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Direct and Site-Selective Palladium-Catalyzed C-7 Acylation of Indolines with Aldehydes

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Abstract: The palladium-catalyzed oxidative acylation of indolines at the C-7 position with aldehydes or alcohols *via* C–H bond activation is described. This protocol represents a facile access to 7-acylated indolines, which can be readily transformed into 7-acylated indoles with diverse biological properties.

Keywords: acylation; C–H activation; indoles; indolines; palladium

The indole and indoline scaffolds have been recognized as privileged structural motifs with diverse biological and medicinal applications.[1] In particular, many pharmaceutical agents include C-7 substituted indole and indoline frameworks.[2] With the development of C–H bond functionalization,[3] it has become the most straightforward protocol leading to C-7 substituted indoles and indolines. Recently, a great deal of effort has been devoted to the formation of C-2 and C-3 functionalized indoles *via* the transition metal-catalyzed C–H bond activation process.[4] Nevertheless, the catalytic C–H bond functionalization of indoles and indolines at the C-7 position remains relatively unexplored. For example, Maleczka and Smith reported the iridium-catalyzed nitrogen-directed C-7 borylation of 2-substituted indoles.[5] Hartwig et al. described the iridium-catalyzed silyl-directed borylation of indoles at the C-7 position.[6] In addition, recent progress has been made on the directing group-assisted C–H arylation,[7] alkenylation,[8] alkylation,[9] and amidation[10] reactions of indolines at the C-7 position.

The C-7 acylated indoles are known as heterocyclic compounds found in a number of natural products and bioactive synthetic molecules (Figure 1).[11] In general, the acylation of indoles occurs preferentially at the more electron-rich C-3 position through electrophilic substitution reactions. Friedel–Crafts acylations,[12] Vilsmeier–Haack reactions,[13] and the coupling reaction between indoles and nitrilium[14] or *N*-(α-haloacyl)-pyridinium salts[15] are common methods for the preparation of C-3 acylated indoles. The catalytic alternatives include the Ru- or Fe-catalyzed carbonylations of the indolic C-3 position with anilines as carbonyl sources,[16] the Pd-catalyzed addition of indoles to nitriles,[17] and the Cu-mediated decarboxylative C-3 acylation of indoles with α-keto acids.[18] The 2-acylated indoles can be generated from the direct addition of acyl equivalents into 2-lithioindoles[19] or

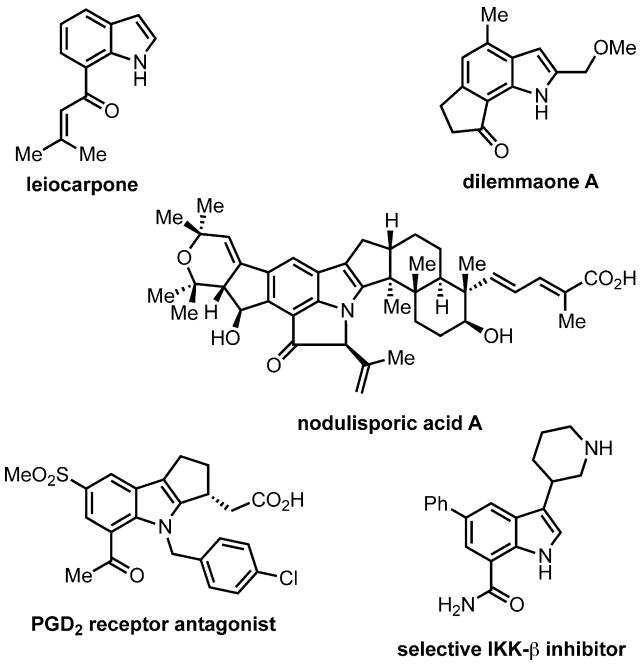
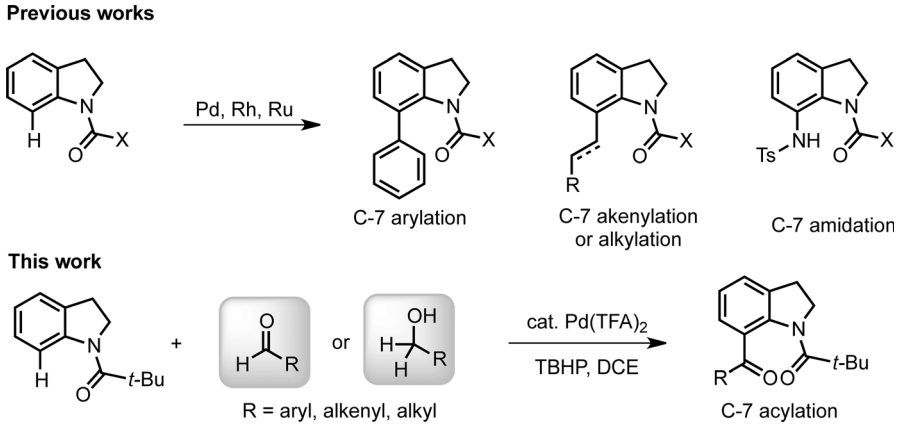


