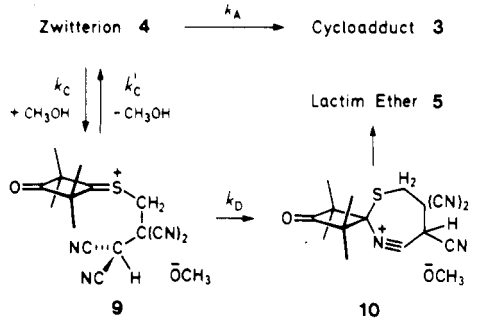

$$(5)/(3) = K_C(CH_3OH)k_D/k_A \quad (1)$$

termined by eq 1. Within the first mechanism, a product ratio independent of the methanol concentration is expected if methanol addition to the ketene imine is fast ($5/3 = k_B/k_A$).

The independence of the product ratio 5/3 from the methanol concentration (Table I) excludes the mechanism via nitrilium ion **10**, and $k_B/k_A = 65/35$ refers to the kinetically controlled formation of **6** and **3** from zwitterion **4**. It is impressive that in the experiment with 0.62 equiv of methanol 90% is consumed by the ketene imine **6**, the yield of **5** being only slightly diminished. Analogous reactions in THF + 0.5 or 1.0 vol % water afforded **7** and **3** in the same ratio 65/35; thus, k_B/k_A is independent of the *nature* of the trapping reagent. We are unaware of an alternative for the ketene imine **6** which fits the data equally well, but some variations in the kinetic scheme are conceivable.[13]

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(13) (a) **2** + TCNE enter competing *concerted* (3 + 2) and (3 + 4) cycloadditions in the ratio 35:65, furnishing **3** and **6**, the latter reversibly. A concerted [$_\pi4_s + _\pi4_s$] cycloaddition violates orbital control and has not been observed for 1,3-dipoles. (b) The concerted formation of **3** from **2** + TCNE and the formation of **6** via **4** compete in the ratio 35:65; in the absence of water or methanol **6** returns via **4** to **2** + TCNE. Schemes a and b fail to explain the nonstereospecificity of a related cycloaddition.[4] (c) As in b but with **6** slowly returning to **4** and channeled to **3**. In this more complex scheme, there is a concerted and a nonconcerted pathway leading to **3**.

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A Novel Preparation of Cyclohepta[*b*]pyrrol-2-ones

Summary: A novel synthesis of the title compounds has been achieved by the base-promoted reaction of diethyl (diazomethyl)phosphonate (**3**) and 2-oxopropanamides **4**.

Sir: The study of enzymatic reactions has stimulated interest in the synthesis of analogues of naturally occurring nucleic acid bases. The interest is driven by the possible consequences of various types of inhibition or induction of enzymatic reactions.[1] In this context, cyclohepta[*b*]-

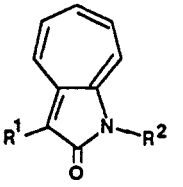
(1) (a) *Burger's Medicinal Chemistry*, 4th ed; Wolff, M. E., Ed.; Wiley Interscience: New York, 1979; Part 2. (b) Baker, B. R. *Design of Active-Site-Directed Irreversible Enzyme Inhibitors*; Wiley: New York, 1967. (c) Leonard, N. J.; Hiremath, S. P. *Tetrahedron* **1986**, *42*, 1917.

Table I. Products Isolated by Reaction of 3 with 4 in Acetonitrile

entry	4	X	2[a,b]	recovered 3[a]
1	a	H	82	34[c]
2	b	Cl	63	36
3[d]	c	CH_3	76	37

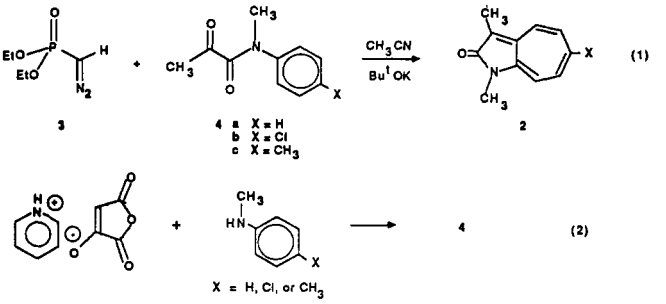
[a] Isolated yield (%). [b] Yield based on recovered starting material. [c] See footnote 7. [d] See footnote 8.

