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Reactivity of cyclic sulfamidates towards phosphonate-stabilised enolates: synthesis and applications of α-phosphono lactams†

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Five and six ring α-phosphono lactams **14–20** are available by reaction of 1,2- and 1,3-cyclic sulfamidates respectively with enolates derived from ethyl dialkylphosphonoacetates **3** and **4**. Subsequent Wadsworth–Emmons olefination provides the enantiomerically pure *exo*-alkylidene variants *e.g.* **25**, which is efficiently converted to vinyl triflate **29** (>98% ee). Suzuki coupling of **29** to a range of aryl and vinyl boronic acids leads to a structurally diverse range of pyrrolidinones exemplified by **30** and **34**. The degree of epimerisation at the base-sensitive *C*(5) stereocentre during the Suzuki coupling of **29** is shown to be dependent on both the nature of the aryl boronic acid and the reaction conditions used.

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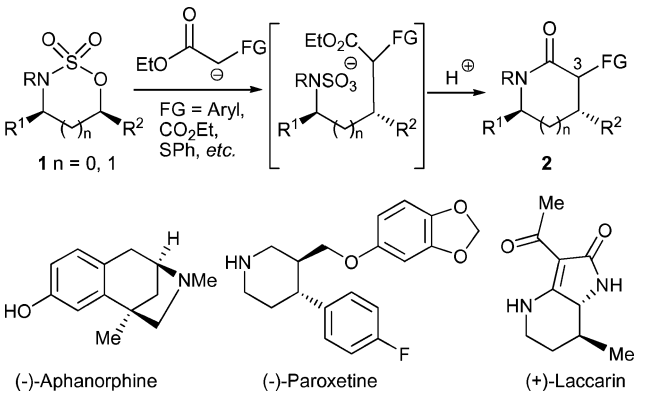
Introduction

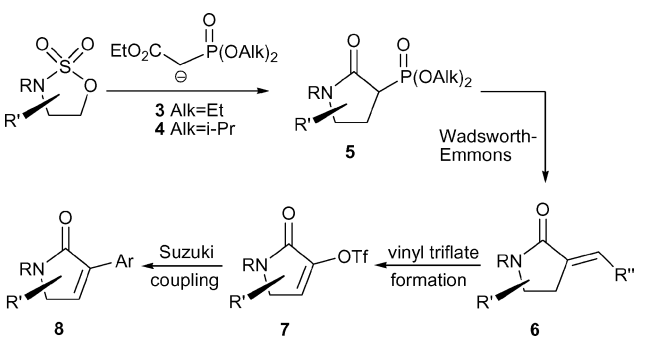
The 1,2- and 1,3-cyclic sulfamidates **1** (n = 0,1 respectively) comprise a grouping of synthetically versatile electrophiles that are accessible *via* readily available (and enantiomerically pure) 1,2- and 1,3-aminoalcohols. Importantly, the reactivity profile of 1,2- and 1,3-cyclic sulfamidates corresponds to that associated with aziridines and azetidines respectively but with several added advantages: (i) cyclic sulfamidates undergo *regiospecific* ring opening (which reflects the higher reactivity of the C–O bond), (ii) there is no significant reliance on ring strain since activation towards nucleophilic attack is "in-built" and (iii) there is no requirement for the presence (and subsequent removal) of an additional activating substituent on the nitrogen.[1] Cyclic sulfamidate reactivity is readily harnessed and in a series of recent papers we have described methodology directed towards the synthesis of a range of different *N*-heterocycles, including pyrrolidines and piperidines.[2]

α-Functionalised enolates, *e.g.* malonates, provide a particularly effective combination with cyclic sulfamidates, leading to efficient and stereospecific C–C bond formation and the potential for down-stream manipulation. The scope of this chemistry has been exemplified by the synthesis of individual heterocyclic classes as well as specific target molecules including (−)-aphanorphine,[3a,3b] (−)-paroxetine[3c] and (+)-laccarin[3c] (Scheme 1).

We have also reported the utility of α-sulfenyl ester enolates, which provide access to enantiomerically pure α-sulfinyl lactams (**2**, FG = SPh) as well as the corresponding and synthetically versatile α,β-unsaturated lactams *via* sulfoxide elimination from **2**.[4] In this paper we describe a comprehensive study‡ of the reactivity of 1,2- and 1,3-cyclic sulfamidates with α-phosphono enolates based on ethyl dialkylphosphonoacetates **3** and **4**. This chemistry provides access to α-phosphono lactams **5** and subsequently *exo*-alkylidene variants **6** (*via* Wadsworth–Emmons reaction) which, in turn, offer an entry to vinyl triflates **7**; the latter are well suited to Suzuki coupling to ultimately provide the α-arylated unsaturated lactams **8** (Scheme 2).



Scheme 1 Cyclic sulfamidates as piperidine and pyrrolidine precursors.



Scheme 2

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† Electronic supplementary information (ESI) available: Full experimental and characterization details of compounds not included in the Experimental. See DOI: 10.1039/b706315f

‡ A portion of this work has been published previously.[2b]

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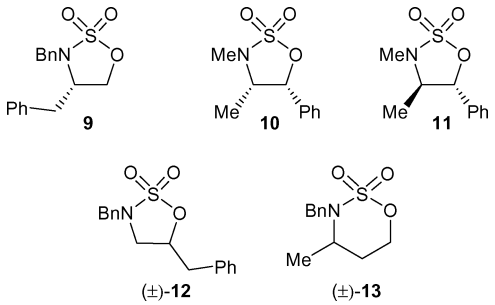
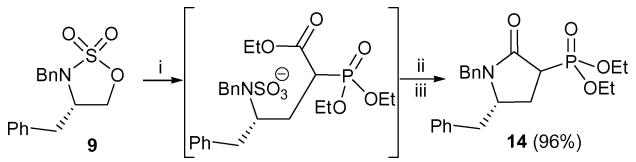
We have employed the same structurally representative selection of 1,2- and 1,3-cyclic sulfamidates **9–13**§ as used in our earlier sulfenyl based work in order to define the scope and potential of this chemistry. However, we identified particular issues within the phosphonate series, and of particular interest to us were the Suzuki coupling reactions of vinyl triflates **7**. With "base vulnerable" substrates, such as **7** or the coupled product **8**, epimerisation at an allylic stereocentre is possible. Consequently, an extensive study of the Suzuki process in terms of the optimal reaction conditions to maintain the level of enantiomeric purity of the products obtained forms a key component of this paper.



Results and discussion

α-Phosphono ester enolates: the role of phosphonate alkyl units

We have previously reported[2b] the reaction of the (*S*)-phenylalanine-derived 1,2-cyclic sulfamidate **9** with ethyl diethylphosphonoacetate **3** to give, after ring opening and thermal lactamisation, α-phosphono pyrrolidinone **14** in 96% yield (Scheme 3 and entry 1, Table 1).



Scheme 3 *Reagents and conditions*: i. **3** (or **4**, see Table 1), *t*-BuOK, either THF, 40 °C or *p*-dioxane, 80 °C (see Table 1 and text); ii. 5 M HCl then $NaHCO_3$; iii. PhMe, reflux.

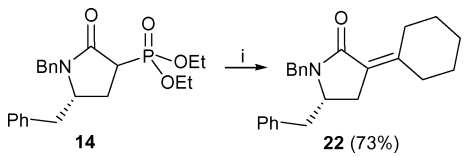
However with **3**, the stereochemically more demanding ephedrine derivative **10** gave low and irreproducible yields of adduct **15** (entry 2, Table 1) despite extensive efforts. The problem here appeared to involve competing nucleophilic attack at the phosphorus promoted by the higher temperatures required to achieve nucleophilic displacement. This prompted us to use the more hindered diisopropyl variant **4**¶ as the enolate component which provided an effective solution. Using **4**, we have successfully isolated a range of α-phosphono lactams **16–20** based on a series of structurally representative cyclic sulfamidates (Table 1).

