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Palladium-Catalyzed Direct and Regioselective C−H Bond Functionalization/Oxidative Acetoxylation of Indoles†

Pui Ying Choy, Chak Po Lau, and Fuk Yee Kwong*

State Key Laboratory of Chirosciences and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong

bcfyk@inet.polyu.edu.hk

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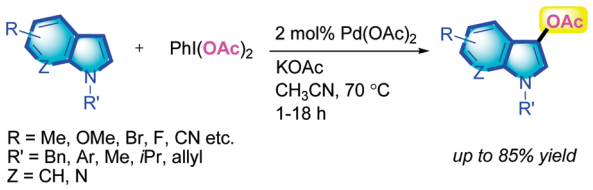

The first general examples of palladium-catalyzed direct and selective oxidative C3-acetoxylation of indoles are presented. The mild reaction conditions (70 °C and with weak base, KOAc) in this indole C−H-acetoxylation are notable.

Introduction

Employing a modular approach for generating a new series of compounds has been one of the most important themes in modern organic synthesis[1] since it offers a direct and simple route to prepare an array of structurally similar yet diversified pharmaceutically attractive molecules.[2] Certainly, the transition-metal-catalyzed C−H bond functionalization sequences have become a cutting-edge methodology in this area for the construction of carbon−carbon and carbon−heteroatom bonds.[3,4]

Among the field of $C_{(sp2)}$−heteroatom cross-couplings, the C−O bond-forming reaction (from ArX electrophile and ROH nucelophile) is the most problematic and difficult process.[5] Thus, it would be of considerable interest if this catalytic process is free of expensive tailor-made phosphine ligand and can be done by applying the more atom-economical C−H cleavage/functionalization cascade protocol. Moreover, it would be advantageous if it is in a highly regioselective manner, yet requiring no chelating-assisted groups.

In regard to the repertoire of acetoxylation (C_{sp2}−O bond-forming reaction), Sanford[6] and Yu[7] recently reported landmark explorations concerning the arene acetoxylation which are directed by *o*-pyridyl or -iminyl moieties and catalyzed by palladium or copper complexes, respectively. 1,2-Disubstituted indoles could be acetoxylated together with 3,3′-biindolyl products using lead tetraacetate.[8] In 2009, one notable example was reported by Suna on an acetoxylation of 2,3-unsubstituted indole to give 3-acetoxyindole accompanying with a mixture of oxidative products.[9] In 2010, Zhang

† Dedicated to Professor Albert S. C. Chan (currently the President of Hong Kong Baptist University) on the occasion his 60th birthday.

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(2) For reviews, see: (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442. (b) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis II, More Targets, Strategies and Methods*; Wiley-VCH: Weinheim, 2003.

(3) For recent reviews, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (d) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (e) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (f) Dyker, G. *Handbook of C−H Transformations*; Wiley-VCH: Weinheim, 2005.

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(5) Specially designed (exceedingly bulky) phosphine ligands are necessary for this C−O bond-forming process (i.e., being proposed to favor the difficult reductive elimination); see: (a) Vorogushin, A. V.; Huang, X. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 8146. (b) Stambuli, J. R.; Weng, Z. Q.; Incarvito, C. D.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7674. (c) Maiti, D.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 17423. (d) Sergeev, A. G.; Schulz, T.; Torborg, C.; Spannenberg, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7595.

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(9) For examples of *ortho*-ester group-directed acetoxylation of indoles under AcOH medium at 100 °C, see: Mutule, I.; Suna, E.; Olofsson, K.; Pelcman, B. *J. Org. Chem.* **2009**, *74*, 7195.

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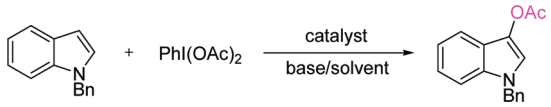
TABLE 1. Initial Optimization of Direct C3-Acetoxylation of Indole[a]



