THE EVOLUTION OF IMMOBILIZED REAGENTS AND THEIR APPLICATION IN FLOW CHEMISTRY FOR THE SYNTHESIS OF NATURAL PRODUCTS AND PHARMACEUTICAL COMPOUNDS

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11.1. BACKGROUND

Underpinning a healthy drug discovery and development programme is the ability to prepare large numbers of structurally diverse molecules. Developing innovative practical chemical techniques to achieve this goal has therefore become essential [1]. Indeed, the incorporation of new technologies for chemical synthesis is now common place and encompasses automation [2], informatics [3], and robotic approaches [4], along with the use of immobilized reagents and catch-and-release [5] strategies together with microfluidic flow reactors [6] and focused microwave techniques [7].

Before discussing the recent evolution of flow chemistry methods, it is helpful to review some of the concepts on which this technology platform is based. One particularly important aspect of flow chemistry for multistep synthesis has been the development of immobilized reagents, scavengers, and catch-and-release techniques.

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There are obvious advantages for the use of immobilized reagents in synthesis, for instance, product isolation and separation can be made easier, since reagents can be used in excess to drive reactions to completion. Furthermore, reaction quenching, aqueous workups, and chromatographic purification are generally not necessary. More often than not, products are obtained in a pure form directly following removal of the resin by filtration and subsequent solvent evaporation. An additional advantage is that the recovered spent reagents can often be recycled, which constitutes an attractive feature especially when using expensive catalysts or precious materials. Supported reagents often have improved safety profiles compared to their nonimmobilized counterparts, meaning toxic, noxious, and flammable compounds become more manageable when tethered to a heterogeneous support. In addition, site isolation effects mean that mutually incompatible reagents such as immobilized acids and bases can be used together in one reaction vessel. Similarly, immobilized scavenger resins can be used during downstream purification processes to negate complicated purification processes. These agents exploit ionic and covalent substrate interactions and bind both organic and inorganic impurities, allowing them to be rapidly sequestered from crude reaction mixtures.

Although some immobilized reagents can react more slowly, reactions times are often improved by using focused microwave heating methods [8]. Alternatively, doping the solution with ionic liquids, which act as good thermal transfer agents in the presence of microwaves, gives greatly improved heating when poor absorbing solvents are used [9].

By seeking to challenge the prevailing dogma of using solid-phase synthesis for the preparation of chemistry compound libraries in the 1990s, the combination of solution-phase chemistry with the versatility and convenience of immobilized reagents has led to a significant shift in improved practices and synthesis concepts. Indeed, to illustrate how these reagents can be used best in multistep synthesis sequences, a few examples are highlighted that demonstrate the breadth and utility in conducting a multitude of chemical transformations. These include the preparation of the amaryllidaceae alkaloids ($\pm$)-oxomaritidine and ($\pm$)-epimaritidine [10], (+)-plicamine [11], ($\pm$)-epibatidine [12], as well as a number of key pharmaceutical compounds, including sildenafil (Viagra®) [13], the β_2 adrenoceptor agonist (*R*)-salmeterol [14], γ -aminobutyric acid (GABA) analogues [15], carpanone [16], and in more recent times the synthesis of the epothilones [17].

11.2. MULTISTEP SYNTHESIS OF NATURAL PRODUCTS AND BIOACTIVE MATERIALS USING IMMOBILIZED REAGENTS

The first multistep synthesis of a natural product to be reported that used immobilized reagents for each transformation was the preparation of the amaryllidaceae alkaloids ($\pm$)-oxomaritidine **7** and ($\pm$)-epimaritidine **8** (Scheme 11.1) [10]. The six-step synthesis route began with the oxidation of benzylic alcohol **1** to the corresponding aldehyde using immobilized perruthenate [18]. The corresponding aldehyde was then reacted with phenolic amine **2** under reductive amination conditions to generate the

SCHEME 11.1 Palladium(O)-catalyzed direct arylation.

norbelladine derivative **3**. Trifluoroacetylation of **3** was achieved with trifluoroacetic anhydride and an immobilized dimethylaminopyridine (DMAP) resin to give the amide **4**. Intramolecular phenolic oxidative cyclization of **4** to form the spirodienone **6** was achieved using immobilized hypervalent iodine **5**, a reagent developed specifically for this task [19]. Finally, treatment of **6** with immobilized carbonate in methanol resulted in a rapid deprotection and spontaneous intramolecular 1,4-addition to give (±)-oxomaritidine **7** in 98% yield. Subsequent borohydride reduction in the presence of an *in situ* copper or nickel boride species delivered the second natural product epimaritidine **8** as its racemate.

The next challenge was to extend the number of sequential reaction steps that could be achieved by these methods; consequently, the analgesic alkaloid (±)-epibatidine **17** was chosen as a suitable proof of principal target. Here, a total of 10 immobilized reagent and sequestering agents were employed in a successive fashion (Scheme 11.2) [12]. Furthermore, **17** was obtained directly from the reaction sequence in >90% purity without any chromatographic purification.

In this work, aldehyde **10** was prepared from **9** via borohydride reduction, followed by oxidation with perruthenate. Using the Henry reaction catalyzed by polymeric base, compound **10** was converted to the corresponding nitrostyrene **11** after elimination of the intermediate trifluoroacetate with an immobilized diethylamine base. Cyclohexanone **13** was obtained via a Diels–Alder reaction of **11** with the silyl-protected 2-oxadiene **12**. Following carbonyl reduction and conversion to the corresponding mesylate, (±)-**14** was obtained. Nickel boride generated on a polymeric support was particularly effective for achieving selective nitro reduction without affecting the aromatic chloride and this method formed the desired amine **15** in high yield. Cyclization of **15** was achieved in the presence of immobilized *N*-phenyl-*tris*(dimethylamino)iminophosphorane (PS-BEMP) using an immobilized benzylamine to scavenge the uncyclized minor mesylate diastereomer. Epimerization of this compound to (±)-epibatidine **17** was mediated using pulsed microwave irradiation in the presence of potassium *tert*-butoxide in *tert*-butanol, furnishing the thermodynamically more stable *exo* isomer. The natural

SCHEME 11.2 Synthesis of the potent analgesic alkaloid (±)-epibatidine 17.

product was purified by a catch-and-release process, catching onto an immobilized sulfonic acid and then releasing by treatment with methanolic ammonia.

A necessary requirement of any new technology is to always compare it with preexisting methods. To exemplify the potential of these new methods during a contemporary drug synthesis, the erectile dysfunction drug sildenafil (Viagra® 27) was chosen as a target (Scheme 11.3) [13].

