Palladium-Catalyzed Synthesis of 3-Indolecarboxylic Acid Derivatives

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Abstract: Indoles having an ester functionality in the 3-position were prepared from 2-(2-nitrophenyl)propenoic acid derivatives via a palladium-catalyzed reductive N-heteroannulation using carbon monoxide as the ultimate reducing agent. The starting materials were prepared either by a Stille coupling of 2-halo-1-nitrobenzenes with ethyl 2-(tributylstannyl)-2-propenoate or by vicarious nucleophilic substitution of nitrobenzenes followed by a Knoevenagel-type condensation with an aldehyde. Synthesis of an example of a 3-nitrile- and a 3-sulfone-substituted indole is also described using the same type of methodologies.

Key words: palladium, catalysis, reductions, indoles, cyclizations

Palladium-catalyzed N-heteroannulation of 1-(2-nitrophenyl)alkenes using carbon monoxide as the ultimate reducing agent is emerging as a powerful methodology for the synthesis of a variety of indoles.[1–4] Applications of this reaction include the synthesis of tjipanazoles,[5] 1*H*-indole-2-yl-1*H*-quinolin-2-ones,[6] murrayaquinone,[7] bauerine A,[8] carbazole alkaloids,[9] and mushroom metabolites.[10]

The annulation reaction is related to the Cadogan–Sundberg type reaction, wherein the same kinds of substrates undergo cyclization using an excess of trialkylphosphites at elevated temperatures. Significant advantages of the palladium-catalyzed methodology are cleaner reactions, often high yielding, with lower reaction temperatures, and compatibility with virtually any functional group on the aromatic ring with little or no difference in reactivity. Synthesis of indoles having a substituent(s) in the 2- and/or 3-position have, to date, mostly been limited to alkyl, aryl, 3-alkoxy, and electron-withdrawing groups including aldehyde, ketone, and ester in the 2-position.

A large variety of practical annulation approaches to functionalized indoles have been developed.[11] However, few direct methods for the preparation of indole 3-carboxylic acids and the corresponding esters have been reported, apart from reactions whereby the carbonyl group is introduced in the 3-position of a preformed indole skeleton. Among these few methods, the classical Nenitzescu indole synthesis using benzoquinone and 3-amino-2-alkenoic acid derivatives is limited to the synthesis of 5-hydroxy-3-carboxylic acids and often affords low yields of product.[12] More recently, Hossain et al. reported a synthesis of ethyl indole-3-carboxylates from 2-nitrobenzaldehydes with ethyl diazoacetate in the presence of a catalytic amount of a Lewis acid, followed by reduction of the formed 2-(2-nitroaryl)-3-hydroxypropenoic acid esters with Pd/C and H_2.[13] Palladium-catalyzed Heck-type reaction of β-(2-halophenyl)amino-substituted α,β-unsaturated esters,[14] and sequential cyclization–carbonylation of 2-alkynylbenzeneamines, in the presence of carbon monoxide and methanol,[15] have also been described. All these methods are limited in scope due to the lack of readily available starting materials.

Indole-3-carboxylic acids, the corresponding esters, indole-3-carboxaldehydes, and indole-3-nitriles have found significant use as pharmaceuticals or as building blocks for more complex compounds. Examples of synthetic, biologically active compounds include the 5-HT_3 receptor blockers tropisetron (Novoban®) and dolasetrone (Anzemet®) used to treat nausea and vomiting caused by cancer chemotherapy or radiotherapy (Figure 1). In addition to the plethora of synthetic compounds reported in the literature, a number of compounds having an electron-withdrawing functionality in the 3-position have been found in nature. Three recently isolated naturally occurring compounds including caulilexine,[16] a phytoalexin, the very unusual bis-indolesulfone echinosulfone,[17] and TMC-205, a transcriptional up-regulator of SV40 promoter,[18] are shown in Figure 1.

In an attempt to extend the scope of the palladium-catalyzed N-heteroannulation reaction to the synthesis of indoles having an electron-withdrawing group in the 3-position of the indole skeleton, methyl 2-(2-nitrophenyl)propenoate (**2**), was prepared in good yield by condensation of commercially available methyl 2-(2-nitrophenyl)ethanoate (**1**) with 1,3,5-trioxane in the presence of calcium oxide and potassium carbonate (Scheme 1).[19] N-Heteroannulation of compound **2** using palladium diacetate (12 mol%), triphenylphosphine (44 mol%), and carbon monoxide (6 atm) in DMF at 110 °C for 72 h, proceeded uneventfully and the expected product, methyl 3-indolecarboxylate (**3**), was obtained in 91% yield. To our knowledge, this is the second example of this type of annulation affording an indole having an electron-withdrawing group in the 3-position.[20]

With this initial result in hand, a number of additional examples were examined. Here is reported a straightforward procedure for the synthesis of 2-(2-nitrophenyl)propenoates and subsequent N-heteroannulation, to give

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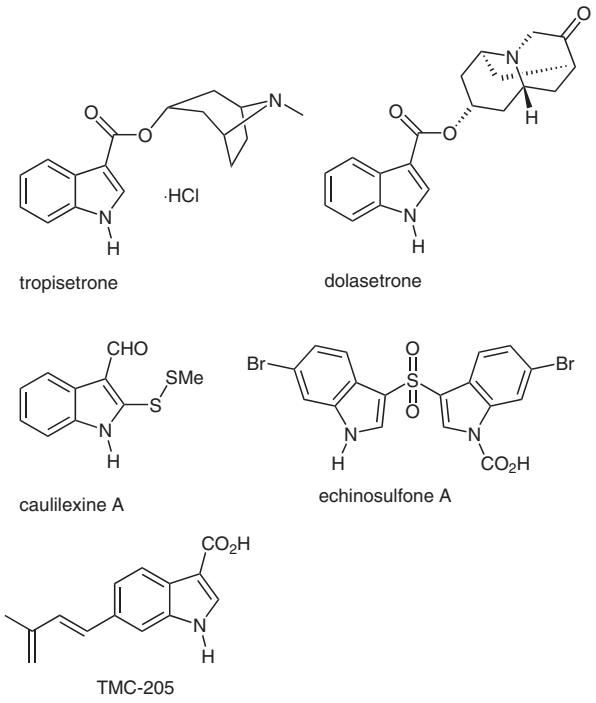
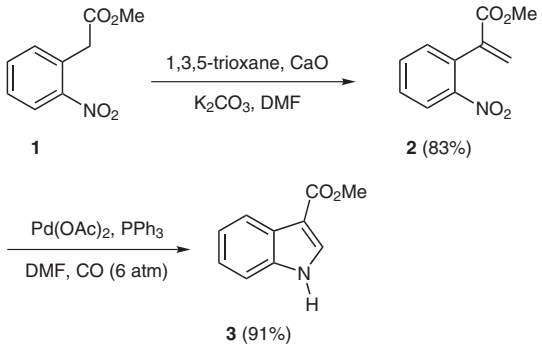


Figure 1 Examples of indoles having an electron-withdrawing substituent in the 3-position



Scheme 1

3-indole carboxylates in two or three synthetic steps starting from commercially available compounds.

A variety of substituted alkyl 2-(2-nitrophenyl)ethanoates are readily available by vicarious nucleophilic substitution (VNS)[21] of nitroaryls with *tert*-butyl chloroacetate in the presence of a base (Table 1). New compounds or previously reported compounds but made under improved conditions, have yields reported in parenthesis in Table 1. In addition to the benzene derivatives, one heteroaromatic compound was also examined. Vicarious nucleophilic substitution (VNS) of 6-methoxy-3-nitropyridine with *tert*-butyl chloroacetate in the presence of potassium *tert*-butoxide gave three 3-nitropyridine products **10**–**12** in an ~11:1:2 ratio (entries 8–10). The major and minor products **10** and **11** formed as a result of VNS in the 2- and 4-position relative to the pyridine nitrogen atom, respectively. Compound **12** is derived from *trans*-etherification of either the starting material followed by a VNS reaction or compound **10**.[22] Substitution in the 2-position of the pyridine ring usually gives rise to the major or sole product from VNS reactions employing 6-methoxy-3-nitropyridine.[23] Due to the close similarity in structure between 3-nitropyridines **10** and **12**, the latter was not further examined.