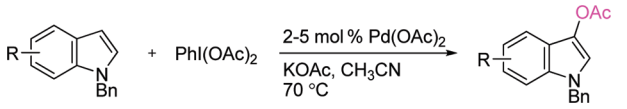
entry	catalyst	solvent	base	% yield[b]
1	$Pd(OAc)_2$	CH_3CN	KOAc	70
2	$PdCl_2$	CH_3CN	KOAc	60
3	Pd_2dba_3	CH_3CN	KOAc	58
4	$Pd(TFA)_2$	CH_3CN	KOAc	59
5		CH_3CN	KOAc	trace
6	$Pd(OAc)_2$	1,2-DCE	KOAc	55
7	$Pd(OAc)_2$	DMF	KOAc	50
8	$Pd(OAc)_2$	dioxane	KOAc	26
9	$Pd(OAc)_2$	toluene	KOAc	22
10	$Pd(OAc)_2$	CH_3CN	K_2CO_3	30
11	$Pd(OAc)_2$	CH_3CN	K_3PO_4	56
12	$Pd(OAc)_2$	CH_3CN	KOH	51
13	$Pd(OAc)_2$	CH_3CN	NaOAc	53
14	$Pd(OAc)_2$	CH_3CN	Et_3N	16
15	$Pd(OAc)_2$	CH_3CN		31

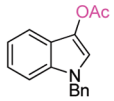
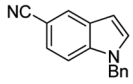
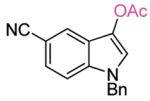
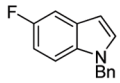
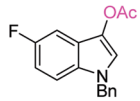
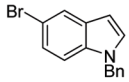
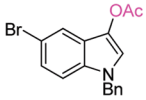
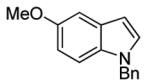
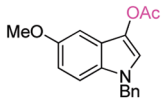
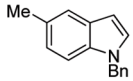
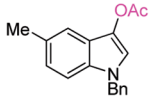
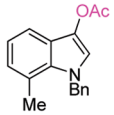
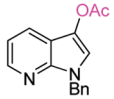
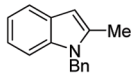
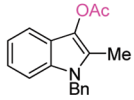
[a]Reaction conditions: catalyst (0.01 mmol, 2 mol %), *N*-benzylindole (0.5 mmol), $PhI(OAc)_2$ (1.0 mmol), base (0.5 mmol), and solvent (2.0 mL) were stirred at 70 °C under nitrogen for 2 h. [b]Calibrated GC yields were reported using dodecane as the internal standard.

disclosed the 2,3′-biindole synthesis together with the C3-acetoxylated products using AgOAc under O_2.[10] Despite these remarkable developments, the direct and regioselective acetoxylation (via C−H bond cleavage/C−O bond coupling sequence) without the assistance from the *ortho*-directing group remained sporadically studied.

Indole is an important class of compounds in the pharmaceutical chemistry as it possesses unique biological activities.[11] In particular, 3-hydroxyindoles (and their alkoxy derivatives) are common scaffolds in medicinal chemistry. They have been used in the development of COX-2 inhibitors[12] as well as applied as Mcl-1 inhibitors in the design of novel antitumor agents.[13] Moreover, they could serve as 5-HT_6 receptor ligand mimics.[14] Literature methods for accessing these 3-hydroxyl(-alkoxyl)indoles in moderate to good yields were mainly from the precursors of 3-bromoindoles[15,16] or 3-formylindoles.[17] Recently, Beller and co-workers reported the Ti- and Zn-mediated hydroamination of silyl-protected propargylic alcohol with arylhydrazine for accessing 3-silyloxy-2-methylindoles.[18] Despite these limited 3-oxyindole syntheses, an exploration of a facile protocol for the direct acetoxylation of indole, and thus hydroxy/alkoxyindoles, would be highly favorable. Herein, we disclose our efforts on direct palladium-catalyzed oxidative C3-acetoxylation of 2-unsubstituted indole in a highly regioselective manner via the C−H bond cleavage/C−O bond formation sequence.

TABLE 2. Palladium-Catalyzed Direct C3-Acetoxylation of Indoles[a]



entry	indole	product	mol%Pd, time(h)	% yield[b]
1			2 mol%, 1 h	70
2			5 mol%, 60 h (RT.)	52
3			2 mol%, 1 h (air)	50
4			2 mol%, 18 h	48
5			2 mol%, 1 h	61
6			5 mol%, 1 h	66
7			2 mol%, 1 h	85
8			2 mol%, 1 h	70
9			2 mol%, 1 h	73
10			2 mol%, 1 h	69
11			2 mol%, 18 h	53
12			2 mol%, 1 h	63

[a]Reaction conditions: $Pd(OAc)_2$ (0.01 mmol, 2 mol %), *N*-benzylindoles (0.5 mmol), $PhI(OAc)_2$ (1.0 mmol), KOAc (0.5 mmol), and CH_3CN (1.0 mL) were stirred at 70 °C under nitrogen for 1−18 h. [b]Isolated yields.

