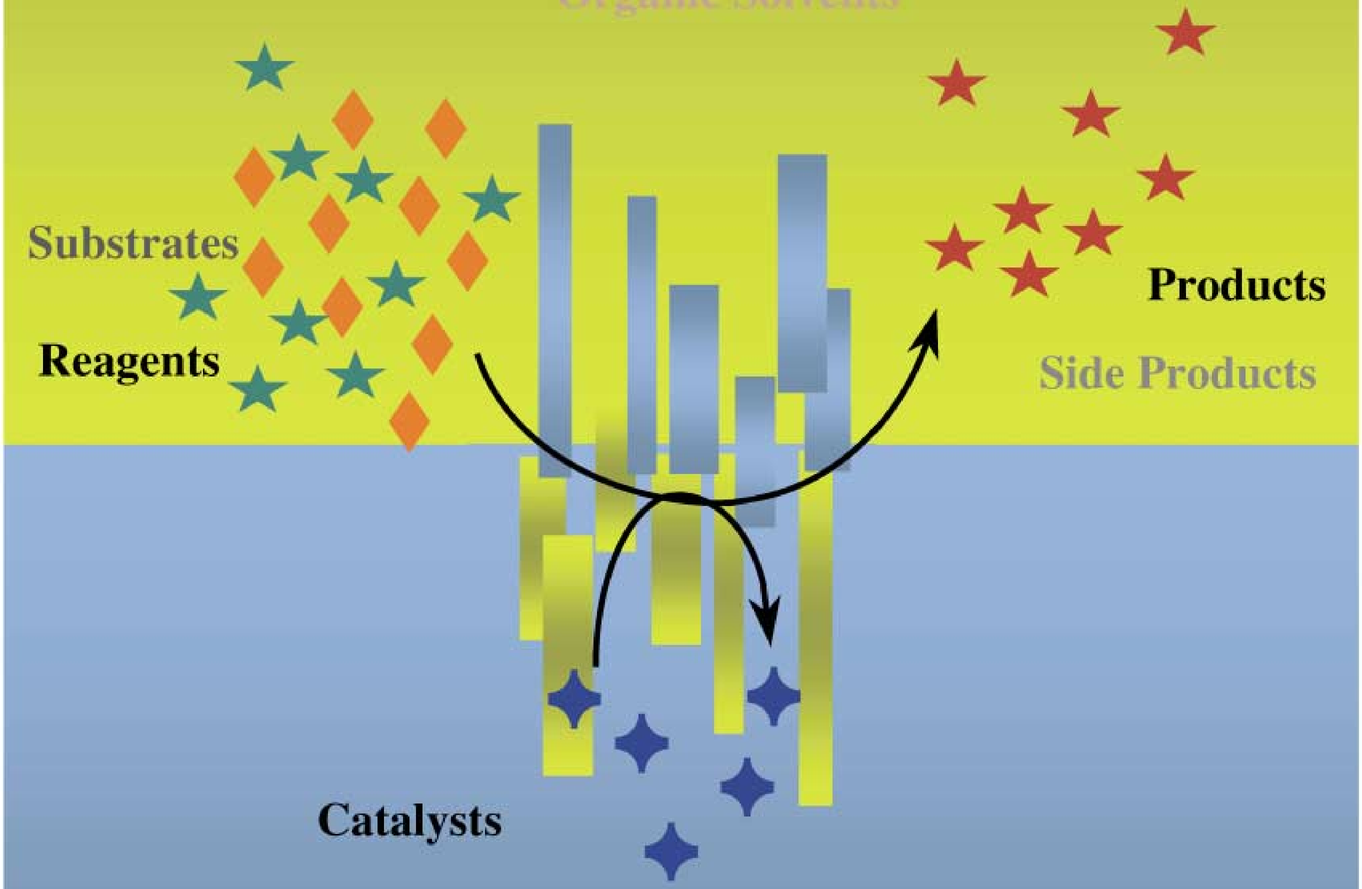
Ionic Liquids

Fluorous Solvents

Supercritical Fluids

Aqueous Solutions

Organic Solvents



Substrates

Reagents

Products

Side Products

Catalysts

Liquid–Liquid Systems

offer a wide variety of separation strategies

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Modern Separation Techniques for the Efficient Workup in Organic Synthesis

Carl Christoph Tzschucke, Christian Markert, Willi Bannwarth,* Sebastian Roller,
André Hebel, and Rainer Haag*

The shift of paradigm in combinatorial chemistry, from large compound libraries (of mixtures) on a small scale towards defined compound libraries where each compound is prepared in an individual well, has stimulated the search for alternative separation approaches. The key to a rapid and efficient synthesis is not only the parallel arrangement of reactions, but simple work-up procedures so as to circumvent time-consuming and laborious purification steps. During the initial development stages of combinatorial synthesis it was believed that rational synthesis of individual compounds could only be achieved by solid-phase strategies. However, there are a number of problems in solid-phase chemistry: most notably there is the need for a suitable linker unit, the limitation of the reaction conditions to certain solvents and reagents, and the heterogeneous reaction conditions. Further disadvantages are: the moderate loading capacities of the polymeric support and the limited stability of the solid support. In the last few years several new separation techniques have been developed. Depending on the chemical problem or the class of compounds to be prepared, one can choose from a whole array of different approaches. Most of these modern separation approaches rely on solution-phase chemistry, even though some of them use solid-phase resins as tools (for example, as scavengers). Several of these separation techniques are based on liquid–liquid phase separation, including ionic liquids, fluorous phases, and supercritical solvents. Besides being benign with respect to their environmental aspects, they also show a number of advantages with respect to the work-up procedures of organic reactions as well as simplicity in the isolation of products. Another set of separation strategies involves polymeric supports (for example, as scavengers or for cyclative cleavage), either as solid phases or as soluble polymeric supports. In contrast to solid-phase resins, soluble polymeric supports allow reactions to be performed under homogeneous conditions, which can be an important factor in catalysis. At the same time, a whole set of techniques has been developed for the separation of these soluble polymeric supports from small target molecules. Finally, miscellaneous separation techniques, such as phase-switchable tags for precipitation by chemical modification or magnetic beads, can accelerate the separation of compounds in a parallel format.

Keywords: biphasic catalysis · combinatorial chemistry · parallel synthesis · polymeric supports · separation techniques

1. Introduction

Combinatorial synthesis[1, 2] is regarded as one of the key disciplines for providing the constant supply of chemical compounds that may be monitored for their biological activity on the vastly increasing number of biological targets. Together with high-throughput screening formats and efficient data management this will undoubtedly lead to an acceleration in the process of drug discovery. The initial focus in combinatorial chemistry was on the rapid synthesis of highly complex mixtures comprising minute amounts of individual compounds. This strategy became prominent because of the ingenious split-and-combine approach and tagging strategies

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to simplify deconvolution once activity on a biological target had been observed. Although this strategy offers a minimum synthetic effort per prepared compound it has been largely substituted by the preparation of individual compounds in amounts of 1–50 mg by the use of parallel synthesis. One reason for this shift of paradigm was the tedious deconvolution process after screening, which resulted quite often in false positives. The individually pure compounds prepared by parallel synthesis can be characterized and stored in easily accessible repositories which contain sets of highly diverse compounds. As a consequence of the high purity of the compounds the screening data are reliable.

During the initial development stages of combinatorial synthesis—possibly biased by the straightforward solid-phase

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Christian Markert was born in 1975 in Freiburg and studied chemistry at the Universität Freiburg from 1995 until 2001, when he completed his Diploma thesis with Prof. W. Bannwarth. During the academic year 1997/98 he studied at UMIST, Manchester (UK), in the group of Prof. S. Holmes. Since March 2002 he has been a PhD student in the research group of Prof. A. Pfalz, Universität Basel (Switzerland).

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synthesis of oligonucleotides and peptides—it was believed that rational synthesis of individual compounds could only be achieved by solid-phase strategies. The main advantage of solid-phase synthesis is that larger excesses of reagents may be applied, thereby driving the reactions to completion. Moreover, the excesses of reagents can be removed after the reaction by simple filtration procedures, thus avoiding time-consuming purification steps. Besides the need for two additional steps involved in chemistry on solid supports, namely the attachment of the starting material and the release of the product, there are a number of difficulties involved in solid-phase chemistry. Most notably there is the need for a suitable linker unit, the limitation of the reaction conditions to certain solvents and reagents, the heterogeneous reaction conditions, the moderate loading capacities (typically $< 1.5\ \mathrm{mmol\,g^{-1}}$), the stability of the solid support, the cumbersome monitoring of the reaction, and the identification of the compounds attached to the solid support. A number of alternative solution approaches and the use of solid-phase-bound reagents and scavengers have emerged because of these difficulties.

The key to a rapid and efficient synthesis is not only the parallel arrangement of reactions, but easy to perform work-up procedures that will circumvent time-consuming and laborious purification steps so that they can be carried out in a parallel fashion. There is no general principle for achieving this goal, but during the last few years several new techniques have been developed. Depending on the chemical problem or the class of compounds to be prepared, one can choose from a whole array of different approaches. In this review we have summarized and compared the latest (since ca. 1999) achievements in this area since the previous review by Curran in 1998.[3] We have also focused on separation techniques which are simple enough that the work-up can be performed in a parallel format and might be suitable for process automation.

2. Liquid–Liquid-Phase Separation

The majority of chemical reactions are carried out in an organic solvent. These solvents can have detrimental effects on the environment and human health as a result of inflammability, volatility, and toxicity. Hence, tremendous efforts have been made during the last decade to replace hazardous organic solvents by alternative reaction media. These encompass water, supercritical media (especially supercritical CO_2), perfluorinated solvents, and ionic liquids. Besides being benign with respect to their environmental aspects, they also show a number of advantages with respect to work-up procedures used in organic reactions as well as simplicity of product isolation.

Ionic liquids and perfluorinated solvents are not miscible with a number of organic solvents. Such combinations can be used to provide biphasic systems for catalysis. In such systems the transition-metal catalyst resides in the second phase (ionic liquid or fluorous phase) whereas the products and starting materials are dissolved in the organic phase. The reactions are carried out under vigorous stirring and/or heating. After the reaction, the layers are reformed and separated by decantation and/or extraction (Figure 1). The catalyst in the ionic liquid or fluorous phase can be reused. The only prerequisite is that the starting materials have to be at least partially soluble in the second phase to guarantee respectable reaction rates. This principle has been demonstrated for a number of catalytic processes. For many applications of reactions in ionic liquids, where the starting material and the product represent liquids themselves, there is no need to add an organic solvent to create the biphasic system. Alternatively, the reaction can be carried out in the ionic liquid and after the reaction it is extracted with an organic solvent to isolate the products. If the products are volatile enough they can be distilled directly from the ionic liquid. In both cases the catalyst remains in the ionic liquid and can be reused. Examples of parallelization and automation in the case of liquid–liquid-phase separation are rare; however, many robotic systems are now able to separate liquid phases which will enhance automation of these techniques in the future.

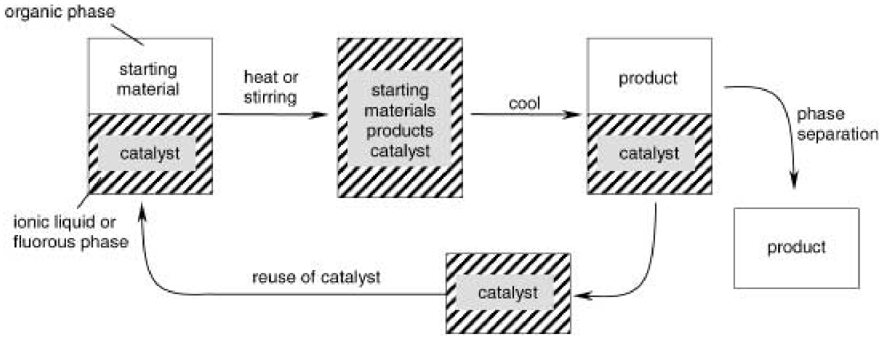


Figure 1. Principle of a simple work-up procedure when using fluorous-phase chemistry or ionic liquids.

2.1. Ionic Liquids

Ionic liquids represent salts with a low melting point ($< 100\,^{\circ}C$). Their vapor pressure is negligible below their decomposition temperatures and, thus, no ionic liquid used as a reaction media is lost by evaporation. Some of the ionic liquids show liquid behavior over a range of several hundred degrees centigrade and thus they can be employed over a wide temperature range.[4–8]

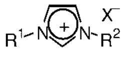
The common classes of ionic liquids comprise: Alkyl ammonium salts (**1**), alkylphosphonium salts (**2**), *N,N'*-dialkyl

$[NR_nH_{4-n}]^+\ X^-$

1

$[PR_nH_{4-n}]^+\ X^-$

2



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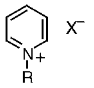


4 X^- = counterion

imidazolium salts (**3**), and *N*-alkyl pyridinium salts (**4**), of which the *N,N'*-dialkyl imidazolium salts have attracted particular attention since they are easily prepared and are liquid over a wide range of temperatures.

Ionic liquids have been used as solvents for numerous organic and inorganic reactions. The physical and chemical properties vary depending on the combination of cation and anion. Hence, their properties can be modulated and adapted to the chemical reaction for which the ionic liquid is envisaged by varying the anions and cations. Ionic liquids composed of weakly coordinating ions represent highly polar, yet noncoordinating solvents. The solvent properties are largely determined by their ability to act as a hydrogen-bond donor or acceptor and the degree of delocalization of the anionic charge. Their ability to form hydrogen bridges also has an influence on the viscosity of the ionic liquids. A low tendency to form hydrogen bridges occurs in parallel with low viscosity. Variation of the chain length of the alkyl substituents on the cation or anion allows the lipophilicity to be adjusted. Increased chain lengths lead to higher lipophilicity.

A number of ionic liquids are air and moisture stable and are relatively easy to handle. Some of them, for example, most of the imidazolium and ammonium salts, are hygroscopic and reactions involving these ionic liquids are best carried out under an inert atmosphere. The nature of the pertinent anion not only has an affect on the melting behavior (Table 1) and the handling properties, it also affects the stability as well as the acidity of the ionic liquid.

Table 1. Effect of the anion on the melting point of $[EMIM]^+X^-$.[a]

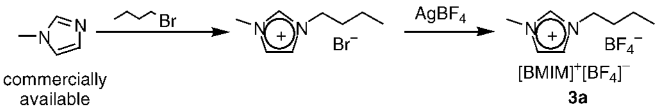
$[X]^-$	M.p. [°C]
Cl^-	87
NO_3^-	55
$AlCl_4^-$	7
BF_4^-	6
$CF_3SO_3^-$	−9

[a] EMIM = 1-ethyl-3-methylimidazolium.

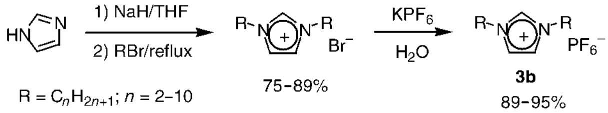
Salts with NO_3^-, $PhSO_3^-$, and $N(SO_2CF_3)_2^-$ counterions are air and moisture stable, while $AlCl_4^-$ salts are hygroscopic and moisture sensitive. Salts with $Al_2Cl_7^-$ counterions show acidic behavior which can have a beneficial effect on activation the catalysts used in ionic liquids. Recently, it was reported that the combination of dicyanamide (dca) anions with cations of the type **1**, **3**, and **4** gave ionic liquids with low viscosity and water miscibility. Furthermore, these ionic liquids show donor characteristics as a consequence of the ligand properties of the anion.[9]

2.1.1. Synthesis of Ionic Liquids

Ionic liquids are prepared starting from the corresponding amine or phosphane in a two-step procedure. Alkylation leads to quarternization of the nitrogen or the phosphorus atom, respectively. This process is usually followed by anion metathesis with an alkali or ammonium salt of the desired anion. This principle is illustrated in Scheme 1 for the preparation of $[BMIM]^+[BF_4]^-$ (**3a**, BMIM = 1-*n*-butyl-3-methylimidazolium).[10, 11] Alternatively, the anion exchange can be achieved by using an ion-exchange resin. If after the alkylation step the anion is a halogenide, it can also react with a Lewis acid to create the desired anion (for example, $AlCl_4^-$). It has been postulated for a long time that the unsymmetrical nature of the cation plays a major role in the low melting point of imidazolium-derived ionic liquids. Recently it was demonstrated that symmetrical imidazolium salts such as **3b** are also room-temperature ionic liquids (Scheme 2).[12]



Scheme 1. Preparation of $[BMIM]^+[BF_4]^-$ (**3a**).



Scheme 2. Synthesis of the C_2-symmetrical ionic liquid **3b**.

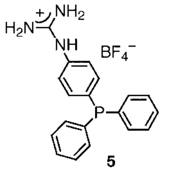
High purity of ionic liquids is of prime importance for achieving reliable synthesis in these media. Therefore, all the steps involved in their preparation have to proceed with high efficiency, since purification after synthesis is extremely tedious. Some of the ionic liquids, especially the ones with imidazolium as the cation, are commercially available. Their price is still very high, which to a certain extent prevents their application for routine synthesis.

2.1.2. Work-Up and Isolation Procedures

The beneficial effects of ionic liquids in regard to environmental aspects that result from their nonvolatility has already been alluded to in Section 2.1. In addition to that, ionic liquids allow for simple work-up procedures and straightforward isolation protocols for products, particularly with respect to transition-metal catalysis.

Ionic liquids with noncoordinating anions represent highly polar organic solvents that dissolve polar transition-metal complexes without usually affecting their properties. In general, they allow immobilization of the complex in the ion liquid without modification of the ligands. In a number of cases, ionic liquids have a beneficial effect on the catalytic reaction, which proceeds more efficiently than in organic solvents. Under these circumstances the ionic liquid acts not only as a solvent but also as a co-catalyst. The reason for this may be a better stabilization of the transition state or activation of the catalyst (as a result of the Lewis acidity of the ionic liquid)[13] or the formation of carbene-like ligand structures.[14]

In applications where the starting material and the product represent liquids themselves, there is no need to add an organic solvent to create the biphasic system. This was demonstrated for the hydrogenation of olefins.[10, 15] Alternatively, the reaction can be carried out in the ionic liquid and the product is isolated by extraction with an organic solvent. The products can be distilled directly from the ionic liquid if they are sufficiently volatile. In both cases the catalyst remains in the ionic liquid and can be reused. In some examples a small leaching of the catalyst out of the ionic liquid into the organic layer was observed. This effect can be minimized by modification of the ligands with ionic groups as shown in the P^{III} ligands **5**–**7**.[16]



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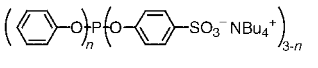

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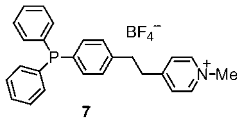

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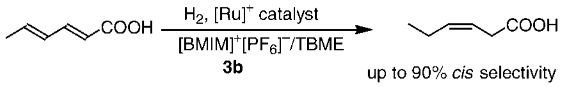
Ionic liquids as reaction media allow for parallel arrangements of reactions followed by straightforward isolation of the products and hence for the rapid synthesis of compounds. So far, this potential has not yet been exploited. This is because of the still limited number of types of reactions which have been carried out in ionic liquids and because of the relatively high costs involved.

2.1.3. Homogeneous Catalytic Reactions in Ionic Liquids

2.1.3.1. Hydrogenations

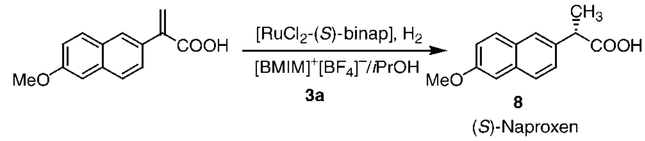
There are a number of catalysts available for homogeneous hydrogenations. In the first reported examples of homogeneous hydrogenations involving ionic liquids the starting material and the product represented highly lipophilic liquids (for example, hydrogenation of hexene or cyclohexene) in which the polar catalyst was immobilized without any modification in the ionic liquid and no additional organic solvents were necessary for the isolation of the product. The solubility of hydrogen in ionic liquids seems to be high enough to obtain respectable reaction rates.[10, 15]

Recently, an interesting example of stereoselective hydrogenation in a biphasic system consisting of $[BMIM]^+[PF_6]^-$/TBME was reported to give high selectivity for *cis*-3-hexanoic acid (Scheme 3).[17]



Scheme 3. Stereoselective hydrogenation in **3b**/TBME to give *cis*-3-hexanoic acid.

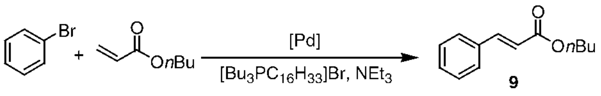
Enantioselective hydrogenation in biphasic systems formed by ionic liquids and organic solvents is also possible. This was first demonstrated for the hydrogenation of acetamidocinnamic acid in a mixture of $[BMIM]^+[BF_4]^-$/isopropanol to give (*S*)-phenylalanine (64% *ee*).[15] The same biphasic system was applied to the hydrogenation of aryl acrylic acids with a [Ru-binap] catalyst as illustrated in the preparation of (*S*)-naproxen (**8**, Scheme 4).[18] The catalyst was reused after phase separation and isolation of the product.