The reaction conditions in each case are similar to those shown in Scheme 3 but with certain substrate-dependent modifications. For example, whereas sulfamidate **9** reacted efficiently with the potassium enolate of **4** at 40 °C in THF, more sterically demanding and/or less reactive substrates (**10–13**) required elevated temperatures (reflux, *p*-dioxane). Once nucleophilic displacement was judged to be complete (by TLC), acid was added (to cleave the intermediate *N*-sulfate) and the target lactams **14–20** were obtained in good to moderate yields after neutralisation and cyclisation. The 3-benzyl variant **12** is a demanding substrate and in our experience shows a propensity towards competing elimination under nucleophilic conditions. Using the conditions defined here, the desired lactam **19** was obtained in 58% isolated yield and we only observed a small (7%) level of the elimination product **21**.

The lactamisation conditions required for the initial ring-opened adducts depend on the substrate involved. For example, monosubstituted derivatives (entries 1, 3 and 6) required thermolysis (PhMe, reflux), whereas disubstituted variants (based on ephedrine and pseudoephedrine; entries 2, 4 and 5) cyclised spontaneously upon neutralisation. 6-Ring lactamisation to form **20** was more challenging and was most efficiently achieved by refluxing the crude material (following neutralisation) in *p*-xylene. In products possessing a *C*(4) substituent, high levels of stereochemical control were observed and lactams **15** and **17–19** were isolated as single diastereomers. In other cases the products were obtained as mixtures of diastereomers at *C*(3).

Wadsworth–Emmons reactions: an entry to α-*exo*-alkylidene lactams

Examples of Wadsworth–Emmons reactions of α-phosphono lactams have been reported earlier.[6] We have evaluated three phosphonates (**14**, **16** and **17**) derived from cyclic sulfamidates **9** and **10** as substrates towards a series of aldehyde and ketone components (Scheme 4, Table 2).



Scheme 4 *Reagents and conditions*: i. NaH, cyclohexanone, THF, rt.

In our hands diethyl phosphonates (entries 1–4, Table 2) reacted more efficiently but the corresponding diisopropyl variants did give a somewhat higher level of *E*/*Z* selectivity (entries 5–7). For example, the sodium enolate of lactam **14** reacted efficiently with cyclohexanone to afford *exo*-alkene **22** in 73% yield whereas the isopropyl variant **16** delivered the same product in only 52% yield. Lactam **14** also underwent efficient reaction with acetaldehyde to deliver trisubstituted alkene **23** in 75% yield but with no stereochemical bias. Switching to the isopropyl variant resulted in a slightly diminished yield (69%) of **23** but allowed greater control over the newly installed double bond (4 : 1 *E* : *Z*). In these cases the isomeric alkene products were readily separable by chromatography and stereochemical assignments were made on

§ Cyclic sulfamidates **9–13** provide a representative series of substrates in terms of substitution pattern and ring size. Substrates **9–11** were prepared starting from the corresponding and commercially available enantiomerically pure 1,2-aminoalcohols. Cyclic sulfamidates **12** and **13** were racemic, but we have already demonstrated an ability to exploit enantiomerically pure 3-substituted 1,3-cyclic sulfamidates in related chemistry.[3c]

¶ Phosphonate **4** is generally employed to allow base-catalysed transesterification of the carboxylate moiety as the diisopropyl groups minimise alkoxy exchange at the phosphorus.[5]

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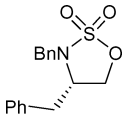
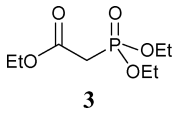
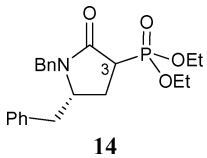
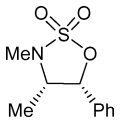
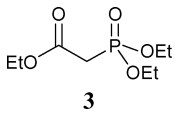
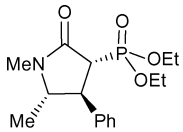
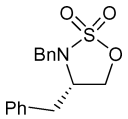
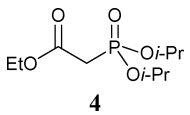
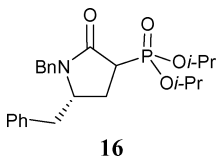
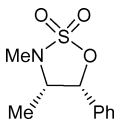
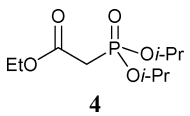
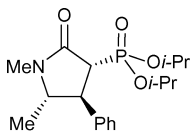
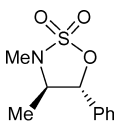
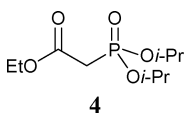
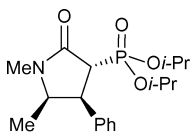
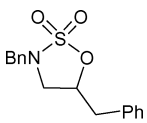
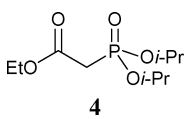
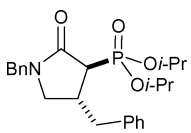
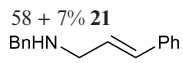
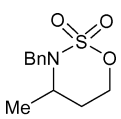
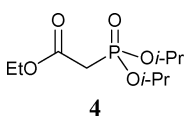
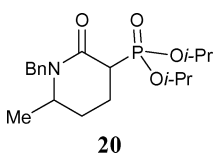
Table 1 Synthesis of α-phosphono lactams **14–20**

Entry	Sulfamidate	Enolate precursor	Product	Yield (%)[a,b]
1	 **9**	 **3**	 **14**	96 (2 : 1 dr at *C*(3))
2	 **10**	 **3**	 **15**	10–31
3	 **9**	 **4**	 **16**	77 (6 : 1 dr at *C*(3))
4	 **10**	 **4**	 **17**	63
5	 **11**	 **4**	 **18**	54
6	 (±)-**12**[c]	 **4**	 **19**	58 + 7% **21**  **21**
7	 (±)-**13**[c]	 **4**	 **20**	50 (3 : 2 dr at *C*(3))

[a] Isolated yields. [b] Diastereomer ratios were determined from the ^{1}H NMR of the crude product. [c] Cyclic sulfamidates **12** and **13** were racemic.

the basis of the diagnostic chemical shift of the alkene proton (*E*: 6.50–6.60 ppm; *Z*: 5.84–5.92 ppm). In the case of trisubstituted lactam **17**, the presence of a bulky *C*(4) substituent caused a reversal in selectivity and lactam **26** was formed as 1 : 8 mixture of *E* : *Z* isomers which were separable by chromatography. Again stereochemical assignments were made on the basis of ^{1}H-NMR (alkenyl proton of *E* isomer: 6.70 ppm; alkenyl proton of *Z* isomer: 5.63 ppm) and were reinforced by diagnostic NOE correlations (see Experimental).

