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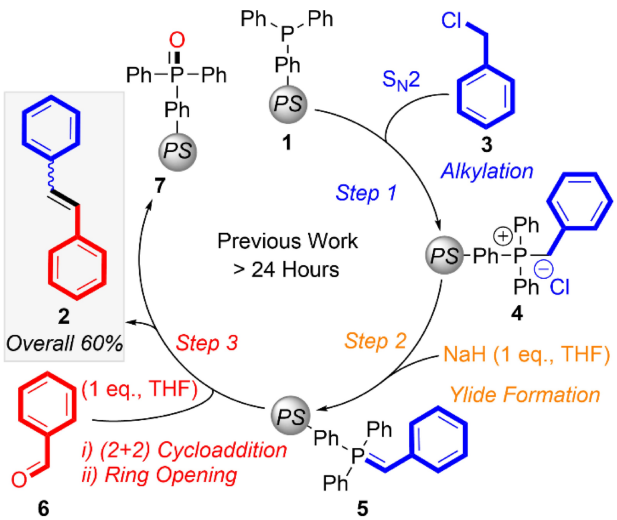
A Solid-Phase Assisted Flow Approach to *In Situ* Wittig-Type Olefination Coupling

Joseph Tadros,[a] Christian Dankers,[a] Janice R. Aldrich-Wright,[a, b] Anastasios Polyzos,[c, d] and Christopher P. Gordon*[a, b, e]

Described herein is the development of a continuous flow, solid-phase triphenylphosphine (PS-PPh_3) assisted protocol to facilitate the in situ coupling of reciprocal pairs of halogen and carbonyl functionalised molecular pairs by a Wittig olefination within 15 mins. The protocol entails injecting a single solution (1:1 $CHCl_3$:EtOH) containing the halogenated and carbonyl-based substrates into a continuously flowing stream of $CHCl_3$:EtOH (1:1), passed through a fixed bed of K_2CO_3 and PS-PPh3. With advancement to the previous PS-PPh_3 coupling procedures, the method employs a traditional polystyrene-based immobilisation matrix, the substrate scope of the protocol extended to substituted ketones, secondary alkyl chlorides, and an unprotected maleimide scaffold.

Introduction

Amongst the initial accounts describing the employment of an immobilised triphenylphosphine (PPh_3) reagent to facilitate solution-phase synthesis, Camps *et al.* detailed the use of a polystyryldiphenylphosphine (PS-PPh_3) resin **1** to mediate a Wittig olefination (Scheme 1).[1] With the utilisation of this resin, stilbene **2** was reportedly afforded in an overall yield of 60% following chromatographic purification. Since this initial study, the use of polystyrene-based PS-PPh_3 **1** has been documented on several occasions.[2] Within a significant number of these reports, often a single sequence of filtration and evaporation is sufficient to afford the desired olefin-based product in high yield and purity. This desirable outcome is primarily a consequence of both PPh_3 and the corresponding triphenylphosphine oxide (Ph_3PO) by-product (i.e. **7**) remaining resin-bound,[1–3] as traditionally the complete isolation of Ph_3PO from the target olefin presents a recurring challenge.[4] Additionally, the use of **1** also offers other benefits beyond simply reducing the requirement for downstream processing. Notably, these include increased reactant stability to moisture and the ability to drive a reaction to completion by using excess reagent without imparting extra purification demands.[5]



Scheme 1. General synthetic protocol for Wittig olefination using PS-PPh_3 **1** to access stilbene **2** reported by Camps *et al.*.[1] Step one involved the neat alkylation of resin **1** with benzyl chloride **3**, affording the polymer-bound benzyltriphenylphosphonium chloride salt **4**. Step two encompassed the formation of the ylide, benzylidene(triphenyl)phosphorane **5**, achieved through the deprotonation of **4** with NaH in THF. Step three entailed the Wittig olefination of **5** with benzaldehyde **6** in THF, affording stilbene **2**, and the resin-bound triphenylphosphine oxide (Ph_3PO) by-product **7**.

Although the above benefits are intrinsic to solid-phase assisted synthesis, it is evident that further efficiency gains can be realised with the integration of immobilised reagents into flow chemistry protocols.[5c,6] For example, the removal of excess materials, the release of final products, and even reagent regeneration by continuous flow are inherently more efficient than standard mixing strategies.[6a,7] As each of these procedures

[a] J. Tadros, C. Dankers, Prof. J. R. Aldrich-Wright, Dr. C. P. Gordon
School of Science
Western Sydney University
1797 Locked Bag, Penrith South DC, Australia
E-mail: c.gordon@westernsydney.edu.au
[b] Prof. J. R. Aldrich-Wright, Dr. C. P. Gordon
Nanoscale Organisation and Dynamics Group
Western Sydney University
1797 Locked Bag, Penrith South DC, Australia
[c] Dr. A. Polyzos
CSIRO Manufacturing
The Commonwealth Scientific and Industrial Research Organisation
Research Way, 3168 Clayton, Victoria, Australia
[d] Dr. A. Polyzos
School of Chemistry
The University of Melbourne
3010 Melbourne, Victoria, Australia
[e] Dr. C. P. Gordon
Molecular Medicine Research Group
Nanoscale Organisation and Dynamics Group
Western Sydney University School of Medicine
Narellan Road & Gilchrist Drive, 2560 Campbelltown, NSW, Australia

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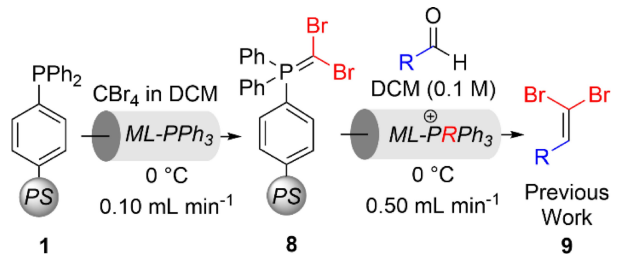
can be sequentially performed in-line, flow methods can also minimise physical handling requirements.[6a,8] Moreover, these processes can all be monitored through spectrophotometric analysis of the elution stream.[7–8]

Fundamentally, the shift from solid-supported batch protocols to flow processing requires careful consideration regarding the reagent immobilisation matrix.[9] Specifically, the matrix should allow for optimal reactant diffusion to the polymer active sites to permit efficient polymer-substrate interactions.[2b,3a,b] Demonstrating this concept, the Ley group have reported the synthesis and application of a monolithic PPh_3 reagent to conduct the Ramirez *gem*-dibromoolefination reaction under mild flow conditions (Scheme 2).[6b]

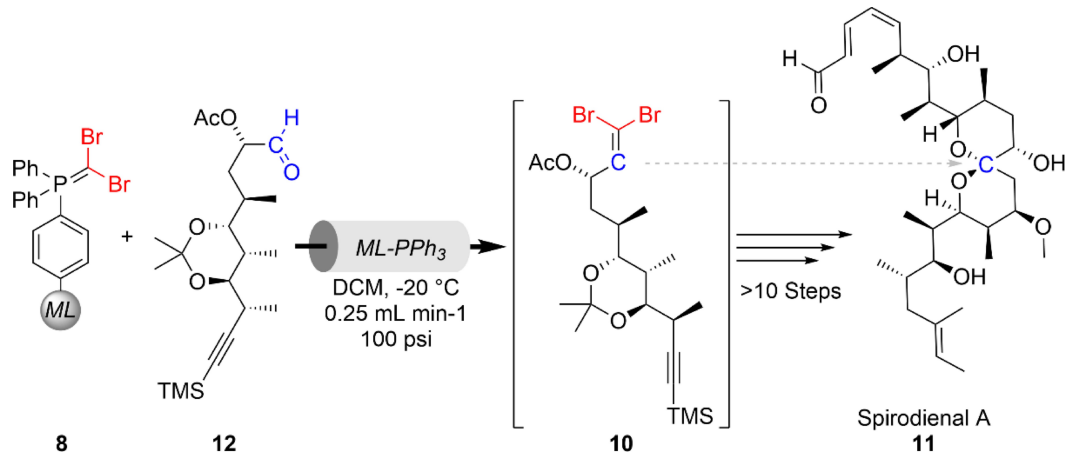
In comparison to the commonly utilised bead-like supports, studies have shown that the internal structure of the monolith consisted of a network of small mesopores within a larger macroporous scaffold.[6b] Reportedly, this resulted in the rapid diffusion of substrates to the active sites for enhanced chemical efficiency over other supports.[6b,10] Expanding upon this study, the Ley group later utilised this monolithic protocol to access the olefin intermediate **10** towards the construction of spirodienal A **11**; a spirocyclic polyketide (Scheme 3).[11] In each instance, the integration of flow chemistry enabled the safe handling of toxic reagents such as CBr_4, and an improvement in reaction efficiency was observed compared to traditional approaches.[6b,11–12] Further, the implementation of in-line reaction monitoring technology towards the synthesis of **11** allowed for the automated dispensing of reactants into the flow stream, expediting the overall reaction sequence.[11]

