# Potassium [1-(*tert*-Butoxycarbonyl)-1*H*-indol-2-yl]trifluoroborate as an Efficient Building Block in Palladium-Catalyzed Suzuki–Miyaura Cross Couplings

Paméla Kassis, Valérie Bénéteau*, Jean-Yves Mérour, Sylvain Routier*

Institut de Chimie Organique et Analytique, Université d'Orléans, UMR CNRS 6005, Rue de Chartres, BP 6759, 45067 Orléans Cedex 2, France

Fax +33(2)38417281; E-mail: sylvain.routier@univ-orleans.fr

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**Abstract:** Potassium [1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl]trifluoroborate (**1**) was used in Suzuki-type coupling reactions. First, the best coupling conditions were assessed using bromobenzene as the electrophile. Then, **1** was successfully coupled with various aryl and hetaryl bromides. Finally, the reactivity of **1** towards coupling partners other than bromide derivatives was evaluated.

**Key words:** Suzuki coupling, organotrifluoroborates, palladium catalysis, indoles

Over the last 25 years, palladium chemistry has deeply modified our retrosynthetic approach to the formation of carbon–carbon bonds, especially for aromatic and heteroaromatic structures.

The palladium-catalyzed Suzuki cross coupling of aryl halides with boronic acids is one of the most extensively used methods, even on industrial scales.[1–3] Nevertheless, some heteroaromatic boronic acids, particularly when the boronic acid group is α to a nitrogen atom, can be subject to degradation by oxidation or deboronation during the coupling process.[4] In these cases, an alternative organoboron coupling partner may be required. Indeed, potassium organotrifluoroborates have emerged lately as efficient and versatile building blocks.[5–10]

Indole is one of the most encountered cores in natural products and a privileged pharmacophore in medicinal chemistry, and new tools to access complex indolic structures are always needed.

For these reasons, we are currently interested in the formation and reactivity in Suzuki-type couplings of potassium [1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl]trifluoroborate (**1**) (Figure 1).[11,12] In a recent paper by Meggers and co-workers, **1** was coupled with various pyridinic derivatives to access pyridocarbazoles.[12] The aim of this report is to compare different catalytic systems in a model reaction, to apply the best system to diverse functionalized bromide compounds, and, finally, to vary the nature of the electrophilic partner.

The preparation of **1** resulted from the transformation of indole **2** into indol-2-ylboronic acid **3**, then conversion into the corresponding potassium trifluoroborate salt (Scheme 1).[13]

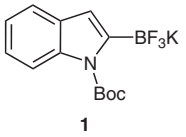


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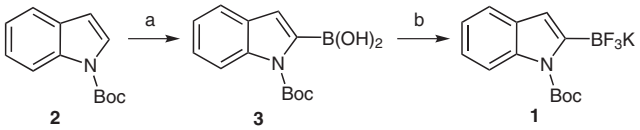
**Figure 1** Potassium [1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl]trifluoroborate

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**Scheme 1** *Reagents and conditions*: (a) (i) LTMP (1.3 equiv), THF, –78 °C, 45 min; (ii) B(O*i*-Pr)$_3$ (3.0 equiv), –78 to r.t., 2 h; (iii) 10% aq HCl, r.t.; (b) 4.5 M aq $KHF_2$ (3.0 equiv), MeOH; 94% over 2 steps.

Indeed, 1-(*tert*-butoxycarbonyl)-1*H*-indole (**2**) treated with lithium 2,2,6,6-tetramethylpiperidide (1.3 equiv) at –78 °C in tetrahydrofuran, followed by addition of triisopropyl borate (3.0 equiv) then acidic hydrolysis, led to the corresponding boronic acid **3**. Alternatively, **3** can be prepared using a noncryogenic method with lithium diisopropylamide at 0 °C.[14] The crude boronic acid **3** was dissolved in methanol and stirred with an aqueous potassium hydrogen fluoride solution (3.0 equiv) to give **1** as a white precipitate in a good overall yield (94%). The $^{11}B$ NMR spectrum of **1** is in agreement with the structure. We noticed that, conveniently, **1** can be stored on the bench at room temperature for several weeks without any decomposition.

As a model reaction, we investigated the Suzuki–Miyaura coupling of **1** with bromobenzene using various palladium species, solvents, and bases (Scheme 2, Table 1).[15] In our search for the best coupling conditions, the use of palladium(II) acetate (in the presence or absence of triphenylphosphine), $PdCl_2(PPh_3)_2$, or $PdCl_2(dppf)\cdot CH_2Cl_2$ did not prove better than the use of $Pd(PPh_3)_4$ (Table 1, entries 1–4, 8).

The most efficient conditions, leading to the 2-phenylindole **4** in 92% yield, involved the use of tetrakis(triphenylphosphine)palladium(0) (10%) in a mixture of 1,2-

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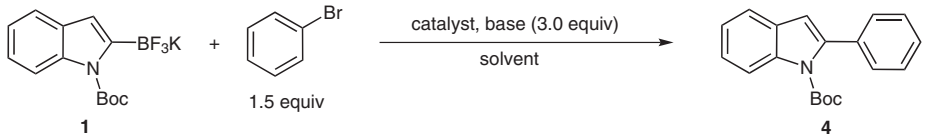