One additional observation does merit comment. An attempt to react **17** with cyclohexanone led to none of the expected alkene, but **27** was isolated in 38% yield (entry 8); this adduct was also formed to a lesser extent (4%) when **17** was treated with the more reactive acetaldehyde (entry 7). When the enolate of **17** was exposed to dry air (in the *absence* of cyclohexanone) α-ketolactam **27** was isolated in 73% yield. Reactions of phosphonate-stabilised anions with oxygen that involve this type of fragmentation have previously been reported[7] although examples possessing an adjacent stabilising group (in this case a lactam) are rare.[7c]

One of our longer term goals is to develop cyclic sulfamidates as versatile heterocyclic building blocks for a range of applications. While it is straightforward to incorporate useful functional

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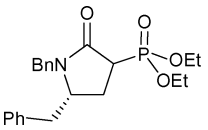
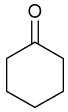
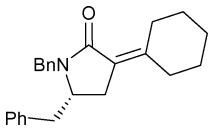
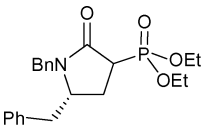
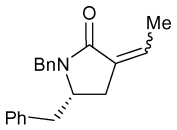
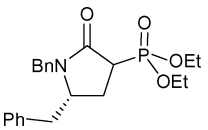
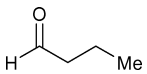
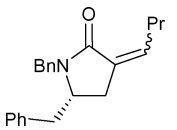
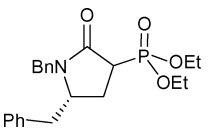
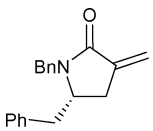
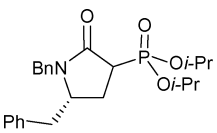
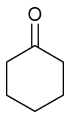
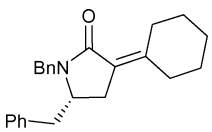
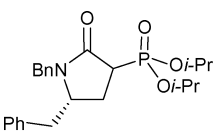
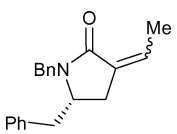
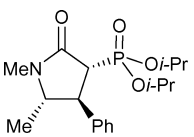
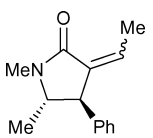
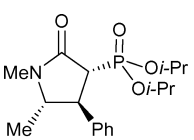
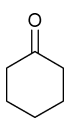
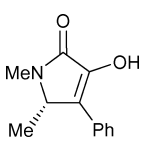
Table 2 Wadsworth–Emmons reactions of α-phosphono lactams

Entry	Phosphono lactam	Aldehyde/ketone	Product	Isolated yield (%)
1	 **14**		 **22**	73
2	 **14**		 **23**	75 (1 : 1 *E* : *Z*)
3	 **14**		 **24**	85 (1 : 1 *E* : *Z*)
4	 **14**		 **25**	65
5	 **16**		 **22**	52
6	 **16**		 **23**	69 (4 : 1 *E* : *Z*)
7	 **17**		 **26**	60 (1 : 8 *E* : *Z*) + 4 % **27**
8	 **17**		 **27**	38, 73[a]

[a] Yield of **27** obtained using 2 equivalents of NaH under dry air and in the *absence* of cyclohexanone.

handles within the enolate nucleophile component, it is also important to explore the viability of any subsequent processes available (*i.e.* diversity oriented transformations). Methods that allow new C–C bond formation and concomitant introduction of a new substituent on the heterocyclic core scaffold are of particular value. The well recognised utility of vinyl triflates made intermediates, such as **29**, attractive targets and these should be readily accessible from the Wadsworth–Emmons adducts shown in Table 2. The simple but enantiomerically pure α-methylidene lactam **25** provided the vehicle for this study (Scheme 5). Lactam

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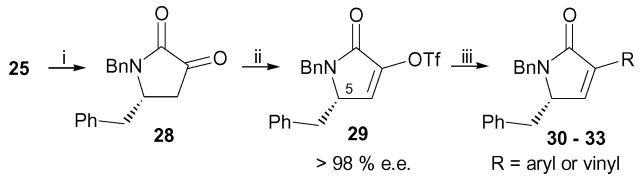


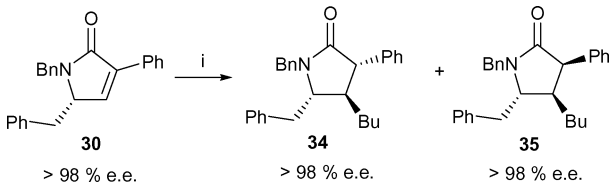
Scheme 5 *Reagents and conditions*: i. O_3, MeOH, −78 °C then Me_2S (98 %); ii. $PhNTf_2$, K_2CO_3, *p*-dioxane, H_2O (63 %); iii. $RB(OH)_2$, 5 mol% $Pd(PPh_3)_4$, Na_2CO_3 or K_3PO_4, *p*-dioxane, H_2O, 90 °C, thermal or microwave, see Table 3.

25, available in 65% yield by reaction of **14** with paraformaldehyde, underwent efficient oxidative cleavage (O_3) to give α-ketolactam **28**. This compound was unstable to chromatography (on either silica or alumina) but was formed cleanly under the conditions described. This factor did, however, necessitate the use of **25** as the precursor to **28** since other alkenes (*e.g.* **23**) did not undergo such clean oxidative cleavage which then affected the efficiency of subsequent steps.

Treatment of **28** with Hendrickson's triflimide[8a] ‖ afforded vinyl triflate **29** in 63% yield. Vinyl triflate **29** was chosen because it represents a demanding substrate in the sense that the *C*(5) stereocentre is potentially labile either during formation of either **28** or **29**, or in any subsequent cross coupling reaction. Importantly, no racemisation was observed during the formation of **29**, the enantiopurity of which was confirmed by chiral HPLC as >98% ee (using the corresponding racemate as a standard). Suzuki coupling of **29** did, however, present more of a challenge, the results of which are shown in Table 3. Reaction of **29** with phenyl boronic acid under standard thermal conditions gave the Suzuki adduct **30** but in poor yield and with a significant level of racemisation. Modification of the base (Na_2CO_3 to K_3PO_4) gave a dramatic improvement in the enantiomeric purity of **30** but the yield remained poor.

The latter problem was solved using microwave irradiation. Under these conditions (*e.g.* entry 3, Table 3), Suzuki coupling was rapid and efficient and no significant level of racemisation was detected. Under the same conditions, coupling of **29** with vinyl boronic acid gave diene **31** in 78% yield and >98% ee. While **30** and **31** could be produced very efficiently, defining the scope and limitations of this Suzuki coupling process was important. With this in mind, we chose to evaluate two particularly demanding substrates incorporating significantly more strongly electron withdrawing aryl units. Under our optimised conditions (K_3PO_4 + MW irradiation) 3-nitrophenyl boronic acid and 3-pyridyl boronic acid underwent Suzuki coupling with **29** to give adducts **32** and **33** in 73% and 38% yields respectively. The strongly electron withdrawing effect of the aryl substituent did, as anticipated, have an impact on the degree of epimerisation observed and **32** and **33** were obtained in 86 and 47% ee respectively; the effect of Na_2CO_3 *vs.* K_3PO_4 under the optimised microwave conditions is aptly illustrated by comparing entries 6 and 7. These observations illustrate current limitations but clearly, with strongly electron withdrawing substrates, use of K_3PO_4 in combination with microwave irradiation provides a validated starting point for optimisation of reactions involving such demanding substrates.††

It is also pertinent to illustrate the capacity of α-arylated α,β-unsaturated lactams to function as electrophiles. We have exemplified this in one case, but as with the Suzuki coupling process, we believe that this has broader applications. Exposure of **30** to an organocuprate[9] gave the 3,4,5-trisubstituted lactams **34** and **35** in 65% yield and as a 3 : 1 mixture of diastereomers (Scheme 6). The stereochemical assignment of each isomer was determined using NOE experiments (see Experimental) and we also established that this 1,4-addition did not cause any erosion of enantiomeric purity; both **34** and **35** were shown by chiral HPLC to have >98% ee.