pyrrol-2-one (**1a**) and its derivatives can be considered as nonbenzenoid analogues of indoles and have been investigated for both their pharmaceutical applications[2] and their chemical and physical properties.[3] The parent compound **1a** has been shown to have inhibitory effects on ascites hepatoma,[2d,e] and the diacid **1b** has recently been found to have potential as an antidiabetic agent as a result of its inhibitory action on aldose reductase.[2c]



1 a $R^1, R^2 = H$
b $R^1 = CO_2H$, $R^2 = CH_2CO_2H$

We report herein a novel and facile synthesis of substituted cyclohepta[*b*]pyrrol-2-ones **2**. The synthetic route involves the base-promoted reaction between diethyl (diazomethyl)phosphonate (**3**)[4] and 2-oxopropanamides **4** (eq 1), themselves prepared by reaction of pyridinium hydroxymaleic anhydride[5] with the appropriately substituted *N*-methylaniline (eq 2).[6]



(2) (a) Abe, N.; Nighiwaki, T. *J. Chem. Res. Synop.* **1984**, 264. (b) Helsley, G. C.; Effland, R. C.; Davis, L. U.S. Patent 3 997 557; *Chem. Abstr.* **1977**, *86*, P139850w. (c) Treasurywala, A.; Palameta, B.; Bogri, T.; Bagli, J. U.S. Patent 4 337 265; *Chem. Abstr.* **1982**, *97*, P162818c. (d) Mirura, Y.; Okamoto, N.; Katayama, H. *J. Biochem.* **1961**, *49*, 502. (e) Mirura, Y.; Okamoto, N.; Goto, M. *Ibid.* **1961**, *49*, 508. (f) Mirura, Y.; Okamoto, N.; Shimanune, A. *Seikagaku* **1960**, *32*, 744; *Chem. Abstr.* **1964**, *60*, 7312f.

(3) (a) Wu, C.; Yang, P. *Hua Hsueh* **1977**, 45. (b) Toda, T.; Ryu, S.; Hagiwara, Y.; Nozoe, T. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 82. (c) Sato, A.; Nozoe, S.; Toda, T.; Seto, S.; Nozoe, T. *Ibid.* **1973**, *46*, 3530. (d) Toda, T.; Seto, S.; Nozoe, T. *Ibid.* **1968**, *41*, 590. (e) Toda, T. *Ibid.* **1967**, *40*, 590. (f) Nakao, H.; Soma, N.; Sunagawa, G. *Chem. Pharm. Bull.* **1965**, 828. (g) Sunagawa, G.; Nakao, H. *Ibid.* **1965**, 450. (h) Ogura, K.; Sasaki, H.; Seto, S. *Bull. Chem. Soc. Jpn.* **1965**, *38*, 306. (i) Seto, S.; Nozoe, T. *Proc. Jpn. Acad.* **1956**, *32*, 756. (j) Nozoe, T.; Seto, S.; Nozoe, S. *Ibid.* **1956**, *32*, 172. (k) Nozoe, T.; Seto, S.; Matsumura, S.; Terasawa, T. *Chem. Ind. (London)* **1954**, 1356.

(4) Seyferth, D.; Mormar, R. M.; Hilbert, P. H. *J. Org. Chem.* **1971**, *36*, 1379.

(5) Ireland, R. E.; Thompson, W. J.; *J. Org. Chem.* **1979**, *44*, 3014.

(6) Wohl, A.; Osterlin, C. *Chem. Ber.* **1907**, *40*, 2312.

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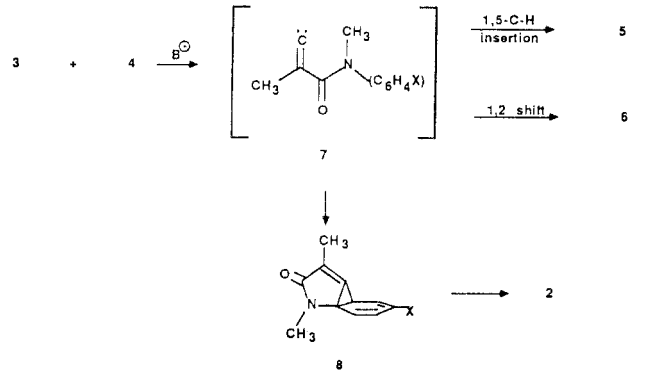
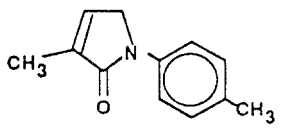
Scheme I



