Hydroxylamine Oxygen as Nucleophile in Palladium(0)- and Palladium(II)-Catalyzed Allylic Alkylation: A Novel Access to Isoxazolidines

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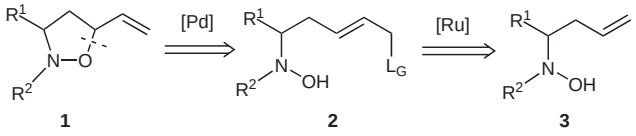
Abstract: In search for novel heterocyclization processes, the intramolecular Pd-mediated allylic alkylation of homoallyl hydroxylamines is described. Depending on both the reaction conditions and the substrates, *cis*- or *trans*-3-substituted-5-vinyl isoxazolidines are preferentially obtained. The corresponding starting materials for the cyclization step are readily obtained through cross-metathesis of the easily accessible unsubstituted homoallyl hydroxylamines.

Key words: palladium, ring closure, hydroxylamines, allyl complexes, isoxazolidines

The use of transition-metal-catalyzed cyclizations in the synthesis of heterocycles has expanded rapidly in recent years thanks to the possibility of achieving multiple and often stereoselective transformations.[1] In this context, although the nucleophilic addition of heteronucleophiles to several types of π-olefin[2] and η[3]-allyl palladium complexes[3] has been amply described, the employ of similar catalytic reactions to add heteroatom-linked oxygen nucleophiles has only very recently been reported. This is the case of oximes[4] and hydroxylamines[5] in which either one of the two heteroatoms can act as the nucleophile.

Isoxazolidines have also attracted considerable attention. For example, these useful intermediates can be converted into 1,3-amino alcohols without loss of stereochemistry.[6] Moreover, the presence of additional functionalities in the ring increases their synthetic value as it allows the obtainment of more elaborated target molecules. In general, isoxazolidines are readily prepared via 1,3-dipolar cycloaddition between nitrones and alkenes.[7] However, in some instances such a general approach cannot be applied owing to functional group incompatibility. This is the case, for instance, of vinyl isoxazolidines **1**, which should be formally prepared through a cycloaddition reaction between a nitrone and a specific double bond of a 1,3-diene. As a consequence, the development of alternative synthetic approaches toward such heterocycles is highly desirable.[8]

In this communication we report the synthesis of 5-vinyl isoxazolidines **1** through a hitherto unknown approach

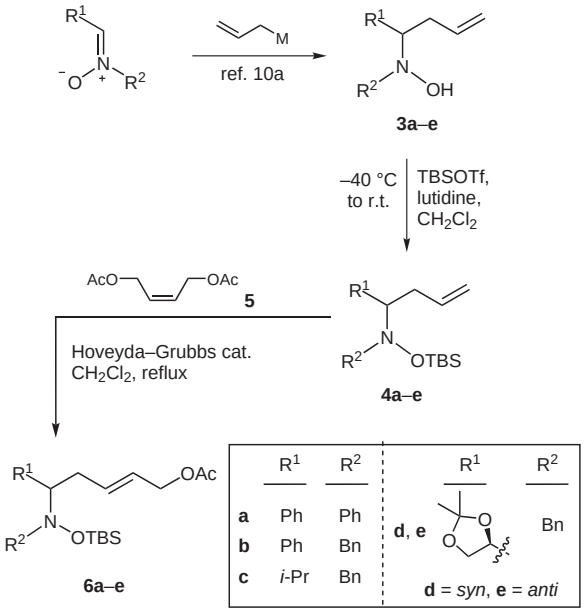


Scheme 1

based on an intramolecular 5-*exo* Pd-catalyzed allylic substitution of hydroxylamines **2** (Scheme 1).[9] We also show here that the cross-metathesis of homoallyl hydroxylamines **3**, in turn easily accessible via nucleophilic allylation of nitrones,[10] provides a useful method to prepare the desired allylically substituted hydroxylamines **2**.

We first prepared the homoallyl hydroxylamines **3** through the direct nucleophilic addition of allyl metals to the corresponding nitrones (Scheme 2).[10a]

Although it is possible to prepare substituted compounds by this method[11] the requirement of a leaving group at the distal allylic position in **2** prompted us to consider a cross-metathesis as the best choice to properly elongate the unsubstituted homoallyl hydroxylamine **3**.