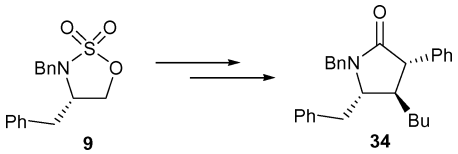


Scheme 6 *Reagents and conditions*: i. *n*-BuLi, CuI, Me_3SiCl, HMPA, THF, rt (65 %, 3 : 1 dr **34** : **35**).

Conclusions

In summary, α-phosphono ester enolates are effective nucleophiles towards a set of structurally representative 1,2- and 1,3-cyclic sulfamidates. Choice of the phosphonate ester alkyl moiety is important in this regard and the reactivity of cyclic sulfamidates provides a new entry to α-phosphono lactams, which themselves are good substrates for Wadsworth–Emmons reactions. The *exo*-methylidene lactam **25** proves a convenient precursor to the corresponding α-ketolactams and, in turn, to the configurationally stable vinyl triflate **29**. Suzuki cross coupling of **29** provides an effective method to functionalise further the heterocyclic core structure and the limitations of this process with respect to the ease of epimerisation at *C*(5) have been probed.

The methodology described in this paper illustrates further the synthetic potential of 1,2- and 1,3-cyclic sulfamidates. These readily available building blocks provide functionalised heterocycles with the capacity to incorporate additional substituents/functionality at a later stage. The full range of the chemistry outlined is illustrated by the overall conversion of **9** to **34** which has been achieved with complete retention of enantiomeric purity.



‖ Other triflating agents such as Tf_2O and Comins' reagent[8b] were significantly less efficient for the formation of **29**.

†† We have also briefly investigated the use of aryl trifluoroborates in this process (*e.g.* $PhBF_3K$) but these have failed to react with vinyl triflate **29** under our optimised conditions.

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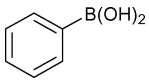
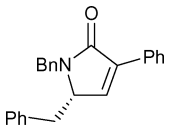
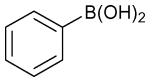
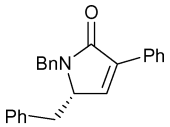
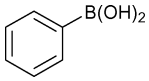
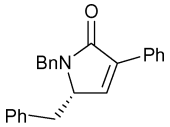
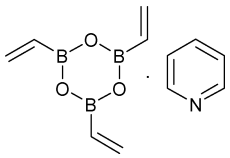
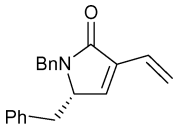
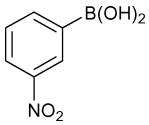
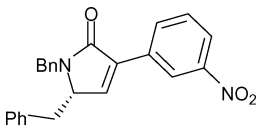
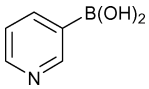
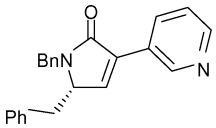
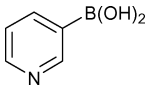
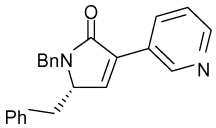
Table 3 Optimisation of Suzuki coupling of vinyl triflate **29**

Entry	Conditions[a]	Base	Boronic acid	Product	Yield (%)	ee (%)[b]
1	90 °C, 14 h	Na_2CO_3		 **30**	29	50
2	90 °C, 14 h	K_3PO_4		 **30**	17	91
3	150 W, 5 min	Na_2CO_3		 **30**	92	>98
4	150 W, 5 min	Na_2CO_3		 **31**	78	>98
5	150 W, 5 min	K_3PO_4		 **32**	73	86
6	150 W, 5 min	K_3PO_4		 **33**	38	47
7	150 W, 5 min	Na_2CO_3		 **33**	50	2

[a] All reactions were performed using 5 mol% $Pd(PPh_3)_4$ (for full details see the Experimental). [b] Enantiomeric excesses were determined by chiral HPLC using the corresponding racemate as standard.

Experimental

General

General experimental details have been reported recently,[4] as has the preparation of the cyclic sulfamidates utilised in this paper.[2] $Pd(PPh_3)_4$ was *freshly* prepared according to Coulson's procedure.[10] Microwave assisted reactions were conducted in sealed pressure tubes using a CEM Discover microwave; the term "powermax" refers to conditions whereby the reaction medium was irradiated at the specified temperature and power whilst being simultaneously cooled with a stream of gaseous nitrogen. FCC refers to flash column chromatography.

(5*S*)-Diethyl(1,5-dibenzylpyrrolidin-2-on-3-yl)phosphonate (14). To a solution of ethyl diethylphosphonoacetate **3** (1.30 mL, 6.6 mmol) in anhydrous THF (30 mL) was added *t*-BuOK (739 mg, 6.6 mmol) and the resulting mixture was heated at 40 °C for 20 minutes to form a colourless solution. Cyclic sulfamidate **9** (1.00 g, 3.3 mmol) was added and the reaction mixture was heated at 40 °C for 13 h. The mixture was cooled to rt, aq. 5 M HCl (3.4 mL) was added and the mixture was stirred for 3 h. The

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reaction mixture was neutralised with saturated aq. $NaHCO_3$, diluted with brine (50 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in PhMe (40 mL) and heated at reflux for 16 h. The reaction mixture was allowed to cool to rt, concentrated *in vacuo* and excess ethyl diethylphosphonoacetate was removed by vacuum distillation (*ca.* 70 °C, 0.01 mm Hg). The residue was purified by FCC (EtOAc) to afford phosphonate **14** (1.27 g, 96%, 2 : 1 dr *A* : *B*) as a colourless oil; ν_{max}/cm^{-1} (film) 2983 (m), 2930 (m), 1689 (s), 1454 (m), 1249 (s), 1024 (s); δ_H (400 MHz, $CDCl_3$) 1.23–1.41 (12H, m, OCH_2CH_3 of *A* and *B*), 1.97–2.34 (4H, m, C4–*H* of *A* and *B*), 2.55 (1H, dd, $J = 13.0$ and 8.5 Hz, C5–CH_2Ph of *A*), 2.66 (1H, dd, $J = 13.0$ and 10.0 Hz, C5–CH_2Ph of *B*), 2.85–3.14 (3H, m, C5–CH_2Ph of *A* and C3–*H* of *A* and *B*), 3.21 (1H, dd, $J = 13.0$ and 4.5 Hz, C5–CH_2Ph of *B*), 3.64 (1H, m, C5–*H* of *B*), 3.78 (1H, m, C5–*H* of *A*), 4.02 (1H, d, $J = 15.0$ Hz, NCH_2Ph of *A*), 4.10–4.36 (9H, m, NCH_2Ph of *B* and OCH_2CH_3 of *A* and *B*), 5.03 (1H, d, $J = 15.0$, NCH_2Ph of *B*), 5.15 (1H, d, $J = 15.0$ Hz, NCH_2Ph of *A*), 7.00–7.09 (4H, m, ArC*H*), 7.19–7.38 (16H, m, ArC*H*); δ_C (75.5 MHz, $CDCl_3$) 16.3–16.6 (4C, m, OCH_2CH_3 × 4), 25.5 (d, $^2J_{PC} = 4.0$ Hz, *C*-4 of *B*), 26.1 (d, $^2J_{PC} = 3.5$ Hz, *C*-4 of *A*), 39.2 (C5–CH_2Ph of *A*), 39.7 (C5–CH_2Ph of *B*), 40.0 (d, $^1J_{PC} = 144.5$ Hz, *C*-3 of *A*), 40.5 (d, $^1J_{PC} = 146.0$ Hz, *C*-3 of *B*), 44.6 (NCH_2Ph of *A*), 44.9 (NCH_2Ph of *B*), 56.3 (d, $^3J_{PC} = 5.0$ Hz, *C*-5 of *A*), 57.3 (d, $^3J_{PC} = 6.0$ Hz, *C*-5 of *B*), 62.1–63.3 (4C, m, OCH_2CH_3 × 4), 126.7, 126.9, 127.6, 127.7, 127.9, 128.1, 128.6, 128.7 (3 signals) and 129.2 (ArCH × 20), 135.9, 136.2, 136.3 and 137.0 (Ar*C* × 4), 169.5 (d, $^2J_{PC} = 3.5$ Hz, *C*-2 of *A* and *B*); δ_P (121 MHz, $CDCl_3$) 24.9 (*B*) and 25.2 (*A*); *m*/*z* (CI^+) 402 ($[M + H]^+$, 100%); HRMS (CI^+): found: $[M + H]^+$ 402.1830, $C_{22}H_{29}NO_4P$ requires 402.1834.

