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Palladium-Catalyzed Direct and Specific C-7 Acylation of Indolines with 1,2-Diketones

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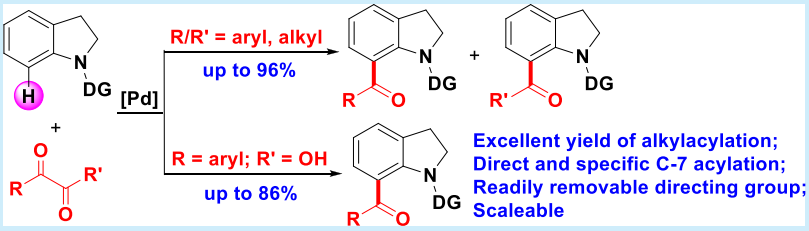

ABSTRACT: The indole scaffold is a ubiquitous and useful substructure, and extensive investigations have been conducted to construct the indole framework and/or realize indole modification. Nevertheless, the direct selective functionalization on the benzenoid core must overcome the high activity of the C-3 position and still remains highly challenging. Herein, a palladium-catalyzed direct and specific C-7 acylation of indolines in the presence of an easily removed directing group was developed. This strategy usually is considered as a practical strategy for the preparation of acylated indoles because indoline can be easily converted to indole under oxidation conditions. In particular, our strategy greatly improved the alkacylation yield of indolines for which only an unsatisfactory yield could be achieved in the previous studies. Furthermore, the reaction can be scaled up to gram level in the standard reaction conditions with a much lower palladium loading (1 mol %).

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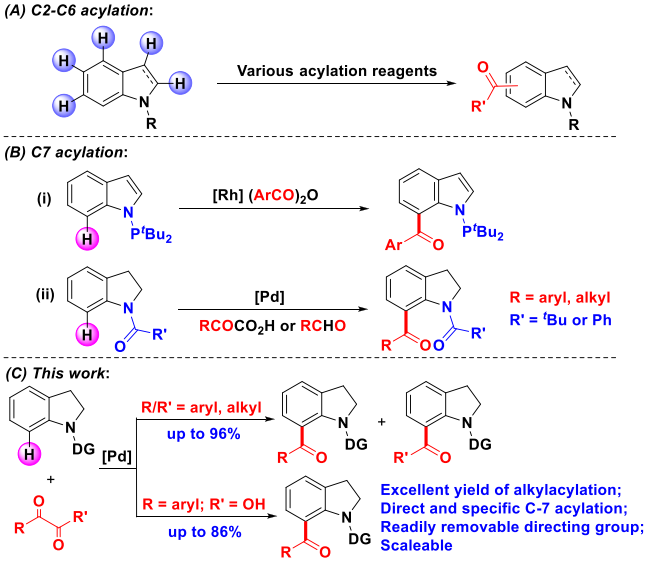
The indole scaffold is one of the most privileged substructures due to its prevalence in bioactive molecules such as commercial drugs and pesticides.[1] Thus, the modification and functionalization of indole derivatives have attracted intense attention, leading to the development of many modification and functionalization strategies among which the metal-catalyzed direct C−H bond functionalization is considered to be the most effective approach.[2] Due to the presence of six independent reaction sites in the indole core, regioselective functionalization is particularly important, and especially, regioselective functionalization on the less reactive benzenoid core rather than on the highly reactive pyrrole ring is still a significant challenge for organic synthesis.[3] To address this issue, various synthesis protocols have been explored via metal-catalyzed strategies involving alkylation,[4] alkenylation,[5] alkynylation,[6] arylation,[7] cyanation,[8] amination,[9] amidation,[10] chalcogenation,[11] borylation,[12] acyloxylation,[13] and sulfonylation.[14]

