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Palladium-catalyzed Heck-type reaction of oxime ether bearing a pendant vinyl iodide moiety†

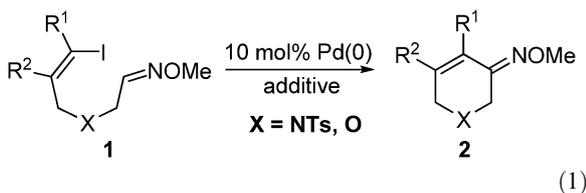
Hui Liu, Limin Wang and Xiaofeng Tong*

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A Pd(0)-catalyzed intramolecular Heck-type reaction of oxime ether has been developed, providing convenient access to heterocyclic oximes.

In the past decades, oxime derivatives have been widely employed as starting materials in palladium catalysis, providing great opportunities to develop numerous novel transformations. For example, various oxime esters can readily undergo oxidative addition to the Pd(0) center to realize amino-Heck reactions¹ or amination of aromatic C–H bonds.² Oxime ethers have been proved to be efficient directing groups to achieve various Pd-catalyzed *ortho*-functionalizations *via* C–H activation.³ Other Pd-catalyzed reactions of oxime, such as allylation of oxime,⁴ deprotection of allyl oxime⁵ and conversion of oxime into nitrile,⁶ have also been well developed.

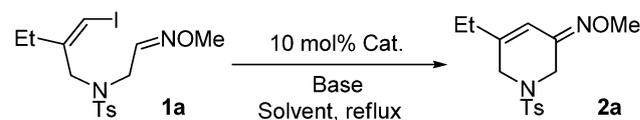


In sharp contrast, the oxime-involving Heck-type reactions are extremely limited. Only two examples, to the best of our knowledge, have been reported till now, which employed an intramolecular strategy to get around the issue⁷ of C=N bond insertion successfully. In 2007, Ohno *et al.* realized the first Pd-catalyzed Heck-type reaction of oxime ethers with an intramolecular aryl halide moiety.⁸ Later, Cheng *et al.* reported a Pd-catalyzed cascade sequence from aromatic aldoxime ether and aryl iodide.⁹ Those precedents elegantly demonstrated that the C=N bond of oxime ether could readily insert into the aryl palladium(II) intermediate. With the combination of those pioneering results and our continuous effort on Pd-catalyzed transformation of (*Z*)-vinyl iodide,¹⁰ we envisioned that the vinyl palladium(II) analogue from the

Pd(0) catalyst and compound **1** bearing vinyl iodide and oxime ether would also be capable of the C=N bond insertion. Herein, we report the Pd(0)-catalyzed intramolecular Heck-type reaction of oxime ether **1** with a pendant vinyl iodide moiety to give heterocyclic oxime **2** (eqn (1)).

We chose to initiate our investigation by using the same system⁸ established by Ohno and co-workers with compound **1a** as the model substrate (Table 1, entry 1). To our delight, the Heck-type cyclisation of **1a** did take place, affording azaheterocyclic oxime **2a** in 23% yield. When the solvent was switched to toluene the isolated yield of **2a** was increased to 35% (Table 1, entry 2). With toluene as solvent, Ag₂O (2 equiv.) as the base was found to be more efficient, affording **2a** in 46% yield (Table 1, entry 3). Interestingly, the combination of Ag₂O (1 equiv.) and K₂CO₃ (1 equiv.) as base additive gave

Table 1 Optimization of reaction conditions^a



Entry	Cat.	Base (equiv.)	Solvent	Yield ^b (%)
1	Pd(PPh ₃) ₄	K ₂ CO ₃ (2)	Dioxane	23
2	Pd(OAc) ₂ + PPh ₃ ^c	K ₂ CO ₃ (2)	Toluene	35
3	Pd(OAc) ₂ + PPh ₃ ^c	Ag ₂ O (2)	Toluene	46
4	Pd(OAc) ₂ + PPh ₃ ^c	Ag ₂ O (1) K ₂ CO ₃ (1)	Toluene	45
5	Pd(OAc) ₂ + BINAP ^d	Ag ₂ O (1) K ₂ CO ₃ (1)	Toluene	7
6	Pd(OAc) ₂ + dppe ^d	Ag ₂ O (1) K ₂ CO ₃ (1)	Toluene	38
7	Pd(OAc) ₂ + dppp ^d	Ag ₂ O (1) K ₂ CO ₃ (1)	Toluene	11
8	Pd(OAc) ₂ + dppe ^d	Ag ₂ O (1) K ₂ CO ₃ (1)	Toluene	24
9	Pd(OAc) ₂ + dppf ^d	Ag ₂ O (1) K ₂ CO ₃ (1)	Toluene	40
10	Pd(dba) ₂ + PPh ₃ ^c	Ag ₂ O (1) K ₂ CO ₃ (1)	Toluene	51
11	PdCl ₂ (MeCN) ₂ + PPh ₃ ^c	Ag ₂ O (1) K ₂ CO ₃ (1)	Toluene	69
12	Pd(PPh ₃) ₂ Cl ₂	Ag ₂ O (1) K ₂ CO ₃ (1)	Toluene	81

^a Reaction conditions: **1a** (0.3 mmol), palladium source (0.03 mmol), solvent (4 mL), 24 hours. ^b Isolated yield. ^c 40 mol% PPh₃ was used.

^d 20 mol% ligand was used.

