An Unexpected Heck Reaction. Inversion of Olefin Geometry Facilitated by the Apparent Intramolecular Carbamate Chelation of the σ-Palladium Intermediate

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Summary: The presence of a carbamate moiety can dramatically alter the outcome of a Heck cyclization, so that the normal exo-cyclization is not followed by β-elimination, but by cyclopropane formation, rearrangement, and elimination.

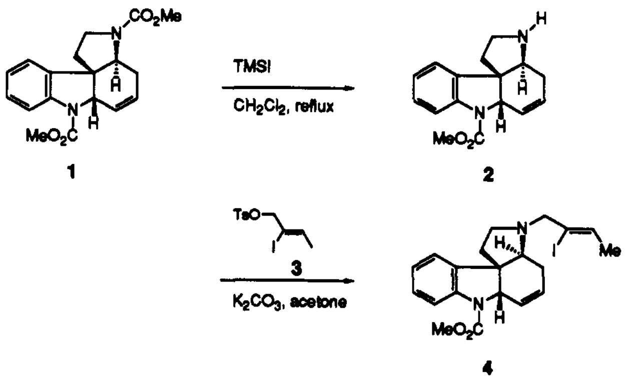
The palladium-catalyzed vinylation of olefins—the Heck reaction—provides a mild, versatile, and efficient method for the construction of carbon-carbon bonds.[1] The intramolecular version of this reaction has been employed with success in the synthesis of a wide variety of carbocycles and heterocycles. Whereas the Heck reaction of simple vinyl halides and triflates is well studied, the course of this reaction in complex systems is not always predictable.[1] Reported here is an unusual Heck reaction in which the normal exo-cyclization is not followed by β-elimination, but by cyclopropane formation, rearrangement, and elimination.

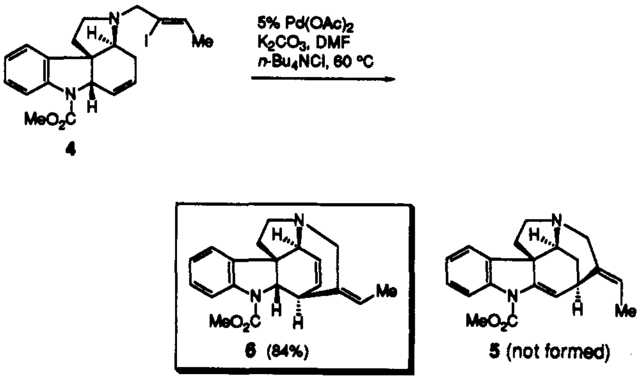
Recently, we reported an efficient new strategy to *Strychnos* alkaloids, in which the challenging bridged azabicyclic subunit was assembled predictably and with complete control of the olefin geometry by an intramolecular Heck reaction.[2,3] In an effort to apply this strategy to another member of the *Strychnos* family, we examined the Heck cyclization of carbamate **4**.[4]

This tetracycle can be prepared by a chemoselective hydrolysis of bis-carbamate **1**, followed by N-alkylation with allylic tosylate **3** (Scheme I).[3,4] The more reactive carbamate in **1** was hydrolyzed preferentially by running the reaction in refluxing dichloromethane with 2.2 equiv of iodotrimethylsilane (TMSI).[5,6] The resulting product, isolated in 95% yield and consisting of a 10:1 mixture of **2** and the fully deprotected tetracycle, was alkylated with tosylate **3** to afford the desired Heck cyclization precursor (**4**) in 75% yield.

Indoline carbamate **4** underwent a smooth cyclization reaction upon subjection to the Jeffery modification of the Heck conditions [$Pd(OAc)_2$, K_2CO_3, cat. n-Bu_4NCl, DMF, 60 °C].[7] Surprisingly, none of the expected Strychnan pentacycle **5** was formed. Instead, the apparent 7-endo cyclization product, **6**, was isolated in 84% yield. This mode of cyclization is in sharp contrast to our earlier results with model systems, which always formed the 2-azabicyclo[3.3.1]nonane framework (*cf.* **5**).[2-4]

Scheme I





The assigned structure is in agreement with the spectroscopic data. The ^1H NMR spectrum indicates the presence of three ethylenic hydrogens, two as (apparent) triplets and one as a quartet, ruling out the expected product, **5**. The ^{13}C NMR spectrum unequivocally revealed the presence of seven sp^2 CH's. Careful analysis of the proton-proton correlation spectrum and NOE experiments confirmed that the alternate Heck cyclization had taken place, affording carbamate **6**. Interestingly, NOE experiments revealed that the cyclization had occurred with inversion of the double-bond geometry, an observation which precludes a direct 7-endo-type mechanism for the coupling reaction.

