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Synthesis of 2-Acylated Indoles through Palladium-Catalyzed Dehydrogenative Coupling of *N*-Pyrimidine-Protected Indoles with Aldehydes and Ethyl Glyoxylate

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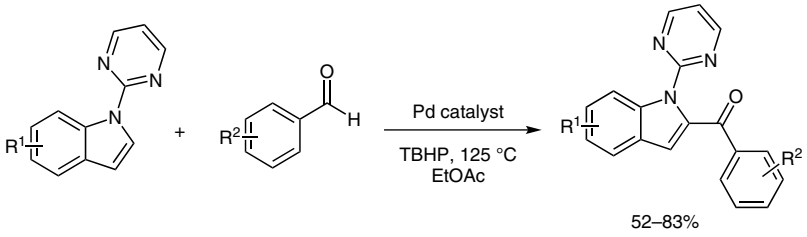

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Abstract C2-Acylated indoles have been synthesized in good yields through palladium-catalyzed dehydrogenative coupling of *N*-pyrimidine-protected indoles using aldehydes as the source of acyl reagent and *tert*-butyl hydroperoxide as the oxidant. 2-Indole carboxylates can be synthesized when aldehydes are substituted by ethyl glyoxylate.

Key words palladium, dehydrogenative coupling, aldehyde, acylation, indoles

Acylated indoles are important substructures in a number of biologically active natural products and pharmaceutical compounds[1] and they have been shown to possess antidiabetic,[1a] anticancer,[1c] and anti-HIV activities.[1b] They have also been frequently used as valuable intermediates in the synthesis of dyes[2a] and pharmaceuticals.[2b] Compared with 2-acylindoles, 3-acylindoles can be conveniently synthesized through Friedel–Crafts reaction,[3] Vilsmeier–Haack reaction,[4] and indole Grignard reaction.[5] In addition, they can be prepared through alternative procedures such as transition-metal-catalyzed formylation[6] or acylations.[7] For example, Wang recently disclosed an elegant copper-promoted decarboxylative C3-selective acylation of N-substituted indoles with α-oxocarboxylic acids.[8] Despite this progress, only a few methods exist for the preparation of 2-acylindoles.[9] The most common method for preparation of 2-acylindole is the Katritsky procedure.[9a] It involves the use of CO_2 to protect the indole nitrogen atom after the hydrogen on the nitrogen atom is abstracted by an organolithium reagent. This in situ protected indole will react further with a strong base such as *t*-BuLi to generate a carbanion at the C2-position, which will subsequently react with an acyl electrophile to generate the desired 2-acylindole. Although the C2-acylation transformation is very efficient and can be run in a one-pot fashion, the need to use CO_2 and organolithium reagent requires stringent exclusion of air and moisture, thus making the reaction less user friendly. Moreover, the use of strong base can severely limit the scope of the reaction.

Recently, several palladium-catalyzed acylation reactions of arenes have been developed by using aldehyde as the source of the acyl group.[10,11] The installation of a carbonyl group on the arenes, i.e., the synthesis of aryl ketones and carboxylates from benzene derivatives through palladium-catalyzed dehydrogenative coupling, has been an area of intense research.[11] For example, Li and others reported dehydrogenative couplings between 2-aryl pyridines and aryl aldehydes to produce aryl ketones.[11a,b] Later, Kwong[11c] successfully extended this protocol to the dehydrogenative coupling between acetanilides with aryl aldehydes. Li, Deng and co-workers were able to successfully use alcohols instead of aldehydes in similar couplings.[11d,e] Even more impressive is that Sun and Patel were able to use toluene derivatives as the acyl source, thus increasing the overall reaction efficiency further.[12] Whereas various protocols based on palladium-catalyzed C–H activation of arenes have been developed for the synthesis of aryl ketones and esters from benzene derivatives, only a few examples involving the use of heterocycles are known.[13,9e,f] Thus it would be highly desirable for palladium-catalyzed dehydrogenative coupling to be applied in the synthesis of acylated heteroaromatic compounds such as indoles.

