compounds between two phases [22]. In SPE, the compounds to be extracted are partitioned between a solid and a liquid. The interactions responsible for the separation between the liquid and solid phase are non-covalent (ionic, van der Waals, hydrophobic) and can be modulated by changing the physical properties of the eluent (liquid phase) and the adsorbent (solid phase).

In principle, there are no major differences between solid-phase extraction and liquid-liquid extraction, but SPE can avoid or reduce some of the disadvantages of liquid-liquid extraction. Thus, SPE can handle small samples and very dilute solutions, it overcomes the formation of emulsions, and can be easily automated. Furthermore, the sorbents that are commonly used are commercially available as cartridges. These sorbents are alumina, silica gel, reversed-phase silica gel, and various ion-exchange resins. It is also possible to pack different adsorbents in layers inside the same cartridge to give a “sandwich-type” extraction column.

1.3.1

Silica Gel and Alumina

A large variety of inorganic salts can be very easily removed by SPE with silica gel or alumina as in an aqueous work-up. Furthermore, it is possible to separate amine hydrochlorides or even an excess of amine or acid from the desired product by silica gel or alumina SPE. Even reagents (e.g., the coupling agent EDC) can be separated by simple filtration of the reaction mixture through silica gel or alumina (Scheme 7).



removal of unreacted amine or acid as well as of excess carbodiimide and formed urea by SPE with "sandwich column" of alumina and silica gel

Scheme 7

A large number of polar reagents, side products, and impurities that are removable by aqueous work-up can also be separated by SPE with alumina or silica gel, and therefore SPE based on these adsorbents offers an easily automated and inexpensive alternative to aqueous work-up.

1.3.2

Fluorous Silica Gel

For the separation of perfluoro-tagged compounds from other molecules, fluorous silica gel (FSG; also called fluorous reversed-phase silica gel, FRPSG) can be employed. Examples of how perfluoroalkyl chains have been attached to silica gel surfaces are shown in Fig. 5.

These FSGs are either commercially available or are easily prepared from silica gel and an appropriate silylating reagent.

The crude reaction mixture is loaded onto an FSG column. First, the organic components are eluted with polar solvents (acetonitrile/water or methanol/water) while the perfluoro-tagged compounds are retained on the column. The fluorous compounds are then eluted with more fluorophilic solvents (acetonitrile, acetonitrile/diethyl ether, diethyl ether, FC-72). How strongly a compound is retained depends on the size of the fluorous tag. Untagged molecules are not significantly retained [27].

By such an SPE, products can be separated from perfluoro-tagged catalysts, by-products or reagents. One example is a Mitsunobu reaction utilizing fluorous azadicarboxylate and triphenylphosphine [28]. Many more examples of the use of this

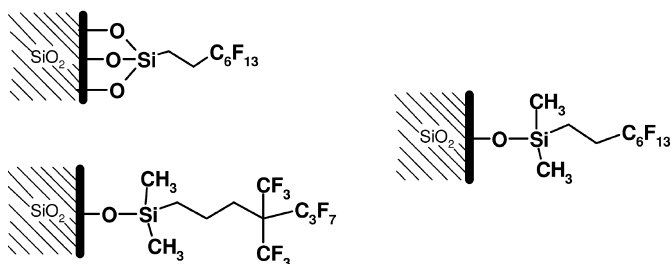


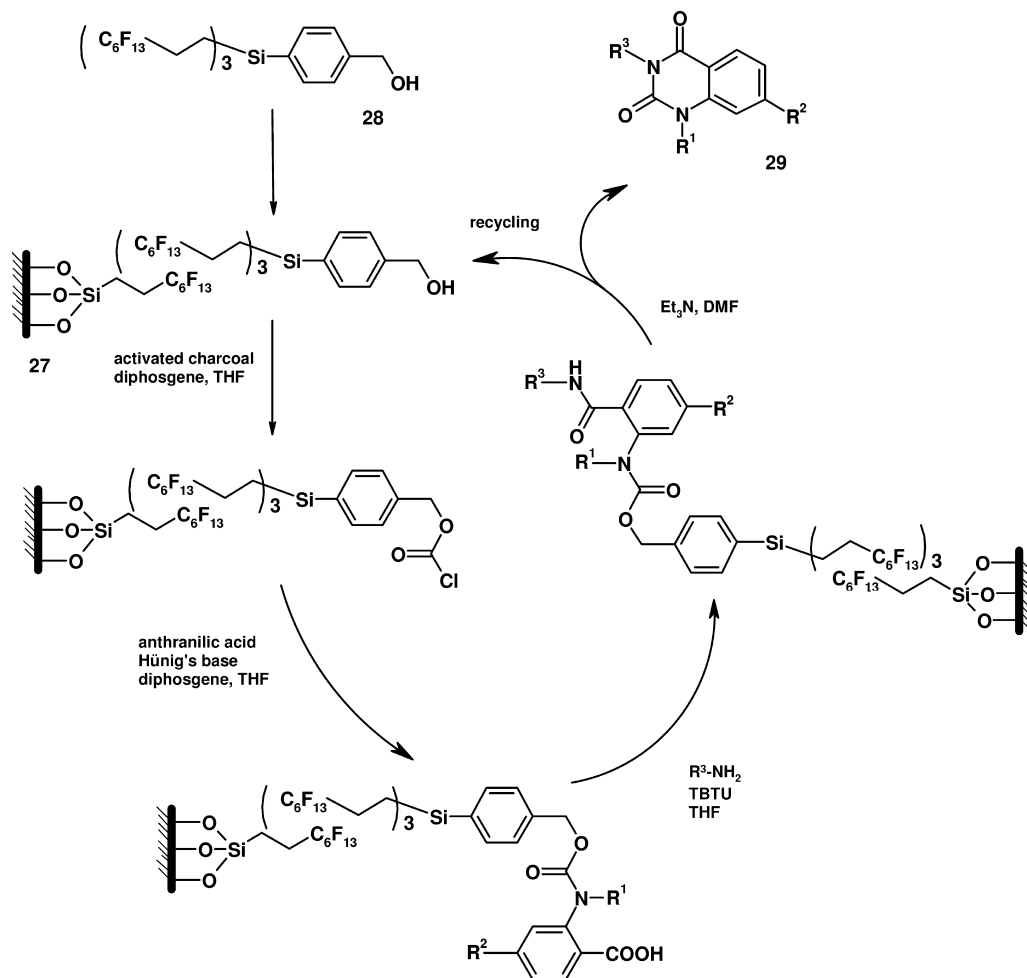
Fig. 5

strategy have been described [15], although few have been applied to the synthesis of combinatorial libraries.

Alternatively, the fluororous tag can be attached to the product via a modified protecting group (Fig. 2). This is useful for longer reaction sequences, in which the product is purified by SPE after each step. After the last step, the fluororous tag is cleaved and separated by SPE on FSG.

A perfluoro-tagged *tert*-butyloxycarbonyl group (^FBoc) has been used for the protection of primary amino functions in the synthesis of a small amide library [29]. The ^FBoc-protected amino acids were coupled with primary or secondary amines. The products were purified by preparative fluororous HPLC. After deprotection by acid treatment, the products were isolated by conventional extractive work-up.

