2-Trifluoromethanesulfonyloxyindole-1-carboxylic Acid Ethyl Ester: A Practical Intermediate for the Synthesis of 2-Carbosubstituted Indoles

Elisabetta Rossi,* Giorgio Abbiati, Valentina Canevari, Giuseppe Celentano, Elsa Magri

Istituto di Chimica Organica 'Alessandro Marchesini', Facoltà di Farmacia, Università degli Studi di Milano, Via Venezian 21, 20133 Milano, Italy
Fax +39(02)50314476; E-mail: elisabetta.rossi@unimi.it

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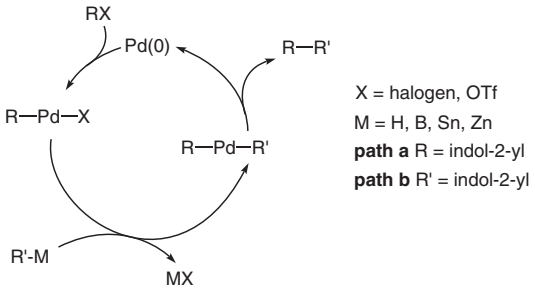
Abstract: Ready accessible 2-trifluoromethanesulfonyloxyindole-1-carboxylic acid ethyl ester undergoes palladium-catalyzed coupling reactions with different partners giving rise to 2-aryl, heteroaryl, vinyl, allyl, and alkynyl indoles in good to excellent yields.

Key words: indoles, palladium-catalyzed, boronic acids/esters, alkynes, heteroarylzinc chlorides

Simple indole derivatives are versatile building blocks in the synthesis of naturally occurring indole alkaloids, polycyclic indoles, and therapeutic agents. Practical synthesis of all these derivatives depends on the existence of available methods to synthesize the functionalized indole nucleus.

In connection with our ongoing interest in developing new synthetic strategies for the construction of polycyclic indole rings[1] we needed to prepare several 3-unsubstituted indoles bearing aryl, heteroaryl, vinyl, allyl, or alkynyl groups at position 2.

As a result of the growth in transition metal catalysis technologies,[2] polycyclic indole rings have been synthesized by palladium-catalyzed coupling reactions from a previously assembled indole nucleus, using 2-halo or pseudohalo-indoles in the oxidative addition step (Scheme 1, path a) or metallated indoles in the transmetallation step (Scheme 1, path b).



Scheme 1

In particular, both 2-iodo-1*H*-indole[3] (**1**) itself, as well as the corresponding *N*-protected derivative[4] **2** (Figure 1), have been exploited as substrates for the synthesis of 2-alkynyl and 2-aryl substituted indoles following Sonogashira[5], Suzuki,[6] or Stille[6] protocols. Both precursors were prepared from the corresponding N-protected indoles by lithiation and subsequent treatment with iodine.

Moreover, only two reports on the synthesis of the corresponding 2-trifluoromethanesulfonyloxy-indoles (Figure 1) are reported in the literature. In 1992, Gribble[7] described a single-step synthesis of the trifluoromethanesulfonic acid 1-trifluoromethanesulfonyl-1*H*-indol-2-yl ester **3** starting from 1,3-dihydroindol-2-one and triflic anhydride. In 1994, Mérour[8] reported a three-step synthesis of the trifluoromethanesulfonic acid 1-benzenesulfonyl-1*H*-indol-2-yl ester **4** starting from 1-benzenesulfonyl-1*H*-indole. However, while compound **4** was tested in palladium-catalyzed coupling reactions with boronic acids following Suzuki methodology,[9] compound **3** has never been tested as a substrate in palladium-catalyzed reactions.

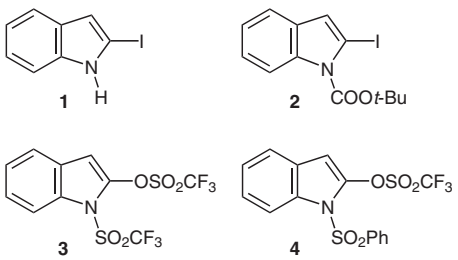


Figure 1

Indole 2-boronic acids,[10] indol-2-ylzinc halogenides,[11] and indol-2-yltributylstannanes[11b,12] have been utilized as organometallic partners in palladium-catalyzed coupling reactions with aryl, heteroaryl, allyl or vinyl halogenides, or triflates.

Nevertheless, taking into consideration both availability and simplicity, the approach to 2-substituted indoles described in Scheme 1, path a, is the most suitable for our purposes although a reinvestigation of the starting 2-halo or pseudohalo indoles is required.

Indeed, several reported starting materials, e.g. **1**, **2**, and **4**, require multistep and complex synthesis[1,2,8] or are unstable[13] (**3**) and decompose when reacted under palladium-catalyzed conditions.