Nevertheless, several drawbacks were observed with the use of the PPh_3 monolith.[6b] For instance, the preparation and functionalisation stages of the monolith were conducted in a non-continuous manner. This approach was a consequence of the protocol requiring prolonged 48-hour reaction periods, a significant degree of physical handling between each step, and the use of multiple reagents. Moreover, pyridine functionalities proved less amenable with the support, affording a moderate 41% yield of *gem*-dibromoolefin. Additionally, the inclusion of the pyridine substrate resulted in the contamination of subsequent products when the same monolith was employed. Regeneration studies were also not conducted on the monolith to establish its recyclability.[6b] Thus, in comparison to the reports available for bead-like PS-PPh_3 supports, it remains unclear whether the monolith would experience the same degree of regenerative success.[13]

Surprisingly, although the previous studies by Ley were non-continuous with regards to the initial generation and application of the active phosphonium species (i.e. **8**),[6b,11] there has been evidence suggesting that this preliminary alkylation step can be achieved *in situ* with the olefination.[2f,i,14] Furthermore, we note that across the existing batch and flow resin **1** mediated studies, the electrophile scope is typically dedicated to primary alkyl bromides for the initial phosphonium salt formation.[2e,f,15] Similarly, solid-supported Wittig reactions on ketones are seldom reported, with these few available reports limited to batch investigations.[2c,15b] Hence, to address these limitations evident with the monolith and electrophile scope, and given our previous experience using commercially available PS-PPh_3 resin **1**,[13a] we were eager to explore the potential of



Scheme 2. Synthetic flow protocol employing the use of monolithic PS-PPh_3 **1** to conduct the Ramirez *gem*-dibromoolefination reaction.[6b] Functionalisation of **1** with CBr_4 in DCM afforded the dibromo functionalised species **8**. Subsequent olefination of **8** with various aldehyde substrates in DCM yielded a library of *gem*-dibromoolefin **9** derivatives in high purities following solvent removal.



Scheme 3. Application of the monolithic flow Ramirez *gem*-dibromoolefination reaction towards the total synthesis of Spirodienal A **11**.[11] Olefination of the functionalised dibromo species **8** with aldehyde **12** afforded the *gem*-dibromoolefin intermediate **10**, which was subjected to a further multi-step reaction sequence to yield Spirodienal A **11**.

developing an *in situ* flow Wittig-type protocol to facilitate the coupling of a variety of halogenated and carbonyl-based substrates *via* olefin-based tethering.

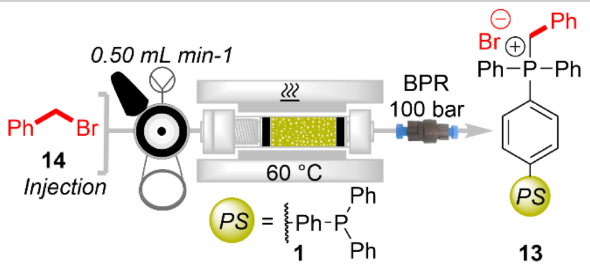
Results and Discussion

PS-PPh_3 Flow Protocol Development: Phosphonium Salt Synthesis

Following our primary goal of developing a flow protocol, we began by assessing the initial S_N2 mediated resin 'capture' reaction (i.e. formation of phosphonium salt **13**) in various solvents (Table 1, entries 1–10). For each of these trials, two equivalents of benzyl bromide (**14**, 0.23 M) was flowed (0.50 mL min^{-1}) through a fixed-bed of commercially available PS-PPh_3 resin **1** (1 molar equivalent) heated to 60 °C. As determined by the mass increase of the resin after washing and drying *in vacuo*, $CHCl_3$ proved most effectual, affording a near-quantitative yield (97%) of **13** (entry 2).

This result was in agreement with previous investigations and is expected to be associated with $CHCl_3$'s superior polystyrene swelling characteristics.[3a] However, the employment of toluene, which induces a similar swelling capacity to dichloromethane (e.g. 5.2 vs. 5.3 cm^3 increase from dry resin),[16] returned a conversion of only 48%, thus demonstrating that the solvent must also facilitate the required S_N2 type substitution reaction.

Table 1. Effect of solvent on the alkylation yield of PS-PPh_3 **1** (1 eq.) with benzyl bromide **14** (2 eq.) [0.23 M] to afford PS-benzyltriphenylphosphonium bromide **13**. Residence time = 1.96 min.



Entry	Solvent	**13** [%][a]
1	Acetonitrile (ACN)	31
2	**Chloroform ($CHCl_3$)**	**97**
3	Dichloromethane (DCM)[b]	95
4	*N,N*-Dimethylformamide (DMF)	90
5	Dimethyl Sulfoxide (DMSO)	81
6	Ethanol (EtOH)	18
7	Ethyl Acetate (EtOAc)	29
8	*n*-Hexane (*n*-Hex)	22
9	Tetrahydrofuran (THF)	79
10	Toluene (MePh)	48

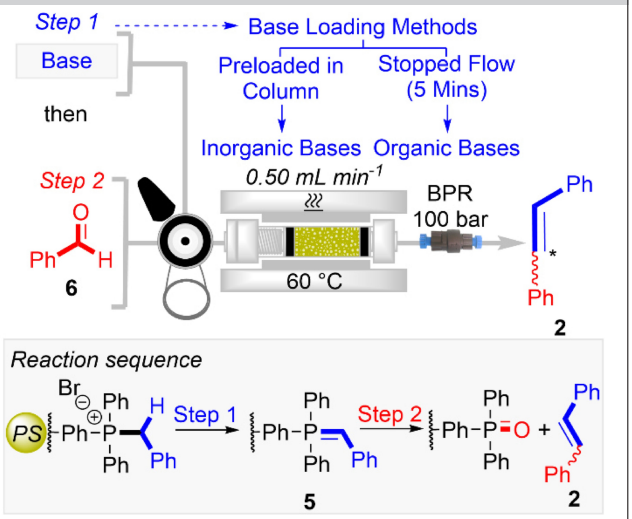
[a] Percent yield (%) determined by the mass increase of the resin. [b] Pressurised (2.75 bar–40 PSI) using an in-line back pressure regulator (BPR) to overcome the low boiling point of DCM (39.6 °C).

PS-PPh_3 Flow Protocol Development: Phosphonium Ylide Formation and Wittig Olefination

With $CHCl_3$ identified as the optimal solvent to mediate the formation of **13**, our focus next turned to ylide formation for the sequential olefination resin 'release' sequence (i.e. formation of phosphonium ylide **5**). Here, a series of bases were evaluated for the generation of **5** under flow conditions (Table 2, entries 1–10), and of the ten bases examined, K_2CO_3 appeared the most effectual (72%, entry 3). Nonetheless, in a bid to further increase conversion, the reaction was repeated, whereby the solution was circulated through the resin for a total of four cycles. This however afforded, at best, a negligible increase in the formation of **2** to 75%. An increase of reaction column temperature to 100 °C and 150 °C afforded minor improvements in conversion to **2**, leading to conversions of 82% and 85%, respectively.