Figure 1. Selected examples of natural and synthetic C-7 acylated indoles.



Scheme 1. Catalytic functionalization of indolines at the C-7 position.

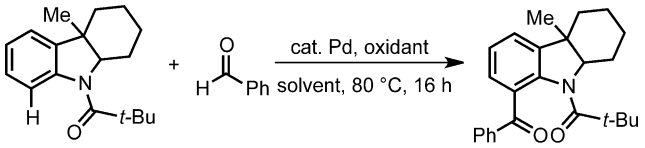
the Pd-catalyzed tandem cyclization reactions.[20] Recently, the directing group-assisted C-2 acylations of indoles using aldehydes[21] or α-oxocarboxylic acids[22] were described. Very recently, our group has reported the Pd-catalyzed decarboxylative acylation of indolines with α-keto acids.[23] However, to the best of our knowledge, there has been only a single example of catalytic C–H acylation at the C-7 position of indoline using arylaldehyde, reported by Yu et al.[24]

Transition metal-catalyzed C–H acylation of indolines using acyl surrogates is a promising synthetic strategy for C-7 acylated indolines, which can be readily converted to C-7 acylated indoles under oxidative conditions. Inspired by recent studies on the catalytic acylation of sp^2 C–H bonds with aldehydes,[25] alcohols,[26] and α-keto acids,[27] we herein disclose the palladium-catalyzed oxidative C-7 acylation of indolines with aldehydes or alcohols *via* C–H bond activation (Scheme 1).

Our examination was initiated by the coupling of *N*-pivaloylindoline **1a** with benzaldehyde (**2a**), and the selected results are summarized in Table 1.

To our delight, the combination of 5 mol% of $Pd(OAc)_2$ and 4 equiv. of TBHP in DCE solvent at 80 °C can promote the coupling of **1a** and **2a** to provide acylated indoline **3a** in 20% yield (Table 1, entry 1). Exclusion of either $Pd(OAc)_2$ or TBHP resulted in no observation of the desired product **3a**. After screening of a range of palladium catalysts, $Pd(TFA)_2$ was found to exhibit the highest reactivity (Table 1, entries 2–4). Further screening of solvents under otherwise identical conditions revealed that DCE was the most effective solvent in this coupling reaction, whereas other solvents such as THF and CH_2Cl_2 were less effective (Table 1, entries 5 and 6). Interestingly, this process provided the coupling product **3a** by the use of aqueous TBHP oxidant in 80% yield (Table 1, entry 7). However, when indoline **1a** was coupled with **2a** under aqueous solvent conditions it afforded our desired product **3a** in low yield (Table 1, entry 8). Further optimization revealed that 2 equiv. of TBHP facilitated high levels of conversion to provide **3a** in high yield (81%) (Table 1, entry 10). Moreover, other oxidants such as DTBP, TBPB, BPO,

