

Cite this: *Chem. Sci.*, 2019, 10, 9292

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## Tertiary amine-directed and involved carbonylative cyclizations through Pd/Cu-cocatalyzed multiple C–X (X = H or N) bond cleavage†

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A novel Pd/Cu-cocatalyzed carbonylative cyclization by C–H activation and *N*-dealkylative C–N bond activation has been developed for the chemoselective construction of synthetically useful heterocycles. The *N,N*-dimethylamine group on *o*-indolyl-*N,N*-dimethylarylamines was found to act as both the directing group and reactive component in this C–H carbonylative cyclization reaction. Furthermore, a unique C–H oxidation/carbonylative lactonization of diarylmethylamines is firstly demonstrated under modified reaction conditions, which could be easily applicable to the one-step synthesis of multi-substituted phthalides bearing an *N,O*-ketal skeleton that is difficult to access by previously reported methods. Mechanistic studies implicate that Pd/Cu-cocatalyzed C–H oxidation/carbonylative lactonization is a sequential reaction system *via* Cu-catalyzed C(sp<sup>3</sup>)–H oxidation and Pd-catalyzed oxidative carbonylation of the C(sp<sup>2</sup>)–H bond. It was found that trace amounts of water are essential to promote the Cu-catalyzed C(sp<sup>3</sup>)–H oxidation of diarylmethylamine for the formation of the hydroxyl group, which could act as an *in situ*-formed directing group in the intramolecular carbonylative lactonization step.

Received 22nd June 2019  
Accepted 17th August 2019

DOI: 10.1039/c9sc03081f

rsc.li/chemical-science

## Introduction

The concept of transition-metal-catalyzed C–H activation/functionalization has re-captured the imagination of chemists and become an exciting field of research in chemistry in the last 20 years.<sup>1</sup> After two decades of effort, dramatic achievements in the field of C–H activation have been achieved and applications of C–H functionalization have permeated and transformed versatile fields including polymer chemistry, materials science, chemical biology and medicinal chemistry.<sup>2</sup> In this regard, by introducing a directing group, numerous catalyst systems have been established to offer direct synthetic methodologies to transform C–H bonds into various valuable C–Z bonds (*e.g.*, C–C, C–O, C–N, C–S, C–P, and C–halides).<sup>3</sup> For instance, Daugulis and Corey demonstrated *N*-heterocycle-

directed palladium-catalyzed  $\beta$ -C(sp<sup>3</sup>)–H arylation of amide derivatives, which realized the synthetic potential of double C(sp<sup>3</sup>)–H activation to give homo-diarylated  $\alpha$ -amino acid derivatives.<sup>4a,b</sup> Yu<sup>4c</sup> and Martin<sup>4d</sup> independently reported carboxyl-directed Pd- and Cu-catalyzed C–H bond activation/C–O bond formation to give lactones and coumarins. The Shi<sup>4e</sup> and Cheng<sup>4f</sup> groups reported hydroxy-directed transition-metal-catalyzed C–H bond activation/carbonylation of 2-aryl-phenols to synthesize benzopyranones.

As a simple yet useful tertiary amine directing group, the *N,N*-dimethylamine group has been widely utilized in C–H activation/functionalization.<sup>5</sup> In this context, nitrogen-directed Pd(II)-catalyzed *ortho*-carbonylation, alkoxycarbonylation of arenes with CO and alcohols, and functionalization of substituted toluenes through *ortho*-olefination of *N,N*-dimethylbenzylamines have been well established in the past years (Scheme 1b).<sup>5</sup> Very recently, You<sup>5a</sup> and Sebesta<sup>5b</sup> independently reported the cross-coupling reaction of ferrocenylmethanamines through Pd-catalyzed C(sp<sup>2</sup>)–H functionalization using *N,N*-dimethylamine as a directing group (Scheme 1a). Notably, Xu<sup>5c</sup> reported a new approach for the synthesis of optically active diarylmethylamines *via* Ir-catalyzed *N,N*-dimethylamine-directed C–H activation/C–B bond formation. Despite these advances, the *N,N*-dimethylamine group was the only used directing group in most of the documented examples. While the *N,N*-dimethylamine group can occasionally become removable in some cases to access further transformation of the C–H

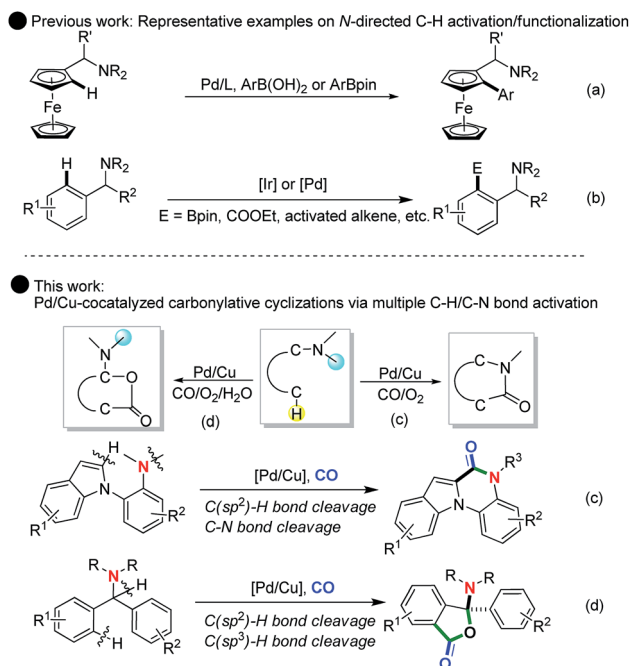
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† Electronic supplementary information (ESI) available: CCDC 1944894. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9sc03081f

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**Scheme 1** Tertiary amine-directed C–H functionalization: single role as the directing group (previous work) and dual role as the directing group and reactive component (this work).

activation products,<sup>5d</sup> its removal reduced the atom-economy and potential derivative diversity of the whole C–H activation process. To overcome these limitations, the combinational use of C–H and C–N activation in *N,N*-dimethylamine-directed C–H functionalization to ensure that the *N,N*-dimethylamine group could work beyond simple directing effects appeared and some rare examples have also been reported.<sup>6</sup> However, in the research area of *N,N*-dimethylamine-directed C–H carbonylation with CO, to date, only the Lei group reported a straightforward oxidative C–H bond activation/*N*-dealkylative carbonylation of tertiary [1,10-biphenyl]-2-anilines, which provided an alternative process to the synthesis of various biologically important lactams and phenanthridin-6(5*H*)-ones.<sup>6d,e</sup>

Notably, the direct transition-metal-catalyzed group-directed C–H activation-initiated carbonylation of diarylmethylamines could provide a convenient and powerful alternative for the construction of new backbones of heterocyclic compounds, such as lactam and lactone skeletons, that have been well identified as potentially useful and bioactive molecules. Herein, we reported a Pd/Cu-cocatalyzed unprecedented and multiple C–H activation/*N*-dealkylative C–N bond activation/carbonylation sequence by using the *N,N*-dimethylamine group as both the directing group and reactive component, allowing for a facile synthesis of biologically important *N*-heterocycles, such as indolo[1,2-*a*]quinoxalin-6-ones. Further studies also offered the first example of Pd/Cu co-controlled hybrid and chemoselective C–H oxidation/carbonylation to access the functionalized *N,O*-ketal-containing phthalides, in which the copper plays a dual role in the first step of  $C(sp^3)$ -H oxidation with the aid of water by single electron transfer (SET) and in the second step of Pd(II)-

catalyzed  $C(sp^2)$ -H carbonylation by oxidation of Pd(0) to Pd(II) respectively. These findings provide a new access to combine the attractive features of C–H functionalization and C–N bond activation/cleavage with catalytic carbonylation for atom-economic synthesis of novel heterocycles.

