Polymeric Scavenger Reagents in Organic Synthesis

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Recent advances in polymeric supported reagents have led to the development of a new synthetic technique. The use of polymeric supports in solid phase synthesis has led to the design and synthesis of ionic and covalent polymeric scavengers. In this Microreview, we discuss the concept of this strategy and comment on the efficiency and versatility of this new purification procedure.

Introduction

Solid phase organic synthesis (SPOS) is now routinely used for the preparation of combinatorial libraries of low molecular weight organic molecules.[1] Recently much of this effort has been focused towards lead optimisation of biologically active frameworks within the pharmaceutical industry.[2] The clear advantage of this biphasic methodology is in the area of purification − simple filtration of the reaction mixture leads to the required compound in high purity.[3] However, this methodology is not without its limitations; excess of at least one reagent is generally required to drive the reaction to completion.[4] There can also be up to two additional synthetic steps required to mount and remove substrates from their solid support, and there are many problems associated with scalability and characterisation of such polymer supports.[5] In many cases, the synthesis of the required compound must be re-optimised in the solution phase.[6]

As a result of the problems associated with SPOS considerable effort has being devoted to the development of new techniques which assist in the rapid purification of solution phase reactions. This has lead to the synthesis of solution phase libraries in a similar parallel fashion.[7] At the forefront of these developments has been the investigation into the applications of solid supported reagents (SSRs).[8] Although many of these supported reagents have been in use since the 1960s,[9] their resurgence in organic synthesis has been initiated by the impact of combinatorial chemistry and associated automated techniques.

In addition to the existing use of solid-supported reagents,[10] a novel extension has recently been reported by several groups and its subsequent application towards more efficient solution phase combinatorial chemistry. This technique involves traditional solution phase chemical synthesis in which the reaction mixture is purified by using a solid support. These solid supported reagents can be used to remove an excess of reactants and thus give the required product in high yield and in a single operation (Scheme 1). This technique offers many of the advantages of solid supported organic synthesis in the ease of reaction workup, and product purification with the additional advantages associated with traditional solution phase synthesis. Previously this strategy has been referred to as either a solid-supported scavenger (SSS), polymer-supported quench (PSQ), or complementary molecular reactivity and molecular recognition (CMR/R)[11] and is the subject of this Microreview, wherein

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MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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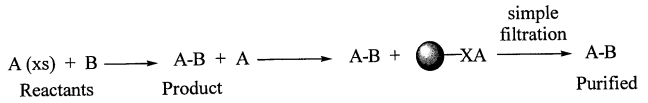
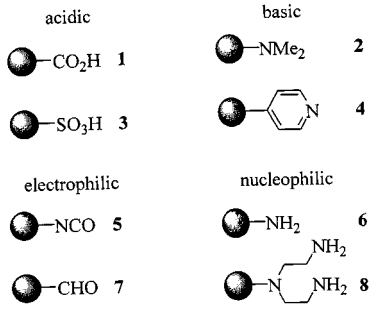
such reagents will be referred to as polymeric scavenger reagents (PSRs). There are only two different classes of scavenger available; those that are ionic (acidic and basic reagents) in origin and those that are covalent (electrophilic and nucleophilic reagents) (Scheme 2).



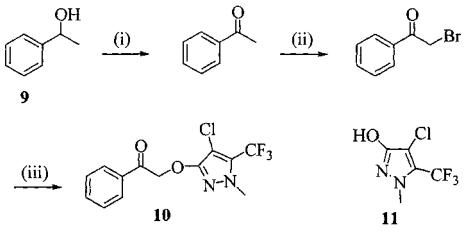
Scheme 1. Schematic representation of a reaction involving a polymer scavenger



Scheme 2. Representative examples of the four different classes of polymeric scavengers

Development of PSRs

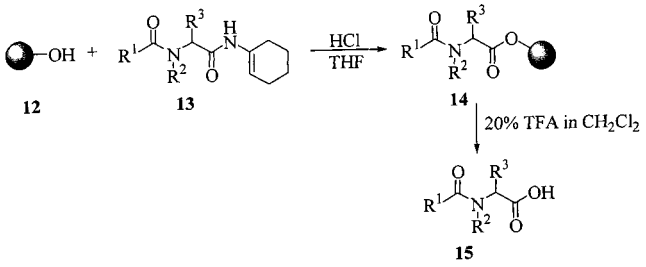
Perhaps central to the development of solid supported reagents was the realisation that cross-linked solid supports with incompatible functionality (commonly known as the "Wolf and Lamb" principle[12]) could be used in a single reaction vessel without compromising the overall reaction sequence.[13] Where the two polymers come into contact, usually on their peripheral surfaces, the functionality may change − but they can generally be treated as though they are individual species. This has been shown by Parlow,[14] who used two polymer supported reagents simultaneously to synthesise a substituted pyrazoyloxy ketone **10** in 48% yield derived from 1-phenylethanol **9** (Scheme 3).



Reagents and conditions: (i) poly(4-vinylpyridinium dichromate); (ii) perbromide on Amberlyst® A-26; (iii) Amberlite® IRA-900 and (4-chloro-1-methyl-5-(trifluoromethyl) -1H-pyrazol-3-ol) **11** in cyclohexane, 65 °C, 16h, (48%).

Scheme 3. The synthesis of substituted pyrazolyloxy-1-phenylethanol **10**

The first report of an application of a polymer supported reagent in synthesis was reported by Keating and Armstrong.[15] They investigated the synthetic utility of the Ugi four component condensation (4CC) using a univeral cyclohexeneamide motif **13** (Scheme 4). Although this procedure was not directed towards the synthesis of a combinatorial library, it clearly demonstrated that the only species trapped was the required pseudo-peptide **14**. Trapping of the unchanged starting material and potential side products did not occur, and subsequently this provided an excellent purification methodology. This can be developed further as a hybrid towards the synthesis of combinatorial libraries since the pseudo-peptide **14** could be further exploited by conventional SPOS chemistry prior to the cleavage step. Nucleophilic resins such as Wang [*p*-(benzyloxy)benzyl alcohol] **12** were employed as a scavenger for the electrophilic cyclohexeneamide motif **13** based on the assumption that it would react similarly to benzyl alcohol. Addition of this resin **12** to the Ugi 4CC intermediate **13** in dry acidic THF gave the polymeric peptide **14**, which was easily cleaved [with 20% (v/v) trifluoroacetic acid (TFA) in dichloromethane] to yield the free pseudo-peptide **15** in greater than 95% purity (Table 1); no further purification was needed.[14] This procedure was shown to be highly efficient, the initial fourfold excess of the cyclohexeneamide **13** was found to be unnecessary and could be reduced to as little as 1.5 equiv. with no real effect on the yield and purity.



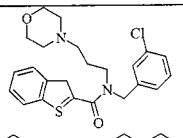
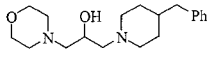
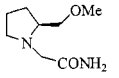
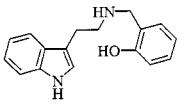
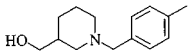
Scheme 4. Postcondensation and modifications of Ugi 4CC condensation products

Table 1. Results of resin capture of Ugi 4CC products and subsequent cleavage

Condensation product **13**			Equivalents	Reaction conditions	Yield
R^1	R^2	R^3	of **13**		(%)
Me	PMB	Ph	4	HCl, toluene, 100 °C	100
Ph	Bu	Ph	4	HCl, toluene, 100 °C	62
Me	PMB	Ph	4	HCl, THF, 55 °C	100
Me	PMB	*i*Pr	4	HCl, THF, 55 °C	100
Me	PMB	*i*Pr	1.5	HCl, THF, 55 °C	96

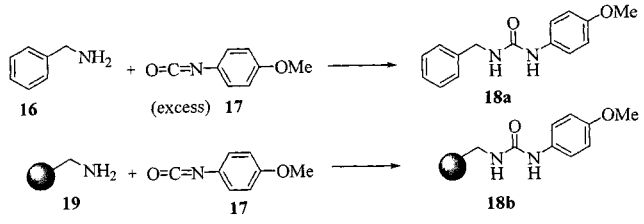
Kaldor and co-workers[12] have reported the applications of both nucleophilic and electrophilic polymer supported reagents. (A nucleophilic polymer is an electrophilic scavenger and vice versa.) They chose to use an amine to demonstrate the applicability of this technique since the chemoselectivity of the electrophilic acylating agent was very much different to both the nucleophilic amine or the amide product (Table 2).