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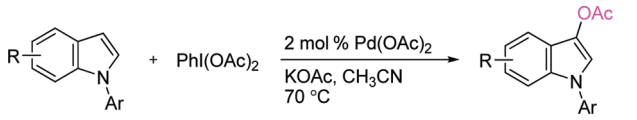
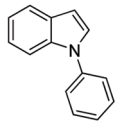
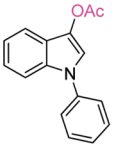
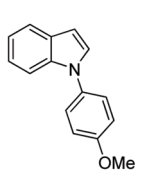
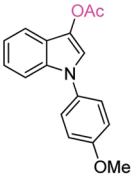
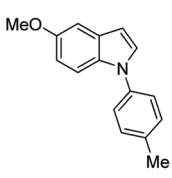
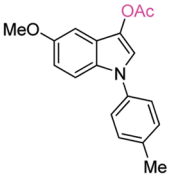
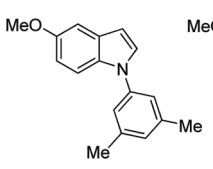
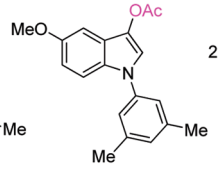
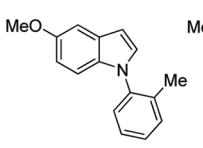
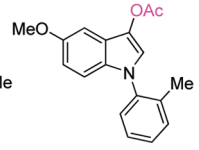
(16) For Pd-catalyzed alkoxylation of 3-bromoindoles, see ref 13.
(17) For a Baeyer−Villiger oxidation sequence, see: (a) Bourlot, A. S.; Desarbre, E.; Merour, J.-Y. *Synthesis* **1994**, 411. (b) Hickman, Z. L.; Sturino, C. F.; Lachance, N. *Tetrahedron Lett.* **2000**, *41*, 8217.
(18) For Ti-mediated protocol, see: (a) Schwarz, N.; Alex, K.; Sayyed, I. A.; Khedkar, V.; Tillack, A.; Beller, M. *Synlett* **2007**, 1091. For Zn-mediated protocol, see: (b) Alex, K.; Tillack, A.; Schwarz, N.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 2304.

TABLE 3. Palladium-Catalyzed Direct C3-Acetoxylation of *N*-Arylindoles[a]



entry	indole	product	mol%Pd, time(h)	% yield[b]
1			2 mol%, 2 h	68
2			2 mol%, 2 h	61
3			2 mol%, 1 h	65
4			2 mol%, 1 h	76
5			2 mol%, 1 h	63

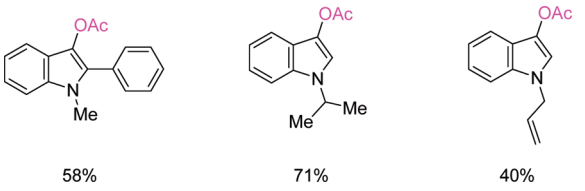
[a]Reaction conditions: $Pd(OAc)_2$ (0.01 mmol, 2 mol %), *N*-arylindoles (0.5 mmol), $PhI(OAc)_2$ (1.0 mmol), KOAc (0.5 mmol), and CH_3CN (1.0 mL) were stirred at 70 °C under nitrogen for 1−2 h. [b]Isolated yields.

Results and Discussion

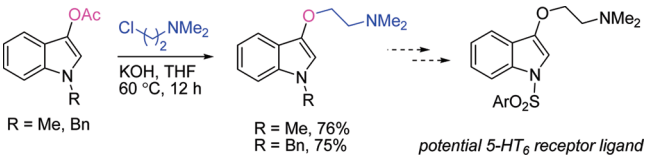
In order to achieve the C-3 indole functionalization, a series of reaction parameter screenings were deployed. *N*-Benzyl-protected indole substrate was chosen in the prototypical trials (Table 1). In the model catalysis, $PhI(OAc)_2$ was used as the oxidant to provide the acetoxy group to indole. An array of commonly used catalyst precursors for coupling reactions were surveyed (Table 1, entries 1−4). $Pd(OAc)_2$ gave the best conversion and yield of the product (entry 1). Control experiments revealed that no product was formed in the absence of palladium catalyst (entry 5). Lewis acids such as $Zn(OTf)_2$, $KAuCl_4$, AuCl, AgOTf, $Cu(OTf)_2$, $Yb(OTf)_3$, and $Eu(fod)_3$ gave only 3−6% yields. Among solvents screened, CH_3CN afforded the best results (entry 1 vs entries 6−9). KOAc base was found to be superior to the other inorganic bases (entry 1 vs entries 10−13). However, poorer yields were obtained when organic base or base-free conditions were used (entries 14 and 15).