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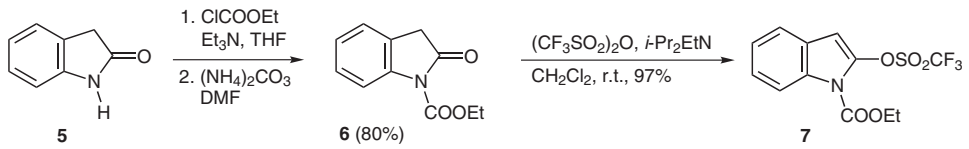


Scheme 2

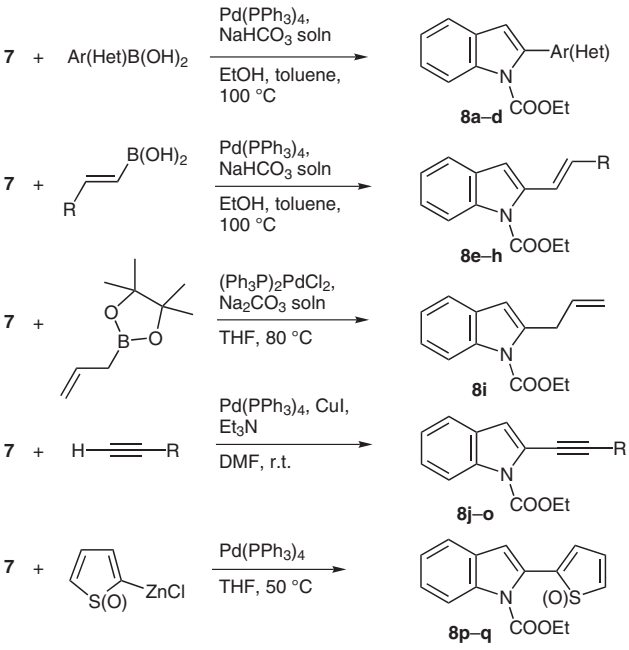
In particular, we envisaged that 2-oxo-2,3-dihydroindole-1-carboxylic acid ethyl ester (**6**) obtained, in 80% yield,[14] from commercially available 1,3-dihydroindol-2-one **5**, could represent a useful building block for the synthesis of the corresponding triflate. Thus, 2-trifluoromethanesulfonyloxyindole-1-carboxylic acid ethyl ester (**7**) was obtained in multigram quantities by the treatment of **6** with triflic anhydride at room temperature in anhydrous dichloromethane in the presence of diisopropylethylamine (Scheme 2).

The reactivity of compound **7** was then tested in order to asses the range of 2-substituted indoles which could be produced. In particular, 2-aryl, 2-heteroaryl, 2-allyl, and 2-vinyl indoles **8a–i** were prepared in good to excellent yield by palladium-catalyzed reactions of **7** with commercially available boronic acids **8a–h** or boronic ester **8i** (Suzuki coupling), whereas 2-alkynyl derivatives **8j–o** were synthesized in excellent yields starting from **7** and 1-alkynes following the Sonogashira protocol (Scheme 3, Table 1).

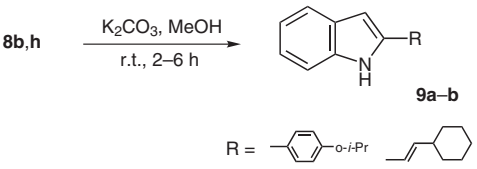
However, whereas the reaction between **7** and 3-thiopheneboronic acid gave the corresponding 2-thiophen-3-yl-indole-1-carboxylic acid ethyl ester (**8d**) in good yield, the related 2-thiophene and 2-furanboronic acids react with **7**, under our standard reaction conditions, giving rise to the desired products in only 25% yields. This is probably related to the low nucleophilicity of C-2 with respect to C-3 in the boronic acids. However, the 2-thiophen(furan)-3-yl-indole-1-carboxylic acid ethyl esters **8p–q** were obtained in good yields by treatment of **7** with the more reactive 2-thienyl and 2-furylzinc chloride[15] (Negishi coupling) (Scheme 3, Table 1).

Furthermore, deprotection of the indolic nitrogen by removal of the ethoxycarbonyl group has been easily achieved by treatment of **8b** and **8h** with potassium carbonate in methanol at room temperature. Under these conditions the corresponding unprotected indoles **9a** and **9b** were isolated in almost quantitative yields (Scheme 4, Table 1).

