Phosphinates as new electrophilic partners for cross-coupling reactions†

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Received 5th June 2008, Accepted 22nd August 2008
First published as an Advance Article on the web 15th September 2008
DOI: 10.1039/b809577a

The use of enol phosphinates as electrophiles for cross-coupling reactions has been explored. Both boronic acids (Suzuki–Miyaura reaction) and stannanes (Stille reaction) couple efficiently with lactam derived phosphinates.

Introduction

Late transition metal (Pd, Ni) mediated cross-coupling reactions represent one of the most common methods for forming C–C bonds.[1] Whilst halides represent the most common electrophilic component, there are a large number of oxygen based leaving groups that have been described.[2] Of these, vinyl and aryl triflates,[2a–c,3] by virtue of their excellent leaving group ability and ease of preparation from phenols and enolates, have become the most widely used in the various cross-coupling strategies. However, these versatile intermediates often suffer from drawbacks, such as a lack of stability and the need to use expensive triflating reagents, which can be difficult to handle and store. An attractive alternative to the triflate group is the analogous phosphate group. Not only are the reagents needed for their preparation cheap and easily stored, phosphates are often found to be superior substrates in cross-coupling reactions. Although previously reported in simple cuprate displacement reactions (Fig. 1a),[4] the first examples of palladium mediated cross-coupling of vinyl phosphates was reported in 1980 by Oshima *et al.*, who coupled a series of vinyl phosphates with trialkyl aluminium species in the presence of a $Pd(PPh_3)_4$ catalyst (Fig. 1b).[5] More recently, amongst others, Nicolaou *et al.*[6] and Coudert *et al.*[7] have successfully used enol-phosphates in a variety of cross-coupling reactions (Fig. 1c and 1d).

Despite these successful applications of the phosphate group in cross-coupling chemistry, the parallel phosphonate and phosphinate groups, Fig. 2, remain unexplored.

Since replacing P–O bonds with P–C bonds lowers the leaving group ability, these groups are predicted to be more stable and thus potentially more suitable for more labile functionality. In this respect, we have begun to explore applications of these other phosphorus groups as electrophiles in synthesis. We have previously shown that both solution and solid phase phosphonates are viable partners in Suzuki and Stille cross-coupling strategies, Fig. 3,[8] and in this paper, we describe the application of lactam derived phosphinates in simple transition metal catalysed cross-coupling strategies.

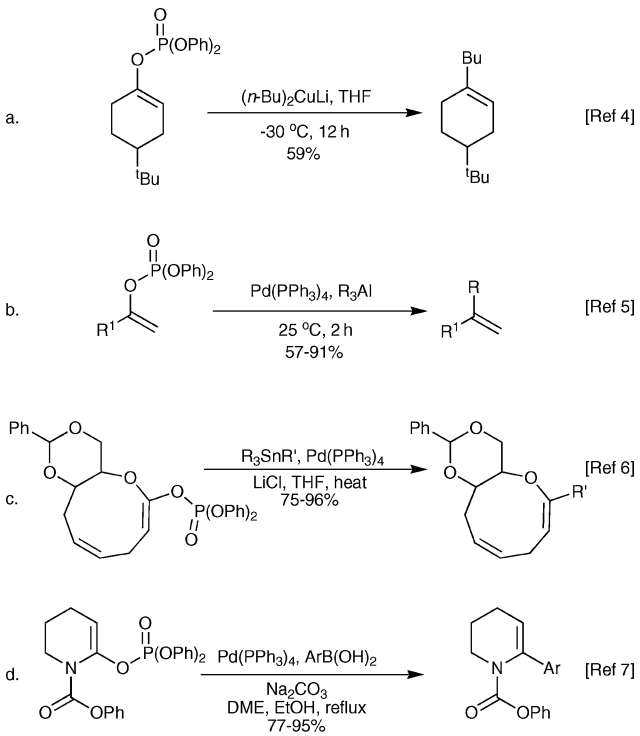

Fig. 1 Phosphate electrophiles in cross-coupling reactions.

Fig. 2

Results and discussion

As a simple system to explore phosphinate based electrophiles in cross-coupling chemistry, we chose to build on our earlier work and use simple N-Boc caprolactam enolates as test substrates. Although reaction with Boc_2O in DCM was unsuccessful, simple treatment of commercially available caprolactam **1** with DMAP and Boc anhydride in THF smoothly furnished **2** in an excellent yield of 92%. Subsequent treatment of a cold THF solution of **2** with LDA and TMEDA and trapping of the resultant anion with diphenylphosphonic chloride afforded the desired phosphinate **3a** in a 77% yield. The formation of the phosphinate was characterised

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† Electronic supplementary information (ESI) available: Experimental. See DOI: 10.1039/b809577a