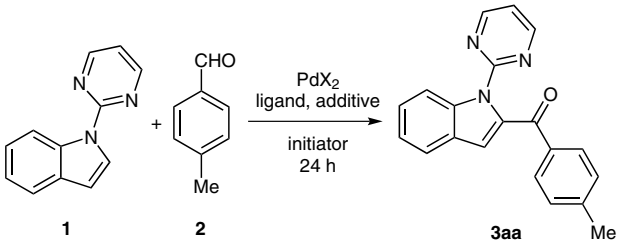
Pyrimidine has been used as a removable protecting group for phenols[14] and anilines.[15] More importantly, it has been shown to be a competent directing group in various transition-metal-catalyzed C–H activations. Hence, a variety of C–C and C–X bond formation reactions based on pyrimidine-directed transition-metal-catalyzed C–H activation have been developed.[16] Inspired by these results, we considered whether pyrimidine could be used to both pro-

tect the nitrogen atom of the indole molecules and serve as the directing group for palladium-catalyzed C2-selective acylation using aldehyde as the acylation reagent. Herein, we report that C2-selective acylation can indeed be achieved in good yields through palladium-catalyzed dehydrogenative coupling between pyrimidine-protected indoles and aldehydes.

We commenced our study by using the reaction of *N*-pyrimidine-protected indole **1** and *p*-methylbenzaldehyde as the model reaction. When **1** was treated with **2** (1.5 equiv) in the presence of $Pd(OAc)_2$ (10 mol%), TBHP (70% in H_2O, 4 equiv) in toluene under N_2 at 125 °C for 24 h, the desired acylation product **3aa** was isolated in 23% yield (Table 1, entry 1). When we replaced the aqueous TBHP with anhydrous TBHP (5 M in decane), the yield increased to 56% (entry 2). A yield of 83% could be obtained when the solvent was switched to EtOAc (entry 3) whereas other solvents such as DMF, DMSO, and MeCN all gave much inferior results (entries 4–6). Given that phosphine ligand was shown to have a beneficial effect on the reaction yield in other palladium-catalyzed acylations, we included phosphine ligands such as dppp, dppe, dppf, and PPh_3 to the reaction mixture as additives. However, the yield actually suffered (entries 7–10). Substituting the catalyst $Pd(OAc)_2$ with $PdCl_2$ or $Pd(TFA)_2$ did not improve the yield (entry 11 and 12). When the reaction temperature was reduced to 100 °C, the yield of **3aa** also dropped, whereas running the reaction at 135 °C gave a yield of 72% (entries 13 and 14). A control reaction also confirmed that no desired product **3aa** was formed when palladium catalyst was absent (entry 15). Based on these results, we established the reaction in EtOAc at 125 °C under N_2 in the presence of $Pd(OAc)_2$ as our standard reaction conditions.[17]

With the optimized protocol in hand, we next set out to explore the scope and the limitations of the reaction (Table 2). We found that the reaction worked satisfactorily with a range of aromatic aldehydes. The desired C2-acylated indoles were obtained in yields ranging from 52 to 83% (Table 2, entries 1–10, 22, and 23) when substituents such as Me, MeO, Ph, NO_2, Br, Cl, and F, as well as acetamino group were placed on the aromatic ring of the aldehyde. Moreover, 1- and 2-naphthaldehyde as well as 2-furfuraldehyde can also participate in the coupling, affording the desired C2-acylated product in 48–78% yields (Table 2, entries 9, 10, 12, and 18). Much to our disappointment, aliphatic aldehydes such as 1-octanal were not viable substrates for this type of coupling (Table 2, entry 11). We surmise that this is due to the fact that alkyl aldehydes can be easily oxidized to acids by the oxidant.[18] We found that substituents such as methyl, fluoro, bromo, chloro, methoxy, cyano, and even carboxylate groups were all well tolerated on the phenyl ring of indole, affording the desired acylated product in 59–85% yields (Table 2, entries 12–21). Notably, a methyl group on the C3-position of the indole did not hinder the desired C2-acylation, demonstrating the versatility of this protocol (Table 2, entry 20).

Table 1 Optimization of the Reaction Conditions[a]