Thus, although the attempts above afforded minimal improvement, the generation of even trace amounts of product is somewhat counterintuitive given the apparent incompatibility of a polystyrene scaffold with the ionic phosphonium intermediates.[2f] Nevertheless, it has been previously revealed that increasing the solvent polarity can prove advantageous,

Table 2. Effect of the base (2 eq.) on PS-benzyltriphenylphosphonium bromide **13** (1 eq.) to generate ylide **5**, followed by subsequent Wittig olefination with benzaldehyde **6** [0.09 M] (0.8 eq.) to afford stilbene **2**. Residence time = 1.96 min.



Entry	Base (2 Eq.)	Conversion **6** to **2** [%][a]
1	1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)	40
2	*N,N*-Diisopropylethylamine (DIPEA)	0
3	**Potassium Carbonate (K_2CO_3)**	**72**
4	Potassium *t*-Butoxide (*t*-BuOK)	45
5	Pyridine (C_5H_5N)	0
6	Sodium Bis(dimethylsilyl)amide (NaHMDS)	58
7	Sodium Hydroxide (NaOH)	5
8	Sodium Hydroxide (NaOH) + Tetrabutyl$^+NH_4$.I (TBAI)	7
9	Sodium Methoxide (NaOMe)	12
10	Triethylamine (Et_3N)	0

[a] Percent conversion (%) determined by the consumption of **6**, as adjudged by HPLC analysis at 254 nm.

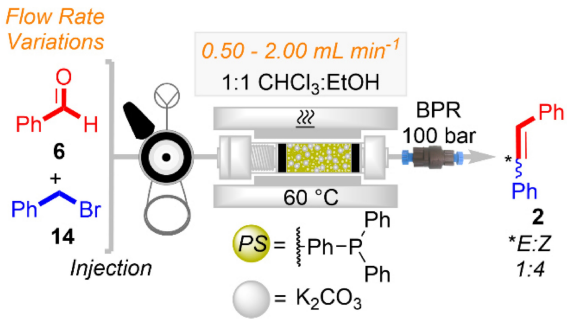
presumably as a result of increasing exposure of the ionic phosphonium sites within the resin matrix.[2f,i] Hence, we reattempted the olefination of **6** to afford **2** using the parameters detailed in entry 3, Table 2, but with increased solvent polarity (1:1 $CHCl_3$:EtOH). Gratifyingly, a near-quantitative conversion (99%) of **6** to **2** was observed in a single cycle. However, in contrast to a previous report using **1** to conduct Wittig reactions under batch conditions,[2f] the use of EtOH alone did not afford complete substrate conversion (68%) under the flow protocol. Consequently, the use of this solvent system (1:1 $CHCl_3$:EtOH) ratio indicated that the balance between matrix swelling and access to the ionic phosphonium sites was essential under a flow setting, as deviations (3:1–1:3) from this mixture failed to afford quantitative substrate conversion.

PS-PPh_3 Flow Protocol Development: *In Situ* Wittig Olefination

Upon establishing flow conditions that returned a near quantitative conversion of **6** to **2**, our attention turned to performing a complete *in situ* sequence. To this end, a solution of **14** and **6** in 1:1 $CHCl_3$:EtOH was directly injected into the pre-heated reaction column (60 °C) containing **1** and solid K_2CO_3 at a flow rate of 0.50 mL min^{-1}. Pleasingly, HPLC analysis of the collected reaction aliquot revealed the quantitative conversion (>99%) of **6** to **2** following a single pass through the immobilised reagent (Table 3, entry 1).

In a bid for further optimisation and to determine the effect of residence time on product formation, additional flow rates were assessed using the *in situ* methodology, and the results of this study are also shown in Table 3, entries 2–4. As deduced, increases in flow rate (0.50–2.00 mL min^{-1}), and therefore a decrease in residence time (1.94–0.49 min), displayed negative impacts on substrate conversion, reinforcing the importance of the duration of polymer-substrate interactions.

Table 3. Effect of residence time on the *in situ* PS-PPh_3 Wittig olefination using a reaction solution consisting of benzyl bromide **14** [0.23 M] and benzaldehyde **6** [0.09 M] in 1:1 $CHCl_3$:EtOH.



Entry	Flow Rate [mL min^{-1}]	Residence Time [min]	Conversion **6** to **2** [%][a]
1	0.50	1.96	>99
2	1.00	0.98	56
3	1.50	0.65	33
4	2.00	0.49	23

[a] Percent conversion (%) determined by the consumption of **6**, as adjudged by HPLC analysis at 254 nm.

PS-PPh_3 Flow Protocol Assessment: Aldehyde Olefinations

To assess the efficacy of the flow procedure against previously reported solution-phase and solid-phase assisted methods, the established Wittig conditions were applied to a series of aldehydes. Here, benzaldehydes encompassing electron-donating and electron-withdrawing functionalities, in addition to aliphatic and heteroaromatic aldehydes, were evaluated (Table 4, entries 1–12). Of these, olefins **2**, **15**–**19** (entries 1–6) have been previously synthesised using resin **1**,[2c,e,f,17] while **20**–**24** (entries 7–11) have been reported using a solution-phase PPh_3 approach.[18] We also highlight that acetamidostilbene **25** (entry 12) has not been previously synthesised using a Wittig reaction but through a reported Matsuda-Heck coupling procedure.[19]

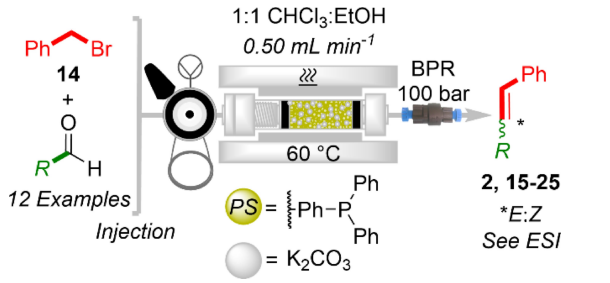
The flow protocol proved amenable across the scope of substrates employed, enabling near-quantitative conversions (> 99%) to the desired olefins **2**, **15**–**25** in high yields and purities (>95%, entries 1–12). In comparison to the corresponding batch methods, which typically required lengthy reaction times, the flow protocol within minutes afforded the target olefins in equal, and in some cases, substantially higher yields (>95%, entries 6–9, 11). Where previously reported, the deduced *E:Z* stereoisomer ratios for products **2**, **15**–**25** were in general agreement (*E:Z*≈3:1–1:3) with those obtained *via* their cited batch methods using resin **1** or solution-phase PPh_3.[2c,e,f,17–18] Hence, under the developed conditions, the flow protocol imparted no significant difference towards the typical stereochemical outcomes previously associated with semi-stabilised ylide **5**.

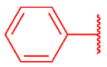
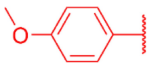
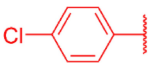
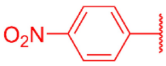
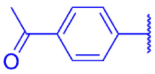
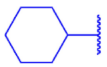
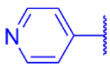
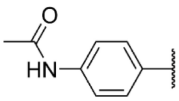
PS-PPh_3 Flow Protocol Assessment: Indole Synthesis

Moving forward with our investigations, we were next eager to deduce whether the flow method could be telescoped to furnish the bioactive indole heterocycle as an additional approach to fragment tethering.[20] Comparatively, this structure has been previously accessed with resin **1** *via* an intramolecular Wittig cyclisation, employing the strong base *t*-BuOK in a refluxing solvent mixture consisting of DMF and toluene.[21] Consequently, we were interested in assessing if the same approach using resin **1** could be accomplished, though under the flow protocol's milder conditions.

To commence our exploration, alkylation of **1** with 2-nitrobenzyl bromide **26** utilising the developed reaction conditions afforded PS-(2-nitrobenzyl)triphenylphosphonium bromide **27** in 95% yield (Scheme 4). With **27** in hand, reduction of the nitro moiety with sodium dithionite following a previously reported method resulted in PS-(2-aminobenzyl) triphenylphosphonium bromide **28**.[21–22] Solid-supported **28** was then placed into the reaction column and injected with ethyl 3-nitrobenzoate **29** under the *in situ* protocol conditions.

Table 4. Continuous flow, *in situ* PS-PPh_3 mediated Wittig olefination on aldehydes. Reagents and conditions: reaction column containing PS-PPh_3 **1** (1 eq.) and K_2CO_3 (2 eq.); injection solution with benzyl bromide **14** [0.23 M] (2 eq.) and aldehyde [0.09 M] (0.8 eq.) in 1:1 $CHCl_3$:EtOH at 60 °C. Flow rate = 0.50 mL min^{-1}, residence time = 1.96 min.