Thus the effectiveness and synthetic application, in palladium-catalyzed reactions, of indol-2-yl triflate has been reported. We have achieved our goal which was to provide a clean, high yielding, general synthesis of 2-carbosubstituted 3-unsubstituted 1*H*-indoles starting from an easy accessible and unique building block. In particular, starting indol-2-yl triflate **7** has been synthesized in multigram quantities, by a straightforward method, starting from a commercially available and inexpensive intermediate. Moreover, we have shown that compound **7** is a reactive, stable, precursor for 2-carbosubstituted indoles, thus providing a valuable alternative to the previously reported synthetic strategies.



Scheme 3



Scheme 4

All chemicals and solvents are commercially available and were distilled or treated with drying agents prior to use. Silica gel F_{254} thin-layer plates were employed for TLC. Silica gel 40–63 μm/60A was employed for flash column chromatography. Mps are uncorrected. ^{1}H NMR spectra were recorded at r.t. in $CDCl_3$ at 200 MHz, with residual $CHCl_3$ as the internal reference (7.27 ppm). ^{13}C NMR spectra were recorded at r.t. in $CDCl_3$ at 50.3 MHz, with the central peak of $CHCl_3$ as the internal reference (77.3 ppm). The APT sequence was used to distinguish the methine and methyl carbon signals from those due to methylene and quaternary carbons.

