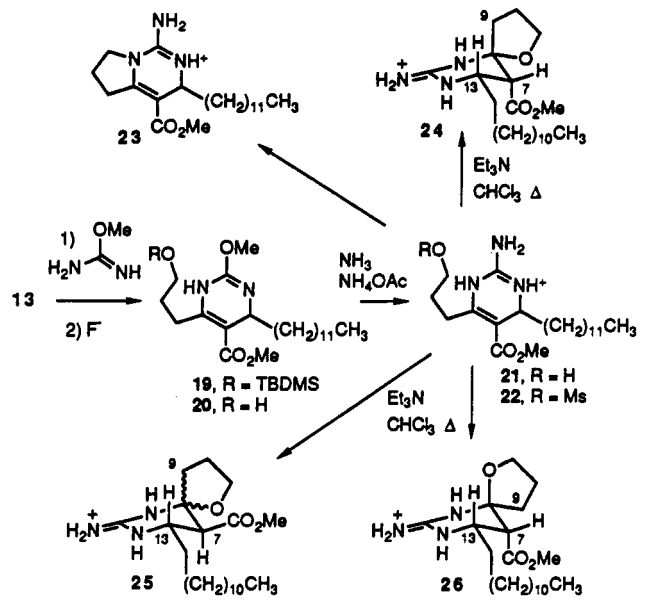

converted to **21** on treatment with K_2CO_3 in 1:1 H_2O–MeOH for 1 d at rt, permitting the recycling of **24** and **25**. The solvent effects on the equilibrium between **21** and **24–26** are similar to those in related hydroxy imines in which polar solvents that can hydrogen bond to the alcohol favor the open form.[22]

The synthesis of the acyl portion of crambine A is completed by reaction of **21** with MsCl and Et_3N in CH_2Cl_2 (30 min, 0 °C; 6 h, rt) to give mesylate **22**. Reaction of **22** with Et_3N in $CHCl_3$ (reflux, 12 h) provides 90% of **23** whose ^1H and ^{13}C NMR spectra[16,19] are virtually identical to those reported for the acyl portion of crambine A (**7**).

The acyl portions of crambine A (six steps, 29% overall yield) and crambine B (six steps, 26% overall yield) have been efficiently and stereospecifically synthesized from methyl acetoacetate. Aminodihydropyrimidine **21** is formed efficiently from enone ester **13** by a two-step procedure involving addition of *O*-methylisourea to give **19** and displacement of the methoxy group of **20** with ammonia to give **21**. Aminal formation from **21** in $CHCl_3$ proceeds in high yield with good selectivity for **26**, the acyl portion of crambine B (**8**). Reaction of alcohol **21** with MsCl and base affords **23**, the acyl portion of crambine A (**7**). The methods developed here should be applicable to the synthesis of the more complex targets ptilomycalin A and the crambescidins.

Acknowledgment. We are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support. We thank Prof. Thomas Pochapsky and Mr. Anping Wang for carrying out the ROESY experiment.

(22) Valters, R. E.; Flitsch, W. *Ring-Chain Tautomerism*; Plenum: New York, 1985; pp 266–267.

A Palladium-Mediated Approach to Construction of Nitrogen Heterocycles

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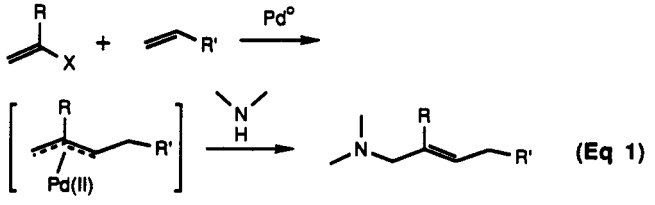
Summary: Sequential regiospecific C–C and C–N bond-forming reactions via a novel variation of the Heck reaction can be used to synthesize nitrogen-containing heterocyclic systems.

The Heck reaction of vinyl or aryl halides with alkenes catalyzed by palladium is a powerful tool for carbon–carbon bond formation.[1] Recently, elegant variations of this methodology have been used for synthesis of complex polycyclic systems.[2] When vinyl halides are used in Heck reactions, a problem which often arises is formation of stable π-allylpalladium intermediates (eq 1) which serve



(Eq 1)

to remove the metal catalyst and thus terminate the catalytic cycle.[1] Heck found that if a secondary amine is included, coupling of a vinyl bromide or iodide and an alkene can be effected catalytically, leading ultimately to an allylic amine (eq 1).[3] In this paper we reveal that this three-component condensation can be effected intramolecularly in a novel, efficient approach to bicyclic nitrogen heterocycles from acyclic precursors.

