NEW TOOLS AND CONCEPTS FOR MODERN ORGANIC SYNTHESIS

Steven V. Ley and Ian R. Baxendale

The increasing need to efficiently assemble small molecules as potential modulators of therapeutic targets that are emerging from genomics and proteomics is driving the development of novel technologies for small-molecule synthesis. Here, we describe some of the general applications and approaches to synthesis using one such technology — solid-supported reagents — that has been shown to significantly improve productivity in the generation of combinatorial libraries and complex target molecules.

COMBINATORIAL CHEMISTRY
The generation of large collections, or 'libraries', of compounds by synthesizing all possible combinations of a set of smaller chemical structures.

PARALLEL SYNTHESIS
Creation of a series of individual compounds through reactions performed simultaneously, rather than one at a time.

Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, UK.
Correspondence to S.V.L.
e-mail: svl1000@cam.ac.uk
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The unprecedented increase in the number of new drug targets arising from genomics and proteomics translates directly into a need for new methods to rapidly assemble highly pure small molecules (M_r ~250–800) that possess an ever-increasing level of structural complexity. These strategically important processes are also required to be environmentally cleaner, more efficient and lead to greater structural variation in as short a period of time as possible. Such demands have driven the development of novel technologies, which have begun to produce compounds at a greater rate than previously thought possible. One such molecule-assembly technology is that of solid-supported reagents. The use of solid-supported reagents in chemical synthesis in a multistep mode has been shown to markedly improve productivity in crucial aspects of the generation of fine chemical entities and complex target molecules. Further studies are under way to show the full range of advantages that these reagents offer — not only because of their significant importance in the field of COMBINATORIAL CHEMISTRY and PARALLEL SYNTHESIS, but also because of the possibilities that they present for a much wider impact generally on all synthetic chemistry.

Solid-supported reagents — summary

Chemists have generally addressed the question of improving their throughput by applying substrate-supported chemistry. In such a strategy, the substrate is temporarily immobilized on a polymeric resin, taken through a synthetic sequence and then cleaved back into solution (FIG. 1a). This makes it possible to drive reactions to completion with excess reagents and to create a high level of molecular diversity, often by the use of a robotic synthesizer. Although this strategy has many advantages, it also has several drawbacks: reactions can be slow and are difficult to monitor in real time compared with solution-phase chemistry; extra steps are required to attach and release the substrate from the resin; part of the resin attachment is often found in the final product; CONVERGENT SYNTHESES are not possible; resin loading is often poor; optimization of reactions can be very time-consuming and long linear sequences are difficult to achieve.

Many of these issues have been addressed by the application of solid-supported reagents. Supported reagents are reactive species that are associated with a support material. They transform a substrate (or substrates) into a new chemical product (or products), and the excess or spent reagent can then be easily removed by filtration. In a similar fashion, impurities can be removed from solution using a 'scavenger' immobilized on a support. A schematic representation of how these concepts work in practice to give clean products is shown in FIG. 1b.

This concept of immobilizing reagents on a solid support provides many advantages over both conventional solution-phase and solid-phase preparative routes (BOX 1). Moreover, it could be argued that this approach actually combines the best attributes from both of these synthetic approaches, which results in a more efficient and powerful methodology. It is certainly conceivable that, with the appropriate choice of support

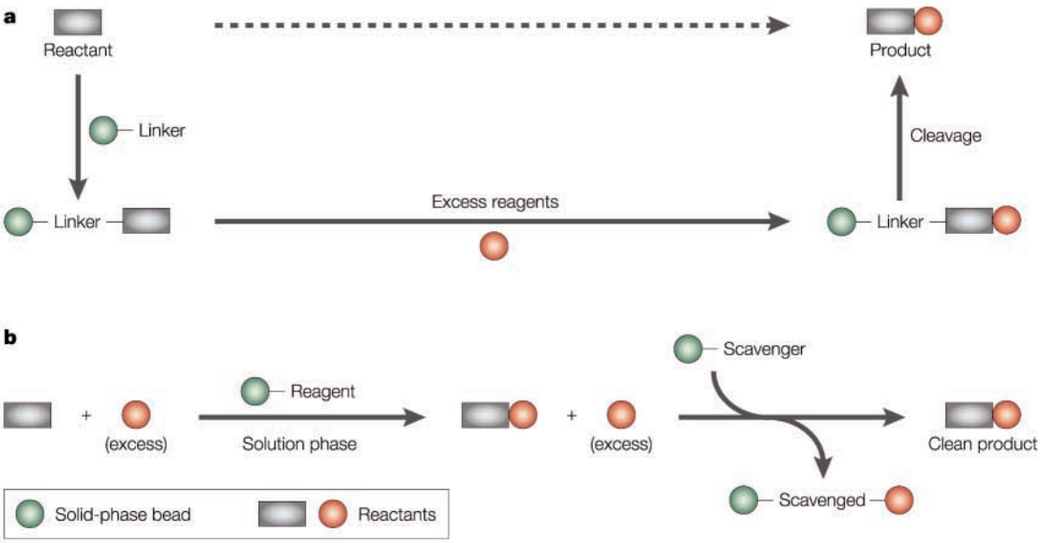

Figure 1 | **Polymer supports in organic synthesis. a** | Conventional solid-supported chemistry as used in combinatorial chemistry programmes. The initial substrate is immobilized on a polymeric resin and taken through a synthetic sequence, with the product being recovered at the end by cleavage back into solution. Reactions can be driven to completion with excess reagents. **b** | Solid-supported reagents in clean synthesis. Here, the reaction between substrates takes place in solution, with the reagent being associated with a support material. Excess or spent reagent can be easily removed by filtration, and impurities or unreacted substrates can be removed from solution using a scavenger that is immobilized on a support.

material, a diverse array of reagents could be tethered. In time, this could result in the entire repertoire of organic reactions and the synthetic flexibility afforded by solution-phase preparation being emulated with supported systems. In addition, the immobilization of the reagents completely obviates any requirement for conventional WORK-UP and purification strategies, resulting in cleaner reactions and easy removal of contaminating by-products by simple scavenging processes. Indeed, not only have supported variants of many commonly used reagents been prepared, but also a growing number of scavenging agents that are capable of sequestering unwanted by-products and excess reactants from solution have been described[1]. This brief review will outline some of the more general applications and approaches to synthesis using solid-supported reagents. It is not envisaged as a complete guide, but as a general overview. For a more detailed description, the authors would like to refer the reader to REFS 1–9 for comprehensive reviews.

Solid-supported reagents. In general, immobilization means tethering the reagent to an insoluble polymeric resin, usually a FUNCTIONALIZED DIVINYLBENZENE-CROSSLINKED POLYSTYRENE, although many other polymer cores and support materials — such as glass beads, silica, cellulose, zeolites and graphite — have also been used. In all cases, the reagent is completely insoluble, but the bound reactive species remains freely accessible within the support matrix to both the solvent and to the solution-dissolved reactants. This means that the reagents can be used in stoichiometric excess to force reactions to completion, resulting in cleaner reactions with recovery of the desired product becoming only the simple operation of filtration and solvent evaporation. This rapid separation of the supported material is particularly important in situations in which the reagent functions as a catalyst or if the spent resin can be regenerated and/or recycled, making the use of these reagents even more advantageous[10–31].

One of the most attractive aspects of this supported reagent approach is that toxic, noxious or hazardous reagents and their by-products can also be immobilized and thereby removed from solution, improving their general acceptability, utility and safety profile. This situation is aptly exemplified by the elimination of the volatile malodourous sulphur components from the commonly employed Swern oxidation reaction[32,33] (FIG. 2a) and by preparation of a heterogeneous version of the Lawessons reagent[34,35] (FIG. 2b). In both cases, the obnoxious stench that is associated with the sulphur by-products is eliminated, making the modified reaction of increased synthetic value, especially when considering the possibilities of using the reagents in scaled-up operations.

A frequently quoted drawback of working both with solid-supported substrates and with reagents is that the reactions involving these heterogeneous systems can often be slower than their solution-phase equivalents. An obvious approach to this problem is to carry out the reactions at slightly elevated temperatures. Unfortunately, many immobilizing supports and, in other cases, the active reagents themselves, are thermally unstable over extended periods of heating. The solution to this problem has been to use rapid, focused and short heating sequences — this is the type of heating mode provided by microwave irradiation. Under these conditions, the thermally enhanced reactions

CONVERGENT SYNTHESIS
Yields of synthetic organic reactions are usually less than 100%. So, for example, a three-step reaction linking the components A, B, C and D to give the linear sequence A–B–C–D, with each step having a 90% yield, would have an overall yield of 73%. But if A was linked to B and C linked to D separately, each with 90% yield, and then A–B and C–D linked with a 90% yield — a convergent synthetic strategy — then the overall yield is improved to 81%.

WORK-UP
Work-up is the phase of synthesis directed at product isolation. On completion of the synthetic transformation, the reaction may be quenched, neutralized or diluted to prevent further reaction(s). This phase of synthesis also incorporates any washing, extraction, separation, drying and, ultimately, solvent-removal steps.

FUNCTIONALIZED DIVINYLBENZENE-CROSSLINKED POLYSTYRENE
2–4% cross-linking produces a swelling resin, referred to as a microporous resin. 30–50% cross-linking produces a non-swelling structure, referred to as a macroporous resin.

proceed without jeopardizing the chemical integrity of the solid supports, but produce enhanced levels of reactivity. We have shown the value of this union of technologies both in the synthesis of small compound libraries[35,36] and also in the preparation of natural products (see below)[37–40].

In all branches of science, the execution of an experiment only has value if adequate planning has been carried out and sufficient means of monitoring and analysing the resulting data exist. This is especially true in chemistry, in which the majority of synthesis time is spent on the constant monitoring of chemical transformations. Such attention allows rapid and effective optimization of the yields, while also minimizing the products of side reactions. A key advantage of the supported-reagent technology over the more traditional solid-supported synthesis is the ease with which the intermediates and reactions can be monitored in real time. The lengthy optimization that traditional solid-phase syntheses require is minimized by the chemistry being carried out in solution, thereby allowing standard analytical techniques to be applied (that is, nuclear magnetic resonance (NMR), liquid chromatography-mass spectrometry (LC-MS), thin-layer chromatography and high-performance liquid chromatography (HPLC)). The process of optimization is now being made even more efficient by the combined application of automation and sophisticated planning techniques such as the 'Design of Experiment' software that is used to calibrate reaction parameters[41]. In general, the integration of robotics and cheminfomatics with this potential core synthetic technology is highly compatible. Many of the chemical steps involved — such as dispensing and weighing of solids (resins) and liquids (reactants/solvents), work-up and isolation (filtration/evaporation) and general manipulation of reaction conditions (mixing, heating/cooling and washing) can be carried out by robotic devices. Coupling this with the ability to monitor reactions online (LC-MS, React-IR, HPLC and others), to interpret the data in real time and then to generate intelligent feedback to the automated process, resulting in reaction modifications and calibration, greatly enhances the potential for advanced synthesis.