Scheme 4. Preparation of (*S*)-naproxen by hydrogenation in **3a**/*i*PrOH.

2.1.3.2. Carbon–Carbon Coupling Reactions

Pd-catalyzed carbon–carbon bond forming reactions have received considerable attention as a consequence of their enormous synthetic potential. The Heck reaction in particular has found widespread application for the synthesis of olefins by Pd-mediated vinylation of aryl halides. The reaction is best performed in polar organic solvents such as DMF or NMP. A relatively large amount of catalyst (> 1 mol%) is required for satisfactory conversions and recycling of the catalyst is hampered by decomposition. It was reported that these shortcomings could be overcome by use of an ionic liquid. The first example involved the coupling of bromobenzene with *n*-butyl acrylate to yield *trans*-cinnamic *n*-butyl ester **9** in tetraalkyl ammonium- and tetraalkyl phosphonium derived ionic liquids of type **2** (Scheme 5).[19] The ionic liquid was reported to have a stabilizing effect on the Pd catalyst such that it could be reused for several consecutive runs.



Scheme 5. Heck reaction leading to *trans*-cinnamic *n*-butyl ester.

The same reaction was also carried out in $[BMIM]^+[PF_6]^-$ as the solvent and $Pd(OAc)_2$ or $PdCl_2$ as the catalyst with NEt_3 as the base. The products were isolated by extraction with hexane and the catalyst could be reused several times.[20] It was also demonstrated that Pd/C and NEt_3 could also be used successfully as the reusable catalyst and base, respectively.[21] Böhm and Herrmann have investigated the Heck reaction in ionic liquids in great detail and have shown impressively the advantages of ionic liquids over conventional solvents. A striking feature is the stabilization and the activation of the Pd catalyst: even $Pd(OAc)_2$ or $Pd(PPh_3)_4$ can be used in the absence of additional phosphanes to couple chloroarenes. The products were either extracted or distilled from the ionic liquid and the catalyst was used for several consecutive runs.[22]

Xiao and co-workers found that Heck reactions carried out in $[BMIM]^+Br^-$ proceeded more efficiently and gave a higher selectivity for the *trans* product than those carried out in $[BMIM]^+[BF_4]^-$.[14] The in situ formation of heterocyclic carbene complexes by deprotonation of BMIM-derived ionic liquids was proposed to explain this finding (Figure 2a). Calò et al. used Pd–benzothiazole carbene complexes directly for Heck reactions in tetrabutylammonium bromide (TBAB;

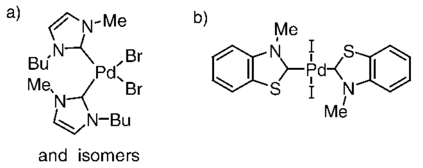
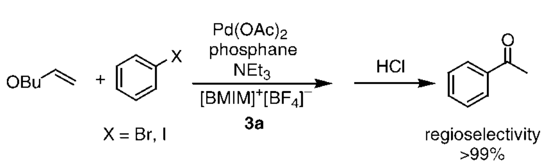


Figure 2. Pd–carbene complexes formed in situ in ionic liquids.

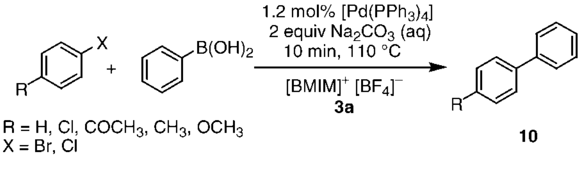
Figure 2b. They demonstrated that very fast and efficient couplings occurred, especially for the preparation of β,β-diaryl acrylates. Recycling of the catalyst was impaired and only three consecutive runs could be performed.[23, 24]

The Heck arylation of electron-rich olefins such as enol ethers leads to a mixture of regioisomers. Regioselective substitution at the olefinic carbon atom α to the oxygen atom can only be achieved when aryl halides are replaced by the corresponding triflates or when a stoichiometric amount of silver triflate or thallium acetate is added. Aryl halides can be transformed in $[BMIM]^+[BF_4^-]$ and the reaction proceeds with high efficiency and high regioselectivity (Scheme 6). The ionic liquid not only promotes the ionic pathway of the Heck reaction to give the α-arylated product but leads at the same time to an acceleration of the reaction.[25] Recently, it was demonstrated that under ultrasonic irradiation the Heck reaction in ionic liquids proceeds at ambient temperature (30 °C) with reaction times of 1.5–3 h.[26] The products were separated from the catalyst by extraction with 10% ethyl acetate in petroleum ether and purified by chromatography. The catalyst could be reused at least three times.



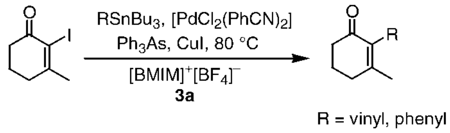
Scheme 6. Heck reaction for the regioselective formation of acetophenone.

The first example of Suzuki cross-coupling reactions in $[BMIM]^+[BF_4]^-$ was reported recently (Scheme 7).[27] Compared to standard protocols for Suzuki couplings, a significantly increased activity of the applied $[Pd(PPh_3)_4]$ complex was observed during the formation of the desired biphenyl derivatives **10**. Only minimal formation of the homocoupling product could be detected, which simplified the work-up. The desired products were obtained by extraction with diethyl ether, by sublimation, or precipitation after the addition of water, with no leaching of the catalyst into the product. The catalyst was recycled at least three times without loss of activity. Suzuki coupling reactions in ionic liquids could also be promoted by ultrasound irradiation to proceed at ambient temperature.[28]



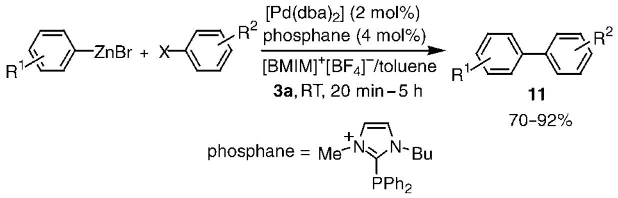
Scheme 7. Suzuki coupling in **3a**.

Stille couplings were also reported (Scheme 8).[29] The products were isolated by extraction with diethyl ether and the $[BMIM]^+[BF_4]^-$ catalyst could be recycled five times with no (for Pd^{II} systems) or only a slight loss in activity (for Pd^0 systems). In addition, the ionic-liquid layer was stored for several weeks after extraction with no special precautions to exclude air or moisture, and gave the same coupling yields as a freshly prepared catalyst solution.



Scheme 8. Stille coupling in **3a**.

The Negishi coupling of organozinc compounds and aryl iodides was demonstrated in a two-phase system composed of $[BMIM]^+[BF_4]^-$ and toluene (Scheme 9).[30] In most cases the reaction proceeded within a few minutes at room temperature and led to the desired cross-coupling products **11**. Aryl bromides and aryl nonaflates required longer reaction times. After the reactions the ionic liquid containing the catalyst was separated from the toluene by decantation and was reused for subsequent coupling reactions. After the third cycle a significant decrease in the yield was observed.



Scheme 9. Negishi coupling in **3a**.

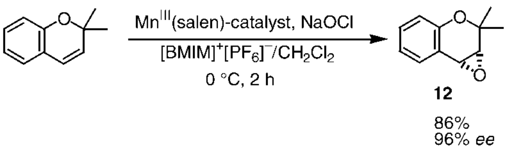
The homocoupling of aryl halides in $[BMIM]^+[PF_6]^-$ with $[(PPh_3)_nNi^0]$ as the catalyst was reported recently.[31] The desired biaryls were obtained in moderate to good yields after extraction with diethyl ether. The catalyst was recycled but in the second run a decrease in activity was already observed.

The Pd^0-catalyzed formation of C–C bonds by allylic nucleophilic substitution with C nucleophiles (Tsuji–Trost coupling) was also performed in ionic liquids. In the reaction of malonic acid derivatives with 3-acetoxy-1,3-diphenylprop-1-ene, the anion was formed with K_2CO_3 or DBU directly in $[BMIM]^+[BF_4]^-$ and the coupling products were obtained in high yields.[32] The recycling of the catalyst was only possible after replacement of PPh_3 by the more polar phosphane $P(m\text{-}C_6H_4SO_3Na)_3$ and reactions could be performed three times. The Tsuji–Trost coupling of ethyl cinnamyl carbonate and ethyl acetoacetate was carried out in a biphasic system of $[BMIM]^+Cl^-$/methyl cyclohexane.[33] The reaction proceeded more efficiently than in water/organic biphasic mixtures and the coupling product was isolated in a yield of 90%. The recycling was hampered by the high solubility of the product in the ionic liquid.

In summary, it can be stated that ionic liquids are ideal media to perform Pd-mediated C–C couplings. In most cases the catalyst can be fixed in the ionic liquid without modification of the ligands. The work-up is easily performed and the products can be separated from the catalyst in the ionic liquid by using lipophilic solvents such as diethyl ether. Both the catalyst and the ionic liquid can be recycled. Ionic liquids can stabilize the Pd catalyst and cause activation, and even unreactive aryl halides can be used. They also allow for the application of "cheap" Pd compounds, such as $PdCl_2$, and the expensive Cs_2CO_3 can often be replaced by less expensive bases.

2.1.3.3. Oxidations

Although a number of ionic liquids are fairly stable towards oxidation, there have been only a very limited number of reports on oxidations in biphasic systems involving ionic liquids. One example is the stereoselective epoxidation using Jacobsen's chiral [Mn^{III}(salen)] complex in a mixture of $[BMIM]^+[PF_6]^-$ and CH_2Cl_2 in a ratio of 1:4 (Scheme 10).[34] A considerable activation of the catalyst by the ionic liquid was reported. The catalyst was recycled five times and a only small decrease in yield and in *ee* values of **12** was observed. Another epoxidation of alkenes and allyl alcohols in $[EMIM]^+[BF_4]^-$ using methyl trioxorhenium (MTO) and urea/H_2O_2 was reported recently.[35] Excellent conversions and selectivities were obtained for a number of substrates. The reaction was performed in a homogeneous fashion since MTO as well as urea/H_2O_2 are completely soluble in $[EMIM]^+[BF_4]^-$. The oxidation solution was anhydrous, and opening of the epoxides to form the diols did not occur. Since MTO as well as the ionic liquid are not soluble in diethyl ether, the remaining reactants and products were isolated by extraction with diethyl ether after the reaction.



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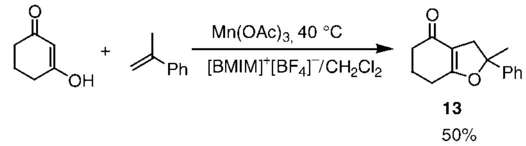
Scheme 10. Stereoselective epoxidation by using the chiral Jacobsen [Mn^{III}salen] complex.

Oxidations of aromatic aldehydes to the corresponding carboxylic acids were carried out in $[BMIM]^+[PF_6]^-$ with oxygen at atmospheric pressure and [Ni(acac)$_2$] (acac = acetyl acetonate) as the catalyst.[36] The yields were lower than the ones obtained for the same type of oxidations carried out in perfluorinated solvents with perfluoroalkyl-tagged acac ligands of Ni^{2+} complexes.[37] The ionic liquid $[BMIM]^+[BF_4]^-$ was used in the oxidation of codeine methyl ether to thebaine with MnO_2.[38] The yield was rather low when the oxidation was carried out directly in the ionic liquid with sonication. Performing the oxidation in THF under sonication followed by selective extraction of MnO_2 and other inorganic byproducts enabled thebaine to be isolated in high yield.

Carbonyl compounds such as *β*-diketones or *β*-ketoesters can be oxidized with $Mn(OAc)_3$ to form radicals which can then undergo carbon–carbon bond-forming reactions. The reaction has to be carried out under harsh conditions which limits its scope of application severely. It was demonstrated that performing the reactions in $[BMIM]^+[BF_4]^-/CH_2Cl_2$ yielded the desired products **13** in respectable yields (Scheme 11).[39] At the end of the reaction the $Mn(OAc)_2$ was recovered by precipitation and after filtration it was reoxidized by $KMnO_4$ and reused. The ionic liquid was also recycled without detriment to the product yields.



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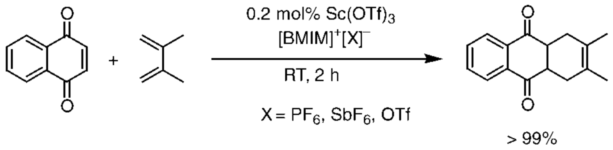
Scheme 11. $Mn(OAc)_3$ oxidations leading to C–C bond formations.

2.1.3.4. Diels–Alder Reactions

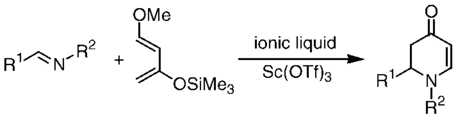
Several authors have investigated Diels–Alder reactions in ionic liquids. The first reported example was the cycloaddition of cyclopentadiene with crotonaldehyde or methacrolein as dienophiles in dialkyl imidazolium salts as ionic liquids.[40] The results clearly demonstrated that the ionic liquid acted as a Lewis acid which allowed the reaction to be performed at low temperature and which led to a high *endo*:*exo* selectivity. These results were confirmed later for the same type of diene and dienophiles.[41–43] A recycling of the ionic liquid was demonstrated as well.

An impressive study on Diels–Alder reactions was reported recently in which a number of different dienophiles were treated with a selection of dienes in $[BMIM]^+[X]^-$ in the presence of 0.2 mol% $Sc(OTf)_3$ (an example is shown in Scheme 12).[13] The reaction proceeded with high yields with PF_6^-, SbF_6^-, and OTf^- counterions. The type of anion had only little effect on the catalytic activity. The *endo*:*exo* selectivity was generally higher than for the same reaction in CH_2Cl_2. After completion of the reaction and extraction of the product with diethyl ether, the ionic liquid phase containing the $Sc(OTf)_3$ was recovered. The ionic-liquid phase was reused 11 times without any loss of activity.



Scheme 12. Diels–Alder reaction in an ionic liquid catalyzed by $Sc(OTf)_3$.

Recently, aza-Diels–Alder reactions for the preparation of 6-aryl-5,6-dihydro-4-pyridones (**14**) in ionic liquids were reported (Scheme 13).[44] The imine dienophiles were prepared in situ from the aldehyde and the amine directly in the ionic liquid. The ionic liquid used was 8-ethyl-1,8-diazabicyclo[5.4.0]-7-undecenium trifluoromethanesulfonates. The yield could be increased significantly by the addition of $Sc(OTf)_3$ in a microencapsulated form. The products were isolated by extraction with diethyl ether and the ionic liquid together with the microencapsulated Lewis acid were reused. The same high yields as observed in the first run were obtained.



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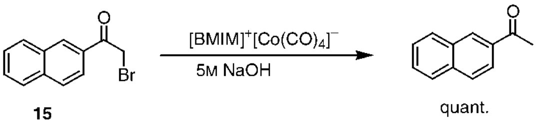
Scheme 13. Aza-Diels–Alder reaction in ionic liquids.

2.1.3.5. *Miscellaneous Reactions*

In the last few years an increasing number of reports have appeared on synthetic methods which take advantage of the favorable properties of ionic liquids. Among the reported reactions are hydroformylations in $[BMIM]^+$-derived ionic liquids in which the aldehydes are formed in remarkably high *n*/*iso* ratios,[45] [Cr(salen)]-catalyzed ring-opening reactions of epoxides with $TMSN_3$,[46] electrophilic nitrations of aromatic compounds,[47] the Biginelli multicomponent reaction for the preparation of 3,4-dihydropyrimidin-2-(1*H*)-ones,[48] and nucleophilic displacement reactions.[49]

It was outlined in Section 2.1 that the anion of the ionic liquid may also be catalytically active, as observed for example with chloroaluminate anions which can act as Lewis acids. An interesting example in this respect is the application of $[BMIM]^+[Co(CO)_4]^-$ as both solvent and reagent for the debromination of 2-bromoketones **15** (Scheme 14).[50]



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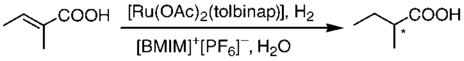
Scheme 14. Debromination of 2-bromoketones in/with $[BMIM]^+[Co(CO)_4]^-$.

2.1.3.6. *Combination of Ionic Liquids and Supercritical CO_2*

Recently, the combination of an ionic liquid and supercritical carbon dioxide ($scCO_2$) has emerged as a new system for biphasic homogeneous catalysis. Supercritical CO_2 is soluble in ionic liquids and decreases their viscosity, thereby enhancing the mass transfer. On the other hand, ionic liquids are not particularly soluble in $scCO_2$. Hence, nonvolatile compounds can be extracted quantitatively out of ionic liquids by $scCO_2$ without any contamination. This was first demonstrated by the extraction of naphthalene from $[BMIM]^+[PF_6]^-$ by $scCO_2$.[51] Recently, the system was applied to batch-wise asymmetric hydrogenation (Scheme 15). The product was extracted out of the ionic liquid by $scCO_2$ after the reaction and the catalyst could be reused for four further runs.[52, 53]



Scheme 15. Asymmetric hydrogenation in an ionic liquid followed by extraction with $scCO_2$.

Another example was reported for the batch-wise hydrogenation of CO_2 and alkenes using Wilkinson's catalyst.[54] Hydroformylation reactions[55] and the Ni-catalyzed hydrovinylation of styrene were reported.[56] More recently, the ionic liquid/$scCO_2$ system was extended to continuous flow processes.[57, 58]

2.2. Perfluorinated Systems

Since the seminal work by Vogt[59] and by Horváth and Rábai[60] perfluorinated solvents and compounds with fluorous labels have emerged as powerful tools in synthetic organic chemistry. Not surprisingly, fluorous systems (Fluorous Biphasic System, FBS) have been the subject of several recent reviews.[61–66]

Perfluoroalkanes and—to a certain degree—perfluorinated ethers and amines show a very low miscibility with common organic solvents. The miscibility is temperature dependent and increases with increasing temperature.[67] This phase behavior can be employed to separate molecules with complementary solubilities in organic and fluorous solvents.[68] Perfluorinated solvents are exceedingly hydrophobic and chemically inert. They are considered to be of low toxicity and they are thought to have no ozone-depletion potential, although they do exhibit long atmospheric lifetimes (>2000 years), which makes them potent greenhouse gases. This situation should be taken into account when using or disposing of perfluorinated solvents.[69]

According to the alchemists rule "similia similibus solvuntur" the solubility of a compound in perfluorinated solvents can be enhanced by attaching long perfluoroalkyl chains (perfluoro tags) to the molecule. The assumption that a fluorine content exceeding 60% (of the molecular weight) is needed to gain differential solubility in fluorous solvents has been reiterated in the literature. This value cannot be more than a rough approximation, since solubilities and partitioning coefficients are dependent on a number of structural features.[70–72] In general, the preferential relative solubility in the fluorous solvent is augmented as the length and number of perfluoroalkyl chains attached to it increase and the polarity of the molecule decreases. However, the absolute solubility of the compound drops as the length of the perfluoroalkyl chains increases. On the other hand common organic compounds, even very unpolar ones such as *n*-alkanes, show very low partitioning into the fluorous phase.

As mentioned above, the immiscibility of fluorous and organic solvents in conjunction with the differential solubilities can be used to separate molecules with a fluorous label from unlabeled compounds. This possibility leads to a multitude of different separation and purification strategies. The common denominator is that one specific component with a fluorous label (for example, catalyst, reagent, by-product, product) is preferentially soluble in the fluorous phase, while the other components of the reaction mixture (product, starting material, reagents, impurities) are soluble in the organic layer. Depending on the application and the partitioning coefficients, the separation can be performed as a conventional liquid–liquid extraction, as a continuous extraction, or as a solid-phase extraction with fluorous reversed-phase silica gel (FRPSG).[73]

In principle, fluorous techniques are similar to other phase-labeling strategies, such as those based on water-soluble reagents or catalysts and solid-phase-bound reagents, catalysts, or substrates. The logic governing such separation strategies has been reviewed.[3]

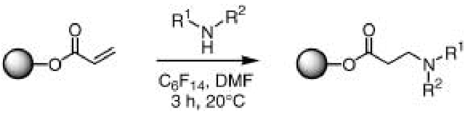
2.2.1. *Perfluorinated Solvents as Reaction Media*

Perfluorinated solvents have found only limited use as reaction media because of their low solvating power. However, this very low miscibility with organic compounds means that products are readily isolated by simple decantation. A perfluorinated solvent can be used to azeotropically remove reaction products and thus shift the equilibrium of the reaction. This principle was demonstrated by Zhu for esterifications and transesterifications as well as for acetal and enamine formation by using a modified Dean–Stark apparatus.[74]

Another interesting feature is the high solubility of gases in perfluorinated solvents;[75] since large amounts of oxygen are soluble they have also been tested as blood substitutes.[76–79] For the same reason they receive attention as reaction media for oxidations. Klement and Knochel have described the oxidation of alkyl zinc compounds to hydroperoxides with molecular oxygen in perfluorohexanes, while mixtures of hydroperoxides and the corresponding alcohols are obtained by the direct oxidation of organometallic compounds in common solvents.[80] Trialkyl boranes have been oxidized to alcohols in a similar manner.[81]

A fluorous biphasic system has been used to spatially separate catalysts in a cascade of ring-closing metathesis (RCM) and a Heck reaction.[82] The RCM was performed at room temperature with the Grubbs catalyst. Since the Grubbs catalysis is not compatible with either palladium acetate nor phosphane ligands, a perfluoro-tagged triphenylphosphane was used. At room temperature the solvent system is biphasic, and the RCM proceeds in the organic phase with the palladium complex residing in the fluorous phase. The mixture becomes homogeneous upon heating and the Heck reaction is catalyzed by the palladium complex. Results obtained with the fluorous phosphane were better than those with a nontagged phosphane, but were not as good as with solid-phase-bound phosphane.

