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COMMUNICATION

Palladium-assisted multicomponent cyclization of aromatic aldehydes, arylamines and terminal olefins under molecular oxygen: an assembly of 1,4-dihydropyridines†

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The palladium-assisted one-pot three-component reactions of aldehydes, amines and olefins proceeded smoothly to give 2,6-unsubstituted 1,4-dihydropyridines (1,4-DHPs) using molecular oxygen as a sole oxidant. It also provides efficient Pd-catalyzed aerobic oxidation access to the anti-Markovnikov oxidative amination products of olefins from primary aromatic amines and alkenes. The method is atom-efficient, using cheap and easily available starting materials and an environmentally benign oxidant.

Multicomponent reactions (MCRs), which directly yield target molecules facilely, fast, and efficiently with minimal workup, have been refined in recent years into a powerful and useful tool in synthetic chemistry. This strategy, highly compatible with the goals of sustainable and green chemistry, is viewed as ideal to assemble large compound libraries in a simple one-pot operation by reacting multiple simple building blocks.[1] On the other hand, transition metal-catalyzed transformations are of increasing importance in synthetic organic chemistry. The outstanding potential of palladium-assisted processes for the development of multicomponent reactions lies in the diversity of bond-forming processes available, the high levels of chemo-, regio-, and stereoselectivity generally observed, and their outstanding functional group tolerance.[2]

One of the emblematic examples of multicomponent reactions is the 1,4-dihydropyridine-yielding Hantzsch reaction reported in 1882.[3] 1,4-Dihydropyridines, regarded as "privileged structures" for drug design, have received a considerable amount of attention in medicinal chemistry and pharmacology due to the wide range of biological activities associated with this heterocyclic scaffold.[4] Furthermore, they are valuable and versatile synthetic intermediates in synthetic chemistry and optimal reducing agents widely employed as a hydride source in hydrogen transfer reactions.[5] Therefore, continuing interest in the more advanced synthetic methodology of 1,4-DHPs has been triggered over the years.[6] However, they do not allow easy access to all possible types of substitution, and in particular the synthesis of 2,6-unsubstituted 1,4-DHPs, which are more suitable as model compounds for the coenzyme NADH,[8e] have received little attention. It is reported that 1,4-DHPs without substituents in the 2- and 6-positions exhibit important pharmaceutical activities. For example, dimers of these compounds are potential inhibitors of HIV-1 protease and possess anticancer activity.[7] While some of the methods afford this type of dihydropyridines efficiently,[8] many of them are still restricted to harsh reaction conditions, relatively low yields of the products, specificity to substituted substrates, or the use of complex or expensive starting materials. Thus, searching for new, facile, and efficient approaches to prepare 1,4-DHPs without substituents in the 2- and 6- positions from easily available inexpensive starting materials is highly desirable. As a part of our ongoing research into the discovery and development of new MCRs to synthesize heterocyclic compound libraries with high diversity,[9] and on the basis of the palladium-assisted aerobic oxidation precedents in our group,[10] herein we report a novel, highly efficient protocol for the synthesis of 2,6-unsubstituted 1,4-DHPs *via* palladium-assisted one-pot three-component reactions of aromatic aldehydes, arylamines and terminal olefins with electron-withdrawing groups under molecular oxygen.

In an exploratory experiment, the reaction conditions of the three-component reaction of benzaldehyde, aniline, and methyl acrylate with O_2 as the oxidant were examined, which included additives, pressure of molecular oxygen, solvents, catalysts, and temperature. As shown in Table 1, the additive seemed to have a dramatic effect on the reaction, since the reaction provided no conversion without any additive. The best result was given when 0.5 equiv of tetrabutyl ammonium bromide (TBAB) was used as additive, and the product was obtained in 93% yield (Table 1, entries 1–6). The reaction could also proceed well under 0.1 MPa O_2 (oxygen was introduced by a balloon), giving 90% yield of product; but the yield decreased to 43% when reacting under air (Table 1, entries 7–8). The reaction without palladium catalyst did not give the desired product at all (Table 1, entries 9), and the Pd source is critical for the success of this reaction. $PdCl_2$ is superior to any other Pd catalyst so far tested (entries 7, 10–11). Subsequently, we further turned to test the effect of solvents, and found acetonitrile was the most effective one (Table 1, entries 7,