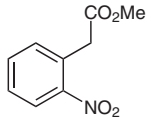
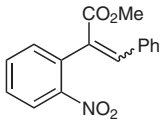
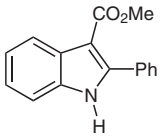
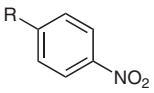
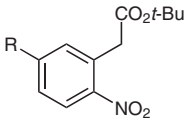
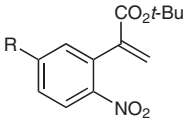
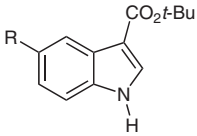
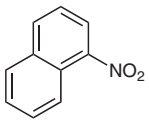
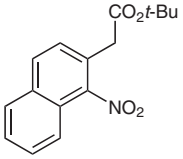
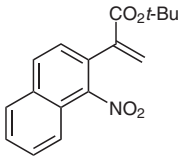
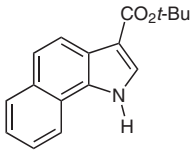
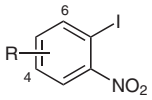
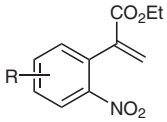
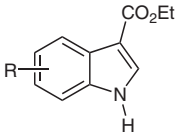
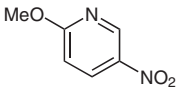
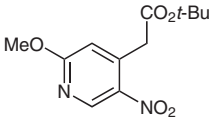
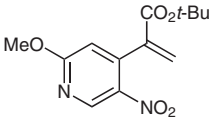
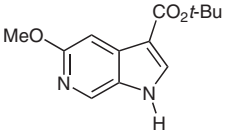
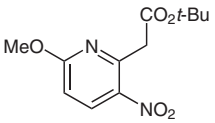
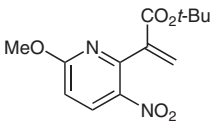
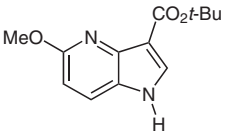
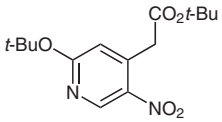
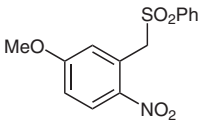
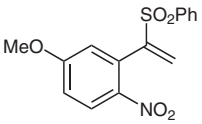
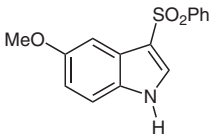
Knoevenagel-type condensation of the VNS products with benzaldehyde (Table 1, entry 1) or 1,3,5-trioxane, afforded the expected annulation precursors **14**–**18** and **21**–**22**; the reactions are also summarized in Table 1.[19,24] In addition to the esters, α,β-unsaturated sulfone **13**, prepared from VNS reaction of chloromethyl phenyl sulfone with 4-nitro-1-methoxybenzene, was reacted with 1,3,5-trioxane to give the unsaturated sulfone **23** (entry 11). Two additional annulation precursors were prepared using a palladium-catalyzed Stille coupling of ethyl 2-(tributylstannyl)-2-propenoate with the corresponding 2-nitro-1-iodobenzenes (entries 6–7).[25]

With an array of substrates in hand, the palladium-catalyzed reductive N-heteroannulation to afford substituted indoles, was then examined (**24**–**33**; Table 1). All reactions forming either new compounds or alternative methods for the preparation of previously described compounds have their yields reported in parenthesis in Table 1.

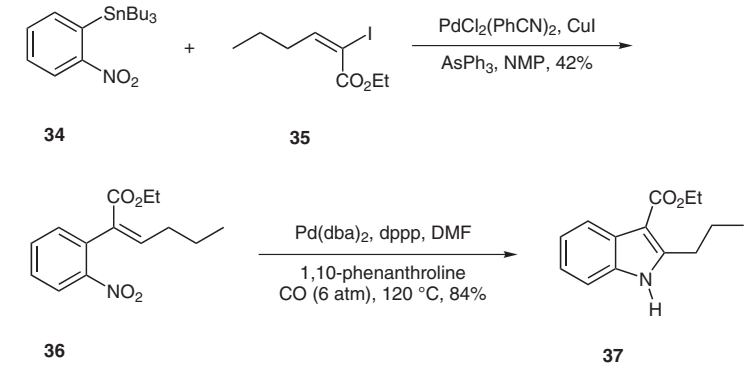
A catalyst system consisting of palladium diacetate and triphenyl phosphine was initially used (Scheme 1). However, bis(dibenzylidene)palladium, bis(1,3-diphenylphosphino)propane and 1,10-phenanthroline as ligands were employed for all other reactions, affording increased yields of products. This catalytic system has previously been succesfully employed in the synthesis of 1,2-dihydro-4(3*H*)-carbazolones[7] and β-carbolines.[8] Methyl 2-phenylindole-3-carboxylate (**24**) was obtained from compound **14** in good yield (entry 1). Functional groups on the aromatic ring including methoxy, bromo, chloro, and methyl ester groups were tolerated, affording the substituted indole-3-carboxylate in 81–99% yield (entries 2–4 and 6–7). Virtually quantitative formation of a 1*H*-benzo[*g*]indole was realized using naphthalene derivative **18** (entry 5). The 3-nitropyridine-derived compounds **21** and **22** also participated in the annulation reactions, affording azaindoles **31** and **32** (entries 9 and 10). As the final example in Table 1, the α,β-unsaturated sulfone **23** also underwent the annulation reaction, affording the sulfone-indole **33** (entry 11).

Compared to previous results using substrates having alkyl or aryl substituents in either the α- or β-position, or an electron-withdrawing group in the β-position of the alkene, the substrates examined here having an electron-withdrawing group in the α-position, underwent cyclization significantly slower. In most cases, three days were required for the reactions to go to completion. An even slower reaction was observed for the pyridine-based compound **22**, requiring six days for all the starting material to be consumed. It is speculated that this may be caused by coordination of the metal to both the alkene and the pyridine nitrogen of compound **22**, thus removing the catalyst

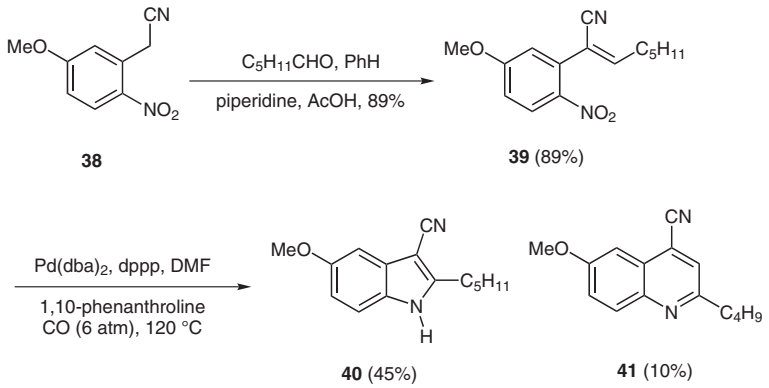
Table 1 Synthesis of 3-Substituted Indoles

Entry[a,b]	Nitroarene	Nitroalkane	Nitroalkene	Indole
1		 **1**	 **14** (67%)	 **24** (74%)
2	 R = Br	 **4** (88%)	 **15** (100%)	 **25** (98%)
3	R = Cl	**5**	**16** (100%)	**26** (92%)
4	R = OMe	**6** (83%)	**17** (70%)	**27** (99%)
5		 **7** (95%)	 **18** (95%)	 **28** (99%)
6		 **8** (R = 4-OMe)	 **19** (74%)	 **29** (81%)
7		**9** (R = 6-CO_2Me)	**20** (43%)	**30** (99%)
8[c]		 **10** (57%)	 **21** (68%)	 **31** (79%)
9[c]		 **11** (5%)	 **22** (58%)	 **32** (96%)
10[c]		 **12** (9%)	not further examined	
11		 **13**	 **23** (94%)	 **33** (74%)

[a] For procedural details, see the experimental section.
[b] Isolated yields are shown in parentheses.
[c] Compounds **10**–**12** were obtained from the same reaction in the yields given.