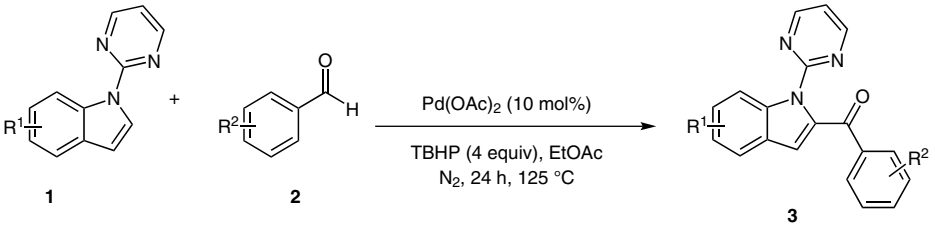
1 **2** **3aa**

Entry	Catalyst	Temp (°C)	Ligand	Initiator	Solvent	Yield (%)[b]
1[c]	$Pd(OAc)_2$	125	–	TBHP	toluene	23
2	$Pd(OAc)_2$	125	–	TBHP	toluene	56
3	$Pd(OAc)_2$	125	–	TBHP	EtOAc	83
4	$Pd(OAc)_2$	125	–	TBHP	DMF	19
5	$Pd(OAc)_2$	125	–	TBHP	DMSO	30
6	$Pd(OAc)_2$	125	–	TBHP	MeCN	38
7	$Pd(OAc)_2$	125	dppp	TBHP	EtOAc	53
8	$Pd(OAc)_2$	125	dppe	TBHP	EtOAc	55
9	$Pd(OAc)_2$	125	dppf	TBHP	EtOAc	48
10	$Pd(OAc)_2$	125	PPh_3	TBHP	EtOAc	32
11	$PdCl_2$	125	–	TBHP	EtOAc	21
12	$Pd(TFA)_2$	125	–	TBHP	EtOAc	60
13	$Pd(OAc)_2$	100	–	TBHP	EtOAc	57
14	$Pd(OAc)_2$	135	–	TBHP	EtOAc	72
15	–	125	–	TBHP	EtOAc	0

[a] Reaction conditions: indole (1 equiv), PdX_2 (10 mol%), anhydrous TBHP (ca. 5 M in decane, 4 equiv), *p*-tolualdehyde (1.5 equiv), solvent (3 mL $mmol^{-1}$), ligand (10 mol%), under N_2, 24 h.
[b] Isolated yield.
[c] TBHP (70% in H_2O) was added.

Given that we have shown that ethyl glyoxylate can also be used to participate in the palladium-catalyzed decarbonylative–dehydrogenative coupling with anilides, and that aryl carboxylate instead of ketones will be obtained,[19] we considered whether ethyl glyoxylate could also be used in our newly developed reaction. Much to our satisfaction, we found that by replacing the aryl aldehyde with ethyl glyoxylate and running the reaction under our standard conditions, decarbonylation indeed took place to give the desired 2-indole carboxylates in good yields; the results are summarized in Table 3. A range of substituted indoles could be used in the palladium-catalyzed decarbonylative-dehydrogenative coupling with ethyl glyoxylate to generate the desired 2-indole carboxylates in 64–82% yields (Table 3, entries 1–9). It is important to note that this type of product is not readily accessible through Friedel–Crafts reaction.

Table 2 Synthesis of 2-Acylated Indoles through Palladium-Catalyzed Dehydrogenative Coupling of *N*-Pyrimidine-Protected Indoles with Aldehydes[a]



1 **2** **3**

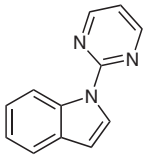
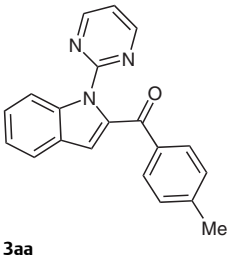
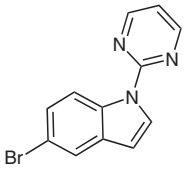
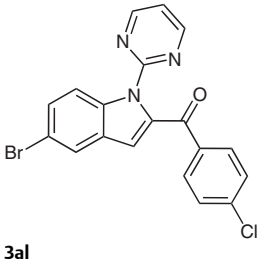
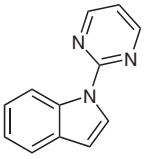
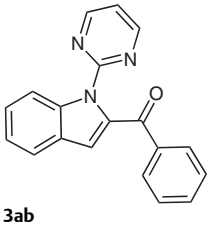
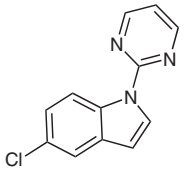
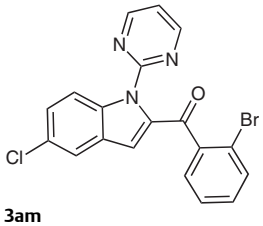
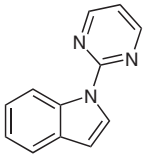
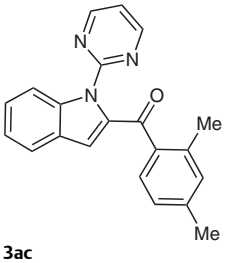
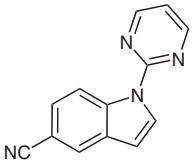
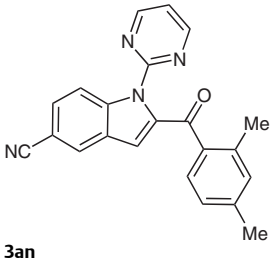
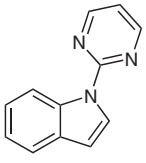
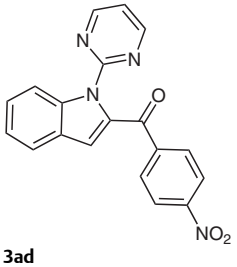
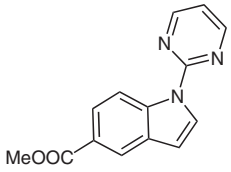
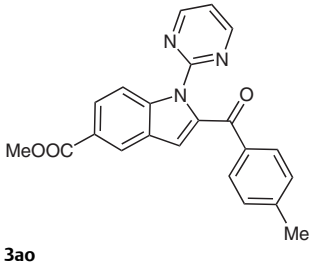
Entry	Indole	Product	Yield (%)[b]	Entry	Indole	Product	Yield (%)[b]
1		 **3aa**	83	13		 **3al**	59
2		 **3ab**	80	14		 **3am**	63
3		 **3ac**	61	15		 **3an**	76
4		 **3ad**	52	16		 **3ao**	85

