

Synthesis of 2-(Arylsulfonyl)-4-hydroxypyridines by Hetero-Diels–Alder Reaction of 1,3-Bis-Silyl Enol Ethers with Arylsulfonyl Cyanides

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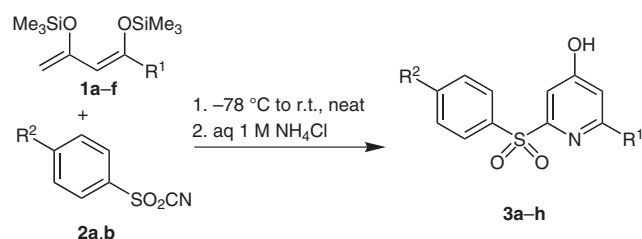
Abstract: 2-(Arylsulfonyl)-4-hydroxypyridines were prepared by Hetero-Diels–Alder reaction of 1,3-bis(trimethylsiloxy)buta-1,3-dienes (1,3-bis-silyl enol ethers) with arylsulfonyl cyanides. The products were transformed into 4-aryl-2-(arylsulfonyl)pyridines by Suzuki cross-coupling reactions of the corresponding enol triflates.

Key words: 1,3-bis-silyl enol ethers, hetero-Diels–Alder, arylsulfonyl cyanide, pyridine

Hetero-Diels–Alder reactions allow the efficient synthesis of heterocyclic frameworks. The hetero-Diels–Alder reaction of aldehydes with Danishefsky's diene or related silyl enol ethers has been widely used for the synthesis of pyran derivatives.¹ In contrast, hetero-Diels–Alder reactions of nitriles are relatively rare, due to the low reactivity of nitriles as hetero-dienophiles.² Some years ago, Breitmaier and Rüffer reported³ an efficient synthesis of functionalized pyridines by cyclization of buta-1,3-dienes, including 2-(siloxy)buta-1,3-dienes, with highly reactive tosyl cyanide.⁴ Pyridines have also been prepared by cyclization of pyran-2-ones with tosyl cyanide with extrusion of carbon dioxide.⁵ The 1,3-dipolar cycloaddition of diazomethane with tosyl cyanide has been reported to give 1,2,3-triazines.⁶ Recently, the synthesis of 1-azabicyclo[2.2.2]oct-1-enes by cyclization of 2-(siloxy)cyclohexa-1,3-dienes with tosyl cyanide has been reported.⁷ Herein, we report, based on the work of Breitmaier,³ the hetero-Diels–Alder reaction of 1,3-bis(trimethylsiloxy)buta-1,3-dienes (1,3-bis-silyl enol ethers)⁸ with tosyl cyanide. These reactions allow the convenient synthesis of 2-(arylsulfonyl)-4-hydroxypyridines, which were transformed into 4-aryl-2-(arylsulfonyl)pyridines by Suzuki reactions of the corresponding enol triflates. It should be noted that 2-(arylsulfonyl)pyridines are of considerable pharmacological importance.⁹ The synthesis of 2-(arylsulfonyl)-4-hydroxypyridines has seldom been reported.^{3,5}

The reaction of tosyl cyanide (**2a**) with 1-methoxy-1,3-bis(trimethylsiloxy)buta-1,3-diene (**1a**), readily available from methyl acetoacetate,¹⁰ afforded 4-hydroxy-2-tosylpyridine **3a** in up to 43% yield. During optimization of

the reaction, it was shown to be important to perform the reaction at $-78\text{ }^{\circ}\text{C}$ without the use of a solvent and to quench the reaction by the addition of aqueous 1 M ammonium chloride solution. No product could be isolated when the reaction was carried out at elevated temperatures ($110\text{ }^{\circ}\text{C}$). This can be explained by thermal $\text{O} \rightarrow \text{C}$ 1,5-silyl shift of the 1,3-bis-silyl enol ether to give a 3-siloxy-4-silylcrotonate.¹¹ The cyclization of 1,3-bis-silyl enol ethers **1a–f** with arylsulfonyl cyanides **2a,b** afforded 2-(arylsulfonyl)-4-hydroxypyridines **3a–h**. The reaction of **2a** with 1,3-bis-silyl enol ethers containing a substituent located at C4 was unsuccessful, presumably for steric reasons. Likewise, the reaction of 1,3-bis-silyl enol ether **1g** (Scheme 2), containing a substituent located at C2, was unsuccessful. This can be explained by the fact that the ester derived 2-substituted 1,3-bis-silyl enol ethers undergo a $\text{O} \rightarrow \text{C}$ 1,5-silyl shift even at ambient temperature. Employment of ethyl cyanoformate rather than **2a** also proved to be unsuccessful, due to its insufficient reactivity; decomposition was observed under forcing conditions (neat, $120\text{ }^{\circ}\text{C}$).



