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Highly efficient Pd-catalyzed synthesis of nitriles from aldoximes

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ABSTRACT

An expedient method of Pd-catalyzed conversion of aldoxime into nitrile was developed. The reaction was carried out under the influence of $Pd(OAc)_2/PPh_3$ in refluxing CH_3CN to provide good to high yields. The use of Cs_2CO_3 (0.1–0.5 equiv) was crucial in some cases.

Palladium-catalyzed reactions of oxime derivatives can be classified into a few categories.[1–5] Allylation of oxime can be carried out by the reaction with π-allylpalladium complex.[1] Deprotection of allyl oxime to oxime can also be catalyzed by Pd under $Et_3N/HCOOH$ conditions.[2] Recently, Heck-type cyclizations of oxime ether have been reported.[3] Various Pd-catalyzed *ortho*-functionalizations via C–H activation have been studied recently.[4] However, conversion of oxime or its derivatives into nitrile with the aid of Pd catalyst has not been reported, to the best of our knowledge.[6] Although many methods for the conversion of oxime or its derivative into nitrile has been reported,[7] the synthesis of nitrile using transition metal catalyst is somewhat limited. The use of $PtCl_4(EtCN)_2$,[6] $[RuCl_2(p\text{-cymene})]_2$,[7a,b] $(HO)ReO_3$,[7c] $Ga(OTf)_3$,[7d] W–Sn hydroxide[7e], and $Cu(OAc)_2$[7f] has been reported.

During our recent studies on the Pd-catalyzed decarboxylative protonation reaction,[8] we imagined the possibility of allyl group migration from oxygen to carbon as shown in Scheme 1. We chose *p*-nitrobenzaldoxime allyl ether (**1**) as the model substrate based on the fact that *p*-nitro group can stabilize the Pd-intermediates as in recent papers of Tunge and co-workers.[9] Initially formed π-allylpalladium complex (**I**) could be changed to (**II**), which might be converted into nitroso compound (**III**) and produced eventually allyl oxime **4**. However, we did not observe the formation of **4** at all. Instead, we isolated *p*-nitrobenzonitrile (**2a**, 26%) and cinnamyl derivative **3** (8%),[10] together with recovered starting material **1** (30%).

The mechanism for the formation of **2a** from **1** could be postulated as depicted in Scheme 1: (i) an oxidative addition of *O*-allyl bond of **1** to Pd(0) to form the π-allylpalladium complex (**I**), (ii) deprotection to oxime by trace water in the reaction mixture,[2,8] (iii) oxidative addition of *N*–*O* bond of oxime to Pd(0),[3] and (iv) the following typical β-H elimination pathway to form nitrile **2a**. Actually, the reaction of *p*-nitrobenzaldoxime ethyl ether did not produce any trace amounts of **2a** under the same conditions. The results state that Pd-catalyzed deprotection of allyl ether and the following Pd-catalyzed dehydration to nitrile could be the plausible mechanism.

The interesting results made us to investigate Pd-catalyzed generation of nitrile from aldoxime (Scheme 2), and we wish to report herein the preliminary successful results. We examined the reaction of *p*-nitrobenzaldehyde oxime (**5a**) and obtained *p*-nitrobenzonitrile (**2a**) in moderate yield (67%) under the influence of $Pd(OAc)_2$ (10 mol %)/PPh_3 (20 mol %) in toluene at refluxing temperature for 24 h (entry 1 in Table 1). Fortunately, the yield was increased to 90% when we replace the solvent to CH_3CN within short time (3 h), as shown in Scheme 2 and in Table 1 (entry 2).[11] The conversion was completely ineffective without Pd catalyst (entry 3). The use of other Pd catalysts including $PdCl_2$ (entry 4) and $Pd(PPh_3)_4$ (entry 5), other phosphine ligands such as $P(o\text{-tolyl})_3$ (entry 6) or PBu_3 (entry 7) did not improve the yield of **2a**. The reaction mechanism could be regarded as shown in Scheme 2, which involve the intermediate (**IV**). As in the Pd-catalyzed β-carbon elimination of cyclobutanone *O*-benzyloximes,[5b] β-H elimination can explain the formation of nitrile.[12] As given in Table 1, the best yield was observed under the conditions comprising $Pd(OAc)_2/PPh_3$ in refluxing CH_3CN (Conditions A, entry 2). This is the first successful results on Pd-catalyzed dehydration of benzaldoxime into nitrile.

