

RESEARCH ARTICLE



Cite this: *Org. Chem. Front.*, 2019, **6**, 627

Cu/Pd-Catalyzed chemoselective synthesis of C-3 dicarbonyl indoles and bis(indolyl)alkanes from aldehydes and indoles†

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A novel and efficient Cu/Pd-catalyzed chemoselective synthesis of C-3 dicarbonyl indoles and bis(indolyl)alkanes from aldehydes and indoles has been achieved. High selectivity for two valuable indole derivatives is achieved by allowing the same substrates to go through different reaction pathways catalyzed by different metal catalysts. Moreover, this mild process affords a wide range of substrates scope and has a high efficacy in large-scale reactions. A plausible mechanism is proposed based on the control experiments.

Received 7th November 2018,
Accepted 9th January 2019

DOI: 10.1039/c8qo01206g

rsc.li/frontiers-organic

Introduction

Indole and its derivatives are biologically active organic motifs that serve as a class of important moieties in natural products, pharmaceuticals and agrochemicals.¹ Owing to their meaningful value and widespread occurrence, functional modification of indoles, especially at the C-3 position, is a hot topic in organic synthesis.² Remarkably, both C-3 dicarbonyl indoles³ and bis(indolyl)alkanes⁴ are valuable indole derivatives that exhibit a wide range of biological and pharmacological activities and act as versatile precursors for a variety of organic transformations (Fig. 1). Consequently, it is greatly desirable to develop novel and efficient methods for the preparation of C-3 dicarbonyl indole and bis(indolyl)alkane derivatives.

In the past few years, novel methods to synthesize bis(indolyl)alkanes were well developed by organo-, transition metal-, ionic liquid- and nanomaterial-catalyzed electrophilic substitution reactions of indoles with various aldehydes or carbonyl compounds.⁵ In addition, recent advances in C-3 dicarbonyl indole preparation generally focused on the development of novel metal/metal-free catalytic oxidative coupling

systems utilizing different starting materials.⁶ However, despite the considerable progress in the easy production of target products in high yields, little attention has been paid to the selectivity of the reactions. Herein, we presented a novel and efficient Cu/Pd-catalyzed chemoselective synthesis of C-3 dicarbonyl indoles and bis(indolyl)alkanes from aldehydes and indoles. In this method, using the same reaction substrates, the selectivity for the synthesis of either dicarbonyl indoles **3** or bis(indolyl)alkanes **4** could be regulated efficiently by changing the metal catalysts: (1) CuBr could contribute to the aerobic oxidative coupling of aldehydes and indoles to produce C-3 dicarbonyl indoles **3**; (2) PdCl₂ catalytic system could more easily promote the condensation and bisindolylolation between aldehydes and indoles to produce bis(indolyl)alkanes **4**.

Dioxygen is a well-known mild, economical and green oxygen source that has been identified as an ideal oxidant in organic synthesis.⁷ To the best of our knowledge, transition-metal catalyzed aerobic oxidative coupling of aryl aldehydes and indoles to synthesize C-3 dicarbonyl indoles has not been reported to date, and the bis(indolyl)alkane syn-

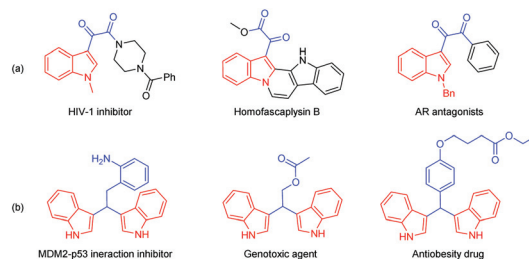


Fig. 1 Representative structures containing C-3 dicarbonyl indoles and bis(indolyl)alkanes.

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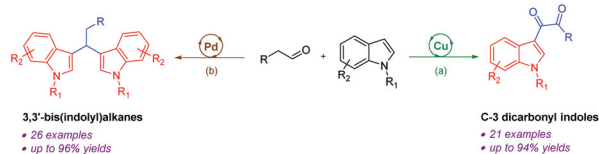
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†Electronic supplementary information (ESI) available: Experimental details, LC-ESI-MS/MS analysis, analytical data and NMR spectra of products. See DOI: 10.1039/c8qo01206g

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Scheme 1 Pd/Cu-Catalyzed chemoselective synthesis of C-3 dicarbonyl indoles and bis(indolyl)alkanes from aldehydes.

thesis employing PdCl_2 as catalyst is also presented for the first time (Scheme 1).