(5*S*)-Diisopropyl(1,5-dibenzylpyrrolidin-2-one-3-yl)phosphonate (16). To a solution of ethyl diisopropylphosphonoacetate **4** (238 μL, 1.00 mmol) in anhydrous THF (5.0 mL) was added *t*-BuOK (112 mg, 1.00 mmol) and the mixture was stirred at 40 °C for 20 minutes to form a colourless solution. Cyclic sulfamidate **9** (150 mg, 0.50 mmol) was added and the mixture was heated at 40 °C for 15.5 h. After cooling to rt, aq. 5 M HCl (0.50 mL) was added and the mixture was stirred at rt for 3 h. The mixture was neutralised with saturated aq. $NaHCO_3$ and then concentrated *in vacuo*. The residue was dissolved in brine (20 mL) and CH_2Cl_2 (15 mL), the organic portion was isolated and the aqueous portion was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford a pale yellow oil. This residue was dissolved in PhMe (8 mL) and heated at 100 °C for 4 h. The mixture was cooled to rt, concentrated *in vacuo* and purified by FCC (EtOAc) to afford phosphonate **16** (165 mg, 77%, 6 : 1 dr *A* : *B*) as a colourless oil; ν_{max}/cm^{-1} (film) 2979 (m), 2932 (m), 1690 (s), 1454 (m), 1248 (s), 1106 (m); δ_H (400 MHz, $CDCl_3$) 1.24–1.44 (24H, m, $OCH(CH_3)_2$ of *A* and *B*), 1.94–2.33 (4H, m, C4–*H* of *A* and *B*), 2.53 (1H, dd, $J = 13.5$ and 8.5 Hz, C5–CH_2Ph of *A*), 2.68–2.83 (2H, m, C3–*H* of *A* and C5–CH_2Ph of *B*), 2.87–3.05 (2H, C3–*H* of *B* and C5–CH_2Ph of *A*), 3.19 (1H, dd, $J =$ 13.0 and 4.0 Hz, C5–CH_2Ph of *B*), 3.55–3.64 (1H, m, C5–*H* of *B*), 3.71–3.79 (1H, m, C5–*H* of *A*), 4.00 (1H, d, $J = 15.0$ Hz, NCH_2Ph of *A*), 4.14 (1H, d, $J = 15.5$ Hz, NCH_2Ph of *B*), 4.65–4.84 (4H, m, $OCH(CH_3)_2$ of *A* and *B*), 5.00 (1H, d, $J = 15.5$ Hz, NCH_2Ph of *B*), 5.15 (1H, d, $J = 15.0$ Hz, NCH_2Ph of *A*), 6.97–7.38 (20H, m, ArC*H*); δ_C (100 MHz, $CDCl_3$) (data for major diastereomer *A* only) 23.8–24.2 (m, $OCH(CH_3)_2$ × 4), 26.3 (d, $^2J_{PC} = 4.0$ Hz, *C*-4), 39.2 (C5–CH_2Ph), 40.5 (d, $^1J_{PC} = 145.5$ Hz, *C*-3), 44.5 (NCH_2Ph), 56.2 (d, $^3J_{PC} = 5.5$ Hz, *C*-5), 70.9 (d, $^2J_{PC} = 5.0$ Hz, $OCH(CH_3)_2$), 71.3 (d, $^2J_{PC} = 5.0$ Hz, $OCH(CH_3)_2$), 126.8, 127.5, 127.9, 128.6 (2 signals) and 129.1 (ArCH × 10), 136.0 and 136.3 (Ar*C* × 2), 169.6 (d, $^2J_{PC} = 4.0$ Hz, *C*-2); δ_P (121 MHz, $CDCl_3$) 22.9 (*B*) and 23.0 (*A*); *m*/*z* (CI^+) 430 ($[M + H]^+$, 80%), 346 (88), 91 (100); HRMS (CI^+): found: $[M + H]^+$ 430.2152, $C_{24}H_{33}NO_4P$ requires 430.2147.

(5*S*)-1,5-Dibenzyl-3-cyclohexylidenepyrrolidin-2-one (22). Procedure A (from ethyl phosphonate **14**): to a suspension of NaH (60% dispersion in mineral oil, 32 mg, 0.80 mmol) in anhydrous THF (5 mL) was added phosphonate **14** (301 mg, 0.75 mmol) and the mixture was stirred for 30 minutes at rt. Cyclohexanone (104 μL, 1.00 mmol) was then added dropwise, and the mixture was stirred for 3 h. The solution was then diluted with Et_2O (25 mL) and water (25 mL) and the phases separated. The aqueous portion was extracted with Et_2O (2 × 25 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by FCC (petrol–Et_2O 4 : 1) afforded the title alkene **22** (188 mg, 73%) as a colourless crystalline solid.

Procedure B (from isopropyl phosphonate **16**): to a solution of phosphonate **16** (229 mg, 0.53 mmol) in anhydrous THF (4.5 mL) was added NaH (60% dispersion in mineral oil, 22 mg, 0.56 mmol) and the mixture was stirred at rt for 15 minutes. The mixture was then cooled to −78 °C and cyclohexanone (68 μL, 0.66 mmol) was added. The mixture was warmed to rt and stirred for 6.5 h. The mixture was then diluted with brine (25 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford a residue which was purified by FCC (hexanes–Et_2O 4 : 1) to yield alkene **22** (95 mg, 52%) as a colourless solid.

Data for **22**: mp 94–97 °C (EtOAc–hexanes); $[\alpha]_D^{20}$ −55.0 ($c = 1.0$, $CHCl_3$); ν_{max}/cm^{-1} (solid) 2920 (m), 2850 (m), 1674 (s), 1655 (s), 1434 (m), 1420 (s), 1262 (s); δ_H (400 MHz, $CDCl_3$) 1.45–1.75 (6H, m), 1.97–2.11 (2H, m), 2.35 (1H, m), 2.43–2.55 (2H, m), 2.89–3.16 (3H, m), 3.60 (1H, m, C5–*H*), 4.08 (1H, d, $J = 15.0$ Hz, NCH_2Ph), 5.14 (1H, d, $J = 15.0$ Hz, NCH_2Ph), 7.00–7.06 (2H, m, ArC*H*), 7.18–7.35 (8H, m, ArC*H*); δ_C (100 MHz, $CDCl_3$) 26.5, 27.9, 28.2 (2 signals), 30.0, 33.4, 40.0 and 44.6 (CH_2 × 8), 54.5 (*C*-5), 120.2 (*C*-3), 126.6, 127.5, 128.3, 128.6, 128.7 and 129.3 (ArCH × 10), 137.3 (Ar*C* × 2), 150.1 (cyclohexyl-*C*), 169.4 (*C*-2); *m*/*z* (EI^+) 345 ($[M]^+$, 20%), 254 ($[M - Bn]^+$ 100); HRMS (EI^+): found: $[M]^+$ 345.2094, $C_{24}H_{27}NO$ requires 345.2093.

