ORGANIC LETTERS

2011
Vol. 13, No. 4
728–731

2,2-Difunctionalization of Alkenes via Pd(II)-Catalyzed Aza-Wacker Reactions

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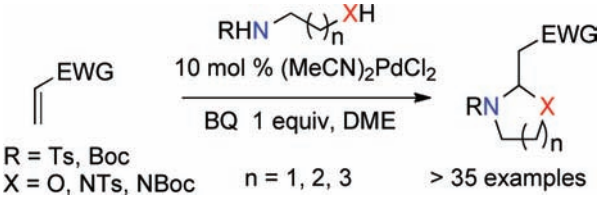
Received December 7, 2010

ABSTRACT



***N*-Ts and *N*-Boc derivatives of 1,2-diamines and 1,2-amino alcohols are shown to undergo efficient Pd(II)-catalyzed aza-Wacker reactions with a large range of electron-deficient alkenes. The resulting enamine intermediate generally undergoes cyclization with the second heteroatom to form 1,3-heterocycles. The sequence facilitates the rapid synthesis of saturated oxazolidines, imidazolidines, and their derivatives. Use of *N*-L-valinol derivatives results in highly diastereoselective reactions, where the net stereochemical outcome diverges between *N*-Ts and *N*-Boc.**

Imidazolidines and oxazolidines are prevalent heterocycles in natural products, in pharmaceuticals,[1] and in ligands of use in organometallic catalysis.[2] In 2005, we reported the first Pd(II)-catalyzed 1,2-diamination of dienes, using ureas as the dinitrogen source.[3] In an attempt to effect an equivalent 1,2-alkoxyamination sequence, we have investigated the Pd(II)-catalyzed addition of a range of aminoalcohol sources across a range of dienes and alkenes. The results we obtained were unexpected, in that 2,2- rather than 1,2-addition was the dominant pathway. The development of this novel process, which facilitates rapid synthesis of saturated oxazolidines, imidazolidines, and their derivatives, forms the subject of the work presented herein.

In initial experiments, we attempted to react 1,3-dienes, simple alkenes (*n*-hexene; cyclohexene), and styrenes with *N*-Ts-ethanolamine, using 10 mol % Pd(II), under the oxidative conditions (benzoquinone, DME, 60 °C) that we had previously found successful for 1,2-addition of ureas[3] (Scheme 1). Of these substrates, only the parent styrene reacted to give oxazolidine **2a**, the product of an oxidative geminal functionalization of the terminal alkenyl carbon, in modest yield (28−36%). To our knowledge, this is the first example of such an alkoxyamination sequence[4,5] with alkenes, and as such, it merited further investigation and development.

On changing to more electron-deficient alkenes, the reaction proceeded much more readily, affording the corresponding oxazolidines (**2**) in good yield (Table 1).

For example, *N*-Ts-ethanolamine (**1**, R = Ts) coupled with butyl acrylate **3** (R′ = CO_2Bu) in under 2 h at 40 °C, to

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(1) (a) Regunathan, S.; Reis, D. *Annu. Rev. Pharmacol. Toxicol.* **1996**, *36*, 511–544. (b) Tomizawa, M.; Casida, J. E. *Annu. Rev. Pharmacol. Toxicol.* **2005**, *45*, 247–268. (c) Brown, D.; Evans, J. R.; Fletton, R. A. *Chem. Commun.* **1979**, *6*, 282–283.

(2) Fache, F.; Schulz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159–2231.

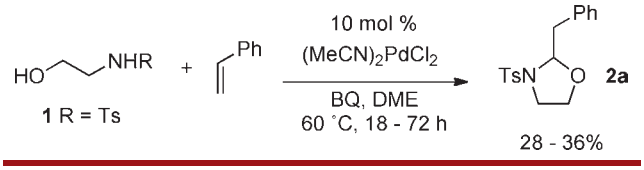
(3) Bar, G. L. J.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 7308–7309.

(4) For Pd(II) mediated reactions of alkenes with diols, see: (a) Hosokawa, T.; Ohta, T.; Kanayama, S.; Murahashi, S. *J. Org. Chem.* **1987**, *52*, 1758–1764. (b) Hosokawa, T.; Ohta, T.; Murahashi, S. *Chem. Commun.* **1983**, *15*, 848–849.

(5) For previous synthesis of oxazolidines, see: Sriramurthy, V.; Barcan, G. A.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 12928–12929.