Our study commenced with optimizing the model reaction of phenylacetaldehyde **1a** and *N*-methylindole **2a**. The results of screening different reaction parameters are summarized in Table 1. First, several Cu and Pd salts as catalysts were examined (Table 1, entries 1–6). We were pleased to find that CuBr (10 mmol%) exhibited the best catalytic effect with 74% yield of C-3 dicarbonyl indole product **3aa**, which was obtained when the model reaction was carried out in 3 mL of toluene at 90 °C for 10 h under oxygen atmosphere (Table 1, entry 3). Meanwhile, it is also noteworthy that PdCl_2 exhibited excellent

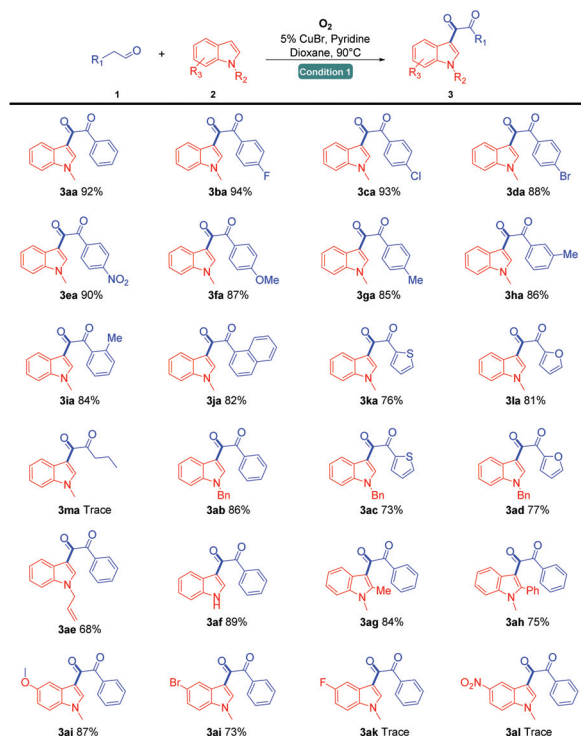
catalytic selectivity to produce bis(indolyl)alkane **4aa** with 76% yield without the generation of **3aa** (Table 1, entry 6), which differed a lot from other catalysts. Encouraged by the above results, various additives were screened to enhance the catalytic effect of CuBr (Table 1, entries 7–10). The results showed that the addition of pyridine could effectively improve the yield of product **3aa** to 86%, which indicated that it may be a useful ligand of CuBr in this reaction (Table 1, entry 10). Next, dioxane was chosen as the best solvent for this reaction, affording 90% yield of product **3aa** (Table 1, entry 12). Further screening experiments afforded the best results to give 92% yield of product **3aa** when 5 mol% CuBr and 1.5 equiv. of 1-methylindole were subjected to the model reaction in the presence of 3 mL of dioxane at 90 °C for 10 h under O_2 atmosphere (Table 1, entry 16), which were considered as the optimal reaction conditions for the synthesis of C-3 dicarbonyl indoles. Subsequently, reaction conditions for the synthesis of bis(indolyl)alkane **4aa** employing PdCl_2 as catalyst were also optimized (Table 1, entries 17–27). To our delight, 83% yield of product **4aa** could be isolated by raising the reaction temperature to 100 °C in 3 mL of toluene for 10 h under O_2 atmosphere (Table 1, entry 19). Some representative solvents were also screened, but no better results were observed when this reaction was conducted in ACN, dioxane or DMF (Table 1, entries 21–23). Subsequently, decreasing the amount of catalyst PdCl_2 to 2 mol% was also favorable for the generation of **4aa** (Table 1, entry 24). Agreeably, when the model reaction employed 2.5 equiv. of **2a** for only 5 h under argon atmosphere, 93% yield of bis(indolyl)alkane product **4aa** was obtained easily (Table 1, entry 27).

With the optimal reaction conditions for the synthesis of dicarbonyl indoles (Condition 1) and bis(indolyl)alkanes (Condition 2) established, a series of substituted aldehydes **1** and indoles **2** were investigated to explore the universality of this method. The results are summarized in Schemes 2 and 3. Generally, both electron-withdrawing and electron-donating (*para*-, *meta*- and *ortho*-) substituted aryl acetaldehydes performed well under the optimized reaction condition 1 and provided the desired dicarbonyl indole products **3aa–3ia** in 84–92% yields (Scheme 2). Furthermore, fused rings and heterocycle-substituted acetaldehydes such as naphthyl-, thienyl- and furyl-substituted acetaldehydes could be transformed into the corresponding target products in 82%, 76% and 81% yields, respectively (Scheme 2, entries **3ja–3la**). In addition, an alkyl aldehyde, valeraldehyde, **1m** was also examined, but no desired dicarbonyl indole product was detected (Scheme 2, entry **3ma**), which indicated that the aromatic aldehydes were indispensable. Subsequently, a variety of substituted indoles were subjected to the optimized reaction condition 1. The results showed that *N*-benzyl and *N*-allyl indoles were both feasible and afforded corresponding products in moderate to good yields (Scheme 2, entries **3ab–3ae**). Notably, *N*-H indole could also be transformed to the corresponding dicarbonyl indole product in high yield (Scheme 2, entry **3af**), which was superior to other reported methods (ref. 6a, d, e and f). Moreover, most of the 2-substituted and the 5-substituted