In a recent example, a perfluoro-tagged bis-alkoxybenzyl group was employed



Scheme 8

as an acid-sensitive protecting group and phase label in the preparation of a library of 27 sulfonamides and 18 carboxamides [30]. The intermediates were purified by fluororous SPE after each step. After cleavage of the fluororous tag, the products were obtained in 42–97% yield with >95% purity (LC/MS).

In a conceptually similar approach, the FSG **27** has been used as a solid support, on which the perfluoro-tagged substrate **28** was adsorbed. This has been demonstrated for the multi-step synthesis of a library of 16 quinazolinediones **29** (Scheme 8) [31].

The reactions were carried out in THF, which desorbed the substrate from the FSG. For work-up, the solvent was evaporated and the FSG was washed with aqueous acetonitrile. While the perfluoro-tagged product remained adsorbed on the FSG, by-products and reagents were washed off. The final reaction was cyclative cleavage of the quinazolinediones. Thereafter, only the pure product was washed from the FSG, while the fluororous tag and any uncyclized precursors were retained.

Similarly, FSG has been used as a support for perfluoro-tagged Pd complexes. The complexes were employed as catalysts in Suzuki couplings and were removed from the product by filtration. No fluororous solvents were used [32].

In a more elaborate scheme, preparative HPLC on FSG columns has been used to deconvolute mixtures of perfluoro-tagged compounds. The synthesis was performed with a mixture of substrates, each uniquely labeled with a perfluoroalkyl chain of different length. Upon completion of the synthesis using the mixture, the individual products were separated by HPLC, with the components being eluted in order of increasing length of the fluororous tag. The utility of this strategy has been demonstrated in the synthesis of mappicine analogues and in the addition of thiolates to acrylates [34, 35]. The advantage is that the number of individual reactions is reduced, since all conversions are carried out with substrate mixtures. A drawback, however, is the use of preparative HPLC for deconvolution of the mixtures. As a final step, the removal of the fluororous tag is necessary.

Procedure

Preparation of FSG [31]: Silica gel (50 g; 35–70 μm ; 550 $\text{m}^2 \text{g}^{-1}$) was activated by stirring with conc. HCl (150 mL) in a rotary evaporator for 2 h at rt and for 3 h at 50 °C. The silica gel was then filtered off, washed with equal volumes of MeOH/H₂O (1:1), MeOH, CH₂Cl₂, and Et₂O (150 mL each), and dried *in vacuo*. The activated silica gel was suspended in toluene (150 mL; 700 ppm H₂O) and *p*-toluenesulfonic acid (1.4 g, 7 mmol) and 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl-triethoxysilane (35.8 g, 70 mmol) were added. The mixture was stirred in a rotary evaporator for 12 h at rt and for 24 h at 100 °C. The product was then filtered off, washed with MeOH (300 mL), CH₂Cl₂ (300 mL), and Et₂O (500 mL), and dried *in vacuo* to give 74 g of FSG.

1.3.3

Ion Exchange

Ion-exchange resins, as well as ion-exchange silica gels, have been more commonly used for combinatorial applications than “traditional” adsorbent materials. The advantage of ion-exchange adsorbents is the possibility of influencing the interaction between the adsorbent and the molecules very selectively. Ion-exchange adsorbents are able to differentiate between charged and neutral molecules, and species capable of undergoing a proton transfer can be retained by ionic interactions. These ionic processes are reversible and can be influenced by the ionic strength of the eluent (pH) as well as the ionic nature of the adsorbent.

A large number of ion-exchange adsorbents based on polystyrene polymers are commercially available, as well as some based on silica gel. The advantage of the silica gel based adsorbents is their much greater stability towards a broad range of organic reagents. Furthermore, they can be used with organic solvents without any problems and even changes of solvent between organic and aqueous solutions are possible without problems due to swelling. These silica gel based ion-exchange sorbents (Fig. 6) are available from various suppliers as prepacked polypropylene cartridges filled with various amounts of sorbent. Since the capacity of the sorbents is given in mequiv. g^{-1} (normally ~ 0.7 mequiv. g^{-1}), how much material can be loaded onto the column can easily be determined.

Thus, products capable of forming ions can be purified by ion-exchange solid-phase extraction in automated solution-phase synthesis. Another possible means of purifying a combinatorial solution-phase library is to selectively separate from the product those reagents, by-products, and impurities that are able to form ions by ion exchange. Both methods have appeared in the literature and a few examples are given here.

Firstly, for the purification of an amide library, a basic ion-exchange resin was used to separate an excess of unreacted acid chloride after the addition of water to the reaction mixture (Scheme 9) [36]. The authors evaluated nine ion-exchange resins and three solvents, and obtained the best results using the weakly basic Amberlite IRA-68 in combination with ethyl acetate. Using this method, they ob-

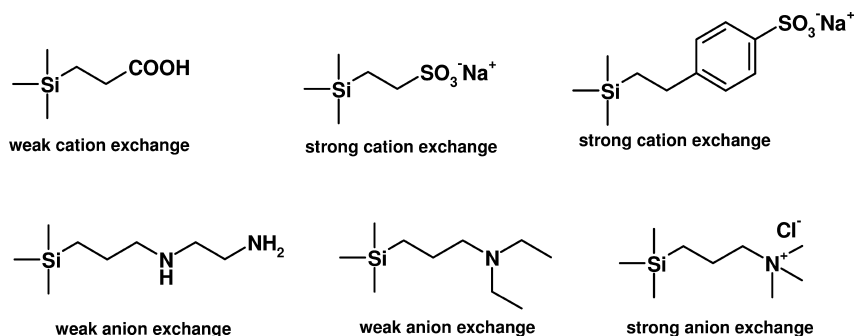
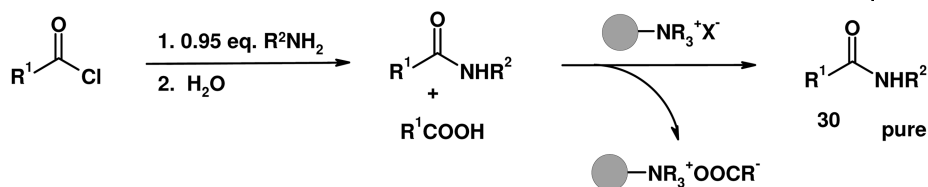
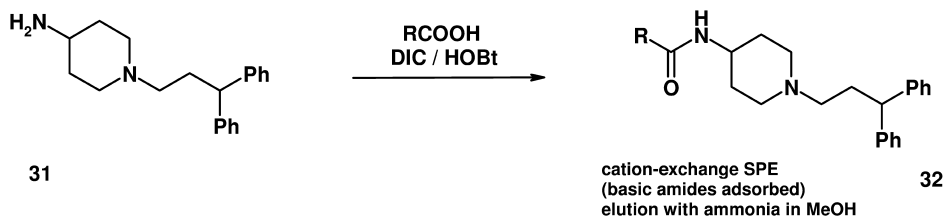


Fig. 6



Scheme 9



Scheme 10

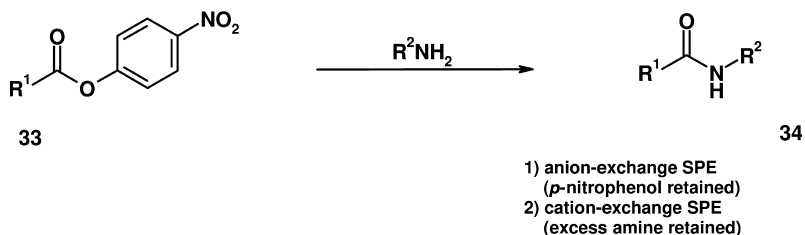
tained the desired products **30** in high yields (84–99%) and with high purities (>95%), but unfortunately only data for a nine-membered library were given.