The results of experiments that yield the 7-substituted cyclohepta[*b*]pyrrol-2-ones **2** are summarized in Table I.[9] The first two entries of Table I show the production of a cyclohepta[*b*]pyrrol-2-one **2** in good yields as the only isolable product. However, two additional products were observed from the reaction of **4c**, namely, 3-methyl-1-(4-methylphenyl)-2(5*H*)-pyrrolone (**5**), in 11% yield and *N*-methyl-*N*-(4-methylphenyl)-2-butynamide (**6**), in 7% yield.[8] It is estimated that as little as 5% of these types



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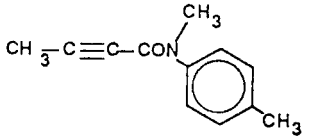


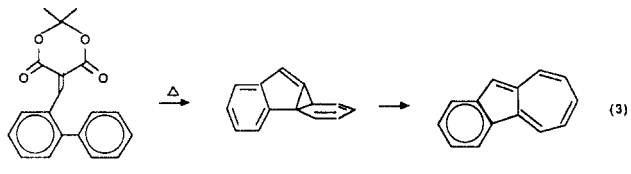
6

of products would have been detected by our spectroscopic analysis (^{1}H NMR) of the crude reaction mixtures had they been formed from the reaction of **3** and **4a** and **4b**.

A general mechanistic rationale for the observed results is portrayed in Scheme I. The reaction between **3** and **4** in the presence of base is expected to give the intermediate alkylidenecarbene **7** by way of the Horner–Emmons modification of the Wittig reaction (eq 1).[10] A 1,5-C–H insertion of **7** affords pyrrolone **5**, whereas a 1,2-shift from the carbene yields the butynamide **6**. Both of these processes are precedented for the type of alkylidenecarbene postulated here.[11]

As for the cyclohepta[*b*]pyrrol-2-ones **2**, they are hypothesized to arise from the intramolecular cycloaddition of **7** to the aromatic ring to give a norcaradiene-type of intermediate, **8**.[12] Subsequently, **8** undergoes an electrocyclic reaction to provide the observed product.

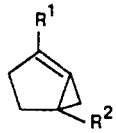
Proposal of intermediate **8** is consistent with the reports of others. For example, Brown and co-workers postulated the intermediacy of **9** in the thermal decomposition of the substrate **10** to **11** (eq 3).[13] Furthermore, insertions into



(3)

10 9 11

aromatic rings by carbenes derived from α-diazocarbonyl compounds, for both inter- and intramolecular reactions, are thought to incorporate intermediates related to **8** along the reaction pathway.[14] Berson and Kobrich, moreover, have independently reported evidence for bicyclo[3.1.0]-hex-1-ene intermediates **12** from intramolecular insertion of an alkylidenecarbene into a carbon–carbon double bond four atoms removed from the carbene center,[15] a process structurally analogous to that required for formation of **8**.



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The unique feature of the synthetic method described here for the generation of the cyclohepta[*b*]pyrrol-2-one skeleton is creation of the seven-membered ring in the final step. All previously described syntheses of this system have started with tropone analogues,[3] as in the case of the four-step synthesis of **2a**, in 31% yield,[3a] starting from the known **1a**, itself derived from 2-aminotropone.[3k] The formation of the seven-membered ring by expansion of an aromatic system should allow for the presence of a broad range of functionalization on the newly formed ring and for the introduction of heteroatoms into it. Such modifications, of course, are defined by the nature of and the

(7) The reaction may be driven to completion by adding four additional equivalents of **3** to the reaction mixture after the first addition of potassium *tert*-butoxide, as described in the text. Base is then added in small portions until evolution of nitrogen is no longer observed upon addition of base. This procedure provided **2a** in 71% yield based on consumption of the 2-oxopropanamide.