Scheme 2



Scheme 3

temporary from the catalytic cycle. The same bidentate coordination is not possible for the regioisomeric pyridine-containing compound **21**, which reacts at a rate comparable to the other substrates in Table 1.

All the indoles discussed above have either a hydrogen or a phenyl group in the β-position. In order to examine the influence of a longer alkyl chain in the β-position of the alkene, compound **36** was prepared via a Stille coupling of 2-nitrophenyl tributylstannane (**34**) with ethyl 2-iodohex-2-enoate (**35**; Scheme 2). Although the yield of coupling product **36** was moderate (42%), this method was used to prepare **36** for the subsequent palladium-catalyzed reaction. Attempted Knoevenagel condensation of methyl 2-(2-nitrophenyl)ethanoate (**1**) with aliphatic aldehydes gave <20% of products, often as complex mixtures.[26] The reductive N-heteroannulation of compound **36** proceeded smoothly and furnished the expected indole **37** in 84% yield. This is a clear indication that 2-alkyl-substituted indoles having an electron-withdrawing group in the 3-position can be prepared using the N-heteroannulation methodology.

As a final example, Knoevenagel-type condensation of the cyanomethyl-substituted nitrobenzene **38** with hexanal, furnished compound **39** as a single stereoisomer in good isolated yield (Scheme 3). The stereochemistry of the alkene was determined to be exclusively *Z* by an NOE experiment whereby irradiation of the alkene-proton produced an NOE enhancement of the resonance for the proton in the 6-position of the aromatic ring (in addition to the adjacent CH_2). Reductive annulation of compound **39** under standard reaction conditions, furnished the expected indole **40** in 45% yield. In addition to **40**, we were surprised to also isolate a small amount of the quinoline **41** in 10% yield. To our knowledge, this is the first time a quinoline has been isolated from a metal-catalyzed reductive N-heteroannulation at a non-functionalized position.[27] The corresponding quinoline by-product was not observed in the reaction converting compound **36** into **37**, based on the ^{1}H NMR spectrum of the crude reaction mixture (Scheme 2).

In summary, an expedient and efficient synthesis of indoles having an electron-withdrawing substituent in the 3-position has been developed. Application of this methodology to the total synthesis of more complex compounds and the development of a quinoline-selective reaction are currently ongoing in this laboratory.

All NMR spectra were recorded in $CDCl_3$ at 270 MHz (^{1}H NMR) and 67.5 MHz (^{13}C NMR) unless otherwise stated. The chemical shifts are expressed in δ values relative to TMS (δ = 0.00 ppm, ^{1}H and ^{13}C) or $CDCl_3$ (δ = 77.0 ppm, ^{13}C) internal standards. Results of attached proton test (APT) ^{13}C NMR experiments are shown in parentheses where, relative to $CDCl_3$, (–) denotes CH_3 or CH and (+) denotes CH_2 or C. Anhydrous solvents were used in all reactions. Chemicals were obtained from commercial sources and used as received or prepared according to literature procedures (referenced where first used). All reactions were performed under a nitrogen at-

mosphere in oven-dried glassware unless otherwise stated. Solvents were removed on a rotary evaporator at water-aspirator pressure.

***tert*-Butyl 2-(5-Bromo-2-nitrophenyl)ethanoate (4)[28]**

To an oven-dried round-bottom flask, *t*-BuOK (7.18 g, 58.7 mmol) was combined with DMF (25 mL) and stirred at r.t. until completely dissolved. The solution was then cooled to –20 °C. In a separate oven-dried flask, 4-bromonitrobenzene (2.00 g, 9.90 mmol), *tert*-butyl chloroacetate (1.49 g, 9.90 mmol) and DMF (25 mL) were combined and stirred at r.t. for 5 min. The contents of this flask were transferred via cannula over a period of 10 min to the dissolved *tert*-butoxide. An immediate color change from a light-tan to purple was observed. The reaction mixture was allowed to react for 30 min at –20 °C and then poured into cold (0 °C) aq HCl (5%, 200 mL). The solution turned from purple-violet to yellow. The resulting reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic phases were washed with H_2O (3 × 50 mL), dried with $MgSO_4$, filtered and the solvents were removed under reduced pressure. The crude product was purified by chromatography (hexanes–EtOAc, 8:2) to afford **4**.

Yield: 2.97 g (88%); yellow solid; mp 69–71 °C.

IR (neat): 1729, 1527, 1348, 1152 cm^{-1}.

^1H NMR: δ = 7.98 (d, *J* = 8.7 Hz, 1 H), 7.56 (dd, *J* = 8.6, 2.0 Hz, 1 H), 7.50 (d, *J* = 2.0 Hz, 1 H), 3.92 (s, 2 H), 1.44 (s, 9 H).

^{13}C NMR: δ = 168.3 (+), 147.5 (+), 136.0 (–), 132.2 (+), 131.3 (–), 128.0 (+), 126.4 (–), 81.9 (+), 40.6 (+), 28.7 (–).

Anal. Calcd for $C_{12}H_{14}BrNO_4$: C, 45.59; H, 4.46; N, 4.43. Found: C, 45.89; H, 4.58; N, 4.45.

***tert*-Butyl 2-(5-Methoxy-2-nitrophenyl)ethanoate (6)**

Reaction of a solution of *t*-BuOK (9.46 g, 77.5 mmol) in DMF (30 mL) with a solution of 4-methoxy-1-nitrobenzene (1.99 g, 13.1 mmol) and *tert*-butyl chloroacetate (1.97 g, 13.1 mmol) in DMF (30 mL), as described for **4**, gave pure product **6** after chromatography (hexanes–EtOAc, 8:2).

Yield: 2.72 g (83%); yellow solid; mp 68.5–70 °C.

IR (neat): 1732, 1614, 1579, 1506, 1338, 1282, 1222, 1146, 1004 cm^{-1}.

^1H NMR: δ = 8.18 (d, *J* = 9.1 Hz, 1 H), 6.89 (dd, *J* = 9.1, 2.8 Hz, 1 H), 6.78 (d, *J* = 2.8 Hz, 1 H), 3.92 (s, 2 H), 3.89 (s, 3 H), 1.45 (s, 9 H).

^{13}C NMR: δ = 169.0 (+), 163.2 (+), 141.6 (+), 133.3 (+), 127.8 (–), 118.5 (–), 112.8 (–), 81.0 (+), 55.7 (–), 41.7 (+), 27.8 (–).

Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.62; H, 6.84; N, 5.07.

***tert*-Butyl 2-(1-Nitronaphthyl)ethanoate (7)[29]**

Reaction of a solution of *t*-BuOK (20.92 g, 171 mmol) in DMF (30 mL) with a solution of 1-nitronaphthalene (5.00 g, 28.8 mmol) and *tert*-butyl chloroacetate (4.35 g, 28.8 mmol) in DMF (30 mL), as described for **4**, gave pure **7** after chromatography (hexanes–EtOAc, 8:2).

Yield: 7.87 g (95%); yellow solid; mp 81–82 °C.

IR (neat): 1728, 1527, 1369, 1332, 1154 cm^{-1}.

^1H NMR: δ = 7.97 (d, *J* = 8.4 Hz, 1 H), 7.91 (d, *J* = 7.9 Hz, 1 H), 7.82 (d, *J* = 8.4 Hz, 1 H), 7.61 (m, 2 H), 7.46 (d, *J* = 8.7 Hz, 1 H), 3.75 (s, 2 H), 1.45 (s, 9 H).

^{13}C NMR: δ = 168.6 (+), 147.6 (+), 132.8 (+), 130.9 (–), 128.5 (–), 127.9 (–), 127.8 (–), 127.2 (–), 125.0 (+), 124.5 (+), 121.6 (–), 81.8 (+), 38.8 (+), 27.8 (–).

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.85; H, 6.29; N, 5.19.