An interesting concept in solid-phase organic synthesis is the use of perfluorinated solvents to accelerate reactions with substrates bound to a polystyrene resin. As a consequence of the low solvating power of the fluorous solvent, the reagent is confined to the resin, thus increasing the local concentration. A small amount of polar cosolvent is needed, possibly to swell the resin (Scheme 16).[83]



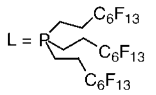
Scheme 16. Increase of the local substrate concentration within the resin by a perfluorinated solvent.

2.2.2. *Perfluoro-Tagged Catalysts*

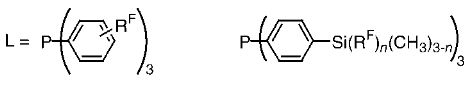
The main field of application for fluorous separation strategies is in fluorous biphasic catalysis (FBC). The catalyst is modified with a fluorous tag, and thus can be removed from the product by extraction with a fluorous solvent. At the beginning of the reaction the perfluoro-tagged catalyst together with the substrate and reagents is present in a biphasic mixture of fluorous and organic solvent. The reaction can proceed either in a heterogeneous fashion with the catalyst in the fluorous phase and the other reactants in the organic phase, or under homogeneous conditions if the reaction temperature is high enough for the biphasic mixture to become monophasic.[84] Upon completion of the reaction, the mixture is cooled to restore the biphasic system. Ideally, the catalyst now remains exclusively in the fluorous layer, while all the product is dissolved in the organic phase. The phases are separated to yield products free of catalyst contaminations, and the fluorous layer containing the catalyst, which can be reused for further reactions.

The importance of such catalyst systems lies mainly in the field of combinatorial synthesis and industrial processes. FBC represents a way to simplify work-up and purification in parallel synthesis to give easy extraction procedures, which even allow for automation. This possibility avoids difficult purification procedures such as chromatography or distillation, which would hamper parallel work-up. Thus, compound libraries can be prepared for high-throughput screening. Products without heavy-metal contaminations, which could impair biological assays, are especially important for such applications. In addition to simplified purification, the option of catalyst recycling plays an important role in industrial processes. Expensive catalysts contribute significantly to the cost of a product. Recycling of such a catalyst as well as a simplified product isolation can greatly reduce the costs of a process. To date, a growing number of catalysts has been modified with perfluoro tags (see for example, structures **16**–**20**).

16: $[HRh(CO)L_3]$

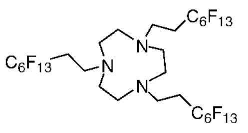


17: $[PdL_2Cl_2]$



17a: R^F = 4-$CH_2CH_2C_8F_{17}$
17b: R^F = 4-C_8F_{17}
17c: R^F = 3-$CH_2CH_2C_8F_{17}$
17d: R^F = 3-C_8F_{17}
17e: R^F = 4-$OCH_2C_7F_{15}$

R^F = $CH_2CH_2C_6F_{13}$
$CH_2CH_2C_8F_{17}$



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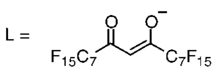
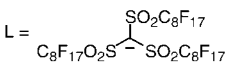
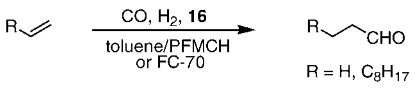
19a: $[NiL_2]$
19b: $[PdL_2]$
19c: $K[RuL_3]$



20: $[LaL_3]$

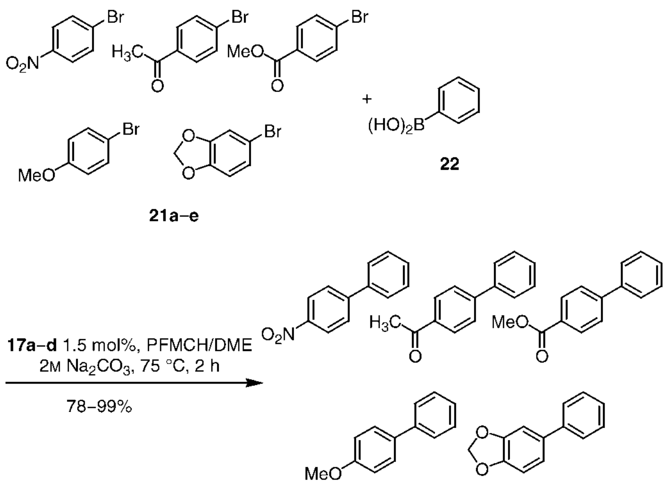


The hydroformylation of terminal olefins was among the first reactions to be performed in FBC.[60, 85] The hydroformylation of 1-decene catalyzed by rhodium complex **16** was studied in detail (Scheme 17). A total turnover number exceeding 35000 with a loss of only 1.18 ppm rhodium per mole of undecanal was achieved in nine consecutive runs using the same fluorous phase containing the catalyst. In the continuous hydroformylation of ethene the resulting propanal was distilled from the high-boiling fluorous phase. No loss of catalyst activity was detected over 60 days. Similar rhodium catalysts have been used for hydrogenations,[86] hydroborations,[87, 88] and hydrosilylations of olefins[89, 90] in fluorous biphasic systems.



Scheme 17. Hydroformylation with an in situ generated fluorous rhodium catalyst.

Hydrogenation of olefins was also achieved with dendrimer-encapsulated palladium nanoparticles that were soluble in fluorous phases.[91] A bimetallic rhodium catalyst was used in the cyclopropanation of alkenes and recovered by fluorous extraction.[92] The palladium-catalyzed C–C bond-forming reactions that have been performed in fluorous biphasic systems include the Heck reaction,[93] benzannulation of conjugated enynes,[94] palladium-catalyzed allylic substitution[95, 96] as well as Negishi,[97] Stille,[98] Suzuki,[99] and Sonogashira reactions.[100] The Suzuki coupling of five different aryl bromides **21** with phenylboronic acid (**22**) was carried out with four different palladium complexes (**17a–d**, Scheme 18).[99] The fluorous phase was extracted with DME and water and the catalysts reused five times without any loss of activity. The yields of the biaryls were generally high and independent of the phosphane employed.



Scheme 18. Suzuki coupling in PFMCH/DME.

Numerous oxidation reactions have been carried out under fluorous biphasic conditions because of the good solubility of oxygen in perfluorinated solvents. Alcohols were oxidized to aldehydes or ketones with molecular oxygen by using a catalyst system of CuBr, perfluoroalkyl-tagged bipyridine, and 2,2,6,6-tetramethylpiperidine-*N*-oxide (TEMPO). Yields were high for benzylic alcohols, and in one example the catalyst was recovered and reused eight times without any significant decrease in yield.[101] A variety of alcohols was oxidized to aldehydes or ketones with palladium(II) acetate and perfluoro-tagged pyridines as ligands.[102] Although only a small amount of leaching of palladium was observed, the catalytic activity in consecutive runs could be retained only if a small amount of additional ligand was added before every other run.[103]

A series of fluorous *β*-diketonates **19** of transition metals were prepared.[104] Nickel complex **19a** was used in the aerobic oxidation of aldehydes to carboxylic acids[37] as well as in combination with *i*PrCHO and oxygen for the oxidation of sulfides to sulfoxides or sulfones.[37] This oxidation could also be catalyzed by cobalt complexes with perfluoro-tagged porphyrin or phtalocyanin ligands, but recycling of the catalyst was unsuccessful.[105] Palladium complex **19b** was used as the catalyst for the oxidation of terminal olefins to methyl ketones with *tert*-butylhydroperoxide (TBHP) as oxidant.[106] Oxidation of cyclohexene to cycohexenol and cyclohexenone was achieved with a manganese complex with ligand **18** using oxygen and substoichiometric amounts of TBHP as the oxidant.[107, 108]

Selective epoxidation reactions of internal olefins in the presence of terminal double bonds was achieved by the use of ruthenium complex **19c** and excess *i*PrCHO/oxygen.[37] The epoxidation of olefins has also been catalyzed by perfluoro-tagged cobalt–porphyrin complexes.[109] Asymmetric epoxidations were achieved with perfluoro-tagged manganese–salen complexes.[110–112] A fluorous aryl selenic acid catalyst for the epoxidation of olefins with hydrogen peroxide could be recycled ten times without loss of catalytic activity.[113]

Friedel–Crafts acylations and other Lewis acid promoted reactions were carried out in FBS using fluorous lanthanide methides **20**. High yields were reported, and the Lewis acid was quantitatively recovered by phase separation and reused in several consecutive runs.[114, 115]

Fluorous tin oxides have been used in transesterifications[116] and in the monotosylation of 1,2-diols.[117] The enantioselective addition of diethylzinc to aldehydes has been performed with different perfluoro-tagged catalysts.[118–121]

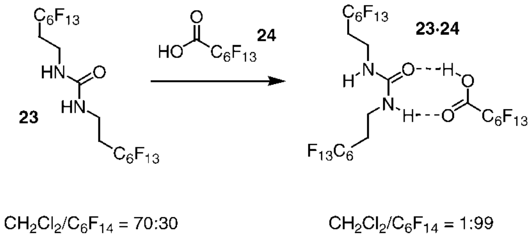
Recently, Gladysz and co-workers employed the fluorous phosphane $P(CH_2CH_2C_8F_{17})_3$ as catalyst for the addition of alcohols to the triple bond of methyl propiolate:[122] During the reaction, the phosphane was dissolved in octane at 65 °C. Subsequently, the catalyst was precipitated at −30 °C and separated by decantation. No fluorous solvent was needed.

2.2.3. *Perfluoro-Tagged Reagents*

After any reaction, chemists are faced with the problem of isolating the product. This is done by exploiting more- or less-pronounced differences in the physical properties of product and impurities. Simple purification procedures are needed in combinatorial syntheses of libraries for high-throughput screening.[123] Furthermore, the procedure should be the same for every compound of a library to allow for automation and parallel synthesis. Similar to the situation of catalysis described in Section 2.2.2, perfluoro-tagged reagents can be used to easily separate reaction by-products and excess reagents from the product. This is achieved either by extraction with a fluorous solvent or by filtration over FRPSG. The resulting solution should now contain only organic molecules while the fluorous phase retains the perfluoro-labeled reagent. Therefore, a large excess of reagent can be used to ensure complete conversion.[124] This approach is especially attractive if reagents or by-products are toxic, expensive, or difficult to remove. The strategy is similar to the use of solid-phase-bound reagents, but since the fluorous reagents are individual soluble molecules their behavior is closer to conventional soluble compounds, and under appropriate conditions the reaction can proceed homogeneously.

The use of trialkyl tin reagents and selenium compounds has been limited by their toxicity. Fluorous tin reagents have been used in radical dehalogenations,[125] in the allylation of aldehydes,[126, 127] and in Stille coupling reactions.[128] Fluorous tin azide was used in the synthesis of tetrazoles.[124] Perfluoro-tagged aryl selenium reagents were employed in the conversion of carbonyl compounds to their α,β-unsaturated derivatives and in the reduction of dimesylates to alkenes.[129, 130]

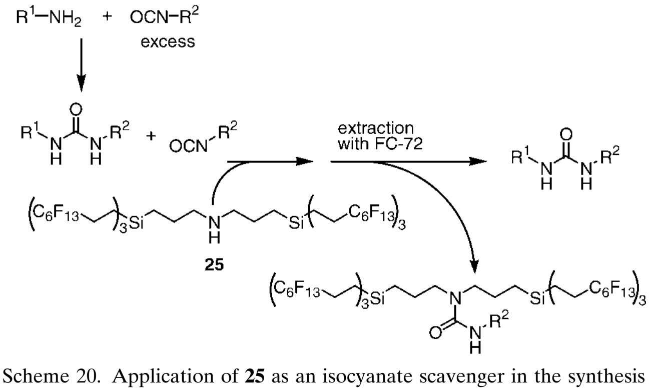
The partitioning coefficient of bis(perfluoroalkyl)ureas **23** between perfluorohexane and CH_2Cl_2 could be significantly increased by the addition of perfluoroalkanoic acids **24** (Scheme 19). This is thought to be the result of hydrogen bonding between the urea and the acid, which results in complex **23**·**24** which is less polar than the individual compounds. The utility as a reagent was demonstrated by dehydration of urea to the corresponding carbodiimide and its subsequent employment as a condensation reagent for the formation of peptide and ester bonds. The urea by-product was removed by extraction with perfluoroheptanoic acid in perfluorohexane, whereas dialkyl ureas formed by conventional carbodiimide reagents are notoriously difficult to remove. The advantage of this strategy is that the reagent itself shows appreciable partitioning into the organic phase, which in turn results in respectable reaction rates. Only upon addition of the perfluoroalkanoic acid scavenger is the partitioning coefficient reversed.[131]



Scheme 19. The partitioning of **23** between CH_2Cl_2 and perfluorohexane is reversed upon addition of **24**.

The application of perfluoro-tagged triphenylphosphanes to Wittig olefinations was suggested initially by Horváth and Rábai.[60] The realization of this idea in the synthesis of substituted ethyl cinnamates and cinnamic nitriles was recently reported.[132] Similarly, perfluoro-tagged triphenylphosphanes, solid-phase-bound phosphane, and triphenylphosphane were compared in an aza-Wittig reaction to give 3*H*-quinazolin-4-ones.[133]

A sulfoxide with a short fluorous tag was employed in Swern oxidations. This reagent is soluble in CH_2Cl_2 and it was removed from the crude product by continuous extraction with FC-72.[134] A perfluoro-tagged binol derivative was employed in the enantioselective protonation of a samarium enolate. The chiral proton source was recovered and could be reused several times.[135] Amine **25** was used to scavenge excess isocyanate from an automated synthesis of a library of ureas (Scheme 20). The product was obtained in high purity after removal of the fluorous urea by extraction with FC-72.[136] Polymers soluble in fluorous solvents efficiently sequester iron ions from organic solvents. Analogous water-soluble polymers have been used to remove trace metals from aqueous solutions.[137]



Scheme 20. Application of **25** as an isocyanate scavenger in the synthesis of ureas.

2.2.4. Perfluoro-Tagged Products

A fluorous label can also be attached to the substrate itself which renders the product soluble in fluorous solvents. Thus, this approach offers an opportunity for easy isolation and makes it particularly attractive for parallel synthesis of compound libraries. After extraction, only the labeled product is found in the fluorous phase, whereas all the other organic compounds remain in the organic phase. As an alternative to liquid–liquid extraction, the reaction mixture can be absorbed on FRPSG (Figure 3). The organic compounds are eluted with a polar organic solvent (methanol/water, acetonitrile/water), while more fluorophilic solvents (diethyl ether, perfluoroalkanes) elute the perfluoro-tagged product.[73] This strategy is conceptually similar to solid-phase synthesis, but offers distinct advantages: 1) The fluorous-tagged substances can be characterized by NMR spectroscopy, 2) reactions can be followed by thin-layer chromatography or HPLC,and 3) homogeneous reactions result in higher reaction rates.[3, 124]

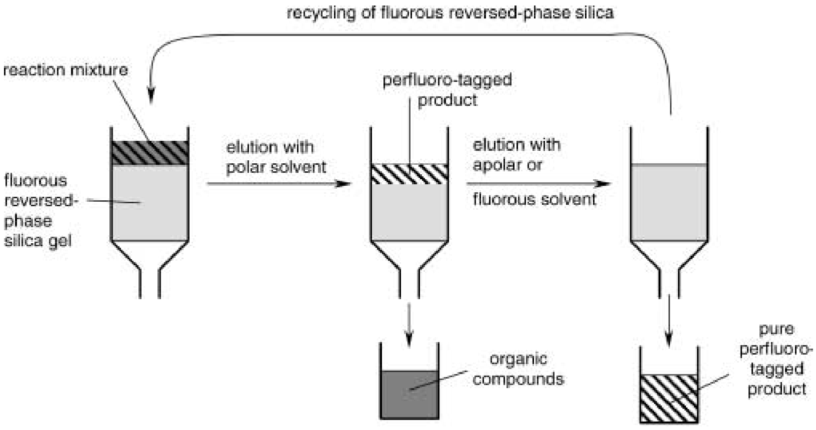
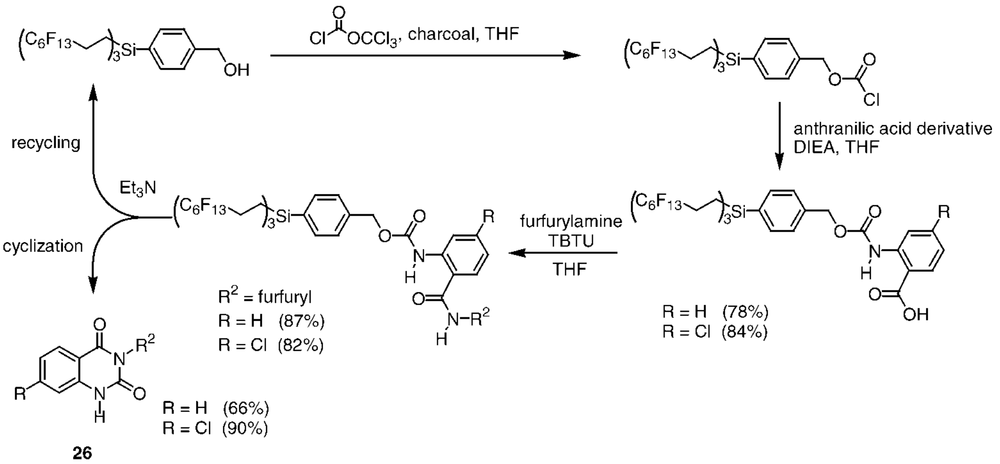


Figure 3. Separation of perfluoro-tagged compounds from organic compounds by solid-phase extraction.

While permanent labeling is necessary for catalysts or reagents, only temporary attachment of the fluorous tag to the substrate is required here (usually through the use of a modified protecting group). A perfluoro-tagged benzyloxycarbonyl protecting group was successfully used in the multistep synthesis of quinazolinediones (Scheme 21). The product was isolated after every step by liquid–liquid extraction with FC-72. Finally, quinazolinedione **26** was removed from the fluorous label by intramolecular cyclization. Since only the desired product undergoes cyclization, all incompletely converted molecules stay attached to the fluorous label and are separated from the product by extraction.[138] Fluorous labeling was employed by Theil and co-workers in the kinetic resolution of 1-phenylethanol. Lipase was used to catalyze the enantioselective esterification of the racemic alcohol with a polyfluoroalkanoic acid. Extraction with FC-72 separated the enantiomerically enriched alcohol from the ester.[139] Polyfluoroalkylsilyl groups were also employed as fluorous labels in the cycloaddition of nitriloxides to allyl silyl ether, in Ugi and Biginelli multicomponent reactions, and in the purification of Grignard products.[124, 140]

Solid-phase extraction with FRPSG is now beginning to replace liquid–liquid extraction procedures.[73] In a recent example amino acids protected by a fluorous Boc group were coupled with different amines by Curran and co-workers. The crude reaction mixtures were adsorbed on FRPSG. The organic reagents and by-products were eluted with methanol/water, the fluorous-tagged amides were eluted with methanol/diethyl ether. Alternatively, preparative HPLC over a fluorous reversed-phase column was used.[141] Preparative HPLC was used to deconvolute product mixtures coded with perfluoroalkyl chains of different length. In this approach, the synthesis is conducted with a mixture of substrates, each uniquely labeled with a perfluoroalkyl group of certain length. Upon completion of the mixture synthesis, the individual products are separated by HPLC over a fluorous reverse-phase column, with the single components eluted in order of increasing length of the fluorous tag (however, other structural features of the product also influence the order of elution). The principle was demonstrated for the synthesis of mappicine analogues and for the addition products of thiolates to acrylates.[142, 143]



Scheme 21. Use of a fluorous protecting group in the synthesis of quinazolinediones.