Table 1 Analytical Data for Indoles **8a–q** and **9a–d**

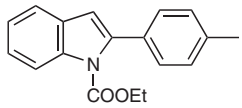
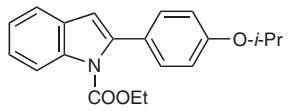
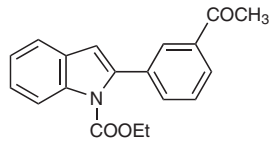
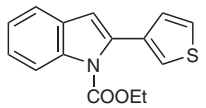
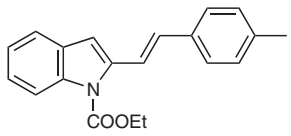
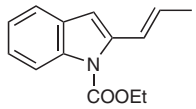
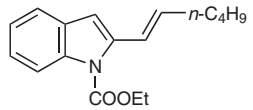
Indole	Structure	Yield (%)[a]	Mp (°C)	MS	^{1}H NMR (200 MHz), $CDCl_3$ [δ, *J* (Hz)]	^{13}C NMR (50.3 MHz), $CDCl_3$ (δ)
8a		84	61	280[b]	1.16 (t, 3 H, CH_3, *J* = 7.3), 2.41 (s, 3 H, CH_3), 4.28 (q, 2 H, OCH_2, *J* = 7.3), 6.57 (s, 1 H, ArH), 7.19–7.35 (m, 6 H, ArH), 7.57 (m, 1 H, ArH), 8.17 (d, 1 H, ArH, *J* = 8.4)	14.2 (CH_3), 21.7 (CH_3), 63.3 (CH_2), 70.2 (CH), 110.7 (ArCH), 115.8 (ArCH), 120.8 (ArCH), 123.5 (ArCH), 124.7 (ArCH), 129.1 (ArCH), 129.9 (ArC), 129.9 (ArCH), 131.9 (ArC), 137.5 (ArC), 138.0 (ArC), 141.2 (ArC), 152.2 (C=O)
8b		98	oil	324[c]	1.15 (t, 3 H, CH_3, *J* = 7.3), 1.38 (d, 6 H, CH_3, *J* = 6.2), 4.27 (q, 2 H, OCH_2, *J* = 7.3), 4.60 [st,[f] 1 H, $(CH_3)_2CH$, *J* = 6.2], 6.54 (s, 1 H, ArH), 6.90 (AA′BB′ system, 4 H, ArH, *J* = 8.8), 7.33 (AA′BB′ system, 4 H, ArH, *J* = 8.8), 7.28 (m, 2 H, ArH), 7.53 (m, 1 H, ArH), 8.18 (d, 1 H, ArH, *J* = 8.4)	14.1 (CH_3), 22.3 (CH_3), 63.1 (CH_2), 70.2 (CH), 110.2 (ArCH), 115.2 (ArCH), 115.7 (ArCH), 120.6 (ArCH), 123.3 (ArCH), 124.4 (ArCH), 126.8 (ArC), 129.7 (ArC), 130.3 (ArCH), 137.3 (ArC), 140.8 (ArC), 152.0 (ArC), 157.9 (C=O)
8c		80	101	308, 330[b,e]	1.13 (t, 3 H, CH_3, *J* = 7.3), 2.64 (s, 3 H, CH_3), 4.27 (q, 2 H, OCH_2, *J* = 7.3), 6.65 (s, 1 H, ArH), 7.28–7.67 (m, 5 H, ArH), 7.97 (dt, 1 H, ArH, *J* = 1.5, 7.7), 8.04 (t, 1 H, ArH, *J* = 1.5), 8.20 (d, 1 H, ArH, *J* = 8.1)	14.0 (CH_3), 26.9 (CH_3), 63.3 (CH_2), 111.6 (ArCH), 115.9 (ArCH), 121.0 (ArCH), 123.6 (ArCH), 125.1 (ArCH), 127.9 (ArCH), 128.2 (ArCH), 128.9 (ArCH), 129.5 (ArC), 133.7 (ArCH), 135.2 (ArC), 136.9 (ArC), 137.5 (ArC), 139.6 (ArC), 152.6 (C=O), 197.9 (C=O)
8d		84	45	272[b]	1.22 (t, 3 H, CH_3, *J* = 7.3), 4.32 (q, 2 H, OCH_2, *J* = 7.3), 6.62 (s, 1 H, ArH), 7.15–7.57 (m, 6 H, ArH), 8.18 (d, 1 H, ArH, *J* = 8.4)	13.9 (CH_3), 63.0 (CH_2), 110.8 (ArCH), 115.6 (ArCH), 120.5 (ArCH), 123.2 (ArCH), 123.5 (ArCH), 124.3 (ArCH), 124.6 (ArCH), 129.0 (ArCH), 129.3 (ArC), 134.5 (ArC), 135.4 (ArC), 137.0 (ArC), 151.7 (C=O)
8e		93	79	306[c]	1.52 (t, 3 H, CH_3, *J* = 7.3), 2.37 (s, 3 H, CH_3), 4.54 (q, 2 H, OCH_2, *J* = 7.3), 7.06 (d, 1 H, =CH, *J* = 16.1), 7.74 (d, 1 H, =CH, *J* = 16.1), 6.87 (s, 1 H, ArH), 7.16–7.55 (m, 7 H, ArH), 8.11 (m, 1 H, ArH)	14.8 (CH_3), 21.7 (CH_3), 63.7 (CH_2), 107.2 (CH), 116.2 (CH), 119.7 (CH), 120.7 (CH), 123.6 (CH), 124.6 (CH), 127.0 (CH), 129.9 (CH), 130.0 (ArC), 131.4 (CH), 134.8 (ArC), 137.1 (ArC), 138.2 (ArC), 140.1 (ArC), 152.6 (C=O)
8f		93	51	230[b]	1.50 (t, 3 H, CH_3, *J* = 7.3), 1.92 (dd, 3 H, CH_3, *J* = 1.8, 6.7), 4.51 (q, 2 H, OCH_2, *J* = 7.3), 6.20 (dq, 1 H, =CH, *J* = 6.7, 15.4), 6.63 (s, 1 H, ArH), 6.97 (m, 1 H, =CH), 7.24 (m, 2 H, ArH), 7.48 (m, 1 H, ArH), 8.07 (m, 1 H, ArH)	14.6 (CH_3), 18.9 (CH_3), 63.4 (CH_2), 106.6 (CH), 115.9 (CH), 120.3 (CH), 123.3 (CH), 123.4 (CH), 124.1 (CH), 129.0 (CH), 129.8 (ArC), 136.5 (ArC), 140.1 (ArC), 152.3 (C=O)
8g		98	oil	272[c]	0.94 (t, 3 H, CH_3, *J* = 7.3), 1.26–1.56 (m, 7 H, CH_3, CH_2), 2.25 (m, 2 H, CH_2C=), 4.51 (q, 2 H, OCH_2, *J* = 7.3), 6.39 (dt, 1 H, =CH, *J* = 6.6, 15.7), 6.64 (d, 1 H, ArH, *J* = 0.7), 6.95 (dd, 1 H, =CH, *J* = 0.7, 15.7), 7.23 (m, 2 H, ArH), 7.48 (m, 1 H, ArH), 8.08 (m, 1 H, ArH)	14.2 (CH_3), 14.6 (CH_3), 22.5 (CH_2), 31.5 (CH_2), 32.9 (CH_2), 63.3 (CH_2), 106.6 (CH), 115.9 (CH), 120.3 (CH), 122.1 (CH), 123.2 (CH), 124.0 (CH), 129.9 (ArC), 136.7 (ArC), 140.2 (ArC), 134.4 (CH), 152.3 (C=O)

Table 1 Analytical Data for Indoles **8a–q** and **9a–d** (continued)

