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PALLADIUM-CATALYZED DIRECT ARYLATION AND ALKENYLATION OF 3-(INDOL-3-YL)PROPIONIC ACIDS THROUGH C–H BOND CLEAVAGE

Daisuke Takeda,[1] Koji Hirano,[1] Tetsuya Satoh,*[1,2] and Masahiro Miura*[1]

[1] Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871, Japan; [2] JST, ACT-C, 4-1-8 Honcho, Kawaguchi, Saitama 332-0012, Japan

E-mail: satoh@chem.eng.osaka-u.ac.jp; miura@chem.eng.osaka-u.ac.jp

Abstract – The palladium-catalyzed direct arylation of 3-(indol-3-yl)propionic acids with aryl bromides proceeds through C–H bond cleavages to give C2-arylated product in good yields. The C2-alkenylation of the substrates can also be performed smoothly under appropriate oxidative conditions.

INTRODUCTION

Indole structures possessing various substituents can be seen in a great number of biologically active natural and unnatural compounds, and thus, their selective syntheses are of considerable importance in organic synthesis field.[1] Among others, 3-(2-substituted indol-3-yl)propionic acid derivatives are of particular interest due to their broad biological activities as well as tangible potential as neurokinin 1 (NK_1) antagonists and antioxidants.[2] Therefore, the development of synthetic methods for C2-functionalization of the indole moiety of 3-(indol-3-yl)propionic acids is of substantial interest. Meanwhile, the transition-metal-catalyzed direct functionalization reactions of (hetero)aromatic compounds via C–H bond cleavage have extensively studied in recent years due to their atom- and step-economical advantages over the conventional cross-coupling strategies.[3] We have investigated the direct arylation, alkenylation, and annulation of heteroaromatics including indoles.[4] In the context of our work, we demonstrated that (indol-3-yl)acetic acids undergo C2-arylation upon treatment with aryl bromides in the presence of a palladium catalyst.[4a,5] The carboxylic function appears to act as an effective director for the reaction. During a further study, it was found that the C2-arylation of 3-(indol-3-yl)-

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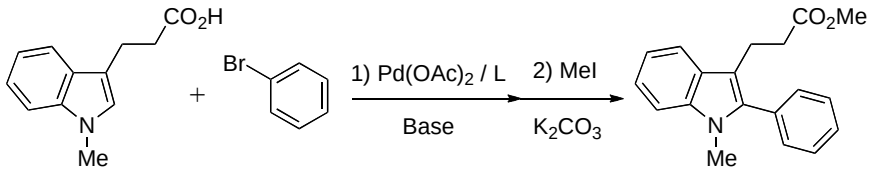
Dedicated to Professor Victor Snieckus on the occasion of his 77th birthday.

propionic acids can be achieved effectively by using a similar catalytic system. Moreover, the substrates also underwent C2-alkenylation with alkenes in the presence of an appropriate oxidant.[6] These new findings are described herein.

RESULTS AND DISCUSSION

In an initial attempt, 3-(1-methylindol-3-yl)propionic acid (**1a**, 0.4 mmol) was treated with bromobenzene (**2a**, 0.8 mmol) in the presence of $Pd(OAc)_2$ (0.02 mmol), CyJohnPhos (2-(dicyclohexylphosphino)-biphenyl, 0.04 mmol), and K_2CO_3 (0.9 mmol) as catalyst, ligand, and base, respectively, in DMAc at 170 ^oC for 9 h. After treatment with MeI (6 mmol) and K_2CO_3 (3 mmol) at room temperature for quantification, methyl 3-(1-methyl-2-phenylindol-3-yl)propionate (**3a**) was obtained in 80% yield (Table 1, Entry 1). Both increase and decrease in the amount of **2a** did not enhance the product yield (Entries 2

Table 1. Reaction of 3-(1-methylindol-3-yl)propionic acid (**1a**) with bromobenzene (**2a**)[a)]