Due to the prevalence of acylated indole frameworks in bioactive molecules,[15] the acylation reaction is one of the most investigated reactions in indole chemistry.[16] Generally, the acylation reaction occurs more easily at the more electron-rich pyrrole-type ring via Friedel−Crafts reactions[17] and Vilsmeier−Haack reactions.[18] Meanwhile, with the development of synthesis techniques, and particularly with the development of metal-catalyzed strategies, indole acylations at the C-4,[16b,19] C-5,[20] and C-6[21] positions have also been well developed (Scheme 1A). However, general strategies for selective direct

Scheme 1. Direct C7-Acylation of Indoles/Indolines



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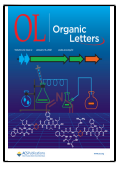

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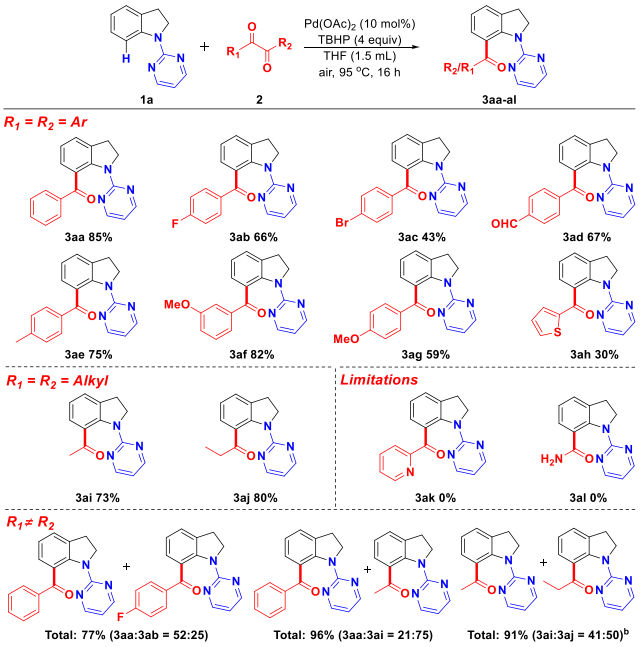
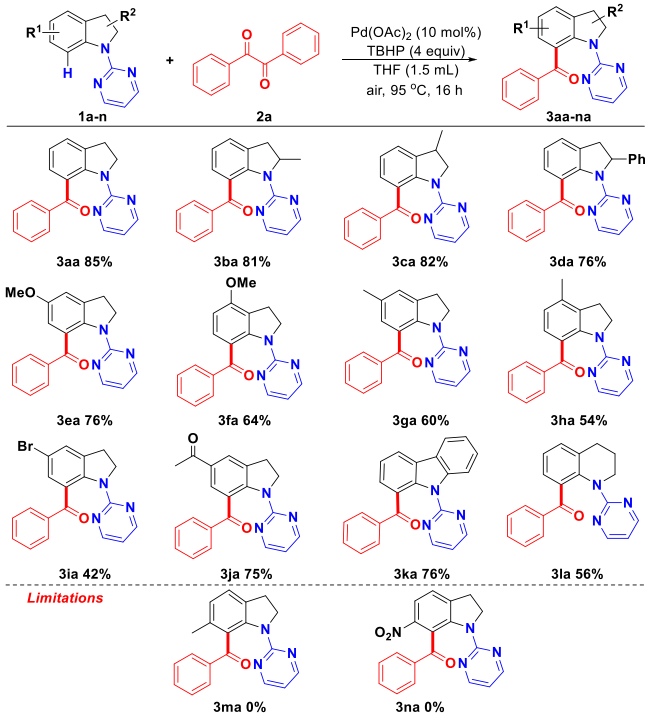
Scheme 2. Scope and Limitations of 1,2-Diketones[a]



[a]Conditions: **1a** (0.1 mmol), **2** (0.15 mmol), $Pd(OAc)_2$ (10 mol %), TBHP (4.0 equiv) in THF (1.5 mL) at 95 °C, 16 h, under air. Isolated yield was given. [b]t = 24 h.

