Electronic Supplementary Information

Ligand Accelerated Indium(III)-Catalyzed Asymmetric Alkynylation of Aldehydes with 2-Methyl-3-butyn-2-ol as an Acetylene Equivalent

Shinji Harada, Ryo Takita, Takashi Ohshima, Shigeki Matsunaga and Masakatsu Shibasaki*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Phone: +81-3-5841-4830, fax: +81-3-5684-5206

E-mail: mshibasa@mol.f.u-tokyo.ac.jp

Experimental Section

General

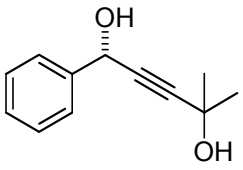
Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. NMR spectra were recorded on JEOL JNM-LA500 spectrometer and JNM-ECX500, operating at 500 MHz for ^{1}H NMR and 125.65 MHz for ^{13}C NMR. Chemical shifts in $CDCl_3$ were reported in the scale relative to $CHCl_3$ (7.26 ppm) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to $CHCl_3$ (77.0 ppm) as an internal reference. Column chromatography was performed with silica gel Merck 60 (230–400 mesh ASTM). Optical rotations were measured on a JASCO P-1010 polarimeter. ESI mass spectra were measured on Waters micromass ZQ. FAB mass spectra were measured on JMS-MS 700V. The enantiomeric excess (ee) was determined by HPLC analysis. HPLC was performed on JASCO HPLC systems consisting of the following: pump, PU-2080 plus; detector, UV-2075 plus, measured at 254 nm. Reactions were carried out in dry solvents under argon atmosphere, unless otherwise stated. $InBr_3$ was purchased from Aldrich. Other solvents and reagents were purified by the usual methods.

General Procedure for the Catalytic Asymmetric Alkynylation Reaction: (*S*)-4-Methyl-1-phenyl-pent-2-yne-1,4-diol (4a): A flame-dried test tube was charged with (*S*)-BINOL (11.45 mg, 0.04 mmol) and $InBr_3$ (14.18 mg, 0.04 mmol) under Argon atmosphere. To the tube was added dry CH_2Cl_2 (0.2 mL) and then benzaldehyde (**3a**) (40.7 μL, 0.4 mmol) at room temperature. The resulting solution was stirred for 10 minutes, and dicyclohexylmethylamine (42.8 μL, 0.2 mmol) was added. After stirring again for 10 minutes, 2-methyl-3-butyn-2-ol (**1a**) (77.5 μL, 0.8 mmol) was added. The mixture was warmed up to 40 °C (oil bath temperature) and stirred for 39 h. The reaction was monitored by TLC analysis. After cooling to room temperature, the reaction was quenched with saturated aqueous NH_4Cl and a small portion of 1 M HCl, and the mixture was extracted with diethyl ether for 3 times. Combined organic layers were washed with brine, and dried over Na_2SO_4. After filtration of Na_2SO_4, the organic solvent was evaporated and the residue was purified by flash column chromatography (silica gel, eluent: hexane/AcOEt = 6/1 – 3/1) to give **4a** (67.2 mg, 0.353 mmol, 88% yield) as a colorless solid. Enantiomeric

excess was determined by chiral HPLC (DAICEL CHIRALCEL OD-H, eluent: hexane/isopropanol = 9/1, flow: 0.5 mL/min, detection at 254 nm, 97% ee).

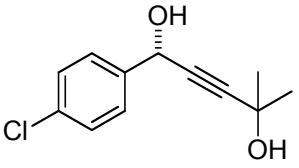
Spectral Data

(*S*)-4-Methyl-1-phenyl-pent-2-yne-1,4-diol (4a): Known compound (CAS No. 321855-44-1)