Using this strategy, over 4500 compounds have been synthesized starting from a series of substituted pyrimidine and benzene acid chlorides [37].

For the purification of a library of amines generated by reductive amination, the use of strong cation-exchange adsorbents based on silica gel has been described [38]. An excess of aldehyde was used to ensure completion of the reaction and the crude reaction mixture was applied to a column of a strong cation-exchange adsorbent. The column was rinsed with methanol to remove the excess aldehyde and other neutral impurities while the basic products remained on the sorbent. The adsorbent was then treated with 2 M anhydrous ammonia in methanol to elute the basic products in high purities.

A similar approach involving selective retention of the product on an ion-exchange adsorbent has been employed for the synthesis of a library of over 225 basic amides **32** (Scheme 10) and a neutral amide library of 150 compounds [39]. For the synthesis of the basic amide library the authors used diisopropylcarbodiimide (DIC) and 1-hydroxybenzotriazole (HOBt) as the coupling agent, because these reagents and the resulting by-products are neutral and therefore compatible with the cationic SPE purification strategy. The reaction stoichiometry was optimized to ensure complete consumption of the basic diamine **31**, as separation of the unreacted diamine from the product amide **32** by cation exchange was not possible. Thus, the reactions were generally performed using 1.5 equiv. each of DIC and HOBt with 4 equiv. of acid.

After 24 h, the reaction mixture was loaded onto a cation-exchange column and eluted with MeOH and 0.1 N ammonia in MeOH to remove the by-product urea, excess acid, and HOBt from the sorbent. The pure product was then eluted with 1 N ammonia in MeOH. The process was automated by using a commercially



Scheme 11

available liquid handler and an SPE workstation. HPLC and MS were used to determine the identity and purity of the products and an average yield of 70% with an average HPLC purity of 90% were quoted.

This robotic method has also been applied to synthesize a neutral amide library (Scheme 11). Nucleophilic acyl substitution of nitrophenyl esters **33** with amines provided mixtures containing the product **34**, *p*-nitrophenol, and excess amine. These products were purified by a dual ion-exchange SPE procedure. First, an anion-exchange sorbent was used to remove the acidic *p*-nitrophenol, and this was followed by cation-exchange to remove the excess amine. The products were eluted with THF and dichloromethane and the desired compounds were obtained in average yields of 75% with average purities of over 90%.

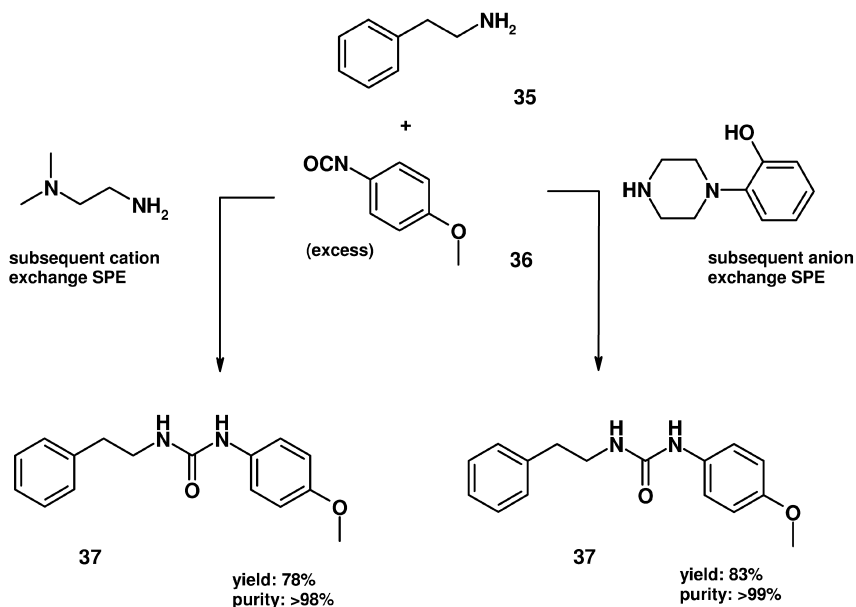
Both basic and neutral amide libraries were prepared in runs of 25 to 100 simultaneous reactions in quantities of up to 0.4 mmol each (25–300 mg).

For the high-throughput synthesis and purification of ethanolamines, the basic products were selectively retained on strong cation-exchange sorbents as ammonium sulfonate salts [40]. An 8 × 6 reaction array employing eight different amines and six different epoxides was performed and the products were obtained in an average yield of 75% with an average purity exceeding 92%.

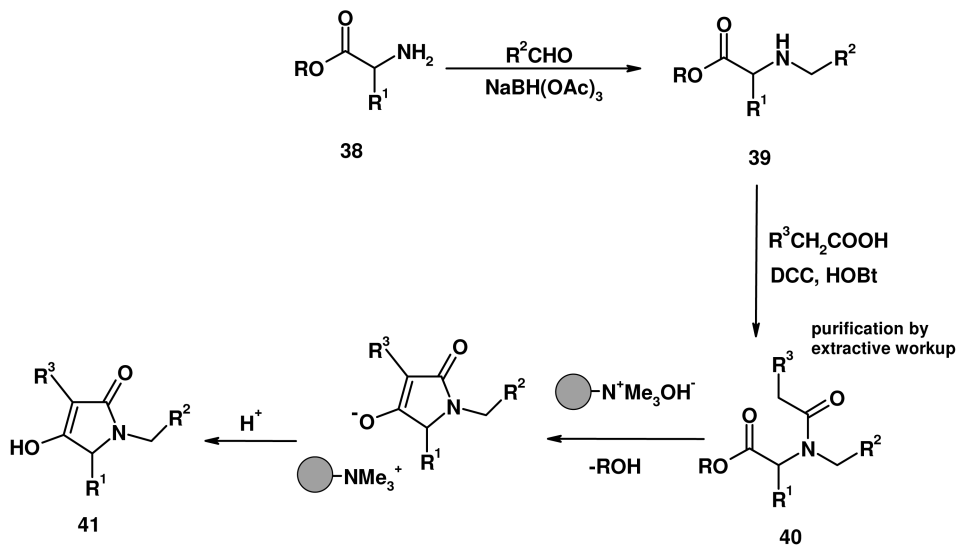
If neither the desired product nor the reagents and impurities are ionizable, the ion-exchange methods described above are not convenient. Nevertheless, the isolation of the desired compound using ion-exchange adsorbents can be performed by a “phase-switch” approach [38]. To achieve this “phase switch”, neutral compounds are converted by the action of quenching reagents into ionizable species that may be captured by an ion-exchange material. The principle is amenable to both anion- and cation-exchange chromatography, depending on the quenching agent employed. An illustration of the method is given in Scheme 12.

