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EVOLUTION OR REVOLUTION: THE CHALLENGE TO TODAY'S MEDICINAL CHEMIST

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ABSTRACT

As the global emphasis towards more eco-efficient and sustainable practices unfolds before us, so does the new remit for chemistry. We are already applying the principles of this new paradigm to environmentally cleaner and more efficient chemical processes, products and services. This discussion looks more deeply into some of the ways this remit will lead to the evolution of new tools for the molecule maker and how it is poised to revolutionize the way in which synthesis chemists will conduct their programmes in the future.

INTRODUCTION

The modern world of drug discovery is a rapidly changing landscape, and despite the new knowledge resulting from the genome, together with advances in high-throughput screening, informatics and automation, we are seeing increasing research and development expenditure with fewer new drugs actually making it to the market place. Consequently the demands made on the modern medicinal chemists are substantial. We can no longer simply depend upon the evolutionary incremental approach to new molecule discovery: we need to revolutionize our thinking. We must recognize and respond to the greater challenges posed by synthesis in general if chemical processes are to have a sustainable future. Strategic planning must incorporate enhanced productivity as well as environmental considerations.

For these reasons we must have far cleaner reaction processes with significantly improved atom efficiencies and this will require the discovery of many more strategically important reactions and the generation of many more new catalytic processes.

We are also required to make these discoveries more rapidly than ever before yet be mindful of costs and downstream processing. We need much greater diversity in not just the molecules we make but in the chemistry and reagents used to create them. We also have to be much better at using compound design tools especially if we upgrade our thinking to go beyond the molecule - towards supramolecular structures. For this we will need to have improved data-mining and knowledge-capture tools than are currently available. The use of internet trading and other innovations will also have a significant impact. The sixty million known compounds are only a drop in the ocean of what we could create if we were to exploit chemical space to the full - it only takes a quick scan of the therapeutic drugs currently on the shelf to realize we have a long way to go.

When they are first discovered in research labs, new healing drugs are generally synthesized in around a dozen steps and utilize up to fourteen different general types of reaction to construct the required chemical architectures. Although this may convey a somewhat limited spectrum of innovation in drug discovery it is not the full picture as, in fact, the techniques and methods for making molecules *have* greatly improved in recent years [1]. We have witnessed the tremendous speed of technological advances and the impact they have had in every aspect of our lives - drug discovery does not escape this. For example the area of combinatorial *bio*-chemistry, encompassing processes such as gene shuffling, phage display, the use of multiple enzymes and directed evolution techniques, is poised to impact considerably upon the molecule maker's tool box (Fig. 1). Many new chemistry devices such as microarrays, calorimetry, flow reactors, mini-reactor wells and microfluidic systems are becoming routine, and the new generation tools for chemists are increasingly aligning with the nano-technological fascination. Novel solvent systems are becoming popular too, such as ionic liquids, supercritical CO_2, H_2O and the use of fluorous phase materials (Fig. 1). Just as wireless devices are revolutionizing the home and workplace they are also impacting on laboratory management and experimental control and these tools are now considered essential to the drug discovery processes.

There is a growing requirement for synthesis automation systems utilizing design of experiment (DoE) and ReactArray software [2] in association with all manner of robotics, computational tools and high-speed chemical manipulation techniques.

This area is expanding at a phenomenal rate (Fig. 1) [3].

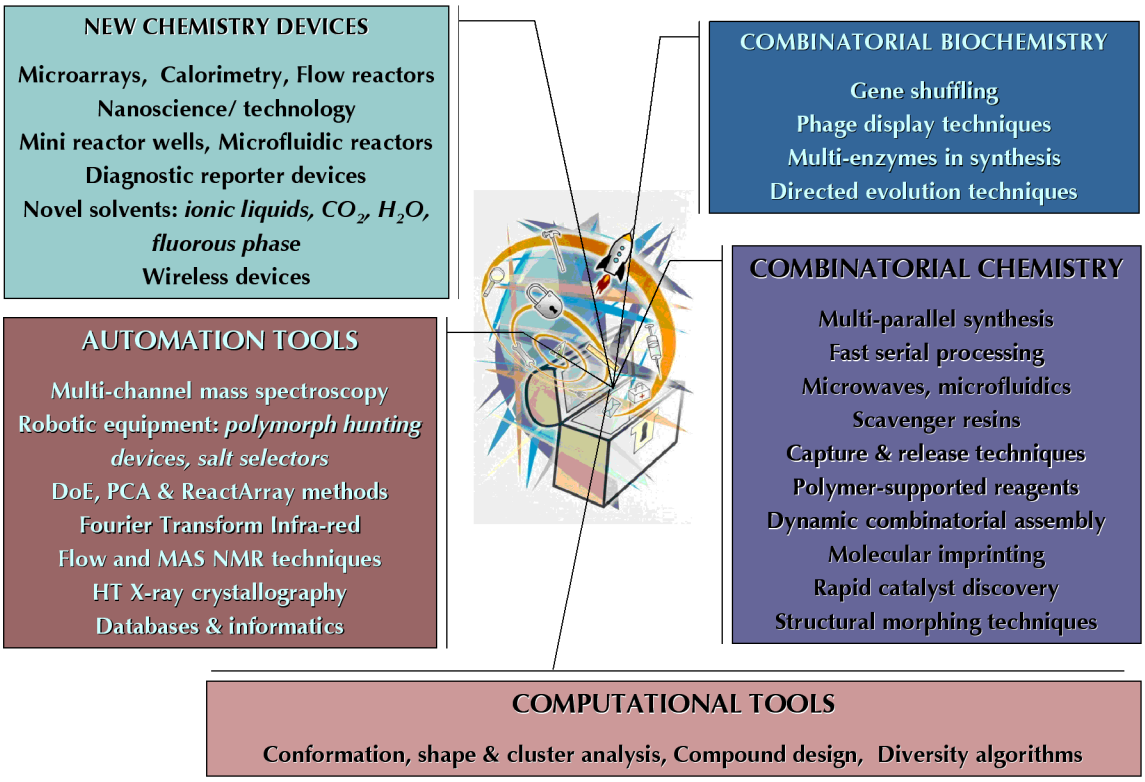


Figure 1. New tools in the molecule maker's tool box.

In order to conduct effective synthesis one needs to recognize that chemistry is part of the continuum from the initial conception and use in the research environment - through the process lab - and on to full-scale production. New synthesis tools should demonstrate applicability across these broad disciplines, even though there can be significant differences in the individual needs and requirements for the chemists involved; speed, safety, scale and cost factors for example.

Over recent years combinatorial chemistry has provided many new opportunities for compound preparation using both parallel processing and fast serial reactions. With the increasing understanding, development of additional practical skills and use of new tools in chemistry such as microwave radiation [4] and microfluidic devices [5], these opportunities will continue to multiply.

Combinatorial chemistry has triggered a renaissance in resin-based synthesis using polymers to support substrates, reagents or scavengers, all of which have aided product work-up and isolation immensely (Fig. 2). In addition, new methods in dynamic assembly of molecules and structural morphing techniques are fast becoming increasingly important drivers for this area of science.

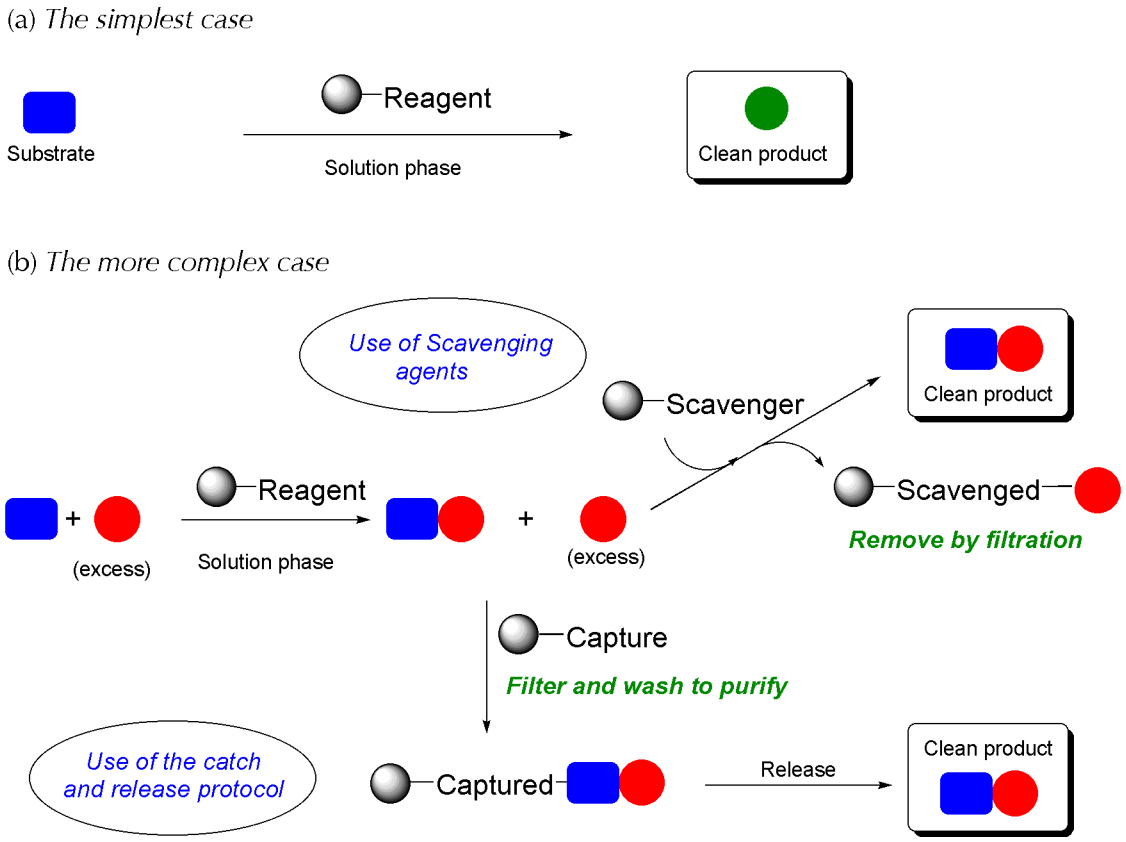


Figure 2. Solid-supported reagents in synthesis. (a) The simple case where no by-products are generated. (b) A more complex case where excess coupling components have been used or by-product removal is needed.

In spite of some successes arising from the use of combinatorial chemistry it has also been responsible for a certain dumbing down of chemistry by its tendency to rely on straightforward and reliable reactions with accepted concomitant compromises in both yield and complexity of the structures that are synthesized. This is no longer acceptable and we must make compounds designed for purpose rather than simply making compounds because we can. In a research laboratory for example, there might be a requirement for greater diversity in the molecules that are made and high attrition rates may be acceptable. In the process environment however, greater reaction versatility and reliability are priorities thus lower attrition rates are essential.