With the preliminary optimized reaction conditions in hand, we next tested the generality of the catalyst system for direct acetoxylation of substituted indoles (Table 2). In general, 2 mol % of $Pd(OAc)_2$ was sufficient to catalyze the reaction. Notably, this direct acetoxylation of indole could be performed at room temperature (entry 2). Functional groups such as cyano, bromo, fluoro, and methoxy were compatible under these reaction conditions, entries 4−8). Notably, the bromo group remained intact throughout this palladium catalysis. This is beneficial for further functionalization using other coupling protocols. Apart from various 5-substituted indoles, 7-substituted indole furnished the desired product smoothly (entry 9). Azaindole was found to be a feasible substrate for this reaction (entry 11).

SCHEME 1. Palladium-Catalyzed Direct Acetoxylation of *N*-Alkylated Indoles (Reaction Conditions are the Same as in Table 2, Entry 1)



SCHEME 2. Cascade Deacetylation−Alkylation Process of Acetoxyindoles



To further evaluate the catalytic system, we examined the acetoxylation of *N*-aryl indoles (Table 3). Moderate to good yields of the corresponding products were obtained (entries 1−5). This protocol was found to be compatible with *ortho*-, *meta*-, and *para*-substituted aryl rings on the indolyl scaffold.

Apart from *N*-benzyl- and *N*-arylindoles, *N*-alkylated indoles were feasible substrates for direct acetoxylation (Scheme 1). *N*-Isopropyl- and *N*-allylindoles were transformed to their corresponding product selectively. Interestingly, no acetoxylation of olefin moiety was observed on the allyl group under our reaction conditions.[19] Sterically congested 2-phenyl-*N*-methylindoles furnished the product in slightly lower yield presumably due to the steric hindrance of the *o*-phenyl ring.

3-Hydroxyindoles are slightly unstable and preferably have silyl or acetyl protection for storage. Indeed, the direct acetoxylation of indole would be a useful way to prepare the protected form of 3-oxyindoles, which can be further functionalized by an easy alkaline hydrolysis to achieve 3-hydroxyindole motifs in situ. In fact, this organic transformation offers a simple protocol to afford a series of potential 5-HT_6 receptor ligands.[14] Thus, the cascade deacetylation and subsequent alkylation processes provide a versatile pathway to access tryptamine-like 5-HT_6 receptor ligand scaffolds, which would be useful for further structural manipulation (Scheme 2).

Conclusion

In summary, we have developed a general palladium-catalyzed direct and regioselective C3-acetoxylation of 2,3-unsubstituted

(19) For the diacetoxylation of styrenes, see: Wang, A.; Jiang, H.; Chen, H. *J. Am. Chem. Soc.* **2009**, *131*, 3846.

indoles, which is complementary to current difficult C−O bond-coupling processes using aryl halides as electrophiles. Moreover, this selective C−H bond-cleavage/C−O bond-coupling sequence is achievable without the aid of *ortho*-directing groups. This protocol provides a facile and direct access to a variety of pharmaceutically useful 3-oxyindole scaffolds under mild reaction conditions (weak base, KOAc; at 70 °C for 1−18 h) and is compatible with the bromo group, which offers potential for further structural modification using other coupling technology. Detailed mechanistic investigations are currently underway.

Experimental Section

General Procedures for Acetoxylation of *N*-Substituted Indoles (Pd Catalyst Loading Range of 2−5 mol %). $Pd(OAc)_2$, PhI-$(OAc)_2$ (1.0 mmol), substituted benzylindoles (0.5 mmol), and KOAc (0.5 mmol) were loaded into a Schlenk tube equipped with a Teflon-coated magnetic stir bar. The tube was evacuated and flushed with nitrogen three times. The solvent acetonitrile (1.0 mL) was then added with stirring at room temperature for several minutes. The tube was then placed into a preheated oil bath (70 °C/25 °C) and stirred for the time as indicated in Tables 2 and 3. After completion of the reaction as judged by GC analysis, the reaction tube was allowed to cool to room temperature and quenched with sodium bisulfate solution and water. EtOAc was then added for dilution. The organic layer was separated, and the aqueous layer was washed with EtOAc. The filtrate was concentrated under reduced pressure. The crude products were purified by flash column chromatography on silica gel (230−400 mesh) to afford the desired product.

