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SYNTHESIS OF 2,3-DISUBSTITUTED INDOLES BY ALKYLATIVE AND ARYLATIVE CYCLIZATION OF 2-ALKENYLPHENYLISOCYANIDES WITH GRIGNARD REAGENTS

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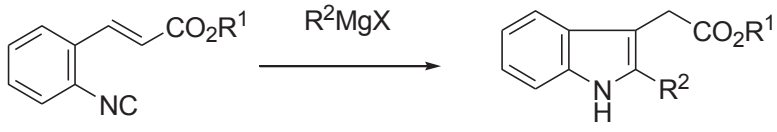
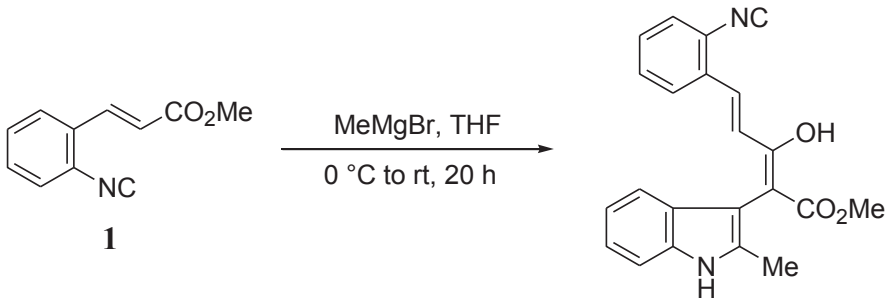
Abstract – Alkylative cyclization of 3-(2-isocyanophenyl)propenoic acid *tert*-butyl ester with Grignard reagents proceeds smoothly to form 2-alkyl-indole-3-acetic acid derivatives in moderate-to-good yields. Substituted 3-(2-isocyanophenyl)propenoic acid *tert*-butyl esters undergo a similar reaction when phenylmagnesium bromide is used to render 2-phenylindole-3-acetic acid derivatives in moderate-to-good yields.

Indoles have received special attention in heterocyclic chemistry, and various methods for their synthesis have been reported.[1] Isocyanides are versatile synthetic intermediates, and are particularly useful for the synthesis of heterocycles, such as pyrroles and oxazoles.[2] The use of isocyanides has also been reported for the synthesis of various indoles.[2,3] On the other hand, Kobayashi and coworkers reported the synthesis of 3-substituted 3*H*-indol-3-ols from the reaction of 2-isocyanophenyl ketones with Grignard reagents.[4] Interestingly, in this reaction, the Grignard reagent reacts with the isocyanide prior to the ketone. We envisaged the application of this reaction to 3-(2-isocyanophenyl)propenoic acid derivatives as an appropriate method for the construction of indole ring systems. Herein, we report the synthesis of 2,3-disubstituted indoles from the reaction of 3-(2-isocyanophenyl)propenoic acid derivatives and Grignard reagents (Scheme 1).



Scheme 1

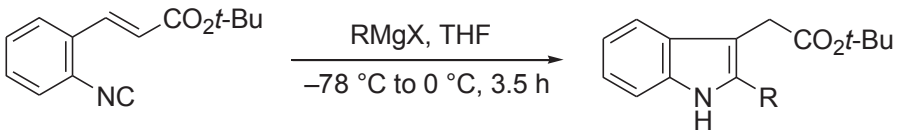
In an initial study, we examined the reaction of isocyanide (**1**) with MeMgBr in THF from 0 °C to rt, and compound (**2**) was obtained as the major product possibly via alkylative cyclization followed by Claisen condensation of the resulting ester enolate to the unreacted starting material (**1**) (Scheme 2).



1 **2**

Scheme 2

In order to avoid the Claisen condensation, the reaction was performed using *tert*-butyl ester (**3**). Thus, treatment of *tert*-butyl ester (**3**) with MeMgBr afforded the 2-methylindole-3-acetic acid derivative (**4a**) in 71% yield. The dimeric product analogous to **2** was not observed. Various Grignard reagents were well tolerated in the cyclization reaction and furnished functionalized indoles (**4b**–**f**) in 53–80% yields (Scheme 3).



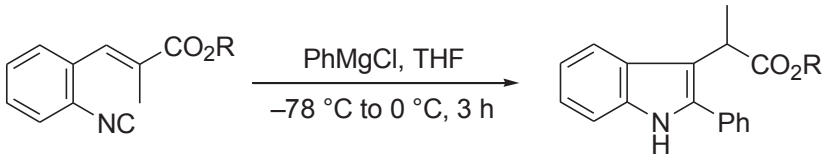
3 **4a–f**

a: R = Me, **b**: R = Ph, **c**: R = *i*-Pr, **d**: R = cyclohexyl, **e**: R = 4-ClC$_6$H$_4$, **f**: R = 4-MeOC$_6$H$_4$

4a: 71% (X = Br)
4b: 72% (X = Br), 80% (X = Cl)
4c: 69% (X = Br), 77% (X = Cl)
4d: 71% (X = Br)
4e: 53% (X = Br)
4f: 59% (X = Br)

