Communications

Palladium-Mediated 6-*endo-trig* Intramolecular Cyclization of *N*-Acryloyl-7-bromoindolines. A Regiochemical Variant of the Intramolecular Heck Reaction†

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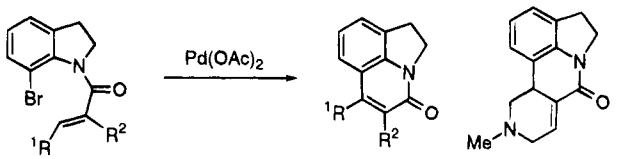
The palladium-catalyzed coupling of haloarenes and haloalkenes with olefins, known as the Heck reaction, has proved to be a general reaction for carbon–carbon bond formation. The utility of this reaction in both inter- and intramolecular variations for the synthesis of carbocyclic and heterocyclic systems is well documented.[1] However, the regiochemical outcome of this intramolecular palladium-catalyzed cyclization nearly always favors the 5-*exo-trig* pathway in those cases where competition between 6-*endo-* and 5-*exo-trig* closures is possible.[2] In an attempt to favor ring closure through a 6-*endo-trig* pathway by increasing the steric hindrance at the α position, Heck and Terpko studied the cyclization of α-substituted *N*-acryloyl-*o*-bromoanilines.[3] It was found that 2-quinolones were in fact produced from these cyclization reactions; however, the products apparently arose from a 5-*exo-trig* closure followed by an aminocarbonyl rearrangement and palladium hydride elimination. Grigg and co-workers cyclized 2-bromo 1,6-dienes using various palladium catalysts to yield products arising from either the 5-*exo-* or 6-*endo-trig* mode of cyclization. Although these reactions generally gave mixtures favoring 5-*exo-trig* closure, in one case a 10:1 ratio favoring the product of 6-*endo-trig* cyclization was observed.[2a] Several other examples have been documented where the 6-*endo-trig* pathway is the preferred mode of cyclization; however, in these cases the elimination of palladium hydride cannot occur if the 5-*exo-trig* cyclization results.[4]

It is herein reported that *N*-acryloyl-7-bromoindolines **1–5**, which plausibly could cyclize via either the 5-*exo* or 6-*endo* pathway, give exclusively 6-*endo* products when subjected to typical Heck conditions.[5] The cyclization of acrylamide **1** proceeded efficiently to give a 6-*endo-trig* product, **1a**.[6] No spectroscopic evidence was found for



1: R^1, R^2 = H
2: R^1 = Me, R^2 = H
3: R^1 = Ph, R^2 = H
4: R^1, R^2 = $CH_2N(Me)(CH_2)_2$
5: R^1,R^2 = $(CH_2)_4$

1a (99%)
2a (95%)
3a (94%)
4a (99%)
5a (88%, isomers)
4b (0%)

the formation of a 5-*exo-trig* product from this reaction.[7] Similarly, crotylamide **2** and cinnamylamide **3** were cyclized in excellent yield to afford quinolones **2a** and **3a**, respectively. Amide **4** provided the tetracyclic quinolone **4a**, again, via a 6-*endo* pathway. It is notable that at short reaction times the palladium-mediated cyclization of **4** produced both **4a** and small amounts of double-bond isomer **4b**; however, allowing the reaction to proceed for longer reaction times (12 h) gave only quinolone **4a**. The apparent isomerization of quinone **4b** to **4a** presumably occurs by readdition and elimination of palladium hydride[1a] to the double bond of amide **4b**; however, isomerization could not be prevented by the use of either silver carbonate[2g] or tetraethylammonium chloride[8] with these typical reaction conditions. Thus, this group has been unsuccessful in efforts to obtain synthetically useful amounts of compound **4b** from palladium-mediated cyclization of **4**. There was an increased tendency toward double-bond isomerization in the palladium-catalyzed cyclization of cyclohexenylamide **5**.[9] Cyclization of **5** appeared to occur by the 6-*endo-trig* pathway; however, all six possible products resulting from double-bond isomerization seemed to have formed.[10]

Increasing substitution of the double bond is known to dramatically reduce yields of intermolecular Heck reactions.[1a] Nevertheless, Overman has demonstrated that cyclization to a tetrasubstituted double bond is effective in the intramolecular variant of the palladium-catalyzed Heck reaction.[2g] It was found that palladium-mediated cyclization of tetrasubstituted amide **6** attempted under the usual conditions provided a mixture of lactams **6a** and **6b** in a 1:1.4 ratio. The cyclization reaction also proceeded slower than the previous cases (substrates **1–5**) presumably due to increased steric

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(1) For recent reviews of the Heck reaction, see: (a) Heck, R. F. *Org. React.* **1982**, *27*, 345. (b) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London, 1985. (c) Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, Chapter 4.3, p 833. (d) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379. (e) Cabri, W. ; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2.