Here, the authors treated phenylethylamine **35** with 1.25 equiv. of 4-methoxyphenyl isocyanate **36** to form a crude reaction mixture of product urea **37** and excess isocyanate. Subsequently, the isocyanate impurity was removed either by quenching with *N,N*-dimethylaminoethylamine followed by cation exchange, or by quenching with 1-(2-hydroxyphenyl)piperazine followed by anion exchange.

Ion-exchange sorbents can also be used as activators or even as reagents for chemical transformations, and in the area of combinatorial chemistry this principle has been applied first for the synthesis of combinatorial libraries of aryl and heteroaryl ethers [41].

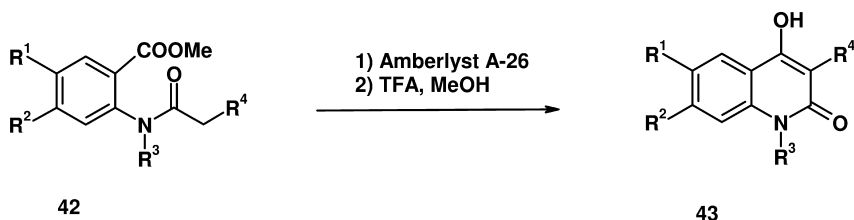


Scheme 12



Scheme 13

In another approach, the two applications were combined and an ion-exchange resin was used both as a reagent and as the purification agent in a synthesis of tetramic acids [42] (Scheme 13). Starting from amino acid esters 38, reductive amination and subsequent coupling with acids led, after extractive work-up, to



Scheme 14

amide esters **40**. The Dieckmann condensation of these amide esters could be achieved using various bases, but the authors established that the cyclization could also be performed with Amberlyst A-26 resin (OH^- form) as base. After the reaction, the tetramic acid was bound to the resin and the rest of the components as well as any impurities could be washed away. Subsequent acidification with trifluoroacetic acid in methanol released the product **41** in high yield (>70%) and with high purity (87% average).

Furthermore, this ion-exchange strategy has been extended to a Dieckmann condensation starting from substituted anthranilic acids **42** [43]. Employing Amberlyst A-26 resin (OH^- form) both as base and as purification sorbent, the authors synthesized a library of 4-hydroxyquinolin-2(1*H*)-ones **43** (Scheme 14).

The desired compounds were again released with trifluoroacetic acid in methanol and the final products were obtained in yields of 72–97% and with purities of 79–99%. The precursors were synthesized by reductive alkylation and subsequent acylation and were purified by extractive work-up.

Procedure

Preparation of 30 [36]: To Amberlite® IRA-68 (approximately 0.05 g, dried under vacuum overnight) was added the amine (0.0475 mmol) in ethyl acetate (0.6 mL) followed by the acid chloride (0.050 mmol) in ethyl acetate (0.6 mL). The reaction mixture was shaken overnight. Water (0.1 mL) was then added and the reaction mixture was shaken for an additional 30 min. Filtration and concentration of the filtrate provided the desired product **30**.

Procedure

Preparation of 32 [39]: The reaction set-up and product purification procedures were carried out using the Zymark Benchmate Robotic Workstation.

Reaction: The variable acid (4 equiv., 0.24–0.8 mmol) was manually added to each 16 × 100 mm tube and the tubes were loosely capped with a polypropylene cap. The liquid handler then carried out the following steps on each tube: 1) Added 500 μL (1.5 equiv., 0.092–0.3 mmol) of a solution of hydroxybenzotriazole in DMF. 2) Added 500 μL (1.5 equiv., 0.092–0.3 mmol) of a solution of diisopropyl carbodiimide in dichloromethane. 3) Added

500 μL (1 equiv., 0.061–0.2 mmol) of a solution of diamine **31** in dichloromethane. 4) Washed syringe with 3 mL of dichloromethane. 5) Mixed tube contents by vortexing at “speed 3” for 15 s. After all of the additions were completed, the workstation cycled through the tubes five times, vortexing each tube for 20 s at speed 3. The reactions were allowed to proceed until all were complete (19 h), as indicated by the disappearance of the diamine by TLC.

Purification: The workstation carried out the following steps for each tube: 1) Conditioned an SPE column (strong cation exchange, 0.5–1.5 g sorbent, 0.6 mequiv. g^{-1}) with 10 mL of methanol. 2) Loaded the reaction mixtures onto the column. 3) Washed the column with 2×10 mL of methanol. 4) Washed the column with 2 mL of 0.1 M ammonia in methanol. 5) Eluted the column with 2–5 mL of 1 M ammonia in methanol and collected the eluate in a tared receiving tube. Aliquots (10–20 μL) were removed for HPLC and MS analyses. The product solutions were concentrated in vacuo and final solvent remnants were removed by further exposure to high vacuum to afford products **32**.

1.4

Covalent Scavengers

Another approach for the removal of unreacted excess starting material, reagents, and impurities is offered by the possibility of performing selective covalent derivatizations of these impurities after the synthesis. These quenching reagents are commonly called scavenger reagents or scavengers. To allow easy separation of the desired products from the selectively formed by-products, the scavenger reagent has to be attached to a suitable support.

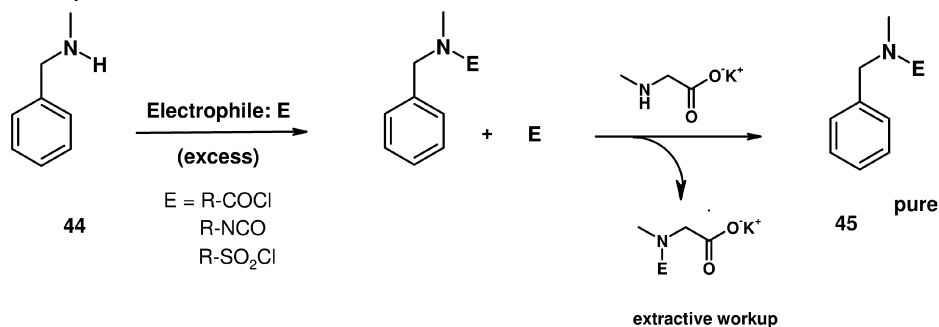
1.4.1

Solution Scavengers

One possibility is a support bearing a functional group that is responsible for a “phase switch” of the impurities, thereby allowing subsequent separation of product and by-product by aqueous extraction or simple filtration.