1-Benzyl-1*H*-indol-3-yl acetate (example from Table 2, entry 1):[20] EA/petroleum ether/Et_3N = 1:9:0.1, R_f = 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 5.30 (s, 2H), 7.16−7.26 (m, 4H), 7.29−7.38 (m, 5H), 7.62−7.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 50.0, 109.6, 117.2, 117.6, 119.5, 120.3, 122.5, 126.7, 127.6, 128.7, 129.7, 133.3, 137.1, 168.4; MS (EI) *m*/*z* (relative intensity) 265 (M^+, 20), 223 (89), 91 (100). (See the Supporting Information for copies of the spectra.)

1-Benzyl-5-cyano-1*H*-indol-3-yl acetate (Table 2, entry 4): EA/petroleum ether/Et_3N = 1:2:0.1, R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 5.29 (s, 2H), 7.13 (dd, J = 1.2, 6.0 Hz, 2H), 7.30−7.41 (m, 5H), 7.50 (s, 1H), 7.96 (dd, J = 0.4, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 50.3, 102.6, 110.5, 119.4, 120.1, 123.5, 125.1, 126.7, 128.0, 128.8, 129.8, 134.2, 135.9; MS (EI) *m*/*z* (relative intensity) 290 (M^+, 9), 248 (57), 91 (100); HRMS calcd for $C_{18}H_{15}N_2O_2^+$ 291.1134, found 291.1140.

1-Benzyl-5-fluoro-1*H*-indol-3-yl acetate (Table 2, entry 5): EA/petroleum ether/Et_3N = 1:9:0.1, R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 5.26 (s, 2H), 6.95−7.00 (m, 1H), 7.14−7.21 (m, 3H), 7.26−7.36 (m, 4H), 7.42 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 50.3, 102.5, 102.7, 110.6, 110.7, 110.9, 111.2, 119.0, 120.4, 120.5, 126.7, 127.7, 128.7, 129.5, 129.9, 136.8, 156.5, 158.8, 168.3; MS (EI) *m*/*z* (relative intensity) 283 (M^+, 14), 241 (69), 91 (100); HRMS calcd for $C_{17}H_{15}NO_2F^+$ 284.1087, found 284.1048.

1-Benzyl-5-bromo-1*H*-indol-3-yl acetate (Table 2, entry 6): EA/petroleum ether/Et_3N = 1:9:0.1, R_f = 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 5.24 (s, 2H), 7.12−7.26 (m, 3H), 7.28−7.33 (m, 4H), 7.38 (s, 1H), 7.76 (dd, J = 0.4, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 50.2, 111.2, 112.8, 118.4, 120.2, 121.9, 125.3, 126.6, 127.8, 128.7, 131.8, 136.6, 168.2; MS (EI) *m*/*z* (relative intensity) 343 (M^+, 8), 301 (43), 91 (100); HRMS calcd for $C_{17}H_{14}NO_2NaBr^+$ 366.0106, found 366.0117.

(20) Haro, T. d.; Nevado, C. *J. Am. Chem. Soc.* **2010**, *132*, 1512.

1-Benzyl-5-methoxy-1*H*-indol-3-yl acetate (Table 2, entry 7): EA/petroleum ether/Et_3N = 1:4:0.1, R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H), 3.90 (s, 3H), 5.24 (s, 2H), 6.89−6.92 (m, 1H), 7.05 (s, 1H), 7.14−7.19 (m, 3H), 7.28−7.36 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 50.1, 55.6, 98.7, 110.7, 113.2, 117.8, 120.4, 126.6, 127.5, 128.6, 129.3, 137.25, 154.0, 168.4; MS (EI) *m*/*z* (relative intensity) 295 (M^+, 25), 253 (100), 162 (26), 91 (90); HRMS calcd for $C_{18}H_{18}NO_3^+$ 296.1287, found 296.1290.

1-Benzyl-5-methyl-1*H*-indol-3-yl acetate (Table 2, entry 8): EA/petroleum ether/Et_3N = 1:6:0.1, R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H), 2.51 (s, 3H), 5.27 (s, 2H), 7.06−7.18 (m, 4H), 7.28−7.36 (s, 4H), 7.42 (t, J = 0.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 21.3, 50.0, 109.4, 117.1, 117.3, 120.5, 124.2, 126.7, 127.5, 128.6, 128.8, 129.2, 131.8, 137.3; MS (EI) *m*/*z* (relative intensity) 279 (M^+, 23), 257 (100), 146 (31), 91 (94); HRMS calcd for $C_{18}H_{18}NO_2^+$ 280.1338, found 280.1339.

