VINYLATION OF THE INDOLE 3-POSITION *VIA* PALLADIUM-CATALYZED CROSS-COUPLING#

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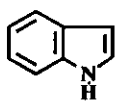
Abstract-The palladium-catalyzed cross-coupling between 3-indoleboronic acids and vinyl triflates is an excellent method for the regioselective introduction of vinyl groups into the indole 3-position. The regioselectivity of the enolization of *N*-substituted 3-piperidones, as dictated by the nitrogen substituent, is far greater than previously reported. *N*-tosyl-3-indoleboronic acids can be easily synthesized using the mercuration-boronation method.

The indole nucleus (**1**) is a building block for more than 1400 naturally occurring alkaloids[1] and its synthesis and functionalization has been the subject of research for more than a century. Many versatile methods for the preparation of indoles, such as the Fischer indole synthesis,[2,3] reductive cyclization of *o*-nitrobenzyl ketones,[4] the Batcho-Leimgruber indole synthesis from *o*-nitrotoluenes and dimethylformamide acetal,[5,6] and the Nenitzescu indole synthesis,[7,8] in particular, have been thoroughly investigated. However, to the best of our knowledge, there are no general methods which can regiospecifically introduce vinylic groups into the important 3-position of an indole nucleus. Functionalization of existing indole ring systems tends to rely heavily on well-established electrophilic substitution reactions.[9] When employed to introduce alkenyl groups into indole rings, many of the classical electrophilic substitutions lead to regioselectivity problems. While the reactions between indole derivatives and symmetric ketones under basic or acidic conditions can be effectively employed to introduce vinylic groups into indole 3-position, product mixtures from non-symmetric ketones can

#This paper is dedicated to Professor A.R. Katritzky on the occasion of his 65th birthday.

sometimes be complicated.[10,11] For example, the direct condensation of indoles with *N*-alkyl-3-piperidones (**2**) is nonregioselective[10,12] and gave extremely low yields (10-30%) of the desired 1,2,5,6-tetrahydropyridyl isomer in our hands.[12] On the other hand, the route that we had devised earlier *via* the corresponding 3-(3-pyridyl)indoles (**3**) prepared by cross-coupling reactions of 3-pyridyltrimethyl- stannane and 5-substituted 3-iodoindoles is lengthy.[12] We therefore investigated the palladium-catalyzed cross-coupling reaction between 3-indoleboronic acids and vinyl triflates derived from the enolates of *N*-substituted 3-piperidones as a more direct, regioselective route. In this paper we wish to report full details or our previous brief communication.[13]



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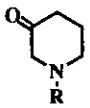

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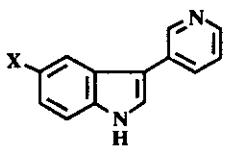


3

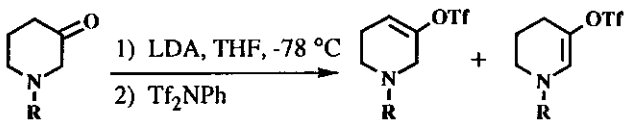
Palladium(0) catalyzed cross-coupling reactions between aryl boronic acids and vinyl triflates have attracted considerable attention recently.[14] In addition to the unambiguity of regiochemistry, mild conditions, and usually good to excellent yields, other advantages of this reaction are the ease of preparation of vinyl triflates from a wide variety of enolizable ketones and their comparable reactivities with that of vinyl halides.

The regiochemistry of enolization of α-amino ketones has been investigated by trapping the enolates as trimethylsilyl ethers.[15] A clear trend emerged based on the nature of the nitrogen substituents. Thus, enolization toward the nitrogen atom predominated when it was substituted with an electron withdrawing group (e.g., CO_2R, SO_2CF_3), and enolization away from the nitrogen atom primarily occurred when it was substituted with an alkyl group (e.g., ethyl, benzyl). In the case of *N*-substituted 3-piperidones, the percentage of minor isomers was in the range of 17-23% when lithium diisopropylamide(LDA) was employed as a base.[15]

In an effort to synthesize enol triflates from *N*-substituted 3-piperidones under kinetic control and with the assumption that enolate formation was the controlling step for the regioselectivity, it was expected that enamine-type vinyl triflates would predominate when the substituents on the nitrogen were electron-withdrawing groups like Cbz and Boc, while allylamine-type vinyl triflates would be favored when the substituents were electron-donating groups like methyl and benzyl. The ratio of the two isomers were anticipated to be comparable to that in the earlier work.[15] To our surprise, only one of the two isomers can be detected by GC-MS and high field ^1H nmr (Scheme-1). When the *N*-substituents are electron donating groups (methyl, benzyl), only allylamine-type isomers (**4a** and **4b**) were detected. If the substituents are electron

withdrawing groups(Cbz, Boc), the enamine-type isomers (**5c** and **5d**) were exclusively observed. These results suggest that the regioselectivity of enolization of 3-piperidones under kinetic control is dictated by the *N*-substituents and is far greater than indicated by the trapping of the enolates as trimethylsilyl enol ethers.[15]

Scheme 1. The Synthesis of Triflates



3a-d 4a-d 5a-d

Entry[a]	R	Yield(%)[b]	4	5
a	Me	81	>97	*c*
b	CH_2Ph	86	>97	*c*
c	Cbz	75	*c*	>97
d	Boc	73	*c*	>97

[a] Compounds (**3**a-d) were prepared according to ref. 16.

