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O-Alkenyl Hydroxylamines: A New Concept for Cyclofunctionalization

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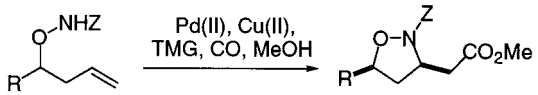
ABSTRACT



Treatment of *O*-homoallylhydroxylamines with palladium(II) and copper(II) in the presence of a base, methanol, and carbon monoxide results in the formation of isooxazolidines. An electron-withdrawing group on the hydroxylamine nitrogen is essential. When carbamate groups are used the products are formed exclusively as their cis isomers.

The cyclofunctionalization[1] of tethered *N*-nucleophiles is a valuable process for the stereo- and regiocontrolled formation of C−N bonds, and it has found numerous uses in synthesis.[2] Typical tethers require an sp^2-hybridized carbon atom and result in 1,2- or 1,3-stereocontrol via a five- or a six-membered-ring heterocyclic intermediate.[3]

Surprisingly, little work has been done concerning the use of transition metal electrophiles as cyclofunctionalization triggers[4] for alkenes with tethered nitrogen despite the potential for concurrent stereocontrolled C−N and C−C bond formation.[5]

We sought to address these issues by employing *O*-,*N*-functionalized hydroxylamines in which the tether would be just an O−N single bond. In this way, a five-membered-ring heterocyclic intermediate might result in 1,3-stereocontrol. With this aim, the hydroxylamines **3** were prepared by Mitsunobu reaction of the corresponding alcohols **1**[6] using *N*-hydroxyphthalimide.[7] Without purification, the phthaloyl group was cleaved by treatment with hydrazine hydrate at room temperature, to give the hydroxylamines **3** in good yield after chromatographic purification (Table 1).

Table 1. Yields (%) for Preparation of Substrates

	2	**3**	**4** Z = CO_2Me	**5** Z = Ns	**6** Z = CBZ	**7** Z = *t*-Boc
a	nd[a]	82[b]	91	92	90	90
b	nd[a]	49[b]			51	56
c	52	51			93	

[a] nd: not determined. [b] Over two steps.

The *N*-unsubstituted hydroxylamine **3a** failed to cyclize under typical conditions. The hydroxylamines were therefore derivatized with a series of standard *N*-protecting groups (**Z1**−**Z4**).[8] With an electron-withdrawing group on nitrogen,

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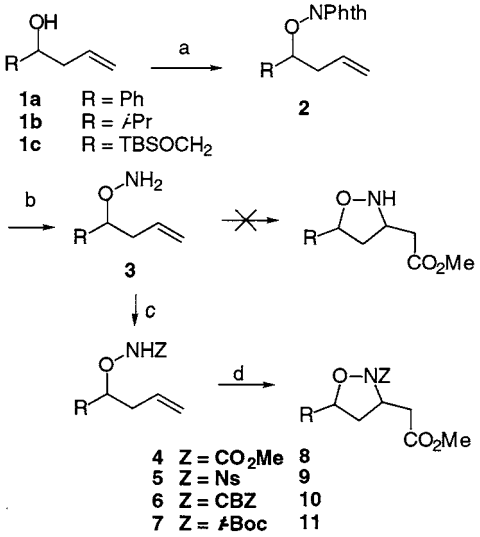
Scheme 1. Preparation and Cyclization of Hydroxylamines[a]



[a] Reagents and conditions: (a) PhthNOH, PPh_3, DEAD, THF, 0 °C to rt; (b) $H_2NNH_2 \cdot xH_2O$, CH_2Cl_2, rt; (c) MeOCOCl, K_2CO_3, CH_2Cl_2, reflux or NsCl, Na_2CO_3, CH_2Cl_2, H_2O, rt or CBZOSuc, $NaHCO_3$, CH_2Cl_2, H_2O or Boc_2O, NaOH, CH_2Cl_2, H_2O.

cyclization−carbonylation proceeded to give the isoxazolidines **8**−**11** (Table 2).

Table 2. Cyclofunctionalization Reactions

entry	substrate	conditions[a]	yield, %	RSM,[c] %
1	**4a**	A	37	31
2	**4a**	D	43	32
3	**5a**	A	61 + 12[b]	1
4	**6a**	A	49	35
5	**6a**	B	28	59
6	**6a**	C	48	19
7	**6a**	D	63	
8	**7a**	A	0	
9	**7a**	D	79	
10	**7a**	E1	75	
11	**7a**	E2	0	
12	**7a**	E3	51	24
13	**7b**	D	30	42
14	**6b**	D	41	16
15	**6c**	D	38	8