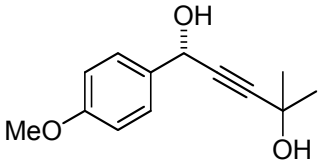
Colorless solid; IR (KBr) 3375, 2981, 1638, 1454, 1379, 1164, 1090, 1059 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.54 (s, 6H), 2.94 (brs, 1H), 3.24 (brs, 1H), 5.46 (d, *J* = 5.5 Hz, 1H), 7.31-7.39 (m, 3H), 7.51 (brd, *J* = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 31.2, 31.3, 64.4, 65.2, 81.8, 91.3, 126.6, 128.3, 128.6, 140.5; ESI-MS *m/z* 213 $[M+Na]^+$; $[\alpha]_D^{25}$ –17.9 (*c* 0.79, $CHCl_3$); HPLC (DAICEL CHIRALCEL OD-H, 2-propanol/hexane 10/90, flow 0.5 mL/min, detection at 254 nm) t_R 12.6 min (major) and 14.7 min (minor).

(*S*)-1-(4-Chloro-phenyl)-4-methyl-pent-2-yne-1,4-diol (4b):



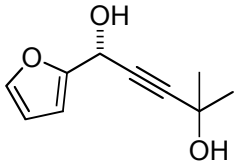
Colorless solid; IR (KBr) 3389, 2982, 1490, 1164, 1091 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.49 (s, 6H), 5.37 (s, 1H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 31.1, 31.1, 63.3, 65.1, 81.5, 91.4, 128.0, 128.6, 134.0, 139.0; ESI-MS *m/z* 247 $[M+Na]^+$; HRMS calcd. for $C_{12}H_{12}ClO$ $[M-OH]^+$: 207.0571, found 207.0569; $[\alpha]_D^{27}$ -15.5 (*c* 0.87, $CHCl_3$); HPLC (DAICEL CHIRALPAK AD-H, 2-propanol/hexane 10/90, flow 0.5 mL/min, detection at 254 nm) t_R 21.3 min (major) and 23.5 min (minor).

(*S*)-1-(4-Methoxy-phenyl)-4-methyl-pent-2-yne-1,4-diol (4c):



Colorless solid; IR (KBr) 3374, 2980, 1611, 1512, 1247, 1173 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.51 (s, 6H), 3.23 (brs, 1H), 3.45 (brs, 1H), 3.78 (s, 3H), 5.38 (s, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 7.41 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 31.2, 31.2, 55.2, 63.8, 65.1, 82.0, 91.1, 113.8, 128.1, 132.9, 159.5; ESI-MS *m/z* 243 $[M+Na]^+$; HRMS calcd. for $C_{13}H_{15}O_2$ $[M+H]^+$: 203.1067, found 203.1067; $[\alpha]_D^{26}$ –22.3 (*c* 0.91, $CHCl_3$); HPLC (DAICEL CHIRALPAK AD-H, 2-propanol/hexane 10/90, flow 0.5 mL/min, detection at 254 nm) t_R 33.0 min (major) and 36.6 min (minor).

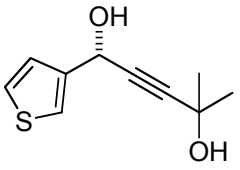
(*S*)-1-Furan-2-yl-4-methyl-pent-2-yne-1,4-diol (4d): Known compound (CAS No. 99186-44-4 (for racemic compound))



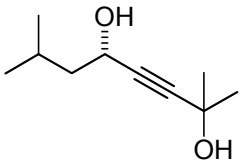
Colorless oil; IR (neat) 3346, 2982, 1379, 1234, 1166 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50 (s, 6H), 3.85 (brs, 1H), 4.29 (brs, 1H), 5.44 (s, 1H), 6.30 (dd, *J* = 1.2, 3.4 Hz, 1H), 6.40 (d, *J* = 3.4 Hz, 1H), 7.36 (d, *J* = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 30.9, 31.0, 57.6, 65.0, 79.4, 90.3, 107.7, 110.3, 142.8, 152.9; ESI-MS *m/z* 203 $[M+Na]^+$; $[\alpha]_D^{25}$ -10.6 (*c* 1.53, $CHCl_3$); HPLC (DAICEL CHIRALCEL OD-H, 2-propanol/hexane 10/90, flow 0.5 mL/min, detection at 254 nm) t_R 28.4 min (minor) and 50.9 min (major).