So far, we have only considered these reagents for a single-step transformation, whereas in reality, iterative multistep synthesis, convergent or various split and recombination approaches might also be adopted, giving increased synthetic scope over traditional substrate-supported chemistry (FIG. 3). Furthermore, as these reagent systems are anchored on a solid, they also allow the simultaneous use of multiple reagents to achieve one-pot transformations where, because of incompatibility of the reagents, no solution-phase equivalent exists. For example, when a reagent is immobilized, the presence of both a powerful oxidizing and a reducing agent in the same reaction becomes a viable option. This is a situation often referred to as a 'wolf and lamb' reaction[42] (FIG. 2c, 3d). In these reactions, a substrate is normally sequentially progressed through a planned sequence of chemical transformations, resulting in activation and immediate chemical modification by a subsequent supported reagent to yield a more advanced product. There have been several extremely persuasive demonstrations of the power of this type of synthetic approach[43–49]; moreover, in many examples in which the reagents were employed sequentially in isolation, the product was obtained in much lower yield[50–52]. With sufficient imagination and planning, there are tremendous opportunities for the generation of very useful chemical cascades, especially for sequences that involve the incorporation of extremely short-lived and reactive intermediates, which under normal synthetic operations would not be viable.

Support material and site effects. In choosing a reagent, it is also important to consider the support material because it confers certain chemical as well as physical characteristics to the immobilized reagent. The polarity of the support will certainly affect the reactivity of the attached functional groups; this could have a more profound influence than any effects that are imparted by a solvent in which the support is suspended. Additionally, the three-dimensional steric environment of the support matrix can also create many pore-like structures and unusual topographies, which exist in complete isolation due to phase partitioning. These factors produce reagent systems with unique kinetics as well as reactivities that are significantly different to those observed in an equivalent homogeneous solution[52–59]. This can lead to several advantages when attempting to overcome solvent-specific reactions or in situations in which the solubility of a reactant/product and the solution reagent is problematic. Furthermore, a structural detail commonly referred to as 'site-specific isolation'[58–60] can allow many reactions that are only possible in solution at extremely low dilution to be conducted at much higher relative concentrations, as a result of restricted intermolecular reactions. A common application of this phenomenon is in cyclization reactions. The standard solution-phase conditions of high dilution are used to reduce the rate

Box 1 | **Advantages of polymer-supported solution-phase synthesis**

Advantages over conventional solution-phase synthesis

- Excess reagents can be used to force the reaction to completion without causing problems with workup.
- Toxic, noxious or hazardous reagents and their by-products can be immobilized and thereby removed from solution.
- Ease of adaptation to automated synthesis.
- Allows the simultaneous use of multiple reagents that would otherwise be incompatible; for example, oxidizing and reducing agents.

Advantages over substrate-immobilized solid-phase synthesis

- As the chemistry is carried out in solution, standard analytical techniques can be easily applied to monitor reactions, allowing rapid optimization.
- Typically, an excess of reagent is used, so not every functional site needs to react to achieve good yields.
- Convergent syntheses are possible.

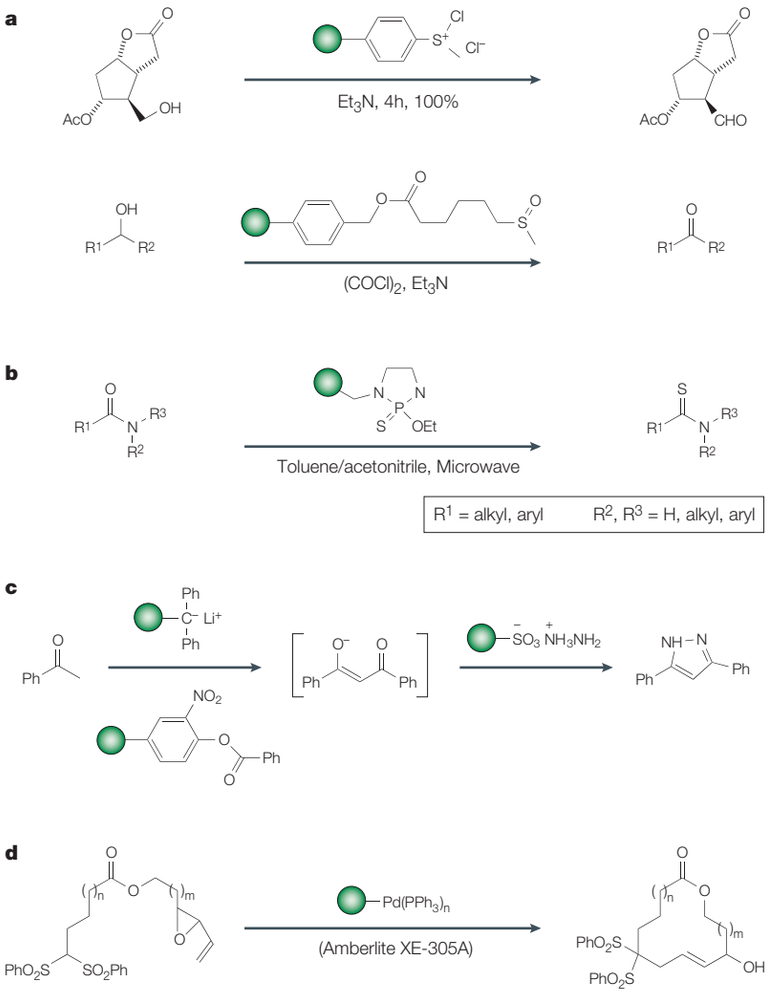

Figure 2 | **Some advantages of solid-supported reagents.** Toxic, noxious or hazardous reagents and their by-products can be immobilized and thereby removed from solution, as shown in **a** | oxidation by immobilized sulphur reagents and **b** | conversion of amides to thioamides using a polymer-supported thionating reagent. In both cases, the obnoxious stench that is associated with the sulphur by-products is eliminated, making the modified reaction of increased synthetic value, especially when considering the possibilities of using the reagents in scaled-up operations. **c** | As the reagents are anchored on a solid, it is possible to simultaneously use multiple reagents to achieve one-pot transformations where, because of incompatibility of the reagents, no solution-phase equivalent exists. For example, it becomes feasible to have both a powerful oxidizing and a reducing agent in the same reaction, which is often referrred to as a 'wolf and lamb' reaction. **d** | Using a bound coupling reagent for intramolecular cyclizations effectively reduces the local concentrations of substrates and thereby increases the amount of the desired cyclic product.

of intermolecular coupling; alternatively, by using a bound coupling reagent, the problem is circumvented by effectively reducing the local concentrations of substrates and thereby increasing the amount of the desired cyclic product[60–64] (FIG. 2d). The same effect has been observed in aldol and related reactions; the self-condensation products can be avoided by the simple technique of pre-forming the enolate of one component with a solid-supported base (in excess). Therefore, once immobilized, the enolate is unable to react until a subsequent addition of the second component occurs[63–66].

Again, in a third example, this same effect can be used for the monoselective protection/modification of equivalently difunctionalized molecules. In this case, either the reactant interacts with the support directly (under high dilution), becoming chemically transformed in the process, or the binding is only temporary for the duration of the reaction but permits the other pendant functional group to react in preference[65,66].

Solid-supported purification processes

Unfortunately, despite many years of effort, only a handful of reactions are known that occur with quantitative conversion and in absolute purity. The work-up and purification of most chemical reactions probably takes up most of a bench chemist's time. So, techniques that simplify and accelerate these operations should greatly free up valuable time, thereby allowing greater creativity and increased levels of output. Here again, supported systems can be used to aid the chemist in the guise of scavengers, quenching agents and catch-and-release protocols.

Scavengers. Supported scavengers are reactive species that selectively quench or sequester by-products of the reaction or remove excess or unreacted starting materials, and can be removed by filtration. These same species are also often referred to as 'sequestering agents' or 'quenching agents' and variants thereof[67–76]. The use of insoluble polymers and other solid-supported agents to scavenge by-products and excess starting materials from complex reaction streams — thereby effecting purification without the need to resort to liquid–liquid extractions or nonspecific column chromatography — is of significant strategic advantage. Two different classes of scavenger are commonly employed, a selection of which are shown in FIG. 4: those that form ionic interactions (acidic and basic resins, normally referred to as ion-exchange resins) and those that form covalent bonds (electrophilic and nucleophilic species)[67–72,77–82].

Most standard scavenging protocols are based on the concept of complementary reactivity. In the simplest cases, electrophilic and nucleophilic species are sequestered via a reciprocally functionalized support; likewise, acids and bases can be removed via salt formation with a solid-supported base or acid. In a similar way, many ion-exchange polymers — especially acidic and basic resins — have been used to work-up/quench reactions as suitable substitutes for aqueous conditions[73–76]. This is especially valuable if the compound in question is moisture sensitive or hydroscopic, or if a rapid quench and work-up procedure is required. Not only have supported reagents been used to scavenge organic fragments, but also the potential for chelation has been exploited to selectively bind ions or inorganic complexes from solution[83–87]. For example, the amine resins in FIG. 4 have been shown to have a high affinity for removing coordinatively unsaturated copper(II) salts from solutions that contain other organic amine compounds[88] (S.V.L. and J. Habermann, unpublished observations). In addition, there is a growing number of commercially available ion-sequestration resins, many of which have their origins in the water treatment and purification industry. The ability