Table 2. Selective scavenging of excess reagents

Entry	Limiting Reagent	Excess Reagent	Scavenger	Representative Product	Yield	Purity
1	R^1R^2NH	R^3NCO R^3COCl[a] R^3OCOCl[a] R^3SO_2Cl[a]	 19		67%	94%
2		R^1R^2NH	 5		94%	93%
3	R^3X[a,b]	R^1R^2NH	 5		96%	>95%[c]
4		R^1NH_2	 7		73%	90%
5		R^1R^2NH	 20		62%	>95%

[a] Piperidinomethyl polystyrene or other solid-supported base added as an acid scavenger. — [b] X = halide or sulfonate ester. — [c] Estimated by ^1H NMR.

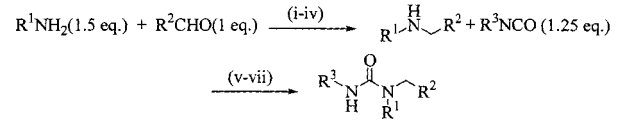
Benzylamine **16** was teated with an excess of *p*-methoxyphenylisocyanate in [D_1]chloroform for 1 h, after which an excess aminomethylpolystyrene **19** (0.8 equiv./g) was added to act as a scavenger for the unchanged isocyanate **17** (Scheme 5). Filtration of the reaction mixture followed by ^1H NMR analysis revealed only the required urea **18b** was present, with no trace of the original isocyanate **17**, indicating that the excess had reacted with the scavenger forming **18b**. The purity was assumed to be greater than 98% by the limits of NMR. This procedure was shown to be quite general by the synthesis of a moderate library containing approximately a thousand different ureas and thioureas (Table 2, Entry 1).



Scheme 5. Synthesis of the substituted urea **18**

This reaction was further extended towards the preparation of amides, sulfonamides, and carbamates. In this case, an additional basic resin[12] like aminomethylated styrene **19** was required to remove HCl from the reaction mixture; thus creating a double scavenger strategy by the combination of both a basic and nucleophilic scavenger. This technique was extended to a wide range of synthetic procedures (see Table 2). Two complementary procedures have been developed for alkylation of secondary amines[12] — both of which involve the use an excess of amine to drive the reaction to completion. This excess was removed from the required tertiary amine using a polymer-supported isocyanate **5** as a nucleophile scavenger under thermodynamic control. This amine scavenger has subsequently been applied in the purification of urea based libraries prepared by SPOS.[16]

As a complementary alternative, secondary amines have also been prepared by reductive amination of primary amines, using a polymer supported borohydride reducing agent (Scheme 6).[12] The excess primary amine was removed using a polymer supported polystyrene carboxaldehyde **7**. The high yield of the substituted piperidine (Table 2, Entry 2) presumably indicates that addition of the primary amine to the polymeric aldehyde **7** was considerably faster than the corresponding reduction involving both polymeric reagents. An analogous procedure was adopted for the formation of tertiary amines, however, a polymer supported acid chloride **20** was employed to scavenge the excess secondary amine, (Table 2, Entry 5). By coupling such procedures together, a series of substituted ureas were synthesised in excellent yield (89−100%) and chemical purity (81−97%) using the procedure shown in Scheme 6.

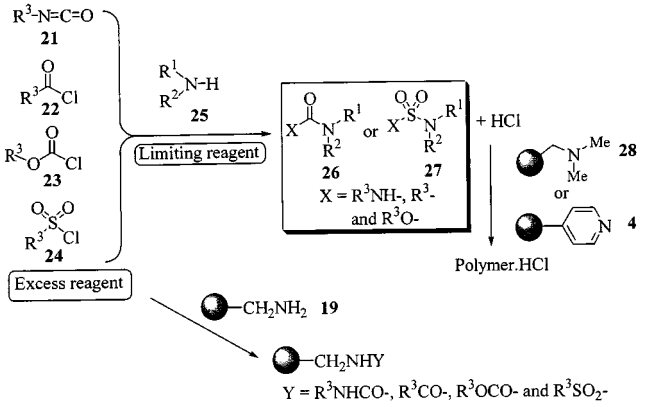


Reagents and conditions: (i) MeOH, r.t., 1 h; (ii) Amberlite® IRA-400 borohydride resin, r.t; (iii) polystyrene carboxaldehyde **7**, CH_2Cl_2, overnight; (iv) filter; (v) ethanol-free $CHCl_3$, 1 h; (vi) **19**, 1 h; (vii) filter.

Scheme 6. Synthesis of unsymmetrical ureas

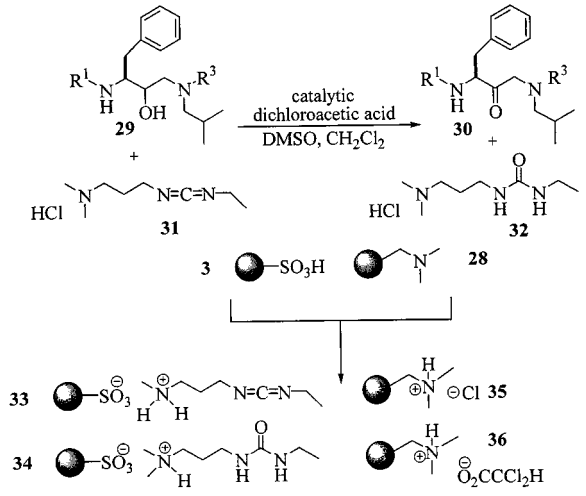
The synthetic application of polymer supported reagents towards the synthesis of a solution phase library was first developed by Flynn and co-workers.[17] They have demonstrated its applicability by synthesising numerous amides **26** and sulfonamides **27** by conducting a series of parallel reactions using a variety of *C*- and *S*-based electrophilic reagents **21**−**24** with a series of amines **25** as shown in Scheme 7. The excess reagents and the resulting HCl were removed using a combination of complementary polymeric scavengers **4**, **19**, and **28**. The yields were excellent (greater than 94%) as well as the chemical purity (greater than 95%). In a subsequent application of this methodology, a moderate library of 4000 ureas was prepared as 400 pools of ten compounds and ten of the pools deconvoluted using an identical approach. This resultant library was later screened for activity against human rhinovirus-14 with at least ten compounds showing significant anti-rhinoviral activity with low to moderate cytotoxicity.[18] This amide bond formation has proved to be the standard bench mark of this polymer scavenger methodology.

