

A Possible Pathway for the Reaction of Triethyl (1-Methylindol-2-yl)borate with Cationic Electrophiles in the Presence of Cuprous Cyanide

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On the preferential formation of 3-substituted indoles from triethyl (1-methylindol-2-yl)borate in the presence of cuprous cyanide and cationic electrophiles, it was supposed that the reaction seems to proceed through a transposition path from boron to copper.

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In our previous paper [1], the preferential formation of 3-pyridylindoles from the reaction of triethyl (1-methylindol-2-yl)borate **1a** and *N*-carbophenoxypyridinium derivatives in the presence of cuprous cyanide was reported. However, the reaction course was tentatively illustrated by a one-electron transfer path involving a redox reaction of copper ion [2]. In the continuation of the study, a transposition from boron to copper [3] was proposed as an alternative mechanistic possibility. Herein, a comparison of the reaction outcome of indolylborates **1** with cationic electrophiles **3** in the presence of cuprous cyanide with that of indolylcuprates **2** was undertaken, and the results are described.

Borates **1** and cuprates **2** were generated *in situ* from treatment of the corresponding 2-lithio-1-methylindoles [4] with triethylborane and cuprous cyanide, respectively, in tetrahydrofuran at -20° under an argon atmosphere (Scheme 1).

As seen in the Table, the reaction outcome of indolylcuprate **2** showed striking resemblance to that of indolylborate **1** in the presence of cuprous cyanide, which showed the exclusive formation of 3-substituted indoles **4** on the runs of **1a** and **2a**, and 2-substituted indoles **5** on the runs of indolylborates **1b,c** and **2b,c**, attributable to the steric interference of the C-3 substituent. On the other hand, by subjecting both **1a** to **3a** and **1b** to **3b** without cuprous cyanide, boranes **6a** and **6b** were isolated through a 1,2-alkyl migration path [5] (Scheme 2).

The reaction of indolylborate **1a** with **3c** [6] in the absence of cuprous cyanide produced **7** as a sole product in 40% yield, whereas **4c** was formed solely from the reaction of **2a** with **3c**. The concomitant formation of **4c** and **7** could be seen in the reaction of **2a** with **3c** in the presence of triethylborane (1.2 molar equivalents) (**4c** in 66% yield and **7** in 10% yield) (Scheme 3), which seems to be deducible from a reversible interconversion between

Scheme 1

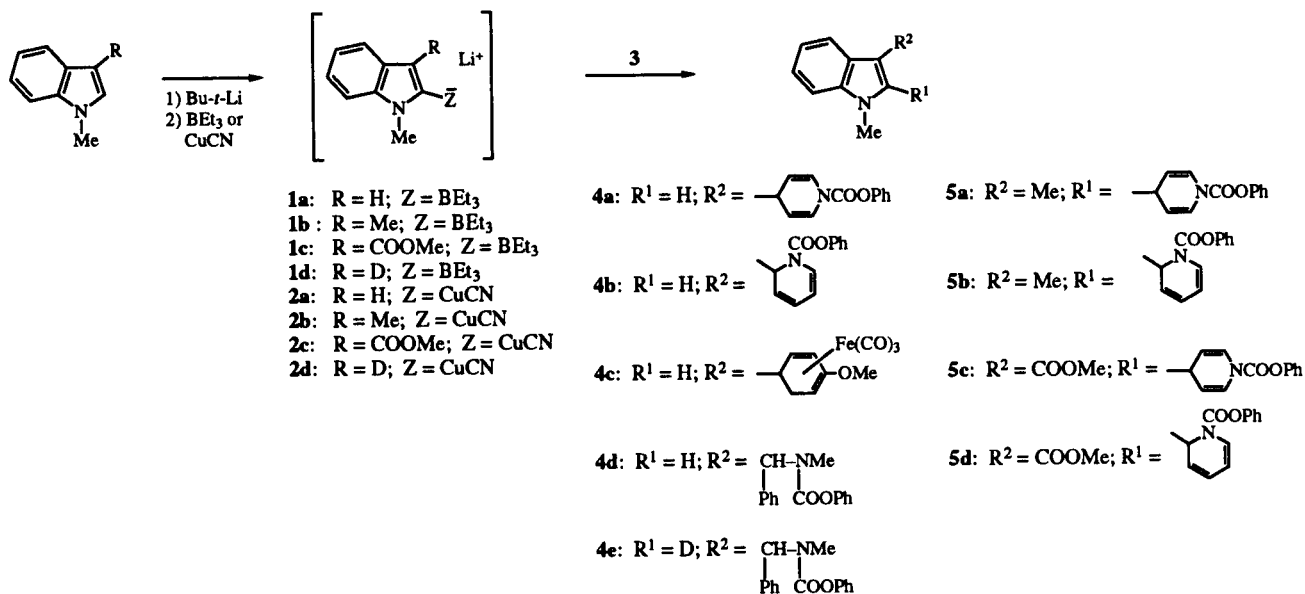
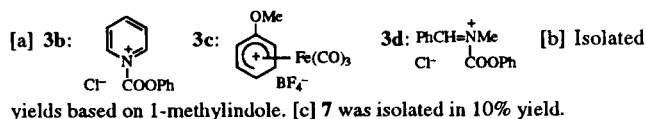