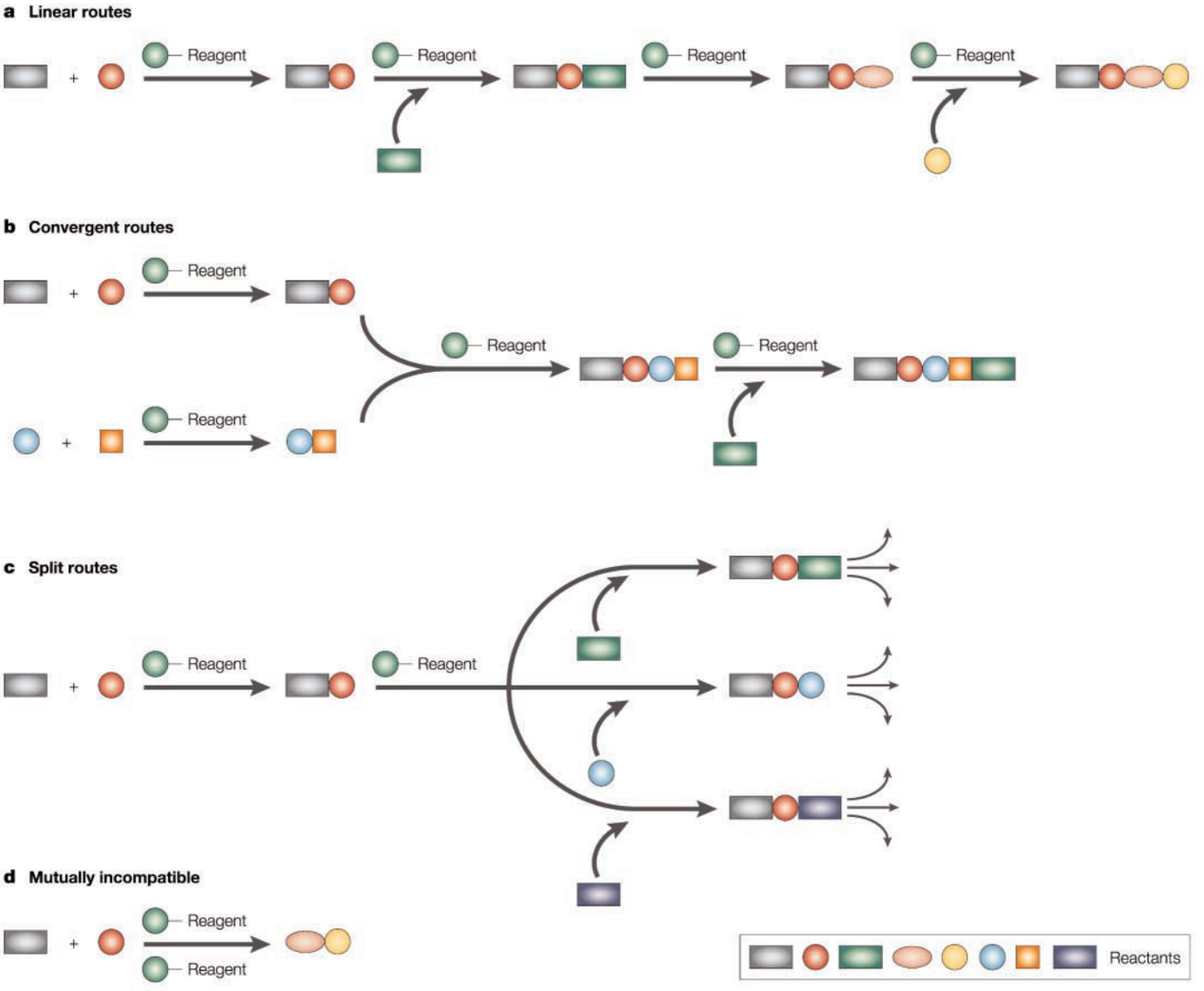

Figure 3 | **Opportunities for solid-supported reagents in clean synthesis. a** | Linear routes. **b** | Convergent routes. **c** | Split routes. **d** | One-pot reactions involving mutally incompatible reagents.

of these systems to be used in excess (and recycled) to ensure the removal of low levels of heavy metals and potentially biologically toxic ions have a direct significance to many applications in pharmaceutical, food and agrochemical manufacture.

Modified scavenging protocols. When reactions are performed using poorly reactive starting materials (for example, anilines or alcohols), product mixtures will contain reactants that are more difficult to remove by using standard scavenging techniques. In these cases, the addition of a highly reactive, bifunctional reagent to the product mixture can quantitatively transform the poorly reactive molecule into an activated intermediate that is subsequently easily trapped by a conventional scavenger. Both electrophilic and nucleophilic reagents have been used in this manner. An example of this strategy is shown in FIG. 5a (REF. 89). Treatment of an excess of amine with the highly electrophilic tetrafluorophthalic anhydride leads to an addition product, which can then be removed with a polymer-supported amine. This approach also enables any excess electrophiles — in this case, unreacted acid chloride (or hydrolysed material) and tetrafluorophthalic anhydride — to be removed in parallel, generating a clean solution of the product. Closely related to the concept of scavenger-enabling is the use of soluble, 'tagged' reagents to mediate chemical transformations[10,90–92]. These reagents bear a functional group that does not affect their reactivity, is preserved in the reagent by-products and reacts with a complementary functionalized supported scavenger at the end of the reaction (FIG. 5b). Only a limited number of soluble tagged reagents have so far been reported. However, their conception creates another interesting variation and tool for modifying synthetic approaches, and allowing facile reaction purification.

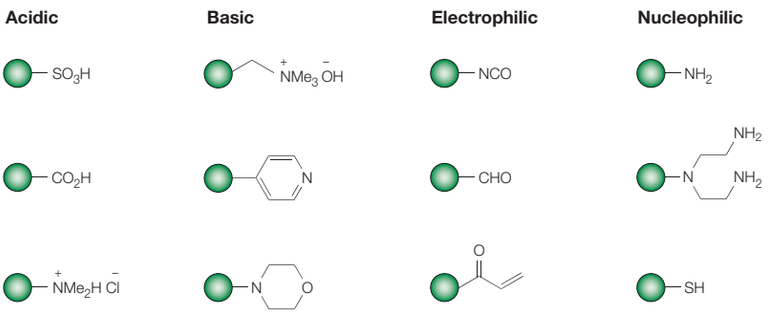

Figure 4 | **Some examples of polymeric scavenger systems.**

It is also worth mentioning under this heading the extensive purification procedures that are based on liquid–liquid phase partitioning, which exploit the immiscibility of fluorous solvents in both aqueous and organic media. In a simple approach, this allows a reagent with a highly fluorinated pendant chain to be used to transform a substrate, which can be easily sequestered into a fluorinated solvent, with the product being retained in the other fraction. Other more elaborate approaches have been demonstrated, which are reviewed in REFS 81,93,94.

Catch-and-release. So far, we have considered only the purification methods for the rapid clean-up of reaction mixtures that are facilitated by sequestration of either by-products, excess reactants or spent reagents. The idea that one can use a suitably functionalized solid-support to selectively capture the required product away from any contaminating impurities, filter and then re-release it (catch-and-release) in a pure form is also an important purification concept. The trapping and subsequent liberation of the product can, in essence, be accomplished using any type of reversible physical or chemical mechanism. Indeed, both ionic and covalent bonding interactions have been used to abstract chemical entities from reaction mixtures[67,77–82]; examples of these are shown in FIG. 5c. This is also the fundamental approach of many of the commercially available solid-phase extraction (SPE) kits that have been developed, which are now available in a myriad of formats and for application in a broad range of situations. The variety and generality of these systems are such that it is now conceivable to purify large chemical libraries in a very clean and efficient manner, ready for direct submission into biological screens.

Another interesting variation on this theme has been to use a hydrophobic absorption technique for the purification of synthetic intermediates and products. An interesting example of this is shown in FIG. 5d (REF. 95). Attachment of the 'tag' onto the amino terminus of a resin-bound peptide, followed by cleavage from the resin, gives the solution species along with several possible impurities. Treatment with porous graphitized carbon (PGC), which absorbs large aromatic structures with high affinity, allows the washing of the now immobilized material and hence removal of the impurities. Subsequent base-catalysed displacement of the 'tag', followed by elution, provides a facile recovery process for the now purified peptide.

As the scope and complexity involved in synthetic pathways increases, so the need for expedient work-up and purification procedures becomes of significant importance. All the above-mentioned methods are valuable additions to the repertoire of rapid purification techniques that can be used either independently or in conjunction with other supported-reagent systems. It is becoming more commonplace to see many of these approaches adopted in all areas of synthetic chemistry, not just in the areas of combinatorial chemistry and parallel synthesis. As the range and understanding of these processes becomes more standard, it will certainly be the case that greater use of these systems will be seen.

Universal scavenging protocols – phase switching. An area that has only received modest attention so far is an alternative approach to product synthesis and purification that combines and modifies the principles of conventional solution-phase chemistry with the catch-and-release and tagged-reagent methodologies. The process involves a reversible and selective interaction between a resin-bound metal and an organic metal-chelating 'tag' that is linked to the molecule of interest (FIG. 6). The tagged functionality can be easily decorated in various sequences in a similar fashion to standard solid-phase synthesis. Immobilization of the tagged material can then be realized by the addition of a resin-bound metal to the reaction media to act as an insolubilizing agent via complexation. The resin can then be isolated by simple filtration and any unbound impurities or reactants washed away. Release and cleavage from the tagging fragment yields the desired product as a mixture with the tagging moiety. Subsequent recapture of the 'tag'-function via re-immobilization facilitates the easy recovery and allows recycling of the material. Various resin-bound metals and metal-chelating organic molecules can be used[96–99]. Of the metal-chelating 'tags' so far explored, bidentate-pyridine containing ligands such as 1,10-phenanthroline and 2,2′-bipyridine have been found to be optimal, not only with respect to their good affinity for various metal ions but also their moderately low reactivity to a wide range of reaction conditions[96]. Both the uptake and release of the bipyridine-tethered material can be easily monitored by either thin-layer or high-performance liquid chromatography techniques, making optimization of the reactions relatively straightforward.

This methodology acts as a bridging technology between traditional solution- and solid-phase synthesis. In turn, this allows the chemist more flexibility to use well-established solution chemistry for difficult or classical transformations, but with a handle for simple purification. In combination with solid-supported reagents, the potential for carrying out extended synthetic routes excluding the usual requirements for purification make this phase-switching concept a key technology for advanced organic synthesis.