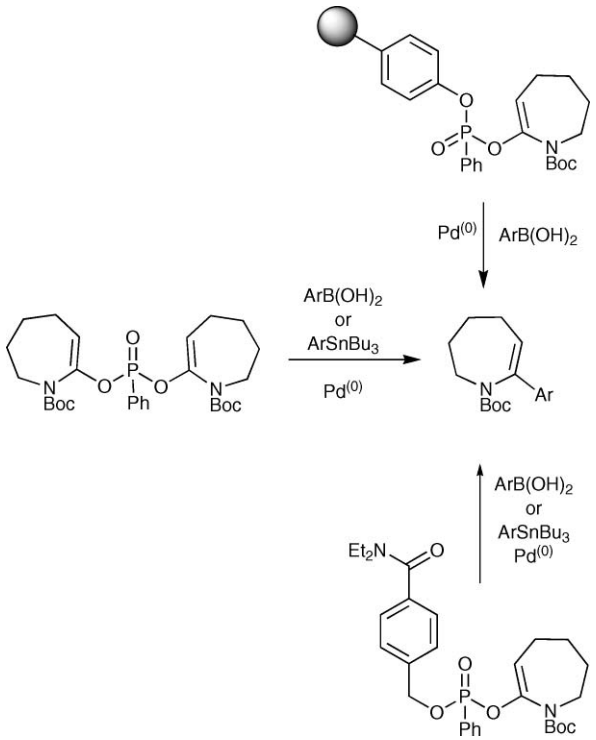
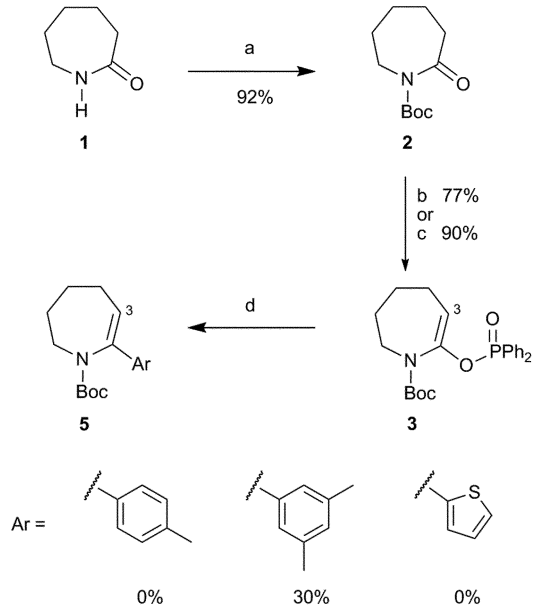


Fig. 3



Reagents: a) DMAP, $(CO_2{}^tBu)_2$, THF, r.t. 3 h. b) i) LDA, TMEDA, THF, -78 °C, ii) $Ph_2P(O)Cl$. c) NaHMDS, THF, -78 °C, ii) $Ph_2P(O)Cl$. d) $ArB(OH)_2$ **4**, $Pd(PPh_3)_4$, Na_2CO_3, DME/H_2O/EtOH (3:2:2), 80 °C, 30 min.

Scheme 1 Initial Suzuki cross-coupling studies with phosphinate **3a**.

by a single peak in the ^{31}P NMR spectrum at 29.7 ppm and a distinctive signal at 5.36 ppm (1H, dt, $J_P = 3$ Hz, $J_H = 7$ Hz) in the ^1H NMR spectrum due to the C-3 vinylic proton. Subsequently replacing LDA–TMEDA by NaHMDS proved to be cleaner and more efficient, providing phosphinate **3a** in 90% yield.

With the phosphinate now readily available, attention then turned to cross-coupling reactions. Reflecting its widespread use, and the low toxicity of the reagents involved, we opted to commence these studies using the Suzuki–Miyaura reaction. Following the protocol successfully applied in the coupling of enol phosphonates (1.5 eq $ArB(OH)_2$, 2 eq Na_2CO_3, 0.05 eq $Pd(PPh_3)_4$, DME–EtOH–H_2O, 80 °C, 1 h), the reaction of phosphinate **3a** with three boronic acids (3,5-dimethylphenyl **4i**, *p*-tolyl **4ii**, and thiophene boronic acid **4iii**) was attempted. Whilst with 3,5-dimethylphenyl boronic acid, the desired product could be isolated, as evidenced by a shift in the resonance for the C-3 vinylic proton to 5.85 ppm (1H, t, $J = 7$ Hz) and a molecular ion at MNa^+ of $m/z = 324.1934$ in the ESI mass spectrum, the yield was low (30%). Moreover, as with the majority of the coupled products *vide infra*, **5a-i** was isolated as a mixture of rotameric isomers (4 : 1 ratio) as characterised by two sets of peaks in the ^1H NMR spectrum. Notably, two peaks due to the C-3 vinyl proton can be seen at 6.11 ppm (t, $J = 7$ Hz). These coalesce to a single broad peak on heating the sample in $CDCl_3$ to 60 °C (see ESI for spectra†). However, reactions with the other boronic acids selected failed to afford any of the desired coupled products (Scheme 1).