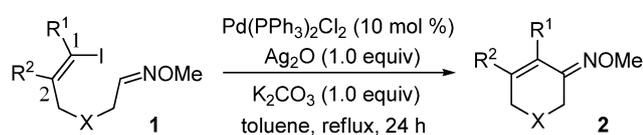
Shanghai Key Laboratory of Functional Materials Chemistry, East China University of Science and Technology, Shanghai 200237, P. R. China. E-mail: tongxf@ecust.edu.cn; Fax: +86-21-64253881; Tel: +86-21-64253881

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almost the same result (Table 1, entry 4). On the basis of these results, we next examined a variety of biphosphine ligands, such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), 1,2-bis(diphenylphosphino)ethane (dppe), and 1,3-bis(diphenylphosphino)propane (dppp), 1,2-bis(diphenylphosphino)benzene (dppb) as well as 1,10-bis(diphenylphosphino)ferrocene (dppf), which, however, did not show any superior performance than PPh_3 (Table 1, entries 5–9) in terms of yield. Fortunately, the use of $\text{Pd}(\text{dba})_2$ and PPh_3 as a catalyst system enabled a promising result with a 51% isolated yield (Table 1, entry 10). This result implied that the palladium source imposed a strong effect on the reaction performance. Indeed, when $\text{PdCl}_2(\text{MeCN})_2$ was used, product **2a** was obtained in 69% yield (Table 1, entry 11). Finally, $\text{PdCl}_2(\text{PPh}_3)_2$ without any additional ligand was identified as the best choice, delivering **2a** in 81% yield (Table 1, entry 12).

With the optimized conditions in hand, we then investigated the scope of this transformation (Table 2). Firstly, various substituted (Z)-vinyl halide oxime ethers with a nitrogen-functionalized tether were tested. Both alkyl and aryl substituents at the C2-position are well tolerated (Table 2, entries 1 and 2). But the reaction of substrate **1c** bearing a butyl group at the C1-position gave lower yield possibly due to steric hindrance (Table 2, entry 3). However, substrates with phenyl substituted at the C1-position, such as **1d** and **1e**, show good reactivity, delivering products with good yield (Table 2, entries 4 and 5). Interestingly, the reaction of substrate **1f** gave five-membered cycle **2f** in 50% yield (Table 2, entry 6). This protocol was also suitable for synthesis of a 7-membered cyclic oxime. Indeed, compound **2g** could be readily obtained albeit in 37% yield (Table 2, entry 7). On the contrary, substrates

Table 2 The results of Heck-type cyclisation of oxime ethers^a

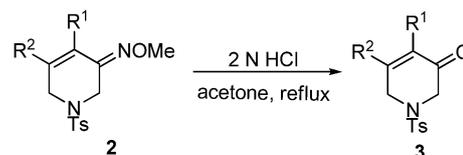


Entry	1 (R ¹ , R ² , X)	2	Yield ^b (%)
1	1a (H, Et, NTs)	2a	81
2	1b (H, Ph, NTs)	2b	68
3	1c (Bu, Et, NTs)	2c	43
4	1d (Ph, Ph, NTs)	2d	70
5	1e (Ph, Et, NTs)	2e	86

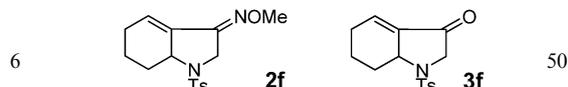
6			50
7			37
8	1h (Ph, Et, O)	2h	34
9	1i (H, Ph, O)	2i	25

^a Conditions: substrate **1** (0.30 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.03 mmol), Ag_2O (0.3 mmol), and K_2CO_3 (0.30 mmol) in toluene (4 mL) under N_2 , 120 °C, 24 h. ^b Isolated yield.

Table 3 Hydrolysis of **2**



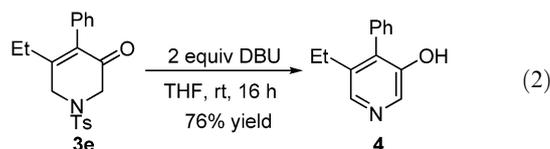
Entry	2 (R ¹ , R ²)	3	Yield ^a (%)
1	2a (H, Et)	3a	70
2	2b (H, Ph)	3b	65
3	2c (Bu, Et)	3c	66
4	2d (Ph, Ph)	3d	68
5	2e (Ph, Et)	3e	71



^a Isolated yield.

with oxygen-functionalized tether, such as **1h** and **1i**, show much less reactivity (Table 2, entries 8 and 9), implying that nitrogen in tether might impose a positive effect on the reaction performance, probably *via* coordination to stabilize the vinyl palladium intermediate. Additionally, a steric effect of the bulky tosylamide group might be important to promote the cyclization by approximating the reaction sites.

To further demonstrate the value of this Heck-type reaction of oxime **1**, the formed aza-cyclic oxime was converted into 1,2-dihydropyridin-3(6H)-one. Indeed, this transformation can be readily achieved *via* hydrolysis with the use of aqueous HCl and the results are summarized in Table 3. Moreover, 3-hydroxypyridine derivative **4** was obtained when **3e** was treated with DBU in THF (eqn (2)). 3-Hydroxypyridines are important structural units found in numerous bioactive compounds.¹¹ Thus, the Heck-type reaction of oxime **1** provides a complementary route to poly-substituted 3-hydroxypyridine from readily available starting materials.¹²



In summary, we have developed a new Heck-type reaction of oxime **1** bearing a vinyl iodide moiety, which allows rapid construction of heterocyclic oxime. This finding demonstrated that the vinylpalladium(II) intermediate is able to undergo insertion of C=N bond, which complements the work related to an arylpalladium(II) analogue and broadens the Heck-type reaction of oxime. Furthermore, this transformation was confirmed to be effective for the synthesis of the 3-hydroxypyridine derivative. Further study on the total synthesis of vitamin B6 by using this reaction as a key step is ongoing and will be reported in due course.

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Specialized Research Fund for the Doctoral Program of Higher Education (20100074120014) is highly appreciated.

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