Table 1 Optimization of the reaction conditions^a

Entry	Catal.	Add.	Sol.	Temp. (°C)	Yield (%) 3aa ^b	Yield (%) 4aa ^b
1	Cu(OAc) ₂	—	Toluene	90	22	6
2	CuCl	—	Toluene	90	67	— ^c
3	CuBr	—	Toluene	90	74	—
4	Pd(OAc) ₂	—	Toluene	90	39	12
5	Pd(TFA) ₂	—	Toluene	90	49	28
6	PdCl ₂	—	Toluene	90	—	76
7	CuBr	AcOH	Toluene	90	65	—
8	CuBr	K ₂ CO ₃	Toluene	90	Trace	—
9	CuBr	Et ₃ N	Toluene	90	47	—
10	CuBr	Pyridine	Toluene	90	86	—
11	CuBr	Pyridine	ACN	90	88	—
12	CuBr	Pyridine	Dioxane	90	90	—
13	CuBr	Pyridine	DMF	90	75	—
14	CuBr (2%)	Pyridine	Dioxane	90	78	—
15	CuBr (5%)	Pyridine	Dioxane	90	91	—
16	CuBr (5%)	Pyridine	Dioxane	90	92 ^d	—
17	PdCl ₂	—	Toluene	30	—	Trace
18	PdCl ₂	—	Toluene	80	—	71
19	PdCl ₂	—	Toluene	100	—	83
20	PdCl ₂	—	Toluene	110	—	81
21	PdCl ₂	—	ACN	100	—	80
22	PdCl ₂	—	Dioxane	100	—	76
23	PdCl ₂	—	DMF	100	—	69
24	PdCl ₂ (2%)	—	Toluene	100	—	83
25	PdCl ₂ (5%)	—	Toluene	100	—	84
26	PdCl ₂ (2%)	—	Toluene	100	—	89 ^e
27	PdCl ₂ (2%)	—	Toluene	100	—	93 ^{e,f,g}

^a Reaction conditions: 1.0 mmol **1a**, 2.0 mmol **2a**, 10% catalyst, 20% additives dissolved in 3 mL solvent stirred at 90 °C for 10 h in a sealed tube with O_2 balloon protection, unless otherwise noted. ^b Isolated yield. ^c No target product was detected. ^d 1.5 mmol **2a**. ^e 2.5 mmol **2a**. ^f Under Ar atmosphere. ^g Reaction time was 5 h.