(8) Selected spectral data of compounds **5** and **6** are listed below. **1,5-Dihydro-3-methyl-1-(4-methylphenyl)-2(5H)-pyrrolone (5)** is a white solid: mp 92–94 °C; ^{1}H NMR ($CDCl_3$) δ 7.62 (d, *J* = 8 Hz, 2 H, ArH), 7.19 (d, *J* = 8 Hz, 2 H, Ar H), 6.79 (br s, 1 H, vinylic H), 4.28 (br s, 2 H, NCH_2CH=), 2.35 (s, 3 H, $ArCH_3$), 1.98 (br s, 3 H, CH_3C=); ^{13}C NMR ($CDCl_3$) 170.73, 170.63, 137.18, 134.38, 133.52, 129.59, 118.73, 51.03, 20.76, 11.24 ppm; IR (CCl_4) 2920, 1700, 1518, 1388 cm^{-1}. ***N*-Methyl-*N*-(4-methylphenyl)-2-butynamide (6)** is an oil: ^{1}H NMR ($CDCl_3$) δ 7.17 (dd, *J* = 17 Hz, 4 H, Ar H), 3.28 (s, 3 H, NCH_3), 2.39 (s, 3 H, $ArCH_3$), 1.75 (s, 3 H, CH_3C=); ^{13}C NMR ($CDCl_3$) 154.33, 140.83, 137.40, 129.63, 126.83, 89.48, 74.26, 36.35, 20.97, 3.73 ppm; IR (CCl_4) 3010, 2905, 2250, 2225, 1656, 1629, 1530, 1388, 1320 cm^{-1}.

(9) All new compounds were characterized by their ^{1}H NMR, ^{13}C NMR, IR, MS, and HRMS data. Selected spectral data for the new cyclohepta[*b*]pyrrol-2-ones are shown below. **1,3-Dimethyl-6-chlorocyclohepta[b]pyrrol-2(1H)-one (2b)** is a red-orange solid: mp 160–161 °C (hexanes, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.20–7.00 (m, 2 H), 6.9 (m, 1 H), 6.45 (m, 1 H), 3.48 (s, 3 H, NCH_3), 2.10 (s, 3 H, CH_3C=); ^{13}C NMR ($CDCl_3$) 168.78 (s), 143.72 (s), 137.86 (s), 133.02 (s), 130.76 (d, *J* = 162.0 Hz), 128.15 (*d*, *J* = 161.9 Hz), 125.08 (d, *J* = 162.4 Hz), 114.85 (s), 106.38 (d, *J* = 156.6 Hz), 26.22 (q, *J* = 139.7 Hz), 7.90 (q, *J* = 128.1 Hz) ppm; IR (CCl_4) 2937, 1691, 1600, 1508, 1446, 1080 cm^{-1}; UV λ (MeOH, max) 276 nm (log ε 4.45) [hyperfine structure 269, 272, 279 nm, shoulder 301 nm], 402 (3.81), 420 (3.80). Anal. Calcd for $C_{11}H_{10}ClNO$: C, 63.51; H, 4.84; N, 6.73. Found C, 63.59; H, 4.91; N, 6.73. **1,3,6-Trimethylcyclohepta[*b*]pyrrol-2(1*H*)-one (2c)** is a red-orange solid: mp 97–99.5 °C, (hexanes, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.21 (dd, *J* = 12 Hz, 1 H), 6.71 (d, *J* = 11 Hz, 2 H), 6.56 (d, *J* = 11 Hz, 1 H), 3.48 (s, 3 H, NCH_3), 2.32 (s, 3 H, $ArCH_3$), 2.10 (s, 3 H, CH_3C=); ^{13}C NMR ($CDCl_3$) 169.01 (s), 142.72 (s), 138.95 (s), 137.39 (s), 132.55 (d, *J* = 157.0 Hz), 128.14 (d, *J* = 158.8 Hz), 125.29 (d, *J* = 154.6 Hz), 111.85 (s), 109.00 (d, *J* = 151.9 Hz), 26.50 (q, *J* = 127.7 Hz), 26.02 (q, *J* = 139.4 Hz), 7.74 (q, *J* = 128.3 Hz) ppm; IR (CCl_4) 3019, 2940, 2920, 1682, 1607, 1575, 1513, 1450, 1380, 1072 cm^{-1}; UV λ (MeOH, max) 275 nm (log ε 4.36) [hyperfine structure 269, 273 nm, shoulder 295 nm], 400 (3.79), 418 (3.81).

(10) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1982**, *47*, 1837.

(11) (a) Gilbert, J. C.; Blackburn, B. K. *Tetrahedron Lett.* **1984**, *25*, 4067. (b) Gilbert, J. C.; Blackburn, B. K. *J. Org. Chem.*, in press.

(12) Reviews: (a) Vogel, E. *Pure Applied Chem.* **1969**, *20*, 237. (b) Maier, G. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 402.

(13) Brown, R. F. C.; Eastwood, F. W.; Harrington, K. J.; McMullen, G. L. *Aust. J. Chem.* **1974**, *27*, 2393.