Encouraged by the results we examined various arylaldoxime derivatives **5b**–**j** and cinnamyl oxime **5k**.[11] When the aromatic nu-

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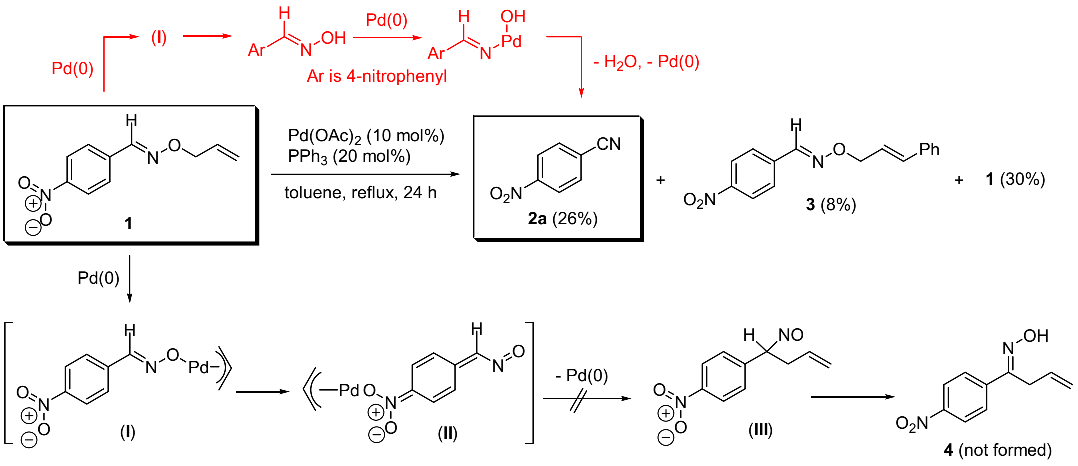
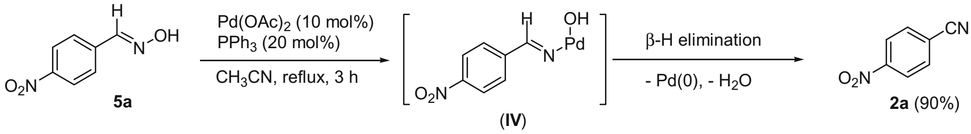


Scheme 1.



Scheme 2.

Table 1

Optimization of conditions for the conversion of **5a** to **2a** and **5e** to **2e**

Entry	Compound	Conditions	Yield (%)
1	**5a**	$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), toluene, reflux, 24 h	67
2[a,b]	**5a**	$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), CH_3CN, reflux, 3 h	90
3	**5a**	no Pd catalyst, PPh_3 (20 mol %), CH_3CN, reflux, 24 h	0
4	**5a**	$PdCl_2$ (10 mol %), PPh_3 (20 mol %), CH_3CN, reflux, 24 h	85
5	**5a**	$Pd(PPh_3)_4$ (10 mol %), PPh_3 (20 mol %), CH_3CN, reflux, 16 h	86
6	**5a**	$Pd(OAc)_2$ (10 mol %), P(o-tol)$_3$ (20 mol %), CH_3CN, reflux, 3 h	83
7	**5a**	$Pd(OAc)_2$ (10 mol %), PBu_3 (20 mol %), CH_3CN, reflux, 18 h	82
8	**5a**	$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), Cs_2CO_3 (0.1 equiv), CH_3CN, 80 °C, 1 h	87
9	**5e**	$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), CH_3CN, reflux, 4 h	49
10[c]	**5e**	$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), Cs_2CO_3 (0.1 equiv), CH_3CN, reflux, 1 h	83

[a] Conditions A.

[b] Without PPh_3 the reaction required longer time (8 h, 84%).