Scheme 3

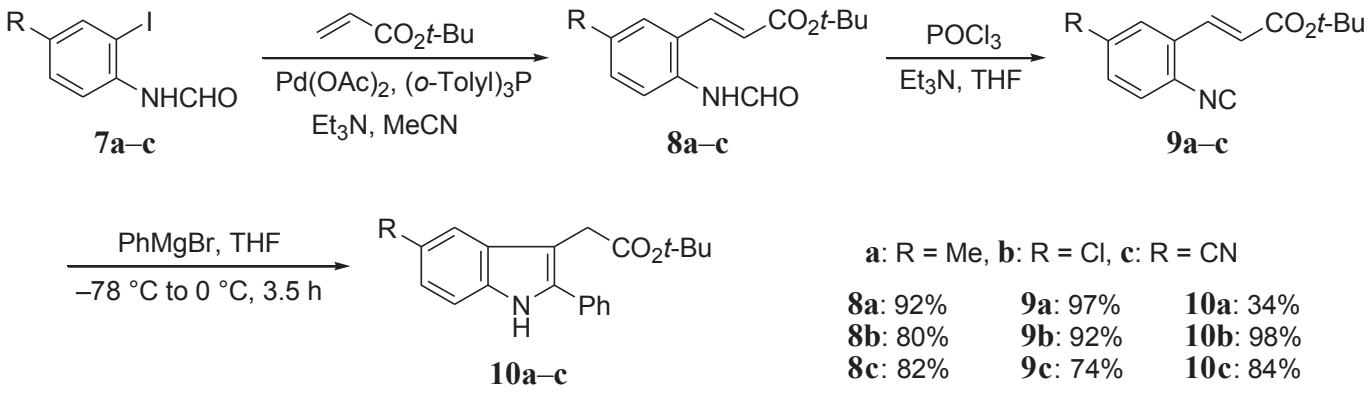
With the optimized reaction conditions in hand, we then examined other Michael acceptors (**5a**,**b**). The reaction of methyl ester (**5a**) with PhMgCl afforded the expected indole (**6a**) in 38% yield. A similar result was obtained using *tert*-butyl ester (**5b**) (Scheme 4). Claisen condensation was unfavorable for **5a** owing to a sterically congested environment on the α-carbon of the ester group.



5a,**b** **a**: R = Me, **b**: R = *t*-Bu **6a**,**b** **6a**: 38% **6b**: 35%

Scheme 4

Finally, we examined substituted 3-(2-isocyanophenyl)propenoic acid derivatives (**9a**–**c**) as Michael acceptors which were prepared as shown in Scheme 5. Thus, Heck reaction of **7a**–**c** with *tert*-butyl acrylate afforded substituted 3-(2-formylaminophenyl)propenoic acid derivatives (**8a**–**c**), which were subsequently dehydrated with $POCl_3$ in the presence of Et_3N to afford substituted 3-(2-isocyanophenyl)propenoic acid derivatives (**9a**–**c**). Treatment of **9a**–**c** with PhMgBr afforded 2-phenylindole derivatives (**10a**–**c**) respectively. The yield of the reaction was moderate for substrate **9a** bearing a methyl group at the para position of the isocyano group, instead substrates **9b** and **9c**, with electron-withdrawing substitutes at the para position of the isocyano group, furnished the corresponding indoles **10b**, and **10c** in high yields.



7a–**c** **8a**–**c** **9a**–**c**

10a–**c**

a: R = Me, **b**: R = Cl, **c**: R = CN

8a: 92%	**9a**: 97%	**10a**: 34%
8b: 80%	**9b**: 92%	**10b**: 98%
8c: 82%	**9c**: 74%	**10c**: 84%

Scheme 5

In conclusion, we have demonstrated that 2-substituted indole-3-acetic acid derivatives can be prepared via an addition / cyclization reaction of 3-(2-isocyanophenyl)propenoic acid derivatives with Grignard reagents. This methodology offers the possibility to introduce substituents on the 2-position of the indole ring and on the benzene ring, thus enabling the synthesis of structural diverse indole-3-acetic acid derivatives.

EXPERIMENTAL

General Notes. All melting points were taken on a Yamato MP-21 capillary melting point apparatus.

Flash chromatography was carried out by using Merck silica gel 60 (No. 9385). The ratios of solvents in mixtures are shown in v/v. Spectra reported herein were recorded on a JEOL JMS-700 mass spectrometer, a Perkin-Elmer Spectrum 100 FT-IR spectrometer, or a JEOL JNM-ECA500 (^{1}H 500 MHz, ^{13}C 125 MHz) NMR spectrometer. Chemical shifts are reported in δ values relative to internal Me_4Si. Rotational isomers based on formamide were observed in NMR for compounds **8a**, **8b** and **8c**.

(*Z*,*E*)-α-[1-Hydroxy-3-(2-isocyanophenyl)-2-propenylidene]-2-methyl-1*H*-indole-3-acetic acid methyl ester (2).

