

Direct and Regioselective C–H  
Alkenylation of  
Tetrahydropyrido[1,2-*a*]pyrimidines

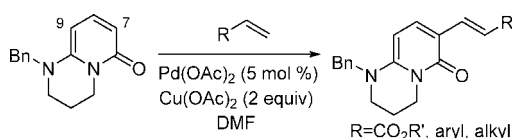
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Received March 25, 2009

## ABSTRACT



The electrophilic C–H palladation and Heck-type alkenylation of the tetrahydro[1,2-*a*]pyrimidine scaffold leads to exclusive formation of the C(7) adducts, and this palladium-catalyzed process is applicable to a broad range of alkenyl components. Mechanistic studies suggest that palladation is selective for C(7), and there was no evidence for C(9) metalation; the latter corresponds to the pathway observed previously with *N*-methylpyridone.

Bicyclic pyridones **1** belong to a class of pharmacologically active heterocycles that have attracted attention initially as potential analgesics and anti-inflammatory agents.<sup>1</sup> More recently, both Bayer AG<sup>2</sup> and Amgen Inc.<sup>3</sup> have disclosed bicyclic pyridones analogous to **1** to be useful in the prophylaxis and treatment of diseases mediated via TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and/or IL-8.

We have recently described two novel approaches to the synthesis of the [5,6], [6,6], and [7,6] bicyclic pyridones **1a–c**, respectively, which encompass versatile methods for achieving aryl substitution within the pyridone ring of these heterocyclic scaffolds (Figure 1).<sup>4</sup>

A key objective of our studies in this area was to define flexible methods for the further substitution and functionalization of these bicyclic scaffolds, and while Suzuki arylation was achieved, alkenylation (via a Heck or analogous process) was more attractive given the significantly increased range

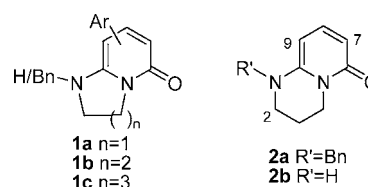


Figure 1. Target bicyclic pyridone scaffolds.

of functionality that Heck products offer. The advantages of the Heck reaction lie in the use of a catalytic process to introduce easily manipulated functionality (e.g., C=C, esters) and low molecular weight units, but as with other Pd-mediated couplings, this reaction usually also necessitates participation of a haloarene (i.e., halopyridone) component. Direct metalation (palladation) of C–H bonds<sup>5</sup> associated with (often but not exclusively) electron-rich arenes offers a very effective alternative to halide-based Heck alkenylation that has attracted widespread interest.<sup>6–8</sup> Itahara's work in

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(2) Alonso-Alija, C.; Michels, M.; Schirok, H.; Schlemmer, K.-H.; Dodd, S.; Fitzgerald, M.; Bell, J.; Gill, A. WO2003053967A1, 2003.

(3) Frohn, M. J.; Hong, F.-T.; Liu, L.; Lopez, P.; Siegmund, A. C.; Tadesse, S.; Tamayo, N. WO 2005/070932A2, 2005.

(4) Cheng, D.; Croft, L.; Abdi, M.; Lightfoot, A.; Gallagher, T. *Org. Lett.* **2007**, *9*, 5175.

(5) For pioneering work in this field, see: Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, 1119. Fujiwara, Y.; Moritani, I.; Danno, S.; Asano, R.; Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166. Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992. Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633.

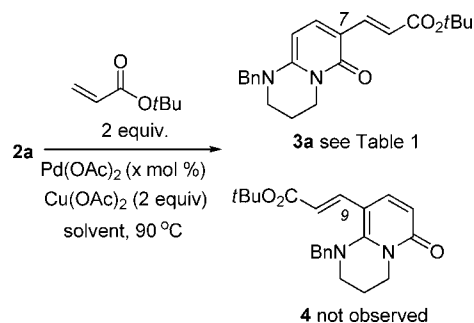
the 1980s is particularly relevant here.<sup>7</sup> For example, alkenylation (using ethyl acrylate) of *N*-toluenesulfonyl indole at C(3) was achieved using palladium(II) acetate (10 mol %) in combination with an excess of copper(II) acetate as the reoxidant (to regenerate Pd(II) after the alkenylation step). More recently, Gaunt<sup>8</sup> has reported that regiocontrol (C(2) vs C(3)) in the oxidative Heck alkenylation of indole itself using butyl acrylate is solvent dependent; a switch from C(3) (as observed by Itahara) to C(2) substitution was achieved by changing the reaction medium from DMF/DMSO to dioxane/acetic acid.