## Results and discussion

To validate our hypothesis that the construction of a novel indolo[1,2-*a*]quinoxalin-6-one moiety could be completed by Pd/Cu-cocatalyzed carbonylation through C–H activation/*N*-dealkylative C–N bond activation, *o*-indolyl-*N,N*-dimethylarylamines (**2a**) was chosen as a model substrate. It should be noted that, among these lactam-containing heterocycles, indolo[1,2-*a*]quinoxalin-6-ones rank as a class of important tetracyclic moieties that represent a diverse range of pharmacological properties, and their synthesis has attracted the interest of many scientists in the past decades.<sup>7,8</sup> Meanwhile, the key motifs of phthalides that bear a lactone scaffold have been found in many potentially bioactive products.<sup>7</sup> Despite the long-standing efforts in the synthesis of the indolo[1,2-*a*]quinoxalin-6-ones<sup>8</sup> and *N,O*-ketal-containing phthalides,<sup>9</sup> most of the reported methods to afford these compounds usually suffer from inherent limitations, including poor reaction efficiency, pre-functionalized substrates, and limited scope or operational simplicity. Nevertheless, to access the indolo[1,2-*a*]quinoxalin-6-ones and *N,O*-ketal-containing phthalides from easily available compounds with the *N,N*-dimethylamine group, the development of practical and one-step processes still remains highly desirable. Thus to overcome the aforementioned challenges, initially we sought to develop a C–H activation/carbonylation process by merging the C–N bond activation and C–H oxidative carbonylation (Scheme 1c).

To establish the Pd/Cu-cocatalyzed carbonylative cyclization of *o*-indolyl-*N,N*-dimethylarylamines (**2a**) by optimizing various reaction parameters, we found that the combination of PdCl<sub>2</sub> (10 mol%), Cu(TFA)<sub>2</sub>·*x*H<sub>2</sub>O (30 mol%) and PivOH (1.0 equiv.) in a dry solvent of dioxane/DMA (3/1) under a mixture of CO/O<sub>2</sub> (1/3, 1 atm) gave the best result (Table 1, entry 1). The reaction did not work in the absence of either PdCl<sub>2</sub> or Cu(TFA)<sub>2</sub>·*x*H<sub>2</sub>O (Table 1, entries 2 and 3). Pd(OAc)<sub>2</sub> and Pd(TFA)<sub>2</sub> were found to be obviously inferior to PdCl<sub>2</sub> in catalytic activity and resulted in trace yields (Table 1, entries 5 and 6). Copper salts also proved to be essential for the reactivity, for example, CuCl<sub>2</sub>, Cu(OAc)<sub>2</sub>, and Cu(acac)<sub>2</sub> gave decreased yields of **3a** (Table 1, entries 7–9). The yield also dropped dramatically, when using AcOH, AdOH, or Boc-Val-OH instead of PivOH (Table 1, entries 10–12). The effect of solvents on the reaction was then investigated, and it was found that protic solvents, such as *i*-PrOH (Table 1, entry 17), impeded the reaction and the polar aprotic solvents proved to work well in this reaction. The mixture of dioxane/DMA appears to be the optimal choice (Table 1, entries 13–16). In addition, a remarkable decrease of the yield of **3a** was observed when adjusting the ratio of CO and O<sub>2</sub> (Table 1, entries 18 and 19). Moreover, we proved that the O<sub>2</sub> is essential for this reaction (Table 1, entries 20–22). Notably, reducing the catalyst loading would result in lower yields of **3a** (Table 1, entries 23–25).

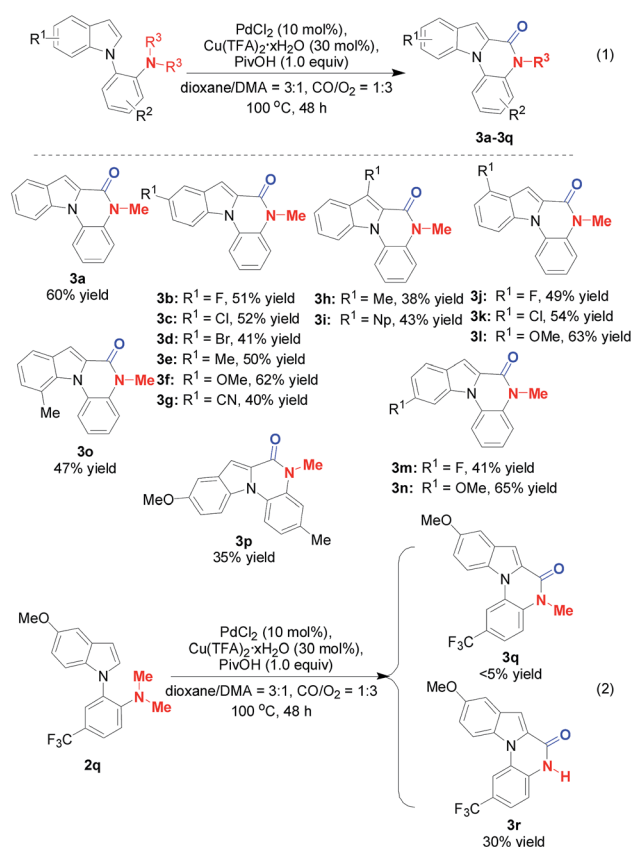


Table 1 Selected optimization of the reaction conditions<sup>a</sup>

Entry	Variation from standard conditions	Yield <sup>b</sup> (%)
1	None	88(60) <sup>e</sup>
2 <sup>c</sup>	Without PdCl <sub>2</sub>	ND <sup>f</sup>
3 <sup>c</sup>	Without Cu(TFA) <sub>2</sub> ·xH <sub>2</sub> O	ND
4 <sup>c</sup>	Without PivOH	60
5 <sup>c</sup>	Pd(OAc) <sub>2</sub> instead of PdCl <sub>2</sub>	Trace
6 <sup>c</sup>	Pd(TFA) <sub>2</sub> instead of PdCl <sub>2</sub>	Trace
7 <sup>c</sup>	CuCl <sub>2</sub> instead of Cu(TFA) <sub>2</sub> ·xH <sub>2</sub> O	Trace
8 <sup>c</sup>	Cu(OAc) <sub>2</sub> instead of Cu(TFA) <sub>2</sub> ·xH <sub>2</sub> O	Trace
9 <sup>c</sup>	Cu(acac) <sub>2</sub> instead of Cu(TFA) <sub>2</sub> ·xH <sub>2</sub> O	Trace
10 <sup>c</sup>	AcOH instead of PivOH	Trace
11 <sup>c</sup>	AdOH instead of PivOH	Trace
12 <sup>c</sup>	Boc-Val-OH instead of PivOH	Trace
13 <sup>d</sup>	Toluene/dioxane = 3 : 1	69
14 <sup>d</sup>	Toluene/DMF = 3 : 1	69
15 <sup>d</sup>	Toluene/NMP = 3 : 1	29
16 <sup>d</sup>	Toluene/DMA = 3 : 1	82
17 <sup>d</sup>	<i>i</i> -PrOH instead of the mixture solvent	Trace
18 <sup>c</sup>	CO/O <sub>2</sub> = 1 : 2	55
19 <sup>c</sup>	CO/O <sub>2</sub> = 1 : 4	57
20 <sup>c</sup>	AgOAc instead of O <sub>2</sub>	Trace
21 <sup>c</sup>	K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> instead of O <sub>2</sub>	Trace
22 <sup>c</sup>	TEMPO instead of O <sub>2</sub>	Trace
23	5 mol% PdCl <sub>2</sub> <sup>g</sup>	55
24	10 mol% Cu(TFA) <sub>2</sub> ·xH <sub>2</sub> O <sup>g</sup>	Trace
25	20 mol% Cu(TFA) <sub>2</sub> ·xH <sub>2</sub> O <sup>g</sup>	25
26	None <sup>h</sup>	46

<sup>a</sup> **2a** (0.1 mmol), PdCl<sub>2</sub> (10 mol%), Cu(TFA)<sub>2</sub>·xH<sub>2</sub>O (30 mol%), PivOH (1.0 equiv.), dioxane/DMA (3 : 1, 2.0 mL), V(CO)/V(O<sub>2</sub>) (1 : 3), 100 °C, 48 h. <sup>b</sup> Determined by GC-MS, isolated yield is given in the parenthesis. The trace by-products are detected as the various demethylated products coming from **2a** and **3a**. And the similar polarity of these products makes the purification by flash column chromatography really difficult, which resulted in a loss of isolated yield. <sup>c</sup> Toluene/dioxane (3 : 1, 2.0 mL), 110 °C. <sup>d</sup> 110 °C. <sup>e</sup> The amount of **2a** is 0.5 mmol in this case. <sup>f</sup> ND = not determined. <sup>g</sup> The amount of Pd or Cu catalyst is reduced and the others are not changed. <sup>h</sup> 1.0 mmol scale of **2a**.