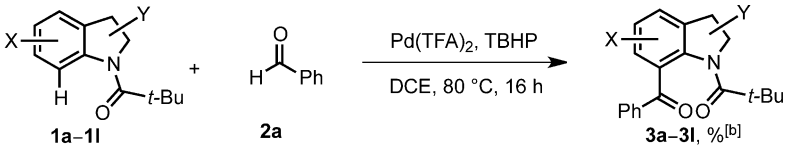
Table 1. Selected optimization of the reaction conditions.[a]



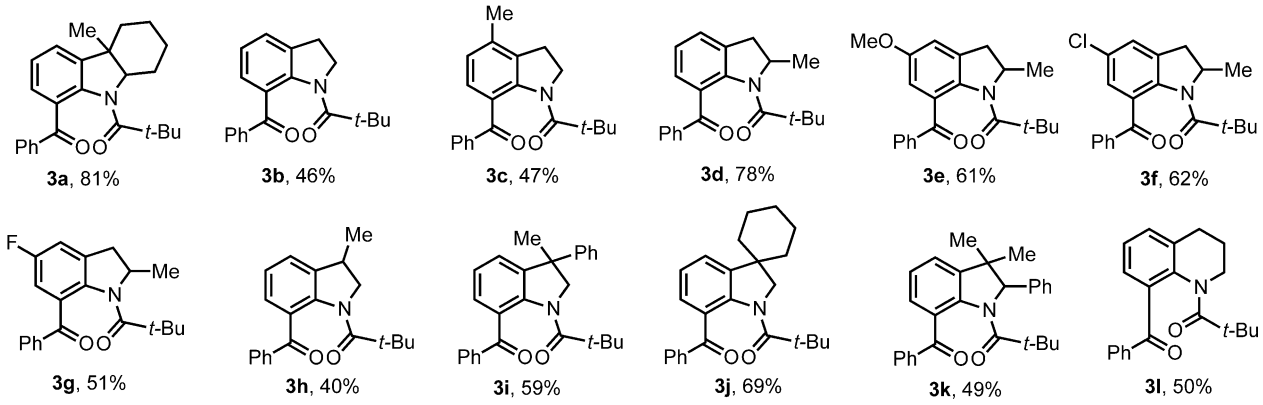
Entry	Catalyst (mol%)	Oxidant (equiv.)	Solvent	Yield[b]
1[c]	$Pd(OAc)_2$ (5)	TBHP (4)	DCE	20%
2[c]	$PdCl_2$ (5)	TBHP (4)	DCE	29%
3[c]	$Pd(TFA)_2$ (5)	TBHP (4)	DCE	78%
4[c]	$Pd(OTf)_2$ (5)	TBHP (4)	DCE	35%
5[c]	$Pd(TFA)_2$ (5)	TBHP (4)	THF	32%
6[c]	$Pd(TFA)_2$ (5)	TBHP (4)	CH_2Cl_2	59%
7[d]	$Pd(TFA)_2$ (5)	TBHP (4)	DCE	80%
8[d]	$Pd(TFA)_2$ (5)	TBHP (4)	H_2O	14%
9[d]	$Pd(TFA)_2$ (5)	TBHP (3)	DCE	79%
10[d]	$Pd(TFA)_2$ (5)	TBHP (2)	DCE	81%
11[e]	$Pd(TFA)_2$ (5)	DTBP (2)	DCE	trace
12[f]	$Pd(TFA)_2$ (5)	TBPB (2)	DCE	12%
13[g]	$Pd(TFA)_2$ (5)	BPO (2)	DCE	trace
14[h]	$Pd(TFA)_2$ (5)	DCP (2)	DCE	16%
15[d]	$Pd(TFA)_2$ (2.5)	TBHP (2)	DCE	46%
16[d,i]	$Pd(TFA)_2$ (5)	TBHP (2)	DCE	trace

