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Organic Synthesis in a Changing World

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ABSTRACT: This article is based on a lecture presented to the Chemical Society of Japan at Wasada University on March 27, 2002, by Professor Steven V. Ley. The lecture, "Organic Synthesis in a Changing World," was a comprehensive account of the ongoing research efforts of professor Ley's group in the development and application of solid-supported reagents and scavengers for use in organic synthesis. © 2002 The Japan Chemical Journal Forum and Wiley Periodicals, Inc. Chem Rec 2: 377–388, 2002: Published online in Wiley InterScience (www.interscience.wiley.com) DOI 10.1002/tcr.10033

Key words: organic synthesis, reagents, seavengers

Introduction

The title of this article suggests we are in a rapidly changing world, which is undoubtedly true. It would also be fair to say that organic synthesis has played a vital role in changing the world and will undoubtedly continue to do so into the future. The benefits afforded by synthesis already considerably enrich our lives: from the development of drugs in the ongoing fight against disease to the more aesthetic aspects of society with preparation of perfumes and cosmetics. Furthermore, the quality and quantity of our food supply relies heavily upon synthesized products, as do almost all aspects of our modern society ranging from paints, pigments, and dyestuffs to plastic, polymers, and materials of all kinds. However, the demands made on science are changing at an unprecedented pace, and synthesis, or molecular assembly, must continue to evolve in response to the new challenges and opportunities that arise.

Regulatory requirements necessitate cleaner and more efficient chemical processes, including better catalysts with lower environmental impact. There is an urgent need for new, strategically important reactions that change the way we plan and think about our synthesis today. We the chemists are under considerable pressure to speed up the discovery process by delivering more and better designed compounds that have important function. Recent interest in combinatorial chemistry and associated automation, computational, analytical, and IT tools are beginning to have a significant impact on synthesis programs. Nevertheless, we still have a long way to go.

One popular approach to making large numbers of compounds in a parallel sense has been to assemble molecules on immobilized supports following the pioneering work first introduced by Merrifield,[1] Letsinger,[2] Patchornik,[3] Leznoff,[4] Rappaport,[5] Camps,[6] Koster[7], and others. This has been a very successful approach and has led to a vast amount of published work. However, the difficulty encountered in optimising and following reactions on solid-supports, together with many other drawbacks, has caused people to reevaluate this approach. There is therefore a need for alternative protocols that can rapidly deliver compounds cleanly, in parallel, and preferably by convergent rather than linear routes. Our view was that multistep organic synthesis programmes would be

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better conducted in solution by using an orchestrated suite of supported reagents to effect all the chemical transformations (Fig. 1).[8] We saw several practical advantages to this approach. However, before commenting on these, it is pertinent to state that though the use of supported reagents, scavengers, and quenching agents to achieve individual reactions was well established,[9] longer multistep syntheses (i.e. in excess of three steps), had not been achieved—especially not with the idea of building combinatorial libraries or even complex natural products.

By combining the power of supported reagents with other techniques such as immobilized scavengers and quenching agents, or catch and release methods, tremendous opportunities present themselves for general organic synthesis programs. Obviously these methods are well suited to parallel synthesis because simple work-up is affected by the filtration of spent reagents and products are isolated by evaporation of solvents. These processes are readily automated, but moreover, can be followed in real-time using LC-MS (and other solution phase analytical techniques) and the information fed back to affect the synthesis and optimisation of the reactions. Much more however is possible. For example, if toxic, obnoxious, or volatile compounds are used, then by immobilisation they become benign and much easier to handle. Furthermore, when by-products co-run with the required materials then conventional chromatography is ineffective, scavenging or catch and release techniques become particularly valuable. Also, many reagents are catalytic or at least the spent reagent can be readily recovered by filtration and recycled to minimise costs. Scale-up of the process is usually straightforward, and in the future

Steve Ley is currently the BP (1702) Professor of Organic Chemistry at the University of Cambridge, and Fellow of Trinity College, Cambridge, England. He studied for his PhD at Loughborough University working with Harry Heaney and then carried out postdoctoral work in the United States with Leo Paquette at Ohio State University. In 1974 he returned to the United Kingdom to continue postdoctoral studies with Sir Derek Barton at Imperial College. He was appointed to the staff at Imperial College in 1975 and was appointed to Professor in 1983 and Head of Department in 1989. In 1990 he was elected to the Royal Society (London) and moved to Cambridge in 1992. Ley's work involves the discovery and development of new synthetic methods and their application to biologically active systems. The group has published extensively on the use of iron carbonyl complexes, organoselenium chemistry, and biotransformations for the synthesis of natural products. So far over 85 major natural products have been synthesised by the group. The group is also developing new methods and strategies for oligosaccharide assembly and combinatorial chemistry. Ley's published work of over 470 papers has been recognised by many awards, including the Hickinbottom Research Fellowship, the Corday Morgan Medal and Prize, the Pfizer Academic Award, the Royal Society of Chemistry Synthesis Award for 1989, the Tilden Lectureship and Medal, the Pedler Medal and Prize, the Simonsen Lectureship and Medal and the Aldolf Windaus Medal of the German Chemical Society and Göttingen University, the Royal Society of Chemistry Natural Products Award, the Flintoff Medal, the Paul Janssen Prize for Creativity in Organic Synthesis, the Rhône-Poulenc Lectureship and Medal of the Royal Society of Chemistry, and the Glaxo-Wellcome Award for Outstanding Achievement in Organic Chemistry. Recently he was awarded the Royal Society of Chemistry Haworth Memorial Lectureship, Medal, and Prize and The Royal Society Davy Medal, and the German Chemical Society August-Wilhelm-von Hofmann Medal together with the Pfizer Award for Innovative Science. He was awarded the CBE in 2002.

