Isoxazolidine Synthesis

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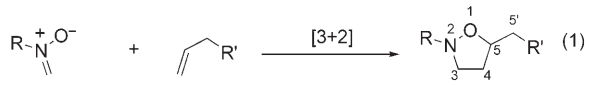
Stereoselective Synthesis of Isoxazolidines through Pd-Catalyzed Carboetherification of *N*-Butenylhydroxylamines**

*Michael B. Hay and John P. Wolfe**

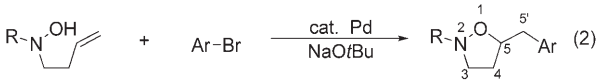
Isoxazolidines are frequently used as intermediates in the synthesis of complex molecules[1] and are found in several interesting biologically active compounds.[2] In addition, the isoxazolidine N–O bond can be easily cleaved under reducing conditions to afford 1,3-amino alcohols, which are also of synthetic utility.[3] The most commonly employed method for the construction of isoxazolidines involves 1,3-dipolar cycloaddition reactions between nitrones and alkenes,[4] which generates the O1–C5 bond and the C3–C4 bond in one step [Eq. (1)]. Although these transformations are very useful, many intermolecular cycloadditions of unactivated alkenes



(1)

generate mixtures of regioisomers.[4] Moreover, the major stereoisomers typically result from *endo* addition on the less hindered face of the alkene, and the selective preparation of stereoisomers resulting from *exo* addition and/or addition to the more substituted alkene face cannot be achieved in a straightforward manner.[4]

Herein, we describe a new approach to the construction of substituted isoxazolidines based on palladium-catalyzed carboetherification reactions of *N*-butenyl hydroxylamine derivatives with aryl bromides [Eq. (2)]. This method represents a new strategy for construction of the isoxazolidine ring, in

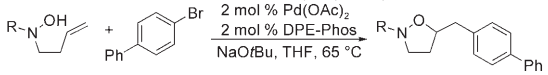


(2)

which the O1–C5 bond and a C5′–Ar bond are formed in one step.[5] These transformations also provide access to isoxazolidine stereoisomers that cannot be generated with currently available methods. The reactions appear to proceed by intramolecular alkene insertion into previously unprecedented palladium alkoxyamine intermediates, which may be of utility in other Pd-catalyzed carbon–heteroatom bond-forming processes.

In preliminary experiments, we examined Pd-catalyzed reactions of *N*-butenyl hydroxylamines **1**–**3** with 4-bromobiphenyl under conditions that were employed in our prior studies on Pd-catalyzed carboetherification reactions of γ-hydroxyalkenes.[6–8] As shown in Table 1, attempts to cyclize unprotected hydroxylamine substrate **1** and *N*-*tert*-butyloxycarbonyl(Boc)-protected derivative **2** were unsuccessful.[9] However, we were gratified to find that treatment of *N*-benzyl-protected substrate **3** with 4-bromobiphenyl and NaO*t*Bu in the presence of catalytic amounts of $Pd(OAc)_2$ and DPE-Phos[10] afforded the desired product **4** in 80% yield.

Table 1: Carboetherification of *N*-butenyl hydroxylamines.[a]



Hydroxylamine	R	Isoxazolidine	Yield [%][b]
1	H	–	0[c]
2	Boc	–	0[c]
3	Bn	**4**	80

[a] Conditions: 1.0 equiv substrate, 1.2 equiv ArBr, 1.2 equiv NaO*t*Bu, 2 mol% $Pd(OAc)_2$, 2 mol% DPE-Phos, THF (0.125 M), 65 °C. [b] Yields represent average yields of isolated product for two or more experiments. [c] Heck arylation products were observed.

With viable reaction conditions and a suitable nitrogen protecting group identified, we examined Pd-catalyzed carboetherification reactions between several different substituted hydroxylamines and a number of aryl bromides. As shown in Table 2, this method is effective with electron-rich (entry 10), electron-neutral (entries 4, 7, 8, and 12), electron-poor (entries 1, 2, 11, and 13), *o*-substituted (entry 8), and heterocyclic (entries 3, 5, 6, and 9) aryl bromides. In addition to the *N*-benzyl-protected derivatives described above, hydroxylamine substrates bearing *N*-methyl or *N*-*tert*-butyl groups also undergo cyclization in good yield.

