Synthesis of 2,3-Disubstituted Indoles by Palladium-Mediated Coupling of 2-Iodoindoles

Hidetoshi Tokuyama, Yosuke Kaburagi, Xiaoqi Chen,[1] Tohru Fukuyama*

Graduate School of Pharmaceutical Sciences, The University of Tokyo CREST, The Japan Science and Technology Corporation, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-0033, Japan

Fax +81(3)58028694; E-mail: fukuyama@mol.f.u-tokyo.ac.jp

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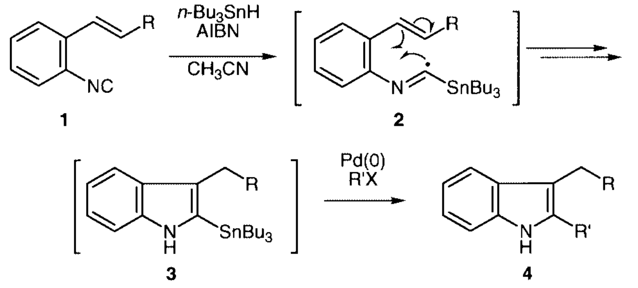
Abstract: *N*-Unprotected 2-iodoindoles are synthesized by treatment of 2-stannylindoles with iodine, which in turn are prepared by tin-mediated radical cyclization of 2-alkenylphenylisocyanides. Palladium-catalyzed coupling reactions of *N*-unprotected 2-iodoindoles with terminal acetylenes, terminal olefins, carbonylation, and the Suzuki coupling reaction with phenyl borate proceed smoothly to furnish the corresponding 2,3-disubstituted indoles in good to excellent yields.

Key words: 2-iodoindole, 2-stannylindole, isonitrile, radical cyclization, palladium-mediated coupling

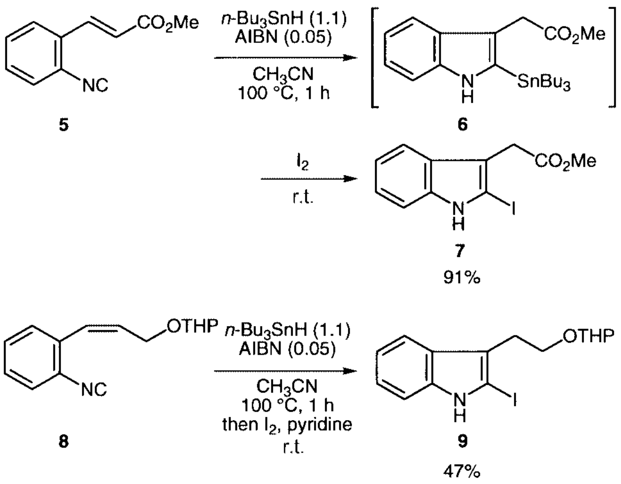
The indole nucleus is present in a wide range of natural products, and the synthesis of this important heterocycle has been a topic of interest for many years.[2] Although numerous methods for the synthesis of indoles have been developed to date,[3] few practical and mild procedures are available for the construction of 2,3-disubstituted indoles.[4] One of the most commonly employed protocols for synthesis of 2,3-disubstituted indoles is introduction of substituents at the C2 position using 2-lithioindoles. This sequence, however, requires protection and deprotection steps of the indole nitrogen.

In our earlier studies we reported the formation of 2-stannylindoles **3** by means of radical cyclization of 2-alkenylphenyl isocyanides **1** (Scheme 1), and **3** could be readily converted to either 3-substituted or 2,3-disubstituted indoles **4** by an acidic workup or palladium mediated coupling reaction, respectively, in a one-pot procedure.[5] Since it is known that the tin-carbon bond is readily oxidized by iodine, we considered that the 2-stannylindole intermediate **3** might be converted to the corresponding 2-iodoindole, which would serve as a substrate for palladium-mediated cross-coupling reactions to furnish a variety of 2,3-disubstituted indoles.



Scheme 1

Following our protocol, we prepared 2-stannylindole by radical cyclization of 2-isocyanocinnamate **5** (Scheme 2). Upon treatment of 2-stannylindole **6** with iodine, 2-iodoindole **7** could be isolated in 91% overall yield from **5**. Compound **7** proved to be relatively stable, and could be stored in a freezer for several weeks without appreciable decomposition. While 2-iodoindole **9** was prepared in moderate yield from **8**, the subsequent conversion to 2,3-disubstituted indole proceeded in good yields (vide infra).



Scheme 2

With the desired 2-iodoindoles in hand, we then examined palladium-mediated cross-coupling reaction with various substrates. The 2-iodoindole underwent smooth palladium-catalyzed coupling reactions with methyl acrylate, terminal acetylene and vinyltin reagents to give excellent yields of the desired coupling products (Table, entries 1–5). It is noteworthy that the cross-coupling reaction can also be conveniently performed in a one-pot procedure without isolating the 2-iodoindole intermediate (Table, entries 4, 5). When the reaction was carried out under an atmosphere of carbon monoxide, carbonylation proceeded smoothly, and subsequent reaction with vinylstannane, methanol, or tri-*n*-butyltin hydride gave the corresponding α,β-unsaturated ketone, methyl ester, or aldehyde, respectively (entries 6–8). In the case of the carbonylation reactions, $PdCl_2$(dppf) gave the best results. In addition, treatment of 2-iodoindole with KCN in the presence of

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Table Synthesis of 2,3-Disubstituted Indoles (**4**) by Palladium-Mediated Cross-Coupling Reaction of 2-Iodoindoles