(*S*)-4-Methyl-1-thiophen-3-yl-pent-2-yne-1,4-diol (4e):

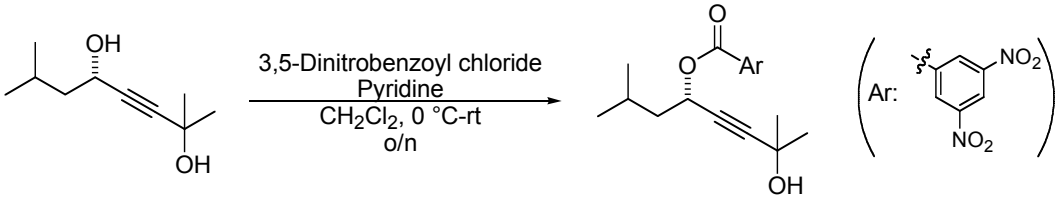
Colorless oil; IR (neat) 3344, 2981, 1628, 1377, 1233, 1164 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.51 (s, 6H), 3.85 (brs, 1H), 4.24 (brs, 1H), 5.46 (s, 1H), 7.16 (d, J = 5.2 Hz, 1H), 7.27 (dd, J = 3.5, 5.2 Hz, 1H), 7.34 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ 31.0, 31.1, 60.0, 65.0, 81.7, 90.3, 122.6, 126.2, 126.4, 141.9; ESI-MS *m/z* 219 $[M+Na]^+$; HRMS calcd. for $C_{10}H_{13}O_2SCs$ $[M+Cs]^+$: 328.9612, found 328.9609; $[\alpha]_D^{25}$ –13.0 (*c* 1.21, $CHCl_3$); HPLC (DAICEL CHIRALCEL OD-H, 2-propanol/hexane 10/90, flow 0.5 mL/min, detection at 254 nm) t_R 14.7 min (major) and 17.0 min (minor).



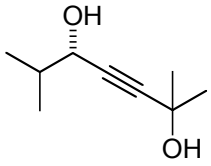
(*S*)-2,7-Dimethyl-oct-3-yne-2,5-diol (4f): Known compound (CAS No. 2398-42-7 (for racemic compound))



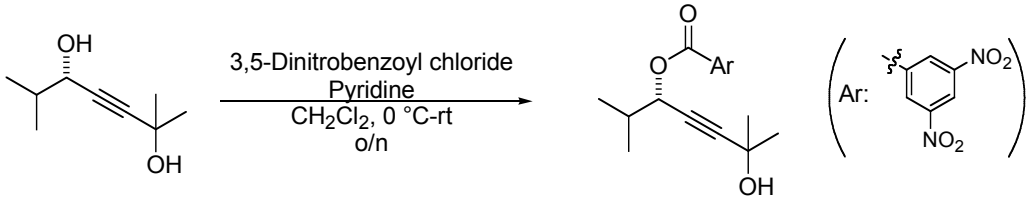
Colorless oil; IR (neat) 3390, 2957, 1366, 1235, 1166 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89-0.92 (m, 6H), 1.49 (s, 6H), 1.51-1.53 (m, 1H), 1.58-1.63 (m, 1H), 1.76-1.84 (m, 1H), 3.27 (brs, 1H), 3.41 (brs, 1H), 4.40 (t, J = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.4, 22.5, 24.7, 31.3, 31.3, 46.7, 60.6, 65.0, 83.4, 89.4; ESI-MS *m/z* 193 $[M+Na]^+$; $[\alpha]_D^{29}$ –11.8 (*c* 1.02, $CHCl_3$); HPLC (after conversion to corresponding 3,5-dinitrobenzoate) (DAICEL CHIRALPAK AD-H, 2-propanol/hexane 10/90, flow 1.0 mL/min, detection at 254 nm) t_R 22.3 min (major) and 24.3 min (minor).