Table
Reaction of 1 and 2 with cationic electrophile 3

R in 1 and 2	3 [a]	Yield(%) of 4 and 5 [b]	
		via 1	via 2
H	3b	40 (4a) 5 (4b)	37 (4a) 7 (4b)
H	3c	63 (4c) [c]	70 (4c)
H	3d	68 (4d)	70 (4d)
Me	3d	22 (5a) 6 (5b)	25 (5a) 7 (5b)
COOMe	3b	19 (5c) 6 (5d)	18 (5c) 9 (5d)

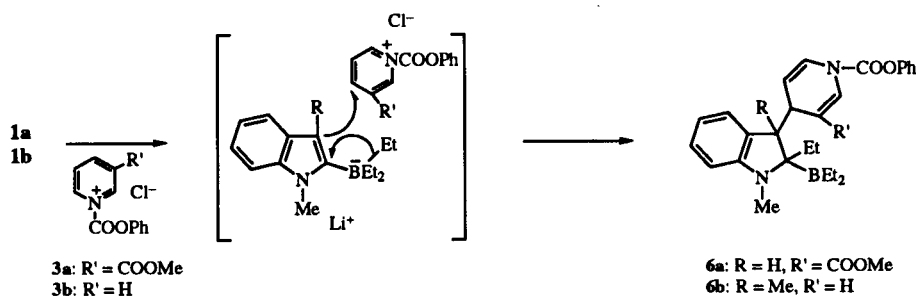


copper indolylborate (A) and indolylcopper (B) species.

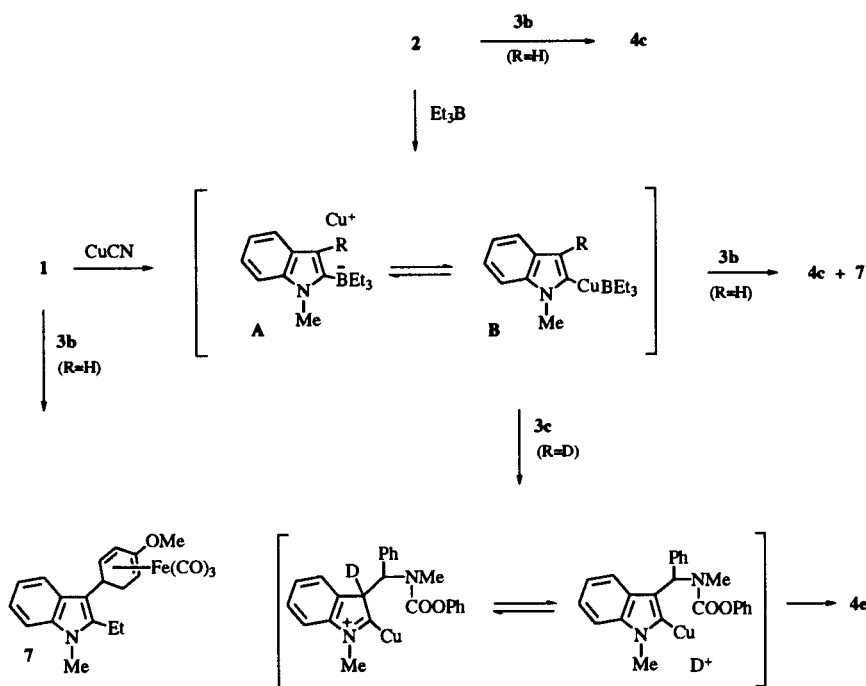
Treatment of 3-deuterated indolylborate 1d with 3d in the presence of cuprous cyanide was found to give 2-deuterated product 4e in 65% yield (deuterium content was determined to be 75% by ^1H nmr), which was also obtained from 2d and 3d in 69% yield. On quenching the reaction of 1a with 3d in the presence of cuprous cyanide with deuterium oxide, no observable incorporation of deuterium in the product 4d could be seen. Possibly, the formation of 4e from 1a and 3d in the presence of cuprous cyanide might be interpreted by the sequence outlined in Scheme 3 [7].