Initial feasibility studies were conducted with cyclization substrates **1** and **2** (eq 2).[4] Exposure of secondary amine **1** to various Pd^0 precursors under a variety of conditions gave bicyclic allylic amine **3**, but only in poor yields (~10%).[5] However, sulfonamide **2** cyclized under the reaction conditions shown[6] to afford bicyclic sulfonamide **4** in good yield. Varying amounts of isomeric bridged compound **5** were also produced (<1–20% of the product mixture). In order to explore some mechanistic issues relevant to these cyclizations (vide infra), isomeric vinyl bromide **6** was prepared[4] and upon subjection to the Heck

(1) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146. Heck, R. F. *Org. React.* **1982**, *27*, 345.

(2) See for example: Larock, R. C.; Yong-de, L.; Bain, A. C. *J. Org. Chem.* **1991**, *56*, 4589. Zhang, Y.; Wu, G.-Z.; Angel, G.; Negishi, E. *J. Am. Chem. Soc.* **1990**, *112*, 8590. Carpenter, N. E.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5846. Grigg, R.; Sridharan, V.; Sukirthalingam, S. *Tetrahedron Lett.* **1991**, *32*, 3855. Meyer, F. E.; de Meijere, A. *Synlett* **1991**, 777. Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1991**, *113*, 701.

(3) (a) Narula, C. K.; Mak, K. T.; Heck, R. F. *J. Org. Chem.* **1983**, *48*, 2792. (b) Shi, L.; Narula, C. K.; Mak, K. T.; Xu, Y.; Heck, R. F. *J. Org. Chem.* **1983**, *48*, 3894. (c) Dieck, H. A.; Heck, R. F. *J. Org. Chem.* **1975**, *40*, 1083. (d) Patel, B. A.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 3898. (e) Kim, J. I.; Patel, B. A.; Heck, R. F. *J. Org. Chem.* **1981**, *46*, 1067. (f) Stakem, F. G.; Heck, R. F. *J. Org. Chem.* **1980**, *45*, 3584.

(4) Cyclization substrates were prepared by short, straightforward routes which will be described in a subsequent full paper. For example, substrates like **6** and **20** can be prepared via alkylation of the dianion of 1-hepten-6-yne followed by conversion of the acetylene to the desired vinyl halide.

(5) A reported attempt by Heck to effect a related cyclization process met with failure.[3b]

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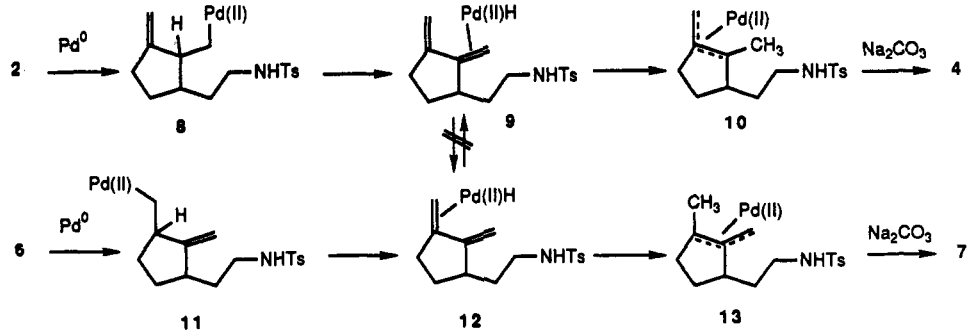
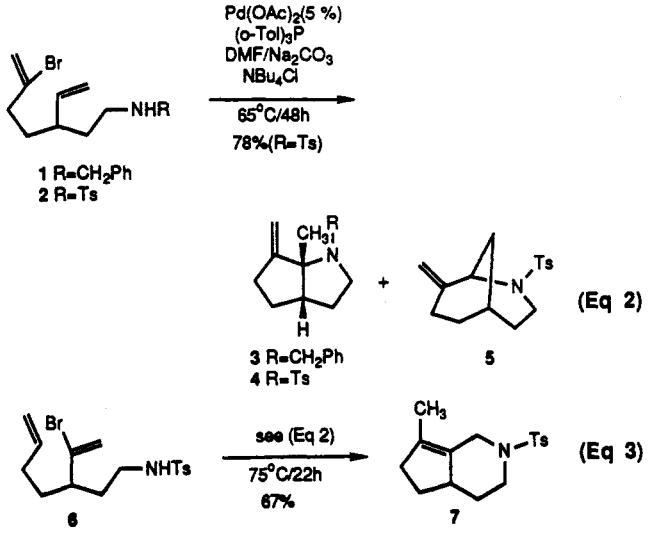
Scheme I