As shown above (Scheme 4), this strategy has been employed for the synthesis of thiohydantoins **18**, as well as for the synthesis of amides and ureas **45** (Scheme 15) [10, 44]. Glycine and potassium sarcosinate were chosen as the quenching agents for their bifunctional nature. The amine end of the amino acid quenches the excess electrophile and the carboxylic acid functionality renders the amino acid bound impurity soluble in aqueous media.

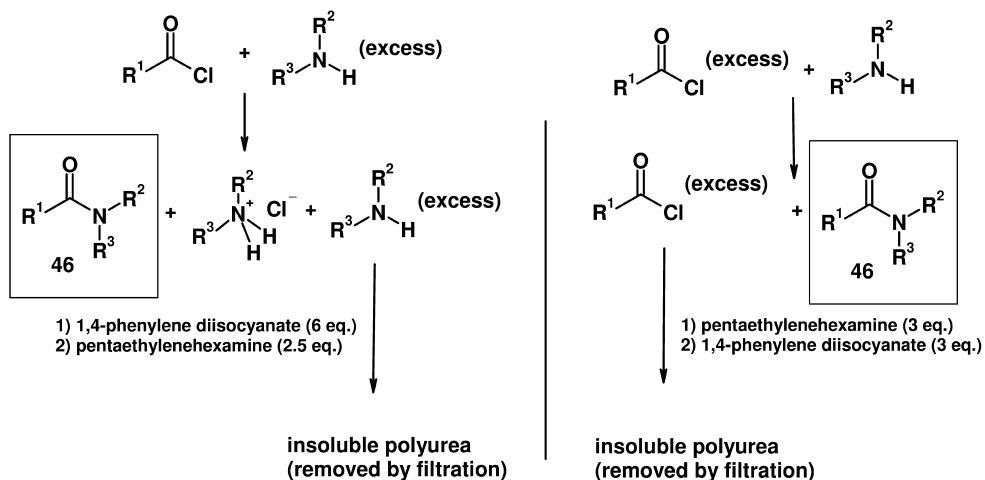
An excess (>1.5 equiv.) of electrophile (acid chloride or isocyanate) in the presence of triethylamine in DMF or THF was used. After stirring for 4 h, potassium sarcosinate (1 equiv.) was added and the reaction mixture was stirred for an addi-



Scheme 15

tional 0.5 h. Water was then added and the product 45 was collected by filtration or extracted with ethyl acetate. Both the ureas and the amides were obtained in high yields (> 72%) and their purities were checked by ^1H NMR and elemental analysis, but no discrete purity data were given. This solution scavenger principle has also been used in combination with ion-exchange purification strategies, as shown for example in Scheme 12 [38].

To purify solution-phase libraries of amides and sulfonamides, a scavenger approach based upon the removal of excess reactants by polymerization and simple filtration has been employed [45]. Co-polymerization of 1,4-phenylene diisocyanate and pentaethylenehexamine was used to remove the excess amine as an insoluble, filterable urea. An excess of acyl or sulfonyl chloride can also be scavenged by polyamine and diisocyanate, depending on the order of addition (Scheme 16). The desired amides 46 and sulfonamides were obtained in good yield (> 64%) and with high purity (87% on average).



Scheme 16

Procedure

Preparation of 45 [44]: The amides and sulfonamides were synthesized by treating *N*-benzylmethylamine **44** (0.302 g, 2.5 mmol) with an acid chloride or sulfonyl chloride (3.5 mmol) in DMF (2 mL) containing triethylamine (5 mmol). The reaction mixture was stirred for 4 h and then quenched with potassium sarcosinate (0.127 g, 1 mmol) and water (6 mL). The product **45** was isolated by filtration in the case of solids, and extracted into ethyl acetate (10 mL) in the case of oils. In the latter case, evaporation of the solvent from the organic extract gave the product.

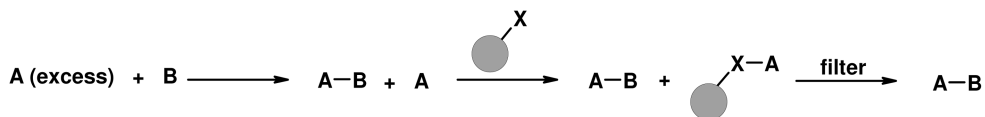
Procedure

Preparation of 46 [45]: *Procedure for the formation of amides 46 or sulfonamides using an acid chloride or sulfonyl chloride, respectively, and excess amine*: To a solution of the acid chloride or sulfonyl chloride (0.1 mmol) in dichloromethane (1 mL) was added a solution of the amine (3 equiv.) in dichloromethane (1 mL). The mixture was stirred at rt for 30 min and then a solution of 1,4-phenylene diisocyanate (6 equiv.) in dichloromethane (4 mL) was added. The resulting mixture was stirred at rt for 40 min and then a solution of pentaethylenhexamine (2.5 equiv.) in dichloromethane (4 mL) was added. After stirring for 1 h, the heterogeneous mixture was filtered. Concentration of the filtrate under reduced pressure afforded the expected amide **46** or sulfonamide.

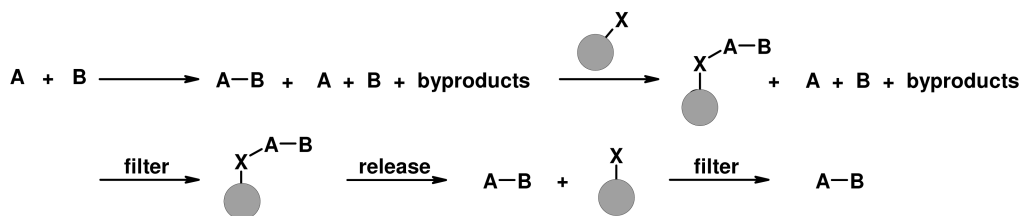
Procedure for the formation of amides 46 or sulfonamides using an amine with excess acid chloride or sulfonyl chloride, respectively: To a solution of the amine (0.1 mmol) in dichloromethane (1 mL) was added a solution of the acid chloride or sulfonyl chloride (3 equiv.) in dichloromethane (1 mL) along with polyvinylpyridine (100 mg). The mixture was stirred at rt for 40 min and then a solution of pentaethylenhexamine (3 equiv.) in dichloromethane (4 mL) was added. The resulting mixture was stirred at rt for 40 min and then a solution of 1,4-phenylene diisocyanate (3 equiv.) in dichloromethane (4 mL) was added. After stirring for 1 h, the heterogeneous mixture was filtered. Concentration of the filtrate under reduced pressure afforded the expected amide **46** or sulfonamide.

1.5**Polymer-Assisted Solution-Phase Chemistry (PASP)**

Another possible means of performing the desired “phase switch” using a covalent scavenger approach is to employ a resin-bound scavenger functionality. Thus, the quenching involves covalent bond formation between the functionalized resin and the unreacted starting materials or other impurities. The resulting resin-bound reactants can be removed by simple filtration and rinsing (Scheme 17). Thus, an



Scheme 17



Scheme 18

excess of one starting material can be utilized to drive the reaction to completion without complicating the isolation and purification of the final product.