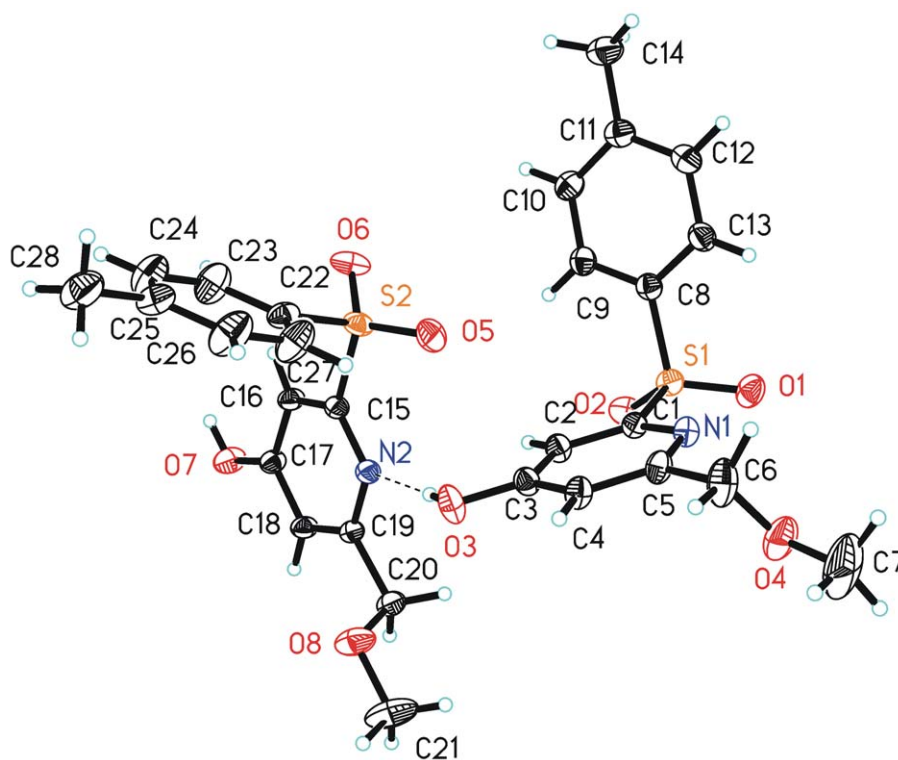
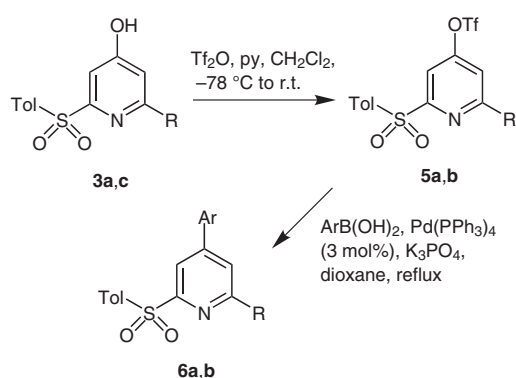
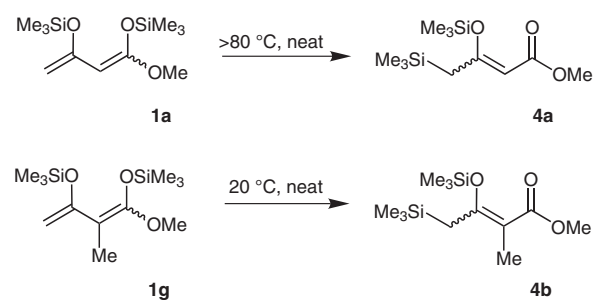
Scheme 1 Synthesis of 2-(arylsulfonyl)-4-hydroxypyridines **3a–h**

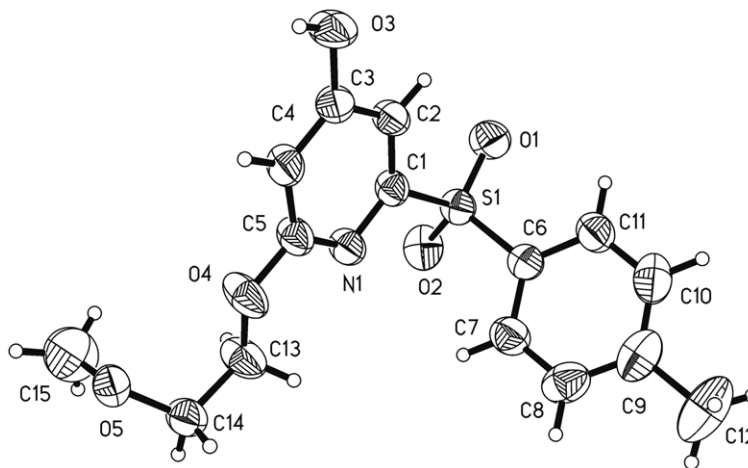
The structures of 2-(arylsulfonyl)-4-hydroxypyridines **3a–h** were confirmed by spectroscopic methods. The structures of **3c** and **3e** were independently confirmed by crystal structure analyses (Figures 1 and 2).¹² Inspection of the crystal lattice showed that an intermolecular hydrogen bond $\text{O} \cdots \text{H} \cdots \text{N}$ was present. The products reside in the form of the hydroxypyridine rather than as the pyridone tautomer.

