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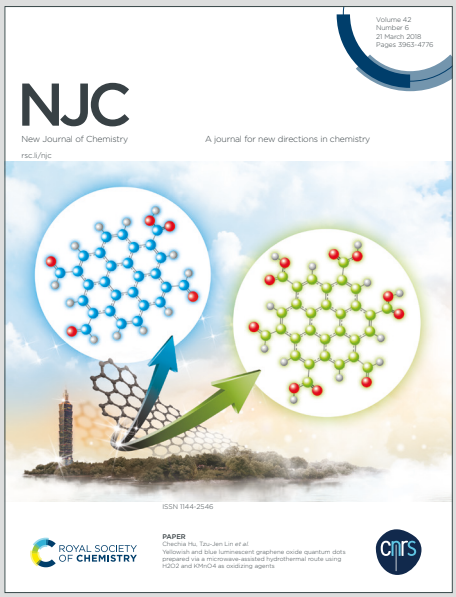

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Palladium-Catalyzed Sequential Acylation/Annulation of Indoles with Acyl Chlorides Using Primary Amine as the Directing Group

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Abstract An attractive and convenient strategy for the direct acylation/annulation of indoles has been developed using Pd(0) as an efficient catalyst. The main feature of this protocol is the use of acyl chlorides as the acylating agents with the primary amine as the directing group. A variety of indolo[1,2-*a*]quinoxalines were readily obtained in reasonable efficiency and satisfactory yields with good functional group tolerance. Based on control experiments, a tentative catalytic mechanism was proposed.

Keywords: palladium-catalyzed; acyl chlorides; acylation/annulation; directing group.

1. Introduction

The reliable and convenient construction of heterocyclic compounds has been a focus of synthetic chemistry because heterocyclic molecules are very significant and widely present in functional materials, pharmaceutical agents, and numerous natural products.[1-7] During the past few decades, transition-metal-catalyzed C-H bond functionalization/annulation under the assistance of the directing group has emerged as an efficient and succinct tool for the synthesis of various heterocyclic compounds.[8-12] For instance, in 2017, Glorius's group reported a facile Mn-catalyzed C(sp^2)-H annulation of imines.[13] In the same year, a study on ruthenium-catalyzed [3+3] annulation of anilines with allyl alcohols appeared for accessing quinolone.[14] Very recently, Song described the cobalt-catalyzed C(sp^2)-H activation/annulations of aromatics with alkynes using *N*,*O*-bidentate group as directing group.[15] In addition, various directing groups have been developed within recent years, such as primary

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amine, aminoquinoline, amino acids, carboxyl, and hydroxyl.[16-21] Among them, primary amine-assisted cyclization of substrates are particularly attractive due to their regioselectivity and practicability.[22,23] Despite such great achievements, investigation on the use of primary amine as directing group to build quinoxalines is very limited.

In addition, as the simple and readily available building blocks, acyl chlorides have received extensive attention in recent years,[24-32] and its participation as an acyl source is mainly accomplished by classic Friedel-Crafts acylation reactions.[33-36] However, the classic Friedel-Crafts acylation reactions generally results in a mixture of products with poor *ortho*/*para* regioselectivity, and usually suffer from narrow substrate scope and poor functional group tolerance.[37,38] The use of stoichiometric Lewis acids is also a deficiency of this type of reaction. In recent years, palladium-catalyzed directing groups assisted acylation of acyl chlorides are particularly attractive due to their remarkable regioselectivity and practicability. In 2019, a Pd-catalyzed acylation of acyl chlorides was elegantly developed by Wu and co-workers (Scheme 1, a).[39] Inspired by this excellent work and as part of our continuing interests in straightforward transition-metal-catalyzed C-H activation,[40,41] herein, we report the first palladium-catalyzed sequential acylation/annulation of indoles using acyl chlorides as the acylating agents with primary amine as the directing group (Scheme 1, b).