[a] *Reaction conditions*: **1a** (0.2 mmol), **2a** (0.6 mmol), Pd catalyst (quantity noted), oxidant (quantity noted), solvent (1 mL) at 80 °C for 16 h in pressure tubes.
[b] Yield isolated by flash column chromatography.
[c] TBHP (5.0–6.0 M in decane).
[d] TBHP (70% in H_2O).
[e] DTBP = di-*tert*-butyl peroxide.
[f] TBPB = *tert*-butyl peroxybenzoate.
[g] BPO = benzoyl peroxide.
[h] DCP = dicumyl peroxide.
[i] At room temperature for 40 h.

Table 2. Scope of the indolines.[a]



1a–1l + 2a → 3a–3l, %[b]



[a] *Reaction conditions*: **1a**–**1l** (0.2 mmol), **2a** (0.6 mmol), $Pd(TFA)_2$ (5 mol%), TBHP (2 equiv.), DCE (1 mL) at 80 °C for 16 h in pressure tubes.
[b] Yield isolated by flash column chromatography.

and DCP were found to be less effective (Table 1, entries 11–14). A decreased loading of palladium catalyst, under otherwise identical conditions, led to relatively decreased formation of **3a** (Table 1, entry 15). Finally, we observed that this coupling reaction did not proceed at room temperature, even for longer reaction times (Table 1, entry 16).

To evaluate the substrate scope of this process, a range of indolines was tested under the optimal reaction conditions (Table 2). The coupling reactions of C-2 or C-3 unsubstituted indolines **1b** and **1c** with **2a** were found to be favored in the acylation reaction to afford the corresponding products **3b** and **3c** in moderate yields. This reaction was also compatible with C-2 methyl-substituted indolines **1d**–**1g** furnishing the corresponding products **3d**–**3g** in moderate to good yields. In addition, mono- or disubstituted indolines **1h**–**1k** at the C-3 position underwent the oxidative acylation reaction to provide **3h**–**3k** with slightly decreased reactivity under the present reaction conditions. We were pleased to observe C-8 acylation of tetrahydroquinoline providing the corresponding product **3l** in 50% yield.

To further explore the substrate scope and limitations, a range of aldehydes was examined under the optimal reaction conditions (Table 3). Electron-rich and electron-deficient benzaldehydes **2b**–**2h** were found to be favored in the acylation reaction, regardless of the position of the substituent on the aromatic ring, affording the corresponding products **4b**–**4h** in good to high yields. Additionally, heteroaromatic aldehyde **2i** and enal **2j** participated in the oxidative acylation reaction to provide **4i** and **4j**, relatively in low yields, under the current reaction conditions. To our pleasure, this reaction is not limited to aryl aldehydes. Aliphatic aldehydes such as cyclohexanecarbaldehyde (**2k**), isobutyraldehyde (**21**), and 1-hexanal (**2m**) were also found to be favored in the oxidative coupling to furnish 7-acylated indolines **4k**–**4m** in 40%, 52% and 60% yields, respectively.

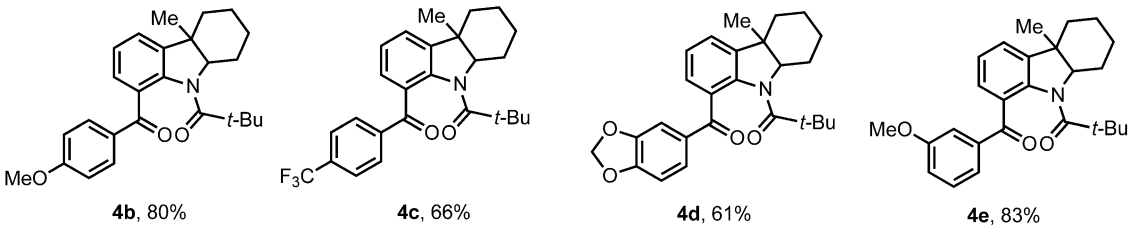
In previous reports, alcohols have been used as efficient acylating agents under various oxidative conditions.[26] Thus we sought to expand the substrate scope from aldehydes to alcohols (Table 4). Subsequently, we found that indoline **1a** was coupled with benzylic alcohols **5a**–**5c** containing electron neutral, electron-donating and electron-withdrawing substituents under slightly modified reaction conditions to afford the corresponding products **3a**, **4b** and **4c** in high yields. Moreover, aliphatic alcohol **5d** also participated in this catalytic acylation to furnish **4m** in 25% yield.