***tert*-Butyl 2-(6-Methoxy-3-nitro-4-pyridyl)ethanoate (10), *tert*-Butyl 2-(6-Methoxy-3-nitro-2-pyridyl)ethanoate (11) and *tert*-Butyl 2-[6-(*tert*-Butoxy)-3-nitro-4-pyridyl]ethanoate (12)**

Reaction of a solution of *t*-BuOK (7.29 g, 65.0 mmol) in DMF (30 mL) with a solution of 2-methoxy-5-nitropyridine (1.68 g, 10.8 mmol) and *tert*-butyl chloroacetate (1.63 g, 10.8 mmol) in DMF (30 mL), as described for **4**, gave **12**, **10** and **11** (order of elution) after chromatography (hexanes–EtOAc, 19:1).

10

Yield: 1.67 g (57%); yellow solid; mp 69–71 °C.

IR (neat): 1728, 1688, 1323, 1153, 912, 736 cm^{-1}.

^1H NMR: δ = 8.27 (d, *J* = 8.9 Hz, 1 H), 6.69 (d, *J* = 8.9 Hz, 1 H), 4.07 (s, 2 H), 3.94 (s, 3 H), 1.38 (s, 9 H).

^{13}C NMR: δ = 168.2 (+), 165.0 (+), 150.7 (+), 140.0 (+), 136.0 (–), 110.1 (–), 81.5 (+), 54.5 (–), 44.7 (+), 27.8 (–).

Anal. Calcd for $C_{12}H_{16}N_2O_5$: C, 53.73; H, 6.01; N, 10.44. Found: C, 53.73; H, 6.41; N, 10.30.

11

Yield: 146 mg (4.6%); yellow solid; mp 92–96 °C.

IR (neat): 1728, 1588, 1474, 1324, 1153 cm^{-1}.

^1H NMR: δ = 9.01 (s, 1 H), 6.64 (s, 1 H), 4.03 (s, 3 H), 3.92 (s, 2 H), 1.44 (s, 9 H).

^{13}C NMR: δ = 168.2 (+), 165.0 (+), 150.7 (+), 139.6 (+), 135.9 (–), 111.1 (–), 81.5 (+), 54.5 (–), 44.7 (+), 27.8 (–).

Anal. Calcd for $C_{12}H_{16}N_2O_5$: C, 53.73; H, 6.01; N, 10.44. Found: C, 54.27; H, 6.44; N, 10.83.

12

Yield: 308 mg (9.3%); yellow solid; mp 51–53 °C.

IR (neat): 1728, 1591, 1512, 1449, 1368, 1328, 1283, 1253, 1225, 1153, 1071 cm^{-1}.

^1H NMR: δ = 8.23 (d, *J* = 9.1 Hz, 1 H), 6.59 (d, *J* = 9.1 Hz, 1 H), 4.06 (s, 2 H), 1.62 (s, 9 H), 1.39 (s, 9 H).

^{13}C NMR: δ = 168.3 (+), 164.9 (+), 149.5 (+), 138.6 (+), 135.1 (–), 111.7 (–), 82.0 (+), 80.8 (+), 44.2 (+), 27.9 (–), 27.5 (–).

HRMS: *m/z* $[M + H]^+$ calcd for $C_{15}H_{23}N_2O_5$: 311.1607; found: 311.1601.

Methyl 2-(2-Nitrophenyl)propenoate (2)[30]

To a solution of methyl (2-nitrophenyl)ethanoate (1.02 g, 5.18 mmol) in DMF (50 mL) was added K_2CO_3 (7.14 g, 51.7 mmol), CaO (1.47 g, 26.2 mmol) and 1,3,5-trioxane (1.56 g, 52.1 mmol). The resulting purple slurry was heated at 40 °C overnight (16 h). Insoluble inorganic material was removed by filtration and washed with Et_2O (50 mL). The filtrate was washed with H_2O (5 × 50 mL) and the organic layer was dried with $MgSO_4$, filtered and the solvents were removed at reduced pressure. The crude product was purified by chromatography (hexanes–EtOAc, 8:2) to give **2**.

Yield: 0.89 g (83%); pale yellow-brown viscous oil.

IR (neat): 1728, 1526, 1349, 1211 cm^{-1}.

^1H NMR: δ = 8.11 (dd, *J* = 8.1, 1.4 Hz, 1 H), 7.65 (dt, *J* = 7.5, 1.2 Hz, 1 H), 7.54 (dt, *J* = 8.1, 1.6 Hz, 1 H), 7.40 (dd, *J* = 7.5, 1.6 Hz, 1 H), 6.54 (s, 1 H), 6.88 (s, 1 H), 3.76 (s, 3 H).

^{13}C NMR: δ = 165.2 (+), 147.7 (+), 139.7 (+), 133.6 (–), 132.8 (+), 132.1 (–), 129.3 (–), 127.5 (+), 124.5 (–), 52.2 (–).

Anal. Calcd for $C_{10}H_9NO_4$: C, 57.97; H, 4.38; N, 6.76. Found: C, 58.34; H, 4.67; N, 7.00.

Methyl 2-(2-Nitrophenyl)-3-phenylpropenoate (14)
Reaction of methyl (2-nitrophenyl)ethanoate (1.00 g, 5.11 mmol), K_2CO_3 (720 mg, 5.21 mmol), CaO (1.68 g, 29.9 mmol) and benzaldehyde (5.70 g, 53.7 mmol) as described above, gave **14**, after chromatography (hexanes–EtOAc, 4:1).

Yield: 970 mg (67%); faint yellow-brown viscous oil.

IR (neat): 1728, 1526, 1349, 1211 cm^{-1}.

^1H NMR: δ = 8.26–8.19 (m, 1 H), 7.92 (s, 1 H), 7.56–7.51 (m, 2 H), 7.25–7.13 (m, 4 H), 7.00 (d, *J* = 7.2 Hz, 2 H), 3.75 (s, 3 H).

^{13}C NMR: δ = 165.2 (+), 147.7 (+), 139.7 (+), 133.6 (–), 132.8 (+), 132.1 (–), 129.3 (–), 127.5 (+), 124.5 (–), 52.2 (–).

HRMS: *m/z* $[M + H]^+$ calcd for $C_{16}H_{14}NO_4$: 284.0923; found: 284.0918.

Anal. Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.25; H, 4.85; N, 4.63.

***tert*-Butyl 2-(5-Bromo-2-nitrophenyl)propenoate (15)**
To a solution of **4** (630 mg, 1.99 mmol) in benzene (100 mL) was added AcOH (1 mL), piperidine (1 mL) and 1,3,5-trioxane (508 mg, 16.9 mmol). The reaction flask was fitted with a Dean–Stark trap and the yellow solution was heated at reflux. After 24 h an additional portion of 1,3,5-trioxane (559 mg, 18.6 mmol) was added and the solution was heated at reflux for 24 h. The solvents were removed under reduced pressure from the resulting brown solution and the crude product was purified by chromatography (hexanes–EtOAc, 9:1) to yield **15**.

Yield: 654 mg (100%); faint yellow solid; mp 132–134 °C.

IR (neat): 1718, 1526, 1348, 1158 cm^{-1}.

^1H NMR: δ = 7.97 (d, *J* = 8.6 Hz, 1 H), 7.64 (dd, *J* = 8.6, 2.2 Hz, 1 H), 7.54 (d, *J* = 2.2 Hz, 1 H), 6.50 (s, 1 H), 5.84 (s, 1 H), 1.42 (s, 9 H).

^{13}C NMR: δ = 163.1 (+), 147.0 (+), 140.4 (+), 135.2 (+), 134.8 (–), 132.1 (–), 128.1 (+), 127.2 (+), 125.8 (–), 82.4 (+), 27.9 (–).

Anal. Calcd for $C_{13}H_{14}BrNO_4$: C, 47.58; H, 4.30; N, 4.27. Found: C, 47.56; H, 4.07; N, 4.44.

***tert*-Butyl 2-(5-Chloro-2-nitrophenyl)propenoate (16)**
Reaction of a solution of **5**[34] (360 mg, 1.32 mmol) in benzene (100 mL) with AcOH (1 mL), piperidine (1 mL) and 1,3,5-trioxane (three portions each 343 mg, 11.43 mmol at 0 h, 48 h and 48 h), as described for **15** (total time 120 h), gave **16**, after chromatography (hexanes–EtOAc, 9:1).