Entry	Substrate	Coupling Partner	Equiv	Conditions	Time (h)	Product	R	R’	Yield (%)
1	**7**	HC≡CH-*n*-Bu	5.0	$Pd(PPh_3)_2Cl_2$ (5 mol%) CuI (10 mol%), Et_2NH, r.t.	8	**4a**	CO_2Me	-C≡C-*n*-Bu	89
2	**9**	CH_2=$CHCO_2Me$	2.0	$Pd(OAc)_2$ (5 mol%) Et_3N (1.1) P(*o*-tol)$_3$ (10 mol%) CH_3CN, 100°C	4	**4b**	CH_2OTHP	-CH=$CHCO_2Me$	83[a]
3	**9**	HC≡CH-*n*-Bu	5.0	$Pd(PPh_3)_2Cl_2$ (5 mol%) CuI (10 mol%), Et_2NH, r.t.	8	**4c**	CH_2OTHP	-C≡C-*n*-Bu	93
4	**5**	CH_2=$CHCO_2Me$	3.0	Bu_3SnH (1.1), AIBN (0.04) 100 °C, CH_3CN; I_2 (1.1); $Pd(OAc)_2$ (3 mol%) P(*o*-tol)$_3$ (12 mol%) Et_3N (2.1), 80 °C	8	**4d**	CO_2Me	-CH=$CHCO_2Me$	81[b,c]
5	**5**	*trans*-Bu_3SnCH=CH-*n*-Bu	2.0	Bu_3SnH (1.1), AIBN (0.04) 100 °C, CH_3CN; I_2 (1.1); $Pd(PPh_3)_4$ (5 mol%) CuI (1.0), 70 °C	10	**4e**	CO_2Me	-CH=CH-*n*-Bu	66[a,b]
6	**7**	*trans*-Bu_3SnCH=CH-*n*-Bu	1.5	$PdCl_2$(dppf) (5 mol%) BHT (trace), CO (1 atm) DMF, 80°C	12	**4f**	CO_2Me	-(C=O)CH=CH-*n*-Bu	78[c]
7	**7**	–	–	$PdCl_2$(dppf) (5 mol%) CO (1 atm), Et_3N (1.5) MeOH, 80 °C	5	**4g**	CO_2Me	CO_2Me	89
8	**7**	Bu_3SnH	1.6	$PdCl_2$(dppf) (5 mol%) CO (1 atm), DMF, 80 °C	3	**4h**	CO_2Me	CHO	85
9	**7**	KCN	1.2	$Pd(PPh_3)_4$ (5 mol%) THF, reflux	6	**4i**	CO_2Me	CN	79
10	**7**	$PhB(OH)_2$	1.1	$Pd(OAc)_2$ (5 mol%) K_2CO_3 (2.5) acetone/H_2O (1:1) 65 °C	0.5	**4j**	CO_2Me	Ph	94

[a] *trans* only.
[b] One-pot procedure.
[c] *trans:cis* = 2.7:1.

$Pd(PPh_3)_4$ furnished 2-cyanoinodole in high yield.[6] Finally, Suzuki coupling with phenylboronic acid took place nicely to afford 2-phenylindole in good yield.[7]

In conclusion, we have developed a preparation of *N*-unprotected 2-iodoindoles by tin-mediated indole synthesis and subsequent oxidation of the 2-stannylindole intermediate with iodine. Furthermore, 2-iodoindoles have been shown amenable to palladium-mediated coupling reactions with a variety of substrates. Our newly developed method compliments the previously reported procedure for the synthesis of 2,3-disubstituted indoles by palladium-mediated coupling reaction of 2-stannylindoles.[5a] Because a wide variety of functional groups are known to tolerate both radical cyclization and palladium-mediated reaction, this synthesis along with the previously reported protocol constitutes a facile and versatile method for the construction of 2,3-disubstituted indoles.

All non-aqueous reactions were carried out in oven-dried glass tubes under slight positive pressure of Ar unless otherwise noted. Toluene and CH_2Cl_2 were distilled from calcium hydride. THF was distilled from Na/benzophenone ketyl under Ar. All other reagents were commercially available and used without further purification. Preparative flash chromatography was performed using Silica Gel 60 (spherical, 40–100 μm) purchased from Kanto Chemical Co., Inc. All products were characterized by ^1H NMR, ^{13}C NMR, and IR spectroscopy. NMR spectra were obtained in $CDCl_3$ on a JEOL LA-400 MHz spectrometer. All ^1H NMR spectra are reported in ppm (δ) relative to TMS. All ^{13}C NMR spectra are reported in ppm relative to the central line of the triplet for $CDCl_3$ at 77 ppm. IR spectra were recorded on a JASCO FT/IR-410, absorptions are reported in cm^{-1}. High resolution mass spectra were obtained on a JEOL JMS-GCmate MS-DIP20 quadrupole at 70 eV using direct probe insertion at temperatures of 70–330 °C. Mps were determined using a Yanako MP-500V melting point apparatus and are uncorrected.

Methyl *o*-(*N*-Formylamino)cinnamate

A mixture of *o*-iodo-*N*-formylaniline (161 mg, 0.65 mmol), methyl acrylate (70 μL, 0.78 mmol), Pd(OAc)$_2$ (1.5 mg, 0.0070 mmol), Et$_3$N (100 μL, 0.72 mmol), and P(*o*-tol)$_3$ (4 mg, 0.01 mmol) in anhyd CH$_3$CN (2 mL) was heated at 100 °C for 2.5 h in a tightly capped culture tube under Ar atm. The mixture was partitioned between Et$_2$O and a 1:1 mixture of 3 N HCl and brine. The extracts were washed with sat. NaHCO$_3$ and brine, dried (Na$_2$SO$_4$), filtered, and evaporated to dryness in vacuo. The crude product was purified by flash column chromatography on silica gel eluting with Et$_2$O/hexane (3:2) to give methyl *o*-(*N*-formylamino)cinnamate (141 mg, 91%) as a white solid: mp 99–100 °C.

IR (film): ν = 3310, 3070, 3050, 3020, 2970, 2890, 1700, 1640, 1580, 1530, 1450, 1400, 1330, 1270, 1200, 1180, 1040, 980, 870, 770 cm^{-1}.