FRPSG was used to purify perfluoralkyl allyl compounds obtained by free-radical addition of perfluoroalkyl iodides to allyl trialkyl tin.[144] A similar synthesis of perfluoroalkylethenes was reported earlier.[145]

2.3. Supercritical Fluids

Although the discovery of the supercritical state dates back to 1822,[146] it was not until the pioneering work of Zosel[147] in 1978 that supercritical fluids (SCFs) found acceptance as solvents. They are now employed on an industrial scale for the extraction of hops, spices, flavors, perfumes, and for the decaffeination of coffee.[148, 149] In the last few years SCFs have been attracting ever increasing attention since they were found to be environmentally and toxicologically benign media for chemical reactions.[150–157] SCFs are particularly attractive in synthesis as they provide some unique properties such as high diffusion rates, enhanced heat transfer, compressibility, and the absence of gas–liquid boundaries. Their solvent properties can be easily tuned by pressure and addition of cosolvents, which provides an attractive means to influence phase behavior as well as the rate and selectivity of catalytic reactions. Product separation is fairly straightforward and essentially solvent-free products are obtained. The use of SCFs are also beneficial in different purification processes such as chromatography, crystallization, or precipitation, on both laboratory and industrial scales, thus reducing the amount of waste organic solvents significantly. However, until now extensive parallelization and automatization has been limited by the need for high-pressure equipment and by safety concerns.

2.3.1. The Concept of Supercritical Fluids

The critical point represents the highest pressure (p_C) and temperature (T_C) at which the vapor and liquid phases of a substance can exist in equilibrium. The distinction between gas and liquid disappears above the p_C and T_C values, and the supercritical fluid has physical properties which are intermediate between those of a liquid and a gas. The critical data for some SCFs are depicted in Figure 4.[158]

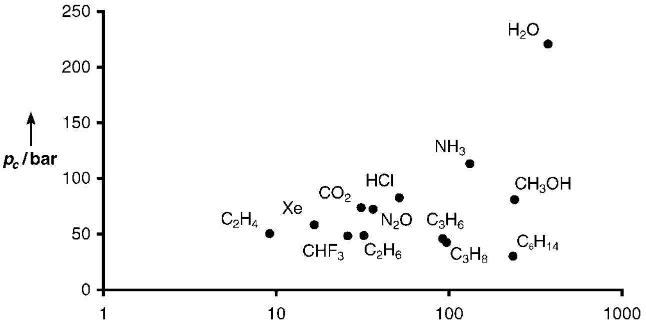


Figure 4. Critical data for some SCFs.

The properties of SCFs such as polarity, dielectric constant, viscosity, and solubility properties can vary dramatically with temperature and pressure.[159] The dielectric constant of a solvent influences chemical reactions whenever the reactants and transition state differ in polarity. The viscosity influences reactions that are diffusion-controlled or in which cage effects are important. Thus, adjusting the temperature and pressure provides a means to control reaction rates and selectivities. Furthermore, reactions can be driven to completion by precipitation of a product, and selective precipitation can be used during reaction work-up. Another important feature of SCFs is their total miscibility with gases. This observation turns SCFs into ideal media for reactions such as hydrogenation, hydroformylation, and oxidation with oxygen, where the solubility of the gaseous reagent is traditionally rate limiting.

Among the different SCFs depicted in Figure 4, $scCO_2$ and scH_2O have found widest acceptance. Supercritical water forms only a few hydrogen bonds and its dielectric constant (ε_r) is reduced from 80 to 5.[160] Hence, scH_2O is attractive for replacing organic solvents at temperatures above 200–350 °C, where it readily dissolves most organic compounds. However, the application of scH_2O is limited not only to reactants and products that are thermally stable, but also by its corrosive properties.

Carbon dioxide becomes supercritical at $T_C = 31.1\,^\circ C$ and $p_C = 73.8$ bar, thus allowing for essentially mild SCF applications. Carbon dioxide is obtained as a by-product of fermentation and combustion processes. It is essentially nontoxic, nonflammable, nonprotic, and chemically inert to a wide range of reaction conditions.[161] Furthermore, $scCO_2$ has been used as a C_1-building block.[162, 163] Since $scCO_2$ is a nonpolar medium, the best solubility is observed for nonpolar solutes. The solubility of polar substances can be substantially increased by adding polar cosolvents or microemulsions.[164] Organic fluorocarbons show a particular high solubility in $scCO_2$. Numerous examples are reported in which so-called perfluoro tags have been used to solubilize substrates, reagents, and catalysts.[157, 165, 166] With $scCO_2$ and perfluorinated solvents both representing very nonpolar media, it is not surprising that their fields of application and research show a certain analogy. In fact, a number of the perfluorotagged reagents, ligands, and catalysts (see Section 2.2) have also been successfully tested in $scCO_2$ applications. Another synthetic SCF strategy makes use of two-phase systems, which allows for SCF transfer catalysis[167] or catalyst immobilization.[56] The combination of $scCO_2$ and ionic liquids is especially attractive (see Section 2.1.3.6).

Product isolation after a reaction in a SCF is straightforward since most SCFs, including CO_2, can be removed by simple depressurization. This is particularly useful in syntheses of thermally unstable compounds or for pharmaceutical syntheses where products have to be free of solvent residues. In analogy, high-quality crystals without any solvent molecules have been generated for X-ray diffraction studies by crystallization from a supercritical solution (CSS).[168] In contrast to conventional batch crystallization, pressure provides a second parameter in addition to temperature to trigger nucleation and growth of crystals.

There are even more elaborate separation protocols which take advantage of the tunable solvent power of SCFs. In particular, the combination of catalysis and extraction with a supercritical solution (CESS) is a new method for the recovery of homogeneous catalysts.[169–171] After venting the reactor the product is extracted from the residue with a SCF whose density is tuned to dissolve the product selectively. Thus, the catalyst remains in the reactor and can be reused. The consecutive use of $scCO_2$ and a perfluorinated solvent has been exploited in a similar strategy.[172] Finally, the rapid expansion of supercritical solutions (RESS)[173] and the supercritical antisolvent precipitation (SASP)[174, 175] processes are mentioned. Both are of relevance in pharmaceutical formulation as they allow for an effective reduction in particle size combined with a narrow size distribution.

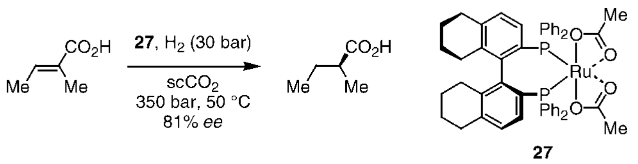
2.3.2. Synthetic Reactions in Supercritical Fluids

SCFs have received only a little attention as reaction media in synthetic organic chemistry. It is noteworthy, however, that a number of large-scale industrial syntheses are performed under supercritical conditions, with the Haber–Bosch synthesis of ammonia and the Fischer–Tropsch reaction, as well as polyethylene, polymethylmethacryate, and polystyrene production[176] probably being the most important ones.

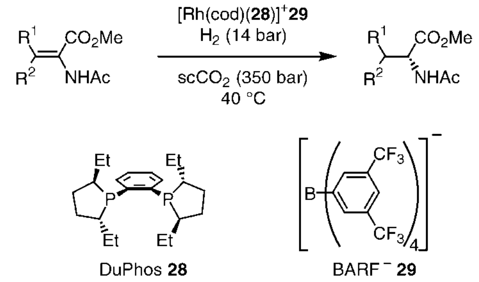
2.3.2.1. Hydrogenation

Hydrogen mass-transfer is often the rate-determining process in hydrogenation reactions. Whereas hydrogen has a rather limited solubility in most organic solvents, it is completely miscible with SCFs and turns them into ideal media for this kind of reaction. SCFs have so far been used beneficially in both homogeneous and heterogeneous hydrogenation reactions of a wide range of substrates.[177–179] Baiker and co-workers observed no increase in the enantioselectivity of a heterogeneous asymmetric hydrogenation in supercritical ethane, but observed a rate enhancement compared to the analogous reaction in toluene.[180, 181] The same effect was reported by Poliakoff and co-workers.[178, 179]

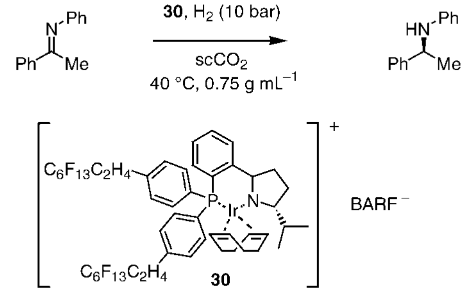
Noyori used Ru catalyst **27** containing a partially hydrogenated binap ligand for improved solubility in $scCO_2$ in homogeneous catalytic asymmetric hydrogenation reactions. The enantiomeric excess obtained was comparable to those obtained in liquid organic solvents (Scheme 22).[182] The bidendate DuPhos ligand (**28**) and the CO_2-philic $BARF^-$ counterion (**29**) were used by Tumas and co-workers (Scheme 23).[183] Asymmetric inductions obtained were comparable to those achieved in methanol or hexane. The perfluoro-tagged cationic iridium(I) complex **30** was tested as a catalyst for the enantioselective hydrogenation of prochiral imines in $scCO_2$.[170] The highest enantioselectivities were obtained with $BARF^-$ as the counterion (Scheme 24). The hydrogenation of $scCO_2$ by soluble rhodium(II) catalysts **31a** or **31b** to yield formic acid, which could be further converted into methyl formate or *N*,*N*-dimethylformamide (Scheme 25) was also reported by Noyori and co-workers.[162, 163]



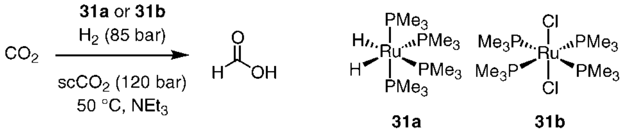
Scheme 22. Asymmetric hydrogenation using a modified Ru–binap complex.



Scheme 23. Asymmetric hydrogenation using a modified Ru–DuPhos complex.



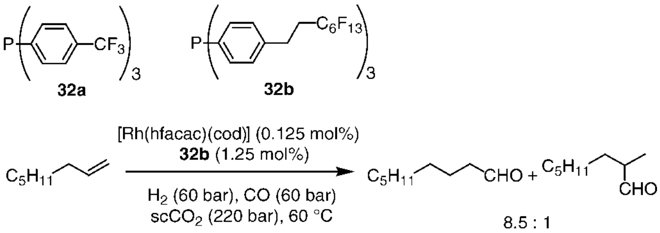
Scheme 24. Asymmetric hydrogenation of prochiral imines.



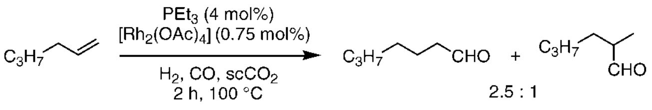
Scheme 25. Hydrogenation of carbon dioxide.

2.3.2.2. Hydroformylation

Hydroformylation of propene in $scCO_2$ was reported as early as 1991.[184, 185] Fluorinated phosphane ligands **32** were used by Palo and Erkey as well as Leitner and co-workers to obtain $scCO_2$-soluble rhodium(I) catalysts for hydroformylation reactions. The results obtained were comparable to those obtained in conventional systems (Scheme 26).[186–188] Similar results were found using commercially available trialkylphosphanes, which also show reasonable solubility in $scCO_2$ (Scheme 27).[189]

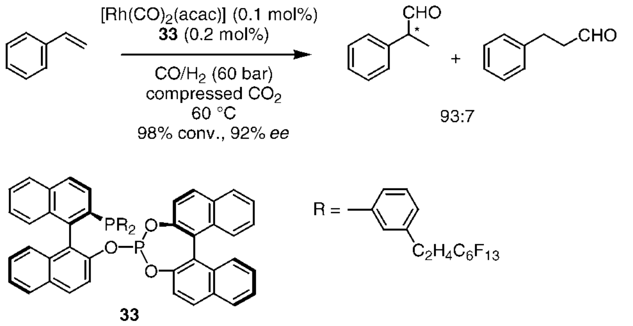


Scheme 26. Hydroformylation using **32a** and **32b**.



Scheme 27. Use of trialkylphosphanes in hydroformylation reactions.

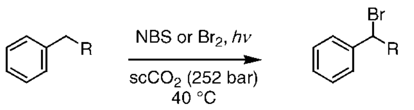
Asymmetric catalytic hydroformylation using the perfluoro-tagged (*R*,*S*)-binaphos ligand **33** and [Rh(CO)$_2$(acac)] in dense CO$_2$ was addressed by Leitner and co-workers as well as by Lin and Akgerman.[169, 190, 191] The products were isolated by using a CESS procedure. The pressure was reduced to give a liquid–gaseous two-phase system, which was consequently extracted with dense CO$_2$, with the active catalyst left behind for subsequent reactions (Scheme 28).



Scheme 28. Asymmetric hydroformylation using a fluorinated binaphos ligand **33**.

2.3.2.3. Halogenation

Tanko and Blackert investigated photo-initiated bromination reactions in scCO$_2$ as a "green" alternative to halogenated solvents.[161] They found selectivities almost identical to the ones observed in chlorinated solvents. Only with molecular bromine as the brominating agent did the competing electrophilic aromatic substitution occasionally produced a small amount of a side product. This problem did not occur in the Ziegler bromination with NBS (Scheme 29).

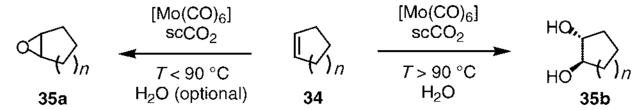


Scheme 29. Bromination in scCO$_2$.

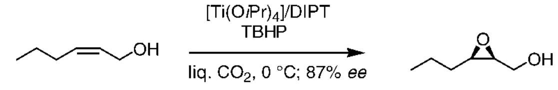
2.3.2.4. Oxidation[192]

As a result of their inertness towards oxidation, scH$_2$O and scCO$_2$ are attractive media for oxidation reactions since they provide safe processes and avoid the formation of side products from solvent oxidation. Supercritical water has found its widest and most important application in the supercritical water oxidation process (SCWO) for the total aerobic oxidation of toxic wastes.[193–196] Oxidation reactions are usually performed in scCO$_2$ and benefit from the expanded explosion limits which allow for higher oxidant/substrate ratios. Even highly exothermic oxidation processes may be controlled efficiently as scCO$_2$ shows better heat-transport capacities than gaseous mixtures.

A number of oxidation reactions in scCO$_2$ have been reported in which a metal catalyst and a TBHP oxidizing agent have been used. For example, cyclic olefins **34** could be oxidized selectively to either epoxides **35a** or *trans*-1,2-diols **35b** with [Mo(CO)$_6$] as the catalyst (Scheme 30).[197, 198] Similarly, allylic and homoallylic alcohols have been epoxidized in liquid CO$_2$ using [VO(O*i*Pr)$_3$] as the catalyst.[198] This epoxidation reaction can also be conducted asymmetrically by employing the Sharpless procedure (Scheme 31).[198]

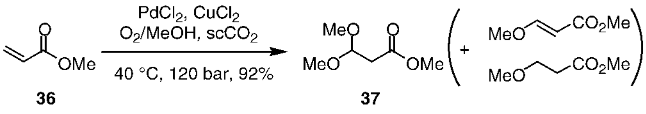


Scheme 30. Oxidation of cyclic olefins in scCO$_2$.



Scheme 31. Asymmetric Sharpless epoxidation in scCO$_2$.

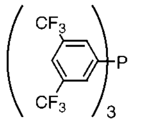
Molecular oxygen is without doubt the most attractive oxidant for selective catalytic oxidation reactions. Again, such reactions can profit from being performed in SCFs, since total miscibility with oxygen is achieved and the oxygen concentration can be easily adjusted.[199] For example, the autoxidation of substituted phenols by Schiff base complexes in scCO$_2$ gave high selectivities for the corresponding quinone at a oxygen/substrate ratio of at least 200/1, which is only practical in SCFs.[200] Scheme 32 shows an example of a palladium(II)-catalyzed oxidation of an acrylic ester **36** to dimethylacetal **37**).[201]



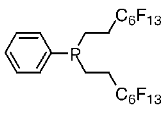
Scheme 32. Pd-catalyzed oxidation of acrylic ester **36** with molecular oxygen.

2.3.2.5. C–C Coupling

Carrol and Holmes applied the perfluoro-tagged phosphane ligand **38** for solubilization of Pd complexes and successfully employed them for Heck, Suzuki, and Sonogashira couplings in scCO$_2$.[202] Ligand **39** was shown to be



38



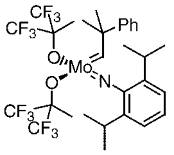
39

suitable for Heck and Stille couplings in $scCO_2$.[203] The two palladium complexes **17a** and **17d** were successfully tested in a Stille coupling.[172] Product purification and catalyst recycling was achieved by extracting the residue with FC-72 after dissipation of the CO_2. In both steps, the difference in solubility between $scCO_2$ and the fluorinated solvent is mediated by the perfluoro tags. The recovered catalyst was reused and showed no loss in activity.

Surprisingly, the catalyst $[Pd(PPh_3)_2]Cl_2$, which is expected not to dissolve in $scCO_2$, also mediated these Stille couplings. Recently, palladium acetate in combination with the non-fluorous ligand tris(*tert*-butyl)phosphane was also reported to give good yields in Heck and Suzuki couplings conducted in $scCO_2$.[204]

2.3.2.6. Olefin Metathesis

Fürstner, Leitner, and co-workers investigated ring-closing metathesis (RCM) reactions in dense CO_2. A 16-membered ring could be closed in yields of over 90% at high pressures, while mainly oligomers were obtained at lower pressures.[205, 206] This observation was explained in terms of the Ziegler–Ruggli principle, with higher pressure corresponding to a higher CO_2 density and, hence, a higher dilution. The complexes used as catalysts or catalyst precursors in $scCO_2$ are shown in structures **40**–**42**.[205, 206] While complex **40** is completely soluble in $scCO_2$, carbenes **41** and **42** showed no visible solubility. Isolation of the product by this process is commonly referred to as selective supercritical fluid extraction (SFE). In principle the organic materials can be collected directly from the gas stream by using appropriate traps to leave the catalyst behind.[147]



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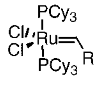
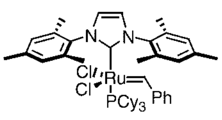


41a (R = CH=CPh$_2$)
41b (R = Ph)



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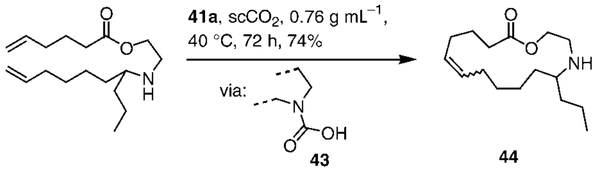
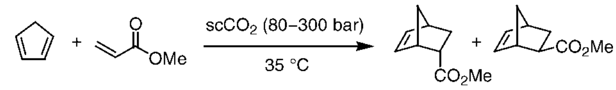
The reversible formation of a carbamic acid in $scCO_2$ from a secondary amine has been used successfully as a protecting strategy in the metathesis approach to the natural product epilachnen (**44**, Scheme 33).[205] Secondary and primary amines deactivate complex **41a** and therefore requires protection. In $scCO_2$, however, the amine is reversibly transformed into the corresponding carbamic acid **43** and good yields of the aza macrocycle **44** are obtained.[205]



Scheme 33. Protecting strategy in the synthesis of epilachnen (**44**).

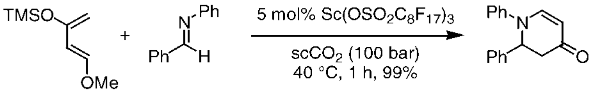
2.3.2.7. Diels–Alder Reactions

A significant increase in the rate constant of the cycloaddition of maleic anhydride and isoprene was observed near the critical pressure.[207–209] Furthermore, Kim and Johnston found a slight pressure dependency of the *exo*/*endo* ratio of Diels–Alder reactions in SCFs (Scheme 34).[210] The transition states leading to the two isomeric products differ in their dipole moments. Interactions with the nonpolar solvent $scCO_2$ are pressure or density dependent, thus causing a difference in diastereoselectivity.



Scheme 34. Example of the pressure dependency of a Diels–Alder reaction.

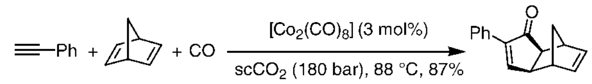
Rayner and co-workers used soluble scandium triflate for a number of Lewis acid catalyzed Diels–Alder reactions in $scCO_2$ and found improved diastereoselectivities compared to those obtained in conventional solvents.[211] For the analogous aza-Diels–Alder reactions, Kobayashi and co-workers were able to show a relationship between catalyst activity and the length of the perfluoroalkyl chains (Scheme 35).[212]



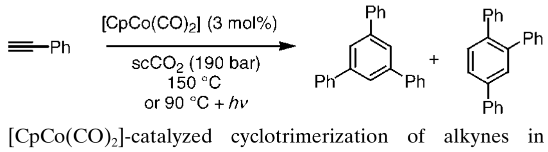
Scheme 35. Aza-Diels–Alder reaction performed in $scCO_2$.