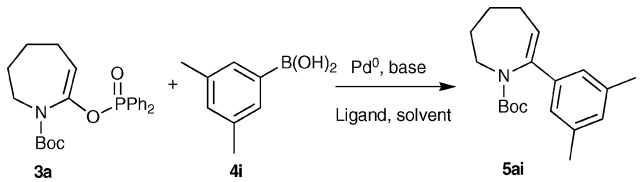
Consequently, we initiated a simple screening strategy to identify conditions to effect the coupling of phosphinate **3a** with a range of boronic acids in good yields. Since the number and range of variables render a complete and systematic screen impractical, we simply selected combinations drawn from a total of 4 palladium salts, 7 ligands 10 bases and 8 solvents.‡ Using the Suzuki reaction between phosphinate **3a** and 3,5-dimethylphenyl boronic acid **4i** as the test transformation, an array of reactions were carried out in parallel on a 0.1 mmol scale in a Radley Technologies Greenhouse Parallel Synthesiser™. The reactions were carried out on a 0.1 mmol scale with analysis *via* GC using dodecane as an internal standard to enable conversion levels and chemical yields to be calculated for each run.

This simple screen revealed that, regardless of the choice of solvent, the use of an organic base (NEt_3) resulted in poor yields of the desired product, ≤11%, indicating that an inorganic/aqueous base is essential to the success of the reaction. Of the seven conditions that fulfilled this requirement and gave yields that merit discussion (Table 1), six employed a protic solvent (EtOH or H_2O) and the five highest yielding entries all employed water as a co-solvent in tandem with an organic solvent with which it is miscible. It is suspected that such an aqueous–organic solvent combination provides greater solubility of all the reagents in the reaction leading to better results. Using the most promising conditions identified from the array (Table 1, A4) the Suzuki cross-coupling of phosphinate **3a** was then carried out on a preparative (0.4 mmol) scale The reaction was followed by TLC analysis and no starting material remained after 1 h. Following a standard work-up, the coupled product **5a-i** was isolated in an excellent 83% yield (Scheme 2, Table 2, entry 1).

Importantly, these optimised conditions proved to be relatively general across a range of boronic acids affording cross coupled products **5a-i** to **5a-ix** in generally excellent yields (Table 2, entries 1–11). Of particular note is the coupling of the highly hindered 2,4,6-trimethylphenyl boronic acid **4vi** giving coupled product

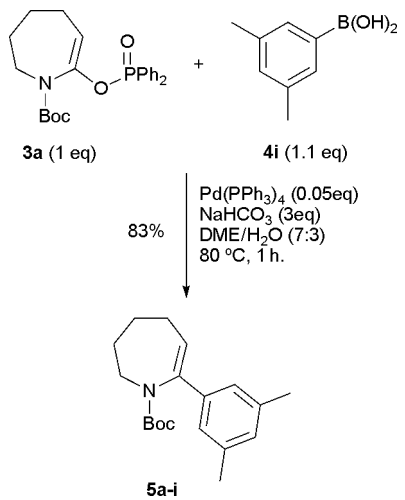
‡ A full listing of all combinations explored can be found in the ESI.†

Table 1 Selected results from the array optimisation of Suzuki cross-coupling protocol using phosphinate **3** and 3,5-dimethylphenyl boronic acid.[a]



Entry	Catalyst	Ligand	Base	Solvent	GC yield
A2	$Pd(PPh_3)_4$		K_3PO_4	DMF	23%
A4	$Pd(PPh_3)_4$		$NaHCO_3$	DME–H_2O	98%
A5	$Pd(PPh_3)_4$		$Ba(OH)_2$	DME–H_2O	72%
C5	$Pd(OAc)_2$	$^tBu_2P$(BiPh)	K_3PO_4	EtOH–H_2O	44%
D1	$Pd_2(dba)_3$		KOAc	Toluene–EtOH	31%
D4	$PdCl_2$(Binap)		$NaHCO_3$	DME–H_2O	46%
D6	$PdCl_2$(Binap)		CsF	THF–H_2O	63%

Reaction conditions: carried out on a 0.1 mmol scale. $ArB(OH)_2$ (1.0 eq), phosphinate **3** (1 eq), dodecane (1 eq), Pd source (0.05 eq), phosphine (0.05 eq), base (3 eq), solvent (1 ml total), 80 °C, 18 h.[a] A full listing of all combinations explored can be found in the ESI.†