The substrate scope was next explored under the optimized reaction conditions. As shown in Scheme 2, *o*-indolyl-*N,N*-dimethylarylamines bearing various substituents at the 3-, 4-, 5-, 6-, and 7-positions of the indole ring were amenable under the optimal conditions and enabled formation of corresponding products in moderate to good yields (**3a–3r**). It is important to note that the functional groups, such as 5-Br (**3d**) and 5-CN (**3g**), could provide handles for further derivation. **3h** and **3i** were also produced in 38% and 43% yields respectively from the reaction of C3-substituted indole partners, suggesting that steric hindrance did not dramatically hamper the transformation. Gratifyingly, introduction of a 7-Me group was also tolerated (**3o**). Switching to disubstituted substrates still furnished the desired products (**3p**). Interestingly, when **2q** is used in the Pd/Cu-cocatalyzed carbonylative cyclization, the major product is **3r**



Scheme 2 Reaction scope. The reactions were run on a 0.5 mmol scale.

but not **3q**, in which double C–N bond cleavage occurs under the optimized reaction conditions (Scheme 2, eqn (2)).

Considering the importance of the isoindolinone and phthalide scaffolds in many pharmaceuticals and bioactive natural products (see Fig. 1),<sup>7</sup> we extended the practicality of this synthetic strategy with diarylmethylamines (**4a**) as the substrate. Surprisingly, the unexpected *N,O*-ketal-containing phthalide **5a** was detected. After judicious optimization of various reaction parameters (see Table 2 and ESI, Tables S1–S9†), the *N,O*-ketal-containing phthalide **5a** was obtained in 90% GC-MS yield upon heating **4a** with a combination of PdCl<sub>2</sub> (10 mol%), Cu(OAc)<sub>2</sub> (30 mol%), Boc-Val-OH (30 mol%) and PivOH (1.0 equiv.) in a dry solvent of toluene/dioxane (5/1) under a mixture of CO/O<sub>2</sub> (2/1, 1 atm).

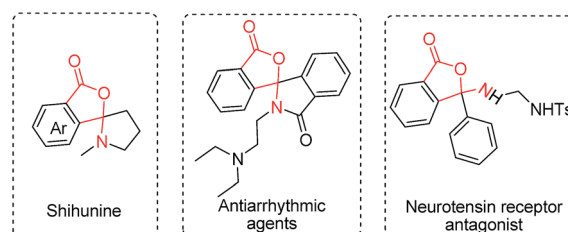
Fig. 1 Representative examples of biologically active molecules based on the *N,O*-ketal-containing phthalide core.

Table 2 Selected optimization of the reaction conditions<sup>a</sup>

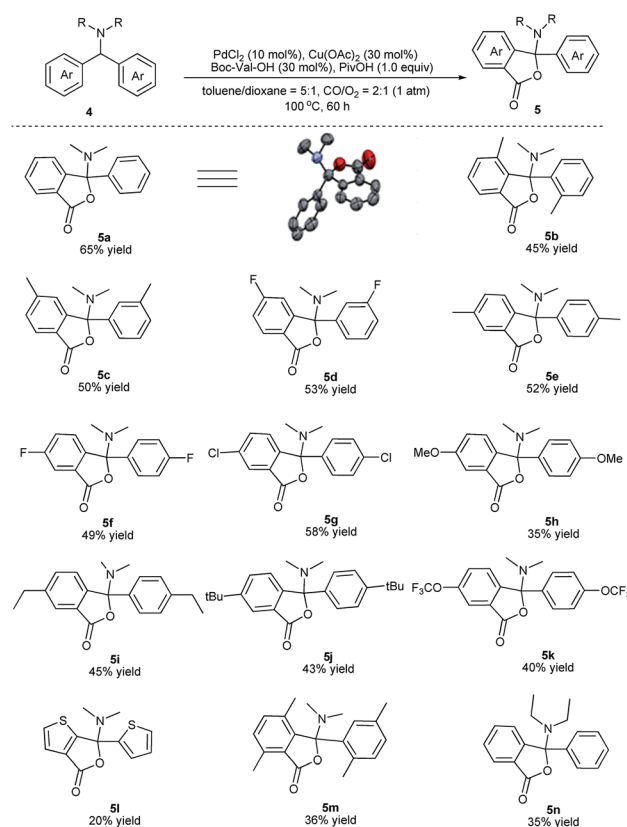
Entry	Variation from standard conditions	Yield <sup>b</sup> (%)
1	None	90(65)
2 <sup>c</sup>	Without PdCl <sub>2</sub>	ND <sup>e</sup>
3 <sup>c</sup>	Without Cu(OAc) <sub>2</sub>	ND
4 <sup>c</sup>	Without PivOH	42
5 <sup>c</sup>	AcOH instead of PivOH	55
6 <sup>c</sup>	Cs <sub>2</sub> CO <sub>3</sub> instead of PivOH	ND
7 <sup>c</sup>	Pd(OAc) <sub>2</sub> instead of PdCl <sub>2</sub>	Trace
8 <sup>c</sup>	Pd(TFA) <sub>2</sub> instead of PdCl <sub>2</sub>	Trace
9 <sup>c</sup>	CuCl <sub>2</sub> instead of Cu(OAc) <sub>2</sub>	Trace
10 <sup>c</sup>	Cu(acac) <sub>3</sub> instead of Cu(OAc) <sub>2</sub>	45
11 <sup>c</sup>	AgOAc as oxidant	Trace
12 <sup>c</sup>	K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> as oxidant	Trace
13 <sup>c</sup>	Toluene instead of mixed solvent	Trace
14 <sup>c</sup>	<i>i</i> -PrOH instead of mixed solvent	Trace
15 <sup>c</sup>	DMA instead of DMF	35
16	110 °C instead of 100 °C	82
17	90 °C instead of 100 °C	55
18	Boc-Phe-OH	80
19	Fomc-Val-OH	72
20	CO/O <sub>2</sub> = 4 : 1	35
21 <sup>d</sup>	Add H <sub>2</sub> O (10 equiv.)	17

<sup>a</sup> **4a** (0.1 mmol), PdCl<sub>2</sub> (10 mol%), Cu(OAc)<sub>2</sub> (30 mol%), Boc-Val-OH (30 mol%), PivOH (1.0 equiv.), toluene/dioxane (5 : 1, 1.2 mL), V(CO)/V(O<sub>2</sub>) (2 : 1), 100 °C, 60 h. <sup>b</sup> Determined by GC-MS, isolated yield is given in the parenthesis. <sup>c</sup> Toluene/DMF (5 : 1, 1.2 mL), 120 °C. <sup>d</sup> 100 °C, 48 h. <sup>e</sup> ND = not determined.

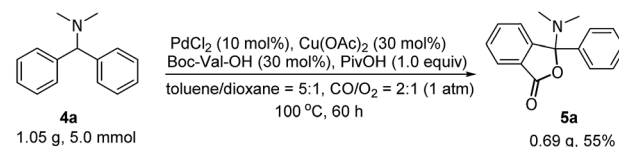
Representative results to support the optimized reaction conditions are shown in Table 2. For example, no product was detected in the absence of either PdCl<sub>2</sub> or Cu(OAc)<sub>2</sub> (Table 1, entries 2 and 3). The yield also dropped dramatically in the absence of PivOH or using AcOH instead of PivOH (Table 1, entries 4 and 5). Although various palladium salts, copper salts and oxidants were screened, no positive results were obtained (Table 1, entries 7–12). Solvent effects on the reaction were also investigated. It was found that both non-polar (*i.e.* toluene) and protic solvents (*i.e.* *i*-PrOH) impeded the reaction, thus resulting in trace amounts of target product **5a**. Only polar aprotic solvents proved to work well in this reaction, and the mixture of toluene/dioxane gave better results (Table 1, entries 1, 13–15). The higher temperature (110 °C) slightly decreased the yield to 80% and the lower temperature led to a lower yield (Table 1, entries 16 and 17). Acid-derived ligands were also screened in this work, and Boc-Val-OH was proved to be the best one (Table 1, entries 1, 18, and 19). In addition, a remarkable change of this transformation was observed by increasing or decreasing the concentration of CO (Table 1, entries 1 and 20). In addition, adding extra water has no benefits but harms the reaction (Table 1, entry 21).