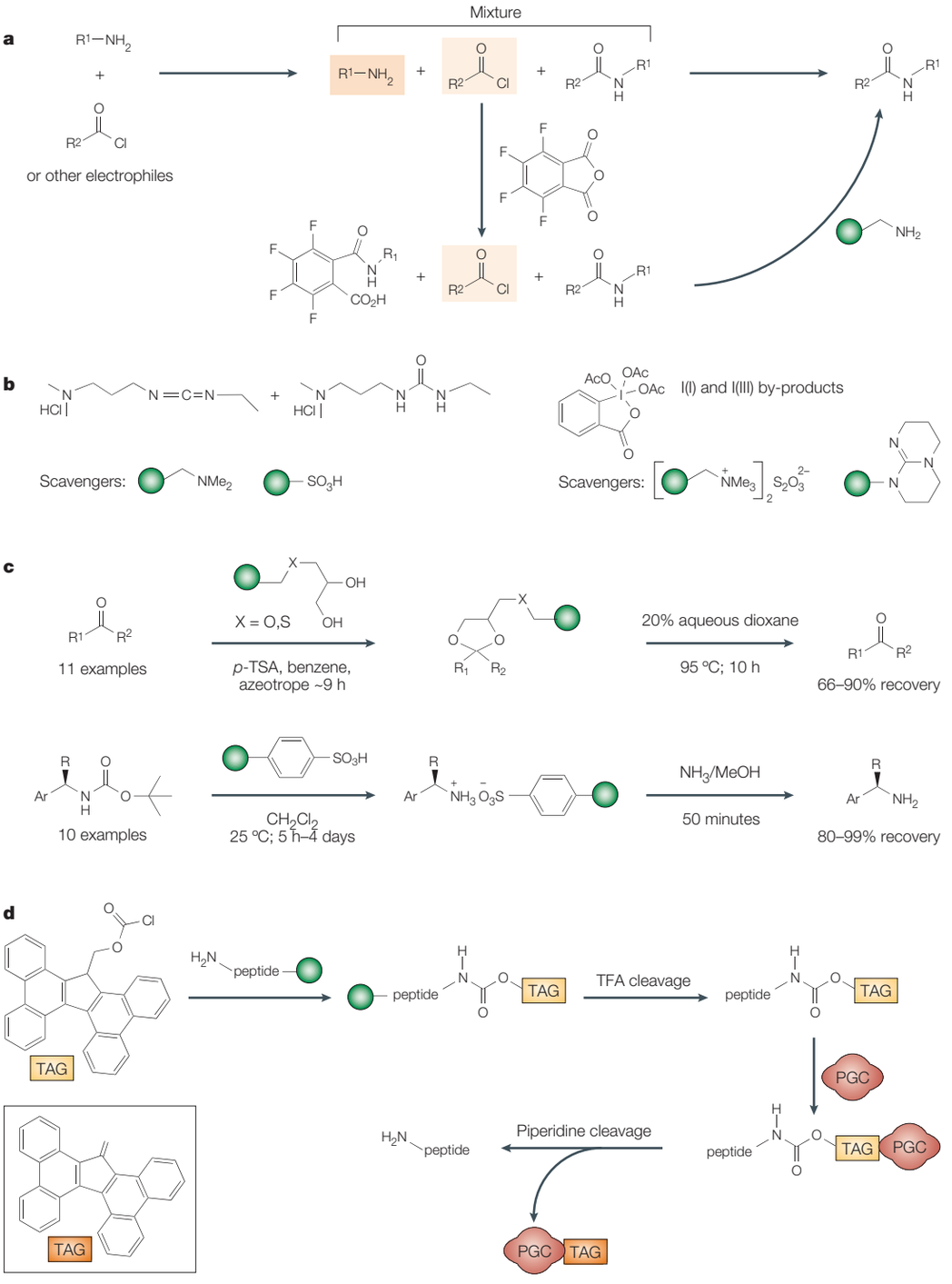

Figure 5 | **Scavenging protocols. a** | Activation of unreactive species towards scavenging. Addition of a highly reactive, bifunctional reagent to the product mixture can quantitatively transform a poorly reactive molecule into an activated intermediate that is subsequently easily trapped by a conventional scavenger. **b** | Tagged reagents. These bear a functional group that does not affect their reactivity, which is preserved in the reagent by-products and reacts with a complementary functionalized supported scavenger at the end of the reaction. **c** | Scavenging via ionic and covalent species: catch-and-release. A suitably functionalized solid support can be used to selectively capture the required product away from any contaminating impurities. After filtration, it can be re-released in a pure form. **d** | Affinity-binding purification of polypeptides and proteins. Attachment of a 'tag' onto the amino terminus of a resin-bound peptide, followed by cleavage from the resin, gives the solution species along with several possible impurities. Treatment with porous graphitized carbon (PGC), which absorbs large aromatic structures with high affinity, allows the washing of the now immobilized material and hence removal of the impurities. Subsequent base-catalysed displacement of the 'tag', followed by elution, provides a facile recovery process for the now purified peptide. TFA, trifluoroacetic acid; *p*-TSA, 4-toluene sulphonic acid.

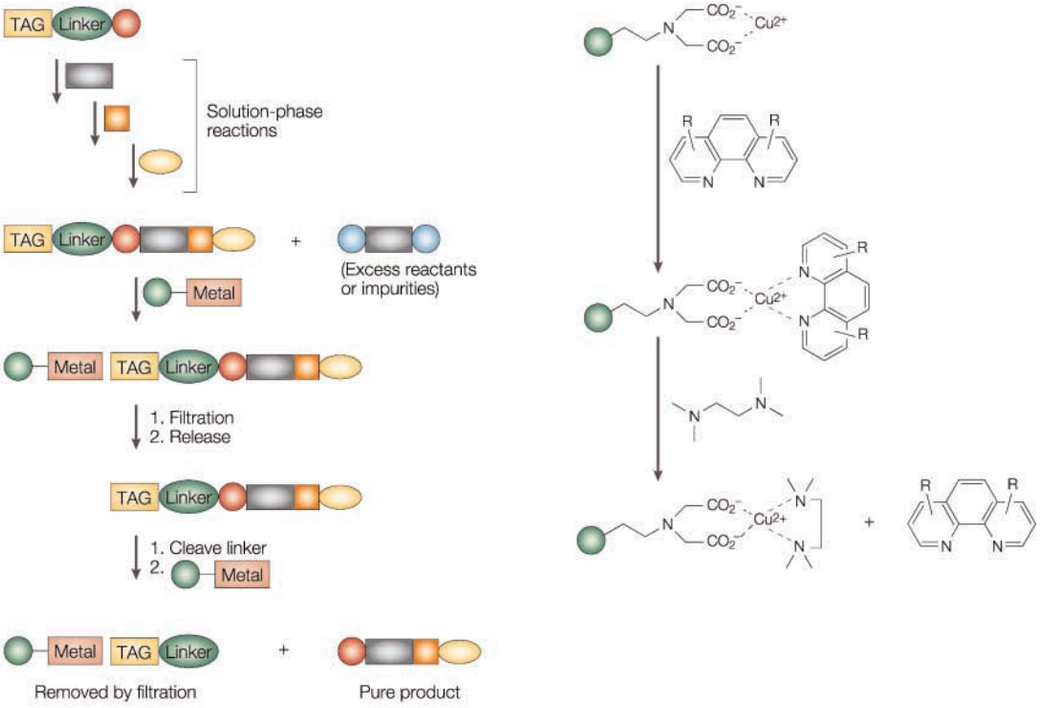

Figure 6 | **Preparation and purification of small molecules using metal tagging — the phase-switch technique.** This technique exploits a reversible and selective interaction between a resin-bound metal (for example, Cu^{2+}; right) and an organic metal-chelating tag (for example; bidentate pyridine-containing ligands; right). The tagged functionality can be taken through a solution-phase synthetic sequence. Addition of a resin-bound metal immobilizes the tagged compound on the resin, which can then be isolated by filtration, and any unbound impurities or reactants washed away. Release from the resin-bound metal gives the product linked to the tag. Cleavage of the linker, followed by recapture of the tag by reimmobilization, facilitates easy recovery of the pure product.

Synthesis of small molecules

Creating diversity. Over the past few years, enormous advances have been made to enhance the synthesis and design of molecules that fit a set of parameters, rather than just indiscriminately and wastefully synthesizing a vast number of compounds. Indeed, the current trend in compound library generation is towards well-designed, individual, pure and fully characterized compounds with quantities in excess of 20 mg. Coupled with this, the quest for increasing chemical diversity in library creation has led to an over-exploitation of commercially available monomers. Therefore, the clean and cost-effective preparation of novel sets of proprietary molecules is of key strategic importance to the chemical industry. Using solid-supported reagents, it is possible — through only simple chemical manipulations — to cleanly prepare a number of novel chemical arrays from readily available starting materials[23–26,100–111] (FIG. 7). These simple products could, in turn, be reacted further to construct more elaborate and highly functionalized molecules.

Target synthesis. There are many advantages provided by utilizing these above methods in synthesis, such as the ability to run reactions at reasonable scale yet to be able to obtain pure products without the need for conventional work-up and purification. Also, because of the ease of optimization, the use of solid-supported reagents is highly beneficial to the assembly of more complex structures and natural products. We have, to this end, carried out several syntheses to show the value of these reagents for the rapid synthesis of natural products and in other targeted syntheses[37,40,112–115] (FIG. 8).

Thinking about the future

The introduction of partial or fully automated procedures allows a more reliable, repeatable and efficient experimental protocol, often resulting in substantially higher throughput. The development of simplified and accelerated systems for chemical synthesis, based on solid-supported reagents in either an integrated or totally automated process, is obviously an area that requires special attention. There already exists a well-established and vast army of companies that build robotic devices capable of conducting many of the repetitive operations that are required in synthesis, especially for the area of solid-phase parallel combinatorial library generation. We will avoid the temptation to discuss the attributes of what could be described as these 'big chemist toys' and instead concentrate our efforts on a small number of evolving synthetic techniques and concepts for the future. For readers who would like to discover more about the use of automation in general synthesis, we recommend consulting REFS 116–121.

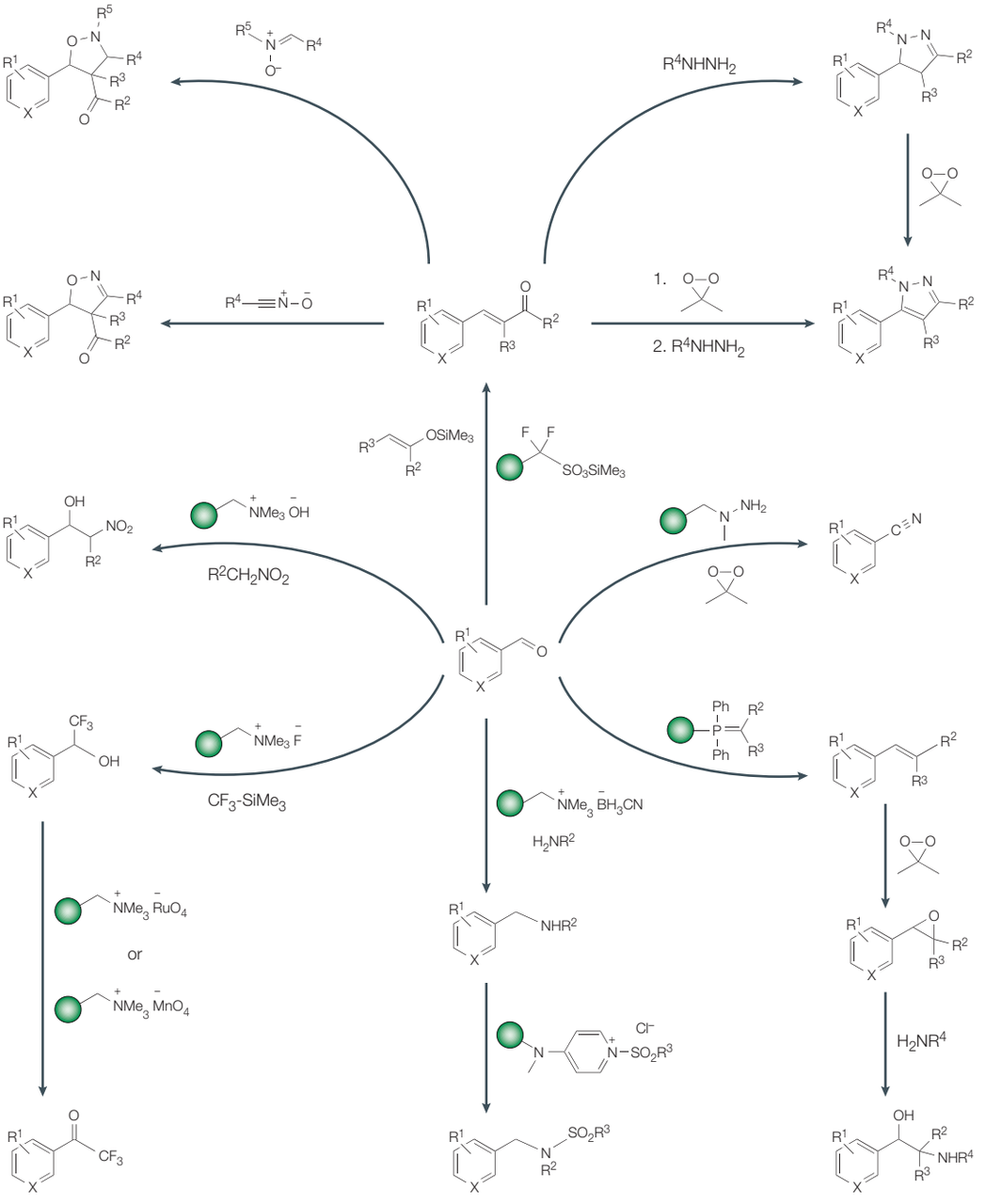

Figure 7 | **Construction of molecular diversity from simple monomers.** Solid-supported reagents can be used to cleanly prepare a number of novel chemical arrays from readily available starting materials through simple chemical manipulations[23–26,100–102,108].