10.1021/ol102956x
Published on Web 01/18/2011

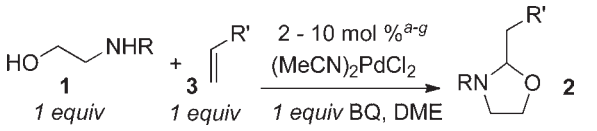
Scheme 1. 2,2-Alkoxyamination of Styrene



give oxazolidine **2b** in 82% yield (Table 1, entry 1); indeed, the reaction even proceeded at ambient temperature, with as little as 2 mol % Pd, in under 18 h (entries 2−4). Attempts to adopt lower catalyst loadings as optimal conditions resulted in inconsistent yields, and as a result 10% catalyst loading was used throughout the study. Interestingly, the alkoxyamination sequence was specific for monosubstituted alkenes as no reaction was observed with methacrylates, crotonates, or cycloalkenones.

A control reaction conducted in the absence of catalyst (entry 5) confirmed the key role of Pd in the process. The reactions of *N*-Ts-ethanolamine and *N*-Boc-ethanolamine (**1**, R = Ts; Boc) both proceeded well under the standard conditions with a range of monosubstituted electron-deficient alkenes (entries 6−22).[6] When the sulfonamide or carbamate moieties were changed to the less NH-acidic *N*-acyl derivative (entry 24) there was no reaction.

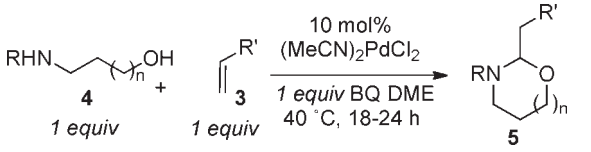
Table 1. Oxyamination of Electron-Deficient Alkenes with Ethanolamine Derivatives



entry	R	R′	product	yield (%)
1	Ts	CO_2Bu	**2b**	82[a]
2	Ts	CO_2Bu	**2b**	75[b]
3	Ts	CO_2Bu	**2b**	73[c]
4	Ts	CO_2Bu	**2b**	78[d]
5	Ts	CO_2Bu	**2b**	0[e]
6	Boc	CO_2Bu	**2c**	60[f]
7	Ts	CONMe(OMe)	**2d**	54[f]
8	Boc	CONMe(OMe)	**2e**	69[f]
9	Ts	CO(morpholinyl)	**2f**	39[f]
10	Boc	CO(morpholinyl)	**2g**	67[f]
11	Ts	SO_2Ph	**2h**	65[g]
12	Boc	SO_2Ph	**2i**	26[g]
13	Ts	CO_2Me	**2j**	79[f]
14	Ts	CO_2tBu	**2k**	72[f]
15	Ts	CO_2H	**2l**	82[f]
16	Boc	CO_2H	**2m**	63[f]
17	Ts	$CON(Me)_2$	**2n**	52[f]
18	Boc	$CON(Me)_2$	**2o**	62[f]
19	Ts	CONH*i*Pr	**2p**	38[f]
20	Ts	COMe	**2q**	53[f]
21	Boc	COMe	**2r**	57[f]
22	Ts	CN	**2s**	18[f]
23	*p*Ns	CO_2Bu	**2t**	77[f]
24	Ac	CO_2Bu	**2u**	0[f]

[a] Catalyst loading: 10 mol %, 40 °C, 2 h. [b] Catalyst loading: 10 mol %, 21 °C, 18 h. [c] Catalyst loading: 5 mol %, 21 °C, 18 h. [d] Catalyst loading: 2 mol %, 21 °C, 18 h. [e] Catalyst loading: 0 mol %, 21 °C, 48 h. [f] Catalyst loading: 10 mol %, 40 °C, 18 h. [g] Catalyst loading: 10 mol %, 60 °C, 18 h.

Table 2. Effect of Chain Length in the Aminoalcohol Derivatives



entry	R	R′	*n*	**5**	yield (%)
1	Ts	CO_2Bu	1	**5a**	83
2	Boc	CO_2Bu	1	**5b**	17
3	Ts	CO_2tBu	1	**5c**	39
4	Ts	CO_2Me	1	**5d**	71
5	Ts	CO_2H	1	**5e**	32
6	Boc	CO_2H	1	**5f**	37
7	Ts	CO_2Bu	2	**5g**	13
8	Boc	CO_2Bu	2	**5h**	30
9	Ts	CO_2H	2	**5i**	9
10	Boc	CO_2H	2	**5i**	14

We then explored the use of homologous reagents (**4**, *n* = 1, 2) to assess the scope for formation of six- and seven-membered heterocycles (Table 2). With *N*-Ts propanolamine, good yields of 1,3-oxazinane **5** (R = Ts, *n* = 1) were obtained with simple acrylates (entries 1 and 4). However, the outcome with *N*-Boc propanolamine (entries 2 and 6) was less clear-cut, with uncyclized Wacker-type products[7] being formed, in addition to **5** (R = Boc, *n* = 1). Yields of seven-membered heterocycles **5** (R = Ts, Boc, *n* = 2) were generally poorer (entries 7−10) possibly due to the greater entropic cost in cyclization.