**Scheme 2** *Reagents and conditions*: see Table 1.

**Table 1** Optimization of Coupling Conditions with Bromobenzene

| Entry | Catalyst | Base (3 equiv) | Solvent | Temp (°C) | Time (h) | Yield[a] (%) of **4** |
|---|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ (10%) | $Na_2CO_3$ | DME–$H_2O$ | 90 | 1 | 41 |
| 2 | $Pd(OAc)_2$ (5%), $Ph_3P$ (10%) | $Na_2CO_3$ | DME–$H_2O$ | 90 | 1 | 60 |
| 3 | $PdCl_2(PPh_3)_2$ (10%) | $Na_2CO_3$ | DME–$H_2O$ | 90 | 1 | 55 |
| **4** | **$Pd(PPh_3)_4$ (10%)** | **$Na_2CO_3$** | **DME–$H_2O$** | **90** | **1** | **92** |
| 5 | $Pd(PPh_3)_4$ (10%) | $Na_2CO_3$ | DME–$H_2O$ | 50 | 4 | 54 |
| 6 | $Pd(PPh_3)_4$ (10%) | $Na_2CO_3$ | toluene–EtOH | 90 | 18 | 44 |
| 7 | $Pd(PPh_3)_4$ (10%) | $NaHCO_3$ | toluene–EtOH | 90 | 5 | 55 |
| 8 | $PdCl_2(dppf)\cdot CH_2Cl_2$ (5%) | *i*-$PrNEt_2$ | EtOH | 90 | 1 | 66 |
| 9 | 10% Pd/C (5%) | NaOH, TBAB | $H_2O$ | 90 | 1 | 0[b] |

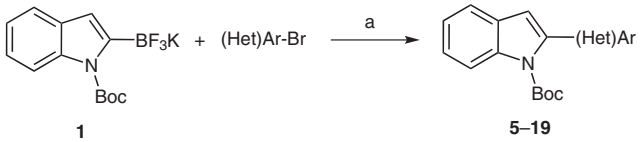
[a] Yield of isolated product.
[b] 18% of indole **2** was recovered.

dimethoxyethane and water, at 90 °C, with sodium carbonate as the base (entry 4). Performing the reaction at a lower temperature for a prolonged time resulted in a lower yield (entry 5). The use of a mixture of toluene and ethanol as the solvent proved detrimental (entries 6, 7). No coupled product was detected when the reaction was carried out in water with sodium hydroxide, tetrabutylammonium bromide, and palladium on carbon as the catalyst.[16] In this case, only the indole **2**, resulting from deboronation of **1**, could be recovered in 18% yield.

As a comparison, this coupling has been reported from the indol-2-ylboronic acid **3** (using iodobenzene)[17,18] and from lithium [1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl]borate in 52% and 80% yield, respectively.

Then, we examined the versatility of **1** in couplings with various aryl and hetaryl bromides using tetrakis(triphenylphosphine)palladium(0) (10%) and sodium carbonate (3.0 equiv) in a mixture of 1,2-dimethoxyethane and water at 90 °C (Scheme 3, Table 2).

The coupling proved to be quite to very efficient with both electron-poor electrophiles (Table 2, entries 1–3, 5–8) and electron-rich electrophiles (entries 4, 9, 11–13). A slight (entry 15) or sharp (entries 10, 14) decrease in the yield was observed when an *ortho*-substituted bromobenzene was used. Satisfyingly, we could achieve a monocoupling reaction in 80% yield starting from 3,5-dibromopyridine




**Scheme 3** *Reagents and conditions*: (a) (Het)ArBr (1.2 equiv), $Pd(PPh_3)_4$ (10%), $Na_2CO_3$ (3.0 equiv), DME–$H_2O$, 90 °C.

**Table 2** Coupling of **1** with Various (Het)aryl Bromides

| Entry | (Het)Ar | Time (h) | Product: Yield (%) |
|---|---|---|---|
| 1 | 3-pyridyl | 3 | **5**: 77 |
| 2 | 5-bromo-3-pyridyl | 5 | **6**: 80 |
| 3 | 2-pyridyl | 3 | **7**: 75 |
| 4 | 4-Tol | 4 | **8**: 73 |
| 5 | 4-$F_3CC_6H_4$ | 4 | **9**: 62 |
| 6 | 4-$NCC_6H_4$ | 6 | **10**: 73 |
| 7 | 4-$O_2NC_6H_4$ | 5[a] | **11**: 65 |
| 8 | 4-$FC_6H_4$ | 5 | **12**: 70 |
| 9 | 3,5-$Me_2C_6H_3$ | 4 | **13**: 77 |
| 10 | 2-$MeOC_6H_4$ | 4 | **14**: 51 |
| 11 | 3-$MeOC_6H_4$ | 4 | **15**: 70 |
| 12 | 4-$MeOC_6H_4$ | 3 | **16**: 76 |
| 13 | 3-thienyl | 6 | **17**: 95 |
| 14 | 2-$NCC_6H_4$ | 6 | **18**: 36 |
| 15 | 2-$FC_6H_4$ | 6 | **19**: 63 |

[a] Reaction with $PdCl_2(dppf)\cdot CH_2Cl_2$ (5%) and *i*-$PrNEt_2$ (3.0 equiv) in refluxing THF.



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(entry 2). It is noteworthy that aprotic conditions [$PdCl_2(dppf)\cdot CH_2Cl_2$ (5%), *i*-$PrNEt_2$ (3.0 equiv), THF, reflux] are needed for the coupling of *para*-bromonitrobenzene (entry 7), with the use of our reference conditions leading to no coupled product at all and recovery of the starting material.

The next issue in our study was to evaluate the reactivity of **1** towards other types of electrophiles (iodide, chloride, triflate, thioether, phosphate, and diazonium salt derivatives) (Schemes 4 and 5, Tables 3 and 4).