The use of other reagent types to enhance the versility of this strategy has led to the use of alternative latent functionalities to promote removal. For example; the use of the "tagged" diimide EDC [1-(3-dimethylaminopropyl)-3-ethylcarbodimide] **31** has been used within a Moffat oxidation[18] which allows the otherwise problematic urea by-product **32** to be removed with ease as an ionic polymer salt **34** (Scheme 8). The oxidation of a series of β-hydroxy diamines



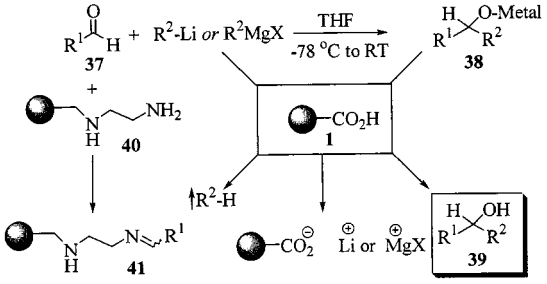
Scheme 7. Application of polymer supported resins for rapid purification

like **29** were used to demonstrate this particular procedure by using the tertiary amine (in the diimine **31**) as the functionality to be scavenged (Scheme 8). After oxidation of the secondary alcohol was complete, both the carbodimide **31** and the urea by-product **32** were removed using a combination of both acidic and basic resins **3** and **28**, respectively. The basic amine resin removed not only the HCl from the reaction mixture, but also the additional reagent dichloroacetic acid by forming **35** and **36**. After simple filtration only the ketone **30** was isolated (determined by ^{13}C NMR analysis of the crude reaction mixture). The yields were reasonable, ranging from 48 to 92%, whilst the purities (determined by HPLC analysis) were slightly disappointing (in excess of 71%). It is worthy of note, the polymeric tertiary amine **28** acts as an anion scavenger (through protonation), whereas the polymeric sulfonic acid **3** acts as a complementary cation scavenger. It appears that are is no recognition between both polymeric cationic and anionic species within the reaction mixture.



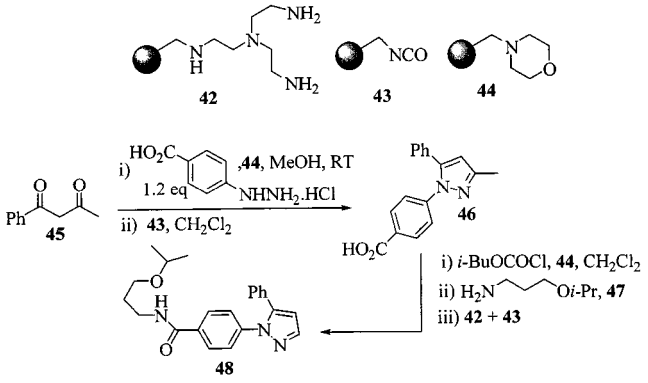
Scheme 8. Parallel oxidation of hydroxy ethyldiamines

Flynn[17] has also elegantly demonstrated a similar use of mutually incompatible polymeric species for quenching and purifying a reaction mixture, thus removing the laborious requirement for solution phase extractive quenching (Scheme 9). This was shown by the addition of a series of aldehydes like **37** to an excess of alkyllithium and -magnesium reagents to give the corresponding metal alkoxide **38**. This was initially quenched with an acidic Amberlite® IRC-50S resin **1** to give the alcohol **39** − thus quenching any remaining excess of the basic organolithium or Grignard reagent. In the event that the reaction did not proceed to completion, an additional amine resin **40** was added to remove the remaining aldehyde **37** in the form of the polymeric imine **41**. This aldehyde **37** could come from competative deprotonation in the original addition step and reprotonation by addition of the acidic Amberlite® IRC-50S resin.



Scheme 9. The use of a polymeric carboxylic acid as a base scavenger

Booth and Hodges[19] have described three separate polymer supported reagents **42**, **43**, and **44**, all of which were derived from commercially available polymers (Scheme 10). They were used either individually or in multiple combinations to aid quenching and further purification during the solution phase synthesis of ureas, thioureas, sulfonamides, amides, and pyrazoles.



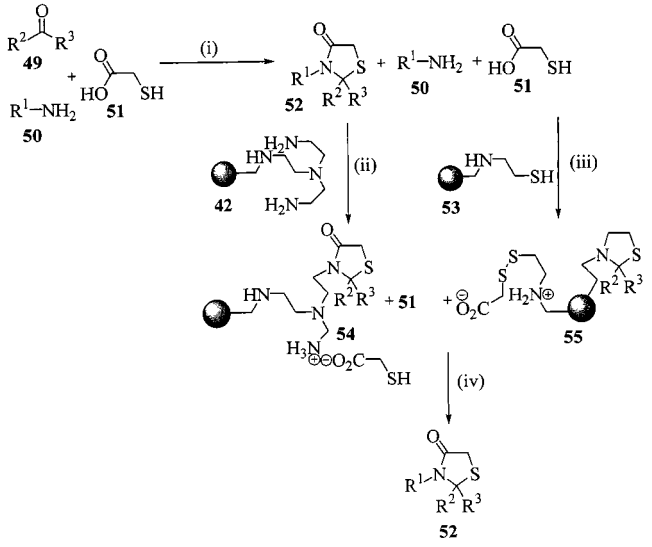
Scheme 10. Pyrazole synthesis involving the polymer scavenger **42**, **43**, and **44**

The utility of the covalent isocyanate scavenger **43** was individually demonstrated in both reactions steps, whilst the polymeric triamine **42** and morpholine **44** were employed as polymeric supported bases. These scavengers were shown to be efficient and reliable methods for removing unwanted reaction impurities, with the advantage that this purification method was experimentally very easy to achieve.

This strategy was also tested within single- and multi-step reactions. As an illustration, they synthesised the substituted pyrazole **48** modifying the traditional method by incorporating their covalent scavenger resin (Scheme 10). Although the yield for the first step of this synthesis involving

the condensation of 1,3-diketone **45** with an excess of phenylhydrazine-4-carboxylic acid in the presence of the two scavengers **43** and **44** was only moderate, the reaction appeared to be very clean and the low yield was accepted in favour of high purity. The second step of the synthesis involved amide bond formation by activation of the carboxylic OH group in **46** (with a mixed anhydride), followed by displacement with a suitable amine, such as **47**, to give the amide **48** − both basic **42** and **44**, and electrophilic **43** scavengers were used to ensure efficiency.[19] The reaction proceeded in good yield (75%) with excellent chemical purity (97%) (Scheme 10).

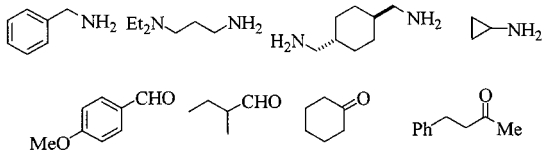
Two nucleophilic scavenger reagents **42** and **53** were used in a succinct one-pot, three-component solution phase synthesis of 2,3-disubstituted and 2,3,5-trisubstituted 4-thiazolidinones (Scheme 11).[20] For high yield an excess of mercaptoacetic acid **51** and the carbonyl component **49** was found to be required. These excess reagents were removed by two sequential reactions; (a) formation of either polymeric 4-thiazolidinone **54** or 2-thiapyrrolidine **55** which removes both the carbonyl component **49** and mercaptoacetic acid **51** and (b) the excess of mercaptoacetic acid **51** was also removed by forming a simple anion exchange resin **54** or by disulfide **55** formation.



Reagents and conditions: (i) **49** (1 equiv), **50** (1.5 equiv), **51** (3 equiv), toluene 75°C; (ii) resin **42**, basic alumina; (iii) resin **53**, basic alumina; (iv) Filter.

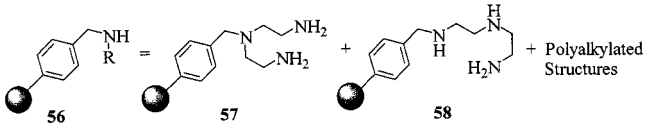
Scheme 11. Generation of a library of 4-thiazolidinones **52**

This cyclisation to give the 4-thiazolidinone framework appears to be independent of the choice of amine and carbonyl component (see Scheme 12).[20] Simple filtration and concentration of the reaction mixture gives the required substituted 4-thiazolidinone **52** in high yield and purity, which were suitable for biological testing. Although both reagents **42** and **53** gave similar results, the cheaper polymeric system **42** was used in library generation due to its lower cost. These libraries were then further elaborated by simple aldol chemistry involving the weakly acidic 5-methylene position of the 4-thiazolidinone nucleus by the addition of aromatic aldehydes in the presence of potassium *tert*-butoxide. The excess carbonyl component **49** was used to drive the reactions to completion, which was again removed by electrophile scavenger **42** and **53**.