In contrast to this method, another PASP strategy, known as the resin-capture approach, makes use of resins that transiently sequester solution-phase products, allowing solution-phase reactants, reagents, and by-products to be filtered from the resin-bound products. The products are subsequently released from the sequestering resin to afford the desired purified solution-phase products (Scheme 18).

1.5.1

Scavenger Resins

The concept of selective sequestration of non-product species was first demonstrated using solid-supported scavengers with electrophilic and nucleophilic character in amine acylation, amine alkylation, and reductive amination protocols [46]. Since then, a wide range of scavenger reagents has become commercially available from various suppliers. The structures and functions of these scavenger resins are shown in Table 1.

Recently, various scavenger resin approaches have appeared in the literature. For the synthesis of 4000 ureas (400 pools of 10-compound mixtures) [47], a solid-supported amino nucleophile was used to quench the excess of isocyanates, yielding the desired products in good purity. A similar concept has been employed in the synthesis of 2-thioxo-4-dihydropyrimidinones using aminomethylated polystyrene beads to quench isothiocyanates as well as aldehydes [48]. To quench an excess of amine in the synthesis of 2,6,9-trisubstituted purines, formyl polystyrene beads were used to form the corresponding polymer-bound imine, which could be filtered off [49].

Furthermore, a pyrazole synthesis with polymer-supported quench (PSQ) purification has been described [50]. Tertiary amine **47**, isocyanate **48**, and primary amine **49** supported on a polymer were used to quench excess acids, an excess of

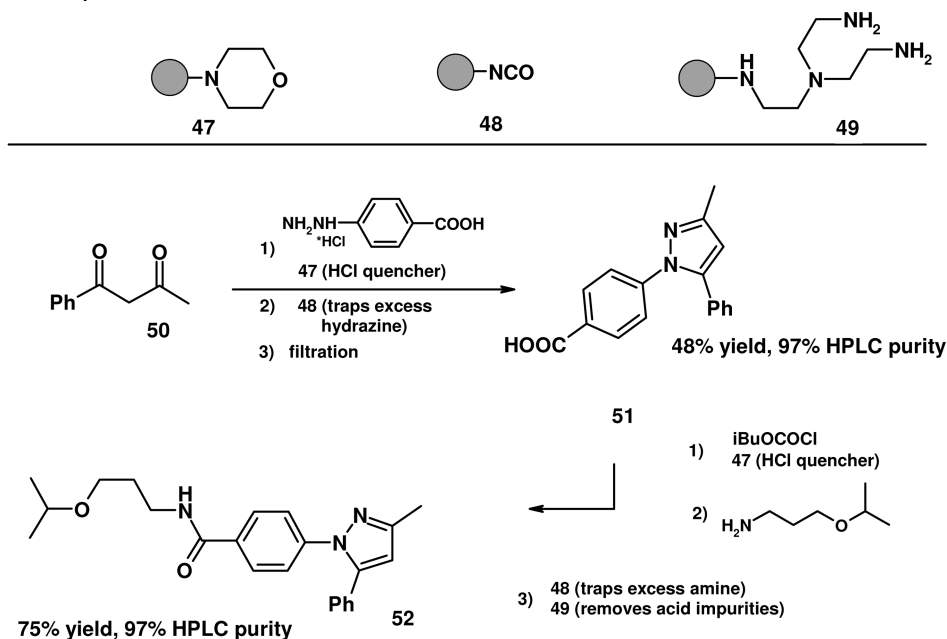
Table 1. Commercially available scavenger resins.

Functional Group of Scavenger Resin	Application as Scavenger for
primary amine	electrophiles: acid chlorides, acid anhydrides, chloroformates, sulfonyl chlorides, isocyanates
tertiary amine	protons, acids
isocyanate	nucleophiles:
isothiocyanate	amines, hydrazines, anilines, thiols, alkoxides, organometallic reagents
benzaldehyde	nucleophiles: hydrazines, hydroxylamines, organometallic reagents
thiol	alkylating agents: halides, mesylates, tosylates, 1,2-unsaturated carbonyl compounds
thiourea	alkylating agents: halides, mesylates, tosylates
hydrazinosulfonylphenyl	electrophiles: aldehydes, ketones
N,N-diethanolamino	boronic acids

hydrazine, and to trap HCl and acid impurities, respectively. The synthesis and purification steps are shown in Scheme 19.

Procedure

Preparation of 52 [50]: A solution of polymer-supported morpholine **47** (170 mg), 1-phenyl-1,3-butanedione **50** (0.5 mmol), and (4-carboxyphenyl)hydrazine hydrochloride (0.6 mmol) in methanol was shaken for 2.5 h. The methanol was then removed under a stream of nitrogen, dichloromethane (4 mL) and polymer-supported isocyanate **48** (350 mg) were added, and the reaction mixture was shaken for a further 16 h. An additional portion of polymer-supported isocyanate **48** (120 mg) was then added. After 4 h, the resin was filtered off and washed with dichloromethane (2 × 1.5 mL). The combined organic phases were concentrated in vacuo to give the desired product, 4-(3-methyl-5-phenylpyrazol-1-yl)benzoic acid **51**. 20 mg (70 μmol) of this benzoic acid was dissolved in dichloromethane and the solution was treated with polymer-supported morpholine **47** (100 mg) and 0.1 M isobutyl chloroformate in dichloromethane (0.75 mL, 75 μmol). The resulting slurry was shaken under nitrogen at rt for 30 min and then treated with a solution of (3-isopropoxypropyl)amine (100 mg, 85 μmol) in dichloromethane



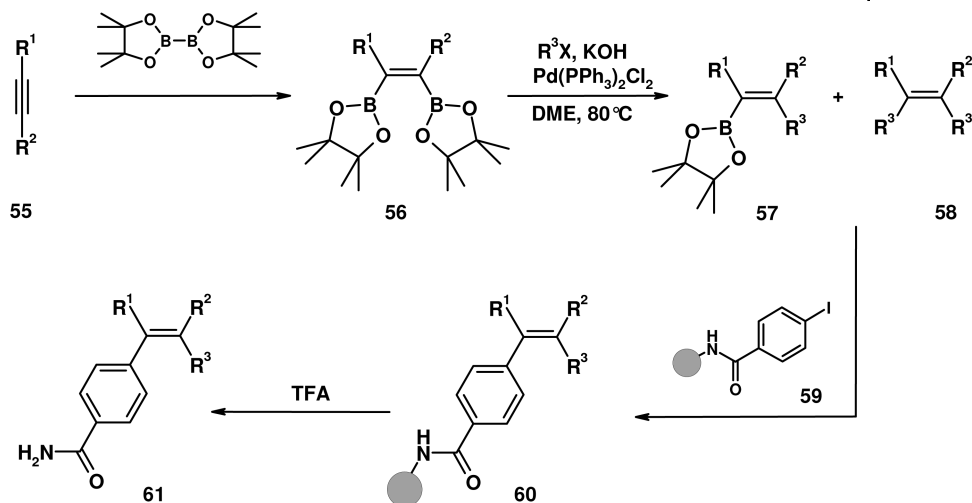
Scheme 19

(0.5 mL). The reaction mixture was shaken at rt for 2.5 h. Polymer-supported isocyanate **48** (75 mg) and polymer-supported tris(2-aminoethyl)amine **49** (100 mg) were added and the mixture was shaken for an additional 2 h. The resins were removed by filtration and rinsed with dichloromethane (2×2.5 mL). The combined filtrate and washings were concentrated to dryness *in vacuo* to yield product **52**.