(*S*)-1,5-Dibenzyl-3-methylenepyrrolidin-2-one (25). To a solution of heterocyclic phosphonate **14** (1.210 g, 3.02 mmol) in anhydrous THF (15 mL) was added, portionwise, at rt, NaH (60% dispersion in mineral oil, 127 mg, 3.17 mmol) to form a light brown suspension. Paraformaldehyde (191 mg, 6.04 mmol) was added and the mixture was stirred at rt for 3.5 h. Aq. 2 M HCl (8 mL) was added, the mixture was diluted with brine (40 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by FCC (Et_2O–hexanes 2 : 1) to afford alkene **25** (544 mg, 65%) as a colourless oil which crystallised on standing; mp 90.5–92 °C (Et_2O–petrol); $[\alpha]_D^{20}$ −71.0 ($c = 1.6$, $CHCl_3$); found: C, 82.28; H, 6.90; N, 5.05. Calc. for $C_{19}H_{19}NO$: C, 82.19; H, 7.12; N, 4.76%; ν_{max}/cm^{-1} (film) 3028 (w), 2924 (w), 1684 (s), 1659 (s), 1416 (s);

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δ_H (300 MHz, $CDCl_3$) 2.41–2.70 (3H, m, C4–*H* and C5–CH_2Ph), 3.08–3.19 (1H, dd, J = 13.5 and 4.0 Hz, C5–CH_2Ph), 3.69 (1H, dddd, J = 12.5, 8.0, 4.0 and 3.5 Hz, C5–*H*), 4.14 (1H, d, J = 15.0 Hz, NCH_2Ph), 5.20 (1H, d, J = 15.0 Hz, NCH_2Ph), 5.31 (1H, t, J = 2.0 Hz, C3–CH_2), 6.04 (1H, t, J = 2.0 Hz, C3–CH_2), 7.06 (2H, dd, J = 6.5 and 1.5 Hz, ArC*H*), 7.19–7.42 (8H, m, ArC*H*); δ_C (100 MHz, $CDCl_3$) 30.7 (C5–*C*H_2Ph), 39.9 (*C*-4), 45.1 (N*C*H_2Ph), 55.3 (*C*-5), 116 (C3–*C*H_2), 126.7, 127.6, 128.2, 128.6, 128.7 and 129.1 (Ar*C*H × 10), 136.4, 136.8 and 138.9 (Ar*C* and *C*-3), 168.1 (*C*-2); m/z (CI^+) 278 ([M + H]$^+$, 100%); HRMS (CI^+): found: [M + H]$^+$ 278.1541, $C_{19}H_{20}NO$ requires 278.1545.

(*S*)-3-Hydroxy-1,5-dimethyl-4-phenyl-1,5-dihydropyrrol-2-one (27). A solution of phosphonate **17** (110 mg, 0.31 mmol) in anhydrous THF (2.8 mL) was added, *via* syringe, to NaH (60% dispersion in mineral oil, 29 mg, 0.72 mmol) in a flask fitted with a drying tube (dry air atmosphere). The resulting cream suspension was stirred at rt for 4 h and then quenched with aq. 1 M HCl (1 mL). The mixture was diluted with brine (10 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford a colourless solid. This residue was purified by FCC (EtOAc–hexanes 2 : 1) to afford oxidised adduct **27** (46 mg, 73%) as a colourless crystalline solid; mp 182–185 °C (Et_2O–hexanes); $[\alpha]_D^{20}$ −74.5 (c = 1.5, $CHCl_3$); ν_{max}/cm^{-1} (film) 3143 (br m), 1661 (s), 1439 (m), 1383 (m), 1132 (m); δ_H (400 MHz, $CDCl_3$) 1.40 (3H, d, J = 6.5 Hz, C5–CH_3), 3.13 (3H, s, NCH_3), 4.37 (1H, q, J = 6.5 Hz, C5–*H*), 7.26–7.32 (1H, m, ArC*H*), 7.43 (2H, dd, J = 7.5 and 7.5 Hz, ArC*H*), 7.66 (2H, d, J = 7.5 Hz, ArC*H*), 8.22 (1H, br s, O*H*); δ_C (100 MHz, $CDCl_3$) 17.9 (C5–*C*H_3), 27.4 (N*C*H_3), 55.6 (*C*-5), 123.1 (*C*-3), 127.3 (2 signals) and 128.5 (Ar*C*H × 5), 131.6 (Ar*C*), 142.1 (*C*-4), 166.7 (*C*-2); HRMS (ESI^+): found: [M + H]$^+$ 204.1027, $C_{12}H_{14}NO_2$ requires 204.1019.

(*S*)-1,5-Dibenzylpyrrolidine-2,3-dione (28). An O_3/O_2 mixture was bubbled through a solution of **25** (232 mg, 0.84 mmol) in MeOH (20 mL) at −78 °C for 30 minutes during which time the solution became lilac. N_2 was bubbled through the reaction mixture for 30 minutes to remove excess O_3 and then Me_2S (0.3 mL) was added. The mixture was stirred at −78 °C for 45 minutes and then allowed to warm to rt over 2.5 h. Solvent was removed *in vacuo* and the residue was dissolved in Et_2O (15 mL), washed with water (4 × 5 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford dione **28** (230 mg, 98%) as a colourless semi-solid. This material was used in the next stage without further purification; ν_{max}/cm^{-1} (film) 3029 (w), 2927 (w), 1763 (s), 1718 (s), 1428 (m); δ_H (300 MHz, $CDCl_3$) 2.42 (2H, m, C4–*H*), 2.69 (1H, dd, J = 13.5 and 8.5 Hz, C5–CH_2Ph), 3.21 (1H, dd, J = 13.5 and 4.0 Hz, C5–CH_2Ph), 3.96 (1H, m, C5–*H*), 4.32 (1H, d, J = 15.0 Hz, NCH_2Ph), 5.34 (1H, d, J = 15.0 Hz, NCH_2Ph), 7.01 (2H, d, J = 6.5 Hz, ArC*H*), 7.15–7.44 (8H, m, ArC*H*); δ_C (68 MHz, $CDCl_3$) 37.1 (C5–*C*H_2Ph), 39.6 (N*C*H_2Ph), 46.2 (*C*-4), 52.0 (*C*-5), 127.5, 128.4, 128.6, 129.0, 129.2 and 129.4 (Ar*C*H × 10), 134.9 and 135.0 (Ar*C*), 160.0 (*C*-2), 197.8 (*C*-3); m/z (CI^+) 280 ([M + H]$^+$, 100%); HRMS (CI^+): found: [M + H]$^+$ 280.1331, $C_{18}H_{18}NO_2$ requires 280.1338.

