Electrophile-mediated Cyclisations involving the Allene π-System. Stereoselectivity and Synthetic Utility of Pd^{II}-Catalysed Heteroatom Cyclisation Reactions. X-Ray Molecular Structure of Methyl 2-[*trans*-3-Phenyl-*N*-(*p*-tolylsulfonyl)pyrrolidin-2-yl]acrylate

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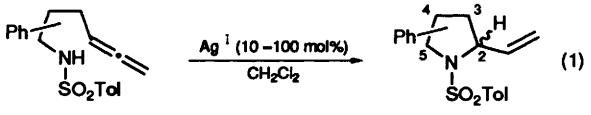
Pd^{II}-Mediated cyclisation and methoxycarbonylation of the phenyl-substituted allenic sulfonamides **4**, **5** and **6** gave the corresponding *N*-sulfonyl 2,3-, 2,4- and 2,5-disubstituted pyrrolidines **9**, **10** and **11**, respectively. With the exception of compound **4**, cyclisations were not highly selective and similar trends were observed with the α-amino allenic esters **7** and **8**. Some improvement, both in yield and diastereoselectivity, was apparent when cyclisations were carried out in the presence of an excess of Et_3N. The isolation of acyclic by-products **14** and **15** from α-amino allenic ester **7** suggests that chloropalladiation may play a key role in the mechanism of this cyclisation sequence and similar by-products were obtained from cyclisation of the unsubstituted allenic sulfonamides **16** and **20** leading to 6- and 7-membered rings, respectively. Other synthetic aspects of this palladium-based chemistry, including efforts directed towards coupling of the cyclisation step with a Heck-type olefination, are also described.

Stereochemical control in electrophile-mediated cyclisations that lead to functionalised heterocycles is important if the full synthetic potential of this methodology is to be realised.[1] Our interest[2] in this area, though varied, has focused primarily on the cyclisation of nitrogen nucleophiles to activated allenes, although these reactions can also be achieved by using a hydroxy group as the nucleophile to give oxygen-containing heterocycles.[3] Stereocontrol in electrophile-mediated cyclisations is, however, usually more difficult to achieve in the nitrogen-based series and, as part of a broader study, we recently described the generation of 2,3-, 2,4- and 2,5-disubstituted pyrrolidines from appropriately substituted *N*-tolylsulfonyl allenic amines [equation (1)].[2a]

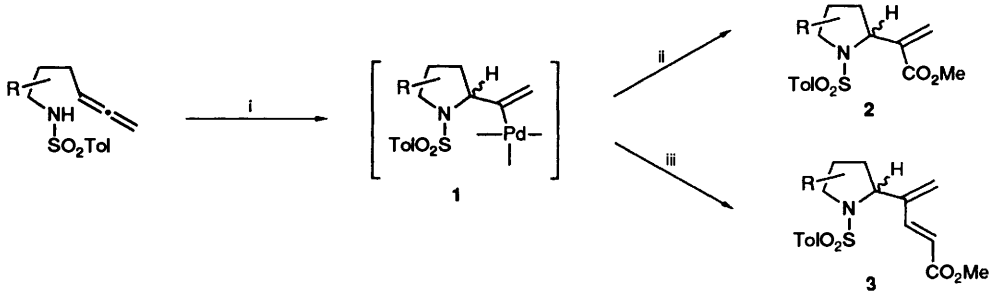


(1)

These transformations, which were carried out under Ag^I-catalysed conditions, were high yielding and also highly stereoselective for the 2,3-series (*trans* product obtained) and the 2,5-series (*cis* product obtained); cyclisation to give a 2,4-disubstituted pyrrolidine was, however, essentially nonselective. The use of Ag^I as the electrophilic trigger is somewhat limiting in terms of the level of functionality that is imparted to the heterocyclic product but other metal-ion electrophiles can be used to activate the allenic moiety.

The cyclisation of allenic alcohols, amines and amides may be carried out using Pd^{II} as the electrophilic trigger and when cyclisation is carried out in the presence of CO and methanol the initially formed η^1-vinylpalladium **1** undergoes insertion of carbon monoxide followed by methanolysis to give heterocyclic acrylates **2** in good-to-moderate yields.[4] This reaction sequence is illustrated in Scheme 1 using the sulfonamide nucleophile, but the general applicability of this process for a wide range of other *N*-nucleophiles should be appreciated.

The Pd^{II}-mediated cyclisation/methoxycarbonylation chemistry was originally developed using alkenyl-based substrates and needs only to utilize a catalytic amount of Pd^{II} if a stoichiometric oxidant, such as $CuCl_2$ is also included.[5] The heterocyclic products **2** are synthetically very attractive but, as with the corresponding Ag^I-catalysed reaction, very little is known regarding the level of stereocontrol that may be exercised in this process. In this paper we describe the cyclisation of a series of substituted allenic sulfonamides under carbonylating conditions in terms of the distribution of *cis*- and *trans*-disubstituted pyrrolidine products that may be obtained. Some of the more general mechanistic and synthetic features of this cyclisation sequence are also presented.



Scheme 1 *Reagents:* i, Pd^{II}; ii, CO, MeOH, $CuCl_2$; iii, $CH_2{=}CHCO_2Me$

We were interested in developing this chemistry in other ways and the alkenylpalladium intermediate **1** shown in Scheme 1 should also be reactive in Heck-type addition processes leading to functionalised dienes **3**.[6] Although this combination of electrophile-mediated cyclisation/Heck addition has not been well explored, both this process and the established CO-based methodology offer attractive solutions to the problems associated with generating functionalised heterocycles. We also outline here some results relating to the combination of the Pd^{II}-mediated cyclisation and Heck addition.

Results and Discussion

The synthesis of the phenyl-substituted sulfonamides **4**, **5** and **6** has already been described.[2a] We have also included in this study results obtained from the *N*-tosyl and *N*-benzyl α-amino esters **7**[2c] and **8**[2c] respectively. Cyclisations were carried out under standard conditions: $PdCl_2$ (0.1 mol equiv.), $CuCl_2$ (3–4 mol equiv.), MeOH, and CO (balloon) at room temperature, and reaction was generally complete within 2–12 h with the products being isolated following work-up with aq. ethanolamine and chromatography. The influence of an added base (Et_3N) was also examined in some cases and this is discussed below.

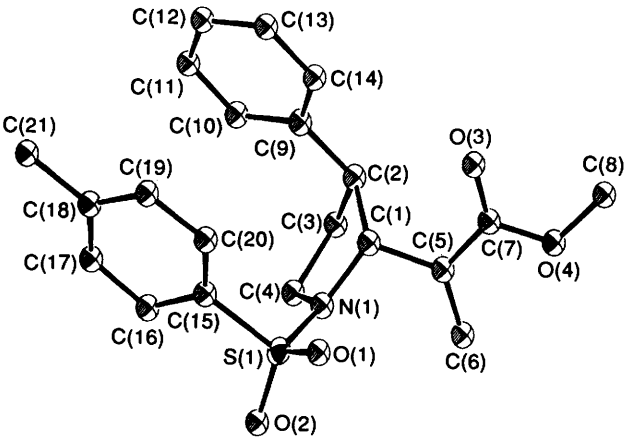
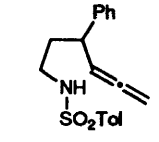
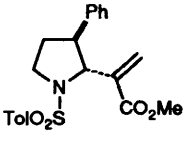
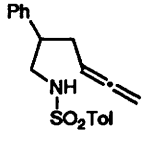
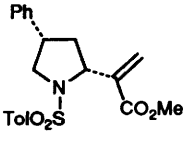
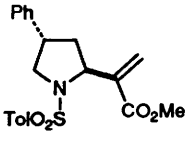
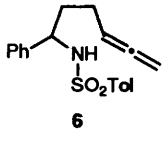
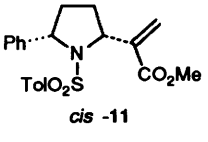
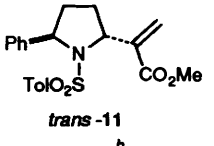
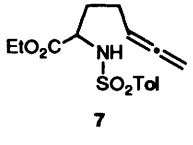
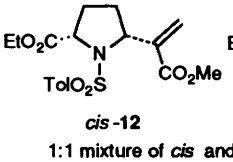
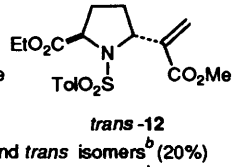
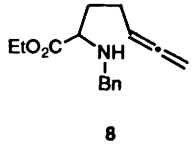
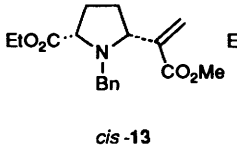
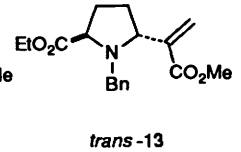