Bromo- and iodobenzene showed similar reactivities, yielding the coupled product **4** in around 90% (Table 3, entries 1, 2). Phenyl triflate[20] proved to be an efficient coupling partner in nonaqueous conditions (Method B, entry 5). During the preparation of this manuscript, Molander and co-workers reported the use of the catalytic system palladium(II) acetate/RuPhos for the coupling of **1** with 4-chlorobenzonitrile.[21] In our hands, chlorobenzene reacted poorly, yielding only 36% of product **4** under conditions using palladium(II) acetate and Xantphos (entry 8).[22] It is noteworthy that the same reaction performed under microwave irradiation overnight resulted mainly in degradation products.

In order to specify the scope and limitations of **1** as a building block in palladium C–C bond-forming methodologies, we considered utilizing less usual coupling partners: thioethers, diazonium salts, and phosphates.

First, we tried two different (het)aryl thioethers: (methylthio)benzene and 3-(methylthio)-1,2,4-triazine.[23] Surprisingly, only (methylthio)benzene was able to undergo coupling with **1**, in a very low yield (10%; Table 3, entry 10), using Method B [$PdCl_2(dppf)\cdot CH_2Cl_2$ (5%), *i*-$PrNEt_2$ (3.0 equiv), THF, reflux].

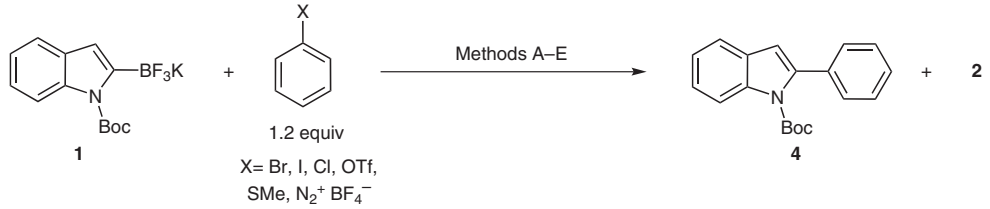
Diazonium salts are described as effective coupling partners with organotrifluoroborates.[10] Despite several attempts, in our case only 22% of product **4** was obtained after reaction of **1** with benzenediazonium tetrafluoroborate salt[24] using Method A (Table 3, entry 12).

Starting from the vinyl phosphates **20a** and **20b**, the coupling reaction proceeded moderately, the best yield (36%) being obtained with the less bulky diethyl phosphate **20b** (Table 4, entry 3). Product **22**, resulting from homocoupling of **1**, was also isolated in 10 to 20% yield. Commonly considered as nonreactive in Suzuki-type couplings,

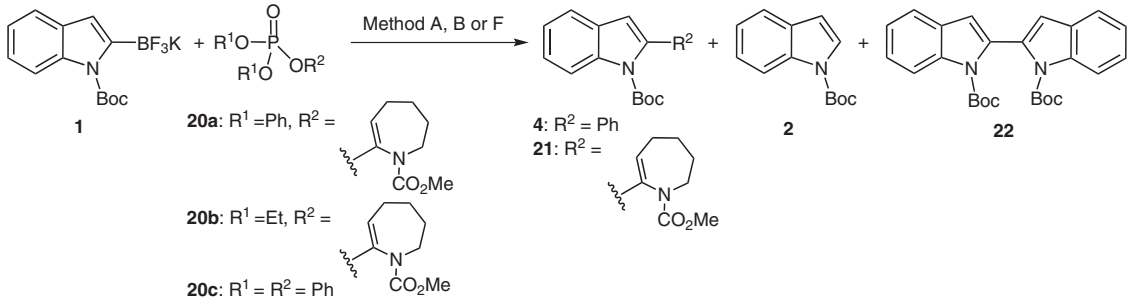
**Table 3** Reaction of **1** with Other Electrophiles

| Entry | X | Method[a] | Time (h) | Yield[b,c] (%) of **4** | Yield[b,c] (%) of **2** |
|---|---|---|---|---|---|
| 1 | Br | A | 1 | **92** | ND |
| 2 | I | A | 1 | **90** | ND |
| 3 | OTf | A | 1 | 64 | ND |
| 4 | | B | 1 | 70 | ND |
| 5 | | B | 6 | **73** | ND |
| 6 | Cl | A | 1 | ND | 44 |
| 7 | | B | 6 | 13[d] | 7[d] |
| 8 | | C | 4 d | **36** | ND |
| 9 | SMe | A | 1 | ND | 44 |
| 10 | | B | 1 | **10**[d] | 26[d] |
| 11 | | D | 1 | ND | 33 |
| 12 | $N_2^+$ | A | 1 | **22**[d] | 4[d] |
| 13 | | B | 6 | 14[d] | 8[d] |
| 14 | | E | 3 | ND | 11 |

[a] A: $Pd(PPh_3)_4$ (10%), $Na_2CO_3$ (3.0 equiv), DME–$H_2O$, 90 °C; B: $PdCl_2(dppf)\cdot CH_2Cl_2$ (5%), *i*-$PrNEt_2$ (3.0 equiv), THF, reflux; C: $Pd(OAc)_2$ (3%), Xantphos (6%), $K_2CO_3$ (3.0 equiv), THF–$H_2O$, reflux; D:[19] $Pd(PPh_3)_4$ (5%), copper(I) thiophene-2-carboxylate (3.0 equiv), THF, reflux; E: $Pd(OAc)_2$ (5%), dioxane, r.t.
[b] Isolated yield, except where indicated.
[c] ND = not detected on TLC.
[d] Determined by $^1H$ NMR spectroscopy.




