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Palladium-catalyzed mono- and double-carbonylation of indoles with amines controllably leading to amides and α-ketoamides†

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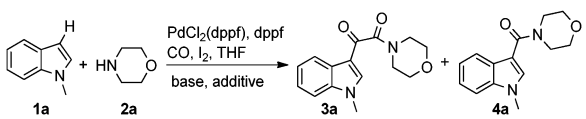
A novel and efficient double-carbonylation of indoles with primary or secondary amines to yield indole-3-α-ketoamides has been developed and bioactive molecules could be one-pot synthesized using the current methodology, which could also be selectively switched to mono-carbonylation to afford indole-3-amides only by a slight modification of reaction conditions.

The amides and α-ketoamides are important targets in organic synthesis because of their ability to serve as building blocks in a wide variety of functional group transformations.[1] They have also been found as a substructure in numerous bioactive natural products and pharmaceutically interesting compounds.[2] Therefore, the development of methods that can construct these two classes of nitrogen containing compounds in an efficient and regioselective manner from readily accessible substrates continues to be a hot research topic. Recently, the Cu-catalyzed aerobic oxidative coupling of terminal alkyne, aryl acetaldehyde, α-carbonyl aldehyde or aryl methylketone with amines to yield α-ketoamides has gained great achievements, however, heteroaryl compounds are much less applicable to these methods.[3]

Alternatively, the direct carbonylation of aryl C–H bonds with different nucleophiles could be a more ideal option to introduce one or two carbonyl moieties onto the resultant compounds including (α-keto)amides,[4] compared with the traditional carbonylation of aryl halides.[5,6] In 2004, Orito and coworkers reported the first Pd-catalyzed intra-carbonylation of aryl C–H bonds with amines to give benzolactams; later, Chatani and Rovis, respectively, disclosed their Ru- or Rh-catalyzed oxidative intra-carbonylation of aromatic amides to form phthalimides.[7] However, to the best of our knowledge, direct inter-carbonylation of (hetero)aryl compounds with amines leading to amides and α-ketoamides has not been established. Furthermore, direct functionalization of indoles through C–C and C–X (X = Si, B, P or O) bond formation has attracted significant attention in the past few years due to the broad applications of functionalized indole derivatives.[8] As the continuous effort on the direct functionalization of heterocycles,[9] we herein present an efficient Pd-catalyzed direct inter-carbonylation of indoles with amines, which could controllably and regioselectively yield heteroaryl α-ketoamides and amides *via* double- and mono-carbonylation by a slight change of the reaction conditions.

We initiated the study by looking for a direct double carbonylation methodology to synthesize indole α-ketoamides. Unlike the reported carbonylation of aryl C–H bonds where oxidants were used to regenerate the metal catalyst; I_2 was herein selected to oxidatively functionalize indole C(3)–H,[10] giving an iodo-3-indole intermediate and followed by further carbonylation to produce the desired product. After extensive screening of reaction parameters in the model carbonylation of *N*-methylindole **1a** and morpholine **2a** (for experimental details, see ESI,† Table S1), the optimal reaction conditions were identified as shown in Table 1, and the target molecule indole-3-α-ketoamide **3a** was obtained in high yield (81%), with only trace amounts (<1%) of monocarbonylated **4a** detected (entry 1). A certain mixture of inorganic and organic bases is vital to synthesize **3a** efficiently. Only Cs_2CO_3 or replacing DBU with DABCO

Table 1 Optimization of reaction conditions



Entry	Variation from the "standard conditions"[a]	Yield[b] (%) 3a	4a
1	None	81	Trace
2	Without DBU	60	10
3	DABCO, instead of DBU	73	12
4	DMAP, instead of DBU	42	15
5	Without CuI/LiCl	74	16
6	$PdCl_2$, instead of $PdCl_2$(dppf)/dppf	Trace	Trace
7	$PdCl_2$(dppp)/dppp, instead of $PdCl_2$(dppf)/dppf	59	Trace
8	$PdCl_2(PPh_3)/PPh_3$, instead of $PdCl_2$(dppf)/dppf	64	Trace
9	1,4-Dioxane, instead of THF	48	5
10	Acetonitrile, instead of THF	Trace	Trace

[a] Standard conditions: **1a** (0.5 mmol), **2a** (2.0 mmol), Cs_2CO_3 (0.25 mmol), I_2 (0.6 mmol), DBU (1.5 mmol), $PdCl_2$(dppf) (5 mol%), dppf (10 mol%), CuI (0.1 mmol), LiCl (0.2 mmol), THF (10 mL), CO (4.0 MPa), 60 °C, 36 h. [b] Isolated yield.