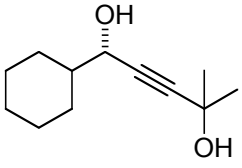
(*S*)-2,6-Dimethyl-hept-3-yne-2,5-diol (4g): Known compound (CAS No. 321903-25-7)



Colorless oil; IR (neat) 3374, 2979, 1380, 1235, 1166 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94-0.97 (m, 6H), 1.48 (s, 3H), 1.49 (s, 3H), 1.79-1.86 (m, 1H), 4.14 (d, J = 5.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 17.5, 18.2, 31.3, 31.4, 34.4, 65.0, 67.5, 81.7, 90.3; ESI-MS *m/z* 157 $[M+Na]^+$; $[\alpha]_D^{31}$ +1.83 (*c* 0.77, $CHCl_3$); HPLC (after conversion to corresponding 3,5-dinitrobenzoate) (DAICEL CHIRALPAK AD-H, 2-propanol/hexane 10/90, flow 1.0 mL/min, detection at 254 nm) t_R 24.2 min (major) and 33.8 min (minor).

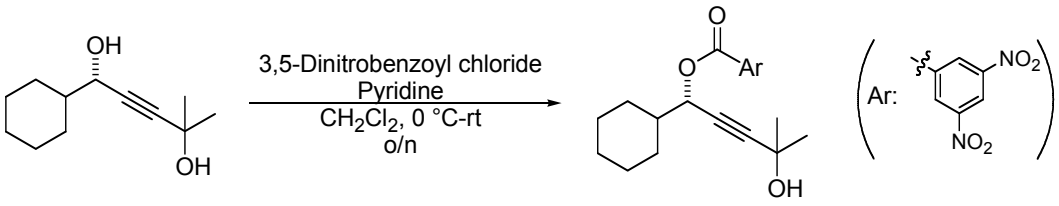


(*S*)-1-Cyclohexyl-4-methyl-pent-2-yne-1,4-diol (4h): Known compound (CAS No. 321855-40-7)

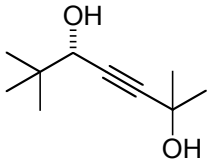


Colorless oil; IR (neat) 3357, 2926, 1450, 1233, 1163, 1084 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96-1.24 (m, 5H), 1.45-1.51 (m, 7H), 1.63-1.83 (m, 5H), 3.27 (brs, 1H), 3.49 (brs, 1H), 4.11 (d, J = 6.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.8, 26.3, 28.1, 28.6, 31.3, 31.3, 43.9, 64.9, 66.8, 82.0, 90.3; ESI-MS *m/z* 219 $[M+Na]^+$; $[\alpha]_D^{29}$

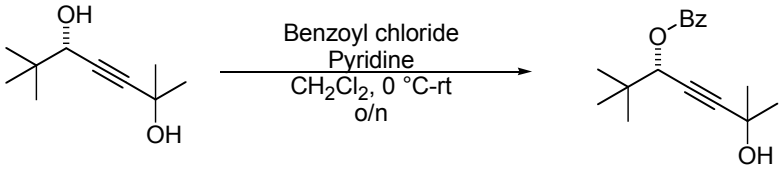
+6.68 (*c* 1.14, $CHCl_3$); HPLC (after conversion to corresponding 3,5-dinitrobenzoate) (DAICEL CHIRALPAK AD-H, 2-propanol/hexane 10/90, flow 1.0 mL/min, detection at 254 nm) t_R 23.5 min (minor) and 47.1 min (major).



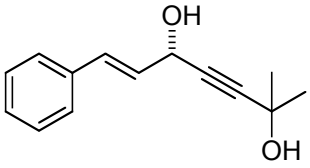
(*S*)-2,6,6-Trimethyl-hept-3-yne-2,5-diol (4i): Known compound (CAS No. 321855-41-8)



Colorless oil; IR (neat) 3374, 2978, 1364, 1233, 1165 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (s, 9H), 1.49 (s, 3H), 1.50 (s, 3H), 2.81 (brs, 1H), 3.11 (brs, 1H), 3.99 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.3, 31.3, 31.4, 35.7, 65.0, 71.0, 81.8, 90.4; ESI-MS *m/z* 193 $[M+Na]^+$; $[\alpha]_D^{31}$ –2.71 (*c* 1.15, $CHCl_3$); HPLC (after conversion to corresponding benzoate) (DAICEL CHIRALPAK AD-H, 2-propanol/hexane 10/90, flow 0.3 mL/min, detection at 254 nm) t_R 18.9 min (minor) and 20.1 min (major).