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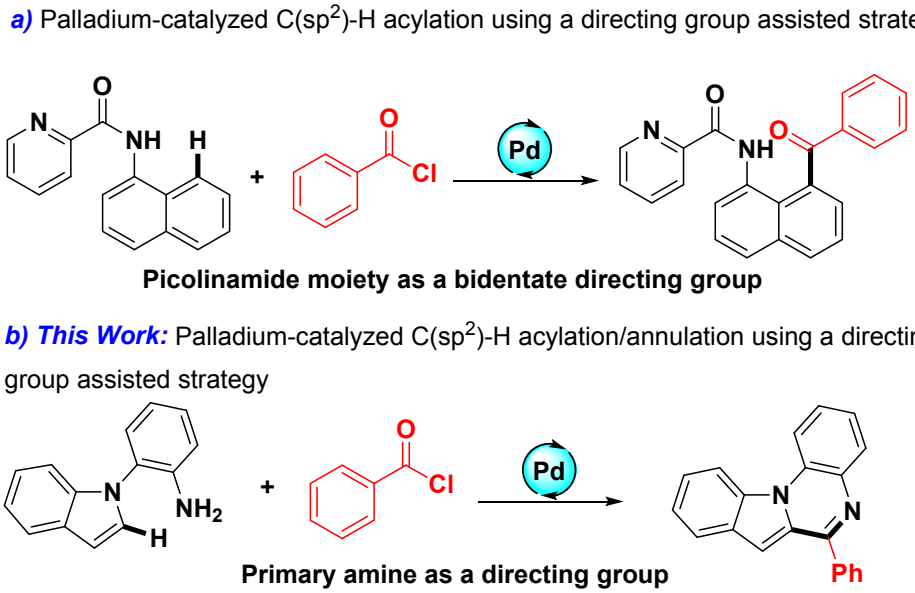
Scheme 1. Coupling Reaction of Acyl Chloride by Using a Directing Group Assisted Strategy.



2. Experimental section

2-(1*H*-indol-1-yl)anilines **1** (0.1 mmol), acyl chloride **2** (0.1 mmol), $Pd(dba)_2$ (10 mol%), $AgSbF_6$ (25 mol%), CsOPiv (0.2 mmol) and anhydrous toluene/1,4-dioxane = 1:1 (1 mL) were sealed in a Schlenk tube under Ar atmosphere. The mixture was then stirred at 130 °C (oil bath temperature) for 24 h. After the condensation was completed (monitored by TLC), the resulting mixture was cooled to room temperature and extracted with ethyl acetate, dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo. The desired products **3** were obtained in the corresponding yields after purified by column chromatography on silica gel with mixture of petroleum ether and ethyl acetate.

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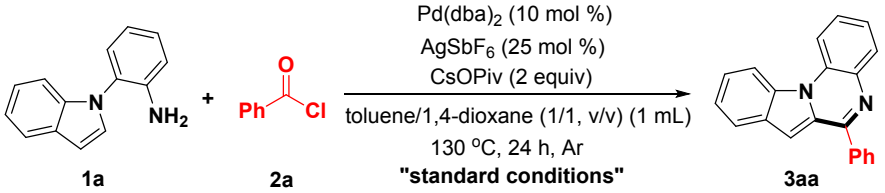
3. Results and discussion

Table 1. Reaction Development[a]



1a 2a 3aa

entry	variations from standard conditions	yield[b] (%)
1	none	**76**
2	$Pd(OAc)_2$ instead of $Pd(dba)_2$	36
3	$Pd(PPh_3)_4$ instead of $Pd(dba)_2$	48
4	$Pd(TFA)_2$ instead of $Pd(dba)_2$	42
5	$PdCl_2$ instead of $Pd(dba)_2$	26
6	AgOAc instead of $AgSbF_6$	47
7	Ag_2CO_3 instead of $AgSbF_6$	50
8	$K_2S_2O_8$ instead of $AgSbF_6$	15
9	$Cu(OAc)_2$ instead of $AgSbF_6$	trace
10	NaOTf instead of CsOPiv	36
11	K_3PO_4 instead of CsOPiv	37
12	NaOH instead of CsOPiv	trace
13	without $Pd(dba)_2$	n.d.
14	without CsOPiv	trace
15	DMF instead of toluene/1,4-dioxane	n.d.
16	CH_3CN instead of toluene/1,4-dioxane	trace

[a]Reaction Conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), catalyst (10 mol %), additive (25 mol %), base (0.2 mmol) and anhydrous toluene/1,4-dioxane (1/1, v/v) (1.0 mL) were sealed in a 25 mL Schlenk tube at 130 °C for 24 h under Ar; [b] Isolated yields; n.d. = not detected.