The unusual cyclization product was difficult to reconcile at first.[4b] On the basis of the seminal paper by Negishi,[8] however, the following mechanism for the formation of pentacycle **6** is proposed (Scheme II). The initial step involves the expected exo-mode carbopalladation to pro-

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(1) (a) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518-5548. (b) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Katritzky, A. R., Ed.; Academic Press: New York, 1985. (c) Heck, R. F. *J. Am. Chem. Soc.* **1969**, *91*, 6707. (d) Heck, R. F. *Org. React.* **1982**, *27*, 345. (e) Tsuji, J. *Organic Synthesis with Pd Compounds*; Springer-Verlag: New York, 1980. (f) Daves, G. D.; Hallberg, A. *Chem. Rev.* **1989**, *89*, 1433. (g) Heck, R. F. Vinyl Substitution with Organopalladium Intermediates. In *Comprehensive Organic Synthesis*; Trost, B., Ed.; Pergamon Press: New York, 1992, Vol. 4, p 842.

(2) Rawal, V. H.; Michoud, C. *Tetrahedron Lett.* **1991**, *32*, 1695.

(3) Rawal, V. H.; Michoud, C.; Monestel, R. *J. Am. Chem. Soc.* **1993**, *115*, 3030.

(4) (a) Taken from: Michoud, C. Ph.D. Thesis, The Ohio State University, 1993. (b) Presented in preliminary form: *Abstracts of Papers*, 24th Central Regional Meeting of the American Chemical Society, Cincinnati, OH, May 1992, paper no. 398.

(5) Both carbomethoxy groups were removed in high yield under more forcing conditions, using an excess of TMSI. See ref 3.

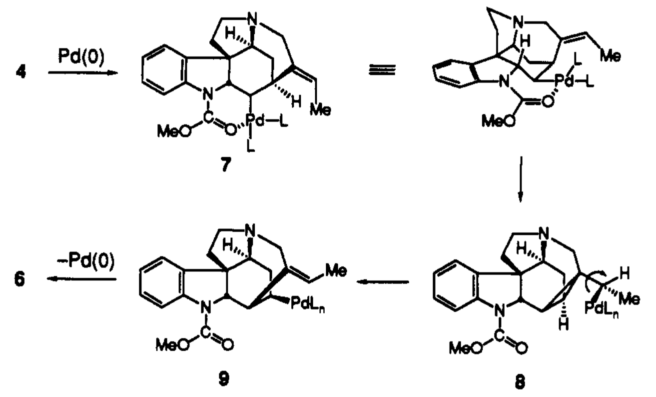
(6) Olah, G. A.; Narang, S. *Tetrahedron* **1982**, *38*, 2225.

(7) (a) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287. (b) Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667. (c) Jeffery, T. *Synthesis* **1987**, 70.

(8) Owczarczyk, Z.; Lamaty, F.; Vawter, E. J.; Negishi, E. I. *J. Am. Chem. Soc.* **1992**, *114*, 10091.

0022-3263/93/1958-5583$04.00/0

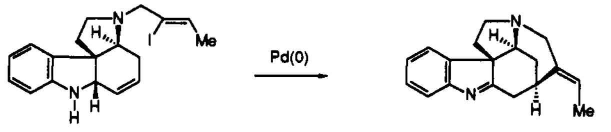
Scheme II



duce σ-alkyl palladium species **7** stabilized by intramolecular chelation. In spite of the availability of a β-hydrogen, the usual β-elimination of palladium hydride does not occur, presumably because chelate formation prevents proper alignment between the syn-β-hydrogen and the carbon–palladium σ-bond. In situ trapping of the reactive carbon–palladium bond by the exocyclic alkene affords cyclopropane **8**. A 120° rotation about the σ-bond allows proper alignment for fragmentation of the other cyclopropane bond. The σ-palladium complex produced after fragmentation is no longer stabilized by chelation and undergoes a fast β-elimination to provide the isolated product, **6**.