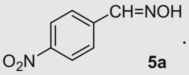
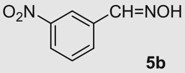
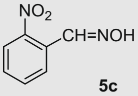
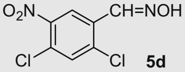
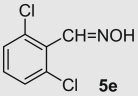
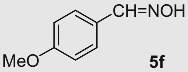
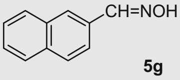
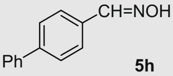
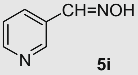
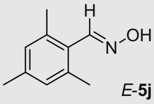
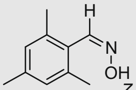
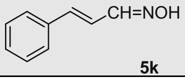
[c] Conditions B.

cleus has a strong electron-withdrawing substituent, the yield of oxime was good to high (entries 1–4 in Table 2). However, 2,6-dichlorobenzaldoxime (**5e**) showed sluggish reactivity under the conditions (entry 9 in Table 1). Thus, we used Cs_2CO_3 (0.1 equiv) as in entry 10 in Table 1 (vide supra) and could improve the yield (Conditions B) although the role of Cs_2CO_3 is not clear at this stage. Thus, we used variable amounts of Cs_2CO_3 (0.1–0.5 equiv) for the substrates which showed sluggish reactivity under the conditions A such as **5e**–**h,** and *E*-**5j**. The results are summarized in Table 2.

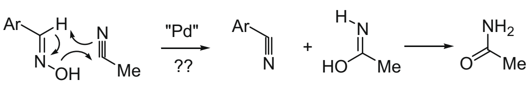
The reaction of **5g** required long reaction time for the completion (entry 7). The reaction of cinnamyl oxime (**5k**) also showed same reactivity to produce **2k** in high yield (entry 12). It is interesting to note that both reactions of *E*- and *Z*-form of 2,4,6-trimethylbenzaldoxime (**5j**) produced nitrile **2j** in similar yields (entries 10 and 11). From the results, we have to reconsider our proposed mechanism (vide supra, Scheme 2) in part. The possibility involving the Pd-catalyzed H_2O transfer from oxime to nitrile, as shown in Scheme 3, could not be excluded at this stage. This type of mechanism was suggested by Maffioli et al. very recently in their $PdCl_2$-catalyzed reversible dehydration of amides.[13] Thus, the clarification of the final mechanism deserved further studies.[14–16]

In summary, we disclosed the first successful Pd-catalyzed dehydration of aldoximes into nitriles. The plausible mechanism involved an oxidative addition of *N*–*O* bond to Pd(0) and the following typical β-H elimination pathway for most of the *E*-oximes. Irrespective of the mechanism as well as the configuration of oxime, Pd-catalyzed dehydration of aldoximes occurred very easily under mild conditions.

Table 2
Pd-catalyzed dehydration of aldoximes.

Entry	Aldoxime[a]	Conditions	Nitrile[b] (%)
1	 **5a**	A(3 h)	**2a** (90)
2	 **5b**	A(3 h)	**2b** (81)
3	 **5c**	A(2 h)	**2c** (87)
4	 **5d**	A(1 h)	**2d** (92)
5	 **5e**	B (1 h)[c]	**2e** (83)
6	 **5f**	B (8 h)[d]	**2f** (88)
7	 **5g**	B (80 h)[d]	**2g** (90)
8	 **5h**	B (8 h)[d]	**2h** (88)
9	 **5i**	A(7 h)	**2i** (87)
10	 *E*-**5j**	B(12 h)[c]	**2j** (87)
11	 *Z*-**5j**	A(1 h)	**2j** (83)
12	 **5k**	A(3 h)	**2k** (91)

[a] The configuration of oximes **5a–k** is *E*-form (>95%) except **Z-5j** (entry 11).
[b] Isolated yield.
[c] Cs_2CO_3 (0.1 equiv) was used.
[d] Cs_2CO_3 (0.5 equiv) was used.



Scheme 3.

Acknowledgments

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15. The reaction of acetophenone oxime under the same reaction conditions (CH_3CN, 0.1 equiv of Cs_2CO_3, reflux, 36 h) showed no reaction.
16. During the evaluation process of this Letter, we carried out the reaction of phenylacetaldehyde oxime (*E*/*Z* = 5:4 mixture), a typical aliphatic oxime, and obtained benzyl cyanide in 56% under the same conditions given in Table 2 (conditions B with 0.5 equiv of Cs_2CO_3, 3 h).