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Intermolecular Oxidative Amination of Olefins with Amines Catalyzed by the Pd(II)/NPMoV/O_2 System

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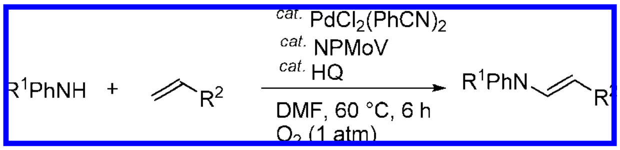
ABSTRACT



A novel and efficient intermolecular aerobic oxidative amination of electron-deficient olefins with secondary aromatic amines has been successfully achieved by a Pd(II)/NPMoV/HQ-catalyzed reaction under dioxygen.

Transition metal-catalyzed amination is an important methodology for synthesizing various nitrogen-containing compounds.[1] In particular, Pd(II)-catalyzed oxidative amination of olefins by using dioxygen, which is referred to as the aza-Wacker reaction, has been the topic of intensive investigation.[1f,2] Currently, the Pd(II)-catalyzed aza-Wacker-type reactions have been utilized to process nitrogen-containing heterocycles like pyrroles and quinolines.[3] Although recent significant developments on the aza-Wacker process have been performed by Stahl and other groups, the existing process generally calls for nonbasic nitrogen nucleophiles such as carboxamides, carbamates, and sulfoneamides.[4] In contrast, the oxidative amination of olefins with simple *amines* as substrate is relatively less explored[5] and generally limited to the intramolecular reaction,[6] owing to deactivation of the Pd catalyst by strong coordination of

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(1) For reviews, see: (a) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675. (b) Brunet, J. J.; Neibecker, D. In *Catalytic Heterofunctionalization*; Togni, A., Grützmacher, H., Eds.; Wiley-VCH: New York, 2001; pp 91−141. (c) Beller, M.; Breindl, C.; Eichberger, M.; Hartung, C. G.; Seayad, J.; Thiel, O. R.; Tillack, A.; Trauthwein, H. *Synlett* **2002**, 1579. (d) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673. (e) Hartwig, J. F. *Pure Appl. Chem.* **2004**, *76*, 507. (f) Kotov, V.; Scarborough, C. C.; Stahl, S. S. *Inorg. Chem.* **2007**, *46*, 1910, and references cited therein.

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(3) For example: (a) Zhang, Z.; Zhang, J.; Tan, J.; Wang, Z. *J. Org. Chem.* **2008**, *73*, 5180. (b) Zhang, Z.; Tna, J.; Wang, Z. *Org. Lett.* **2008**, *10*, 173. (c) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 6328.

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(6) For intramolecular oxidative anmination reactions with simple amines, see: (a) van Benthem, R. A. T. M.; Hiemstra, H.; Longarela, G. R.; Speckamp, W. N. *Tetrahedron Lett.* **1994**, *35*, 9281. (b) Rönn, M.; Bäckvall, J.-E.; Andersson, P. G. *Tetrahedron Lett.* **1995**, *36*, 7749. (c) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, *61*, 3584. (d) Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 164. (e) Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2892.

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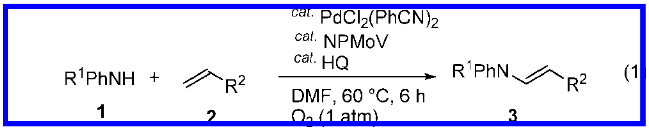
amines. Therefore, the investigation of the novel efficient catalytic system for the intermolecular aza-Wacker reaction with amines as a substrate is highly desirable.