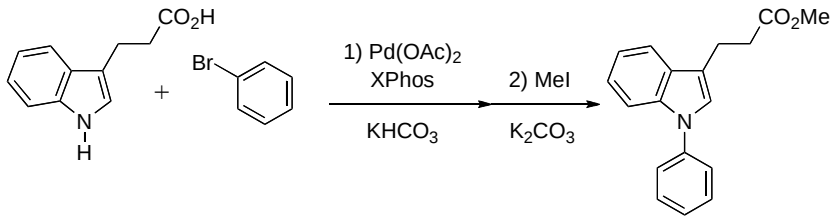
1a **2a** **3a**

Entry	L	Base	Yield of **3a** /%[b)]
1[c)]	CyJohnPhos	K_2CO_3	80 (70)
2[c,d)]	CyJohnPhos	K_2CO_3	69
3[c,e)]	CyJohnPhos	K_2CO_3	78
4	CyJohnPhos	K_2CO_3	78
5	CyJohnPhos	Na_2CO_3	15
6	CyJohnPhos	Cs_2CO_3	47
7	CyJohnPhos	$KOBu^t$	55
8	CyJohnPhos	KOAc	31
9	CyJohnPhos	KH_2PO_4	2
10	CyJohnPhos	$KHCO_3$	81 (71)
11	CyJohnPhos	K_3PO_4	81
12	JohnPhos	$KHCO_3$	50
13	SPhos	$KHCO_3$	3
14	DavePhos	$KHCO_3$	80
15	XPhos	$KHCO_3$	98 (85)
16	PPh_3	$KHCO_3$	43
17	PCy_3	$KHCO_3$	37
18[f)]	dppb	$KHCO_3$	50
19[f)]	Xantphos	$KHCO_3$	72

a) Reaction conditions: 1) **1a** (0.4 mmol), **2a** (0.8 mmol), $Pd(OAc)_2$ (0.02 mmol), L (0.04 mmol), Base (0.9 mmol), in DMAc (2.5 mL) at 170 ^oC for 3 h under N_2; 2) with the addition of MeI (6 mmol) and K_2CO_3 (3 mmol) at room temperature for 3 h. b) GC yield based on the amount of **1a** used. Value in parentheses indicates yield after isolation. c) For 9 h. d) With **2a** (0.5 mmol). e) With **2a** (1.2 mmol). f) With L (0.02 mmol).

and 3). A comparable result was found to be obtained within 3 h (Entry 4 vs 1). Although the use of other bases such as Na_2CO_3, Cs_2CO_3, $KOBu^t$, KOAc, and KH_2PO_4 in place of K_2CO_3 decreased the product yield (Entries 5-9), $KHCO_3$ and K_3PO_4 were found to be as effective as K_2CO_3 (Entries 10 and 11). Next, the reaction was conducted with various mono- and diphosphine ligands using $KHCO_3$ as base (Entries 12-19). Among the ligands examined, XPhos (2-(dicyclohexylphosphino)-2',4',6'-triisopropylbiphenyl) was found to be the most effective (Entry 15). Thus, with XPhos (0.04 mmol), **3a** was obtained in 98% yield.

Under the optimized reaction conditions (Table 1, Entry 15), the reactions of a series of 4-substituted bromobenzenes **2b-f** with **1a** were next examined (Table 2, Entries 1-7). While 4-bromotoluene (**2b**) reacted with **1a** smoothly (Entry 1), the reaction of 4-bromoanisole (**2c**) was somewhat sluggish (Entry 2). By increasing the amount of $KHCO_3$ (1.5 mmol) and extending reaction time (20 h), product **3c** was obtained in 97% yield (Entry 4). Under similar conditions, 4-chloro- (**2d**), 4-fluoro- (**2e**), and 4-trifluoromethyl- (**2f**) bromobenzenes also underwent the reaction with **1a** efficiently to produce the corresponding methyl 3-(1-methyl-2-arylindol-3-yl)propionates **3d-f** in good yields (Entries 5-7). 3-(1-Phenylindol-3-yl)propionic acid (**1b**) also reacted with **2a** to afford methyl 3-(1,2-diphenylindol-3-yl)propionate (**3g**) (Entry 8). In contrast, 3-(1-unsubstituted indol-3-yl)propionic acid (**1c**) underwent phenylation on N1 rather than C2 upon treatment with **2a** (Scheme 1).

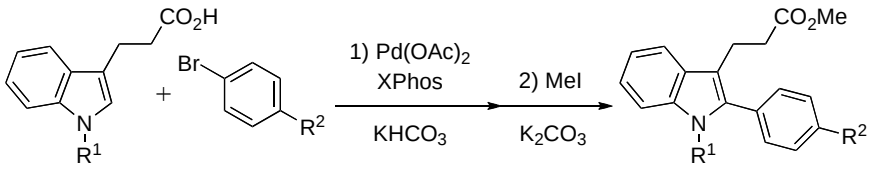


1c **2a** **3a'**, 52% (49%)[a)]