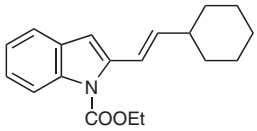
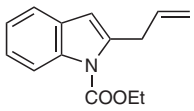
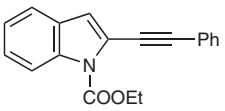
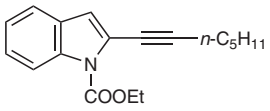
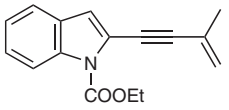
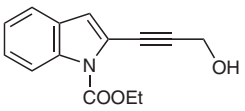
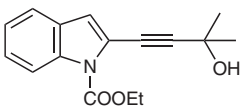
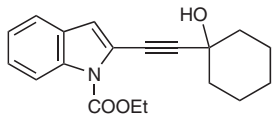
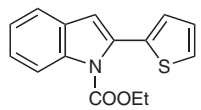
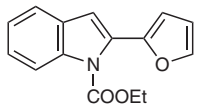
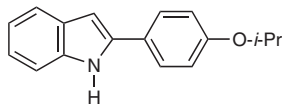
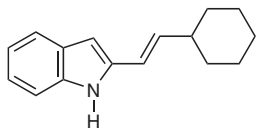
Indole	Structure	Yield (%)[a]	Mp (°C)	MS	^{1}H NMR (200 MHz), $CDCl_3$ [δ, *J* (Hz)]	^{13}C NMR (50.3 MHz), $CDCl_3$ (δ)
8h		75	oil	298[b]	1.10–1.38 (m, 6 H, CH_2), 1.50 (t, 3 H, CH_3, *J* = 7.3), 1.7–1.92 (m, 4 H, CH_2), 2.16 (m, 1 H, CH), 4.50 (q, 2 H, OCH_2, *J* = 7.3), 6.16 (dd, 1 H, =CH, *J* = 6.7, 15.8), 6.64 (s, 1 H, ArH), 6.97 (d, 1 H, =CH, *J* = 15.8), 7.23 (m, 2 H, ArH), 7.46 (m, 1 H, ArH), 8.08 (m, 1 H, ArH)	14.8 (CH_3), 26.4 (CH_3), 26.6 (CH_2), 33.1 (CH_2), 41.3 (CH_2CH), 63.8 (CH_2), 106.6 (CH), 116.1 (CH), 120.0 (CH), 120.4 (CH), 123.6 (CH), 124.2 (CH), 130.0 (ArC), 136.8 (ArC), 140.0 (CH), 140.6 (ArC), 152.5 (C=O)
8i		77	oil	230[c]	1.44 (t, 3 H, CH_3, *J* = 7.3), 3.79 (dd, 2 H, CH_2, *J* = 1.1, 6.2), 4.48 (q, 2 H, OCH_2, *J* = 7.3), 5.14 (m, 2 H, $=CH_2$), 6.10 (m, 1 H, =CH), 6.41 (d, 1 H, ArH, *J* = 1.1), 7.20 (m, 2 H, ArH), 7.43 (m, 1 H, ArH), 8.08 (m, 1 H, ArH)	14.7 (CH_3), 34.7 (CH_2), 63.4 (CH_2), 108.8 (CH), 116.0 (CH), 117.1 ($=CH_2$), 120.3 (CH), 123.3 (CH), 124.0 (CH), 129.8 (ArC), 135.5 (CH), 137.0 (ArC), 140.3 (ArC), 152.3 (C=O)
8j		98	oil	289[d]	1.50 (t, 3 H, CH_3, *J* = 7.3), 4.56 (q, 2 H, OCH_2, *J* = 7.3), 6.99 (s, 1 H, ArH), 7.22–7.59 (m, 8 H, ArH), 8.19 (m, 1 H, ArH)	14.6 (CH_3), 63.3 (CH_2), 82.2 (C≡C), 95.5 (C≡C), 115.9 (ArCH), 116.7 (ArCH), 120.7 (ArCH), 120.8 (ArC), 123.2 (ArC), 123.7 (ArCH), 125.9 (ArCH), 128.7 (ArCH), 128.8 (ArCH), 129.1 (ArC), 131.6 (ArCH), 136.4 (ArC), 151.3 (C=O)