Ley sits on many national and international boards, among which is the Chemicals Innovation and Growth Team. He is also chairman of the EPSRC International Review of Chemistry Steering Group. He is presently the chairman of the Novartis Foundation Executive Committee and immediate president of the Royal Society of Chemistry. ■

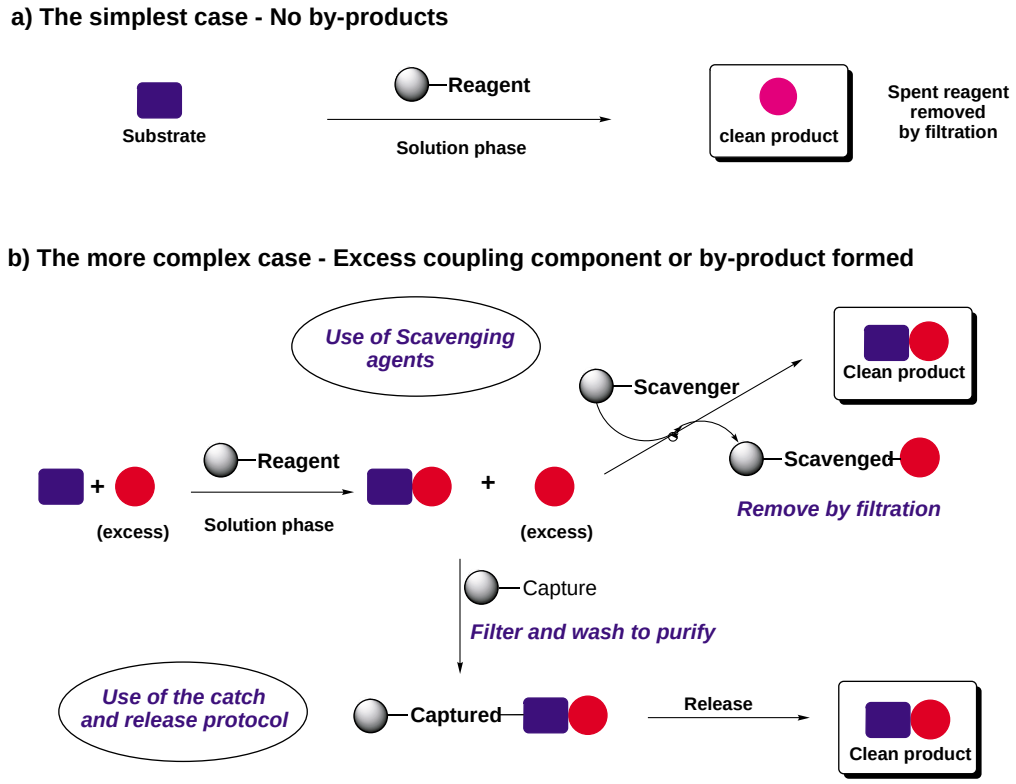


Fig. 1. Solid-supported reagents in synthesis. (**a**) The simple case—no by-products generated. (**b**) A more complex case—the use of excess coupling components or by-product removal.

one can envisage much more use being made of flow reactors. Another aspect that makes these systems attractive in synthesis is the potential to pilot new reaction schemes on small quantities. The ability to investigate sequentially a number of new steps in a synthetic pathway by simply removing the contaminating spent reagents and by-products rather than having to use the standard protocols of water-quenching, solvent extraction, drying, evaporation, and chromatography at each stage generates substantial time savings. Even more exciting opportunities arise when one considers combining several reagents in a single pot to effect multiple transformations. This is possible of course because of the site isolation of reagents by immobilization, so that even mutually incompatible reagents in solution (e.g., oxidants and reductants) do not react together.

Using these concepts one can imagine how they could be harnessed to discover new chemistry, but without doubt they do minimise long-winded conventional procedures and simplify the tasks to create time for more profitable planning, thinking, and innovation in synthesis. What is also important to recognise is that not only are one-pot linear synthesis routes possible but that one can perform convergent synthesis or batch splitting to maximise product variation (Fig. 2). All these are attractive components of modern synthetic design.

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 properly. What follows constitutes a selection of topics to give a flavour of what can be achieved using these systems.

Some years ago we recognised the importance of developing a catalytic oxidant for alcohols because the products of these reactions constitute useful building blocks for synthesis. Following our previous studies on tetra-N-propyl ammonium perruthenate (TPAP)[10] we prepared a polymer-supported version of this reagent (PSP) by ion exchange of an Amberlyst 27 resin with potassium perruthenate (Scheme 1).[11]

This has proven to be a very effective oxidant that is now commercially available.[12] Oxidation of alcohols with catalytic PSP can be best achieved using toluene as a solvent in the pres-

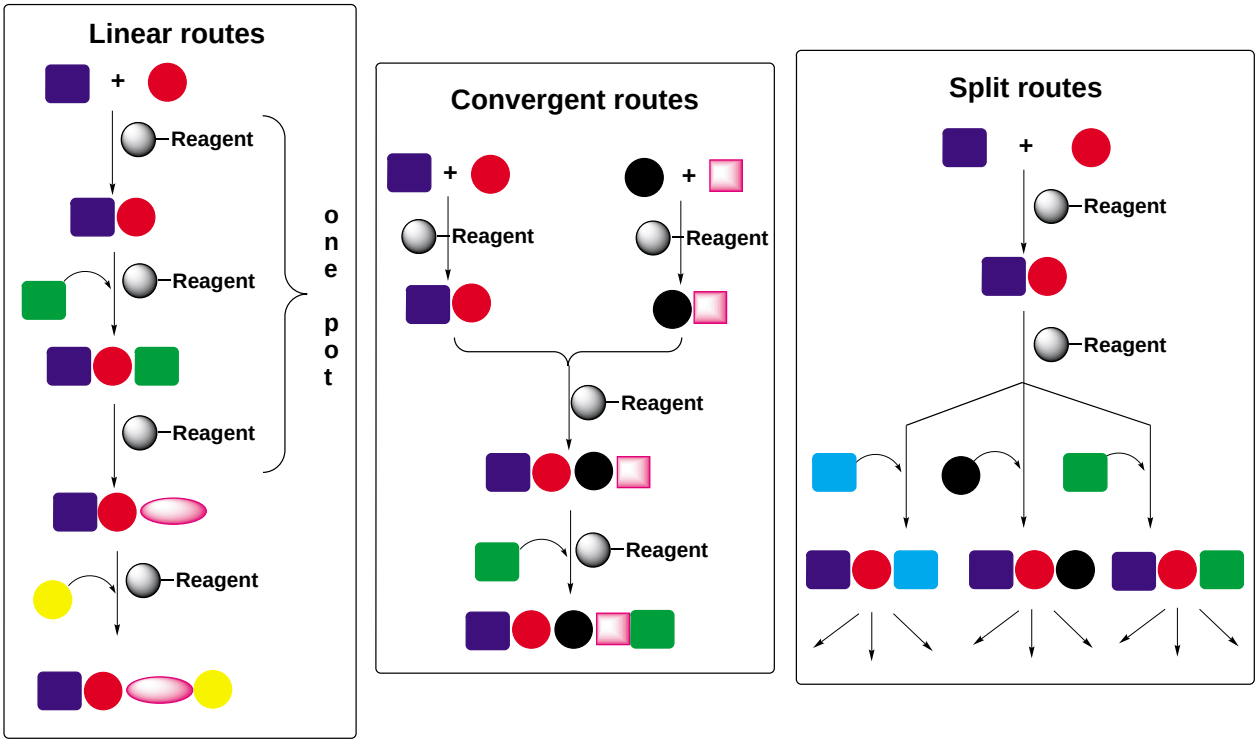
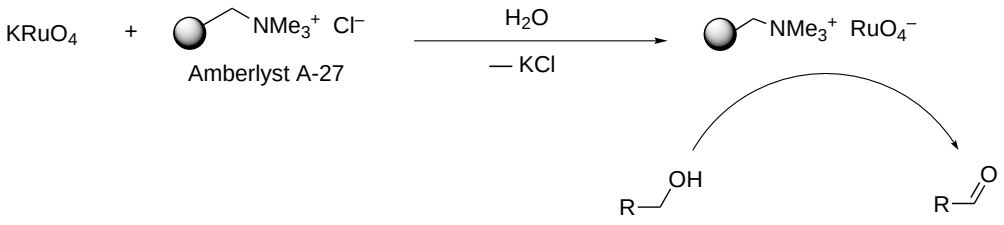