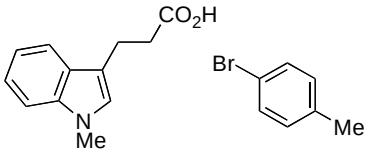
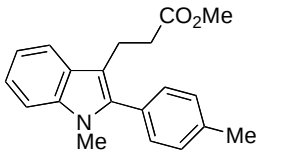
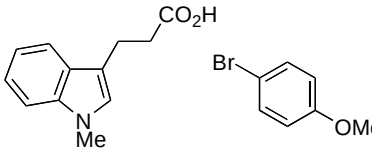
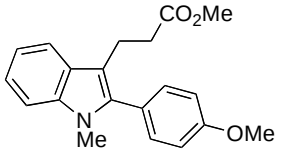
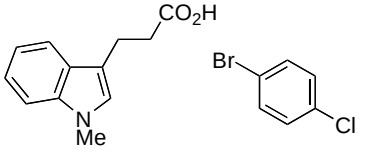
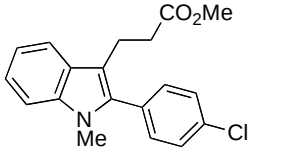
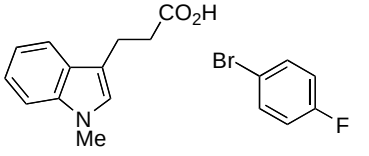
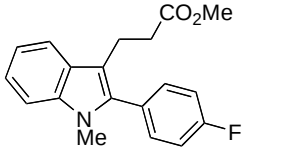
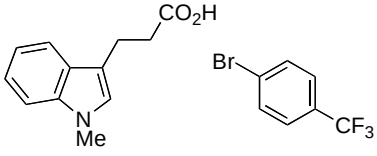
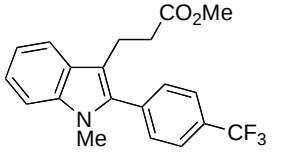
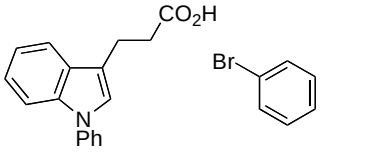
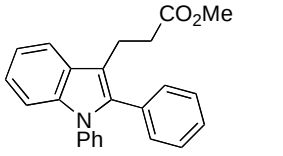
Scheme 1. Reaction of **1c** with **2a**. Reaction conditions: 1) **1c** (0.4 mmol), **2a** (0.8 mmol), $Pd(OAc)_2$ (0.02 mmol), XPhos (0.04 mmol), $KHCO_3$ (1.5 mmol), in DMAc (2.5 mL) at 170 °C for 20 h under N_2; 2) with the addition of MeI (6 mmol) and K_2CO_3 (3 mmol) at room temperature for 3 h. a) GC yield based on the amount of **1c** used. Value in parentheses indicates yield after isolation.

The present arylation of **1** with **2** appears to proceed through similar reaction pathways to those of the direct arylation of indole derivatives.[4a,7] It should be noted that treatment of methyl 3-(1-methylindol-3-yl)propionate (**1d**) with **2a** gave **3a** only in a moderate yield (Scheme 2). Therefore, the existence of the carboxylic group in **1** appears to promote the reaction at least partly.

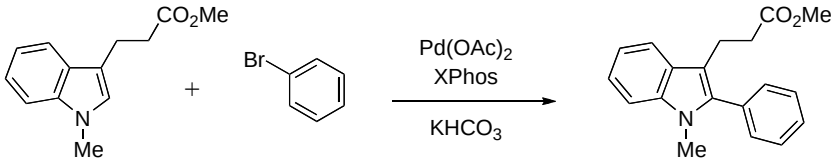
Table 2. Reaction of (indol-3-yl)-3-propionic acids **1** with aryl bromides **2**[a]



1 **2** **3**

Entry	**1**	**2**	Time / h	Product, % yield[b]
1[c]			6	 **3b**, 78 (77)
2[c]			6	 **3c**, 67
3			6	**3c**, 81
4			20	**3c**, 97 (82)
5	 **1a**	**2d**	20	 **3d**, 74 (63)
6	 **1a**	**2e**	20	 **3e**, 79 (79)
7	 **1a**	**2f**	20	 **3f**, >99 (85)
8	 **1b**	**2a**	20	 **3g**, 66 (66)

a) Reaction conditions: 1) **1** (0.4 mmol), **2** (0.8 mmol), $Pd(OAc)_2$ (0.02 mmol), XPhos (0.04 mmol), $KHCO_3$ (1.5 mmol), in DMAc (2.5 mL) at 170 °C under N_2; 2) with the addition of MeI (6 mmol) and K_2CO_3 (3 mmol) at room temperature for 3 h. b) GC yield based on the amount of **1** used. Value in parentheses indicates yield after isolation. c) With $KHCO_3$ (0.9 mmol).