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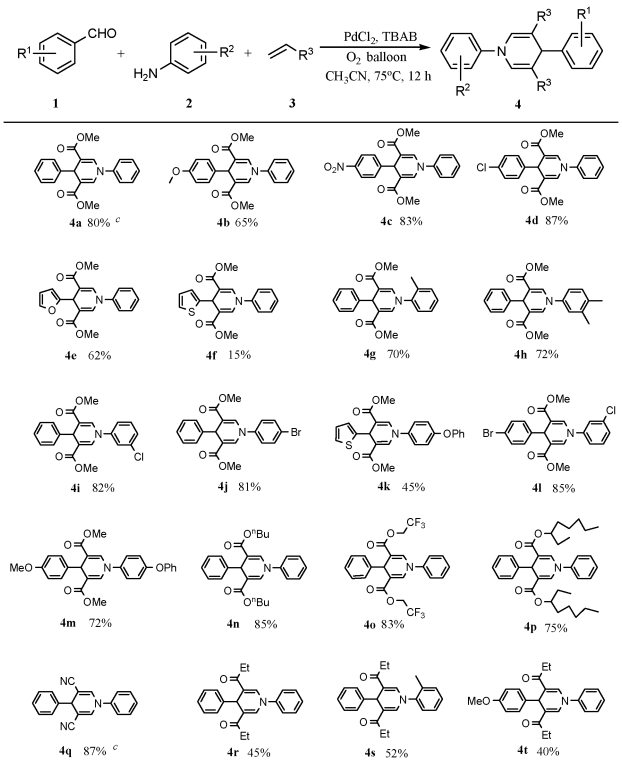
Table 1 Optimization of reaction conditions[a]

Entry	Catalyst	Additive (equiv)	Solvent	O_2 (MPa)	T/°C	Yield (%)[b]
1[c]	$PdCl_2$	—	CH_3CN	1.2	80	trace
2[c]	$PdCl_2$	LiCl (2)	CH_3CN	1.2	80	11
3[c]	$PdCl_2$	NaBr (2)	CH_3CN	1.2	80	73
4[c]	$PdCl_2$	LiBr (2)	CH_3CN	1.2	80	85
5[c]	$PdCl_2$	TBAB (2)	CH_3CN	1.2	80	92
6[c]	$PdCl_2$	TBAB (0.5)	CH_3CN	1.2	80	93
7	**$PdCl_2$**	**TBAB (0.5)**	**CH_3CN**	**0.1**	**75**	**90**
8	$PdCl_2$	TBAB (0.5)	CH3CN	—	75	43
9	—	TBAB (0.5)	CH_3CN	0.1	75	0
10	$Pd(OAc)_2$	TBAB (0.5)	CH_3CN	0.1	75	8
11	$Pd_2(dba)_3$	TBAB (0.5)	CH_3CN	0.1	75	10
12	$PdCl_2$	TBAB (0.5)	DMF	0.1	75	21
13	$PdCl_2$	TBAB (0.5)	toluene	0.1	75	41
14	$PdCl_2$	TBAB (0.5)	CH_3CN	0.1	50	29

[a] Reaction conditions: benzaldehyde **1a** (1 mmol), aniline **2a** (1 mmol), methyl acrylate **3a** (2 mmol), catalyst (10 mol%) based on **1a**, in 2 mL solvent for 12 h, oxygen was introduced by a balloon. [b] GC yield based on **1a**. [c] The reaction was performed in an HF-15 autoclave.

12–13). Moreover, a lower temperature (50 °C) decreased the yield to 29% with 65% benzaldehyde recovered. (Table 1, entries 7, 14).

Encouraged by the above success, we next turned our attention to explore the scope of the reaction under the optimal reaction conditions (Table 1, entry 7). As summarized in Scheme 1, various aromatic aldehydes, arylamines and terminal olefins with electron-withdrawing groups could smoothly and successfully react to afford the corresponding 1,4-DHPs in moderate to excellent yields under the optimized conditions. Generally, the electron-deficient



Scheme 1 Synthesis of 1,4-DHPs with various substrates[a,b]. [a]Reaction conditions: aldehyde **1** (1 mmol), amine **2** (1 mmol), olefin **3** (2 mmol), $PdCl_2$ (10 mol%), TBAB (0.5 equiv), oxygen was introduced by a balloon, MeCN (2 mL), 75 °C, 12 h. [b] Isolated yields. [c] Crystallographic data available.

aromatic aldehydes gave higher yields of the corresponding DHPs (**4c–4d**) than the electron-rich one (**4b**). Heteroaryl aldehydes such as furan-2-carbaldehyde and thiophene-2-carbaldehyde were also compatible under the reaction conditions, furnishing **4e**, **4f**, and **4k** in relatively lower yields. As for the arylamines, it was found that the arylamines used could afford the corresponding products (**4g–4j**) in 70–82% yields. Furthermore, different alkenes with electron-withdrawing groups, including various acrylates, acrylonitrile and pent-1-en-3-one, afforded the corresponding 1,4-DHPs successfully. When pent-1-en-3-one was used, the yields of DHPs (**4r–4t**) were lower than that of acrylates and acrylonitrile, probably because of the weaker electron-withdrawing ability of acetyl than ester and cyano. Many useful substituting groups, such as halogen, trifluoroethyl and cyano, were successfully introduced into the product. Unfortunately, no desirable product could be obtained from alkyl aldehydes or alkyl amines. The structures of **4a** and **4q** were further characterized by X-ray crystal diffraction measurement (Fig. 1).