Fig. 2. The opportunities for solid-supported reagents in synthesis.



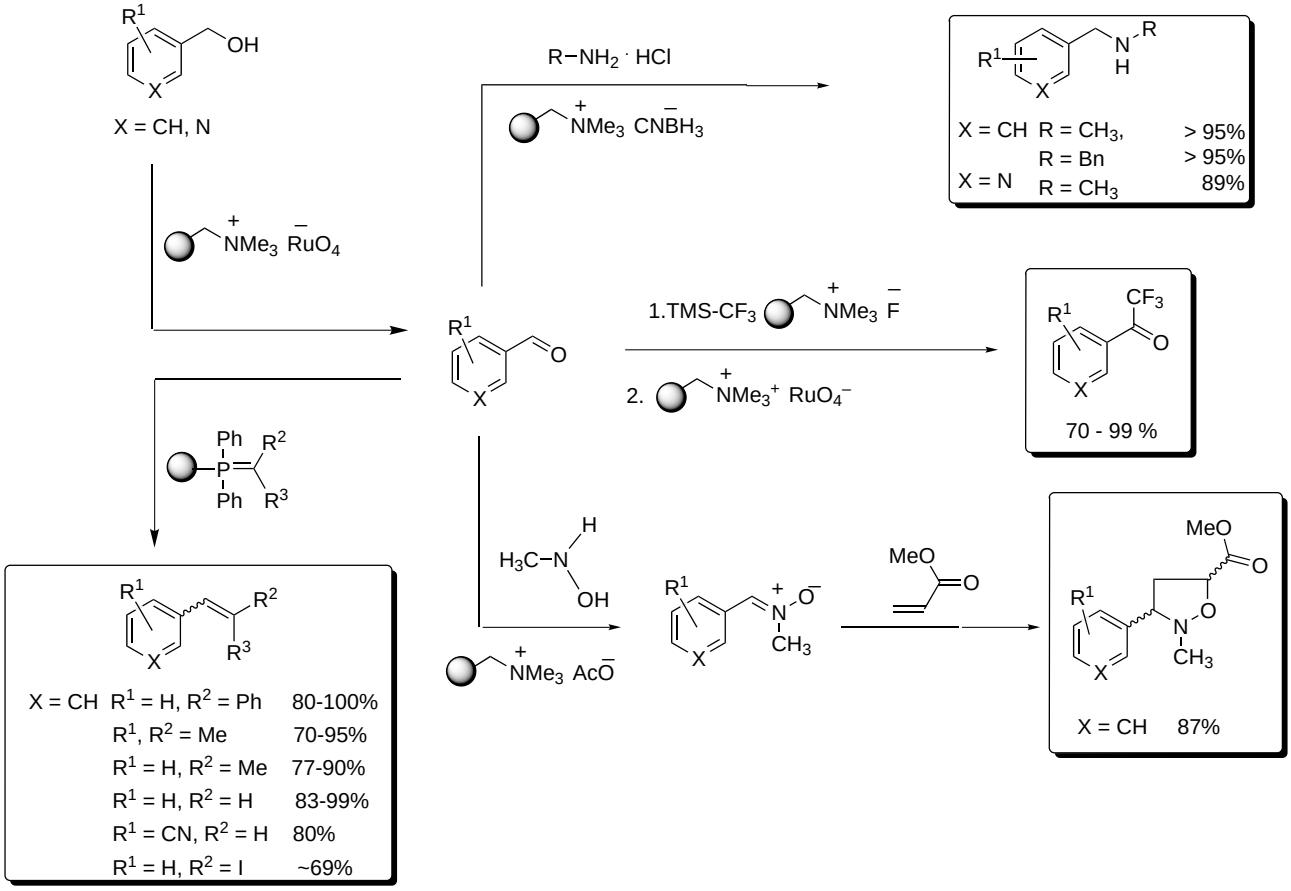
Scheme 1.

ence of molecular oxygen as the co-oxidant. In favourable cases the spent reagent can be recovered and reused. The aldehyde products can then be directed to many other synthesis programmes by batch splitting (Scheme 2).[13]

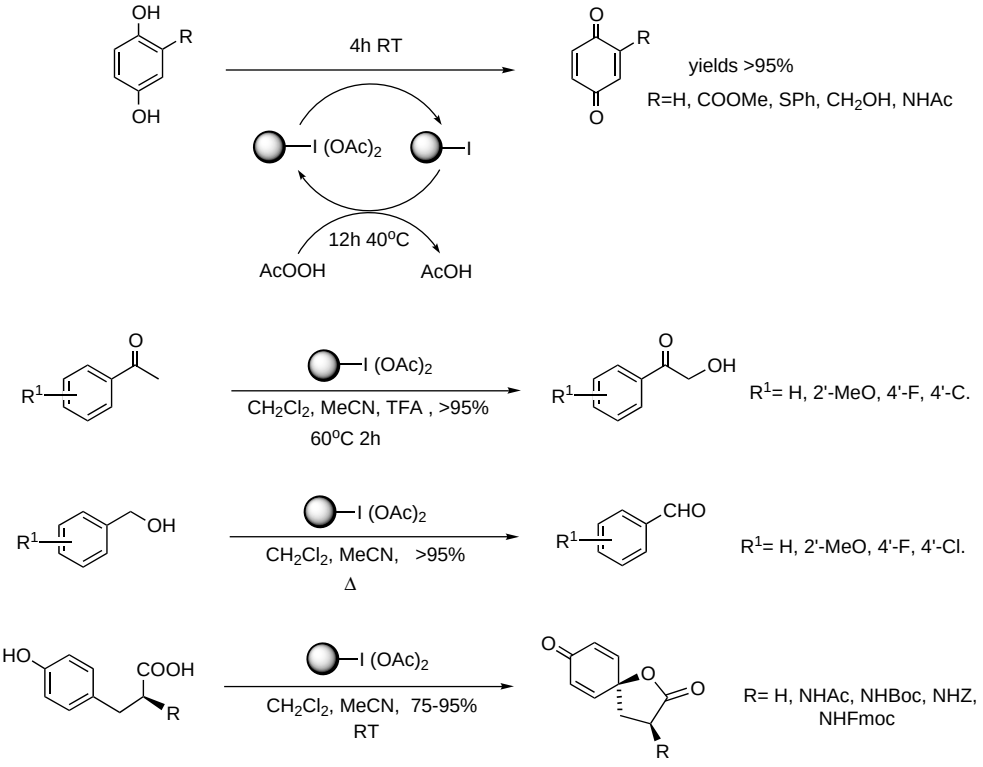
Hypervalent iodine reagents are also similarly useful in a wide range of synthetic applications. Accordingly we have prepared a number of these systems on an immobilised format and used these for oxidation.[14] What is attractive is that the spent solid supported aryliodide by-product can be readily recovered by filtration and recycled by oxidation with peracids (Scheme 3).

