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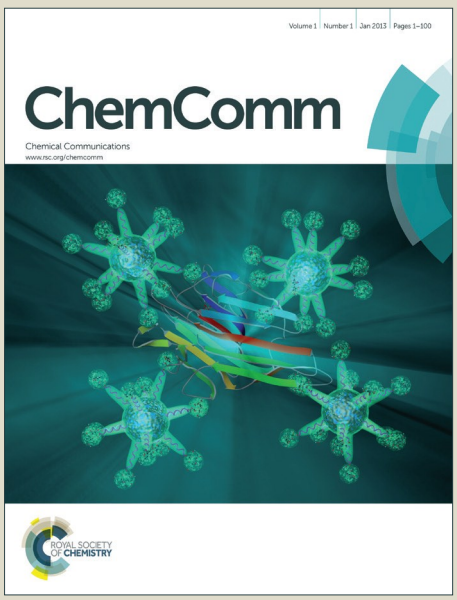

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C8-H Bond Activation vs C2-H Bond Activation: From Naphthyl Amines to Lactams

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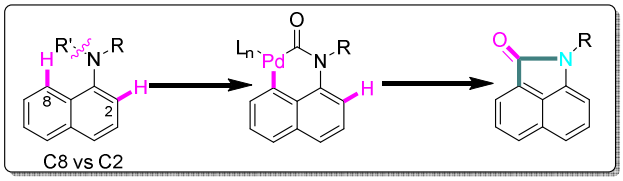
Pd-catalyzed selective amine-oriented C8-H bond functionalization/*N*-dealkylative carbonylation of naphthyl amines has been achieved. The amine group from dealkylation is proposed to be the directing goup to promote this process. It represents a straightforward and easy method to various biologically important benzo[*cd*]indol-2(1*H*)-one derivatives. Moreover, O_2 is utilized as the terminal oxidant to promote the oxidative carbonylation process. Preliminary mechanism studies were conducted indicating the possible route of this transformation.

During the past decade, Pd catalyzed aromatic C-H functionalization to form C-C and C-X bonds has been intensively investigated.[1] While developing regioselective C-H bond functionalization still remains a great challenge. To enhance the site-selectivity of C-H bond activation, extensive efforts have been made to develop C-H activation reactions of broadly useful substrates using various directing groups.[2] As one of the valuable commodity chemicals and useful synthetic building blocks for agrochemicals, active pharmaceutical ingredients and process chemicals, aromatic amines have been widely utilized in chemical synthesis. However the *ortho*-selective C-H bond functionalization of these amines still remains less developed.[3] Compared with anilines, Pd-catalyzed directed C8-H functionalization of the commonly employed naphthyl amines remains even more difficult for the site-selectivity between C2-H and C8-H bond.

Carbonylation, the incorporation of CO into an organic molecule, is now widely recognized as a very important tool in industrial and organic chemistry, which meets the requirement of "atom economy" and "green chemistry".[4] It allows the direct synthesis of important carbonyl compounds starting from the simplest C-1 unit.[3a, 5] Based on our continuous interest in oxidative carbonylation reactions,[3d, 6] it might be a reasonable approach to synthesize benzo[*cd*]indol-2(1*H*)-ones utilizing Pd-catalyzed intramolecular C-H oxidative carbonylation. Yet, it remains difficult to use *N*-methylnaphthalen-1-amines as the substrate in the direct oxidative carbonylation, which urges us to solve the problem in other ways.[7] In our previous work, Pd/Cu-catalyzed aerobic *N*-dealkylative carbonylation of olefins and tertiary amines has been demonstrated.[3c, 8] But it remains a great challenge to expand this novel *N*-dealkylative carbonylation protocol to direct amine-oriented aromatic C-H bond functionalization of naphthyl amines.



Scheme 1.

The chemical structure of benzo[*cd*]indol-2(1*H*)-ones constitutes central core which widely exists in dyes, electronic typing materials and DNA intercalative antitumors.[9] Recently the extraordinary biological and pharmaceutical properties of benzo[*cd*]indol-2(1*H*)-ones have attracted more and more attention.[10] Despite the great importance of benzo[*cd*]indol-2(1*H*)-one derivatives, there are few synthetic routes to access this structure. Among the known synthetic routes, reaction of 1, 8-naphthalic anhydride with hydroxylammonium chloride is the most popular method, which suffers from harsh conditions and narrow substrate scope. It still remains a great challenge to develop an efficient and general synthetic approach to construct various benzo[*cd*]indol-2(1*H*)-ones. Herein, we reported the first Pd/Cu-catalyzed aerobic selective C-H bond activation/*N*-dealkylative carbonylation of naphthalen-1-amines to access biologically important benzo[*cd*]indol-2(1*H*)-ones.