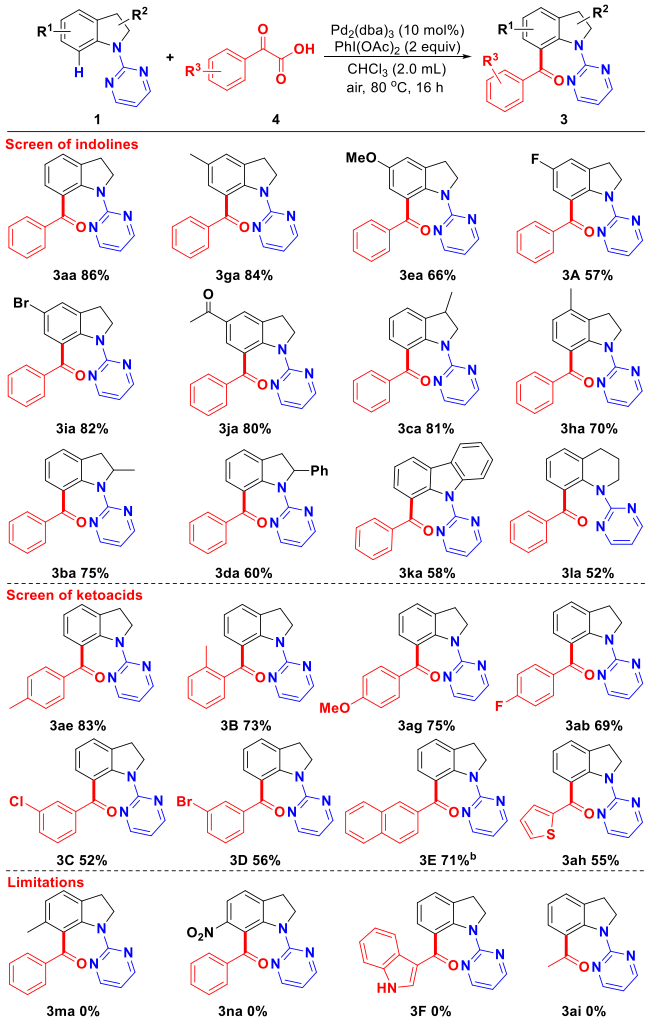
Scheme 3. Scope and Limitations of *N*-Pyrimidinyl Indolines[a]



[a]Conditions: **1** (0.1 mmol), **2a** (0.15 mmol), $Pd(OAc)_2$ (10 mol %), TBHP (4.0 equiv) in THF (1.5 mL) at 95 °C, 16 h, under air. Isolated yield was given.

catalytic C−H acylation at the C-7 position of indoles are still scarce (Scheme 1B). Recently, Shi's group developed a rhodium-catalyzed P(III)-directed indole C7-functionalization, and using aromatic carboxylic anhydrides as reagents, the

Scheme 4. Scope and Limitations of Acylation Reaction Using α-Keto Acids as the Acyl Source[a]



[a]Conditions: **1** (0.1 mmol), **4** (0.25 mmol), $Pd_2(dba)_3$ (10 mol %), $PhI(OAc)_2$ (2.0 equiv) in $CHCl_3$ (2.0 mL) at 80 °C, 16 h, under air. Isolated yield was given. [b]t = 24 h.

corresponding aromatic ketones were obtained in 40−61% yields (Scheme 1B, i).[16a] The acylation of indolines has also been considered a practical strategy for the synthesis of acylated indoles because acylated indolines can be easily converted to acylated indoles via the oxidation reaction. In 2014, Kim and co-workers reported the palladium-catalyzed direct acylation at the C-7 position of indolines using either α-keto acids[16c] or aldehydes[16d] as the acyl source (Scheme 1B). When aryl ketoacids/aldehydes were used as the acyl source, moderate to good yields were obtained, while when alkyl ketoacids/aldehyde were used as the reagents, poor yields were obtained in most cases. Inspired by these excellent studies, we herein report a palladium-catalyzed direct and specific C-7 acylation of indolines with *o*-dicarbonyl compounds as the acylation reagent via C−H activation (Scheme 1C). Significantly, when dialkyl substituted 1,2-diketones were used as the acyl source, good to excellent yields were obtained, overcoming the shortcomings of the previously reported synthetic methods.