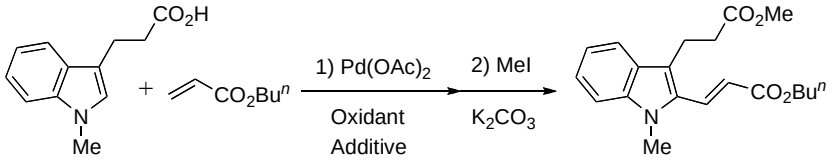


1d **2a** **3a**, 57 (54%)[a)]

Scheme 2. Reaction of **1d** with **2a**. Reaction conditions: **1d** (0.4 mmol), **2a** (0.8 mmol), $Pd(OAc)_2$ (0.02 mmol), XPhos (0.04 mmol), $KHCO_3$ (1.5 mmol), in DMAc (2.5 mL) at 170 °C for 3 h under N_2. a) GC yield based on the amount of **1d** used. Value in parentheses indicates yield after isolation.

Next, we examined the C2-alkenylation of 3-(indol-3-yl)propionic acid.[8] Treatment of **1a** (0.4 mmol) with butyl acrylate (**4a**, 0.8 mmol) in the presence of $Pd(OAc)_2$ (0.02 mmol), $Cu(OAc)_2•H_2O$ (0.8 mmol), and LiOAc (1.2 mmol) as catalyst, oxidant, and additive, respectively, in DMF at 140 °C for 6 h and subsequent esterification with MeI gave (*E*)-butyl 3-[3-(3-methoxy-3-oxopropyl)-1-methyl-1*H*-indol-2-yl]acrylate (**5a**) in 21% yield (Table 3, Entry 1).

Table 3. Reaction of 3-(1-methylindol-3-yl)propionic acid (**1a**) with butyl acrylate (**4a**)[a)]



1a **4a** **5a**

Entry	Oxidant (mmol)	Additive (mmol)	Yield of **5a** /%[b)]
1[c)]	$Cu(OAc)_2•H_2O$ (0.8)	LiOAc (1.2)	21
2	$Cu(OAc)_2•H_2O$ (0.8)	LiOAc (1.2)	45
3	$Cu(OAc)_2•H_2O$ (1.2)	LiOAc (1.2)	54 (48)
4	$Cu(OAc)_2•H_2O$ (1.6)	LiOAc (1.2)	51
5	$Cu(2\text{-}EtHexCO_2)_2$ (1.2)	LiOAc (1.2)	34
6	AgOAc (1.6)	LiOAc (1.2)	6
7	Ag_2CO_3 (0.8)	LiOAc (1.2)	9
8	$Cu(OAc)_2•H_2O$ (1.2)	–	6
9	$Cu(OAc)_2•H_2O$ (1.2)	NaOAc (1.2)	56
10	$Cu(OAc)_2•H_2O$ (1.2)	KOAc (1.2)	54
11	$Cu(OAc)_2•H_2O$ (1.2)	CsOAc (1.2)	43
12	$Cu(OAc)_2•H_2O$ (1.2)	Li_2CO_3 (1.2)	4
13	$Cu(OAc)_2•H_2O$ (1.2)	$KHCO_3$ (1.2)	7
14[d)]	$Cu(OAc)_2•H_2O$ (1.2)	LiOAc (1.2)	0
15[e)]	$Cu(OAc)_2•H_2O$ (1.2)	LiOAc (1.2)	0

a) Reaction conditions: 1) **1a** (0.4 mmol), **4a** (0.8 mmol), $Pd(OAc)_2$ (0.02 mmol), in DMAc (2.5 mL) at 170 °C for 6 h under N_2; 2) with the addition of MeI (6 mmol) and K_2CO_3 (3 mmol) at room temperature for 3 h. b) GC yield based on the amount of **1a** used. Value in parentheses indicates yield after isolation. c) In DMF at 140 °C. d) $[RuCl_2(p\text{-cymene})]_2$ (0.01 mmol) was used in place of $Pd(OAc)_2$. e) $[Cp^*RhCl_2]_2$ (0.01 mmol) was used in place of $Pd(OAc)_2$.