The functionalization of 2-(arylsulfonyl)-4-hydroxypyridines by Suzuki cross-coupling reactions was next studied (Scheme 3, Table 2). Pyridines **3a,c** were transformed into the corresponding enol triflates **5a,b**. The Suzuki reaction of **5a** with phenylboronic acid afforded 2-methoxy-4-phenyl-6-tosylpyridine (**6a**). The reaction of **5b** with

Table 1 Synthesis of 2-(Arylsulfonyl)-4-hydroxypyridines **3a–h**

Substrates	Product	R ¹	R ²	Temp (°C)	Time ^a (h)	Yield ^b (%)
1a + 2a	3a	OMe	Me	–78 to r.t.	24	43
1b + 2a	3b	OEt	Me	–78 to r.t.	2.5	30
1c + 2a	3c	CH ₂ OMe	Me	0 to r.t.	96	30
1d + 2a	3d	Me	Me	r.t.	48	33
1e + 2a	3e	O(CH ₂) ₂ OMe	Me	–78 to r.t.	24	12
1a + 2b	3f	OMe	H	–78 to r.t.	24	10
1b + 2b	3g	OEt	H	–78 to r.t.	24	38
1f + 2a	3h	O <i>i</i> -Pr	Me	–78 to r.t.	28	31

^a Reaction time after warming to r.t.^b Yield of isolated product.**Figure 1** ORTEP plot of **3c**

Figure 2 ORTEP plot of **3e**Table 2 Synthesis of 4-Aryl-2-(arylsulfonyl)pyridines **6a,b**

5,6	R	Ar	Yield ^a (%)	
			5	6
a	OMe	Ph	87	87
b	CH ₂ OMe	3,4-(MeO) ₂ C ₆ H ₃	92	94

^a Yield of isolated product.

3,4-dimethoxyphenylboronic acid gave 4-(3,4-dimethoxyphenyl)-2-(methoxymethyl)-6-tosylpyridine (**6b**).

2-(Arylsulfonyl)-4-hydroxypyridines **3a–h**; General Procedure

To the arylsulfonyl cyanide **2a,b** (1.0 equiv) was added dropwise the 1,3-bis-silyl enol ether **1a–f** (2.0–2.5 equiv) at the temperature given. The mixture was allowed to warm to r.t. and was stirred until the arylsulfonyl cyanide was no longer detected by TLC. To the mixture was added aq 1 M NH₄Cl (30 mL) and CH₂Cl₂ (30 mL). The organic and aqueous layers were separated and the aqueous layer was extracted with CH₂Cl₂ (30 mL). The combined organic layers were dried (Na₂SO₄) and filtered and the solvent was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexanes–EtOAc).

4-Hydroxy-2-methoxy-6-tosylpyridine (**3a**)

Compound **1a** (574 mg, 2.21 mmol) was added to **2a** (200 mg, 1.10 mmol) at –78 °C. The mixture was allowed to warm r.t. over 30 min and then stirred at this temperature for 24 h. Product **3a** was isolated by chromatography (silica gel, *n*-hexane–EtOAc, 3:1) as a colorless solid; yield: 132 mg (43%); mp 126 °C.

IR (KBr): 3357 (w), 3090 (w), 3066 (w), 3024 (w), 2959 (w), 2919 (w), 2856 (w), 2794 (w), 2715 (w), 2685 (w), 2626 (w), 2581 (w), 2521 (w), 1611 (s), 1562 (s), 1475 (s), 1436 cm^{–1} (s).

¹H NMR (300 MHz, acetone-*d*₆): δ = 2.41 (s, 3 H, Ar-CH₃), 3.79 (s, 3 H, OCH₃), 6.29 (d, ⁴*J* = 1.9 Hz, 1 H, Py), 7.31 (d, ⁴*J* = 1.9 Hz, 1 H, Py), 7.43 (d, ³*J* = 8.4 Hz, 2 H, Ar), 7.94 (d, ³*J* = 8.4 Hz, 2 H, Ar), 10.28 (s, 1 H, OH).