Scheme 2

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First attempt of direct cross-metathesis between the free hydroxylamine **3a** and alkene **5**[12] in the presence of the second generation phosphine-free Hoveyda–Grubbs catalyst [$Cl_2Ru(H_2IMes)(2\text{-}i\text{-}PrOC_7H_5)$][13] failed, the corresponding *N*-phenyl homoallyl amine being obtained as the only product. An identical result was obtained with Grubbs' I and II catalysts and in a $Ti(Oi\text{-}Pr)_4$-assisted reaction.[14] Treatment of **3a** with excess *tert*-butyldimethylsilyltriflate (3.0 equiv) in the presence of lutidine readily gave the corresponding O-silylated hydroxylamine **4a** in 81% yield.[15]

Treatment of the silylated hydroxylamine **4a** with 1,4-diacetoxy-but-2-ene (**5**) in the presence of 5 mol% of the above-mentioned Hoveyda–Grubbs catalyst in CH_2Cl_2 at reflux for 4 hours, and then at room temperature for 12 hours, gave the expected metathesis *E*-adduct **6a**[16] in 90% yield (Table 1, entry 1). We next examined the generality of the reaction with the more synthetically useful *N*-benzyl derivatives **4b** and **4c** (Table 1, entries 2 and 3) and the enantiopure homoallyl hydroxylamines **4d** and **4e** (Table 1, entries 4 and 5). The metathesis reactions proceeded in good yield to afford the corresponding *E*-compounds **6** as the only products.

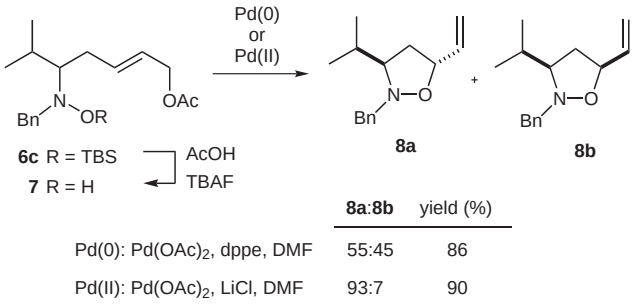
Table 1 Cross-Metathesis between Hydroxylamines **4** and **5**[a]

Entry	R^1	R^2	Hydroxylamine	Yield (%)
1	Ph	Ph	**6a**	90
2	Ph	Bn	**6b**	90
3	*i*-Pr	Bn	**6c**	83
4	*syn*-DMDO[c]	Bn	**6d**	85[b]
5	*anti*-DMDO[c]	Bn	**6e**	86[d]

[a] All the reactions were carried out in CH_2Cl_2 (reflux 4 h, then r.t. 12 h).
[b] The *syn* (*S*,*R*) isomer.
[c] DMDO: 2,2-dimethyl-4-dioxolanyl.
[d] The *anti* (*S*,*S*) isomer.

Since initial attempts of in situ desilylation prior to the cyclization step were unsuccessful, compounds **6a**–**c** were first desilylated by TBAF in THF. Under these conditions, aromatic derivatives **6a** and **6b** proved to be unstable. On the other hand, compound **6c** afforded free hydroxylamine **7** in 99% yield. The planned palladium-catalyzed intramolecular cyclization was next tackled by choosing **7** as the model substrate for a preliminary study (Scheme 3). Since such a compound could theoretically undergo cyclization activated by Pd(0)[17] catalysis but also by nonoxidative Pd(II),[18] we decided to undertake a comparative study of both conditions.[19]

Pd(0) conditions were first tested by treatment of the precursor **7** with $Pd(OAc)_2$ (10 mol%) in the presence of dppe (0.1 equiv).[20] These conditions gave rise to an almost equimolar mixture of the desired *trans* and *cis* 5-*exo*-cyclization adducts **8a** and **8b** in 86% yield, which could not



	8a:8b	yield (%)
Pd(0): $Pd(OAc)_2$, dppe, DMF	55:45	86
Pd(II): $Pd(OAc)_2$, LiCl, DMF	93:7	90