Our investigation commenced with the coupling of 1-(pyrimidin-2-yl)indoline (**1a**) and benzil (**2a**) in the presence

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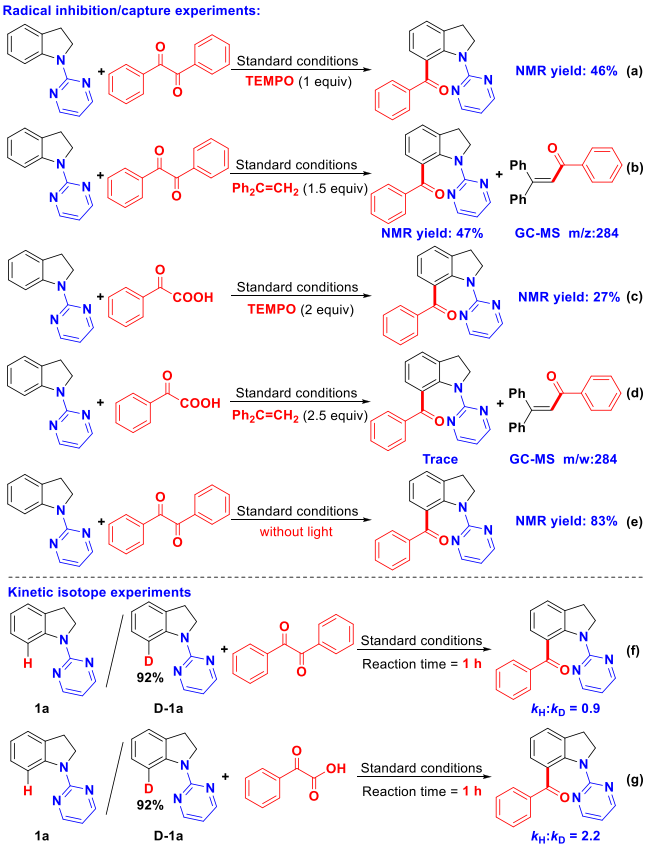
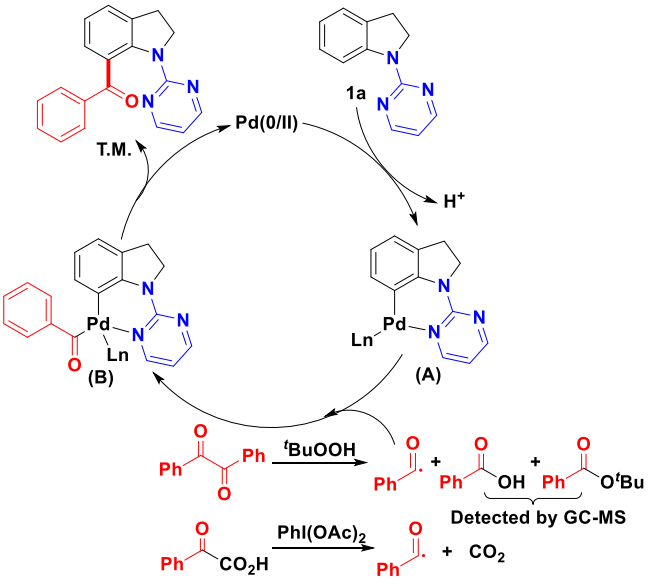
Scheme 5. Control Experiments