Initially, we chose 2-(1*H*-indol-1-yl)aniline (**1a**) as the model substrate and benzoyl chloride (**2a**) as the acylating agent to identify the optimal reaction conditions, and significant results are summarized in Table 1. During the screening of several reaction conditions, including additive, catalysts, bases, and solvents, the expected acylation/annulation proceeded smoothly to give the corresponding product **3aa** in

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76% isolated yield under the following reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $Pd(dba)_2$ (10 mol%), $AgSbF_6$ (25 mol %) and CsOPiv (0.2 mmol) were stirred in 1 mL of solvent (toluene/1,4-dioxane =1:1) for 24 h at 130 °C under an atmosphere of argon (Table 1, entry 1). Notably, the isolated yield of the reaction was highly dependent on the palladium(II) generated in situ, and the optimal result was observed with $Pd(dba)_2$ (Table 1, entries 2-5). $Pd(dba)_2$ supported by other corresponding additives were inferior (Table 1, entries 6-9). Bases, such as NaOTf and K_3PO4, showed a moderate reactivity, whereas NaOH was ineffective (Table 1, entries 10-12). Control experiments suggested that both $Pd(dba)_2$ and CsOPiv were vital for this acylation/annulation reaction (Table 1, entries 13 and 14). Finally, the efficiency of this transformation could not be improved by changing the reaction solvent (Table 1, entries 15 and 16, see Supporting Information for details).

With the optimal reaction condition in hand, the scope of the transformation with respect to the acyl chlorides was also observed (Table 2). Generally, this reaction afforded the corresponding products in modest to excellent yield and with unique regioselectivity. The acyl chlorides with *para*-substituted electron-donating groups gave the desired indolo[1,2-*a*]quinoxalines **3ba-3ea** in 69-80% yields. In addition, acyl chlorides with halogen-substituted worked well and obtained expected products **3fa** and **3ga** in moderate yields, which could be used for further transformation via cross coupling reactions. Other functional groups, such as *meta*-F, *meta*-Br and *meta*-OCH_3 can also be compatible with the reaction system, providing the corresponding indolo[1,2-*a*]quinoxalines **3ha-3ja** in good yields. The reaction of **2k**,

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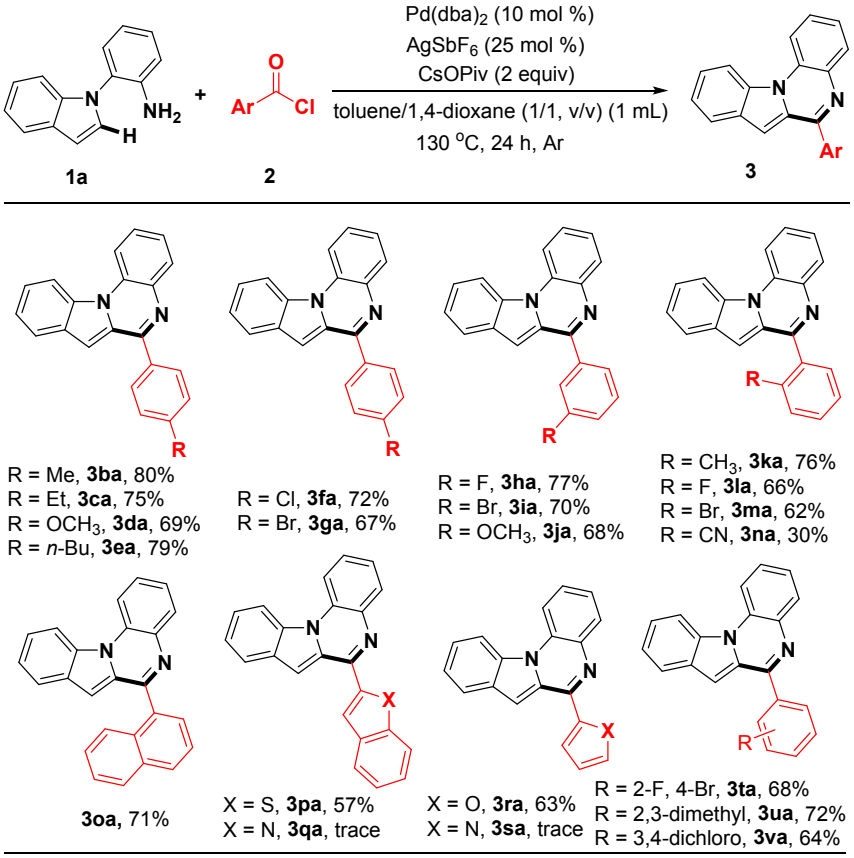
2l, **2m** and **2n** gave the desired products **3ka**, **3la**, **3ma** and **3na** respectively, even though the reaction site is sterically hindered. When the 1-naphthoyl chloride, benzo[*b*]thiophene-2-carbonyl chloride, and furan-2-carbonyl chloride were used as the substrates, the desired products **3oa**, **3pa**, **3ra** were obtained in yields of 57-71%. Unfortunately, nitrogen-containing acyl chlorides are not compatible with the reaction system (**3qa**, **3sa**). Finally, double-substituted acyl chlorides also gave the highly functional products **3ta-3va** in reasonable yield.