Yield: 375 mg (100%); pale-yellow crystals; mp 107.5–108.5 °C.

IR (neat): 1719, 1602, 1560, 1518 cm^{-1}.

^1H NMR: δ = 8.06 (d, *J* = 8.6 Hz, 1 H), 7.47 (dd, *J* = 8.9, 2.5 Hz, 1 H), 7.37 (d, *J* = 2.2 Hz, 1 H), 6.50 (s, 1 H), 5.85 (s, 1 H), 1.42 (s, 9 H).

^{13}C NMR: δ = 163.0 (+), 146.4 (+), 140.4 (+), 139.6 (+), 135.0 (+), 131.8 (–), 128.9 (–), 127.1 (+), 125.7 (–), 82.3 (+), 28.6 (–).

Anal. Calcd for $C_{13}H_{14}ClNO_4$: C, 55.04; H, 4.97; N, 4.94. Found: C, 55.43; H, 5.46; N, 4.56.

HRMS: *m/z* $[M + H]^+$ calcd for $C_{13}H_{14}ClNO_4Na$: 306.0509; found: 306.0504.

***tert*-Butyl 2-(5-Methoxy-2-nitrophenyl)propenoate (17)**
Reaction of a solution of **6** (175 mg, 0.70 mmol) in benzene (100 mL) with AcOH (1 mL), piperidine (1 mL) and 1,3,5-trioxane (three portions of each 180 mg, 6.00 mmol at 0 h, 48 h and 24 h), as described for **15** (total time 120 h), gave **17** after chromatography (hexanes–EtOAc, 9:1).

Yield: 129 mg (70%); pale-yellow crystals; mp 97 °C.

IR (neat): 1710, 1582, 1507, 1457, 1342, 1254 cm^{-1}.

^1H NMR: δ = 8.15 (d, *J* = 8.9 Hz, 1 H), 6.93 (dd, *J* = 8.6, 2.5 Hz, 1 H), 6.82 (d, *J* = 2.7 Hz, 1 H), 6.43 (s, 1 H), 5.78 (s, 1 H), 3.91 (s, 3 H), 1.42 (s, 9 H).

^{13}C NMR: δ = 163.6 (+), 163.3 (+), 142.0 (+), 141.0 (+), 136.0 (+), 127.0 (–), 125.8 (+), 117.3 (–), 113.1 (–), 81.8 (+), 55.9 (–), 27.7 (–).

Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.05. Found: C, 59.72; H, 6.50; N, 5.21.

***tert*-Butyl 2-(1-Nitro-2-naphthyl)propenoate (18)**
Reaction of a solution of *tert*-butyl 2-(1-nitro-2-naphthyl)ethanoate[30] (666 mg, 2.57 mmol) in benzene (100 mL) with AcOH (1 mL), piperidine (1 mL) and 1,3,5-trioxane (three portions of each 666 mg, 22.2 mmol), as described for **15** (total time 48 h), gave **18** after chromatography (hexanes–EtOAc, 9:1).

Yield: 662 mg (95%); pale-yellow crystals; mp 95–97 °C.

IR (neat): 1719, 1511, 1345, 1149 cm^{-1}.

^1H NMR: δ = 8.00–7.91 (m, 3 H), 7.69–7.58 (m, 2 H), 7.41 (d, *J* = 8.4 Hz, 1 H), 6.57 (d, *J* = 0.7 Hz, 1 H), 5.88 (d, *J* = 1.0 Hz, 1 H), 1.48 (s, 9 H).

^{13}C NMR: δ = 163.4 (+), 146.3 (+), 139.4 (+), 133.2 (+), 131.0 (+), 129.0 (+), 128.7 (–), 127.9 (–), 127.3 (–), 127.1 (–), 124.2 (+), 122.1 (–), 82.0 (+), 27.6 (–).[31]

Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.43; H, 6.02; N, 4.59.

Ethyl 2-(4-Methoxy-2-nitrophenyl)propenoate (19)
To a solution of 2-nitro-4-methoxyiodobenzene (**8**; 273 mg, 1.01 mmol) in 1-methyl-2-pyrrolidinone (NMP; 2 mL) was added ethyl 2-(tributylstannyl)prop-2-enoate (538 mg, 1.36 mmol), bis(benzonitrile)dichloropalladium [$PdCl_2(PhCN)_2$, 19 mg, 0.05 mmol], $AsPh_3$ (34 mg, 0.11 mmol) and CuI (20 mg, 0.10 mmol). The resulting red solution was heated at 80 °C for 72 h. The solvents were removed under reduced pressure and the crude product was purified by chromatography (hexanes–EtOAc, 9:1) to give **19**.

Yield: 187 mg (74%); pale-yellow oil.

IR (neat): 1715, 1626, 1531, 1352, 1303, 1236, 1202, 1099, 1028 cm^{-1}.

^1H NMR: δ = 7.63 (d, *J* = 2.7 Hz, 1 H), 7.30 (d, *J* = 8.4 Hz, 1 H), 7.16 (dd, *J* = 8.4, 2.5 Hz, 1 H), 6.49 (d, *J* = 0.7 Hz, 1 H), 5.83 (d, *J* = 1.0 Hz, 1 H), 4.19 (q, *J* = 7.2 Hz, 2 H), 3.90 (s, 3 H), 1.23 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 165.0 (+), 159.9 (+), 148.5 (+), 139.7 (+), 132.9 (–), 126.6 (+), 125.2 (+), 119.7 (–), 109.4 (–), 61.3 (+), 55.9 (–), 13.9 (–).

Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.36; H, 5.63; N, 6.07.

Ethyl 2-(6-Carbomethoxy-2-nitrophenyl)propenoate (20)
Reaction of a solution of methyl 2-iodo-3-nitrobenzoate[32] (**9**; 285 mg, 0.93 mmol) in NMP (2 mL) with ethyl 2-(tributylstannyl)prop-2-enoate (547 mg, 1.41 mmol), $PdCl_2(PhCN)_2$ (20 mg, 0.06 mmol), $AsPh_3$ (33 mg, 0.10 mmol) and CuI (23 mg, 0.11 mmol), as described for **19** (80 °C, 72 h), gave **20** after chromatography (hexanes–EtOAc, 9:1).

Yield: 112 mg (43%); pale-yellow oil.

IR (neat): 1729, 1535, 1296, 1205, 1132 cm^{-1}.

^1H NMR: δ = 8.17 (d, *J* = 7.9 Hz, 1 H), 8.08 (d, *J* = 8.2 Hz, 1 H), 7.59 (t, *J* = 7.9 Hz, 1 H), 6.47 (s, 1 H), 5.54 (s, 1 H), 4.27 (q, *J* = 7.2 Hz, 2 H), 3.85 (s, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 165.6 (+), 164.4 (+), 150.0 (+), 140.5 (+), 132.9 (–), 137.5 (+), 133.9 (–), 128.8 (–), 127.1 (–), 125.7 (+), 61.2 (+), 52.5 (–), 14.0 (–).

Anal. Calcd for $C_{13}H_{13}NO_6$: C, 55.91; H, 4.69; N, 5.02. Found: C, 56.43; H, 5.05; N, 4.38.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}NO_6$: 280.0821; found: 280.0816.

***tert*-Butyl 2-(6-Methoxy-3-nitro-4-pyridyl)propenoate (21)**
Reaction of a solution of **10** (180 mg, 0.67 mmol) in benzene (100 mL) with AcOH (1 mL), piperidine (1 mL) and 1,3,5-trioxane (three portions of each 174 mg, 5.8 mmol at 0 h, 48 h and 48 h), as described for **15** (total time 120 h), gave **21** after chromatography (hexanes–EtOAc, 9:1).

Yield: 128 mg (68%); pale-yellow crystals; mp 81 °C.

IR (neat): 1722, 1610, 1543, 1512, 1348, 1287, 1244, 1024 cm^{-1}.

^{1}H NMR: δ = 8.91 (s, 1 H), 6.63 (s, 1 H), 6.45 (s, 1 H), 5.81 (s, 1 H), 4.01 (s, 3 H), 1.37 (s, 9 H).