The convergent strategy adopted for this synthesis of sildenafil 27 brought together compounds 22 and 25 as the major coupling components that in turn were easily derived from simple starting materials (18 and 23). The activated immobilized ester 25 and aminopyrazole 22 underwent amide bond formation, while the excess amine was scavenged with an immobilized isocyanate resin in a separate step. Cyclodehydration was achieved using sodium ethoxide under an early example of focussed microwave conditions to afford multigram quantities of analytically pure sildenafil in excellent overall yield.

A further example of these methods in contemporary drug synthesis was the preparation of the bronchodilator (*R*)-salmeterol 34. Here, an alternative synthetic pathway was used to avoid the problem of diastereomers encountered in previous syntheses [20], allowing 34 to be prepared without any chromatographic purification steps required (Scheme 11.4) [14]. Each transformation and product purification was effected using immobilized reagents, although one recrystallization of 30 was needed to enhance the diastereomeric purity of the product. The initial condensation of phenol 28 with an immobilized methylene iminium salt to eventually form compound 29 was also an important aspect of this synthesis. This involved a sequence of reactions using an immobilized carbonate resin to effect deprotonation of 28, followed by reaction with Eschenmoser's salt to *ortho*-aminomethylate the phenol,

SCHEME 11.3 Synthesis of sildenafil (Viagra® 27).

hydrolysis in the presence of acetic anhydride, and bromination using an immobilized perbromide.

Since alkaloids often provide interesting synthetic challenges, the preparation of (+)-plicamine **41** using the new methods is particularly instructive

SCHEME 11.4 Synthesis of the bronchodilator (*R*)-salmeterol **34**.

SCHEME 11.5 The first synthesis of (+)-pilocarpine **41** using a combination of immobilized reagents and scavengers.

(Scheme 11.5) [11]. Impressively, the entire synthesis including optimization was complete within 6 weeks. A key feature of this synthesis was the use of immobilized hypervalent iodine **5** for the oxidative transformation to the spiridienone **38**. Also, the conjugate addition of the amidic nitrogen atom to complete the natural product scaffold (**38** to **39**) using Nafion-H fluorosulfonic acid resin as an acid source was an attractive feature. Similarly, the use of an immobilized sulfonic acid resin in combination with trimethylsilyl diazomethane proved to be a particularly efficient way to methylate the hindered alcohol and afford **39**.

Enzymes are valuable tools for asymmetric synthesis, most notably in the desymmetrization of *meso*-compounds, where achiral starting materials can be converted into enantiomerically enriched materials. Since enzyme preparations are expensive, being able to recycle them using immobilization techniques is important. To do so, enzymes can be covalently attached to insoluble supports and adsorbed onto various materials, thereby facilitating recovery through filtration. In 2002, the first reported combined application of immobilized enzymes together with supported reagents in the preparation of GABA analogues appeared (Scheme 11.6) [15].

Here, the synthesis used commercially available Eupergit-immobilized pig liver esterase to terminally differentiate *meso*-diester **42** in an asymmetric fashion. Also of note in this work is the conversion of bromide **45** into azide **46** by application of immobilized reagents. The resulting hazardous azide product **46** was not isolated

SCHEME 11.6 Representative synthesis of GABA analogues.

but directly reduced with palladium on carbon to the amine derivative itself, being trapped as its Boc-protected derivative **47** in an excellent 95% yield after scavenging of the excess reagents. An acid catch-and-release using a sulfonic acid resin finally afforded the hydrolyzed hydrochloride salt of the cyclopropyl GABA analogue **48**.

A further illustration of the power of immobilized reagents was during the synthesis of the natural product carpanone **55**. Beguiling in its apparent complexity, carpanone was obtained in a simple series of reactions from commercially available sesamol **49** (Scheme 11.7) [16].

Sesamol **49** was first *O*-alkylated with allyl bromide in the presence of immobilized phosphazine base BEMP to give **50**, which then underwent a Claisen rearrangement to **51** using focused microwave heating with a combined solvent

SCHEME 11.7 Synthesis of carpanone **55**.

SCHEME 11.8 Retrosynthesis of the epothilone core.

system of ionic liquid and toluene. Double bond isomerization was achieved using an immobilized iridium catalyst **52**, which was specifically developed for this synthesis. The yield and selectivity of the process were excellent, affording the phenolic styrene **53** with a *trans* to *cis* ratio of 11:1. Final conversion of the styrene to **55** was achieved effectively using an immobilized cobalt salen catalyst **54** in the presence of molecular oxygen that effected an oxidative dimerization process to give a compound that underwent spontaneous intramolecular Diels–Alder reaction to generate carpanone **55** in excellent overall yield as a crystalline product.

The most challenging target from this period, however, was the synthesis of the epothilones A **56** and C **57** [17]. Here, it was envisaged the epothilone core could be assembled from the coupling of three main fragments, A **58**, B **59**, and C **60** (Scheme 11.8).

The key step in the preparation of fragment A **58** involved a modified Mukaiyama aldol used to set up the C-3 stereochemistry in compound **66** (Scheme 11.9). This reaction was mediated by formation of a chiral borane complex with **63**, which catalyzed the asymmetric coupling of aldehyde **62** with the trimethylsilyl enol ether **64**. The reaction proceeded in excellent yield and high ee ($\geq 92\%$). The workup required a small amount of water and polyol resin **65** to quench the reaction and remove boric acid contaminants. Filtration and concentration provided a suspension of amino acid **63** and the aldol product **66**. Subsequent

SCHEME 11.9 Synthesis of fragment A **58**.

SCHEME 11.10 Synthesis of fragment B 59.

filtration allowed the chiral amino acid catalyst **63** to be recovered and recycled, while concentration of the filtrate afforded the pure adduct **66**. Following TBS protection of **66** to give **67**, homologation was achieved in two steps. First, treatment with (trimethylsilylmethyl)lithium followed by an immobilized acid quench provided **68**. After monomethylation and again quenching with an immobilized acid, fragment A (**58**) was obtained in excellent yield without requiring any chromatographic purification.

Fragment B, **59**, was prepared in five steps from the bromide **69** (Scheme 11.10). Following acid-catalyzed tetrahydropyranyl protection and conversion to iodide **70**, displacement with the cuprate derived from 3-butenylmagnesium bromide gave **71**. Addition of a carboxylic acid and a trisamine resin, together, quenched the reaction and simultaneously scavenged the dissolved copper salts. Following filtration and evaporation, compound **71** was deprotected and the resulting alcohol was oxidized to its corresponding aldehyde, fragment B **59**, using chlorochromate absorbed onto basic alumina.

