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A palladium-catalyzed cascade reaction of N-H insertion and oxidative dehydrogenative aromatization under an air atmosphere has been developed under relatively mild conditions.

ARTICLE TYPE

Pd-Catalyzed Cascade Reaction of N-H Insertion and Oxidative Dehydrogenative Aromatization: A New Entry to 2-Amino-phenols

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A palladium-catalyzed cascade reaction of N-H insertion (NHI) and oxidative dehydrogenative aromatization (ODA) has been developed, which affords a straightforward and efficient way to access the carbazole precursors (2-arylamino-
10 **phenols) as well as to prepare 2-alkylamino-phenols from non-aromatic substrates.**

The carbazole nucleus is an important motif found in numerous natural products and synthetic molecules with biological and pharmaceutical activities.[1] Meanwhile, the
15 alkaloids bearing 1-oxygenated carbazole core which have been found mainly in plants of the *Rutaceae* family (Fig. 1), have received considerable attention due to their diverse and significant biological activities.
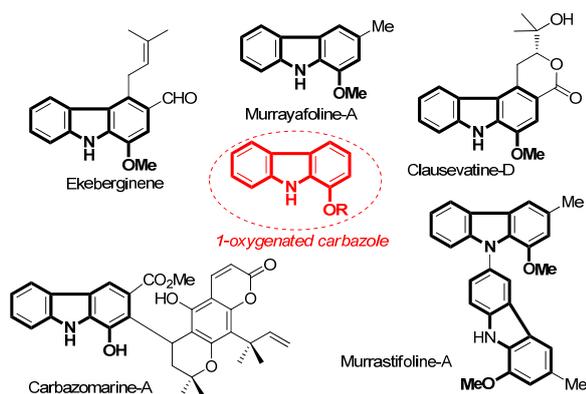

Fig. 1 Natural 1-oxygenated carbazole alkaloids.

Owing to the importance of 1-oxygenated carbazole, many
25 studies have been directed toward a general and flexible approach to access this scalffold.[2] Clearly, the most used way is the well-known palladium-catalyzed annulation of 2-arylamino-phenols (Scheme 1), while classical approaches for 2-arylamino-phenol formation include metal-catalyzed cross-coupling such as
30 Buchwald-Hartwig amination,[3] Ullmann-type reaction[4] and others.[5] Despite these valuable methods, the development of an straightforward and practical methodology towards the synthesis of 2-amino-phenols, which can be further employed for the synthesis of 1-oxygenated carbazole alkaloids and the discovery
35 of new bioactive compounds, is still an interesting and practical research area.

Scheme 1 Retrosynthesis of 1-oxygenated carbazol.

40
On the other hand, oxidative dehydrogenative aromatization remains a powerful way to prepare the aromatic compounds from non-aromatic substrates.[6] Recently, Yoshikai[7] and Li[8] independently reported the Pd-catalyzed intermolecular ODA of
45 cyclic ketones with amines. Stahl described a Pd(TFA)$_2$-mediated ODA system (TFA = trifluoroacetate).[9] In these reports, the cyclohexanone can be transferred to phenol and cyclohexenone under an O$_2$ atmosphere catalyzed by Pd(TFA)$_2$. Just recently, Zhai reported a cross-coupling of aryl iodides and 6-diazo-2-
50 cyclohexenones, which featured Pd(0)-catalyzed tandem reaction of C=C bond formation/aromatization to produce 2-aryl-phenols (Scheme 2, **A**).[10] Our group has independently developed the first Pd-catalyzed NHI from diazo compounds, in which palladium can serve as efficient catalysts for this transformation.[11] Feng and
55 Zhou reported the first highly enantioselective Pd-catalyzed NHI and O-H insertion respectively. Just recently, we reported a copper-catalyzed cascade reaction of NHI and ODA to produce 2-arylamino-phenols,[14] which must be conducted under an oxygen atmosphere in a sealed tube with a view to obtaining high yields.
60 Based on the former reports,[6-12,13,14] we envisioned that the formation of 2-amino-phenols might be possible through a Pd-catalyzed cascade reaction of NHI and ODA from diazo-cyclohexenones (Scheme 2, **B**).[14] Clearly, challenges remained before we achieved this goal. Not only were the difficulties
65 within every single step, but also the means to realize these different transformations through a cascade process by using one single palladium complex. Furthermore, different with Zhai's former reports, our strategy includes a Pd-catalyzed NHI as well as a tandem process of oxidative dehydrogenation/aromatization.
70 Herein, we wish to present a practical one-pot procedure for the preparation of 2-amino-phenols. Moreover, compared with our former report on the copper-catalyzed approach, this Pd-catalyzed protocol features the use of molecular oxygen in air as oxidant under very mild reaction conditions rather than an oxygen
75 atmosphere in a sealed tube.
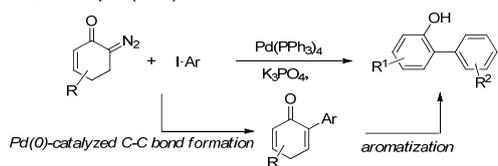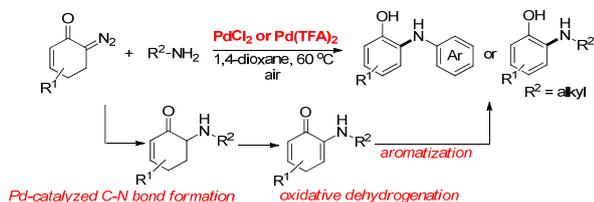
**Scheme 2** Previous report and our synthetic plan.