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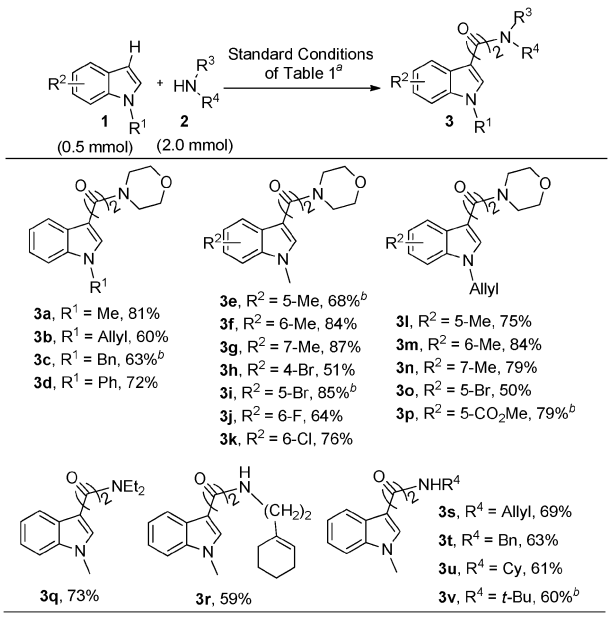
or DMAP would dramatically reduce the selectivity of **3a** (entries 2–4). The absence of CuI/LiCl resulted in a lower yield of **3a** (74%) and the yield of **4a** could be as high as 16% (entry 5). The phosphine ligand of the palladium complex also plays an important role, $PdCl_2$ alone gave no reaction, and the Pd-complexes with other mono- or bi-dentate phosphines led to an obvious lower yield of **3a** (entries 6–8). Among solvents screened, THF provided the highest reactivity (entries 9 and 10). As observed in the previously reported literature, higher CO pressure could obviously facilitate the present double carbonylation to form α-ketoamides,[11] and it was also assumed that the addition of CuI/LiCl could promote the double CO insertion. Furthermore, presence or absence of the organic base could also affect the selectivity to **3** or **4**.

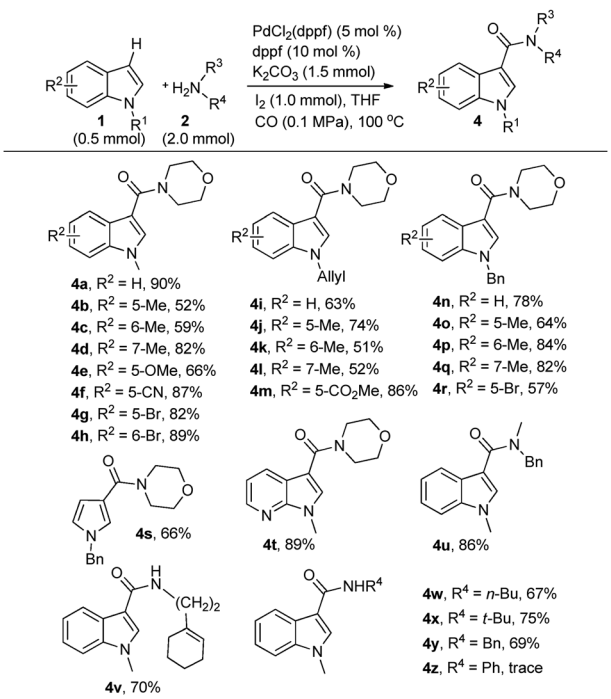
With the optimized conditions in hand, we then turned to explore the substrate scope of the double-carbonylation of indoles with amines. As shown in Scheme 1, carbonylation of indoles with different *N*-protective groups proceeded smoothly, giving moderate to good yields of indole-3-α-ketoamides (**3a–3d**), and among them, *N*-methyl indole was proved to be the most efficient. Subsequently, the influence of substituents on the benzene ring was examined. Generally, indoles bearing electron-donating groups (**3e–3g**) showed better reactivity when compared with those having halide moieties (**3h–3k**) except for **3i**, which could be obtained in 85% yield after extending the reaction time. Additionally, it is worth mentioning that these halide substituents could be well preserved during the reaction, thus affording the potential functionalized position for further transformation. The substituent effect of *N*-allyl indole was also investigated (**3l–3p**), and a similar result confirmed that the electron-giving groups are more favorable for the double carbonylation (**3l–3n**), and the yield of **3p** with an electron-withdrawing 5-CO_2Me group could be increased from 57% to 79% when prolonging the reaction duration. Unfortunately, *N*-H indole (R^1 = H) did not give the desired carbonylation product.