Some other solid supported reagents we have developed to solve problems when the products or the by-products are particularly obnoxious or hazardous are shown in Scheme 4.[15]

In many of these reactions we have also found the use of focused microwaves to be particularly beneficial in driving the reactions to completion.[16] The combined use of toluene and an ionic liquid to achieve both a rapid heating cycle and ease of work-up is also advantageous in parallel solid-supported synthesis projects.[17] In the two examples above, the odorous products of the reaction, thioamides or isocyanides, were used immediately as starting points for other syntheses and

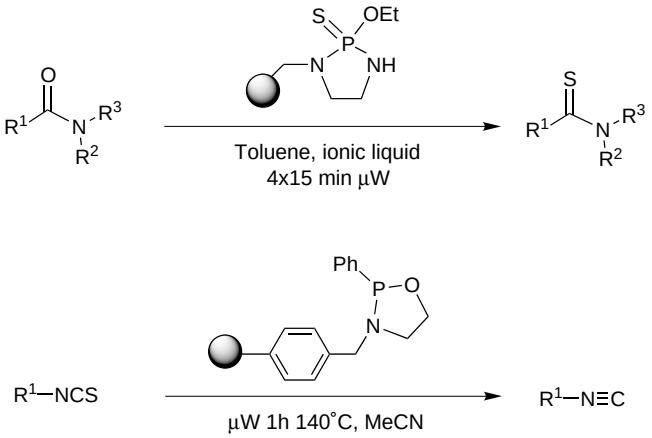


Scheme 2.



Scheme 3.

consequently did not require complex isolation and therefore worker exposure was minimised. The availability of appropriate starting materials is always an issue in the preparation of chemical libraries, and many of these compounds that contain desirable features are often not commercially available and need to be synthesised. There is a demand therefore to produce compounds with other common functional groups from readily available species. We have therefore developed a number of these pro-cesses, which can be illustrated by two examples, namely the conversion of aldehydes to nitriles[18] and the direct transformation of alcohols to acids[19] (Scheme 5). Both examples lead to clean products and are therefore suitable for automation.



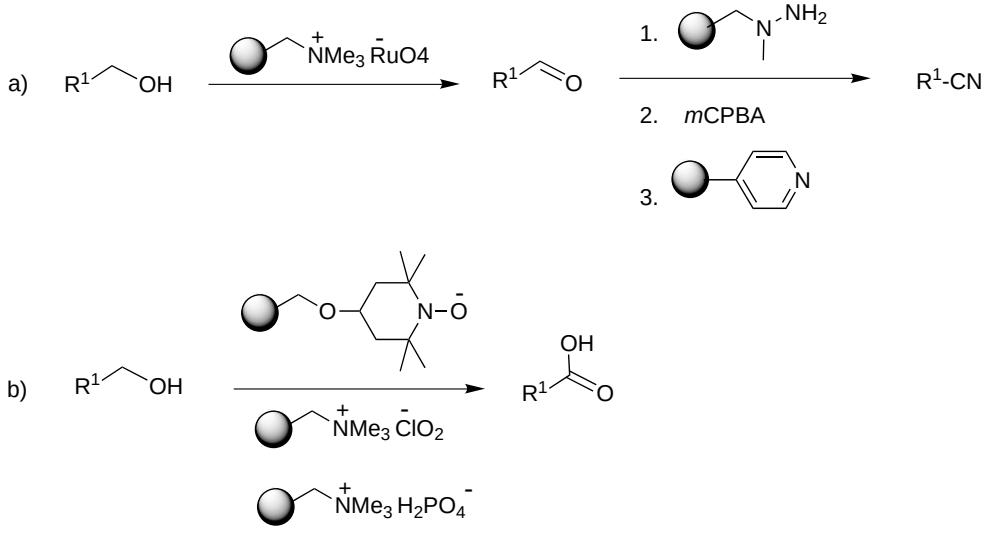
Scheme 4.

The last example in this scheme is interesting in that while the conversion of alcohol to acid is straightforward using conventional reagents, the isolation and work-up of the product is often laborious. In the immobilised reagent version all the compounds are added together at the start of the process and the product acid is isolated by simple filtration through a silica cartridge.