^{1}H NMR (CDCl$_3$), observed as a mixture of two amide rotamers: δ = 3.71 (s, 3H), 3.74 (s, 3H), 6.36 (d, 1H, *J* = 15.8 Hz), 6.39 (d, 1H, *J* = 15.8 Hz), 7.10–7.41 (m, 8H), 7.55 (m, 2H), 7.88 (m, 2H), 8.43 (m, 1H), 8.63 (s, 1H).

^{13}C NMR (CDCl$_3$), observed as a mixture of two amide rotamers: δ = 51.7, 119.7, 120.4, 122.8, 124.4, 125.6, 126.8, 127.6, 130.8, 131.1, 135.0, 139.0, 139.4, 163.9, 166.8, 167.4, 168.7, 168.9.

EI-LRMS: *m/z* (%) = 205 (M$^+$, 22), 146 (79), 128 (63), 118 (95), 117 (99), 91 (31), 90 (37), 89 (36), 39 (19).

EI-HRMS: *m/z* calc for $C_{11}H_{11}NO_3$ (M$^+$) 205.0739. Found: 205.0734.

Methyl *o*-Isocyanocinnamate (5)

To a solution of methyl *o*-(*N*-formylamino)cinnamate (141 mg, 0.680 mmol) and Et$_3$N (287 μL, 2.06 mmol) in CH$_2$Cl$_2$ at 0 °C was added dropwise a solution of phosgene in CH$_2$Cl$_2$. The reaction was monitored closely by TLC until completion. The mixture was partitioned between Et$_2$O and sat. NaHCO$_3$, and then brine. The combined extracts were dried (Na$_2$SO$_4$), filtered, and evaporated to dryness in vacuo. The crude product was purified by flash column chromatography on silica gel eluting with Et$_2$O/hexane (1:4) to give **5** (106 mg, 87%) as a white solid: mp 57–59 °C.

IR (KBr): ν = 3430, 3050, 3010, 2960, 2120, 1750, 1640, 1480, 1430, 1330, 1290, 1200, 1040, 990, 780 cm^{-1}.

^{1}H NMR (CDCl$_3$): δ = 3.84 (s, 3H), 6.55 (d, 1H, *J* = 16.0 Hz), 7.46 (m, 2H), 7.67 (m, 2H), 7.98 (d, 1H, *J* = 16.0 Hz).

^{13}C NMR (CDCl$_3$): δ = 51.9, 121.9, 125.8, 126.8, 127.6, 129.6, 130.4, 130.7, 137.8, 166.3, 168.7

EI-LRMS: *m/z* (%) = 187 (M$^+$, 6), 156 (30), 143 (14), 142 (13), 139 (99), 138 (99), 101 (61), 75 (43), 51 (30), 28 (31).

EI-HRMS: *m/z* calc for $C_{11}H_9NO_2$ (M$^+$) 187.0633. Found: 187.0635.

Methyl 2-(2-Iodo-1*H*-indol-3-yl)acetate (7)

A mixture of isonitrile (**5**, 202 mg, 1.08 mmol), *n*-Bu$_3$SnH (320 μL, 1.19 mmol), and AIBN (2,2′-azobisisobutyronitrile) (9 mg, 0.05 mmol) in anhyd CH$_3$CN (6 mL) was heated at 100 °C for 1 h in a tightly capped culture tube under Ar. After the mixture was cooled to r.t., I$_2$ (302 mg, 1.19 mmol) was added in one portion. The mixture was stirred at r.t. for 10 min before the mixture was partitioned twice between hexane and CH$_3$CN. The combined CH$_3$CN extracts were evaporated to dryness in vacuo. The crude product was purified by flash column chromatography on silica gel eluting with Et$_2$O/hexane (3:2) to give **7** (308 mg, 91%) as a colorless oil.

IR (film): ν = 3350, 3050, 3000, 2950, 2850, 1730, 1440, 1340, 1270, 1200, 1170, 1010, 940, 750 cm^{-1}.

^{1}H NMR (CDCl$_3$): δ = 3.70 (s, 3H), 3.74 (s, 2H), 7.13 (m, 2H), 7.26 (m, 1H), 7.54 (m, 1H), 8.22 (s, 1H).

^{13}C NMR (CDCl$_3$): δ = 32.9, 52.1, 79.9, 110.5, 114.7, 118.0, 120.3, 122.3, 127.2, 138.6, 171.7.

EI-LRMS: *m/z* (%) = 315 (M$^+$, 69), 256 (86), 188 (12), 145 (13), 129 (99), 117 (14), 102 (56), 75 (22), 59 (9).

EI-HRMS: *m/z* calc for $C_{11}H_{10}NO_2I_1$ (M$^+$) 314.9756. Found: 314.9755.

Isonitrile **8** was prepared from *o*-iodo-*N*-formanilide in a two-step sequence.

(1) Sonogashira-Coupling Reaction of *o*-Iodo-*N*-formanilide with Propargyl Alcohol THP Ether

A mixture of *o*-iodo-*N*-formanilide (4.17 g, 16.8 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (236 mg, 0.34 mmol), CuI (257 mg, 1.35 mmol), and propargyl alcohol THP ether (4.26 g, 30.4 mmol) in anhyd Et$_2$NH (20 mL) was stirred for 8 h at r.t., under Ar. The mixture was then partitioned between Et$_2$O and 3 N HCl. The extracts were washed with sat. NaHCO$_3$ and then with brine, dried (Na$_2$SO$_4$), filtered, and evaporated to dryness in vacuo. The crude product was purified by flash column chromatography on silica gel eluting with Et$_2$O/hexane (1:4) to give 3-(*o*-(*N*-formylamino)phenyl)propargyl alcohol THP ether (3.98 g, 91%) as a yellow oil.