¹³C NMR (75 MHz, acetone-*d*₆): δ = 22.2 (Ar-CH₃), 54.8 (OCH₃), 100.2, 106.9 (CH, Py), 130.4, 131.1 (CH, Ar), 138.0, 146.2 (C, Ar), 158.9, 167.5, 168.7 (C, Py).

MS (CI, isobutane): *m/z* (%) = 280 (100) [M + 1]⁺.

HRMS (MALDI, DHBA): *m/z* [M + H]⁺ calcd for C₁₃H₁₄NO₄S⁺: 280.06381; found: 280.06398.

UV/Vis (MeCN): λ_{max} (log ε) = 203 (4.4), 232 (4.0), 246 nm (3.9).

Anal. Calcd for C₁₃H₁₃NO₄S: C, 55.90; H, 4.69; N, 5.01. Found: C, 56.21; H, 5.08; N, 4.98.

4-Hydroxy-2-ethoxy-6-tosylpyridine (**3b**)

Compound **1b** (756 mg, 2.76 mmol) was added to **2a** (200 mg, 1.10 mmol) at –78 °C. The mixture was allowed to warm to r.t. over 1 h and then stirred at this temperature for 2.5 h. Product **3b** was isolated by chromatography (silica gel, *n*-hexane–EtOAc, 3:1) as a colorless solid; yield: 95 mg (30%); mp 123 °C.

IR (KBr): 3610 (w), 3544 (w), 3394 (w), 3090 (m), 3049 (m), 2986 (m), 2930 (m), 2897 (m), 2795 (w), 2736 (w), 2671 (w), 2606 (w), 2552 (w), 2508 (w), 1606 (s), 1554 (s), 1490 cm^{–1} (m).

¹H NMR (300 MHz, acetone-*d*₆): δ = 1.23 (t, ³*J* = 7.0 Hz, 3 H, OCH₂CH₃), 2.42 (s, 3 H, Ar-CH₃), 4.23 (q, ³*J* = 7.0 Hz, 2 H, OCH₂CH₃), 6.26 (d, ⁴*J* = 1.9 Hz, 1 H, Py), 7.28 (d, ⁴*J* = 1.9 Hz, 1 H, Py), 7.44 (d, ³*J* = 8.4 Hz, 2 H, Ar), 7.92 (d, ³*J* = 8.4 Hz, 2 H, Ar), 10.26 (s, 1 H, OH).

¹³C NMR (75 MHz, acetone-*d*₆): δ = 15.3 (OCH₂CH₃), 22.2 (Ar-CH₃), 63.7 (OCH₂CH₃), 100.4, 106.6 (CH, Py), 130.4, 131.1 (CH, Ar), 138.1, 146.2 (C, Ar), 159.1, 167.1, 168.6 (C, Py).

MS (CI, isobutane): *m/z* (%) = 294 (100) [M + 1]⁺.

HRMS (MALDI, DHBA): *m/z* [M + H]⁺ calcd for C₁₄H₁₆NO₄S⁺: 294.07946; found: 294.07968.

UV/Vis (MeCN): λ_{max} (log ε) = 267 (3.6), 248 (3.8), 232 (3.9), 202 nm (4.3).

4-Hydroxy-2-(methoxymethyl)-6-tosylpyridine (**3c**)

Compound **1c** (945 mg, 3.45 mmol) was added to **2a** (250 mg, 1.38 mmol) at 0 °C. The mixture was warmed to r.t. and then stirred at this temperature for 4 d. Product **3c** was isolated by chromatography (silica gel, *n*-hexane–EtOAc, 4:1) as a colorless solid; yield: 120 mg (30%); mp 137 °C.

IR (KBr): 3427 (s), 3097 (w), 3071 (w), 3067 (w), 2991 (w), 2931 (w), 2830 (w), 1602 (s), 1442 cm^{–1} (m).

¹H NMR (300 MHz, acetone-*d*₆): δ = 2.41 (s, 3 H, Ar-CH₃), 3.37 (s, 3 H, OCH₃), 4.39 (s, 2 H, PyCH₂OCH₃), 7.06 (d, ⁴*J* = 2.3 Hz, 1 H, Py), 7.42 (d, ³*J* = 8.5 Hz, 2 H, Ar), 7.54 (d, ⁴*J* = 2.3 Hz, 1 H, Py), 7.89 (d, ³*J* = 8.5 Hz, 2 H, Ar), 10.32 (s, 1 H, OH).

¹³C NMR (75 MHz, acetone-*d*₆): δ = 21.5 (Ar-CH₃), 58.8 (OCH₃), 75.0 (PyCH₂OCH₃), 109.3, 111.7 (CH, Py), 129.7, 130.5 (CH, Ar), 137.6, 145.6 (C, Ar), 160.8, 163.0, 167.0 (C, Py).