We next evaluated the scope and generality of this novel lactonization by Pd/Cu-cocatalyzed C–H carbonylation. As

shown in Scheme 3, both substrates bearing electron-rich and electron-poor substituents on the aryl ring could be activated and a C–H carbonylation process occurred to give corresponding *N,O*-ketal-containing phthalides in moderate to good yields. The steric hindrance of substituents on the phenyl rings exhibited an important effect on the yields. For instance, while the substrate bearing a *meta*- or *para*-methyl substituent gave yields greater than 50% (**5c**, **5e**), *ortho*-methyl substituted substrates decreased the yields of the corresponding products to 36–45% (**5b**, **5m**). Substrates bearing either an electron-donating or electron-withdrawing substituent on the *para*-position of the aryl rings were well-tolerated under the current conditions (**5e**–**5k**). A wide range of functional groups, including fluoride (**5f**), chloride (**5g**), methoxy (**5h**), and trifluoromethoxy (**5k**), were well compatible with the reaction. Furthermore, the gram-scale reaction of **4a** has been pursued and the desired product **5a** was obtained in 55% isolated yield (Scheme 4).



Scheme 3 Reaction scope. The reactions were run on a 0.5 mmol scale.



Scheme 4 Gram-scale reaction.



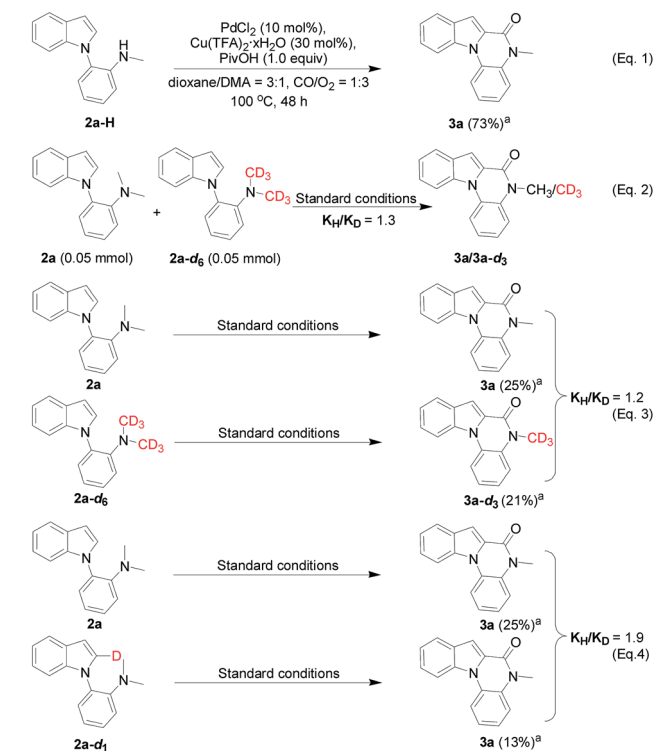


## Mechanistic studies

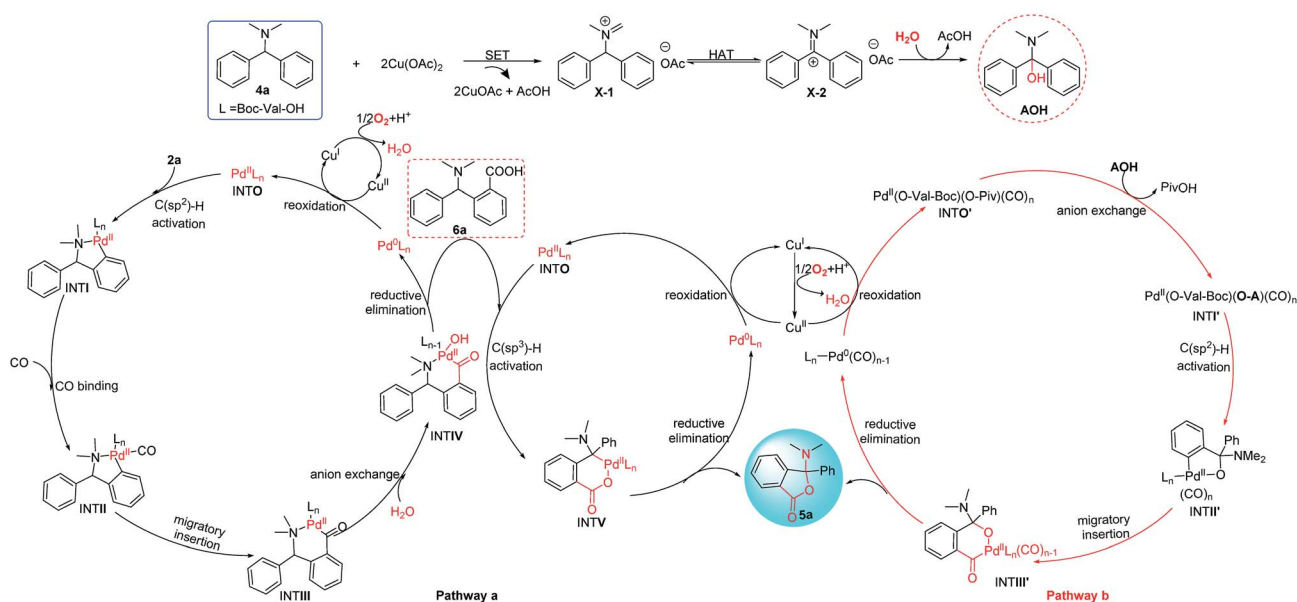
To gain more insight into the *N*-dealkylative C–N bond activation/carbonylation, various control experiments and kinetic isotope effect (KIE) studies were conducted. Firstly, compound

**3a** was detected by GC-MS using **2a-H** as the substrate under the standard conditions, which clearly indicated that **2a-H** was the key intermediate during the reaction (Scheme 5, eqn (1)). As shown in eqn (2) and (3),  $K_H/K_D = 1.3$  and 1.2 were observed respectively for the intermolecular KIE experiments, suggesting that C–N bond cleavage might not be involved in the rate-determining step, while the C–H bond cleavage step did ( $K_H/K_D = 1.9$ , eqn (4)). All these experiments suggested C–N bond cleavage as the key step, which led to the intermediate **2a-H** in the initial step, and the resulting –NHMe group of **2a-H** worked as the directing group in the following C–H activation/carbonylation sequence.

Furthermore, to clarify the highly attractive protocol for the unexpected synthesis of phthalides bearing an *N,O*-ketal skeleton, two plausible mechanisms of Pd/Cu-cocatalyzed C–H functionalization are proposed in Scheme 6. Palladium-catalyzed C–H activation has been well studied and normally needs the presence of directing groups. For instance, the C(sp<sup>2</sup>)-H bond activation with the *N,N*-dimethylamine group as the directing group has been successfully used in catalytic carbonylation, olefination, and cross-coupling reactions. According to the literature precedence, it is supposed that the reaction may proceed through pathway a shown in Scheme 6, which involves two sequential C(sp<sup>2</sup>)-H and C(sp<sup>3</sup>)-H activation *via* two independent catalytic cycles by Pd/Cu-based cooperative catalysis directed by the *N,N*-dimethylamine group and carboxyl group respectively.<sup>5a,d,6a</sup> The carbonylation process was considered to occur in the first C(sp<sup>2</sup>)-H activation cycle (left), which is followed by anion exchange and reductive elimination to form intermediate **6a**. In this pathway, **6a** is proposed to be a key intermediate and the final product **5a** is released by the reductive elimination in the subsequent cycle of the C(sp<sup>3</sup>)-H activation (pathway a, right cycle).<sup>10a</sup> However, we did not detect



Scheme 5 Control experiments and KIE experiments. <sup>a</sup>Determined by GC-MS.



Scheme 6 Two proposed mechanisms of the double C–H functionalization for Pd/Cu-cocatalyzed oxidative carbonylation/lactonization of diarylmethylamines.