Fig. 1 ORTEP Diagram of *trans*-**9**

Table 1

Allenic sulfonamide or amine	Products (isomer distribution; yield)
 **4**	 *trans*-**9** (23%,57%[a] see text)
 **5**	 *cis*-**10**  *trans*-**10** 1:1 mixture of *cis* and *trans* isomers[b] (63%)
 **6**	 *cis*-**11**  *trans*-**11** 1.4:1 mixture of *cis* and *trans* isomers[b] (24%) 2:1 mixture of *cis* and *trans* isomers[a] (68%)
 **7**	 *cis*-**12**  *trans*-**12** 1:1 mixture of *cis* and *trans* isomers[b] (20%) 3:1 mixture of *cis* and *trans* isomers[b] (68%)[a]
 **8**	 *cis*-**13**  *trans*-**13** 3:1 mixture of *cis* and *trans* isomers[b] (55%)

[a] Yield and product distribution when cyclisation was carried out in the presence of Et_3N (4 mol equiv.). [b] The *cis*/*trans* assignment of isomers was not carried out.

The results of this aspect of the study—yields and *cis*/*trans* distribution of pyrrolidine products—are shown in Table 1. Of the substrates studied only compound **4** showed a high degree of selectivity, leading exclusively to the *trans*-2,3-disubstituted pyrrolidine *trans*-**9**, though in low (23%) yield. When the cyclisation was carried out in the presence of Et_3N (4 mol equiv.) the yield of the cyclisation reaction was improved significantly and a 5:1 mixture (by NMR spectroscopy) of *trans*-**9** and another component (possibly *cis*-**9**) was obtained. *trans*-**9** Was isolated following chromatography in 57% yield and the *trans*-configuration of this major component was confirmed by X-ray crystallographic analysis (Fig. 1).† However, we were unable to isolate the minor component of this mixture and there is a possibility that this corresponds to an acyclic by-product (see below) and not to *cis*-**9**.

Cyclisation of sulfonamides **5** and **6** showed a low level of diastereoselectivity, leading to *cis*/*trans*-**10** and *cis*/*trans*-**11**,

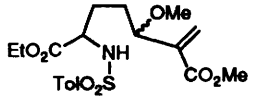
† A blocky crystal of approximate dimensions 0.2 × 0.2 × 0.2 mm was selected for data collection. *Crystal data*: $C_{21}H_{23}NO_4S$, M = 385.5, triclinic, a = 8.042(2), b = 11.091(1), c = 11.377(2) Å, α = 105.44(1)°, β = 100.32(3)°, γ = 96.74(1)°, V = 959.0 Å^3, space group $P\bar{1}$, Z = 2, D_c = 1.33 g cm^{-3}, μ(Mo-Kα) = 1.53 cm^{-1}, F(000) = 408. Data were measured at room temperature on a Hilger and Watts Y290 four-circle diffractometer in the range $2 < \theta < 22°$. 2361 Reflections were collected of which 1887 were unique with $I \geq 3\sigma(I)$. Data were corrected for Lorentz and polarisation effects but not for absorption. The structure was solved by conventional Direct methods and refined using the SHELX suite of programs (G. M. Sheldrick, SHELX86, a Computer Program for Crystal Structure Determination, University of Goetingen, 1986; G. M. Sheldrick, SHELX76, a Computer Program for Crystal Structure Determination, University of Cambridge, 1976). In order to account for the thermal motion the sulfur and oxygen atoms and carbons 5–8 were allowed to vibrate anisotropically in the final stages of convergence. Hydrogens were included at calculated positions. Final residuals after 19 cycles of full-matrix least-squares were $R = R_w$ = 0.0786 for unit weights. The total number of parameters varied was 154. Maximum final shift/esd was 0.008, and the maximum and minimum residual densities were 0.19 and −0.14 e Å^{-3}, respectively. Final fractional atomic co-ordinates are given in Table 2 and isotropic thermal parameters, bond distances and angles, and tables of anisotropic temperature factors and hydrogen-atom position factors and hydrogen-atom positions have been submitted to the Cambridge Crystallographic Data Centre. (See section 5.6.3. of 'Instructions for Authors, issue 1.)

Table 2 Fractional atomic co-ordinates for acrylate **9**

Atom	*x*	*y*	*z*
S(1)	−0.0137(2)	0.2669(1)	0.8076(1)
O(1)	0.1361(6)	0.3513(4)	0.8784(4)
O(2)	−0.0519(6)	0.1408(4)	0.8220(4)
O(3)	−0.6195(6)	0.0832(4)	0.8163(4)
O(4)	−0.6072(5)	0.1445(4)	1.0208(3)
C(5)	−0.4031(7)	0.2507(5)	0.9354(5)
C(6)	−0.3293(9)	0.3204(6)	1.0481(5)
C(7)	−0.5546(8)	0.1514(5)	0.9163(5)
C(8)	−0.7530(9)	0.0485(7)	1.0087(6)
N(1)	−0.1744(6)	0.3367(4)	0.8413(4)
C(1)	−0.3475(7)	0.2642(5)	0.8173(5)
C(2)	−0.4574(8)	0.3424(5)	0.7548(5)
C(3)	−0.3644(8)	0.4782(5)	0.8201(5)
C(4)	−0.1778(8)	0.4685(5)	0.8309(5)
C(9)	−0.4682(7)	0.3001(5)	0.6150(5)
C(10)	−0.4004(8)	0.3760(5)	0.5476(5)
C(11)	−0.4127(9)	0.3332(6)	0.4211(6)
C(12)	−0.4960(8)	0.2132(6)	0.3566(6)
C(13)	−0.5646(9)	0.1371(6)	0.4218(6)
C(14)	−0.5507(8)	0.1798(6)	0.5491(5)
C(15)	−0.0038(7)	0.2525(5)	0.6507(5)
C(16)	0.0869(8)	0.3491(6)	0.6171(5)
C(17)	0.0892(9)	0.3399(6)	0.4962(6)
C(18)	0.0044(8)	0.2346(6)	0.4027(6)
C(19)	−0.0841(9)	0.1388(6)	0.4372(6)
C(20)	−0.0880(8)	0.1474(6)	0.5606(5)
C(21)	0.0096(11)	0.2249(8)	0.2696(7)

respectively. This selectivity was not improved by carrying out the cyclisation in the presence of an excess of Et_3N although in the case of sulfonamide **6** the yield of *cis*/*trans*-**11** was improved to 60%. The lack of selectivity observed for sulfonamide **5** in the formation of the 2,4-disubstituted pyrrolidines **10** was not unexpected but we were surprised by the presence of both *cis*- and *trans*-**11** from cyclisation of compound **6**; under the Ag^I-catalysed cyclisation conditions examined earlier this substrate had shown essentially complete *cis*-selectivity.[2a]

The α-amino esters **7** and **8** did show a more useful level of diastereoselectivity, but this was still significantly lower than had been observed in the corresponding Ag^I-catalysed process.[2c] Cyclisation of amino-ester **8** proceeded smoothly to give an inseparable 3:1 mixture of isomers (*cis*/*trans*-**13**) in 55% yield. Under the standard conditions (no added base) sulfonamide **7** gave *cis*- and *trans*-**12** as a 1:1 mixture in 20% yield, together with two by-products, the allylic ether **14** and the allylic chloride **15** in a 1:2.4 ratio in 20% yield. These two



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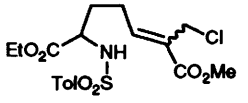

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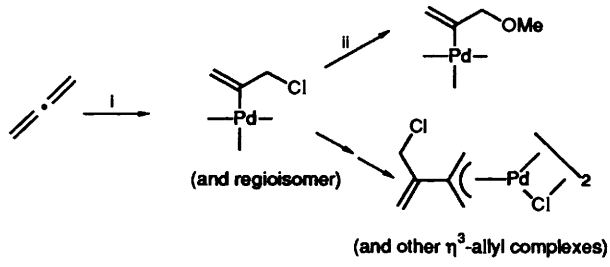
by-products could not be separated from one another and structural assignment is based on ^1H NMR analysis and the presence in the mass spectrum (CI) of peaks at *m*/*z* 382 (**14**, $M^+ + 1$) and *m*/*z* 386/388 (**15**; $M^+ + 1$). The incorporation of a base (Et_3N, 4 mol equiv.) improved the efficiency of the cyclisation sequence to give acrylate **12** in 68% and as a 3:1 mixture of *cis* and *trans* isomers. Unambiguous stereochemical assignment of the major isomer has not, however, been possible.