A central aspect to progress in the area of supported reagents is the creation of new presentation formats; small beads, fine solids or dusty powders are difficult to manipulate, and so novel alternatives such as plug-in cartridges, reagent tablets, woven fabrics and various porous pouches have been developed[122–127].

In addition to chemical immobilization of reagents and substrates, it is also possible to consider the physical containment of reactive intermediates on the molecular level through microencapsulation. In the broadest sense, microencapsulation can provide a means of packaging, separating and storing material on a microscopic scale for later release or in restricted access under controlled and predetermined conditions. The general concept is to create a physical barrier to envelop the species of interest behind either an impervious capsule wall or a semi-permeable membrane that provides restricted directional movement. Having created species of this nature, there are many potential applications. A major field of interest is in catalysis; in this case, we can envisage a reacting species penetrating the capsule wall and undergoing chemical modification with a trapped

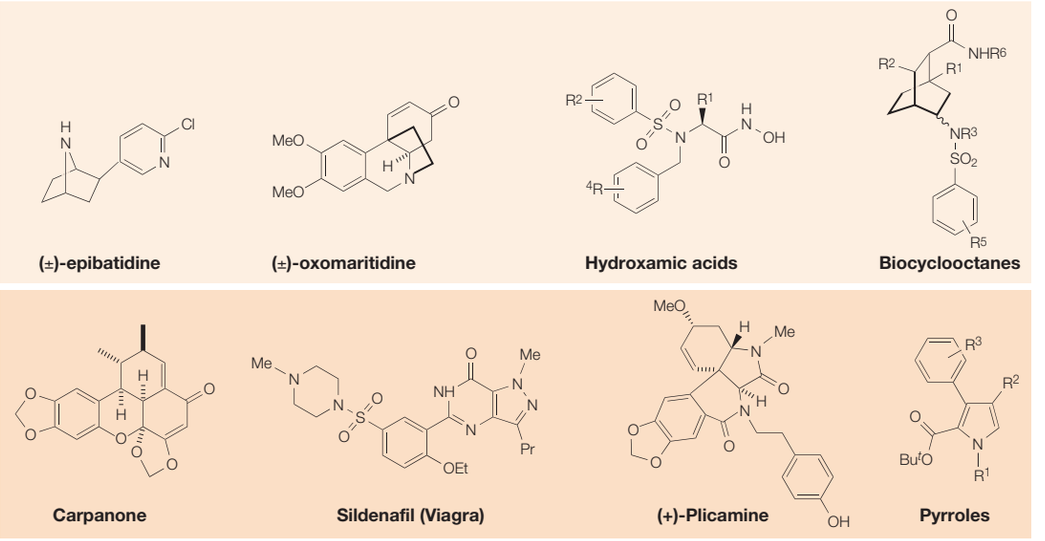

Figure 8 | **Polymer-supported total synthesis of alkaloid natural products and other targets.** Several syntheses have been carried out that show the value of solid-supported reagents for the rapid synthesis of natural products and in other targeted syntheses: epibatidine[115], oxomaritidine[114], hydroxamic acids[104], bicyclooctanes[100], carpanone[39,40,113], sildenafil[112], plicamine[37,38] and pyrroles[103].

active catalyst before being released back to the outside environment; this approach provides many advantages for purification, and easy recovery and recycling of the reagent[128,129]. As well as using these systems as mini reactor wells, we could also apply the systems to act as vehicles for reactant/reagent delivery. This could be arranged through a capsule construction that allows the slow leaching of the reagents/reactants into a reactor over a set period of time (a time-release mechanism); it would be a relatively simple process of controlling the wall permeability through thickness and choice of fabrication material. Alternatively, a disruption of the shell integrity could be triggered or designed into the system to invoke a more total release of the nucleus material. Here, a number of possible methods could be considered, including mechanical rupture, slow dissolution (that is, dissolving) of the capsule or wall disintegration facilitated by electrical, thermal, photochemical and sonication processes. Considering the scope for activation and release, the next stage of development could see the creation of multipurpose layered capsules, with orthogonal mechanisms for their rupture (FIG. 9a). In this mode, each layer could contain a separate reactant/reagent, so that a programmed sequence of releases would allow multistep synthesis in a single reaction vessel without the need for physical transfer of chemicals. In general, this technology could provide the chemical industry with a range of new chemical delivery, purification and isolation capabilities, which would greatly aid synthesis.

New approaches to process-scale synthesis can also be envisaged, using stacked reactors, flow systems and integrated batch processors. Indeed, system design is only limited by imagination; reactors such as that shown in FIG. 9b could be constructed. In such a set-up, individual plug-in cartridges containing supported reagents could be assembled in appropriate synthetic sequences and reagent streams flowed through. Small discs of functionalized fibres could be introduced to act as both filters and scavenging agents to ensure that unreacted material was not progressed through to the next chamber. In this way, multistep clean synthesis could be carried out in a flow-process manner, and is readily applicable to automation. Additional features, such as regions of heating and cooling, could be engineered into the system and product purities could be monitored by coupling the outflow to analytical systems. So far, we have not reached such levels of sophistication, although a number of mini-flow reactors have been produced that are capable of single-step transformations[130,131].

Another idea is to use reactors based not on flow systems but on centripetal force. The idea of having impregnated coatings or immobilized reagents that are attached directly to the surface of a disc that can be revolved, thereby creating radial movement of a liquid phase from the centre to the outside, is an interesting one. This concept will be familiar to many users of purification devices such as the chromatotron (see Analtech Technical Data Sheet — Rotors and Accessories in the online links box). Here, a sample of material to be purified is trickled onto a silica-layered disc, and a reservoir of solvent is used to slowly elute and separate the sample as it moves across the face of the device. Eventually, the individual components reach the edge and are scattered from the disc to be collected in fractions (FIG. 9c). It takes only a small leap of imagination to consider the functionalization of the silica on these spinning discs (many different types of functionalized silica are commercially available), and their application to synthesis rather than purification. Indeed, such a system would give many benefits not only in terms of efficient mixing and control of concentrations, but also from the

high surface area (greater reactivity) and reduced quantities of solvent required. Additionally, with the desire to conduct successive multiple reactions, the question is: why not have these systems banded with multiple reagents placed at different circumferences on a single disk, creating the potential for multistep synthesis from a single reactor? As well as rotating wafers of immobilized reagents, it is also possible to create related systems based on cones[132,133] (S.V.L., I.R.B. and A. Flewitt, unpublished observations). This approach creates advantages in solvent and substrate flow, resulting in beneficial changes in the parameters of lag time, substrate/reagent concentrations, and also greater penetration of the immobilized layer and so better overall reaction kinetics.

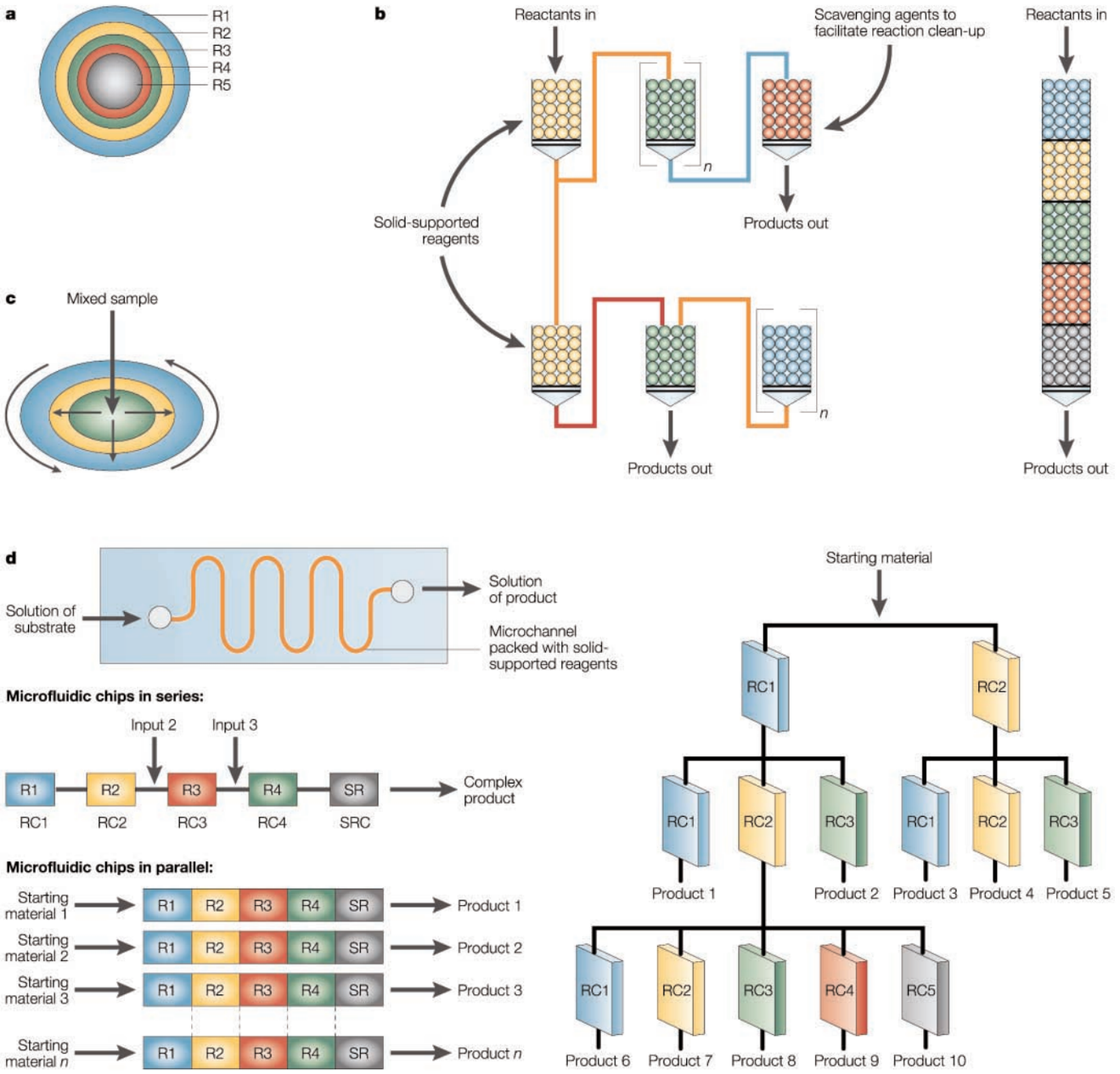

Figure 9 | **Evolving synthetic techniques and concepts. a** | Concept of multilayered microencapsulated reagents. Each layer could contain a separate reactant/reagent so that a programmed sequence of releases would allow multistep synthesis in a single reaction vessel without the need for physical transfer of chemicals. **b** | Flow systems and stacked reactors. Individual plug-in cartridges containing supported reagents could be assembled in appropriate synthetic sequences and reagent streams flowed through. **c** | Reactors based on centripetal force. The liquid phase would move from the centre to the outside of rotating wafers or cones of immobilized reagents. **d** | Lab-on-a-chip concept. At its simplest level, a solution of substrate could be pushed through a microchannel packed with solid-supported reagents (or its surface functionalized), and the product would emerge at the far end. A diverse tool kit of such functionalized chips could be combined in various ways to facilitate multistep synthetic sequences.

