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**UPDATE**

# Pd/Mn Bimetallic Relay Catalysis for Aerobic Aldoxime Dehydration to Nitriles

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**Abstract:** A Pd/Mn bimetal system was found to be an effective catalyst for dehydration of aldoximes to the useful nitriles under mild aerobic conditions. Different to the known metal-catalyzed aldoxime dehydration reactions, this reaction very possibly proceeded via an alternative mechanism of Pd/Mn bimetal relay catalysis involving a Mn-catalyzed aerobic oxidation of aldoximes to nitrile oxides by air and a Pd-catalyzed oxygen transfer from the nitrile oxides to the solvent acetonitrile. This method tolerates a variety of substrates including sterically bulky ones and also the natural product derivative.

**Keywords:** aldoxime; dehydration; nitrile; nitrile oxide; Pd/Mn bimetal catalyst; relay catalysis

Nitriles not only occur in natural products and bioactive molecules, they are also important intermediates in organic and pharmaceutical synthesis, agricultural chemistry, as well as materials science.[1] Preparation and utilization of nitriles are thus one of the hottest topics in chemistry.[1-7] In comparison with classic nitrile preparation methods especially those using highly toxic cyanides,[2] dehydration of aldoximes is an attractive approach[3-6] due to the easy availability of the aldoximes, simplicity of the method, and production of water as the byproduct. Although various methods have been developed for aldoxime dehydration,[3-6] drawbacks still remain. For example, some methods require harsh reaction conditions,[3] the use of special reagents[4] or large amounts of dehydrants,[4,5] or suffer from problems of low functional group tolerance, waste production, and difficult product purification. Transition metal-catalyzed methods using Ru, Re, Pt, Pd, W-Sn, Ni, Cu, Zn, Ga, and Fe catalysts have also received much attention in recent years,[6] but inert 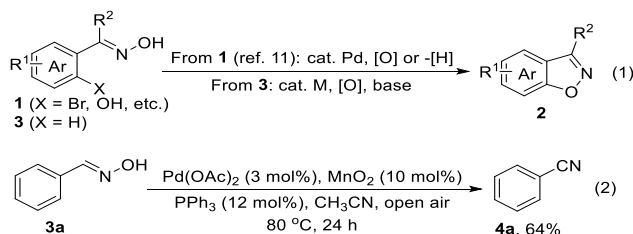atmosphere protection, high catalyst loadings, high reaction temperatures ($\geq$ 100 °C), and requirement of capricious ligands were mostly inevitable. Therefore, developing more active catalysts that can be used in lower loadings and/or under milder conditions is still highly desirable in the research.

For interested in developing green catalytic methods for the synthesis of useful organic molecules[7-10] including the preparation and synthetic applications of nitriles,[7] herein we report an serendipitously developed Pd/Mn bimetal-catalyzed aerobic aldoxime dehydration reaction for the synthesis of nitriles. This reaction tolerates a variety of substrates including the sterically bulky ones and also a natural product derivative. The reaction very possibly proceeds via a mechanism of Pd/Mn bimetal relay catalysis involving a Mn-catalyzed aerobic oxidation of aldoximes to nitrile oxide intermediates by air and a Pd-catalyzed oxygen transfer from the nitrile oxides to the solvent acetonitrile.

Initially,[10] since benzo[*d*]isoxazole (**2**) is a versatile heterocycle used to be obtained by intramolecular coupling of the less available *ortho*-functionalized aldoximes (**1**),[11] we envisioned that the non-functionalized aldoximes (**3**) may be used as promising substrates for direct synthesis of **2** [Eq. (1)] based on recent developments in *ortho* C-H activation of organoheteroatom acids from one of us and other groups.[12] We thus firstly attempted various Pd catalysts, ligands, and oxidants including oxygen or air to obtain **2** from the reaction of **3**. However, the attempts failed. On the other hand, we noticed that, when Pd(OAc)$_2$, MnO$_2$, and PPh$_3$ were used as the catalyst, a new product could be obtained in a good yield under a mild condition in air. The product was later determined to be benzonitrile **4a** [Eq. (2)]. Clearly, **4a** was produced by a catalytic dehydration reaction of **3a**. This abnormal result led us to further investigate the Pd/Mn bimetal-catalyzed aldoxime

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dehydration reaction and its mechanism in detail, because our literature survey revealed the known Pd-catalyzed methods usually require much higher loadings of the catalyst, the use of ligands, and inert conditions.[6f-h] In contrast, the above abnormal finding suggested that an air-insensitive aerobic catalytic method maybe achieved by adding $MnO_2$ as the co-catalyst and by readily running the reaction in air.