[b] Isolated yields after chromatography on silica gel

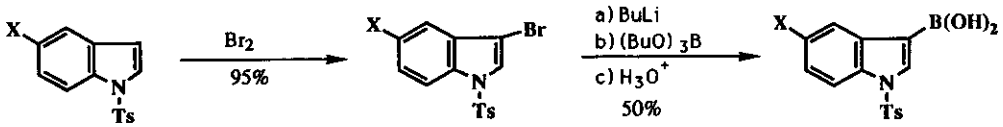
[c] Unable to be detected by gc-ms (detection limit is 3%)

Although numerous papers describing the chemistry of aryl boronic acids appeared in the last three decades, limited work has been done in indoles wherein halogen-metal exchange methodology was applied.[17] This approach has two major drawbacks. First, many functional groups are sensitive to the organolithium reagents; second, when the method is used to prepare 3-indoleboronic acid derivatives, the intermediate 3-indolylithium has a potential to isomerize to 2-indolyllithium.[18] We, therefore, investigated the mercuration-boronation method[19] to synthesize 1-tosyl-3-indoleboronic acids as shown in Scheme 2. Compared with the halogen-metal exchange, this method proved a more suitable route since a much wider range of functional groups can be tolerated, no isomerization is observed, the yields are higher, and the reactions are easier to perform. The versatility of aryl boronic acids, the structural diversity and broad spectrum of biological properties of indole derivatives give this route potential significance in both medicinal and indole chemistry.

Finally, the *N*-tosyl-3-indolylboronic acids (**8**a) or (**8**b) were cross-coupled with the triflates (**4**) or (**5**) in the presence of sodium carbonate, lithium chloride and tetrakis(triphenylphosphine)palladium(0) to give the desired products. As shown in Scheme 3 and Table 1, high regioselectivity, mild conditions, and good yields prove the cross-coupling reaction between the 3-indoleboronic acids and the readily available vinyl triflates to be an excellent method for the introduction of vinyl groups into the indole 3-position.