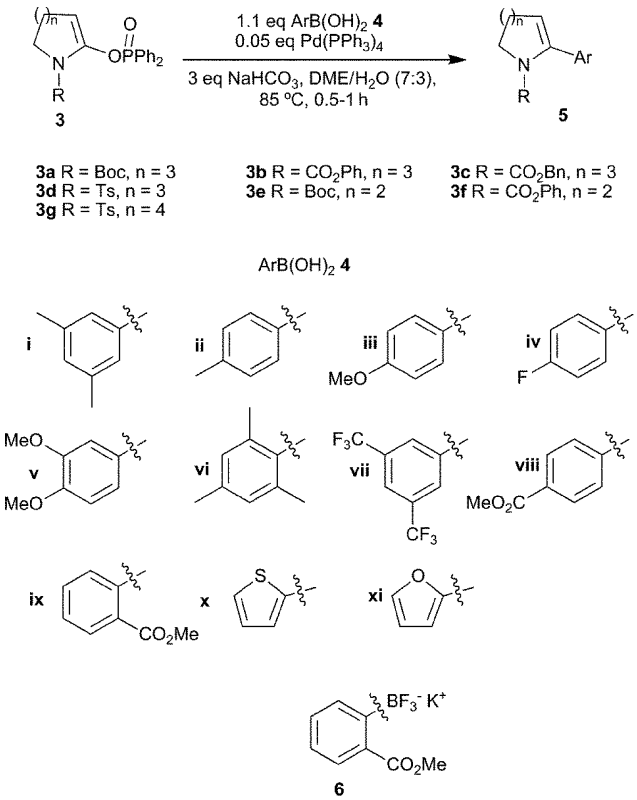
Scheme 2

5a-vi in a 65% yield (Table 2, entry 6) as well as electron poor boronic acids yielding coupled products **5a-vii** and **5a-viii** in 87% and 72% respectively (entries 7 and 8). Unsurprisingly, however, employing an electron poor and sterically hindered boronic acid **4ix** resulted in a marked drop in yield giving **5a-ix** in a moderate 32% (entry 9). Significantly, in contrast to our preliminary studies, the electron rich heterocyclic boronic acids **4x** and **4xi** could also be successfully employed in the Suzuki reaction, furnishing the corresponding coupled products in 68% and 90% yield respectively (entries 10 and 11).

Having established the viability of N-Boc caprolactam phosphinate **3a** as the electrophilic component in cross-coupling reactions, the scope and limitations of the process were investigated by varying the protecting group and the lactam ring.

Initial attempts to use simple alkyl protecting groups (Me and Bn) were unsuccessful, owing to an inability to form the enol phosphinate. However, preparation of, and subsequent phosphinate formation with the more electron withdrawing N-phenyl carbamate, N-benzyl carbamate and N-tosyl protected caprolactams proceeded smoothly, following analogous procedures to that employed for Boc protected phosphinate **3a**. In each case, the phosphinates (**3b–d**) were isolated in good to excellent yields, 90%, 58% and 73% respectively. All three phosphinates were then investigated in the thermal Suzuki reaction. Using the

Table 2 Suzuki–Miyaura cross-coupling reactions of phosphinates **3**



Entry	Phosphinate **3**	Boronic acid **4**	Enamide **5**	Yield
1	**3a**	**4i**	**5a-i**	83%
2	**3a**	**4ii**	**5a-ii**	81%
3	**3a**	**4iii**	**5a-iii**	99%
4	**3a**	**4iv**	**5a-iv**	89%
5	**3a**	**4v**	**5a-v**	75%
6	**3a**	**4vi**	**5a-vi**	65%[a]
7	**3a**	**4vii**	**5a-vii**	87%
8	**3a**	**4viii**	**5a-viii**	72%
9	**3a**	**4ix**	**5a-ix**	32%
10	**3a**	**4x**	**5a-x**	68%[a]
11	**3a**	**4xi**	**5a-xi**	90%
12	**3b**	**4iii**	**5b-iii**	81%
13	**3b**	**4i**	**5b-i**	75%
14	**3b**	**4vi**	**5b-vi**	69%
15	**3b**	**4viii**	**5b-viii**	37%
16	**3c**	**4viii**	**5c-viii**	20%
17	**3c**	**6**	**5c-viii**	58%
18	**3d**	**4ii**	**5d-ii**	64%
19	**3e**	**4iii**	**5e-iii**	41%
20	**3e**	**4x**	**5e-x**	29%
21	**3f**	**4ii**	**5f-ii**	~10%
22	**3f**	**4iii**	**5f-iii**	~10%
23	**3g**	**4ii**	**5g-ii**	86%[a]

[a] Quoted yield based on recovered starting material.