To a stirred solution of **1**[3b,5] (187 mg, 1.0 mmol) in THF (5 mL) at 0 °C was added dropwise MeMgBr (1.0 mL, 1.1 mmol; 1.1 M in THF). The mixture was gradually warmed to rt, stirred at rt for 20 h, and quenched with saturated aqueous NH_4Cl (15 mL). The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by flash chromatography (AcOEt-Hexane; 1:4) to give **2** (89 mg, 50%) as a yellow amorphous powder. IR (ATR) ν, cm^{-1}: 3377 (OH), 2116 (NC), 1621 (CO); ^{1}H-NMR ($CDCl_3$) δ: 2.29 (3H, s, CMe), 3.72 (3H, s, OMe), 6.59 (1H, dd, *J* = 15.9, 1.6 Hz, ArCH=C<u>H</u>), 7.07–7.35 (8H, m, two Ar's), 7.78 (1H, d, *J* = 15.9 Hz, ArC<u>H</u>=CH), 8.03 (1H, s, NH), 13.10 (1H, d, *J* = 1.6 Hz, OH); ^{13}C-NMR ($CDCl_3$) δ: 12.5 (CH_3), 52.2 (CH_3), 98.1 (C), 105.6 (C), 110.4 (CH), 119.1 (CH), 120.0 (CH), 121.5 (CH), 124.8 (CH), 126.6 (CH), 127.6 (CH), 129.38 (CH), 129.42 (CH), 129.6 (C), 130.1 (CH), 132.3 (C), 134.6 (C), 135.2 (C), 167.2 (C), 168.1 (C), 174.0 (C); HRFABMS *m*/*z* calcd for $C_{22}H_{18}N_2O_3$ (M^+): 358.1317, found: 358.1313.

2-Methyl-1*H*-indole-3-acetic acid *tert*-butyl ester (4a).

To a stirred solution of **3**[6] (229 mg, 1.0 mmol) in THF (4 mL) at -78 °C was added dropwise MeMgBr (1.4 mL, 1.3 mmol; 0.95 M in THF). The mixture was gradually warmed to 0 °C during 3.5 h, and quenched with saturated aqueous NH_4Cl (5 mL). The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by flash chromatography (AcOEt-Hexane; 1:3) to give **4a** (175 mg, 71%) as a yellow oil. MS *m*/*z*: 245 (M^+); IR (ATR) ν, cm^{-1}: 3394 (NH), 1718 (CO); ^{1}H-NMR ($CDCl_3$) δ: 1.42 (9H, s, *tert*-Bu), 2.37 (3H, s, Ar-<u>Me</u>), 3.58 (2H, s, CH_2), 7.06–7.12 [2H, m, C(5)-H, C(6)-H], 7.23 and 7.53 [1H each, br d, *J* = 7.2 Hz, C(4)-H, C(7)-H], 7.84 (1H, s, NH); ^{13}C-NMR ($CDCl_3$) δ: 11.6 (CH_3), 28.2 (CH_3), 31.9 (CH_2), 80.7 (C), 104.9 (C), 110.5 (CH), 118.2 (CH), 119.3 (CH), 121.0 (CH), 128.6 (C), 132.8 (C), 135.3 (C), 171.8 (C); HRMS *m*/*z* calcd for $C_{15}H_{19}NO_2$: 245.1416, found: 245.1415.

2-Phenyl-1*H*-indole-3-acetic acid *tert*-butyl ester (4b).

Prepared from **3** (115 mg, 0.5 mmol) and PhMgCl (0.33 mL, 0.65 mmol; 2.0 M in THF) according to the procedure described for the preparation of **4a**. Purification by flash chromatography (AcOEt-Hexane; 1:6)

gave **4b** (123 mg, 80%) as a pale yellow solid. mp 111.5–112 °C; MS *m*/*z*: 307 (M^+); IR (ATR) ν, cm^{-1}: 3359 (NH), 1708 (CO); ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s, *tert*-Bu), 3.75 (2H, s, CH_2), 7.16 and 7.22 [1H each, dd, *J* = 7.5, 7.5 Hz, C(5)-H, C(6)-H], 7.36–7.72 [7H, m, C(4)-H, C(7)-H, Ph], 8.12 (1H, s, NH); ^{13}C-NMR ($CDCl_3$) δ: 28.1 (CH_3), 32.5 (CH_2), 80.9 (C), 106.4 (C), 110.8 (CH), 119.5 (CH), 119.9 (CH), 122.5 (CH), 128.0 (CH), 128.3 (CH), 128.9 (CH), 129.2 (C), 132.6 (C), 135.8 (C), 136.0 (C), 171.6 (C); HRMS *m*/*z* calcd for $C_{20}H_{21}NO_2$: 307.1572, found: 307.1571.

2-Isopropyl-1*H*-indole-3-acetic acid *tert*-butyl ester (4c).