The application of this C–H activation variant of the Heck reaction to pyridones is, however, less straightforward. Itahara applied direct C–H palladation and Heck alkenylation to *N*-methyl-2-pyridone, and (using acrylates) the C(5) adducts were the exclusive products (see below).<sup>7</sup> However, this chemistry reported use of stoichiometric amounts of palladium(II) and failed for other (useful) alkenyl substrates, such as styrene and methyl vinyl ketone. More recently, one example of an oxidative Heck alkenylation (using catalytic Pd(II)) of a dihydro-4-pyridone using methyl acrylate has been described.<sup>9</sup>

Building on Itahara's initial studies with *N*-methyl-2-pyridone, we have sought to develop an efficient and economical method for C–H palladation and functionalization of bicyclic pyridones **1**. Using *N*-benzylated tetrahydropyrido[1,2-*a*]pyrimidine **2a** as a representative substrate, reaction with *tert*-butyl acrylate, a variety of alkenylation conditions were examined (Scheme 1 and Table 1).

Optimal conditions proved to be palladium(II) acetate (5 mol %) and copper(II) acetate (200 mol %) in DMF for 10 h at 90 °C (entry 3, Table 1), which gave the C(7)-substituted adduct **3a** in 93% yield. The impact of an acidic solvent was also examined (entries 4–6, Table 1), but this only resulted in slower and less efficient reactions; no change in regiochemistry or product distribution was observed. Inter-

**Scheme 1.** Oxidative Heck Alkenylation of Bicyclic **2a**



estingly, none of the isomeric C(9) adduct **4** was observed under any of the conditions examined; this isomer corresponds to the regioisomer observed by Itahara with *N*-methyl-2-pyridone.<sup>7</sup>

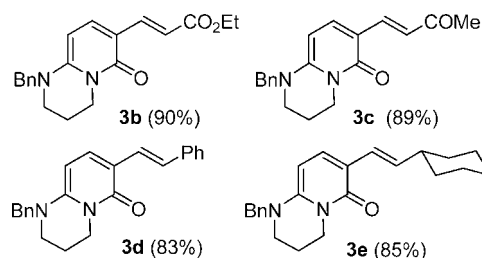
The scope of this process (in terms of the range of compatible alkenes) has been explored, and a series of C(7) alkenylated adducts (**3b–e**, Figure 2) have been prepared using ethyl acrylate, methyl vinyl ketone, styrene, and 2-cyclohexylethene, respectively. These reactions proceed in good yield under essentially the same conditions as described for **3a**, and this is particularly noteworthy in the case of **3e**, which involves a simple alkyl-substituted alkene, which are traditionally regarded as poor substrates for Heck reactions.

Interestingly, 2-vinylpyridine failed to give the expected Heck adduct **3f**, and based on Narahashi and Shimizu's earlier work, it is likely that palladation is followed by formation of a stable chelate **5** (involving the pyridine lone

**Table 1.** Optimization of Oxidative Alkenylation of **2a**

entry <sup>a</sup>	solvent	Pd(OAc) <sub>2</sub> (x mol %)	time (h)	<b>3a</b> <sup>b</sup> (%)
1	DMF	0	6	0
2	DMF	10	2	92
3	<b>DMF</b>	5	<b>10</b>	<b>93</b>
4	AcOH	20	10	35
5	dioxane/AcOH	10	10	45
6	DMSO/AcOH	10	10	51

<sup>a</sup> No evidence was observed for formation of the C(9) adduct **4** under any of these conditions. <sup>b</sup> Isolated yield.



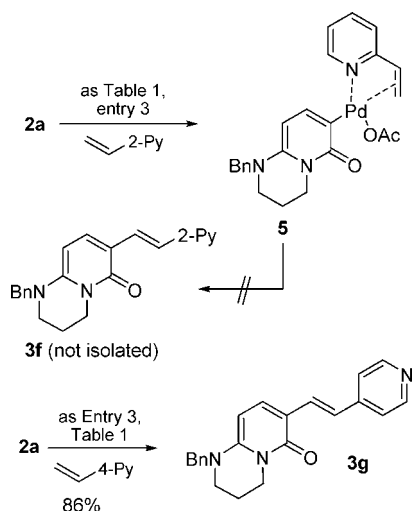
**Figure 2.** Alkenylation products derived from **2a**.

(6) For examples of Pd-mediated C–H activation and alkenylation of aryl and heteroaryl substrates, see: Trost, B. M.; Godleski, S. A.; Genet, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 3930. Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586. Baran, P.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 7904. Dams, M.; De Vos, D. E.; Celen, S.; Jacobs, P. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3512. Ma, S.; Yu, S. *Tetrahedron Lett.* **2004**, *45*, 8419. Capito, E.; Brown, J. M.; Ricci, A. *Chem. Commun.* **2005**, 1854. Wang, J.-R.; Yang, C.-T.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* **2007**, *48*, 5449. Cai, G.; Fu, Y.; Li, Y.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 7666. Maehara, A.; Satoh, T.; Miura, M. *Tetrahedron* **2008**, *64*, 5982. Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 6452. Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. Houlden, C. E.; Bailey, C. D.; Ford, J. G.; Gagne, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2008**, *130*, 10066. Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072.