Table 2 (continued)

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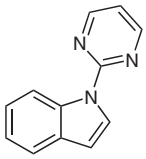
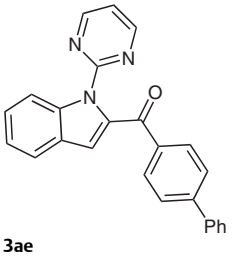
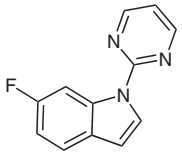
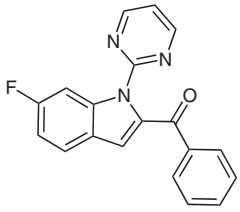
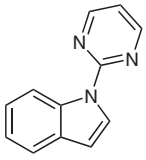
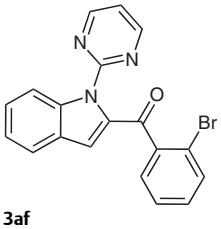
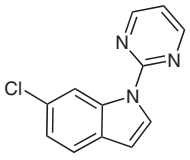
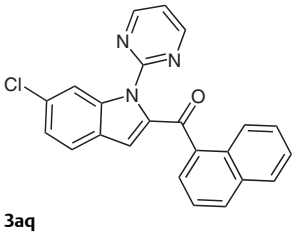
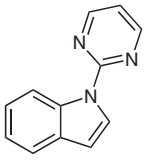
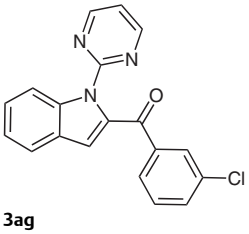
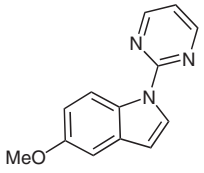
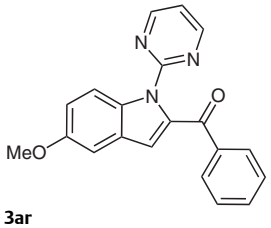
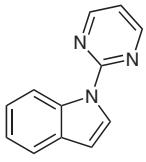
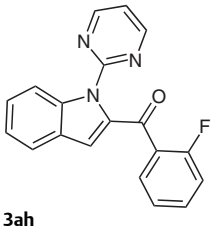
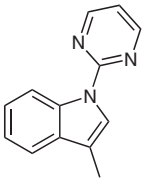
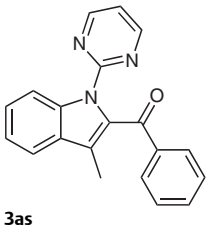
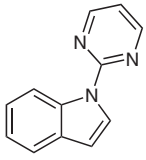
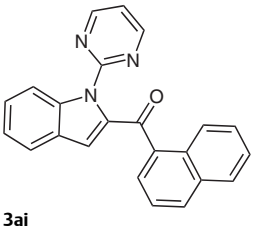
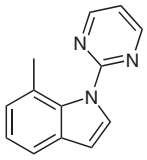
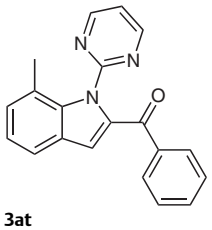
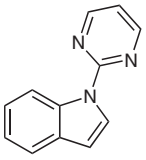
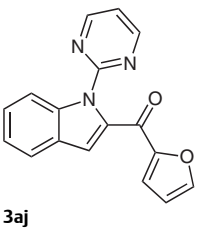
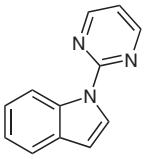
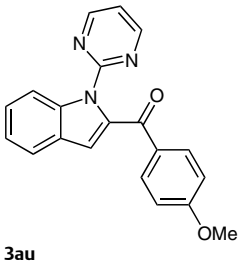
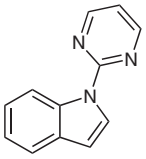
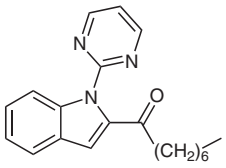
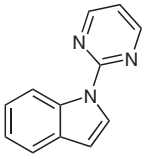
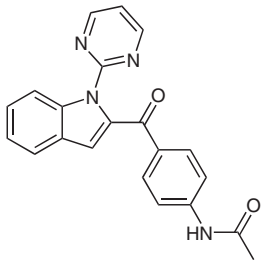
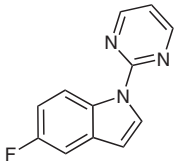
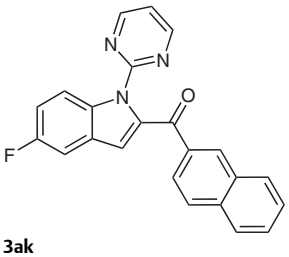
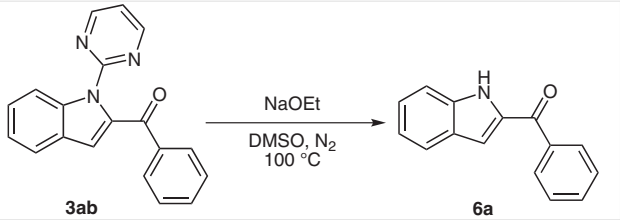
5		 **3ae**	72	17		 **3ap**	70
6		 **3af**	63	18		 **3aq**	72
7		 **3ag**	65	19		 **3ar**	78
8		 **3ah**	61	20		 **3as**	82
9		 **3ai**	62	21		 **3at**	80
10		 **3aj**	78	22		 **3au**	76