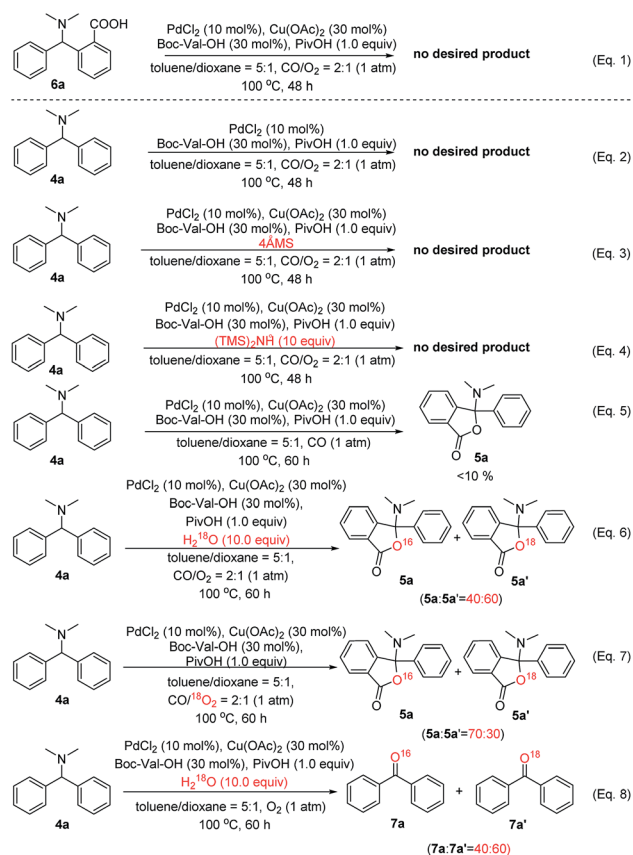


**6a** or a related intermediate during the reaction process. In addition, the desired product **5a** was not formed when **6a** was used as a starting material under the standard reaction conditions (Scheme 6, eqn (1)). Thus on the basis of the above experimental results, the proposed pathway is not a major process and could be excluded.

Then we proposed an alternative mechanism (pathway b) that is shown in Scheme 6 (the third cycle). In this case, the C(sp<sup>3</sup>)-H bond of *N,N*-dimethylphenylamine is activated *via* Cu-catalyzed a single electron transfer (SET) together with a hydrogen-migration process.<sup>11</sup> Substrate **4a** was initially considered to be converted into intermediate **X-1** with the assistance of Cu(OAc)<sub>2</sub> through the SET pathway.<sup>11a-c</sup> And it could be transformed into **X-2** through a proton transfer process because intermediate **X-1** lies in an equilibrium with intermediate **X-2**.<sup>11d</sup> Hydrolysis of **X-2** would help shift the equilibrium to form **AOH** by the nucleophilic attack of H<sub>2</sub>O to **X-2**. Then the active CO-ligated Pd(II) intermediate (**INTO'**) is allowed to react with **AOH** by anion exchange that induced by chelating of the hydroxyl group to Pd center, which can make C(sp<sup>2</sup>)-H bond activation more easily by the Pd(II) center of **INTI'**. The resulting five-membered palladacycle (**INTII'**) becomes a key intermediate in the subsequent carbonylation in this pathway. Then the migratory insertion of one coordinated CO into the aryl-Pd bond forms the six-membered palladacycle (**INTIII'**). Reductive elimination from **INTIII'** leads to **5a** and generates the Pd(0) species, which will be reoxidized to form the active palladium(II) complex by Cu(OAc)<sub>2</sub> in the presence of O<sub>2</sub>.

To gain more insights into the reaction mechanism that **5a** was produced through C(sp<sup>3</sup>)-H oxidation and the subsequent C(sp<sup>2</sup>)-H activation, oxidative carbonylation of **AOH**, followed by reductive elimination (Scheme 5, pathway b),<sup>10b-d</sup> various control experiments, kinetic isotope effect (KIE) studies and density functional theory (DFT) investigations were conducted. According to the above proposed mechanism (pathway b), the following speculations may be deduced: (1) the starting material **4a** cannot be activated through the SET process without the Cu catalyst; (2) in the absence of CO, the whole reaction may stop at intermediate **AOH**; (3) trace water is important for the successful hydrolysis of **X-2** to **AOH**, whose hydroxyl group is derived from water or oxygen in the reaction system. To verify these assumptions, several control experiments were carefully designed and carried out. As shown in Scheme 7, all controlled experiments were performed under standard conditions unless notified.

Firstly, it was found that no lactonization reaction was observed in the absence of Cu(OAc)<sub>2</sub> (Scheme 7, eqn (2)), suggesting that Cu(II) species indeed act as the initiator involved in the transformation of substrate **4a**. Secondly, we have tried to completely remove the trace amount of water in the reaction system with a 4 Å molecular sieve or hexamethyldisilazane (Scheme 7, eqn (3) and (4)). Interestingly, almost no desired product was observed in these two cases. On the other hand, if an excessive amount of water (up to 15 equiv.) is added to the reaction system (see Table S9 in the ESI†), the yield of product **3a** decreased from 72% to lower than 10%, suggesting that water plays an important role in the whole catalytic cycle. As



Scheme 7 Mechanistic studies with control experiments.

such, we postulate that the catalytic generation of the **AOH** intermediate in this system is facilitated by the copper catalyst and water in the presence of O<sub>2</sub> and can undergo rapid C(sp<sup>3</sup>)-H oxidation of **4a**. It was noteworthy that, in pathway b of Scheme 3, the O<sub>2</sub> was initially introduced into the reaction system *via* a Cu-promoted redox reaction in the presence of carboxylic acid (PivOH). In accord with this expectation, the yield of **5a** was lower than 10% in the absence of O<sub>2</sub>, indicating that the oxygen atom in O<sub>2</sub> exists in the catalytic cycle in the form of water (Scheme 7, eqn (5)). To support the importance of water in the formation of product **5a** *via* intermediate **AOH**, an experiment was carried out in the presence of trace amounts of H<sub>2</sub><sup>18</sup>O under the standard reaction conditions (Scheme 7, eqn (6)). As expected, both the **5a** and O<sup>18</sup>-containing **5a'** were obtained in the ratio of 40 : 60 (**5a**/**5a'**). Another <sup>18</sup>O labelled experiment was conducted with the <sup>18</sup>O<sub>2</sub> as the oxidant to give the different ratio of **5a** and **5a'** (Scheme 7, eqn (7)). Additionally, in the absence of CO, the isolation of diphenylketone, a byproduct that formed *via* the C-N bond cleavage approach, is surprising, as its existence would normally be thought as potent evidence for hydrolysis of starting material **4a**. Therefore, these control experiments strongly support the unprecedented potential of ppm levels of water-driven Pd/Cu catalysis, which will be an innovative process to understand the mechanism of catalytic C-H oxidation/carbonylation reaction featuring trace water as the carrier of oxygen (O<sub>2</sub>) in this reaction.



Furthermore, a complicated mixture of diphenylketone  $O^{16}$ -7a and  $O^{18}$ -7a' (40 : 60) can be detected when  $H_2^{18}O$  was added to the system (Scheme 7, eqn (8)). These results seem to further suggest that diphenylketone is mostly likely generated by removing one dimethylamine from intermediate AOH and water may participate in the reaction through the hydrolysis process of intermediate X-2. These experimental observations clearly indicated that both the trace amounts of  $H_2O$  and  $O_2$

were the source of the oxygen atom for the formation of 5a, and  $O_2$  was involved in the reaction in the form of  $H_2O$  which was transformed into intermediate AOH by nucleophilic addition to intermediate X-2. The subsequent reaction of this AOH would then occur smoothly in the presence of palladium and copper catalysts. These control experiments suggest the possibility of pathway b as the mechanism for the catalytic C–H functionalization/carbonylation reaction.