The carboetherification reactions are also effective with substrates bearing substituents along the tether between the hydroxylamine moiety and the alkene. Transformations of these substrates provide access to disubstituted isoxazolidines with moderate to excellent stereocontrol. Importantly, in many cases these cyclizations provide a means to generate isoxazolidines that could not be prepared using 1,3-dipolar

[*] M. B. Hay, Prof. J. P. Wolfe
University of Michigan
Department of Chemistry
Ann Arbor, MI 48109-1055 (USA)
Fax: (+1) 734-763-2307
E-mail: jpwolfe@umich.edu

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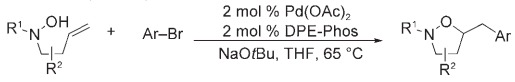
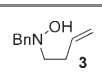
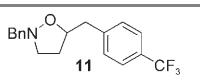
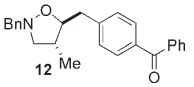
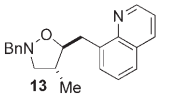
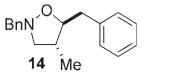
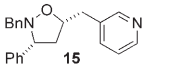
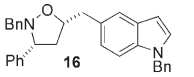
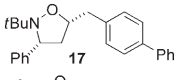
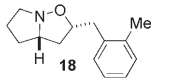
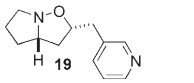
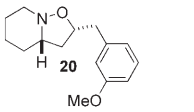
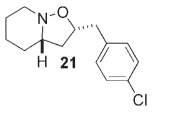
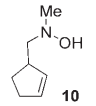
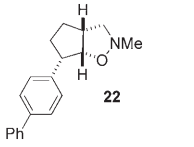
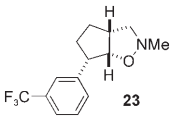
Table 2: Pd-catalyzed synthesis of substituted isoxazolidines.[a]

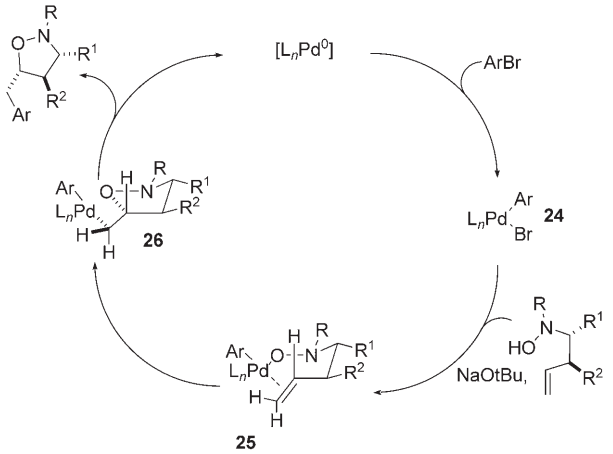


Entry	Substrate	Isoxazolidine	d.r.[b]	Yield [%][c]
1			–	85
2			>20:1 (5:1)	56
3	**5**		3:1 (3:1)	70
4	**5**		>20:1 (3:1)	57
5			3:1 (3:1)	77
6	**6**		3:1 (3:1)	78
7			3:1 (3:1)	61
8			>20:1 (10:1)	82
9	**8**		>20:1 (10:1)	85
10			19:1 (9:1)	94
11	**9**		>20:1 (9:1)	89
12[d]			>20:1 (>20:1)	78
13[d]	**10**		>20:1 (>20:1)	69

[a] Conditions: 1.0 equiv substrate, 1.2 equiv ArBr, 1.2 equiv NaO*t*Bu, 2 mol% $Pd(OAc)_2$, 2 mol% DPE-Phos, THF (0.125 M), 65 °C. [b] d.r. = diastereomeric ratio of isolated material. Numbers in parentheses are the observed diastereomeric ratios for the crude reaction mixture. [c] Yields represent average yields of product isolated in two or more experiments. [d] The reaction was conducted at 110 °C in toluene solvent with $[Pd_2(dba)_3]$ (1 mol%) used in place of $Pd(OAc)_2$ (dba = dibenzylideneacetone).

cycloaddition methods. For example, Pd-catalyzed reactions of **10** with 4-bromobiphenyl and 3-bromobenzotrifluoride provide **22** and **23**, respectively, in 78% and 69% yields, with >20:1 diastereoselectivity and regioselectivity (Table 2, entries 12 and 13). In contrast, a 1,3-dipolar cycloaddition reaction between a nitrone and a 3-arylcyclopentene would be expected to occur on the less hindered face of the alkene to afford a different stereoisomer and would likely generate mixtures of regioisomers.[4] In addition, reactions of **8** with aryl bromides proceed in 82–85% yield and 10:1 d.r. to afford the (2*R**,3a*S**)-hexahydropyrrolo[1,2*b*]isoxazole isomers **18** and **19** (Table 2, entries 8 and 9). However, dipolar cycloadditions between 3,4-dihydropyrrole-1-oxide and allylbenzene derivatives instead generate stereoisomeric (2*S**,3a*S**)-hexahydropyrrolo[1,2*b*]isoxazoles.[11] The hydroxylamine carboetherifications can also be used to prepare *trans*-4,5-disubstituted isoxazolidines **12**–**14** and *cis*-3,5-disubstituted isoxazolidines **15**–**17** in good yield with 3:1 to 5:1 diastereoselectivity.