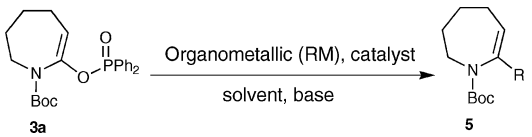
standard conditions identified for the N-Boc derivative **3a**, coupled products **5** were isolated in moderate to good yields (Table 2, entries 12–18). Again, electron rich and electron poor boronic acids both perform well, although coupling of the sterically demanding and deactivated 2-carboxymethylphenyl boronic acid **4viii** with both **3b** and **3d** under thermal conditions afforded the corresponding coupled product **5b-viii** and **5c-viii** in poor yields of 37% and 20% respectively (Table 2, entries 15 and 16). Given that similar observations had been made with phosphinate **3a** (Table 2, entry 9), we then explored the use of the corresponding potassium trifluoroborate salts, which are often more reactive in Suzuki coupling reactions than their boronic acid equivalents.[9] Consequently, 2-carboxymethylphenyl boronic acid was treated with KHF_2 in a MeOH–H_2O mixture; recrystallisation from acetonitrile afforded the trifluoroborate salt **6** in a 75% yield. Pleasingly, use of this in a Suzuki coupling with **3d** under identical conditions resulted in a threefold increase in yield, affording the desired product in a now reasonable 58% yield (Table 2, entry 17).

We then turned to consider the effect of lactam ring size. Whilst attempts to generate the five-membered ring enol phosphinates appeared successful by LCMS analysis of the crude material, all attempts to purify these proved unsuccessful, leading only to recovered lactams. Similar results were obtained on using the phosphinates directly in cross-coupling experiments and we surmise that the 5-membered enol phosphinate is highly strained, making it very prone to hydrolysis. Although the six-membered ring analogue protected as the N-Ts also exhibited some degree of hydrolytic instability, both the N-Boc and N-CO_2Ph derivatives **3e** and **3f** were stable to flash column chromatography and could be isolated in excellent yields, 89% and 95% respectively, but proved to be unstable with respect to prolonged storage or acidic media. Similar problems complicated applications in cross-coupling reactions, which provided modest yields of the desired arylenamides (Table 2, entries 19–22). This instability persisted in the products, which, although stable in the solid state, as solutions in $CDCl_3$ were found to gradually convert to the corresponding acyclic amino ketones over a period of days.

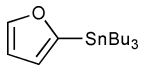
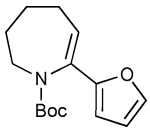
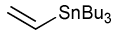
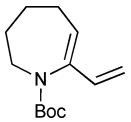
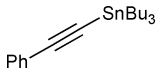
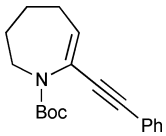
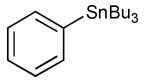
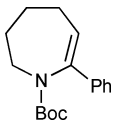
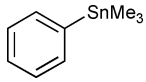
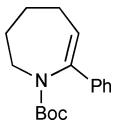
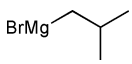
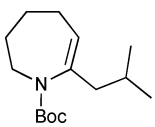
In contrast, ring strain appears to be much reduced in the eight membered phosphinate **3g**, which could be prepared in a moderate 51% yield from the corresponding N-Ts protected 8-membered ring lactam and was successfully coupled with *p*-tolylboronic acid **4ii** (Table 2, entry 23). Notably, this substrate performed better in the Suzuki reaction than the analogous N-Ts 7-membered ring phosphinate **3d** (Table 2, entry 18).

Having demonstrated the viability of phosphinate electrophiles in the Suzuki–Miyaura reaction, we then considered other common cross-coupling methods. Initially exploring the Stille cross-coupling, aryl, heteroaryl, vinyl and alkynyl tributylstannanes were all coupled in moderate to good yields using standard literature conditions (Table 3, entries 1–4). Trimethylstannanes can also be employed, although in the single example explored, the reaction proved to be less efficient than the analogous tributylstannane (Table 3, entries 4 and 5). Both thermal and microwave protocols performed equally well, however, carrying out the reactions in a microwave has the advantage of drastically shortened reaction times and dispensing with the need to degas solvents before the reaction. Whilst Kumada–Hayashi type coupling with isopropylmagnesium bromide in the presence of a Ni salt and phosphine ligand afforded the very hydrolytically labile alkyl enamide **5aq** in a moderate 37% yield (Table 3, entry 6), all attempts to utilise **3** in Heck and Sonogashira coupling protocols have, to date, been unsuccessful.