To further clarify the mechanism of the Pd-catalyzed  $C(sp^2)$ –H carbonylation process, the catalytic cycle starting from intermediate AOH to product 5a has been explored with density functional theory (DFT) calculations. Our calculation results show that the reaction may proceed through the catalytic cycle shown in Fig. 2. The corresponding free energy profiles are shown in Fig. 3. The Pd(II) carboxylic acid salt (O) coordinated with one molecule of CO, which can be formed by deprotonation and ligand exchange of  $PdCl_2$  in the presence of Boc-Val-OH, PivOH and CO, was considered as the active catalyst in this reaction. It is set to a relative zero value. O was firstly transformed into the Pd(II) complex (Int1') by the ligand exchange of AOH with PivO-. In Int1', the *ortho*- $C(sp^2)$ –H bond of the AO-fragment was slightly activated *via* the weak  $\pi$  interactions between the phenyl group and Pd center. Int1' then undergoes  $C(sp^2)$ –H activation *via* a six-membered transition state TS1 with a free energy barrier of 19.5 kcal mol<sup>-1</sup>, generating the Pd(II) Int2. In this step, a new Pd– $C(sp^2)$  bond is formed and the proton is transferred to the carbonyl of the Boc fragment. If the carbonyl group on the carboxylate fragment acts as the base, the calculated free energy barrier increases to 28.8 kcal mol<sup>-1</sup> (see

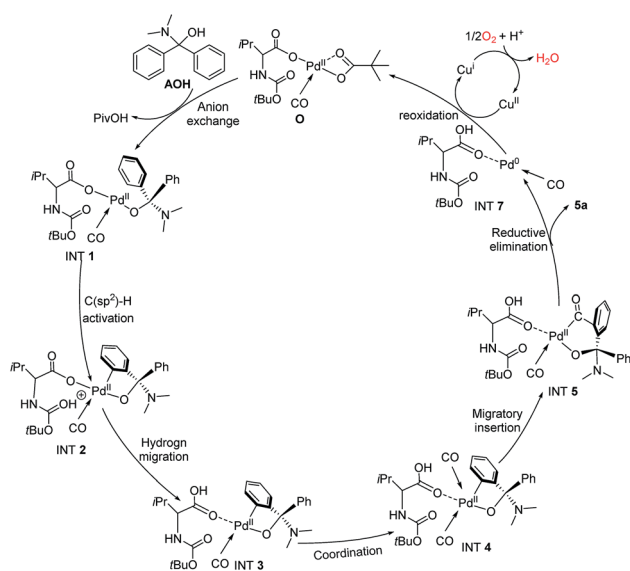


Fig. 2 Calculated catalytic cycle for the double C–H functionalization of diarylmethylamines (4a) catalyzed by the Pd(II) catalyst.

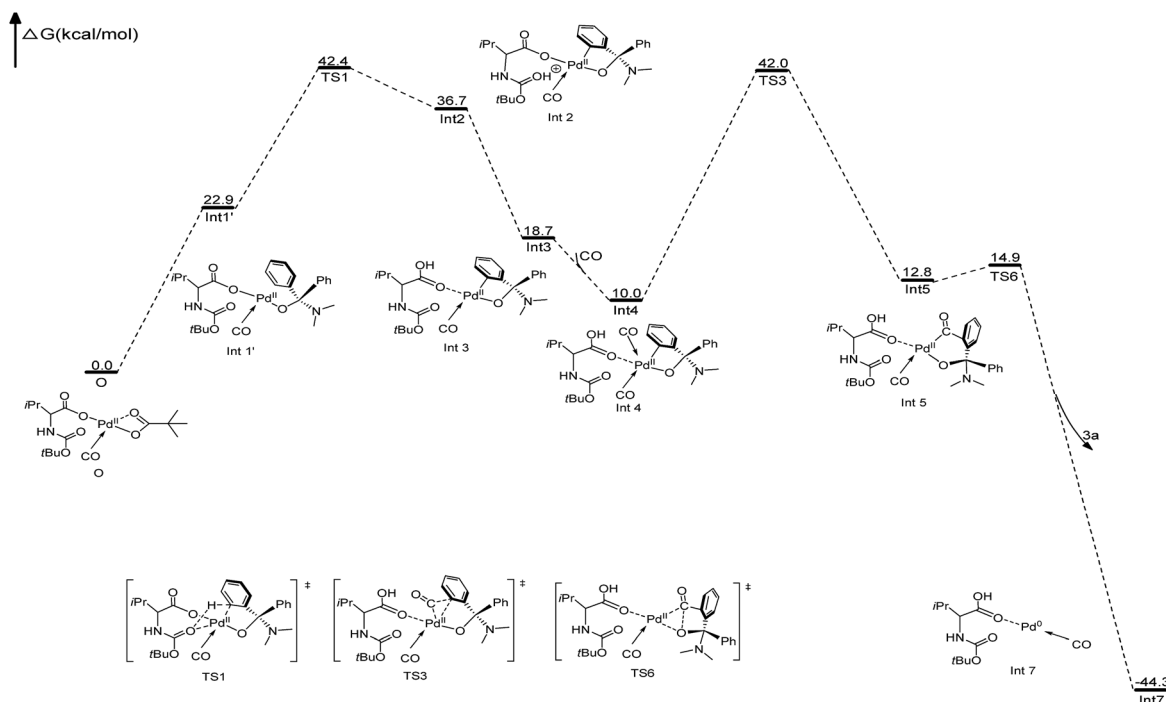
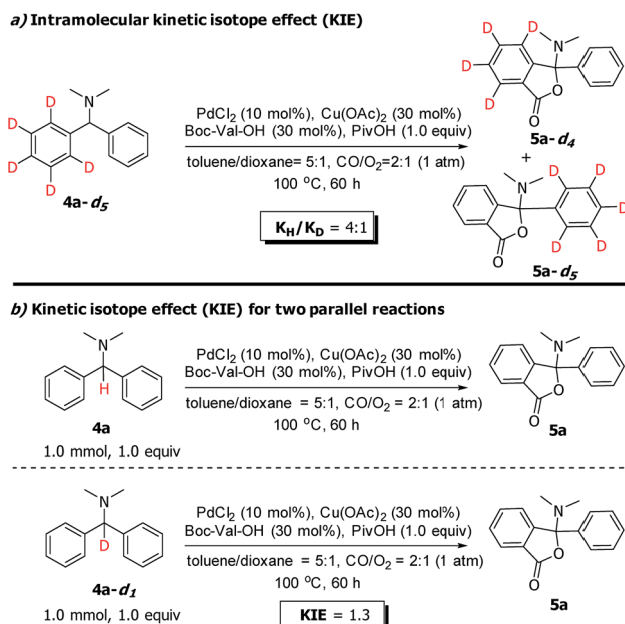


Fig. 3 The free energy profiles for the Pd/Cu-cocatalyzed double C–H functionalization/carbonylation. The free energies (in kcal mol<sup>-1</sup>) are calculated at the B3lyp and BS (BS = 6–31 g (d,p) for main group elements and LanL2DZ for Pd) level of theory.





Scheme 8 KIE experiments.

Fig. S9 in the ESI<sup>†</sup>), indicating that the Boc-based carbonyl group is a better base to activate the C(sp<sup>2</sup>)-H. The proton on the carbonyl oxygen of **Int2** will rapidly transfer to the carboxylate oxygen of Boc-Val-O-, yielding energetically more stable intermediate **Int3**. Interestingly, progressing from **Int3**, a second CO molecule will coordinate to **Int3** leading to the reactive intermediate **Int4**, which is exergonic by only 8.7 kcal mol<sup>-1</sup>. After that, the carbonyl insertion into the Pd-C(sp<sup>2</sup>) bond can occur easily *via* the transition state **TS3** with a free energy barrier of 32.0 kcal mol<sup>-1</sup> to form the intermediate **Int5**, while the carbonyl insertion into the Pd-O bond was found to be unfavourable by 7.4 kcal mol<sup>-1</sup>. Subsequently, **Int5** rapidly undergoes a rapid reductive elimination *via* **TS6** with an energy barrier of 2.1 kcal mol<sup>-1</sup> to give the final product **3a** and release the Pd(0) catalyst (**Int7**). This process is exergonic by 57.1 kcal mol<sup>-1</sup>. Finally, Pd(0) species could be re-oxidized to release the active center Pd(II) with the aid of copper as well as the presence of O<sub>2</sub> to close the catalytic cycle.

In order to identify the rate-determining step of the whole reaction cycle, we carried out two parallel experiments to compare the kinetic isotope effect for the C(sp<sup>3</sup>)-H and C(sp<sup>2</sup>)-H functionalization, respectively (Scheme 8). The results clearly show that the migratory insertion step of the C(sp<sup>2</sup>)-H bond is the rate-limiting step and the cleavage of C(sp<sup>2</sup>)-H is more difficult than that of C(sp<sup>3</sup>)-H oxidation, which is in agreement with the DFT calculations (Fig. 2, the free energy barrier of **TS3** is 12.5 kcal mol<sup>-1</sup>, and it is higher than that of **TS1**).