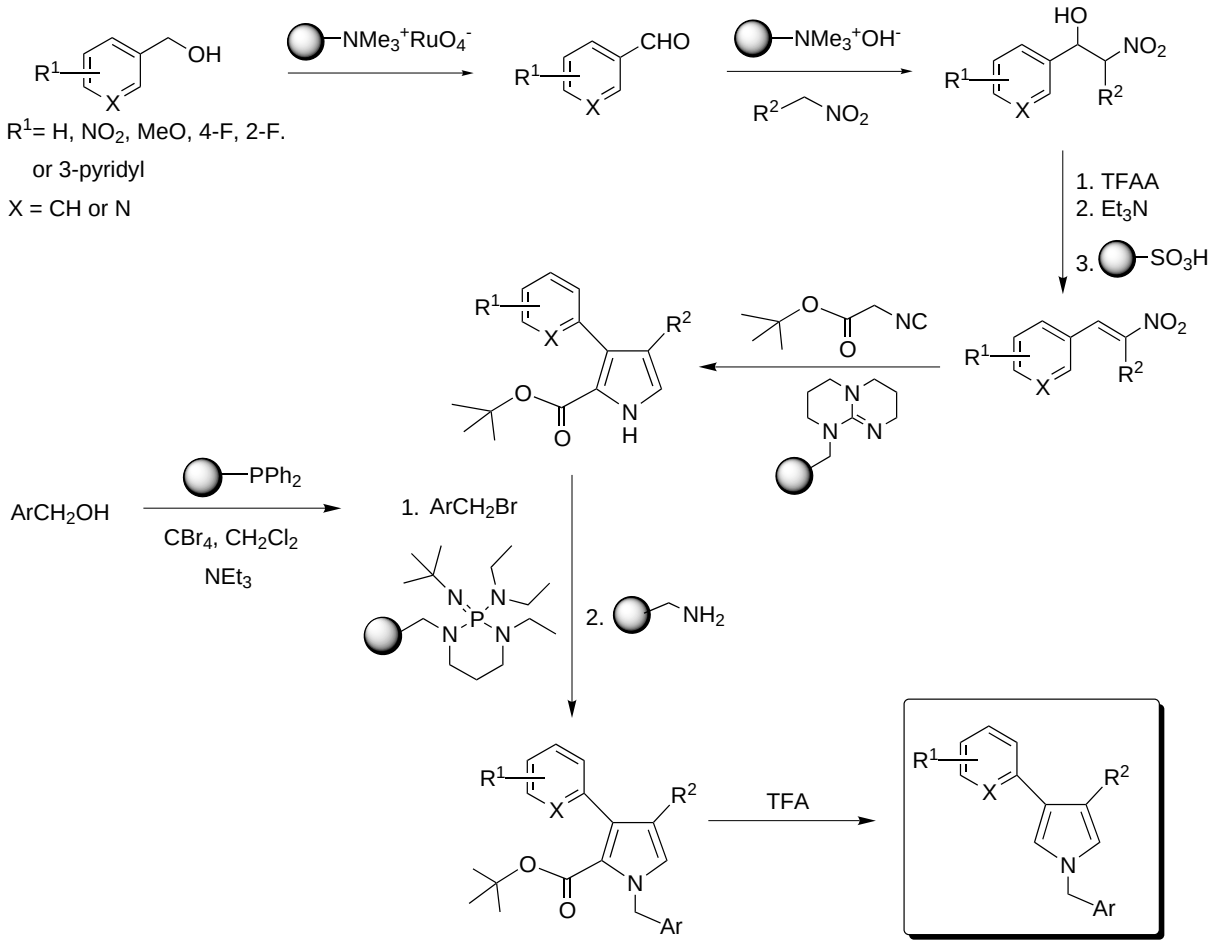
Most of our work however has focused on multistep syntheses using solid-supported reagents and scavengers.[8] The aim of this approach has been to develop enhanced efficient synthetic sequences to the more complex species that are found in biologically active systems—either pharmaceutical drugs, agrochemicals, or natural products. Implicit in this methodology is the desire to avoid conventional methods of product isolation such as chromatography, distillation, or crystallisation, as these are often consuming, expensive, and are tasks not easily performed in parallel using automated methods.

We have reported many multistep sequences to potentially useful targets that use combinations of solid-supported reagents, scavengers, catch and release, and other phase-switching processes.[20] Shown below are three Schemes 6, 7, and 8, which demonstrate the versatility of these concepts leading to a pyrrole library[21] (Scheme 6), a collection of matrix metalloproteinases (MMP) inhibitors[22] (Scheme 7), and the synthesis of sildenafil (Viagra™)[23] (Scheme 8).

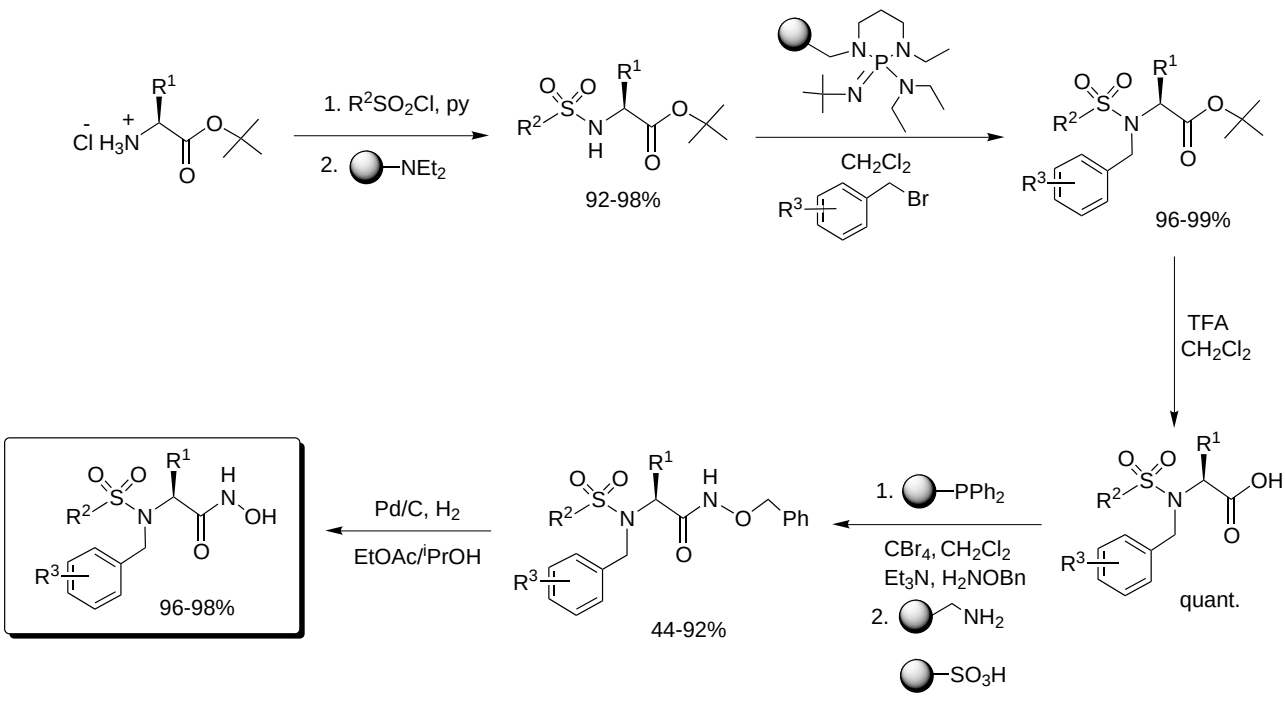
Though these examples illustrate routes to molecules of interest to the pharmaceutical industry and point the way in which these multistep syntheses can be accomplished in future discovery programs, we have also used these procedures to prepare natural products. Needless to say, if natural systems can be prepared simply and in quantity, then it follows that