IR (film): ν = 3300, 2950, 2870, 2860, 2230, 1700, 1580, 1520, 1450, 1400, 1350, 1300, 1270, 1200, 1120, 1090, 1160, 1030, 900, 870, 820, 760 cm^{-1}.

^{1}H NMR (CDCl$_3$), observed as a mixture of two amide rotamers: δ = 1.56–1.90 (m, 4H), 3.60 (m, 2H), 3.91 (m, 2H), 4.56 (m, 2H), 4.90 (m, 1H), 7.06 (m, 1H), 7.22–7.48 (m, 3H), 7.28 (s, 1H), 8.42 (d, 1H, *J* = 8.3 Hz), 8.47 (d, 1H, *J* = 1.6 Hz), 8.82 (d, 1H, *J* = 11.3 Hz).

^{13}C NMR (CDCl$_3$), observed as a mixture of two amide rotamers: δ = 18.9, 25.2, 29.6, 30.3, 54.9, 55.4, 62.2, 80.9, 92.9, 97.5, 97.9, 113.3, 115.8, 119.8, 123.7, 124.3, 129.8, 131.7, 133.1, 138.6, 159.1, 161.2.

EI-LRMS: *m/z* (%) = 259 (M$^+$, 3), 243 (2), 175 (45), 158 (34), 146 (10), 130 (99), 102 (23), 101 (23), 77 (23), 55 (22), 41 (39).

EI-HRMS: *m/z* calc for $C_{15}H_{17}NO_3$ (M$^+$) 259.1208. Found: 259.1206.

(2) Conversion to Isonitrile (8)

A mixture of 3-(*o*-(*N*-formylamino)phenyl)propargyl alcohol THP ether (3.98 g, 15.3 mmol), and Pd/BaSO$_4$ (200 mg) in EtOH (40 mL) was stirred for 2.5 h at r.t., under atmospheric pressure of H$_2$. The reaction was monitored closely by TLC until completion. The reaction mixture was passed through a pad of Celite, and evaporated to dryness in vacuo. The crude product was purified by flash column chromatography on silica gel eluting with Et$_2$O/hexane (3:7) to give *cis*-3-(*o*-(*N*-formylamino)phenyl)propen-1-ol THP ether (2.53 g, 63%) as a dark yellow oil. To a mixture of *cis*-3-(*o*-(*N*-formylamino)phenyl)propen-1-ol THP ether (2.53 g, 9.68 mmol), and Et$_3$N (4.07 mL, 29.3 mmol) in CH$_2$Cl$_2$ at 0 °C was added drop-wise a solution of phosgene in CH$_2$Cl$_2$. The reaction was monitored closely by TLC until completion. The mixture was partitioned between Et$_2$O and sat. NaHCO$_3$, and washed with brine. The combined extracts were dried (Na$_2$SO$_4$), filtered, and evaporated to dryness in vacuo. The crude product was purified by flash column chromatography on silica gel eluting with Et$_2$O/hexane (1:9) to give **8** (2.27 g, 97%) as a colorless oil:

IR (film): ν = 3040, 2950, 2860, 2140, 1730, 1450, 1375, 1340, 1270, 1200, 1130, 1030, 970, 900, 770 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.45–1.88 (m, 4H), 3.49 (m, 1H), 3.86 (m, 1H), 4.18 (dd, 2H, J = 6.5, 12.9 Hz), 4.43 (dd, 2H, J = 6.5, 12.9 Hz), 4.65 (t, 1H, J = 3.0 Hz), 6.12 (dt, 1H, J = 6.5, 11.9 Hz), 6.74 (d, 1H, J = 11.9 Hz), 7.30 (m, 4H).

^{13}C NMR ($CDCl_3$): δ = 19.3, 25.3, 30.6, 62.2, 63.9, 98.4, 126.1, 126.8, 128.1, 128.9, 129.8, 132.4, 133.3.

EI-LRMS: *m/z* (%) = 243 (M$^+$, 1), 214 (2), 200 (4), 199 (30), 143 (55), 142 (99), 130 (36), 115 (82), 85 (96), 43 (57), 41 (62).

EI-HRMS: *m/z* calc for $C_{15}H_{17}NO_2$ (M$^+$) 243.1259. Found: 243.1259.

2-(2-Iodo-*1H*-indol-3-yl)ethanol THP Ether (9)

A mixture of isonitrile (**8,** 216 mg, 0.90 mmol), *n*-Bu_3SnH (264 µL, 0.98 mmol), and AIBN (7 mg, 0.04 mmol) in anhyd CH_3CN (6 mL) was heated at 100 °C for 1 h in a tightly capped culture tube under Ar. After cooling to r.t., pyridine (80 µL, 0.99 mmol) and I_2 (249 mg, 0.98 mmol) were added to the mixture. The mixture was stirred for 10 min at r.t., then partitioned twice between hexane and CH_3CN. The combined CH_3CN extracts were evaporated to dryness in vacuo. The crude product was purified by flash column chromatography on silica gel eluting with Et_2O/hexane (2:3) to give **9** (156 mg, 47%) as a colorless oil.

IR (film): ν = 3390, 3250, 3050, 2940, 2860, 1450, 1350, 1280, 1200, 1140, 1120, 1070, 1020, 900, 870, 800, 740 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.25–1.89 (m, 6H), 3.02 (t, 2H, J = 7.4 Hz), 3.47 (m, 1H), 3.61 (q, 1H, J = 9.6 Hz), 3.81 (m, 1H), 3.93 (q, 1H, J = 9.6 Hz), 4.64 (t, 1H, J = 3.2 Hz) 7.07 (t, 1H, J = 7.4 Hz), 7.12 (t, 1H, J = 7.0 Hz), 7.27 (d, 1H, J = 7.0 Hz), 7.58 (d, 1H, J = 7.4 Hz), 8.20 (s, 1H).