With the optimized conditions in hand(see SI), the carbonylation of a variety of naphthalen-1-amine compounds were tested (Scheme 2). In general, tertiary naphthalene-1-amine substituted with alkyl group at the 4th position could go the standard reaction smoothly to give **2d** in 61% yield. While electron-rich group could be well tolerated (**2h**). Substrate substituted with halogens including Cl and Br furnished the corresponding carbonylation products in good yields (**2b** and **2c**), which can provide useful handles for further synthetic transformations. Unfortunately, substrates substituted with -NO2, -COOMe and other electron-withdrawing group gave less products in this protocol. Both electron-donating and electron-withdrawing substituents on benzene ring of 4-phenylnaphthalen-1-amine derivatives were well tolerated under the current conditions (**2e, 2f** and **2g**). The same results were found in 5-phenylnaphthalen-

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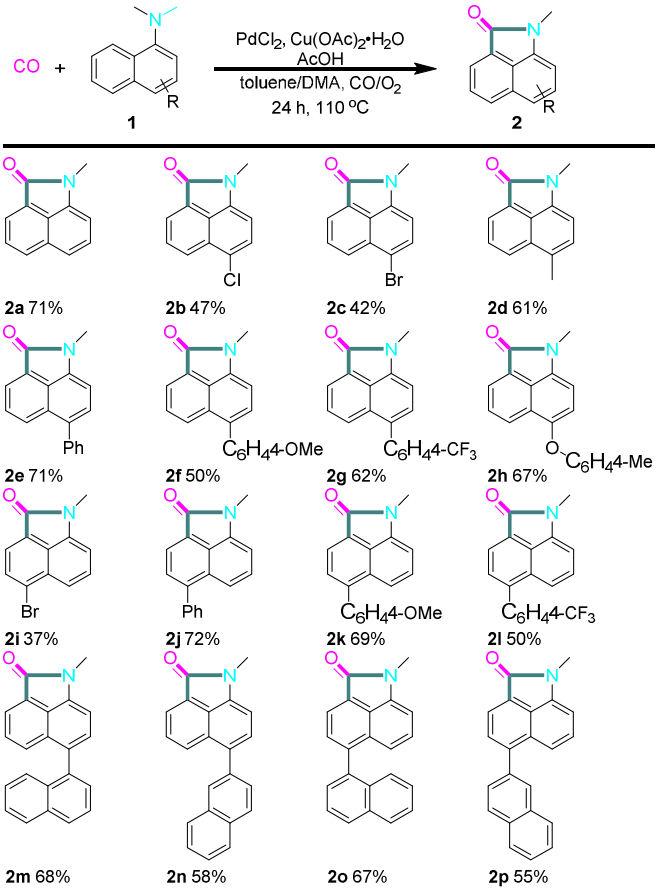
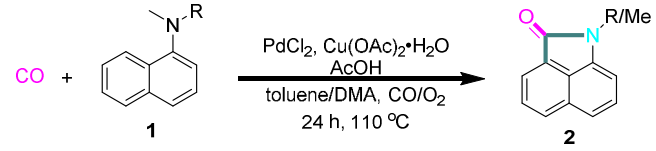
1-amine derivatives (**2j, 2k** and **2l**). 5-Bromo-*N, N*-dimethylnaphthalen-1-amine could give the desired product in 37% yield under the standard conditions (**2i**).



Scheme 2. Palladium/copper-catalyzed intramolecular oxidative *N*-dealkylative carbonylation of naphthalen-1-amine derivatives **1**. Standard reaction conditions: **1** (0.2 mmol), $PdCl_2$ (10 mol%), $Cu(OAc)_2$ •H_2O (30 mol%), AcOH (40 mol%), CO/O_2 = 2/1, toluene/DMA =1.0/0.2, 110 °C, 24 h. Isolated yield.