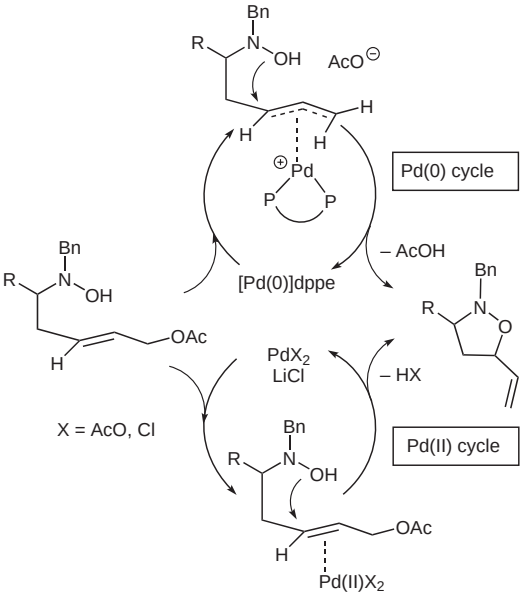
Scheme 3

be separated by silica gel chromatography. No 1,2-oxazepane coming from a 7-*endo* cyclization was detected.

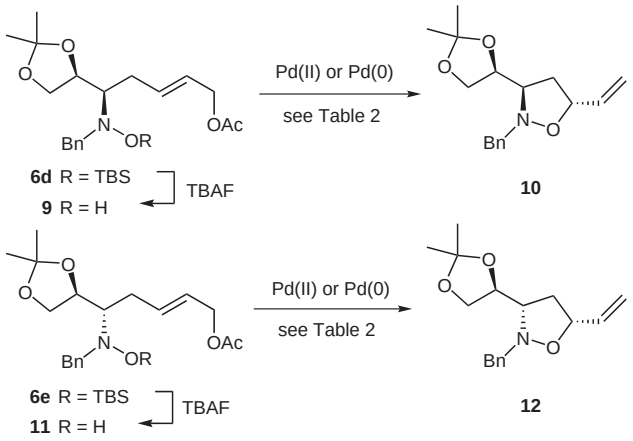
Pd(II) catalysis was then tested by treatment of **7** with $Pd(OAc)_2$ (5 mol%) and LiCl (1.0 equiv).[21] This gave the same products in a 93:7 *trans*:*cis* ratio and a 90% yield.[22]

The different stereochemical result between the Pd(II)- and the Pd(0)-catalyzed cyclization of **7** is not surprising, as the two protocols involve fundamentally different reaction mechanisms. Indeed, in the former protocol addition of the hydroxylamine hydroxyl takes place *anti* to the Pd(II)-activated alkene. Deacetoxypalladation of the newly formed σ-alkyl palladium complex affords the final product and regenerates Pd(II) [Scheme 4, Pd(II) cycle].[18] On the other hand, when dppe is added to $Pd(OAc)_2$ before the addition of the substrate, Pd(0) is rapidly generated.[23] Following oxidative addition of the latter gives a transient electrophilic η^3-allyl palladium complex which is in turn intramolecularly intercepted by the hydroxylamine oxygen atom. This affords the final product and Pd(0)/dppe, which can reenter the catalytic cycle [Scheme 4, Pd(0) cycle].

Having demonstrated the feasibility of the Pd-mediated cyclization of homoallyl hydroxylamines, the prospects of



Scheme 4



Scheme 5

this reaction were next explored in the case of the enantiopure derivatives **9** and **11**, arising from desilylation of **6d** (85%) and **6e** (86%, Scheme 5).

Pd(II)-catalyzed tests were conducted both in the absence of any additive (Table 2, entries 1 and 4) and in the presence of lithium halides (Table 2, entries 2, 3, 5 and 6).[24] Pd(0)-catalyzed reactions were carried out in the presence of dppe under base-free conditions (Table 2, entries 7 and 9), or using NaH as the base (Table 2, entries 8 and 10). Tiny differences in the respective diastereoselectivities were observed depending on both the substrate and the reagent.