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(9) Ge, H.; Niphakis, M. J.; Georg, G. I. *J. Am. Chem. Soc.* **2008**, *130*, 3708.

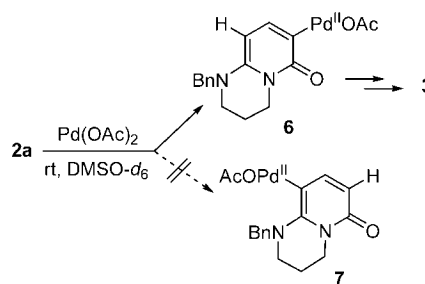
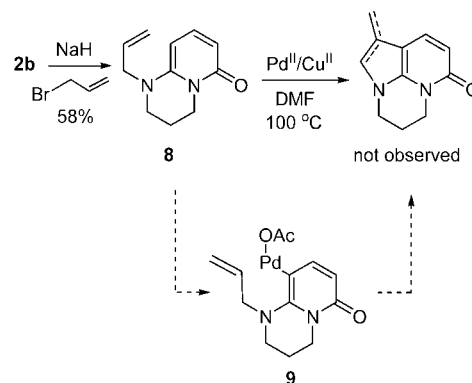
**Scheme 2.** Oxidative Alkenylation: 2- vs 4-Vinylpyridine

pair and the adjacent  $\pi$ -bond) that retard this process (Scheme 2).<sup>10</sup> The corresponding 4-substituted pyridine did, however, give the expected Heck adduct **3g** in 86% isolated yield.

Mechanistic options<sup>11</sup> associated with this process have also been studied. As pointed out above, increasing the acidity of the solvent system (which has been associated with the interconversion of  $\sigma$ -Pd intermediates) had no impact on the distribution of regioisomers (entries 4–6, Table 1). In our hands, the C(9) adduct was never detected, although electrophilic halogenation of **2a** (and **2b**) does produce both the C(7) and C(9) regioisomers.<sup>12</sup>

The initial interaction of Pd(II) with **2a** was examined by <sup>1</sup>H NMR (in DMSO-*d*<sub>6</sub>). Using 20 mol % of Pd(OAc)<sub>2</sub>, the resulting spectrum showed formation of approximately 16% of the C(7)  $\sigma$ -Pd species **6** (with the remainder being unreacted **2a**) (Scheme 3). With 1 equiv of Pd(OAc)<sub>2</sub> (and after 4 h), a 10:1 ratio of **6** to **2a** was observed (see the Supporting Information for details of assignments and copies of relevant spectra). We obtained no evidence for the formation or intermediacy of the C(9)-palladated adduct **7**, although these experiments cannot exclude involvement of this species.<sup>13</sup>

Nevertheless, if formed, **7** would need to be unstable with respect to protodemetalation in order to account for the high

**Scheme 3.** Palladation Pathway Observed by <sup>1</sup>H NMR**Scheme 4.** Failed Attempt To Trap a C(9)-Palladated Species

yields of the C(7) alkenylation products (i.e., **3**) that we have observed. Further support for a lack of involvement of a C(9)-palladated species comes from a failure of the *N*-allylated variant **8** (prepared from **2b**) to undergo an internal (5-exo) Heck reaction<sup>14</sup> (via **9**) under these oxidative conditions (Scheme 4).

In summary, the oxidative Heck reaction which likely involves initial and highly regioselective electrophilic palladation (given the electron-rich nature of **2a**), provides a robust, efficient and economical method for the functionalization of bicyclic pyridone scaffolds, as represented by *N*-benzyltetrahydropyrido[1,2-*a*]pyrimidine **2a**. The intermediate  $\sigma$ -Pd species **6** has been characterized by <sup>1</sup>H NMR and regeneration of the key electrophilic Pd(II) reagent is readily achieved using Cu(II) as oxidant.

**Acknowledgment.** Financial support from the University of Bristol is gratefully acknowledged.

**Supporting Information Available:** . Experimental details and spectroscopic data for all new compounds and <sup>1</sup>H NMR studies relating to the regioselective palladation of **2a** are available. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(11) Various mechanistic possibilities exist for C–H activation with Pd(II). These most frequently link electrophilic aromatic substitution to electron-rich,  $\pi$ -excessive (hetero)arenes and, more recently, concerted metalation–deprotonation for simple and electron-deficient arenes. For a summary of mechanistic possibilities and leading references, see: Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848.

(12) Reaction of **2a** with NCS or NBS gave mixtures of C(7) and C(9) regioisomers and C(7)/C(9) bishalogenation products: Cheng, D. Unpublished results.

(13) The possibility that the C=O group directs palladation at C(7) has been raised by a reviewer, and carbonyl directing effects have been recently reported: Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14082. Delcamp, J. H.; Brucks, A. P.; White, C. M. *J. Am. Chem. Soc.* **2008**, *130*, 11270. However, such a directing effect should also have operated in Itahara's work, but this does not appear to be the case.<sup>7</sup>