^{13}C NMR ($CDCl_3$): δ = 19.4, 25.4, 27.6, 30.6, 62.1, 66.9, 78.5, 98.6, 110.2, 118.2, 119.0, 119.6, 122.1, 127.6, 138.8.

EI-LRMS: *m/z* (%) = 371 (M$^+$, 1), 256 (8), 193 (22), 176 (14), 165 (13), 158 (17), 148 (55), 130 (33), 85 (99), 55 (99), 39 (29).

EI-HRMS: *m/z* calc for $C_{15}H_{18}NO_2I_1$ (M$^+$) 371.0382. Found: 371.0381.

Methyl (2-(Hex-1-ynyl-1*H*-indol-3-yl)acetate (4a)

To a mixture of iodoindole (**7**; 50 mg, 0.16 mmol), $Pd(PPh_3)_2Cl_2$ (6 mg, 0.01 mmol), and CuI (3 mg, 0.02 mmol) in anhyd Et_2NH (2 mL) was added hex-1-yne (92 µL, 0.80 mmol) at r.t. under Ar. The reaction mixture was stirred for 8 h and then partitioned between Et_2O and 3 N HCl. The combined extracts were washed with sat. $NaHCO_3$ and then with brine, dried (Na_2SO_4), filtered, and evaporated to dryness in vacuo. The crude product was purified by preparative TLC (silica gel) eluting with Et_2O/hexane (2:3) to give **4a** (38 mg, 89%) as a light yellow oil.

IR (film): ν = 3350, 3050, 2950, 2920, 2870, 2320, 1730, 1460, 1430, 1350, 1300, 1270, 1250, 1170, 1010, 750 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.98 (t, 3H, J = 7.2 Hz), 1.46–1.66 (m, 4H), 2.49 (t, 2H, J = 6.7 Hz), 3.70 (s, 3H), 3.87 (s, 2H), 7.14 (m, 2H), 7.23 (m, 1H), 7.56 (d, 1H, J = 7.6 Hz), 8.18 (s, 1H).

^{13}C NMR ($CDCl_3$): δ = 13.6, 19.3, 21.9, 30.6, 31.0, 51.9, 71.5, 96.9, 110.7, 112.8, 118.8, 119.0, 120.1, 123.1, 127.0, 135.3, 172.0.

EI-LRMS: *m/z* (%) = 269 (M$^+$, 53), 210 (99), 170 (13), 167 (25), 154 (16), 139 (10), 49 (4).

EI-HRMS: *m/z* calc for $C_{17}H_{19}NO_2$ (M$^+$) 269.1416. Found: 269.1418.

2-(2-(2-Carbomethoxy)vinyl-1*H*-indol-3-yl)ethanol THP Ether (4b)

A mixture of iodoindole (**9,** 42 mg, 0.11 mmol), methyl acrylate (21 µL, 0.23 mmol), $Pd(OAc)_2$ (1 mg, 0.005 mmol), Et_3N (17 µL, 0.12 mmol), and (*o*-tol)$_3$P (4 mg, 0.01 mmol) in anhyd CH_3CN (2 mL) was heated at 100 °C for 4 h in a tightly capped culture tube under Ar. After cooling to r.t., the mixture was partitioned between Et_2O and a 1:1 mixture of 3 N HCl and brine. The combined extracts were washed with sat. $NaHCO_3$ and then with brine, dried (Na_2SO_4), filtered, and evaporated to dryness in vacuo. The crude product was purified by preparative TLC (silica gel) eluting with Et_2O/hexane (2:3) to give **4b** (31 mg, 83%) as a light yellow solid: mp 121–122 °C.

IR (film): ν = 3350, 3060, 2950, 2880, 1700, 1620, 1460, 1440, 1330, 1290, 1200, 1180, 1040, 980, 920, 740 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.49 (m, 4H), 1.79 (m, 2H), 3.17 (t, 2H, J = 6.8 Hz), 3.46 (m, 1H), 3.60 (q, 1H, J = 7.0 Hz), 3.77 (m, 1H), 3.81 (s, 3H), 3.97 (q, 1H, J = 7.0 Hz), 4.58 (t, 1H, J = 2.5 Hz), 6.19 (d, 1H, J = 15.9 Hz), 7.08 (t, 1H, J = 7.5 Hz), 7.26 (m, 1H), 7.27 (d, 1H, J = 7.5 Hz), 7.61 (d, 1H, J = 7.5 Hz), 7.85 (d, 1H, J = 15.9 Hz), 8.61 (s, 1H).

^{13}C NMR ($CDCl_3$): δ = 19.3, 24.9, 25.3, 30.5, 51.6, 62.0, 67.5, 98.8, 110.9, 113.5, 119.8, 119.9, 124.8, 128.3, 130.5, 132.7, 137.3, 167.6.

EI-LRMS: *m/z* (%) = 329 (M$^+$, 21), 227 (29), 214 (33), 201 (99), 167 (69), 154 (75), 128 (6), 115 (6), 85 (67), 67 (19), 57 (19), 28 (23).

EI-HRMS: *m/z* calc for $C_{19}H_{23}NO_4$ (M$^+$) 329.1627. Found: 329.1630.

(2-(Hex-1-ynyl-1*H*-indol-3-yl)ethanol THP Ether (4c)

A mixture of iodoindole (**9,** 45 mg, 0.12 mmol), $Pd(PPh_3)_2Cl_2$ (4 mg, 0.006 mmol), CuI (2 mg, 0.01 mmol), and hex-1-yne (70 µL, 0.61 mmol) in anhyd Et_2NH in (1 mL) was stirred for 8 h at r.t., under Ar. Then, the mixture was partitioned between Et_2O and 3 N HCl. The combined extracts were washed with sat. $NaHCO_3$ and then with brine, dried (Na_2SO_4), filtered, and evaporated to dryness in vacuo. The crude product was purified by preparative TLC (silica gel) eluting with Et_2O/hexane (1:4) to give **4c** (37 mg, 93%) as a light yellow oil.