^{13}C NMR: δ = 166.7 (+), 162.7 (+), 145.2 (–), 144.3 (+), 140.0 (+), 139.6 (–), 127.5 (+), 112.7 (+), 82.5 (+), 54.7 (–), 27.7 (–).

Anal. Calcd for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.99. Found: C, 55.99; H, 6.29; N, 9.63.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{17}N_2O_5$: 281.1138; found: 281.1132.

***tert*-Butyl 2-(6-Methoxy-3-nitro-2-pyridyl)propenoate (22)**
Reaction of a slurry of **11** (231 mg, 0.85 mmol) in benzene (100 mL) with AcOH (1 mL), piperidine (1 mL) and 1,3,5-trioxane (two portions of each 226 mg, 7.53 mmol at 0 h and 48 h), as described for **15** (total time 72 h), gave **22** after chromatography (hexanes–EtOAc, 8:2).

Yield: 139 mg (58%); pale-yellow crystals; mp 60–62 °C.

IR (neat): 1725, 1583, 1516, 1470, 1320 cm^{-1}.

^{1}H NMR: δ = 8.24 (d, *J* = 8.9 Hz, 1 H), 6.76 (d, *J* = 8.9 Hz, 1 H), 6.53 (s, 1 H), 6.16 (s, 1 H), 3.99 (s, 3 H), 1.13 (s, 9 H).

^{13}C NMR: δ = 165.2 (+), 163.3 (+), 150.0 (+), 141.6 (+), 139.7 (+), 135.4 (–), 129.6 (+), 110.9 (–), 82.3 (+), 54.7 (–), 27.8 (–).

Anal. Calcd for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.99. Found: C, 56.00; H, 6.18; N, 10.00.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{16}N_2O_5Na$: 303.0957; found: 303.0951.

1-(5-Methoxy-2-nitrophenyl)ethenyl Phenylsulfone (23)
Reaction of a solution of **13**[33] (1.046 g, 3.39 mmol) in benzene (100 mL) with AcOH (1 mL), piperidine (1 mL) and 1,3,5-trioxane (three portions of each 880 mg, 29.33 mmol at 0 h, 48 h and 48 h), as described for **15** (total time 120 h), gave **23** after chromatography (hexanes–EtOAc, 9:1).

Yield: 1.02 g (94%); red solid; mp 105–108 °C.

IR (neat): 1588, 1519, 1343, 1323, 1152 cm^{-1}.

^{1}H NMR: δ = 8.00 (d, *J* = 9.2 Hz, 1 H), 7.70 (d, *J* = 7.4 Hz, 2 H), 7.61 (t, *J* = 7.4 Hz, 1 H), 7.46 (t, *J* = 7.9 Hz, 2 H), 6.98 (dd, *J* = 9.2, 2.7 Hz, 1 H), 6.76 (d, *J* = 2.7 Hz, 1 H), 6.64 (s, 1 H), 5.94 (s, 1 H), 3.85 (s, 3 H).

^{13}C NMR: δ = 162.5 (+), 148.3 (+), 141.4 (+), 138.0 (+), 133.9 (–), 129.5 (+), 129.0 (–), 128.8 (–), 127.2 (–), 126.7 (+), 118.0 (–), 115.3 (–), 56.1 (–).

Anal. Calcd for $C_{15}H_{13}NSO_5$: C, 56.42; H, 4.10; 4.39. Found: C, 56.48; H, 4.61; 4.22.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{14}NO_5S$: 320.0593; found: 320.0587.

Ethyl 2-(2-Nitrophenyl)hexenoate (36)
Reaction of a solution of 2-nitrophenyl tributylstannane[34] (**34**; 635 mg, 1.61 mmol), ethyl 2-iodohexenoate[35] (**35**; *E*/*Z* = 9:1, 437 mg, 1.63 mmol), $PdCl_2(PhCN)_2$ (24 mg, 0.07 mmol), $AsPh_3$ (35 mg, 0.11 mmol) and CuI (27 mg, 0.08 mmol) in 1-methyl-2-pyrrolidone (NMP, 2 mL), as described for **19** (80 °C, 72 h), gave **36** after chromatography (hexanes–EtOAc, 9:1).

Yield: 177 mg (42%); pale-yellow oil.

IR (neat): 2962, 1710, 1524, 1346, 143, 1222, 1187, 1031, 709 cm^{-1}.

^{1}H NMR (600 MHz): δ = 8.06 (d, *J* = 8.4 Hz, 1 H), 7.56 (dt, *J* = 8.4, 1.2 Hz, 1 H), 7.44 (dt, *J* = 8.4, 1.2 Hz, 1 H), 7.18 (dd, *J* = 8.4, 1.2 Hz, 1 H), 7.04 (t, *J* = 7.8 Hz, 1 H), 4.06 (m, 2 H), 1.92 (m, 2 H), 1.39 (sext, *J* = 7.2 Hz, 2 H), 1.12 (t, *J* = 7.2 Hz, 3 H), 0.80 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz): δ = 165.4, 148.6, 144.5, 133.1, 132.6, 131.5, 131.4, 128.7, 124.7, 61.0, 31.6, 21.8, 14.0, 13.8.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{17}NO_4Na$: 286.1055; found: 286.1050.

(*Z*)-5-Methoxy-2-nitro-α-hexylidenebenzeneacetonitrile (39)
Reaction of 5-methoxy-2-nitrobenzeneacetonitrile[29] (**38**; 540 mg, 2.82 mmol) in benzene (10 mL) with AcOH (60 μL), piperidine (50 μL) and hexanal (284 mg, 2.82 mmol) as described for **15**, gave **39** after chromatography (hexanes–EtOAc, 8:2).

Yield: 659 mg (89%); pale-yellow oil.

IR (neat): 2223, 1514, 1300 cm^{-1}.

^{1}H NMR (600 MHz): δ = 8.14 (d, *J* = 9.0 Hz, 1 H), 6.99 (dd, *J* = 9.0, 3.0 Hz, 1 H), 6.81 (d, *J* = 3.0 Hz, 1 H), 6.46 (t, *J* = 7.8 Hz, 1 H), 3.92 (s, 3 H), 2.58 (q, *J* = 7.2 Hz, 2 H), 1.58 (pent, *J* = 7.2 Hz, 2 H), 1.38 (m, 4 H), 0.93 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz): δ = 163.0, 151.3, 140.4, 132.6, 127.9, 117.4, 115.1, 114.2, 113.6, 56.1, 31.8, 31.2, 27.9, 22.3, 13.9.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{18}N_2O_3$: 275.1396; found: 275.1396.

Methyl Indole-3-carboxylate (3)
To an oven-dried, threaded ACE glass pressure tube was added **2** (123 mg, 0.59 mmol), $Pd(OAc)_2$ (15 mg, 0.07 mmol), Ph_3P (67 mg, 0.26 mmol) and DMF (7 mL). The tube was fitted with a pressure head, the solution was saturated with CO (four cycles to 6 atm of CO) and the reaction mixture was heated to 110 °C (oil bath temperature) under CO (6 atm) until all starting material was consumed (72 h) as judged by TLC. The solvent was removed by bulb-to-bulb distillation under reduced pressure and the crude product was purified by chromatography (hexanes–EtOAc, 6:4) to give **3**.

Yield: 95 mg (91%); brownish solid; mp 148–149 °C (Lit.[36] 142–144 °C).

Methyl 2-Phenylindole-3-carboxylate (24)
Reaction of **14** (69 mg, 0.24 mmol), $Pd(dba)_2$ (8 mg, 0.01 mmol), 1,3-bis(diphenylphosphino)propane (dppp; 6 mg, 0.01 mmol), 1,10-phenanthroline monohydrate (phen; 6 mg, 0.03 mmol), in DMF (5 mL), as described for **3** (100 °C, 6 atm CO, 72 h), gave **24** after chromatography (hexanes–EtOAc, 9:1).

Yield: 45 mg (74%); yellow solid; mp 145 °C (Lit.[37] 149–151 °C).

IR (neat): 1684, 1450, 1213, 1128 cm^{-1}.