Table 1. Palladium/copper-catalyzed intramolecular oxidative N-dealkylative carbonylation of naphthalen-1-amine derivatives **1**.



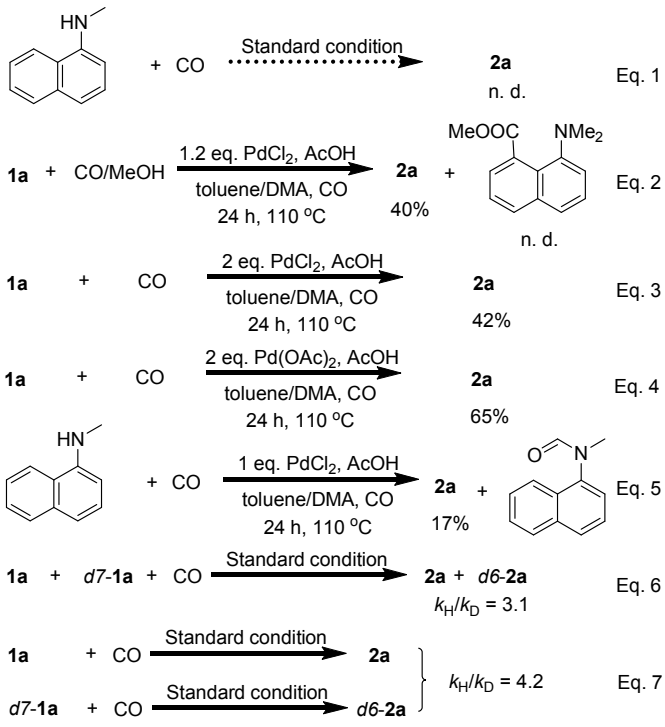
Entry	R	Yield%
1	-Et	56%(**2q/2a**=1.16/1)
2	-Bu	51%(**2r/2a**=1.13/1)
3	-Oct	47%(**2s/2a**=1.47/1)

Standard reaction conditions: **1** (0.2 mmol), $PdCl_2$ (10 mol%), $Cu(OAc)_2$ •H_2O (30 mol%), AcOH (40 mol%), CO/O_2 = 2/1, toluene/DMA =1.0/0.2, 110 °C, 24 h. Isolated yield.

On the other hand, we tested naphthyl substituted substrates to construct conjugated molecules which might have great potential in photoelectric material(Scheme 2). Both 1-methyl-4-(naphthalen-1-yl)benzo[*cd*]indol-2(1*H*)-one and 1-methyl-4-(naphthalen-2-yl)benzo[*cd*]indol-2(1*H*)-one could be obtained in moderate to good yields (**2m** and **2n**). The same phenomenon would be detected with 5-naphthyl-N, N-dimethylnaphthalen-1-amine (**2o** and **2p**).

Furthermore, this protocol could also be applied to *N, N*-dialkyl naphthalen-1-amines with different *N*-alkyl substituents (Table 1). Different alkyl groups like -Et, -Bu, -Oct, were tolerated to obtain a mixture of desired products in moderate yields.

To get some detailed information of the mechanism, control experiments were carried out. Firstly, no desired product was detected by utilizing *N*-methylnaphthalen-1-amine as the substrate under the standard conditions (Scheme 3, Eq. 1). However, when **1a** was used to react with MeOH using 1.2 eq. $PdCl_2$, no product of oxidative C-H alkyloxycarbonylation was detected, yet **2a** was afforded (Eq. 2). It indicates that the *N, N*-dimethylamino group might not be directly used as the directing group. Besides, formaldehyde (CH_2O) was detected by GC in this *N*-dealkylative carbonylation reaction of **1a**. Therefore, we assumed that C-N bond cleavage occurs during the reaction, which leads to the selective C-H bond activation and carbonylation.



Scheme 3. Control experiments.