As obvious from all the above results, the exclusive formation of a 3-substituted indole from 1a and cationic electrophile 3 in the presence of cuprous cyanide seems to involve an intervention of an indolyl copper species arising from a transposition path from boron to copper.

Scheme 2



Scheme 3



EXPERIMENTAL

All melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. Tetrahydrofuran (THF) was distilled from sodium/benzophenone before use. The ir spectra were recorded with a Hitachi 270-30 spectrometer. The nmr spectra were determined with a JEOL FX90Q spectrometer. Chemical shifts are given in δ -value down field from tetramethylsilane. Tetramethylsilane was used as internal reference. The mass spectra were recorded on JEOL JMS-QH100 and JEOL JMS-D300 spectrometers. Medium pressure liquid chromatography (mplc) was performed on a Merck lobar column (LiChroprep Si 60).

The reaction of indolylborate **1** with cationic electrophile **3** in the presence of cuprous cyanide was accomplished according to the previous report [1]. The product **4a** and **4b** were separated by mplc with ethyl acetate-hexane as eluent, and the results are shown in the Table.

Typical Procedure: The Reaction of Cuprate 2a with Cationic Electrophile 3a.

Cuprous cyanide (3 mmoles) was added to a solution of 2-lithio-1-methylindole [5] [derived from the corresponding 1-methylindole (2 mmoles) and *tert*-butyllithium (2.4 mmoles)] in THF (10 ml) at -20° under an argon atmosphere, and the mixture was stirred for 20 minutes. After pyridinium chloride **3a** (3 mmoles) [1] was added, the whole was gradually warmed to room temperature and stirred overnight. The mixture was diluted with ethyl acetate (70 ml), washed with brine, and dried over magnesium sulfate. The solvent was removed, and the residue was separated by mplc to give **4a** and **4b** (Table).

Compound **4b** had mp 148-150 $^\circ$ (recrystallized from ethyl acetate-hexane); ir (chloroform): ν 1718, 1642 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 3.72 (s, 3H), 6.03 (ddd, 1H, $J = 2, 6, 8.5$ Hz), 6.28 (d, 1H, $J = 6$ Hz), 6.78 (dd, 1H, $J = 6, 11$ Hz), 6.85 (dd, 1H, $J = 6, 11$ Hz), 7.08 (d, 1H, $J = 8.5$ Hz), 6.95-7.70 (m, 9H), 7.70-8.10 (m, 1H); ^{13}C nmr (deuteriochloroform): δ 32.8, 49.1, 106.7, 109.3, 113.2, 119.6, 120.5, 121.8, 123.1, 125.6, 126.3, 129.4, 137.5, 151.2; ms: (ei) 330 (M^+).

Anal. Calcd. for $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.35; H, 5.47; N, 8.40.

Compound **4c** had mp 87-88 $^\circ$ (recrystallized from ethyl acetate-hexane); ir (chloroform): ν 2048, 1966 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.97 (ddd, 1H, $J = 2.2, 3.5, 18$ Hz), 2.42 (ddd, 1H, $J = 4, 11, 18$ Hz), 2.88 (dd, 1H, $J = 3.5, 6.6$ Hz), 3.30-3.60 (m, 2H), 3.68 (s, 3H), 3.70 (s, 3H), 5.16 (dd, 1H, $J = 2.2, 6.6$ Hz), 6.78 (s, 1H), 7.00-7.35 (m, 3H), 7.55 (dd, 1H, $J = 2, 6.6$ Hz); ^{13}C nmr (deuteriochloroform): δ 32.5, 32.9, 34.8, 53.1, 54.4, 55.4, 67.1, 109.3, 118.8, 119.2, 120.6, 121.7, 125.1, 126.6, 137.4, 140.2, 211.4; ms: (ei) 379 (M^+).

Anal. Calcd. for $\text{C}_{19}\text{H}_{17}\text{NO}_4\text{Fe}$: C, 60.18; H, 4.52; N, 3.69. Found: C, 60.12; H, 4.54; N, 3.82.

Compound **7** had mp 133-135 $^\circ$ (recrystallized from ethyl acetate-hexane); ir (chloroform): ν 2044, 1968 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.18 (t, 3H, $J = 7.5$ Hz), 1.90-2.50 (m, 2H), 2.60 (dd, 1H, $J = 3.5, 6.6$ Hz), 2.74 (q, 2H, $J = 7.5$ Hz), 3.30-3.60 (m, 2H), 3.63 (s, 3H), 3.73 (s, 3H), 5.13 (dd, 1H, $J = 2.2, 6.6$ Hz), 7.00-7.35 (m, 3H), 7.40-7.60 (m, 1H); ^{13}C nmr (deuteriochloroform): δ 15.2, 17.7, 29.4, 31.1, 35.4, 53.5, 54.4, 56.5, 67.9, 109.0, 113.6, 118.8, 119.0, 120.7, 125.2, 137.1, 138.8, 140.2, 211.6; ms: (ei) 407 (M^+).