The optimized conditions (Table 1, entry 8) were then employed to extend the scope of the method. As shown in Table 2, like **1a** (entry 1), both electron-deficient (entries 2-7) and -rich (entries 8-14) aromatic aldoximes, including those with relatively bulky substituents (entries 5, 13-14) and reactive halo, and OH groups (entries 2-7, 10), all reacted smoothly to give the target nitriles in moderate to good yields. The reactions of electron-deficient aromatic aldoximes were found generally a bit faster than those of the electron-rich ones, but giving slightly lower yields of the products (entries 2-7 vs entries 8-14). This Pd/Mn-catalyzed method could also be applied to $\alpha,\beta$-unsaturated, heterocyclic, and alkyl aldoximes (entries 15-19) to give moderate to high yields of the products, showing a relatively wide scope of the method. The method can be successfully employed in the natural product modification, i.e., the reaction of the aldoxime of natural product *veratraldehyde* also readily afforded the desired nitrile **4t** in good yield (entry 20). This reaction could be magnified to at least 100 mmol scale without affecting the reaction's efficiency obviously (entry 21). Moreover, functional group tolerance of the method was also examined by using carboxylate- and cyano-substituted aromatic aldoximes as the substrates. Acceptable yields of the corresponding nitriles could be obtained under the same conditions (entries 22-23), which showed the good functional group tolerance of the present method.

As shown in Table 1, further catalyst screenings revealed that ligand $PPh_3$ was not necessary, since the reactions with and without $PPh_3$ gave close results (entries 1-2). However, without either $Pd(OAc)_2$ or $MnO_2$, the yields of the product decreased dramatically (entries 3-4), revealing the key roles of both $Pd(OAc)_2$ and $MnO_2$ in the reaction. $Pd(OAc)_2$ alone was found to be a less active catalyst as reported in the literature,[6f-h] which gave a decreased yield of **4a** (entry 5). $MnO_2$ alone was lowly active and only a very low yield of **4a** could be obtained (entry 6). By using the $Pd(OAc)_2/MnO_2$ combination, the catalyst loading can be reduced without affecting the yield of **4a** (entry 7). Moreover, by enhancing the reactant's concentration by using reduced solvent volume, both the use of solvent can be saved and the reaction rate improved (entry 8). Thus, with only 1/3 mol % of $Pd(OAc)_2/MnO_2$, the dehydration of **3a** completed in only 16 h to give 75% yield of **4a** (entry 8).

**Table 1.** Catalyst screening and condition optimization.[a]



| entry | Cat. (mol %) | t (h) | 4a%[b] |
|---|---|---|---|
| 1 | $Pd(OAc)_2/MnO_2/PPh_3$ (3/10/12) | 24 | 64 |
| 2 | $Pd(OAc)_2/MnO_2$ (3/10) | 24 | 69 |
| 3 | $Pd(OAc)_2/PPh_3$ (3/12) | 24 | 38 |
| 4 | $MnO_2/PPh_3$ (10/12) | 24 | 12 |
| 5 | $Pd(OAc)_2$ (3) | 24 | 57 |
| 6 | $MnO_2$ (10) | 24 | 6 |
| 7 | $Pd(OAc)_2/MnO_2$ (1/3) | 24 | 76 |
| 8[c] | $Pd(OAc)_2/MnO_2$ (1/3) | 16 | 75 |

[a] The mixture of **3a** (1 mmol) and the catalyst such as $Pd(OAc)_2$, $MnO_2$ and $PPh_3$ in $CH_3CN$ (2 mL) was heated at 80 °C in open air.
[b] Isolated yields based on **3a**.
[c] 0.5 mL of $CH_3CN$.