Scheme 2 The Synthesis of 1-Tosyl-3-indoleboronic Acids

A. Halogen-Metal Exchange Method[17a]

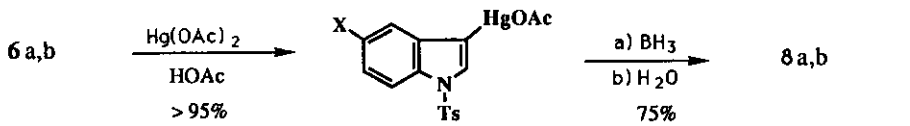


6a X = MeO
6b X = H

7a,b

8a,b
total yield: ~ 50%

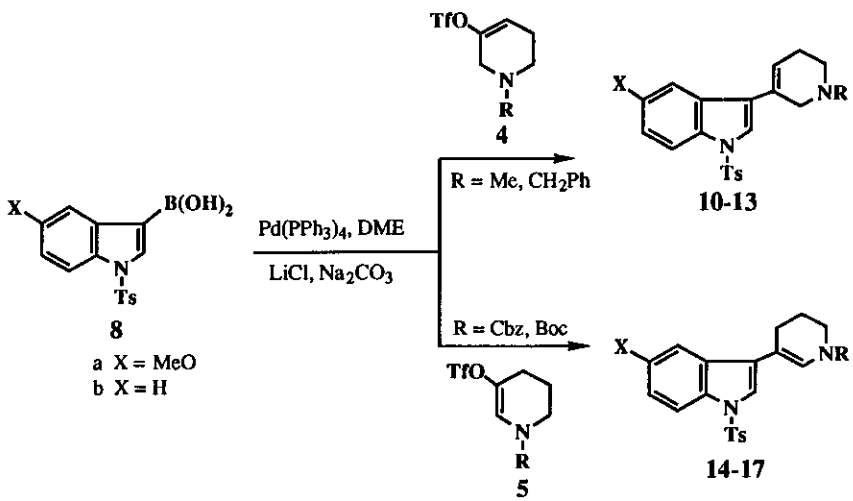
B. Mercuration-Boronation Method



9a,b

total yield: ~ 70%

Scheme 3 Cross-Coupling Reactions



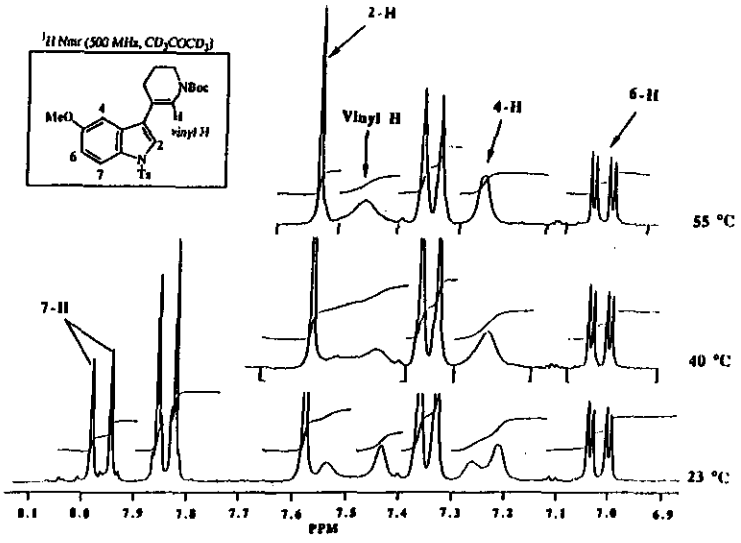
In the ^{1}H nmr spectra of those products carrying Boc or Cbz group on tetrahydropyridine nitrogen (**14-17**), each vinyl and indole 4-proton presented two broad peaks while the indole 2-proton always appeared as a single sharp peak. Variable temperature nmr studies performed between 23 and 60°C in acetone-d_6 showed coalescence of the pairs of broad peaks as shown in Scheme 4. This is presumably a result of restricted rotation about the amide bond between the Boc or Cbz group and the nitrogen atom. Support for this conclusion is the

observation that the allylamine compounds (**10-13**), all exhibited simple and sharp ^1H nmr absorption for both the indole-4 and vinyl protons.

Table 1 *N*-Tosyl-3-(tetrahydropyridin-3-yl)indoles

Compound	X	R	mp °C	Yields %
10	H	Me	101-102	90
11	H	CH_2Ph	124-126	92
12	MeO	Me	106-107	86
13	MeO	CH_2Ph	127-128	76
14	H	Cbz	125-127	80
15	H	Boc	139-140	89
16	MeO	Cbz	112-113	82
17	MeO	Boc	154-156	79

Scheme 4



EXPERIMENTAL

General Methods: Melting points were determined with an Electrothermal capillary melting point apparatus and are uncorrected. Proton magnetic resonance spectra were obtained for all compounds using Bruker AM500 (500 MHz), Bruker AM-250 (250 MHz), or JEOL FX-90Q (90 MHz) spectrometers. Gas-chromatography/mass spectra were obtained on Hewlett Packard 5970 MSD and Varian MAT 90 spectrometers. Infrared spectra were recorded on a Beckman ir-33 spectrophotometer with samples prepared as

potassium bromide pellets or as thin films on NaCl plates. Elemental analyses were performed by Desert Analytics, Tucson, AZ. All the chemical reactions requiring inert atmosphere were carried out under nitrogen in oven-dried glassware using septum techniques.

1-Methyl-3-hydroxy-1,2,5,6-tetrahydropyridine Triflate (4a) A solution of freshly distilled diisopropylamine (2.31 g, 22 mmol) in 20 ml of dry THF in a 100 ml flask was purged with N_2, then cooled to -78 °C. n-BuLi (2.5 M in hexanes, 9.3 ml, 23.2 mmol) was added and the solution was agitated at -78 °C for 15 min, then at 0 °C for 45 min. It was cooled to -78 °C, and a solution of 1-methyl-3-piperidinone (2.5 g, 22 mmol) in 20 ml of dry THF was added along the flask wall within 5 min. After stirring at -78 °C for 60 min, a solution of *N*-phenyltrifluoromethanesulfonimide (8.3 g, 23.2 mmol) in 60 ml of dry THF was quickly added to the clear solution at -78 °C. After agitating at -78 °C for 10 min, the slurry was warmed slowly to 0 °C and stirred at 0 °C for 3 h. The solvent was removed at 40 °C under reduced pressure. The yellow oil was eluted on a basic Al_2O_3 column with CH_2Cl_2 and 4.41 g of light yellow oil was obtained (80%). An analytical sample was obtained by vaccum distillation: bp 81-82 °C/10 mm Hg. R_f = 0.8 (10% MeOH/CH_2Cl_2). The product was kept under N_2 in a refrigerator. ^{1}H Nmr (250 MHz, CD_3COCD_3): δ 2.31 (2 H, m, 5-H), 2.35 (3 H, s, CH_3), 2.50 (2 H, t, 6-H, J = 5.5 Hz), 3.08 (2 H, m, 2-H), 5.93 (1 H, m, vinyl H). Mass spectrum: *m/z* 245 (M^+, 10%), 134 (0.8%), 112 (42%), 84 (33%), 69 (62%), 42 (100%). Anal. Calcd for $C_7H_{10}N_1O_3F_3S$: C, 34.27; H, 4 .11; N, 5.71; F, 23.25; S, 13.08. Found: C, 34.42; H, 4.02; N, 5.69; F, 23.33; S, 13.38.

1-Benzyl-3-hydroxy-1,2,4,5-tetrahydropyridine Triflate (4b) was prepared similarly in an yield of 74% after vaccum distillation. bp 93-102 °C/0.05-0.075 mm Hg. The product decomposed at room temperature and thus was kept under N_2 at < -10 °C. R_f = 0.55 (30% CH_2Cl_2/hexane). ^{1}H Nmr (500 MHz, $CDCl_3$): δ 2.30 (2 H, m, 5-H), 2.61 (2 H, t, 6-H, J = 5.5 Hz), 3.14 (2 H, q, 2-H), 3.65 (2 H, s, -CH_2Ph), 5.84 (1 H, m, vinyl H), 7.33 (5 H, s, phenyl). Mass spectrum, *m/z* 321 (M^+, 5.2%), 230(5.4%), 188(22%), 91(100%), 69(15%).