MS (CI, isobutane): m/z (%) = 294 (100) $[M + 1]^+$.

UV/Vis (MeCN): λ_{\max} (log ϵ) = 245 (4.0), 228 (4.1), 203 nm (4.5).

Anal. Calcd for $C_{14}H_{15}NO_4S$: C, 57.32; H, 5.15; N, 4.77. Found: C, 57.42; H, 5.17; N, 5.01.

4-Hydroxy-2-methyl-6-tosylpyridine (3d)

Compound **1d** (671 mg, 2.75 mmol) was added to **2a** (265 mg, 1.46 mmol) at r.t. The mixture was stirred for 48 h at this temperature. Product **3d** was isolated by chromatography (silica gel, *n*-hexane–EtOAc, 3:1) as a colorless solid; yield: 127 mg (33%); mp 140 °C (dec).

IR (KBr): 3098 (w), 3065 (w), 3027 (w), 2959 (w), 2928 (w), 2872 (w), 1609 (s), 1550 (s), 1458 cm^{-1} (s).

1H NMR (300 MHz, acetone- d_6): δ = 2.37, 2.41 (s, 2×3 H, Ar-CH₃, Py-CH₃), 6.85 (d, 4J = 2.1 Hz, 1 H, Py), 7.42 (d, 3J = 8.1 Hz, 2 H, Ar), 7.47 (d, 4J = 2.1 Hz, 1 H, Py), 7.89 (d, 3J = 8.1 Hz, 2 H, Ar), 10.15 (s, 1 H, OH).

^{13}C NMR (75 MHz, acetone- d_6): δ = 22.1 (Ar-CH₃), 24.8 (Py-CH₃), 108.8, 114.7 (CH, Py), 130.4, 131.1 (CH, Ar), 138.4, 146.1 (C, Ar), 161.5, 163.0, 167.1 (C, Py).

MS (CI, isobutane): m/z (%) = 264 (100) $[M + 1]^+$.

HRMS (MALDI, DHBA): m/z $[M + H]^+$ calcd for $C_{13}H_{14}NO_3S^+$: 264.06889; found: 264.06897.

UV/Vis (MeCN): λ_{\max} (log ϵ) = 238 (4.0), 228 (4.1), 203 nm (4.5).

Anal. Calcd for $C_{13}H_{13}NO_3S$: C, 59.30; H, 4.98; N, 5.32. Found: C, 59.92; H, 5.68; N, 5.47.

4-Hydroxy-2-(2-methoxyethoxy)-6-tosylpyridine (3e)

Compound **1e** (1.25 g, 4.13 mmol) was added to **2a** (300 mg, 1.65 mmol) at –78 °C. The mixture was allowed to warm up to r.t. over 1.5 h and then stirred at this temperature for 24 h. Product **3e** was isolated by chromatography (silica gel, *n*-hexane–EtOAc, 3:1) as a colorless solid; yield: 63 mg (12%); mp 105 °C.

IR (KBr): 3512 (w), 3333 (m), 3178 (w), 3146 (w), 3098 (w), 2975 (m), 2930 (m), 1605 (s), 1567 (m), 1441 cm^{-1} (s).

1H NMR (300 MHz, acetone- d_6): δ = 2.41 (s, 3 H, Ar-CH₃), 3.27 (s, 3 H, OCH₃), 3.57 (t, 3J = 4.6 Hz, 2 H, OCH₂CH₂OCH₃), 4.32 (t, 3J = 4.6 Hz, 2 H, OCH₂CH₂OCH₃), 6.31 (d, 4J = 2.0 Hz, 1 H, Py), 7.31 (d, 4J = 2.0 Hz, 1 H, Py), 7.44 (d, 3J = 8.2 Hz, 2 H, Ar), 7.50 (d, 3J = 8.2 Hz, 2 H, Ar), 10.33 (s, 1 H, OH).

^{13}C NMR (75 MHz, acetone- d_6): δ = 22.1 (Ar-CH₃), 59.3 (OCH₃), 67.1, 71.7 (OCH₂CH₂OCH₃, OCH₂CH₂OCH₃), 100.4, 106.8 (CH, Py), 130.4, 131.1 (CH, Ar), 137.9, 146.2 (C, Ar), 158.9, 167.0, 168.7 (C, Py).

MS (CI, isobutane): m/z (%) = 324 (100) $[M + 1]^+$.

UV/Vis (MeCN): λ_{\max} (log ϵ) = 246 (3.9), 231 (4.0), 204 nm (4.4).

Anal. Calcd for $C_{15}H_{17}NO_5S$ (323.08): C, 55.71; H, 5.30; N, 4.33. Found: C, 55.99; H, 5.31; N, 4.67.