The final fragment C (**60**) was generated as its immobilized phosphonium salt (**80**) using a convergent process (Scheme 11.11). The Horner–Wadsworth–Emmons

SCHEME 11.11 Synthesis of fragment C 60.

coupling of **74** and **76** proceeded well with very high stereoselectivity to give **77**, with excess phosphonate being scavenged with an immobilized benzaldehyde resin. Selective removal of the primary silyl group with camphor sulfonic acid (CSA) followed by carbonate resin workup afforded the alcohol **78**. The latter was then converted to **79** by treatment with iodine and immobilized triphenylphosphine. Fragment C was eventually captured onto a phosphine resin to give the phosphonium salt (**80**) ready for later release from the resin via a further Wittig reaction.

The impressive convergent coupling of the three fragments is shown in Scheme 11.12. In brief, deprotonation of fragment A **58** with LDA and coupling with fragment B (**59**) gave the aldol product **80**. Quenching with acetic acid was followed by addition of an immobilized diamine to scavenge residual acid and any unreacted aldehyde. Simple filtration and evaporation then afforded **80**. Following TBS protection, alkene cleavage by ozonolysis, and workup using immobilized triphenylphosphine, aldehyde **81** could be isolated. The resin-bound phosphonium salt **60** was next treated with sodium hexamethyldisilylazide (NaHMDS) and washed with THF to give a salt-free ylide. This was then coupled with the aldehyde **81** to give exclusively the *cis*-olefin. Selective deprotection of the primary TBS-protected ether

SCHEME 11.12 Total synthesis of epothilones C **56** and A **57**.

was achieved with CSA, followed by an immobilized carbonate workup to quench and scavenge unwanted acidic residues to give **82**. Oxidation of the primary alcohol in **82** was realized in two steps: TPAP oxidation to the aldehyde and then a modified Pinnick oxidation using an immobilized reagent combination incorporating immobilized chlorite to furnish the acid. Although selective deprotection to access **83** required aqueous tetrabutylammonium fluoride (TBAF), no further purification protocol was necessary. Finally, successful Yamaguchi macrolactonization using immobilized DMAP followed by a catch-and-release protocol gave the macrocycle epothilone C (**56**), which was conveniently converted to the natural product epothilone A **57** via a final oxidation using dimethyldioxirane (DMDO).

This synthesis constitutes a record for the use of immobilized systems in complex molecule assembly, effecting no less than 29 overall steps where the longest linear sequence was 17 steps from available starting materials in 55% overall yield.

11.3. FLOW CHEMICAL SYNTHESIS

As can be seen from the previous discussion, the use of immobilized reagents, catalysts, and scavenging techniques provide viable and practical alternative tools to linear substrate-bound synthesis. Furthermore, these methods can incorporate many of the advantages of conventional solution-phase chemistry, such as real-time reaction monitoring, convergency, and rapid sequence optimization. The approach is highly amenable to multistep telescoped processes, parallel array preparation, batch splitting methods, and reaction scale-up. However, the real value of immobilized reagents in chemical processing is certainly in the area of flow chemistry. Flow-based synthesis is emerging as a powerful technology platform that is steadily gaining acceptance in the modern laboratory for multistep processes and scale-up operations [21].

As a technique, flow chemistry replaces traditional glassware practices conducted in batch mode with continuously flowing systems integrating connective tubing, preloaded columns, and cartridges containing immobilized reagents, catalysts, and scavengers (Figure 11.1a and b). Additionally, by building precision

FIGURE 11.1 (a) A column packed with an immobilized copper(I) reagent as used in the Bestmann–Ohira synthesis of triazoles (shown later); (b) column containing two regions of different inorganic scavengers; (c) a mesofluidic static mixing chip.

manufactured microfluidic reactor chips into flow systems, controlled mixing and exact temperature regulation of reaction sequences can be achieved (Figure 11.1c). This essentially translates conventional batch reaction sequences into a continuous flowing, dynamic cascade by passing flow streams of the starting materials through various immobilized reagents or combining intermediates and reagents in appropriately designed/combined reactor blocks. In this way, material generated *in situ* can be involved in a series of consecutive reactions and scavenging purification protocols before exiting the reactor into a chemically inactive environment ready to be collected as a pure product. Throughout this processing, the reactors and packed cartridges can be heated or cooled. In addition, the application of oscillation, ultrasound, electrical currents, or microwave irradiation can be used. Furthermore, catalysts have been deposited on reactor surfaces or tethered onto their surfaces, opening up new opportunities for flow synthesis development; for example, a new polymer tubing reactor that has palladium tethered to the inner wall has been developed that enables Pd-catalyzed reactions to be conducted in flow [22].

Systems to conduct flow chemistry can be assembled from individual components such as HPLC or syringe-driven pumps with appropriate connective tubing, glass microreactor chips, tubular heating coils, fritted columns and other units, for example, microwave machines, and hydrogen or ozone gas generators. Commercial flow systems are available for micro- and mesoscale reactions that can be reconfigured quite readily to suit the specific needs of the reaction. Microsystems (e.g., Advion NanoTek LF™) have multiple syringe pumps and microfluidic heating blocks and can be used to quickly screen reaction conditions on a small scale (Figure 11.2a). Mesosystems, such as the Uniqsis FlowSyn™ and Vapourtec™ R2 + R4 system, consist of at least two HPLC pumps, internal pressure monitors, and coil and column heating facilities (Figure 11.2b and c). These systems have various onboard automation features and mechanical safety features, for example, pressure sensors that trigger automatic shutdown when a blockage or leak is detected.

For the heating and cooling of flow streams, tubular coils are often used as these can operate across a wide temperature range of -78 to 250°C (Figure 11.3a). Furthermore, they can be connected in parallel (Figure 11.3b) to scale-up reaction productivity or set in series (Figure 3c) to increase the reaction residence time or create sequential but different temperature zones. Microscale reactions can be scaled up by increasing throughput using stacks of coils of microcapillary tubing that can be heated using a specialized heating unit [23,24].

Microwave reactors can be used to heat reaction streams as they pass through columns containing an immobilized reagent. Reactions with metal-tethered catalysts, for example, polyurea microencapsulated palladium species (Pd EnCat), are a good example, whereby microwave heating activates the active palladium species [25]; a number of reaction types using Pd EnCat have been explored, for example, transfer hydrogenations [26], hydrogenations of epoxides [27], and Suzuki reactions [28]. Being able to perform microwave reactions in flow readily facilitates the transition from batch to continuous flow processing. Gas generators

FIGURE 11.2 (a) Advion NanoTek™ LF; (b) Uniqsis FlowSyn™; (c) Vapourtec™ R2 + R4.