**Table 2.** Pd/Mn-catalyzed aerobic dehydration of aldoximes.[a]



| entry | R | t (h) | 4%[b] |
|---|---|---|---|
| 1 | $C_6H_5$ | 16 | 75 (**4a**) |
| 2 | $p$-$FC_6H_4$ | 16 | 65 (**4b**) |
| 3 | $p$-$ClC_6H_4$ | 8 | 72 (**4c**) |
| 4 | $m$-$ClC_6H_4$ | 14 | 61 (**4d**) |
| 5 | $o$-$ClC_6H_4$ | 12 | 70 (**4e**) |
| 6 | $p$-$BrC_6H_4$ | 20 | 84 (**4f**) |
| 7 | $p$-$CF_3C_6H_4$ | 4 | 40 (**4g**) |
| 8 | $p$-$MeC_6H_4$ | 23 | 92 (**4h**) |
| 9 | $p$-$MeOC_6H_4$ | 22 | 91 (**4i**) |
| 10 | $p$-$HOC_6H_4$ | 20 | 88 (**4j**) |
| 11 | $p$-$t$-$BuC_6H_4$ | 20 | 71 (**4k**) |
| 12 | $p$-$Me_2NC_6H_4$ | 20 | 74 (**4l**) |
| 13 | $1$-$C_{10}H_7$ | 30 | 90 (**4m**) |
| 14 | $2$-$C_{10}H_7$ | 48 | 75 (**4n**) |
| 15 | $(E)$-$C_6H_5CH=CH$ | 12 | 78 (**4o**) |

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| 16 | 2-furan- | 12 | 51 (**4p**) |
|---|---|---|---|
| 17 | 2-thiophene- | 2 | 62(**4q**) |
| 18 | C$_6$H$_5$CH$_2$CH$_2$ | 24 | 87(**4r**) |
| 19 | *n*-C$_6$H$_{13}$ | 22 | 82 (**4s**) |
| 20 | 3,4-(MeO)$_2$C$_6$H$_3$ | 16 | 82 (**4t**) |
| 21[c] | | 18 | 80 (**4t**) |
| 22 | *p*-MeOC(O)C$_6$H$_4$ | 24 | 57 (**4u**) |
| 23 | *p*-CNC$_6$H$_4$ | 24 | 51 (**4v**) |

[a] See entry 8 of Table 1 for detailed conditions.
[b] Isolated yields based on **3**.
[c] Reaction magnified to 100 mmol scale.

The requirement of air and the high catalytic activity of the Pd(OAc)$_2$/MnO$_2$ bimetallic system suggested that the mechanism of this aerobic aldoxime dehydration reaction may be interesting. Control reactions under N$_2$ were then firstly investigated to get more insights about the role of air in the reaction. As shown in Table 3, the reactions under N$_2$ using either Pd(OAc)$_2$ or MnO$_2$ or both of them were all less effective (entries 1-4)[13] than the parallel reactions in air (Table 1, entries 1, 5, 7), which suggested that air can greatly facilitate the reaction, very possibly working as an oxidant in the reaction. If this is the case, similar to air, other oxidants should also work in the reaction. Indeed, addition of a stoichiometric amount of MnO$_2$, a well known mild oxidant, promoted the reaction efficiently to give 79% yield of **4a** under N$_2$ (Table 3, entry 5). Similarly, addition of another oxidant diacetateiodobenzene (DIB) also improved the reaction to give 42% yield of **4a** under the same conditions (entry 6). We also investigated a reaction using pure O$_2$ as the oxidant (entry 7). Like the reaction in air, this reaction also gave a much higher yield of the product (entry 7) than the parallel reaction in N$_2$ (entry 4), suggesting that pure O$_2$ played the same role in the reaction as air. However, very likely due to the more oxidative ability of pure O$_2$ that may lead to side reactions, the yield of the product obtained in O$_2$ (63%) was lower than the one obtained in air (76%, Table 1, entry 7) under the same conditions, as some unidentified by-products was also observed. These contrastive results clearly showed the promoting effect of the oxidants on the reactions.