1-Benzyloxycarbonyl-3-hydroxy-1,4,5,6-tetrahydropyridine Triflate (5c) was prepared similarly with an yield of 75% after chromatography on a silica gel column (hexane : EtOAc = 20 : 1). R_f = 0.5 (10% EtOAc/hexane). ^{1}H Nmr (500 MHz, $CDCl_3$): δ 2.00 (2 H, m, 5-H, J = 6.2 Hz), 2.46 (2 H, t, 6-H, J = 6.2 Hz), 3.60 (2 H, m, 4-H), 5.21 (2 H, s, OCH_2), 7.27 (1 H, s, vinyl H), 7.39 (5 H, s, phenyl). Mass spectrum: *m/z* 365 (M^+, 1.2%), 232, 188, 181, 142, 116, 91 (100%), 69. Anal. Calcd for $C_{14}H_{14}NO_5F_3S$: C, 46.00; H, 3.86; N, 3.84; F, 15.61; S, 8.73. Found: C, 46.60; H, 4.08; N, 3.67; F, 14.95; S, 9.00.

1-*tert*-Butoxycarbonyl-3-hydroxy-1,4,5,6-tetrahydropyridine Triflate (5d) was prepared similarly in an yield of 73% purified by chromatography with a silica gel column (hexane : EtOAc = 20 : 1). R_f = 0.45 (6%

EtOAc/hexane). ^{1}H Nmr (250 MHz, CD_3COCD_3): δ 1.49 (9 H, s, Boc CH_3), 1.95 (2 H, m, 5-H), 2.5 (2 H, t, 6-H, J = 6.3 Hz), 3.66 (2 H, m, 4-H), 7.22 (1 H, b, vinyl H). Anal. Calcd for $C_{11}H_{16}NO_5F_3S$: C, 39.86; H, 4.79; N, 4.23; F, 17.21; S, 9.68. Found: C, 40.29; H, 5.01; N, 4.21; F, 17.60; S, 9.68.

5-Methoxy-1-tosylindole (6a) Into a 1 liter flask were placed 5-methoxyindole (5 g, 33.6 mmol), *p*-toluenesulfonyl chloride (10.1 g, 39.4 mmol), tetrabutylammonium bisulfate (1 g, 0.3 mmol), toluene (200 ml), and a solution of NaOH (40 g in 390 ml of H_2O). The two-phase mixture was stirred vigorously at room temperature for 2 h. The organic phase was washed with water until it was neutral. After being dried with anhydrous Na_2SO_4, the organic phase was concentrated under reduced pressure to a brown oil. Recrystallization from 120 ml of hot methanol afforded 9.76 g (96%) of a white crystalline solid. mp 111-113 °C. R_f = 0.5 (25% hexane/CH_2Cl_2). Mass spectrum: m/z 301 (M^+, 45%), 146 (100%). ^{1}H Nmr (500 MHz, $CDCl_3$): δ 2.33 (3 H, s, tosyl CH_3), 3.8 (3 H, s, OCH_3), 6.57 (1 H, dd, indole 3-H, J = 0.7 and 3.7 Hz), 6.91 (1 H, dd, indole 6-H, J = 2.7 and 9 Hz), 6.95 (1 H, d, indole 4-H, J = 2.2 Hz), 7.20 (2 H, d, tosyl H adjacent to methyl, J = 8 Hz), 7.5 (1 H, d, indole 2-H, J = 3.7 Hz), 7.72 (2 H, d, tosyl H adjacent to sulfonyl, J = 6.7 Hz), 7.87 (1 H, d, indole 7-H, J = 9.2 Hz). ir (KBr, cm^{-1}): 3140, 3100, 3000, 2950, 2840, 1615, 1590, 1470, 1365, 1228. Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.75; H, 5.02; N, 4.65; S, 10.65. Found: C, 63.34; H, 5.04; N, 4.60; S, 10.63.

1-Tosylindole (6b) was prepared similarly in 82% yield. mp 86-86.5 °C (lit.,[20] 83-84 °C). R_f = 0.63 (50% hexane/CH_2Cl_2).

5-Methoxy-1-tosyl-3-indoleboronic Acid (8a) To a suspension of 5-methoxy-3-acetoxymercurio-1-tosylindole (280 mg, 0.5 mmol) in 14 ml of THF purged with N_2 was added borane solution (1M in THF, 5 ml, 5 mmol) at room temperature and the mixture was stirred at room temperature for 1 h, followed by the addition of 2.8 ml of H_2O. A clear solution and elemental mercury were obtained. The mercury was removed by filtration, and the solvent was evaporated at 40 °C under reduced pressure. To the white residue was then added 30 ml of THF/EtOAc (1/9) and the insoluble material was removed by filtration. The filtrate was extracted with H_2O (2 x 10 ml, and concentrated to give 170 mg white solid. Recrystallization from MeOH afforded 130 mg (77%) of a crystalline solid. mp 120-122 °C. (the melting point and elemental analysis are not reliable for characterization since an anhydride may form). R_f = 0.70 (10% MeOH/CH_2Cl_2). ^{1}H Nmr (500 MHz, CD_3COCD_3+D_2O): δ 2.34 (3 H, s, tosyl CH_3), 3.81 (3 H, s, OCH_3), 6.94 (1 H, dd, indole 6-H, J = 8.95 and 2.6 Hz), 7.39 (2 H, d, tosyl H adjacent to methyl, J = 8.4 Hz), 7.57 (1 H, d, indole 4-H, J = 2.6 Hz), 7.85 (1