**Scheme 4** *Reagents and conditions*: see Table 3.




**Scheme 5** *Reagents and conditions*: see Table 4.



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**Table 4** Reaction of **1** with Phosphate Derivatives

| Entry | Phosphate | Method[a] | Time (h) | Yield[b] (%) of coupled product | Yield[b] (%) of byproducts |
|---|---|---|---|---|---|
| 1 | **20a** | A | 1 | **21**: 2 | **22**: 11 |
| 2 | | F | 1 | **21**: 0 | **2**: 13; **22**: 21 |
| 3 | **20b** | A | 12 | **21**: 36 | **22**: 12 |
| 4 | **20c** | A | 1 | **4**: **31**[c] | **2**: 24[c] |
| 5 | | B | 6 | **4**: 10[c] | **2**: 13[c] |

[a] A and B: see Table 3; F: $PdCl_2(PPh_3)_2$ (10%), $Na_2CO_3$ (2.0 equiv), THF, reflux.
[b] Isolated yield, except where indicated.
[c] Determined by $^1$H NMR spectroscopy.

triphenyl phosphate (**20c**) underwent the reaction with **1** in 31% yield when Method A was used (entry 4). To our knowledge, this is the first example of an aryl transfer from a phosphate via a palladium catalysis. These preliminary results encourage us to further explore the coupling of **1** with various types of phosphate derivatives.

In conclusion, potassium [1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl]trifluoroborate (**1**) proved to be a convenient substitute for its boronic acid counterpart in Suzuki–Miyaura cross couplings with various electron-poor and electron-rich functionalized aryl and hetaryl bromides. The main limitation may arise from the use of *ortho*-substituted phenyl derivatives as coupling partners, which afford the reaction products in low to modest yields. As far as other electrophiles are concerned, iodobenzene and phenyl triflate reacted efficiently with **1** when tetrakis(triphenylphosphine)palladium(0) was used. Moderate yields (around 35%) were obtained for vinyl and aryl phosphates, as well as for chlorobenzene when a bulky ligand was used. In a continuation of this work, we will focus our efforts toward the use of potassium [1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl]trifluoroborate (**1**) in accessing complex indolic structures for biological applications.

All reagents were purchased from Sigma–Aldrich, Acros Organics, and Alfa Aesar, and were used without further purification. Melting points are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker Avance DPX 250 spectrometer ($^1$H, 250.19 MHz; $^{13}$C, 62.89 MHz) or a Bruker Avance II 400 spectrometer ($^1$H, 400 MHz; $^{13}$C, 100 MHz) using tetramethylsilane as the internal standard; multiplicities were determined using the DEPT 135 sequence. Chemical shifts are reported in parts per million (ppm, δ units) and coupling constants are reported in units of hertz (Hz). Splitting patterns are designated as s: singlet, d: doublet, t: triplet, and m: multiplet. IR absorption spectra were recorded on a Nicolet iS10 Smart iTR apparatus and the values are reported in cm$^{-1}$. High-resolution mass spectra (HRMS) were recorded with a Waters micro Q-TOF spectrometer in the electrospray ionization (ESI) mode or with a Finnigan MAT 95 XL spectrometer in the chemical ionization (CI) mode at the Regional Center of Physical Measurement, Blaise Pascal University. Column chromatography was carried out using silica gel 60 (spherical, neutral, 40–63 μm, Merck). Thin-layer chromatography was carried out on Merck silica gel 60F254 precoated plates. Visualization was undertaken with UV light. Spectroscopic data for compounds **4**,[25] **5**,[26] **7**,[19] **8**,[27] **9**,[28] **10**,[26] **11**,[28] **12**,[29] **14**,[28] and **16**[29] are in agreement with the literature.

**1-(*tert*-Butoxycarbonyl)-1*H*-indol-2-ylboronic Acid (3)[17]**

2,2,6,6-Tetramethylpiperidine (3.10 mL, 18.2 mmol) in anhyd THF (35 mL) was cooled to –78 °C under an atmosphere of argon and treated dropwise with 2.5 M *n*-BuLi in THF (8.30 mL, 20.70 mmol). The mixture was stirred at –78 °C for 10 min, then a soln of 1-(*tert*-butoxycarbonyl)-1*H*-indole[30] (**2**; 3.00 g, 13.8 mmol) in THF (15 mL) was added dropwise. The mixture was stirred at –78 °C for 45 min. B(O*i*-Pr)$_3$ (9.55 mL, 41.4 mmol) was added dropwise, and the reaction mixture was stirred for 30 min at –78 °C before being warmed to r.t. The reaction mixture was quenched with $H_2O$ (30 mL), acidified with 10% aq HCl, and extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with brine, dried ($MgSO_4$), and filtered. The solvents were removed under reduced pressure to afford **3** as an off-white solid, in quantitative yield, which was used without further purification; mp 105 °C.

$^1$H NMR (250 MHz, $CDCl_3$): δ = 1.65 (s, 9 H, COO*t*-Bu), 6.62 (s, 1 H, $H_3$), 7.16–7.30 (m, 2 H, $H_5$ + $H_6$), 7.56 (d, *J* = 7.5 Hz, 1 H, $H_4$), 8.08 (d, *J* = 10 Hz, 1 H, $H_7$), 8.18 (s, 2 H, OH).