Entry	Compound	R	Conversion [%][a]	Yield [%][b]
1	2		>99	97 (98)
2	15		>99	99 (100)
3	16		>99	98 (95)
4	17		>99	97 (97)
5	18		>99	96 (99)
6	19		>99	97 (83)
7	20		>99	98 (58)
8[c]	21		>99	98 (50)
9[c]	22		>99	98 (<10)
10[c]	23		>99	97 (ND)
11	24		>99	95 (34)
12	25		>99	96 (ND)

[a] Percent conversion (%) determined *via* HPLC analysis at 254 nm. [b] Product yields (%) reported are isolated yields following silica gel filtration. Yields in (parentheses) refer to reported literature yields. ND = No Data. [c] Percent conversions (%) based on the consumption of the starting material aldehydes, as deduced *via* $KMnO_4$ staining. Compounds in red (**2**, **15**–**19**) have been previously synthesised using PS-PPh_3 **1**. Compounds in blue (**20**–**24**) have been previously synthesised using solution-phase PPh_3. Compound **25** has not been previously synthesised using a Wittig reaction.

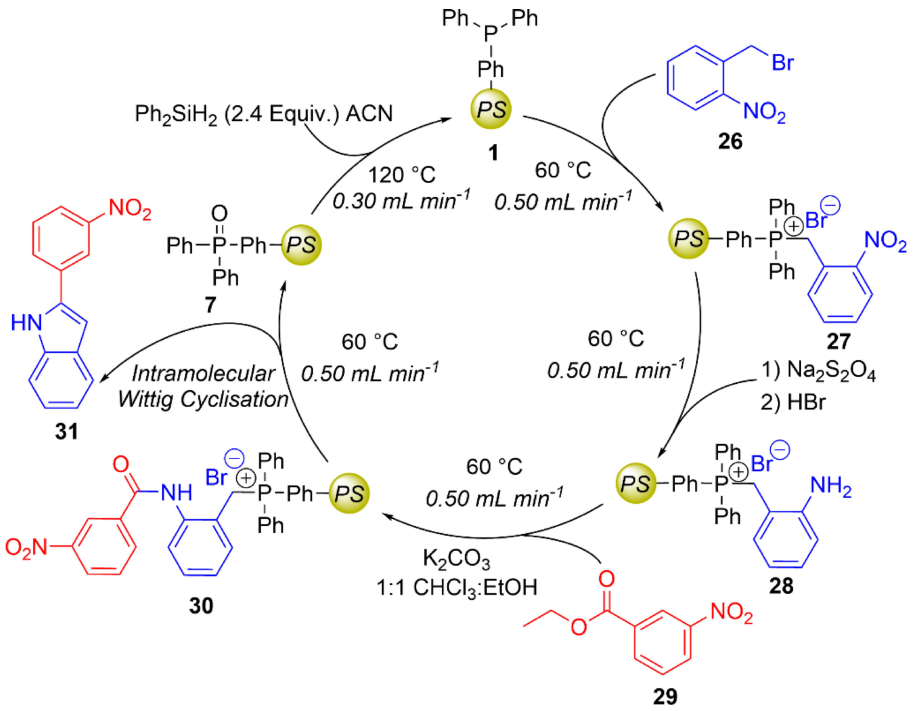
Subsequent amide formation yielded PS-(2-(3-nitrobenzamido) benzyl)triphenylphosphonium bromide **30**, followed by *in situ* cyclisation and concomitant cleavage from the solid-support, yielding 2-(3-nitrophenyl)-1*H*-indole **31** (95%). Furthermore, following the release of **31**, **1** was regenerated from the immobilised PS-Ph_3PO **7** *via* our previously described Ph_2SiH_2 mediated reduction,[13a] and was reutilised in our upcoming electrophile study.

Hence, as a summary, and by comparison with existing Wittig olefinations employing resin **1**, the established flow protocol afforded similar olefin-tethered scaffolds in near-quantitative conversions. Utilising K_2CO_3, a continuous solvent stream of 1:1 $CHCl_3$:EtOH, a flow rate of 0.50 mL min^{-1}, and a temperature of 60 °C, a broad series of alkene derivatives displaying various alkyl, aromatic, halide, and heteroaromatic functionalities, in addition to an indole scaffold, have each been accessed in a residence time of ≈2 minutes.

PS-PPh_3 Flow Protocol Assessment: Electrophile Scope Evaluation

Having benchmarked the efficacy of the flow Wittig protocol against existing synthetic methods that utilise resin **1** and solution-phase PPh_3, we then explored the formation and application of additional polymer-bound phosphonium salts. As stated previously, the available literature Wittig reports using **1** are limited mainly to unfunctionalised and undemanding primary alkyl bromides (e.g. benzyl bromide, ethyl bromide) for the initial phosphonium salt formation.[2e,f,15] Moreover, with the exception of the aforementioned monolithic PPh_3 protocols,[6b,c,11] these Wittig studies using **1** have not been performed under flow conditions. Hence, we decided to explore the flow-assisted reaction of **1** with an allyl and furanyl substituted primary bromide (Table 5, entries 1 and 2), in addition to the less commonly explored secondary alkyl chlorides, here incorporating diphenyl and ester groups (entries 3 and 4). Further, given the reported biological utilities of maleimide-based derivatives,[23] and that only *N*-protected maleimide structures had previously been examined under solid-phase conditions,[24] we also elected to investigate the reaction of **1** with maleimide (entry 5).

Administering our established conditions, all of the olefinations proceeded smoothly using **6** as the model aldehyde substrate, affording the olefin products **32**–**36** in high yields and purities (entries 1–5). In agreement with reports that use solution-phase PPh_3, the formation of *E* isomer was favoured for **32**, **35** and **36** under the flow method.[25] Notably, our specific approach for using the furanyl(triphenyl)phosphonium ylide on **6** to access styrylfuran **33** has not been previously reported. Further, an additional benefit over current batch methods is illustrated through the synthesis of trisubstituted triphenylethylene **34**, derived from the phosphonium salt obtained *via* the sterically hindered chlorodiphenylmethane (entry 3). To the best of our knowledge, this flow-based approach towards the traditional Wittig synthesis of **34** in high yield has not been earlier described using resin **1** or solution-phase PPh_3.

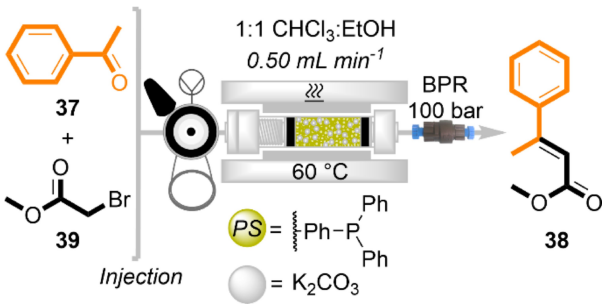


Scheme 4. Synthetic flow protocol to access the 2-substituted indole **31**. Treatment of PS-PPh_3 **1** (1 eq.) with 2-nitrobenzyl bromide **26** (2 eq.) afforded PS-(2-nitrobenzyl)triphenylphosphonium bromide **27**. Treatment of **27** (1 eq.) with excess sodium dithionite ($Na_2S_2O_4$) followed by HBr provided PS-(2-aminobenzyl) triphenylphosphonium bromide **28**. Amide formation between **28** (1 eq.) with ethyl 3-nitrobenzoate **29** (0.8 eq.) yielded the solid-supported PS-(2-(3-nitrobenzamido)benzyl)triphenylphosphonium bromide **30**. Subsequent K_2CO_3 promoted intramolecular Wittig cyclisation of **30** furnished 2-(3-nitrophenyl)-1*H*-indole **31**.