1.5.2

Resin Capture

As mentioned above, the second PASP strategy for purifying a crude reaction mixture after a synthesis is to separate the desired product by selective covalent derivatization with a functionalized resin followed by filtration and rinsing. After the formation of the product in solution, it reacts selectively with a solid support while impurities and unreacted substrate remain in solution and are washed away. This resin-capture concept has been demonstrated in the context of the Ugi four-component condensation [51]. After the condensation, the reactivity of the enamide allowed the specific reaction with Wang resin under anhydrous acidic conditions. The resin was washed with methanol and dichloromethane and the subsequent cleavage was performed with trifluoroacetic acid in dichloromethane. The final carboxylic acids were characterized without further purification and were found to be > 95% pure.



Scheme 20

Another resin-capture approach has been published in relation to the synthesis of tetrasubstituted ethylenes via Suzuki coupling reactions (Scheme 20) [42, 53]. A 25-member library was synthesized using five alkynes, five aryl halides, and a polymer-bound aryl iodide. The alkynes **55** were converted into bis(boryl)alkenes **56** in solution, and the crude intermediates were used in Suzuki reactions with an excess of aryl halide. When all of the bis(boryl)alkene **56** had been consumed, the aryl iodide resin **59** was added to the reaction mixture and the reaction continued on the solid support. Side products such as **58**, arising from a double Suzuki reaction, remained in solution and could be washed away. Compounds **60** were cleaved from the polymer using trifluoroacetic acid and products **61** were obtained in > 90% purity.

The resin-capture approach combines the ease of solution synthesis with the ease of solid-supported isolation and purification (Section 6.3), but the unreacted starting materials and possible side products have to be inert to the capture.

Procedure

Preparation of 61 [42]: A small test tube was charged with **56** (10 equiv.), organohalide (15 equiv.), $[Pd(PPh_3)_2Cl_2]$ (0.3 equiv.), 3 M KOH (20 equiv.), and enough dimethoxyethane to bring the concentration of **56** to 0.5 M. The test tube was covered with a septum, flushed with N_2 , and heated overnight. Another test tube was charged with 100 equiv. of KOH and 1 equiv. of **59** and flushed with N_2 . The dimethoxyethane/KOH solution was then transferred by means of a syringe into the tube containing the polymer and the mixture was heated overnight. The polymer was then filtered from the solution and washed successively with water, methanol, ethyl acetate, and dichlorome-

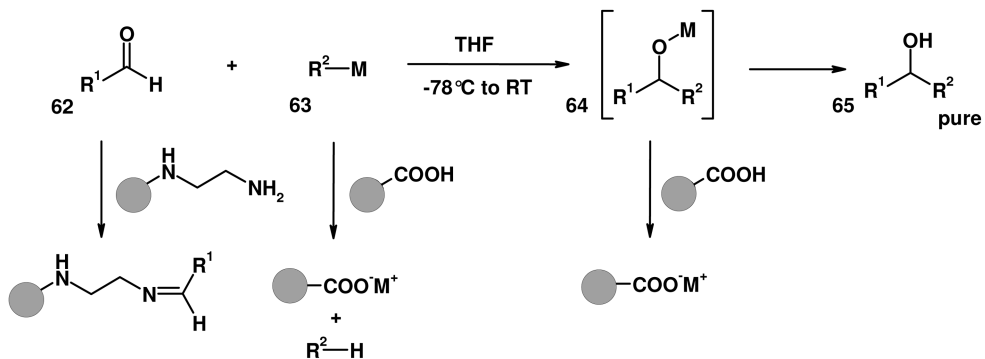
thane. The solid-bound products **60** were cleaved from the polymer with 30% TFA in dichloromethane to give **61**.

1.6 Complex Purification Strategies

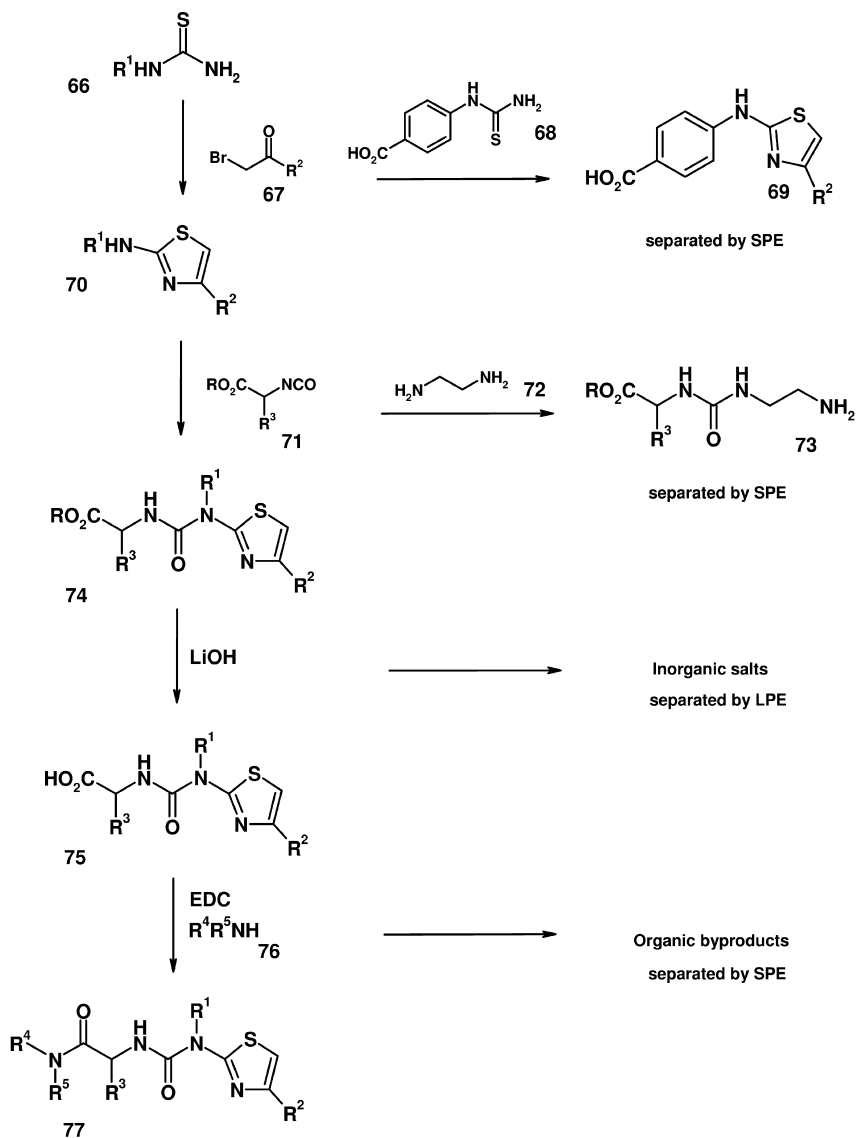
Covalent scavenger and resin-capture strategies rely on covalent bond formation for the phase switch, whereas solid-phase extraction is based on noncovalent interactions between the product, the impurities, and the two phases.