Anal. Calcd. for $\text{C}_{21}\text{H}_{21}\text{NO}_4\text{Fe}$: C, 61.93; H, 5.19; N, 3.44. Found: C, 61.93; H, 5.21; N, 3.51.

Compound **4d** had mp 143-144 $^\circ$ (recrystallized from ethyl acetate-hexane); ir (chloroform): ν 1714 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 2.93 (s, 3H), 3.73 (s, 3H), 6.77 (s, 1H), 6.99 (s, 1H), 6.90-7.65 (m, 14H); ^{13}C nmr (deuteriochloroform): δ 31.1, 32.7, 57.1, 109.4, 113.0, 119.6, 121.8, 122.1, 125.1, 127.3, 127.5, 128.4, 129.1, 137.3, 139.8, 151.6, 155.1; ms: (ei) 370 (M^+).

Anal. Calcd. for $\text{C}_{24}\text{H}_{22}\text{N}_2\text{O}_2$: C, 77.81, H, 5.99; N, 7.56. Found: C, 78.00; H, 5.94; N, 7.53.

Compound **5a** had ir (film): ν 1728, 1698 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 2.30 (s, 3H), 3.79 (s, 3H), 4.70-4.90 (m, 1H), 4.90-5.20 (m, 2H), 6.90-7.65 (m, 11H); ^{13}C nmr (deuteriochloroform): δ 8.7, 30.4, 107.8, 108.4, 108.6, 118.5, 118.9, 121.4, 122.8, 126.0, 128.2, 129.5, 135.9, 137.0, 149.9, 150.7; ms: (ei) Calcd. for $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_2$: 344.15241. Found: 344.15201.

Compound **5b** had mp 123-125 $^\circ$ (recrystallized from ethyl acetate-hexane); ir (chloroform): ν 1726, 1654 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 2.33 (s, 3H), 3.81 (s, 3H), 5.32 (dd, 1H, $J = 5, 9$ Hz), 5.43 (dd, 1H, $J = 4, 8$ Hz), 5.97 (dd, 1H, $J = 5, 8$ Hz), 6.85 (d, 1H, $J = 4$ Hz), 6.70-7.40 (m, 9H), 7.55 (dd, 1H, $J = 2, 6$ Hz); ^{13}C nmr (deuteriochloroform): δ 8.9, 30.1, 50.9, 103.4, 109.1, 110.1, 118.9, 119.6, 120.6, 121.6, 121.9, 125.1, 125.8, 128.3, 129.4, 135.9, 137.0, 150.7, 152.7; ms: (ei) 344 (M^+).

Anal. Calcd. for $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.60; H, 5.88; N, 8.04.

Compound **5c** had mp 178-179 $^\circ$ (recrystallized from ethyl acetate-hexane); ir (chloroform): ν 1730, 1690 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 3.93 (s, 6H), 4.90-5.20 (m, 2H), 6.10-6.30 (m, 1H), 6.95-7.55 (m, 10H), 8.00-8.25 (m, 1H); ^{13}C nmr (deuteriochloroform): δ 30.5, 31.2, 50.8, 103.7, 107.6, 109.2, 121.4, 122.1, 122.7, 123.5, 126.1, 129.5, 137.4, 146.8, 149.8, 150.6, 166.4; ms: (ei) 388 (M^+).

Anal. Calcd. for $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_4$: C, 71.12; H, 5.19; N, 7.21. Found: C, 71.20; H, 5.20; N, 7.10.

Compound **5d** had mp 208-210 $^\circ$ (recrystallized from ethyl acetate-hexane); ir (chloroform): ν 1726, 1688, 1680 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 3.85 (s, 3H), 3.94 (s, 3H), 5.33 (ddd, 1H, $J = 1.5, 5, 7$ Hz), 5.55 (ddd, 1H, $J = 1.5, 4, 10$ Hz), 5.95 (ddd, 1H, $J = 1.5, 5, 10$ Hz), 6.70-7.50 (m, 9H), 7.73 (dd, 1H, $J = 1.4, 4$ Hz), 8.00-8.20 (m, 1H); ^{13}C nmr (deuteriochloroform): δ 31.3, 50.9, 51.4, 103.2, 104.3, 109.5, 120.5, 121.0, 121.2, 122.1, 122.5, 123.1, 125.7, 126.1, 129.2, 137.4, 145.9, 150.6, 152.4, 166.0; ms: (ei) 388 (M^+).