Increasing the reaction temperature to 170 °C in DMAc improved the yield of **5a** (Entry 2). The optimization of the amount of $Cu(OAc)_2•H_2O$ (1.2 mmol) led to further enhancement of the yield of **5a** up to 54% (Entries 3 and 4). Even in these cases, significant amounts of **1a** were recovered (ca. 20%). At a relatively high temperature, palladium active species tend to be deactivated.[9] Other oxidants such as $Cu(2\text{-ethylhexylCO}_2)_2$, AgOAc, and Ag_2CO_3 were found to be less effective (Entries 5-7). The addition of LiOAc was essential to conduct the reaction smoothly (Entry 8). While comparable results were obtained with NaOAc and KOAc (Entries 9 and 10), CsOAc, Li_2CO_3, and $KHCO_3$ were less effective as an additive (Entries 11-13). The alkenylation did not proceeded at all in the presence of a Ru- or Rh-catalyst in place of the Pd catalyst (Entries 14 and 15), although all of them have been employed as catalysts in the C2-alkenylation of indole-3-carboxylic acids.[4b,c,p]

The reactions of **1a** with various alkenes **4** were conducted under the conditions used for Entry 3 in Table 3. The corresponding C2-alkenylated products **5b-d** were obtained by using isobutyl (**4b**) and cyclohexyl (**4c**) acrylates and *N*,*N*-dimethylacrylamide (**4d**) (Table 4, Entries 1-3). As observed in the arylation, the existence of the carboxylic group was essential for conducting the alkenylation smoothly. Thus, treatment of **1d** with **4a** gave **5a** in a lower yield (Entry 4).

In summary, we have demonstrated that the C2-arylation and alkenylation of 3-(indol-3-yl)propionic acids can occur through C–H bond cleavage under palladium catalysis. The relatively more remote carboxylic group in the substrates appears to be still capable of promoting the reactions.

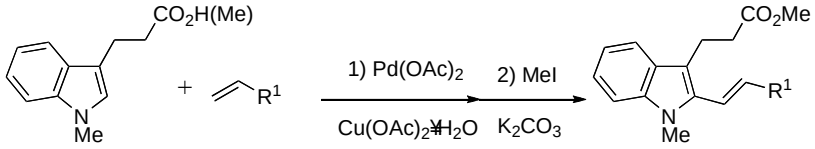
EXPERIMENTAL

General. ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz for $CDCl_3$ solutions. MS data were obtained by EI. GC analysis was carried out using a silicon OV-17 column (i. d. 2.6 mm x 1.5 m). GC-MS analysis was carried out using a CBP-1 capillary column (i. d. 0.25 mm x 25 m). The structures of all products listed below were unambiguously determined by ^1H and ^{13}C NMR with the aid of NOE, COSY, HMQC, and HMBC experiments.

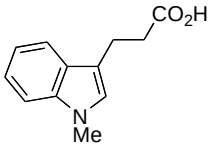
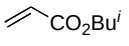
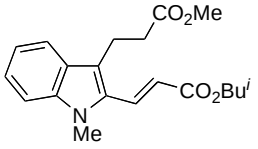
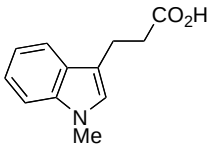
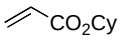
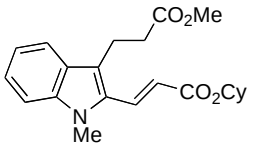
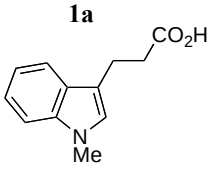
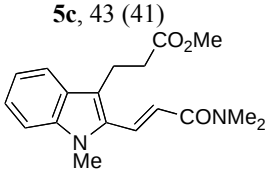
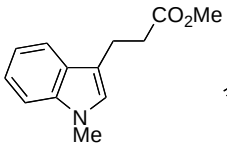
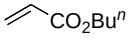
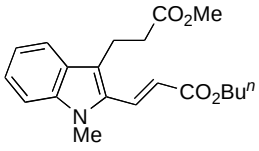
Starting Materials. Indole-3-propionic acids **1a**,[10] **1b**,[11] and **1d**[10] were prepared according to published procedures. Other starting materials were commercially available.