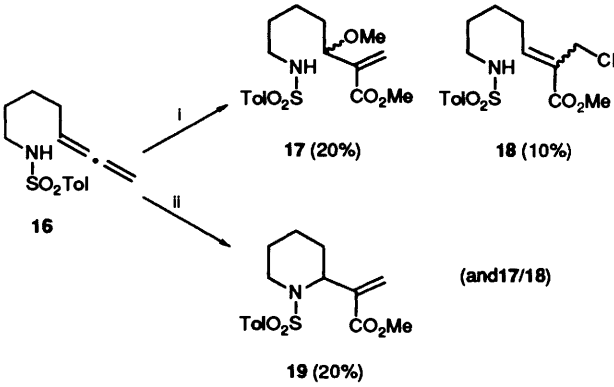
The reasons behind the divergence in *cis*/*trans* product distribution observed for Ag^I *vs.* Pd^{II}-mediated cyclisation are most likely due to a basic difference in mechanism. Some years ago Shaw[7] and Schultz[8] demonstrated in independent studies that allene reacted with $Pd^{II}Cl_2L_2$ complexes to give products that were suggested to arise from net addition of 'Pd–Cl' across one π-bond. The resulting η^1-complexes then underwent further reaction leading to various dimeric products containing a η^3-allyl unit (Scheme 2). The susceptibility of the intermediate complex towards external nucleophiles, such as methanol, was also demonstrated though it is not clear whether nucleophilic displacement takes place directly or *via* ligand transfer from the metal centre. Substituted allenes are also known to undergo similar transformations.[9]



Scheme 2 *Reagents:* i, $PdCl_2L_2$; ii, MeOH

The isolation of products **14** and **15** provides evidence for the participation of this mode of activation in this present study. In the case of substrate **7** the nucleophilicity of nitrogen is lowered by both the sulfonamide residue and the adjacent ester function although neither of the by-products are thought to be important intermediates in the principle cyclisation pathway. When the mixture of products **14** and **15** was resubjected to the standard Pd^{II}-mediated cyclisation conditions, ^1H NMR analysis indicated that while the ether **14** was unreactive, chloride **15** did cyclise to give a 1:1 mixture of *cis*- and *trans*-**12**. However, cyclisation was much slower compared with direct cyclisation of substrate **7** under the same conditions. We have briefly examined the use of palladium(II) complexes lacking nucleophilic ligands and have studied the ability of the commercially available complex $[Pd(MeCN)_4(BF_4)_2]$ to effect cyclisation/methoxycarbonylation of allenic ester **7** with and without Et_3N being present. In both cases a 1:1 mixture of *cis*- and *trans*-**12** was observed together with allylic ether **14** in varying amounts; these reactions were monitored by ^1H NMR spectroscopy and no yields were recorded.

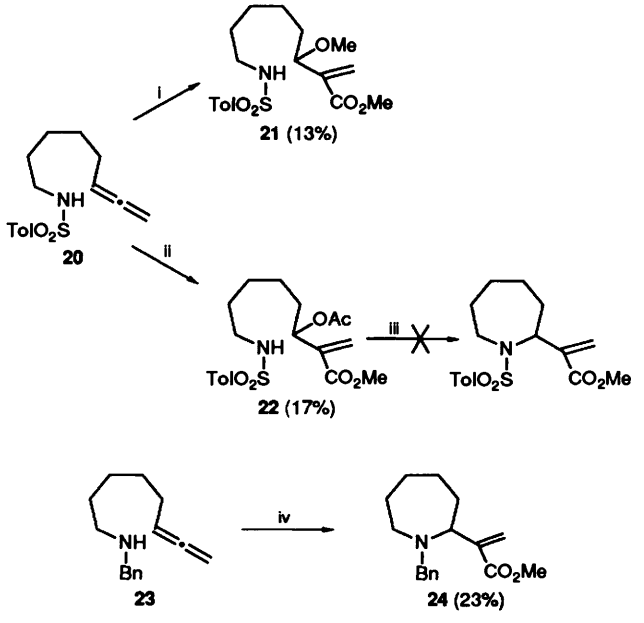
The formation of related by-products was also observed when this chemistry was applied to the synthesis of 6- and 7-membered rings. For example, attempts to cyclise the unsubstituted sulfonamide **16** in the *absence of* Et_3N failed and a 2:1 mixture of allylic ether **17** and allylic chloride **18** was isolated in 30% combined yield. When this reaction was repeated with Et_3N (4 mol equiv.), the piperidine **19** was isolated but only in 20% yield (Scheme 3). The ether **17** and the chloride **18** were observed (by TLC) in the crude reaction



Scheme 3 *Reagents:* i, $PdCl_2$, CO, MeOH, $CuCl_2$; ii, $PdCl_2$, CO, Et_3N, MeOH, $CuCl_2$

mixture together with a number of other components that could not be characterised.*

To date, efforts to apply electrophile-mediated cyclisation methodology to the synthesis of 7-membered rings has not been particularly successful.[10] The Pd^{II}-mediated cyclisation/methoxycarbonylation of sulfonamide **20** was examined under a wide variety of conditions but we were unable to obtain any evidence for the formation of the desired 7-membered ring (Scheme 4). Generally, complex reaction mixtures were obtained but with $PdCl_2$ we were able to isolate allylic ether **21** in 13% yield, and when $Pd(OAc)_2$ was used, with a limited amount (1 mol equiv.) of methanol, the allylic acetate **22** was obtained in 17% yield. Attempts to generate a 7-membered ring by reaction of the acetate **22** with $Pd(PPh_3)_4$ were unsuccessful. Use of a more nucleophilic substrate, the *N*-benzylamine **23**, was more profitable and the 7-membered heterocyclic acrylate **24** was produced, albeit in only 23% yield.



Scheme 4 *Reagents and conditions:* i, $PdCl_2$, CO, MeOH, 70 °C; ii, $Pd(OAc)_2$, Et_3N, CO, MeOH; iii, $Pd(PPh_3)_4$; iv, $Pd(PhCN)_2Cl_2$, Et_3N, CO, MeOH

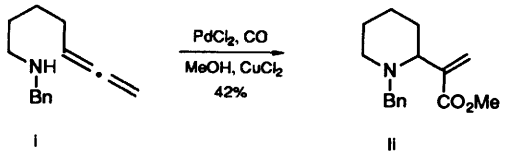
In terms of the diastereoselectivity observed in cyclisations involving sulfonamides, then, the participation of a chloropalladiation step (see Scheme 2) has important implications as outlined in Scheme 5. Ring formation may involve either direct or allylic nucleophilic displacement on the chloropalladiated intermediates **25a/b**. Alternatively, CO-insertion to give an acylpalladium species **26a/b** may precede the cyclisation step itself. The role of the corresponding chloroacrylates, such as **15**, is less clear although the control experiment described above suggests that this type of intermediate does not play a major part in the cyclisation process. The stereochemical outcome of the overall sequence in terms of the *cis/trans* heterocyclic product (Table 1) is predetermined to some extent by the distribution of diastereoisomeric chlorides present.† With compounds **25a** and **26a** the stereochemistry of the heterocyclic product is effectively defined, assuming that the cyclisation step does not involve a free allylic carbocation as an intermediate. If a significant amount of cyclisation proceeds *via* the primary allylic chlorides **25b** or **26b** then addition of the nitrogen nucleophile to an sp^2-centre is unlikely to be subject to the same steric demands of reactions involving a π-complex, which is the situation likely to be operating with Ag^I; this statement is supported by the control experiment involving cyclisation of allylic chloride **15** to give a 1:1 mixture of *cis*- and *trans*-**12**. The *trans*-selectivity observed in the cyclisation of sulfonamide **4** is reasonable given the proximity of the phenyl substituent to the activated allylic moiety and a significant degree of facial differentiation might be expected to operate in this case in both the chloropalladiation step (leading to **25a**) or in the allylic displacement of an intermediate analogous to **25b** or **26b**.