Prepared from **3** (115 mg, 0.5 mmol) and *i*-PrMgCl (0.33 mL, 0.65 mmol; 2.0 M in THF) according to the procedure described for the preparation of **4a**. Purification by flash chromatography (AcOEt-Hexane; 1:6) gave **4c** (106 mg, 77%) as a pale yellow solid. mp 56–56.5 °C; MS *m*/*z*: 273 (M^+); IR (ATR) ν, cm^{-1}: 3384 (NH), 1718, 1701 (CO); ^{1}H-NMR ($CDCl_3$) δ: 1.32 (6H, d, *J* = 7.0 Hz, CH$\underline{Me}_2$), 1.40 (9H, s, *tert*-Bu), 3.30 (1H, m, C$\underline{H}Me_2$), 3.61 (2H, s, CH_2), 7.06–7.13 [2H, m, C(5)-H, C(6)-H], 7.27 and 7.57 [1H each, br d, *J* = 7.5 Hz, C(4)-H, C(7)-H], 7.89 (1H, s, NH); ^{13}C-NMR ($CDCl_3$) δ: 22.6 (CH_3), 25.6 (CH), 28.1 (CH_3), 31.8 (CH_2), 80.4 (C), 103.5 (C), 110.4 (CH), 118.6 (CH), 119.4 (CH), 121.1 (CH), 128.6 (C), 135.0 (C), 141.9 (C), 171.4 (C); HRMS *m*/*z* calcd for $C_{17}H_{23}NO_2$: 273.1729, found: 273.1727.

2-Cyclohexyl-1*H*-indole-3-acetic acid *tert*-butyl ester (4d).

Prepared from **3** (115 mg, 0.5 mmol) and $C_6H_{11}MgBr$ (0.65 mL, 0.65 mmol; 1.0 M in THF) according to the procedure described for the preparation of **4a**. Purification by flash chromatography (AcOEt-Hexane; 1:7) gave **4d** (95 mg, 71%) as a pale yellow solid. mp 130–131 °C; MS *m*/*z*: 313 (M^+); IR (ATR) ν, cm^{-1}: 3415 (NH), 1711 (CO); ^{1}H-NMR ($CDCl_3$) δ: 1.24–1.49 (5H, m), 1.77–1.98 (5H, m), and 2.88–2.94 (1H, m) (C_6H_{11}), 1.41 (9H, s, *tert*-Bu), 3.61 (2H, s, CH_2), 7.06–7.13 [2H, m, C(5)-H, C(6)-H], 7.28 and 7.57 [1H each, d, *J* = 7.2 Hz, C(4)-H, C(7)-H], 7.86 (1H, s, NH); ^{13}C-NMR ($CDCl_3$) δ: 26.1 (CH_2), 26.7 (CH_2), 28.1 (CH_3), 31.9 (CH_2), 33.2 (CH_2), 35.8 (CH), 80.5 (C), 103.7 (C), 110.4 (CH), 118.6 (CH), 119.4 (CH), 121.1 (CH), 128.6 (C), 135.0 (C), 141.5 (C), 171.5 (C); HRMS *m*/*z* calcd for $C_{20}H_{27}NO_2$: 313.2042, found: 313.2035.

2-(4-Chlorophenyl)-1*H*-indole-3-acetic acid *tert*-butyl ester (4e).

Prepared from **3** (458 mg, 2.0 mmol) and 4-ClPhMgBr (2.8 mL, 2.8 mmol; 1.0 M in THF) according to the procedure described for the preparation of **4a**. Purification by flash chromatography (AcOEt-Hexane; 1:7) gave **4e** (365 mg, 53%) as a pale yellow solid. mp 133–133.5 °C; MS *m*/*z*: 341, 343 (M^+); IR (ATR) ν, cm^{-1}: 3354 (NH), 1709 (CO); ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s, *tert*-Bu), 3.71 (2H, s, CH_2), 7.16 and 7.23 [1H each, dd, *J* = 8.0, 7.0 Hz, C(5)-H, C(6)-H], 7.38 and 7.70 [1H each, d, *J* = 8.0 Hz, C(4)-H, C(7)-H], 7.46 and 7.65 (2H each, d, *J* = 8.3 Hz, C_6H_4Cl), 8.11 (1H, s, NH); ^{13}C-NMR ($CDCl_3$) δ: 28.1 (CH_3), 32.4 (CH_2), 81.1 (C), 106.8 (C), 110.9 (CH), 119.5 (CH), 120.1 (CH), 122.8 (CH), 129.07 (C),

129.12 (CH), 129.4 (CH), 131.0 (C), 134.0 (C), 134.8 (C), 135.9 (C), 171.5 (C); HRMS *m*/*z* calcd for $C_{20}H_{20}ClNO_2$: 341.1183, found: 341.1179.

2-(4-Methoxyphenyl)-1*H*-indole-3-acetic acid *tert*-butyl ester (4f).