Scheme 12. Representative carbonyls and amines used in the synthesis of the 4-thiazolidinone **52**

In a related report Parlow and co-workers[21] also used high loading polymeric amine scavengers **57** and **58** (represented by **56**) which were formed by the reaction of Merrifield resin with diethylene triamine (Scheme 13). Analysis of the polymer formed indicated that all chlorine had been displaced from the Merrifield resin and that approximately 64% was monoalkylated whilst 36% was dialkylated and therefore cross-linked. The scavenging capacities of **57** and **58** were estimated to be 2−3 times that of commercial polymeric amines (e.g. **6**) and they are also much cheaper. The utility of this polymeric scavenger was demonstrated as a covalent scavenger for the removal of excess reactants and also for the removal of unchanged starting materials. In addition this resin could be used as a thermodynamic trap by removing protic acids during the course of the reaction.

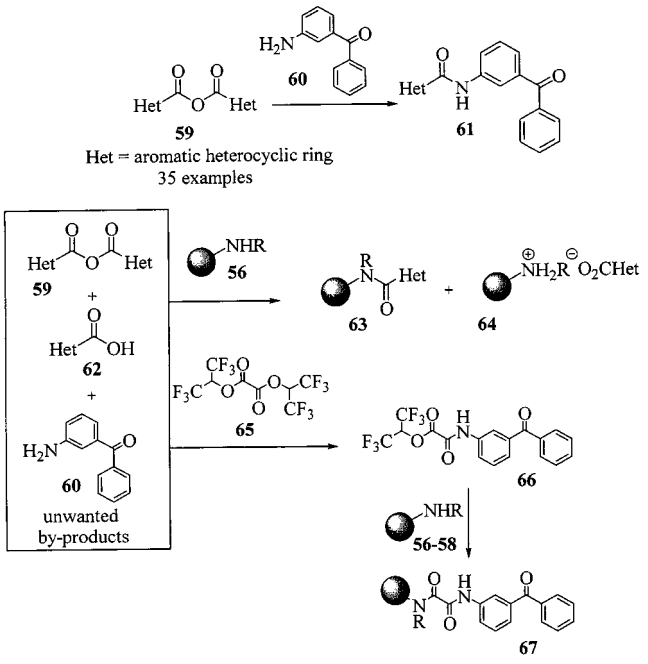


Scheme 13. High loading acid and electrophilic scavengers **56**

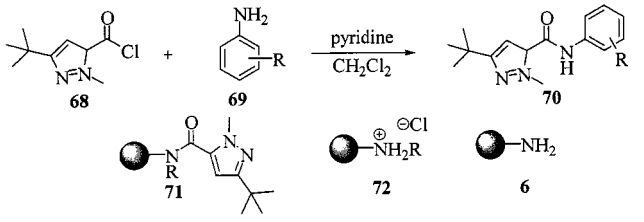
The general utility of the scavenger was elegantly demonstrated in the parallel synthesis of a series of heterocyclic carboxamides **61** by the addition of the generic heterocyclic anhydride **59** to a substituted aniline **60** (Scheme 14).[21] Two of the possible three by-products **59** and **62** were removed by a scavenging amine **56** by the formation of the polymeric amide **63** or ammonium salt **64**. The removal of the unchanged aniline **60** proved to be more difficult − this had to be encapsulated in the form of an unsymmetrical oxalate **66** for efficient removal. Addition of the activated ester, hexafluroisopropyl oxalate **65** to the reaction mixture gave the mono-addition activated ester product **66**. This was removed by the addition of the nucleophilic amine scavenger **56**, which resulted in the formation of the polymeric oxalate **67**. All polymeric intermediates **63**, **64**, and **67** were easily removed by simple filtration giving the required heterocyclic carboxamides **61** in high yield and purity.

A similar method involved the use of heterocyclic acid chlorides (Scheme 15).[22] For example, pyrazole **70** was synthesised by the addition of the unusual heterocyclic acid chloride **68** to the aniline **69**. Unreacted acid chloride **68** and HCl were removed by addition of the polymeric amine **6** and filtering the resulting amide **71**. The by-product, pyridinium chloride was converted back to free pyridine using the more basic polymeric amine **6** to give **72**.

Related analogues could also be synthesised using a Friedel−Crafts acylation and reduction strategy

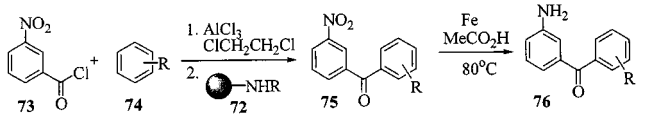


Scheme 14. Solid phase synthesis of heterocyclic carboxamides



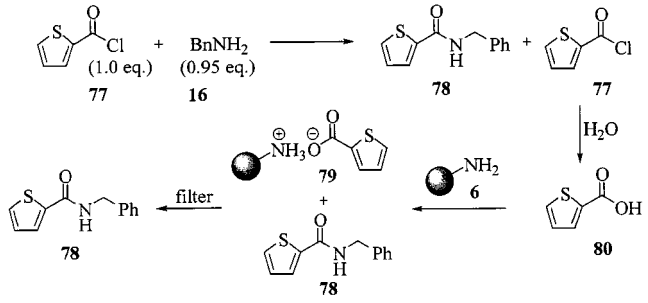
Scheme 15. The synthesis pyrazole analogue by using traditional acid chloride methodology

(Scheme 16).[22] After aqueous extraction, the scavenger amine **72** was used to purify the substituted 3-nitrobenzophenones **75** by removing the formed HCl and the excess 3-nitrobenzoyl chloride **73**. These substrates were converted into the required anilines using a metal dissolving reduction.



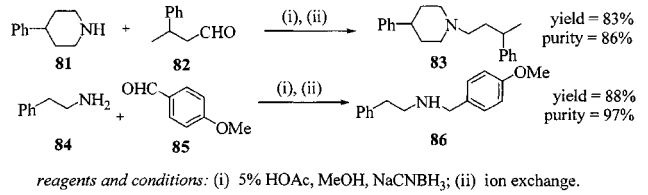
Scheme 16. Friedel–Crafts approach to substituted anilines **76** using a scavenger base **72**

Gayo and Suto[22] have developed a reliable ion exchange resin for capturing carboxylic acids and have used this strategy in the synthesis of amides (Scheme 17). By adding less than 1 equiv. of amine **16** (0.95 equiv.) to the acid chloride **78** (1 equiv.) the required amide **79** was formed leaving a small amount of unchanged acid chloride **78** behind. After hydrolysis, this resulting carboxylic acid **80** was removed by a basic ion-exchange resin to give the required amide **79** in high yield and purity. The reaction conditions were optimised using a multitude of resins (ranging from weakly to strongly basic). It was found that weakly basic Amberlite® IRA-68 in ethyl acetate provided the optimum system for the formation and purification of amides. In total, sixty reactions were run in parallel – using an automised 96-well plate. These conditions were then applied to the reaction of a variety of alcohols with acid chlorides to give substituted esters in good yield and high purity (> 97%). A further extension has revealed that acidic ion-exchange resins such as Amberlite®IR-120 and Amberlyst 15 are superb amine scavengers in the synthesis of ureas.[22] It is worthy of note, from these limited reports into ionic scavengers, that ionic scavengers appear to be less predictable than their covalent counterparts and generally require optimisation experiments. This is an important aspect to consider prior to undertaking such a study and presumably results from differences in polymer structure, porosity, and charge effects. Although ionic scavengers are clearly extremely useful reagnets in synthesis these difficulties should not be underestimated.



