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A simple solid phase diversity linker strategy using enol phosphonates†

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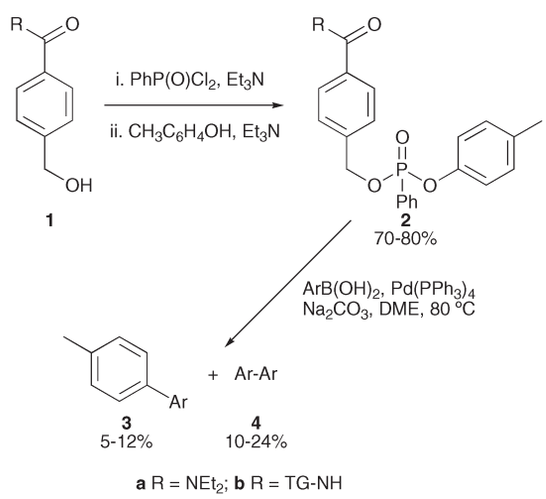
Polymer bound lactam enol phosphonates can be easily generated using simple phenol on polystyrene resin. These stable, storable compounds can be released in a diversity cleavage strategy, using Suzuki cross coupling conditions, to provide 2-arylenamides in moderate to good overall yields.

Owing to the developments stimulated by combinatorial (medicinal) chemistry, solid phase organic synthesis (SPOS) now has an accepted place in the armoury of the synthetic and medicinal chemist.[1] A key component of a SPOS procedure is the linker unit which must be stable under the reaction conditions and also provide a mild method for the release of the desired product at the end of the synthesis. Traditionally, SPOS linkers resemble protecting groups with the product to linker connection being, most commonly, an ester or amide.[2] Drawbacks to this approach exist in that, following cleavage, the target library structure contains a common auxiliary polar functionality which can adversely affect the functional (pharmacological) profile and that the process of attachment and cleavage represent non-productive chemical steps. To address the first of these issues 'traceless' linkers, in which cleavage produces a hydrogen atom at the site of resin attachment, have been developed.[3–5] An enhanced version of the 'traceless' approach is to use the linker as a means to introduce additional diversity into the product library. In these cases the additional steps are compensated by increased product complexity in the library. One particularly attractive approach to generate diversity in the cleavage step is to use transition metal mediated cross coupling strategies.[6] In this, both the nucleophilic (organometallic)[4] and electrophilic components[5] have been polymer supported with the latter generally providing greater scope for substrate stability during the reaction sequence. Despite this, relatively few electrophilic tethers have been reported.

Enol phosphates have long been known to be effective cross coupling partners for organocopper reagents[7] and, more recently, in various palladium or nickel catalysed strategies.[8,9,10] Importantly these are reported to exhibit higher stability than many other enol derivatives but have not been used in the context of a solid phase synthetic strategy. Recognising that enhanced stability of the linker and a reduction in the potential for competing reactions would be achieved by replacement of the spectator P(OR) units in a phosphate linker with alkyl or aryl substituents we opted to explore the use of alternative phosphorus ester derived activating groups, *i.e.* phosphinites and phosphonates. In this communication we report our preliminary results that demonstrate that simple effective diversity cleavage strategies are feasible with readily accessible phosphonate based linker groups.[11]

Initial studies commenced with benzyl alcohol **1a** as a simple solution phase model of a hydroxyl functionalised resin. Reaction with 1.25 equivalents of phenylphosphonic dichloride (PPDC; $PhP(O)Cl_2$) in the presence of Et_3N gave a mixture of mono and bis phospho-esters. Without purification, the mono substituted product was directly combined with *p*-cresol to afford the desired phenyl phosphonate **2a** in an overall yield of 70–80%, Scheme 1. In a similar fashion *p*-cresol could be loaded onto Tentagel® resin using 4-hydroxymethylbenzoic acid as a simple spacer group. Although both systems underwent the desired Suzuki cross coupling reaction [$Pd(PPh_3)_4$, Na_2CO_3, DME, 80 °C] this was accompanied by significant amounts of the biaryl **4** derived from homo coupling of the boronic acid. Attempts to circumvent this problem through screening of alternative catalysts (metal sources and ligands), bases and solvents were not successful with the homo-coupling pathway always occurring more readily. Suspecting that the low reactivity of the Ar–OP bond to oxidative addition towards the metal centre was contributing to this problem we explored alternative substrates.