H, d, indole 7-H, J = 9.2 Hz), 7.86 (2 H, d, tosyl H adjacent to sulfonyl, J = 8.42 Hz), 8.10 (1 H, s, indole 2-H). ir (KBr, cm^{-1}): 3520, 3140, 2950, 1600, 1570, 1480, 1380, 1160.

1-Tosyl-3-indoleboronic Acid (8b) was prepared similarly in an yield of 75%. R_f = 0.70 (10% MeOH/CH_2Cl_2). ^1H Nmr (500 MHz, $CDCl_3$+D_2O): δ 2.35 (3 H, s, tosyl CH_3), 5.75 (br, OH), 7.22 (2 H, d, tosyl H adjacent to Me, J = 7.97 Hz), 7.30 (1 H, dd, 7-H, J = 7.21 and 1.51 Hz), 7.45-7.38 (1 H, m, 5-H), 7.9-7.75 (2 H, two doublets, tosyl H adjacent to sulfonyl, J = 8.4 Hz), 7.98-7.90 (1 H, m, 6-H), 8.29 and 8.03 (1 H, two multiplets, 4-H), 8.45 and 7.96 (1H, two singlets, 2-H).

5-Methoxy-3-acetoxymercurio-1-tosylindole (9a)[20] A mixture of mercuric acetate (5.45 g, 16.6 mmol) and 150 ml of glacial HOAc was stirred at room temperature for 30 min. The insoluble material was removed by filtration. To the filtrate was added 5-methoxy-1-tosylindole (5 g, 16.6 mmol). The clear solution was stirred at room temperature for 4 h and became a white slurry. Filtration gave 6.4 g of a white heavy crystalline material, along with another 2.26 g of crystals from the filtrate. Recrystallization from HOAc (the temperature was controlled below 40 °C) afforded 9.2 g of crystal (product·HOAc). Yield: 90%. mp 130-132 °C. ^1H Nmr (500 MHz, $CDCl_3$): δ 2.11 (6 H, s, 2 acetoxy CH_3), 2.33 (3 H, s, CH_3 of the tosyl), 3.80 (3 H, s, OCH_3), 6.93 (1 H, dd, indole 6-H, J = 2.3 and 9.5 Hz), 6.95 (1 H, s, indole 4-H), 7.21 (2 H, d, tosyl H adjacent to methyl, J = 8.5 Hz), 7.41 (1 H, s, indole 2-H), 7.73 (2 H, d, tosyl H adjacent to sulfonyl, J = 6.6 Hz), 7.87 (1 H, d, indole 7-H, J = 9.6 Hz). ir (KBr, cm^{-1}): 3170, 3130, 2990, 1720, 1600, 1480, 1385, 1220, 1140. Anal. Calcd for $C_{20}H_{21}NO_7HgS$ (product·HOAc):C, 38.72; H, 3.41; N, 2.26; S, 5.17. Found C, 39.09; H, 3.10; N, 2.15; S, 4.69.

3-Acetoxymercurio-1-tosylindole (9b) was prepared similarly in a yield of 91%. Recrystallization from CH_2Cl_2 afforded the pure product. mp 92-94 °C (partial melting; gradual decomposition was observed when the temperature was slowly raised above 100 °C). ^1H Nmr (250 MHz, $CDCl_3$): δ 2.11 (3 H, s, acetoxy CH_3), 2.33 (3 H, s, CH_3 of the tosyl), 7.22 (2 H, d, tosyl H adjacent to methyl, J = 8.2 Hz), 7.24 (1 H, t, indole 5-H, J = 7.1 Hz), 7.33 (1 H, t, indole 6-H, J = 7.2 Hz), 7.47 (1 H, s, indole 2-H), 7.51 (1 H, d, 4-H, J = 8.3 Hz), 7.77 (2 H, d, tosyl H adjacent to sulfonyl, J = 8.3 Hz), 8.01 (1 H, d, indole 7-H, J = 8 Hz). ir (KBr, cm^{-1}): 3170, 3130, 2990, 1720, 1600, 1480, 1385, 1220, 1140.