Scheme 17. Synthesis of amide **78** using a basic ion-exchange resin

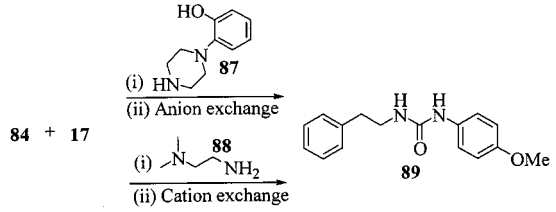
Siegel and co-workers[23] have reported an application of ion exchange chromatography which allows rapid workup and purification of small organic libraries synthesised in solution following automated construction (Scheme 18). These substituted amines, **83** and **86**, were synthesised by addition of a less substituted amine **81** and **84** to a carbonyl component, such as an aldehyde **82** and **85**, in 5% acetic acid in methanol, followed by in-situ reduction of the resultant imine with an excess of sodium cyanoborohydride.



Scheme 18. Synthesis of substituted amines **83** and **86** using a reductive amination procedure

The reaction mixture was monitored by TLC, and once complete (no amine **81** or **84** detected), the reaction mixture was poured onto a Varian strong acid exchange column. The column was rinsed with methanol to remove neutral impurities and then eluted with 2 M anhydrous ammonia (in methanol) to give the required substituted amine **83** or **86**. This procedure was applied to the synthesis of a small library of over a hundred secondary and tertiary amines. The yields were good and this was further shown to be a very efficient method for the purification of a reductive amination protocol.

The applicability of ion-exchange scavengers was further demonstrated by the purification of the urea **89** − synthesised by the addition of a isocyanate **17** to an amine **84** − using tagged reagents to remove the unchanged and excess isocyanate **17**. Two complementary nucleophilic scavengers 1-(2-hydroxyphenyl)piperazine **87** and (dimethylamino)ethylamine **88** were developed, one utilising either an anion exchange resin (for **87**), or a cation exchange resin (for **88**), Scheme 19.



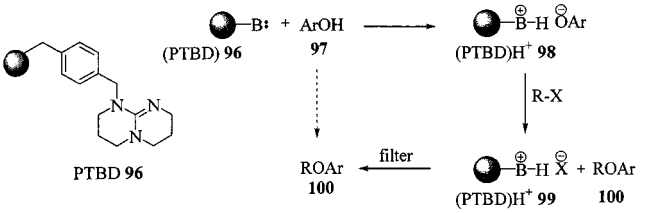
Scheme 19. Synthesis of a urea **89** using either an anion- or cation-exchange resin

Three of these secondary amines **93**−**95** were further subjected to a small combinatorial experiment involving a [3 × 3] matrix with three different substrates; an aldehyde **90**, an epoxide **91**, and an isocyanate **92**.[23] The excess reagents were used such that the product was the only ionisable component (by reaction with the aldehyde or epoxide) and the only non-ionisable component (by reaction with isocyanate) (Table 3). When the reactions were complete as judged by TLC analysis of the limiting reagent, the nine solutions were purified using automated ion exchange. In all cases after both purification steps, the purity was greater than 80% and in many cases greater than 90%. The yields were also impressive ranging from 72−92%.

Table 3. [3 × 3] matrix of reactions purified by ion exchange

	90	**91**	**92**
93	yield = 72% purity = 98%	yield = 85% purity = 99%	yield = 90% purity = 91%
94	yield = 84% purity = 88%	yield = 81% purity = 80%	yield = 92% purity = 86%
95	yield = 71% purity = 95%	yield = 92% purity = 86%	yield = 87% purity = 87%

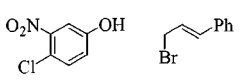
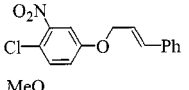
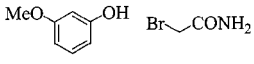
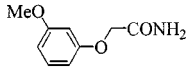
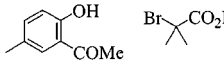
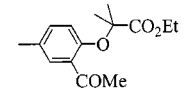
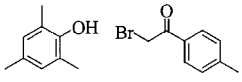
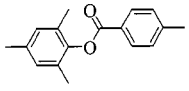
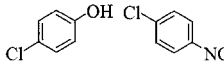
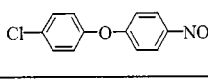
Further demonstrations of the utility of ion exchange resins in combinatorial chemistry can be seen using a highly basic polymeric base PTBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene) **96** in a series of *O*- and *N*-alkylation experiments (Scheme 20).[24]



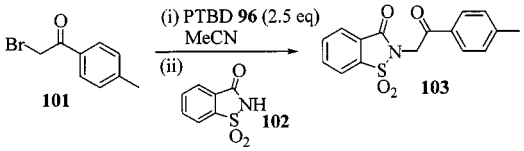
Scheme 20. The synthesis of aryl ethers **100** using an ionic-scavenger resin

For example, deprotonation of a series of substituted phenols like **97** with this polymeric base PTBD **96** forms the ionic polymeric species **98** containing the more nucleophilic phenolate. Addition of a suitably activated electrophile (RX) gives the aryl ethers **100** by an S_N2 mechanism in reasonable yield and in near perfect purity (Table 4, Entries 1−4). Alternatively biaryl ethers can be synthesised using a similar approach involving direct addition and elimination of electron deficient aryl system, such as 4-chloronitrobenzene (Table 4, Entry 5). Overall the basic polymeric scavenger PTBD **96** removes all the HX produced within the reaction mixture and eliminates the need for an aqueous extractive workup procedure.

Table 4. Synthesis of aryl ethers by forming an in-situ ionic scavenger

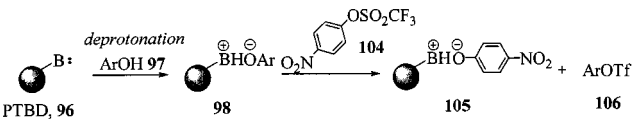
Entry	Phenol	Halide	Product	Yield	Purity
1				92%	92%
2				70%	95%
3				32%	95%
4				64%	90%
5				73%	99%

This technology has been further extended towards the synthesis of sulfimides and imides by conducting an analogues *N*-alkylation (Scheme 21).[25] For example, addition of the sulfimide **102** to the polymeric base **96** in acetonitrile, followed by treatment with the acetyl bromide **101** gave the corresponding substituted sulfimide **103**, formed via a



Scheme 21. The synthesis of substituted sulfimides **103** using the polymeric base PTBD **96**

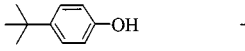
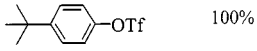
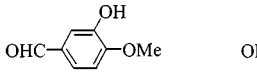
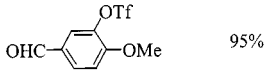
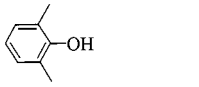
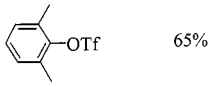
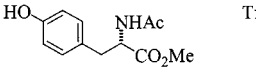
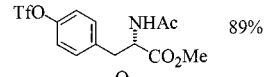
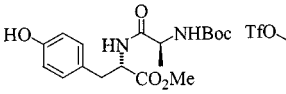
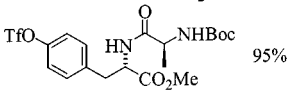
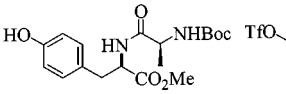
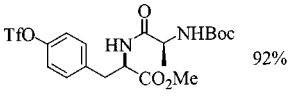
simple S_N2 reaction. The yield and purity of such alkylation reactions were near identical to that of the aryl ethers.