On the other hand, we found that molybdovanadophosphoric acid (HPMoV) served as a good reoxidant of Pd(0) to Pd(II).[7,8] Thus, the Pd(II)/HPMoV/O_2 system showed an efficient catalyst for an oxidative coupling reaction of benzenes with olefins (direct Mizoroki−Heck-type reaction) and a reaction of acrylate and vinyl carboxylates, through direct aromatic or alkenyl C−H bond activations.[7] The same catalyst system was also effective for carboxylation of arenes with CO and O_2.[8]

Alternatively, molybdovanadophosphate (NPMoV), which is partly replaced with an ammonium cation of the acidic complex, HPMoV, has also been utilized as an efficient reoxidation system for the Pd(II)-catalyzed oxidation of alkenes.[9] We reported that the Pd(II)/NPMoV/O_2 or Pd(II)/NPMoV/HQ/O_2 (HQ:hydroquinone) system showed the effective catalytic activity for reactions of acetoxylation and acetalization of olefins under mild conditions.[9] The Pd(II)/NPMoV/O_2 catalyst system could be extended to the Waker-type oxidation and a carbomethoxylation of olefins.[10,11]

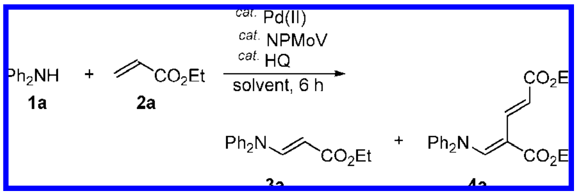
In this letter, our attention has been focused on the aza-Wacker-type reaction of amines with olefins and we found that the Pd(II)/NPMoV/HQ/O_2 system realized an efficient catalytic activity to the intermolecular aza-Wacker reaction of secondary amines with electron-deficient olefins to give oxidative amination products in good yields (eq 1). In addition, we would like to show an unusual formation of 1-amino-2,4-dicarboxylate-substituted 1,3-dienes by using the present catalyst system.



We first chose the reaction of diphenylamine (**1a**) with ethyl acrylate (**2a**) as a model reaction and the results under various reaction conditions are summarized in Table 1. When **1a** (2 mmol) was allowed to react with **2a** (6 mmol) in the presence of $PdCl_2(PhCN)_2$ (0.1 mmol, 5 mol %), $(NH_4)_5H_4PMo_6V_6O_{40}{\cdot}23H_2O$ (NPMoV) (0.02 mmol, 1 mol %), and hydroquinone (HQ) (0.4 mmol, 20 mol %) in DMF (2 mL) under atmospheric oxygen (1 atm) at 60 °C for 6 h ethyl-3-(diphenylamino)propenoate (**3a**) was produced in 90% yield (Table 1, entry 1).[12]

This reaction was successfully performed by using 3 equiv of **2a** to **1a**, while the yield of **3a** was decreased to 18% when an equimolar reaction was carried out (entry 2). The optimized reaction temperature was 60 °C, but the reaction at an elevated temperature (80 °C) under these reaction conditions gave almost the similar result (entry 3). Removal of either NPMoV or hydroquinone from the catalytic system resulted in sluggish reactions (entries 4 and 5). Needless to say, no reaction occurred in the absence of Pd(II) catalyst. The reaction under air or argon resulted in low yields of **3a**, owing to difficulty of regenerating Pd(II) from the reduced

Table 1. Oxidative Amination of Diphenylamine (**1a**) with Ethyl Acrylate (**2a**) Catalyzed by the Pd(II)/NPMoV/HQ System[a]



entry	Pd-catalyst	solvent	yield/%[b] 3a	4a
1	$PdCl_2(PhCN)_2$	DMF	90 (84)	<1
2[c]	$PdCl_2(PhCN)_2$	DMF	18	n.d.[d]
3[e]	$PdCl_2(PhCN)_2$	DMF	86	<1
4[f]	$PdCl_2(PhCN)_2$	DMF	35	<1
5[g]	$PdCl_2(PhCN)_2$	DMF	14	<1
6[h]	$PdCl_2(PhCN)_2$	DMF	24	<1
7[i]	$PdCl_2(PhCN)_2$	DMF	10	n.d.[d]
8	$Pd(OAc)_2$	DMF	7	<1
9	$Pd(acac)_2$	DMF	14	<1
10	$PdCl_2$	DMF	56	<1
11	$Pd(OCOCF_3)_2$	DMF	62	<1
12	$PdCl_2(PhCN)_2$	DME	66	8
13	$PdCl_2(PhCN)_2$	PhCN	34	28
14	$PdCl_2(PhCN)_2$	MeCN	59	26
15	$PdCl_2(PhCN)_2$	*t*-BuOH	54	8