The cyclisation step itself, which is presumed to involve an intramolecular displacement of an allylic chloride, is also interesting. In the case of, for example, allylic chloride **25a** cyclisation could occur to give the 5-membered ring (the observed reaction pathway) or the corresponding 7-membered ring by either an S_N2 or S_N2'-type nucleophilic displacement, respectively. Similarly, the cyclisation sequence shown in Scheme 3 could also lead to competition between 6- and 8-membered-ring formation, and 9-membered-ring formation may also compete in the sequences shown in Scheme 4. We have not found any evidence for the formation of the larger of the two possible ring sizes. However, this mode of reaction *has* been observed in a related series of cyclisations and can, under appropriate circumstances, provide an efficient entry to medium rings.[12]

While the Pd^{II}-mediated cyclisation/methoxycarbonylation is attractive in terms of the level of functionality that is imparted to the heterocyclic product, the putative alkenylpalladium species **1** should also be exploitable in other ways. This allene-based chemistry also offers the advantage that compound **1** is relatively stable, unlike the corresponding σ-alkylpalladium complexes that are generated when cyclisation to an alkene π-bond is carried out. We were interested in exploring the reactivity of complexes related to compound **1** and have described some early results in this final section. When cyclisation of the α-amino ester **7** was carried out in the presence of either ethyl acrylate or styrene (in either methanol or dichloromethane solution), cyclisation appeared to proceed smoothly (substrate **7** was consumed) but we were unable to isolate any products resulting from a Heck-type addition.‡ Attempts to stabilise a σ-alkenylpalladium intermediate by carrying out the reaction in the presence of triphenylphosphine also led to complex product mixtures.§

The compatibility of oxygen nucleophiles has also been examined by using hepta-5,6-dien-1-ol **27**[13] as a readily available model substrate and our results in this case are more encouraging (Scheme 6). Under the usual methoxycarbonylation

* Cyclisation of *N*-benzylhepta-5,6-dienylamine i to give the corresponding piperidine **ii** proceeds in 42% yield, with no acyclic by-products corresponding to either the allyl ether **17** or the piperidine **18** being observed. Details for the preparation and cyclisation of amine i are also included in the Experimental section.

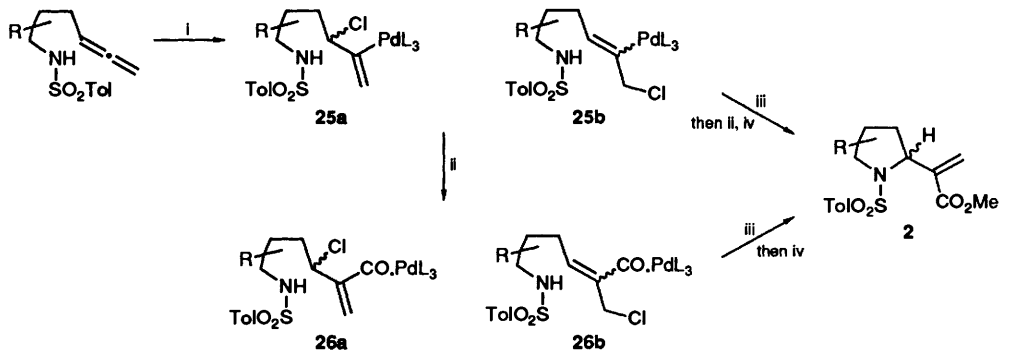


i ii

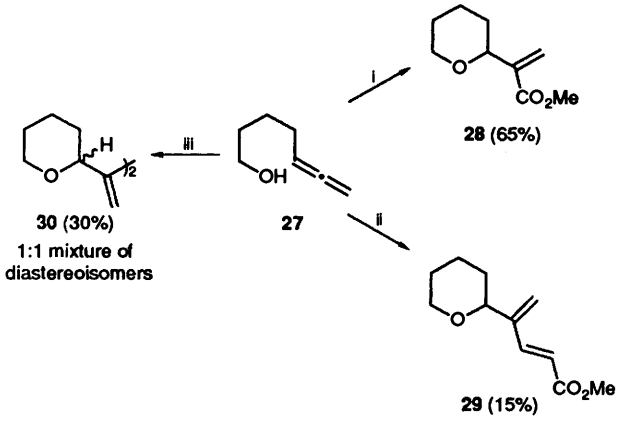
† A reasonable level of 1,3-asymmetric induction (up to 71% d.e.) has been observed in cyclisation involving primary allylic halides in the presence of Ag^I.[11]

‡ The only products observed correspond to dimers [*m/z* (EI) 644] which are analogous to compound **30**. The product mixture was, however, a complex mixture of diastereoisomers (by ^1H NMR analysis) and has not been properly characterised.

§ The synthesis of dienes **3** has been achieved but in a two-step process. This involves the use of I_2 as the electrophilic trigger for the initial cyclisation step and then a conventional Heck olefination of the resulting alkenyl iodide (I. W. Davies and R. Wisedale, University of Bath, unpublished results).



Scheme 5 *Reagents and conditions:* i, $PdCl_2$; ii, CO; iii, cyclisation step; iv, MeOH



Scheme 6 *Reagents:* i, $PdCl_2$, CO, MeOH, $CuCl_2$; ii, $PdCl_2$ (1 mol equiv.), Et_3N, CH_2=$CHCO_2Me$, CH_2Cl_2; iii, $PdCl_2$, $CuCl_2$, MeOH

conditions, acrylate **28** was isolated in 65% yield. By omitting carbon monoxide and carrying out the cyclisation step in dichloromethane in the presence of methyl acrylate and using 1 mol equiv. of $PdCl_2$, the Heck product **29** was obtained albeit in low (15%) yield. Interestingly, when cyclisation of compound **27** was carried out in the absence of *both CO and methyl acrylate*, the dimer **30** was obtained in 30% yield by a process that is presumed to arise by reductive elimination of a bis(σ-alkenyl)palladium species.[6b] It should be stressed that the tandem Pd^{II}-mediated cyclisation–Heck reaction has not yet been optimised although this sequence would extend what is already a synthetically useful process and further work in this area is being pursued.

Experimental

General experimental and instrument specifications have been described previously.[2a] $CDCl_3$ was used as solvent for ^1H and ^{13}C NMR spectroscopy throughout.

General Procedure for Pd^{II}*-Mediated Cyclisation/Methoxycarbonylation.*—Cyclisations were typically carried out by using 0.2–1 mmol of the allenic sulfonamide/amine. A mixture of allenic sulfonamide/amine in methanol (0.1 mmol cm^{-3}), $PdCl_2$ (0.1 mol equiv.) and $CuCl_2$ (3 mol equiv.) was stirred under carbon monoxide for 2–12 h. Following aqueous work-up using 10% ethanolamine in water the products were extracted with diethyl ether. The combined extracts were dried ($NaSO_4$), concentrated under reduced pressure, and the products were isolated following flash chromatography with ethyl acetate–light petroleum. Essentially the same procedure was followed when cyclisation was carried out in the presence of Et_3N as an added base. Yields and isomer distribution of the heterocyclic products are shown in Table 1.