Scheme 22. Synthesis of aryl triflates **106** using PTBD **96** and the transfer reagent **104**

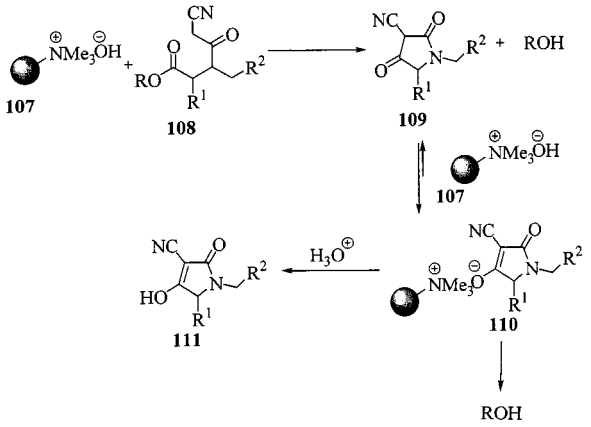
In a very similar report[26] it was demonstrated that aryl triflates could be readily synthesised using 4-nitrophenyl triflate **104** as the transfer reagent with this intermediate ionic scavenger derived from PTBD **96** (Scheme 22). Deprotonation of the phenol **97** with PTBD **96** in acetonitrile at elevated temperature (80 °C), followed by the addition of 4-nitrophenyl triflate **104** gave the required aryl triflate **106** with the remaining unchanged phenol still attached to the polymer **105** (Table 5).

Table 5. Synthesis of substituted aryl triflates using a transfer reagent **104**

Entry	Starting material	Product	Yield
1			100%
2			95%
3			65%
4			89%
5			95%
6			92%

It was found that initial deprotonation of the phenol was not necessary for optimal reactivity and that epimerisation of base sensitive compounds was not a problem.[26] Racemisation of D-Try and epimerisation of the diastereoisomeric L-*N*-Boc-Ala-L-Try methyl ester/L-*N*-Boc-Ala-D-Try methyl ester does not occur (Table 5, Entries 4, 5, and 6, respectively). The chemoselectivity of this reaction was quite remarkable when considering the nucleophilic behaviour of the amide groups.

A library of 2,4-pyrrolidinediones **111** were synthesised by employed a Dieckman condensation using a quaternary ammonium ion exchange resin **107** [Amerlyst®A-26 resin (hydroxide form)] (Scheme 23).[27] This polymeric base **107** served not only to promote cyclisation, but also to retain the cyclised product **110**, all the unchanged starting materials were simply removed by filtration. When treated with acid, the product 2,4-pyrrolidinedione **111** could be eluted in good yield from the resin. The purity was also found to be excellent (86−94%) (Table 6).

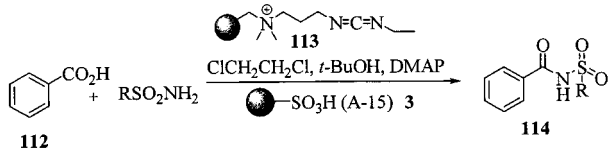


Scheme 23. Synthesis of a combinatorial library of 2,4-pyrrolidinediones **111**

Table 6. Yield and purity of formed 2,4-pyrrolidinediones **111**

Entry	R^1	R^2	Yield	Purity
1	H	Ph	72%	92%
2	*i*-Pr	Ph	80%	94%
3	CH_2Ph	*p*-$MeOC_6H_4$	75%	86%

During the combinatorial synthesis of acyl-sulfonamide **114**, it was found that Amberlyst® A-15 (**3**) was a practical proton source to protonate both the required acylsulfonamide and to remove the unwanted DMAP. Generally, greater than 95% of the DMAP was removed from the reaction mixture, following addition of the Amberlyst® A-15 and filtration.[28] The excess carboxylic acid always remains bound to the resin (carbodiimide) and does not lower the product purity. The yield and purity were acceptable (Scheme 24).

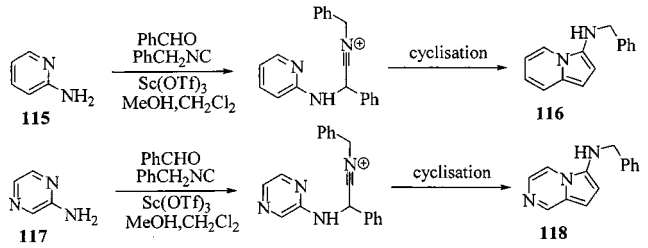


Entry	Sulfonamide	Yield	Purity
1	methanesulfonamide	66%	85%
2	2-(carboxymethyl)-benzenesulfonamide	75%	92%
3	*o*-toluenesulfonamide	75%	85%
4		68%	88%
5	benzenesulfonamide	56%	92%
6	2-fluorobenzenesulfonamide	79%	92%

Scheme 24. Synthesis of acylsulfonamide library

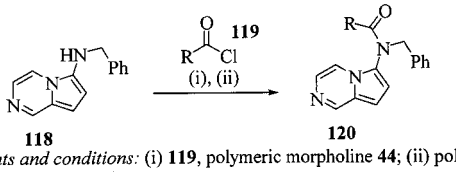
Isolation of 3-aminoimidazo[1,2-*a*]pyridines and -pyrazines (**116** and **118**) from their corresponding reaction mixtures was also achieved by capturing them on a solid support (Scheme 25).[29] There products were synthesised using a three component condensation (3CC) involving either 2-aminopyridine **115** or aminopyrazine **117** with a series of

aldehydes (e.g. PhCHO) and isonitriles (e.g. $PhCH_2NC$). It was found that providing the primary amine was kept as the limiting reagent, only the required 3CC product (e.g. **116**) was absorbed on the Dowex 50WX 2-200 cation exchange resin. After initial washing with methanol to remove all the neutral impurities, ammonia (2 M) in methanol was slowly added to elute the required heterocyclic 3-aminoimidazo[1,2-*a*]pyridine **116** or -pyrazine **118**. The yields were excellent (75−95%) and the purity exceeded 85% in all cases studied.



Scheme 25. Synthesis of 3-aminoimidazo[1,2-*a*]pyridine **116** or pyrazine **118**

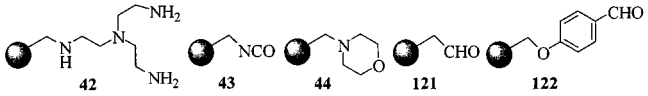
These substituted pyridines and pyrazines were further functionalised by additional amide bond formation to give amides like **120**.[30] This was performed by adding an excess of acid chloride, such as acetyl chloride in the presence of polymer supported morpholine **44**, which acts as a proton scavenger. When the reaction was complete, the polymer supported tris(2-aminoethyl)amine **57** (electrophile scavenger) was added to remove all traces of the excess acid chloride.[30] This methodology has also been extended towards the synthesis of substituted ureas (derived from isocyanates) using the same reaction conditions (Scheme 26).



Reagents and conditions: (i) **119**, polymeric morpholine **44**; (ii) polymeric tris(2-aminoethyl) amine **57**.