Table 3 Further cross-coupling reactions of phosphinate **3**



3a **5**

Entry	RM	Product **5**	Yield
1			89%[a] 91%[b]
2			82%[a] 85%[b]
3			49%[a] 54%[b]
4			45%[a] 45%[b]
5			29%[a]
6			37%[c]

Reaction conditions:[a] 1.5 eq R′SnR_3, 2.5 eq LiCl, 0.05 eq $Pd(PPh_3)_4$, THF, reflux, 2 h. [b] 1.5 eq R′SnR_3, 2.5 eq LiCl, 0.05 eq $Pd(PPh_3)_4$, THF, microwave, 15 min. [c] 1.5 eq ^{i}PrMgBr, 0.05 eq Ni(dppe)Cl_2, Et_2O–THF (1 : 1), r.t., 18 h.

In conclusion, lactam derived enol phosphinates with electron withdrawing groups on the nitrogen atom have been shown to be excellent partners for both Suzuki and Stille cross-coupling protocols and also show some activity in nickel catalysed Kumada type coupling reactions. Both electron rich and electron poor boronic acids couple equally efficiently, with the only restriction being those combining deficiency with steric hindrance. However, this problem may be circumvented by use of the corresponding aryltrifluoroborate salt. Whilst six- to eight-membered rings are tolerated, a limitation appears to be ring strain, which results in hydrolysis being competitive for smaller rings. Overall, these results suggest that phosphinates represent a viable alternative to the more commonly used triflate group.

Experimental section

All reactions were carried out under an argon atmosphere unless otherwise stated. Solvents were purified following established protocols. Petrol refers to petroleum spirit boiling in the 40–60 °C range. Ether refers to diethyl ether. Commercially available reagents were used as received unless otherwise stated. Flash column chromatography was performed according to the method of Still *et al.* using 200–400 mesh silica gel. Yields refer to isolated yields of products of greater than 95% purity as determined by ^{1}H + ^{13}C NMR spectroscopy or elemental analysis (Durham University Microanalytical Laboratory).

Melting points were determined using Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded as thin films between KBr plates (liquids) or using an ATR attachment (golden gate apparatus) on a Perkin-Elmer FT-IR 1600 spectrometer. Unless otherwise stated, ^{1}H NMR spectra were recorded in $CDCl_3$ on Varian Mercury 200, Varian Unity-300, Mercury-400 or Varian Inova-500 and are reported as follows: chemical shift δ (ppm) (number of protons, multiplicity, coupling constant J (Hz), assignment). Residual protic solvent $CHCl_3$ (δ_H = 7.26 ppm) was used as the internal reference. ^{13}C NMR spectra were recorded at 101 MHz or 126 MHz on Mercury-400 or Varian Inova-500 respectively, using the central resonance of $CDCl_3$ (δ_c = 77.0 ppm) as the internal reference. All chemical shifts are quoted in parts per million relative to tetramethylsilane (δ_H = 0.00 ppm) and coupling constants are given in Hertz to the nearest 0.3 Hz. All ^{13}C spectra were proton decoupled. Assignment of spectra was carried out using DEPT, COSY, HSQC and NOESY experiments. Low-resolution electrospray mass spectra (ES) were obtained on a Micromass LCT Mass Spectrometer or a Thermo-Finnigan LTQ. High-resolution mass spectra (ES) were obtained on a Thermo-Finnigan LTQFT Mass Spectrometer in Durham. Procedures for the reaction screen and characterisation data for compounds **3b–3e**, **5a-i** to **5a-xv** can be found in the ESI.†

N-(*tert*-Butyloxycarbonyl)-2-oxo-azepane 2

To a solution of caprolactam (11.47 g, 0.10 mol) and DMAP (13.62 g, 0.11 mol) in dry THF (120 ml) was added a solution of di-*tert*-butyldicarbonate (24.33 g, 0.11 mol) in dry THF (60 ml). The reaction mixture was stirred at RT for 3 h. The mixture was concentrated and extracted with EtOAc (150 ml). The organic phase was washed with 5% HCl (3 × 25 ml), brine (3 × 25 ml) and $NaHCO_3$ (3 × 25 ml), dried over $MgSO_4$ and concentrated. Kugelrohr distillation (50 °C, 0.4 mbar) afforded the title compound as a yellow oil (19.87 g, 93.17 mmol, 92%). ν_{max} (NaCl) 1768 (CH_2C=O), 1716 (O=C-O), 1457, 1367, 1299, 1152 cm^{-1}. δ_H (500 MHz, $CDCl_3$) 1.50 (9H, s, C(CH_3)3), 1.72 (6H, m, 4-H_2, 5-H_2, 6-H_2), 2.62 (2H, m, 7-H_2), 3.75 (2H, m, 3-H_2). δ_C (125 MHz, $CDCl_3$) 23.7 (CH_3)$_3$), 28.3 (*C*-5), 28.9 (*C*-6), 29.5 (*C*-4), 39.7 (*C*-3), 46.4 (*C*-7), 83.0 ($C(CH_3)_3$), 153.1 (*C*-2), 176.0 (O*C*=O). *m*/*z* (ES+) 236.1 (MNa^+), 449.1 ($2MNa^+$).