1-Benzyl-7-methoxy-1*H*-indol-3-yl acetate (Table 2, entry 9): EA/petroleum ether/Et_3N = 1:6:0.1, R_f = 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 3.88 (s, 3H), 5.63 (s, 2H), 6.7 (d, J = 7.6 Hz, 1H), 7.05−7.10 (m, 1H), 7.18−7.34 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 52.4, 55.2, 103.3, 110.2, 118.0, 120.0, 122.4, 123.1, 126.7, 127.1, 128.4, 129.8, 139.2, 147.4, 168.3; MS (EI) *m*/*z* (relative intensity) 295 (M^+, 33), 253 (100), 162 (16), 91 (64); HRMS calcd for $C_{18}H_{18}NO_3^+$ 296.1287, found 296.1293.

1-Benzyl-7-methyl-1*H*-indol-3-yl acetate (Table 2, entry 10): EA/petroleum ether/Et_3N = 1:9:0.1, R_f = 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 2.54 (s, 3H), 5.55 (s, 2H), 6.92−6.98 (m, 3H), 7.04 (t, J = 7.2 Hz, 1H), 7.25−7.45 (m, 4H), 7.47 (d, J = 0.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 20.9, 52.2, 115.5, 118.9, 119.8, 121.2, 121.4, 125.4, 127.3, 128.8, 129.7, 132.2, 139.2, 168.4; MS (EI): *m*/*z* (relative intensity) 279 (M^+, 25), 237 (83), 146 (41), 91 (100); HRMS calcd for $C_{18}H_{17}NO_2Na^+$ 302.1157, found 302.1157.

1-Benzyl-1*H*-pyrrolo[2,3-b]pyridine-3-yl acetate (Table 2, entry 11): EA/petroleum ether/Et_3N = 1:6:0.1, R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 5.50 (s, 2H), 7.10−7.14 (dd, J = 0.8, 3.2 Hz, 1H), 7.24−7.35 (m, 6H), 7.89 (dd, J = 1.6, 6.4 Hz, 1H), 7.10−8.40 (t, J = 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 47.5, 112.7, 115.7, 116.7, 126.2, 127.4, 127.6, 127.9, 128.6, 137.3, 143.8, 144.0; MS (EI) *m*/*z* (relative intensity) 266 (M^+, 16), 224 (92), 147 (18), 91 (100); HRMS calcd. for $C_{16}H_{15}N_2O_2^+$ 267.1134, found 267.1130.

1-Benzyl-2-methyl-1*H*-indol-3-yl acetate (Table 2, entry 12). EA/petroleum ether/Et_3N = 1:4:0.1, R_f = 0.7; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3H), 2.44 (s, 3H), 5.31 (s, 2H), 7.04 (d, J = 6.8 Hz, 2H), 7.14−7.20 (m, 2H), 7.25−7.34 (m, 4H), 7.45−7.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.0, 20.5, 46.4, 109.3, 116.7, 119.6, 120.7, 121.4, 125.6, 125.9, 126.5, 127.3, 128.7, 133.9, 137.5, 169.3; MS (EI) *m*/*z* (relative intensity) 279 (M^+, 23), 237 (100), 146 (35), 91 (91); HRMS calcd for $C_{18}H_{18}NO_2^+$ 280.1338, found 280.1341.

1-Phenyl-1*H*-indol-3-yl acetate (Table 3, entry 1):[21] EA/petroleum ether/Et_3N = 1:9:0.1, R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 7.25−7.33 (m, 2H), 7.37−7.41 (m, 1H), 7.54−7.70 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 110.5, 116.9, 117.7, 120.3, 121.1, 123.1, 124.3, 126.3, 129.5, 131.4, 132.7, 139.3, 168.3; MS (EI) *m*/*z* (relative intensity) 251 (M^+, 18), 209 (100), 180 (33), 77 (20).