Scheme 26. Synthesis of substituted pyrazine **120** using a basic and nucleophilic scavenger

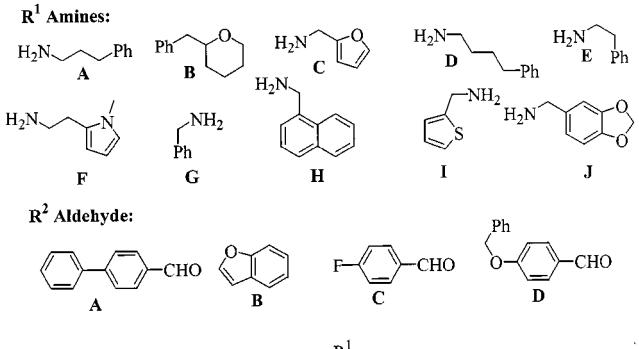
Cresswell and co-workers[31] used a combination of both covalent and ionic scavengers to achieve an efficient synthesis of a diverse library of dihydropyridones **126** using a Lewis acid catalysed hetero-Diels−Alder reaction. Their investigations used a total of five different scavengers (Scheme 27). The first scavenger resin **42** was used to remove any unchanged imine **123** and any hydrolysed product resulting from Danishefsky's diene **124**, following the acid workup (1 M HCl) required to remove the ytterbium catalyst. Attempts to make this procedure more efficient using a polymer bound scandium catalyst, unfortunately only promoted hydrolysis.



Scheme 27. Five different scavengers used in the synthesis of acylaminopiperidines

A series of fourty dihydropyridones **126** were prepared using a representative group of building blocks (4 × 10) in an average yield of 64% yield with excellent purity, always greater than 95% (Table 7). Chemoselective reduction of the carbon−carbon double bond **125** using L-Selectride gave the piperidone **126**.

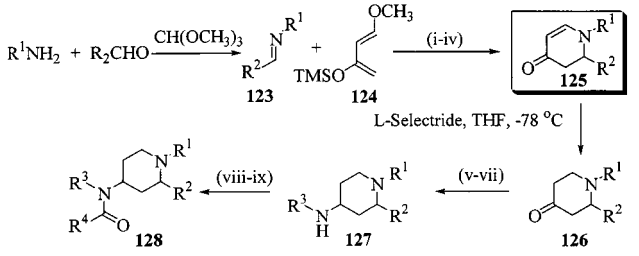
Table 7. Yields and purity of synthesised dihydropyridones **AA−JD**



Dihydropyridone Array (Yields and Purities)

R^1R^2	Yield	Purity	R^1R^2	Yield	Purity	R^1R^2	Yield	Purity	R^1R^2	Yield	Purity
AA	75%	99%	CC	52%	97%	FA	60%	53%	HC	75%	97%
AB	74%	98%	CD	65%	93%	FB	46%	66%	HD	73%	97%
AC	71%	98%	DA	60%	96%	FC	23%	32%	IA	67%	96%
AD	71%	97%	DB	69%	99%	FD	66%	37%	IB	67%	94%
BA	74%	99%	DC	70%	99%	GA	73%	99%	IC	56%	89%
BB	74%	97%	DD	67%	98%	GB	66%	98%	ID	69%	97%
BC	49%	93%	EA	51%	91%	GC	65%	99%	JA	39%	97%
BD	65%	99%	EB	69%	97%	GD	73%	99%	JB	68%	97%
CA	70%	96%	EC	66%	99%	HA	41%	84%	JC	69%	95%
CB	70%	90%	ED	70%	99%	HB	61%	86%	JD	68%	99%

These were further converted into a series of aminopiperidines **127** by employing a reductive amination procedure developed by Kaldor using the polymeric amine scavengers **121** or **122** (Scheme 28). The resulting aminopiperidine **127** was then converted into the corresponding amide **128** using an excess of acid chloride in the presence of the morpholine proton scavenger **44**. The unchanged acid chloride was removed by the electrophilic scavanger **42**. The yields for this two step procedure were moderate, averaging 48%, however, purities were excellent (80−90%). As a result of this success, the approach was further extended to the five-step synthetic route (shown in Scheme 28) used to generate eight acyl-aminopiperidines in moderate yield (34−58%) and purity (73−83%).

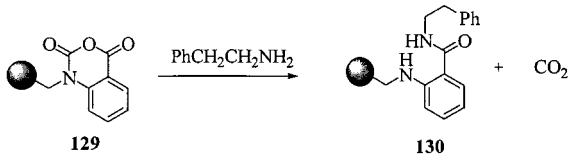


Reagents and conditions: (i) $Yb(OTf)_3$ (0.1 eq.), CH_3CN; (ii) **42**, CH_2Cl_2; (iii) filter; (iv) EtOAc/1N HCl; (v) R^3NH_2 (1.5 eq.), MeOH, 4 h; (vi) polymer supported BH_4^-, 24 h; (vii) **121** or **122**, CH_2Cl_2, 24 h (viii) R^4COCl, **44**; (ix) **42** and **43**.

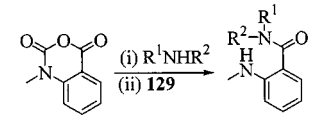
Scheme 28. The combinatorial synthesis of acylaminopiperidines **128**

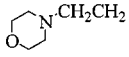
As the area of polymer supported reagents continue to expand the complexity of the polymeric supported resins has increased.[32] Although electrophilic supported reagents like the isocyanate **5** and acid chloride **20** are efficient reagents for the covalent capture for primary and secondary amines (Table 2), they are not without their difficulties. The isocyanate resin is particularly expensive and the loading is rather low (approximately 1 mmol NCO/g).

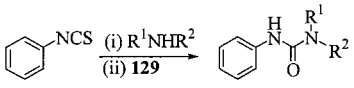
In an attempt to solve this problem, Coppola has designed a novel electrophilic scavanger **129** on an isatoic anhydride motif. This reactive mixed anhydride was shown to be particularly effective towards, primary and secondary amines (Scheme 29). The loading for this polymer was also shown to be high (3.2 mmol/g) − which is excellent for good mass efficiency. A series of amides **132** and ureas **134** were synthesised using a variety of amines (a representative selection is given in Scheme 30) using this approach, both the yield and purity were excellent.



Scheme 29. A novel polymer supported isatoic anhydride scavanger for amine removal



Entry	R^1	R^2	Yield	Purity
1	$PhCH_2$	H	96%	99%
2		H	99%	99%
3	$PhCH_2$	CH_3	97%	98%

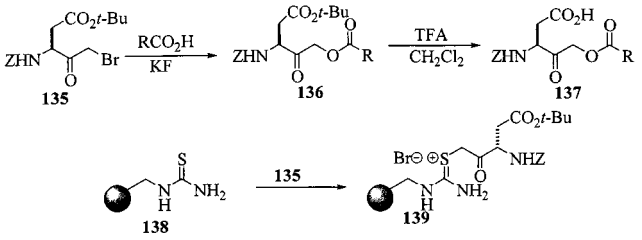


Entry	R^1	R^2	Yield	Purity
1	$PhCH_2$	H	91%	99%
2		H	99%	97%
3	$PhCH_2$	H	97%	98%

Scheme 30. The combinatorial synthesis of amides **132** and ureas **134** using the scavenger **129**

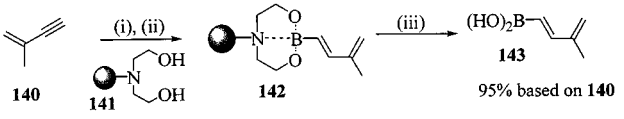
A thiourea scavenger[33] was developed in the preparation of competitive *pseudo*-peptide based inhibitors for N-His (D381E) ICE. There were concerns that unchanged electrophiles, such as the acetyl bromide **135** might lead to false positives in the study due to it irreversibly binding to the assay.

The nucleophilic polymer supported[33] thiourea **138** was used in the step prior to the extractive workup in the synthesis of the acyloxy ketone **136**, deprotection of the β-acid using TFA in dichloromethane gave the required substrate **137** for biological testing (Scheme 31). This resin **138** was used rather than a conventional scavenger like the thiol resin, which complicated matters by causing additional ester hydrolysis. No such problematic reaction was observed using the polymeric urea based scavenger **138**, which removes the electrophilic bromide by chemoselective alkylation on sulfur to form the sulfonium ion **139**.