Typical procedure for the formation of enol phosphinates. *N*-(*tert*-Butyloxycarbonyl)-4,5,6,7-tetrahydro-1*H*-azepin-2-yl diphenylphosphinate 3a

To a cold solution (−78 °C) of the N-protected lactam **2** (0.1 M, 1 eq) in dry THF was added NaHMDS (2 M 1.2 eq) slowly *via* syringe and the reaction mixture was stirred at −78 °C for 1 h. Diphenylphosphonic chloride (1.2 eq) was added dropwise *via* syringe and the reaction mixture was stirred at −78 °C for an additional 2 h before warming to room temperature and quenching with H_2O. The resulting mixture was concentrated and the aqueous layer extracted into EtOAc (3 ×). The combined organics were washed with brine, dried over $MgSO_4$ and concentrated, affording the crude product as a yellow oil. Purification by flash chromatography ([1 : 1] dichloromethane–ethyl acetate) afforded the title compound as a white solid (90%). Mp 81–83 °C. Found; C, 66.70; H, 6.82; N, 3.22%; Calc. for $C_{23}H_{28}NO_4P$; C, 66.82; H, 6.83; N, 3.39%. ν_{max} (KBr) 2932 (C–H), 1703 (C=O), 1681 (enol ether), 1440 (P–Ph), 1356 (P=O), 1226 (P-O–Ar), 1159, 1131, 1059, 541, 524 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.44 (13H, m, (CH_3)$_3$C, 5-H_2, 6-H_2), 1.56 (2H, m, 4-H_2), 1.99 (2H, m, 7-H_2), 5.36 (1H, dt, JP = 3 Hz, JH = 7 Hz, 3-*H*), 7.38–7.58 (6H, m, Ar–*H*), 7.78–7.92 (4H, m, Ar–*H*). δ_C (100 MHz, $CDCl_3$) 24.3 (*C*-5), 24.8 (*C*-6), 28.5 (C(CH_3)$_3$), 29.4 (*C*-4), 46.4 (*C*-7), 81.0 ($C(CH_3)_3$), 110.1 (*C*-3), 128.6, 128.7 (Ar*C*–H), 130.9, 131.9 and 132.0 (Ar*C*–H), 132.3 and 132.5 (Ar*C*), 144.9 (*C*-2), 153.4 (*C*=O). δ_P (162 MHz, $CDCl_3$) 29.7. *m*/*z* (ES+) 436.2 (MNa^+), 849.0 ($2MNa^+$).

Typical Suzuki cross-coupling protocols. *N*-[(4′-Methylphenyl)sulfonyl]-2-(4′-methylphenyl)-4,5,6,7-tetrahydro-azepane 5d-ii

Method A. A solution of phosphonite **3d** (1 eq), $NaHCO_3$ (3 eq), and 3′,5′-dimethylphenylboronic acid (1 eq) in DME–H_2O (7 : 3) was degassed *via* the freeze–pump–thaw method. $Pd(PPh_3)_4$ (0.05 eq) was added and the reaction mixture stirred at reflux (85 °C) for 1 h. The reaction mixture was cooled to room temperature, concentrated and extracted into EtOAc (3 ×). The combined organics were washed with H_2O (3 ×) then brine (3 ×), dried over $MgSO_4$ and concentrated. Purification on a Horizon® column chromatography system (1.5% ethyl acetate–DCM) afforded recovered starting material (33%) and the title compound as a white solid (43%).