There is also the scope of conducting these reactions under inert or even active atmospheres of gases where an extremely high percentage of the surface layer is in continual contact with the gaseous phase; therefore, in combination with a supported oxidizing or reducing catalyst we would be presented with a reactor of significant interest. Systems based on these or similar concepts are already envisaged, and in certain cases prototypes have been developed[135].

A complementary approach lies in miniaturization with concomitant multi-parallelization to access very large, diverse compound libraries on a micro-scale. The science of microfluidics and the concept of the 'lab-on-a-chip', which will facilitate this, is still in its infancy. As illustrated (FIG. 9d), at its simplest level, one can envisage a micro-channel etched onto a centimetre-scale glass or plastic chip, the topology of which is such that the chip contains many metres of channel. If the channel is packed with a supported reagent (or its surface functionalized), a solution of substrate introduced and pushed through with a pumping system would emerge at the far end as a solution of the product. If developed, a diverse tool kit of such functionalized chips could be combined to facilitate multistep synthetic sequences. For example, used in series, the chips could be arranged such that a multitude of reactions could be carried out on each substrate (a splitting of the reaction flow approach), possibly with further monomer inputs at different points allowing access to multiple products. Alternatively, when used in parallel, the chip arrays could be sequenced for the production of very large libraries of compounds. Clearly, this is an area that is ideally suited to supported reagents — synthesis in this format is hard to envisage using any other technique as, purification on this scale, although not impossible, would make parallelization prohibitively expensive.

Conclusion

In all these systems, the main thrust is directed not at isolation of the compounds after each individual step, but, instead, at telescoping the intermediates through a sequence of transformations ending up with more-advanced products. These methods really will revolutionize the way we think, plan and optimize chemical processes. Gone are the days when a multistep synthesis required the laborious retrieval and characterization of each successive fragment and by-product. Now, the potential for simultaneous analysis and reaction modification, coupled with the rapid progression of intermediates, means we could produce a full array of compounds in the same time. So, in summary, the world of organic synthesis is evolving and it would be wise to embrace these new technologies or be left struggling with conventional methodologies.

1. Ley, S. V. *et al*. Multi-step organic synthesis using solid-supported reagents and scavengers:a new paradigm in chemical library generation *J. Chem. Soc. Perkin Trans. 1* 3815–4195 (2000).
This review constitutes the most comprehensive coverage of supported reagents in the literature, as well as a full list of all other reviews. It contains a historical account of the area followed by a full tabulated and cross-referenced section on the use of individual supported reagents.
2. Thompson, L. A. Recent applications of polymer-supported reagents and scavengers in combinatorial, parallel, or multistep synthesis *Curr. Opin. Chem. Biol.* **4**, 324–337 (2000).
3. Kobayahi, S. Immobilized catalysts in combinatorial chemistry. *Curr. Opin. Chem. Biol.* **4**, 338–345 (2000).
4. Kirschning, A., Monenschein, H. & Wittenberg, R. Functionalized polymers — emerging versatile tools for solution-phase chemistry and automated parallel synthesis. *Angew. Chem. Int. Edn Engl.* **40**, 650–679 (2001).
5. Ley, S. V. & Baxendale, I. R. *Supported Catalysts and their Applications* 9 (Royal Society of Chemistry, Cambridge, UK, 2000).
6. Ley, S. V. & Baxendale, I. R. Organic synthesis in a changing world *Acc. Chem. Res*. (in the press).
7. Ley, S. V. *et al.* Solid-supported reagents for multi-step organic synthesis: preparation and application. *Il Farmaco* **57**, 231–330 (2002).
8. Hall, B. *et al*. Preparation of compounds using polymer supported reagents. WO Patent 9,958,475 (1999).
9. Sherrington, D. C. Polymer-supported reagents, catalysts, and sorbents: evolution and exploitation — a personalised view. *J. Poly. Sci. Poly. Chem*. **39**, 2364–2377 (2001).
A very stimulating walk through the archives of polymer-supported reagent technology from the personal viewpoint of D. Sherrington — a major contributor to the area.
10. Parlow, J. J., Case, B. L. & South, M. S. High-throughput purification of solution-phase periodinane mediated oxidation reactions utilizing a novel thiosulfate resin. *Tetrahedron* **55**, 6785–6796 (1999).
11. Drewry, D. H., Coe, D. M. & Poon, S. Solid-supported reagents in organic synthesis. *Med. Res. Rev*. **19**, 97–148 (1999).
An excellent review aimed at the medicinal chemist, slightly dated now, but containing some good descriptions of the concepts and ideas that have subsequently evolved in the area.
12. Hinzen, B., Lenz, R. & Ley, S. V. Polymer supported perruthenate (PSP): clean oxidation of primary alcohols to carbonyl compounds using oxygen as cooxidant. *Synthesis* 977–979 (1998).
13. Flynn, D. L. *et al*. Polymer-assisted solution phase (PASP) chemical library synthesis. *Med. Chem. Res*. **8**, 219–243 (1998).
14. Patchnornik, A. & Kraus, M. A. Reactive species mutually isolated on insoluble polymeric carriers. 1. The direct monoacylation of esters. *J. Am. Chem. Soc.* **92**, 7587–7589 (1970).
15. Rapoport, H. & Crowley, J. I. Cyclization via solid phase synthesis. Unidirectional Dieckmann products from solid phase and benzyl triethylcarbinyl pimelates. *J. Am. Chem. Soc.* **92**, 6363–6365 (1970).
One of the original supported reagent papers that describes the concept of selective monoprotection of symmetrical systems through the use of insoluble support systems.
16. Shuttleworth, S. J., Allin, S. M. & Sharma, P. K. Functionalised polymers: recent developments and new applications in synthetic organic chemistry. *Synthesis* 1217–1239 (1997).
17. Hinzen, B. & Ley, S. V. Polymer supported perruthenate (PSP): a new oxidant for clean organic synthesis. *J. Chem. Soc. Perkin Trans.* **1** 1907–1908 (1997).
18. Akelah, A. & Sherrington, D. C. Heterogeneous organic synthesis using functionalized polymers. *Synthesis* **6**, 413–438 (1981).
19. Akelah, A. & Sherrington, D. C. Recent developments in the application of functionalised polymers in organic synthesis. *Polymer* **24**, 1369–1386 (1983).
20. Akelah, A. & Sherrington, D. C. Application of functionalized polymers in organic synthesis. *Chem. Rev.* **81**, 555–589 (1981).
21. Booth, R. J. & Hodges, J. C. Polymer-supported quenching reagents for parallel purification. *J. Am. Chem. Soc.* **19**, 4882–4886 (1997).
22. Hinzen, B. & Ley, S. V. Synthesis of isoxazolidines using polymer supported perruthenate (PSP) *J. Chem. Soc. Perkin Trans. 1* 1–2 (1998).
23. Haunert, F., Bolli, M. H., Hinzen, B. & Ley, S. V. Clean three-step synthesis of 4,5-dihydro-1H-pyrazoles starting from alcohols using polymer-supported reagents *J. Chem. Soc. Perkin Trans. 1* 2235–2237 (1998).
24. Ley, S. V., Bolli, M. H., Hinzen, B., Gervois, A.-G. & Hall, B. J. Use of polymer supported reagents for the clean multi-step organic synthesis: preparation of amines and amine derivatives from alcohols for use in compound library generation. *J. Chem. Soc. Perkin Trans. 1* 2239–2241 (1998).
25. Bolli, M. H. & Ley, S. V. Development of a polymer bound Wittig reaction and use in multi-step organic synthesis for the overall conversion of alcohols to β-hydroxyamines. *J. Chem. Soc. Perkin Trans. 1* 2243–2246 (1998).
26. Habermann, J., Ley, S. V. & Scott, J. S. Clean six-step synthesis of a piperidino-thiomorpholine library using polymer-supported reagents. *J. Chem. Soc. Perkin Trans. 1* 3127–3130 (1998).
27. Sussman, S. Catalysis by acid-regenerated cation exchangers. *Ind. Eng. Chem*. **38**, 1228–1230 (1946).
A seminal paper describing one of the earliest applications of polymer-supported reagents used in a recyclable fashion.
28. Pittman, C. U. & Smith, L. R. Sequential multistep reactions catalysed by polymer-anchored homogeneous catalysts. *J. Am. Chem. Soc*. **97**, 1749–1754 (1975).
29. Virgilio, A. A., Schuerer, S. C. & Ellman, J. A. Expedient solid-phase synthesis of putative β-turn mimetics incorporating the i+1, i+2, and i+3 sidechains. *Tetrahedron Lett*. **37**, 6961–6964 (1996).
30. Laszlo, P. (ed.) *Preparative Chemistry using Supported Reagents* (Academic Press, New York, 1987).
31. Hodge, P., Hunt, B. J., Khoshdel, E. & Waterhouse, J. Polymer-supported organophosphorus chemistry. *Nouveau J. de Chemie* **12**, 617–621 (1982).
32. Crosby, G. A., Weinshenker, N. M. & Uh, H.-S. Polymeric reagents. III. Synthesis of an insoluble polymeric thioanisole and its utilisation for the oxidation of alcohols. *J. Am. Chem. Soc*. **97**, 2232–2235 (1975).
References 32,33,35 are excellent examples of the ability to substitute polymer-supported reagents into standard chemical applications with the effect of reducing the exposure of the chemist to toxic or obnoxious systems.
33. Harris, J. M., Liu, Y., Chai, S., Andrews, M. D. & Vederas, J. C. Modification of the Swern oxidation: use of a soluble polymer-bound, recyclable, and odorless sulfoxide. *J. Org. Chem*. **63**, 2409–2409 (1998).
34. Pedersen, B. S., Scheibye, S., Clausen, K. & Lawesson, S, O. Studies on organophosphorus compounds XXII. The dimer of *p*-methoxyphenylthionophosphine sulfide as thiation reagent. A new route to *o*-substituted thioesters and dithioesters. *Bull. Soc. Chim. Belg.* **87**, 293–297 (1978).