(14) (a) McKervey, M. A.; Sarbajna, M. T.; Twohig, M. F. *J. Chem. Soc., Chem. Commun.* **1984**, 129. (b) Gordon, M. *Chem. Rev.* **1952**, 127. (c) Treibs, W.; Quarg, M.; Poppe, E. J. *Ann.* **1956**, *598*, 32.

(15) (a) Berson, J. A.; Salinaro, R. F. *Tetrahedron Lett.* **1982**, *23*, 1451. (b) Rule, M.; Salinaro, R. F.; Pratt, D.; Berson, J. A. *J. Am. Chem. Soc.*, **1982**, *104*, 2223. (c) Salinaro, R. F.; Berson, J. A. *Ibid.* **1982**, *104*, 2228. (d) Kobrich, G.; Heinemann, H. *J. Chem. Soc., Chem. Commun.* **1969**, 493. (e) Kobrich, G. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 464.

substitution on the aromatic ring of **4**.

A slight drawback of this procedure is the production of minor products when electron-releasing groups are present on the aromatic ring.[8] These materials, however, are easily removed by column chromatography.

The general experimental procedure for the production of pyrrolones **2** is as follows. To a stirred solution of 2 mmol (0.28 mL, 0.356 g) of diethyl (diazomethyl)-phosphonate (**3**), 1 mmol of 2-oxopropanamide **4**, and 2 mL of acetonitrile at 0 °C was added powdered potassium *tert*-butoxide (1.5 mmol, 0.18 g) over a period of 1.5 h. After 2 min, the reaction mixture was quenched with 10 mL of water, and extracted with five 15-mL portions of ethyl acetate. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to yield the crude products. Purification was achieved by high-pressure liquid chromatography.

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Registry No. **2a**, 72788-60-4; **2b**, 104422-25-5; **2c**, 104422-26-6; **3**, 25411-73-8; **4a**, 61110-50-7; **4b**, 61110-54-1; **4c**, 61110-53-0; **5**, 104422-27-7; **6**, 104422-28-8.

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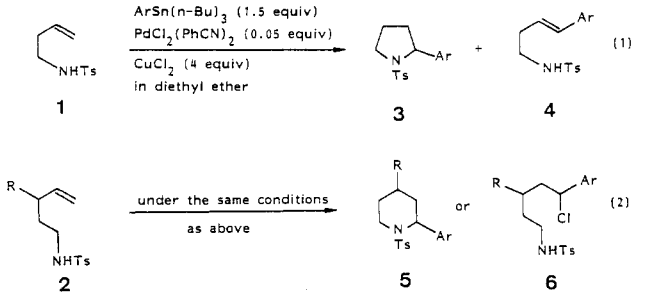
Synthesis of Five- and Six-Membered Nitrogen Heterocycles via a Palladium(II)-Catalyzed Cyclization of Unsaturated Amides

Summary: Palladium(II)-catalyzed arylation of *N*-4-pentenyl-*p*-toluenesulfonamides **2** with $ArSn(n\text{-}Bu)_3$ under oxidative conditions ($CuCl_2$ in ether) provides either 2-arylpiperidines **5** or *N*-(chloro-5-arylpentyl)-*p*-toluenesulfonamides **6** depending on the kind of arylating agents. Under the similar conditions, *N*-3-butenyl-*p*-toluenesulfonamides (**1**) are converted to a mixture of 2-arylpyrrolidines **3** and *N*-(4-aryl-3-butenyl)-*p*-toluenesulfonamides **4**.

Sir: Palladium(II) usually mediates addition reactions at the vicinal positions of olefins.[1] For example, Heck reaction selectively provides 1,2-arylchlorination[2] or 1,2-oxyarylation products.[3] In separate papers, 1,1-difunctionalization has been noted in some special cases.[4,5]

Recently we have found that a slight modification of conditions of Heck reaction (catalytic $PdCl_2(PhCN)_2$, ArHgCl or $ArSn(n\text{-}Bu)_3$, $CuCl_2$ in diethyl ether) dramatically alters the reaction pattern, and 1,1-difunctionalization becomes the main course of the reaction as exemplified by the formation of 2-aryltetrahydropyrans from 4-pentenols.[6] In this paper, we describe the first example of the palladium(II)-catalyzed regiospecific 1,1-arylamination of unsaturated amides, which provides 2-arylated five- and six-membered nitrogen heterocycles (eq 1 and 2). These products share the partial structure with many interesting alkaloids.[7]