2.3.2.8. Miscellaneous Synthetic Reactions

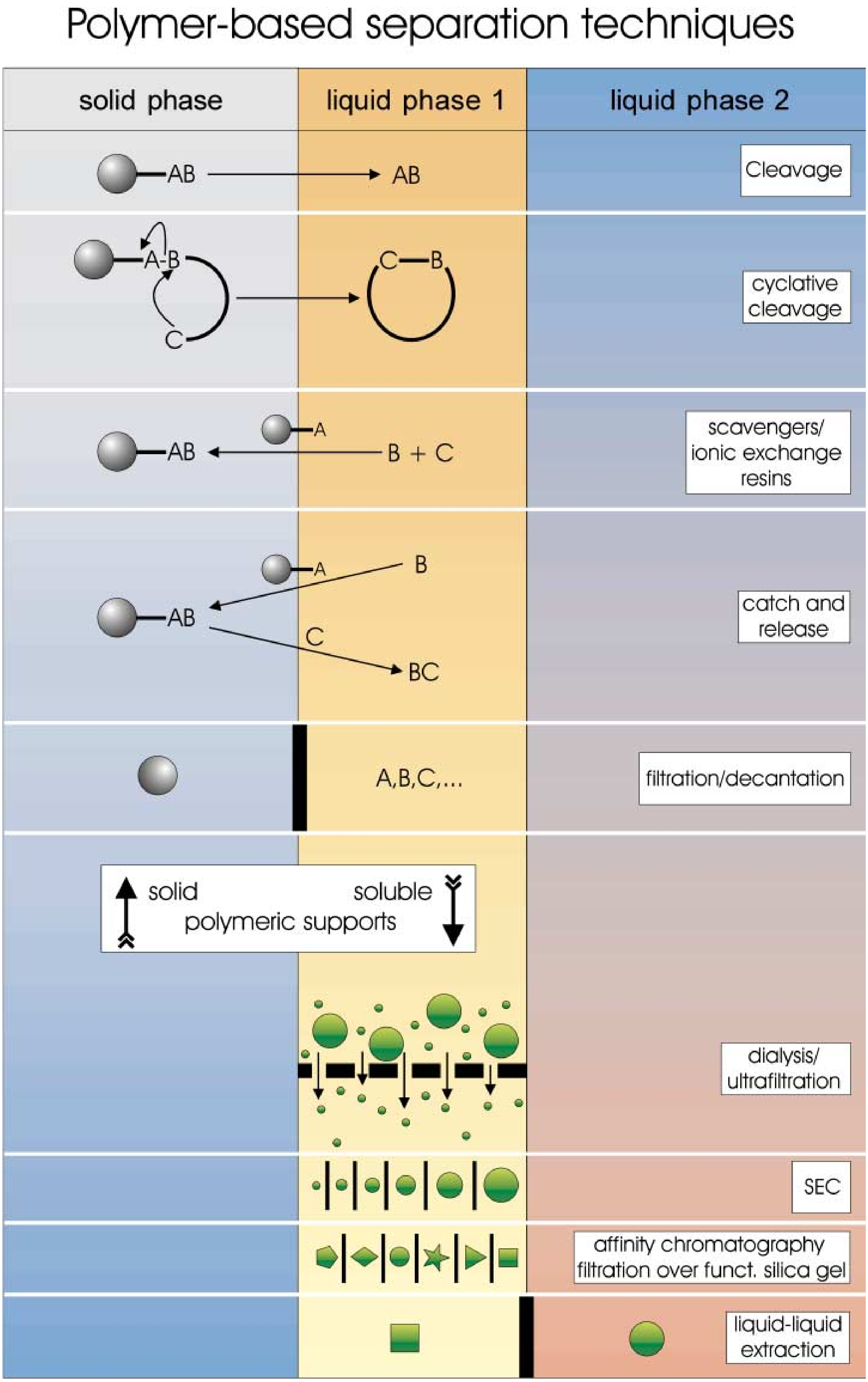
Jeong et al. reported the synthesis of a substituted cyclopentenone by a Pauson–Khand reaction (Scheme 36).[213] A $[CpCo(CO)_2]$-catalyzed cyclotrimerization of alkynes in $scCO_2$ was reported by Avilés and co-workers (Scheme 37).[214] Tumas and co-workers applied an in situ generated rhodium catalyst with fluorinated trialkylphosphane ligands to hydroboration of alkenes.[215] Similarly, ruthenium- and rhodiumphosphane complexes were successfully used as catalysts for the hydrosilation of olefins in dense CO_2.[216] The great interest in utilizing SCFs for polymerization processes has been described in a series of review articles.[157, 217, 218]



Scheme 36. Pauson–Khand reaction in $scCO_2$.



Scheme 37. $[CpCo(CO)_2]$-catalyzed cyclotrimerization of alkynes in $scCO_2$.


Polymer-based separation techniques
solid phase
liquid phase 1
liquid phase 2
AB
AB
Cleavage
A-B
C
C—B
cyclative cleavage
AB
A
B + C
scavengers/ ionic exchange resins
A
B
AB
C
BC
catch and release
A,B,C,...
filtration/decantation
solid
soluble
polymeric supports
dialysis/ ultrafiltration
SEC
affinity chromatography filtration over funct. silica gel
liquid-liquid extraction

3. Polymer-Based Separation and Purification Techniques

Polymeric supports have been used for over 50 years to simplify and accelerate the work-up of organic reactions. Initially ion-exchange resins dominated the field, while in the last decade more specific polymeric supports and linker systems have been used. A number of different polymers, cross-linked (insoluble) and non-cross-linked (soluble), have been used for many different applications.[219]

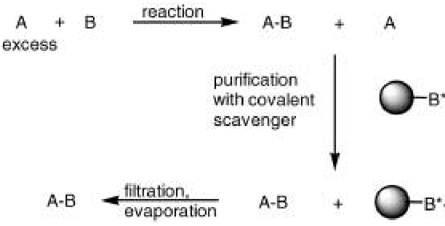
3.1. Polymer-Supported Scavenger Reagents

The ability to use multiparallel purification techniques is of great importance to solution-phase combinatorial synthesis. Polymer-supported scavenger reagents can be used since they allow for an automated purification protocol for a large number of parallel reactions.[220–224] In general, one or more solid-supported reagents which selectively bind to impurities, either covalently or ionically, are added to a reaction mixture. The choice of scavenger depends on the nature of both the impurity as well as the desired product.

This work-up procedure has frequently been performed in a parallel format. However, most of the employed scavengers have relatively small loading capacities and hence this approach is useful only for small-scale reactions. Even though the protocol can be performed by a robotic system, the automated addition of beads is still problematic. To circumvent the handling problems associated with beads, a so-called pass-flow system has recently been developed by Kirschning et al.[225] Here the beads are immobilized on a porous glass fritt sealed in a pressure tubing. This reactor can be operated by an automated HPLC system.

3.1.1. Covalent Scavengers

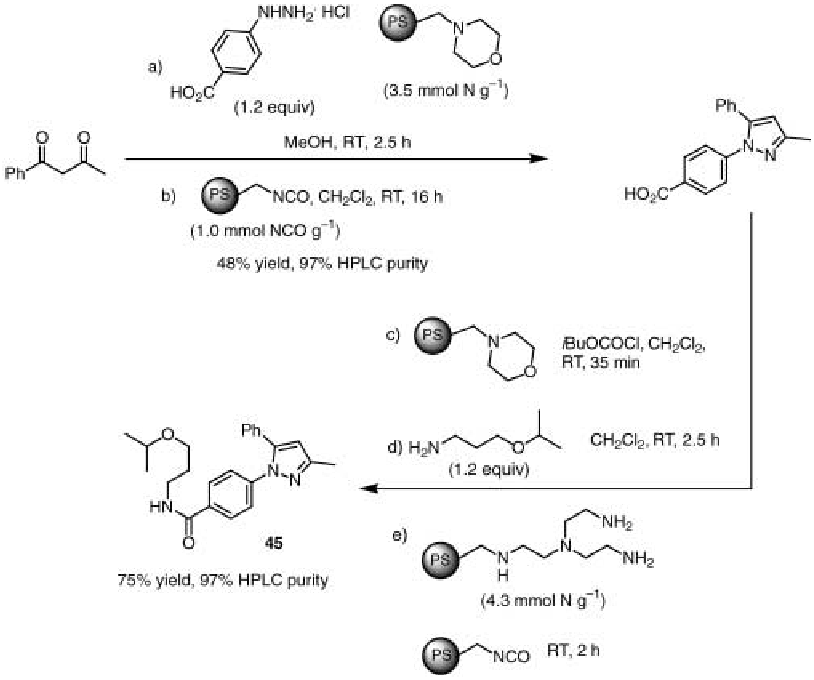
The general concept of covalent scavengers is shown in Scheme 38: Reagent **A** is present in an excess to drive the reaction to completion. The resulting reaction mixture contains the product **AB** and the remaining reagent **A**. Subsequently, the polymer-supported scavenger is added, which bears a reactive functionality **B*** that is similar to compound **B**, to consume the remaining starting material **A**. The isolation of the product is achieved by filtration and solvent evaporation.[226] Covalent scavengers have been designed for the removal of electrophiles in the presence of nucleophiles and vice versa.



Scheme 38. Schematic representation of a reaction purification with covalent scavengers.

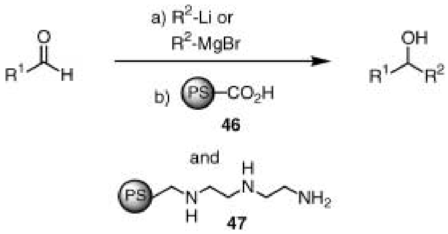
3.1.1.1. Removal of Electrophiles by Nucleophilic Resins

Booth and Hodges described the preparation of polystyrene-supported derivatives of tris(2-aminoethyl)amine for the scavenging of ureas, thioureas, sulfonamides, amides, and pyrazoles.[227] The multistep synthesis of a pyrazole **45** is shown in Scheme 39. In the first reaction, a polymer-bound amine is used to remove hydrochloric acid. Excess hydrazine is scavenged by a polymer-bound isocyanate. In the subsequent step the acid is activated, again in the presence of a polymer-supported base, and coupled with an amine. After this reaction, the polymer-bound amine and isocyanate are used together to remove any residual activated acid and amine. The simultaneous use of electrophilic and nucleophilic scavengers is possible, since they cannot react with each other because they are immobilized on different beads. These resins have also been used successfully for removing acid chlorides, sulfonyl chlorides, and isothiocyanates from solutions.[228]



Scheme 39. Synthesis of pyrazole by using polymer-supported scavengers.

Aldehydes have been separated from alcohols through formation of an imine with a primary amine resin **47** (Scheme 40).[229] In this reaction a carboxylic acid resin **46**

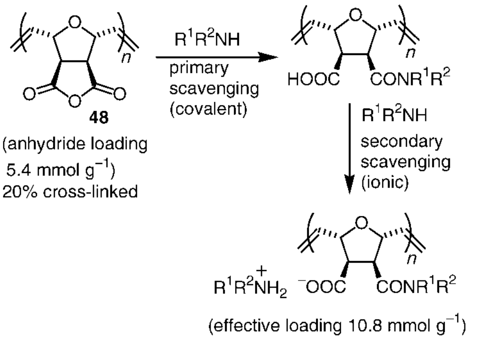


Scheme 40. Separation of aldehydes from alcohols by formation of an imine with a primary amine resin.

was used to remove any excess Grignard reagent, reprotonate the metal alkoxide, and scavenge the metal ions as salts of the resin. In another example, derivatized cellulose beads with a high loading of primary amines were used to scavenge amides and ureas.[230] In contrast to common polystyrene materials, this support can be degraded by enzymes, which could solve disposal problems.

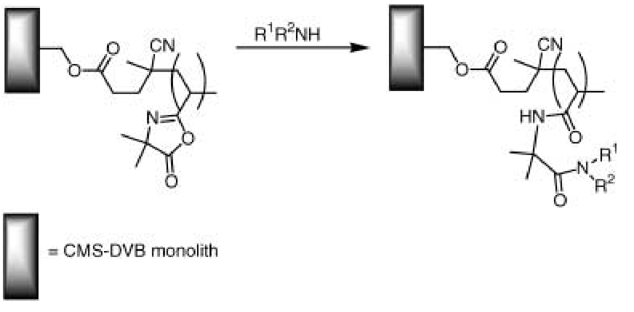
3.1.1.2. Removal of Nucleophiles by Electrophilic Resins

A number of resins have been developed for the removal of amines or hydrazines from solution (Scheme 39). A good choice are polymer-bound isocyanates[231] since no by-products are released from the resin during the quenching reaction. Furthermore they can be used for scavenging excess primary and secondary amines during the formation of amides and sulfonamides,[227, 232–234] as well as for the separation of secondary amines from tertiary amines and tertiary amino alcohols. Other electrophilic resins are polymer-supported aldehydes and acid chlorides.[232] Another alternative for removing excess amines and hydrazines are the so called ROMPGEL scavengers **48**, which are high-loading supported anhydrides (Scheme 41).[235]

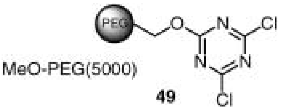


Scheme 41. Sequestration of excess amine with a ROMPGEL scavenger.

Another approach uses grafted macroporous polymer monolith disks as scavengers for amines (Scheme 42).[236, 237] These materials consist of poly(chloromethylstyrene-*co*-divinylbenzene) and are activated by graft polymerization of 4-vinyl-2,2-dimethylazlactone to its porous surface. Falchi and Taddei described polyethylene glycol–dichlorotriazine (PEG-DCT, **49**) as a soluble electrophilic scavenger.[238] It can be obtained from reaction of trichlorotriazine with MeO-PEG-OH ($M_w = 5.000\ \mathrm{g\,mol^{-1}}$) and can be used as a scavenger for primary, secondary, and tertiary alcohols, as well as for diols, polyalcohols (for example, D-mannitol), and for thiols in different kinds of reactions such as the formation of esters, silyl ethers, acetals, thioacetals, and thioglycosides. (For further properties and separtion techniques for soluble polymers see Section 3.4.)

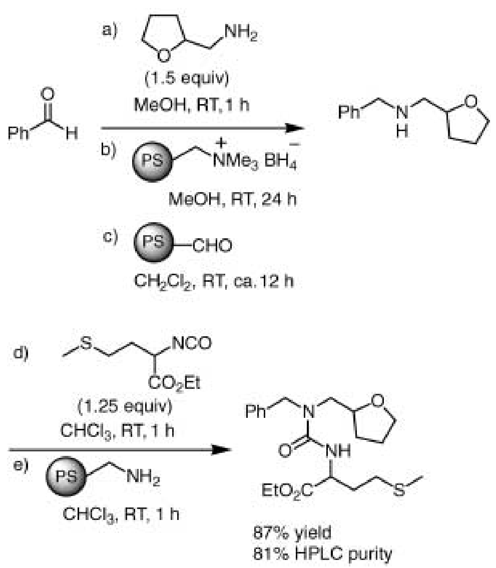


Scheme 42. Macroporous polymeric CMS-DVB monolith scavengers for the separation of amines.



49

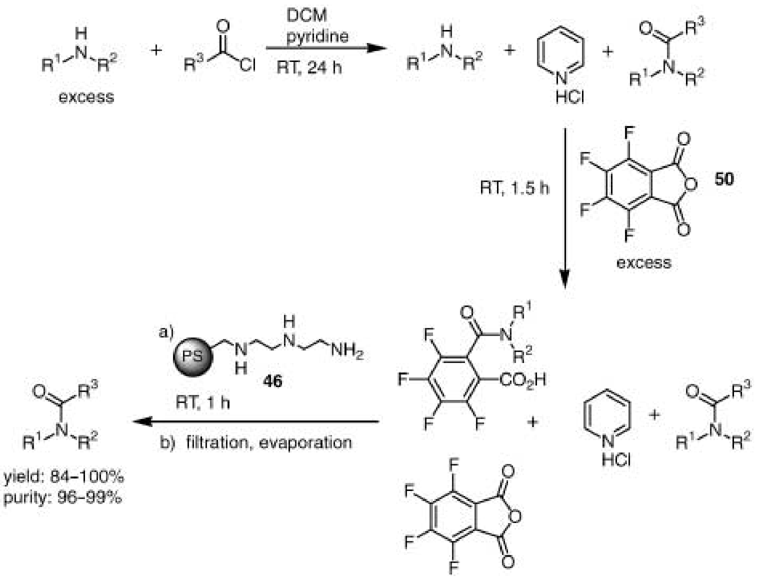
The simultaneous use of both nucleophilic and electrophilic scavengers has been reported by Kaldor, Siegel et al.[232] for the alkylation and acylation of amines. Purification of the products was achieved through the use of immobilized amines, isocyanates, aldehydes, and acid chlorides. Although a complex distribution of products is obtained, purities up to 95% can be reached. Another example is shown in Scheme 43. In the first step the reductive amination requires the use of an excess of amine to drive the imine formation to completion. Then polymer-bound borohydride is added for imine reduction and subsequently the excess of primary amine can be scavenged by a polystyrene-bound carbaldehyde. Reaction of the resulting secondary amine with excess of a functionalized isocyanate yielded the desired urea. Residual isocyanate was removed with an aminomethylated polystyrene resin.[223]



Scheme 43. Simultaneous use of electrophilic and nucleophilic scavenger resins for purification.

3.1.2. Purification by Sequestration-Enabling Reagent Technique

Another form of separation using covalent scavengers is the so-called sequestration-enabling (SER) technique. For example, an excess of amine in a crude product can be derivatized to a carboxylic acid by reaction with surplus tetrafluorophthalic anhydride (**50**, Scheme 44).[229] The polymeric amine scavenger **46** is then added. This reagent plays three different roles: eliminating the HCl formed during the first reaction step, thus allowing the pyridine to be removed by evaporation, and removing the hemitetrafluorophthalic acid and the excess



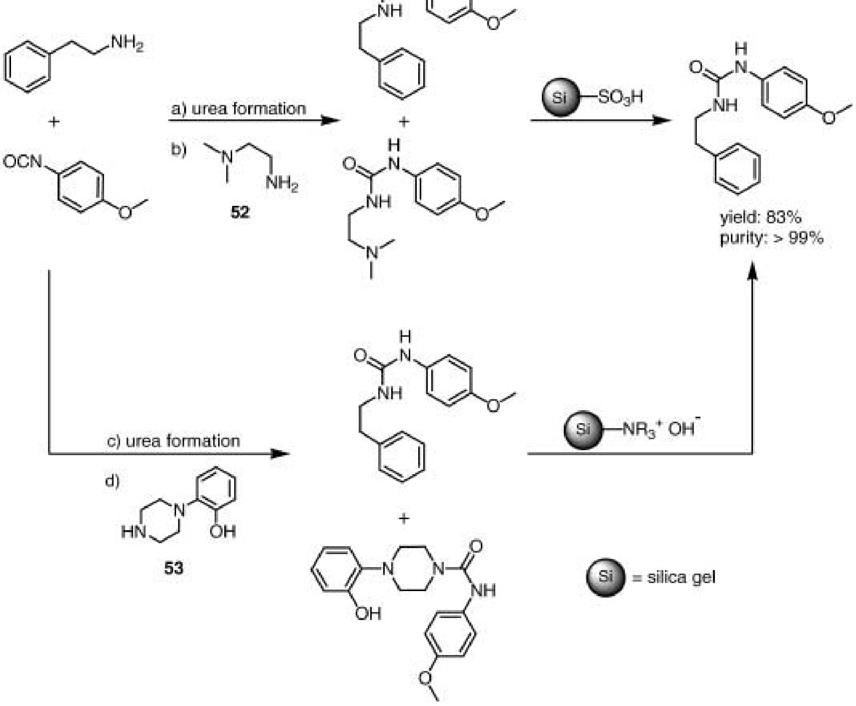
Scheme 44. Derivatization of excess amine with tetrafluorophthalic anhydride as a SER.

of SER reagent **50** by ionic interaction and covalent binding, respectively. This technique using electrophilic SER reagents allows for the creation of products with high purity.

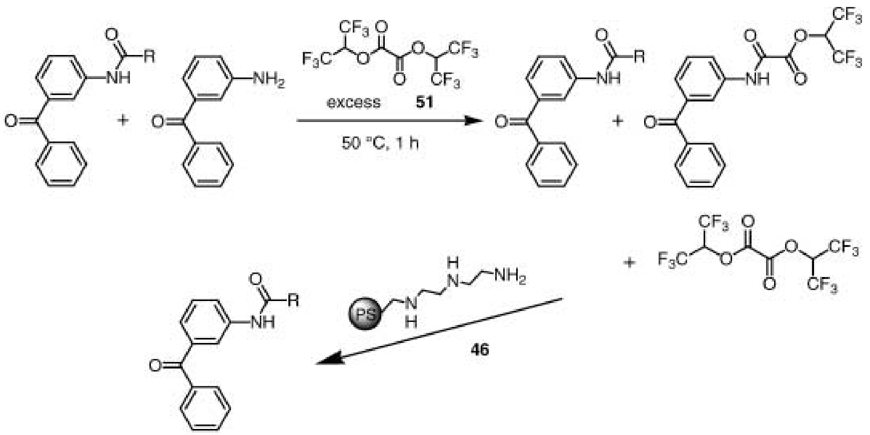
A variation of the SER technique uses bis(hexafluoroisopropyl) oxalate (**51**) to form a hemiamide with an excess of amine.[239] Subsequently, the remaining active ester functionality is covalently sequestered along with excess of **51** by treatment with the polymer-bound amine **46** (Scheme 45). These SER methods are superior to the use of polymer-supported isocyanates for the removal of anilines.