Scheme 1

In contrast to the low reactivity of aryl phosphates, vinyl phosphates have been reported as being viable substrates for various cross coupling reactions although other phosphorus activating groups have not been explored. In particular, Nicolaou and Coudert have demonstrated the potential of lactam enol phosphates in both the Stille and Suzuki reactions.[8,9] Consequently, following these precedents, *N*-Boc caprolactam **5** was treated with LDA and TMEDA to generate the corresponding enolate and then combined with the model support **1a** to afford phosphonate **6** in modest yield. Although acid labile, decomposing in chloroform overnight, **6** underwent efficient cross coupling reactions, Scheme 2. In the hope that immobilisation on a polymer support would provide enhanced stability we then explored the preparation of the analogous supported phosphonates. However, analysis of the resins by ^{31}P NMR showed no evidence for the presence of the phosphonate. Suspecting that this instability was due to the benzylic nature of the linkage, preparation of the alkyl derivative **9** was attempted albeit with no success.

During these solution phase studies it had proved possible to prepare the bis enol phosphonate **10**. Surprisingly, this proved

† Electronic supplementary information (ESI) available: characterisation data for Suzuki products **15** from diversity cleavage of resin **14**. See http://www.rsc.org/suppdata/ob/b4/b411111g/

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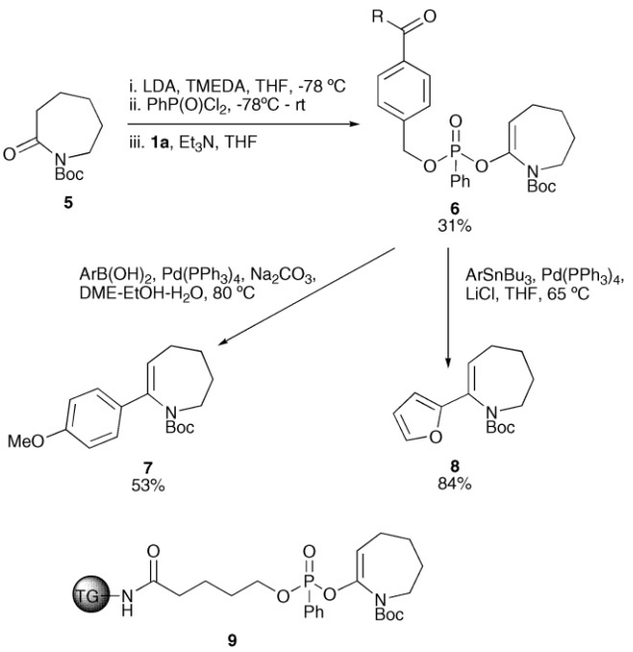
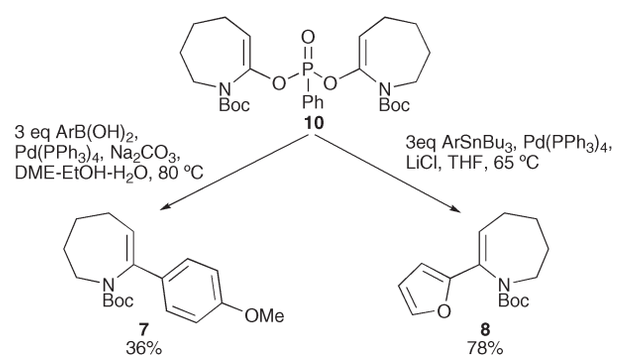