PS-PPh_3 Flow Protocol Assessment: Ketone Olefinations

In accordance with our aims, our final investigation focused on the polymer-supported olefination of ketones under flow conditions. Reports of resin **1** mediated olefinations on ketone structures are extremely limited owing to their reduced electrophilic nature, with only a handful of batch resin **1** studies currently disclosed.[2c,3b,15b] Furthermore, these few available reports predominantly utilise the unfunctionalised ylide methylene(triphenyl)phosphorane ($Ph_3P{=}CH_2$), offering little insight into the range of ylides amenable to ketone olefination using resin **1**.[2c,3b,15b] Therefore, it would be desirable to utilise ylides that incorporate other functionalities, such as esters, to provide opportunities for rapid derivatisation. Hence, using acetophenone **37** as the model ketone substrate, we proposed to access the target α,β-unsaturated ester **38** through the flow olefination of **37** with **1** and methyl bromoacetate **39** (Scheme 5).

Employing our previously defined conditions, only a trace amount (<5%) of the unsaturated ester product **38** was detected *via* HPLC analysis. Having anticipated the requirement for more forcing conditions, the olefination was thus reattempted with an increase in the column reaction temperature to 100 °C, affording a ≈25% conversion to **38**. Extending upon this result, the aforementioned reaction conditions were replicated, and the residence time of the reaction was doubled (1.96–3.92 min, flow rate = 0.25 mL min^{-1}), revealing a further

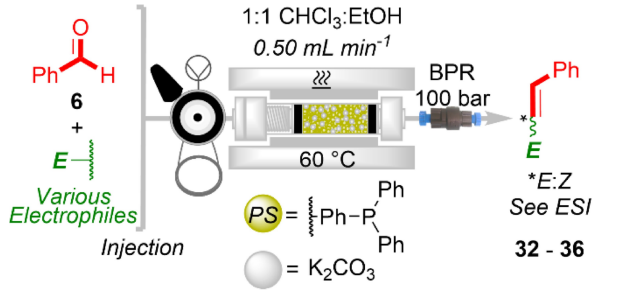


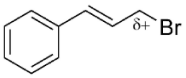
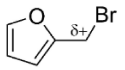
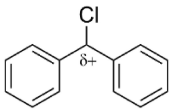
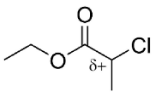
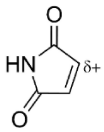
Scheme 5. Proposed flow olefination of acetophenone **37** using PS-PPh_3 **1** and methyl bromoacetate **39** to access the α,β-unsaturated ester **38**.

increase in **38** conversion to ≈50%. In a subsequent attempt to promote complete consumption of **37**, the reaction was again repeated using the adjusted parameters, and the reaction solution was allowed to recirculate through the reaction column for a total of two cycles. Gratifyingly, HPLC analysis of the reaction solution revealed the near quantitative conversion (> 99%) of **37** to **38**.

With our previous result in hand, and to further assess the scope of the amended protocol, a small selection of additional ketones was investigated. Here, a further five ketones substituted with phenyl, methyl, benzyl, pyridyl, cyclopentyl, and camphor scaffolds were assessed (Table 6, entries 1–6). Of these, product esters **38**, **40**, and **41** (entries 1–3) have been previously accessed using solution-phase PPh_3 with **39**,[26] while the Wittig

Table 5. Continuous flow, *in situ* PS-PPh_3 mediated Wittig olefination of benzaldehyde **6** with a series of electrophiles. Reagents and conditions: reaction column containing PS-PPh_3 **1** (1 eq.) and K_2CO_3 (2 eq.); injection solution containing electrophile [0.23 M] (2 eq.) and benzaldehyde **6** [0.09 M] (0.8 eq.) in 1:1 $CHCl_3$:EtOH at 60 °C. Flow rate = 0.50 mL min^{-1}, residence time = 1.96 min.



Entry	Compound	Electrophile (E)	Conversion [%][a]	Yield [%][b]
1	32		> 99	97 (87)
2	33		> 99	93 (ND)
3	34		> 99	89 (ND)
4	35		> 99	94 (99)
5	36		> 99	94 (75)

[a] Percent conversion (%) determined *via* HPLC analysis at 254 nm. [b] Product yields (%) reported are isolated yields following silica gel filtration. Yields in (parentheses) refer to reported literature yields. ND = No Data.

syntheses of **42** and **43** (entries 3–6) have only been reported under Horner-Emmons conditions.[27] Further, the proposed olefination to access camphor methyl ester **44** has not been prior described using traditional Wittig or Horner-Emmons methods.

Across the examined series of unsaturated ester products **38**, **40**–**43** (entries 1–5), high yields and purities were generally observed. Specifically, in comparison to the moderate yields previously reported using solution-phase PPh_3 for accessing esters **38** (35%),[26c] **40** (62%),[26b] and **41** (45%),[26a] the flow protocol employing resin **1** afforded individual yields of greater than 85% for all products. Esters **42** and **43** were also accessed in high yields (> 85%) and purities (> 94%) *via* **1**, with pyridyl-substituted ester **42** obtained in 94% yield, exceeding the previously reported 81% associated with the Horner-Emmons synthesis (entry 4).[27] A strict preference for the *E* isomers of **38** and **42** was identified using the stabilised ylide derived from **1** and **39** (entries 1 and 4), in agreement with a former report which detailed the synthesis of **38** through the employment of solution-phase PPh_3.[27]

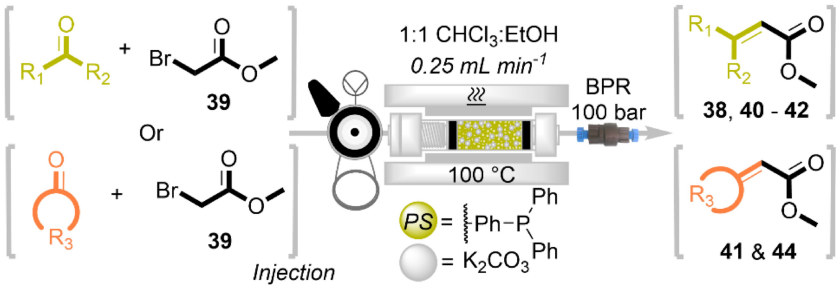
Unfortunately, although the Wittig olefination proceeded quantitatively with the cyclic ketone cyclopentanone (entry 3), no olefin product was detected with the more sterically demanding camphor (entry 6). Consequently, this result indicates that both the steric nature and electrophilicity of the ketone influence its amenability towards Wittig olefinations using resin **1**.[3a] On the other hand, and to the best of our knowledge, this preliminary investigation details the first continuous flow, polymer-supported olefination of ketones employing a stabilised ylide in distinctly high yields and purities.

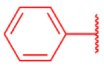
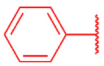
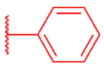
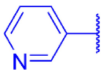
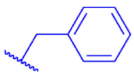
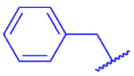
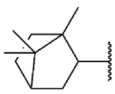
Conclusion

Through an extensive screening process entailing commonly utilised solvents and bases, in concert with residence time and temperature evaluations, a single injection and *in situ* flow processing procedure to effect the PS-PPh_3 mediated Wittig olefination was derived. Benchmarking of the developed flow protocol revealed near-quantitative substrate conversions, affording numerous olefin products in high yields and purities from a diverse range of substituted aldehydes, in addition to the construction of a heterocyclic scaffold. In comparison to previous studies that utilise PPh_3 immobilised supports, prolonged reaction and handling periods were not required. Moreover, the protocol remained viable across multiple heteroatom-containing functionalities.

Further, an expansion of the currently limited PS-PPh_3 Wittig substrate scope to more elaborate primary and secondary alkyl halides incorporating various functional groups was achieved. From these investigations, a series of di and tri-substituted olefins were accessed in generous yields and purities, with scaffolds such as triphenylethylene **34** not previously obtained *via* the classical Wittig reaction. Finally, ketone functionalities, which have frequently demonstrated resistance to PPh_3 mediated olefinations, were successfully implemented within the flow protocol. For the first time, the Wittig reaction of ketone moieties employing a generated PS-PPh_3 stabilised ylide produced an assortment of α,β-unsaturated esters in substantial yields and purities under the adapted flow conditions. Additional olefination studies conducted from elaborate halogen and carbonyl-based building blocks are currently in progress within our laboratories, with an emphasis on the design of advanced and highly decorated olefin-tethered derivative libraries.