Meanwhile, it seemed the Pd catalyst is essential for the reaction (entries 5-6), since the reactions of these oxidants without the Pd catalyst were not effective (entries 8-9). Moreover, in contrast to the effective reactions with oxidants MnO$_2$ or DIB (entries 5-6), the reactions using either stoichiometric or catalytic amounts of non-oxidative MnO only gave trace yields of **4a** under the same conditions (entries 10-11). This suggested again the oxidant's crucial

role in the reaction. For comparison, the reaction with catalytic amounts of Pd(OAc)$_2$ and MnO under air was also investigated. Surprisingly, it afforded an improved 68% yield of **4a** (entry 12), suggesting that air most likely oxidized MnO to the oxidative MnO$_2$, which then works again as the active oxidant in the reaction. Consequently, a close result (entry 12) with that of Pd(OAc)$_2$/MnO$_2$-catalyzed reaction (Table 1, entry 7) was obtained. All these results suggested that, like stoichiometric amounts of MnO$_2$ or DIB, air (or O$_2$) should also work as an oxidant in the reaction, via the MnO/MnO$_2$ oxidative cycle, to transform aldoximes into certain reactive intermediates (*vide infra*).

**Table 3.** Control reactions.[a]

$$Ph\diagup N^{OH} \xrightarrow[80\ ^\circ C,\ 24\ h]{cat.,\ conditions} Ph-C\equiv N$$
**3a** → **4a**

| entry | Cat. (mol%) | atm., solvent | **4a**%[b] |
|---|---|---|---|
| 1 | Pd(OAc)$_2$ (3) | N$_2$, CH$_3$CN | 26(28)[c] |
| 2 | MnO$_2$ (10) | N$_2$, CH$_3$CN | 10(12)[c] |
| 3 | Pd(OAc)$_2$/MnO$_2$ (3/10) | N$_2$, CH$_3$CN | 34(38)[c] |
| 4 | Pd(OAc)$_2$/MnO$_2$ (1/3) | N$_2$, CH$_3$CN | 28(30)[c] |
| 5 | Pd(OAc)$_2$/MnO$_2$ (1/100) | N$_2$, CH$_3$CN | 79 |
| 6 | Pd(OAc)$_2$/DIB (1/100) | N$_2$, CH$_3$CN | 42[d] |
| 7 | Pd(OAc)$_2$/MnO$_2$ (1/3) | O$_2$, CH$_3$CN | 63 |
| 8 | MnO$_2$ (100) | N$_2$, CH$_3$CN | 0(23)[c,d] |
| 9 | DIB (100) | N$_2$, CH$_3$CN | 7(34)[c,d] |
| 10 | Pd(OAc)$_2$/MnO (1/100) | N$_2$, CH$_3$CN | 6 (10)[c] |
| 11 | Pd(OAc)$_2$/MnO (1/3) | N$_2$, CH$_3$CN | 9(11)[c] |
| 12 | Pd(OAc)$_2$/MnO (1/3) | air, CH$_3$CN | 68(75)[c] |
| 13 | Pd(OAc)$_2$/MnO$_2$ (1/3) | air, solvents[e] | 0(<10)[c] |
| 14 | Pd(OAc)$_2$/MnO$_2$ (1/3) | air, *n*-BuCN | 82 |

[a] 1 mmol of **3a** and 2 mL of solvent were employed.
[b] Isolated yields of **4a** based on **3a** (conversion of **3a** were shown in the parentheses).
[c] Reactions not completed.
[d] A series of unidentified byproducts were observed.
[e] MeOH, DMF, DMSO, or toluene was used as the solvent.

Moreover, solvent effect was also investigated to obtain more information. Different to other non-effective solvents including the polar protonic, polar non-protonic, and non-polar ones (entries 13), like acetonitrile, another nitrile solvent *n*-BuCN was found very effective in the reaction and gave 82% yield of **4a** (entry 14). This distinctive role of nitrile solvents suggested that an interesting mechanism involving the nitrile solvent may take place in the reaction.