[a] Conditions: **1a** (2 mmol) was allowed to react with **2a** (6 mmol) in the presence of Pd-catalyst (5 mol %) combined with $(NH_4)_5H_4PMo_6V_6O_{40}{\cdot}23H_2O$ (NPMoV) (1 mol %) and hydroquinone (20 mol %) in DMF (2 mL) under O_2 (1 atm) at 60 °C for 6 h. [b] GC yields based on **1a** used. The number in parentheses shows the isolated yield. [c] The reaction was performed with **1a** (2 mmol) and **2a** (2 mmol). [d] Not detected by GC. [e] Reaction was performed at 80 °C. [f] Reaction was performed in the absence of NPMoV. [g] Reaction was performed in the absence of hydroquinone. [h] Reaction was performed under air (1 atm). [i] Reaction was performed under Ar (1 atm).

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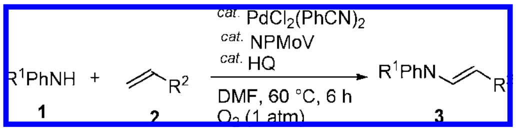
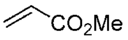
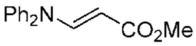
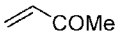
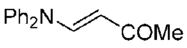
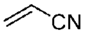
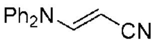
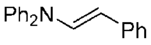
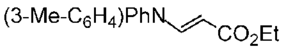
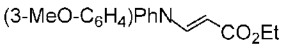
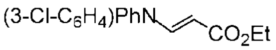
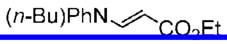
(12) **Typical experimental procedure for the oxidative amination (entry 1, Table 1):** A mixture of **1a** (338 mg, 2 mmol) and **2a** (600 mg, 6 mmol) was allowed to react in the presence of $PdCl_2(PhCN)_2$ (38 mg, 0.1 mmol, 5 mol %), $(NH_4)_5H_4PMo_6V_6O_{40}{\cdot}23H_2O$ (NPMoV) (35 mg, 0.02 mmol, 1 mol %), and hydroquinone (HQ) (44 mg, 0.4 mmol, 20 mol %) in DMF (2 mL) under atmospheric oxygen (1 atm) at 60 °C for 6 h in a 30 mL round-bottomed flask. The conversions and yields of products were estimated from peak areas based on an internal standard using GC and the product **3a** was obtained in 90% yield along with a trace amount of **4a**. The product **3a** was isolated by column chromatography (230−400 mesh silica gel, *n*-hexane/ethyl acetate = 9/1) in 84% yield (224 mg).

Table 2. Oxidative Amination of Amines (**2**) and Electron-Deficient Olefins (**2**) Catalyzed by the Pd(II)/NPMoV/HQ System[a,d]



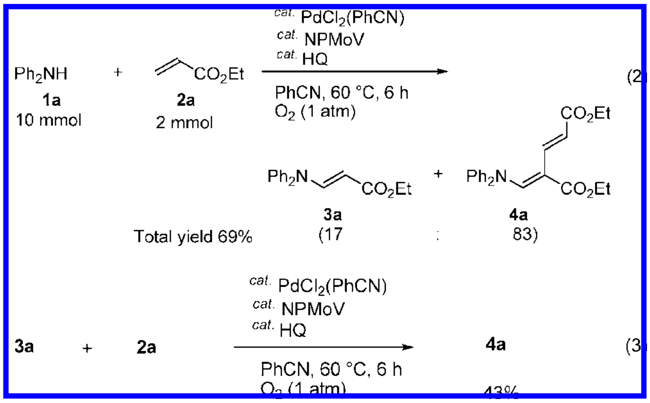
Entry	Amine (**1**)		Olefin (**2**)		Product (**3**)		Yield/%[b,c]
1	Ph_2NH	(**1a**)		(**2b**)		(**3b**)	74
2	**1a**			(**2c**)		(**3c**)	76
3	**1a**			(**2d**)		(**3d**)	53
4	**1a**			(**2e**)		(**3e**)	41
5	(3-Me-C_6H_4)PhNH	(**1b**)	**2a**			(**3f**)	70
6	(3-MeO-C_6H_4)PhNH	(**1c**)	**2a**			(**3g**)	81
7	(3-Cl-C_6H_4)PhNH	(**1d**)	**2a**			(**3h**)	56
8[d]	*n*-BuPhNH	(**1e**)	**2a**			(**3i**)	60

