Tagged phosphine reagents to assist reaction work-up by phase-switched scavenging using a modular flow reactor

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The use of three orthogonally tagged phosphine reagents to assist chemical work-up *via* phase-switch scavenging in conjunction with a modular flow reactor is described. These techniques (acidic, basic and Click chemistry) are used to prepare various amides and tri-substituted guanidines from *in situ* generated iminophosphoranes.

One of the most time-consuming and work-intensive aspects of a chemical synthesis is the isolation of the desired product in high purity. Indeed, the necessity for repeated purification can be a major productivity limiting factor when conducting multi-step synthetic sequences. We have held a longstanding interest in the development[1] and use[2] of immobilised reagents[3] to alleviate these purification bottlenecks. We and others have also been advocating their integration into flow based processes.[4] However, it is recognised that these immobilised systems often react more slowly than their solution phase counterparts. Elevated temperatures, particularly utilising focused microwave heating,[5] can sometimes compensate for this loss of reactivity; however, another solution which circumvents the problem involves the development of specially designed soluble 'tagged' reagents (solution phase reagents with designed functionality that allows their facile removal from the reaction medium).[6] Recent examples include the use of bipyridyl or boronic acids which can be selectively scavenged from the reaction solution.[7,8] Alternatively, concepts such as 'impurity annihilation' can be applied by, for example, metathesis induced polymerisation of unwanted by-products and waste components.[9] In addition, Curran has pioneered the use of appending polyfluorinated chains to chemically active species to facilitate a phase-switch of the undesired impurities by fluorous phase extraction.[10]

Phosphorus reagents are well recognised as being extremely useful for effecting a variety of chemical transformations,[11] but their by-products, typically phosphine oxides, are notoriously difficult to completely remove and often require multiple chromatographic cycles. Here we describe how tagged phosphine reagents can be used to bring about useful chemical reactions and then be transformed by orthogonal processes that allow phase-switching of spent reagents from solution to a scavenging support material in a modular flow reactor system. In this way products can be obtained in good yields and high purities without the need for conventional manual work-up and purification protocols.

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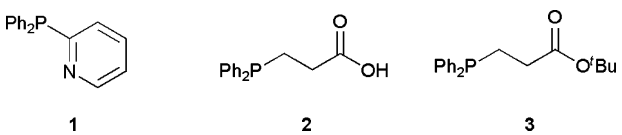
Our initial investigations were concerned with the use of simple acidic or basic tags. For example, phosphine **1**[12] (Fig. 1) could be removed using macroporous polymer supported toluene sulfonic acid (MP-TsOH).[13] This molecule (**1**) was of particular interest because of our earlier success in using bipyridine tagged species with selective metal chelating phase-switch mediators for conducting organic synthesis.[8]