^{1}H NMR: δ = 8.64 (br s, 1 H), 78.24–8.15 (m, 1 H), 7.69–7.18 (m, 8 H), 3.81 (s, 3 H).

^{13}C NMR: δ = 165.8 (+), 144.6 (+), 135.1 (–), 131.9 (+), 129.5 (–), 129.2 (–), 128.1 (–), 127.5 (+), 123.2 (–), 122.1 (–), 122.1 (–), 111.0 (+), 104.4 (+), 50.9 (–).

***tert*-Butyl 5-Bromoindole-3-carboxylate (25)**
Reaction of **15** (59.3 mg, 0.20 mmol), $Pd(dba)_2$ (7 mg, 0.01 mmol), dppp (5 mg, 0.01 mmol) and phen (5 mg, 0.02 mmol) in DMF (5 mL), as described for **3** (100 °C, 6 atm CO, 72 h), gave **25** after chromatography (hexanes–EtOAc, 9:1).

Yield: 52.1 mg (98%); pale-yellow solid; mp 148 °C.

IR (neat): 1669, 1651, 1522, 1436, 1357, 1152, 1129 cm^{-1}.

^{1}H NMR: δ = 8.60 (br s, 1 H), 8.31 (d, *J* = 1.7 Hz, 1 H), 7.85 (d, *J* = 3.0 Hz, 1 H), 7.35 (dd, *J* = 8.6, 1.7 Hz, 1 H), 7.27 (d, *J* = 6.4 Hz, 1 H), 1.64 (s, 9 H).

^{13}C NMR: δ = 164.3 (+), 134.7 (+), 131.5 (–), 127.5 (+), 126.0 (–), 124.3 (–), 115.4 (+), 112.9 (–), 110.4 (+), 80.6 (+), 28.5 (–).

Anal. Calcd for $C_{13}H_{14}BrNO_2$: C, 52.72; H, 4.76. Found: C, 52.85; H, 4.52.

***tert*-Butyl 5-Chloroindole-3-carboxylate (26)**
Reaction of **16** (85 mg, 0.31 mmol), $Pd(dba)_2$ (16 mg, 0.02 mmol), dppp (10 mg, 0.02 mmol) and phen (10 mg, 0.04 mmol) in DMF (5 mL), as described for **3** (120 °C, 6 atm CO, 72 h), gave **26** after chromatography (hexanes–EtOAc, 9:1).

Yield: 70 mg (92%); pale-yellow solid; mp 134–135 °C.

IR (neat): 1666, 1532, 1456, 1361, 1153 cm^{-1}.

^{1}H NMR: δ = 8.88 (br s, 1 H), 8.13 (d, *J* = 2.0 Hz, 1 H), 7.85 (d, *J* = 2.7 Hz, 1 H), 7.31 (d, *J* = 8.7 Hz, 1 H), 7.20 (dd, *J* = 8.6, 2.0 Hz, 1 H), 1.69 (s, 9 H).

^{13}C NMR: δ = 164.5 (+), 134.5 (+), 131.8 (–), 127.7 (+), 126.9 (+), 123.4 (–), 121.2 (–), 112.5 (–), 110.4 (+), 80.6 (+), 28.5 (–).

Anal. Calcd for $C_{13}H_{14}ClNO_2$: C, 62.03; H, 5.61; N, 5.56. Found: C, 62.40; H, 6.07; N, 5.18.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{14}ClNO_2Na$: 274.0611; found: 274.0605.

***tert*-Butyl 5-Methoxyindole-3-carboxylate (27)**
Reaction of **17** (186 mg, 0.67 mmol), $Pd(dba)_2$ (24 mg, 0.03 mmol), dppp (14 mg, 0.03 mmol) and phen (14 mg, 0.07 mmol) in DMF (5 mL), as described for **3** (120 °C, 6 atm CO, 72 h), gave **27** after chromatography (hexanes–EtOAc, 9:1).

Yield: 164 mg (99%); pale-yellow solid; mp 110–112 °C.

IR (neat): 1717, 1684, 1653, 1558, 1540, 1522, 1457, 1151 cm^{-1}.

^{1}H NMR: δ = 8.28 (br s, 1 H), 7.77 (s, 1 H), 7.64 (d, *J* = 2.2 Hz, 1 H), 7.25 (d, *J* = 8.9 Hz, 1 H), 6.87 (dd, *J* = 8.6, 2.5 Hz, 1 H), 3.85 (s, 3 H), 1.63 (s, 9 H).

^{13}C NMR: δ = 165.1 (+), 155.6 (+), 131.1 (–), 131.0 (+), 126.5 (+), 113.4 (–), 112.3 (–), 110.0 (+), 102.7 (–), 80.0 (+), 55.6 (–), 28.5 (–).

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.91; H, 7.52; N, 5.25.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{17}NO_3Na$: 270.1106; found: 270.1101.

***tert*-Butyl 1*H*-Benzo[*g*]indole-3-carboxylate (28)**
Reaction of **18** (55.9 mg, 0.20 mmol), $Pd(dba)_2$ (7 mg, 0.01 mmol), dppp (5 mg, 0.01 mmol) and phen (5 mg, 0.02 mmol) in DMF (5 mL), as described for **3** (100 °C, 6 atm, 72 h), gave **28** after chromatography (hexanes–EtOAc, 9:1).

Yield: 53.0 mg (99%); yellow solid; mp 155 °C.

IR (neat): 1700, 1669, 1529, 1391, 1155, 1126 cm^{-1}.

^{1}H NMR: δ = 9.59 (br s, 1 H), 9.25 (d, *J* = 8.9 Hz, 1 H), 8.03 (d, *J* = 7.9 Hz, 1 H), 7.95 (d, *J* = 7.4 Hz, 1 H), 7.87 (d, *J* = 3.2 Hz, 1 H), 7.64 (d, *J* = 8.7 Hz, 1 H), 7.55–7.43 (m, 2 H), 1.68 (s, 9 H).

^{13}C NMR: δ = 165.7 (+), 131.1 (+), 130.6 (+), 128.8 (–), 125.9 (–), 124.5(–), 122.6 (–), 122.2 (+), 121.6 (+), 120.7 (–), 119.7 (–), 112.0 (+), 80.5 (+), 28.6 (–).[31]

Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.21; H, 6.12; N, 5.57.

Ethyl 6-Methoxyindole-3-carboxylate (29)[38]
Reaction of **19** (30 mg, 0.12 mmol), $Pd(dba)_2$ (4.9 mg, 0.009 mmol), dppp (5 mg, 0.01 mmol) and phen (4 mg, 0.02 mmol) in DMF (5 mL), as described for **3** (100 °C, 6 atm CO, 72 h), gave **29** after chromatography (hexanes–EtOAc, 9:1).

Yield: 21.3 mg (81%); pale-yellow solid; mp 141–142 °C (Lit.[38] 141–142 °C).

3-Ethyl 4-Methyl Indole-3,4-dicarboxylate (30)[38]
Reaction of **20** (94 mg, 0.34 mmol), $Pd(dba)_2$ (14 mg, 0.02 mmol), dppp (9 mg, 0.02 mmol) and phen (8 mg, 0.04 mmol) in DMF (5 mL), as described for **3** (120 °C, 6 atm CO, 72 h), gave **30** after chromatography (hexanes–EtOAc, 9:1).

Yield: 81 mg (99%); pale-yellow solid; mp 142–143 °C (Lit.[38,39] 93–94 °C).

IR (neat): 3318, 1711, 1689, 1244, 1175, 750 cm^{-1}.

^{1}H NMR: δ = 7.96 (dd, *J* = 7.4, 1.0 Hz, 1 H), 7.83 (dd, *J* = 2.2, 1.0 Hz, 1 H), 7.64 (d, *J* = 8.2 Hz, 1 H), 7.38 (t, *J* = 7.4 Hz, 1 H), 4.44 (q, *J* = 7.2 Hz, 2 H), 4.01 (s, 3 H), 1.44 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 167.4, 162.0, 137.3, 129.0, 124.5, 124.4, 116.8, 109.5, 61.3, 52.0, 14.4.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}NO_4$: 248.0938; found: 248.0917.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{13}NO_4Na$: 270.0742; found: 270.0736.