[a] Conditions: **1** (2 mmol) was allowed to react with **2** (6 mmol) in the presence of $PdCl_2(PhCN)_2$ (5 mol %) combined with NPMoV (1 mol %) and hydroquinone (20 mol %) in DMF (2 mL) at 60 °C for 6 h. [b] Isolated yields based on **1** used. [c] GC analysis of the reaction mixture showed a negligible amount of **4** (<1%) was obtained under these reaction conditions. [d] Reaction time was 24 h.

Pd(0) during the reaction (entries 6 and 7). $Pd(OAc)_2$ and $Pd(acac)_2$, which showed high catalytic activity in previously reported $Pd(II)/HPMoV/O_2$[7,8] or $Pd(II)/NPMoV/O_2$[9−11] catalytic system, only showed lower catalytic activity for the present oxidative amination reaction (entries 8 and 9). However, the use of $PdCl_2$ and $Pd(OCOCF_3)_2$ under these reaction conditions gave a moderate yield of **3a** (entries 10 and 11). Among the solvents examined, DMF was found to be the best solvent and **3a** was obtained in high selectivity and yield, while the reactions in DME, PhCN, MeCN, and *t*-BuOH under these reaction conditions afforded **3a** in fair to moderate yields (34−66%) along with 1-amino-2,4-dicarboxylate-substituted 1,3-dienes, (2*E*,4*E*)-diethyl-4-((diphenylamino)methylene)pent-2-enedioate (**4a**), in 8−28% yields (entries 12−15). In this reaction, the choice of the solvent and the ratio of **1a** to **2a** affected markedly the selectivity of **3a** and **4a**. Thus, we tried the optimization of the reaction conditions for the formation of **4a** and found that the use of an excess (5 equiv) of **1a** toward **2a** in PhCN resulted in **4a** in maximum yield (57%) with 83% selectivity (eq 2). The best choice of solvent to obtain the highest yield of **4a** was PhCN.

It was considered that compound **4a** would be formed from a successive reaction of the resulting **3a** with **2a**. Hence, the reaction of **3a** with **2a** under similar reaction conditions was carried out (eq 3). As expected, **4a** was obtained in 43% yield.

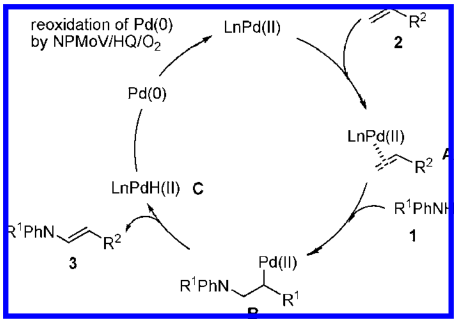
Under the optimized reaction conditions, the reaction of various olefins with amines was examined (Table 2). As a result, the reaction with **1a** with various electron-deficient olefins, such as methyl acrylate (**2b**), methyl vinyl ketone (**2c**), acrylonitrile (**2d**), and styrene (**2e**), was found to progress smoothly to give the corresponding products (**3b−e**) in good yields (entries 1−4). In addition the reaction was tolerated with secondary aromatic amines such as 3-methyldiphenylamine (**1b**), 3-methoxydiphenylamine (**1c**), 3-chlorodiphenylamine (**1d**), and *n*-butylphenylamine (**1e**) to afford the corresponding aza-Wacker product (**3f−i**), exclusively, in good yields (entries 5−8). As for the amine substrates in the present reaction, secondary amines having a phenyl group can also be utilized as a substrate. Unfortunately, the reaction with aromatic primary amines like aniline was sluggish to afford low yield (<10%) of the oxidative amination product along with a mixture of several unidentified compounds.