(H₂ or O₃) can also be integrated into flow systems. Flow ozonolysis methods can also incorporate immobilized reagents as safe workup steps for excess ozone without contaminating the product [29]. The commercially available ThalesNano H-Cube® generates hydrogen *in situ* by electrolysis of water and employs cartridges of immobilized heterogeneous catalysts (including Pd EnCat) to perform hydrogenations in flow with minimal workup.

Working in flow creates large amounts of data that can be usefully harvested. For a given reaction, real-time inline analysis can give data on multiple reaction parameters, which in turn enables rapid optimization, as well as important kinetic and physical chemical data. Qualitative spectral data can also be acquired using adjustable wavelength photodiode detectors (or similar spectrometers) that can be assembled as inline analysis cells. Other diagnostic devices can be used to report on reaction progress, for example, impedance measurements, Raman spectroscopy, near or ReactIR, fluorescence measurements, and various bioassays. Alternatively,

FIGURE 11.3 (a) A flow coil; (b) flow coils connected in parallel; (c) flow coils connected in series.

or in addition, automated sampling techniques can be used to divert aliquots of reaction media into auxiliary monitoring equipment, allowing LCMS or GCMS to be assimilated into the system. The Mettler Toledo ReactIR™ Flow Cell is one example of such equipment that can be used to analyze flow streams in real-time, showing reactive intermediates and the scavenger efficiencies of immobilized reagents (Figure 11.4) [30].

With these new tools, multistep, convergent synthetic sequences in flow are now possible, conducting multiple individual steps (Scheme 11.13).

FIGURE 11.4 Mettler Toledo ReactIR Flow Cell.

SCHEME 11.13 A concept diagram illustrating a convergent flow synthesis incorporating flow coils, microfluidic chips, scavengers, and immobilized reagents in cartridges using five individual starting inputs.

11.4. FLOW SYNTHESIS OF CHEMICAL BUILDING BLOCKS

Appropriate chemical building blocks form the necessary starting points for all chemical synthesis programmes. They can be simple structures or specially tailored for a particular functionality. Their availability and cost ultimately determine their usage; consequently, more automated ways of preparing these materials is important. The following sections highlight some of the flow chemistry methods that can be employed to generate specific classes of useful building blocks.

11.4.1. Butane-2, 3-Diacetal-Protected Diols

Various 1,2-diacetals and specifically butane-2,3-diacetals (BDAs) have been used extensively in natural product syntheses to effect selective vicinal diol and α -hydroxy acid protection, diastereoselective, and facially selective processes. They have also been used to prepare a variety of chiral building blocks [31] for use in the syntheses of natural products, such as (+)-aspicillin [32] and bengazole A [33]. Useful key members of the BDA building block series have been assembled by flow chemistry methods in higher yields and higher reproducibility than the corresponding batch process employing minimal manual workup when immobilized reagent cartridges are used to purify the reaction stream exiting from the flow reactor [34]. The BDA-protected tartrate **85**, for example, was obtained from mixing a stream of dimethyl-L-tartrate derivative **84** and trimethyl orthoformate with a second stream containing butane-2,3-dione together with a catalytic amount of CSA and heated at 90°C for 47 min in a flow coil (Scheme 11.14). Premixing **84** and trimethyl orthoformate resulted in formation of an intermediate orthoester that can be observed using the ReactIR™ flow cell. This premixing is thought to be an important requirement for diol activation, thus allowing the reaction to proceed. The product was purified

SCHEME 11.14 Flow synthesis of BDA-protected tartrate **85**.

using an immobilized benzylamine to scavenge the remaining butanedione and CSA catalyst. Periodate resin was then employed to perform rapid glycol cleavage of the remaining tartrate ester **84** to generate volatile by-products that could be easily removed.

The BDA-protected tartrate **85** was subsequently transformed to the unsaturated system **87** by subjecting it to a strong base in the presence of iodine (Scheme 11.15). The product stream was purified by scavenging (quenching lithium salts, removing diisopropylamine using a sulfonic acid resin, and removing residual iodine using a thiosulfate resin). Finally, a short plug of silica gel was used to remove inorganic lithium salts.

The corresponding crystalline *meso*-BDA-protected derivative **89** was readily generated from **87** in quantities using the H-Cube Midi™ system with a Rh/Al₂O₃ catalyst under recycling conditions (Scheme 11.16).

The preparation of the BDA-protected glyceraldehyde **91** as a building block for synthesis proved more challenging. It was finally found that premixing mannitol **90**, trimethyl orthoformate, and CSA greatly aided solubility such that a flow synthesis could be achieved (Scheme 11.17). When only a small excess of butanedione was used with gentle warming of the stream to 40°C, an optimum yield was obtained. This process also reduced the propensity for the formation of the *tris*-protected by-product. A final column of benzylamine was used to scavenge excess reagents; however, a

SCHEME 11.15 Flow synthesis of BDA-protected alkene (**87**). SCHEME 11.16 Flow synthesis of *meso*-BDA-protected derivative **89**.

SCHEME 11.17 Flow synthesis of BDA-protected glyceraldehyde **91**.

simple silica-based column chromatography step was found beneficial to obtain analytically pure **91**.

The subsequent aldehyde **93** and ester **95** were then readily obtained from the hemiacetal produced using a recycling procedure through a resin-bound periodate. The aldehyde **93** was obtained following passage through a short plug of magnesium sulfate to remove any residual water (Scheme 11.18).

Similarly, the analogous methyl ester **95** was formed from **91** under oxidizing conditions via oxidation of the *in situ*-generated aldehyde intermediate using an immobilized perbromide resin (Scheme 11.19).

Finally, the BDA-protected glycolate **100**, a useful building block, was synthesized using related procedures (Scheme 11.22). Here, using conditions similar to the tartrate protection reaction described above, chloropropanediol **96** was converted to **97** in 95% yield, without any substrate racemization being observed. Also, since this conversion proceeded so efficiently, it was not necessary to use the periodate cleavage protocol to remove excess diol **96** (Scheme 11.20).

Chloride **97**, which was formed as a single product, was then subjected to a strong base to effect elimination to give the *exo* alkene **98**. Unfortunately, owing to the ease of isomerization of the double bond, it was not possible to scavenge all the excess base with an immobilized acid, and instead the product stream was collected into a flask containing water and extracted in a typical batch fashion (Scheme 11.21).

SCHEME 11.18 Corresponding aldehyde (**93**) of BDA-protected glyceraldehyde. SCHEME 11.19 Corresponding ester (**95**) of BDA-protected glyceraldehyde.

SCHEME 11.20 First step in the synthesis of BDA-protected glycolate **100**. SCHEME 11.21 Second step in the synthesis of BDA-protected glycolate **100**. SCHEME 11.22 Synthesis of BDA-protected glycolate **100**.