For these many reasons our group has focused on immobilized reagents, scavengers and catch-and-release techniques as a better practical approach for making chemical compounds, either in a library format or being capable of rapid reaction optimization and eventual scale-up [6].

SUPPORTED-REAGENTS IN SYNTHESIS

Although immobilized reagents have been known since 1946, we saw several advantages and opportunities of this approach when applied to multi-step synthesis programmes. By combining the power of supported reagents, enzymes and other methods such as immobilized scavengers, quenching agents or the catch-and-release principle, tremendous opportunities present themselves. Obviously these methods are well suited to parallel synthesis because of the work-up procedures that simply involve filtration of spent reagents and evaporation to give pure products [7]. The processes are readily automated and the reactions can be followed in real-time using LC-MS and other solution phase analytical techniques. By feeding back information the reaction could also be self-optimizing. Other advantages are that if toxic or volatile compounds must be used, then by immobilizing them on resins they become benign and far easier to handle. Furthermore, when plagued with by-products, co-running impurities, excess reactants or reagents (where conventional chromatography is not only ineffective but also time-consuming) scavenging or catch-and-release techniques become particularly valuable. Many immobilized reagents are also catalytic, or at least the spent reagent can be readily recovered by filtration and recycled to minimize costs. Scale-up is usually straightforward and in the future one could envisage far greater use being made of these supported systems in flow reactors devices [8].

Immobilized reagents are attractive as they allow the piloting of new synthesis schemes on very small quantities of compound. The ability to investigate sequentially a number of new steps in a synthetic pathway by removing the contaminating spent reagents and by-products in this way (rather than using standard protocols of water-quenching, solvent extraction, drying, evaporation and chromatography at each stage) saves considerable time and materials. Even more exciting opportunities arise when the idea of combining several reagents in a single pot to facilitate multiple transformations is considered. The site isolation of reagents (resulting from their immobilization) means that even otherwise mutually incompatible reagents in solution (e.g. oxidants and reductants) do not react together [9].

Without doubt these methods minimize the use of long-winded conventional procedures and create time for more profitable planning, thinking and innovation in the synthesis process. It should also be recognized that not only are one-pot linear synthesis routes possible, but that one can perform convergent syntheses or batch splitting to maximize product variation (Fig. 3). All these are essential components to good synthetic practice.

In a short article such as this it is not possible to cite all the relevant literature, nor can all the work that we have done in the area be covered thoroughly [10] what follows therefore, constitutes a selection of topics to give a flavour of what can be achieved using these systems.

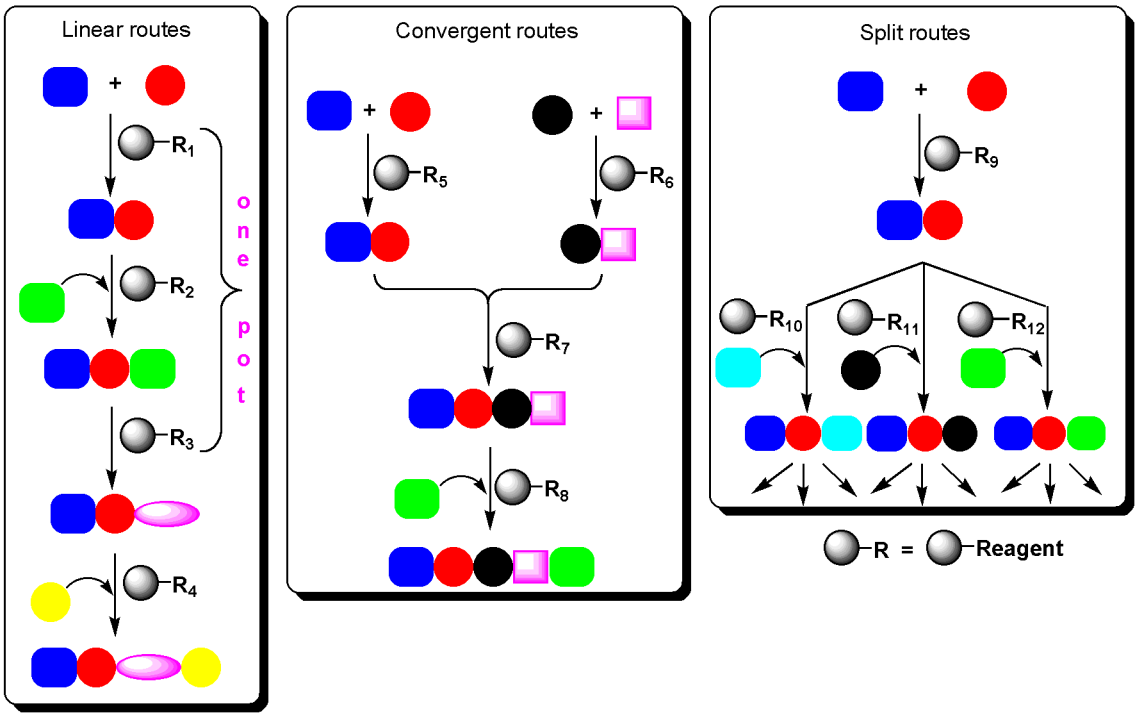


Figure 3. Opportunities for supported reagents.

Firstly, to illustrate the power of these methods we have studied the conversion of a readily available alcohol to an aldehyde using alkylammonium perruthenate resin (Fig. 4) [11]. In this way we generate an aldehyde cleanly by the simple process of filtering away spent reagent. This process can be conducted in real time and monitored using *in situ* methods. The reaction is especially attractive for the generation of unstable aldehydes which are often prone to form hydrates, over oxidize or racemize. The aldehyde thus produced can be used directly in other synthesis programmes by batch-splitting. In this case seven different routes lead to a variety of different products ranging from nitro olefins [12], alkenes and epoxides [13], acids [14], nitriles [15] and enones to isoxazoles [16] (Fig. 4).

All these processes use immobilized reagents and scavengers to effect individual transformations and as a consequence conventional work-up procedures (chromatography, distillation, aqueous washes or crystallization) are unnecessary.

This approach to on-demand synthetic intermediates could be extremely useful in future synthesis programmes as it minimizes waste and compound storage problems particularly as many of the reagents are readily recycled. We have published extensively in this area and suggest the reader consults one of our reviews for further details [6a].

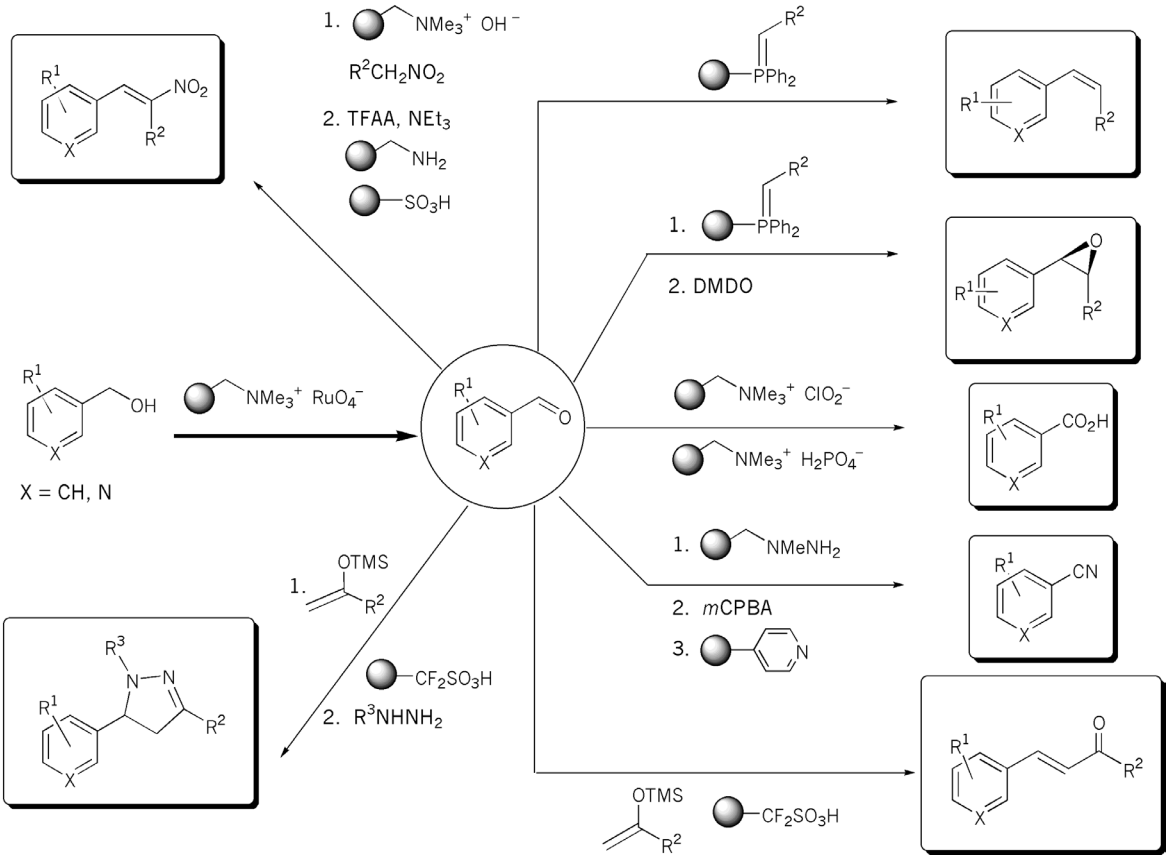


Figure 4. Multiple use of polymer supported reagents by a seven-way split.

MICROENCAPSULATION

Metal-catalysed organic synthesis, especially using palladium, has become common practice, however, product contamination by metal atoms is often problematic and considerable skill and expense are necessary to obtain products with less than 10 ppm of metal contamination.

In order to address this issue we have investigated an approach that effectively entraps the metals within a polymer matrix [17]. Our aim was to generate a system that was inexpensive to operate and would lead directly to clean products by straightforward extraction and a ready recycling of the expensive metal component.

Micro-encapsulation of materials in polymeric coatings is an attractive procedure for drug delivery, radiation therapy, cell entrapment and for the controlled release of pesticides. Microcapsules can be prepared using a variety of chemical and physical methods, and one such method is an *in situ* interfacial polymerization [18]. This involves dispersing an organic phase (containing poly-functional monomers and/or oligomers) into an aqueous phase (containing a mixture of emulsifiers and protective colloid stabilizers) along with the material to be encapsulated.