Methyl 2-[trans-3-*phenyl*-N-(p-*tolylsulfonyl*)*pyrrolidin*-2-*yl*]-*acrylate* **9**. Isolated in 57% yield (by using 4 mol equiv. of Et_3N) as *crystals*, m.p. 98 °C (from MeOH) (Found: M^+, 385.131. $C_{21}H_{23}NO_4S$ requires M, 385.134); $\nu_{max}(CHCl_3)/cm^{-1}$ 1705 and 1610; δ_H(270 MHz) 7.60 (2 H, d, *J* 7, part of AA′BB′), 7.28–7.04 (5 H, m), 6.88 (2 H, d, *J* 7, part of AA′BB′), 6.35 (1 H, s), 5.94 (1 H, t, *J* 0.5), 4.60 (1 H, d, *J* 4.5), 3.76–3.54 (5 H, m, including OMe), 3.31 (1 H, m), 2.42 (3 H, s), 2.17 (1 H, m) and 1.90 (1 H, m); *m/z* (EI) 385 (M^+).

Methyl 2-[cis- *and* trans-4-*phenyl*-N-(p-*tolylsulfonyl*)*pyrrolidin*-2-*yl*]*acylate* **10**. Isolated as a 1:1 mixture of diastereoisomers in 63% yield as a *solid* (Found: C, 65.5; H, 6.05; N, 3.6. $C_{21}H_{23}NO_4S$ requires C, 65.43; H, 6.03; N, 3.63%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1700 and 1610; δ_H(270 MHz) 7.76 (2 H, d, *J* 7, part of AA′BB′), 7.35–7.18 (5 H, m, both isomers), 7.04 (2 H, d, *J* 7, part of AA′BB′, both isomers), 6.48/6.34 (1 H, s), 6.18/6.14 (1 H, t, *J* 1), 4.81/4.65 (1 H, m), 3.98 (1 H, m, both isomers), 3.78/3.74 (3 H, s), 3.46/3.08 (1 H, br t, *J* 11), 3.34 (0.5 H, m), 2.67 (1 H, m, both isomers), 2.45 (3 H, s, both isomers), 2.02 (0.5 H, m), and 1.87 (1 H, m, both isomers); *m/z* (CI) 386 (M^+ + 1).

Methyl 2-[cis- *and* trans-5-*phenyl*-N-(p-*tolylsulfonyl*)*pyrrolidin*-2-*yl*]*acrylate* **11**. Isolated as 2:1 mixture of diastereoisomers in 60% yield (by using 4 mol equiv. of Et_3N) as a *solid* (Found: C, 65.3; H, 6.0; 3.6%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1700 and 1640; δ_H(270 MHz) 7.75–6.90 (9 H, m, ArH, both isomers), 6.44 (1 H, br s, major isomer) and 6.42 (1 H, t, *J* 1, minor isomer), 6.25 (1 H, t, *J* 1, minor isomer) and 5.98 (1 H, br s, major isomer), 5.19–5.10 (1 H, m, both isomers), 4.80 (1 H, m, minor isomer) and 4.65 (1 H, m, major isomer), 3.80 (3 H, s, both isomers), 2.55–2.45 (1 H, m, both isomers), 2.42 (3 H, s, major isomer) and 2.33 (3 H, s, minor isomer), 2.00–1.85 (3 H, m, both isomers); *m/z* (CI) 386 (M^+ + 1).

Methyl 2-[cis- *and* trans-5-(*ethoxycarbonyl*)-N-(p-*tolylsulfonyl*)*pyrrolidin*-2-*yl*]*acrylate* **12**. Isolated as a 3:1 mixture of diastereoisomers in 68% yield (by using 4 mol equiv. of Et_3N) as an *oil*. A small quantity of each individual isomer (designated isomer A and isomer B) was isolated in reasonably pure form by chromatography to enable ^1H NMR spectroscopic assignment [Found: M^+ + 1, 382.135. ($C_{18}H_{23}NO_6S$ + H) requires *m/z*, 382.132]; $\nu_{max}(CHCl_3)/cm^{-1}$ 1720 and 1640; *m/z* (CI) 382 (M^+ + 1); δ_H(270 MHz) isomer A: 7.79 (2 H, d, *J* 7, part of AA′BB′), 7.34 (2 H, d, *J* 7, part of AA′BB′), 6.62 (1 H, br s), 6.40 (1 H, br s), 4.70 (1 H, m), 4.25 (2 H, m), 4.15 (1 H, m), 3.78 (3 H, s), 2.42 (3 H, s), 1.98 (1 H, m), 1.92–1.68 (3 H, m) and 1.34 (3 H, t, *J* 7); δ_H(270 MHz) isomer B: 7.66 (2 H, d, *J* 7, part of AA′BB′), 7.26 (2 H, d, *J* 7, part of AA′BB′), 6.20 (1 H, br s), 5.59 (1 H, br s), 4.96 (1 H, d, *J* 8), 4.55 (1 H, d, *J* 8), 4.18–3.97 (2 H, m), 3.70 (3 H, s), 2.43 (1 H, m), 2.41 (3 H, s), 2.10 (1 H, m), 1.89 (1 H, m), 1.67 (1 H, m) and 1.24 (3 H, t, *J* 7).

Allylic ether **14** *and allylic chloride* **15**. Allylic ether **14** and allylic chloride **15** were isolated in 20% combined yield from substrate **12** as a 1:2.4 mixture which could not be separated:

δ_H(270 MHz) 7.74 (2 × 2 H, d, *J* 7, part of AA'BB', both **14** and **15**), 7.28 (2 × 2 H, d, *J* 7, part of AA'BB', both **14** and **15**), 6.90 (1 H, t, *J* 8, **15**, $CH_2CH{=}CCO_2Me$), 6.35 (1 H, s, **14**, $=CHH$), 5.80 (1 H, s, **14**, $=CHH$), 5.41 (1 H, d, *J* 9, **15**, NH), 5.33 (1 H, d, *J* 9, **14**, NH), 4.30 (2 H, s, **15**, CH_2Cl), 3.96 (2 H, q, *J* 7, CO_2CH_2Me, **15**), 3.92 (2 H, q, *J* 7, CO_2CH_2Me, **14**), 3.96–3.90 [3 H, m, combination of **14**, CH(OMe) and both **14** and **15**, CHNHTs], 3.80 (3 H, s, **15**, CO_2Me), 3.76 (3 H, s, **14**, CO_2Me), 3.22 [3 H, s, **14**, CH(OMe)], 2.41 (2 × 3 H, s, both **14** and **15**), 2.40–1.60 (2 × 4 H, both **14** and **15**), 1.13 (3 H, t, *J* 7, CO_2CH_2Me, **15**) and 1.10 (3 H, t, *J* 7, CO_2CH_2Me, **14**); *m/z* (CI) 386/388 ($M^+ + 1$, **15**), 382 ($M^+ + 1$, **14**).

Methyl 2-[cis- *and* trans-N-*benzyl*-5-(*ethoxycarbonyl*)*pyrrolidin*-2-*yl*]*acrylate* **13**. Isolated as a 3:1 mixture of diastereoisomers in 55% yield as an *oil* [Found: $M^+ + 1$, 318.170. ($C_{18}H_{23}NO_3 + H$) requires *m/z*, 318.171]; ν_{max}($CHCl_3$)/cm^{-1} 1710 and 1612; δ_H(270 MHz) 7.31–7.23 (5 H, m, both isomers), 6.48 (1 H, dd, *J* 2 and 1, minor isomer), 6.32 (1 H, d, *J* 2, minor isomer), 6.32 (1 H, d, *J* 2, major isomer), 6.04 (1 H, dd, *J* 2 and 1, major isomer), 4.22–4.08 (2 H, m, both isomers), 3.95–3.64 (4 H, m, both isomers), 3.77 (3 H, s, minor isomer), 3.75 (3 H, s, major isomer), 2.55–1.60 (4 H, m, both isomers), 1.20 (3 H, t, *J* 7, major isomer) and 1.13 (3 H, t, *J* 7, minor isomer); *m/z* (CI) 318 ($M^+ + 1$).

Preparation of N-*Tosylhepta*-5,6-*dienylamine* **16**.—*Hepta*-5,6-*dienylamine*. A solution of hepta-5,6-dienal oxime[14] (2 g, 17 mmol, mixture of *E*/*Z* isomers) in diethyl ether (10 cm^3) was added to a stirred suspension of $LiAlH_4$ (1.2 g, 31 mmol) in diethyl ether (30 cm^3) at 0 °C. The reaction mixture was allowed to warm to room temperature and was then stirred at room temperature for 6 h. The reaction was then quenched with aq. NaOH, the mixture then filtered, and the filtrate was carefully concentrated under reduced pressure to give *hepta*-5,6-*dienylamine* (960 mg, 50%) as an oil, b.p. 130 °C (water-pump) [Found: $M^+ + 1$, 112.108. ($C_7H_{13}N + H$) requires *m/z*, 112.112]; ν_{max}(thin film)/cm^{-1} 3300 and 1950; δ_H(300 MHz) 5.09 (1 H, pentet *J* 7), 4.60–4.68 (2 H, m), 2.66 (2 H, t, *J* 6) and 1.31–2.10 (8 H, m); *m/z* (CI) 112 ($M^+ + 1$).