1-Tosyl-3-(1'-methyl-1',2',5',6'-tetrahydropyridin-3'-yl)indole (10) A mixture of 1-tosyl-3-indoleboronic acid (0.46 g, 1.45 mmol), 1,2,5,6-tetrahydro-1-methyl-3-hydroxypyridine triflate (0.36 g, 1,45 mmol), Na_2CO_3 (2M, 1.5 ml), 1,2-dimethoxyethane (DME, 4 ml), LiCl (130 mg, 3 mmol), and tetrakis(triphenylphosphine)palladium(0) catalyst (60 mg, 0.05 mmol) was placed in a 10 ml flask which was purged with N_2 immediately. The mixture was heated to reflux for 1.5 h and the solvent was then removed

under reduced pressure at 65 °C. The green-black residue was partitioned with 20 ml of CH_2Cl_2 and 20 ml of 2 M Na_2CO_3 containing 1 ml of concentrated NH_4OH. The aqueous phase was extracted with CH_2Cl_2 (4 x 20 ml). The CH_2Cl_2 phases were combined and dried with anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified with silica gel (MeOH/CH_2Cl_2 = 1 : 25) yielding 395 mg of product (90%). mp 101-102 °C. R_f = 0.65 (CH_2Cl_2 : MeOH = 10 : 1). ^1H Nmr (250 MHz, $CDCl_3$): δ 2.33 (3 H, s, tosyl CH_3), 2.50-2.40 (2 H, m, 5'-CH_2), 2.48 (3 H, s, *N*-CH_3), 2.63 (2 H, t, 6'-CH_2, J =5.83 Hz), 3.28 (2 H, q, 2'-H, J = 7.4 Hz), 6.28 (1 H, m, 4'-vinyl H), 7.21 (2 H, d, tosyl H adjacent to Me, J = 8.22 Hz), 7.38-7.15 (2 H, m, indole 5- and 6-H), 7.47 (1 H, s, indole 2-H), 7.75 (3 H, d, tosyl H adjacent to sulfonyl and indole 4-H, J = 8.22 Hz), 7.99 (1 H, d, indole 7-H, J = 7.4 Hz). ir (KBr, cm^{-1}): 3140, 2940, 1765, 1600, 1445, 1370, 1170. Anal. Calcd for $C_{21}H_{22}N_2O_2S$: C, 68.82; H, 6.01; N, 7.65; S, 8.76. Found: C, 68.92; H, 5.97; N, 7.54; S, 8.67.

1-Tosyl-3-(1'-benzyl-1',2',5',6'-tetrahydropyridin-3'-yl)indole (11) was prepared similarly from 1-tosyl-3-indoleboronic acid (0.46 g, 1.45 mmol) and 1,2,5,6-tetrahydro-1-benzyl-3-hydroxypyridine triflate (0.47 g, 1,45 mmol). Recrystallization with ether/hexane yielded 589 mg (92%) of product with mp 124-126 °C. R_f = 0.7 (CH_2Cl_2 : MeOH = 10 : 1). ^1H Nmr (500 MHz, CD_3COCD_3): δ 2.32 (3 H, s, CH_3), 2.40-2.30 (2 H, m, 5'-H), 2.60 (2 H, t, 6'-H, J = 5.5 Hz), 3.40 (2 H, q, 2'-H, J = 8.1 Hz), 3.69 (2 H, s, CH_2Ph), 6.33 (1 H, m, vinyl H), 7.45-7.20 (9 H, m, phenyl, indole 5-,6-H, tosyl H adjacent to methyl), 7.61 (1 H, s, indole 2-H), 7.81 (1 H, d, indole 4-H, J = 7.4 Hz), 7.86 (2 H, d, tosyl H adjacent to sulfonyl, J = 8.4 Hz), 8.03 (1 H, d, indole 7-H, J = 8 Hz). ir (KBr, cm^{-1}): 3060, 2920, 2800, 1600, 1450, 1370, 1300, 1180. Mass spectrum: m/z 442 (M^+, 1.2%), 351 (1.5%), 323 (100%), 287 (27%), 195 (6%), 167 (90%), 91 (98%).

5-Methoxy-1-tosyl-3-(1'-methyl-1',2',5',6'-tetrahydropyridin-3'-yl)indole (12) was prepared similarly from 5-methoxy-1-tosyl-3-indoleboronic acid (0.5 g, 1.45 mmol) and 1,2,5,6-tetrahydro-1-methyl-3-hydroxypyridine triflate (0.36 g, 1,45 mmol). After recrystallization from ether, 491 mg of product was obtained (86%). mp 106-107 °C. R_f = 0.50 (CH_2Cl_2 : MeOH = 10 : 1). ^1H Nmr (250 MHz, $CDCl_3$): δ 2.33 (3 H, s, tosyl Me), 2.46-2.37 (2 H, m, 5'-H), 2.49 (3 H, s, *N*-Me), 2.63 (2 H, t, 6'-H, J = 5.9 Hz), 3.22 (2 H, q, 2'-H, J = 8.9 Hz), 3.76 (3 H, s, OCH_3), 6.16 (1 H, m, vinyl H), 6.92 (1 H, dd, indole 6-H, J = 8.8 Hz), 7.15 (1 H, d, indole 4-H, J = 2.4 Hz), 7.18 (2 H, d, tosyl H adjacent to Me), 7.43 (1 H, s, indole 2-H), 7.71 (2 H, d, tosyl H adjacent to sulfonyl, J = 8.4 Hz), 7.83 (1 H, d, indole 7-H, J = 8.2 Hz). ir (KBr, cm^{-1}): 2900, 2820, 2760, 1605, 1590, 1460, 1355, 1210, 1165. Mass spectrum: m/z 396 (M^+, 9.2%), 353 (100%), 241 (27%), 198 (50%), 183 (63%), 155 (37%), 128 (8%), 91 (23.7%). Anal. Calcd for $C_{22}H_{24}N_2O_3S$: C, 66.62,;H, 6.10; N, 7.07; S, 8.09. Found: C, 66.39; H, 6.00; N, 6.89; S, 8.36.