To demonstrate the practicable preparation of 7-acylated indolines, we successfully scaled the reactions to 2.5 mmol using benzaldehyde (**2a**) or benzyl alcohol (**5a**), and obtained 0.75 g (80% isolated yield from **2a**) and 0.73 g (76% isolated yield from **5a**) of **3a**, respectively, after 28 h (Scheme 2).

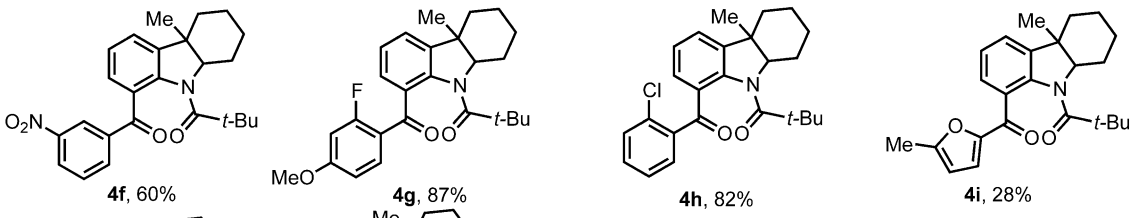
To highlight the transformation of C-7 acylated indolines, the removal of the *N*-pivaloyl group of **3b** under basic hydrolysis conditions was first performed to provide the free (NH)-indoline **6a** in 87% yield (Scheme 3). In addition, we performed the oxidation of **3b** using DDQ to furnish 7-acylated indole **6b** in 57% yield.

Table 3. Scope of the aldehydes.[a]

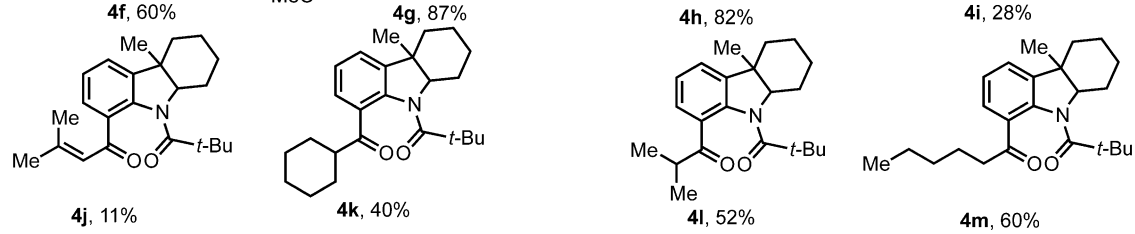
1a **2b–2m** **4b–4m**, %[b]



4b, 80% **4c**, 66% **4d**, 61% **4e**, 83%



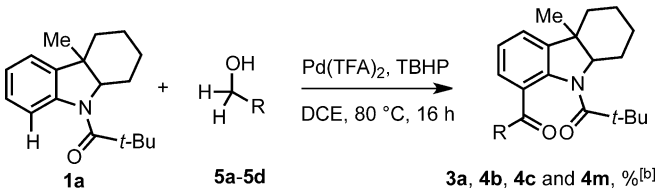
4f, 60% **4g**, 87% **4h**, 82% **4i**, 28%