N-*Tosylhepta*-5,6-*dienylamine* **16**. Tosyl chloride (2.5 g, 16 mmol) was added to a solution of hepta-5,6-dienylamine (1.48 g, 13 mmol) in pyridine (40 cm^3) at 0 °C and the solution was stored at 4 °C for 40 h. The excess of pyridine was neutralised by addition of 2 mol dm^{-3} hydrochloric acid and the mixture was then extracted with diethyl ether (3 × 100 cm^3). The combined extracts were dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography to give, on elution with light petroleum–diethyl ether (3:2), the *sulfonamide* **16** (2.2 g, 62%) as a yellow oil [Found: $M^+ + 1$, 266.121. ($C_{14}H_{19}NO_2S + H$) requires *m/z*, 266.122]; ν_{max}(thin film)/cm^{-1} 3300, 1950 and 1600; δ_H(300 MHz) 7.73 (2 H, d, *J* 8, part of AA'BB'), 7.30 (2 H, d, *J* 8, part of AA'BB'), 5.00 (1 H, p, *J* 7), 4.59–4.67 (3 H, m), 2.92 (2 H, q, *J* 7), 2.41 (3 H, s), 1.88–1.98 (2 H, m) and 1.30–1.55 (4 H, m); *m/z* (CI) 266 (M^+).

Methyl 2-[1-*Methoxy*-5-(p-*tolylsulfonamido*)*pentyl*]*acrylate* **17**.—Isolated in 20% yield as an *oil* [Found: $M^+ + 1$, 356.154. ($C_{17}H_{25}NO_5S + H$) requires *m/z*, 356.153]; ν_{max}(thin film)/cm^{-1} 3300 and 1710; δ_H(270 MHz) 7.73 (2 H, d, *J* 7, part of AA'BB'), 7.30 (2 H, d, *J* 7, part of AA'BB'), 6.30 (1 H, d, *J* 1.5), 5.79 (1 H, t, *J* 1.5), 4.30 (1 H, br t, *J* 7), 4.02 (1 H, m), 3.76 (3 H, s), 3.24 (3 H, s), 2.92 (2 H, q, *J* 7), 2.42 (3 H, s) and 1.58–1.37 (6 H, m); *m/z* (CI) 356 ($M^+ + 1$).

Methyl 2-(*Chloromethyl*)-7-(p-*tolylsulfonamido*)*hept*-2-*enoate* **18**.—Isolated in 10% yield as an *oil* [Found: $M^+ + 1$, 360.105. ($C_{16}H_{22}{}^{35}ClNO_4S + H$) requires *m/z*, 360.103]; ν_{max}(thin film)/cm^{-1} 3300 and 1710; δ_H(270 MHz) 7.74 (2 H, d, *J* 7, part of AA'BB', 7.32 (2 H, d, *J* 7, part of AA'BB'), 6.91 (1 H, t, *J* 7), 4.36 (1 H, br t, *J* 7), 4.29 (2 H, s), 3.79 (3 H, s), 2.96 (2 H, q, *J* 6), 2.43 (3 H, s), 2.30–2.35 (2 H, m) and 1.64–1.42 (4 H, m); *m/z* (CI) 362/360 ($M^+ + 1$).

Methyl 2-[N-(p-*Tolylsulfonyl*)*piperidin*-2-*yl*]*acrylate* **19**.—Isolated in 20% yield as an *oil* (Found: M^+, 323.119. $C_{16}H_{21}NO_4S$ requires M, 323.119); ν_{max}($CHCl_3$)/cm^{-1} 1710; δ_H(270 MHz) 7.73 (2 H, d, *J* 7, part of AA'BB'), 7.30 (2 H, d, *J* 7, part of AA'BB'), 6.26 (1 H, d, *J* 1.5), 5.70 (1 H, d, *J* 2), 5.01 (1 H, m), 3.80 (1 H, m), 3.74 (3 H, s), 3.20 (1 H, m), 2.42 (3 H, s), 2.22 (1 H, m), 1.91 (1 H, m) and 1.64–1.18 (4 H, m); *m/z* (EI) 323 (M^+).

Preparation and Cyclisation of N-*Benzylhepta*-5,6-*dienylamine*.—N-*Benzylhepta*-5,6-*dienylamine*. Benzaldehyde (83 mg, 0.78 mmol) was added to a stirred solution of hepta-5,6-dienylamine (87 mg, 0.78 mmol) in absolute ethanol (2 cm^3) and the solution was stirred overnight. After this time $NaBH_4$ (25 mg) was added and after being stirred for 1 h the mixture was diluted with diethyl ether (50 cm^3), washed with water (2 × 10 cm^3), and dried ($MgSO_4$). The dried solution was concentrated under reduced pressure and the residue was purified by flash chromatography (EtOAc) to give *N*-benzylhepta-5,6-dienylamine (95 mg, 60%) as an oil, ν_{max}(thin film)/cm^{-1} 3250, 1940 and 1580; δ_H(60 MHz) 7.50–7.30 (5 H, m), 5.04 (1 H, m), 4.45–4.80 (2 H, m), 3.70 (2 H, s), 2.90–2.40 (2 H, m) and 2.35–1.30 (7 H, m). Satisfactory analytical or high-resolution mass data could not be obtained for this compound.

Under the standard conditions described above (no added base) *N*-benzylhepta-5,6-dienylamine (85 mg, 0.32 mmol) underwent cyclisation to give *methyl* 2-(N-*benzylpiperidin*-2-*yl*)*acrylate* (46 mg, 42%) as an oil (Found: M^+, 259.156. $C_{16}H_{21}NO_2$ requires M, 259.157); ν_{max}(thin film)/cm^{-1} 1720 and 1615; δ_H(60 MHz) 7.25 (5 H, s), 6.30 (1 H, d, *J* 2), 6.16 (1 H, m), 4.02 (1 H, d, *J* 13, part of AB), 3.76 (3 H, s), 3.35–2.80 (3 H, m), 2.75 (1 H, d, *J* 13, part of AB) and 2.15–1.50 (6 H, m); *m/z* (EI) 259 (M^+).

Synthesis of N-*Tosylocta*-6,7-*dienylamine* **20** *and* N-*Benzylocta*-6,7-*dienylamine* **23**.—*Octa*-6,7-*dienenitrile*. A solution of methanesulfonyl chloride (2.5 cm^3, 32 mmol) in CH_2Cl_2 (10 cm^3) was added slowly to a mixture of hepta-5,6-dienol **27**[13] (3.30 g, 29 mmol) and triethylamine (5.8 cm^3, 40 mmol) in CH_2Cl_2 (200 cm^3) at −30 °C. The reaction mixture was stirred at −10 °C for 1 h and then poured onto aq. sodium hydrogencarbonate (100 cm^3). The resulting mixture was extracted with CH_2Cl_2 (3 × 50 cm^3) and the extracts were then combined, washed with brine (50 cm^3), and dried ($MgSO_4$). The dried solution was concentrated under reduced pressure to give the crude mesylate which was used without further purification.

A stirred solution of the crude mesylate (prepared above) and KCN (7.5 g, 116 mmol) in dimethyl sulfoxide (100 cm^3) was heated at 75 °C for 2 h. The reaction mixture was cooled and then poured onto water (100 cm^3) and the product was extracted with diethyl ether (3 × 50 cm^3). The combined extracts were washed with water (50 cm^3), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography to give, on elution with CH_2Cl_2, *octa*-6,7-*dienenitrile* (3.30 g, 94%) as an oil (Found: M^+, 121.089. $C_8H_{11}N$ requires M, 121.089); ν_{max}(thin film)/cm^{-1} 2200, 1950 and 850; δ_H(300 MHz) 5.05 (1 H, p, *J* 7), 4.70–4.60 (2 H, m), 2.34 (2 H, t, *J* 7.5), 2.07–1.96 (2 H, m), 1.76–1.61 (2 H, m) and 1.61–1.50 (2 H, m); *m/z* (CI) 122 ($M^+ + H$).