Scheme 2

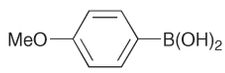
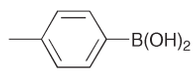
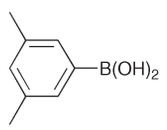
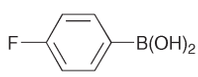
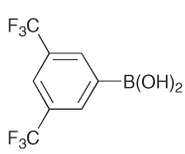
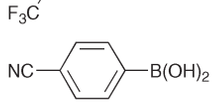
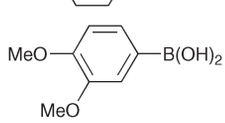
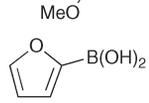
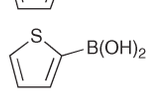
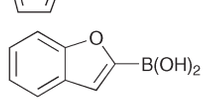
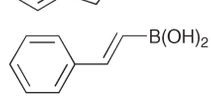
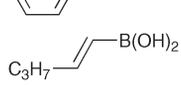
to be considerably more stable than the benzylic derivative **6**. Moreover, preliminary studies reveal this to be a viable substrate for cross coupling reactions – providing an atom economical method for activation of two equivalents of an enol with a single equivalent of the phosphorus reagent, Scheme 3.



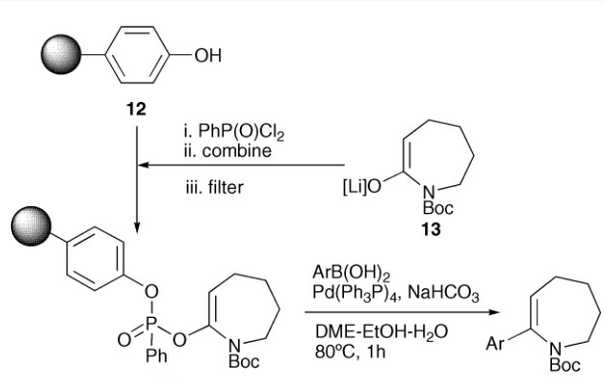
Scheme 3

These results and the earlier work using phenyl phosphates suggested that an sp^2C–O–P linkage would be stable and attention turned to the use of a phenolic linker unit. Initial attempts to sequentially treat polystyrene bound phenol resin **12** with PPDC and the lactam enolate **13** failed to produce a resin exhibiting a significant response in the ^{31}P NMR spectrum. However, simply reversing the order of addition, combining the enolate with PPDC at −78 °C and then transferring this solution to a slurry of the resin in THF afforded the desired immobilised enolate, Scheme 4. Analysis by ^{31}P NMR spectra revealed a major broad peak at $\delta = 12$ for the desired enol phosphonate **14** accompanied by a minor component corresponding to a cross-linked bis phenyl phosphonate at $\delta = 16$. Importantly, this resin is stable, giving identical analysis and performance in cross coupling reactions (*vide infra*) even after storage for several months. Treatment of the resin with a range of boronic acids under the standard Suzuki reaction conditions afforded the desired 2-substituted enamides **15** in modest to good yields, Table 1.[12] The quoted yields refer to the overall process of resin activation, loading and cross coupling cleavage. Whilst the 2-aryl and styryl products derived from caprolactam are stable compounds attempts to isolate the vinyl derivative derived from pent-1-enylboronic acid failed (entry xii). Similarly the more electron rich aryl derivatives hydrolyse in mild acidic conditions ($CDCl_3$) to afford the corresponding keto amine and this may

Table 1 Suzuki reaction results

Entry	$ArB(OH)_2$	Yield[a]
i		49%
ii		46%
iii		57%
iv		53%
v		48%
vi		35%
vii		32%
viii		72%
ix		42%
x		21%
xi		34%
xii		0%

[a] Yield of purified, isolated product based on initial resin **12** used.



Scheme 4

account for some of the lower yields for these derivatives under these standard reaction conditions.

In summary, we have demonstrated that resin bound phosphonates can provide a simple catch-and-release strategy for lactam enolates. These supported enolates are amenable to prolonged storage and can be employed in a diversity cleavage strategy in solid phase synthesis. Applications of this new methodology and studies to further enhance the use of phosphorus based linkers to permit the use of aryl substrates are in progress and results will be reported in due course.