**Potassium [1-(*tert*-Butoxycarbonyl)-1*H*-indol-2-yl]trifluoroborate (1)[12]**

A soln of 1-(*tert*-butoxycarbonyl)-1*H*-indol-2-ylboronic acid (**3**; 2.42 g, 9.26 mmol) in MeOH (50 mL) was cooled to 0 °C. A 4.5 M soln of $KHF_2$ in $H_2O$ (6.20 mL, 27.78 mmol) was slowly added and the resulting thick suspension was stirred at r.t. for 4 h, then filtered under reduced pressure and washed with a minimum of cold MeOH. The solid was dried on a high-vacuum line to afford **1** as a white solid; yield: 2.82 g (94%).

IR (film): 1730, 1450, 1368, 1330, 1249, 1213, 1144, 1121, 964 (s), 893 cm$^{-1}$.

$^1$H NMR (250 MHz, acetone-$d_6$): δ = 1.67 (s, 9 H, COO*t*-Bu), 6.62 (s, 1 H, $H_3$), 7.04–7.11 (m, 2 H, $H_5$ + $H_6$), 7.39 (d, *J* = 7.5 Hz, 1 H, $H_4$), 8.02 (d, *J* = 7.5 Hz, 1 H, $H_7$).

$^{11}$B NMR (123.37 MHz, acetone-$d_6$): δ = 1.34–2.29 (relative to $BF_3$·$OEt_2$) (1:3:3:1 quartet, $J_{B\text{-}F}$ = 40.16 Hz).

**Palladium-Catalyzed Cross-Coupling Reactions; General Procedures**

**Method A**

A soln of the electrophile (0.37 mmol, 1.2 equiv), potassium [1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl]trifluoroborate (**1**; 100 mg, 0.31 mmol), and $Na_2CO_3$ (98 mg, 0.93 mmol) in a mixture of DME (2.5 mL) and $H_2O$ (0.8 mL) was degassed by argon bubbling for 30 min. $Pd(PPh_3)_4$ (10 mol%, 0.031 mmol) was added and the mixture was immediately plunged in a preheated oil bath and refluxed for the indicated time. After hydrolysis with $H_2O$ (5 mL), the crude product was extracted with EtOAc (2 × 5 mL), and the combined organic layer was washed with brine (5 mL), then dried ($MgSO_4$) and filtered. The solvents were removed under reduced pressure and the residue was purified by flash chromatography.



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**Method B**

A soln containing the electrophile (0.37 mmol, 1.2 equiv), potassium [1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl]trifluoroborate (**1**; 100 mg, 0.31 mmol), *i*-PrNEt$_2$ (0.16 mL, 0.93 mmol), and PdCl$_2$(dppf)·CH$_2$Cl$_2$ (5 mol%, 0.015 mmol) in THF (5 mL) was plunged in a preheated oil bath and refluxed for the indicated time. After hydrolysis with H$_2$O (5 mL), the crude product was extracted with EtOAc (2 × 5 mL), and the combined organic layer was washed with brine (5 mL), then dried (MgSO$_4$) and filtered. The solvents were removed under reduced pressure and the residue was purified by flash chromatography.

**Method C**

A soln of the electrophile (0.37 mmol, 1.2 equiv), potassium [1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl]trifluoroborate (**1**; 100 mg, 0.31 mmol), and K$_2$CO$_3$ (128 mg, 0.93 mmol) in a mixture of THF (2.5 mL) and H$_2$O (0.25 mL) was degassed by argon bubbling for 30 min. Pd(OAc)$_2$ (3 mol%, 9.3 μmol) and Xantphos (11 mg, 0.019 mmol) were added and the mixture was immediately plunged in a preheated oil bath and refluxed for the indicated time. After hydrolysis with H$_2$O (5 mL), the mixture was extracted with EtOAc (2 × 5 mL), and the combined organic layer was washed with brine (5 mL), then dried (MgSO$_4$) and filtered. The solvents were removed under reduced pressure and the residue was purified by flash chromatography.

**Method D**

A soln of the electrophile (0.37 mmol, 1.2 equiv), potassium [1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl]trifluoroborate (**1**; 100 mg, 0.31 mmol), and copper(I) thiophene-2-carboxylate (77 mg, 0.4 mmol) in THF (2.5 mL) was degassed by argon bubbling for 30 min. Pd(PPh$_3$)$_4$ (18 mg, 15.5 μmol) was added and the mixture was immediately plunged in a preheated oil bath and refluxed for the indicated time. After hydrolysis with H$_2$O (5 mL), the mixture was extracted with EtOAc (2 × 5 mL), and the combined organic layer was washed with brine (5 mL), then dried (MgSO$_4$) and filtered. The solvents were removed under reduced pressure and the residue was purified by flash chromatography.

**Method E**

A soln of the electrophile (0.37 mmol, 1.2 equiv) and potassium [1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl]trifluoroborate (**1**; 100 mg, 0.31 mmol) in dioxane (2.5 mL) was degassed by argon bubbling for 30 min. Pd(OAc)$_2$ (4 mg, 15.5 μmol) was added and the mixture was stirred at r.t. for the indicated time. After hydrolysis with H$_2$O (5 mL), the mixture was extracted with EtOAc (2 × 5 mL), and the combined organic layer was washed with brine (5 mL), then dried (MgSO$_4$) and filtered. The solvents were removed under reduced pressure and the residue was purified by flash chromatography.