***tert*-Butyl 5-Methoxy-6-azaindole-3-carboxylate (31)**
Reaction of **21** (57.5 mg, 0.21 mmol), $Pd(dba)_2$ (7 mg, 0.01 mmol), dppp (5 mg, 0.01 mmol) and phen (5 mg, 0.02 mmol) in DMF (5 mL), as described for **3** (100 °C, 6 atm, 72 h), gave **31** after chromatography (hexanes–EtOAc, 9:1).

Yield: 40.0 mg (79%); pale-yellow solid; mp 204 °C.

IR (neat): 1696, 1649, 1555, 1343, 1284, 1049 cm^{-1}.

^{1}H NMR: δ = 8.92 (br s, 1 H), 8.42 (s, 1 H), 7.98 (d, *J* = 3.0 Hz, 1 H), 7.38 (s, 1 H), 3.98 (s, 3 H), 1.64 (s, 9 H).

^{13}C NMR: δ = 164.3 (+), 159.8 (+), 136.2 (–), 135.4 (+), 130.7 (–), 119.4 (+), 98.0 (–), 80.6 (+), 54.5 (–), 28.5 (–).[31]

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{17}N_2O_3$: 249.1239; found: 249.1234.

***tert*-Butyl 5-Methoxy-4-azaindole-3-carboxylate (32)**
Reaction of **22** (76 mg, 0.27 mmol), $Pd(dba)_2$, (10 mg, 0.015 mmol), dppp (8 mg, 0.016 mmol) and phen (9 mg, 0.036 mmol) in DMF (5 mL), as described for **3** (120 °C, 6 atm CO, 144 h), gave **32** after chromatography (hexanes–EtOAc, 9:1).

Yield: 67 mg (96%); pale-yellow solid; mp 174–178 °C.

IR (neat): 2979, 1690, 2581, 1478, 907 cm^{-1}.

^{1}H NMR: δ = 8.83 (br s, 1 H), 7.90 (d, *J* = 3.2 Hz, 1 H), 7.58 (d, *J* = 8.9 Hz, 1 H), 6.66 (d, *J* = 8.9 Hz, 1 H), 4.04 (s, 3 H), 1.63 (s, 9 H).

^{13}C NMR: δ = 163.9 (+), 161.2 (+), 140.3 (+), 132.3 (–), 125.0 (+), 122.4 (–), 108.4 (–), 106.6 (–), 80.0 (+), 53.2 (–), 28.5 (–).

Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.85; H, 7.19; N, 10.97.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{17}N_2O_3$: 249.1239; found: 249.1234.

5-Methoxyindol-3-yl Phenyl Sulfone (33)

Reaction of **23** (100 mg, 0.31 mmol), $Pd(dba)_2$ (15 mg, 0.02 mmol), dppp (11 mg, 0.02 mmol) and phen (10 mg, 0.04 mmol) in DMF (5 mL), as described for **3** (120 °C, 6 atm CO, 72 h), gave **33** after chromatography (hexanes–EtOAc, 9:1).

Yield: 65 mg (74%); pale-yellow solid; mp 91 °C.

IR (neat): 1506, 1487, 1293, 1213, 1144, 909, 732 cm^{-1}.

^{1}H NMR: δ = 9.36 (br s, 1 H), 7.99 (dd, *J* = 7.7, 1.2 Hz, 1 H), 7.79 (s, 1 H), 7.56–7.39 (m, 4 H), 7.32 (d, *J* = 2.5 Hz, 1 H), 7.28 (d, *J* = 9.2 Hz, 1 H), 6.90 (dd, *J* = 8.9, 2.5 Hz, 1 H), 3.82 (s, 3 H).

^{13}C NMR: δ = 156.0 (+), 143.2 (+), 132.5 (–), 131.1 (+), 130.2 (–), 129.0 (–), 126.5 (–), 124.3 (+), 115.8 (+), 114.4 (–), 113.1 (–), 100.9 (–), 55.8 (–).

Anal. Calcd for $C_{15}H_{13}NO_3S$: C, 62.70; H, 4.56; N, 4.87. Found: C, 63.13; H, 4.41; N, 4.49.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{13}NO_3S$: 310.0514; found: 310.0508.

Ethyl 2-Propylindole-3-carboxylate (37)

Reaction of ethyl 2-(2-nitrophenyl)hexenoate (130 mg 0.44 mmol), $Pd(dba)_2$ (14 mg, 0.02 mmol), dppp (10 mg, 0.02 mmol) and phen (11 mg, 0.04 mmol) in DMF (5 mL), as described for **3** (120 °C, 6 atm CO, 72 h), gave **37** after chromatography (hexanes–EtOAc, 9:1).

Yield: 96 mg (84%); pale-yellow solid; mp 108 °C.

IR (neat): 2965, 2925, 1726, 1267, 1118, 1973, 740 cm^{-1}.

^{1}H NMR (600 MHz): δ = 8.28 (s, 1 H), 8.06 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.24 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.13 (m, 2 H), 4.33 (q, *J* = 7.2 Hz, 2 H), 3.07 (t, *J* = 7.8 Hz, 2 H), 1.71 (sext, *J* = 7.8 Hz, 2 H), 1.37 (t, *J* = 7.2 Hz, 3 H), 0.94 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz): δ = 165.9, 148.2, 144.5, 134.5, 127.3, 122.3, 121.7, 121.5, 110.5, 59.4, 29.9, 22.5, 14.6, 14.0.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{18}NO_2$: 232.1338; found: 232.1333.

3-Cyano-2-pentyl-5-methoxyindole (40) and 2-Butyl-4-cyano-6-methoxyquinoline (41)

Reaction of **39** (110 mg, 0.40 mmol), $Pd(dba)_2$ (16 mg, 0.02 mmol), dppp (15 mg, 0.02 mmol) and phen (19 mg, 0.03 mmol) in DMF (5 mL), as described for **3** (120 °C, 6 atm, 72 h), gave **40** and **41** (in order of elution), after chromatography (hexanes–EtOAc, 8:2).

40

Yield: 40 mg (45%); pale-yellow solid; mp 98–99 °C.

IR (neat): 3249, 2210, 1477, 1221 cm^{-1}.

^{1}H NMR (600 MHz): δ = 8.44 (br s, 1 H), 7.24 (d, *J* = 8.4 Hz, 1 H), 7.09 (d, *J* = 2.4 Hz, 1 H), 6.86 (dd, *J* = 9.0, 2.4 Hz, 1 H), 3.86 (s, 3 H), 2.92 (t, *J* = 7.8 Hz, 2 H), 1.78 (pent, *J* = 7.2 Hz, 2 H), 1.38–1.35 (m, 4 H), 0.90 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz): δ = 155.8, 149.2, 129.2, 128.6, 116.5, 113.7, 112.1, 100.7, 84.9, 55.8, 31.2, 28.7, 27.6, 22.3, 13.9.

Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 73.88; H, 8.04; N, 11.45.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{19}N_2O$: 243.1497; found: 243.1492.

41

Yield: 10 mg (10%); pale-yellow solid; mp 51–52 °C.

IR (neat): 2228, 1619, 1479, 1213, 1072 cm^{-1}.

^{1}H NMR (600 MHz): δ = 8.00 (d, *J* = 9.0 Hz, 1 H), 7.58 (s, 1 H), 7.44 (dd, *J* = 9.0, 3.0 Hz), 7.34 (d, *J* = 3.0 Hz, 1 H), 3.99 (s, 3 H), 2.97 (t, *J* = 7.8 Hz, 2 H), 1.79 (pent, *J* = 7.8 Hz, 2 H), 1.44 (sext, *J* = 7.8 Hz, 2 H), 0.97 (t, *J* = 7.8 Hz, 3 H).

^{13}C NMR (150 MHz): δ = 159.6, 159.3, 144.2, 131.2, 125.7, 125.2, 124.0, 117.2, 102.1, 55.9, 38.4, 31.9, 22.5, 13.9.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{17}N_2O$: 241.1341; found: 241.1335.

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