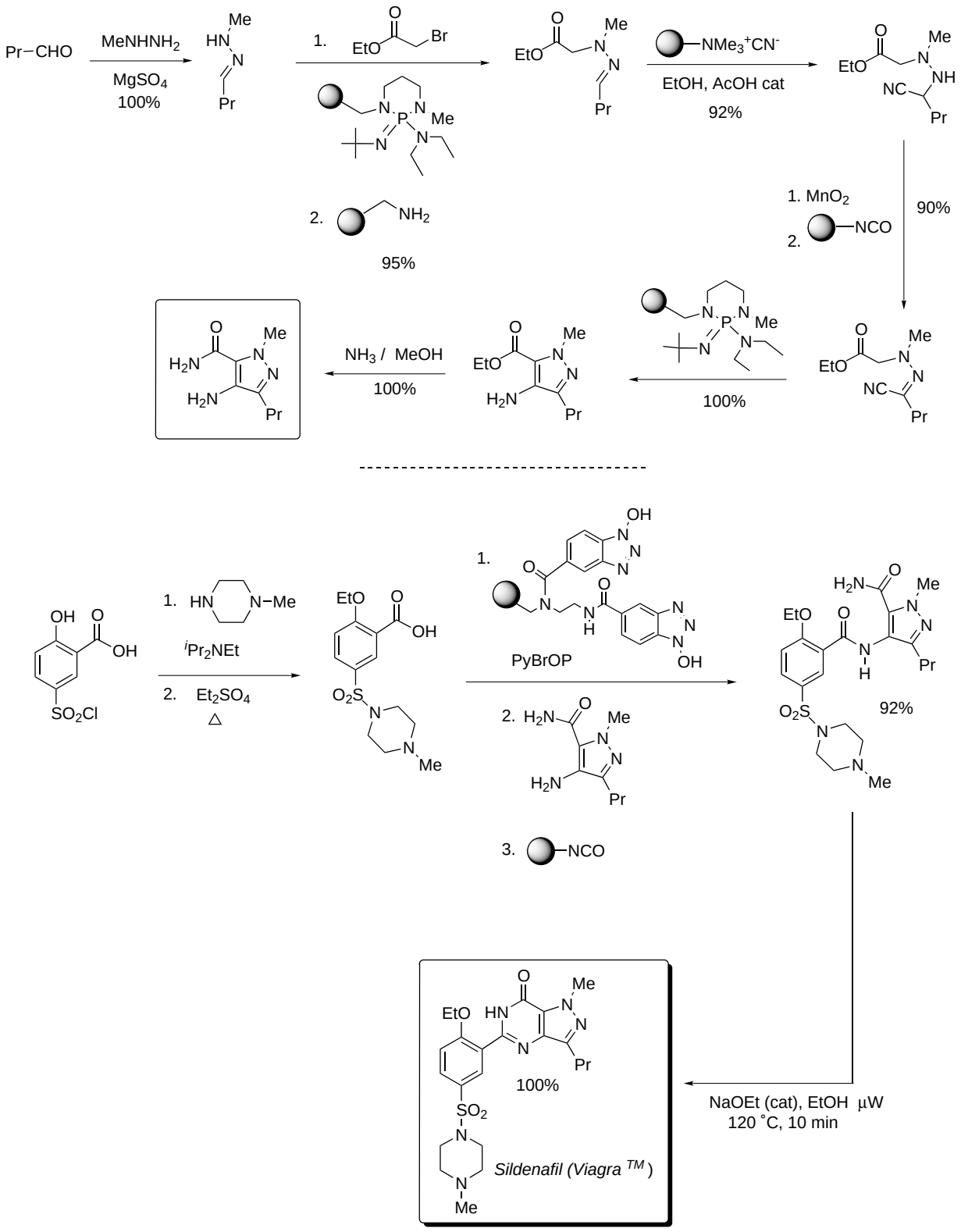
Scheme 5.



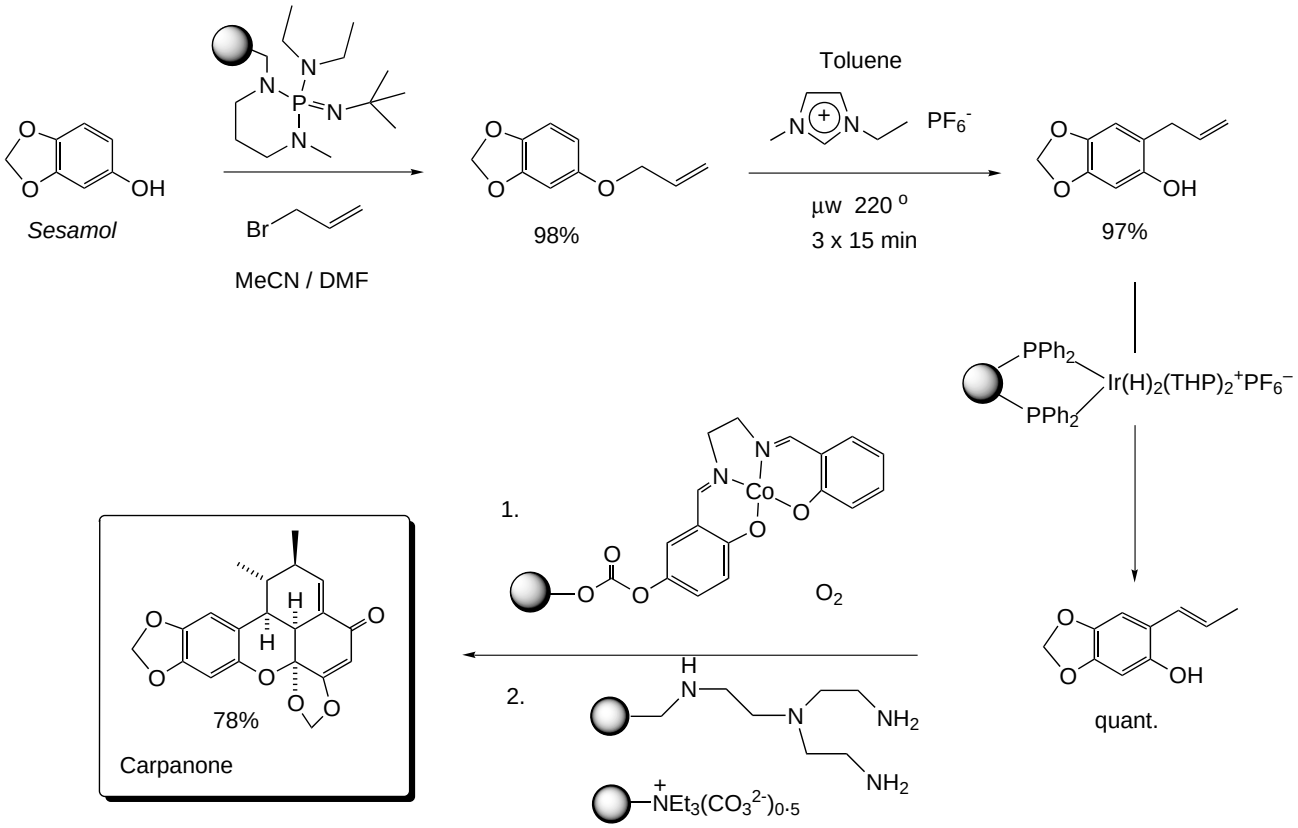
Scheme 6.