This new flow procedure, nevertheless, consistently produced more of the desired product in an *exo/endo* ratio of 24:1 compared to between 15:1 and 5:1 for the batch procedure. The final double bond cleavage employed a combination of osmium EnCat™ and sodium periodate to give the corresponding lactone (Scheme 11.22) [35]. However, when periodate in solution was used for this transformation, formation of a side product was noticed due to periodic acid fragmentation of **99**. The optimized procedure, therefore, involved a recycling procedure through a mixed bed of OsEnCat™ and immobilized periodate, with morpholine as a solution-phase reoxidant. The reaction stream was then passed through a sulfonic acid resin to scavenge the morpholine and an immobilized thiourea to scavenge any leached osmium in order to generate the pure lactone **100** (Scheme 11.22).

11.4.2. Yne-Ones and Pyrazoles as Primary Building Blocks

The flow synthesis of yne-ones with inline purification provides reactive building blocks for further transformation to numerous heterocyclic scaffolds [36]. The nice feature of this process is the ability to split the product stream and divert these to different product outcomes by varying the subsequent coupling agents.

After a rapid screen, conditions were found that could transform an acid chloride and acetylene into an yne-one using palladium catalysis (Scheme 11.23).

SCHEME 11.23 Synthesis of yne-ones **101**. SCHEME 11.24 Synthesis of pyrazoles **102**.

Here, the desired acyl chloride and acetylene in one reagent stream were combined with a second stream containing a catalytic amount of $\text{Pd}(\text{OAc})_2$ and base. The combined reagent stream was heated at 100°C for 30 min and the reactor output was then purified by passage through a series of four solid reagents and scavengers. First, a polyol resin was used to remove excess acyl chloride followed by a column of CaCO_3 to trap the HCl formed during the reaction and to deprotonate any ammonium salts. The resultant tertiary amine by-product was then trapped on the sulfonic acid resin before a column of immobilized thiourea finally removed residual palladium contamination. The yne-one products **101** were obtained in moderate to high yield (41–95%) and purity following removal of the solvent (Scheme 11.23).

The yne-one can then be combined with an additional input stream containing, for example, a hydrazine (or guanidine) derivative. The mixed stream is heated before passage through a column of calcium carbonate, resulting eventually in the formation of simple pyrazoles (**102**) or aminopyrimidines (from guanidine) as final products or as starting materials for other medicinal chemistry programmes (Scheme 11.24). Excess hydrazine or guanidine can be removed by acidic resins, thereby preventing the larger dispersion curve normally observed at the end of multiple column sequences. In this way, a collection of pyrimidines, pyrazoles, oximes, guanidines, and flavones was obtained, all in high yield and purity.

11.4.3. Curtius Rearrangement

The Curtius rearrangement transforms carboxylic acids or acid chlorides to the corresponding isocyanate functionality. The reaction proceeds via an intermediate acyl azide that undergoes rearrangement to give a reactive isocyanate that can be attacked by a nucleophile to give functionalized product. The continuous production and immediate quenching of the isocyanate also exemplifies another advantage of flow chemistry, namely, the preparation and immediate consumption

SCHEME 11.25 Synthesis of an azide monolith **105**.

of reactive or, in this case, hazardous intermediates, which in batch mode could be a serious safety risk.

To solve potential safety problems, an azide monolith has been developed and used to synthesize acyl azides in flow, which can then undergo Curtius rearrangements to give a variety of aryl isocyanates [37]. An alternative method has also been used to produce the acyl azides on a 25 g scale, continuously, from diphenylphosphoryl azide (DPPA) and a carboxylic acid [38]. Performing this reaction continuously on a small scale or with an immobilized azide source greatly increases the safety during the generation of these compounds and demonstrates the potential for scaling up these reactions safely and easily.

Azide monolith **105** was prepared from a Merrifield-type monolith **103** made by polymerizing vinyl benzyl chloride and divinylbenzene using AIBN, with 1-dodecanol used as the porogen. Monolith **103** was then converted to its quaternary ammonium form using triethylamine, resulting in a chloride counterion to the monolith **104**. This monolith can subsequently be ion exchanged with an aqueous solution of sodium azide to give the stable azide monolith **105**, which can be safely stored and handled (Scheme 11.25).

The utility of this monolith was demonstrated when an acid chloride was eluted through the monolith at ambient temperature, followed by a plug of drying agent to remove any water released from the monolith to generate the acyl azide **106**, which can be isolated in high yield and purity (Scheme 11.26).

In order to obtain the Curtius rearrangement products, the acyl azide intermediate continues its passage through a heated coil at 120°C, whereupon rearrangement to the corresponding isocyanate **107** occurs. The output stream was collected into a microwave vial containing the desired nucleophile and heated to 100°C for 10 min. The resulting products **108** were obtained in high yield and purity.

SCHEME 11.26 Synthesis of acyl azides **106** and derivatives **108**.

SCHEME 11.27 Curtius rearrangements using diphenylphosphoryl azide.

Typically, the azide monolith has been used to create between 1 and 10 mmol of acyl azides **106**. It can also be regenerated easily by treatment with an aqueous solution of sodium azide.

The Curtius rearrangement using DPPA as a source of azide with a variety of carboxylic acids in flow has also been reported (Scheme 11.27) [38]. Here, a solution of a carboxylic acid with triethylamine plus a suitable nucleophile was loaded as one reaction stream, which was then combined with a second stream containing DPPA in the same solvent. An excess of the carboxylic acid was used to ensure complete consumption of the DPPA. On mixing of the streams, an acyl azide was generated that on heating in a coil produced the isocyanate that was quenched immediately with an *in situ* nucleophile to give the desired products **109**. A mixed acid/base scavenger workup was used to remove the base, excess carboxylic acid, and the by-product. For nitrogen-containing heterocyclic carboxylic acid starting materials, it was found necessary to use a catch-and-release protocol to afford the purified products.

To produce a Boc-protected **110** or Fmoc-protected amine **111**, heating to 120°C for 2 min in a flow microwave was required. For **111**, a more hindered base (2,6-lutidine) and more hindered basic resin (polymer-immobilized 2,6-di-*tert*-butylpyridine) were required to prevent *in situ* protecting group removal under basic conditions (Scheme 11.28).

Mixed semicarbazide products **113**, on the other hand, were prepared using a procedure similar to that described in Scheme 11.26. Here, the isocyanate stream **107** was directed into a collecting vial containing a hydrazine derivative **112**. This proved necessary owing to the low solubility of the resulting semicarbazide products in acetonitrile. Analytically pure material could then be obtained upon filtration of the precipitated compound (Scheme 11.29).

SCHEME 11.28 Production of Boc- or Fmoc-protected amines **110** and **111**.