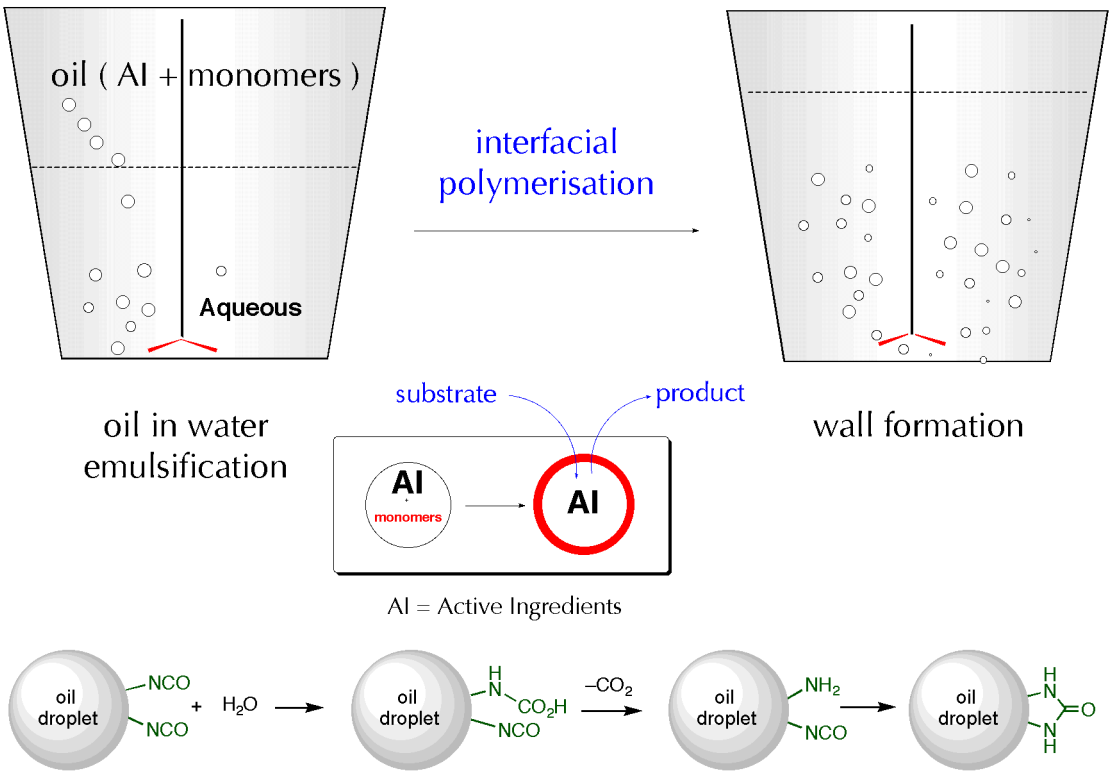


Figure 5. Microcapsule manufacture by interfacial polymerisation.

The resulting oil-in-water emulsion undergoes interfacial polymerization, with the monomers/ oligomers reacting spontaneously at the phase boundary to form microcapsule polymer walls.

The permeability and size of these microcapsules and the coordinating properties of the polymer matrix can be tuned by varying the identity of the monomers/oligomers, the presence of additives and the specific reacting conditions used in the encapsulation such as temperature, concentration or pH. Efficient entrapment of transition metal-based catalysts requires the design of systems possessing ligating functionality in order to retain the metal species. These systems should be physically robust and chemically inert to reaction conditions whilst also being cost effective.

Polyurea microcapsules [19] were found to be suitable by virtue of their chemical structure as they could ligate and retain palladium or other metallic species readily. The micro-encapsulation procedure is straightforward. A solution containing polymethylene polyphenylene diisocyanate (SUPRASEC 5025) and palladium diacetate in dichloroethane was stirred with an aqueous solution of sodium lignosulfonate (Reax 100M), polyvinyl alcohol (Goshenol GL03) and the polyoxypropylene polyoxyethylene ether of butyl alcohol (Tergitol XD) using a standard laboratory overhead stirrer which results in an oil-in-water micro-emulsion. The wall-forming reaction is initiated when some of the peripheral isocyanate groups are hydrolysed at the oil-water interface to form amines; these in turn react with other unhydrolysed isocyanates to form a urea-linked polymeric coating yielding, insoluble and permeable, polyurea microcapsules with a particle distribution of 20-250 microns (average size 150 microns) (Fig. 5). According to X-ray fluorescence (XRF) and inductively coupled plasma (ICP) analysis the average palladium content in the polyurea microcapsules (MC-[Pd]) we made was found to be 0.4 mmol g^{-1}.

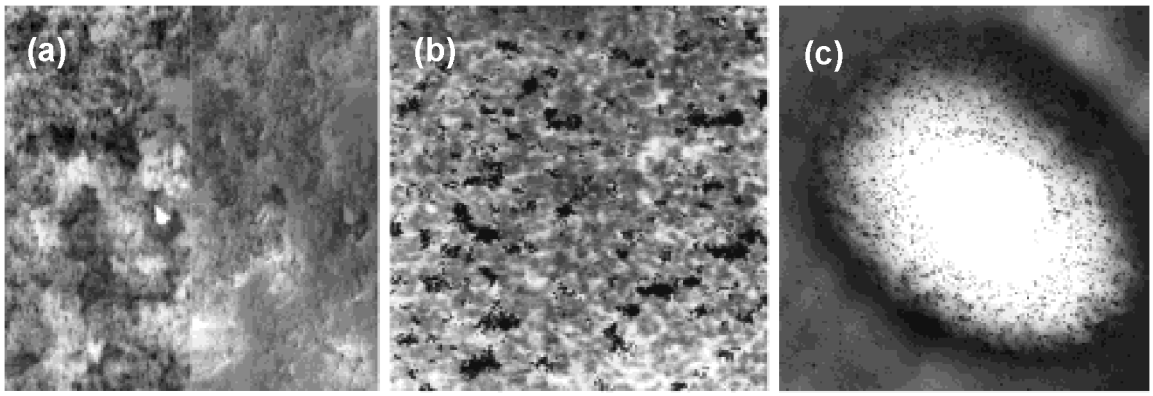
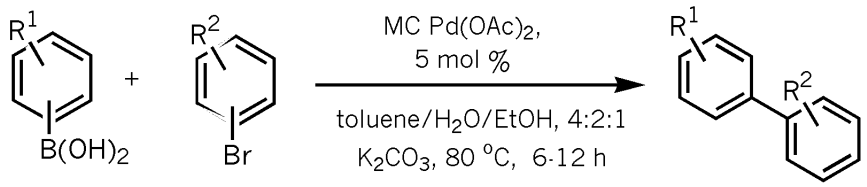


Figure 6. (a) Scanning electron micrograph (SEM) showing the interior of a palladium diacetate containing polyurea microcapsule (magnification 3 x 2500). (b) TEM of a sliced palladium diacetate microcapsule after chemical reaction (magnification 3 x 14.000). (c) TEM of a sliced microcapsule showing the distribution of palladium nanoparticles (dark spots) along a channel fromed within the polyurea matrix (magnification 3 x 46.000).

Our palladium-containing microcapsules, [Pd^0EnCat], were examined as catalysts in Suzuki cross-coupling reactions of aryl boronic acids with aryl bromides [17], as this is a particularly important transformation. The reactions proceeded extremely well (Fig. 7).

What is important to note is the catalysts were readily recovered by filtration through a polyethylene frit (20 micron). The products of the reaction were examined by ICP analysis and were found to have very low residual palladium content (0.5 - 5 ppm).

Since these early experiments, subsequent reactions have shown the catalysts to be extremely versatile and reliable. They have also found application in super-critical CO_2 in either batch or flow modes [8b, 17b]. To date over 300 different examples of reactions promoted by these catalysts have been conducted. Furthermore, modified catalysts displaying enhanced activity can be made that incorporate additional coordinating ligands, leading to acceleration and tailored selectivity in the reactions.



Entry	R^1	R^2	Yield/(%)†
1	*p*-OMe	*p*-OMe	87
2	*p*-OMe	*p*-F	89
3	*p*-OMe	*p*-NO_2	91
4	*p*-OMe	*p*-OMe	71
5	*p*-Ac	*p*-OMe	84
6	*p*-Ac	*p*-F	90
7	*p*-Ac	*p*-NO_2	97
8	H	*p*-OMe	94
9	H	*p*-F	93
10	H	*p*-NO_2	97

†(%) based on isolated products. ICP Pd analysis typically 0.5-5 ppm

Figure 7. Synthesis of biaryls using palladium diacetate encapsulated in polyurea.

We have also studied other palladium-catalysed processes such as the Heck and carbonylation reactions with some measure of success (Fig. 8) [17a].

We have demonstrated that these palladium-containing microcapsules function well as catalysts in the hydrogenation of double bonds (Fig. 9) [20].

This important chemical transformation is especially useful when double bond selectivity is required in the presence of other functional features on the molecule which can be sensitive to more commonly used catalysts i.e. palladium on charcoal.

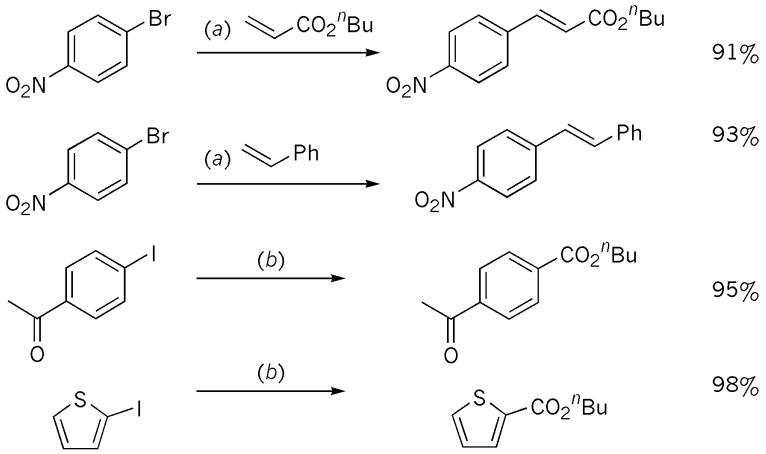


Figure 8. *Conditions*: (a) (Heck 2.5 mol% MC-[Pd], IPA, $^{n}BuN_4OAc$, 90º C plus olefin. (b) (Carbonylation) 3 mol% MC-[Pd], CO, $^{n}BuOH$, Et_3N, 90º C.

These new catalysts are recyclable and can be reused at least thirty times. They are also chemoselective; working in the presence of benzyl groups, carbamates, nitriles, epoxides and even aromatic halides. Recovery of the catalyst does not require special filteration procedures nor do we need to wet the catalyst to prevent ignition, as is the case for Pd/C. This safety feature is a significant advantage especially for scale-up applications.