(*S*)-Trifluoromethanesulfonic acid 1,5-dibenzyl-2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl ester (29). To a solution of **28** (40 mg, 0.14 mmol) in *p*-dioxane (2.0 mL) at rt were added K_2CO_3 (22 mg, 0.16 mmol) and water (0.5 mL) to form a yellow solution. After 10 minutes *N*-phenyltriflimide (57 mg, 0.16 mmol) was added and the resulting suspension was stirred at rt for 2 h during which time the mixture became an orange solution. The mixture was diluted with brine (10 mL) and extracted with CH_2Cl_2 (4 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by FCC (petrol–Et_2O 3 : 1) to afford triflate **29** (36 mg, 63%) as a yellow crystalline solid; mp 82–84 °C (Et_2O–petrol); $[\alpha]_D^{20}$ +91.7 (c = 1.0, $CHCl_3$); ν_{max}/cm^{-1} (film) 3013 (w), 2929 (w), 1712 (s), 1644 (m), 1429 (s), 1217 (s), 1136 (s); δ_H (400 MHz, $CDCl_3$) 2.44 (1H, dd, J = 13.5 and 9.0 Hz, C5–CH_2Ph), 3.26 (1H, dd, J = 13.5 and 5.0 Hz, C5–CH_2Ph), 4.12 (1H, ddd, J = 9.0, 5.0, and 2.0 Hz, C5–*H*), 4.22 (1H, d, J = 16.0 Hz, NCH_2Ph), 5.23 (1H, d, J = 16.0 Hz, NCH_2Ph), 6.66 (1H, d, J = 2.0 Hz, C4–*H*), 7.03 (2H, d, J = 6.5 Hz, ArC*H*), 7.20–7.39 (8H, m, ArC*H*); δ_C (75 MHz, $CDCl_3$) 37.6 (C5–*C*H_2Ph), 44.9 (N*C*H_2Ph), 58.2 (*C*-5), 118.6 (q, J_{FC} = 320.0 Hz, C3–OSO_2*C*F_3), 127.6, 128.2 (2 signals), 129.0, 129.1 and 129.2 (Ar*C*H × 10), 130.3 (*C*-4), 134.7, 136.2 and 141.7 (Ar*C* and *C*-3), 162.3 (*C*-2); δ_F (70 MHz, $CDCl_3$) −72.9 (s, C3–OSO_2CF_3); m/z (CI^+) 412 ([M + H]$^+$, 100%); HRMS (CI^+): found: [M + H]$^+$ 412.0848, $C_{19}H_{17}NO_4SF_3$ requires 412.0825. The enantiomeric purity of this compound was determined by chiral HPLC (Chiralpak AD-H, isocratic hexanes–i-PrOH 98 : 2, 1.0 mL min^{-1}, 20 °C); t_R (major) = 47.1 min and t_R (minor) = 37.4 min.

(*S*)-1,5-Dibenzyl-3-phenyl-1,5-dihydropyrrol-2-one (30). A solution of vinyl triflate **29** (100 mg, 0.24 mmol), phenyl boronic acid (34 mg, 0.28 mmol), Na_2CO_3 (39 mg, 0.37 mmol) and freshly prepared $Pd(PPh_3)_4$ (13 mg, 5 mol%) in *p*-dioxane (3 mL) and water (1 mL) was heated under microwave conditions for 5 minutes (90 °C, 150 W, Powermax). The mixture was cooled to rt and extracted with Et_2O (4 × 2 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford a yellow oil. This residue was purified by FCC (Et_2O–hexanes 1 : 1) to yield arylated lactam **30** (75 mg, 92%, >98% ee) as a yellow oil; $[\alpha]_D^{20}$ −59.7 (c = 0.7, $CHCl_3$); ν_{max}/cm^{-1} (film) 3307 (m), 2926 (m), 1679 (s), 1494 (m), 1410 (m), 1226 (m), 1080 (m); δ_H (400 MHz, $CDCl_3$) 2.59 (1H, dd, J = 13.0 and 9.0 Hz, C5–CH_2Ph), 3.27 (1H, dd, J = 13.0 and 5.0 Hz, C5–CH_2Ph), 4.12 (1H, ddd, J = 9.0, 5.0 and 1.5 Hz, C5–*H*), 4.25 (1H, d, J = 15.0 Hz, NCH_2Ph), 5.30 (1H, d, J = 15.0 Hz, NCH_2Ph), 7.02 (1H, d, J = 1.5 Hz, C4–*H*), 7.10 (2H, d, J = 7.0 Hz, ArC*H*), 7.22–7.43 (11H, m, ArC*H*), 7.85 (2H, d, J = 7.0 Hz, ArC*H*); δ_C (100 MHz, $CDCl_3$) 38.1 (C5–*C*H_2Ph), 44.4 (N*C*H_2Ph), 60.3 (*C*-5), 127.1, 127.2, 127.6, 128.2, 128.5, 128.6, 128.8 (2 signals) and 129.2 (Ar*C*H × 15), 131.7, 136.3, 136.4 and 137.6 (Ar*C* × 3 and *C*-3), 140.2 (*C*-4), 170.0 (*C*-2); m/z (CI^+) 340 ([M + H]$^+$, 100%); HRMS (CI^+): found: [M + H]$^+$ 340.1703, $C_{24}H_{22}NO$ requires 340.1701. The enantiomeric purity of this compound was determined by chiral HPLC (Chiralcel OJ-H, isocratic hexanes–i-PrOH 90 : 10, 1.0 mL min^{-1}, 20 °C); t_R (major) = 74.3 min and t_R (minor) = 65.5 min.

(*S*)-1,5-Dibenzyl-3-vinyl-1,5-dihydropyrrol-2-one (31). A solution of vinyl triflate **29**[11] (75 mg, 0.18 mmol), vinyl boroxane (48 mg, 0.20 mmol), Na_2CO_3 (29 mg, 0.27 mmol) and freshly prepared $Pd(PPh_3)_4$ (10 mg, 5 mol%) in *p*-dioxane (1.5 mL) and water (0.5 mL) was heated under microwave conditions for 5 minutes (90 °C, 150 W, Powermax). The mixture was cooled to rt and extracted with Et_2O (4 × 2 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford

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a yellow oil. This residue was purified by FCC (petrol–Et_2O 2 : 1) to yield diene **31** (41 mg, 78%) as a yellow oil; $[\alpha]_D^{20}$ −57.1 (c = 0.8, $CHCl_3$); ν_{max}/cm $^{-1}$ (film) 2922 (w), 1677 (s), 1603 (w), 1408 (m), 1028 (m); δ_H (270 MHz, $CDCl_3$) 2.52 (1H, dd, J = 13.5 and 10.0 Hz, C5–CH_2Ph), 3.21 (1H, dd, J = 13.5 and 5.5 Hz, C5–CH_2Ph), 4.01–4.10 (1H, m, C5–*H*), 4.20 (1H, d, J = 15.0 Hz, NCH_2Ph), 5.22 (1H, d, J = 15.0 Hz, NCH_2Ph), 6.20 (1H, dd, J = 11.0 and 1.5 Hz, CH=CH_2), 6.30 (1H, dd, J = 17.5 and 1.5 Hz, CH=CH_2), 6.44 (1H, dd, J = 17.5 and 11.0 Hz, CH=CH$_2$), 6.68 (1H, s, C4–*H*), 7.05–7.15 (2H, m, ArC*H*), 7.20–7.43 (8H, m, ArC*H*); δ_c (100 MHz, $CDCl_3$) 38.0 (C5–*C*H$_2$Ph), 44.1 (N*C*H$_2$Ph), 60.5 (*C*-5), 119.8 (*C*-8), 127.0, 127.3, 127.6, 128.1, 128.7, 128.8 and 129.2 (Ar*C*H × 10 and *C*-3), 134.5, 136.4 and 137.5 (Ar*C* × 2 and *C*-4), 140.7 (*C*-7), 170.0 (*C*-2); HRMS (ESI$^+$): found [M + Na]$^+$ 312.1359, $C_{20}H_{19}NONa$ requires 312.1359. The enantiomeric purity of this compound was determined by chiral HPLC (Chiralcel OJ-H, isocratic hexanes–i-PrOH 95 : 5, 1.0 mL min^{-1}, 20 °C); t_R (major) = 41.3 min and t_R (minor) = 25.1 min.