Table 6. Continuous flow, *in situ* PS-PPh_3 mediated Wittig olefination on a series of ketones. Reagents and conditions: reaction column containing PS-PPh_3 **1** (1 eq.) and K_2CO_3 (2 eq.); injection solution containing methyl bromoacetate **39** [0.23 M] (2 eq.) and ketone [0.09 M] (0.8 eq.) in 1:1 $CHCl_3$:EtOH at 100 °C. Flow rate = 0.25 mL min^{-1}, residence time = 3.92 min, two reaction cycles.



Entry	Compound	R_1	R_2	R_3	Conversion [%][a]	Yield [%][b]
1	38				>99	90 (35)
2	40				97	86 (62)
3[c]	41				>99	88 (45)
4	42				>99	94 (81)
5	43				95	85 (100)
6	44				0	N/A

[a] Percent conversion (%) determined *via* HPLC analysis at 254 nm. [b] Product yields (%) reported are isolated yields following silica gel filtration. Yields in (parentheses) refer to reported literature yields. [c] Percent conversions (%) based on the consumption of the starting material ketone, as deduced *via* dinitrophenylhydrazine (DNP) staining. Compounds in red (**38**, **40**, **41**) have been previously synthesised using solution-phase PPh_3. Compounds in blue (**42**, **43**) have been previously synthesised using the Horner-Emmons reaction. Compound **44** has not been synthesised *via* a Wittig reaction using PS-PPh_3 **1**, solution-phase PPh_3, or Horner-Emmons reagents.

Experimental Section

General Information

General Experimental

All reactants and reagents were purchased from Sigma-Aldrich and were utilised without further purification. Polymer-supported triphenylphosphine (PS-PPh_3, 1% cross-linked poly (styrene-co-divinylbenzene), loading = 2.35 mmol/g) was purchased from Biotage and stored around 4 °C. All anhydrous solvents were purchased from Chem-Supply and were distilled under reduced pressure before use, with chromatography grade solvents utilised for silica gel filtration procedures. Deuterated solvents were purchased from Cambridge Isotope Laboratories and stored in a desiccator.

All ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 'Avance' AMX 400 MHz spectrometer. All obtained spectra were recorded in the stated deuterated solvents at 25 °C. Chemical shifts (δ) are represented in parts per million (ppm) and are referenced to $CDCl_3$ (^1H = 7.26 ppm and ^{13}C = 77.16 ppm) or DMSO-d_6 (^1H = 2.50 ppm and ^{13}C = 39.52 ppm) as indicated. All coupling constants (*J*) are expressed in hertz (Hz). Multiplicities are indicated as singlet (s), doublet (d), doublet of doublets (dd), doublet of triplets (dt), doublet of doublet of doublets (ddd), doublet of quartets (dq), triplet (t), pentet (p) and multiplet (m). Spectral data, including chemical shifts, multiplicities, coupling constants, and integrations, were calculated and processed using Mestrelab Research's "MestReNova" V11.0 NMR analysis software. All ^1H spectral peaks are characterised and represented according to the following convention: chemical shift, multiplicity, coupling constant, integration, proton assignment, and *isomer identification*: δ = 7.52 (d, *J* = 7.4, 1H, Ar–H2/H6, *E-isomer*). Aromatic protons (Ar–H1/H2') are assigned per the atom numbers illustrated on each compound, with the remaining proton assignments self-indicated, e.g. CH_3. To clearly represent the obtained *E:Z* stereoisomer ratios, all ^1H NMR integrations were reported as calculated.

All high-performance liquid chromatography (HPLC) applications were performed on an Agilent Technologies '1260 Infinity Series' LC fitted with a diode-array detector (DAD). All samples were prepared at a concentration of 1.00 mg/mL, with a 1.50 or 3.00 μL injection utilised for analyses. Solvent A consisted of 0.06% trifluoroacetic acid (TFA) as a modifier in H_2O, and solvent B consisted of 0.06% TFA in CH_3CN:H_2O (90:10). Analytical conditions consisted of a 1.00 mL min^{-1} flow rate, 30–100% gradient increase of solvent B over 15 minutes, curve = 6, with UV detection at 214 and 254 nm. Analytical RP-HPLC was performed using a Phenomenex® Onyx Monolithic C18 (100 × 4.6 mm) analytical column.

Continuous Flow System

A continuous stream of solvent was pumped through an attached in-line glass reaction column (Omnifit®, L × I.D. = 100 mm × 10 mm, bed volume = 5.6 mL, adjustable ends) containing polymer-supported triphenylphosphine (PS-PPh_3) and base (K_2CO_3) using a HPLC pump (Waters 600 Controller). The reaction column was heated and its temperature maintained using a heating block (FRX Volcano). A sample injector (Rheodyne®) fitted with a 2 mL injection loop was attached in-line for direct sample injection to the reaction column. The injected sample solution was pumped through the heated reaction coil before traversing through the reaction column. Collection of the resulting eluent, followed by silica gel filtration and concentration *in vacuo*, afforded the pure olefin products as detailed within the characterisation data.

General and Experimental Procedures

General Procedure A: Flow-Assisted Alkylation of PS-PPh_3

To a pre-assembled reaction column was added PS-PPh_3 resin **1** (0.100 g, 0.235 mmol, loading = 2.35 mmol/g, 1 eq.), and the column was placed in-line under a continuous stream of anhydrous $CHCl_3$. Following resin swelling, which was effected at a flow rate of 0.50 mL min^{-1} with a column temperature of 60 °C, the Rheodyne® injection loop was loaded with a 2.00 mL solution consisting of benzyl bromide **14** (0.080 g, v = 0.055 mL, 0.470 mmol, 0.23 M, 2 eq.) in $CHCl_3$ (1.945 mL). The solution was then injected into the continuous solvent stream through the resin bed (0.50 mL min^{-1}, 60 °C). After this period, the reaction column was flushed with additional $CHCl_3$ at a flow rate of 2.00 mL min^{-1} for 15 minutes, and the resulting alkylated resin was collected and dried *in vacuo* for 16 hours. The desired PS-benzyltriphenylphosphonium bromide resin **13** was obtained in 97% yield (0.136 g), as deduced by the mass increase of the resin.

General Procedure B: Flow-Assisted Base Optimisation for Wittig Olefination

To a pre-assembled reaction column was added resin **13** (0.136 g, 0.228 mmol, 1 eq.), base (0.456 mmol, 2 eq.) and anhydrous $CHCl_3$ (1.00 mL), and the resin was allowed to swell for 10 minutes. Following this initial period of resin swelling and ylide generation, the column was placed in-line under a continuous stream of anhydrous $CHCl_3$ at a flow rate of 0.50 mL min^{-1} with a column temperature of 60 °C. To the Rheodyne® injection loop was loaded a 2.00 mL solution consisting of benzaldehyde **6** (0.019 g, v = 0.019 mL, 0.188 mmol, 0.09 M, 0.8 eq.) in $CHCl_3$ (1.981 mL), and the solution injected into the continuous solvent stream through the resin bed (0.50 mL min^{-1}, 60 °C). Analysis of the resulting column eluent *via* HPLC revealed a varying 5–72% conversion (NaOH–K_2CO_3) of **6** to stilbene **2**.

General Procedure C: Flow-Assisted Solvent Optimisation for Wittig Olefination

To a pre-assembled reaction column was added resin **13** (0.136 g, 0.228 mmol, 1 eq.), K_2CO_3 (0.063 g, 0.456 mmol, 2 eq.) and anhydrous 1:1 $CHCl_3$:EtOH (1.00 mL), and the resin was allowed to swell for 10 minutes. Following this initial period of resin swelling and ylide generation, the column was placed in-line under a continuous stream of anhydrous 1:1 $CHCl_3$:EtOH at a flow rate of 0.50 mL min^{-1} with a column temperature of 60 °C. To the Rheodyne® injection loop was loaded a 2.00 mL solution consisting of benzaldehyde **6** (0.019 g, v = 0.019 mL, 0.188 mmol, 0.09 M, 0.8 eq.) in 1:1 $CHCl_3$:EtOH (1.981 mL), and the solution injected into the continuous solvent stream through the resin bed (0.50 mL min^{-1}, 60 °C). Analysis of the resulting column eluent *via* HPLC revealed a near-quantitative (99%) conversion of **6** to stilbene **2**.