## Conclusion

In summary, we reported an unprecedented and multiple C-H activation/*N*-dealkylative C-N bond activation/carbonylative cyclization sequence by Pd/Cu-based bimetallic catalysis,

allowing for the direct and facile preparation of a wide variety of novel heterocycles, such as indolo[1,2-*a*]quinoxalin-6-ones and phthalides, in good chemoselectivity. This novel protocol showed good functional group tolerance and broad substrate scope and will contribute substantially to the preparation of heterocyclic compounds bearing the lactam skeleton. On the other hand, we have also developed a unique palladium/copper-cocatalyzed double C(sp<sup>3</sup>)-H/C(sp<sup>2</sup>)-H functionalization/carbonylation/lactonization of diarylmethylamines to form *N,O*-ketal-containing phthalide derivatives in promising yields with good substrate scope. This serendipitously discovered reaction is found to be the combined sequential C(sp<sup>3</sup>)-H/C(sp<sup>2</sup>)-H cleavage and oxidative carbonylation. This protocol could be easily applicable to the one-step synthesis of multi-substituted phthalides bearing an *N,O*-ketal skeleton, which is difficult to access by previously reported methods. The experimental results suggested that the novel Pd/Cu-cocatalyzed C-H carbonylative cyclization is a sequential reaction system by Cu-catalyzed C(sp<sup>3</sup>)-H oxidation and Pd-catalyzed oxidative carbonylation of the C(sp<sup>2</sup>)-H bond. Mechanistic insights also implicate that ppm levels of water are essential to promote the Cu-catalyzed C(sp<sup>3</sup>)-H oxidation of diarylmethylamine for the formation of the hydroxyl group during the construction of the key *N,O*-ketal intermediate. Thus, this C(sp<sup>3</sup>)-H oxidation process is proved to be a key step for the catalytic cycle of C(sp<sup>2</sup>)-H carbonylation, which further supported the mutual importance of sequential and hybrid C(sp<sup>3</sup>)-H oxidation and C(sp<sup>2</sup>)-H carbonylation in the hydroxyl-directed intramolecular oxidative carbonylative lactonization. We believe that this work strongly supports the unprecedented and new potential of trace water as the carrier of oxygen (O<sub>2</sub>) in transition-metal catalysis, which will be an innovative process to understand the mechanism of the catalytic C-H oxidation/carbonylation reaction.

## Conflicts of interest

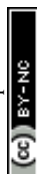
There are no conflicts to declare.

## Acknowledgements

We thank the National Natural Science Foundation of China (NSFC 21702211, 21773051, 21703051, and 21801056), Natural Science Foundation of Jiangsu Province (BK20170421), and Zhejiang Provincial Natural Science Foundation of China (LZ18B020001 and LY17B030005) for financial support of this work. We also thank Dr K. Z. Jiang, Dr K. F. Yang, Dr C. Q. Sheng, Dr X. Q. Xiao, Dr Z. J. Zheng, Dr J. Cao, and Dr G. W. Yin (all at HZNU) for their technical and analytical support.

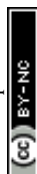
## Notes and references

- For recent examples on the C-H functionalization, see: (a) F. Berger, M. B. Plutschack, J. Riegger, M. W. Yu, S. Speicher, M. Ho, N. Frank and T. Ritter, *Nature*, 2019, **567**, 223; (b) X. Zhang, G. Lu, M. Sun, M. Mahankali, Y. Ma, M. Zhang, W. Hua, Y. Hu, Q. Wang, J. Chen, G. He,





- X. Qi, W. Sheng, P. Liu and G. Chen, *Nat. Chem.*, 2018, **10**, 540; (c) R. G. Kinney, J. Tjutrins, G. M. Torres, N. J. Liu, O. Kulkarni and B. A. Arndtsen, *Nat. Chem.*, 2018, **10**, 193; (d) P. Wang, P. Verma, G. Xia, J. Shi, J. X. Qiao, S. Tao, P. T. W. Cheng, M. A. Poss, M. E. Farmer, K.-S. Yeung and J.-Q. Yu, *Nature*, 2017, **551**, 489; (e) K. Liao, S. Negretti, D. G. Musaev, J. Bacsá and H. M. Davies, *Nature*, 2016, **533**, 230; (f) J. C. K. Chu and T. Rovis, *Nature*, 2016, **539**, 272; (g) D. Willcox, B. G. N. Chappell, K. F. Hogg, J. Calleja, A. P. Smalley and M. J. Gaunt, *Science*, 2016, **354**, 851; (h) F. L. Zhang, K. Hong, T. J. Li, H. Park and J.-Q. Yu, *Science*, 2016, **351**, 252; (i) M. H. Shaw, V. M. Shurtleff, J. A. Terrett, J. D. Cuthbertson and D. W. C. Macmillan, *Science*, 2016, **352**, 1304; (j) A. K. Cook, S. D. Schimler, A. J. Matzger and M. S. Sanford, *Science*, 2016, **351**, 1421; (k) B. Shao, A. L. Bagdasarian, S. Popov and H. M. Nelson, *Science*, 2017, **355**, 1403; (l) X. Li, X. Li and N. Jiao, *J. Am. Chem. Soc.*, 2015, **137**, 9246; (m) B. Xiao, T.-J. Gong, Z.-J. Liu, J.-H. Liu, D.-F. Luo, J. Xu and L. Liu, *J. Am. Chem. Soc.*, 2011, **133**, 9250.
- 2 For selected reviews on C-H functionalization, see: (a) J. B. Williamson, S. E. Lewis, R. R. Johnson III, I. M. Manning and F. A. Leibfarth, *Angew. Chem., Int. Ed.*, 2019, **58**, 8654; (b) D. J. Abrams, P. A. Provencher and E. J. Sorensen, *Chem. Soc. Rev.*, 2018, **47**, 8925; (c) H. M. L. Davies and D. Morton, *ACS Cent. Sci.*, 2017, **3**, 936; (d) K. Murakami, S. Yamada, T. Kaneda and K. Itami, *Chem. Rev.*, 2017, **117**, 9302; (e) H. M. L. Davies and D. Morton, *J. Org. Chem.*, 2016, **81**, 343; (f) M. P. Doyle and K. I. Goldberg, *Acc. Chem. Res.*, 2012, **45**, 777; (g) J. Yamaguchi, A. D. Yamaguchi and K. Itami, *Angew. Chem., Int. Ed.*, 2012, **51**, 8960; (h) H. M. L. Davies, J. D. Bois and J.-Q. Yu, *Chem. Soc. Rev.*, 2011, **40**, 1855; (i) W. R. Gutekunst and P. S. Baran, *Chem. Soc. Rev.*, 2011, **40**, 1976; (j) X.-F. Wu, H. Neumann and M. Beller, *ChemSusChem*, 2013, **6**, 229; (k) B. Gabriele, R. Mancuso and G. Salerno, *Eur. J. Org. Chem.*, 2012, 6825.
- 3 For selected reviews, see: (a) P. Gandeeepan and L. Ackermann, *Chem*, 2018, **4**, 199; (b) C. Ma, P. Fang and T.-S. Mei, *ACS Catal.*, 2018, **8**, 7179; (c) W. Ye, P. Hu, M. Zhang and W. Su, *Chem. Rev.*, 2017, **117**, 8864; (d) J. He, M. Wasa, K. S. L. Chan, Q. Shao and J.-Q. Yu, *Chem. Rev.*, 2017, **117**, 8754; (e) J. A. Labinger, *Chem. Rev.*, 2017, **117**, 8483; (f) X.-X. Guo, D.-W. Gu, Z. Wu and W. Zhang, *Chem. Rev.*, 2015, **115**, 1622; (g) B. Ye and N. Cramer, *Acc. Chem. Res.*, 2015, **48**, 1308; (h) S. A. Girard, T. Knauber and C.-J. Li, *Angew. Chem., Int. Ed.*, 2014, **53**, 74; (i) G. Rouquet and N. Chatani, *Angew. Chem., Int. Ed.*, 2013, **52**, 11726; (j) S. R. Neufeldt and M. S. Sanford, *Acc. Chem. Res.*, 2012, **45**, 936; (k) K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788; (l) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord and F. Glorius, *Angew. Chem., Int. Ed.*, 2012, **51**, 10236; (m) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev.*, 2012, **112**, 5879; (n) C. Liu, H. Zhang, W. Shi and A. Lei, *Chem. Rev.*, 2011, **111**, 1780; (o) J. F. Hartwig, *Chem. Soc. Rev.*, 2011, **40**, 1992; (p) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (q) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (r) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094; (s) O. Daugulis, H.-Q. Do and D. Shabashov, *Acc. Chem. Res.*, 2009, **42**, 1074; (t) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem., Int. Ed.*, 2009, **48**, 9792; (u) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel and J.-Q. Yu, *Chem. Soc. Rev.*, 2009, **38**, 3242; (v) H. M. L. Davies and J. R. Manning, *Nature*, 2008, **451**, 417; (w) C. Sambiasi, D. Schonbauer, R. Blicke, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes and M. Schnurch, *Chem. Soc. Rev.*, 2018, **47**, 6603.
- 4 (a) V. G. Zaitsev, D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.*, 2005, **127**, 13154; (b) B. V. S. Reddy, L. R. Reddy and E. J. Corey, *Org. Lett.*, 2006, **8**, 3391; (c) X.-F. Cheng, Y. Li, Y. M. Su, F. Yin, J.-Y. Wang, J. Sheng, H. U. Vora, X. S. Wang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2013, **135**, 1236; (d) J. Gallardo-Donaire and R. Martin, *J. Am. Chem. Soc.*, 2013, **135**, 9350; (e) S. Luo, F.-X. Luo, X.-S. Zhang and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2013, **52**, 10598; (f) T.-H. Lee, J. Jayakumar, C.-H. Cheng and S.-C. Chuang, *Chem. Commun.*, 2013, **49**, 11797.
- 5 For selected reports, see: (a) Z.-J. Cai, C.-X. Liu, Q. Gu, C. Zheng and S.-L. You, *Angew. Chem., Int. Ed.*, 2019, **58**, 2149; (b) K. Plevova, B. Mudrakova, E. Rakovsky and R. Sebesta, *J. Org. Chem.*, 2019, **84**, 7312; (c) X. Zou, H. Zhao, Y. Li, Q. Gao, Z. Ke and S. Xu, *J. Am. Chem. Soc.*, 2019, **141**, 5334; (d) G. Cai, Y. Fu, Y. Li, X. Wan and Z.-J. Shi, *J. Am. Chem. Soc.*, 2007, **129**, 7666; (e) H. Li, G.-X. Cai and Z.-J. Shi, *Dalton Trans.*, 2010, **39**, 10442; (f) B. Liu and B. F. Shi, *Synlett*, 2013, **24**, 2274; (g) Z. Wang, Y. Li, F. Zhu and X.-F. Wu, *Adv. Synth. Catal.*, 2016, **358**, 2855.
- 6 (a) H. Li, G.-X. Cai and Z.-J. Shi, *Dalton Trans.*, 2010, **39**, 10442; (b) R. Shi, L. Lu, H. Zhang, B. Chen, Y. Sha, C. Liu and A. Lei, *Angew. Chem., Int. Ed.*, 2013, **52**, 10582; (c) X. Li, J. Pan, H. Wu and N. Jiao, *Chem. Sci.*, 2017, **8**, 6266; (d) R. Shi, H. Niu, L. Lu and A. Lei, *Chem. Commun.*, 2017, **53**, 1908; (e) R. Shi, L. Lu, H. Xie, J. Yan, T. Xu, H. Zhang, X. Qi, Y. Lan and A. Lei, *Chem. Commun.*, 2016, **52**, 13307; (f) S. Shi, S. P. Nolan and M. Szostak, *Acc. Chem. Res.*, 2018, **51**, 2589.
- 7 For selected reports, see: (a) H. Iqbal and F. Xua, WO 2016/179505 A1, 2016; (b) O. Key, O. Etsuo, O. Hiroyuki, O. Yoshimasa, N. Massaki and K. Kazuhiro, *Eur. Pat. Appl.*, EP 273401 A1, 1988; (c) M. Snider, D. A. Pereira, K. P. Longo, R. E. Davidson, F. J. Vinick, K. Laitinen, K. Genc-Sehitoglu and J. N. Crawley, *Bioorg. Med. Chem. Lett.*, 1992, **2**, 1535; (d) E. Breuer and S. Zbaida, *Tetrahedron*, 1975, **31**, 499; (e) A. Brossi, W. Kloetzel, S. Teitel and J. F. Blount, *J. Am. Chem. Soc.*, 1971, **93**, 4321; (f) G. Campiani, S. Butini, F. Trotta, C. Fattorusso, B. Catalanotti, F. Aiello, S. Gemma, V. Nacci, E. Novellino, J. A. Stark, A. Cagnotto, E. Fumagalli, F. Carnovali, L. Cervo and T. Mennini, *J. Med. Chem.*, 2003, **46**, 3822.
- 8 For selected reports, see: (a) A. Gogoi, P. Sau, W. Ali, S. Guin and B. K. Patel, *Eur. J. Org. Chem.*, 2016, 1449; (b) Q. Yuan and D. Ma, *J. Org. Chem.*, 2008, **73**, 5159; (c) A. Huang, F. Liu,