Prepared from **3** (115 mg, 0.5 mmol) and 4-MeOPhMgBr (1.3 mL, 0.65 mmol; 0.5 M in THF) according to the procedure described for the preparation of **4a**. Purification by flash chromatography (AcOEt-Hexane; 1:4) gave **4f** (99 mg, 59%) as a pale yellow solid.mp 134–134.5 °C; MS *m*/*z*: 337 (M^+); IR (ATR) ν, cm^{-1}: 3362 (NH), 1712 (CO); ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s, *tert*-Bu), 3.71 (2H, s, CH_2), 3.87 (3H, s, OMe), 7.02 and 7.63 (2H each, d, *J* = 8.7 Hz, $C_6\underline{H}_4$OMe), 7.14 and 7.19 [1H each, dd, *J* = 8.0, 7.0 Hz, C(5)-H, C(6)-H], 7.36 and 7.68 [1H each, d, *J* = 8.0 Hz, C(4)-H, C(7)-H], 8.06 (1H, s, NH); ^{13}C-NMR ($CDCl_3$) δ: 28.2 (CH_3), 32.6 (CH_2), 55.5 (CH_3), 80.9 (C), 105.7 (C), 110.8 (CH), 114.4 (CH), 119.4 (CH), 119.9 (CH), 122.2 (CH), 125.1 (C), 129.3 (C), 129.6 (CH), 135.7 (C), 136.1 (C), 159.6 (C), 171.8 (C); HRMS *m*/*z* calcd for $C_{21}H_{23}NO_3$: 337.1678, found: 337.1671.

α-Methyl-2-phenyl-1*H*-indole-3-acetic acid methyl ester (6a).

Prepared from **5a**[3b,e] (101 mg, 0.5 mmol) and PhMgCl (0.33 mL, 0.65 mmol; 2.0 M in THF) according to the procedure described for the preparation of **4a**. Purification by flash chromatography (AcOEt-Hexane; 1:15) gave **6a** (54 mg, 38%) as a pale yellow oil. MS *m*/*z*: 279 (M^+); IR (ATR) ν, cm^{-1}: 3358 (NH), 1713 (CO); ^{1}H-NMR ($CDCl_3$) δ: 1.61 (3H, d, *J* = 7.2 Hz, CH$\underline{Me}$), 3.65 (3H, s, OMe), 4.15 (1H, q, *J* = 7.2 Hz, C$\underline{H}$Me), 7.13 and 7.21 [1H each, dd, *J* = 8.0, 7.1 Hz, C(5)-H, C(6)-H], 7.38 and 7.77 [1H each, d, *J* = 8.0 Hz, C(4)-H, C(7)-H], 7.40–7.64 (5H, m, Ph), 8.08 (1H, s, NH); ^{13}C-NMR ($CDCl_3$) δ: 17.6 (CH_3), 36.7 (CH), 52.0 (CH_3), 110.0 (CH), 112.0 (C), 120.0 (CH), 120.5 (CH), 122.4 (CH), 127.2 (C), 128.3 (CH), 128.8 (CH), 129.0 (CH), 132.8 (C), 135.4 (C), 136.0 (C), 175.5 (C); HRMS *m*/*z* calcd for $C_{18}H_{17}NO_2$: 279.1259, found: 279.1263.

α-Methyl-2-phenyl-1*H*-indole-3-acetic acid *tert*-butyl ester (6b).

Prepared from **5b**[3e] (78.5 mg, 0.34 mmol) and PhMgCl (0.22 mL, 0.44 mmol; 2.0 M in THF) according to the procedure described for the preparation of **4a**. Purification by flash chromatography (AcOEt-Hexane; 1:15) gave **6b** (37 mg, 35%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (9H, s, *tert*-Bu), 1.55 (3H, d, *J* = 7.2 Hz, CH$\underline{Me}$), 4.04 (1H, q, *J* = 7.2 Hz, C$\underline{H}$Me), 7.11 and 7.19 [1H each, dd, *J* = 8.0, 6.8 Hz, C(5)-H, C(6)-H], 7.36 and 7.82 [1H each, d, *J* = 8.0 Hz, C(4)-H, C(7)-H], 7.38–7.67 (5H, m, Ph), 8.04 (1H, s, NH); ^{13}C-NMR ($CDCl_3$) δ: 17.4 (CH_3), 28.0 (CH_3), 38.0 (CH), 80.5 (C), 110.8 (CH), 112.6 (C), 119.6 (CH), 120.9 (CH), 122.1 (CH), 127.3 (C), 128.0 (CH), 128.77 (CH), 128.83 (CH), 132.9 (C), 135.2 (C), 136.0 (C), 174.2 (C).

(2*E*)-3-[2-(Formylamino)-5-methylphenyl]-2-propenoic acid *tert*-butyl ester (8a).