8k		92	oil	284[b]	0.93 (t, 3 H, CH_3, *J* = 7.3), 1.25–1.75 (m, 9 H, CH_3, CH_2), 2.49 (t, 2 H, CH_2, *J* = 7.0), 4.51 (q, 2 H, OCH_2, *J* = 7.3), 6.81 (s, 1 H, ArH), 7.17–7.36 (m, 2 H, ArH), 7.48 (m, 1 H, ArH), 8.13 (d, 1 H, ArH, *J* = 8.1)	14.2 (CH_3), 14.5 (CH_3), 20.1 (CH_2), 22.5 (CH_2), 28.5 (CH_2), 31.4 (CH_2), 63.4 (CH_2), 73.1 (C≡C), 97.0 (C≡C), 115.7 (ArCH), 115.8 (ArCH), 120.6 (ArCH), 121.5 (ArC), 123.5 (ArCH), 125.4 (ArCH), 129.1 (ArC), 136.0 (ArC), 151.4 (C=O)
8l		78	oil	254, 276[b,e]	1.50 (t, 3 H, CH_3, *J* = 7.3), 2.02 (m, 3 H, CH_3), 4.52 (q, 2 H, OCH_2, *J* = 7.3), 5.36 (m, 1 H, =C*H*H), 5.44 (m, 1 H, =CH*H*), 6.90 (s, 1 H, ArH), 7.31 (m, 2 H, ArH), 7.49 (m, 1 H, ArH), 8.16 (m, 1 H, ArH)	14.6 (CH_3), 23.3 (CH_3), 63.5 (CH_2), 79.3 (C≡C), 94.0 (C≡C), 115.8 (ArCH), 116.7 (ArCH), 119.7 (C), 120.9 (ArCH), 122.8 ($=CH_2$), 123.6 (ArCH), 125.8 (ArCH), 126.8 (C), 128.7 (C), 136.2 (C), 150.9 (C=O)
8m		87	oil	266[b,e]	1.50 (t, 3 H, CH_3, *J* = 7.3), 1.90 (br s, 1 H, OH, D_2O exchange), 4.52 (q, 2 H, OCH_2, *J* = 7.3), 4.57 (s, 2 H, CH_2), 6.91 (s, 1 H, ArH), 7.25 (m, 2 H, ArH), 7.46 (m, 1 H, ArH), 8.10 (m, 1 H, ArH)	14.5 (CH_3), 51.9 (CH_2), 63.8 (CH_2), 78.1 (C≡C), 93.7 (C≡C), 115.8 (ArCH), 117.1 (ArCH), 120.2 (ArC), 121.6 (ArCH), 123.7 (ArCH), 126.0 (ArCH), 128.9 (ArC), 136.1 (ArC), 151.3 (C=O)
8n		92	72	271[d]	1.38 (t, 3 H, CH_3, *J* = 7.3), 1.65 (s, 6 H, CH_3), 2.28 (br s, 1 H, OH, D_2O exchange), 4.52 (q, 2 H, OCH_2, *J* = 7.3), 6.87 (s, 1 H, ArH), 7.40 (m, 2 H, ArH), 7.50 (d, 1 H, ArH, *J* = 7.3), 8.13 (d, 1 H, ArH, *J* = 8.4)	14.6 (CH_3), 31.4 (CH_3), 64.5 (CH_2), 65.9 (COH), 74.8 (C≡C), 99.8 (C≡C), 115.9 (ArCH), 116.7 (ArCH), 120.3 (ArC), 120.9 (ArCH), 123.6 (ArCH), 125.8 (ArCH), 128.9 (ArC), 136.2, (ArC), 151.3 (C=O)