[a] Conditions (all using 1:1 CH_3CN/MeOH unless otherwise indicated and 10 mol % of $PdCl_2$): A—$PdCl_2$, $CuCl_2 \cdot 2H_2O$, NaOAc, MeOH, CO; B—$PdCl_2$, $CuCl_2 \cdot 2H_2O$, K_2CO_3, CO; C—$PdCl_2$, $Cu(OAc)_2 \cdot 2H_2O$, K_2CO_3, CO; D—$PdCl_2$, $Cu(OAc)_2 \cdot 2H_2O$, TMG, CO; E1—addition of NaOMe to $PdCl_2$, $Cu(OAc)_2 \cdot 2H_2O$, CO; E2—as E1, but using $CuCl_2 \cdot 2H_2O$; E3—addition of $PdCl_2$, $Cu(OAc)_2 \cdot 2H_2O$ to NaOMe, CO. [b] Cis + trans isomers. Isolated yields of chromatographically separated compounds. [c] Recovered starting material.

Under the original conditions employed with sodium acetate as the base,[9] the reactions terminated (formation of Pd black) prior to completion (entries 1, 4, and 8). We attributed this to premature reduction of the active palladium(II) species to palladium(0) by carbon monoxide[10] and inefficient reoxidation by the (only slightly soluble) cupric complexes. Use of a stronger base, a more soluble copper salt (copper acetate: compare entries 5 and 6), a good coordinating solvent, acetonitrile,[11] and a lower temperature improved matters. Tetramethylguanidine (TMG) was selected as the base due to its relative strength compared to other organic bases and the absence of copious precipitates when added to methanol solutions of cupric chloride. Sodium methoxide could give similar yields to TMG in certain cases (entries 10−12). Potassium carbonate proved to be only moderately effective (entries 5 and 6). Despite these improvements, starting material was still recovered in most experiments.

In all cases with carbamate groups on nitrogen, a single diastereoisomer was obtained. In the case of isoxazolidine **8a**, this was shown to be the cis isomer by nOe experiments (Figure 1). Irradiation of one of the H4 protons led to no

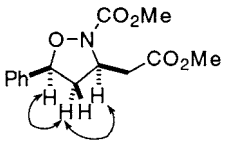


Figure 1. Significant nOe interactions for isoxazolidine **8a**.

enhancement of either proton α to a heteroatom (H3, H5). Irradiation of the other H4 proton led to clear enhancement of both protons α to heteroatoms. This experiment is slightly complicated by the fact that this H4 proton signal is very close to the signal for a side chain methylene proton, preventing selective irradiation. The assignment is, however, comfirmed by irradiation of either H3 or H5. In both cases the same H4 proton is enhanced. The sulfonamide **5a** was less selective leading to an approximately 5:1 mixture of separable diastereoisomers.

The predominant formation of the cis isomer can be explained by appeal to an envelope-like reactive conformation, in which A is favored over B due to the lesser crowding of the alkene moiety (Figure 2). The stereochemical outcome can be compared to the nitrone−alkene cycloaddition, which can be used to form similar isoxazolidines. The cycloaddition, however, results in the trans isomer as the major product, usually as a mixture when acyclic nitrones are employed.[12] An isomerically pure trans isoxazolidine has been prepared by Michael addition.[13] The reaction may not be extended to

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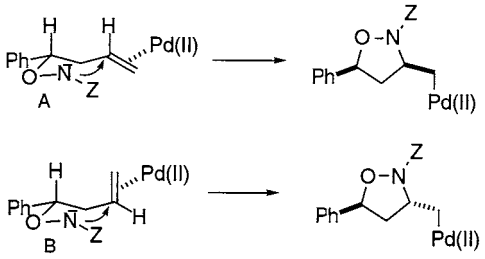

Figure 2. Reaction intermediate conformations.

the formation of six-membered rings, as the hydroxylamine **12**, prepared in the standard way in overall 46% yield from the corresponding alcohol,[14] was recovered unchanged (conditions D).

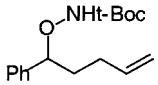

Figure 3. Hydroxylamine (**12**).

Although oximes have been previously employed in palladium-catalyzed cyclizations as both *N*-nucleophiles[5,15] and *O*-nucleophiles,[16] this is the first example to our knowledge of the use of *O*-substituted hydroxylamines. Isoxazolidines have been found to be valuable synthetic intermediates.[12,13,17] The clean, diastereoselective formation of isoxazolidines by the novel cyclofunctionalization reported here is a potentially useful procedure and its application in synthesis is in hand. Other modes of cyclization of these and related compounds are being examined.

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Supporting Information Available: Spectroscopic data for hydroxylamines and isoxazolidines, nOe experiments for compound **8a**, and experimental procedures for the preparation and cyclization of hydroxylamines. This material is available free of charge via the Internet at http://pubs.acs.org.

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