Scheme 7.



Scheme 8.



Scheme 9.

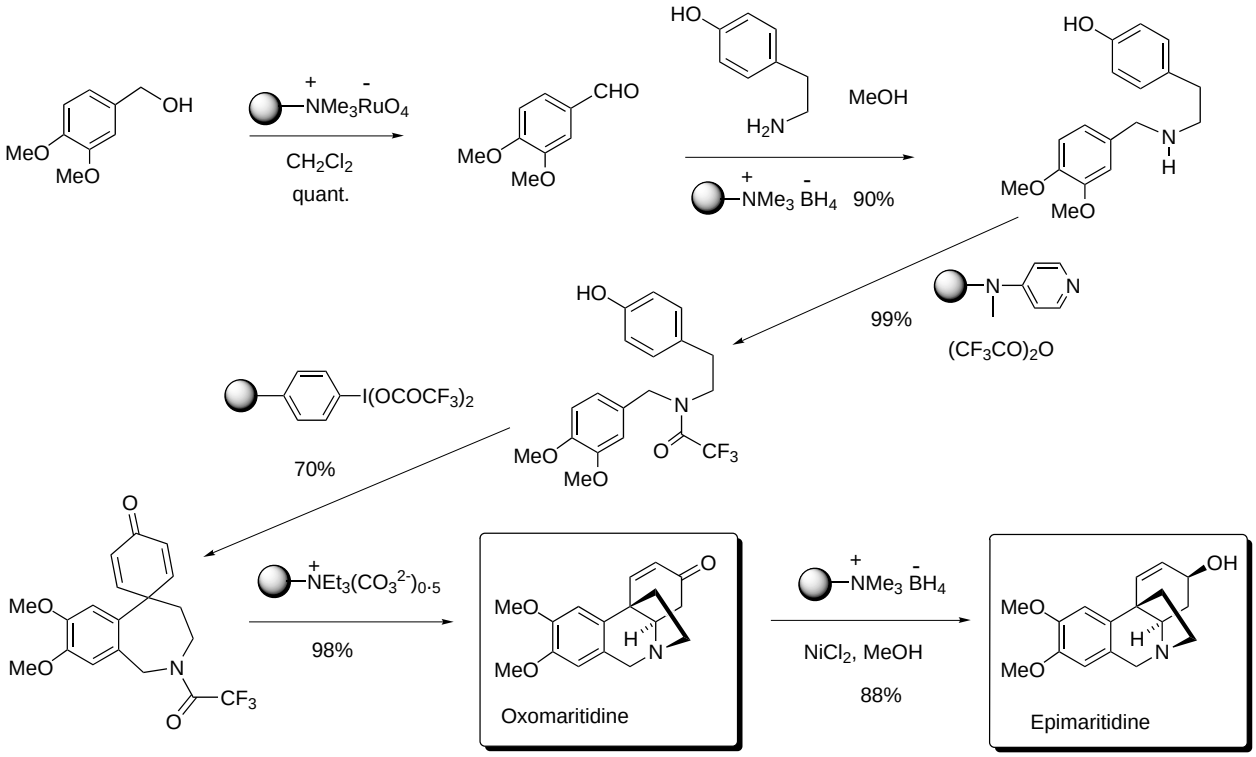
novel natural product-like analogs can be made to probe cellular mechanisms and signal transduction pathways using related approaches.

The synthesis of the natural product carpanone (Scheme 9) is based on an early synthesis by Chapman[24] but uses supported reagents, some of which were new and designed for this particular synthesis. It also reports the use of microwaves and ionic liquids to enhance the Claisen rearrangement step and makes use of scavengers to give a final clean, crystalline product.[25] Likewise the route to epimaritidine (Scheme 10) utilises no less than six solid-supported reagents in an orchestrated sequential fashion. The route is based on a solution phase conventional multistep process nicely developed by Kita[26] that required chromatography to give a clean product. The new route requires no chromatography and can deliver grams of product in less than one week.[27]

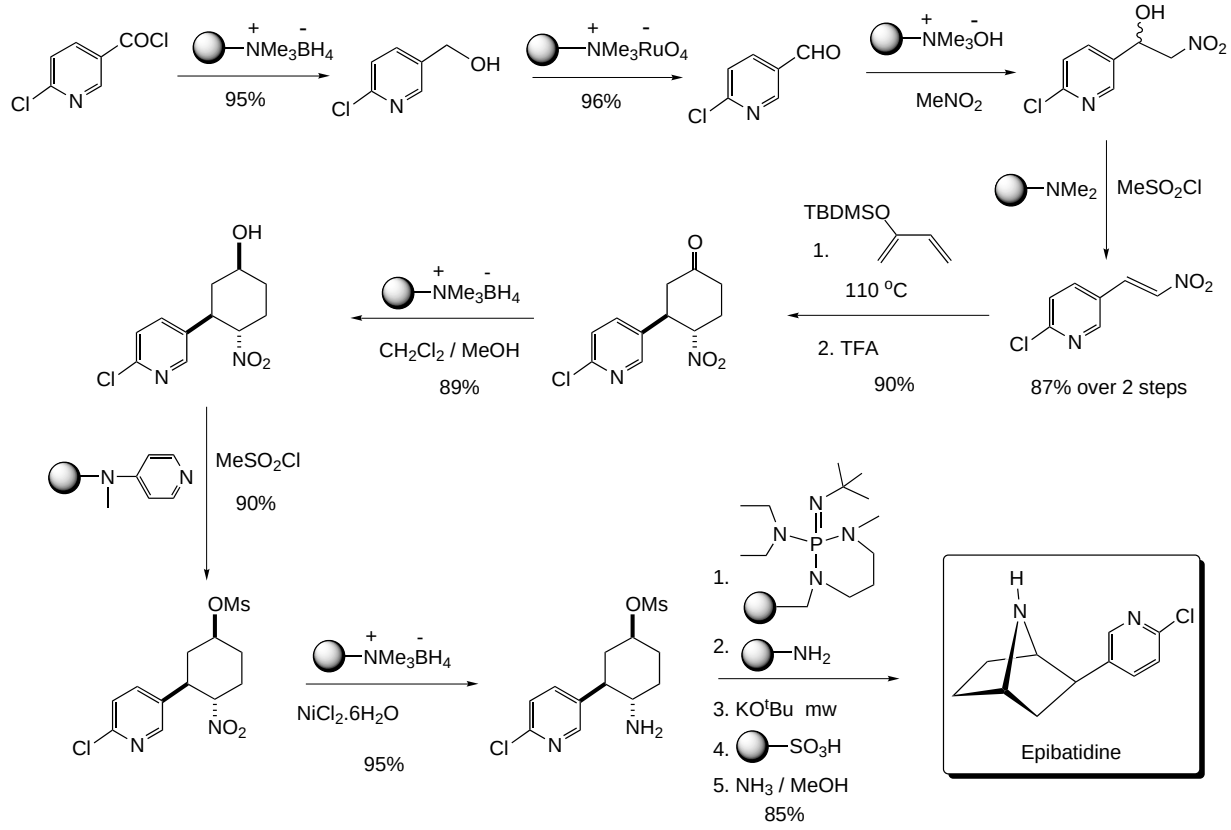
Similarly, the route to epibatidine is attractive and uses 10 solid-supported reagents including a scavenger, catch and release, and microwaves to enhance one of the synthetic steps (Scheme 11).[28]