(*S*)-2-Methyl-7-phenyl-hept-6-en-3-yne-2,5-diol (4j): Known compound (CAS No. 321855-45-2)



Colorless solid; IR (KBr) 3332, 2980, 1449, 1378, 1232, 1164 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.54 (s, 6H), 3.70 (brs, 1H), 3.97 (brs, 1H), 5.07 (d, *J* = 5.7 Hz, 1H), 6.27 (dd, *J* = 5.7, 15.5 Hz, 1H), 6.71 (d, *J* = 15.5 Hz, 1H), 7.22-7.30 (m, 3H), 7.36 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 31.2, 31.2, 62.5, 65.1, 81.1, 91.0, 126.7, 128.0, 128.0, 128.3, 128.4, 128.5, 131.7, 136.0; ESI-MS *m/z* 239 $[M+Na]^+$; $[\alpha]_D^{27}$ +4.58 (*c* 2.88, $CHCl_3$); HPLC (DAICEL CHIRALCEL OD-H, 2-propanol/hexane 10/90, flow 0.5 mL/min, detection at 254 nm) t_R 19.4 min (major) and 21.4 min (minor).

Deprotection:

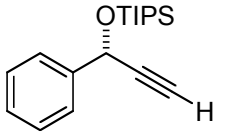
To a 20 mL round-bottomed flask, **4a** (500 mg, 2.63 mmol) and DMF (5.0 mL) was charged. To the resulting solution was added imidazole (537.2 mg, 7.89 mmol) and TIPSCl (0.843 mL, 3.94 mmol) was added at 0 ^oC successively. Then the mixture was warmed up to room temperature and stirred over night. The reaction was quenched with water and extracted with diethyl ether for 3 times. Collected organic layer was washed with water then brine, and dried over Na_2SO_4. After filtration of Na_2SO_4, the organic solvent was evaporated and the residue was purified by flash column chromatography (silica gel, eluent: hexane/Et_2O = 100/0 – 85/15) to give **5a** as a colorless oil.

To a test tube, MS 5A (6.5 mg) and K_2CO_3 (2.81 mg, 25.9 μmol) was charged and dried with heat gun under reduced pressure. After cooling down to room temperature, argon was charged in the test tube and xylenes (0.7 mL) was added. The resulting slurry was stirred for 1 minute, then 18-crown-6 (2.74 mg, 10.4

μmol) was added. Again stirring for 1 minute, **5a** (22.5 mg, 64.8 μmol) in xylenes (0.2 mL) was added by syringe, followed by washing with xylenes 3 times (0.2 mL x 3). The reaction mixture was stirred for 44 h at 145 ^{o}C (oil bath temperature). The reaction was monitored by TLC analysis. After cooling to room temperature, the reaction was quenched with water, extracted with diethyl ether for 3 times. Combined organic layers were washed with brine, and dried over Na_2SO_4. After filtration of Na_2SO_4, the organic solvent was evaporated and the residue was purified by flash column chromatography (silica gel, eluent: hexane 100%) to give **6a** (14.26 mg, 49.4 μmol, 76% yield) as a colorless oil.

Spectral Data

(*R*)-Triisopropyl-(1-phenyl-prop-2-ynyloxy)-silane (6a): Known compound (CAS No. 321855-62-3)



Colorless oil; IR (neat) 2944, 2867, 1093, 1065 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.08 (d, *J* = 7.3 Hz, 9H), 1.13 (d, *J* = 7.0 Hz, 9H), 1.17-1.25 (m 3H), 2.54 (d, *J* = 2.2 Hz, 1H), 5.57 (d, *J* = 2.2 Hz, 1H), 7.29 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.36 (d, *J* = 7.4, 7.7 Hz, 2H), 7.52 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 12.2, 18.0, 64.7, 73.4, 85.2, 125.8, 127.7, 128.3, 141.9; ESI-MS *m/z* 311 $[M+Na]^+$; $[\alpha]_D^{25}$ –5.7 (*c* 1.21, $CHCl_3$).