4-Hydroxy-2-methoxy-6-(phenylsulfonyl)pyridine (3f)

Compound **1a** (466 mg, 1.80 mmol) was added to **2b** (150 mg, 0.90 mmol) at –78 °C. The mixture was allowed to warm to r.t. over 30 min and then stirred at this temperature for 24 h. Product **3f** was isolated by chromatography (silica gel, *n*-hexane–EtOAc, 5:1) as a colorless solid; yield: 24 mg (10%); mp 140 °C.

IR (KBr): 3441 (w), 3271 (w), 3267 (w), 3259 (w), 3252 (w), 3092 (w), 3065 (m), 3015 (w), 2956 (m), 2924 (m), 2853 (m), 2797 (w), 2682 (m), 2628 (m), 2582 (w), 2522 (w), 2479 (w), 1613 (s), 1556 (s), 1472 (s), 1435 cm^{-1} (s).

1H NMR (300 MHz, acetone- d_6): δ = 3.78 (s, 3 H, OCH₃), 6.29 (d, J = 1.9 Hz, 1 H, Py), 7.32 (d, J = 1.9 Hz, 1 H, Py), 7.62–7.73 (m, 3 H, Ar), 8.05–8.08 (m, 2 H, Ar), 10.33 (s, 1 H, OH).

^{13}C NMR (75 MHz, acetone- d_6): δ = 54.2 (OCH₃), 99.7, 106.4 (CH, Py), 129.8, 129.9 (CH, Ar), 134.6 (CH, Ar), 140.3 (C, Ar), 158.1, 166.9, 168.0 (C, Py).

MS (CI, isobutane): m/z (%) = 266 (100) $[M + 1]^+$.

UV/Vis (MeCN): λ_{\max} (log ϵ) = 273 (3.6), 267 (3.6), 243 nm (3.7).

Anal. Calcd for $C_{12}H_{11}NO_4S$: C, 54.33; H, 4.18; N, 5.28. Found: C, 54.59; H, 4.03; N, 5.10.

2-Ethoxy-4-hydroxy-6-(phenylsulfonyl)pyridine (3g)

The compound **1b** (327 mg, 1.20 mmol) in the presence of hydroquinone (0.5 mol%) was added to **2b** (100 mg, 0.6 mmol) at –78 °C. The mixture was allowed to warm to r.t. over 1 h and then stirred at this temperature for 24 h. Product **3g** was isolated by chromatography (silica gel, *n*-hexane–EtOAc, 2:1) as a yellow-tinged solid; yield: 64 mg (38%); mp 114 °C; the product was contaminated with hydroquinone which could not be completely removed.

IR (KBr): 3327 (w), 3238 (w), 3090 (w), 3064 (w), 3043 (w), 3034 (w), 2987 (w), 2926 (m), 2863 (w), 2689 (w), 2615 (w), 1608 (s), 1560 (m), 1510 (w), 1460 cm^{-1} (s).

1H NMR (300 MHz, acetone- d_6): δ = 1.21 (t, 3J = 7.0 Hz, 3 H, OCH₂CH₃), 4.22 (q, 3J = 7.0 Hz, 2 H, OCH₂CH₃), 6.27 (d, 4J = 1.9 Hz, 1 H, Py), 7.30 (d, 4J = 1.9 Hz, 1 H, Py), 7.61–7.73 (m, 3 H, Ar), 8.03–8.07 (m, 2 H, Ar), 10.19 (s, 1 H, OH).

^{13}C NMR (75 MHz, acetone- d_6): δ = 15.2 (OCH₂CH₃), 63.7 (OCH₂CH₃), 100.5, 106.6 (CH, Py), 130.4, 130.6 (CH, Ar), 135.2 (CH, Ar), 141.0 (C, Ar), 158.8, 167.2, 168.5 (C, Py).

MS (EI, 70 eV): m/z (%) = 279 (5) $[M]^+$, 264 (100) $[M - CH_3]^+$, 251 (38) $[M - C_2H_4]^+$, 235 (30) $[M - C_2H_5O]^+$.

HRMS (MALDI, DHBA): m/z $[M + H]^+$ calcd for $C_{13}H_{14}NO_4S^+$: 280.06381; found: 280.06396.

UV/Vis (MeCN): λ_{\max} (log ϵ) = 274.04 (3.5), 267.68 (3.5), 223.43 nm (3.9).

4-Hydroxy-2-isopropoxy-6-tosylpyridine (3h)

Compound **1f** (795 mg, 2.76 mmol) was added to **2a** (200 mg, 1.10 mmol) at –78 °C. The mixture was allowed to warm up to r.t. over 1 h and then stirred at this temperature for 28 h. Product **3h** was isolated by column chromatography (*n*-hexane–EtOAc, 3:1) as a yellow highly viscous oil; yield: 106 mg (31%); the product was contaminated with isopropyl acetoacetate which could not be completely removed.