1-(4-Methoxyphenyl)-1*H*-indol-3-yl acetate (Table 3, entry 2):[22] EA/petroleum ether/Et_3N = 1: 4: 0.1, R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 3.90 (s, 3H), 7.04−7.08 (m, 2H), 7.21−7.30 (m, 2H), 7.43−7.44 (m, 3H), 7.45 (s, 1H), 7.47−7.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

(21) Moltzen, E. K.; Perregaard, J. K. EP 518805 A1 19921216.

(22) Bellina, F.; Calandri, C.; Cauteruccio, S.; Rossi, R. *Eur. J. Org. Chem.* **2007**, *13*, 2147.

20.8, 55.4, 110.3, 114.6, 117.3, 117.6, 120.0, 120.7, 122.9, 125.9, 130.9, 132.2, 133.2, 158.1, 168.3; MS (EI) *m*/*z* (relative intensity) 281 (M^+, 22), 239 (100), 210 (15), 77 (12).

5-Methoxy-1-(4-methylphenyl)-1*H*-indol-3-yl acetate (Table 3, entry 3): EA/petroleum ether/Et_3N = 1:4:0.1, R_f = 0.5; ^1H NMR (400 MHz, $CDCl_3$) δ 2.44 (d, J = 6.8 Hz, 3H), 3.92 (s, 3H), 6.93 (dd, J = 2.0, 6.8 Hz, 1H), 7.07 (d, J = 2.8 Hz, 1H), 7.32 (d, J = 4.0, 2H), 7.39−7.46 (m, 5H), 7.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 20.9, 55.7, 98.8, 111.6, 113.5, 117.5, 121.2, 123.9, 128.1, 130.0, 130.9, 136.0, 136.9, 154.4, 158.3; MS (EI) *m*/*z* (relative intensity) 295 (M^+, 22), 253 (100), 210 (15); HRMS calcd for $C_{18}H_{18}NO_3^+$ 296.1287, found 296.1295.

1-(3,5-Dimethylphenyl)-5-methoxy-1*H*-indol-3-yl acetate (Table 3, entry 4): EA/petroleum ether/Et_3N = 1:4:0.1, R_f = 0.5; ^1H NMR (400 MHz, $CDCl_3$) δ 2.43 (d, J = 3.6 Hz, 9H), 3.93 (s, 3H), 6.95 (dd, J = 2.8, 6.4 Hz, 1H), 7.00 (s, 1H), 7.07 (d, J = 2.4 Hz, 1H), 7.14 (s, 2H), 7.50 (d, J = 8.8 Hz, 1H), 7.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 21.2, 55.7, 98.7, 111.7, 113.5, 117.4, 121.3, 121.7, 127.8, 128.0, 131.0, 139.2, 139.3, 154.4, 158.3; MS (EI) *m*/*z* (relative intensity) 309 (M^+, 24), 267 (100), 251 (18); HRMS calcd for $C_{19}H_{20}NO_3^+$ 310.1443, found 310.1454.

5-Methoxy-1-*o*-tolyl-1*H*-indol-3-yl acetate (Table 3, entry 5): EA/petroleum ether/Et_3N = 1:4:0.1, R_f = 0.7; ^1H NMR (400 MHz, $CDCl_3$) δ 2.13 (s, 3H), 2.43 (s, 3H), 3.92 (s, 3H), 6.88−6.97 (m, 2H), 7.09 (d, J = 2.0 Hz, 1H), 7.33−7.43 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 20.9, 55.7, 98.7, 111.6, 113.5, 118.3, 120.2, 126.6, 128.1, 128.1, 129.3, 130.4, 131.1, 135.7, 137.8, 154.3, 168.2; MS (EI) *m*/*z* (relative intensity) 295 (M^+, 23), 253 (100), 238 (20); HRMS calcd for $C_{18}H_{17}NO_3Na^+$ 318.1106, found 318.1093.

1-Allyl-1*H*-indol-3-yl acetate (Scheme 1). EA/petroleum ether/Et_3N = 1:9:0.1, R_f = 0.5; ^1H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 4.70−4.72 (m, 2H), 5.12−5.14 (m, 1H), 5.17−5.18 (m, 1H), 5.22−5.26 (m, 1H), 5.96−6.06 (m, 1H), 7.14−7.18 (m, 1H), 7.24−7.28 (m, 1H), 7.31−7.33 (m, 2H), 7.58−7.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 48.7, 109.5, 116.8, 117.4, 117.5, 119.4, 120.3, 122.3, 129.5, 133.1, 133.1, 168.3; MS (EI) *m*/*z* (relative intensity) 215 (M^+, 28), 173 (100), 132 (76); HRMS calcd for $C_{13}H_{13}NO_2Na^+$ 238.084, found 238.0851.