Typical Procedure for the Reactions of Indole-3-propionic Acids 1 with Aryl Bromides 2. A mixture of indole-3-propionic acid **1** (0.4 mmol), aryl bromide **2** (0.8 mmol), $Pd(OAc)_2$ (0.02 mmol, 4.5 mg), XPhos (0.04 mmol, 19 mg), $KHCO_3$ (0.9-1.5 mmol), and dibenzyl (ca. 40 mg) as internal standard was stirred in DMAc (2.5 mL) under nitrogen at 170 °C for 6-20 h. After the mixture was cooled, iodomethane (6 mmol, 852 mg) and K_2CO_3 (3 mmol, 415 mg) were added, and the resulting mixture was stirred under air at room temperature for 3 h. GC and GC-MS analyses of the mixtures confirmed formation of product **3**. The reaction mixture was extracted with EtOAc (100 mL). The organic layer was

Table 4. Reaction of indole-3-propionic acid derivatives **1** with alkenes **4**[a]



1 **4** **5**

Entry	**1**	**4**	Product, % yield[b]
1	 **1a**	 **4b**	 **5b**, 43 (40)
2	 **1a**	 **4c**	 **5c**, 43 (41)
3	 **1a**	 **4d**	 **5d**, 32 (32)
4	 **1d**	 **4a**	 **5a**, 34 (25)

a) Reaction conditions: 1) **1** (0.4 mmol), **4** (0.8 mmol), $Pd(OAc)_2$ (0.02 mmol), $Cu(OAc)_2$•H_2O (1.2 mmol), LiOAc (1.2 mmol), in DMAc (2.5 mL) at 170 °C for 6 h under N_2; 2) with the addition of MeI (6 mmol) and K_2CO_3 (3 mmol) at room temperature for 3 h. b) GC yield based on the amount of **1** used. Value in parentheses indicates yield after isolation.

washed with water (100 mL, three times), and dried over Na_2SO_4. After evaporation of the solvent under vacuum, the product **3** was isolated by column chromatography on silica gel using hexane-EtOAc as eluant.

Typical Procedure for the Reactions of Indole-3-propionic Acids 1 with Alkenes 4. A mixture of indole-3-propionic acid **1** (0.4 mmol), alkene **4** (0.8 mmol), $Pd(OAc)_2$ (0.02 mmol, 4.5 mg), $Cu(OAc)_2$ • H_2O (1.2 mmol), LiOAc (1.2 mmol), and dibenzyl (ca. 40 mg) as internal standard was stirred in DMAc (2.5 mL) under nitrogen at 170 °C for 6 h. After the mixture was cooled, iodomethane (6 mmol, 852 mg) and K_2CO_3 (3 mmol, 415 mg) were added, and the resulting mixture was stirred under air at room temperature for 3 h. GC and GC-MS analyses of the mixtures confirmed formation of product **5**. The

reaction mixture was extracted with EtOAc (100 mL). The organic layer was washed with water (100 mL, three times), and dried over Na_2SO_4. After evaporation of the solvent under vacuum, the product **5** was isolated by column chromatography on silica gel using hexane-EtOAc as eluant and gel permeation chromatography using chloroform as eluant.

Characterization Data of Products.

Methyl 3-(1-Methyl-2-phenyl-1*H*-indol-3-yl)propanoate (3a): oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56-2.60 (m, 2H), 3.03-3.07 (m, 2H), 3.57 (s, 3H), 3.60 (s, 3H), 7.14-7.18 (m, 1H), 7.24-7.28 (m, 1H), 7.33-7.38 (m, 3H), 7.42-7.51 (m, 3H), 7.64 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 30.7, 35.4, 51.5, 109.4, 111.4, 118.7, 119.3, 121.8, 127.2, 128.2, 128.5, 130.5, 131.7, 137.0, 138.1, 173.7; HRMS *m/z* (M^+) Calcd for $C_{19}H_{19}NO_2$: 293.1416. Found 293.1417.

Methyl 3-(1-Methyl-2-(4-methylphenyl)-1*H*-indol-3-yl)propanoate (3b): mp 117-119 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 2.55-2.60 (m, 2H), 3.02-3.06 (m, 2H), 3.56 (s, 3H), 3.61 (s, 3H), 7.13-7.17 (m, 1H), 7.23-7.34 (m, 6H), 7.62 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 21.3, 30.7, 35.5, 51.5, 109.4, 111.2, 118.7, 119.2, 121.6, 127.2, 128.7, 129.2, 130.4, 137.0, 138.0, 138.2, 173.8; HRMS *m/z* (M^+) Calcd for $C_{20}H_{21}NO_2$: 307.1572. Found 307.1570.