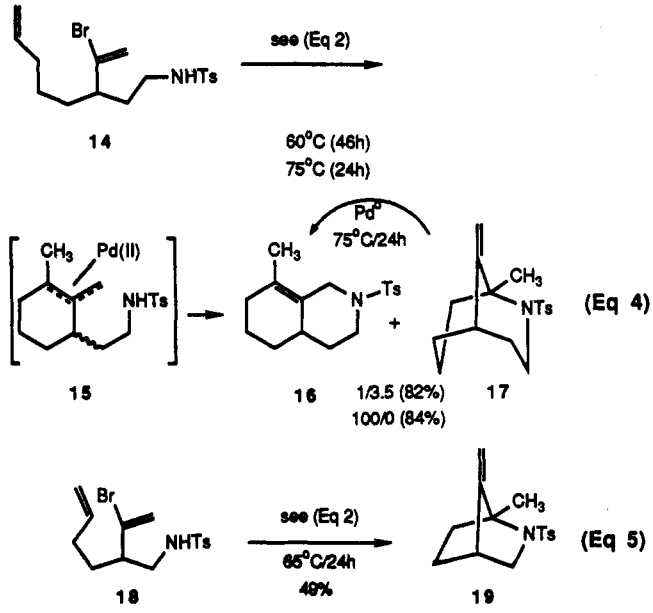


conditions indicated afforded allylic sulfonamide **7** as the only isolable product.[7]



Scheme I outlines a proposed mechanism for the cyclizations. Palladium-mediated addition of the vinyl bromide moiety in substrate **2** to the adjacent olefin via an exo mode affords **8**, which upon β-hydride elimination gives the putative η^2-diene complex **9**. Readdition of palladium hydride to **9** occurs regiospecifically leading to π-allylpalladium intermediate **10**,[8] which upon nucleophilic attack by the sulfonamide anion[9,10] yields product **4**. Initial cyclization of **2** via an endo mode ultimately yields minor product **5** by a similar sequence. Similarly, isomeric vinyl bromide **6** cyclizes via **11** and **12**, leading to π-allylpalladium species **13**, which closes to bicyclic product **7**. *The key point of this mechanistic proposal is that intermediate π-complexes **9** and **12** do not interconvert faster than they rearrange to isomeric π-allylpalladium complexes **10** and **13**, respectively, since no crossover product was found in cyclizations of **2** and **6**.* This postulate can be used to explain similar results recorded by Heck in reactions of the type shown in eq 1.[3] However, formation of an anomalous Heck product has been rationalized to occur via fluxional isomerization of diene-π-Pd complexes like **9** and **12**.[3e] It is thus possible to regiospecifically generate and trap π-allylpalladium complexes by Heck reactions of vinyl halides and simple olefins in a completely predictable manner as evidenced by the reactions in eqs 2 and 3, as well as the additional examples described below.

Substrate **14** cyclized at 60 °C to afford a 1/3.5 mixture of fused [6,6]-allylic sulfonamide **16** and bridged product **17** via attack of the sulfonamide anion at either of the two termini of the π-allylpalladium unit in intermediate **15** (eq 4). Interestingly, when the cyclization was conducted at



75 °C, *only* fused isomer **16** was produced. Upon resubjection to the reaction conditions at 75 °C, bridged compound **17** rearranged to **16**, presumably via π-allylpalladium species **15**. To our knowledge, π-allylpalladium complexes have not previously been generated from allylic sulfonamides.[8] Vinyl bromide olefin **18** cyclized to yield only the bridged product **19** (eq 5). None of the strained [5,5]-fused bicyclic product was found.

The cyclization strategy can also be applied to terminal *Z*-vinyl halides. Thus, cyclization of substrate **20** produced the hexahydroindole derivative **21** (eq 6).