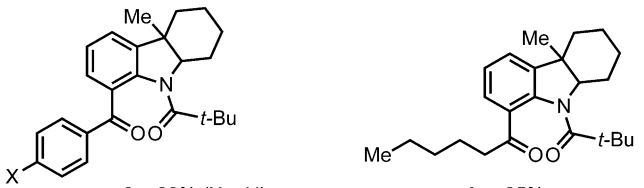
4j, 11% **4k**, 40% **4l**, 52% **4m**, 60%

[a] *Reaction conditions*: **1a** (0.2 mmol), **2b–2m** (0.6 mmol), $Pd(TFA)_2$ (5 mol%), TBHP (2 equiv.), DCE (1 mL) at 80 °C for 16 h in pressure tubes.
[b] Yield isolated by flash column chromatography.

Table 4. Scope of the alcohols.[a]



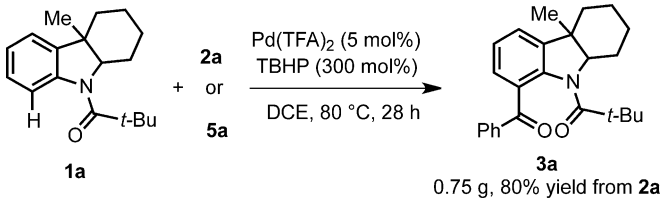
1a **5a-5d** **3a**, **4b**, **4c** and **4m**, %[b]



3a, 83% (X = H)
4b, 78% (X = OMe)
4c, 41% ($X = CF_3$)

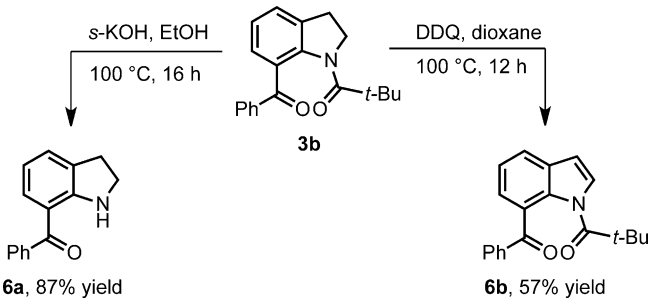
4m, 25%

[a] *Reaction conditions*: **1a** (0.2 mmol), **5a–5d** (0.6 mmol), $Pd(TFA)_2$ (5 mol%), TBHP (3 equiv.), DCE (1 mL) at 80 °C for 16 h in pressure tubes.
[b] Yield isolated by flash column chromatography.



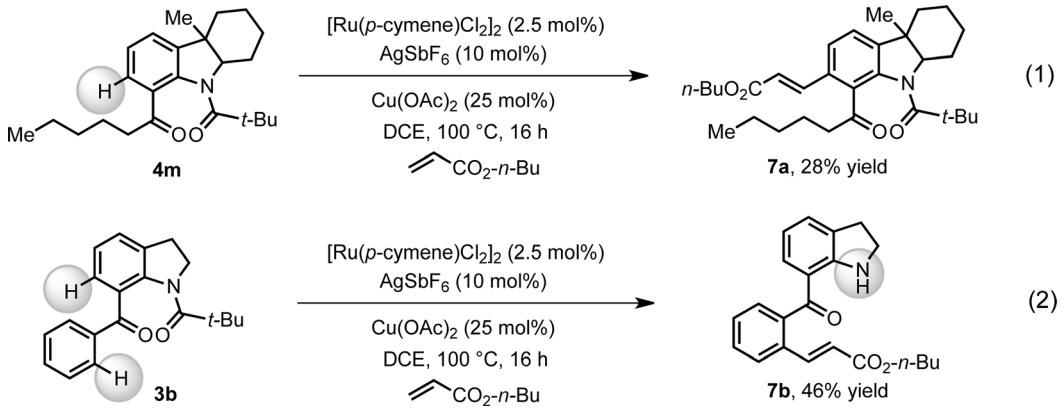
1a **3a**
0.75 g, 80% yield from **2a**
0.73 g, 76% yield from **5a**

Scheme 2. Scale-up experiments using aldehyde or alcohol.