Table 2 (continued)

Entry	Indole	Product	Yield (%)[b]	Entry	Indole	Product	Yield (%)[b]
11			0	23		 **3av**	67
12		 **3ak**	61				

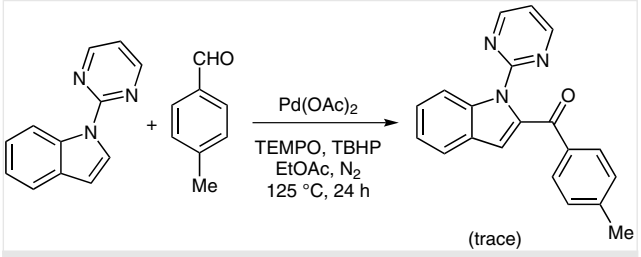
[a] Reaction conditions: indole (0.3 mol), aldehyde (0.45 mmol), $Pd(OAc)_2$ (10 mol%), TBHP (4 equiv), EtOAc (2.0 mL), 125 °C, 24 h.
[b] Isolated yield.

To demonstrate the synthetic utility of our reaction and authenticate the product, **3ab** was treated with NaOEt for 24 hours,[20] the pyrimidine group was removed, and **6a** was isolated in 80% yield (Equation 1). The identity of **3ab** was confirmed by comparison of its ^{1}H NMR spectrum with reported data.[9e] This result proved that acylation took place at the C2-position.