Initially, we conducted the reaction between 6-diazo-2-cyclohexenone (**1a**) and aniline (**2a**) in 1,4-dioxane in the presence of palladium complexes at 60 °C under air (Table 1). After 3 h, the use of PdCl$_2$ provided the best result (**3a** in 90% yield, entry 2) and Pd(TFA)$_2$ gave slightly lower yield (entry 6), while Pd(OAc)$_2$ afforded **3a** in 81% yield. However, other palladium complexes showed poor catalytic activity. Of the solvents screened, the use of dichloromethane (DCM) resulted in moderate yield (entry 7). Others such as DMF, DMSO, toluene, CH$_3$CN and THF gave low yields (entries 8 to 12). In addition, lower catalyst loading and lower temperature were found to be detrimental to the transformation (entries 14 and 16). Furthermore, when the reaction was carried out under an oxygen atmosphere, almost the similar yield as with entry 2 was observed (entry 13).

Table 1 Optimization of the reaction conditions[a]
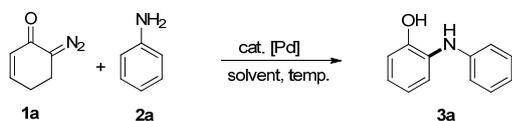
| Entry	[Pd]	Solvent	T (°C)	Yield (%)[b]
1	Pd(OAc)$_2$	1,4-dioxane	60	81
2	PdCl$_2$	1,4-dioxane	60	90
3	Pd(PPh$_3$)$_4$	1,4-dioxane	60	20
4	Pd$_2$(dba)$_3$	1,4-dioxane	60	<5
5	Pd(dppf) Cl$_2$	1,4-dioxane	60	35
6	Pd(TFA)$_2$	1,4-dioxane	60	88
7	PdCl$_2$	DCM	40	80
8	PdCl$_2$	DMF	60	51
9	PdCl$_2$	DMSO	60	32
10	PdCl$_2$	toluene	60	64
11	PdCl$_2$	CH$_3$CN	60	66
12	PdCl$_2$	THF	60	47
13[c]	PdCl$_2$	1,4-dioxane	60	91
14	PdCl$_2$	1,4-dioxane	40	81
15	PdCl$_2$	1,4-dioxane	80	87
16[d]	PdCl$_2$	1,4-dioxane	60	83

[a] All reactions were carried out with **1a** (0.75 mmol), **2a** (0.5 mmol), catalyst (0.05 mmol), solvent (3mL) under air for 3 h unless otherwise noted. [b] Isolated yields of **3a**. [c] Reaction was carried out under O$_2$ in a sealed tube at 60 °C for 3 h. [d] With 5 mol% PdCl$_2$

Under the above optimized conditions, the reaction proceeded smoothly and appeared to tolerate a wide range of functionalized anilines (Table 2). In general, the anilines bearing electron-donating substituents gave higher yields than those with electron-withdrawing substituents. Different 6-diazo-2-cyclohexenones reacted smoothly and afforded the corresponding 2-arylamino-phenols in moderate to high yields. Even for the more congested anilines as well as the hindered diazo substrate (Table 2, **3d**, **3j** to **3l**), the reaction still worked well.

Table 2 Substrate scope[a, b]
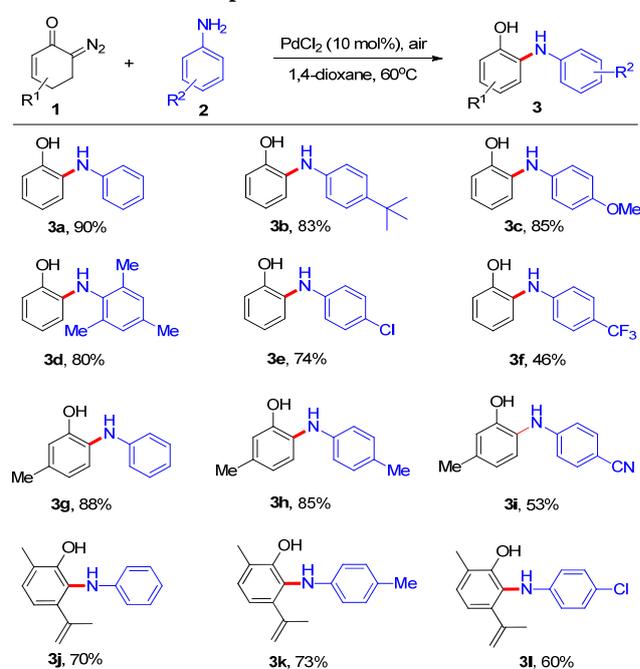
[a] All reactions were carried out with **1** (0.75 mmol), **2** (0.5 mmol), PdCl$_2$ (0.05 mmol), in 1,4-dioxane (3mL) at 60°C under air for 3 hours. [b] Isolated yields of **3**.