We have continued to develop and evolve these palladium-polyurea catalysts and have extended their application to hydrogen transfer reductions in highly efficient and chemoselective conversions of aryl ketones to the corresponding alcohols (Fig. 10). The most effective conversions were carried out using the encaps with formic acid and triethylamine in the presence of ethyl acetate at room temperature [21].

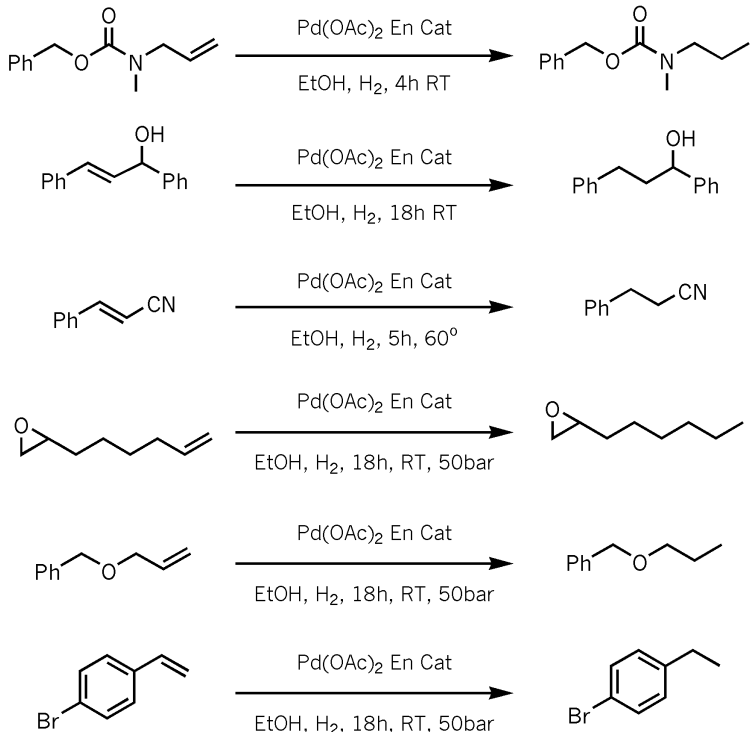


Figure 9. Palladium diacetate En Cats in hydrogenation reactions.

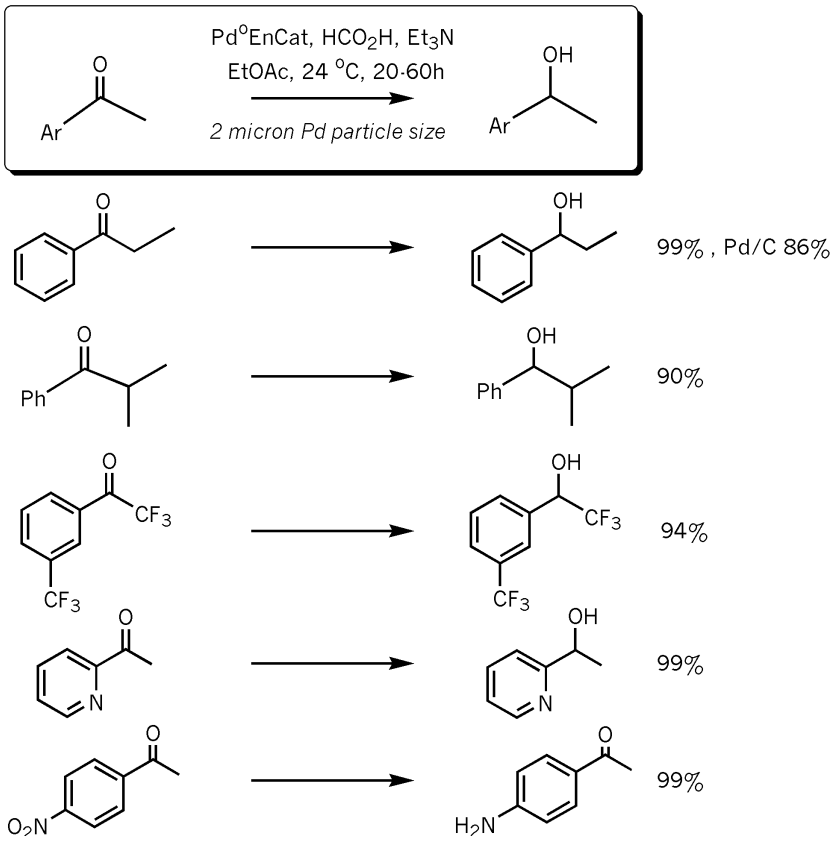


Figure 10. Micro-encapsulated Pd(0) for hydrogenation transfer reduction of aryl ketones.

A further application of this catalytic system is in the reductive ring-opening of benzylic epoxides via transfer hydrogenation (Fig. 11) [22]. Hydrogenolysis of terminal epoxides with conventional hydrogenation conditions was also examined, although this was found to be less effective than the hydrogen transfer process.

It is also noteworthy that these catalysts out-performed palladium/charcoal in any comparison reactions. In conclusion, encapsulated systems are being extended to incorporate many other metals [23], enzymes and even whole cells. With adaptation we can incorporate chiral ligands for asymmetric processes or design cavities suitable for selective scavenging processes. We are also investigating mixed metal perovskites as interesting new catalysts for clean organic synthesis programmes [24].

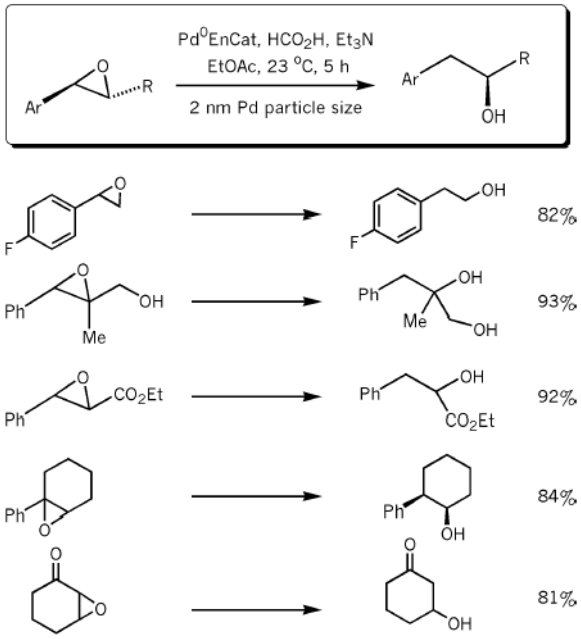


Figure 11. Pd(0) nanoparticles micro-encapsulated for the hydrogenolysis of epoxides.

In order to demonstrate the full potential of these immobilized reagents and scavenging agents, we have used them in orchestrated multi-step syntheses of a wide range of building blocks [25] and products such as drug substances [26], azo dyes [27], heterocycles [28] alkaloids and a selection of natural products, some of which are discussed below, highlighting just a few of these applications to demonstrate how useful supported reagents are and how wide ranging their applicability is.

In the first of these projects we wanted to prepare a library of potential anti-proliferative agents histone deacetylase (HDAc) inhibitors in the form of sulfonamide hydroxamic acids [29]. Imbalance in the level of histone acetylation in the body is associated with malignant disease and HDAc inhibitors lead to a reversal of the transcriptional repression and an associated upregulation of tumour suppressors. They have also been observed to result in inhibition of angiogenesis and are therefore of considerable interest as potential new anticancer agents. The sulfonamide hydroxamic acids chosen for study bear a close structural relationship to the natural product *trichostatin A*, a known HDAc inhibitor.

It is also known that the hydroxamic group in these structures could be problematic owing to their propensity to bind metal atoms leading to difficulties in purification; the supported reagent strategy was therefore a logical choice. Accordingly we devised a very efficient set of synthesis protocols for the construction of the three diversity point sulfonamide hydroxamic acid library whereby we were able to use a Zinsser Sofas robotic synthesizer to prepare these compounds with no manual intervention at any intermediate stage (Fig. 12).

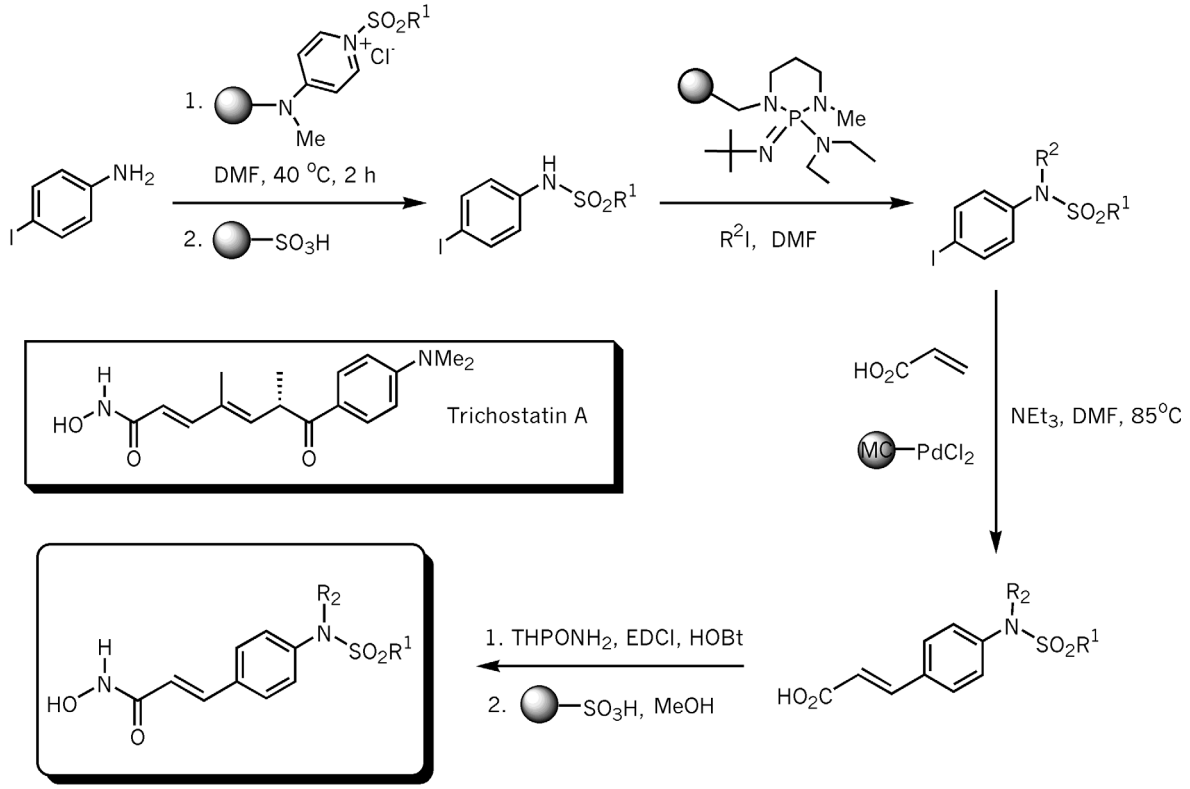


Figure 12. Synthesis of histone deacetylase inhibitors.