- C. Zhan, Y. Liu and C. Ma, *Org. Biomol. Chem.*, 2011, **9**, 7351; (d) M. J. Beach, R. Hope, D. H. Klaubert and R. K. Russell, *Synth. Commun.*, 1995, **25**, 2165; (e) W. Liu, J. Bang, Y. Zhang and L. Ackermann, *Angew. Chem., Int. Ed.*, 2015, **54**, 14137; (f) L. Kong, Y. Sun, Z. Zheng, R. Tang, M. Wang and Y. Li, *Org. Lett.*, 2018, **20**, 5251.
- 9 For selected reports, see: (a) K. Mitobe, T. Kawasaki-Takasuka, T. Agou and T. Kubota, *J. Fluorine Chem.*, 2019, **218**, 3647; (b) K. Kasamatsu, T. Yoshimura, A. Mandi, T. Taniguchi, K. Monde, T. Furuta and T. Kawabata, *Org. Lett.*, 2017, **19**, 352; (c) C. Engelbert, *Organic Reactions*, Hoboken, NJ, United States, 2008, vol. 72, pp. 1–366; (d) Y. Nagao, M. Tachikawa and K. Kozawa, *Shikizai Kyokaishi*, 2001, **74**, 339; (e) M. Sakamoto, N. Sekine, H. Miyoshi, T. Mino and T. Fujita, *J. Am. Chem. Soc.*, 2000, **122**, 10210; (f) K. Bowden, S. P. Hiscocks and A. Perjess, *J. Chem. Soc., Perkin Trans. 2*, 1998, 291; (g) K. Unverferth, R. Dorre, B. Korner, H. Scheibe and E. Morgenstern, *Arch. Pharm.*, 1991, **324**, 809; (h) T. Hisato and E. Shoji, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2149; (i) K. Akiba, Y. Negishi and N. Inamoto, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 2188; (j) P. L. Faye, K. Vaughan and D. L. Hooper, *Can. J. Chem.*, 1983, **61**, 179; (k) M. V. Bhatt, K. M. Kamath and M. Ravindranathan, *J. Chem. Soc. C*, 1971, 1772.
- 10 (a) X.-F. Cheng, Y. Li, Y. M. Su, F. Yin, J.-Y. Wang, J. Sheng, H. U. Vora, X. S. Wang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2013, **135**, 1236; (b) S. Luo, F.-X. Luo, X.-S. Zhang and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2013, **52**, 10598; (c) T.-H. Lee, J. Jayakumar, C.-H. Cheng and S.-C. Chuang, *Chem. Commun.*, 2013, **49**, 11797; (d) Y. Wang and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2015, **54**, 2255; (e) J. Zhang, Y. Hou, Y. Ma and M. Szostak, *J. Org. Chem.*, 2019, **84**, 338; (f) L. Ren, X. Li and N. Jiao, *Org. Lett.*, 2016, **18**, 5852.
- 11 For selected reports, see: (a) J. Shearer, C. X. Zhang, L. Q. Hatcher and K. D. Karlin, *J. Am. Chem. Soc.*, 2003, **125**, 12670; (b) X. Li, J. Pan, H. Wu and N. Jiao, *Chem. Sci.*, 2017, **8**, 6266; (c) R. K. Kawade, D. B. Huple, R. J. Lin and R. S. Liu, *Chem. Commun.*, 2015, **51**, 6625; (d) M. L. Deb, C. D. Pegu, P. J. Borpatra and P. K. Baruah, *RSC Adv.*, 2016, **6**, 40552; (e) S. Guo, B. Qian, Y. Xie, C. Xia and H. Huang, *Org. Lett.*, 2011, **13**, 522; (f) J.-S. Tian and T.-P. Loh, *Angew. Chem., Int. Ed.*, 2010, **49**, 8417; (g) L. Huang, X. Zhang and Y. Zhang, *Org. Lett.*, 2009, **11**, 3730.