To further broaden the scope of substrates, we next examined benzylamine (**4a**) in this reaction (Table 3). However, unlike former observations for anilines, Pd(TFA)$_2$ exhibited the best catalytic activity and gave **5a** in 80% yield (entry 6). In contrast, PdCl$_2$ provided **5a** in very low yield (entry 2), while Pd(OAc)$_2$, Pd(MeCN)$_2$Cl$_2$ and Pd(PhCN)$_2$Cl$_2$ showed moderate to high reaction activity. So we utilized Pd(TFA)$_2$ for further studies.

Table 3 Optimization of the reaction conditions for benzylamine[a]
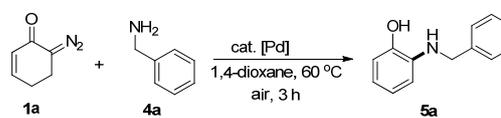
Entry	[Pd]	Yield (%)[b]
1	Pd(OAc)$_2$	66
2	PdCl$_2$	15
3	Pd(MeCN)$_2$Cl$_2$	57
4	Pd(PhCN)$_2$Cl$_2$	73
5	Pd(PPh$_3$)$_2$Cl$_2$	35
6	Pd(TFA)$_2$	80

a All reactions were carried out with **1a** (0.75 mmol), **4a** (0.5 mmol), Pd-catalyst (0.05 mmol), 1,4-dioxane (3mL) at 60 ºC under air for 3 h unless otherwise noted. *b* Isolated yields of **5a**.

Under the optimized condition for benzylamine, various aliphatic amines were subjected to the cascade procedure (Table 4). For the amines investigated, (*tert*-butyldimethylsilyl)oxy-ethanamine delivered the corresponding products in highest yield (**5l**, 88%). The more hindered *tert*-butylamine was also tolerated and gave **5h** in 60% yield. Clearly, this approach afforded a straightforward pathway to prepare 2-*N*-substituted-aminophenols from the non-aromatic substrates. Unfortunately, further investigation in the use of piperidine and pyrrolidine as amine substrates failed to afford the desired product.

### Table 4 Substrate scope[a,b]
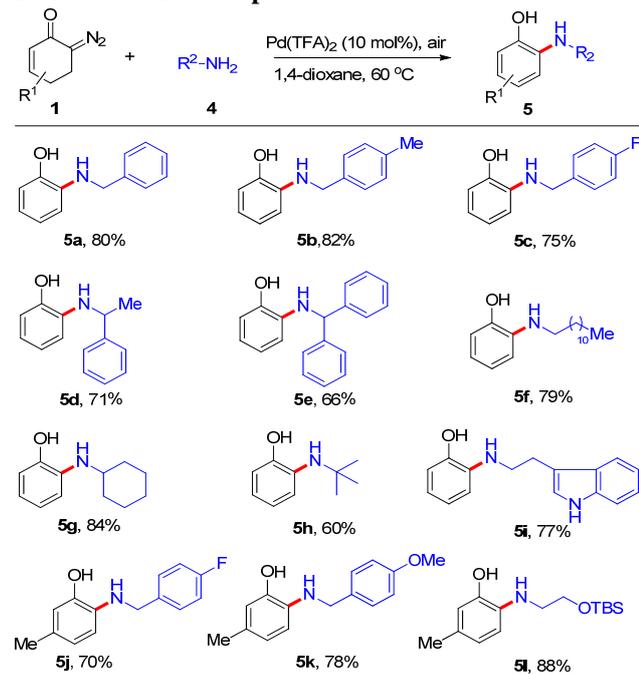
a All reactions were carried out with **1** (0.75 mmol), **4** (0.5 mmol), Pd(TFA)₂ (0.05 mmol), in 1,4-dioxane (3mL) at 60 ºC under air for 3 h. *b* Isolated yields.