A combination of both methodologies has been introduced as the “complementary molecular reactivity and recognition” (CMR/R) purification approach [54]. The CMR/R approach allows the rapid purification of products by incubation with various resins simultaneously, avoiding serial and more time-consuming purification procedures. By quenching all of the undesired by-products of the reaction mixture simultaneously, the desired product is obtained in solution after a simple filtration. This strategy has been illustrated in relation to amine acylations, the Moffat oxidation, and the reaction of organometallics with carbonyl compounds. In the case of amine acylation, commercially available aminomethyl polystyrene resin was utilized to react with the excess electrophile and Amberlyst A-21 or polyvinylpyridine was used to sequester HCl. The parallel Moffat oxidations of secondary alcohols to ketones were worked-up by simultaneously adding sulfonic acid substituted resin and tertiary amine substituted resin. Simple filtration afforded the ketone products. The reaction of organometallics with carbonyl compounds and their CMR/R work-up is illustrated in Scheme 21.

Aldehydes **62** were reacted with an excess of either *n*-butyllithium or allylmagnesium chloride **63** to give the metal alkoxides **64**, which were quenched with carboxylic acid functionalized resin. This resin also served a dual role in quenching the excess organometallic reactant. The excess carbonyl compound was quenched with a primary amine substituted resin and the products were obtained > 95%



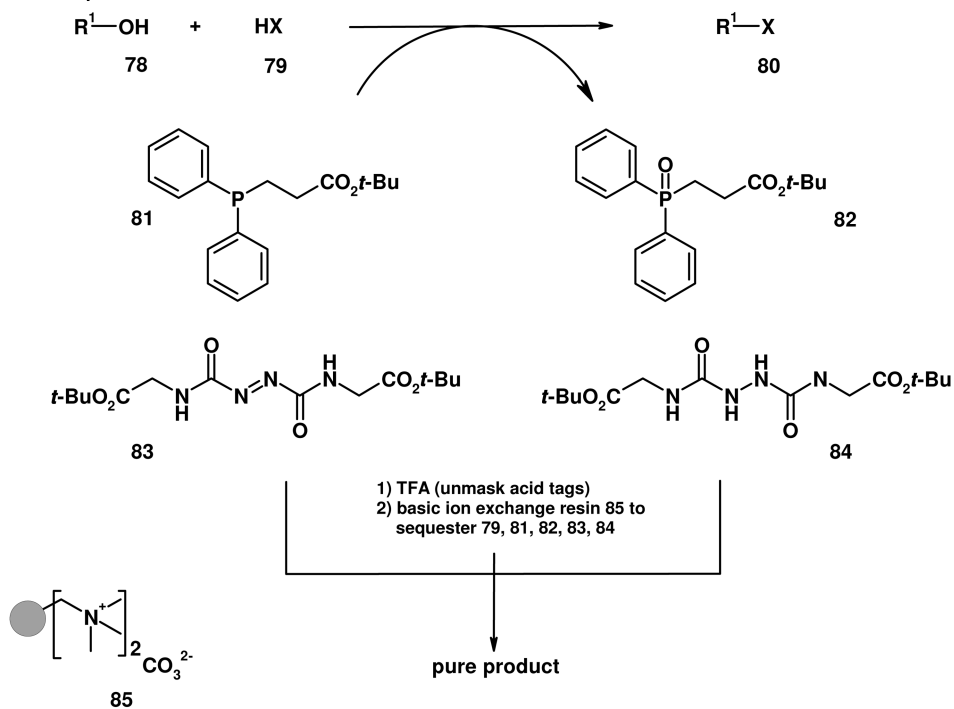
Scheme 21



Scheme 22

pure. Other examples of the application of the CMR/R strategy have also been published, and for the synthesis of heterocyclic carboxamides this strategy has been combined with the use of resin-bound reagents [55, 56].

A combination of solid-phase extraction, liquid-phase extraction, and the use of solution scavengers has been employed for the synthesis of thiazole libraries (Scheme 22) [57].



Scheme 23

The synthesis was based on the Hantzsch condensation of thioureas **66** with 2-bromo ketones **67** to give the 2-aminothiazoles **70**. The excess of **67** was trapped with *N*-(4-carboxyphenyl)thiourea **68** and removed by SPE. Subsequent treatment of the aminothiazoles **70** with a series of amino acid derived isocyanates **71** gave the second generation of thiazoles **74**. The excess **71** was quenched with 1,2-diaminoethane **72** and removed by SPE. Saponification gave the third generation of thiazole acids **75**, which were transformed into the corresponding amides **77** using EDC and amine **76**. Again, the excesses of all of the reagents could be removed by SPE or LPE. Liquid-phase extractions were performed with aqueous citric acid, and all of the solid-phase extractions were realized using neutral alumina [58].

Another approach using chemically tagged reagents in combination with ion-exchange resin has recently been published in relation to high-throughput purification of the products of Mitsunobu reactions [59]. Masked carboxylic acid tags (*t*-butyl esters) were attached to both the phosphine and the azodicarboxylate. Upon post-reaction unmasking with trifluoroacetic acid, a base-functionalized ion-exchange resin **85** was used to sequester the carboxy-tagged reagents **81** and **83**, the carboxy-tagged by-products **82** and **84**, as well as the excess nucleophile **79**. An overview is given in Scheme 23.

Procedure

Preparation of 65 [54]: Under conditions of parallel reaction synthesis, a solution of allylmagnesium chloride **63** (2.0 M in THF, 0.30 mL, 0.60 mmol) was added to a set of vials containing a solution of aldehyde **62** (0.5 mmol) in THF at $-78\text{ }^{\circ}\text{C}$ and the resulting mixtures were stirred at rt for 2.5 h. Amberlite IRC-50S (8–10 mmol, ~ 10 mequiv g^{-1}) was then added to each vial and the respective mixtures were stirred for an additional 4 h. Each mixture was then filtered and the polymer was rinsed with THF. The solvent was removed in vacuo to afford the carbinols **65**.

1.7

Conclusion and Outlook

Various purification methods have been developed for high-speed solution-phase chemistry within a very short time. These methodologies offer a very valuable alternative to the solid-phase approach. One of the major goals of these product isolation strategies is to simplify the operational procedures so as to enable automation. The phase switch of products or impurities and the ensuing phase separation offers a basis for automated purification. As documented above, this phase differentiation can be performed by various liquid-liquid extraction methods as well as by liquid-solid extraction strategies. In particular, the wise combination of covalent scavengers, resin capture, and solid-phase extraction can represent a very efficient and powerful tool for high-speed solution-phase synthesis. Furthermore, these strategies may be combined with resin-bound reagents or chemically tagged reagents to optimize automated solution-phase synthesis.

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