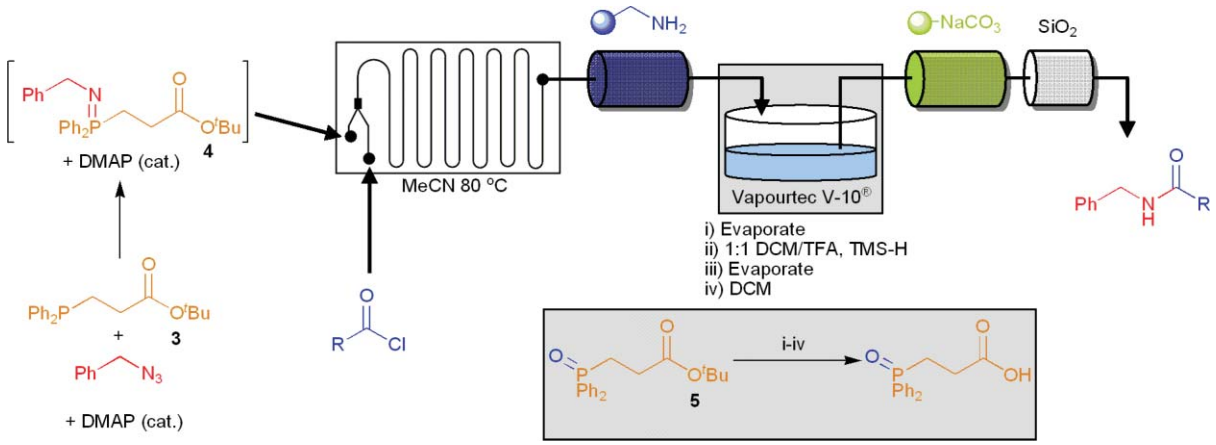


1 **2** **3**

Fig. 1 Tagged phosphine species **1**, **2** and **3**.

Similarly, an acidic tag such as that present in phosphine **2** could be trapped using polymer supported carbonate (PS-$NaCO_3$).[14] However, the reactive nature of the acidic functionality means it is incompatible with many desired chemistries. As a result, modified phosphine **3**[15] was prepared and used as a masked tagged reagent which required removal of the *tert*-butyl group before sequestering onto the solid phase. This deprotection was readily achieved following Douglas's[16] procedure (treatment with TFA and trimethylsilane) followed by evaporation of the TFA and removal of phosphine **2** with the addition of a supported carbonate base and passage through a short plug of silica. During this research programme a modified procedure was devised enabling complete removal of the *tert*-butyl group *via* treatment with MP-TsOH in DCM under microwave heating at 120 °C for 30 minutes. In batch mode this enables a one-pot deprotection and scavenging protocol to be employed using a mixed acid–base resin bed as a consequence of the site isolation of the immobilised reagents.[17] Thus, the procedure offers immediate advantages for speed of reaction work-up and reagent handling.

Other masked carboxylic acids were also examined (Fmoc and SEM ester functionalities)[18] but these capping units were generically less stable and proved to be problematic in the subsequent chemical transformations. We therefore selected phosphine **3** as our reagent of choice with the added advantage that it was easy to prepare in multigram quantities. This tagged reagent **3** as well as pyridine **1** were then applied to the preparation of various amides and guanidines using a modular flow reactor.



Scheme 1 Flow approach to amide formation.

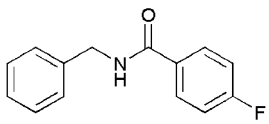
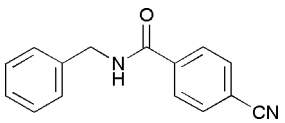
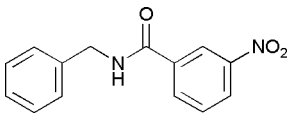
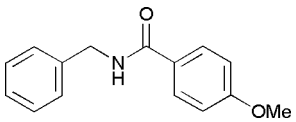
Iminophosphorane reaction with acid chlorides

Our initial experiments involved the evaluation of the tagged reagents **1** and **3** as phosphine sources in a reaction with benzyl azide to yield the corresponding iminophosphorane **4.** This was in turn reacted with an acid chloride to furnish an intermediate imidoyl chloride.[19,20] Under the reaction conditions the reactive imidoyl chloride spontaneously hydrolysed on the microfluidic chip to give the corresponding amide derivative which was isolated (Scheme 1).

The pumping system employed for this chemistry was either a Syrris AFRICA® unit,[21] or a pair of standard HPLC pumps.[22] The phosphine (0.1 M, 1 equiv.), azide (0.1 M, 1 equiv.) and DMAP (0.05 equiv.) (which was found to dramatically accelerate the reaction) were premixed as a solution in MeCN and loaded into an in-line reagent loop (1–5 mL). A second matching sample reservoir containing the acid chloride component (0.3 M, 3 equiv.) was also charged and the two feeds brought together at a flow rate of 25 μL min^{-1} on a 250 μL microfluidic chip which was heated to 80 °C. An excess of the acid chloride was found to be necessary as the reaction did not proceed to completion with equal stoichiometry. Two volume equivalents of the reagent loops were pumped through the reactor to permit the starting materials to react on the chip and allow sufficient time for scavenging the excess acid chloride with a prepacked column[23] of Quadrapure™ BZA (QP-BZA),[24] a benzylamine resin (3 equiv.). The flow rate was then increased to 250 μL min^{-1} to elute the products. This was required due to a significant retention of the reaction components, however this was easily compensated for by the increased flow rates. A back pressure regulator of ~7 bar (100 psi) was installed in-line at the exit of the flow stream in order to ensure a uniform flow profile.