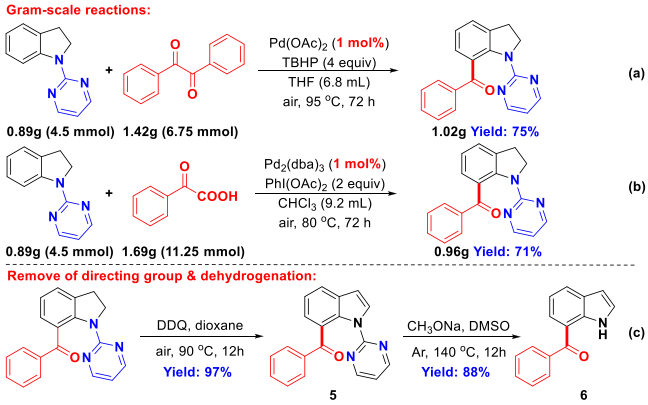


Scheme 6. Proposed Mechanism of C-7 Direct Acylation of Indoline



of a palladium catalyst to yield the C7-acylation product **3aa**. After extensive and meticulous optimization of the reaction conditions, a satisfactory yield of the desired product **3aa** was obtained with $Pd(OAc)_2$ (10 mol %) as the catalyst and TBHP as the oxidant in THF within 16 h at 95 °C without the use of any external ligands or bases (please see Supporting Information (SI) for the details in Table S1).

Scheme 7. Scale-up Reactions and Remove of Directing Group



With the optimized conditions identified, the scope and limitations of 1,2-diketones were examined (Scheme 2). When symmetric diaryl substituted 1,2-diketones were applied as the acyl source, moderate to good yields were achieved (**3aa**–**ag**).

We were pleased to see that heteroaroyl could also be introduced to the C-7 position of indoline (**3ah**). Significantly, highly active functional groups such as aldehyde (**3ad**) and bromo (**3ac**) are tolerated in this reaction. Excitingly, the coupling reaction of dialkyl substituted 1,2-diketones with indoline proceeded well, and good yields of the corresponding acylated produces were achieved (**3ai**–**aj**). Thus, this synthetic strategy advances beyond the previously reported strategies in which lower yields were found in the alkacylation of indole/indoline.[16] Subsequently, asymmetric 1,2-diketones were studied (last line of Scheme 2). When 1-(4-fluorophenyl)-2-phenylethane-1,2-dione was used, **3aa** and **3ab** were obtained with the yields of 52% and 25%, respectively, consistent with the reactivity of the corresponding symmetric ketones (**1a** vs **1b**). It is possible that the presence of electron-withdrawing substituents on aromatic rings is unfavorable for the reaction. Interestingly, when the reaction proceeded with 1-phenylpropane-1,2-dione as the acyl source, the yield of the acetylated product **3ai** (75%) was much higher than that of the benzoylated product **3aa** (21%), indicating that alkacylation of indoline is easier than aroylation. When asymmetric dialkyl substituted 1,2-diketone was used, similar yields of **3ai** (41%) and **3aj** (50%) were obtained. Unfortunately, electron-deficient heteroaromatic-substituted 1,2-diketone (**3ak**) and other types of 1,2-diketones such as oxalamide (**3al**) are not compatible with this reaction.

Subsequently, the scope and limitations of *N*-pyrimidinyl indolines were evaluated (Scheme 3). The results indicated that C2-, C3-, C4-, or C5-substituted indolines were converted to the corresponding acylated product in good yield (**3aa**–**ja**). However, we found that it is difficult to acylate the C6-substituted indolines in this catalytic system due to steric hindrance (**3ma**–**na**). It was also found that this method was also compatible with carbazole-type substrates and other nitrogen-containing benzo-heterocycles such as tetrahydroquinoline, furnishing the corresponding acylated products **3ka** and **3la** in satisfactory yields.