IR (film): ν = 3410, 3290, 3060, 2940, 2860, 2220, 1620, 1580, 1460, 1350, 1300, 1200, 1120, 1070, 1020, 900, 870, 810, 740 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.96 (t, 3H, J = 7.2 Hz), 1.45–1.89 (m, 10H), 2.47 (t, 2H, J = 6.8 Hz), 3.15 (t, 2H, J = 7.6 Hz), 3.50 (m, 1H,), 3.70 (q, 1H, J = 9.3 Hz), 3.86 (m, 1H), 4.02 (q, 1H, J = 9.3 Hz), 4.68 (t, 1H, J = 3.8 Hz), 7.06 (m, 2H), 7.22 (m, 1H), 7.61 (d, 1H, J = 7.7 Hz), 8.27 (s, 1H).

^{13}C NMR ($CDCl_3$): δ = 13.5, 19.2, 19.4, 21.9, 25.4, 25.6, 30.6, 62.1, 67.3, 72.2, 96.0, 98.6, 110.5, 117.3, 117.5, 117.8, 119.1, 119.5, 122.8, 127.4, 135.4.

EI-LRMS: *m/z* (%) = 325 (M$^+$, 38), 283 (3), 223 (51), 210 (99), 197 (62), 170 (50), 168 (21), 167 (21), 155 (14), 85 (5).

EI-HRMS: *m/z* calc for $C_{21}H_{27}NO_2$ (M$^+$) 325.2042. Found: 325.2041.

Methyl 2-(2-(2-Carbomethoxy)vinyl-1*H*-indol-3-yl)acetate (4d)

A mixture of isonitrile (**5**; 52 mg, 0.28 mmol), *n*-Bu_3SnH (82 µL, 0.30 mmol), and AIBN (2 mg, 0.01 mmol) in anhyd CH_3CN (2 mL) was heated at 100 °C for 1.5 h in a tightly capped culture tube under Ar. After cooling to r.t., the mixture was treated with I_2 (78 mg, 0.31 mmol) in one portion. The mixture was stirred at r.t. for 10 min prior to the addition of methyl acrylate (75 µL 0.84 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), Et_3N (84 µL, 0.60 mmol), and (*o*-tol)$_3$P (10 mg, 0.03 mmol). After heating at 80 °C for 8 h under Ar, the mixture was partitioned between Et_2O and a 1:1 mixture of 3 N HCl and brine. The combined extracts were washed with sat. $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and evaporated to dryness in vacuo. The crude product was purified by preparative TLC (silica gel) eluting with Et_2O/hexane (2:3) to give *cis*-**4d** (17 mg, 22%) as a light yellow oil and *trans*-**4d** (45 mg, 59%) as white crystals.

cis-**4d**

IR (film): ν = 3300, 3050, 3030, 3010, 2970, 1740, 1700, 1600, 1530, 1500, 1450, 1430, 1340, 1270, 1200, 1030, 1010, 830, 750 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.66 (s, 3H), 3.83 (s, 3H), 3.89 (s, 2H), 5.86 (d, 1H, *J* = 12.9 Hz), 7.09 (d, 1H, *J* = 12.9 Hz), 7.12 (t, 1H, *J* = 8.1 Hz), 7.29 (t, 1H, *J* = 8.1 Hz), 7.43 (d, 1H, *J* = 8.1 Hz), 7.65 (d, 1H, *J* = 8.1 Hz), 11.99 (s, 1H).

^{13}C NMR ($CDCl_3$): δ = 30.4, 52.0, 52.1, 112.0, 112.7, 114.8, 119.7, 120.1, 125.2, 127.2, 130.9, 132.0, 136.4, 169.0, 171.4.

EI-LRMS: *m/z* (%) = 273 (M^+, 31), 241 (5), 214 (18), 182 (26), 154 (99), 127 (10), 77 (5), 44 (14).

EI-HRMS: *m/z* calc for $C_{15}H_{15}NO_4$ (M^+) 273.1001. Found: 273.1001.

trans-**4d**: mp 145–146 °C.

IR (film): ν = 3350, 3070, 3050, 3010, 2960, 2850, 1720, 1690, 1630, 1620, 1460, 1440, 1320, 1290, 1200, 1150, 1030, 970, 850, 750 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.71 (s, 3H), 3.80 (s, 3H), 3.88 (s, 2H), 6.12 (dd, 1H, *J* = 1.1, 15.8 Hz), 7.09 (t, 1H, *J* = 6.1 Hz), 7.28 (m, 2H), 7.58 (d, 1H, *J* = 8.0 Hz), 7.70 (dd, 1H, *J* = 2.3, 15.8 Hz), 8.65 (s, 1H).

^{13}C NMR ($CDCl_3$): δ = 30.1, 51.8, 52.3, 111.2, 114.1, 114.9, 119.8, 120.5, 125.1, 128.2, 130.9, 131.7, 137.2, 167.3, 173.8.

EI-LRMS: *m/z* (%) = 273 (M^+, 36), 241 (8), 214 (61), 182 (29), 154 (99), 127 (13), 77 (11), 44 (6), 28 (14).

EI-HRMS: *m/z* calc for $C_{15}H_{15}NO_4$ (M^+) 273.1001. Found: 273.1003.