N-(2-Iodo-4-methylphenyl)formamide (**7a**)[7a,b] (5.30 g, 20.3 mmol), $Pd(OAc)_2$ (300 mg, 1.3 mmol),

tri-*o*-tolylphosphine (816 mg, 2.7 mmol) were placed in a dry three necked flask under Ar. Then, MeCN (116 mL), Et_3N (4.0 mL, 29 mmol), *tert*-butyl acrylate (4.7 mL, 32 mmol) were added and the mixture was refluxed for 20 h under Ar. The mixture was evaporated, diluted with EtOAc and washed water and brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by flash chromatography (AcOEt-Hexane; 1:2) to give **8a** (4.90 g, 92%) as a colorless solid. mp 140–141 °C; MS *m*/*z*: 261 (M^+); IR (ATR) ν, cm^{-1}: 3227 (NH), 1703 (ester CO), 1662, 1633 (amide CO); ^{1}H-NMR ($CDCl_3$) δ: 1.51 and 1.52 (9H, s each, *tert*-Bu), 2.33 and 2.36 [3H, s each, C(5)-Me], 6.34 and 6.35 [1H, d each, *J* = 15.8 Hz, C(α)-H], 7.09 and 7.78 [1H, d each, *J* = 8.0 Hz, C(3)-H], 7.19 [1H, br d, *J* = 8.0 Hz, C(4)-H], 7.36 and 7.40 [1H, s each, C(6)-H], 7.73 and 7.76 [1H, d each, *J* = 15.8 Hz, C(β)-H], 7.69 (br s) and 8.06 (br d, *J* = 11.1 Hz) (1H, NH), 8.43 (d, *J* = 11.1 Hz) and 8.44 (d, *J* = 1.8 Hz) (1H, CHO); ^{13}C-NMR ($CDCl_3$) δ: 20.90 (CH_3), 20.93 (CH_3), 28.1 (CH_3), 28.2 (CH_3), 80.9 (C), 81.0 (C), 122.4 (CH), 123.0 (CH), 123.2 (CH), 124.5 (CH), 126.9 (C), 127.4 (CH), 128.22 (C), 128.23 (CH), 131.4 (CH), 131.6 (CH), 132.4 (C), 132.7 (C), 135.5 (C), 136.5 (C), 137.7 (CH), 138.2 (CH), 159.9 (CH), 163.8 (CH), 165.8 (C), 166.4 (C); HRMS *m*/*z* calcd for $C_{15}H_{19}NO_3$: 261.1365, found: 261.1360.

(2*E*)-3-[5-Chloro-2-(formylamino)phenyl]-2-propenoic acid *tert*-butyl ester (8b).

Prepared from **7b**[6,7] (5.73 g, 20.4 mmol) according to the procedure described for the preparation of **8a**. Purification by flash chromatography (AcOEt-Hexane; 1:2) gave **8b** (4.58 g, 80%) as a pale yellow solid. mp 154–156 °C; MS *m*/*z*: 281, 283 (M^+); IR (ATR) ν, cm^{-1}: 3230 (NH), 1705 (ester CO), 1664, 1632 (amide CO); ^{1}H-NMR ($CDCl_3$) δ: 1.526 and 1.530 (9H, s each, *tert*-Bu), 6.35 and 6.36 [1H, d each, *J* = 15.8 Hz, C(α)-H], 7.15 and 7.96 [1H, d each, *J* = 8.6 Hz, C(3)-H], 7.35 and 7.36 [1H, dd each, *J* = 8.6, 2.4 Hz, C(4)-H], 7.45 (br s) and 7.75 (br d, *J* = 11.1 Hz) (1H, NH), 7.51 and 7.57 [1H, d each, *J* = 2.4 Hz, C(6)-H], 7.65 and 7.67 [1H, d each, *J* = 15.8 Hz, C(β)-H], 8.46 (s) and 8.47 (d, *J* = 11.1 Hz) (1H, CHO); ^{13}C-NMR ($CDCl_3$) δ: 28.09 (CH_3), 28.11 (CH_3), 81.3 (C), 81.4 (C), 123.8 (CH), 124.3 (CH), 124.4 (CH), 125.5 (CH), 126.7 (CH), 127.5 (CH), 128.2 (C), 129.9 (C), 130.4 (CH), 130.7 (CH), 130.9 (C), 132.3 (C), 133.5 (C), 133.9 (C), 136.4 (CH), 136.8 (CH), 160.0 (CH), 163.8 (CH), 165.4 (C), 166.0 (C); HRMS *m*/*z* calcd for $C_{14}H_{16}ClNO_3$: 281.0819, found: 281.0826.

(2*E*)-3-[5-Cyano-2-(formylamino)phenyl]-2-propenoic acid *tert*-butyl ester (8c).

Prepared from **7c**[7c,8] (1.03 g, 3.77 mmol) according to the procedure described for the preparation of **8a**. Purification by flash chromatography (AcOEt-Hexane; 1:2) gave **8c** (845 mg, 82%) as a pale yellow solid. mp 142–143 °C; MS *m*/*z*: 272 (M^+); IR (ATR) ν, cm^{-1}: 3318 (NH), 2226 (CN), 1708 (ester CO), 1685, 1635 (amide CO); ^{1}H-NMR ($CDCl_3$) δ: 1.51 and 1.52 (9H, s each, *tert*-Bu), 6.40 and 6.43 [1H, d each, *J* = 15.7 Hz, C(α)-H], 7.38 and 8.40 [1H, d each, *J* = 8.4 Hz, C(3)-H], 7.65 and 7.68 [1H, d each, *J* = 8.4 Hz, C(4)-H], 7.75 and 7.78 [1H, d each, *J* = 15.7 Hz, C(β)-H], 7.80 and 7.89 [1H, s each, C(6)-H], 8.43