In the first experiment using phosphine **1** as the tagged reagent, an additional column of MP-TsOH (3 equiv.) was placed after the QP-BZA column. Interestingly it was discovered that both the pyridine tagged reagent and the resultant amide coupling products were captured by the immobilised acid. Even when substituting a weaker carboxylic acid (PS-CO_2H)[25] into the system and using repeated washing sequences with different solvents (DCM, MeOH and MeCN) the amide product could never be isolated free from the pyridine tagged reagent (**1**).

Table 1 Amides synthesised in flow

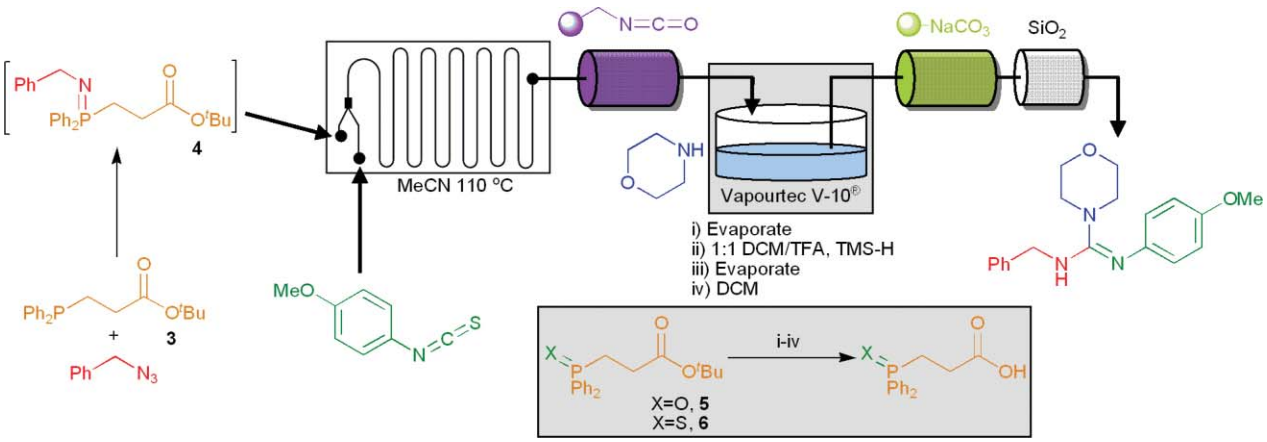
Amide	Isolated yield (%)[a]
	81
	73
	76
	71

[a] Based on the phosphine reagent used. Purity >95% by NMR and LC-MS.

Phosphine **3** proved more successful; following unmasking of the acid tag (steps ii–iv; Scheme 1) the removal of the phosphine oxide by-product **5** could be selectively achieved using PS-$NaCO_3$ (3 equiv.). A small example series of amides were prepared in good yields and high purities (Table 1).

Iminophosphorane reaction with isothiocyanates

Following the successful generation of amides in flow (described above), a more ambitious three component coupling sequence was investigated. This involved a preliminary reaction between an isothiocyanate and an aza-Wittig substrate (**4**) leading to a reactive carbodiimide intermediate along with a phosphine sulfide by-product **6**.[19,26] The carbodiimide could then be intercepted with various amines to afford tri-substituted guanidines (Scheme 2).



Scheme 2 Formation of guanidines in flow.