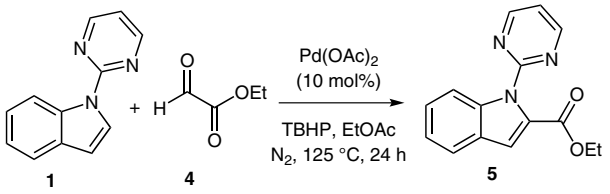
Equation 1

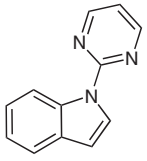
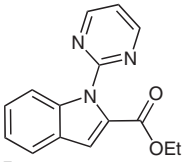
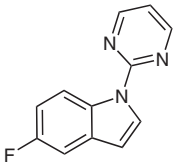
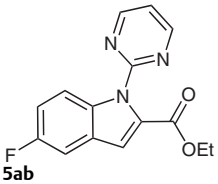
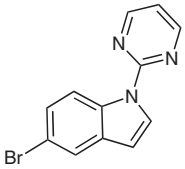
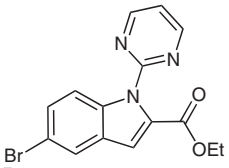
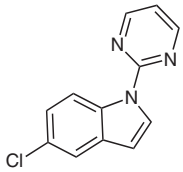
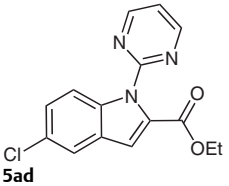
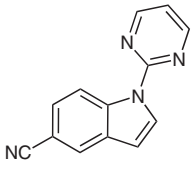
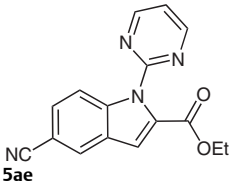
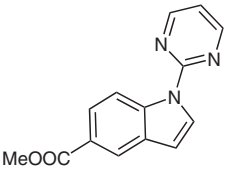
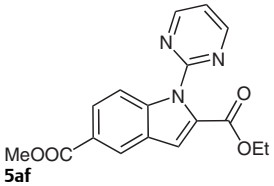
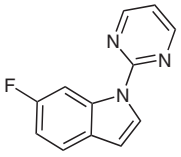
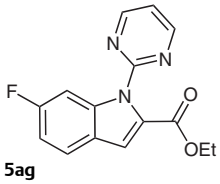
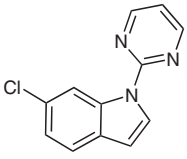
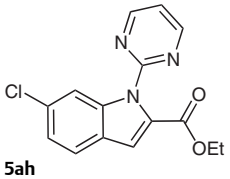
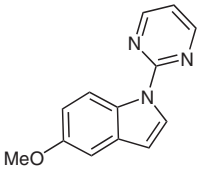
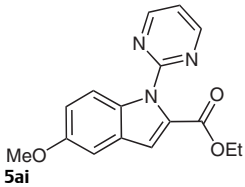
Although the exact mechanism remains unclear, some information has been gathered. When a free-radical scavenger (e.g., TEMPO) was added to the reaction mixture, the reaction was almost completely stopped (Equation 2), suggesting this reaction may involve a radical intermediate. This observation is consistent with reports by others.[10e,11a,c,21] On the other hand, the usually invoked palladation–addition to the carbonyl group–dehydropalladation mechanism cannot explain the loss of one molecule of CO during the reaction with ethyl glyoxylate. Based on these results, we reason that the reaction may be initiated with the palladium(II)-mediated *ortho*-palladation of the indole to form intermediate **A** (Scheme 1). TBHP is decomposed into RO· radicals, which subsequently abstract the hydrogen from the aldehyde to form acyl radicals. As in the case of glyoxylate, an extra step of decarbonylation is involved after the hydrogen abstraction. The generated acyl radicals will subsequently react with intermediate **A** to produce a palladium(IV)[22] or palladium(III) intermediate **B** (**B1** for glyoxylate and **B2** for benzaldehyde).[23] After reductive elimination, **B** will be transformed into the desired ketone and ester products, and palladium(II) is regenerated, thus completing the catalytic cycle.



Equation 2

Table 3 Synthesis of 2-Indole Carboxylates through Palladium-Catalyzed Dehydrogenative/Decarbonylative Coupling of *N*-Pyrimidine-Protected Indoles with Ethyl Glyoxylate[a]



Entry	Indole	Product	Yield (%)[b]
1		 **5aa**	82
2		 **5ab**	67
3		 **5ac**	68
4		 **5ad**	72
5		 **5ae**	65
6		 **5af**	70
7		 **5ag**	73
8		 **5ah**	78
9		 **5ai**	64

[a] Reaction conditions: indole (0.3 mol), ethyl glyoxylate (0.45 mmol), $Pd(OAc)_2$ (10 mol%), TBHP (4 equiv), EtOAc (2.0 mL), 125 °C, 24 h.
[b] Isolated yield.

In summary, a novel way of synthesizing C2-acylated indoles was developed with palladium catalysis using TBHP as the oxidant and aldehydes as the source of acyl reagent. We also found that 2-indole carboxylates can be synthesized when aldehydes were substituted with ethyl glyoxylate.[9f] This method offers an alternative route for the synthesis of 2-acylated indoles because the pyrimidine group can be easily removed. Efforts are underway to elucidate the reaction mechanism and the results will be reported in due course.