Mass Spectrometry Analyses:

A flame-dried test tube was charged with (*S*)-BINOL (28.6 mg, 0.1 mmol) and $InBr_3$ (35.4 mg, 0.1 mmol) under Argon atmosphere. To the tube was added dry CH_2Cl_2 (0.5 mL), and the mixture was stirred for 1 h. Then, benzaldehyde (**3a**) (40.7 μL, 0.4 mmol) was added at room temperature. After the resulting solution was stirred for 15 minutes, a portion of the resulting solution (75 μL) was then diluted with CH_2Cl_2 (1.0 mL) and *i*PrOH (0.1 mL). The resulting clear solution was analyzed by Waters micromass ZQ (ESI-MS). ESI-MS analysis was performed in cation mode under the following conditions: capillary: 3.8 kV; cone: 95 V; source temp: 80 °C; desolvation temp.: 100 °C; syringe pump: 10 μL/min. The obtained spectrum is shown in Figure S1.

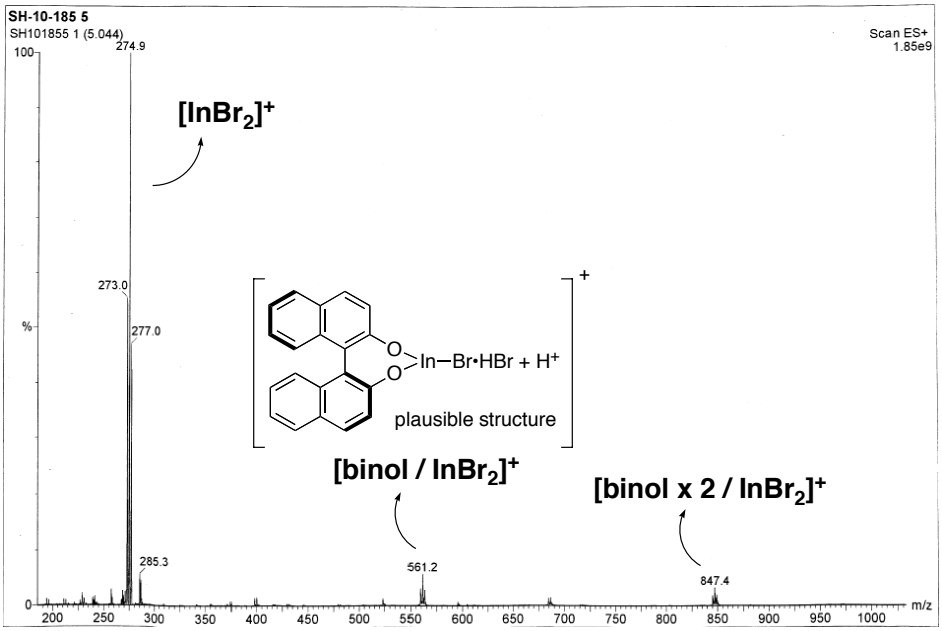


Figure S1. ESI-MS of indium(III)/binol = 1:1 mixture in CH_2Cl_2/*i*PrOH. *m/z*: 275 $[InBr_2]^+$, 561 $[binol/InBr_2]^+$, 847 $[binol\ x\ 2/InBr_2]^+$.

In addition to a major of $InBr_2^+$ (*m/z* 275), peaks corresponding to $[binol/InBr_2]^+$ (*m/z* 561) and $[binol\ x\ 2/InBr_2]^+$ (*m/z* 847) were observed. Although the chart supported the complexation of indium(III) with BINOL, further mechanistic studies are required to elucidate the structure of the $InBr_3$/BINOL complex.