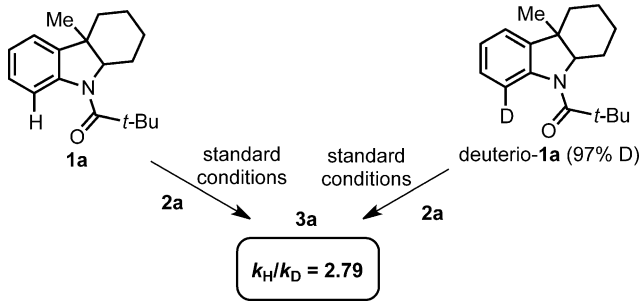


6a, 87% yield **3b** **6b**, 57% yield

Scheme 3. Transformations of 7-acylated indoline.



Scheme 4. Site-selective olefinations of C-7 acylated indolines.



Scheme 5. Kinetic isotope experiments.

Next, the sequential C–H functionalization was performed by using a newly installed ketone functionality as a directing group. We were delighted to find that the olefination site can be controlled by using different acyl groups such as hexanoyl and benzoyl. As shown in Scheme 4, the olefination of **4m** using *n*-butyl acrylate under ruthenium catalysis[28] afforded C-6 olefinated indoline **7a** [Eq. (1)]. Furthermore, in the case of **3b**, the olefination preferentially occurs on the phenyl moiety, concomitant with unexpected cleavage of the pivaloyl group, to provide the free (NH)-indoline **7b** in 46% yield [Eq. (2)].

To gain a mechanistic insight, two parallel reactions of **1a** and deuterio-**1a** with benzaldehyde (**2a**) under standard reaction conditions were performed, which resulted in the kinetic isotope effect (k_H/k_D) of 2.79 (see the Supporting Information for details), thus indicating that C–H cleavage might be involved in the rate-limiting step (Scheme 5).[29]

In conclusion, we have described an efficient method for the palladium-catalyzed oxidative C-7 acylation of highly substituted indolines with aldehydes or alcohols as acyl equivalents *via* C–H bond activation. These transformations allow the generation of an array of C-7 acylated indoles, which are known to be crucial scaffolds of biologically active compounds. Our ongoing studies seek to expand the scope to the acylation of sp^2 C–H bonds without directing groups and unactivated sp^3 C–H bonds.

Experimental Section

Typical Procedure for C-7 Acylation of *N*-Pivaloylindolines with Aldehydes

To an oven-dried sealed tube charged with *N*-pivaloylindoline (**1a**) (54.3 mg, 0.2 mmol, 100 mol%), $Pd(TFA)_2$ (3.3 mg, 0.01 mmol, 5 mol%) and TBHP (0.06 mL, 0.4 mmol, 200 mol%, 70% in H_2O) in DCE (1 mL) was added benzaldehyde (**2a**) (63.7 mg, 0.6 mmol, 300 mol%). The reaction mixture was allowed to stir at 80 °C for 16 h, and was then cooled to room temperature. The reaction mixture was diluted with EtOAc (3 mL) and saturated $NaHCO_3$ solution (3 mL). The resulting mixture was extracted with EtOAc (5 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc = 6:1) to afford **3a**; yield: 60.8 mg (81%).

Acknowledgements

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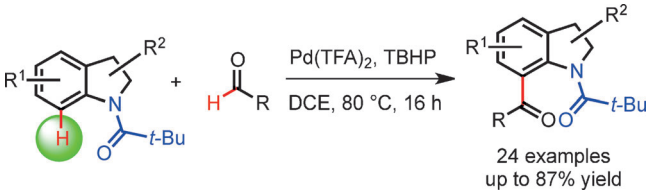

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