A typical reaction was performed as follows: Into an argon-purged and ice-cooled flask, containing $PdCl_2(PhCN)_2$ (0.05 mmol) and $CuCl_2$ (4 mmol), was introduced a solution of 4-pentenyl-*p*-toluenesulfonamide (**1**, R = H, 1 mmol) in 20 mL of dry ether. Then $4\text{-}MeOC_6H_4Sn(n\text{-}Bu)_3$ was added via a syringe in one portion, and the heterogeneous mixture was stirred at 0 °C for 5 h, during which the color of the mixture turned from dark brown to gray and finally to light brown. The mixture was diluted with 20 mL of ether and washed thoroughly with three portions of 10 mL of saturated KF and then with 10 mL of 2 N HCl, followed by 5 mL of saturated $NaHCO_3$. The ethereal layer was dried over anhydrous $MgSO_4$ and condensed to leave a sticky oil, which was subjected to flash column chromatography over silica gel (benzene–ethyl acetate gradient) to provide *N*-tosyl-2-(*p*-methoxyphenyl)piperidine (**5b**, 70%). **5b**: mp 116.9–117.1 °C (hexane–benzene); IR (KBr disk) 2940, 1615, 840, 815 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11–1.82 (m, 6 H), 2.40 (s, 3 H), 3.04 (m, 1 H), 3.75 (s, 3 H), 3.77 (m, 1 H), 5.22 (br s, 1 H), 6.82 (d, J = 9.0 Hz, 2 H), 7.24 (m, 4 H), 7.72 (d, J = 8.3 Hz, 2 H) [the resonances at δ 3.04, 3.77, and 5.22 collapse to d (J = 13.7 Hz), d (J = 13.7 Hz), and s by irradiation at δ 1.42, respectively]; ^{13}C NMR ($CDCl_3$) δ 18.9, 21.4, 24.3, 27.3, 41.7, 54.8, 55.2, 113.9, 127.0, 128.1, 129.5, 130.8, 138.8, 142.7, 158.4.

The results examined with *N*-3-butenyl- (**1**) and *N*-4-pentenyl-*p*-toluenesulfonamides (**2**) according to the procedure described above are summarized in Table I. From this table the following points readily emerge. First, the present reaction is applicable not only for the formation of 2-arylpiperidines **5** but also for the formation of 2-arylpyrrolidines **3**. However, we have not succeeded yet in the formation of 2-aryl-1-azacycloheptanes using *N*-5-hexenyl-*p*-toluenesulfonamide as a substrate. Second, all the reactions are complete at 0 °C or room temperature within 5–8 h with a Pd^{II} catalyst as small amount as 5 mol %. Arylmercuric chlorides may be used as arylation agents instead of aryltins (**6a** was obtained in 60% yield by the use of PhHgCl, cf. run 4, Table I). Third, depending on the structure of substrate and the substituent on the aromatic ring of the arylating agent, the course of the reactions dramatically changes. Thus, 2-arylpyrrolidines **3** are formed as major products together with **4** from *N*-3-butenyl-*p*-toluenesulfonamides (**1**), irrespective of the kind of the arylating agents. On the other hand, *N*-4-pentenyltosylamides **2** give either 2-arylpiperidines **5** or *N*-(5-aryl-5-chloropentyl)-*p*-toluenesulfonamides **6**. Aryltins with electron donating substituents provide **5**, and

(1) Heck, R. F. *Palladium Reagents in Organic Syntheses*; Academic: New York, 1985.
(2) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5538.
(3) Horino, H.; Inoue, N. *J. Chem. Soc., Chem. Commun.* **1976**, 500.
(4) (a) Bäckvall, J.-E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1980**, *102*, 393. (b) Larock, R. C.; Liu, C.-L.; Lau, H. H.; Varaprath, S. *Tetrahedron Lett.* **1984**, *25*, 4459.
(5) For the other types of functionalization, see: (a) Trost, B. M.; Burgess, K. *J. Chem. Soc., Chem. Commun.* **1985**, 1085. (b) Bäckvall, J.-E.; Nyström, J.-E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1985**, *107*, 3676.
(6) Tamaru, Y.; Hojo, M.; Higashimura, H.; Yoshida, Z. *Angew. Chem.*, in press.
(7) Stevens, R. V. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: 1977; Vol. 3, Chapter 3.

0022-3263/86/1951-4089$01.50/0