Nucleophilic SER reagents have also been described.[229, 240, 241] Scheme 46 shows an example of amine SERs **52** and **53** to remove excess isocyanate. In the case of **52**, the resulting basic compounds can be separated by cation-exchange chromatography. Alternatively, when **53** is used as the SER, the generated phenolic component is removable by anion-exchange chromatography. In general, it is often more cost-effective to perform a SER reaction so as to take advantage of a readily available and inexpensive purification resin than to spend time in developing a special scavenger resin for the same purpose.[226] The same limitations apply for parallelization and automation of the SER technique as already mentioned for polymer-supported scavenger reagents.

3.1.3. Purification with Ion-Exchange Resins



Scheme 46. Removal of excess isocyanate with a nucleophilic amine SER.

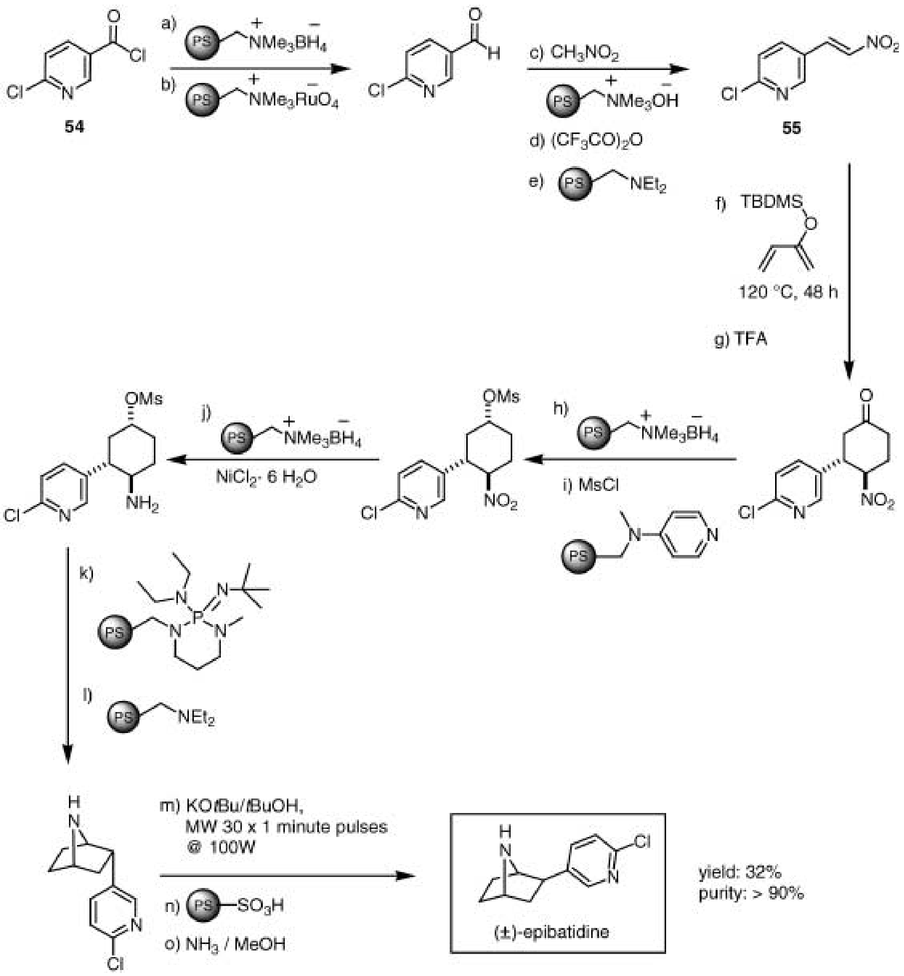


Scheme 45. Removal of amines with hexafluoroisopropyl oxalate (**51**) through formation of a hemiamide.

Polystyrene-based macroporous resins functionalized with quaternized amines and sulfonates, so-called ion-exchange resins, have been known since the 1950s and used in a wide variety of applications. Typical usages include purification of water,[242] serum analysis,[243] and protein purification.[244] In addition, they can also be used as reagents and scavengers in solid-phase organic synthesis and the purification of extremely hydrophilic molecules such as peptides and amino acids which are often difficult to purify by other methods.[245, 246] An advantage of ion-exchange chromatography over traditional methods such as HPLC or flash chromatography is that one can reliably predict the elution characteristics of a broad range of molecules solely by the presence or absence of an ionizable site in the molecule.

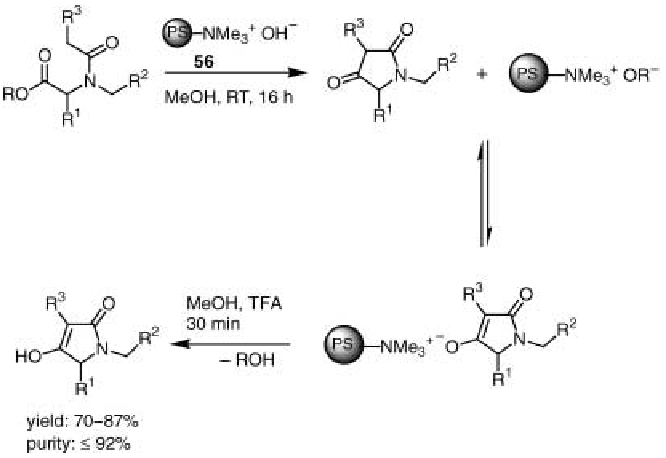
The typical way of using a strong cation ion exchange column is depicted in Scheme 47.[240] Two neutral molecules A and B pass through a sulfonic acid based cation-exchange column, while the protonated molecule C is retained. In a similar way, a cationic ion-exchange resin can be used as a scavenger for the purification of organic reactions containing, for example, amines or ammonium salts. In contrast to covalent scavenger reagents, which are mainly based on gel-type microporous PS beads with relatively moderate loading capacities (1–2 mmol g^{-1}), ion-exchange resins can have much higher loading capacities (up to 5 mmol g^{-1}). An impressive example by Ley and co-workers[247] demonstrates the high potential of scavengers in natural product synthesis, namely, the use of cation-exchange resins as scavengers in the final purification of the multistep synthesis. Scheme 48 describes the linear ten step sequence of the potent analgesic (±)-epibatidine. This compound was accessible in an overall yield of 32 % and in more than 90 % purity without column chromatography. This example demonstrates once more the utility of polymer-supported reagents in combination with polymer-supported scavengers for combinatorial synthesis. For example, the conversion of the acid chloride **54** to the intermediate nitroalkene **55** (five steps!) could be performed in a one-pot procedure.

Scheme 47. Interaction with a strong cationic ion exchange resin.

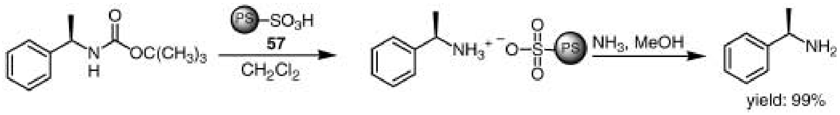


Scheme 48. Synthesis of (±)-epibatidine by using supported reagents and scavengers.

Ion-exchange resins can not only be used in purification steps but may also be included in a chemical reaction. Kulkarni and Ganesan described the application of Amberlyst A-26 (OH$^-$ form, **56**) for effecting both ring closure and purification of libraries of 2,4-pyrrolidinediones (Scheme 49).[248] Cyclization yields the desired products as their ionically bound enolates, which were cleaved by treatment with trifluoroacetic acid. Ten compounds with yields of 70–87 % and good purities of up to 92 % were reported. A combination of purification and deprotection of a Boc protecting group was described by Bergbreiter, Romo, and co-workers.[249] They used an Amberlyst-15 exchange resin **57** in its SO$_3^-$ form. As depicted in Scheme 50 the products were treated with an excess of resin **57** at room temperature in CH$_2$Cl$_2$. This process resulted in deprotection and allowed the free amino group to bind ionically to the polymeric support. By-products and impurities were subsequently washed off. Release of the primary amines were



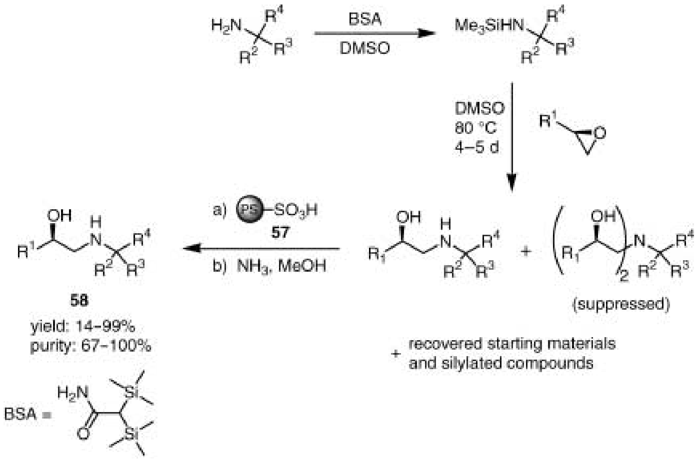
Scheme 49. Synthesis of 2,4-pyrrolidinediones using a basic ion-exchange resin.



Scheme 50. A combination of purification and deprotection with a sulfonic acid based Amberlyst-15 exchange resin.

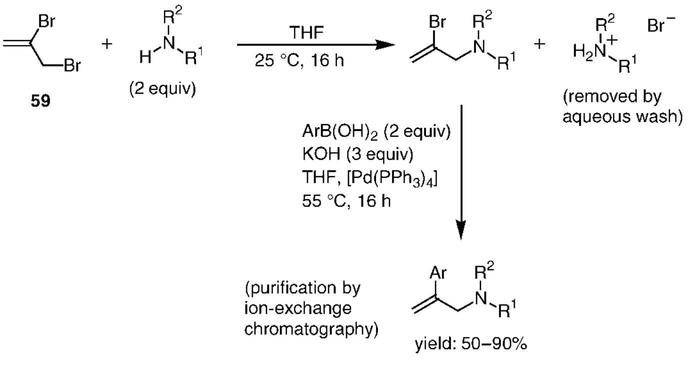
achieved with ammonia in methanol. Ten amines were synthesized with yields of up to 99%.

Siegel and co-workers reported the synthesis of a library of 48 β-amino alcohols **58** by using a parallel synthesis approach.[250] In the first step the primary amine is silylated in situ with bis(trimethylsilyl)acetamide (BSA) in DMSO, before adding an epoxide to the reaction mixture (Scheme 51). Isolation of the desired ethanolamine was achieved using a strongly acidic ion-exchange resin **57**. The amine was retained on the column while residual epoxide, silicon by-products, and DMSO were removed by washing with methanol. Subsequently, the method was applied to an array of 8 × 6 reactions with yields up to 99% and purities up to 100%. Recently, Siegel, Organ, and co-workers described the synthesis of a 1344-member allylic amine library.[251] First, the alkylation of an excess of secondary amine with 2,3-dibromopropene (**59**) was achieved (Scheme 52). The HBr salt of the excess amine was then removed either by filtration or aqueous extraction. A subsequent Suzuki cross-coupling reaction yielded the allylamine which was purified by ion-exchange chromatography.

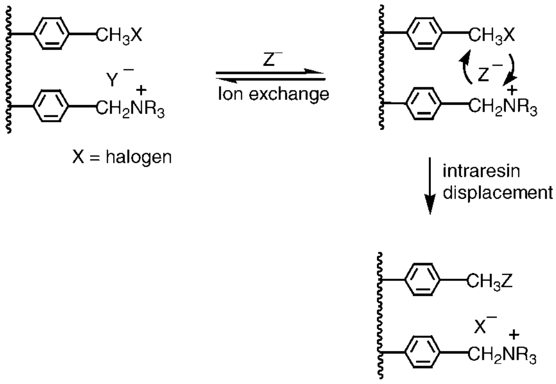


Scheme 51. Synthesis of a 48 compound library of β-aminoalcohols, purified by a strong ion-exchange chromatography.

Another recent application of cation-exchange resins as scavengers is the removal of boronic acids from solution.[252] In this application the complexed boronic acid can be subsequently released by cyclative cleavage (see Section 3.2.1.2). Regen et al. reported on a chloromethylated polystyrene for the scavenging of organic anions by covalent and ionic interactions.[253] Scheme 53 shows how such partially quaternized anion-exchange resins can be used. The pendant quaternary ammonium groups concentrate organic anions and therefore assist the nucleophilic displacement at the chloromethyl sites.[254–256] The ammonium groups allow for the swelling of the resin in aqueous media and thus make the chloromethyl groups accessible. Another possible way of purification is based on polymer-supported reagents. A polystyrene resin is generally used as the support and different ligands are immobilized on it. Typical ligands include amines, pyridines, imidazoles, oximes, hydroxylamines, Schiff bases, thiols, crown ethers, and a varity of phosphorus ligands.[257] This procedure thus allows a wide range of different metal ions to be recovered from solution.



Scheme 52. Purification of a library of allylic amines by ion-exchange chromatography.



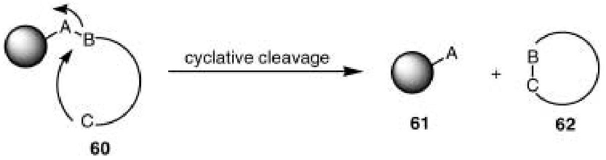
Scheme 53. General concept using partially quaternized anion-exchange resins as covalent scavengers; X = Cl, Y$^-$ = Cl$^-$, Z$^-$ = cholate anion.

3.2 Selective Cleavage from the Polymeric Support

An attractive feature of polymer-supported multistep organic synthesis is that the desired products can be selectively cleaved from the polymeric support. If a supported compound has not successfully passed every single step of the executed reaction sequence it will not be cleaved from the polymer support. Completion of a polymer-supported multistep synthesis with a selective cleavage reaction can yield products of high purity even if the previous transformations did not proceed quantitatively.[3] Thus, one of the decisive disadvantages of polymer-supported chemistry, the inability to purify polymer-bound intermediates from each other, can be overcome. Selective cleavage provides final products which ideally do not require purification, thus greatly facilitating rapid synthesis[258] and making this separation strategy ideal for parallel and automated synthesis.

3.2.1. Cyclative Cleavage

As shown in Scheme 54, cyclative cleavage is the result of an intramolecular reaction that yields a cyclized product. The polymer-bound side products are incapable of cyclizing, and thus remain attached to the polymeric support on release of the desired material.[259] Those groups which undergo intermolecular reactions during the cleavage step also remain



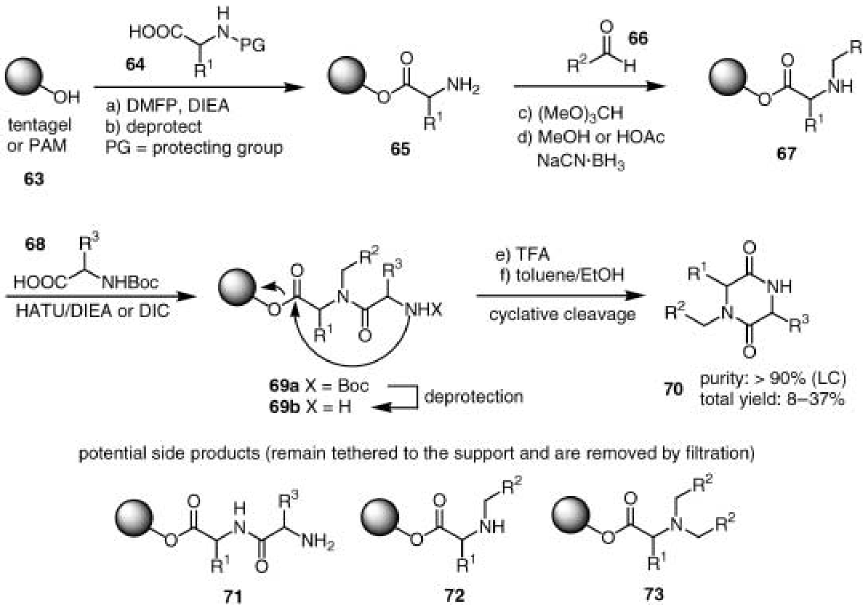
Scheme 54. The principle of cyclative cleavage.

bound to the polymeric support.[260] Cyclative cleavage often involves formation of a carbon–heteroatom bond during the cyclization step, but there are also examples of carbon–carbon bond-forming cyclizations.[261]

3.2.1.1. Cyclative Cleavage with Carbon–Heteroatom Bond Formation

Several polymer-supported approaches to heterocycles obtained by cyclative cleavage have been described. Examples include benzazepinones,[262] benzodiazepinones,[258, 263] diazepindiones,[264–266] hydantoins,[258, 263, 267–274] thiohydantoins,[268] thiazolylhydantoins,[275] benzopyrones,[276] benzoisothiazolones,[258] benzisoxazoles,[277, 278] diketopiperazines,[265, 279–281] diketomorpholines,[280] quinazolindiones,[282, 283] hydroxyquinolinones,[284] pyrazolones,[285–287] dihydropyridines,[288] dihydropyrimidindiones,[289] pyridine-fused heterocycles,[290] oxazines,[291, 292] oxazolines,[291, 292] oxazolidinones,[293–296] phthalides,[297] lactones,[298–300] lactams,[301] cyclic sulfonamides,[302] cyclic ethers,[303–306] cyclic imides,[307] tetrahydro-β-carbolines,[308, 309] 2-quinolone,[310] coumarin,[310] indolyl diketopiperazine alkaloids,[311, 312] and cyclic peptides.[313–315] Photoinduced cyclative cleavage reactions have also been reported.[310, 316]

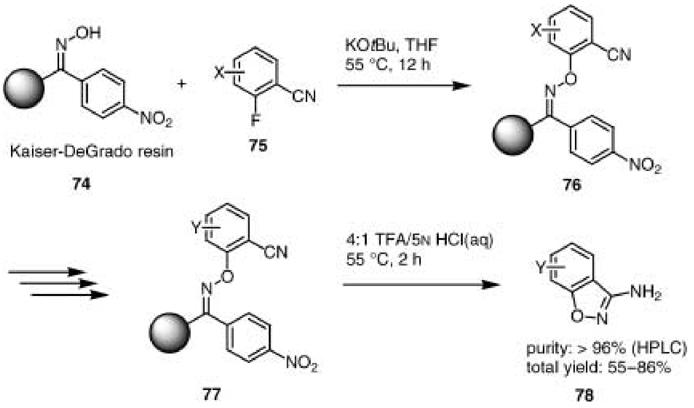
Diketopiperazines are quite common in nature and many natural products have been isolated with a wide range of biological activities. Szardenings et al. described two methods for the solid-phase-supported synthesis of diketopiperazines with three or four centers of diversity.[280] Each of them includes a cyclative cleavage step. The first method (Scheme 55) starts with the esterification of a protected amino acid **64**. Deprotection and reductive amination furnishs a secondary amine **67**, which is then acylated with a Boc-protected amino acid **68**. Successive deprotection results in the cyclization precursor **69b**. The cleavage-mediated cyclization yielded pure compounds **70** (>90% by LC). Potential side products, including nonalkylated **71**, nonacylated **72**, or over-alkylated **73**, remain attached to the resin and do not contaminate the library mixtures. Alternatively, these structures can also be prepared by a one-step Ugi multicomponent reaction and subsequent cyclative cleavage. Other than the building blocks, no further reagents are required, which makes this procudure especially attractive for high-throughput synthesis.



potential side products (remain tethered to the support and are removed by filtration)

Scheme 55. Preparation of diketopiperazines.

Lepore and Wiley reported on the synthesis of 3-aminobenzisoxazoles **78** (Scheme 56).[277, 278] Several on-resin modifications such as hydrolysis and amide-bond formation, Mitsunobu reactions, nucleophilic aromatic substitutions, Suzuki reactions, Sonogashira couplings, and Horner–Wadsworth–Emmons olefinations are possible, depending on the group X. Cyclative cleavage is induced by aqueous acidic conditions.

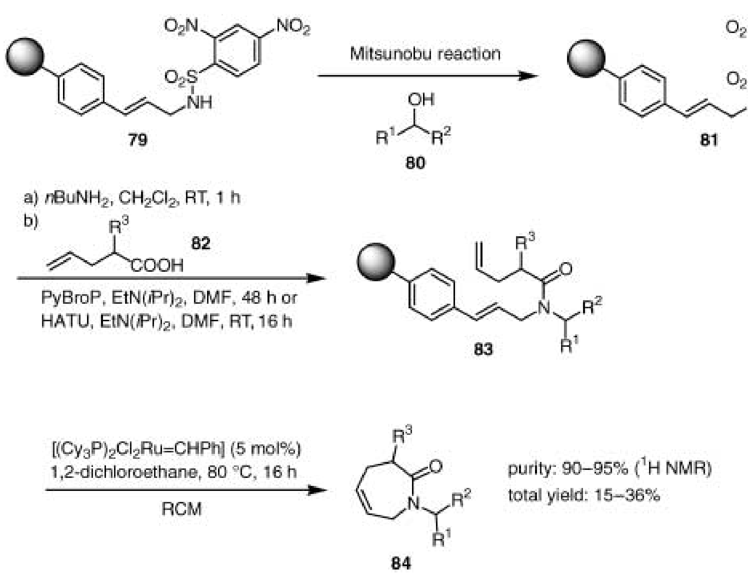


Scheme 56. Synthesis of 3-aminobenzisoxazoles.