However, the reaction to prepare the intermediate carbodiimide failed to reach completion when equimolar quantities of the isothiocyanate and iminophosphorane were employed. The use of an excess of isothiocyanate required an in-line nucleophilic scavenging cartridge *e.g.* QP-BZA to eliminate the excess but this also resulted in removal of the desired carbodiimide. Employing excesses of the isothiocyanate and the secondary amine input resulted in the formation of thiourea by-products which proved impossible to selectively sequester from the reaction stream. Ultimately a sub-stoichiometric amount of the isothiocyanate compared to the iminophosphorane was used to ensure that the reaction went to completion on the microfluidic reactor chip. The excess iminophosphorane was subsequently quenched by passage through an immobilised isocyanate resin yielding an immobilised carbodiimide and the derivatised phosphine oxide **5** as a contaminant.

The final optimised experimental procedure involved initial formation of the iminophosphorane **4** through the reaction of phosphine **3** (0.1 M, 1 equiv.) and an azide (0.1 M, 1 equiv.) in acetonitrile for 15 minutes prior to its introduction to the reactor. The aza-Wittig component was then injected along with a stream of the isothiocyanate (0.075 M, 0.75 equiv.) at equal flow rates of 25 μL min^{-1} into a 1000 μL microfluidic chip heated to 110 °C. The system was maintained with a constant backpressure (7 bar) to suppress any solvent boiling, with the elevated temperatures also helping to preserve the solubility of the substrates and intermediates. The resulting solution was directly eluted into a connected glass column containing immobilised isocyanate (PS-NCO; 6 equiv.),[27] heated to 90 °C using a Vapourtec R-4 column heater (Fig. 2).[28] The PS-NCO resin reacted with the remaining iminophosphorane creating the tagged by-product **5** which could be scavenged in a subsequent step. Twice the combined volume of the sample loops was metered through the reactor supplying the required residence times before the flow rate was increased to 250 μL min^{-1} to elute the product from the column. The solution was dispensed into a vial containing the volatile amine (5 equiv.), which reacted with the carbodiimide to form the desired guanidine. The solution was then evaporated using a Vapourtec V-10® solvent evaporator[28] to remove the solvent and excess amine. The tagged reagent was then unmasked using the Douglas procedure (steps ii–iv; Scheme 2) prior to sequestering with an immobilised carbonate base. The guanidines (Table 2) were isolated as their free bases in good yields and excellent purities following passage through a short plug of silica.

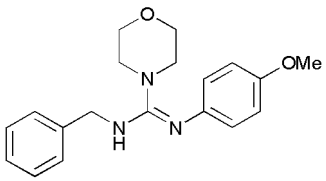
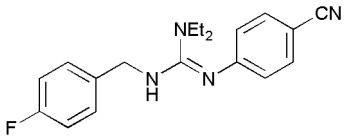
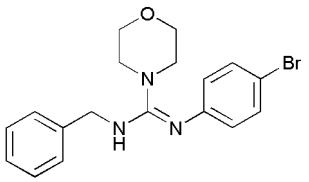
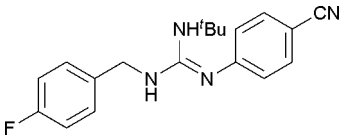
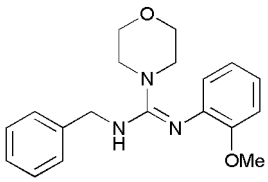
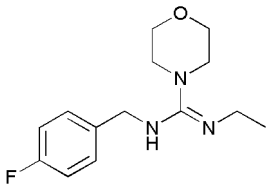
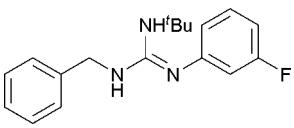
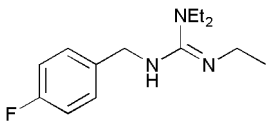
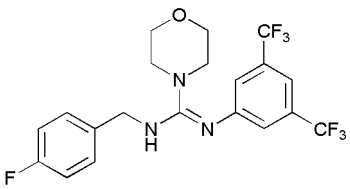
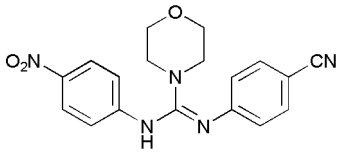
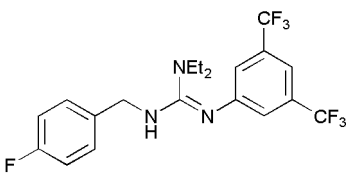
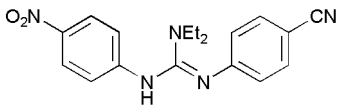
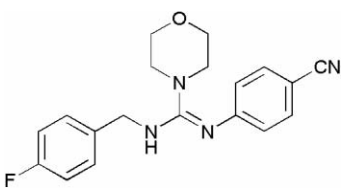
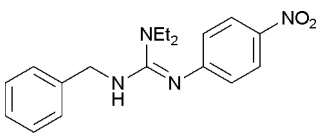
Fig. 2 System set-up.