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On the other hand, the literature has revealed that oxidation of aldoximes using oxidants such as $MnO_2$ and DIB can afford the reactive and versatile nitrile oxides.[14-15] This suggested that nitrile oxide intermediates are very possibly generated and involved in the present Pd/Mn-catalyzed aerobic aldoxime dehydration reaction. To certify this hypothesis, nitrile oxide **5a**, obtained *in situ* by treating **3a** with trichloroisocyanuric acid according to the literature method,[14d-e] was then treated with 1 mol % $Pd(OAc)_2$. As shown in Scheme 1, the reaction readily afforded **4a** in 42% yield. This suggested that the nitrile oxide intermediates, generated by oxidation of the aldoximes,[14] can be readily converted into the nitriles under the present Pd-catalyzed conditions in acetonitrile. Meanwhile, to confirm the formation of nitrile oxides in the present aldoxime dehydration reaction, the mixture of aldoxime **3i** and phenylacetylene was treated with catalyst $Pd(OAc)_2$ in the presence of oxidant DIB. Hopefully, 5-phenyl-3-(*p*-tolyl)isoxazole **6i** may be obtained by a typical [3+2] cycloaddition reaction of nitrile oxides[15] if nitrile oxide **5i** is generated *in situ* through the oxidation by DIB and react with phenylacetylene. As shown in Eq. (3), the reaction indeed afforded the target heterocycle **6i**, albeit the yield is not high.[16] Thus, as can be inferred by the above results [Scheme 1, and Eq. (3)], nitrile oxides **5** should most likely be generated as the intermediates in the present aldoxime dehydration reaction under the Pd-catalyzed oxidative conditions.
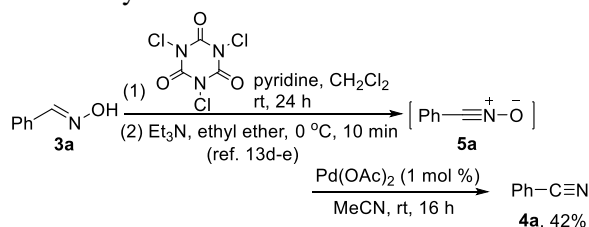


**Scheme 1.** Pd-catalyzed deoxygenation of the *in situ* generated nitrile oxide.
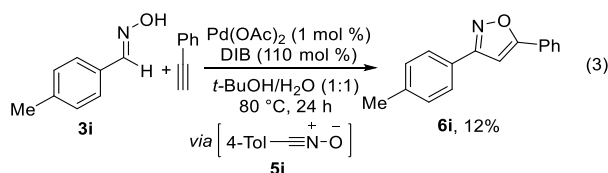


As to the determination of Pd's valence in the reaction, the catalyst residue recovered from the standard reaction was subjected to X-ray photoelectron spectroscopy (XPS) study. The result (Figure 1, image a) showed that only Pd(II) and Pd(0) species presented in the catalyst residue (see the SI for detail). More importantly, the lone reaction of **3a** with 1.0 equiv. of $Pd(OAc)_2$ without any oxidant ($MnO_2$ or air) not only afforded 72% yield of **4a** under the same conditions [Eq. (4)], XPS analysis of

the Pd catalyst residue recovered from this reaction also showed that, similar to image a, it also consists of Pd(0)/Pd(II) species only (Figure 1, image b). Images a and b suggested that Pd(0)/Pd(II) species should most likely be the working catalyst in the reaction and the possibility of the formation of potential Pd(IV) species might be excluded.[17]
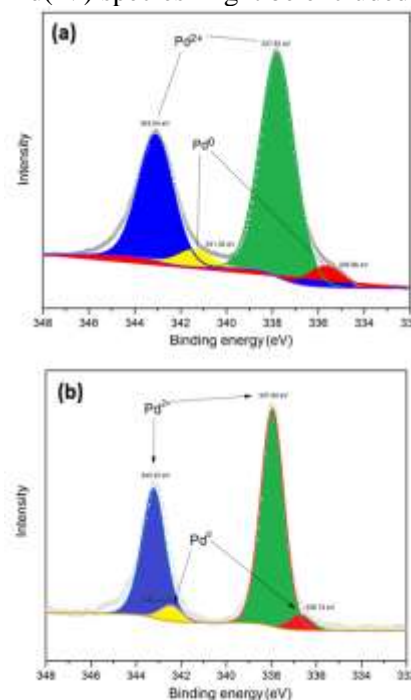


**Figure 1.** XPS spectra of: (a) Pd catalyst residue recovered from the standard reaction; (b) Pd catalyst residue recovered from the reaction of benzaldoxime **3a** with 1.0 equiv. of $Pd(OAc)_2$ [Eq. (4)].
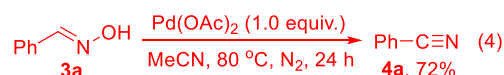