Methyl 3-(2-(4-Methoxyphenyl)-1-methyl-1*H*-indol-3-yl)propanoate (3c): mp 90-92 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57 (t, J = 8.2 Hz, 2H), 3.03 (t, J = 8.0 Hz, 2H), 3.55 (s, 3H), 3.61 (s, 3H), 3.88 (s, 3H), 7.01-7.03 (m, 2H), 7.14 (t, J = 7.6 Hz, 1H), 7.22-7.33 (m, 4H), 7.62 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 30.6, 35.4, 51.5, 55.3, 109.3, 111.1, 114.0, 118.6, 119.2, 121.6, 123.9, 127.2, 131.7, 136.9, 138.0, 159.5, 173.8; HRMS *m/z* (M^+) Calcd for $C_{20}H_{21}NO_3$: 323.1521. Found 323.1523.

Methyl 3-(2-(4-Chlorophenyl)-1-methyl-1*H*-indol-3-yl)propanoate (3d): mp 142-144 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57 (t, J = 8.0 Hz, 2H), 3.03 (t, J = 8.0 Hz, 2H), 3.56 (s, 3H), 3.61 (s, 3H), 7.16 (t, J = 7.4 Hz, 1H), 7.27-7.35 (m, 4H), 7.48 (d, J = 8.2 Hz, 2H), 7.63 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 30.7, 35.3, 51.5, 109.5, 111.8, 118.8, 119.5, 122.1, 127.1, 128.8, 130.2, 131.8, 134.4, 136.7, 137.2, 173.5; HRMS *m/z* (M^+) Calcd for $C_{19}H_{18}ClNO_2$: 327.1026. Found 327.1023.

Methyl 3-(2-(4-Fluorophenyl)-1-methyl-1*H*-indol-3-yl)propanoate (3e): oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.55-2.59 (m, 2H), 3.00-3.04 (m, 2H), 3.54 (s, 3H), 3.61 (s, 3H), 7.14-7.22 (m, 3H), 7.24-7.28 (m, 1H), 7.32-7.36 (m, 3H), 7.63 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 30.7, 35.3, 51.5, 109.4, 111.6, 115.6 (d, J = 22.1 Hz), 118.8, 119.4, 121.9, 127.1, 127.7 (d, J = 2.9 Hz), 132.3 (d, J = 7.7 Hz), 136.95, 137.01, 162.7 (d, J = 247.2 Hz), 173.6; HRMS *m/z* (M^+) Calcd for $C_{19}H_{18}FNO_2$: 311.1322. Found 311.1322.

Methyl 3-(1-Methyl-2-(4-(trifluoromethyl)phenyl)-1*H*-indol-3-yl)propanoate (3f): mp 114-116 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.59 (t, J = 8.0 Hz, 2H), 3.05 (t, J = 8.2 Hz, 2H), 3.58 (s, 3H), 3.60 (s, 3H), 7.16-7.20 (m, 1H), 7.27-7.31 (m, 1H), 7.36 (d, J = 8.2 Hz, 1H), 7.52 (d, J = 8.2 Hz, 2H), 7.65 (d, J = 8.3

Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 30.9, 35.3, 51.6, 109.6, 112.4, 119.0, 119.7, 122.4, 125.5 (q, *J* =3.8 Hz), 126.8 (q, *J* = 273.2 Hz), 127.1, 130.2 (q, *J* =32.6 Hz), 130.9, 135.5, 136.4, 137.4, 173.5; HRMS *m/z* (M^+) Calcd for $C_{20}H_{18}F_3NO_2$: 361.1290. Found 361.1287.

Methyl 3-(1,2-Diphenyl-1*H*-indol-3-yl)propanoate (3g): mp 85-87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68 (t, *J* = 8.2 Hz, 2H), 3.19 (t, *J* = 8.2 Hz, 2H), 3.64 (s, 3H), 7.15-7.34 (m, 13H), 7.68-7.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 35.2, 51.6, 110.6, 113.3, 118.8, 120.2, 122.5, 126.8, 127.5, 127.7, 127.9, 128.1, 129.0, 130.5, 131.7, 137.47, 137.54, 138.2, 173.6; HRMS *m/z* (M^+) Calcd for $C_{24}H_{21}NO_2$: 355.1572. Found 355.1574.

Methyl 3-(1-Phenyl-1*H*-indol-3-yl)propanoate (3a'): oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (t, *J* = 7.8 Hz, 2H), 3.16 (t, *J* = 7.8 Hz, 2H), 3.69 (s, 3H), 7.16-7.25 (m, 3H), 7.31-7.34 (m, 1H), 7.46-7.52 (m, 4H), 7.56 (d, *J* = 8.3 Hz, 1H), 7.65 (d, *J* = 7.3Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 34.6, 51.7, 110.6, 116.0, 119.0, 120.0, 122.5, 124.1, 125.3, 126.2, 128.6, 129.6, 136.0, 139.8, 173.8; HRMS *m/z* (M^+) Calcd for $C_{18}H_{17}NO_2$: 279.1259. Found 279.1260.