3.2.1.2. Cyclative Cleavage with Formation of a C−C Bond

Formation of a C−C bond in the cyclative cleavage step can occur in several ways. Ring-closing metathesis has been used most frequently, for example, in the synthesis of dihydropyranes,[317] pipecolinnic acid derivatives,[317] Freidinger lactams,[317–320] and other N heterocycles,[321] furans,[322] phenols,[323] and macrocycles.[324–326] The advantages of this cyclization reaction are the chemical stability of an olefinic linker, the mild conditions required for cleavage, and the tolerance of the catalyst to a wide range of functional groups (for example, -COOH, -CONH-, -CHO, -CO-, -OH, -SONH-).[261]

Piscopio et al. described the synthesis of Freidinger lactams **84** by using an initial Mitsunobu loading step to obtain an intermediate resin-bound sulfonamide **81** (Scheme 57).[318] After cleavage of the sulfo-



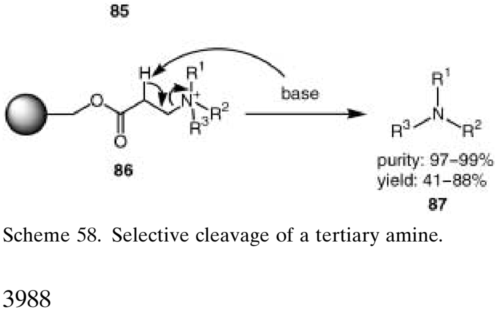
Scheme 57. Synthesis of Freidinger lactams.

namide group and acylation with an ω-unsaturated pentenoic acid derivative **82**, ring-closing metathesis with concomitant substrate cleavage provided the desired lactam **84** in high purity (90–95% by ^{1}H NMR spectroscopy). The ring-closing step can also include formation of a bond between the carbon atoms of a nucleophilic and an electrophilic. In this way, cyclic ketones,[327] tetramic acid derivatives,[328–331] indols (through the Wittig reaction),[332] and macrocycles (through the Horner–Wadsworth–Emmons reaction) have been prepared.[333] Ring closure by a transition-metal-mediated C–C coupling reaction has also been reported.[334, 335]

A cyclative cleavage based on a catch-and-release strategy was recently reported by Vaultier and co-workers.[252] In this case, a boronic acid was trapped by a cationic ion-exchange resin and subsequently released by an intramolecular Suzuki-type reaction.

3.2.2. Noncyclative Selective Cleavage

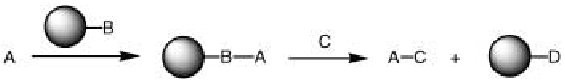
Noncyclative selective cleavage is mostly limited to selective elimination and fragmentation reactions.[303–305, 336–339] Morphy and co-workers described the synthesis of tertiary amines **87** in which a selective β-elimination cleaving step was applied (Scheme 58).[336] Coupling of the starting amine to an acrylate-functionalized polystyrene resin (Michael addition) and quaternization furnished the precursor for cleavage (**86**). Each step in the sequence has to proceed successfully for the final Hofmann elimination to occur. The purity of the final product **87** was found to be similar whether or not the individual reactions were driven to completion.



Scheme 58. Selective cleavage of a tertiary amine.

3.3. Catch-and-Release

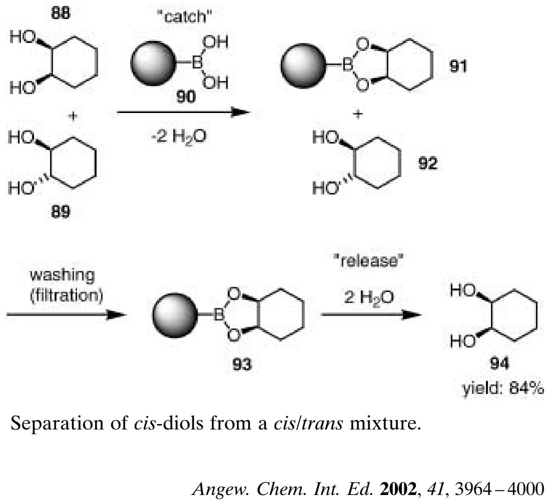
The catch-and-release strategy combines the features of both solution-phase chemistry and solid-phase chemistry. The principle of the catch-and-release strategy is shown in Scheme 59:[340] A desired low-molecular-weight compound **A** (which was synthesized in solution) is immobilized on a functionalized polymeric support to yield an activated polymer intermediate. Soluble impurities such as by-products, excess reactants, or solvent are removed by a simple filtration/washing protocol. By using this strategy merely for purification purpose, the next step will release the desired product into a new solution environment. However, it is also possible to carry out one or several modification steps on the polymer-bound compound before performing the final release step. In the latter case, catch-and-release implies a transformation to the desired compound A-C and, as such, combines solution and solid-phase synthesis.



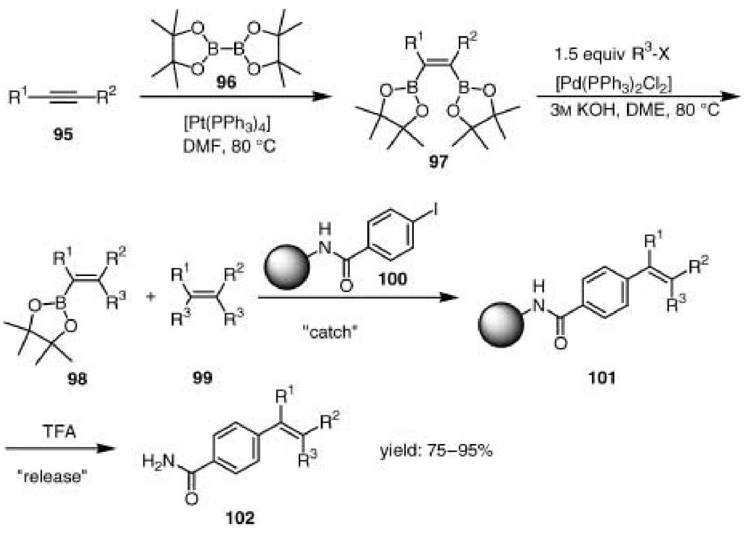
Scheme 59. The principle of the "catch-and-release" strategy.

The use of this method as a separation technique can facilitate the work-up, and is therefore particularly well-suited for multiparallel chemistry. Several applications in automated synthesis have been reported.[341–343] Since a comprehensive overview of this technique was recently published[340] we will describe only a few instructive applications.

An early example using "catch-and-release" as a purification strategy was reported by Seymour and Fréchet.[344] They separated *cis*-diol **88** from *cis/trans* mixtures using polystyrene resin **90** functionalized with boronic acid groups (Scheme 60). Brown and Armstrong used the catch-and-release strategy for



Scheme 60. Separation of *cis*-diols from a *cis*/*trans* mixture.



Scheme 61. Separation of Suzuki coupling products.

the separation of compounds resulting from a Suzuki coupling reaction (Scheme 61).[345] The bis(boryl)alkene **97** is transformed with 1.5 equivalents of an organo halide to give the monoaddition product **98** along with the diaddition product **99**. The mixture is combined with a resin-bound aryl iodide **100** to initiate a second Suzuki reaction. Only the monoaddition product **98** is captured on the solid support. Several coupling products **102** were obtained in high yields (75–95%) after cleavage with TFA. This route was applied to the parallel synthesis of tamoxifen derivatives.[346]

Aronov and Gelb described a procedure to "catch" alcohols and "release" amines (Scheme 62).[347] The "catch" step is realized by a Mitsunobu reaction of the alcohol **103** with a phthalimide-containing resin **104**. After washing off the soluble compounds from the resin, a hydrazinolysis "release" step releases the corresponding amine **106** in high yield (>96%) and purity. This polymer-supported phthalimide could be used for the selective conversion of less sterically hindered alcohols into corresponding primary amines or the generation of a resin-based combinatorial library starting with an alcohol. Combinations of both catch-and-release and cyclative cleavage have been employed to synthesize oxazolines, oxazines,[291, 292] and benzopyrones.[276] Table 2 gives a selection of further examples of the application of the catch-and-release strategy.

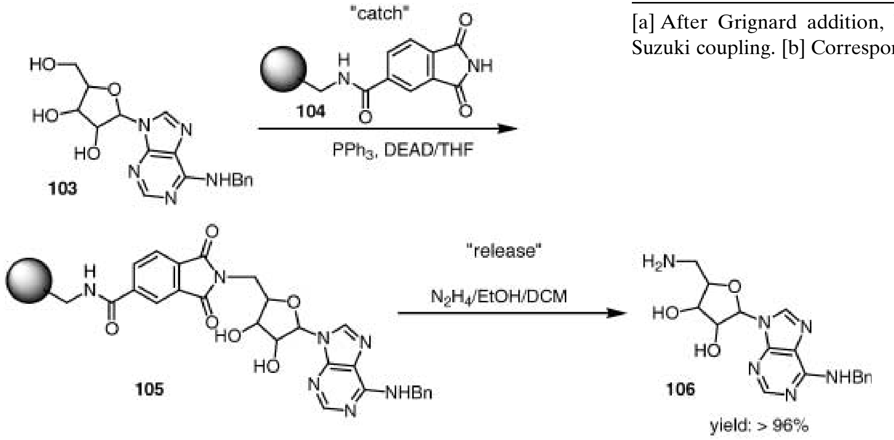
3.4. Purification and Separation with Soluble Polymeric Supports

It is generally believed that soluble polymeric supports are difficult to separate from the reaction mixture. However, this disregards their advantages (for example, homogeneous reaction conditions, standard analytical techniques, and high-loading capacities in some cases).

Table 2. Examples for the application of the catch-and-release strategy.

"Caught" compound	"Released" compound
acyl chlorides	amides[342]
	heterocyclic amides[387]
alcohols	alcohols (purification)[388]
	heteroatom-substituted amines, thiolates, imidazoles[a] [389]
	amines[347]
	oxazines, oxazolines[291]
aldehydes	secondary and tertiary amines[391]
alkenes	alkenes (purification), alcohols[392]
alkynyl ketones	benzopyrones[276]
9-anthrylmethyl-tagged esters	methyl esters[393]
amines	amines (purification)[240, 250]
	ureas[394]
	secondary and tertiary amines[391]
	guanidines[395]
β-amino alcohols	β-amino alcohols (purification)[396]
aryl boronic acids	macroheterocycles[252]
aryl carboxylic acids	aryl amines[397]
borylalkenes	tetrasubstituted ethylenes[345, 346]
carboxylic acids	*N*-hydroxysuccinimide esters[398]
carbonyl compounds	enones
iodoalkanes	alkanes, alkenes[392]
lithioaryls	arenes
ketones	1,2,3-thiadiazoles (after Stille coupling)[341]
phenols	aryl triflates and aryl nonaflates[399]
pyridines	alkylated dihydropyridones[400]
sulfonyl chlorides	sulfonamides[342]
α,β-unsaturated carbonyls	α,β-unsaturated carbonyls (purification)[b] [401]

[a] After Grignard addition, Wittig reactions, NaBH$_4$ reduction, reductive amination, Suzuki coupling. [b] Corresponding Diels–Alder adducts obtainable.[390]



Scheme 62. Synthesis of primary amines by the catch-and-release strategy.

Several techniques for the separation of soluble polymers from low-molecular-weight compounds have been evaluated (see Table 3).[348–351] There are various methods that separate macromolecules by size (preparative SEC, dialysis, membrane filtration and centrifugation).[352–354] All of them are suitable for automation, however, little effort has been undertaken, compared to the progress made in solid-phase synthesis, for multiparallel automation in this area. Also, other separation techniques, such as precipitation,

Table 3. Separation techniques for soluble polymeric supports.

	Dialysis[a]	Ultrafiltration[a]	SEC[a]	Precipitation/filtration[b]	Liquid-phase separation[b]
M_W of polymer [g mol^{-1}]	> 1000	> 1000	–	> 3000	–
sample volume [mL]	10 – 1000	1 – 100	< 1	1 – 100	10 – 1000
commercially available	yes	yes	yes	no	no
suitable for automation	yes	yes	yes	no	yes
suitable for high-throughput	no	yes	yes	no	yes
limitations	unsuitable for final cleavage step	–	–	unsuitable for multistep syntheses	different solubilities required

[a] Separation by differences in hydrodynamic volume; SEC = size-exclusion chromatography. [b] Separation by differences in solubility.

phase separation, and filtration through a silica cartridge have been reported. However, the application of these techniques to solution-phase synthesis depends on the physiochemical properties of each individual polymer. In addition, these techniques are sensitive to the change of functional groups on the polymeric support during the synthesis. Therefore, the use of soluble polymeric supports in combinatorial synthesis requires the careful selection of the appropriate separation technique.

3.4.1. *Separation of Soluble Polymeric Supports by Size*

For efficient and fast separations by size (hydrodynamic volume) homogenous polymeric supports should have medium molecular weights (5000 – 50 000 g mol^{-1}) and narrow molecular weight distributions (< 1.5). In addition, macromolecules with a persistent three-dimensional structure (for example, highly branched polymers) are preferable to a linear polymer structure. Purification based on size is general, since it does not rely on other physical differences between support-bound compounds, reagents, and catalysts. However, the eluent must be carefully chosen for the individual problem.

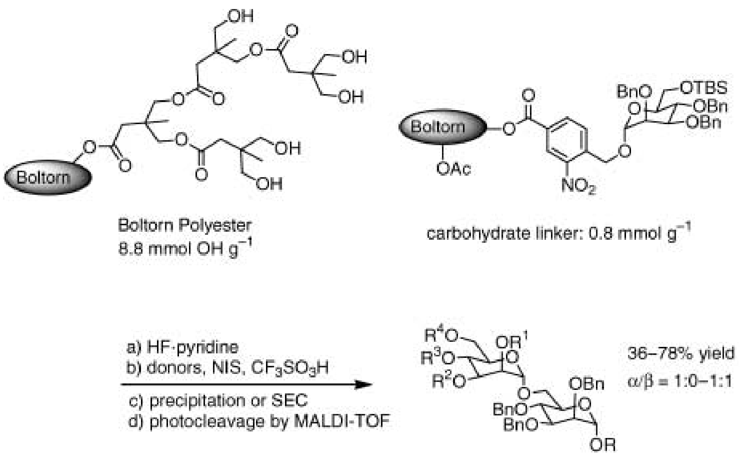
3.4.1.1. Size-Exclusion Chromatography

Size-exclusion chromatography (SEC; also known as gel permeation chromatography (GPC)) is used for the separation and fractionation of macromolecules on analytical and preparative scales.[350] The separation occurs predominantly by the difference in the hydrodynamic volume of the macromolecules in solution, however, in some cases the polarity of the molecules can also influence the retention times. The SEC technique, like HPLC, generally gives very reproducible elution times (typically of < 1 h) and hence can be used for automated synthesis. However, the high cost of an automated SEC system means it must be considered as a serial separation technique.

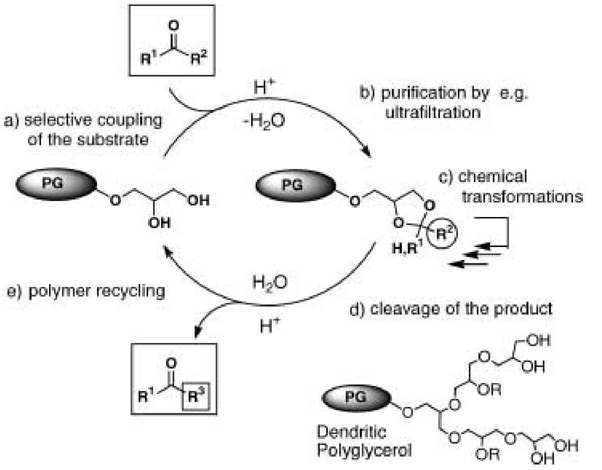
Nevertheless, SEC has been applied in combinatorial synthesis to the separation of dendritic high-loading polymeric supports from low-molecular-weight reaction products.[355, 356] Monodisperse polyamidoamine (PAMAM) dendrimers (generation 1) with an HMB-linker have been used to generate a small library (27 compounds) of indoles in a split-and-pool synthesis.[356] Separation was performed on a 25 mg (10 μmol) scale on a Sephadex LH-20 stationary phase to give good yields (> 90 %) for individual examples.

Carbosilane dendrimers (generation 0 and 1)[357] and star-like PEGs[358] have been used as multifunctional supports for the synthesis of β-lactams and guanidines, respectively. Preparative SEC was again used for the purification of the lactam and guanidine products, however, it was noted[357] that the application of membrane technology (see Section 3.4.1.2) could make an improvement. Another example of the use of SEC is the purification of dendrimer-bound salen ligands, which where employed in the enantioselective opening of epoxides.[359]

Most synthetic applications do not require the use of monodisperse polymeric supports (that is, perfect dendrimers) as long as the molecular-weight distribution of the polymer is narrow (< 1.5).[348] For example, dendritic aliphatic polyesters and polyethers have been used for the parallel syntheses of disaccharides (Scheme 63)[355] and functional carbonyl compounds (Scheme 64),[360] respectively. In the case of the dendritic polyesters, separation was performed by SEC on a 50 mg scale, and high purities (> 90 %) and moderate yields (40 – 60 %) were obtained. MALDI-TOF analysis of the reaction products could be directly performed on the polyester support by using a photolabile linker. A general problem of polyester supports, however, is their limited chemical stability for a general application in organic synthesis. Although the separation of dendritic polyethers by SEC can be successfully performed, membrane separation techniques (dialysis and ultrafiltration) seem to be more promising with respect to parallelization and automation of the process.[360]



Scheme 63. Synthesis of disaccharides using a dendritic polyester support and SEC purification. In all cases thioglycoside donors were employed.



Scheme 64. Usage and separation of dendritic aliphatic polyethers as high-loading supports, for example, carbonyl compounds.

3.4.1.2. Dialysis

Dialysis is a fairly established technique for the purification of soluble polymers.[354] Originally, dialysis was mainly used for the separation of biopolymers in aqueous media because of the incompatibility of the membrane materials with organic solvents. Nowadays, however, dialysis can be performed in nearly any organic solvent as a result of improved membrane materials. Typical molecular weight cut-offs (MWCO) are 1000, 5000, and 20000 $g\,mol^{-1}$ (based on linear polymer standards in water). In organic solvents, however, the MWCO can slightly vary because of the different swelling ability of the membrane materials in different solvents.

Recently, Haag et al. introduced dialysis as a multiparallel separation technique for soluble polymers on a multigram scale (Figure 5a, b).[360] In this way, dendritic polyglycerol,[361] a chemically stable, high-loading, soluble polymeric support, can be separated from low-molecular-weight impurities in multistep reactions. A fundamental advantage of this technique is the separation of large quantities (up to 10 mmol of substrate) in multiparallel approaches. Hence this material is attractive for the preparation of smaller libraries (10–100 compounds) on a relatively large scale. The limitations of this technique are the relatively long separation times (typically 12–36 h) and in some cases incompatibility with membrane materials, for example, for the separation of highly reactive or ionic compounds. Dialysis is also unsuitable for the final cleavage step of a multistep polymer-supported synthesis because the cleaved low-molecular-weight compound would be diluted into a large amount of solvent when diffusing through the membrane. In this case, ultrafiltration (see Section 3.4.1.3) can be used advantageously.

3.4.1.3. Ultrafiltration

A very efficient membrane separation technique for soluble macromolecules is ultrafiltration (UF), which was originally introduced by Bayer and co-workers for the automated synthesis of peptides in solution.[362] Like dialysis, it can be employed for the separation of low-molecular-weight compounds from soluble polymeric supports. Membrane materials (organic and inorganic) with high chemical stability and compatibility to most organic solvents are now commercially available.[363] In contrast to dialysis, much shorter separation times (ca. 1–3 h) can be achieved with UF because of the application of pressure (3–30 bar). It is necessary to use stirred UF cells or continuous flow systems for efficient separations to avoid clogging of the membrane. A chemically stable and commercially available set-up for pressures up to 6 bar is shown in Figure 5c.[364] For higher pressures and continuous flow membrane reactors, however, it is necessary to use HPLC-type systems to avoid gas bubbles in the system (Figure 5d). As a result of the high costs of the automated systems, UF must be considered as a serial separation technique.