Acknowledgment

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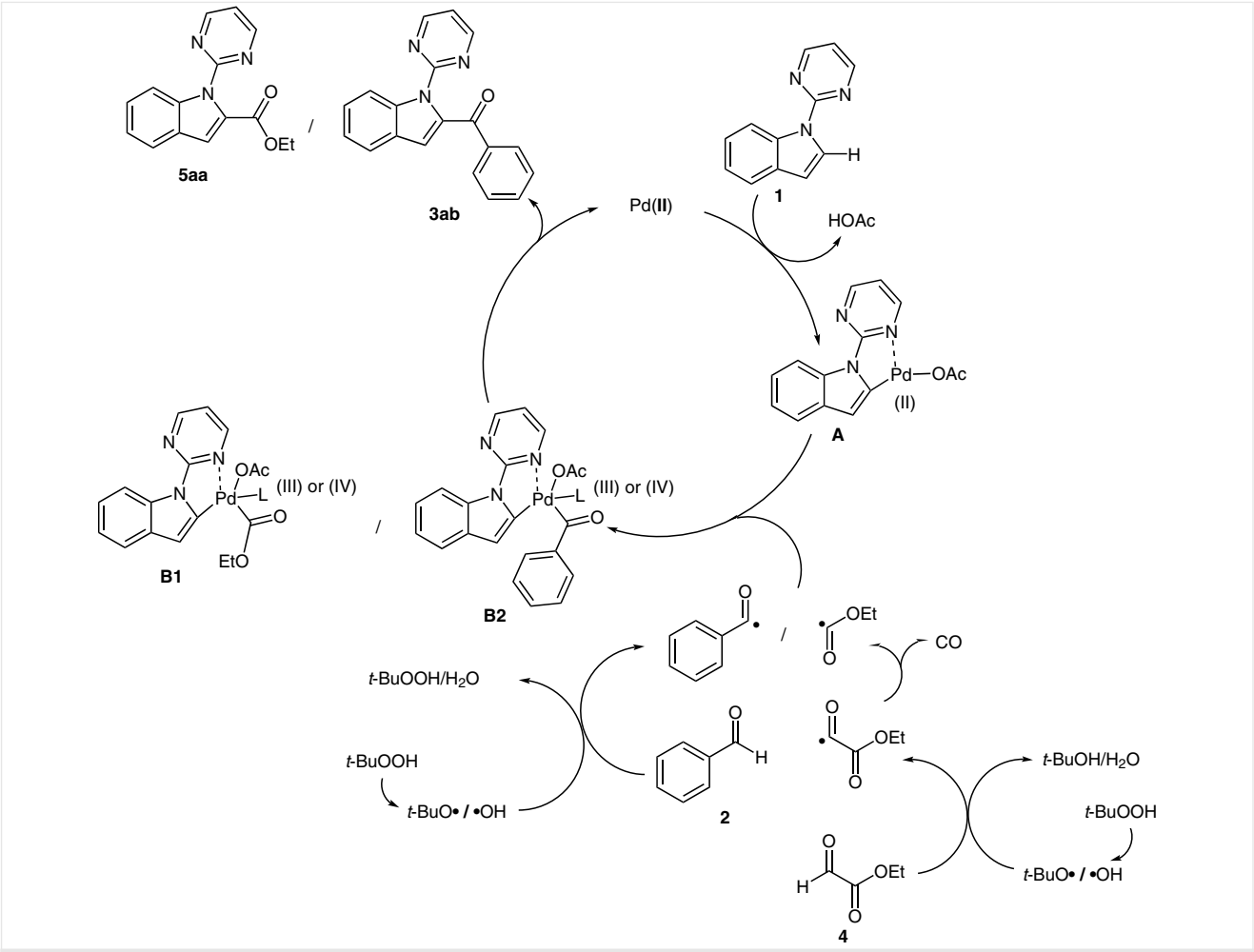

Scheme 1 Proposed mechanism for palladium-catalyzed dehydrogenative coupling of *N*-pyrimidine-protected indoles with aldehydes and ethyl glyoxylate

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379935. Included are experimental procedures, characterization data, and copies of ^{1}H NMR and ^{13}C NMR spectra.