Finally, we describe the synthesis of a newly isolated alkoloid plicamine[29] utilizing no less than 12 immobilised systems (Scheme 12).[30] This route constitutes the first synthesis of this molecule but was achieved rapidly using the new methods. Both enantiomeric forms have been prepared, and intermediates can be diverted into other unnatural product synthesis programs. The complexity of plicamine as a target molecule nicely confirms the power and effectiveness of these new approaches and these new tools for organic synthesis.

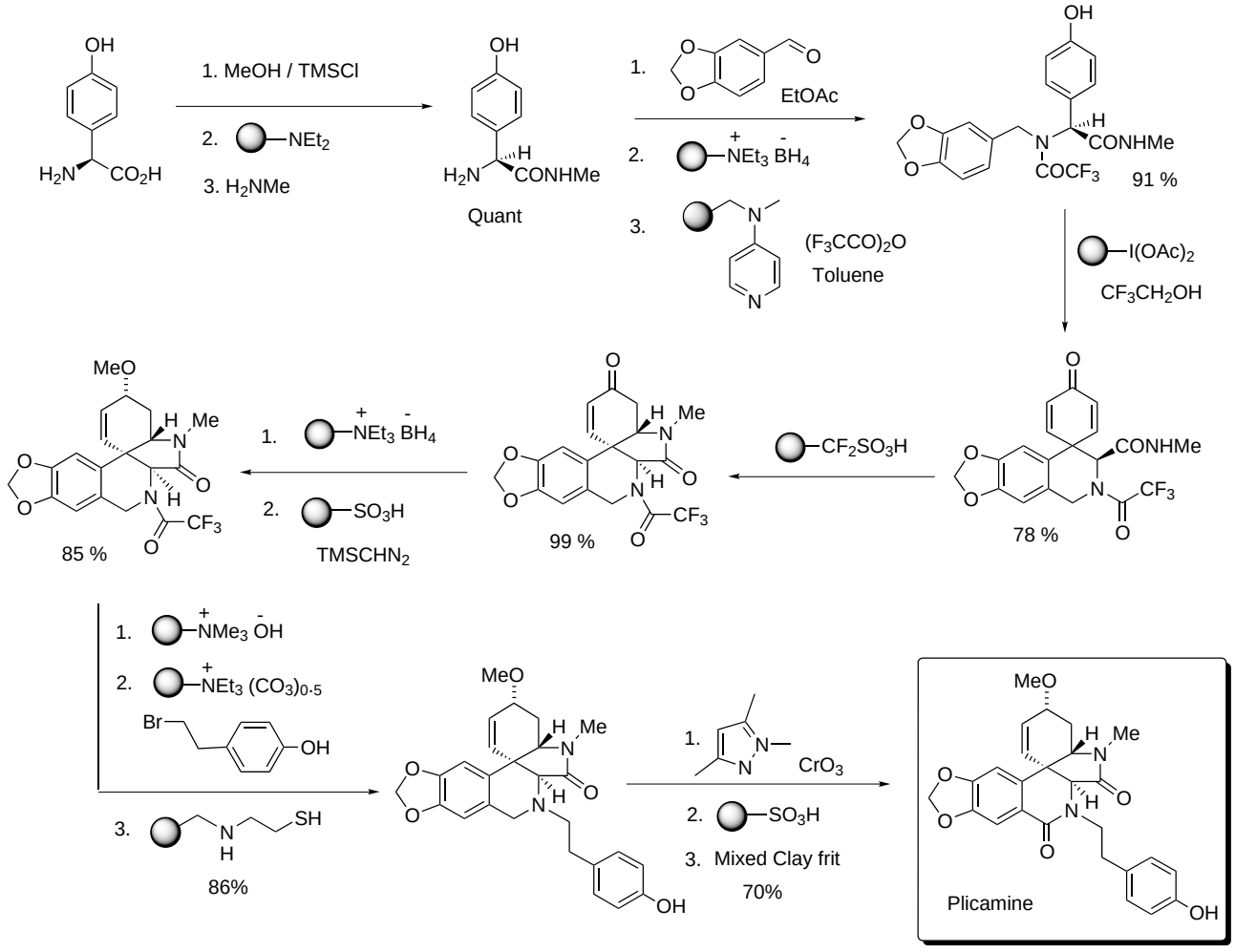
As to the future we can expect many exciting developments. We will see many new reagents being developed—reagents that have been designed for immobilisation rather than being first developed for traditional solution phase chemistry. Many more catalytic and fully recyclable systems are required along with more effective and or selective scavenging agents. These systems will be developed as plug-in reagent cartridges or stacked/parallel flow reactors. The idea of using reagent stirrer bars is already a reality. The ability to link the product formation with real-time feedback of information should lead to rapid and even self-optimising systems. It is also



Scheme 10.



Scheme 11.



Scheme 12.

exciting to think how to use designed one-pot multi-solid-supported reagent sequences for synthesis and the possible invention of new reactions. Given that informatics and automation will play an ever-increasing role in synthesis, the opportunities are limited only by our imagination.

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