To better understand the reaction process, further explorations have been conducted (Scheme 3). Firstly, under a nitrogen atmosphere, the reaction of **1a** and **2a** afforded **3a'** as the major product (93%) (Scheme 3, **I**). Additionally, no reaction occurred when **3a'** was subjected to an oxygen atmosphere and further oxidation of **3a'** in the presence of PdCl₂ in air gave **3a** in 36% yield. These phenomenon indicated that the whole transformation would cease to the NHI stage in the absence of O₂ and the oxidation dehydrogenation is a complicate process. Furthermore, the reaction of **1a** and phenol did not give any product which confirmed that the Pd-catalyzed cascade process would not allow extra side reaction, namely the O-H insertion. Next, to test the practical utility of this methodology, a gram-scale reaction was carried out. The reaction of **1b** and **2a** afforded 1.77g of **3g** in 89% yield (Scheme 3, **III**). Then following the literature method,[2b] we obtained 1.2 g of murrayafoline A within three steps from the diazo substrate (total 57% yield). Notably, this synthetic route could be completed only in the presence of the palladium complexes; no other metals were needed.
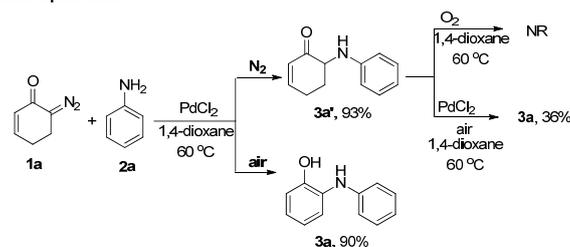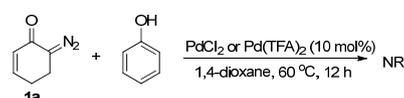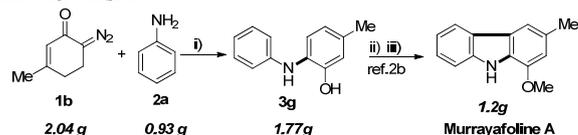

Scheme 3 Further explorations.

A plausible Pd(II)-mediated reaction mechanism is proposed (Fig. 2, Path **a**). The first catalytic cycle is the Pd-catalyzed NHI to give the NHI intermediate **C**, which has been confirmed by the isolation of insertion intermediate in the absence of oxygen. Although the exact mechanism of ODA step is unclear at this moment, as identified by Stahl's and co-workers on the Pd(II)-catalyzed oxidative dehydrogenation of cyclohexanone and cyclohexenone,[9] we thought the Pd(II) species still served as active catalyst for the whole transformation in our approach. Firstly, reaction of **1a** with PdL₂ (L = Cl or TFA) generates intermediate **A** and loss of N₂ to deliver Pd-carbene **B**. Then nucleophilic addition of amine affords **C** and regenerates PdL₂ to the next catalytic cycle. Secondly, **C** is activated by PdL₂ and releasing of HL to generate intermediate **E**, which undergoes *β*-H elimination to afford dienone **F** as well as another HL and Pd(0) species. Finally, **F** would quickly tautomerize to its more stable isomer **G** and the Pd(0) species could be reoxidized to Pd(II) by O₂ and HL to complete the second catalytic cycle.
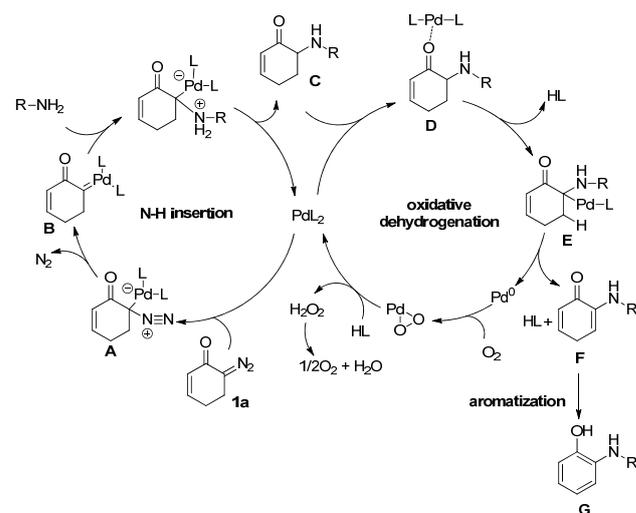
Fig. 2 Plausible catalytic cycle

In summary, we have developed a new strategy for accessing 2-amino-phenols. This approach includes Pd-catalyzed NHI and a tandem oxidative dehydrogenation/aromatization under an air atmosphere. In addition, this method allows a straightforward access to the key precursors for synthesizing 1-oxygenated carbazoles, as well as an efficient way to prepare 2-alkylamino-phenols from nonaromatic substrates. Furthermore, this newly established methodology was expanded to the synthesis of murrayafoline A on a gram scale.

Notes and references

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† Electronic Supplementary Information (ESI) available: [details of experiment procedures, NMR and HRMS data for new compounds. See DOI: 10.1039/b000000x/

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