(3*S*,4*R*,5*S*)-1,5-Dibenzyl-4-butyl-3-phenylpyrrolidin-2-one (34) and (3*R*,4*R*,5*S*)-1,5-dibenzyl-4-butyl-3-phenylpyrrolidin-2-one (35). To a suspension of CuI (112 mg, 0.59 mmol) in anhydrous THF (0.5 mL) at 0 °C was added, *via* syringe, *n*-BuLi in hexanes (1.6 M, 1.12 mmol) to form a brown suspension. After 10 min the mixture was cooled to −78 °C and TMSCl (35 μL, 0.282 mmol) and hexamethylphosphoramide (HMPA, 65 μL, 0.37 mmol) were sequentially added *via* syringe. After a further 5 minutes a solution of arylated lactam **30** (53 mg, 0.16 mmol) in anhydrous THF (0.75 mL) was added, *via* syringe, and the mixture was stirred at rt for 5 h. Saturated aq. NH_4Cl (10 mL) was added and the mixture was diluted with Et_2O (15 mL). The organic portion was isolated and washed with saturated aq. NH_4Cl (10 mL) and water (2 × 10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford a yellow oil. This residue was purified by FCC (hexanes–Et_2O 2 : 1) to yield *trans*-lactam **34** (28 mg, 50%, >98% ee) and subsequently *cis*-lactam **35** (9 mg, 15%, >98% ee) as colourless solids.

Data for *trans* product **34**: mp 106–107 °C ($CHCl_3$–hexanes); $[\alpha]_D^{20}$ +10.4 (c = 1.2, $CHCl_3$); ν_{max}/cm^{-1} (film) 2927 (m), 1686 (s), 1496 (m), 1453 (m); δ_H (400 MHz, $CDCl_3$) 0.58 (3H, t, J = 7.0 Hz, $(CH_2)_3CH_3$), 0.73–1.23 (6H, m, $(CH_2)_3CH_3$), 2.04 (1H, dddd, J = 6.0, 6.0, 6.0 and 6.0 Hz, C4–*H*), 2.60 (1H, dd, J = 13.5 and 8.0 Hz, C5–CH_2Ph), 2.97 (1H, dd, J = 13.5 and 4.5 Hz, C5–CH_2Ph), 3.25 (1H, ddd, J = 8.0, 6.0 and 4.5 Hz, C5–*H*), 3.31 (1H, d, J = 6.0 Hz, C3–*H*), 4.03 (1H, d, J = 15.0 Hz, NCH_2Ph), 5.14 (1H, d, J = 15.0 Hz, NCH_2Ph), 6.89–6.93 (2H, m, ArC*H*), 7.01–7.05 (2H, d, J = 7.5 Hz, ArC*H*), 7.12–7.31 (11H, m, ArC*H*); δ_C (100 MHz, $CDCl_3$) 13.8 ($(CH_2)_3CH_3$), 22.4, 28.7 and 34.6 ($(CH_2)_3CH_3$), 39.8 (C5–*C*H$_2$Ph), 45.1 (N*C*H$_2$Ph), 45.2 (*C*-4), 55.1 (*C*-3), 62.4 (*C*-5), 126.8, 126.9, 127.7, 128.1, 128.3, 128.7, 128.8 (2 signals) and 129.5 (Ar*C*H × 15), 136.6, 137.1 and 140.7 (Ar*C* × 3), 174.8 (*C*-2); HRMS (ESI$^+$): found: [M + H]$^+$ 398.2489, $C_{28}H_{32}NO$ requires 398.2478. The enantiomeric purity of this compound was determined by chiral HPLC (Chiralpak AD-H, isocratic hexanes–i-PrOH 95 : 5, 1.0 mL min^{-1}, 20 °C); t_R (major) = 49.1 min and t_R (minor) = 24.1 min. The relative stereochemical assignment of this product was assigned on the basis of field gradient NOE experiments. Observed NOE correlations: C3–*H* → C4–*H*, C4–*Bu*; C4–*H* → C5–CH_2Ph, C5–*H*, C3–*H*, C3–*Ph*, C4–*Bu*; C5–*H* → C4–*H*, C4–*Bu*, C5–CH_2Ph; C5–CH_2Ph → C4–*H*, C5–*H*, C3–*Ph*.

Data for *cis* product **35**: mp 96.5–98 °C (Et_2O–hexanes); $[\alpha]_D^{20}$ +17.1 (c = 0.7, $CHCl_3$); ν_{max}/cm^{-1} (film) 2929 (m), 1686 (s), 1496 (m), 1455 (m), 1249 (m), 1079 (m); δ_H (400 MHz, $CDCl_3$) 0.52 (3H, t, J = 7.0 Hz, $(CH_2)_3CH_3$), 0.56–0.97 (6H, m, $(CH_2)_3CH_3$), 2.17–2.26 (1H, m, C4–*H*), 2.82 (1H, dd, J = 13.5 and 8.0 Hz, C5–CH_2Ph), 3.06 (1H, dd, J = 13.5 and 4.5 Hz, C5–CH_2Ph), 3.34–3.41 (1H, m, C5–*H*), 3.84 (1H, d, J = 8.5 Hz, C3–*H*), 4.56 (1H, d, J = 14.5 Hz, NCH_2Ph), 5.30 (1H, d, J = 14.5 Hz, NCH_2Ph), 7.08–7.18 (4H, m, ArC*H*), 7.20–7.43 (11H, m, ArC*H*); δ_C (100 MHz, $CDCl_3$) 13.6 ($(CH_2)_3CH_3$), 22.1, 28.6 and 29.0 ($(CH_2)_3CH_3$), 38.4 (C5–*C*H$_2$Ph), 42.0 (*C*-4), 44.8 (N*C*H$_2$Ph), 50.8 (*C*-3), 61.1 (*C*-5), 126.8, 126.9, 127.8, 128.3, 128.6, 128.7 (2 signals), 129.4 and 129.9 (Ar*C*H × 15), 136.2, 136.7 and 137.5 (Ar*C* × 3), 174.3 (*C*-2); HRMS (ESI$^+$): found: [M + H]$^+$ 398.2490, $C_{28}H_{32}NO$ requires 398.2478. The enantiomeric purity of this compound was determined by chiral HPLC (Chiralpak AD-H, isocratic hexanes–i-PrOH 96 : 4, 1.0 mL min^{-1}, 20 °C); t_R (major) = 43.8 min and t_R (minor) = 41.7 min. The relative stereochemical assignment of this product was assigned on the basis of field gradient NOE experiments. Observed NOE correlations: C3–*H* → C4–*H*, C5–CH_2Ph; C4–*H* → C5–CH_2Ph, C5–*H*, C3–*H*, C3–*Ph*, C4–*Bu*; C5–*H* → C4–*H*, C4–*Bu*, C3–*Ph*, C5–CH_2Ph; C5–CH_2Ph → C3–*H*, C4–*H*, C5–*H*; C3–*Ph* → C4–*Bu*.

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