5-Methoxy-1-tosyl-3-(1'-benzyl-1',2',5',6'-tetrahydropyridin-3'-yl)indole (13) was prepared similarly from 5-methoxy-1-tosyl-3-indoleboronic acid (0.5 g, 1.45 mmol) and 1,2,5,6-tetrahydro-1-benzyl-3-hydroxypyridine triflate (0.47 g, 1,45 mmol). Recrystallization of the solid residue with EtOAc/MeOH yielded 520 mg of product (76%). mp 127-128 °C. R_f = 0.4 (5% MeOH/CH_2Cl_2). ^{1}H Nmr (500 MHz, CD_3COCD_3): δ 2.32 (3 H, s, tosyl Me), 2.34 (2 H, m, 5'-H), 2.6 (2 H, t, 6'-H, J = 5.6 Hz), 3.37 (2 H, q, 2'-H, J = 9.0 Hz), 3.68 (2 H, s, benzyl-CH_2), 3.78 (3 H, s, OCH_3), 6.30 (1 H, m, vinyl H), 6.97 (1 H, dd, indole 6-H, J = 2.3 and 9 Hz), 7.22 (1 H, d, indole 4-H, J = 2.4 Hz), 7.45-7.23 (7 H, m, phenyl H, tosyl H adjacent to Me), 7.57 (1 H, s, indole 2-H), 7.81 (2 H, d, tosyl H adjacent to sulfonyl, J = 8.5 Hz), 7.92 (1 H, d, indole 7-H, J = 9 Hz). ir (KBr, cm^{-1}): 3105, 3000, 2900, 2795, 1595, 1450, 1365, 1205, 1168. Mass spectrum: m/z 472 (M^+, 2.4%), 353 (95%), 317 (28%), 225 (7.3%), 183 (40%), 155 (23.7%), 91 (100%). Anal. Calcd for $C_{28}H_{28}N_2O_3S$: C, 71.14; H, 5.97; N, 5.93; S, 6.79. Found: C, 70.99; H, 5.75; N, 5.80; S, 6.78.

1-Tosyl-3-(1'-benzyloxycarbonyl-1',4',5',6'-tetrahydropyridin-3'-yl)indole (14) was prepared similarly from 1-tosyl-3-indoleboronic acid (0.46 g, 1.45 mmol) and 1,4,5,6-tetrahydro-1-benzyloxycarbonyl-3-hydroxypyridine triflate (0.53 g, 1.45 mmol). After being recrystallized from MeOH, 563 mg of product was obtained (80%). mp 125-127 °C. R_f = 0.6 (CH_2Cl_2). ^{1}H Nmr (250 MHz, CD_3COCD_3): δ 2.01 (2 H, m, 5'-H, J = 5.7 Hz), 2.32 (3 H, s, CH_3), 2.53 (2 H, t, 6'-H, J = 5 Hz), 3.07 (2 H, br, 4'-H), 5.24 (2 H, s, Cbz-CH_2), 7.3-7.83 (11 H, phenyl, vinyl, indole 4-, 5-, 6-H, tosyl H adjacent to Me), 7.64 (1 H, s, indole 2-H), 7.87 (2 H, d, tosyl H adjacent to sulfonyl, J = 8.0 Hz), 8.06 (1 H, d, indole 7-H, J = 8 Hz). ir (KBr, cm^{-1}): 3140, 2945, 1710, 1650, 1600, 1400, 1170, 1145. Mass spectrum: m/z 486 (M^+, 3.3%), 351 (9.7%), 331 (1.8%), 287 (17%), 260 (0.4%), 196 (4.6%), 155 (7.9%), 91 (100%). Anal. Calcd for $C_{28}H_{26}N_2O_4S$: C, 69.10; H, 5.39; N, 5.76; S, 6.59. Found: C, 68.90; H, 5.12; N, 5.57; S, 6.92.

1-Tosyl-3-(1'-*tert*-butoxycarbonyl-1',4',5',6'-tetrahydropyridin-3'-yl)indole (15) was prepared similarly from 1-tosyl-3-indoleboronic acid (0.46 g, 1.45 mmol) and 1,4,5,6-tetrahydro-1-*tert*-butoxycarbonyl-3-hydroxypyridine triflate (0.48 g, 1,45 mmol). After recrystallization from ether, 583 mg of product was obtained (89%). mp 139-140 °C. R_f = 0.6 (30% CH_2Cl_2/hexane). ^{1}H Nmr (500 MHz, CD_3COCD_3): δ 1.52 (9 H, s, *tert*-Bu), 1.97 (2 H, m, 5'-H, J = 5.8 Hz), 2.31 (3 H, s, tosyl Me), 2.50 (2 H, t, 6'-H, J = 6.3 Hz), 3.64 (2 H, br, 4'-H), 7.32 (2H, d, tosyl H adjacent to Me, J = 7.9 Hz), 7.42-7.27 (2 H, m, indole 5-, 6-H), 7.60-7.48 (1 H, two broad peaks, vinyl H), 7.61 (1 H, s, indole 2-H), 7.80 (1 H, 2 broad peaks, indole 4-H), 7.87 (2 H, d, tosyl H adjacent to sulfonyl, J = 8.4 Hz), 8.08 (1 H, dd, indole 7-H, J= 7.4 Hz and 1.2 Hz). ir (KBr, cm^{-1}): 3140, 2970, 2940, 1700, 1645, 1595, 1450, 1370, 1315, 1170, 1140, 1115. Mass spectrum: m/z 452 (M^+, 1.4%), 396