Finally, the methodology can be used efficiently in spirocyclizations. For example, both vinyl bromide *E*-olefin **22** and vinyl iodide *Z*-olefin **23** cyclized to afford the

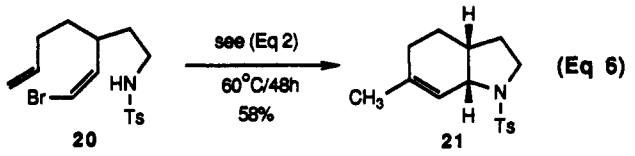
(6) (a) Reaction conditions used are essentially those of Jeffery: Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287. (b) See also: Larock, R. C.; Berrios-Pena, N.; Narayanen, K. *J. Org. Chem.* **1990**, *55*, 3447.

(7) Compound **7** possesses the skeleton of the skytanthine-type alkaloids: Snieckus, V. Mono- and Sesqui-terpenoid Alkaloids. In *International Review of Science*; Wiesner, K., Ed.; Organic Chemistry Series 2; Butterworths: London, 1976; Vol. 9, p 208.

(8) For reviews of π-allylpalladium chemistry see: Hegedus, L. S. Nucleophilic Attack on Transition Metal Organometallic Compounds. In *The Chemistry of the Metal-Carbon Bond*; Hartley, F. R., Patai, S., Eds.; Wiley: New York, 1985; Vol. 2, p 401. Tsuji, J. η^3-Allylpalladium Complexes. *Ibid.* Vol. 3, p 163. Pearson, A. J. Transition Metal-Stabilized Carbocations in Organic Synthesis. *Ibid.* Vol. 4, p 889.

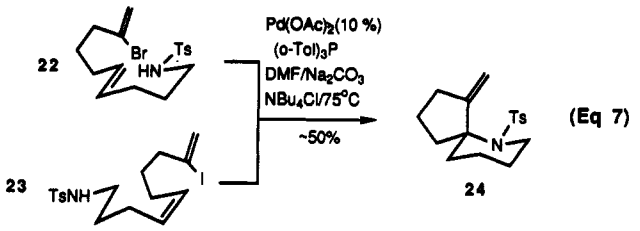
(9) For nucleophilic displacements with amides and sulfonamides onto π-allylpalladium complexes see inter alia: Bäckvall, J. E.; Andersson, P. G. *J. Am. Chem. Soc.* **1990**, *112*, 3683. Bystrom, S. E.; Aslanian, R.; Bäckvall, J. E. *Tetrahedron Lett.* **1985**, *26*, 1749. See also ref 6b.

(10) For mechanistic studies of amination of π-allyl palladium complexes see: Akermark, B.; Akermark, G.; Hegedus, L. S.; Zetterberg, K. *J. Am. Chem. Soc.* **1981**, *103*, 3037.



(Eq 6)

same spirocyclic system **24** (eq 7). This cyclization, which could provide a strategically new and rapid entry to the histrionicotoxins,[11] is presently being pursued further.



(Eq 7)

The chemistry described here provides a method for synthesis of diverse, functionalized bicyclic nitrogen compounds from readily available acyclic precursors via sequential C–C and C–N bond-forming processes involving an unactivated olefin. It should be noted that quaternary centers are also easily formed via this methodology (cf. eqs 2, 5, 7). The work has confirmed that useful π-allylpalladium compounds can be regioselectively produced by intramolecular Heck reactions of vinyl halides with simple alkenes. We are currently investigating extensions of this methodology and applications in alkaloid total synthesis.[7,11]

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Registry No. **1**, 139705-39-8; **2**, 139705-40-1; **3**, 139705-41-2; **4**, 139705-42-3; **5**, 139705-43-4; **6**, 139705-44-5; **7**, 139705-45-6; **14**, 139705-46-7; **16**, 139705-47-8; **17**, 139705-48-9; **18**, 139705-49-0; **19**, 139705-50-3; **20**, 139705-51-4; **21**, 139705-52-5; **22**, 139705-53-6; **23**, 139705-54-7; **24**, 139705-55-8; $Pd(OAc)_2$, 3375-31-3; $(o\text{-}Tol)_3P$, 6163-58-2.

Supplementary Material Available: Cyclization procedure and compound characterization data (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(11) For other Pd-mediated routes to the histrionicotoxin spirocyclic system see: Tanner, D.; Sellen, M.; Bäckvall, J. E. *J. Org. Chem.* **1989**, *54*, 3374. Godleski, S. A.; Heacock, D. J.; Meinhart, J. D.; van Wallendael, S. *J. Org. Chem.* **1983**, *48*, 2101. For a review of synthetic strategies to histrionicotoxins see: Kotera, M. *Bull. Soc. Chim. Fr.* **1989**, 370.