Table 2. Synthesis of Indolo[1,2-*a*]quinoxalines Derivatives from a Range of Acyl Chlorides and 2-(1*H*-indol-1-yl)aniline[a,b]



[a]A mixture of **1a** (0.1 mmol), **2** (0.2 mmol), $Pd(dba)_2$ (10 mol %), $AgSbF_6$ (25 mol%), CsOPiv (0.2 mmol), and anhydrous toluene/1,4-dioxane (1/1, v/v) (1.0 mL) were

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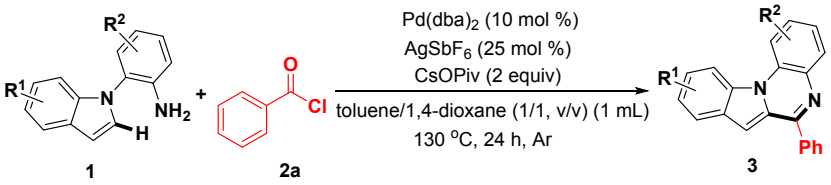
sealed in a 25 mL Schlenk tube at 130 °C for 24 h under Ar; [b]Yields refer to isolated yield.

Table 3. Synthesis of Indolo[1,2-*a*]quinoxalines Derivatives from a Range of Indoles and Benzoyl Chloride[a,b]



1 2a 3

Entry	R^1	R^2	Product	Yield[b] (%)
1	3-CH_3	H	**3ab**	82%
2	4-CH_3	H	**3ac**	84%
3	4-OCH_3	H	**3ad**	72%
4	4-benzyloxy	H	**3ae**	76%
5	5-OCH_3	H	**3af**	71%
6	6-OCH_3	H	**3ag**	67%
7	4,6-di-CH_3	H	**3ah**	80%
8	4-F	H	**3ai**	70%
9	4-Cl	H	**3aj**	78%
10	5-F	H	**3ak**	67%
11	6-F	H	**3al**	65%
12	5-CN	H	**3am**	45%
13	H	4-CH_3	**3an**	85%
14	H	4-Cl	**3ao**	76%
15	H	5-Cl	**3ap**	73%
16	H	4-F	**3aq**	69%
17	H	4-Cl-6-F	**3ar**	56%
18	H	4-CF_3	**3as**	38%

[a]A mixture of **1** (0.1 mmol), **2a** (0.2 mmol), $Pd(dba)_2$ (10 mol %), $AgSbF_6$ (25 mol %), CsOPiv (0.2 mmol), and anhydrous toluene/1,4-dioxane (1/1, v/v) (1.0 mL) were sealed in a 25 mL Schlenk tube at 130 °C for 24 h under Ar; [b]Yields refer to isolated yield.

Subsequently, the scope of indoles were investigated under the optimal reaction conditions. As the data of Table 3 shown, indole rings substituted with 3- Me, 4-Me,

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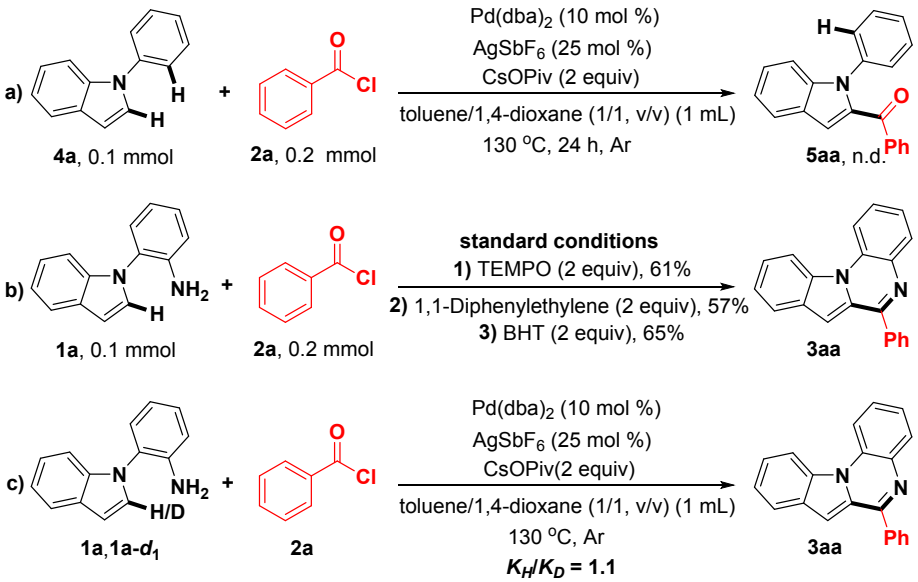
4-OCH_3, 4-benzyloxy, 5-OCH_3, and 6-OCH_3 groups successfully participated in this transformation to give the corresponding products in moderate to good yields (**3ab-3ag**). Further, 2-(4,6-dimethyl-1*H*-indol-1-yl)aniline reacted well to afford the expected product (**3ah**) with excellent yield. Noticeably, the halogen atoms were compatible with this reaction system (**3ai-3al**). In addition, 1-(2-aminophenyl)-1*H*-indole-5-carbonitrile was also investigated, and to our delight, the target product **3am** was synthesized, albeit in relatively lower yield (45%). Remarkably, 2-(1*H*-indol-1-yl)-4-methylaniline was a suitable substrate, affording the corresponding product **3an** in 85% yield. The indoles **1o-1q** bearing a halogen (F, Cl) at aniline rings were compatible for the transformation, providing the expected products **3ao-3aq** in 76%, 73%, and 69% yields, respectively. In addition, the dihalogen-substituted starting materials could be functionalized under standard reaction condition. It should be noted that **1s** containing a CF_3 group was suitable, albeit resulting in obviously decreased reactivity (38%).