General Procedure D: Flow-Assisted In Situ *PS-Wittig Reaction (Aldehyde)*

To a pre-assembled reaction column was added PS-PPh_3 resin **1** (0.100 g, 0.235 mmol, loading = 2.35 mmol/g, 1 eq.) and K_2CO_3 (0.065 g, 0.470 mmol, 2 eq.), and the column was placed in-line under a continuous stream of anhydrous 1:1 $CHCl_3$:EtOH. Following resin swelling, which was effected at a flow rate of 0.50 mL min^{-1} with a column temperature of 60 °C, the Rheodyne® injection loop was loaded with a 2.00 mL solution consisting of benzyl bromide **14** (0.080 g, v = 0.055 mL, 0.470 mmol, 0.23 M, 2 eq.) and aldehyde (0.188 mmol, 0.09 M, 0.8 eq.) in 1:1 $CHCl_3$:EtOH. The solution was then injected into the continuous solvent stream through the resin bed (0.50 mL min^{-1}, 60 °C). Collection of the resulting column eluent, followed by silica gel filtration and concentration *in vacuo*, afforded the desired olefin products as described within the characterisation details.

Procedure E: Synthesis of PS-(2-nitrobenzyl) triphenylphosphonium Bromide

Synthesised according to 'General Procedure A' using a 2.00 mL solution consisting of 2-nitrobenzyl bromide **26** (0.101 g, 0.470 mmol, 0.23 M, 2 eq.) in $CHCl_3$ (2.00 mL). PS-(2-nitrobenzyl) triphenylphosphonium bromide resin **27** was obtained in 95% yield (0.143 g), as deduced by the mass increase of the resin.

Procedure F: Synthesis of PS-(2-aminobenzyl) triphenylphosphonium Bromide

Following literature precedence,[22] to a 50 mL two-neck round bottom flask was added resin **27** (0.143 g, 0.223 mmol, 1 eq.) in EtOH (15 mL), and the reaction was heated to reflux for 20 minutes. Following this period, a solution of sodium dithionite (0.194 g, 1.115 mmol, 5 eq.) in H_2O (10 mL) was added dropwise to the refluxing mixture over 30 minutes and heating was continued for a further 90 minutes. After this time, a sample of polymer was taken from the reaction mixture, and treatment with dilute NaOH in MeOH (0.1 M, 1 mL) provided a negative nitro-ylide result (no dark coloration of the resin was observed). Following filtration of the reaction mixture, the resin was washed successively with H_2O (2 × 10 mL), EtOH (2 × 10 mL), and Et_2O (2 × 10 mL), and the resin was resuspended in a 1:1 Dioxane:MeOH solvent system (20 mL). To the suspended reaction mixture was added 48% HBr (aq) (10 mL) dropwise and the reaction was left to stir for 6 hours. The reaction mixture was then filtered and the resin was washed with dioxane (2 × 5 mL), MeOH (2 × 5 mL), and Et_2O (2 × 5 mL). Upon drying of the resin *in vacuo* for 16 hours, the desired PS-(2-aminobenzyl)triphenylphosphonium bromide resin **28** was obtained in quantitative yield (0.136 g), as deduced by the mass decrease of the resin.

*Procedure G: Synthesis of 2-(3-nitrophenyl)-1*H*-indole*

To a pre-assembled reaction column was added resin **28** (0.136 g, 0.223 mmol, 1 eq.) and K_2CO_3 (0.062 g, 0.446 mmol, 2 eq.), and the column was placed in-line under a continuous stream of anhydrous 1:1 $CHCl_3$:EtOH. Following resin swelling,

which was effected at a flow rate of 0.50 mL min^{-1} with a column temperature of 60 °C, the Rheodyne® injection loop was loaded with a 2.00 mL solution consisting of ethyl 3-nitrobenzoate **29** (0.035 g, 0.178 mmol, 0.09 M, 0.8 eq.) in 1:1 $CHCl_3$:EtOH (2.00 mL). The solution was then injected into the continuous solvent stream through the resin bed (0.50 mL min^{-1}, 60 °C). Collection of the resulting column eluent and silica gel filtration (1:9 EtOAc:Hexanes), followed by concentration *in vacuo*, afforded 2-(3-nitrophenyl)-1*H*-indole **31** in 95% yield.

General Procedure H: Flow-Assisted In Situ *PS-Wittig Reaction (Electrophile Scope)*

To a pre-assembled reaction column was added PS-PPh_3 resin **1** (0.100 g, 0.235 mmol, loading = 2.35 mmol/g, 1 eq.) and K_2CO_3 (0.065 g, 0.470 mmol, 2 eq.), and the column was placed in-line under a continuous stream of anhydrous 1:1 $CHCl_3$:EtOH. Following resin swelling, which was effected at a flow rate of 0.50 mL min^{-1} with a column temperature of 60 °C, the Rheodyne® injection loop was loaded with a 2.00 mL solution consisting of benzaldehyde **6** (0.019 g, v = 0.019 mL, 0.188 mmol, 0.09 M, 0.8 eq.) and the relevant alkyl halide/maleimide (0.470 mmol, 0.23 M, 2 eq.) in 1:1 $CHCl_3$:EtOH. The solution was then injected into the continuous solvent stream through the resin bed (0.50 mL min^{-1}, 60 °C). Collection of the resulting column eluent, followed by silica gel filtration and concentration *in vacuo*, afforded the desired olefin products as described within the characterisation details.

General Procedure I: Flow-Assisted In Situ *PS-Wittig Reaction (Ketone)*

To a pre-assembled reaction column was added PS-PPh_3 resin **1** (0.100 g, 0.235 mmol, loading = 2.35 mmol/g, 1 eq.) and K_2CO_3 (0.065 g, 0.470 mmol, 2 eq.), and the column was placed in-line under a continuous stream of anhydrous 1:1 $CHCl_3$:EtOH. Following resin swelling, which was effected at a flow rate of 0.25 mL min^{-1} with a column temperature of 100 °C, the Rheodyne® injection loop was loaded with a 2.00 mL solution consisting of methyl bromoacetate **39** (0.072 g, v = 0.044 mL, 0.470 mmol, 0.23 M, 2 eq.) and ketone (0.188 mmol, 0.09 M, 0.8 eq.) in 1:1 $CHCl_3$:EtOH. The reaction solution was then injected into the continuous solvent stream through the resin bed (0.25 mL min^{-1}, 100 °C) for two reaction cycles. Collection of the resulting column eluent, followed by silica gel filtration and concentration *in vacuo*, afforded the desired olefin products as described within the characterisation details.

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Conflict of Interest

The authors declare no conflict of interest.