The previously described procedure was also modified to permit the incorporation of non-volatile amine components. In this alternative sequence the product output from the PS-isocyanate column was combined directly with a solution of the amine (0.5 equiv.). The reaction mixture was treated with QP-BZA (3 equiv.) to facilitate removal of the excess carbodiimide. Following filtration of the QP-BZA the solution was subjected to the same unmasking and scavenging routine as employed above (Scheme 2), allowing isolation of the desired products in good yields and excellent purities (Table 3).

Terminal alkyne substituted phosphine as an orthogonal tagging strategy

The use of an acid (**2**) or base (**1**) tagged phosphine reagent is not always suitable, particularly with substrates sensitive to these functionalities or possessing similar properties themselves. We therefore examined a neutral tagging strategy. The attachment of the terminal alkyne functionalised phosphine such as **7**[29] (or

Table 2 Guanidines synthesised using phosphine **3**

Product	Isolated yield (%)	Product	Isolated yield (%)[a]
	82		74
	85		77
	70		61
	73		65
	79		59
	81		63
	83		65

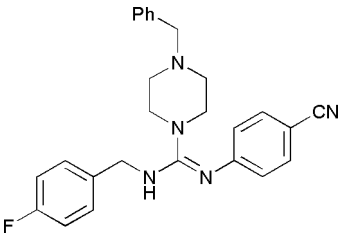
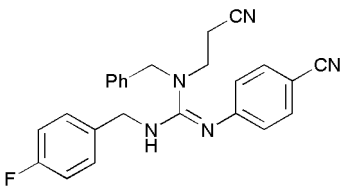
[a] Calculated compared to the isothiocyanate used. Purity >95% as measured by LC-MS and NMR.

the phosphine oxide **8**) onto an azide capped solid phase is an especially mild process, requiring only catalytic base and a copper(I) salt (Schemes 3, 4).

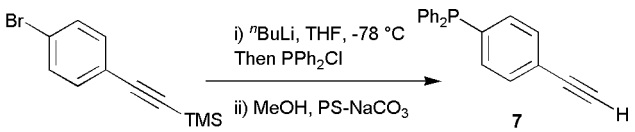
This third tagged reagent **7** was devised to take advantage of our proceeding communication[30] on the preparation of 1,2,3-triazoles[31] commonly referred to as Click chemistry. Phosphine **7** was prepared in 91% isolated yield over two steps (Scheme 3) utilising a lithium–halogen exchange followed by a PS-$NaCO_3$ in MeOH induced silyl deprotection.