Finally, we explored 2,2-diamination of electron-deficient alkenes using *N*,*N*′-derivatized 1,2-ethylenediamine sources.

In general, the Boc disubstituted ethylenediamines gave the best results. Overall, however, the reactions proved to be less selective than with ethanolamines, since mixtures of the imidazolidines **7** and the aza-Wacker products **8** were obtained in moderate to good overall yield (Table 3).

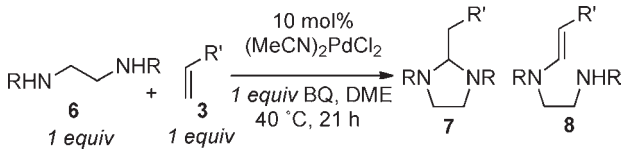
Palladium-catalyzed intermolecular aza-Wacker additions to alkenes have been extensively studied by Stahl[8] and others. We envisage an analogous aza-Wacker sequence (Scheme 2) for the first stage of the 2,2-alkoxyamination reaction, with an off-cycle conjugate addition leading to the final product (**2**). In this model, activation of the electron-deficient alkene by coordination to Pd(II) is

(6) In general the yields were moderate to good. In the case of the lower yielding examples in Table 1, increasing the amount of alkene and/or benzoquinone did not significantly improve overall yields.

(7) For example, see **13** in the Supporting Information.

(8) (a) Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2003**, *125*, 12996–12997. (b) Brice, J. L.; Harang, J. E.; Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2005**, *127*, 2868–2869. (c) Timokhin, V. I.; Stahl, S. S. *J. Am. Chem. Soc.* **2005**, *127*, 17888–17893. (d) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 6328–6335. (e) Liu, X.; Hii, K. K. *Eur. J. Org. Chem.* **2010**, *27*, 5181–5189.

Table 3. Diamination of Electron-Deficient Alkenes



entry	R	R′	**7** (%)	**8** (%)
1	Ts	CO_2Bu	**7a** (46)	**8a** (11)
2	Boc	CO_2Bu	**7b** (57)	**8b** (10)
3	Ts	CONMe(OMe)	**7c** (24)	**8c** (12)
4	Boc	CONMe(OMe)	**7d** (63)	**8d** (13)
5	Ts	CO(morpholinyl)	**7e** (10)	**8e** (29)
6	Boc	CO(morpholinyl)	**7f** (63)	**8f** (16)
7[a]	Ts	SO_2Ph	**7g** (34)	**8g** (4)
8[b]	Boc	SO_2Ph	**7h** (0)	**8h** (17)

[a] 70 °C, 48 h. [b] 60 °C, 48 h.

followed by amino-palladation leading to the σ-Pd(II) species ***II***. β-Hydride elimination leads to the enamide ***III*** and Pd(0) which is then reoxidized by BQ to the active Pd(II) catalyst. In the majority of cases, the final cyclization (***III***→**2**) is efficient under the reaction conditions, such that no ***III*** or ***IV*** accumulates. However, during a larger scale reaction (Table 1, entry 10, 5 mmol of **3**, 1% Pd), we were able to isolate enamide **9**. This proved to be stable on heating, but on addition of 10 mol % $(MeCN)_2PdCl_2$ with no added BQ, it underwent efficient cyclization to **2g**. Similar reasults were then observed with TsOH and BF_3•Et_2O. This suggests Lewis or Bronsted acid catalysis for this step (***III***→**2**) under the reaction conditions. A separate experiment showed hydroquinone, a reaction coproduct, to be insufficiently acidic in catalyzing the cyclization of **9** to **2g**.

The prochiral nature of intermediate ***III*** raises interesting questions concerning kinetic and thermodynamic diastereoselectivity in the cyclization when the ethanolamine backbone is appropriately substituted. To probe this issue we reacted *N*-Ts- and *N*-Boc-L-valinol (**10a** and **10b**) with butyl acrylate and found complementary stereogenic outcomes (Figure 1).