**Method F**

A soln of the electrophile (0.37 mmol, 1.2 equiv), potassium [1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl]trifluoroborate (**1**; 100 mg, 0.31 mmol), and 2 M Na$_2$CO$_3$ (0.32 mL) in THF (2.5 mL) was degassed by argon bubbling for 30 min. PdCl$_2$(PPh$_3$)$_2$ (22 mg, 0.031 mmol) was added and the mixture was immediately plunged in a preheated oil bath and refluxed for the indicated time. After hydrolysis with H$_2$O (5 mL), the mixture was extracted with EtOAc (2 × 5 mL), and the combined organic layer was washed with brine (5 mL), then dried (MgSO$_4$) and filtered. The solvents were removed under reduced pressure and the residue was purified by flash chromatography.

**2-(5-Bromo-3-pyridyl)-1-(*tert*-butoxycarbonyl)-1*H*-indole (6)**

Method A was used, starting from compound **1** (100 mg, 0.31 mmol) and 3,5-dibromopyridine (88 mg, 0.37 mmol). The mixture was refluxed for 5 h. The residue was purified by flash chromatography (petroleum ether–EtOAc, 9:1) to afford **6** as a white solid; yield: 92 mg (80%).

Mp 134 °C; $R_f$ = 0.41 (petroleum ether–EtOAc, 9:1).

IR (film): 3031, 2974, 1730, 1453, 1318, 1226, 1159, 1132, 1028, 1011, 845, 741 cm$^{-1}$.

$^1$H NMR (250 MHz, CDCl$_3$): δ = 1.39 (s, 9 H, 3 × CH$_3$), 6.65 (s, 1 H, H$_3$), 7.28 (t, *J* = 7.5 Hz, 1 H, H$_5$), 7.39 (t, *J* = 7.5 Hz, 1 H, H$_6$), 7.59 (d, *J* = 7.5 Hz, 1 H, H$_4$), 7.88 (t, *J* = 2.5 Hz, 1 H, H$_{4'}$), 8.25 (d, *J* = 7.5 Hz, 1 H, H$_7$), 8.61 (d, *J* = 2.5 Hz, 1 H, H$_{2'}$), 8.66 (d, *J* = 2.5 Hz, 1 H, H$_{6'}$).

$^{13}$C NMR (100.61 MHz, CDCl$_3$): δ = 27.7 (3 × CH$_3$), 84.3 (C), 112.0 (CH), 115.6 (CH), 119.7 (C), 120.9 (CH), 123.3 (CH), 125.3 (CH), 128.8 (C), 132.4 (C), 134.8 (C), 137.6 (C), 138.5 (CH), 147.4 (CH), 149.4 (CH), 149.6 (C).

HRMS: *m*/*z* calcd for C$_{18}$H$_{18}$$^{79}$BrN$_2$O$_2$: 373.0552; found: 373.0540.

**1-(*tert*-Butoxycarbonyl)-2-(3,5-dimethylphenyl)-1*H*-indole (13)**

Method A was used, starting from compound **1** (100 mg, 0.31 mmol) and 1-bromo-3,5-dimethylbenzene (0.050 mL, 0.37 mmol). The mixture was refluxed for 4 h. The residue was purified by flash chromatography (petroleum ether–EtOAc, 98:2) to afford **13** as a red oil; yield: 76 mg (77%).

$R_f$ = 0.82 (petroleum ether–EtOAc, 8:2).

IR (film): 2975, 1727, 1605, 1452, 1324, 1250, 1209, 1158, 1130, 1066, 1021, 851, 810, 744 cm$^{-1}$.

$^1$H NMR (250 MHz, CDCl$_3$): δ = 1.31 (s, 9 H, 3 × CH$_3$), 2.35 (s, 6 H, 2 × CH$_3$), 6.53 (s, 1 H, H$_3$), 6.98 (s, 1 H, H$_{4'}$), 7.03 (s, 2 H, H$_{2'}$ + H$_{6'}$), 7.19–7.34 (m, 2 H, H$_5$ + H$_6$), 7.53 (d, *J* = 7.5 Hz, 1 H, H$_4$), 8.20 (d, *J* = 7.5 Hz, 1 H, H$_7$).

$^{13}$C NMR (62.5 MHz, CDCl$_3$): δ = 21.2 (2 × CH$_3$), 27.5 (3 × CH$_3$), 83.1 (C), 109.4 (CH), 115.0 (CH), 120.3 (CH), 122.8 (CH), 124.1 (CH), 126.5 (2 × CH), 129.1 (CH), 129.2 (C), 134.6 (C), 137.1 (2 × C), 137.4 (C), 140.8 (C), 150.2 (C).

HRMS: *m*/*z* calcd for C$_{21}$H$_{23}$NO$_2$Na: 344.1626; found: 344.1643.

**1-(*tert*-Butoxycarbonyl)-2-(3-methoxyphenyl)-1*H*-indole (15)**

Method A was used, starting from compound **1** (100 mg, 0.31 mmol) and 1-bromo-3-methoxybenzene (0.047 mL, 0.37 mmol). The mixture was refluxed for 4 h. The residue was purified by flash chromatography (petroleum ether–EtOAc, 98:2) to afford **15** as a yellow oil; yield: 70 mg (70%).

$R_f$ = 0.57 (petroleum ether–EtOAc, 8:2).

IR (film): 2925, 2874, 1729, 1597, 1452, 1366, 1322, 1246, 1214, 1158, 1129, 1048, 1027, 848, 746 cm$^{-1}$.