(br s) and 9.02 (br d, J = 10.6 Hz) (1H, NH), 8.54 (s) and 8.68 (d, J = 10.6 Hz) (1H, CHO); ^{13}C-NMR ($CDCl_3$) δ: 28.2 (CH_3), 81.7 (C), 81.8 (C), 108.3 (C), 109.9 (C), 117.9 (C), 118.3 (C), 121.9 (CH), 123.2 (CH), 125.6 (CH), 125.7 (CH), 126.3 (C), 128.3 (C), 131.4 (CH), 132.1 (CH), 133.9 (CH), 134.1 (CH), 135.7 (CH), 136.0 (CH), 139.1 (C), 139.4 (s), 160.3 (CH), 163.5 (CH), 165.2 (C), 165.7 (C); HRMS *m*/*z* calcd for $C_{15}H_{16}N_2O_3$: 272.1161, found: 272.1166.

(2*E*)-3-(2-Isocyano-5-methylphenyl)-2-propenoic acid *tert*-butyl ester (9a).

To a cooled mixture of **8a** (2.78 g, 10.6 mmol), Et_3N (5.3 mL, 38 mmol) and THF (98 mL) was added dropwise $POCl_3$ (1.22 mL, 13.3 mmol) and the mixture was stirred at rt for 2 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (18 mL) and the resultant mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by flash chromatography (AcOEt-Hexane; 1:4) to give **9a** (2.50 g, 97%) as a pale yellow solid. mp 64–65 °C; IR (ATR) ν, cm^{-1}: 2118 (NC), 1703 (CO); ^{1}H-NMR ($CDCl_3$) δ: 1.55 (9H, s, *tert*-Bu), 2.39 [3H, s, C(5)-Me], 6.45 [1H, d, J = 16.0 Hz, C(α)-H], 7.19 [1H, d, J = 8.1 Hz, C(4)-H], 7.31 [1H, d, J = 8.1 Hz, C(3)-H], 7.45 [1H, s, C(6)-H], 7.85 [1H, d, J = 16.0 Hz, C(β)-H]; ^{13}C-NMR ($CDCl_3$) δ: 21.3 (CH_3), 28.1 (CH_3), 81.0 (C), 123.9 (CH), 127.2 (CH), 127.4 (CH), 130.6 (C), 131.2 (CH), 136.8 (CH), 139.9 (C), 165.3 (C), 167.9 (C); HRFABMS *m*/*z* calcd for $C_{15}H_{18}NO_2$ (MH^+): 244.1338, found: 244.1337.

(2*E*)-3-(5-Chloro-2-isocyanophenyl)-2-propenoic acid *tert*-butyl ester (9b).

Prepared from **8b**[9] (3.00 g, 10.6 mmol) according to the procedure described for the preparation of **9a**. Purification by flash chromatography (AcOEt-Hexane; 1:10) gave **9b** (2.58 g, 92%) as a pale yellow solid. mp 114–116 °C; IR (ATR) ν, cm^{-1}: 2126 (NC), 1703 (CO); ^{1}H-NMR ($CDCl_3$) δ: 1.55 (9H, s, *tert*-Bu), 6.47 [1H, d, J = 16.0 Hz, C(α)-H], 7.34–7.39 [2H, m, C(3)-H, C(4)-H], 7.63 [1H, br s, C(6)-H], 7.80 [1H, d, J = 16.0 Hz, C(β)-H]; ^{13}C-NMR ($CDCl_3$) δ: 28.1 (CH_3), 81.5 (C), 124.3 (C), 125.6 (CH), 126.9 (CH), 128.8 (CH), 130.4 (CH), 132.7 (C), 135.4 (CH), 135.7 (C), 164.8 (C), 170.0 (C); HRFABMS *m*/*z* calcd for $C_{14}H_{15}ClNO_2$ (MH^+): 264.0791, found: 264.0781.

(2*E*)-3-(5-Cyano-2-isocyanophenyl)-2-propenoic acid *tert*-butyl ester (9c).

Prepared from **8c** (610 mg, 2.23 mmol) according to the procedure described for the preparation of **9a**. Purification by flash chromatography (AcOEt-Hexane; 1:10) gave **9b** (419 mg, 74%) as a pale yellow solid. mp 134–136 °C; IR (ATR) ν, cm^{-1}: 2242 (CN), 2112 (NC), 1699 (CO); ^{1}H-NMR ($CDCl_3$) δ: 1.55 (9H, s, *tert*-Bu), 6.54 [1H, d, J = 16.0 Hz, C(α)-H], 7.56 [1H, d, J = 8.2 Hz, C(3)-H], 7.69 [1H, dd, J = 8.2, 1.7 Hz, C(4)-H], 7.82 [1H, d, J = 16.0 Hz, C(β)-H], 7.96 [1H, d, J = 1.7 Hz, C(6)-H]; ^{13}C-NMR ($CDCl_3$) δ: 28.1 (CH_3), 81.8 (C), 113.9 (C), 116.9 (C), 126.9 (CH), 128.6 (CH), 130.9 (CH), 132.6 (C), 133.3 (CH),

134.4 (CH), 164.5 (C), 173.2 (C); HRFABMS *m*/*z* calcd for $C_{15}H_{15}N_2O_2$ (MH^+): 255.1134, found: 255.1137.