Also of importance in this synthesis was that the chosen palladium-encapsulated catalysts for the Heck coupling (involving reaction of the substituted aryl iodides with acrylic acid in DMF) performed especially well. Moreover, in separate experiments with other supported palladium catalysts using a Gilson 233 ReactArray profiling system, the encaps gave a much reduced level of by-products and of course very low levels of palladium contamination in the products. In a similar fashion we have completed the synthesis of a matrix metalloproteinase (MMP) compound collection where once again the final products are hydroxamic acids (Fig. 13) [30]. This synthesis makes use of supported reagents and scavengers in all stages of the process and again leads to very clean products.

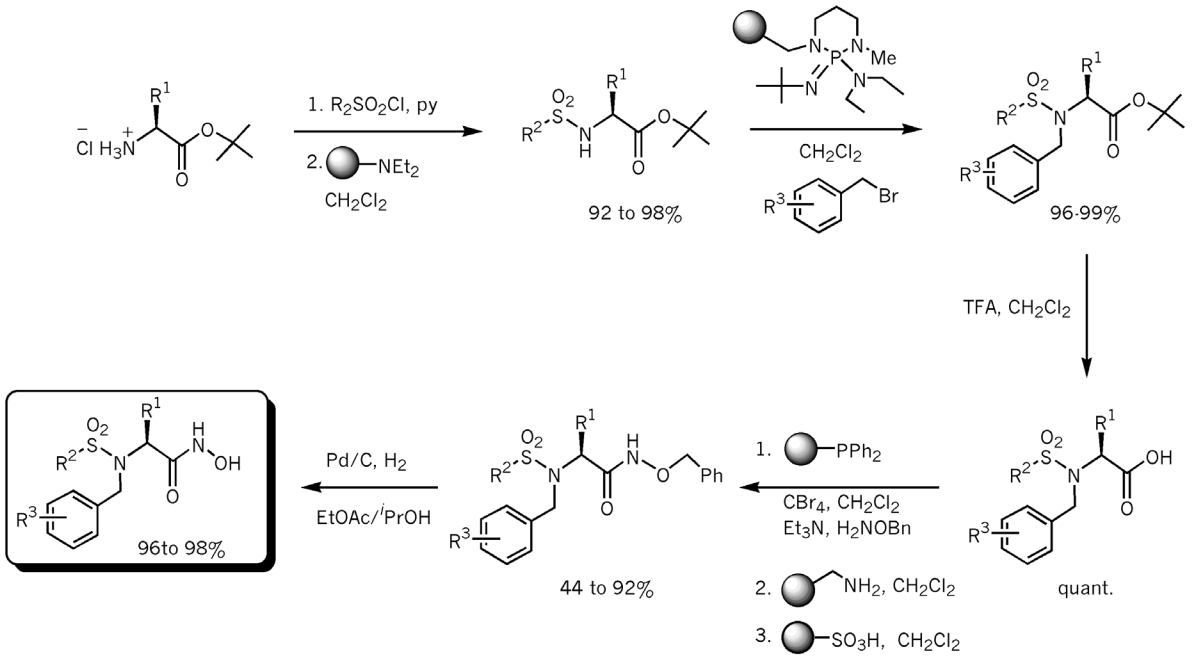


Figure 13. Synthesis of potential matrix metalloproteinase (MMP) inhibitors.

In order to evaluate other supported catalysts for organic synthesis programmes we have carried out initial investigations into how immobilized enzymes would perform during multi-step synthesis operations. This was important as supported enzymes are appealing reagents for synthesis and many of them are already becoming commercially available. Accordingly we have used pig liver esterase (PLE) immobilized on Eupergit® as a key step in the preparation of some g-amino butyric acid analogues (GABA) (Fig. 14) [31]. This reagent efficiently accomplished the resolution of a cyclopropyl *meso*-diester to a highly enantio-enriched carboxylic acid. This was elaborated through a series of transformations to the corresponding GABA derivative. Noteworthy is the conversion of an aliphatic bromide to a protected amine using an immobilized azide. Direct reductive work-up and Boc-protection was achieved in a single reaction vessel avoiding any need to isolate the potentially hazardous azide intermediates. Although only the cyclopropane ring system has been shown in the scheme, the chemistry translates well to 4, 5 and 6 rings. We believe this application of an immobilized enzyme together with other supported reagents, scavengers and catch-and-release techniques is the first of such sequences to be reported and constitutes a conceptually attractive strategy for complex molecule assembly in the future.

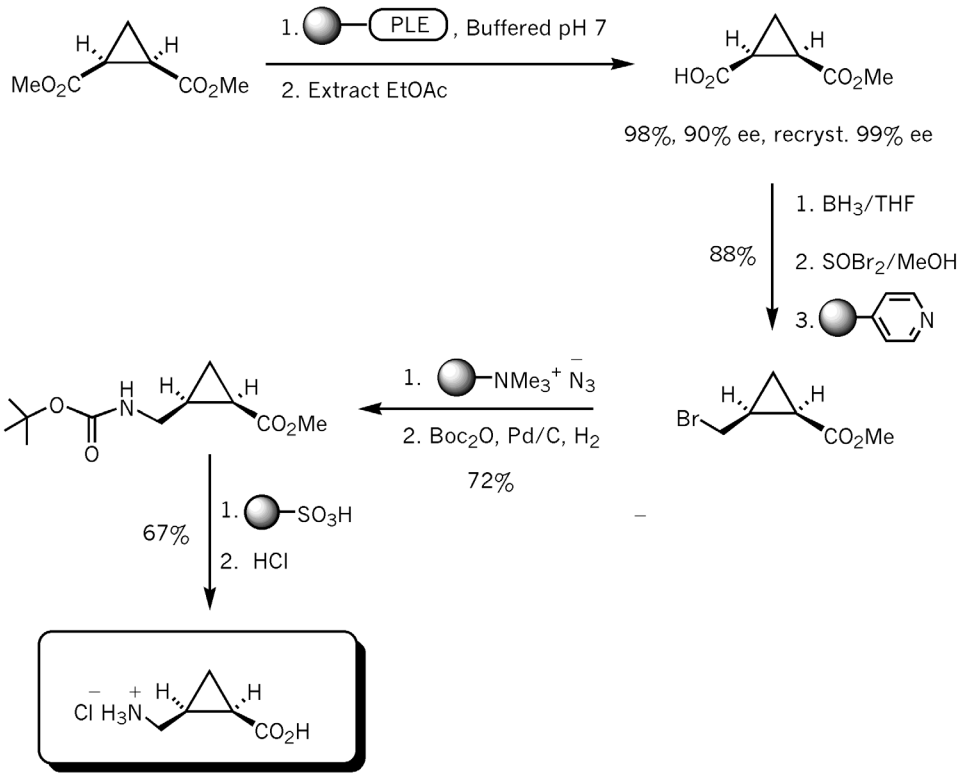


Figure 14. Using immobilised enzymes, in this case pig liver esterase (PLE), in the synthesis of GABA analogues.

The use of these approaches can be illustrated further as in the synthesis of the GSK bronchodilator *salmeterol*, a known β2 agonist used in the treatment of asthma (Fig. 15) [32]. The particular feature of this multi-step process is the convergent strategy and the bringing together two different synthesis streams resulting in a more elaborate, advanced intermediate. This tactic, crucial for the practice of good organic synthesis programmes, is not possible by the more typically used on-bead approach to chemical library generation. During the synthesis of *salmeterol* we also discovered an excellent way of introducing the hydroxymethyl acetal group early on in the synthesis, using a new version of the Mannich reaction. Also of note is the stereoselective introduction of the benzylic hydroxyl group by directed calcium chelation using an immobilized borohydride reagent (Fig. 15).

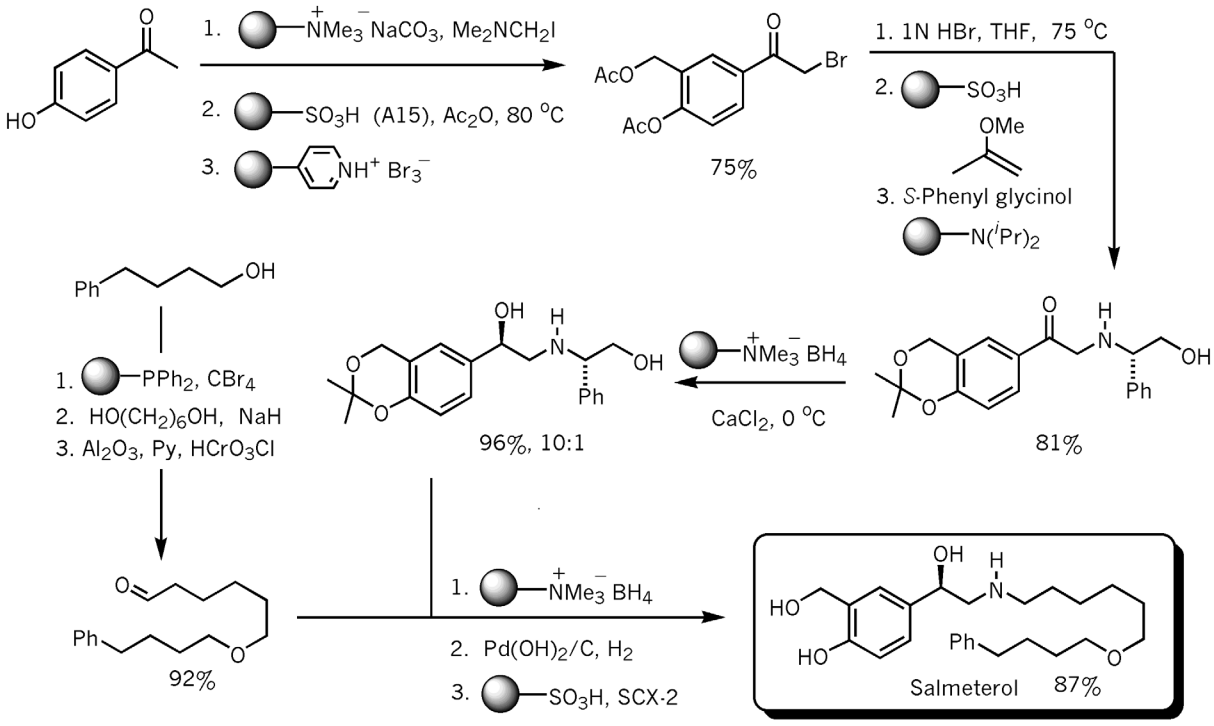


Figure 15. Synthesis of the GSK β2 agonist bronchodilator *salmeterol*.