As shown in Eq. 3, stoichiometric reaction was also performed. With 2 eq. $PdCl_2$, **1a** could undergo the C-N oxidative dealkylative carbonylation smoothly to give the desire product in 42% yield, which indicates that $PdCl_2$ could promote the C-N bond cleavage in the absence of Cu salt.[7d, 7g, 7k, 7l, 11] When 2 eq. $Pd(OAc)_2$ was used, 65% yield was obtained (Eq. 4). On the other hand, when stoichiometric $PdCl_2$ and *N*-methylnaphthalen-1-amine were used in this process, *N*-methyl-*N*-(naphthalen-1-yl)formamide was detected by GC-MS as shown in Eq. 5, suggesting the existence of the insertion process of CO to the Pd-N bond to obtain the carbamoyl palladium intermediate. k_H/k_D=3.1 and 4.2 were observed for the intermolecular KIE experiment, suggesting that C-H bond cleavage might be involved in the rate-determining step (Eq. 6 and Eq. 7). All these results indicates that C-N bond activation occurs firstly to

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obtain carbamoyl palladium intermediate which is the key to C-H bond activation.

To step further in studying the mechanism of CO insertion step and C-H activation, DFT calculations were also carried out. Two possible pathways were proposed and calculated (Figure 1, see SI) In Path-A, the intramolecular CO insertion first occurs before C-H

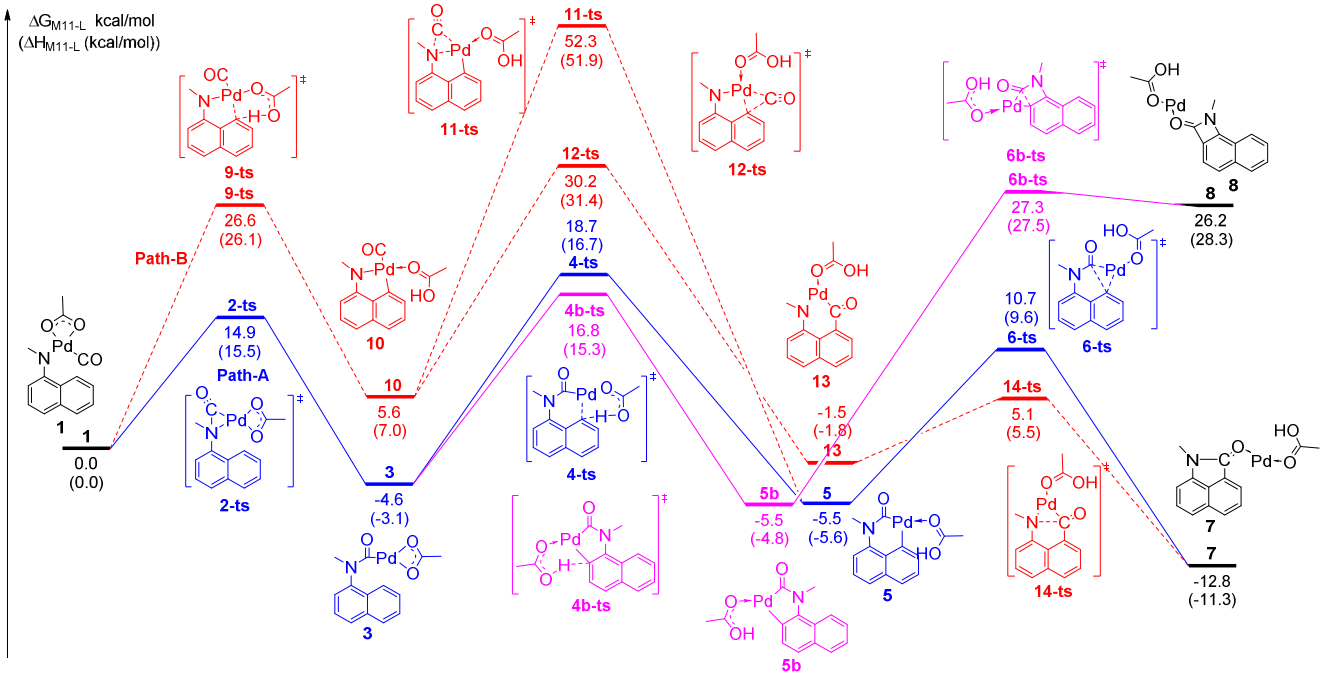
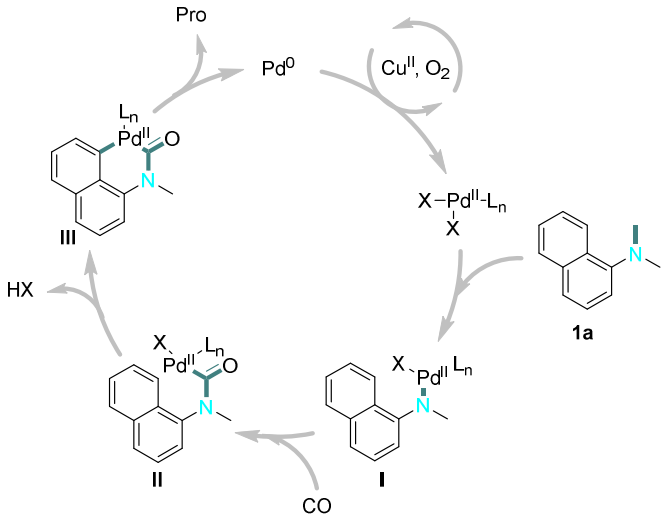