35. Ley, S. V., Leach, A. G. & Storer, R. I. A polymer-supported thionating reagent. *J. Chem. Soc. Perkin Trans. 1* 358–361 (2001).
36. Taylor, S. J. & Ley, S. V. A Polymer-supported [1,3,2]oxazaphospholidine for the conversion of isothiocyanates to isocyanides and their subsequent use in an Ugi reaction. *Bioorg. Med. Chem. Lett.* (in the press).
37. Baxendale, I. R., Ley, S. V. & Piutti, C. Total synthesis of the amaryllidaceae alkaloid (+)-plicamine and its unnatural enantiomer by using solid-supported reagents and scavengers in a multistep sequence of reactions. *Angew. Chem. Int. Edn Engl*. **41**, 2194–2197 (2002).
This paper effectively demonstrates the use of supported reagents in target-orientated total synthesis.
38. Baxendale, I. R., Ley, S. V., Piutti, C. & Nessi, M. Total synthesis of the amaryllidaceae alkaloid (+)-plicamine using solid-supported reagents. *Tetrahedron* (in the press).
39. Baxendale, I. R., Lee, A. L. & Ley, S. V. A concise synthesis of the natural product carpanone using solid-supported reagents and scavengers. *Synlett* 1482–1484 (2001).
This paper describes the total synthesis of the natural product carpanone; it also contains references to the solution- and solid-phase synthesis of this molecule for comparison of the various synthetic methods.
40. Baxendale, I. R., Lee, A. L. & Ley, S. V. A concise synthesis of the natural product carpanone using solid-supported reagents and scavengers. *Synlett* 2004 (2001).
41. Jamieson, C., Congreve, M. S., Emiabata-Smith, D. F. & Ley, S. V. A rapid approach for the optimisation of polymer supported reagents in synthesis. *Synlett* 1603–1607 (2000).
This paper describes techniques for the rapid optimization of polymer-supported reactions. The technology is also directly applicable to both solution- and solid-phase synthetic operations.
42. Cohen, B. J., Kraus, M. A. & Patchornik, A. Organic synthesis involving multipolymer reactions. Polymeric tritylithium. *J. Am. Chem. Soc*. **99**, 4165–4167 (1977).
43. Cohen, B. J., Kraus, M. A. & Patchornik, A. Wolf and Lamb reactions — equilibrium and kinetic effects in multi-polymer systems. *J. Am. Chem. Soc*. **103**, 7620–7629 (1981).
References 42 and 43 demonstrate the feasibility of using multiple supported reagents in a single pot to facilitate sequential synthetic transformations, and are the first examples of such work.
44. Cainelli, G., Contento, M., Manescalchi, F. & Regnoli, R. Polymer-supported phosphonates. Olefins from aldehydes, ketones, and dioxolanes by means of polymer-supported phosphonates. *J. Chem. Soc. Perkin Trans. 1* 2516–2519 (1980).
45. Frechet, J. M. J., Darling P. & Farrall, M. J. Poly(vinylpyridinium dichromate): an inexpensive recyclable polymeric reagent. *J. Org. Chem*. **46**, 1728–1730 (1985).
46. Bergbreiter, D. E. & Chandran, R. Concurrent catalytic reduction stoichiometric oxidation using oligomerically ligated catalysts and polymer-bound reagents. *J. Am. Chem. Soc*. **107**, 4792–4793 (1985).
47. Hebert, N., Beck, A., Lennox, R. B. & Just, G. A new reagent for the removal of the 4-methoxybenzyl ether — application to the synthesis of unusual macrocyclic and bolaform phosphatidylcholines. *J. Org. Chem*. **57**, 1777–1783 (1992).
48. Choi, J. & Yoon, N. M. Synthesis of thiols via palladium-catalyzed methanolysis of thioacetates with borohydride exchange resin. *Synth. Commun*. **25**, 2655–2663 (1995).
49. Cardillo, G., Orena, M. & Sandri, S. Oxazolidin-2-ones from allylic amines by means of iodine and carbonate anion on polymeric support — a convenient synthesis of (+/–)-propranolol. *J. Org. Chem*. **51**, 713–717 (1986).
50. Regen, S. L. & Kodomari, M. Polymer-supported chain homologation. *J. Chem. Soc. Chem. Commun*. 1428–1429 (1987).
51. Parlow, J. J. Simultaneous multistep synthesis using polymeric reagents. *Tetrahedron Lett*. **36**, 1395–1396 (1995).
52. Bessodes, M. & Antonakis, K. One pot solid-phase cleavage of α-diols to primary alcohols — an attractive route to trihydroxy-nucleosides, antiviral precursors. *Tetrahedron Lett*. **26**, 1305–1306 (1985).
53. Solaro, R., D'antone, S. & Chiellini, E. Anion exchange-type resins in preparative organic chemistry: structure–activity relationship. *Reac. Poly*. **9**, 155–179 (1988).
54. Hodge, P. Polymer-supported organic reactions: what takes place in the beads? *Chem. Soc. Rev.* **26**, 417–424 (1997).
55. Chakrabarti, A. & Sharma, M. M. Cationic ion exchange resins as catalysts. *React. Poly.* **20**, 1–45 (1993).
56. Akelah, A. Review: technological applications of functionalized polymers. *J. Mat. Sci.* **21**, 2977–3001 (1986).
57. Kraus, M. A. & Patchornik, A. Polymeric reagents. *Chemtech* 119–128 (1979).
58. Patchornik, A. & Kraus, M. A. Recent advances in the use of polymers as chemical reagents. *Pure Appl. Chem.* **46**, 183–186 (1976).
59. Patchornik, A. Synthesis using polymeric reagents. *Chemtech* 58–63 (1987).
60. Overberger, C. G. & Sannes, K. N. Polymers as reagents in organic synthesis. *Angew. Chem. Int. Edn Engl*. **13**, 99–104 (1974).
61. Trost, B. M. & Warner, R. W. Macrolide formation via an isomerization reaction — an unusual dependence on nucleophile. *J. Am. Chem. Soc*. **105**, 5940–5942 (1983).
62. Mathur, N. K. & Williams K. F. Organic synthesis using polymeric supports, polymeric reagents, and polymeric catalysts. *J. Macromol. Sci. Rev. Macromol. Chem.* **C15**(1), 117–142 (1976).
63. Leznoff, C. C. The use of insoluble polymer supports in organic chemical synthesis. *Chem. Soc. Rev*. 65–85 (1974).
64. Kraus, M. A. & Patchnornik, A. The use of polymeric reagents in organic synthesis. *Pure Appl. Chem*. 503–526 (1976).
65. Leznoff, C. C. The use of insoluable polymeric supports in general organic synthesis. *Acc. Chem. Res*. **11**, 327–333 (1978).
66. Leznoff, C. C. & Dixit, D. M. The use of polymer supports in organic synthesis XI. The preparation of monoethers of symmetrical dihydroxy aromatic compounds. *Can. J. Chem*. **55**, 3351–3355 (1977).
67. Flynn, D. L., Devraj, R. V. & Parlow, J. J. Recent advances in polymer assisted solution-phase chemical library synthesis and purification. *Curr. Opin. Drug Discov. Dev*. **1**, 41–50 (1998).
68. Kaldor, S. W., Siegel, M. G., Fritz, J. E., Dressmann, B. A. & Hahn, P. J. Use of supported nucleophiles and electrophiles for the purification of non-peptide small molecule libraries. *Tetrahedron Lett*. **37**, 7193–7196 (1996).
69. Kaldor, S. W., Fritz, J. E., Tang, J. & McKinney, E. R. Discovery of antirhinoviral leads by screening a combinatorial library of ureas prepared using covalent scavengers. *Bioorg. Med. Chem. Lett.* **6**, 3041–3044 (1996).
70. Booth, R. J. & Hodges, J. C. Polymer-supported quenching reagents for parallel purification. *J. Am. Chem. Soc.* **119**, 4882–4886 (1997).
71. Flynn, D. L. *et al*. Recent advances in polymer-assisted solution-phase chemical library synthesis and purification. *J. Am. Chem. Soc.* **119**, 4874–4881 (1997).
72. Parlow, J. J., Mischke, D. A. & Woodard, S. S. Utility of complementary molecular reactivity and molecular recognition (CMR/R) technology and polymer-supported reagents in the solution-phase synthesis of heterocyclic carboxamides *J. Org. Chem.* **62**, 5908–5919 (1997).
73. Siegel, M. G. *et al.* Rapid purification of small libraries by ion exchange chromatography. *Tetrahedron Lett.* **38**, 3357–3360 (1997).
74. Booth, R. J. & Hodges, J. C. Solid-supported reagent strategies for rapid purification of combinatorial synthesis products. *Acc. Chem. Res.* **32**, 18–26 (1999).
A comprehensive paper that describes the applications of supported scavengers and quenching reagents to effect the purification of compound libraries. The paper also contains references to many of the other important contributors to this area. See also references 75 and 77.
75. Nikam, S. S., Kornberg, B. E., Ault-Justus, S. E. & Rafferty, M. F. Novel quenchers for solution phase parallel synthesis. *Tetrahedron Lett*. **39**, 1121–1124 (1998).
76. Ault-Justus, S. E., Hodges, J. C. & Wilson, M. W. Generation of a library of 4-thiozolidinones utilizing polymer supported quench (PSQ) reagent methodology. *Biotechnol. Bioeng*. **1**, 17–22 (1998).
77. Eames, J. & Watkinson, M. Polymeric scavenger reagents in organic synthesis. *Eur. J. Org. Chem.* 1213–1224 (2001).
78. Parlow, J. J., Devraj, R. V. & South, M. S. Solution-phase chemical library synthesis using polymer-assisted purification techniques. *Curr. Opin. Drug Discov. Dev.* **3**, 320–336 (1999).
79. Shuttleworth, S. J., Allin, S. M., Wison, R. D. & Nasturica, D. Functionalised polymers in organic chemistry; Part 2. *Synthesis* 1035–1074 (2000).
80. Oliver, S. F. & Abell, C. Combinatorial synthetic design. *Curr. Opin. Chem. Biol.* **3**, 299–306 (1999).
81. Curran, D. P. Strategy-level separations in organic synthesis: from planning to practice. *Angew. Chem. Int. Edn Engl.* **37**, 1175–1196 (1998).
An excellent review on alternative purification strategies, including fluorous-phase reactions and work-up.
82. Ferritto, R. & Seneci, P. High throughput purification methods in combinatorial solution phase synthesis. *Drugs Future* **23**, 643–654 (1998).
83. Melby, L. R. Polymers for selective chelation of transition metal ions. *J. Am. Chem. Soc*. **97**, 4044–4051 (1975).
84. Palmer, V., Zhou, R. N. & Geckeler, K. E. Cetylpyridinium chloride-modified poly(ethyleneimine) for the removal and separation of inorganic-ions in aqueous-solution. *Angew. Makromol. Chem*. **215**, 175–188 (1994).
85. Schuttenberg, H. & Schulz, R. C. Hertellung und Eigenschaften von Poly-(N-chlor-amiden). *Makromol. Chem*. **143**, 153–161 (1971).
86. Hoshi, S. *et al*. Preparation of Amberlite Xad resins coated with dithiosemicarbazone compounds and preconcentration of some metal-ions. *Talanta* **41**, 503–507 (1994).
87. Phillips, R. J. & Fritz, J. S. Extraction of metal-ions by n-phenylhydroxamic, n-methylhydroxamic, and n-unsubstituted hydroxamic acid resins. *Anal. Chim. Acta* **139**, 237–246 (1982).
88. Shumbhu, M. B., Theodorakis, M. C. & Digenis, J. Polstyrene resins with immobilised polyamines: preparation, characterization and ability to bind Cu(ii) Ions. *J. Polym. Sci. Poly. Chem. Ed*. **15**, 525–531 (1977).
89. Parlow, J. J., Naing, W., South, M. S. & Flynn, D. L. *In situ* chemical tagging: tetrafluorophthalic anhydride as a 'sequestration enabling reagent' (SER) in the purification of solution-phase combinatorial libraries. *Tetrahedron Lett.* **38**, 7959–7962 (1997).
Describes the concept of sequestration of multiple species or inherently unreactive compounds from solution by initial chemical activation followed by a universal scavenging protocol — some very interesting ideas that have not been fully exploited or elaborated on.
90. Flynn, D. L. *et al*. Chemical library purification stratagies based on principles of complimentary molecular recognition. *J. Am. Chem. Soc.* **119**, 4874–4881 (1997).
91. Parlow, J. J. & Flynn, D. L. Solution-phase parallel synthesis of a benzoxazinone library using complementary molecular reactivity and molecular recognition (CMR/R) purification technology. *Tetrahedron* **54**, 4013–4031 (1998).
92. Starkey, G. W., Parlow, J. J. & Flynn, D. L. Chemically-tagged Mitsunobu reagents for use in solution-phase chemical library synthesis. *Bioorg. Med. Chem. Lett.* **8**, 2385–2390 (1998).
93. Studer, A. *et al*. Fluorous synthesis: a fluorous-phase strategy for improving separation efficiency in organic synthesis. *Science* **275**, 823–826 (1997).
94. Curran, D. P. Parallel synthesis with fluorous reagents and reactants. *Med. Res. Rev.* **19**, 432–438 (1999).
95. Brown, A. R., Irving, S. L., Ramage, R. & Raphy, G. (17-Tetrabenzo[A,C,G,I]fluorenyl)methylchlororformate (TBFMOCCl) a reagent for the rapid and efficient purification of synthetic peptides and proteins. *Tetrahedron* **51**, 11815–11830 (1995).
96. Ley, S. V. *et al*. A new phase-switch method for application in organic synthesis programs employing immobilization through metal-chelated tagging. *Angew. Chem. Int. Edn Engl.* **40**, 1053–1057 (2001).
97. Toy, P. H. & Janda, K. D. Soluble polymer-supported organic synthesis. *Acc. Chem. Res.* **33**, 546–554 (2000)
98. Han, H. S., Wolfe, M. M., Brenners, S. & Janda, K. D. Liquid-phase combinatorial synthesis. *Proc. Natl Acad. Sci. USA* **92**, 6419–6423 (1995).
99. Gravert, D. J. J., Datta, A., Wentworth, P. & Janda, K. D. Soluble supports tailored for organic synthesis: parallel polymer synthesis via sequential normal/living free radical processes. *J. Am. Chem. Soc*. **120**, 9481–9495 (1998).
100. Ley, S. V. & Massi, A. Polymer supported reagents in synthesis: preparation of bicyclo[2. 2. 2]octane derivatives via tandem michael addition reactions and subsequent combinatorial decoration. *J. Comb. Chem*. **2**, 104–107 (2000).
101. Caldarelli, M., Baxendale, I. R. & Ley, S. V. Clean and efficient synthesis of azo dyes using polymer-supported reagents. *J. Green Chem*. **2**, 43–45 (2000).
102. Ley, S. V., Lumeras, L., Nesi, M. & Baxendale, I. R. Synthesis of trifluoromethyl ketones using polymer-supported reagents. *Comb. Chem. High Throughput Screening* **5**, 197–199 (2002).
103. Caldarelli, M., Habermann, J. & Ley, S. V. Clean five-step synthesis of an array of 1,2,3,4-tetra-substituted pyrroles using polymer-supported reagents. *J. Chem. Soc. Perkin Trans. 1* 107–110 (1999).
104. Caldarelli, M., Habermann, J. & Ley, S. V. Synthesis of an array of potential matrix metalloproteinase inhibitors using a sequence of polymer-supported reagents. *Biorg. Med. Chem. Lett*. **9**, 2049–2052 (1999).
105. Habermann, J., Ley, S. V. & Smits, R. Three-step synthesis of an array of substituted benzofurans using polymer-supported reagents. *J. Chem. Soc. Perkin Trans. 1* 2421–2423 (1999).