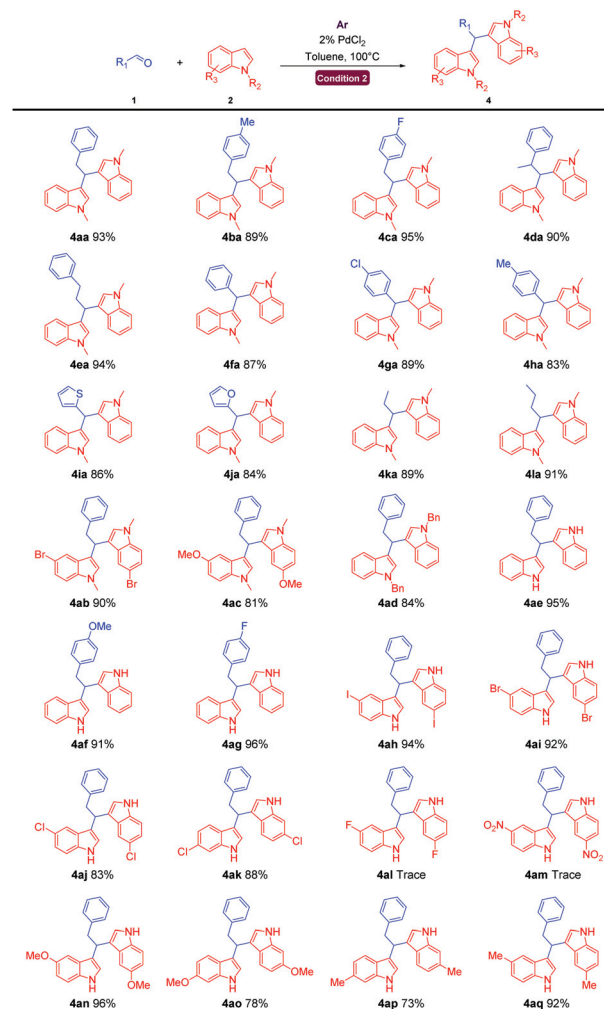


Scheme 2 Cu-Catalyzed synthesis of C-3 dicarbonyl indoles from substituted aldehydes 1, 1.5 mmol indoles 2, 5% CuBr, 0.2 mmol pyridine dissolved in 3 mL 1,4-dioxane stirred at 90 °C for 10 h in a sealed tube with O₂ balloon protection.

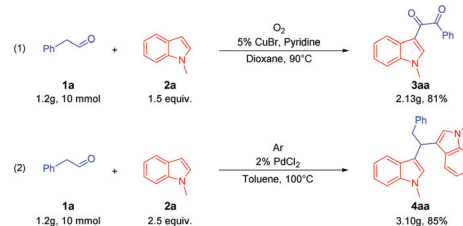
indoles could react smoothly with phenylacetaldehyde **1a** to produce the desired products in 73%–85% yields (Scheme 2, entries **3ag–3aj**) except for indoles with strong electron-withdrawing substituents, probably due to their decreased electron density in the indolyl ring (Scheme 3, entries **3ak** and **3al**).

The extended bisindolylolation of substituted aldehydes **1** and indoles **2** was also explored. As shown in Scheme 3, a variety of aldehydes, including aromatic and aliphatic aldehydes, reacted smoothly with *N*-methylindole **2a** to afford the corresponding bis(indolyl)alkane products in good yields (Scheme 3, entries **4aa–4la**). Then, 5-Br and 5-OMe substituted *N*-methyl indoles were subjected to the optimized reaction condition 2, which afforded the desired bis(indolyl)alkane products in 90% and 81% yields, respectively (Scheme 3, entries **4ab** and **4ac**). Furthermore, *N*-benzyl and *N*-H indole substrates could also survive well in this method (Scheme 3, entries **4ad–4ag**). Most of the electron-rich and electron-deficient (at 5- or 6- position) *N*-H indoles could be transformed into the desired bis(indolyl)alkane products in moderate to good yields (Scheme 3, entries **4ah–4aq**), but 5-F and 5-NO₂ substituted *N*-H indole substrates failed.

In order to further demonstrate the practical application of this methodology, gram-scale reactions were carried out using 1.2 g of substrate **1a** under corresponding optimized reaction conditions. We were pleased that 81% and 85% yields of the desired products **3aa** and **4aa** could be isolated (Scheme 4,



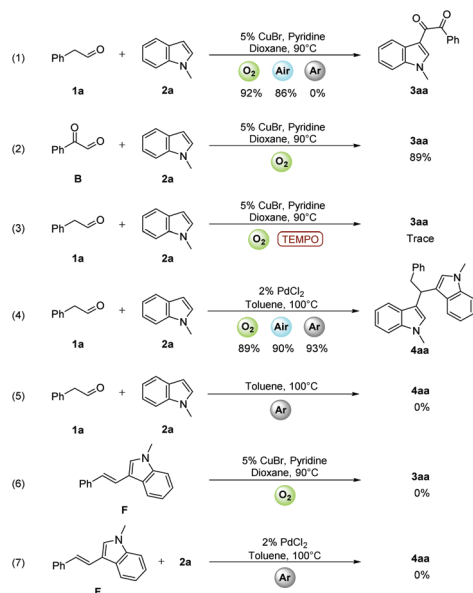
Scheme 3 Pd-Catalyzed synthesis of bis(indolyl)alkanes from substituted aldehydes and indoles. Reaction conditions: 1 mmol aldehydes **1**, 2.5 mmol indoles **2**, 2% PdCl₂ dissolved in 3 mL toluene stirred at 100 °C for 5 h in a sealed tube under Ar condition.



Scheme 4 Gram-scale reaction.

eqn. (1) and (2)), respectively, implying that it is suitable for enlarged scale preparations.