SCHEME 11.29 Synthesis of mixed semicarbazide products **113**.

11.4.4. Fluorination Reactions

Fluorine atoms in drug molecules are typically used to improve binding or provide greater metabolic stability. However, the introduction of fluorine to molecules can prove difficult due to the hazards associated with the most commonly used fluorinating reagents. Using a flow microreactor system with immobilized inline purification, many of these hazards are eliminated owing to the contained environment and the robustness of the reactor tubes [39].

Trifluoromethylation of aldehydes has been demonstrated using TMSCF_3 (Ruppert's reagent) as a source of nucleophilic CF_3 when an immobilized fluoride was used as the initiating agent [40]. In particular, a fluoride monolith **114** provided a versatile source of fluoride anions that can be readily prepared using ion exchange procedures (Scheme 11.30) [37].

The fluoride monolith **114** may then be used to transform aldehydes into their corresponding trifluoromethylated derivatives (Scheme 11.31). Hence, it was found that gentle heating of the monolith and the sequential use of heating coils improved yields in these reactions. The reaction stream was purified using an immobilized aldehyde to trap any unreacted Ruppert's reagent, while an immobilized acid deprotects the intermediate silylated product initially formed. Finally, an immobilized hydrazine then sequesters any unreacted aldehyde. The desired products **115** were obtained in high yields after solvent removal (Scheme 11.31).

Alternative flow chemistry methods for the introduction of fluorine involves the use of other common fluorinating agents such as Selectfluor[®] and diethylamino sulfurtrifluoride (DAST). The safe workup of these reactions was achieved by the application of flow synthesis and immobilized reagents. Fluorine atoms may also be introduced α to an activated ketone using the Selectfluor[®] reagent, while similarly

SCHEME 11.30 Synthesis of a fluoride monolith **114**. SCHEME 11.31 Synthesis of trifluoromethylated alcohols **115** using a fluoride monolith **114**.

SCHEME 11.32 Electrophilic fluorine reactions with Selectfluor®.

the fluoro-Ritter reaction with olefinic substrates can be realized in the same reactor setup. In the first reaction, a stream of the activated carbonyl was combined with a stream of Selectfluor® and heated between 100 and 120°C (Scheme 11.32). Then the product stream was purified using immobilized sulfonic acid and dimethylamine resins to scavenge excess reagents and by-products. This process afforded the desired products **116** in high yield and excellent purity (Scheme 11.32).

An identical reactor arrangement was then used for the Ritter reaction, whereby an alkene starting material in the presence of wet acetic acid (< 5 mol% water) reacts with acetonitrile. This mixture was heated to 120°C to furnish the desired mono-fluorinated products **117** (Scheme 11.33).

The reagent DAST is a useful source of fluorine for the transformation of an alcohol or a carbonyl functionality (aldehyde or activated ketone) to the corresponding mono- or difluorinated products [41]. For example, an alcohol or carbonyl input stream was combined with DAST in DCM and heated between 70 and 90°C (Scheme 11.34). Excess DAST along with any residual HF was scavenged using a calcium carbonate quench, immediately followed by a silica gel plug to trap inorganic salts. Although this scavenging procedure produces carbon dioxide, this is managed easily using the continuous flow environment as the generated gas is progressed through the reactor, avoiding a buildup of pressure. While yields were affected by the electronics of the carbonyl moiety, the reaction was found to be tolerant of a wide

SCHEME 11.33 Ritter reactions with Selectfluor®.

SCHEME 11.34 Synthesis of mono- or difluorinated products **118** using DAST.

SCHEME 11.35 Synthesis of oxazolines **119** using DAST.

range of functional groups, for example, epoxides, alkenes, acetals, amines, esters, amides, and various heterocycles.

DAST has also been used in cyclodehydration reactions where starting β -hydroxy amines were converted to the corresponding oxazolines **119** in excellent yields compared to previously reported procedures (Scheme 11.35).

11.4.5. Seyferth–Gilbert Homologation Using the Bestmann–Ohira Reagent for the Formation of Acetylenes and Triazoles

The Seyferth–Gilbert homologation using the Bestmann–Ohira reagent **121** has been used for the production of acetylenes in a flow microreactor (Scheme 11.36) [42]. The reaction proceeds well but requires extensive purification with immobilized reagent cartridges owing to the large number and quantities of by-products produced in this reaction sequence.

The aldehyde component and the Bestmann–Ohira reagent **121** were combined with a secondary stream of potassium *tert*-butoxide and introduced to a heating coil at 100°C. The exiting flow stream was first scavenged with immobilized benzylamine heated to 70°C to remove excess aldehyde, then a sulfonic acid resin to both remove excess base and protonate any phosphoric residues, and finally a dimethylamine cartridge to remove any acidic material. The pure acetylic compound **120** could then be collected in high yield. For nitrogen-containing heterocyclic starting materials, the sulfonic acid resin cartridge was substituted for an alumina packed tube to avoid partial capture and hydrolysis of the acetylene to a methyl ketone. The reaction was generally tolerant of functional groups (e.g., halides, nitro compounds, esters, and cyanides).

The procedure was further extended to prepare triazoles by using azides following an already established procedure (Scheme 11.37) [43]. The cyclization was initiated by passage through a copper(I) catalyst supported on a dimethylamine resin. Copper impurities that potentially leached from the resin were subsequently scavenged using immobilized thiourea, while the products **122** could be isolated in high yield by crystallization (Scheme 11.37).

SCHEME 11.36 Synthesis of acetylenes **120** using the Bestmann–Ohira reagent **121**.

SCHEME 11.37 Synthesis of triazoles **122** using the Bestmann–Ohira reagent **121**. SCHEME 11.38 Synthesis of triazole **123** from the corresponding alcohol using the Bestmann–Ohira reagent **121**.

Finally, the Bestmann–Ohira reagent **121** was used in a multistep sequence involving the transformation of alcohols to the corresponding triazoles (Scheme 11.38). In this work, a benzyl alcohol mixed with **121** and an azide were passed through a column of immobilized TEMPO to selectively oxidize the alcohol to the aldehyde. Next, potassium butoxide in methanol was introduced to the flow line that then progresses through a series of scavengers and reaction cartridges to finally afford the triazole **123** in high purity and 55% yield after crystallization.