Methyl [2-(*trans*-Hex-1-enyl)-1*H*-indol-3-yl]acetate (4e)

To a mixture containing 2-iodoindole prepared as above from isonitrile (**5**, 52 mg, 0.28 mmol), *n*-Bu_3SnH (82 μL, 0.30 mmol), AIBN (2 mg, 0.01 mmol), and I_2 (78 mg, 0.31 mmol) were added 1-tri-*n*-butylstannylhexene (247 mg, 0.56 mmol), $Pd(PPh_3)_4$ (16 mg, 0.01 mmol), and CuI (53 mg, 0.28 mmol). The mixture was heated at 80 °C for 10 h under Ar, and then partitioned between Et_2O and a 1:1 mixture of 3 N HCl and brine. The combined extracts were washed with sat. KF and then with brine, dried (Na_2SO_4), filtered, and evaporated to dryness in vacuo. The crude product was purified by preparative TLC (silica gel) eluting with Et_2O/hexane (3:7) to give **4e** (50 mg, 66%) as a light yellow oil.

IR (film): ν = 3400, 3030, 2950, 2930, 2860, 1730, 1450, 1310, 1270, 1160, 1020, 960, 740 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.94 (t, 3H, *J* = 7.0 Hz), 1.42 (m, 4H), 2.27 (dd, 2H, *J* = 6.6, 6.9 Hz), 3.66 (s, 3H), 3.77 (s, 2H), 6.03 (dt, 1H, *J* = 6.9, 16.0 Hz), 6.52 (d, 1H, *J* = 16.0 Hz), 7.08 (t, 1H, *J* = 6.9 Hz), 7.16 (t, 1H, *J* = 7.0 Hz), 7.27 (d, 1H, *J* = 7.0 Hz), 7.55 (d, 1H, *J* = 7.1 Hz), 8.06 (s, 1H).

^{13}C NMR ($CDCl_3$): δ = 13.9, 22.2, 30.1, 31.4, 32.9, 52.0, 106.0, 110.4, 118.4, 118.7, 119.7, 122.5, 128.7, 130.8, 133.7, 135.7, 172.2.

EI-LRMS: *m/z* (%) = 271 (M^+, 71), 228 (11), 212 (99), 198 (13), 182 (11), 168 (94), 154 (31), 130 (23), 28 (46).

EI-HRMS: *m/z* calc for $C_{17}H_{21}NO_2$ (M^+) 271.1572. Found: 271.1574.

Methyl 2-(2-(*trans*-1-Oxo-2-heptenyl)-1*H*-indole-3-yl)acetate (4f)

A mixture of iodoindole (**7,** 62 mg, 0.20 mmol), 1-tri-*n*-butylstannylhexene (131 mg, 0.30 mmol), $PdCl_2(dppf)•CH_2Cl_2$ (7 mg, 0.01 mmol), and a trace amount of 2,6-di-*t*-butyl-4-methylphenol (BHT) in dry DMF (1 mL) was heated at 70 °C under atmospheric pressure of CO. The mixture was stirred for 12 h, then partitioned between Et_2O and a one third sat. KF. The combined extracts were washed with diluted brine, dried (Na_2SO_4), filtered, and evaporated to dryness in vacuo. The crude product was purified by preparative TLC (silica gel) eluting with Et_2O/hexane (2:3) to give **4f** (46 mg, 78%) as a light yellow solid: mp 78–79 °C.

IR (film): ν = 3320, 3050, 2950, 2920, 2860, 1730, 1650, 1600, 1540, 1430, 1340, 1250, 1210, 1170, 1020, 930, 740 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.93 (t, 3H, *J* = 7.1 Hz), 1.42 (m, 4H), 2.27 (q, 2H, *J* = 6.6 Hz), 3.75 (s, 3H), 4.16 (s, 2H), 6.83 (d, 1H, *J* = 15.3 Hz), 7.03 (t, 1H, *J* = 6.7 Hz), 7.13 (m, 1H), 7.32 (m, 2H), 7.66 (d, 1H, *J* = 8.1 Hz), 9.58 (s, 1H).

^{13}C NMR ($CDCl_3$): δ = 13.8, 22.2, 27.8, 30.0, 31.2, 32.4, 52.1, 112.2, 114.2, 120.6, 126.1, 126.5, 129.4, 133.2, 136.1, 148.2, 171.8, 182.8.

EI-LRMS: *m/z* (%) = 299 (M^+, 22), 242 (38), 240 (55), 226 (19), 210 (22), 196 (45), 182 (99), 168 (60), 156 (34), 128 (34), 101 (9).

EI-HRMS: *m/z* calc for $C_{18}H_{21}NO_3$ (M^+) 299.1521. Found: 299.1519.

Methyl 2-(2-Methoxycarbonyl-1*H*-indol-3-yl)acetate (4g)

A mixture of iodoindole (**7**; 109.9 mg, 0.349 mmol) and $PdCl_2(dppf)•CH_2Cl_2$ (14.2 mg, 0.0174 mmol) in MeOH (1.7 mL) in a culture tube equipped with septum was bubbled with CO for 3 min. After bubbling, Et_3N (73 μL, 0.524 mmol) was added, and then the tube was capped, and heated at 80 °C for 5 h under atmospheric pressure of CO. The reaction mixture was partitioned between Et_2O and a 1:2 mixture of 3 N HCl and brine. The organic layer was washed with 1:1 mixture of sat. $NaHCO_3$ and brine, and with brine, dried ($MgSO_4$), filtered, and evaporated to dryness in vacuo. The crude product was purified by preparative TLC (silica gel) eluting with EtOAc/hexane (3:7) to give **4g** (76.9 mg, 89%) as a white solid: mp 130–131 °C.

IR (neat): ν = 3343, 1714, 1559, 1457, 1330, 1256 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.70 (s, 3H), 3.94 (s, 3H), 4.12 (s, 2H), 7.17 (t, 1H, *J* = 7.2 Hz), 7.32–7.41 (m, 2H), 7.65 (d, 1H, *J* = 7.6 Hz), 8.85 (br s, 1H).

^{13}C NMR ($CDCl_3$): δ = 30.4, 51.8, 52.0, 111.9, 115.8, 120.5, 120.6, 124.1, 125.7, 127.7, 135.8, 162.3, 171.8.