Furthermore, the reaction of **2a** with primary aliphatic amines such as hexylamine and secondary aliphatic amines like dibutylamine resulted in only conjugated addition (Michael addition) products[13] in place of the formation of the desired oxidative amination products.

Although a detailed reaction mechanism remains to be further elucidated, a plausible path is shown in Scheme 1.

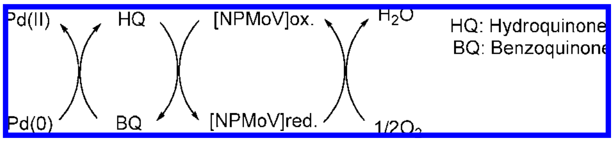
Scheme 1. A Plausible Pathway of the Aza-Wacker Process



The reaction is thought to be initiated by the coordination of the olefin (**2**) to Pd(II), forming a Pd(II)−olefin complex (**A**). Then, **A** is subjected to intermolecular nucleophilic attack of amine (**1**), leading to aminopalladation adducts **B**. The intermediate **B** is likely to undergo *β*-hydride elimination leading to **3** and LnPdH(II) intermediate (**C**), which subsequently resulted in Pd(0).

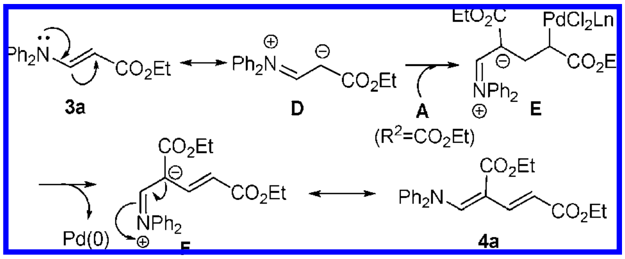
The reoxidation step of Pd(0) to Pd(II) is outlined in Scheme 2. Here, benzoquinone (BQ) serves as a good oxidizing agent of the reduced palladium(0) in the reaction cycle to disproportionate to palladium(II) and hydroquinone (HQ), which then dehydrogenated to BQ with dioxygen by NPMoV, as we previously reported.[9]

Scheme 2. A Mechanism of Regeneration of Pd(II) from Pd(0) under the Influence of NPMoV, Hydroquinone (HQ), and O_2



Considering the formation of **4a** under these reaction conditions, it is assumed that the formation of a zwitterionic structure **D** as a resonance form of **3a** would serve as a carbon nucleophile. Subsequently, the aminopalladation proceeds through nucleophilic attack of **D** to the Pd(II)−olefin complex **A** leading to the intermediate **E**, followed by *β*-hydride elimination leading to **4a** as a product with the formation of Pd(0) (Scheme 3).

Scheme 3. A Plausible Reaction Pathway for the Formation of **4a** from **3a**



In conclusion, we found an efficient catalyst system for an intermolecular aza-Wacker reaction of olefins and secondary aromatic amines by employing a Pd(II)/NPMoV/HQ/O_2 system that affords oxidative amination products in good yields. In addition, by tuning the reaction solvent and the substrate ratio, we could obtain 1-amino-2,4-dicarboxylate-substituted 1,3-dienes as a major adduct.

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Supporting Information Available: Experimental procedures and characterization data for the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[13] For examples of the conjugate addition of amines with electron-deficient olefins, see: (a) Khan, A. T.; Parvin, T.; Gazi, S.; Choudhury, L. H. *Tetrahedron Lett*. **2007**, *48*, 3805. (b) Xu, L. W.; Li, L.; Xia, C.-G. *Helv. Chim. Acta* **2004**, *87*, 1522, and references cited therein.