(2) 6-*Endo-trig* cyclizations: (a) Grigg, R.; Stevenson, P.; Worakun, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1073. (b) Grigg, R.; Stevenson, P.; Worakun, T. *Tetrahedron* **1988**, *44*, 2033. (c) Odle, R.; Blevins, B.; Ratcliff, M.; Hegedus, L. S. *J. Org. Chem.* **1980**, *45*, 2709. (d) Negishi, E.; Zhang, Y.; O'Connor, B. *Tetrahedron Lett.* **1988**, *29*, 2915. 5-*Exo-trig* cyclizations: (e) Grigg, R.; Sridharan, V.; Stevenson, P. *Tetrahedron* **1990**, *46*, 4003. (f) Larock, R. C.; Babu, S. *Tetrahedron Lett.* **1987**, *28*, 5291. (g) Abelman, M. O.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130.

(3) Terpko, M. O.; Heck, R. F. *J. Am. Chem. Soc.* **1979**, *101*, 5281.

(4) (a) Grigg, R.; Sridharan, V.; Stevenson, P.; Worakun, T. *J. Chem. Soc., Chem. Commun.* **1986**, 1697. (b) Ishibashi, H.; Ito, K.; Hirano, T.; Tabuchi, M.; Ikeda, M. *Tetrahedron* **1993**, *49*, 4173.

(5) A typical procedure: The unsaturated amide **1** (256 mg, 1.02 mmol) was dissolved in acetonitrile (20 mL), and TEA (0.29 mL, 2.03 mmol) was added. The reaction was charged with triphenylphosphine (53 mg, 0.2 mmol) and palladium acetate (23 mg, 0.1 mmol), and the solution was refluxed for 10 h. The volatiles were removed under vaccum, and the crude material was purified by flash chromatograghy with silica gel to provide 173 mg of **1a** (99%).

(6) Complete experimental details and physical characterization of isolated compounds may be found in the supplementary material.

(7) Approximate limit by 300 MHz NMR.

(8) Jeffrey, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287.

(9) The use of either silver carbonate or tetraethylammonium chloride in the Heck cyclization of **5** provided several double-bond isomers which were not further characterized.

(10) Chromatography of the crude reaction mixture was attempted; however, purification for full spectroscopic identification was not feasible.

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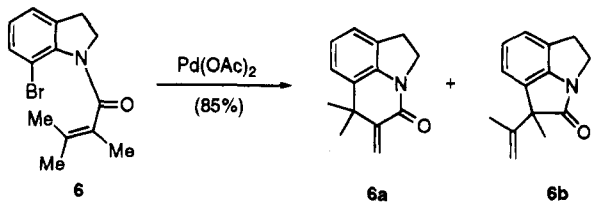
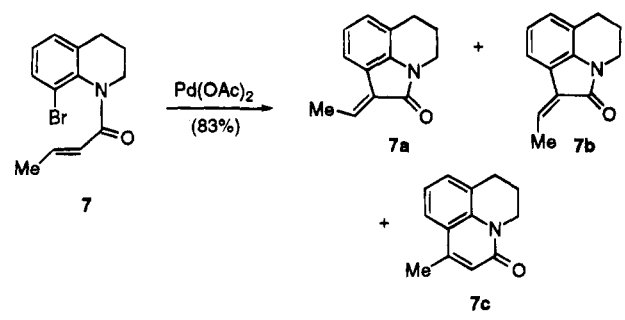


hindrance. The slightly predominant formation of compound **6b** via a 5-*exo* pathway is possibly due to relief of nonbonded interactions between the *cis*-β-methyl group and the ligands on palladium in the π-complex.

The palladium-catalyzed cyclization of **1**–**5** through a 6-*endo* pathway is presumably due to strain involved in the approach of the palladium species to the α position of the double bond of these acrylamides, thus generally disfavoring the 5-*exo-trig* mode of closure. In order to probe the effect of ring size on the regiochemistry of cyclization, amide **7** was subjected to the palladium cyclization conditions to provide the lactams **7a**, **7b**, and **7c** in a 5:1.3:1 mixture. Thus a 6.3:1 mixture of products favoring the 5-*exo-trig* pathway dominated in the reaction mixture. The indoline system in **1**–**5** is therefore apparently crucial for the 6-*endo-trig* Heck cyclization pathway. In summary, the results described here demonstrate that the regiochemistry of the palladium-mediated cyclization of *N*-acrylamides is profoundly influenced by incorporating the amide nitrogen into a benzofused ring and that indoline-based substrates generally favor



ring closure through a 6-*endo* pathway. Studies to further define the scope of the reaction and applications to natural product synthesis will be pursued in future work.

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Supplementary Material Available: Experimental procedures for all reaction products and complete spectral and analytical data for compounds **1**–**6**, **1a**–**4a**, **7**, and **7a**–**7c**. Products from the reactions of **5** and **6** were characterized as mixtures (11 pages).

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