EI-LRMS: *m/z* = 247 (M^+).

FAB-HRMS: *m/z* calc for $C_{13}H_{13}NO_4$ (M^+) 247.0844. Found: 247.0844.

Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15, H, 5.30, N, 5.67. Found C, 62.89, H, 5.33, N, 5.62.

Methyl 2-(2-Formyl-1*H*-indol-3-yl)acetate (4h)

A mixture of iodoindole (**7**; 150.3 mg, 0.477 mmol) and $PdCl_2(dppf)•CH_2Cl_2$ (19.5 mg, 0.0239 mmol) in DMF (3.4 mL) was heated at 80 °C for 15 min under atmospheric pressure of CO, and then *n*-Bu_3SnH (156 μL, 0.770 mmol) was added dropwise over 3 h using a syringe pump. The mixture was evaporated and partitioned between Et_2O and 1 N HCl. The combined organic extracts were washed with sat. KF, sat. $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and evaporated to dryness in vacuo. The crude product was purified by preparative TLC (silica gel) eluting with EtOAc/benzene (1:19) to give **4h** (88.2 mg, 85%) as a white solid: mp 122.7–123.1 °C.

IR (neat): ν = 3318, 1737, 1657 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.72 (s, 3H), 4.11 (s, 2H), 7.18–7.22 (m, 1H), 7.41 (d, 2H, *J* = 4.0 Hz), 7.76 (d, 1H, *J* = 8.8 Hz), 8.97 (br s, 1H), 10.07 (s, 1H).

^{13}C NMR ($CDCl_3$): δ = 29.7, 52.5, 112.5, 119.5, 121.1, 121.3, 127.4, 127.6, 132.6, 137.2, 170.9, 180.8.

EI-LRMS: *m/z* = 217 (M^+).

FAB-HRMS: *m/z* calc for $C_{12}H_{11}NO_3$ (M^+) 217.0739. Found: 271.0740.

Anal: Calcd. for $C_{12}H_{11}NO_3$: C; 66.35, H; 5.10, N; 6.45. Found: C; 66.07, H; 5.27, N; 6.40.

Methyl 2-(2-Cyano-1*H*-indol-3-yl)acetate (4i)

A mixture of iodoindole (**7**; 115.3 mg, 0.366 mmol), pulverized KCN (28.1 mg, 0.432 mmol), and $Pd(PPh_3)_4$ (21.0 mg, 0.0182 mmol) in THF (1.2 mL) was refluxed for 6 h under Ar. After cooling to r.t., the mixture was filtered and evaporated to dryness. The crude product was purified by preparative TLC (silica gel) eluting with $MeOH/CH_2Cl_2$/hexane (7:63:30) to give **4i** (59.2 mg, 79%) as a light orange solid: mp 81.0–82.0 °C.

IR (neat): ν = 3324, 2953, 2224, 1728, 1437, 1347, 1213, 1174, 746.

^{1}H NMR ($CDCl_3$): δ = 3.73 (s, 3H), 3.95 (s, 2H), 7.21–7.25 (m, 1H), 7.39 (m, 2H), 7.66 (d, 1H, *J* = 7.6 Hz), 8.60 (br s, 1H).

^{13}C NMR ($CDCl_3$): δ = 30.7, 52.4, 106.0, 111.9, 113.4, 120.4, 120.9, 121.6, 125.8, 126.5, 136.8, 170.5.

EI-LRMS: *m/z* = 214 (M^+).

FAB-HRMS: *m/z* calc for $C_{12}H_{10}N_2O_2$ (M^+) 214.0742. Found: 214.0744.

Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28, H, 4.71, N, 13.08. Found C, 67.07, H, 4.72, N, 13.03.

Methyl 2-(2-Phenyl-1*H*-indol-3-yl)acetate (4j)

A mixture of iodoindole (**7**, 100 mg, 0.318 mmol), $PhB(OH)_2$ (42.2 mg, 0.346 mmol), K_2CO_3 (110 mg, 0.798 mmol), and $Pd(OAc)_2$ (3.5 mg, 0.016 mmol) in a 1:1 mixture of acetone/H_2O (1.6 mL) was stirred at 65 °C for 30 min under Ar. After cooling to r.t., the mixture was partitioned between Et_2O and 1 N HCl. The organic layers were washed with sat. $NaHCO_3$, and then with brine, dried ($MgSO_4$), filtered, and evaporated to dryness in vacuo. The crude product was purified by preparative TLC (silica gel) eluting with $MeOH/CH_2Cl_2$/hexane (4:36:60) to give **4j** (79.6 mg, 94%) as a light yellow foam: mp 106–107 °C.

IR (film): ν = 3480, 3050, 2950, 2860, 1730, 1610, 1450, 1320, 1270, 1170, 1010, 750, 700 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.75 (s, 3H), 3.91 (s, 2H), 7.21 (t, 1H, *J* = 5.8 Hz), 7.26 (t, 1H, *J* = 5.8 Hz), 7.36 (d, 1H, *J* = 8.8 Hz), 7.45 (t, 1H, *J* = 7.3 Hz), 7.51 (t, 2H, *J* = 6.8 Hz), 7.67 (d, 2H, *J* = 7.5 Hz), 7.72 (d, 1H, *J* = 6.8 Hz), 8.32 (s, 1H).

^{13}C NMR ($CDCl_3$): δ = 30.9, 52.0, 105.3, 110.9, 119.1, 120.0, 122.5, 128.0, 128.2, 128.8, 129.0, 132.2, 135.7, 136.1, 172.8.

EI-LRMS: *m/z* (%) = 265 (M^+, 19), 206 (99), 178 (19), 102 (4), 59 (5).

EI-HRMS: *m/z* calc for $C_{17}H_{15}NO_2$ (M^+) 265.1103. Found: 265.1102.

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