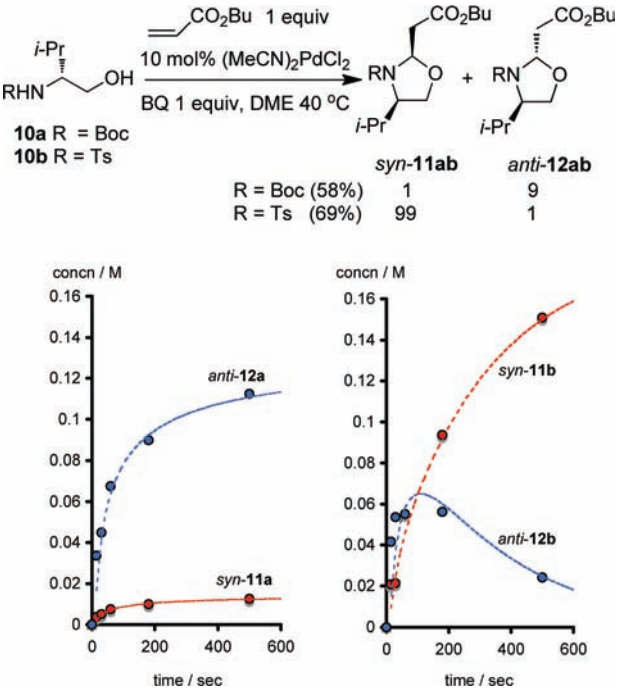
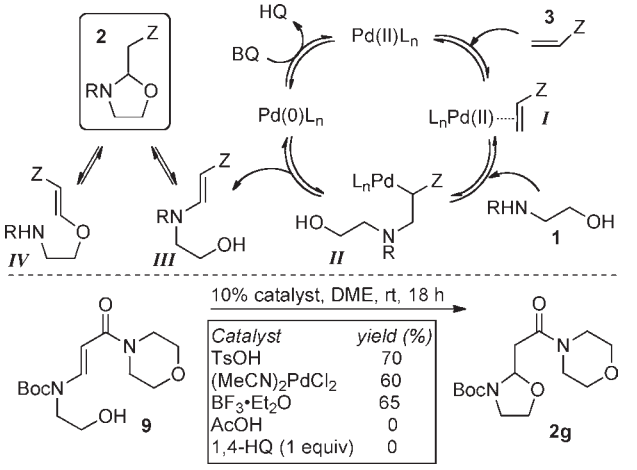


Figure 1. Oxyamination with *N*-L-valinol derivatives.

Scheme 2. Proposed Pd(II)-Catalyzed Aza-Wacker Mechanism and Acid-Catalyzed Cyclization of **9**



Analysis of the evolution of two reactions during the first 10 min revealed a constant 9/1 selectivity for the formation of the *anti* isomer **12a**, when R = Boc. The *anti* isomer was also favored when R = Ts (**12b**), albeit with lower selectivity (k_{rel} = 2). However, in contrast to **12a**, the *anti* isomer **12b** epimerized, via pseudo-first-order equilibrium kinetics, to eventually give almost pure *syn*-**11b** (K_{eq} > 98). No enamide (***III***) or enol ether (***IV***) intermediates were detected, and neither $(MeCN)_2PdCl_2$ (10 mol %) nor hydroquinone (1 equiv) had any effect on reference samples of *anti*-**12b**/*syn*-**11b** in DME. However, under the reaction conditions (Figure 1) the rate of epimerization of **12b** to **11b** was found to be inversely dependent on the stoichiometry of the benzoquinone. This suggested that increasing the efficiency of Pd-reoxidation ([Pd(0)] + BQ + 2 HCl → [Pd(II)]Cl_2 + hydroquinone) reduces the concentration of free HCl and thus the rate of epimerization via a ring-opened oxonium intermediate. This conclusion was supported by the observation of a rapid increase in the rate of epimerization when 10 mol % anhydrous HCl was added to the reaction.

In summary, we report an oxidative aza-Wacker methodology for the conversion of electron-deficient alkenes into functionalized, saturated heterocycles. The reaction has broad scope for a range of amino-alcohol and diamine nucleophiles. Reactions with valinol nucleophiles show an interesting switch in diastereoselectivity, and further studies on the mechanism of this process, including other amino acid derived substrates, will be reported in full in due course.

Acknowledgment. We thank Novartis for provision of a PhD studentship to J.W.W. and EPSRC for funding (EP/E061575/1). G.C.L.J. is a Royal Society Wolfson Research Merit Award Holder.

Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.