This mechanism is consistent with other observations. The recent report by Negishi provided the mechanistic rationale for Heck reactions that afford products of an apparent endo-mode cyclization with inversion of the alkene geometry.[8] It should be noted, however, that in those examples the initial exo-cyclization gives a neopentyl alkylpalladium species lacking β-hydrogens. With no possibility for a β-elimination, the homoallyl palladium species cyclizes to the cyclopropylcarbinyl palladate.[9] Several groups have reported the formation of cyclopropanes by a double Heck cyclization.[10] Finally, the intermediacy of a carbonyl-coordinated palladium complex, such as **7**, is very plausible, since a stable σ-alkyl palladium complex possessing a β-hydrogen has been reported by Daves.[11]

On the basis of these mechanistic considerations, it would be expected that the Heck cyclization of the carbamate free analog of **4** should give the normal exo-cyclization product. This is indeed the case. As was recently reported, vinyl iodide **10** undergoes a smooth intramolecular Heck coupling reaction to provide, after tautomerization of the intermediate enamine, dehydrotubifoline (**11**) as the sole product.[3]



10 **11** (79%)

The influence of chelating functional groups on the Heck reaction has not been investigated extensively, although some recent reports suggest that esters and, even, alkenes can affect the course of these reactions.[12] The results described here show that the presence of a carbamate moiety can dramatically alter the outcome of Heck cyclizations, so that the normal cyclization is followed not by a β-elimination, but by a cyclopropanation, rearrangement, and elimination. This outcome suggests that by judicious placement of coordinating groups it may be possible to intercept the σ-palladium Heck cyclization intermediate.

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Supplementary Material Available: Experimental details and ^{1}H and ^{13}C NMR spectra of key compounds (13 pages). This material is contained in 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.

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(9) The cyclopropylcarbinylpalladate to homoallylpalladate rearrangement is well documented. See, for example: (a) Green, M.; Hughes, R. P. *J. Chem. Soc., Dalton Trans.* **1976**, 1880. (b) Larock, R. C.; Varaprath, S. *J. Org. Chem.* **1984**, *49*, 3432. (c) Donaldson, W. A.; Brodt, C. A. *J. Organomet. Chem.* **1987**, *330*, C33.

(10) (a) Zhang, Y.; Negishi, E. I. *J. Am. Chem. Soc.* **1989**, *111*, 3454. (b) Grigg, R.; Dorrity, M.; Malone, J. F.; Sridharan, V.; Sukirthalingam, S. *Tetrahedron Lett.* **1991**, *31*, 1343. (c) Grigg, R.; Sridharan, V.; Sukirthalingam, S. *Tetrahedron Lett.* **1991**, *32*, 3855. (d) Meyer, F. E.; Parsons, P. J.; de Meijere, A. *J. Org. Chem.* **1991**, *56*, 6487. (e) Grigg, R.; Sridharan, V. *Tetrahedron Lett.* **1992**, *33*, 7965. (f) Carpenter, N. E.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5846. (g) Trost, B. M.; Dumas, J. *Tetrahedron Lett.* **1993**, *34*, 19. (h) Terpko, M. O.; Heck, R. F. *J. Am. Chem. Soc.* **1979**, *101*, 5281.

(11) (a) Daves, G. D. *Acc. Chem. Res.* **1990**, *23*, 201. (b) Arai, I.; Daves, G. D. *J. Am. Chem. Soc.* **1981**, *103*, 7683. (c) Hacksell, U.; Kalinoski, H. T.; Barofski, D. F.; Daves, G. D. *Acta Chem. Scand. B* **1985**, *39*, 469. See also: (d) Newkome, G. R.; Kawato, T.; Kohli, D. K.; Puckett, W. E.; Olivier, B. D.; Chiari, G.; Fronczek, F. R.; Deutsch, W. A. *J. Am. Chem. Soc.* **1981**, *103*, 3423.

(12) (a) Earley, W. G.; Oh, T.; Overman, L. E. *Tetrahedron Lett.* **1988**, *29*, 3785. (b) Madin, A.; Overman, L. E. *Tetrahedron Lett.* **1992**, *33*, 4859. (c) A carbamate unit not positioned for coordination does not affect the normal Heck reaction: Ableman, M. M.; Overman, L. E.; Tran, V. D. *J. Am. Chem. Soc.* **1990**, *112*, 6959. **Note added in proof:** Masters, J. J.; Hegedus, L. S. *J. Org. Chem.* **1993**, *58*, 4547.