A plausible mechanism for the isoxazolidine-forming reactions is shown in Scheme 1. These transformations appear to be mechanistically related to Pd-catalyzed carboetherification reactions of γ-hydroxy alkenes with aryl bromides[6] and are likely initiated by oxidative addition of the aryl bromide to Pd^0 to afford **24**. The $[L_nPd(Ar)(Br)]$ complex can then be transformed to intermediate **25** by reaction with the hydroxylamine substrate and NaO*t*Bu. Intramolecular *syn* oxypalladation[6,12] of the tethered alkene moiety of **25** would generate **26**, which can undergo C–C bond-forming reductive elimination[13] to afford the observed isoxazolidine products. The conversion of **10** to *syn*-addition products **22** and **23** is consistent with this hypothesis. Moreover, this model also accounts for the observed stereochemistry of **12**–**21**, as the *syn* oxypalladation likely occurs from an organized cyclic transition state in which nonbonding interactions are minimized by pseudoequatorial orientation of the substrate R^1 and R^2 groups. This transition state arrangement would provide *cis*-3,5-disubstituted products ($R^2 = H$) and *trans*-4,5-disubstituted compounds ($R^1 = H$).



Scheme 1. Catalytic cycle of the Pd-catalyzed carboetherification reaction of *N*-butenylhydroxylamines.

Although palladium(aryl)alkoxides have been shown to be important intermediates in a number of catalytic processes,[6,14,15] the analogous complexes derived from hydroxylamines (e.g. **25**) are unknown. The reactions described in this paper represent the first examples of catalytic transforma-

tions involving [Pd(Ar)(ONRR′)] species. These previously unknown intermediates will likely find additional applications in other metal-catalyzed carbon–heteroatom bond-forming reactions.[15]

In conclusion, we have developed a new stereoselective method for the construction of substituted isoxazolidines through Pd-catalyzed carboetherification reactions of unsaturated hydroxylamine substrates. In many cases the stereochemical outcome of these transformations is complementary to that of nitrone cycloadditions, and this method provides a new strategic disconnection that can be used for retrosynthetic analysis of substituted isoxazolidines.

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[5] A recent report described Pd^0- and Pd^{II}-catalyzed syntheses of 2-vinyl isoxazolidines by cyclizations of hydroxylamines bearing tethered allylic acetate groups. In contrast to the reactions described in this paper, the cyclizations of the allyl acetate derivatives do not lead to C–C bond formation concomitant with ring closure. The cyclizations of the allylic acetate derivatives are also mechanistically distinct, as the Pd^0-catalyzed transformation proceeds via a π-allylpalladium intermediate which is likely captured by an outer-sphere nucleophilic attack on the allyl ligand, and the Pd^{II}-catalyzed transformation proceeds by alkene activation followed by outer-sphere *anti*-oxypalladation. No evidence exists for the intermediacy of $[L_nPd(ONR_2)(allyl)]$ complexes that bear a Pd–O bond. See: a) P. Merino, T. Tejero, V. Mannucci, G. Prestat, D. Madec, G. Poli, *Synlett* **2007**, 944 – 948. For additional discussion of Pd-catalyzed allylations of nucleophiles containing an N–O bond, see: b) H. Miyabe, K. Yoshida, V. K. Reddy, A. Matsumura, Y. Takemoto, *J. Org. Chem.* **2005**, *70*, 5630 – 5635.

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[7] For a review on Pd-catalyzed carboetherification and carboamination reactions of γ-hydroxy and γ-amino alkenes, see: J. P. Wolfe, *Eur. J. Org. Chem.* **2007**, 571 – 582.

[8] Two recent reports have described a related approach to the synthesis of *cis*-3,5-disubstituted isoxazolidines in which the N–C3 bond is generated by Pd-catalyzed carboamination of *O*-homoallyl hydroxylamines. The scope of these transformations has not been fully explored. See: a) K. G. Dongol, B. Y. Tay, *Tetrahedron Lett.* **2006**, *47*, 927 – 930; b) J. Peng, W. Lin, S. Yuan, Y. Chen, *J. Org. Chem.* **2007**, *72*, 3145 – 3148.

[9] The major products observed in these reactions resulted from Heck arylation of the alkene.

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[14] For examples of well-characterized $[L_nPd(Ar)(OR)]$ complexes, see: a) G. Mann, J. F. Hartwig, *J. Am. Chem. Soc.* **1996**, *118*, 13109 – 13110; b) R. A. Widenhoefer, H. A. Zhong, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 6787 – 6795.

[15] In addition to carboetherification reactions of γ-hydroxyalkenes, synthetically useful reactions that are believed to proceed via $[L_nPd(Ar)(OR)]$ complexes include Pd-catalyzed *O*-arylation reactions and oxidation reactions. It is likely that the analogous hydroxylamine complexes $[L_nPd(Ar)(ONRR')]$ will find similar applications. For lead references on useful catalytic transformations involving $[L_nPd(Ar)(OR)]$ intermediates, see: a) A. V. Vorogushin, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 8146 – 8149; b) N. Kataoka, Q. Shelby, J. P. Stambuli, J. F. Hartwig, *J. Org. Chem.* **2002**, *67*, 5553 – 5566; c) A. S. Guram, X. Bei, H. W. Turner, *Org. Lett.* **2003**, *5*, 2485 – 2487.