Method B. The desired phosphinate (1 eq), boronic acid (1.1 eq), Na_2CO_3 (3 eq) and catalyst (0.05 eq) were placed in a standard 2 ml microwave vial, the solvent (DME–H_2O–EtOH, [7 : 3 : 1]) was added and the vial sealed. Reaction parameters; Prestir = 10 s, reaction time = 300 s, temperature = 100 °C. The reaction was allowed to cool to room temperature, concentrated and extracted into EtOAc (3 ×). The combined organics were washed with H_2O (3 ×) then brine (3 ×), dried over $MgSO_4$ and concentrated, affording the crude product. Purification on a Horizon® column chromatography system (1. 5% ethyl acetate–DCM) afforded recovered starting material (32%) and the title compound as a white solid (35%). ν_{max} (ATR) 2938, 2918, 1440, 1334, 1150, 1087, 1058, 950, 814, 763, 704 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.43 (2H, m, 5-H_2), 1.83 (2H, quint, J = 6 Hz, 6-H_2), 2.06 (2H, q, J = 7 Hz, 4-H_2), 2.34 (3H, s, CH_3), 2.41 (3H, s, CH_3), 6.04 (1H, t, J = 7 Hz, 3-*H*), 7.04 (2H, d, J = 8 Hz, Ar–*H*), 7.18 (4H, d, J = 8 Hz, Ar–*H*), 7.55 (2H. d, J = 8 Hz, Ar–*H*). δ_C (100 MHz, $CDCl_3$) 19.8 (CH_3), 20.2 (CH_3), 22.3 (*C*-5), 25.3 (*C*-4), 28.6 (*C*-6), 49.3 (*C*-7), 124.7 (Ar–*C*H), 126.1 (Ar–*C*H), 126.9 (*C*-3), 127.4 (Ar–*C*H), 127.9 (Ar–*C*H), 134.4 (Ar–*C*), 136.2 (*C*-2), 137.4 (Ar–*C*), 141.6 (Ar–*C*), 141.7 (Ar–*C*). *m*/*z* (ES^+) 342.3 (MH^+), 359.4 (MH_2O^+), 700.6 ($2MH_2O^+$). HRMS

(ES) found MH^+ 342.1523, $C_{20}H_{24}NO_2S$ requires 342.1522, found MNa^+ 364.1342, $C_{20}H_{23}NO_2SNa$ requires 364.1342.

Stille protocols. *N-tert*-Butyloxycarbonyl-2-vinyl-4,5,6,7-tetrahydro-azepane 5a-xii

Method A. A solution of **3a** (0.413 g, 1.0 mmol) and LiCl (0.106 g, 2.50 mmol) in THF (15 ml) was degassed by purging Ar for 10 minutes before CH_2=$CHSnBu_3$ (1.5 mmol) and $Pd(PPh_3)_4$ (0.058 g, 0.05 mmol) were added. The mixture was refluxed for 2 h before cooling to room temperature. The solution was concentrated and extracted with EtOAc–(1 M aqueous KF), the organic phase was combined, dried ($MgSO_4$), filtered and evaporated. Flash chromatography on silica (19 : 1 to 9 : 1 petroleum ether–EtOAc) gave the coupled compound as a colourless oil (82%).

Method B. A solution of **3** (0.413 g, 1.0 mmol) and LiCl (0.106 g, 2.50 mmol) in THF (7 ml) was degassed by purging with Ar for 10 minutes before $ArSnR_3$ (1.5 mmol) and $Pd(PPh_3)_4$ (0.058 g, 0.05 mmol) was added. The reaction mixture was sealed in a standard 10 ml microwave vial and was heated in a Biotage microwave oven with stirring (irradiation power; 50 W; temperature ramped to 150 °C in 2 min and held for 15 min), then cooled to rt. The solution was extracted with EtOAc–(1 M aqueous KF), the organic phase was combined, dried ($MgSO_4$), filtered and evaporated. Flash chromatography on silica (19 : 1 to 9 : 1 petroleum ether–EtOAc) gave the title compound (85%). *R*f (19 : 1 petroleum ether–EtOAc): 0.30. Found; C, 69.11; H, 9.31; N, 6.09%: Calc. for $C_{13}H_{21}NO_2$; C, 69.92; H, 9.48; N, 6.27%. ν_{max} (NaCl film) 3092, 2926, 2933, 2853, 1703, 1698, 1645, 1445, 1391, 1253, 1166, 985, 896 and 779 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.37 (9H, s, $(CH_3)_3C$), 1.47 (2H, br, 5-H_2), 1.78 (2H, quintet, $J = 6$ Hz, 6-H_2), 2.15 (2H, m, 4-H_2), 2.90–3.70 (2H, br, 7-H_2), 4.95 (1H, d, $J = 10$ Hz), 5.07 (1H, d, $J = 17$ Hz), 5.67 (t, 1H, $J = 7$ Hz, 3-H), 6.18 (1H, dd, $J1 = 17$ Hz, $J2 = 10$ Hz). δ_C (100 MHz, $CDCl_3$) 24.5 (*C*-4), 27.1 (*C*-5), 28.3 ($(CH_3)_3C$), 29.8 (*C*-6), 46.7 (*C*-7), 80.0 ($(CH_3)_3C$), 111.9 (CH_2=CH), 127.8 (*C*-3), 134.3 (CH_2=*C*H), 144.3 (*C*-2), 154.1 (O-*C*=O). *mlz* (ES+) 246.0 MNa^+.

Acknowledgements

We thank the EPSRC (GR/M75990/01 - JG), and Glaxo-SmithKline for financial support of this work (CASE award to TMW); the EPSRC Mass Spectrometry Service for accurate mass determinations, Dr A. M. Kenwright for assistance with NMR experiments and Dr M. Jones for mass spectra.

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