Experimental

Enol phosphonate resin 14

To a cold (−78 °C) solution of lactam **5** (14 mmol, 4 eq) and TMEDA (16.8 mmol, 4.8 eq) in dry THF (50 ml) was added a solution of LDA (16.8 mmol, 4.8 eq). This mixture was stirred at −78 °C for 40 minutes and phenylphosphonic dichloride (12.6 mmol, 3.6 eq) was added dropwise. The reaction mixture was stirred for 0.5 h at −78 °C and then at room temperature for 1 h. It was then transferred *via* a cannula into a suspension of phenol on polystyrene resin **12** (3.5 mmol g^{-1}, 1.0 g, 3.5 mmol) and dry TEA (7 mmol, 2 eq) in THF (10 ml). The suspension was stirred at room temperature for 18 h. The reaction mixture was then filtered. The beads were washed with MeOH (3 × 20 ml), DMF (3 × 20 ml), THF (3 × 20 ml), and dry ether (3 × 20 ml), and then dried to give the title resin. δ_P (121 MHz, $CDCl_3$) 11.96, 15.93.

Typical Suzuki reaction with resin 14. Preparation of 7-(4′-methylphenyl)-2,3,4,5-tetrahydro-azepine-1-carboxylic acid *tert*-butyl ester (15ii)

A suspension of resin **14** (1 g, 1.61 mmol), tolylboronic acid (4.83 mmol, 3 eq) and Na_2CO_3 (6.44 mmol, 4 eq) in DME (20 ml), H_2O (8 ml), EtOH (8 ml) was degassed with Ar for 30 minutes. $Pd(PPh_3)_4$ (0.16 mmol, 0.1 eq) was added and the reaction mixture was refluxed for 1 h and then cooled to room temperature. The resin was filtered and washed with THF and ether. The combined filtrate was concentrated and extracted with EtOAc/brine. The organic phase was dried ($MgSO_4$), filtered and evaporated. Flash chromatography on silica gel (1%–3% EtOAc/petrol ether) gave the title compound as a white solid as a 4:1 mixture of two rotomers (56%). mp. 94–95 °C. Found C 75.17%, H 8.78%, N 4.86%. $C_{18}H_{25}NO_2$ requires C 75.26%, H 8.71%, N 4.88%. ν_{max} 2963 (C–H), 1690 (O–C=O), 1385, 1363, 1333, 1156, 1115, 810, 770 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.11 (9H, s, $(CH_3)_3C$), 1.47 (2H, m, 4-H_2), 1.84 (2H, m, 3-H_2), 2.28 (4H, m, 5-H_2 + 2-H_2), 2.34 (3H, s, CH_3), 5.84 (0.8H, t, J_1 = 6.4 Hz, 6-*H*), 6.02 (0.2H, t, J_1 = 6.4 Hz, 6-*H*), 7.10 (2H, m, Ar-*H*), 7.26 (2H, m, Ar-*H*). δ_C (125 MHz, $CDCl_3$) *Rotamer 1*: 21.10 (CH_3), 27.42 (C4), 27.93 ($(CH_3)_3C$), 28.39 (C5) 29.70 (C3), 47.86 (C2), 79.60 ($(CH_3)_3C$), 121.65 (C6), 124.78 (2 × Ph C–H), 128.69 (2 × Ph C–H), 136.73 (C4′), 136.90 (C1′), 144.35 (C7), 154.12 (O–*C*=O). *Rotamer 2*: 21.11 (CH_3), 27.46 (C4), 28.93 ($(CH_3)_3C$), 28.39 (C5), 29.98 (C3), 49.02 (C2), 79.60 ($(CH_3)_3C$), 123.11 (C6), 124.78 (2 × Ph C–H), 128.69 (2 × Ph C–H), 136.73 (C4′), 136.90 (C1′), 144.39 (C7), 154.12 (O–*C*=O). *m/z* (ES^+) 310.2 (MNa^+), 597.4 (M_2Na^+).

Acknowledgements

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12 In all cases the 2-arylenamide products **15** are isolated as rotomeric mixtures interconvertable at 60 °C as ascertained by simple VT NMR studies.