5-Methyl-2-phenyl-1*H*-indole-3-acetic acid *tert*-butyl ester (10a).

Prepared from **9a** (122 mg, 0.5 mmol) and PhMgBr (0.63 mL, 0.70 mmol; 1.1 M in THF) according to the procedure described for the preparation of **4a**. Purification by flash chromatography (AcOEt-Hexane; 1:7) gave **10a** (55 mg, 34%) as a pale yellow solid. mp 132–133 °C; MS *m*/*z*: 321 (M^+); IR (ATR) ν, cm^{-1}: 3362 (NH), 1718 (CO); ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s, *tert*-Bu), 2.47 [3H, s, C(5)-Me], 3.72 (2H, s, CH_2), 7.04 [1H, d, *J* = 8.2 Hz, C(6)-H], 7.26 [1H, d, *J* = 8.2 Hz, C(7)-H], 7.36–7.70 [6H, m, C(4)-H, Ph], 8.02 (1H, s, NH); ^{13}C-NMR ($CDCl_3$) δ: 21.6 (CH_3), 28.1 (CH_3), 32.5 (CH_2), 80.8 (C), 105.9 (C), 110.4 (CH), 119.2 (CH), 124.0 (CH), 127.8 (CH), 128.2 (CH), 128.9 (CH), 129.1 (C), 129.4 (C), 132.7 (C), 134.1 (C), 136.1 (C), 171.6 (C); HRMS *m*/*z* calcd for $C_{21}H_{23}NO_2$: 321.1729, found: 321.1724.

5-Chloro-2-phenyl-1*H*-indole-3-acetic acid *tert*-butyl ester (10b).

Prepared from **9b** (132 mg, 0.5 mmol) and PhMgBr (0.63 mL, 0.70 mmol; 1.1 M in THF) according to the procedure described for the preparation of **4a**. Purification by flash chromatography (AcOEt-Hexane; 1:7) gave **10b** (169 mg, 98%) as a pale yellow solid. mp 157–158 °C; MS *m*/*z*: 341, 343 (M^+); IR (ATR) ν, cm^{-1}: 3343 (NH), 1710 (CO); ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s, *tert*-Bu), 3.69 (2H, s, CH_2), 7.14 [1H, dd, *J* = 8.6, 2.0 Hz, C(6)-H], 7.26 [1H, d, *J* = 8.6 Hz, C(7)-H], 7.38–7.67 (5H, m, Ph), 7.68 [1H, d, *J* = 2.0 Hz, C(4)-H], 8.19 (1H, s, NH); ^{13}C-NMR ($CDCl_3$) δ: 28.1 (CH_3), 32.4 (CH_2), 81.1 (C), 106.1 (C), 111.8 (CH), 119.1 (CH), 122.7 (CH), 125.6 (C), 128.2 (CH), 128.3 (CH), 129.0 (CH), 130.3 (C), 132.0 (C), 134.1 (C), 137.4 (C), 171.3 (C); HRMS *m*/*z* calcd for $C_{20}H_{20}ClNO_2$: 341.1183, found: 341.1186.

5-Cyano-2-phenyl-1*H*-indole-3-acetic acid *tert*-butyl ester (10c).

Prepared from **9c** (127 mg, 0.5 mmol) and PhMgBr (0.63 mL, 0.70 mmol; 1.1 M in THF) according to the procedure described for the preparation of **4a**. Purification by flash chromatography (AcOEt-Hexane; 1:7) gave **10b** (140 mg, 84%) as a pale yellow solid. mp 137–139 °C; MS *m*/*z*: 332 (M^+); IR (ATR) ν, cm^{-1}: 3307 (NH), 2219 (CN), 1710 (CO); ^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s, *tert*-Bu), 3.73 (2H, s, CH_2), 7.38 and 7.42 [1H each, d, *J* = 8.3 Hz, C(6)-H, C(7)-H], 7.41–7.66 (5H, m, Ph), 8.04 [1H, s, C(4)-H], 8.57 (1H, s, NH); ^{13}C-NMR ($CDCl_3$) δ: 28.1 (CH_3), 32.2 (CH_2), 81.5 (C), 103.0 (C), 106.9 (C), 111.7 (CH), 120.8 (C), 125.1 (CH), 125.4 (CH), 128.3 (CH), 128.7 (CH), 128.9 (C), 129.1 (CH), 131.3 (C), 137.4 (C), 138.3 (C), 171.0 (C); HRMS *m*/*z* calcd for $C_{21}H_{20}N_2O_2$: 332.1525, found: 332.1519.

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