11.4.6. 3-Nitropyrrolidine Building Blocks

Another useful functionalized heterocycle for potential incorporation into medicinally relevant products are the 3-nitropyrrolidines [44]. The compounds can be prepared using TFA or a fluoride monolith to facilitate dipole formation, followed by dipolar cycloaddition with alkenes. In an early example, a stream of the nitroalkene with TFA was combined with a second stream containing the *N*-(methoxymethyl)-*N*-(trimethylsilyl)benzylamine **124** coupling partner. The combined flow stream was heated between 60 and 120°C for 30–90 min, depending on the substrate, and then

SCHEME 11.39 Synthesis of 3-nitropyrrolidines **125** from the nitroalkene. SCHEME 11.40 Synthesis of pyrrolidines **126** from the corresponding alkenes.

purified by scavenging with benzylamine and a plug of silica gel. This also served a dual purpose of removing unreacted nitroalkene and releasing the product from its initially formed TFA salt, giving the desired pure nitropyrrolidines **125** (Scheme 11.39).

Further optimization studies revealed that nitropyrrolidines could be obtained under milder conditions when a fluoride monolith was used to generate the dipole component. Here, the starting materials were flown through a fluoride monolith **114** that heated the solution to 50–80 °C before purifying the exiting stream using benzylamine resin to afford the pure products in high yields. Furthermore, the new procedure allowed other electron-withdrawing groups such as esters, sulfonates, and phosphonates to replace the nitro group on the olefinic coupling partner. By adjusting the reaction parameters of the flow reactor, even more sensitive nitropyrrolidines were synthesized (Scheme 11.40).

The H-Cube® flow hydrogenator was then used to selectively reduce the nitro group to an amine function, while leaving the benzyl group intact using a Raney nickel catalyst. Alternatively, by swapping to a Pd/C cartridge, dual reduction of the nitro group and a debenzyl reaction was facilitated.

11.4.7. 4,5-Disubstituted Oxazoles as Building Blocks

An immobilized strong base in a packed flow tube has been used to transform acid chlorides and isocyanides to useful 4,5-disubstituted oxazole building blocks for medicinal or agrochemical programmes (Scheme 11.41) [45]. For example, in order to prepare the oxazoles **127**, a flow stream containing an acid chloride was mixed with

SCHEME 11.41 Flow synthesis of 4,5-disubstituted oxazoles (**127**).

alkyl isocynoacetate containing an electron-withdrawing ethyl ester moiety in a microfluidic chip as the initial reactor. The prior mixing before the introduction of the immobilized base was important to ensure high yields. Furthermore, NMR studies of the reaction showed that formation of an adduct occurs exclusively via the methylene unit, which is in contrast to the batch process [46]. The reactive intermediate then cyclizes in the presence of polymer-immobilized BEMP at 50°C. The product output stream was finally purified using a benzylamine resin to furnish the 4,5-disubstituted oxazole derivatives **127**. Sulfonates (from the corresponding tosyl substituent) could also be prepared (nine examples, 81–94%), as well as phosphonates (three examples, 84–85%), by using a similar synthesis strategy. The immobilized BEMP column could be regenerated using solution-phase BEMP in hexane or NaOMe/*t*-BuOK in MeOH.

11.5. MULTISTEP FLOW SYNTHESIS OF NATURAL PRODUCTS AND PHARMACEUTICAL COMPOUNDS

The first application of a flow process for the multistep synthesis of a natural product was achieved in 2006 for (±)-oxomaritidine using a combination of scavengers and reagents to effect product formation at all individual steps [47]. In this work, microfluidic pumping systems were used to direct material through various packed columns, containing immobilized reagents, catalysts, scavengers, or catch-and-release agents. The route involved seven separate synthetic steps linked to a continuous flow sequence. No column chromatography or aqueous workups were required at any stage and the automated sequence employed readily available starting materials to produce (±)-oxomaritidine **7** in less than a day (Scheme 11.42), which compares extremely well with the four day batch process of this natural product.

The first step of the oxomaritidine synthesis involved passage of the bromide 4-(2-bromoethyl)phenol **128** through a packed column containing an azide exchange resin to give **129**. The output stream containing azide **129** was then coupled directly with a second column containing an immobilized phosphine, furnishing a corresponding trapped aza-Wittig intermediate. In a separate but convergent channel, the aldehyde coupling partner **131** was prepared. Here, a prepacked column of tetra-*N*-alkylammonium perruthenate (PSP) was used to oxidize 3,4-dimethoxybenzyl alcohol **130** and the product stream was then passed through the column containing the immobilized aza-Wittig intermediate, thus producing the desired imine **132**. The exiting THF solution of imine **132** was then subjected to continuous flow hydrogenation using the Thales H-Cube flow hydrogenator, containing a cartridge of 10% palladium on carbon as a catalyst. The product of this reaction **133** was then collected and the THF solvent removed using a Vapourtec V-10 solvent evaporator. After being redissolved in dichloromethane, the secondary amine **133** was passed into a microfluidic reaction chip that combined an additional stream of trifluoroacetic anhydride (TFAA) in dichloromethane, resulting in trifluoroacetylation of the amine to give the amide **134**. After a short scavenging process whereby a silica gel-immobilized primary amine removed any excess TFAA or residual trifluoroacetic acid (TFA), the product was then directed into a column containing immobilized (ditrifluoroacetoxyiodo)benzene, which performed the oxidative coupling, generating a seven-

SCHEME 11.42 A new paradigm for molecular assembly: a flow process for the multistep synthesis of the alkaloid natural product (±)-oxomaritidine 7.

membered tricyclic spirodieneone intermediate **135**. The product was then released directly into a column that contained an immobilized base to effect hydrolysis and the free amine spontaneously generates the target compound (±)-oxomaritidine (**7**) in 40% overall yield and high purity.

SCHEME 11.43 Flow synthesis of grossamide **140**.

The preparation of the natural product grossamide **140** by flow chemistry methods involved amide coupling of tyramine **138** and ferulic acid **137** using an immobilized HOBt cartridge, followed by oxidative dimerization and intramolecular cyclization (Scheme 11.43) [48]. The reaction progression to **139** was followed by inline LC–MS.

For the oxidation step, precursor **139** was diluted (3:1) with a second input solution containing hydrogen peroxide urea complex and sodium dihydrogen phosphate buffer (pH 4.5). The combined flow stream was passed through a prepacked column with the enzyme horseradish peroxidase (II) supported on silica gel. Automated LC–MS sampling enabled the reaction progress to be monitored and provided an opportunity for rapid optimization of flow rates, dilution ratios, and reagent concentrations.

11.5.1. Casein Kinase I Inhibitors

A four-component coupling flow synthesis of a series of casein inhibitors has been described (Scheme 11.44) [49]. This was achieved by varying substituents at positions C2, C3, and C6 of the imidazopyridazine core structure **145**, leading to a collection of 20 analogues. The first important step necessitated the development of a continuous flow method to safely scale-up an organometallic reaction at low temperature. This led to the use of a dual loop system that enabled pumping of the organometallic species in a continuous fashion. The second step made use of an immobilized perbromide to ensure monobromination and automated flow device was equipped with specialized software to effect the third step and optimize the reaction conditions. Finally, an autosampler was used to perform an automated S_NAr reaction to give a collection of diversified imidazopyridazine derivatives **145** (Scheme 11.44).