(*E*)-Butyl 3-(3-(3-Methoxy-3-oxopropyl)-1-methyl-1*H*-indol-2-yl)acrylate (5a): oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, *J* = 7.3 Hz, 3H), 1.46 (qt, *J* = 7.5, 7.4 Hz, 2H), 1.72 (tt, *J* = 7.3, 7.1 Hz, 2H), 2.66 (t, *J* = 7.8 Hz, 2H), 3.27 (t, *J* = 7.8 Hz, 2H), 3.67 (s, 3H), 3.82 (s, 3H), 4.24 (t, *J* = 6.6 Hz, 2H), 6.31 (d, *J* = 16.5 Hz, 1H), 7.10-7.14 (m, 1H), 7.29 (d, *J* = 3.7 Hz, 2H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.88 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 19.2, 20.4, 30.8, 31.2, 35.0, 51.7, 64.6, 109.6, 118.0, 119.0, 119.6, 119.9, 124.3, 127.0, 131.1, 132.3, 138.8, 167.3, 173.2; HRMS *m/z* (M^+) Calcd for $C_{20}H_{25}NO_4$: 343.1784. Found 343.1784.

(*E*)-Isobutyl 3-(3-(3-Methoxy-3-oxopropyl)-1-methyl-1*H*-indol-2-yl)acrylate (5b): oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, *J* = 6.9 Hz, 6H), 2.04 (tqq, *J* = 6.9, 6.7, 6.7 Hz, 1H), 2.66 (t, *J* = 7.8 Hz, 2H), 3.27 (t, *J* = 7.8 Hz, 2H), 3.67 (s, 3H), 3.83 (s, 3H), 4.03 (d, *J* = 6.9 Hz, 2H), 6.32 (d, *J* = 16.0 Hz, 1H), 7.11-7.15 (m, 1H), 7.30 (d, *J* = 3.7 Hz, 2H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.89 (d, *J* = 16.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 20.4, 27.8, 31.3, 35.0, 51.7, 70.8, 109.6, 118.0, 119.1, 119.6, 119.9, 124.3, 127.0, 131.2, 132.3, 138.8, 167.3, 173.2; HRMS *m/z* (M^+) Calcd for $C_{20}H_{25}NO_4$: 343.1784. Found 343.1782.

(*E*)-Cyclohexyl 3-(3-(3-Methoxy-3-oxopropyl)-1-methyl-1*H*-indol-2-yl)acrylate (5c): oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26-1.61 (m, 6H), 1.78-1.95 (m, 4H), 2.66 (t, *J* = 8.0 Hz, 2H), 3.27 (t, *J* = 7.8 Hz, 2H), 3.67 (s, 3H), 3.83 (s, 3H), 4.89-4.94 (m, 1H), 6.29 (d, *J* = 16.0 Hz, 1H), 7.10-7.14 (m, 1H), 7.30 (d, *J* = 3.7 Hz, 2H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.87 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 23.9, 25.4, 31.3, 31.8, 35.0, 51.7, 73.0, 109.5, 118.6, 118.9, 119.6, 119.8, 124.2, 127.0, 131.2, 132.1, 138.8, 166.6, 173.2; HRMS *m/z* (M^+) Calcd for $C_{22}H_{27}NO_4$: 369.1940. Found 369.1943.

(*E*)-Methyl 3-(2-(3-(Dimethylamino)-3-oxoprop-1-en-1-yl)-1-methyl-1*H*-indol-3-yl)propanoate (5d): mp 94-96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64-2.68 (m, 2H), 3.11 (s, 3H), 3.21 (s, 3H), 3.26-3.30 (m, 2H), 3.68 (s, 3H), 3.81 (s, 3H), 6.85 (d, J = 15.6 Hz, 1H), 7.10-7.14 (m, 1H), 7.26-7.29 (m, 2H), 7.61 (d, J = 8.2 Hz, 1H), 7.87 (d, J = 15.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 30.7, 34.8, 36.1, 37.3, 51.7, 109.5, 116.4, 118.6, 119.2, 119.7, 123.6, 127.2, 130.4, 132.2, 138.0, 166.5, 173.4; HRMS *m/z* (M^+) Calcd for $C_{18}H_{22}N_2O_3$: 314.1630. Found 314.1632.

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