Figure 1. Free energy profiles of Path-A and Path-B for Pd-catalyzed carbonylation

bond activation. Through transition state **2-ts**, intermediate **3** is formed with a barrier of 14.9 kcal/mol. Subsequent concerted metallation-deprotonation (CMD) takes place via transition state **4-ts**, generating complex **5**; the activation free energy of this process is 23.3 kcal/mol. Finally, the C-N bond reductive elimination through transition state **6-ts** can afford lactam coordinated Pd^0 complex **7** with an activation free energy of 16.2 kcal/mol. The relative free energy of complex **7** is 12.8 kcal/mol exothermic compared with complex **1**. Alternatively, the C2-H bond activation might take place through transition state **4b-ts**, generating the complex **5b** reversibly. Although the corresponding activation free energy is 21.4 kcal/mol, which is very close to that of transition state **4-ts**, subsequent reductive elimination is unfavored to occur because of the higher energy barrier (32.8 kcal/mol). Thus, the C-H bond activation prefers to occur on C8 site.

On the other hand, the deprotonation might first occur through transition state **9-ts**, generating complex **10** with a barrier of 26.6 kcal/mol (Path-B). Followed by CO insertion into N-Pd bond via transition state **11-ts** leads to the formation of complex **5**. The overall barrier reaches up to 52.3 kcal/mol, which is 29.0 kcal/mol higher than that in Path-A. Besides, CO can also insert into the C-Pd bond through transition state **12-ts**, generating complex **13**. Subsequent reductive elimination via transition state **14-ts** gives complex **7** with a barrier of 16.6 kcal/mol. As the activation free energy of CO insertion via **12-ts** is 11.5 kcal/mol higher than that in Path-A, Path-B can be safely ruled out. Consequently, Pd-catalyzed carbonylation is most likely to proceed through CO insertion, concerted metallation-deprotonation on C8 site, and C–N bond reductive elimination to give the product.

Based on the above observations and related mechanistic studies, we proposed the following catalytic cycle for this intramolecular oxidative C-H bond activation/*N*-dealkylative carbonylation reaction (Scheme 4). Taking the reaction of *N, N*-dimethylnaphthalen-1-amine **1a** as an example, the Pd-catalyzed aerobic C-N bond activation of **1a** released the intermediate **I**. Then, Pd (II) complex **I** underwent sequential CO insertion to generate the key intermediate **II**, followed by C-H bond activation to achieve six-members palladacycle **III**. Finally, reductive elimination occurs to form the product **2a**, and releases the Pd(0) species, which was re-oxidized by O_2 with the assistance of the copper co-catalyst to regenerate Pd(II) complex.



Scheme 4. Proposed mechanism

In conclusion, we have developed a novel palladium-catalyzed intramolecular aerobic oxidative amine-directed C-H bond activation/*N*-dealkylative carbonylation reaction of tertiary naphthalen-1-amines utilizing O_2 as the terminal oxidant. This transformation provides an effective and straightforward protocol towards the synthesis of biologically and synthetically useful

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benzo[*cd*]indol-2(1*H*)-one derivatives from widely available substrates. Therefore, we anticipate that this work will contribute substantially to the development of next generation carbonylation of amines. Preliminary mechanism studies revealed that amine-directed C-H bond cleavage might be involved in the rate-determining step after the Pd-catalyzed C-N bond activation. Further studies on substrate scope and C-N bond activation mechanism are currently underway and will be reported in due course.

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Notes and references

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