Moreover, image b also showed that Pd(0) species can be directly generated from the reaction of $Pd(OAc)_2$ with lone aldoxime, with aldoxime working as the reductant. The obtained 72% yield of **4a** also suggests that stiochiometric amount of $Pd(OAc)_2$ can also work as the oxidant in the reaction, similar to oxidant $MnO_2$ or air and very possibly by transferring aldoxime **3** into nitrile oxide intermediate **5**, to finally gave a good result of the reaction [Eq. (4)]. This result further supports the findings and conclusions obtained in the preceding control reactions and mechanistic studies [Table 3, Scheme 1, and Eq. (3)].

Therefore, although the conventional metal-catalyzed mechanisms including the $H_2O$ transfer process between aldoximes and solvent acetonitrile may simultaneously work in the present Pd/Mn bimetal-catalyzed aerobic aldoxime dehydration reaction according to the metal-catalyzed precedents,[6] an interesting new mechanism should most likely be involved in the present reaction based on the observed aerobic and ligand-free conditions

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(Tables 1 and 3), the above mechanistic findings [Table 3, Scheme 1, and Eqs. (3-4)], and the XPS studies (Figure 1). As shown in Scheme 2, aldoximes **3** may firstly be oxidized by $MnO_2$ to give nitrile oxide intermediates **5** and MnO. MnO is then reoxidized by air to regenerate the active oxidant $MnO_2$. Meanwhile, $Pd(OAc)_2$ may firstly be reduced to Pd(0) species by aldoxime and then coordinate with acetonitrile to give a Pd complex **7** due to the strong ligating ability of the nitriles.[18] **7** may then couple with **5** to give a Pd-nitrile oxide complex **8**. Transfer of the oxygen from the nitrile oxide ligand to the acetonitrile ligand, possibly via certain kind of Pd-O complexes **9**,[19] may afford a new Pd-nitrile oxide complex **10**, which then, by coordinating with the high concentration of the solvent acetonitrile, releases the final nitrile product **4**.
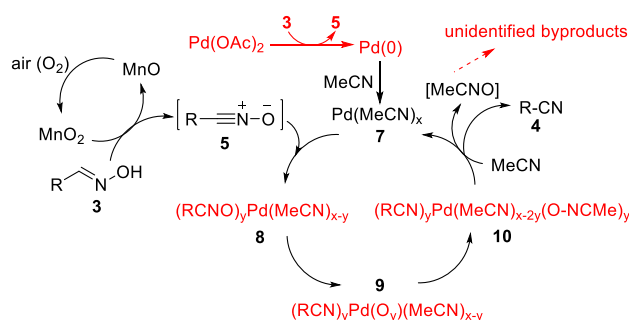


**Scheme 2.** A newly discovered possible mechanism.

In conclusion, a $Pd(OAc)_2/MnO_2$ bimetallic system is found to be an effective catalyst for dehydration of aldoximes to produce the useful nitriles under mild aerobic conditions. Mechanistic studies revealed that the reaction very possibly proceeds via a new mechanism of Pd/Mn bimetal relay catalysis involving an Mn-catalyzed aerobic oxidation of aldoximes to nitrile oxides by air and a Pd-catalyzed oxygen transfer from the nitrile oxides to the solvent acetonitriles to finally give the target nitrile products. Deeper mechanistic studies and further applications of the new findings in this work are our next concern.

## Experimental Section

**Typical Procedures for Pd/Mn-Catalyzed Aerobic Dehydration of Aldoximes to Nitriles.**
The mixture of **3a** (121 mg, 1 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01mmol), $MnO_2$ (2.61 mg, 0.03 mmol), and MeCN (0.5 mL) in a reaction tube was stirred in open air at 80 ˚C for 16 h. MeCN was then evaporated under vacuum and the residue purified by column chromatography (eluent: petroleum ether/EtOAc 6:1 for **4j**; 9:1 for **4l**; pure petroleum ether for the rest products) to give the nitrile product **4a** in 75% yield. The characterization data as well as NMR spectra of the products were given in Supporting information.

## Acknowledgements

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## UPDATES

Pd/Mn Bimetallic Relay Catalysis for Aerobic Aldoxime Dehydration to Nitriles

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