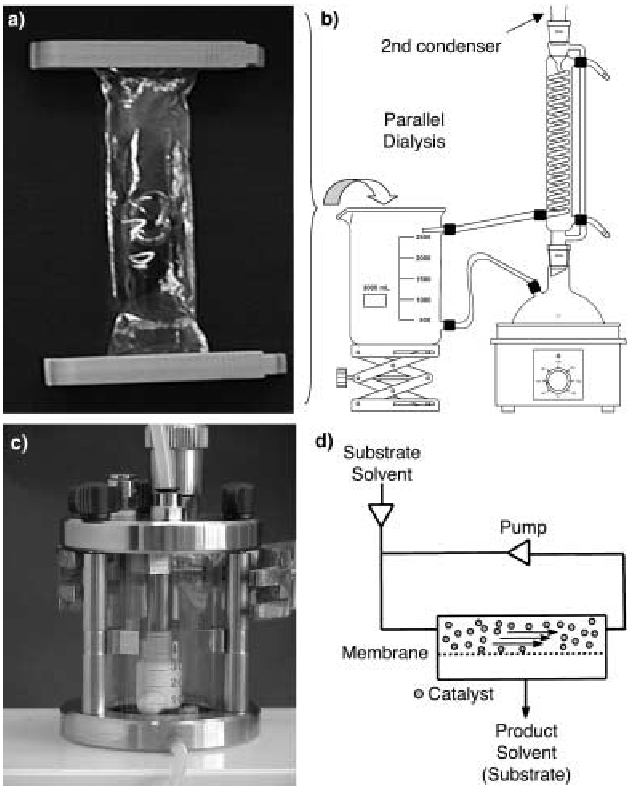


Figure 5. a) Dialysis tubing for the separation of soluble polymeric supports on a millimolar scale, b) apparatus for parallel dialysis for up to 12 reaction mixtures, c) chemically resistant UF unit for pressures up to 6 bar, d) continous flow setup for a membrane reactor (with kind permission from Dr. S. Mecking).

Ultrafiltration has been used for the separation of polymeric supports during multistep syntheses as well as for the separation of products after the final cleavage step (Scheme 64).[348, 360] However, this technique is employed most frequently for the separation of polymer-supported catalysts.[352] In this case, continuous flow UF systems (so-called membrane reactors) have been used for homogeneous catalysis. In these cases, the catalysts are complexed to amphiphilic dendritic macromolecules[365, 366] or attached covalently through ligands to dendritic macromolecules.[367–371] Although UF was originally introduced for the separation of linear polymeric supports, dendritic polymeric supports have been employed in many recent applications. Oxazaborolidine-functionalized microgels have also been used as homogeneous catalysts in enantioselective reduction of prochiral ketones and separated by UF.[372]

3.4.1.4. Centrifugation

Centrifugation can also be used to generate the required "pressure" for ultrafiltration and is frequently used in biochemistry in multiparallel approaches for purification of biopolymers (for example, proteins, DNA).[373] A major drawback of this technique, however, is the limited availability of membrane vials which are stable towards a broad range of organic solvents. Also, for analytical purposes, ultracentrifugation can directly separate large molecules from small molecules, similar to SEC. In both cases the separation times depend on the rotation speed of the centrifuge.[373]

3.4.2. Separation of Soluble Polymeric Supports Based on Physiochemical Properties

3.4.2.1. Precipitation/Filtration

Other separation techniques for soluble polymers, such as precipitation/filtration and liquid–liquid phase separation, rely on polymer properties (for example, solubility) rather than their hydrodynamic volume. Precipitation is frequently used in polymer chemistry to purify the respective polymer from low-molecular-weight impurities. This method works especially well when the polymer is crystalline and the glass transition temperature is above room temperature. It has been frequently applied to the separation of functionalized PEG and non-cross-linked PS supports.[349] Precipitation, however, is less suitable for multistep syntheses because impurities often remain trapped in the precipitated polymer. In addition, large solvent volumes are required to perform quantitative precipitation and hence automation of the process is difficult.

3.4.2.2. Liquid–Liquid-Phase Separation of Polymers

Another simple separation technique which is suitable for the separation of organic molecules from water-soluble polymers is based on liquid–liquid-phase separation between an organic phase (which contains the cleaved organic product) and an aqueous phase (containing the water soluble polymer).[348, 360] Bergbreiter also used these biphasic systems for the recovery of polymer-supported catalysts.[374] Although phase separation can be performed by a robot in a serial fashion, it is limited to systems in which the components have different solubilities in the two phases. Further examples of biphasic systems for simple separation (ionic liquids, fluorous phases, and supercritical fluids) are discussed in Section 2.

3.4.2.3. Column Filtration for Separation of Soluble Polymeric Supports

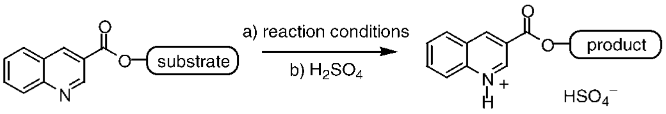
Although column filtration does not offer any advantages over conventional work-up protocols, filtration through a small amount of silica is often used as an additional purification step after the final cleavage of the product from the polymeric support. It also has been used for the separation of polymer-supported reagents from low-molecular-weight unpolar products.[375]

4. Miscellaneous Separation Techniques

The techniques mentioned in the following section are rather specific and so far have only been described for a limited number of examples. Many of them are restricted to certain functionalities or can be used only under special reaction conditions. The potential of these techniques to be automated has not yet been explored.

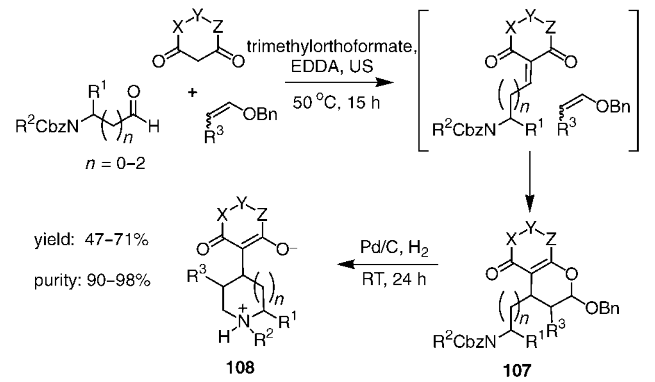
4.1. Phase Switch

Phase-switchable tags can be used to precipitate a product from organic solutions either through salt formation[376, 377] or by configurational change (for example, *cis*/*trans* isomerization).[378, 379] Perrier and Labelle described a simple solution-phase/solid-phase work-up protocol in which a phase-switchable tag was employed.[377] They covalently linked a substrate to a quinoline derivative, which is soluble in many organic solvents (Scheme 65). However, the conjugate can be precipitated after each reaction step in good yield (68–91%) by protonation to the corresponding quinolinium salt. Cleavage of the quinoline after the final reaction step, followed by precipitation liberates the desired products in high purities (>95%). In many cases the quinoline derivative was sufficiently pure for reuse in the next synthesis. Several benzylic alcohols and aromatic carboxylates have been prepared by this approach as individual compounds and also as mixtures. This purification strategy, however, might be limited by incomplete reactions, which result in mixtures of quinoline derivatives.



Scheme 65. Application of a quinoline tag for phase switching.

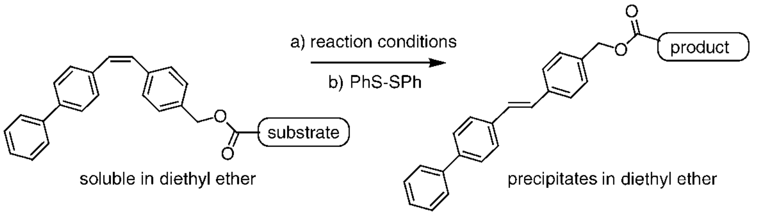
A very elegant phase-switch approach was recently described by Tietze et al. for the preparation of pyrrolidine, piperidine, and azepan derivatives.[376] In this case, the formation of a zwitterionic compound induces precipitation after a multicomponent domino reaction (Scheme 66). Sev-



Scheme 66. Synthesis of pyrrolidine, piperidine, and azepan derivatives as betains..

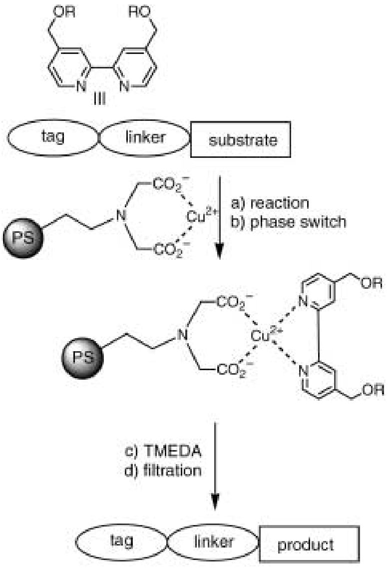
eral functionalized bicyclic compounds **107** can be formed from aminoaldehydes, 1,3-dicarbonyl compounds, and enol ethers through a Knoevenagel condensation and a hetero-Diels–Alder reaction. After hydrogenolytic cleavage of the protective groups and subsequent reductive amination, the corresponding betaines **108** are obtained in good yields (47–71%) and high purities (90–98%) as mixtures of diastereomers. The products are readily soluble in water and methanol and can easily be precipitated by the addition of diethyl ether. Although this approach is limited to betain formation, it does not require any coupling or cleavage of a phase-switchable tag, and hence saves time and synthetic effort.

A rather unconventional phase-switchable tag was recently designed by Wilcox and co-workers.[378, 379] In this case, *cis*/*trans* isomerization of a stilbene derivative was used to induce precipitation from the reaction mixture (Scheme 67). 4-Phenylstilbene was chosen as the phase-switchable tag because the *cis* isomer is readily soluble in many organic solvents, while the *trans* isomer can be precipitated with, for example, diethyl ether or methanol. The isomerization can be induced either photolytically or by addition of diphenyldisulfide. A small library of isoxazolines was prepared in high yields (73–90%) and high purities (88–95%) by this approach.



Scheme 67. Stilbene tags for phase switching by *cis*/*trans* isomerization.

Recently, Ley et al. introduced a solid-phase Cu complex as a scavenger for dipyridyl tags (Scheme 68).[380] This method is related to metallochelate chromatography in biochemistry in which $(His)_6$ tags, which are isolated by stationary Ni complexes bound to a dicarboxylate resin, are used.[373] The commercially available iminoacetic acid resin is first used to immobilize copper salts. This solid-phase Cu complex can now be used as a phase switch for the bipyridyl derivatives. Cleavage from the resin is easily induced in excellent yields (92–95%) and high purities (>90%) with TMEDA. The broad utility of this approach was demonstrated in the synthesis of hydantoine and benzodiazepine derivatives.

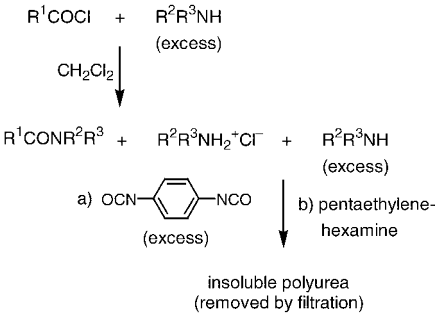


Scheme 68. Solid-phase bound Cu complex as a phase switch for bipyridyl tags.

Although all these phase-switchable-tag protocols seem rather complicated they allow for reactions to be performed under homogenous conditions with monitoring by standard methods, as well as in concentrated solutions on a large or small scale.

4.2. Purification through In Situ Polymerization

Another purification strategy is the removal of excess reagent by polymerization. A recent example of the removal of secondary amines from the reaction mixture was presented by Barrett et al.[381] Six simple amines were converted into the corresponding 3,5-dichlorobenzoic amides in high yields (85–96%) and purities (92–99%, Scheme 69). The excess amine was removed by subsequent addition of 1,4-phenylene diisocyanate (excess) and the cross-linking agent pentaethylenehexamine. The insoluble polyurea can then be filtered off and the product isolated.



Scheme 69. Removal from impurities by in situ polymerization.

4.3. Nanofiltration

While ultrafiltration (see Section 3.4.1.3) typically requires particle sizes above 1 nm, nanofiltration can separate even smaller species. Vankelecom and co-workers described a simple approach in which Ru and Rh catalysts with bulky binap-type ligands ($M_W > 300\ \mathrm{g\,mol^{-1}}$) were separated directly with a nanofiltration membrane in a continuous system.[382] They obtained very high turnover frequencies and *ee* values for the hydration of unsaturated carbonyl compounds. Although the system is limited by the working conditions, such as solvent, temperature, and pressure, it can be applied to a number of catalysts and substrates, especially in the field of fine-chemical synthesis.

4.4. Magnetic Bead Separation

Magnetic particles that have been encapsulated within highly cross-linked polystyrene beads and then functionalized with, for example, antibodies have found various applications in the area of immunodiagnostics.[383] The use of magnetic separation in the field of solid-phase organic synthesis has been limited because of the instability and/or relatively poor loading capacities exhibited by the currently available paramagnetic supports.[384] Recently, Sucholeiki and Perez[385] as well as Bradley and co-workers[386] independently presented an approach for the preparation of higher loading (up to 1 $\text{mmol}\,\text{g}^{-1}$) magnetic solid-phase beads. The composite beads were found to compare favorably with the standard Merrifield resin under typical chemical conditions in organic solvents. These materials were used as scavengers in the synthesis of sulfonamides and tetrapeptides.[385, 386]

5. Summary and Outlook

The separation techniques presented in this review illustrate alternatives for the traditional methods, such as cristallization, distillation, and column chromatography. While solid-phase chemistry has successfully demonstrated that it can be employed for the high-throughput synthesis and purification of large compound libraries on a small scale, it has several limitations. Thus, the various solution-phase techniques available should be reconsidered. This shift in paradigm is also observed in the pharmaceutical industry, which has partially returned to the solution-phase synthesis of individual compounds in a parallel format. In addition, sustainability (recycling of the support, catalyst, etc.), which was almost forgotten in the area of solid-phase chemistry, has become increasingly important.

Also, there are great industrial efforts towards a "green chemistry". Consequently, maximum efficiency of all resources and minimum environmental impact are crucial features for all future chemical processes. Ionic liquids are among the few reaction media which could contribute to reaching these goals by replacing volatile organic solvents, minimizing the consumption of catalyst, and enhancing the overall activity and selectivity of chemical processes. Although there is little parallelization and automation in this area yet, the work-up protocols are simple enough to fulfill the requirements.

Fluorous-phase strategies must be viewed in comparison with other phase-labeling strategies. As with any of those, fluorous biphasic systems do not provide solutions to all the conceivable problems encountered in organic synthesis. Rather they should be seen as a possible specialized solution for a specific problem.

Combinatorial chemistry might become a major application for perfluoro-tagged catalysts, reagents, and products, since they offer a quite general method for work-up. Here, it is likely that solid-phase extraction will replace liquid–liquid extraction, because a lower fluorine content in the molecule is needed and because such filtration steps are easily performed in a parallel fashion, either manually or by a robot. The widespread use of perfluorinated solvents is undesirable because of their negative long-term environmental impact. Fluorous silica gel certainly is a less problematic, easily recovered, and reusable alternative for small-scale operations. Besides combinatorial chemistry, fluorous-tagged catalysts may find application in industrial-scale operations either in fluorous biphasic systems or in synthesis in $scCO_2$. In contrast to laboratory-scale synthesis, where efficient containment and recovery of fluorous solvents can hardly be ensured, high-boiling fluorocarbons can be used in industrial processes for catalyst immobilization in closed circuit operations. Efficient quantitative recovery of fluorocarbons is imperative because of environmental concerns and the high cost of such solvents as well.

While fluorous reagents are a viable alternative in combinatorial chemistry, they are not likely to enter rapidly into the broad field of everyday synthesis, since they have to compete with established conventional reagents and a variety of solid-phase-bound reagents. Again, they might find specialized application in the commercial synthesis of fine chemicals, where their easy separation and regeneration presents a significant advantage.

One major advantage of SCF techniques over all other solution-phase techniques is the ease of product isolation. Simple depressurization suffices to obtain completely dry products if SCFs are used that are gaseous at normal pressure. This is an extremely important aspect, especially for the production of pharmaceuticals, where traces of solvents are not tolerated. Also, the tunable solvent power of SCFs allows for the development of a number of more elaborate separation schemes which are attractive for the separation from catalysts. Furthermore, $scCO_2$ has the potential to become the ideal "green solvent" which can be used to replace many potentially hazardous organic solvents. This may prove to be particular advantageous in the preparation of pharmaceuticals, cosmetics, and food additives.

In contrast to these alternative solution-phase systems, solid-phase supports have so far dominated the field of combinatorial chemistry as well as the automation of separation techniques. After ten years of intensive research, however, there is still no polymeric support for general application in combinatorial chemistry. Every polymer has its drawbacks (for example, chemical stability, polarity, loading capacity). Soluble polymeric supports have also had a similar, but less pronounced, revival over the past decade. Aliphatic polyethers and non-cross-linked polystyrene are among the most promising candidates in terms of stability. Dendritic and linear polyfunctional soluble polymers have by far the highest loading capacities and show great potential as supports for reagents and catalysts in combinatorial synthesis. Although many separation techniques for soluble polymeric supports have been developed for solution-phase organic synthesis (some, even in a parallel format), further progress in the automation of solution-phase separation techniques is required. For example, membrane stability towards all organic solvents and better size selectivity are still insufficient in the case of membrane separation (dialysis, ultrafiltration).

There are still many new developments in the field of polymer-based separation techniques, such as smart cleavage protocols and phase-switching protocols (including catch-and-release). Even though predictions about the future impact of this area are very speculative, the number of polymeric support based separations will certainly increase tremendously.

Among the various alternative separation approaches presented, there is nothing approaching "the best method"! Instead, it is more a search for an appropriate separation technique. Each individual chemical problem can only be successfully solved if the separation technique has been well-chosen and optimized. This becomes even more important for parallel approaches where small separation problems are amplified into a whole library. In the search for new separation strategies one should always bear in mind that it has to be a general tool for achieving the synthetic goal and not vice versa.

Abbreviations

acac	acetylacetonate
BARF	tetrakis(3,5-di(trifluoromethyl)phenyl)borate
binap	2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl
binaphos	2-(diphenylphosphanyl)-1,1′-binaphthyl-2-yl-1,1′-binaphthyl-2,2′-diyl-phosphite
binol	2,2′-dihydroxy-1,1′-binaphthyl
BMIM	1-*n*-butyl-3-methylimidazolium
Boc	*tert*-butyloxycarbonyl
BSA	bis(trimethylsilyl)acetamide
CESS	catalysis and extraction using supercritical solution
CMS-DVB	poly(chloromethylstyrene-*co*-divinylbenzene)
cod	cyclooctadiene
CSS	crystallization from supercritical solution
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dca	dicyanamide anion
DCT	dichlortriazene
DIC	5-(3,3-dimethyl-1-triazenyl)-1*H*-imidazole-4-carboxamide
DIEA	diisopropylethylamine
DIPT	diisopropyl tartrate
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMFP	1,3-dimethyl-2-fluoropyridinium 4-toluenesulfonate
DMSO	dimethylsulfoxide
DuPhos	1,2-bis(2,5-dimethylphospholanyl)benzene
EDDA	ethylenediammonium diacetate
ee	enantiomeric excess
EMIM	1-ethyl-3-methylimidazolium
FBC	fluorous biphasic catalysis
FBS	fluorous biphasic system
FC-72	perfluoroalkane solvent, mainly C_6H_{14}
FRPSG	perfluorous reversed-phase silica gel
GPC	gel permeation chromatography
HATU	*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate
hfacac	hexafluoroacetylacetonate
HMB	4-hydroxymethylbenzoic acid
HPLC	high pressure liquid chromatography
LC	liquid chromatography
MTO	methyl trioxorhenium
MWCO	Molecular weight cut-off
NBS	*N*-bromosuccinic imide
NMP	*N*-methylpyrrolidone
PAM	phenylacetamidomethyl
PAMAM	polyamidoamine
PEG	polyethylene glycol
PFMCH	perfluoromethylcyclohexane
PG	protecting group
PS	polystyrene
PyBroP	bromo-tris(pyrrolidine)phosphonium hexafluorophosphate
RCM	ring-closing metathesis
RESS	rapid expansion of supercritical solutions
ROMP	ring-opening methathesis polymerization
salen	*N*,*N*′-bis(2-hydroxybenzylidene)-1,2-diaminoethane
SASP	supercritical antisolvent precipitation
$scCO_2$	supercritical carbon dioxide
SCWO	supercritical water oxidation process
SEC	Size-exclusion chromatography
SER	sequestration-enabling technique
SFE	supercritical fluid extraction
TBAB	tetrabutylammonium bromide
TBHP	*tert*-butylhydroperoxide
TBME	*tert*-butyl methyl ether
TBTU	benztriazolyl-tetramethyluronium tetrafluoroborate
TEMPO	2,2,6,6-tetramethylpiperidin-*N*-oxide
TFA	trifluoroacetic acid
T_g	glass transition temperature
THF	tetrahydrofuran
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TLC	thin-layer chromatography
tolbinap	2,2′-bis(ditoluylphosphanyl)-1,1′-binaphthyl
UF	ultrafiltration
US	ultrasonication

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[1] The original meaning of "combinatorial synthesis" has partially disappeared and it is nowadays used as a synonym for (automated) synthesis of compound libraries in a parallel format.
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