Octa-6,7-*dienylamine*. A solution of octa-6,7-dienenitrile (2.0 g, 16.0 mmol) in diethyl ether (10 cm^3) was added to a

stirred suspension of $LiAlH_4$ (0.63 g, 16.0 mmol) in diethyl ether (40 cm^3) at −20 °C. The reaction mixture was allowed to warm to room temperature and was then stirred at room temperature for 2 h. The reaction was quenched with aq. NaOH and the mixture then filtered, and the filtrate was carefully concentrated under reduced pressure to give *octa-6,7-dienylamine* (1.60 g, 84%) as a pale yellow oil (Found: $M^+ + 1$, 126.128. $C_8H_{15}N + H$ requires *m/z*, 126.128); ν_{max}(thin film/cm^{-1} 3300br, 1950 and 840; δ_H(300 MHz) 5.08 (1 H, p, *J* 7), 4.69–4.60 (2 H, m), 2.68 (2 H, t, *J* 7), 2.05–1.92 (2 H, m) and 1.24–1.64 (8 H, m): *m/z* (CI) 126 (M + 1).

N-*Tosylocta-6,7-dienylamine* **20**. Tosyl chloride (3 g, 16 mmol) was added to a solution of octa-6,7-dienylamine (2 g, 16 mmol) in pyridine (60 cm^3) at 0 °C and the solution was stored at 4 °C for 40 h. The excess of pyridine was neutralised by addition of 2 mol dm^{-3} hydrochloric acid and the mixture was extracted with diethyl ether (3 × 100 cm^3). The combined extracts were dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography to give, on elution with light petroleum–diethyl ether (3:2), the *sulfonamide* **20** (3.37 g, 76%) as a yellow oil [Found: $M^+ + 1$, 280.137. ($C_{15}H_{21}NO_2S + H$) requires *m/z*, 280.137]; ν_{max} (thin film)/cm^{-1} 3300, 1950 and 1595; δ_H(300 MHz) 7.74 (2 H, d, *J* 8, part of AA′BB′), 7.28 (2 H, d, *J* 8, part of AA′BB′), 5.10 (1 H, m), 5.00 (1 H, p, *J* 7), 4.65–4.55 (2 H, m), 2.88 (2 H, q, *J* 7), 2.39 (3 H, s), 1.95–1.85 (2 H, m), 1.49–1.36 (2 H, m) and 1.36–1.20 (4 H, m); *m/z* (CI) 280 ($M^+ + 1$).

Methyl 2-[1-*Methoxy*-6-(p-*tolylsulfonamido*)*hexyl*]*acrylate* **21**. A solution of sulfonamide **20** (25 mg, 0.089 mmol) and palladium(II) chloride (16 mg, 0.089 mmol) in methanol (15 cm^3) under carbon monoxide was heated at 70 °C for 2 days. 10% Aq. ethanolamine (3 cm^3) was added and the reaction mixture was diluted with diethyl ether (20 cm^3). The organic layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography to give, on elution with light petroleum–diethyl ether (3:2), the *allylic ether* **21** (4 mg, 13%) as an oil [Found: $M^+ + 1$, 370.168. ($C_{18}H_{27}NO_5S + H$) requires *m/z*, 370.164]; ν_{max}(thin film)/cm^{-1} 3300, 1710, 1430 and 1160; δ_H(300 MHz) 7.72 (2 H, d, *J* 8, part of AA′BB′), 7.30 (2 H, d, *J* 8, part of AA′BB′), 6.30 (1 H, s), 5.80 (1 H, s), 4.35 (1 H, br s), 4.02 (1 H, m), 3.76 (3 H, s), 3.24 (3 H, s), 2.91 (2 H, q, *J* 7), 2.92 (3 H, s) and 1.20–1.50 (8 H, m); *m/z* (CI) 370 ($M^+ + 1$).

Methyl 2-[1-*Acetoxy*-6-(p-*tolylsulfonamido*)*hexyl*]*acrylate* **22**. Palladium(II) acetate (102 mg, 0.45 mmol) was added to a stirred solution of sulfonamide **20** (127 mg, 0.45 mmol), triethylamine (0.063 cm^3, 0.45 mmol), and methanol (0.081 cm^3, 0.45 mmol) in CH_2Cl_2 (25 cm^3) at room temperature and the reaction mixture was stirred for 18 h under carbon monoxide. The solution was filtered through Celite, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography to give, on elution with light petroleum–diethyl ether (3:2), the *allylic acetate* **22** (30 mg, 17%) as an oil [Found: $M^+ + 1$, 398.163. ($C_{19}H_{27}NO_6S + H$) requires *m/z*, 398.164]; ν_{max}(thin film)/cm^{-1} 3300, 1720, 1625 and 1595; δ_H(300 MHz) 7.60 (2 H, d, *J* 8, part of AA′BB′), 7.29 (2 H, d, *J* 8, part of AA′BB′), 6.25 (1 H, s), 5.71 (1 H, s), 5.55 (1 H, dd, *J* 5 and 7), 4.50 (1 H, m), 3.74 (3 H, s), 2.89 (2 H, q, *J* 7), 2.40 (3 H, s), 2.06 (3 H, s) and 1.75–1.20 (8 H; m); *m/z* (CI) 398 ($M^+ + H$).

N-*Benzylocta-6,7-dienylamine* **23**. A solution of octa-6,7-dienylamine (900 mg, 7.2 mmol) and benzaldehyde (0.73 cm^3, 7.2 mmol) in ethanol (20 cm^3) was stirred at room temperature for 16 h. Sodium borohydride (270 mg, 7.2 mmol) was added and this solution was stirred for 1 h. Diethyl ether (100 cm^3) was then added and the reaction mixture was washed successively with water (10 cm^3) and brine (10 cm^3), dried ($MgSO_4$), and then concentrated under reduced pressure. The residue was purified by flash chromatography to give, on elution with CH_2Cl_2 and then CH_2Cl_2–MeOH (10:1), *amine* **23** (910 mg, 61%) as a yellow oil [Found: $M^+ + 1$, 216.716. ($C_{15}H_{21}N + H$) requires *m/z*, 216.175]; ν_{max}(thin film)/cm^{-1} 3300 and 1950; δ_H(300 MHz) 7.35–7.20 (5 H, m), 5.08 (1 H, p, *J* 7), 4.68–4.61 (2 H, m), 3.79 (2 H, s), 2.62 (2 H, t, *J* 7), 2.05–1.95 (2 H, m), 1.65 (1 H, s) and 1.58–1.30 (6 H, m); *m/z* (CI) 216 ($M^+ + H$).

Methyl 2-[N-*Benzylazepan*-2-*yl*]*acrylate* **24**.—$Pd(PhCN)_2Cl_2$ (50 mg, 0.13 mmol) was added to a stirred solution of *N*-benzylocta-6,7-dienylamine **23** (28 mg, 0.13 mmol) and triethylamine (0.017 cm^3, 0.13 mmol) in methanol (30 cm^3). The mixture was stirred at room temperature for 3 h under carbon monoxide. The reaction mixture was then diluted with diethyl ether (100 cm^3) and washed with 10% aq. ethanolamine (20 cm^3). The aq. layer was extracted with diethyl ether (3 × 20 cm^3) and the extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography to give, on elution with light petroleum–diethyl ether (4:1), *compound* **24** (8 mg, 23%) [Found: $M^+ + 1$, 274.182. ($C_{17}H_{23}NO_2 + H$) requires *m/z*, 274.180]; ν_{max}(thin film)/cm^{-1} 1720 and 1625; δ_H(300 MHz) 7.32–7.18 (5 H, m), 6.25 (1 H, s), 6.12 (1 H, s), 3.77 (3 H, s), 3.70 (1 H, d, *J* 14), 3.50 (1 H, d, *J* 14), 2.82–2.62 (3 H, m) and 1.94–1.40 (8 H, m); *m/z* (CI) 274 ($M^+ + 1$).