Interestingly, $Pd(OAc)_2$/LiCl turned out to be the most selective Pd(II)-based catalytic system for both the substrates, giving exclusively the *trans* isomer **10**[25] from the *syn* precursor **9** (Table 2, entry 2), and a 92:8 *cis*:*trans* ratio from the *anti* isomer **11** (Table 2, entry 5). On the other hand, when the $Pd(OAc)_2$/dppe system was applied [Pd(0) catalysis], the *syn* isomer **9** showed a 10:90 *cis*:*trans* preference (Table 2, entry 7), while the *anti* precursor **11** afforded exclusively the *cis* isomer **12**[26] (Table 2, entry 9). It should be noted that, in contrast to what previously observed with **7**, the selectivity of cyclization of **9** and **11** turned out to be independent of the cyclization mechanism, indicating that **9** and **11** are intrinsically biased to favor *trans* and *cis* patterns, respectively.

The ensemble of these results suggests that when studying diastereoselectivity in palladium-catalyzed O-allylations, both Pd(0)- and Pd(II)-catalyzed protocols are worthy to be tested, as different, and sometimes opposite stereochemical results may be obtained. Furthermore, switching from one protocol to the other simply requires replacement of the phosphine for LiCl.

In conclusion, we have reported a versatile method for the synthesis of functionalized isoxazolidines, otherwise inaccessible via conventional methods such as 1,3-dipolar cycloadditions. The methodology successfully exploited a cross-metathesis reaction to initially provide the allylically substituted homoallyl hydroxylamines. Cyclization of the latter intermediates by the action of catalytic Pd(II) or Pd(0) gave rise, via different and alternative mechanistic paths, to the target 5-vinyl-substituted isoxazolidines. These novel allylic alkylations demonstrate that hydroxylamines, even lacking an N-bound electron-withdrawing group,[5] can act as efficient oxygen nucleophiles toward transiently generated π-olefin palladium complexes or η^3-allyl palladium complexes. Since homoallyl hydroxylamines are readily prepared from commercially available reagents, the present strategy provides a novel, useful and straightforward method for constructing complex organic molecules. Further use of this synthetic approach is under study in our laboratories.

Table 2 Intramolecular Allylic Alkylation of **9** and **11** to **10** and **12**[a]

Entry	Hydroxylamine		Additive	Isoxazolidine (*cis*:*trans*)	Yield (%)
1	**9**	Pd(II)	–	**10** (10:90)	66
2	**9**	Pd(II)	LiCl	**10** (<5:95)	92
3	**9**	Pd(II)	LiBr	**10** (6:94)	90
4	**11**	Pd(II)	–	**12** (89:11)	70
5	**11**	Pd(II)	LiCl	**12** (92:8)	90
6	**11**	Pd(II)	LiBr	**12** (90:10)	88
7	**9**	Pd(0)	dppe	**10** (10:90)	96
8	**9**	Pd(0)	dppe[b]	**10** (12:88)	>99
9	**11**	Pd(0)	dppe	**12** (>95:5)	92
10	**11**	Pd(0)	dppe[b]	**12** (>95:5)	90

[a] All the reactions have been carried out at 80 °C in DMF for 3 h and using $Pd(OAc)_2$ as the palladium source.
[b] Previous treatment of **9** with NaH.