Scheme 2 Control experiments



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In order to elucidate the reaction mechanism, a few preliminary control experiments were carried out (Scheme 2). First, the designed substrates **4a** was conducted under the standard reaction conditions, and no corresponding product **5aa** was observed (Scheme 2, a), suggesting that the primary amine as a directing group should be essential in this reaction. When 2.0 equiv. of TEMPO, 1,1-diphenylethylene, and BHT were added under the optimal reaction conditions, the target product 6-phenylindolo[1,2-*a*]quinoxaline (**3aa**) was obtained in 61%, 57% and 65% yields, respectively (Scheme 2, b). These results indicate that a radical process is not involved in this transformation.[42-44] Furthermore, by employing deuterium-labeled compound **1a-*d*$_1$** and **1a** as substrates, the experiment for calculating the KIE (kinetic isotope effect) value was performed (see the Supporting Information),[45,46] and the result (KIE = 1.1) may suggest that the C(sp^2)-H bond cleavage of 2-(1*H*-indol-1-yl)aniline (**1**a) should not involved in the rate-limiting step (Scheme 2, c).

Based on our control experiments and previous literature reports,[47-49] a possible catalytic cycle is outlined in Fig S2. We proposed that the acylation/annulation process may proceed a Pd(II)/Pd(IV) catalytic cycle. First, the treatment of Pd(dba)$_2$ with silver salts gives rise to the activated Pd(II) catalyst, which undergoes C(sp^2)-H functionalization with 2-(1*H*-indol-1-yl)aniline (**1a**) to obtain a six-membered palladacyclic intermediate **B**.[50-53] Subsequently, the oxidative addition of benzoyl chloride (**2a**) to intermediate **B** gives the probable Pd(IV) intermediate **C**, which undergoes reductive elimination to obtain the acylating product **D** along with

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regeneration of the activated Pd(II) species. Simultaneously, the final product **3aa** was obtained by an intramolecular dehydration reaction.

4. Conclusions

In summary, we have reported a unique, directing group protocol for a one-pot synthesis of functionalized indolo[1,2-*a*]quinoxalines from acyl chloride and indoles, utilizing a palladium-catalyzed C(sp^2)-H acylation method as the crucial step. This protocol exhibits a good functional group tolerance, high regioselectivity, and convenient operation. Dramatically, simple and readily available acyl chlorides and high step economy make this strategy particularly attractive. In addition, we believe that these transformation proceed via a classical Pd(II)/Pd(IV) catalytic cycle. Further studies on the construction of heterocyclic compounds via C-H activation as well as acylation/annulation are underway in our laboratory.

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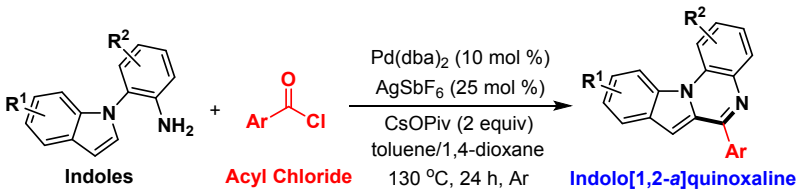

An efficient, palladium(II)-catalyzed, C(sp^2)-H acylation/annulation of indoles with acyl chlorides for the synthesis of substituted indolo[1,2-*a*]quinazolines is reported.