Salmeterol and related molecules are not always easy to purify by conventional methods owing to their combination of polar heads and lipophilic tails, however the use of supported reagents goes a long way towards overcoming these difficulties. Although we have published the syntheses of several other medicinally relevant molecules including Pfizer's famous erectile dysfunction agent *Sildenafil* (Viagra™) [33], these systems can also be used for complex natural product synthesis [34]. Again we have published extensively in this area, but here we will report only a few selected examples.

NATURAL PRODUCT SYNTHESIS

The synthesis of *carpanone*, a methylenedioxy natural product, constitutes an interesting example as we had to develop new immobilized reagents specifically for the task [35]. Our initial attraction to this particular molecule was the opportunity to effect an oxidative coupling reaction using a substituted phenolic styrene to lead directly to carpanone after an intramolecular Diels-Alder cyclization.

This was achieved using a modified cobalt oxidant as a catalyst in the presence of molecular oxygen giving the natural product in 78% yield as a crystalline material following filtration to remove the spent reagents (Fig. 16).

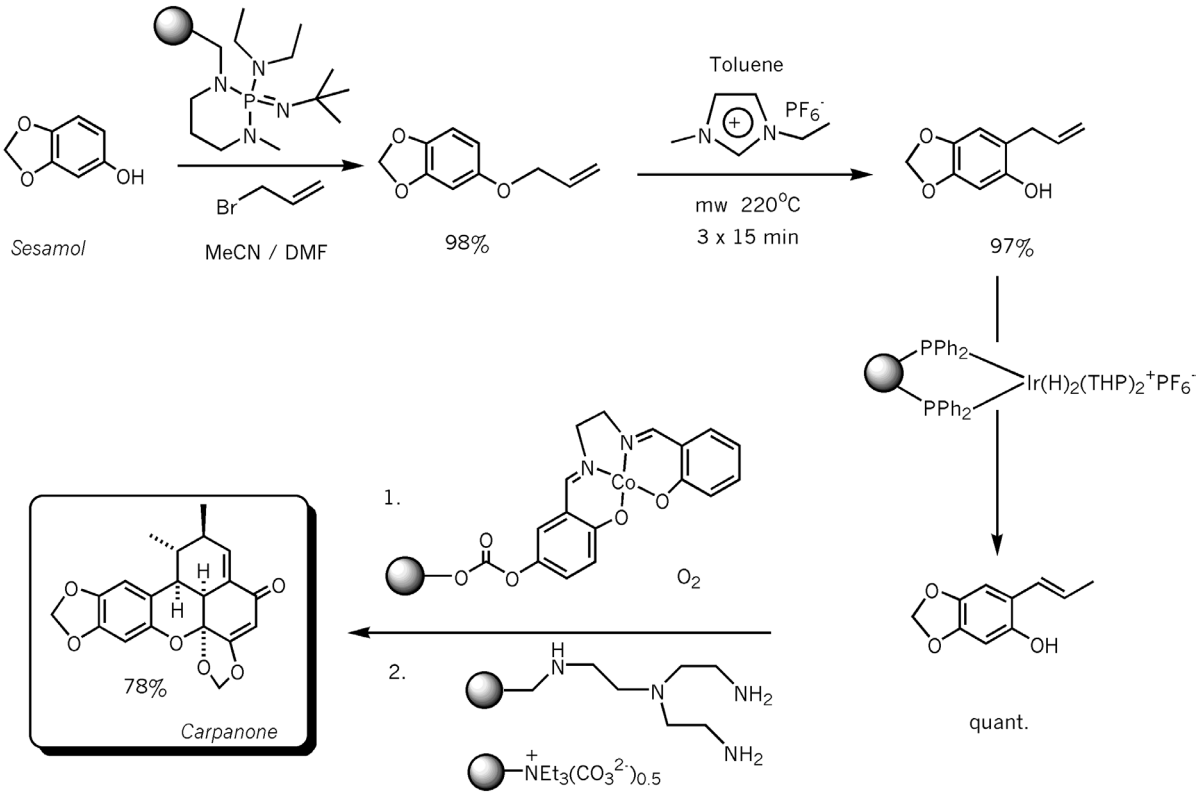


Figure 16. Synthesis of carpanone.

This synthesis neatly demonstrates how simple building blocks can be rapidly transformed into architecturally complex materials. In this work we also invented the use of an immobilized iridium catalyst for the room temperature isomerization of carbon-carbon double bonds, and we have gone on to use it successfully in many other related reactions [36]. Another key step of this synthesis pathway to *carpanone* is the Claisen reaction conducted using a focused microwave reactor (using toluene and an ionic liquid to absorb the microwave energy thus rapidly enabling temperatures of around 200°C). We were one of the early pioneers to use ionic liquids and microwaves in this manner. They were used to effect the smooth conversion of amides to thioamides using a new supported thionlyation catalyst [37] and the first to use immobilized reagents under these conditions.

The next synthesis allowed us to develop extremely efficient methods for alkaloid preparation of some quite challenging structures. Again the emphasis is on ease of operation (with no generation of by-products and reactions amenable to scale-up) using only filtration and evaporation to obtain pure products. A simple six-step synthesis of epimaritidine and oxomaritidine [38] portrays the speed and efficiency of these concepts (Fig. 17).

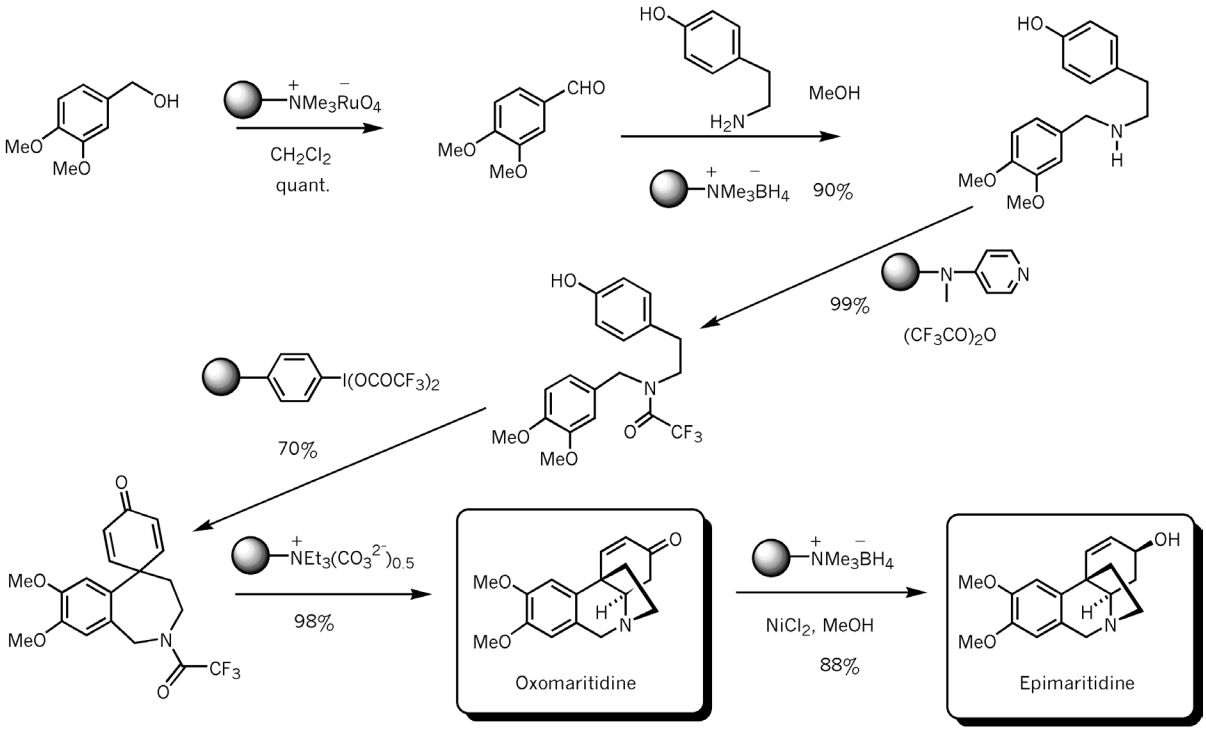


Figure 17. Synthesis of (±)-oxomaritidine and (±)-epimaritidine.

The choice of reagents in the scheme broadly exploits processes we have used for other syntheses. The action of our immobilized perruthenate reagents for example, is both catalytic and recyclable at room temperature and efficiently converts alcohols to aldehydes. Also of more general importance is the polymer-supported hypervalent iodine oxidant [39] used to bring about the phenol oxidative coupling to form the spirodienone product. The last reductive step involving the conversion *oxomaritidine* to *epimaritidine* is new and employs the use of nickel chloride to dope the supported borohydride, presumably to prepare nickel boride *in situ* which then effects the reduction process.

In a more complex example of multi-step natural product synthesis we have prepared the analgesic agent epibatidine [40] (Figs 18-22). This published work makes use of supported reagents, scavengers and catch-and-release techniques.

It also effectively uses microwaves in a key epimerization reaction towards the end of the synthesis, the whole synthesis uses many reagent systems developed by our group. Those skilled in synthesis methods will also appreciate the IRA 420 immobilized base-catalysed Henry reaction leading to nitrostyrenes which are known building blocks for many drug discovery programmes. Once again supported perruthenate and nickel-doped borohydride reagents are exploited to obtain high yield transformations. This synthesis used these reagents in porous polymer pouches to facilitate a more easy removal of the spent reagents on completion of the reaction.