$^1$H NMR (250 MHz, CDCl$_3$): δ = 1.33 (s, 9 H, 3 × CH$_3$), 3.83 (s, 3 H, OCH$_3$), 6.57 (s, 1 H, H$_3$), 6.91 (dd, *J* = 7.5 Hz, *J*′ = 2.5 Hz, 1 H, H$_{4'}$), 6.96–7.03 (m, 2 H, H$_{Ar}$), 7.25–7.36 (m, 3 H, H$_{Ar}$), 7.56 (d, *J* = 7.5 Hz, 1 H, H$_4$), 8.21 (d, *J* = 7.5 Hz, 1 H, H$_7$).

$^{13}$C NMR (62.5 MHz, CDCl$_3$): δ = 27.6 (3 × CH$_3$), 55.3 (CH$_3$), 83.3 (C), 109.8 (CH), 113.2 (CH), 114.3 (CH), 115.1 (CH), 120.4 (CH), 121.3 (CH), 122.9 (CH), 124.3 (CH), 128.8 (CH), 128.9 (C), 136.2 (C), 137.4 (C), 140.3 (C), 150.1 (C), 159.1 (C).

HRMS: *m*/*z* calcd for C$_{20}$H$_{21}$NO$_3$Na: 346.1419; found: 346.1435.

**1-(*tert*-Butoxycarbonyl)-2-(3-thienyl)-1*H*-indole (17)**

Method A was used, starting from compound **1** (100 mg, 0.31 mmol) and 3-bromothiophene (0.034 mL, 0.37 mmol). The mixture was refluxed for 6 h. The residue was purified by flash chromatography (petroleum ether–EtOAc, 98:2) to afford **17** as a red oil; yield: 89 mg (95%).

$R_f$ = 0.51 (petroleum ether–EtOAc, 98:2).



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IR (film): 3113, 2929, 1727, 1453, 1326, 1224, 1156, 1127, 1030, 849, 783, 767, 744 $cm^{-1}$.

$^1H$ NMR (250 MHz, $CDCl_3$): δ = 1.47 (s, 9 H, 3 × $CH_3$), 6.63 (s, 1 H, $H_3$), 7.18–7.20 (m, 1 H, $H_{5'}$), 7.26–7.42 (m, 4 H, $H_{Ar}$), 7.59 (d, *J* = 7.5 Hz, 1 H, $H_4$), 8.26 (d, *J* = 7.5 Hz, 1 H, $H_7$).

$^{13}C$ NMR (100.61 MHz, $CDCl_3$): δ = 27.7 (3 × $CH_3$), 83.4 (C), 110.1 (CH), 115.3 (CH), 120.3 (CH), 122.9 (2 × CH), 124.3 (CH), 124.5 (CH), 129.0 (CH), 129.1 (C), 135.0 (C), 135.3 (C), 137.2 (C), 150.1 (C).

HRMS: *m*/*z* calcd for $C_{17}H_{18}NO_2S$: 300.1058; found: 300.1042.

**1-(*tert*-Butoxycarbonyl)-2-(2-cyanophenyl)-1*H*-indole (18)**

Method A was used, starting from compound **1** (100 mg, 0.31 mmol) and 2-bromobenzonitrile (68 mg, 0.37 mmol). The mixture was refluxed for 6 h. The residue was purified by flash chromatography (petroleum ether–EtOAc, 98:2) to afford **18** as a white solid; yield: 35 mg (36%).

Mp 147 °C; $R_f$ = 0.45 (petroleum ether–EtOAc, 98:2).

IR (film): 2982, 2929, 2161, 1715, 1449, 1364, 1332, 1254, 1217, 1157, 1120, 1027, 848, 819, 769, 740 $cm^{-1}$.

$^1H$ NMR (250 MHz, $CDCl_3$): δ = 1.24 (s, 9 H, 3 × $CH_3$), 6.65 (s, 1 H, $H_3$), 7.22–7.49 (m, 5 H, $H_{Ar}$), 7.57 (d, *J* = 7.5 Hz, 1 H, $H_4$), 7.66 (ddd, *J* = 12.5 Hz, *J*′ = 5 Hz, *J*″ = 2.5 Hz, 1 H, $H_{3'}$), 8.32 (d, *J* = 7.5 Hz, 1 H, $H_7$).

$^{13}C$ NMR (100.61 MHz, $CDCl_3$): δ = 27.7 (3 × $CH_3$), 83.3 (C), 111.2 (CH), 115.7 (CH), 115.9 (C), 117.1 (C), 120.5 (CH), 122.8 (CH), 124.8 (CH), 125.3 (C), 127.6 (CH), 128.7 (C), 132.1 (C), 133.2 (CH), 133.9 (CH), 134.3 (CH), 137.0 (C), 149.8 (C).

HRMS: *m*/*z* calcd for $C_{20}H_{18}N_2O_2Na$: 341.1266; found: 341.1261.

**1-(*tert*-Butoxycarbonyl)-2-(2-fluorophenyl)-1*H*-indole (19)**

Method A was used, starting from compound **1** (100 mg, 0.31 mmol) and 1-bromo-2-fluorobenzene (0.040 mL, 0.37 mmol). The mixture was refluxed for 6 h. The residue was purified by flash chromatography (petroleum ether–EtOAc, 98:2) to afford **19** as a red oil; yield: 61 mg (63%).

$R_f$ = 0.48 (petroleum ether–EtOAc, 98:2).

IR (film): 2982, 1729, 1451, 1367, 1325, 1218, 1157, 1132, 1019, 800, 744 $cm^{-1}$.

$^1H$ NMR (250 MHz, $CDCl_3$): δ = 1.40 (s, 9 H, 3 × $CH_3$), 6.65 (s, 1 H, $H_3$), 7.12–7.31 (m, 3 H, $H_{Ar}$), 7.37–7.52 (m, 3 H, $H_{Ar}$), 7.62 (d, *J* = 7.5 Hz, 1 H, $H_4$), 8.31 (d, *J* = 7.5 Hz, 1 H, $H_7$).