Scheme 31. The synthesis of pseudo-peptides ICE inhibitors

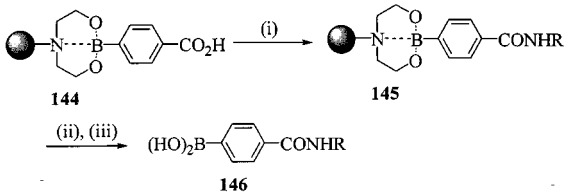
Despite the wide use of boronic acids as intermediates in Suzuki cross-coupling reactions, and in the biological application to sugar recognition, there are limited scavengers available for this functional group. Hall has subsequently designed and developed[34] a novel polymer scavenger resin DEAM-PS [(*N*,*N*′-diethanolaminomethyl)polystyrene] **141** for solution phase parallel synthesis of aryl boronic acids (Scheme 32). This resin was used to purify the crude dienylboronic acid **143** which was previously known to be difficult. Resin **141** was used to capture the boronic acid **143** and facilitates purification of **143** through simple rinsing of the resin bound form **142**.



Reagents and conditions: (i) addition of $(C_6H_{11})_2BH$ (1.0 equiv.), then Me_3NO; (b) DEAM-PS resin **141**; (iii) H_2O, THF.

Scheme 32. Purification of dienylboronic acid **143** with diethanolamine resin **141**

Of particular interest to combinatorial chemistry is the use of immobilised functionalised boronic acid templates which are capable of further transformations.[35] For instance, an arylcarboxylic acid **144** could be converted into the corresponding amide **145** (Scheme 33), whilst still being attached to the resin. Benzylamine and butylamine were coupled efficiently to afford the corresponding amides **146** in high yield after cleavage.

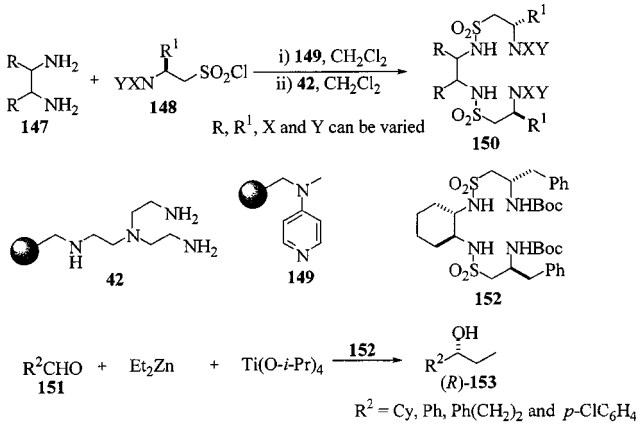


Reagents and conditions: (i) RNH_2 (2.5 equiv), *N*-hydroxbenzotriazole (2.5 equiv) *N*,*N*′-diisopropylcarbodiimide (2.5 equiv); (ii) DEAM-PS resin **141**; (iii) H_2O, THF.

Scheme 33. Immobilisation and solid-phase transformations of resin bound arylboronic acid **144**

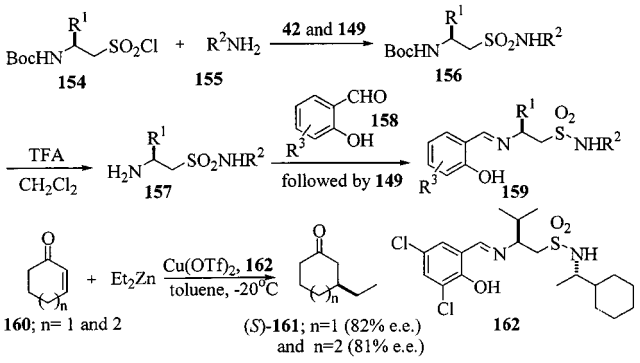
All the polymer supported scavengers encountered so far have been removed by filtration, however, this may now change following the report of an amino scavenger reagent in which magnetite has been encapsulated during suspension polymerisation.[35] The beads produced in this way were shown to compare favourably with standard Merrifield resin under a wide range of reactions. Iron leaching was not found to occur unless the beads were treated with 12 M HCl. Classical Gabriel amination yielded the first magnetic PSR whose applicability as a scavenger in the synthesis of a series of sulfonamides was demonstrated. The beads were removed with small magnets and the final products were shown to be resin free and in near perfect purity.

The majority of these reports into the applications of polymeric scavengers have been within the pharmaceutical field. Recently, this technology has been used to assist in the development of new catalysts. In particular, the ability of high throughput catalyst screening for improving efficiency has generated a lot of excitement. The use of a polymeric amine **42** and pyridine **149** as scavengers in the synthesis of substituted sulfonamides **150** and **159**, which were known to catalyse Et_2Zn addition to carbonyl derivatives has been reported by Gennari and Piarulli (Scheme 34).[36,37] The required sulfonamide ligands **150** were efficiently synthesised by addition of a 1,2-diamine **147** to an excess of substituted chloride **148** to ensure complete conversion. The use of a polymeric nucleophilic covalent catalyst, dimethylaminopyridine **149**, not only accelerates the rate of addition but all scavenges the HCl by-product. The excess sulfonyl chloride was removed using the polymeric bound tris(2-aminoethyl)amine **42**. Thirty of the possible thirty-six component library were screened against the enantioselective Ti(O-*i*Pr)$_4$-mediated addition of Et_2Zn to a series of four aldehydes **151**. This screening revealed a number of interesting points; the best ligand was shown to be **152** − using the (1*S*,2*S*)-diaminocyclohexane scaffold and the sulfonyl chloride derived from L-phenylalanine giving in all cases studied the (*R*)-alcohol **153** in high selectivity (86−96% *ee*). The effect of varying the R^1 substituent has revealed the selectivity to increase in the following order $CH_2Ph > CH_3 > iBu > iPr > -(CH_2)_3-$, which may assist in the design of future catalysts.



Scheme 34. High speed parallel synthesis of substituted sulfonamide **150**

The related related sulfonamide ligands **159** have been used in the $Cu(OTf)_2$ catalysed enantioselective 1,4-addition of Et_2Zn to a series of enones **160**; n = 1 and 2 (Scheme 35).[37] Similar scavenger methodology was used to synthesise the sulfonamide component **156**. This was further functionalised by incorporation of a substituted salicylaldehyde **158** to generate a library of chiral Schiff base ligands, which contain three different metal binding sites (imine, phenol, and secondary sulfonamide). The acid scavenger **149** was used to purify this library to remove the generated HCl from the Boc deprotonation step. Screening this 100 or so component library, revealed that the ligand **162** [R^1 = *i*Pr; R^2 = (*S*)-CH(Me)Cy; R^3 = 3,5-Cl_2] gave the best selectivity for 2-cyclohexanone (82% *ee*) and 2-cycloheptenone (81% *ee*). These results have shown the importance of combinatorial techniques for probing the efficiency of a particular reaction to allow further optimisation.



Scheme 35. High speed parallel synthesis of substituted sulfonamide ligands **159**

The importance of this new area is further emphasised by the publication of a thematic issue of *J. Chem. Soc., Perkin Trans. 1* on the application of solid-supported reagents and scavengers in multi-step reactions, which came to our attention after this Microreview article had been written.[38]

Conclusion

The use of polymer supported reagents and scavengers has greatly improved the efficiency of classical solution phase chemistry. This development has allowed combinatorial solution phase chemistry to be further extended. The advantages being:

− Use of excess reagents or reactants to drive the solution phase reaction to completion.
− Avoidance of the need for substrate linkage to the polymer support.
− Avoidance of a liquid phase extraction procedure for reaction quenching and/or workup.
− Obviates the need of chromatography for purification.
− The minimisation of pre-library validation time.

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