SCHEME 11.44 Flow synthesis of one of a series of casein kinase I inhibitors **145**.

FIGURE 11.5 Automated flow synthesis equipment used to prepare casein kinase I inhibitors [49].

11.5.2. A Quinolone 5HT_{1B} Antagonist

The quinolone derivative **151**, which is a potent 5HT_{1B} antagonist developed by AstraZeneca, was prepared by a seven-step batch synthesis with an overall yield of 7% in 2007 [50], thus setting a benchmark for improvement by flow chemistry [51].

The flow synthesis was achieved by combining streams of nitroanisole **146** and piperazine **147** at 135°C. The exiting reaction products were scavenged with benzylamine to remove the hydrofluoric acid by-product before subsequent transmission to continuous flow hydrogenation. The outflow was scavenged with thiourea to remove any leached palladium to give aniline **148** (Scheme 11.45).

After a solvent switch from ethanol to toluene, flow streams containing **148** and dicarboxylate **149** were combined and heated to 130°C (Scheme 11.46). This was followed by inline scavenging for residual dicarboxylate and use of anhydrous potassium carbonate to remove traces of water. The stream was then subjected to a high-temperature cyclocondensation reaction in a stainless steel flow coil at 250°C. Since this was much higher than the boiling point of the toluene, an inline back pressure regulator (BPR) operating at 250 psi was fitted to the system. The output stream from the stainless steel reactor was rapidly cooled to ambient temperature prior to being mixed with a third input of THF/H₂O. The combined stream was then progressed through a column containing immobilized trimethylamine with a hydroxide

SCHEME 11.45 Flow synthesis of aniline intermediate **148**.

SCHEME 11.46 Flow synthesis of quinoline carboxylic acid intermediate trapped on resin.

SCHEME 11.47 Flow synthesis of a 5HT_{1B} antagonist **151**.

counterion. The presence of the third stream was necessary to promote efficient ester hydrolysis within the column. The resulting carboxylic acid **150** was immediately deprotonated and retained within the basic resin column (Scheme 11.45).

The final step involved an amide coupling reaction and a catch-and-release purification. This arose by use of a solution of *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) and HOBT in DMF, being flowed through the column containing immobilized intermediate **150** that activated and released the carboxylic acid. The output stream from this step containing the newly generated activated ester was then coupled directly with a second stream of 4-morpholinoaniline in DMF. The flow stream was maintained at ambient temperature for 50 min and then passed through a sulfonic acid column that trapped the product that could be released by washing with methanolic ammonia, thus completing the catch-and-release purification. The final solution was concentrated and the crude inhibitor **151** was recrystallized to obtain an 18% overall yield of product and thereby nearly trebling the yield of the batch process (Scheme 11.47).

11.5.3. Imatinib Mesylate

The synthesis of the tyrosine kinase inhibitor imatinib mesylate (Gleevec®) **158**, which is used to treat chronic myeloid leukemia and gastrointestinal stromal tumors, is a significant test of the flow chemistry methods since the batch method had been optimized to provide very insoluble intermediates. Nevertheless, a flow synthesis

SCHEME 11.48 A flow process for the synthesis of imatinib **158**.

route has been developed that uses a reverse coupling strategy to the batch route but was more suitable to continuous processing (Scheme 11.48) [52].

Acid chloride **152** was preloaded onto immobilized DMAP and a solution of aniline **153** was then passed through the column to release the amide **154**. The output from this stream was collected by an automatic fraction collector (triggered by a UV detector) after scavenging the acid byproduct with immobilized dimethylamine. Collecting fractions in this manner enabled only the most concentrated output peak area to be collected and subsequently aliquoted directly into a vial containing methylpiperazine in DMF. This process also facilitated the automated solvent switch (from chloroform to DMF) and produced a homogeneous mixture of known relative stoichiometry ready to form amide **155**. The stream was passed through a basic calcium carbonate column maintained at 80°C and scavenged with isocyanate to remove excess methylpiperazine. The stream was then directed into a column containing silica-immobilized sulfonic acid for catch-and-release purification.

Intermediate **155** was released from the silica-supported sulfonic acid by elution with a DBU solution directly into the subsequent Buchwald–Hartwig coupling with **156** using the BrettPhos Pd precatalyst **157**. Fortunately, at the elevated temperatures required, no decomposition of the catalyst to Pd black was observed. The addition of a water stream aided dissolution of the NaBr precipitate. A series of scavenging columns at the end of the coupling sequence was envisaged to clean up the reaction stream and furnish pure material. However, analysis revealed that the output stream contained not only product **158** but also unreacted starting materials. Differentiating between these was problematic so the reactor output was concentrated *in vacuo* and directly loaded onto a silica samplelet cartridge for automated flash chromatography to give **158** in 32% yield with better than 95% purity.

11.6. CONCLUSION

As can be seen in this chapter which covers literature to 2010, immobilized reagents have become valuable tools for powerful organic transformations with simple separation procedures and recovery of catalysts from reaction mixtures. The area has grown exponentially over the past decade with great interest being shown into different support forms [53], immobilized catalysts [54], and asymmetric reactions [55] increasing the synthetic possibilities. All these different reactions have then been utilized in batch mode, in combination with microwave reactors [56], with simple trickle bed reactors [57], or complex automated flow systems to give multistep syntheses of complex molecules and pharmaceutically active compounds.

The combination of immobilized reagents and flow chemistry is beginning to have a significant impact on how modern synthesis is being conducted. These methods constitute a change in technology as well as a massive change in philosophy. The adaptability and ease of scaling-up automated these chemical processes during a 24/7 working environment using remote monitoring or control devices is especially attractive [58]. Furthermore, as our knowledge of these methods improves, we can envisage extensive multistep synthesis sequences coming within range of this equipment in a relatively short time. The benefits that accrue using this equipment are extensive, ranging from improved safety, hazardous molecule containment, high pressure and temperature tolerances, improved heat/mass transfer, ease of optimization, and reaction consistency.

The ability to rapidly scale-up (scale-out) processes combined with telescoped reaction steps and the reduction in solvent use are also attractive features to the new technology. However, one should not underestimate that considerable experience and synthesis knowledge are still required to derive the full benefits that the equipment has to offer. Furthermore, we can expect considerable advances to be made in the area, which will involve improved downstream processing methods, the use of gas reactors, and how best to incorporate new strategically important chemistries.

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