Table 1 Analytical Data for Indoles **8a–q** and **9a–d** (continued)

Indole	Structure	Yield (%)[a]	Mp (°C)	MS	^{1}H NMR (200 MHz), $CDCl_3$ [δ, *J* (Hz)]	^{13}C NMR (50.3 MHz), $CDCl_3$ (δ)
8o		97	oil	334[b,e]	1.49 (t, 3 H, CH_3, *J* = 7.3), 1.55–2.08 (m, 10 H, CH_2), 2.31 (br s, 1 H, OH, D_2O exchange), 4.52 (q, 2 H, OCH_2, *J* = 7.3), 6.89 (d, 1 H, ArH, *J* = 0.7), 7.20–7.51 (m, 3 H, ArH), 8.13 (m, 1 H, ArH)	14.7 (CH_3), 23.5 (CH_2), 25.4 (CH_2), 40.0 (CH_2), 63.6 (OCH_2), 69.5 (COH), 76.8 (C≡C), 99.1 (C≡C), 115.9 (ArCH), 116.9 (ArCH), 120.5 (ArC), 120.9 (ArCH), 123.6 (ArCH), 125.8 (ArCH), 129.0 (ArC), 136.2 (ArC), 151.3 (C=O)
8p		84	oil	272[b]	1.21 (t, 3 H, CH_3, *J* = 7.3), 4.32 (q, 2 H, OCH_2, *J* = 7.3), 6.72 (s, 1 H, ArH), 7.04–7.57 (m, 6 H, ArH), 8.17 (d, 1 H, ArH, *J* = 8.4)	14.1 (CH_3), 63.3 (CH_2), 129.2 (ArC), 112.7 (ArCH), 115.8 (ArCH), 120.8 (ArCH), 123.5 (ArCH), 125.1 (ArCH), 126.5 (ArCH), 126.7 (ArCH), 128.2 (ArCH), 133.0 (ArC), 135.1 (ArC), 137.4 (ArC), 151.7 (C=O)
8q		81	oil	256[b]	1.28 (t, 3 H, CH_3, *J* = 7.3), 4.37 (q, 2 H, OCH_2, *J* = 7.3), 6.46 (m, 1 H, ArH), 6.57 (m, 1 H, ArH), 6.80 (s, 1 H, ArH), 7.22–7.59 (m, 4 H, ArH), 8.21 (m, 1 H, ArH)	14.3 (CH_3), 63.4 (CH_2), 129.1 (ArC), 110.2 (ArCH), 111.1 (ArCH), 112.1 (ArCH), 115.8 (ArCH), 121.1 (ArCH), 123.5 (ArCH), 125.4 (ArCH), 130.1 (ArC), 137.3 (ArC), 142.8 (ArCH), 146.9 (ArC), 151.5 (C=O)
9a		98	144	252[b]	1.37 (d, 6 H, CH_3, *J* = 6.2), 4.59 [st,[f] 1 H, $(CH_3)_2CH$, *J* = 6.2], 6.71 (s, 1 H, ArH), 6.85 (AA′BB′ system, 2 H, ArH, *J* = 8.8), 7.57 (AA′BB′ system, 2 H, ArH, *J* = 8.8), 7.14 (m, 2 H, ArH), 7.36 (m, 1 H, ArH), 7.57 (m, 1 H, ArH), 8.22 (s, 1 H, NH)	22.3 (2 × CH_3), 70.3 (CH), 98.9 (CH), 110.9 (ArCH), 116.6 (ArCH), 120.4 (ArCH), 120.6 (ArCH), 122.1 (ArCH), 125.2 (ArC), 126.7 (ArCH), 129.7 (ArC), 136.9 (ArC), 138.3 (ArC), 157.9 (ArC)
9b		92	oil	226[c]	1.08–1.37 (m, 6 H, CH_2), 1.57–1.86 (m, 4 H, CH_2), 2.16 (m, 1 H, CH), 6.01 (dd, 1 H, =CH, *J* = 6.7, 15.8), 6.38 (d, 1 H, =CH, *J* = 15.8), 6.38 (s, 1 H, ArH), 7.09 (m, 2 H, ArH), 7.28 (m, 1 H, ArH),7.52 (d, 1 H, ArH, *J* = 7.3), 8.07 (s, 1 H, NH)	25.3 (CH_2), 25.4 (CH_2), 33.2 (CH_2), 40.3 (CH), 100.8 (CH), 109.7 (CH), 115.5 (CH), 117.6 (CH), 119.1 (CH), 121.4 (CH), 128.0 (ArC), 132.9 (ArC), 135.4 (CH), 135.7 (ArC)

[a] Yields are of pure isolated products after chromatography.
[b] ESI-MS.
[c] APCI-MS.
[d] EI-MS.
[e] $[M + Na]^+$.
[f] st = septet.

2-Trifluoromethanesulfonyloxyindole-1-carboxylic Acid Ethyl Ester (7)

To a N_2-flushed solution of **6**[14] (500 mg, 2.44 mmol) and *i*-Pr_2EtN (0.66 mL, 3.66 mmol) in anhyd CH_2Cl_2 (12.5 mL), Tf_2O (0.52 mL, 3.17 mmol) was added dropwise at 0–5 °C. The reaction was stirred for 3 h at r.t. and then was quenched with H_2O (12.5 mL). The pH of the solution was adjusted to 7 by the addition of an aq solution of Na_2CO_3 (1 N) and extracted with CH_2Cl_2 (2 × 12.5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent evaporated under reduced pressure. The crude was purified by flash chromatography (hexane–EtOAc, 99:1) to give pure **7** (895 mg, 97%) as a white solid; mp 50 °C.

IR (KBr): 3006, 1758, 1741, 1382 cm^{-1}.

^{1}H NMR: δ = 1.50 (t, 3 H, CH_3, *J* = 7.3 Hz), 4.58 (q, 2 H, OCH_2 *J* = 7.3 Hz), 6.47 (s, 1 H, ArH), 7.45–7.26 (m, 2 H, ArH), 7.50 (dd, 1 H, ArH, *J* = 1.3, 6.0 Hz), 7.55 (dd, 1 H, ArH, *J* = 0.7, 7.7 Hz), 8.17 (d, 1 H, ArH, *J* = 8.4 Hz).

^{13}C NMR: δ = 14.4 (CH_3). 64.5 (CH_2), 99.0 (ArCH), 115.7 (ArCH), 119.0 (CF_3, J_{C-F} = 160 Hz), 121.5 (ArCH), 124.3 (ArCH), 125.4 (ArC), 126.1 (ArCH), 133.1 (ArC), 138.2 (ArC), 149.8 (C=O).