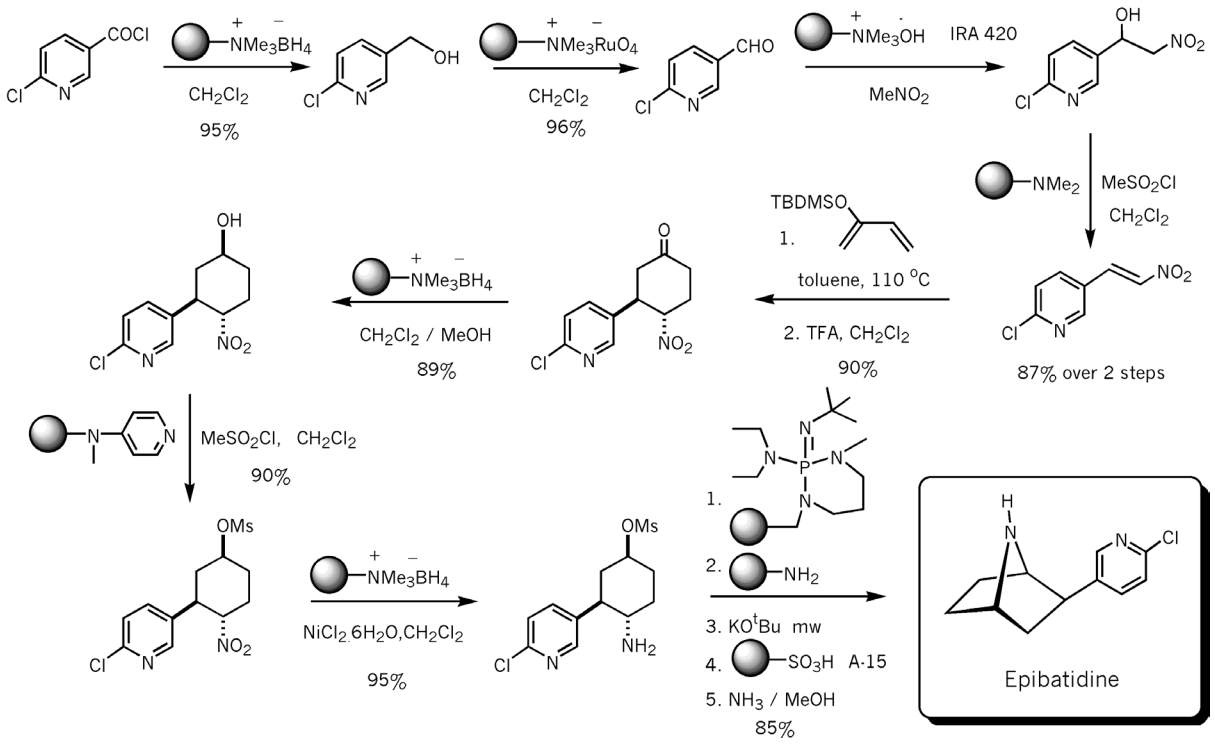


Figure 18. Synthesis of *epibatidine*.

One of the most recent alkaloids we have made using this technology is *plicamine* (Fig. 19) [41]. The route involves a total of fifteen steps carefully designed to afford high quality materials, representing a showcase for the various techniques and immobilized reagents previously described. Once again effective use of the immobilized hypervalent oxidant to give spirodienones is crucial. The use of Nafion, the fluorosulfonylated resin, to bring about the piperidone ring closure is extremely efficient and could be useful in other transformations. Also of note is the new method used to methylate very hindered alcohols with TMS-diazomethane and a sulfonic acid resin, which has many potential applications as a less hazardous alkylation methodology.

The reader is encouraged to consult the full details of this synthesis in which we describe the importance of design of experiment (DoE) and parallel reaction and reagent scanning to optimize many of the reactions. The extensive utilization of focused microwave machinery as described earlier also plays a significant role in this synthesis. One should also recognize that, while this synthesis was targeted at a single molecule, all reaction intermediates can be batch split and diverted into a whole raft of combinatorial chemistry programmes.

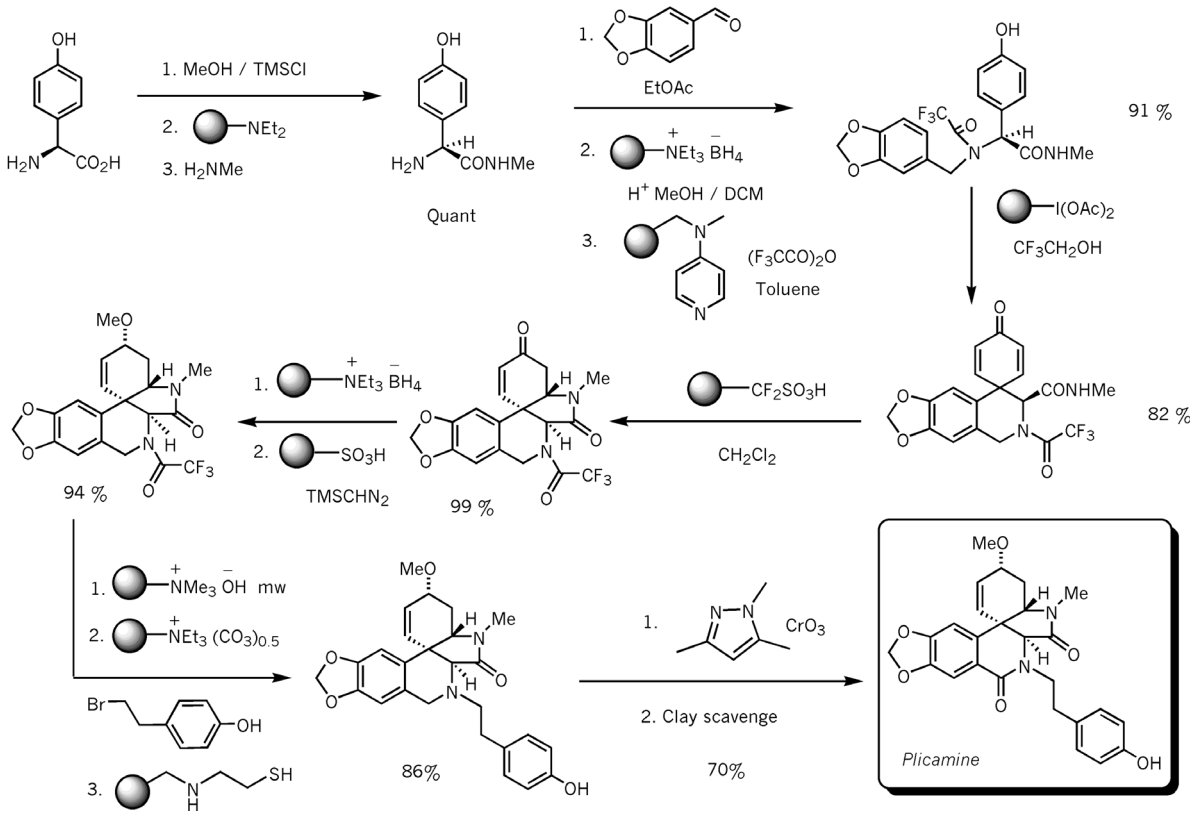


Figure 19. Synthesis of *plicamine*.

Finally the state-of-the-art of these supported reagent methods can be illustrated in the synthesis of the tubulin binder *epothilone C* (Figs 20-23) [42]. The multi-step, multi-convergent approach leads to the natural product more efficiently than any previously described 'in solution' methods. Many of the steps can be optimized rapidly using automated equipment and therefore releases skilled laboratory staff for other tasks. Indeed complex molecule syntheses in the future are likely to be conducted by using a combination of these new tools and techniques especially where routine tasks can be relegated to robotic equipment.

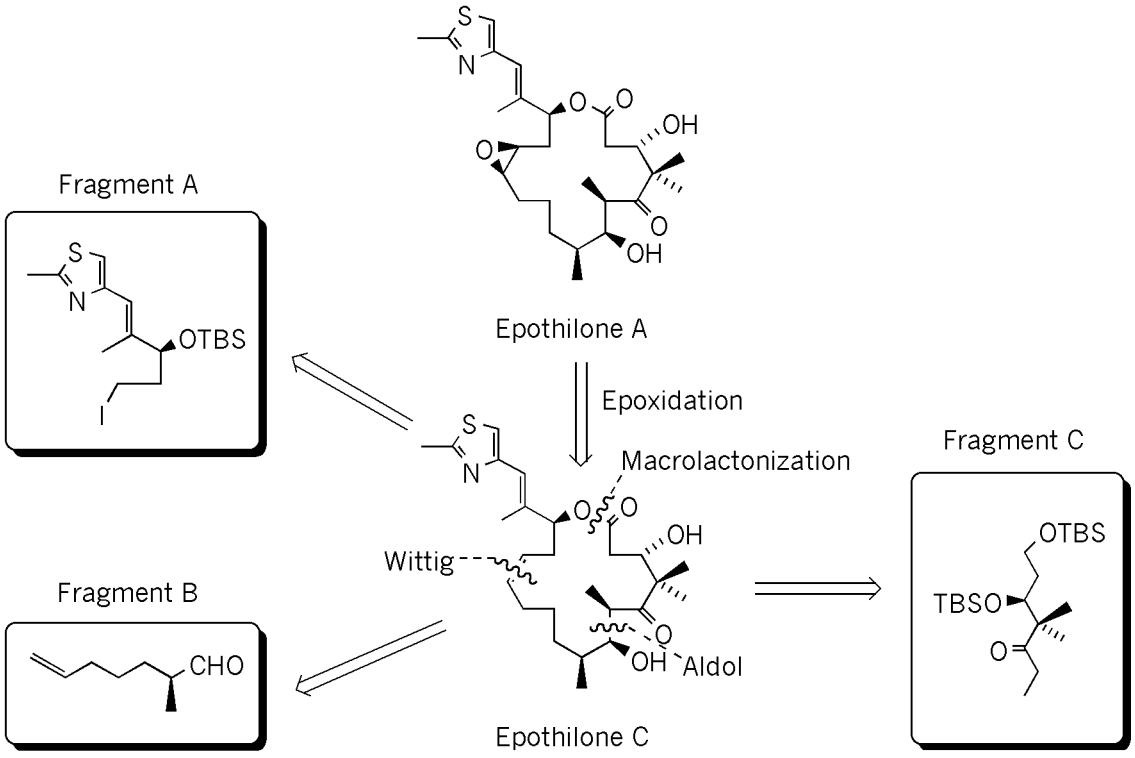


Figure 20. Synthesis plan for *epothilone C*.