1-Isopropyl-1*H*-indol-3-yl acetate (Scheme 1): EA/petroleum ether/Et_3N = 1:9:0.1, R_f = 0.45; ^1H NMR (400 MHz, $CDCl_3$) δ 1.56 (d, J = 6.8 Hz, 6H), 2.41 (s, 3H), 4.68−4.75 (m, 1H), 7.16−7.20 (m, 1H), 7.27−7.31 (m, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.47 (s, 1H), 7.63 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 22.5, 47.0, 109.3, 112.7, 117.5, 119.1, 120.1, 121.9, 129.5, 132.4, 168.5; MS (EI) *m*/*z* (relative intensity) 217 (M^+, 34), 175 (89), 160 (100), 132 (44); HRMS calcd for $C_{13}H_{15}NO_2Na^+$ 240.1000, found 240.1002.

(23) Capon, B; Kwok, F. C. *J. Am. Chem. Soc.* **1989**, *111*, 5346.

1-Methyl-2-phenyl-1*H*-indol-3-yl acetate (Scheme 1): EA/petroleum ether/Et_3N = 1:9:0.1, R_f = 0.5; ^1H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 3.72 (s, 3H), 7.21−7.25 (m, 1H), 7.31−7.35 (m, 1H), 7.41−7.57 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 30.8, 109.7, 117.3, 119.9, 120.5, 122.4, 126.4, 128.2, 128.5, 129.4, 130.0, 134.9, 169.8; MS (EI) *m*/*z* (relative intensity) 265 (M^+, 13), 223 (100); HRMS calcd for $C_{17}H_{16}NO_2^+$ 266.1181, found 266.1173.

1-Methyl-1*H*-indol-3-yl acetate (Scheme 2):[23] EA/hexane/Et_3N = 1:4:0.1, R_f = 0.5; ^1H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 3.77 (s, 3H), 7.14−7.18 (m, 1H), 7.26−7.34 (m, 3H), 7.57−7.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 32.7, 109.2, 117.4, 117.8, 119.2, 120.0, 122.2, 129.0, 133.6, 168.7; MS (EI) *m*/*z* (relative intensity) 189 (M^+, 21), 147 (100), 132 (11), 77 (13).

***N*,*N*-Dimethyl-2-(1-methyl-1*H*-indol-3-yloxy)ethanamine (Scheme 2):** MeOH/$CHCl_3$ = 1:9, R_f = 0.45; ^1H NMR (400 MHz, C_6D_6) δ 2.18 (s, 6H), 2.64 (t, J = 6.0 Hz, 2H), 2.97 (s, 3H), 3.98 (t, J = 6.0 Hz, 2H), 6.11 (s, 1H), 6.98 (d, J = 8.0 Hz, 1H), 7.09−7.22 (m, 2H), 7.94 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 31.9, 46.0, 58.7, 70.0, 109.2, 110.0, 118.5, 118.7, 120.6, 122.5, 135.3, 140.4; MS (EI) *m*/*z* (relative intensity) 218 (M^+, 8), 146 (10), 72 (100), 58 (33) ; HRMS calcd for $C_{13}H_{19}N_2O^+$ 219.1497, found 219.1506.

***N*,*N*-Dimethyl-2-(1-benzyl-1*H*-indol-3-yloxy)ethanamine (Scheme 2):** MeOH/$CHCl_3$ = 1:9, R_f = 0.5; ^1H NMR (400 MHz, C_6D_6) δ 2.16 (s, 6H), 2.62 (t, J = 6.0 Hz, 2H), 3.93 (t, J = 8.0 Hz, 2H), 4.68 (s, 2H), 6.27 (s, 1H), 6.81−6.84 (m, 2H), 6.97−7.03 (m, 4H), 7.07−7.16 (m, 2H), 7.96−7.98 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 46.6, 50.1, 59.2, 70.4, 109.6, 110.2, 119.4, 119.5, 121.5, 123.6, 127.4, 128.1, 128.3, 129.4, 135.7, 139.1, 141.6; MS (EI) *m*/*z* (relative intensity) 294 (M^+, 7), 91 (32), 72 (100), 58 (23); HRMS calcd for $C_{19}H_{23}N_2O^+$ 295.1810, found 295.1796.

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Supporting Information Available: Detail experimental procedures and copies of ^1H NMR, ^{13}C NMR, and HRMS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.