$^{13}C$ NMR (100.61 MHz, $CDCl_3$): δ = 27.7 (3 × $CH_3$), 83.4 (C), 110.7 (CH), 115.3 (d, *J* = 20 Hz, CH), 120.5 (CH), 122.8 (CH), 123.4 (d, *J* = 10 Hz, C), 123.8 (CH), 124.5 (CH), 128.9 (d, *J* = 10 Hz, CH), 129.6 (CH), 130.5 (d, *J* = 10 Hz, CH), 134.1 (C), 137.3 (C), 149.9 (C), 158.7 (C), 161.2 (d, *J* = 251 Hz, C).

HRMS: *m*/*z* calcd for $C_{19}H_{19}FNO_2$: 312.1400; found: 312.1383.

**Methyl 7-[(Diethoxyphosphinyl)oxy]-2,3,4,5-tetrahydro-1*H*-azepine-1-carboxylate (20b)**

A soln of methyl 2-oxoazepane-1-carboxylate (600 mg, 3.50 mmol) in THF (10 mL) was cooled to –78 °C under an atmosphere of argon and treated with 2 M LDA in heptane–THF–ethylbenzene (2.10 mL, 4.20 mmol). The mixture was stirred at –78 °C for 2 h, diethyl chlorophosphate (0.60 mL, 4.20 mmol) was added, and the reaction was stirred for 2 h at –78 °C before being warmed to r.t. The reaction mixture was quenched with $H_2O$ (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine, dried ($MgSO_4$), and filtered. The solvents were removed under reduced pressure to afford **20b** as a colorless oil; yield: 661 mg (60%).

$R_f$ = 0.45 (petroleum ether–EtOAc, 1:1).

IR (film): 2982, 2933, 2851, 1718, 1685, 1450, 1374, 1352, 1327, 1284, 1253, 1203, 1020, 979, 925, 902, 772 $cm^{-1}$.

$^1H$ NMR (250 MHz, $CDCl_3$): δ = 1.34 (t, *J* = 8.0 Hz, 6 H, 2 × $CH_3$), 1.52 (s, 2 H, $CH_2$), 1.74 (s, 2 H, $CH_2$), 2.07 (s, 2 H, $CH_2$), 3.60 (s, 2 H, $CH_2$), 3.75 (s, 3 H, $CH_3$), 4.12–4.16 (m, 4 H, 2 × $CH_2$), 5.43 (s, 1 H, $H_6$).

$^{13}C$ NMR (100.61 MHz, $CDCl_3$): δ = 16.0 (2 × $CH_3$), 24.0 ($CH_2$), 24.2 ($CH_2$), 29.4 ($CH_2$), 47.3 ($CH_2$), 53.0 ($CH_3$), 64.3 (2 × $CH_2$), 69.2 (CH), 109.1 (C), 154.5 (C).

MS (ion spray): *m*/*z* = 308 $[M + H]^+$.

**1-(*tert*-Butoxycarbonyl)-2-[1-(methoxycarbonyl)-4,5,6,7-tetrahydro-1*H*-azepin-2-yl]-1*H*-indole (21)**

Method A was used, starting from compound **1** (100 mg, 0.31 mmol) and methyl 7-[(diethoxyphosphinyl)oxy]-2,3,4,5-tetrahydro-1*H*-azepine-1-carboxylate (**20b**; 114 mg, 0.37 mmol). The mixture was refluxed for 12 h. The residue was purified by flash chromatography (petroleum ether–EtOAc, 9:1) to afford **21** as an oil; yield: 44 mg (36%).

$R_f$ = 0.55 (petroleum ether–EtOAc, 1:1).

IR (film): 2933, 1737, 1702, 1449, 1367, 1317, 1253, 1222, 1157, 1120, 1093, 1029, 845, 767, 744 $cm^{-1}$.

$^1H$ NMR (250 MHz, DMSO-$d_6$): δ = 1.61 (s, 9 H, 3 × $CH_3$), 1.76–1.79 (m, 2 H, $H_{4'}$), 2.28–2.33 (m, 2 H, $H_{5'}$), 3.22–3.24 (m, 2 H, $H_{6'}$), 3.40 (s, 3 H, $CH_3$), 3.70 (t, *J* = 6.0 Hz, 2 H, $H_{7'}$), 5.77 (t, *J* = 5.9 Hz, 1 H, $H_{3'}$), 6.63 (s, 1 H, $H_3$), 7.18–7.32 (m, 2 H, $H_5$ + $H_6$), 7.53 (d, *J* = 4.8 Hz, 1 H, $H_4$), 7.82 (d, *J* = 5.3 Hz, 1 H, $H_7$).

$^{13}C$ NMR (100.61 MHz, DMSO-$d_6$): δ = 23.2 ($CH_2$), 23.6 ($CH_2$), 27.1 ($CH_2$), 27.5 (3 × $CH_3$), 28.0 ($CH_2$), 52.3 ($CH_3$), 83.8 (C), 113.9 (CH), 120.6 (CH), 122.5 (CH), 123.2 (C), 124.0 (CH), 124.6 (C), 128.4 (CH), 128.6 (C), 138.6 (CH), 149.4 (C), 154.3 (C), 159.4 (C).

HRMS: *m*/*z* calcd for $C_{21}H_{26}N_2O_4Na$: 393.1790; found: 393.1809.

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