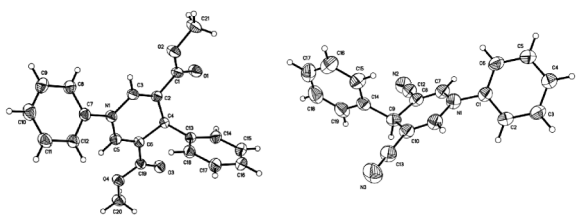
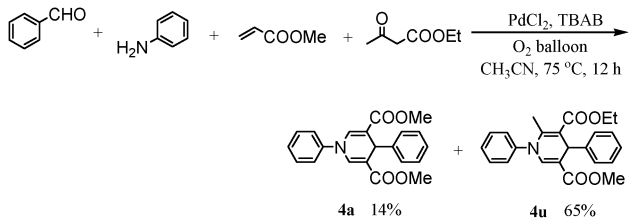


Fig. 1 X-Ray crystal structure of **4a** and **4q**.

Finally, we carried out the reaction of benzaldehyde, aniline, methyl acrylate and ethyl 3-oxobutanoate (1 : 1 : 1 : 1) under the optimized conditions, and 65% yield of 3-ethyl 5-methyl 2-methyl-1,4-diphenyl-1,4-dihydropyridine-3,5-dicarboxylate **4u** was obtained, along with 14% yield of dimethyl 1,4- diphenyl-1,4-dihydropyridine-3,5-dicarboxylate **4a** (Scheme 2).

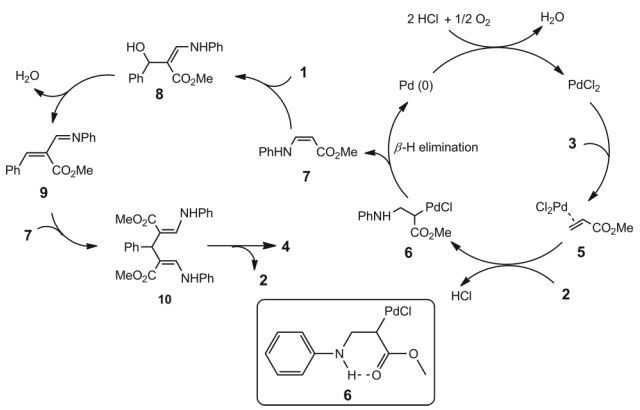
To explore the possible pathways of this reaction, we carried out the reaction of aniline and methyl acrylate under the optimized conditions, and methyl 3-(phenylamino)acrylate **7** was isolated in 87% yield (the ratio of the Z/E isomers was 5 : 1),[11] which could react with benzaldehyde smoothly to give the product in excellent



Scheme 2 Reaction of benzaldehyde, aniline, methyl acrylate and ethyl 3-oxobutanoate.

yield. On the basis of the above results, we proposed **7** as the key intermediate of the reaction. There are few successful precedents of the anti-Markovnikov oxidative amination of olefins from primary aromatic amines and alkenes to our knowledge, because primary aromatic amines such as anilines tend to deactivate palladium catalyst by strong coordination to the palladium species.[12] For example, Hegedus and Bozell reported palladium-catalyzed reactions of substituted anilines and methyl acrylate to produce vinylogous arylamino esters with benzoquinone as an oxidant; however, aniline failed to react completely and most primary aromatic amines reacted poorly affording the products in low yields.[12b] Therefore, this catalytic system could be used to prepare the anti-Markovnikov oxidative amination products of olefins from primary aromatic amines and alkenes, which are useful synthetic intermediates, particularly in the construction of heterocyclic compounds.

A plausible mechanism is shown in Scheme 3. First, a Pd^{II} catalyst coordinates the olefin which undergoes nucleophilic attack by the amine to generate the σ-alkylpalladium complex **6**. The σ-alkylpalladium complex **6** then undergoes β-H elimination to give an unstable palladium hydride complex and anti-Markovnikov oxidative amination product **7**. The palladium hydride complex ultimately forms Pd^{0}, which is reoxidized by molecular oxygen to regenerate the Pd^{II} catalyst. Next, nucleophilic addition of the previously formed enamine **7** to the carbonyl group of the aldehyde occurs to form **8**. Compound **8**, which possibly undergoes dehydration to imine **9**, reacts with a second molecule of enamine **7** to give bisenamine (*Z*)-**10**, which would isomerize into (*E*)-**10** and then lead to cyclized DHP **4** by nucleophilic attack of the amino group to the enone moiety.[8b]



Scheme 3 Plausible reaction mechanism.

In conclusion, we have established a novel, highly efficient protocol for the synthesis of 2,6-unsubstituted 1,4-DHPs *via* palladium-assisted one-pot three-component reactions of aromatic aldehydes, arylamines and terminal olefins with electron-withdrawing groups using molecular oxygen as a sole oxidant. Besides, this method also provides efficient access to the anti-Markovnikov oxidative amination products of olefins *via* Pd-catalyzed reactions of primary aromatic amines and alkenes under molecular oxygen. The use of cheap and easily available starting materials and environmentally benign oxidant would make this atom-efficient method particularly attractive. We expect this method to be useful in the total synthesis of more complex molecules with potential for extensive pharmaceutical and biological applications. Further investigation of the reaction scope including the synthesis of unsymmetrical substituted 1,4-DHPs and its applications in organic synthesis is ongoing in our laboratory and the results will be reported in due course.

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