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[1] F. Camps, J. Castells, J. Font, F. Vela, *Tetrahedron Lett.* **1971**, *12*, 1715–1716.
[2] a) .A. Akelah, *Eur. Polym. J.* **1982**, *18*, 559–561; b) .M. Bernard, W. T. Ford, E. C. Nelson, *J. Org. Chem.* **1983**, *48*, 3164–3168; c) .M. Bolli, S. Ley, *J. Chem. Soc. Perkin Trans. 1* **1998**, *15*, 2243–2246; d) .D. Castro, L. Boiani, D. Benitez, P. Hernandez, A. Merlino, C. Gil, C. Olea-Azar, M. Gonzalez, H. Cerecetto, W. Porcal, *Eur. J. Med. Chem.* **2009**, *44*, 5055–5065; e) .S. D. Clarke, C. R. Harrison, P. Hodge, *Tetrahedron Lett.* **1980**, *21*, 1375–1378; f) .W. C. Shearouse, J. Mack, *Green Chem.* **2012**, *14*, 2771–2775; g) .R. I. Storer, T. Takemoto, P. S. Jackson, D. S. Brown, I. R. Baxendale, S. V. Ley, *Chem. Eur. J.* **2004**, *10*, 2529–2547; h) G. L. Thomas, C. Böhner, M. Ladlow, D. R. Spring, *Tetrahedron* **2005**, *61*, 12153–12159; i) J. Westman, *Org. Lett.* **2001**, *3*, 3745–3747.
[3] a) .W. T. Ford in *Polymeric Reagents and Catalysts*, (Ed.: W. T. Ford)ACS Symposium Series; American Chemical Society, Washington, **1986**, pp. 155–185; b) M. Bernard, W. T. Ford, *J. Org. Chem.* **1983**, *48*, 326–332; c) L. Szabó, P. Tétényi Jr, *React. Polym. Ion Exch. Sorbents* **1988**, *8*, 193–199.
[4] a) .Z. Moussa, Z. M. A. Judeh, S. A. Ahmed, *RSC Adv.* **2019**, *9*, 35217–35272; b) .P. H. Toy, *Pure Appl. Chem.* **2014**, *86*, 1651–1661.
[5] a) J. W. Labadie, *Curr. Opin. Chem. Biol.* **1998**, *2*, 346–352; b) .S. V. Ley, I. R. Baxendale, R. N. Bream, P. S. Jackson, A. G. Leach, D. A. Longbottom, M. Nesi, J. S. Scott, R. I. Storer, S. J. Taylor, *J. Chem. Soc. Perkin Trans. 1* **2000**, *23*, 3815–4195; c) L. Rokhum, G. Bez, *Curr. Org. Chem.* **2019**, *23*, 643–678.
[6] a) .P. Hodge, *Ind. Eng. Chem. Res.* **2005**, *44*, 8542–8553; b) .K. A. Roper, M. B. Berry, S. V. Ley, *Beilstein J. Org. Chem.* **2013**, *9*, 1781–1790; c) .K. A. Roper, H. Lange, A. Polyzos, M. B. Berry, I. R. Baxendale, S. V. Ley, *Beilstein J. Org. Chem.* **2011**, *7*, 1648–1655.
[7] L. K. Spare, M. Menti, D. G. Harman, J. R. Aldrich-Wright, C. P. Gordon, *React. Chem. Eng.* **2019**, *4*, 1309–1317.
[8] C. Dankers, J. Tadros, D. G. Harman, J. R. Aldrich-Wright, T. V. Nguyen, C. P. Gordon, *ACS Comb. Sci.* **2020**, *22*, 255–267.
[9] a) .D. C. Sherrington, *Chem. Commun.* **1998**, *21*, 2275–2286; b) .U. Kunz, A. Kirschning, H. L. Wen, W. Solodenko, R. Cecilia, C. O. Kappe, T. Turek, *Catal. Today* **2005**, *105*, 318–324; c) F. Svec, J. M. J. Fréchet, *Science* **1996**, *273*, 205–211.
[10] E. C. Peters, F. Svec, J. M. J. Fréchet, *Adv. Mater.* **1999**, *11*, 1169–1181.
[11] S. Newton, C. Carter, C. Pearson, L. Alves, H. Lange, P. Thansandote, S. Ley, *Angew. Chem. Int. Ed.* **2014**, *53*, 4915–4920; *Angew. Chem.* **2014**, *126*, 5015–5020.
[12] N. B. Desai, N. McKelvie, F. Ramirez, *J. Am. Chem. Soc.* **1962**, *84*, 1745–1747.
[13] a) .U. P. Tran, K. J. Hock, C. P. Gordon, R. M. Koenigs, T. V. Nguyen, *Chem. Commun.* **2017**, *53*, 4950–4953; b) .S. L. Regen, D. P. Lee, *J. Org. Chem.* **1975**, *40*, 1669–1670; c) .R. Caputo, C. Ferreri, G. Palumbo, *Synth. Commun.* **1987**, *17*, 1629–1636; d) .R. Caputo, E. Corrado, C. Ferreri, G. Palumbo, *Synth. Commun.* **1986**, *16*, 1081–1087.
[14] X. Xia, P. H. Toy, *Synlett* **2015**, *26*, 1737–1743.
[15] a) .W. Heitz, R. Michels, *Angew. Chem. Int. Ed.* **1972**, *11*, 298–299; *Angew. Chem.* **1972**, *84*, 296–297; b) .S. V. McKinley, J. W. Rakshys, *J. Chem. Soc. Chem. Commun.* **1972**, *3*, 134–135; c) .K. L. Denlinger, L. Ortiz-Trankina, P. Carr, K. Benson, D. C. Waddell, J. Mack, *Beilstein J. Org. Chem.* **2018**, *14*, 688–696.
[16] E. Bayer, *Angew. Chem. Int. Ed.* **1991**, *103*, 30, 113–129.
[17] P. Hodge, J. Waterhouse, *Polymer* **1981**, *22*, 1153–1154.
[18] a) .T. Matsushima, S. Kobayashi, S. Watanabe, *J. Org. Chem.* **2016**, *81*, 7799–7806; b) .D. W. Allen, *Zeitschrift für Naturforschung B* **1980**, *35*, 1455–1458; c) .M. Fukazawa, F. Takahashi, K. Nogi, T. Sasamori, H. Yorimitsu, *Org. Lett.* **2020**, *22*, 2303–2307; d) .J.-F. Poon, J. P. Alao, P. Sunnerhagen, P. Dinér, *Org. Biomol. Chem.* **2013**, *11*, 4526–4536; e) F.-L. Hu, S.-L. Wang, B. F. Abrahams, J.-P. Lang, *CrystEngComm.* **2015**, *17*, 4903–4911.
[19] B. Schmidt, N. Elizarov, N. Riemer, F. Hölter, *Eur. J. Org. Chem.* **2015**, *2015*, 5826–5841.
[20] a) .S. Suzen, *Curr. Org. Chem.* **2017**, *21*, 2068–2076; b) .M.-Z. Zhang, Q. Chen, G.-F. Yang, *Eur. J. Med. Chem.* **2015**, *89*, 421–441.
[21] I. Hughes, *Tetrahedron Lett.* **1996**, *37*, 7595–7598.
[22] I. Hughes, Smithkline Beecham Plc, UK . WO9618592 A1 **1996**.

[23] a) .N. Salewska, J. Boros-Majewska, I. Łącka, K. Chylińska, M. Sabisz, S. Milewski, M. J. Milewska, *J. Enzym. Inhib. Med. Chem.* **2012**, *27*, 117–124; b) .M. Hanif, A. A. Nazarov, A. Legin, M. Groessl, V. B. Arion, M. A. Jakupec, Y. O. Tsybin, P. J. Dyson, B. K. Keppler, C. G. Hartinger, *Chem. Commun.* **2012**, *48*, 1475–1477.
[24] M. Bayat, S. R. Hosseini, E. Asmari, *Phosphorus Sulfur Silicon Relat. Elem.* **2017**, *192*, 98–102.
[25] a) M. H. Kunzmann, N. C. Bach, B. Bauer, S. A. Sieber, *Chem. Sci.* **2014**, *5*, 1158–1167; b) W.-L. Yang, Y.-Z. Liu, S. Luo, X. Yu, J. S. Fossey, W.-P. J. C. C. Deng, *Chem. Commun.* **2015**, *51*, 9212–9215; c) .Z. Wang, J. G. Verkade, *Heteroat. Chem.* **1998**, *9*, 687–689.
[26] a) R. Brown, N. Browne, K. Coulston, F. Eastwood, M. Irvine, A. Pullin, U. Wiersum, *Aust. J. Chem.* **1989**, *42*, 1321–1344; b) D. Konrádová, H. Kozubíková, K. Doležal, J. Pospíšil, *Eur. J. Org. Chem.* **2017**, *2017*, 5204–5213; c) M. Wijtmans, D. Maussang, F. Sirci, D. J. Scholten, M. Canals, A. Mujić-Delić, M. Chong, K. L. S. Chatalic, H. Custers, E. Janssen, C. de Graaf, M. J. Smit, I. J. P. de Esch, R. Leurs, *Eur. J. Med. Chem.* **2012**, *51*, 184–192.
[27] a) L. Chu, A. Ogawa, H. O. Ok, F. Ujjainwalla, Merck Sharp & Dohme Corp., USA . WO2010051245 A1 **2010**; b) P. A. Jacobi, L. M. Armacost, H. L. Brielmann, R. O. Cann, J. I. Kravitz, M. J. Martinelli, *J. Org. Chem.* **1994**, *59*, 5292–5304.

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