1H NMR (300 MHz, acetone- d_6): δ = 1.19 and 1.24 [d, 3J = 6.3 Hz, 6 H, OCH(CH₃)₂], 2.42 (s, 3 H, Ar-CH₃), 5.00–5.12 [m, 1 H, OCH(CH₃)₂], 6.21 (d, 4J = 2.0 Hz, 1 H, Py), 7.25 (d, 4J = 2.0 Hz, 1 H, Py), 7.44 (d, 3J = 8.1 Hz, 2 H, Ar), 7.91 (d, 3J = 8.1 Hz, 2 H, Ar), 10.30 (s, 1 H, OH).

^{13}C NMR (75 MHz, acetone- d_6): δ = 21.8, 21.9 ($3 \times$ CH₃), 70.7 [OCH(CH₃)₂], 100.1, 105.5 (CH, Py), 129.8, 130.4 (CH, Ar), 137.4, 145.5 (C, Ar), 158.4, 166.0, 168.0 (C, Py).

2-Methoxy-6-tosyl-4-[(trifluoromethylsulfonyl)oxy]pyridine (5a); Typical Procedure

To a soln of **3a** (123 mg, 0.44 mmol) and pyridine (70 mg, 0.88 mmol) in CH₂Cl₂ (10 mL) was added Tf₂O (0.11 mL, 0.66 mmol) at –78 °C. The mixture was allowed to warm up to r.t. over 4 h and then stirred at this temperature for 1 h. The mixture was directly purified by chromatography (CH₂Cl₂) to give **5a** as a colorless oil that crystallized upon standing overnight at –20 °C; yield: 156 mg (87%).

1H NMR (300 MHz, CDCl₃): δ = 2.45 (s, 3 H, Ar-CH₃), 3.92 (s, 3 H, OCH₃), 6.77 (d, 4J = 1.9 Hz, 1 H, Py), 7.36 (d, 3J = 8.5 Hz, 2 H, Ar), 7.68 (d, 4J = 1.9 Hz, 1 H, Py), 7.96 (d, 3J = 8.5 Hz, 2 H, Ar).

^{13}C NMR (75 MHz, CDCl_3): δ = 21.7 ($\text{CH}_3\text{-Ar}$), 55.0 (OCH_3), 107.1, 108.4 (CH, Py), 118.5 (q, $^1J_{\text{C-F}}$ = 319.1 Hz, OSO_2CF_3), 129.3, 129.8 (CH, Ar), 134.7, 145.5 (C, Ar), 157.9, 158.7, 165.8 (C, Py).

2-(Methoxymethyl)-6-tosyl-4-[(trifluoromethylsulfonyl)oxy]pyridine (**5b**)

The reaction was carried out following the procedure as given for the synthesis of **5a**. Starting with **3c** (70 mg, 0.24 mmol), Ti_2O (0.06 mL, 0.36 mmol), and pyridine (38 mg, 0.48 mmol) in CH_2Cl_2 (7 mL), **5b** was isolated as a colorless oil that crystallized upon standing overnight at -20°C ; yield: 93 mg (92%).

^1H NMR (300 MHz, CDCl_3): δ = 2.44 (s, 3 H Ar-CH_3), 3.47 (s, 3 H, OCH_3), 4.59 (s, 2 H, $\text{Py-CH}_2\text{OCH}_3$), 7.35 (d, 3J = 8.7 Hz, 2 H, Ar), 7.54 (d, 4J = 2.3 Hz, 1 H, Py), 7.94 (d, 3J = 8.7 Hz, 2 H, Ar), 7.97 (d, 4J = 2.3 Hz, 1 H, Py).

^{13}C NMR (75 MHz, CDCl_3): δ = 21.7 ($\text{CH}_3\text{-Ar}$), 59.0 (OCH_3), 73.8 (Py- CH_2OCH_3), 113.3, 116.2 (CH, Py), 118.5 (q, $^1J_{\text{C-F}}$ = 318.8 Hz, OSO_2CF_3), 129.2, 129.9 (CH, Ar), 134.8, 145.5 (C, Ar), 157.7, 161.1, 164.7 (C, Py).

2-Methoxy-4-phenyl-6-tosylpyridine (**6a**); Typical Procedure

To a soln of **5a** (60 mg, 0.145 mmol), K_3PO_4 (60 mg, 0.28 mmol), and $\text{Pd}(\text{PPh}_3)_4$ (5 mg, 4.4 μmol) in dioxane (1 mL) under an inert atmosphere was added a soln of phenylboronic acid (24 mg, 0.20 mmol) in dioxane (5 mL). The mixture was heated under reflux for 5 h. The mixture was allowed to cool and CH_2Cl_2 (100 mL) and sat. aq NH_4Cl (100 mL) were added. The organic and the aqueous layer were separated and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were dried (Na_2SO_4) and filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (*n*-hexane–EtOAc, 3:1 to 0:1) to give **6a** as a slight brownish, highly viscous oil; yield: 43 mg (87%).