EI-MS: *m/z* (%) = 337.2 [M^+] (30), 204.2 (77), 132.1 (100), 104.1 (69).

2-Substituted Indoles 8a–h; General Procedure

To a N_2-flushed solution of **7** (300 mg, 0.89 mmol) in anhyd toluene (15 mL), $Pd(PPh_3)_4$ (51 mg, 0.045 mmol, 5%) was added. The reaction was stirred for 30 min at r.t., then a solution of the appropriate

boronic acid (0.89 mmol) in EtOH–sat. Na_2HCO_3 (3:2, 15 mL) was added dropwise at r.t. The mixture was then heated at reflux for 2 h, cooled to r.t., and washed with brine. The organic layer was dried ($MgSO_4$), filtered, and the solvent evaporated under reduced pressure. The crude was purified by flash chromatography (hexane–EtOAc, 98:2) to furnish pure **8a–h** (Table 1).

2-Allylindole-1-carboxylic Acid Ethyl Ester (8i)

To a N_2-flushed solution of **7** (100 mg, 0.30 mmol) in anhyd THF (4 mL), $(Ph_3P)_2PdCl_2$ (10 mg, 0.015 mmol), allylboronate (75 mg, 0.45 mmol) and an aq solution of Na_2CO_3 (2 M; 1 mL) were added at r.t. The reaction was stirred at reflux for 6 h, then poured into H_2O (10 mL), and extracted with Et_2O (2 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent evaporated under reduced pressure. The crude was purified by flash chromatography (hexane–EtOAc, 97:3) to furnish pure **8i** (Table 1).

2-Alkynylindole-1-carboxylic Acid Ethyl Esters (8j–o)

To a N_2-flushed solution of **7** (100 mg, 0.30 mmol) in anhyd DMF (2 mL) the appropriate 1-alkyne (0.30 mmol), Et_3N (0.8 mL, 6 mmol), CuI (12 mg, 0.006 mmol), and $Pd(PPh_3)_4$ (28 mg, 0.024 mmol) were added at r.t. The mixture was then stirred for 1 h at r.t., poured into HCl (0.1 M; 150 mL), and extracted with EtOAc (2 × 70 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent evaporated under reduced pressure. The crude was purified by flash chromatography (hexane–EtOAc, 9:1) to furnish pure **8j–o** (Table 1).

2-Thiophen-2-ylindole-1-carboxylic Acid Ethyl Ester (8p) and 2-Furan-2-ylindole-1-carboxylic Acid Ethyl Ester (8q)

To a N_2-flushed solution of thiophene (0.06 mL, 0.74 mmol) or furan (0.05 mL, 0.74 mmol) in THF (0.5 mL), *n*-BuLi (2.5 M solution in hexanes; 0.3 mL) was added dropwise at 0 °C. After stirring for 3 h at 0 °C a solution of $ZnCl_2$ (162 mg, 0.012 mmol) in THF (1 mL) was added. The mixture was stirred for an additional 30 min and then added to a second flask containing **7** (100 mg, 0.3 mmol), and $Pd(PPh_3)_4$ (14 mg, 0.02 mmol) in THF (0.7 mL). The reaction mixture was then heated at 50 °C for 3 h, cooled to r.t., quenched by the addition of a sat. aq solution of NH_4Cl (5 mL), and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with H_2O (10 mL), and brine (10 mL), dried ($MgSO_4$), and the solvent evaporated under reduced pressure. The crude was purified by flash chromatography (hexane–EtOAc, 98:2) to furnish pure **8p** or **8q** (Table 1).

2-(4-Isopropoxyphenyl)-1*H*-indole (9a) and 2-[(*E*)-2-cyclohexylvinyl]-1*H*-indole (9b)

To a solution of the appropriate indole **8b** or **8h** (0.3 mmol) in anhyd MeOH (3 mL), K_2CO_3 (41.5 mg, 0.3 mmol) was added and the mixture was stirred at r.t. for 6 h. The solvent was then removed under reduced pressure and the crude taken up in H_2O–EtOAc (1:1, 20 mL). The organic layer was dried (Na_2SO_4), filtered, and the solvent evaporated under reduced pressure. The crude was purified by flash chromatography (hexane–EtOAc, 8:2) to furnish pure **9a** or **9b** (Table 1).

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(13) We synthesized the trifluoromethanesulfonic acid 1-trifluoromethanesulfonyl-1*H*-indol-2-yl ester **3** from 1,3-dihydroindol-2-one(**5**) in 70% yield following the procedure described by Gribble.[7] However, **3** is stable only at low temperatures and after reaction with phenylacetylene or with 2-methyl-3-butyn-2-ol under Sonogashira conditions at 60 °C, the corresponding coupled products were isolated in poor yields (31% and 32%, respectively).

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