Two methods were found to be effective for the removal of the phosphine oxide by-product **8** (Scheme 4). Firstly, treatment with an immobilised azide (PS-BnN_3;[32] 5 equiv.) and catalytic amounts of copper(I) iodide (3 mol%) and *N*,*N*-diisopropylethylamine (DIPEA),[33] permanently bound the phosphine oxide **8** to the solid

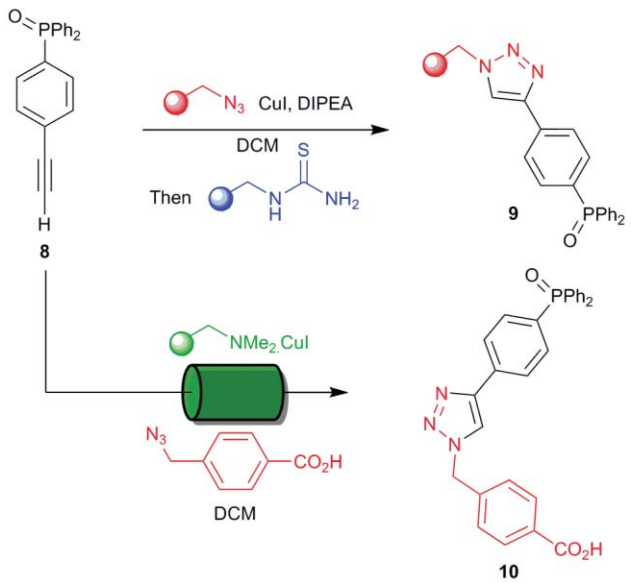
Table 3 Guanidines made using non-volatile amines and phosphine **3**

Product	Isolated yield (%)[a]
	85
	71

[a] Calculated compared to the amine used. Purity >95% by NMR and LC-MS.



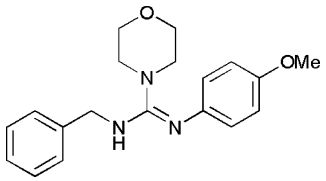
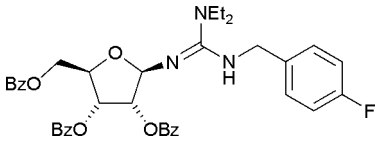
Scheme 3 Formation of terminal alkyne functionalised phosphine **7**.



Scheme 4 Removal of phosphine oxide **8**.

phase as **9** (Scheme 4). The flow stream was subsequently passed through a column containing QP-TU[34] to remove any copper residues. The second capture method involves attaching phosphine oxide **8** to a functionalised azide; this method is outlined in our preceding paper using copper(I)-mediated cycloaddition reactions.[30] In this example, a carboxylic acid functionalised azide was used and the newly functionalised phosphine oxide by-product **10** was removed using PS-$NaCO_3$ (5 equiv.). This reversible

Table 4 Guanidines synthesised using phosphine **7**

Product	Isolated yield (%)[a]
	84
	74

[a] Calculated compared to isothiocyanate used. Purity >95% by NMR and LC-MS.

binding mechanism (release by treatment with AcOH) allows the phosphine oxide **10** to be recovered. In principle this molecule could be reduced to the phosphine with or without protection of the carboxylic acid and used as a tagged reagent itself.

Phosphine **7** was evaluated using a similar procedure as described above for the formation of the guanidines (Scheme 2). The oxide or sulfide by-product of phosphine **7** was successfully scavenged by covalent attachment to the solid phase using the PS-BnN_3 resin (5 equiv.). No additional base catalyst was necessary in these examples due to the inherent basicity of the guanidine products (Table 4).

In conclusion, it has been shown that various tagged phosphines and their by-products, especially those bearing a masked carboxylic acid, can be easily removed by phase-switch scavenging from the reaction stream in a modular flow reactor system. As an application of these methods a three component coupling of isothiocyanates, azides and amines delivers guanidines in good yields and high purities. However, the concepts developed here have wider-ranging implications for flow chemistry in general. For example, the generation and *in situ* use of reactive intermediates, coupled with the simplification of the purification procedure using tagged reagents and the on-demand synthesis of compounds through high levels of automation.

Acknowledgements

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