Compared with secondary amines, the double carbonylation of aromatic halides with primary amines to produce α-ketoamides has been less established.[6c] Using *N*-methyl indole as a heterocyclic substrate, the reactivities of different amines were examined, as expected, secondary amines gave better results (**3a** and **3q**). To our delight, primary amines such as allylamine and benzylamine could be tolerated in the current double carbonylation as well, generating desired products in moderate yields (**3r–3t**), and a representative structure of **3t** was confirmed by the X-ray single crystal structure analysis (CCDC 895174, ESI†). Moreover, double carbonylation of **1a** with primary amines bearing a large steric hindrance group also proceeded smoothly, affording the desired products in about 60% yield (**3u** and **3v**).

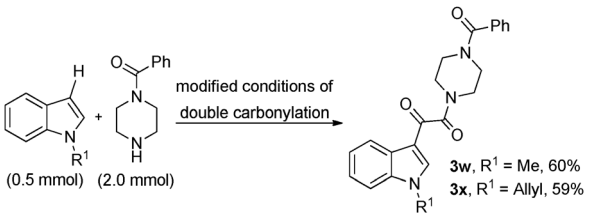
From the viewpoint of synthetic chemistry, to achieve catalyst- or condition-controlled diversity-oriented synthesis from the same substrates is a very fascinating theme. Interestingly, the above Pd-catalyzed double-carbonylation catalyst system could be readily switched to catalyze the mono-carbonylation to produce indole-3-amides through slight modification of the reaction conditions (for details, see ESI,† Table S2). As shown in Scheme 2, *N*-methyl indole (**1a**) could be efficiently carbonylated with morpholine (**2a**) in the presence of the $PdCl_2$(dppf)/I_2/K_2CO_3 catalyst system under 1 atm of CO at 100 °C in THF, affording the desired indole-3-amide (**4a**) in 90% yield. Different substituents on the benzene ring of **1a** could be readily tolerated (**4b–4h**), unlike the substituent effect shown in the double-carbonylation, the electron-pulling groups (**4f–4h**) seemed to facilitate the reaction, giving better results (82–89%) than those with electron-pushing groups (**4b–4e**). Again, when employing *N*-allyl indole derivatives, similar consequences to those of *N*-methyl indoles could be obtained, and the expected amides (**4i–4m**) could be selectively carbonylated in good to excellent yields (51–86%). In contrast, *N*-benzyl indoles with electron-donating groups behaved much better (**4o–4q**) than those with electron-attracting groups (**4r**).



Scheme 1 The substrate scope of indole-3-α-ketoamides. [a] The standard conditions of Table 1. [b] Reaction time was prolonged to 48 hours.



Scheme 2 The substrate scope of indole-3-amides.



Scheme 3 The preparation of bioactive compounds. Reaction conditions: $PdCl_2(PhCN)_2$ (5 mol%), Xantphos (10 mol%) and other conditions are the same as the standard conditions given in Table 1.

Interestingly, *N*-methyl-7-azaindole and *N*-benzyl pyrrole could also undergo the reaction efficiently (**4s** and **4t**).

As for the investigation of the amines, both primary and secondary amines could be the appropriate partners (**4u–4y**), and stronger electron-donating *N*-methylbenzylamine could generate the target product **4u** with a yield as high as 86%. Surprisingly, *t*-$BuNH_2$ performed slightly better than *n*-$BuNH_2$ (**4w** and **4x**), indicating that the hindrance of amines may not be the key factor for the monocarbonylation, while the nucleophilicity played a more important role, and that hypothesis could possibly be further clarified when only a trace amount of product **4z** was achieved. To further verify the structure of indole-3-amide, the single crystal structure of **4v** was analyzed (CCDC 895173, ESI†).

Indole-3-ketoamide has been proved to be the nucleus skeleton of a large number of molecules with biological activity such as **3w** (Scheme 3), which belongs to a group of HIV-1 inhibitors targeting the glycoprotein gp120 situated in the viral envelope.[2] To further extend the practical application of the present carbonylation method, we focused our efforts to synthesize compounds **3w** and **3x** from indoles and *N*-benzoylpiperazine. Unfortunately, using the above double carbonylation procedure, only 29% yield of **3x** was obtained, thus reoptimization of the Pd-catalyst is necessary to obtain high yield of the pharmaceutically interesting product. We finally found that 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) could be a more favorable assisting ligand with the presence of $PdCl_2(PhCN)_2$ to replace $PdCl_2$(dppf), and moderate yields of **3w** and **3x** could be obtained (for experimental details, see ESI†). Thus, this methodology would be of importance to the facile synthesis of these bioactive HIV-1 inhibitors from readily available starting substrates.

In conclusion, we have developed an efficient carbonylative synthesis of indole-3-α-ketoamides and indole-3-amides with good tolerance of both secondary and primary amines as nucleophiles. Complete control of product selectivity in the carbonylation of unfunctionalized (hetero)aromatics was proved to be possible through slight modification of reaction conditions. Further investigations to understand the reaction mechanism and the synthetic applications to other heteroaromatic C–H bonds are ongoing in our laboratory.

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