Anal. Calcd. for $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_4$: C, 71.12; H, 5.19; N, 7.21. Found: C, 70.91; H, 5.23; N, 7.00.

Reaction of **1a,b** with **3a,b** in the Absence of Cuprous Cyanide.

A solution of **3a,b** [1] [derived from pyridine (3 mmoles) and phenyl chloroformate (468 mg, 3 mmoles)] in THF (5 ml) was added to a solution of **1a,b** [derived from the corresponding indole (290 mg, 2 mmoles) and *tert*-butyllithium (2.4 mmoles)], followed by treatment with triethylborane (2.4 mmoles)] in THF (10 ml) under an argon atmosphere at -20° . After 30 minutes, the whole was gradually warmed to room temperature, and stirred overnight. After treatment with 10% aqueous sodium hydroxide (10 ml) and 30% aqueous hydrogen peroxide (1 ml) under ice-cooling, the mixture was diluted with ethyl acetate (70 ml), washed with brine, and dried over magnesium sulfate. The solvent was removed, and the residue was separated by mplc with hexane:ethyl acetate (20:1) as eluent to give **6a** and **b**.

Compound **6a** was obtained in 20% yield based on 1-methylindole; mp 130-132° (recrystallized from ethyl acetate-hexane); ir (potassium bromide): ν 1744, 1704, 1680 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 0.69 (t, 3H, $J = 8$ Hz), 1.05-1.15 (m, 8H), 1.19 (q, 2H, $J = 8$ Hz), 1.76 (dq, 1H, $J = 7, 15$ Hz), 2.06 (dq, 1H, $J = 7, 15$ Hz), 2.55 (d, 1H, $J = 3$ Hz), 3.04 (s, 3H), 3.73 (dd, 1H, $J = 3, 5$ Hz), 3.84 (s, 3H), 4.99 (m, 1H), 6.44 (d, 1H, $J = 8$ Hz), 6.65 (d, 1H, $J = 7.5$ Hz), 6.73 (dd, 1H, $J = 1.5, 7.5$ Hz), 6.90 (d, 1H, $J = 8.5$ Hz), 6.99 (dd, 2H, $J = 1.5, 8.5$ Hz), 7.18 (ddd, 1H, $J = 1.5, 7.5, 8.5$ Hz), 7.25 (d, 1H, $J = 7$ Hz), 7.37 (dd, 2H, $J = 7, 8.5$ Hz), 7.78 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 5.8, 9.3, 10.0, 10.7, 21.8, 26.1, 30.3, 34.2, 35.0, 51.7, 52.0, 110.1, 112.1, 114.1, 120.3, 121.2, 121.6, 126.1, 127.1, 128.2, 129.4, 132.0, 134.9, 144.7, 149.0, 150.4, 167.2; ms: (ei) 258 (base), 455 and 456 ($\text{M}^+ - \text{C}_2\text{H}_5$).

Anal. Calcd. for $\text{C}_{29}\text{H}_{35}\text{N}_2\text{O}_4\text{B}$: C, 71.61; H, 7.25; N, 5.76. Found: C, 71.75; H, 7.42; N, 5.64.

Compound **6b** was obtained in 27% yield based on 1,3-dimethylindole, mp 128-130° (recrystallized from ethyl acetate-hexane); ir (chloroform): ν 1728, 1692 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 0.10-1.30 (m, 10H), 1.11 (t, 3H, $J = 7$ Hz), 1.48 (s, 3H), 1.70-2.10 (m, 2H), 2.78 (s, 3H), 3.36 (dd, 1H, $J = 3.8, 4$ Hz), 4.50-4.80 (br, 1H), 5.05-5.45 (br, 1H), 6.43 (d, 1H, $J = 7.5$ Hz), 6.70-7.60 (m, 10H); ^{13}C nmr (deuteriochloroform): δ 7.5, 10.5, 12.8, 20.5, 22.2, 34.0, 40.3, 53.7, 108.4, 109.2, 114.7, 121.4, 123.0, 123.8, 124.4, 125.9, 126.6, 129.4, 141.3, 148.7, 149.5, 150.7; ms: (ei) 412 and 413 ($\text{M}^+ - \text{C}_2\text{H}_5$).

Anal. Calcd. for $\text{C}_{28}\text{H}_{35}\text{N}_2\text{O}_2\text{B}$: C, 76.02; H, 7.97; N, 6.33. Found: C, 75.81; H, 8.02; N, 6.09.

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