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(17) **General Procedure:** To a 25-mL sealed tube were added indole (0.3 mmol), aldehyde (0.45 mmol), $Pd(OAc)_2$ (6.72 mg, 10 mmol%), anhydrous TBHP (ca. 5 M in decane, 4 equiv), and EtOAc (2.0 mL). The tube was capped and stirred under N_2 at 125 °C for 24 h. The reaction mixture was cooled to room temperature and diluted with CH_2Cl_2, filtered through a short pad of Celite, and washed with brine and CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, concentrated in vacuo, and the resulting residue was purified by silica gel column chromatography to afford the desired product.
[3-Methyl-1-(pyrimidin-2-yl)-1*H*-indol-2-yl](phenyl)methanone (3as): Yield: 82%; white solid; mp 153–154 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.63 (d, *J* = 8.0 Hz, 1 H), 8.44 (d, *J* = 4.0 Hz, 2 H), 7.77 (d, *J* = 8.0 Hz, 2 H), 7.68 (d, *J* = 8.0 Hz, 1 H), 7.48–7.40 (m, 2 H), 7.32 (q, *J* = 8.0 Hz, 3 H), 6.84 (t, *J* = 4.0 Hz, 1 H), 2.37 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 189.4, 157.5, 157.0, 139.2, 136.4, 133.2, 132.2, 130.2, 128.5, 128.3, 126.1, 122.5, 121.7, 120.1, 116.1, 115.2, 9.3; HRMS: *m*/*z* [M]$^+$ calcd for $C_{20}H_{15}N_3O$: 313.1207; found: 313.1210.
[7-Methyl-1-(pyrimidin-2-yl)-1*H*-indol-2-yl](phenyl)methanone (3at): Yield: 80%; yellow solid; mp 36–37 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.85 (d, *J* = 4.0 Hz, 2 H), 7.92 (d, *J* = 8.0 Hz, 2 H), 7.60–7.55 (m, 2 H), 7.48–7.45 (m, 2 H), 7.39 (t, *J* = 4.0 Hz, 1 H), 7.20 (s, 1 H), 7.13–7.11 (m, 2 H), 1.96 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 187.0, 159.7, 158.1, 138.3, 138.2, 136.0, 132.4, 129.6, 129.2, 128.2, 127.2, 122.4, 121.9, 121.1, 120.1, 116.4, 19.3. HRMS: *m*/*z* [M]$^+$ calcd for $C_{20}H_{15}N_3O$: 313.1207; found: 313.1210.
(4-Methoxyphenyl)[1-(pyrimidin-2-yl)-1*H*-indol-2-yl]methanone (3au): Yield: 76%; white solid; mp 39–40 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.61 (d, *J* = 4.0 Hz, 2 H), 8.39 (d, *J* = 8.0 Hz, 1 H), 7.97 (d, *J* = 8.0 Hz, 2 H), 7.68 (d, *J* = 8.0 Hz, 1 H), 7.41 (t, *J* = 8.0 Hz, 1 H), 7.27 (t, *J* = 8.0 Hz, 1 H), 7.07 (s, 1 H), 7.02 (t, *J* = 4.0 Hz, 1 H), 6.91 (d, *J* = 8.0 Hz, 2 H), 3.83 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 186.4, 163.3, 157.9, 157.2, 138.0, 137.2, 131.8, 130.7, 127.9, 126.1, 122.6, 122.2, 117.3, 114.5, 114.1, 113.5, 55.4; HRMS: *m*/*z* [M]$^+$ calcd for $C_{20}H_{15}N_3O_2$: 329.1152; found: 329.1159.
***N*-{4-[1-(Pyrimidin-2-yl)-1*H*-indole-2-carbonyl]phenyl}acetamide (3av):** Yield: 67%; yellow solid; mp 138–139 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.11 (s, 1 H), 8.56 (d, *J* = 4.0 Hz, 2 H), 8.37 (d, *J* = 8.0 Hz, 1 H), 7.89 (d, *J* = 8.0 Hz, 2 H), 7.68–7.61 (m, 3 H), 7.41 (t, *J* = 8.0 Hz, 1 H), 7.26 (t, *J* = 8.0 Hz, 1 H), 7.07 (s, 1 H), 6.99 (t, *J* = 4.0 Hz, 1 H), 2.09 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 186.8, 169.4, 157.8, 157.0, 142.9, 138.0, 136.9, 132.7, 130.7, 127.8, 126.4, 122.7, 122.3, 118.7, 117.3, 115.1, 114.1, 24.28; HRMS: *m*/*z* [M]$^+$ calcd for $C_{21}H_{16}N_4O_2$: 356.1273; found: 356.1268.
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