Methyl 2-(*Tetrahydropyran*-2-*yl*)*acrylate* **28**.—A suspension of $PdCl_2$ (35 mg, 0.2 mmol), $CuCl_2$ (800 mg, 6 mmol) and hepta-5,6-dienol[13] **27** (220 mg, 2 mmol) in MeOH (10 cm^3) were stirred under CO at room temperature for 4 h. The reaction mixture was filtered, then concentrated under reduced pressure, and the residue was extracted with hexane. The combined extracts were carefully concentrated and the residue was then purified by distillation to give *compound* **28** (220 mg, 65%) as an oil, b.p. (bulb-to-bulb) 120 °C (20 mmHg) (Found: M^+, 170.094. $C_9H_{14}O_3$ requires M, 170.094); ν_{max}(thin film)/cm^{-1} 1720 and 1630; δ_H(60 MHz) 6.28 (1 H, br s), 5.92 (1 H, br s), 4.19 (1 H, m), 3.80 (3 H, s), 3.79–3.45 (2 H, m) and 2.02–1.20 (6 H, m); *m/z* (EI) 170 (M^+).

Methyl 4-(*Tetrahydropyran*-2-*yl*)*penta*-2,4-*dienoate* **29**.—A suspension of $PdCl_2$ (470 mg, 2.6 mmol), triethylamine (0.56 cm^3, 3.9 mmol), methyl acrylate (1 cm^3, 13 mmol) and hepta-5,6-dienol[13] **27** (300 mg, 2.6 mmol) in CH_2Cl_2 (10 cm^3) was stirred at room temperature for 24 h. The reaction mixture was diluted with CH_2Cl_2 (30 cm^3), washed with 10% aq. ethanolamine, and extracted with CH_2Cl_2 (3 × 50 cm^3). The extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was then purified by flash chromatography to give, on elution with light petroleum–diethyl ether (2:1), the *diene* **29** (80 mg, 15%) as an oil [Found: $M^+ + 1$, 197.117. ($C_{11}H_{16}O_3 + H$) requires *m/z*, 197.118]; ν_{max}(thin film)/cm^{-1} 1730 and 1625; δ_H(300 MHz), 7.25 (1 H, d, *J* 15), 6.00 (1 H, d, *J* 15), 5.55 (1 H, s), 5.42 (1 H, s), 4.10–3.95 (2 H, m), 3.71 (3 H, s), 3.50 (1 H, m), 1.50–1.92 (2 H, m) and 1.37–1.65 (4 H, m); *m/z* (CI) 197 ($M^+ + 1$).

2,3-*Bis*(*tetrahydropyran*-2-*yl*)*buta*-1,3-*diene* **30**.—A suspension of $PdCl_2$ (30 mg, 0.178 mmol), $CuCl_2$ (710 mg, 5.3 mmol) and hepta-5,6-dienol[13] **27** (200 mg, 1.78 mmol) in methanol (10 cm^3) was heated at 65 °C for 30 min. The reaction mixture was diluted with diethyl ether (50 cm^3), then washed with 10% aq. ethanolamine, and the aq. phase was extracted with diethyl ether (3 × 20 cm^3). The combined organic phases were dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography to give, on elution with light petroleum–diethyl ether (6:1), the *dimer* **30** (60 mg, 30%) as a mixture of diastereoisomers which could not be

separated [Found: $M^+ + 1$, 223.171. ($C_{14}H_{22}O_2$ + H) requires *m/z*, 223.170]; ν_{max}(thin film)/cm^{-1} 1590; δ_H(300 MHz) 5.19 (2 H, d, *J* 7), 5.06 (2 H, d, *J* 7), 4.05 (2 H, br d, *J* 12), 3.95 (2 H, br t, *J* 9), 3.49 (2 H, br t, *J* 10), 1.69–1.91 (4 H, m), 1.40–1.68 (4 H, m) and 1.20–1.40 (4 H, m); δ_C 149.2/148.8, 111.7/110.9, 78.1/77.7, 68.8 (2 coincident signals), 31.6/31.5, 25.9 (2 coincident signals) and 23.8/23.7; *m/z* (CI) 223 (M^+ + H).

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References

1 P. A. Bartlett in *Asymmetric Synthesis*, ed. J. D. Morrison, Academic Press, New York, 1984, vol. 3, p. 411; L. S. Hegedus, *Tetrahedron*, 1984, **40**, 2415; M. B. Gasc, A. Lattes and J. J. Perie, *Tetrahedron*, 1983, **39**, 703; G. Cardillo and M. Orena, *Tetrahedron*, 1990, **46**, 3321.

2 (*a*) T. Gallagher, S. W. Jones, M. F. Mahon and K. C. Molloy, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2193; (*b*) R. Kinsman, D. Lathbury, P. Vernon and T. Gallagher, *J. Chem. Soc., Chem. Commun.*, 1987, 243; (*c*) N. J. S. Huby, R. G. Kinsman, D. Lathbury, P. G. Vernon and T. Gallagher, *J. Chem. Soc., Perkin Trans. 1*, 1991, 145.

3 R. D. Walkup and G. Park, *Tetrahedron Lett.*, 1988, **29**, 5505; T. Gallagher, *J. Chem. Soc., Chem. Commun.*, 1984, 1554; P. A. Audin, A. Doutheau and J. Gore, *Bull Soc. Chim. Fr.*, 1984, 297.

4 D. Lathbury, P. Vernon and T. Gallagher, *Tetrahedron Lett.*, 1986, **27**, 6009; R. D. Walkup and G. Park, *Tetrahedron Lett.*, 1987, **28**, 1023.

5 L. S. Hegedus, G. F. Allen, J. J. Bozell and E. L. Waterman, *J. Am. Chem. Soc.*, 1978, **100**, 5800; L. S. Hegedus, G. F. Allen and D. J. Olsen, *J. Am. Chem. Soc.*, 1980, **102**, 3583.

6 (*a*) R. F. Heck, *Org. React.*, 1982, **27**, 345; (*b*) R. F. Heck, *Palladium Reagents in Organic Synthesis*, Academic Press, New York, 1985; (*c*) H.-U. Reissig, 'Palladium-Catalysed Arylation and Vinylation of Alkenes', in *Organic Synthesis Highlights*, J. Mulzer, H.-J. Altenbach, M. Braun, K. Krohn and H.-U. Reissig, VCH, Weinheim, 1991, p. 174. The tandem intra/intermolecular palladium-mediated alkenyl coupling sequence has been studied: see R. C. Larock and N. H. Lee, *J. Am. Chem. Soc.*, 1991, **113**, 7815.

7 M. S. Lupin and B. L. Shaw, *Tetrahedron Lett.*, 1964, 883.

8 R. G. Schultz, *Tetrahedron Lett.*, 1964, 301; *Tetrahedron*, 1964, **20**, 2809.

9 L. S. Hegedus, N. Kambe, Y. Ishii and A. Mori, *J. Org. Chem.*, 1985, **50**, 2240. See also D. R. Coulson, *J. Org. Chem.*, 1973, **38**, 1483.

10 R. M. Williams and T. D. Cushing, *Tetrahedron Lett.*, 1990, **31**, 6325; M. J. Kurth, M. J. Rodriguez and M. M. Olmstead, *J. Org. Chem.*, 1990, **55**, 283; L. Xiang and A. P. Kozikowski, *Synlett*, 1990, 279.

11 Y. Ohfune, K. Hori and M. Sakaitani, *Tetrahedron Lett.*, 1986, **27**, 6079.

12 T. Tsuda, T. Kiyoi and T. Saegusa, *J. Org. Chem.*, 1990, **55**, 3388; R. Shaw, M. Anderson and T. Gallagher, *Synlett*, 1990, 584.

13 L. Brandsma and H. D. Verkruijsse in *'Synthesis of Acetylenes, Allenes and Cumulenes'*, in *Studies in Organic Chemistry*, Elsevier, Amsterdam, 1981, vol. 8.

14 D. C. Lathbury, R. W. Shaw, P. A. Bates, M. B. Hursthouse and T. Gallagher, *J. Chem. Soc., Perkin Trans. 1*, 1989, 2415.

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