106. Habermann, J. *et al*. Clean synthesis of alpha-bromo ketones and their utilisation in the synthesis of 2-alkoxy-2,3-dihydro-2-aryl-1,4-benzodioxanes, 2-amino-4-aryl-1,3-thiazoles and piperidino-2-amino-1,3-thiazoles using polymer-supported reagents. *J. Chem. Soc. Perkin Trans. 1* 2425–2427 (1999).
107. Hinzen, B. & Ley, S. V. Synthesis of isoxazolidines using polymer-supported perruthenate (PSP). *J. Chem. Soc. Perkin Trans. 1* 1–2 (1998).
108. Baxendale, I. R., Ley, S. V. & Sneddon, H. A clean conversion of aldehydes to nitriles using a solid-supported hydrazine. *Synlett*. 775–777 (2002).
109. Ley, S. V., Takemoto, T. & Yasuda, K. The simultaneous use of immobilised reagents for the one-pot conversion of alcohols to carboxylic acids. *Synlett* 1555–1556 (2001).
110. Baxendale, I. R., Ernst, M., Krahnert, W.-R. & Ley, S. V. Application of polymer-supported enzymes and reagents in the synthesis of GABA-analogues. *J. Chem. Soc. Perkin Trans. 1* (in the press).
111. Baxendale, I. R., Ley, S. V., Brusotti, G. & Matsuoka, M. Synthesis of nornicotine, nicotine and other functionalised derivatives using solid-supported reagents and scavengers. *J. Chem. Soc. Perkin Trans. 1* 143–154 (2002).
112. Baxendale, I. R. & Ley, S. V. Polymer-supported reagents for multi-step organic synthesis: application to the synthesis of Sildenafil. *Bioorg. Med. Chem. Lett*. **10**, 1983–1986 (2000).
113. Baxendale, I. R., Lee, A.-L. & Ley, S. V. A concise synthesis of Carpanone using solid-supported reagents and scavengers. *J. Chem. Soc. Perkin Trans. 1* (in the press).
114. Ley, S. V., Schucht, O., Thomas, A. W. & Murray, P. J. Synthesis of the alkaloids (+/–)-oxomaritidine and (+/–)-epimaritidine using an orchestrated multi-step sequence of polymer supported reagents. *J. Chem. Soc. Perkin Trans. 1* 1251–1252 (1999).
115. Habermann, J., Ley, S. V. & Scott, J. S. Synthesis of the potent analgesic compound (+/–)-epibatidine using an orchestrated multi-step sequence of polymer-supported reagents *of J. Chem. Soc. Perkin Trans. 1* 1253–1255 (1999).

References 114 and 115 are the first two papers in a series from our group that show the use of supported reagents to facilitate all of the steps in an organized synthetic sequence targeted at the formation of natural products.

116. Hird, N. W. Automated synthesis: new tools for the organic chemist. *Drug Discov. Today* **4**, 265–274 (1999).
117. Ripka, W. C., Barker, G. & Krakover, J. High-throughput purification of compound libraries. *Drug Discov. Today* **6**, 471–477 (2001).
118. Dolle, R. E. Comprehensive survey of combinatorial library synthesis: 2000. *J. Comb. Chem*. **2**, 383–433 (2001).
119. Dolle, R. E. Comprehensive survey of combinatorial library synthesis: 1999. *J. Comb. Chem*. **3**, 477–517 (2001).
120. An, H. Y. & Cook, P. D. Methodologies for generating solution-phase combinatorial libraries. *Chem. Rev*. **100**, 3311–3340 (2000).
121. Powers, D. G. & Coffen, D. L. Convergent automated parallel synthesis. *Drug Discov. Today* **4**, 377–383 (1999).
122. Tripp, J. A., Svec, F. & Frechet, J. M. J. Solid-phase acylating reagents in new format: macrooporous polymer disks. *J. Comb. Chem*. **3**, 604–611 (2001).
123. Hafez, A. M., Taggi, A. E., Dudding, T. & Lectka, T. Asymmetric catalysis on sequentially-linked columns. *J. Am. Chem. Soc*. **123**, 10853–10859 (2001).
124. White, R. S. & Bradley, M. Synthesis of magnetic beads for solid phase synthesis and reaction scavenging. *Tetrahedron Lett*. **40**, 8137–8140 (1999).
125. Kobylecki, R. Porous device. WO Patent 0,021,658 (2000).
126. Kobylecki, R. & Gardner, J. M. F. Method of making a library of compounds using a functionalised polymer support resin affixed to a laminar material. US Patent 6,153,375 (2000).
127. Kobylecki, R., Cowell, D., Bradley, M. & Kronfli, E. Solid support materials. WO Patent 9,932,705 (1999).
128. Ramarao, C., Ley, S. V., Smith, S. C., Shirley I. M. & DeAlmeida, N. Encapsulation of palladium in microcapsules. *J. Chem. Soc. Chem. Commun.* 1132–1133 (2002).
129. Ley, S. V. *et al*. Polyurea-encapsulated palladium(acetate): a robust and recyclable catalyst for use in conventional and supercritical media. *J. Chem. Soc. Chem. Commun.* 1134–1135 (2002).
130. Haswell, S. J. *et al*. The application of micro reactors to synthetic chemistry. *J. Chem. Soc. Chem. Commun*. 391–398 (2001).
131. Kirschning, A. *et al.* PASSflow syntheses using functionalized monolithic polymer/glass composites in flow-through microreactors. *Angew. Chem. Int. Edn Engl.* **40**, 3995–3998 (2001).
132. Oxley, P., Brechtelsbauer, C., Richard, F., Lewis, N. & Ramshaw, C. Evaluation of spinning disk reactor technology for the manufacture of pharmaceuticals. *Ind. Eng. Chem. Res*. **39**, 2175–2182 (2000).
133. Boodhoo, K. V. K. & Jachuck, R. J. Spinning disk technology. *App. Therm. Eng*. **20**, 1127–1136 (2000).

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