Acknowledgment

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(15) Use of *tert*-butyldimethylsilyl chloride in the presence of several tertiary amines failed to give the corresponding protected hydroxylamine.
(16) Data for **6a**: (90%). R_f = 0.55 (hexane–EtOAc, 4:1); oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, mixture of conformers): δ = 7.27–7.22 (m, 3 H), 7.21–7.13 (m, 4 H), 7.04–6.98 (m, 3 H), 5.61–5.55 (m, 1.6 H), 5.54–5.43 (m, 0.4 H), 4.58–4.50 (m, 0.4 H), 4.41–4.37 (m, 1.6 H), 4.20 (t, 1 H, *J* = 7.5 Hz), 2.79 (t, 2 H, *J* = 6.7 Hz), 2.06 (br, 0.6 H), 2.02 (br, 2.4 H), 0.3 (br, 9 H), –0.07 (br, 3 H), –0.31 (br, 0.6 H), –0.34 (br, 2.4 H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, selected signals for the major conformer): δ = 170.7, 152,5, 137.8, 133.3, 131.9, 127.9, 127.5, 127.4, 125.8, 123.7, 121.2, 74.3, 65.0, 32.9, 26.1, 21.0, 18.0, –4.7, –5.5. Anal Calcd for $C_{25}H_{35}NO_3Si$: C, 70.55; H, 8.29; N, 3.29. Found: C, 70.59; H, 8.45; N, 3.22.
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(20) **General Procedure for the Pd(0)-Mediated Intramolecular Allylic Alkylation**
The proper homoallylhydroxylamine (1 mmol) and (if needed) NaH (60% dispersion in a mineral oil, 1 mmol) were dissolved in DMF (20 mL) under an argon atmosphere and the resulting mixture was cooled to 0 °C. In a separate flask, $Pd(OAc)_2$ (5 mol%) and dppe (10 mol%) were mixed in DMF (5 mL) and stirred for ca 5 min. After having carefully verified that the initially brown solution turned into a paler brown suspension, the thus formed Pd(0) catalyst was added into the solution of hydroxylamine. The resulting mixture was stirred at r.t. for 30 min, then heated at 80 °C for 3 h. After cooling to r.t., the solution was poured into Et_2O (125 mL) and H_2O (50 mL) was added. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure to give a residue which was purified by radial chromatography.
(21) **General Procedure for the Pd(II)-Mediated Intramolecular Allylic Alkylation**
The corresponding homoallylhydroxylamine (1 mmol), $Pd(OAc)_2$ (10 mol%) and lithium halide (5 mmol; if needed) were dissolved in DMF (20 mL) under an argon atmosphere. The resulting mixture was stirred at r.t. for 30 min, then heated at 80 °C for 3 h. After cooling to r.t., the solution was poured into Et_2O (125 mL) and H_2O (50 mL) was added. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure to give a residue which was purified by radial chromatography.
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(25) Data for **10**: R_f = 0.36 (hexane–EtOAc, 4:1); $[\alpha]_D^{20}$ +92 (*c* 0.16, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.45–7.40 (m, 2 H), 7.37–7.31 (m, 2 H), 7.30–7.24 (m, 1 H), 5.85 (ddd, 1 H, *J* = 17.2, 10.3, 7.1 Hz), 5.29 (d, 1 H, *J* = 17.2 Hz), 5.18 (d, 1 H, *J* = 10.3 Hz), 4.47 (dt, 1 H, *J* = 7.6, 7.1 Hz), 4.34 (d, 1 H, *J* = 14.0 Hz), 4.15 (dt, 1 H, *J* = 7.1, 6.5 Hz), 4.04 (dd, 1 H, *J* = 8.3, 6.5 Hz), 4.00 (d, 1 H, *J* = 14.0 Hz), 3.74 (dd, 1 H, *J* = 8.3, 7.1 Hz), 3.13 (dt, 1 H, *J* = 8.2, 7.1 Hz), 2.21–2.04 (m, 2 H), 1.44 (s, 3 H), 1.36 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 137.6, 137.2, 129.2, 128.2, 127.2, 117.5, 109.8, 78.4, 77.2, 67.2, 66.9, 62.2, 37.5, 26.7, 25.4. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.47; H, 8.13; N, 4.76.

(26) Data for **12**: R_f = 0.42 (hexane–EtOAc, 4:1); $[\alpha]_D^{20}$ +21 (*c* 1.38, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.31–7.17 (m, 5 H), 5.89–5.79 (ddd, 1 H, *J* = 17.1, 10.2, 7.4 Hz), 5.20 (dt, 1 H, *J* = 17.1, 1.2 Hz), 5.10 (dt, 1 H, *J* = 10.2, 1.2 Hz), 4.50 (q, 1 H, *J* = 7.4 Hz), 4.04 (d, 1 H, *J* = 12.8 Hz), 3.98–3.92 (m, 2 H), 3.77 (d, 1 H, *J* = 12.8 Hz), 3.47–3.40 (m, 1 H), 3.16–3.10 (t, 1 H, *J* = 6.9 Hz), 2.48 (dddd, 1 H, *J* = 12.8, 9.2, 7.4, 1.6 Hz), 2.15 (ddd, 1 H, *J* = 12.8, 9.2, 7.4 Hz), 1.27 (s, 3 H), 1.24 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 138.2, 137.0, 129.3, 128.5, 127.6, 117.3, 109.3, 80.4, 75.7, 68.0, 67.4, 63.6, 36.1, 26.8, 25.3. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.70; H, 7.88; N, 5.01.