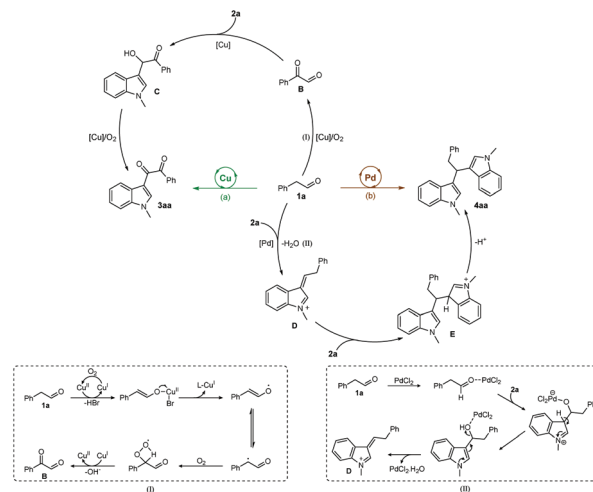
A series of control experiments were conducted to get an insight into the reaction mechanism (Scheme 5). First, the optimized reaction condition 1 was modified to be under a different gas atmosphere. And the results demonstrated that the reactions carried out under O₂ and air atmosphere could



Scheme 5 Control experiments.

proceed smoothly, while no desired product **3aa** was observed under argon atmosphere and the *N*-methylindole was barely consumed, indicating that O₂ may serve as an essential oxidant and as a reactant to promote this oxidative coupling in this transformation (Scheme 5, eqn (1)). In addition, it was speculated that phenyl glyoxal **B** may be the important intermediate during the process of dicarbonyl indole generation, which was verified by control experiment (Scheme 5, eqn (2)). Subsequently, when the radical scavenger 2,2,6,6-tetramethyl piperidine-*N*-oxyl (TEMPO) was added to the optimized reaction condition 1, only trace amounts of desired product **3aa** were detected, which indicated that free radical process was present in the catalytic process (Scheme 5, eqn (3)). Moreover, it was found that the reaction condition 2 of bis(indolyl)alkane synthesis was not air-sensitive (Scheme 5, eqn (4)). No product **4aa** was detected in the absence of catalyst PdCl₂ (Scheme 5, eqn (5)). Additionally, when C3-alkenylated indole **F** was subjected to optimized reaction conditions 1 and 2, it failed to be transformed to the corresponding products **3aa** and **4aa** (Scheme 5, eqn (6) and (7)), which suggests that compound **F** was not the key intermediate in these two reactions.

Based on the abovementioned results and reported literatures, the possible mechanism was proposed in Scheme 6. Initially, in the Cu-catalyzed dicarbonylation reaction (a), phenyl glyoxal **B** as the key intermediate was first generated from the oxidation of phenylacetaldehyde **1a** by a combined effect of CuBr and O₂. Then a Friedel–Crafts type reaction occurred between **B** and **2a** resulting in compound **C**, which further underwent copper-catalyzed aerobic oxidation to produce the target C-3 dicarbonyl product **3aa**. In the Pd-catalyzed bisindolylalkane reaction (b), the condensation between phenylacetaldehyde **1a** and *N*-methylindole **2a** occurred first, affording an excellent Michael-acceptor for nucleophilic enamine **D** with the elimination of a H₂O molecule, where



Scheme 6 Possible mechanism.

PdCl₂ may serve as a Lewis acid to activate the aldehyde substrate. Subsequently, enamine **D** underwent the aza-Michael addition with a second indole molecule to produce the double indolylated intermediate **E**. Further deprotonation of **E** led to the target bis(indolyl)alkane product **4aa**.

Conclusions

In summary, we have presented a novel and efficient Cu/Pd-catalyzed chemoselective synthesis of C-3 dicarbonyl indoles and bis(indolyl)alkanes from aldehydes and indoles, which achieve high selectivity to both two functional C3-substituted indole derivatives. Molecular oxygen serves as an ideal oxidant and as a reactant in the dicarbonylation process, which is very practical and mild. A wide range of dicarbonyl indoles and bis(indolyl)alkanes could be obtained in moderate to good yields, exhibiting good substrate universality. Furthermore, this method has high efficacy in large-scale reactions. Further investigations on the synthetic applications of this methodology are still in progress in our group.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The research has been supported by the National Key Research and Development Program of China (2016YFB0301501); The National Natural Science Foundation of China (Grant No. 21776130); The Jiangsu National Synergetic Innovation Center for Advanced Bio-Manufacture (No. X1821 & X1802); Top-notch Academic Programs Project of Jiangsu Higher Education Institutions (TAPP); and Postgraduate Research and Practice Innovation Program of Jiangsu Province.

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