(12%), 351 (3.7%), 271 (1.5%), 241 (100%), 197 (50%), 168 (11%), 155 (7.6%), 91 (23%), 57 (26%). Anal. Calcd for $C_{25}H_{28}N_2O_4S$: C, 66.33; H, 6.24; N, 6.19; S, 7.09. Found: C, 66.34; H, 6.19; N, 5.82; S, 6.99.

5-Methoxy-1-tosyl-3-(1'-benzyloxycarbonyl-1',4',5',6'-tetrahydropyridin-3'-yl)indole (16) was prepared similarly from 5-methoxy-1-tosyl-3-indoleboronic acid (0.5 g, 1.45 mmol) and 1,4,5,6-tetrahydro-1-benzyloxycarbonyl-3-hydroxypyridine triflate (0.53 g, 1,45 mmol). The product was recrystallized from ether yielding 0.62 g of white crystalline solid (82%). mp 112-113 °C. R_f = 0.42 (10% MeOH/CH_2Cl_2). ^{1}H Nmr (500 MHz, CD_3COCD_3): δ 2.04 (2 H, m, 5'-H), 2.33 (3 H, s, tosyl CH_3), 2.52 (2 H, t, 6'-H, J = 6.3 Hz), 3.61-3.85 (3 H, 2 peaks, OCH_3), 3.73 (2 H, m, 4'-H), 5.26 (2 H, s, Cbz-CH_2), 6.94-7.06 (1 H, m, indole 6-H), 7.08-7.3 (1 H, two broad peaks, indole 4-H), 7.3-7.58 (8 H, m, vinyl H, phenyl H, tosyl H adjacent to methyl), 7.61 (1 H, s, indole 2-H), 7.84 (2 H, d, tosyl H adjacent to sulfonyl, J = 8.3 Hz), 7.94 (1 H, d, indole 7-H, J = 9.2 Hz). ir (KBr, cm^{-1}): 2940, 2000, 1700, 1680, 1600, 1470, 1405, 1250, 1170. Mass spectrum: m/z 516 (M^+, 3%), 381 (5.5%), 362, 317 (21%), 226 (19%), 91 (100). Anal. Calcd for $C_{29}H_{28}N_2O_5S$: C, 67.40; H, 5.47; N, 5.43; S, 6.21. Found: C, 67.45; H, 5.63; N, 5.63; S, 6.71.

5-Methoxy-1-tosyl-3-(1'-*tert*-butoxycarbonyl-1',4',5',6'-tetrahydropyridin-3'-yl)indole (17) was prepared similarly from 5-methoxy-1-tosyl-3-indoleboronic acid (0.5 g, 1.45 mmol) and 1,4,5,6-tetrahydro-1-*tert*-butoxycarbonyl-3-hydroxypyridine triflate (0.48 g, 1,45 mmol). Recrystallization was performed from MeOH, and 553 mg of product was obtained (79%). mp 154-156 °C. R_f = 0.6 (30% CH_2Cl_2/hexane). ^{1}H Nmr (500 MHz, CD_3COCD_3): δ 1.52 (9 H, s, *tert*-Bu), 1.98 (2 H, m, 5'-H, J = 2.2 Hz), 2.34 (3 H, s, tosyl CH_3), 2.49 (2 H, t, 6'-H, J = 5.9 Hz), 3.64 (2 H, br, 4'-H), 3.84 (3 H, s, OCH_3), 7.02 (1 H, dd, indole 6-H, J = 2.5 and 9 Hz), 7.3-7.18 (1 H, two broad peaks, indole 4-H), 7.35 (2 H, d, tosyl H adjacent to Me, J = 8.6 Hz), 7.56-7.42 (1 H, two broad peaks, vinyl-H), 7.58 (1 H, s, indole 2-H), 7.84 (2 H, d, tosyl H adjacent to sulfonyl, J = 8.4 Hz), 7.97 (1 H, d, indole 7-H, J = 9.1 Hz). ir (KBr, cm^{-1}): 2960, 2000, 1700, 1655, 1470, 1370, 1250, 1170. Mass spectrum: m/z 482 (M^+, 1.6%), 426 (11%), 382 (3.9%), 271 (100%), 227 (73%). Anal. Calcd for $C_{26}H_{30}N_2O_5S$: C, 64.69; H, 6.27; N, 5.81; S, 6.65. Found: C, 64.21; H, 6.04; N, 6.09; S, 6.65.

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