Our further research showed that the decarboxylation of α-keto acids proceeds well in a slightly modified palladium-catalyzed system and this system can also be used as the acylation source for the acylation of indolines. The C-7

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acylated indolines were generated by the coupling of 1-(pyrimidin-2-yl)indoline (**1a**) and α-aryl ketoacids (**4a**) in the presence of $Pd_2(dba)_3$ (10 mol %) and $PhI(OAc)_2$ (2 equiv) in chloroform (2.0 mL) within 16 h at 80 °C (the details of the reaction condition optimization are provided in Table S2 in SI). The substrates scope and limitations were also examined (Scheme 4). It was found that the reactions proceeded smoothly using alkyl-, aryl-, halogen-, and acetyl-substituted indoline derivatives as the substrates (**3aa**−**da**). Carbazole-type substrates and a tetrahydroquinoline derivative also could be converted to the desired products with satisfactory yields (**3ka**, **3la**). Furthermore, several kinds of aryl ketoacids including alkyl-, alkoxy-, and halogen-substituted aryl ketoacids were investigated and good yields were achieved in most cases (**3ae**−**ah**). However, the substituent at the C6-site still shows resistance to this acylation reaction (**3ma**−**na**), and for the same reason, **3F** could not be obtained via this reaction. Unfortunately, the acylation reaction is not applicable to alkyl-substituted ketoacids (**3ai**).

Generally, this conversion proceeds via a radical-based mechanism. To elucidate the mechanism, radical inhibition/capture experiments were conducted (Scheme 2). As expected, when 1,2-diketones were used as the acyl source, the yield of the desired product was reduced from 85% to 46% by the addition of 1 equiv of TEMPO, and the yield decreased to 47% in the presence of 1.5 equiv of 1,1-diphenylethylene (Scheme 5, eqs a and b). In particular, the benzoyl radicals were captured by 1,1-diphenylethylene (Scheme 5, eq b). Similar results were found when α-ketoacids were used as the acyl source (Scheme 5, eqs c and d). Li's group reported the photoinduced acylation reaction using 1,2-diketones as acyl source via a radical procedure.[22] To investigate the interference of light on our strategy, the reaction under dark conditions was carried out. And the yield of acylation product is almost the same as that under standard conditions. The result indicated that this reaction is independent of light (Scheme 5, eq e). Subsequently, to study the kinetics of this reaction, the parallel reactions of **1a** and **D-1a**[23] with benzyl and phenylglyoxylic acid were performed, which resulted in the KIE (kinetic isotope effect) of 0.9 and 2.2 (k_H/k_D), respectively (Scheme 5, eqs f and g). These results indicated that C−H cleavage in the C-7 acylation of indolines using benzyl as the acyl source might not be a rate-limiting step, while in the case of phenylglyoxylic acid as the acyl source the C−H cleavage may be involved in the rate-limiting step.

Based on these results and the reported work,[24] a plausible mechanism was proposed (Scheme 6) that involves the coordination of the pyrimidinyl group with Pd(II) followed by the generation of the palladacycle intermediate **A** via C−H activation. Next, the oxidative addition of the benzoyl radical produced in the presence of an initiator with palladacycle intermediate occurs and the trivalent palladacycle intermediate **B** is formed. The target molecule (**T.M.**) is formed by a reductive elimination procedure, and the palladium catalyst is regenerated.

To confirm the feasibility of this strategy for practical use, gram-scale reactions were conducted and good yields were achieved in the presence of only 1 mol % palladium catalyst (Scheme 7, eqs a and b). These results indicated that this reaction has good potential for scaled-up production with a low loading of palladium catalyst. In addition, the indole derivatives can be produced by a dehydrogenation process, and the protecting group can be removed easily in the presence of CH_3ONa (Scheme 7, eq c).

In summary, a direct and specific C-7 acylation of indolines catalyzed by palladium is reported here. Most importantly, the low alkacylation yields obtained by previous methods were improved by our strategy. In addition, the directing group of this reaction can be removed easily, and the acylated indolines can be converted to the corresponding indoles under oxidative conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03922.

Experimental procedures, spectral and analytical data, copies of ^{1}H and ^{13}C NMR spectra for new compounds (PDF)

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Author Contributions

‡G.X. and Y.Z. contributed equally.

Notes

The authors declare no competing financial interest.

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