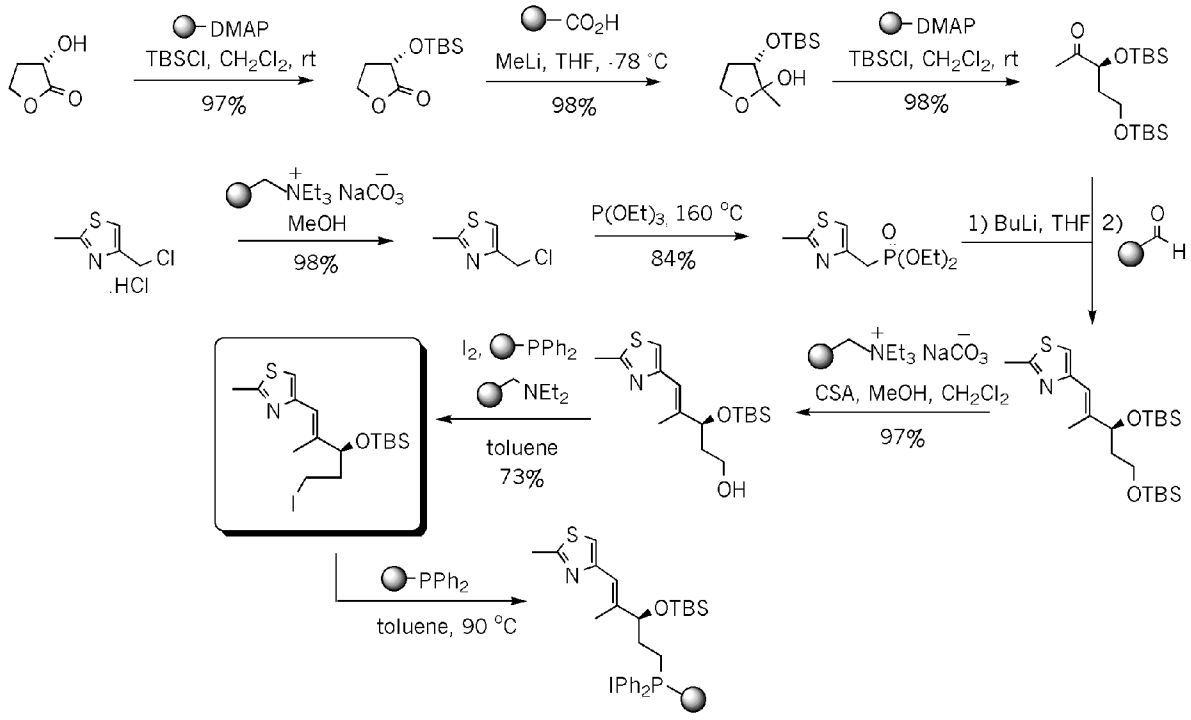


Figure 21. Synthesis of fragment A of *epothilone C*.

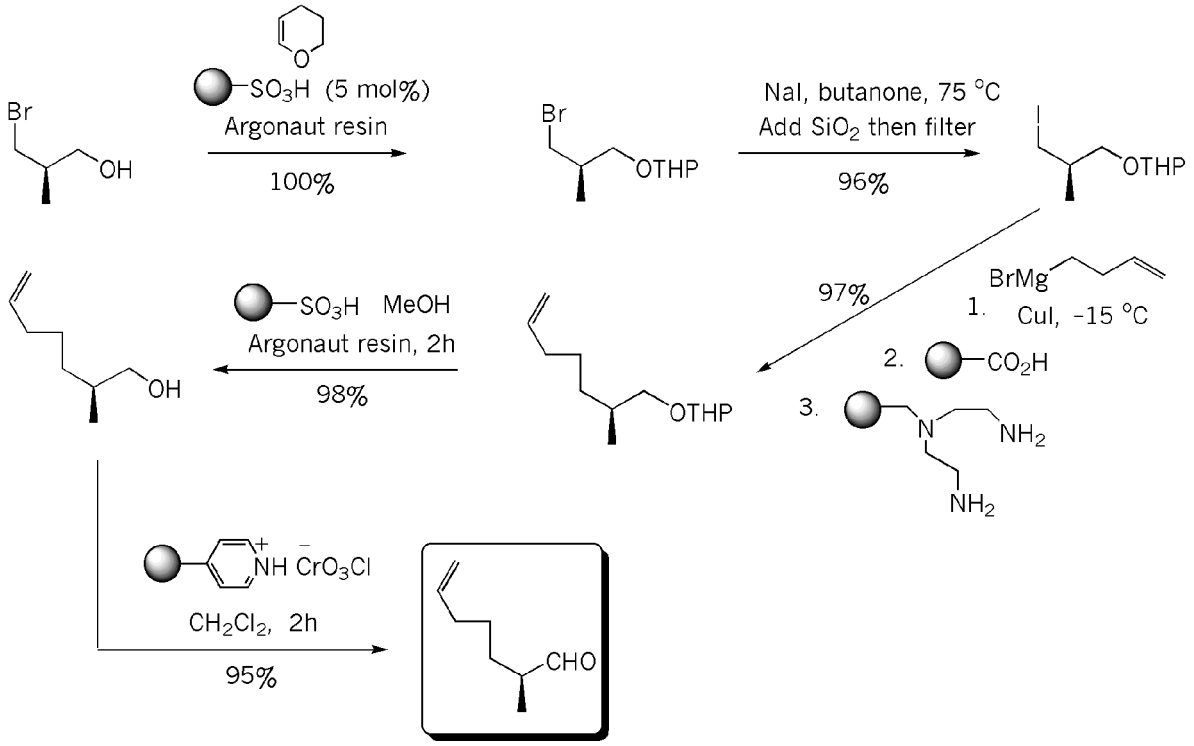


Figure 22. Synthesis of fragment B of *epothilone C*.

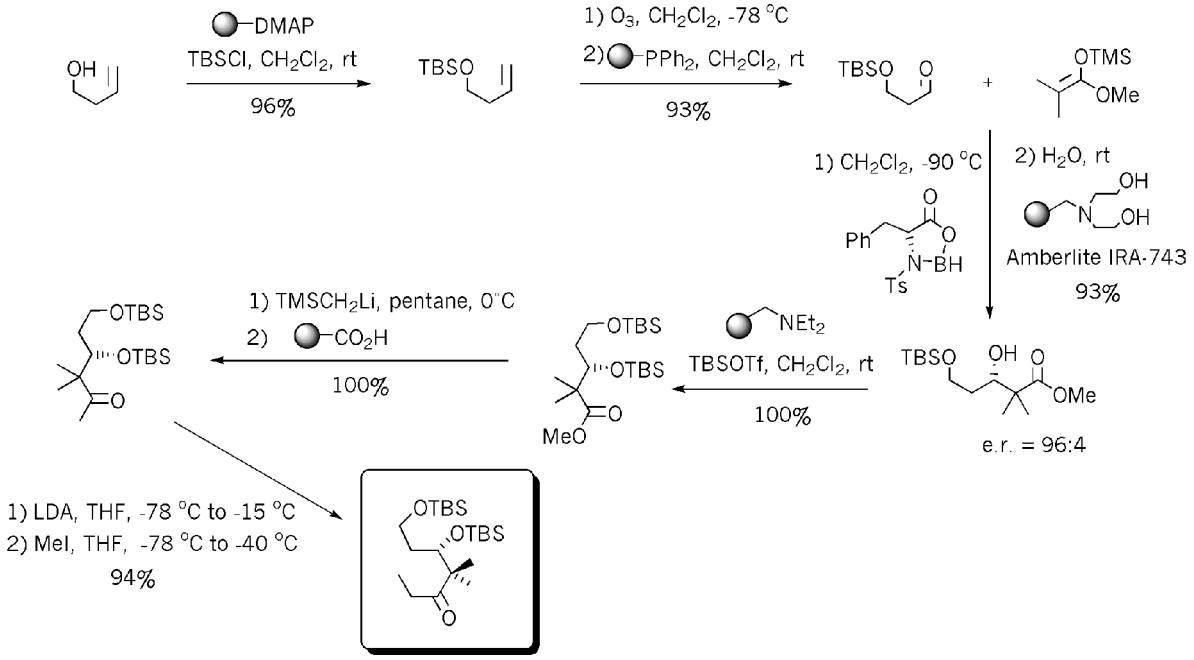


Figure 23. Synthesis of fragment C of *epothilone C*.

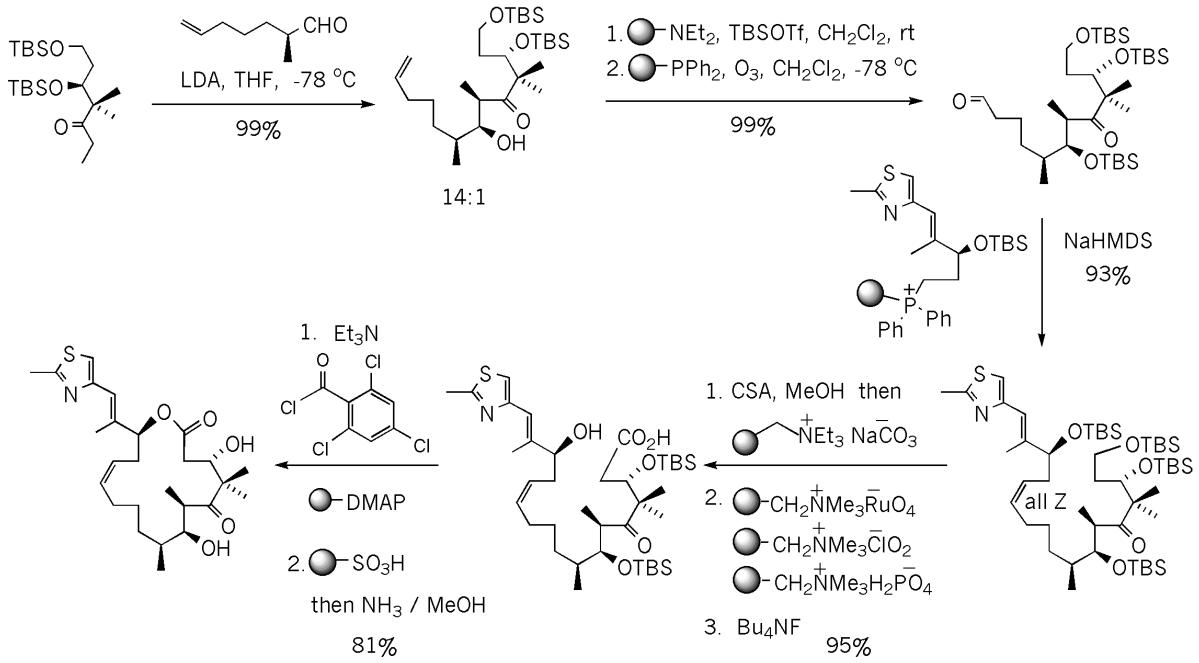


Figure 24. Final steps in the synthesis of epothilone C.

CONCLUSIONS

We remain very excited by the potential of these supported systems for compound synthesis. Future opportunities where stacked or flow reactors can be designed to deliver compounds to order are especially important. Furthermore, the miniaturization of these tools to microfluidic channels or mini-reactor vessels will also be a key driver for future applications. The idea of running one-pot multi-step sequences is now much more feasible. We can envisage using intelligent feed-back mechanisms, the use of robotics and even reagent stirrer bars and other devices to discover new reactions. We have only scratched the surface of synthesis for what will be possible in the years to come [43].

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