IR (KBr): 3419 (w), 2977 (w), 2933 (w), 1653 (w), 1604 (s), 1540 (m), 1462 cm^{-1} (s).

^1H NMR (300 MHz, CDCl_3): δ = 2.43 (s, 3 H, Ar-CH_3), 3.91 (s, 3 H, OCH_3), 7.04 (d, 4J = 1.3 Hz, 1 H, Py), 7.34 (d, 3J = 8.1 Hz, 2 H, Ar), 7.42–7.54 (m, 3 H, Ar, Py), 7.58–7.68 (m, 2 H, Ar), 7.98–8.02 (m, 3 H, Ar).

^{13}C NMR (75 MHz, CDCl_3): δ = 21.6 (Ar-CH_3), 54.1 (OCH_3), 112.2, 113.5 (CH, Py), 127.0, 129.1, 129.2, 129.5, 129.8 (C, Ar), 135.9, 136.7, 144.6 (C, Ar), 152.7, 156.4, 164.8 (C, Py).

UV/Vis (MeCN): λ_{max} (log ϵ) = 242 nm (4.4).

MS (EI, 70 eV): m/z (%) = 339 (3) [M^+], 338 (5), 275 (100).

Anal. Calcd for $\text{C}_{19}\text{H}_{17}\text{NO}_3\text{S}$: C, 67.24; H, 5.05. Found: C, 67.38; H, 5.35.

4-(3,4-Dimethoxyphenyl)-2-(methoxymethyl)-6-tosylpyridine (**6b**)

The reaction was carried out following the procedure as given for the synthesis of **6a**. Starting with **5b** (41 mg, 0.096 mmol), 2,3-dimethoxyphenylboronic acid (23 mg, 0.13 mmol), K_3PO_4 (33 mg, 0.15 mmol), and $\text{Pd}(\text{PPh}_3)_4$ (3 mg, 2.9 μmol) in dioxane (5 mL), **6a** was isolated as a colorless oil; yield: 37 mg (94%).

IR (KBr): 3422 (m), 3075 (w), 2974 (m), 2928 (s), 2859 (m), 1735 (m), 1647 (w), 1596 (s), 1521 (s), 1452 cm^{-1} (s).

^1H NMR (300 MHz, CDCl_3): δ = 2.42 (s, 3 H, Ar-CH_3), 3.47 (s, 3 H, Py- CH_2OCH_3), 3.95 (s, 3 H, ArOCH_3), 3.99 (s, 3 H, ArOCH_3), 4.61 (s, 2 H, Py- CH_2OCH_3), 6.98 (d, 3J = 8.4 Hz, 1 H, Ar), 7.18 (d, 4J = 2.1 Hz, 1 H, Ar), 7.28–7.38 (m, 1 H, Ar), 7.32 (d, 3J = 8.3 Hz, 2 H, Ar), 7.76 (d, 4J = 1.5 Hz, 1 H, Py), 7.97 (d, 3J = 8.3 Hz, 2 H, Ar), 8.26 (d, 4J = 1.5 Hz, 1 H, Py).

^{13}C NMR (75 MHz, CDCl_3): δ = 21.6 (Ar-CH_3), 56.0, 56.2 (ArOCH_3), 58.9 (Py- CH_2OCH_3), 74.7 (Py- CH_2OCH_3), 109.8, 111.5,

117.9, 120.2, 120.9 (CH, Ar, Py), 128.9 (CH, Ar), 129.3 (C, Ar), 129.6 (CH, Ar), 136.1, 144.6, 149.6, 150.8, 151.0, 158.6, 160.7 (C, Py, Ar).

MS (EI, 70 eV): m/z (%) = 413 (20) [M^+], 383 (100), 334 (35).

HRMS (EI): m/z [M^+] calcd for $\text{C}_{22}\text{H}_{23}\text{NO}_5\text{S}$: 413.1291; found: 413.1298.

UV/Vis (MeCN): λ_{max} (log ϵ) = 314 (3.9), 283 (3.8), 237 nm (4.2).

Fluorescence (MeCN): $F\lambda_{\text{max}}$ (λ_{ex}): 442 nm (318).

Anal. Calcd for $\text{C}_{22}\text{H}_{23}\text{NO}_5\text{S}$: C, 63.90; H, 5.61. Found: C, 64.08; H, 6.31.

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- Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-295095(3c) and CCDC-297417(3e). Copies of this data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk or via www.ccdc.cam.ac.uk/conts/retrieving.html.