Counterion Effects in the Catalytic Stereoselective Synthesis of 2,3'-Pyrrolidinyl Spirooxindoles

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I. General Information

Materials. Commercially available reagents were obtained from (Aldrich, Acros, AKSci) and used without further purification. Iminooxindoles were synthesized according to the literature. \(^1\) Crotylsilane \(^2\) was synthesized according to the literature procedure. \(^2\) Racemic standards were prepared using a racemic variant of crotylsilane \(^2\).

Dry \(\text{CH}_2\text{Cl}_2\) was dispensed from a solvent purification system that passes \(\text{CH}_2\text{Cl}_2\) through two columns of dry neutral alumina. Anhydrous acetonitrile was purchased from EMD (drisolv® bottle). The following abbreviations are used throughout: ethyl acetate (EtOAc), dichloromethane (DCM), dimethylformamide (DMF), diastereomeric ratio (dr), \(\text{para}-\text{methoxyphenyl} (\text{PMP})\), \(\text{para}-\text{methoxybenzyl} (\text{PMB})\), benzyl (Bn), enantiomeric excess (ee), isopropyl alcohol (IPA), \(N\)-tert-butoxycarbonyl (Boc), sodium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (NaBArF).

Synthesis, Purification, and Analysis. All reactions were performed in oven-dried and Ar-purged glassware (including 4- and 8-mL vials fitted with PTFE caps). All \(^1\)H and \(^13\)C spectra were recorded at ambient temperature at 400 (or 300, 600) and 100 (or 75, 150) MHz, respectively, using a Varian Mercury 300, Varian Inova 400, or Varian 600 spectrometer. The \(^1\)H spectral data are reported as follows: chemical shift in ppm downfield from tetramethylsilane on the \(\delta\) scale, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; sep, septet; m, multiplet; dd, doublet of doublets; dt, doublets of triplets; td, triplet of doublets, and b, broadened), coupling constant (Hz), and integration. Carbon NMR chemical shifts are reported in ppm from tetramethylsilane with the solvent reference employed as the internal standard (deuterochloroform (CDCl\(_3\)) at 77.16 ppm).

Compounds were analyzed for MS (ESI) using an Applied Biosystems Qtrap (Foster City, CA) in the positive ion mode. Source parameters were 5kV spray voltage, with a curtain plate temperature of 275 °C and sheath gas setting of 15. Samples were analyzed via flow injection analysis by injecting 20 µL samples into a stream of 80% MeOH/20% aqueous solution of 0.1% formic acid, flowing at 200 µL/min. When indicated, the progress of reactions was monitored by analytical thin layer chromatography using glass or aluminum backed plates pre-coated with EMD silica gel 60 F254 and visualized with UV light. Flash chromatography was performed either on Acros silica gel 60 Å (0.035-0.070 mm), Aldrich silica gel 150 Å grade 62 (60-200 mesh), or using a CombiFlash Companion system (Teledyne ISCO, Inc.) with pre-packed FLASH silica columns (RediSep, Rf®). All HPLC analyses were performed on a Shimadzu LC-20AB system with a Daicel CHIRALPAK® AD-H column (4.6 x 250 mm, 5 µm), CHIRALPAK® AS-H column (4.6 x 250 mm, 5 µm) or CHIRALPAK® OD-H column (4.6 x 250 mm, 5 µm), each attached to a guard column, at a flow rate of 1 mL/min (isopropanol/hexanes isocratic system) using a Shimadzu SPD-M20A photodiode array detector and 40 °C column oven temperature. Optical rotations were obtained on a Rudolph AUTOPOL IV polarimeter at a wavelength of 589 nm (sodium D line) using a 1.0 dm cell. Specific rotations are reported in degrees per decimeter at 23 °C and the concentrations are given in grams per 100 mL of solvent. Solvents used for optical rotations were MeOH (reagent grade), and CHCl\(_3\) (stabilized with 0.5% - 1% EtOH, and filtered through basic alumina). X-ray powder diffraction was measured on a Bruker D8 Advance diffractometer with Cu Ka radiation (\(\lambda = 1.5418\) Å) operating at 40 kV and 40 mA. Samples were collected on a zero background quartz plate.


II. Experimental Procedures and Characterization Data

a. General Procedures

**General Procedure for the Cu(II)-catalyzed Preparation of Spiropyrrrolidine-oxindoles:**
To an oven dried, Ar-purged 4-mL vial equipped with a stir bar was added activated 4 Å molecular sieves (100 mg/mmol), CuCl$_2$ (20 mol %) and NaBArF (22 mol %) in dry CH$_2$Cl$_2$ (0.1 M). This solution was stirred at room temperature for 0.5-1 h, then cooled to –20 ºC where the appropriate N-Boc-iminooxindole (1 equiv) and crotylsilane (3 equiv) were added to the solution. The reaction was monitored by TLC until full consumption of the iminooxindole was observed, then the reaction mixture was loaded directly onto a flash silica gel column and eluted using a gradient of DCM/EtOAc.

**General Procedure for the deprotection of N-Boc Protected Spiropyrrrolidines:**
Montmorillonite K10 was activated under vacuum at 200 ºC for 1 h. To a flame dried, Ar-purged 4-mL vial charged with a stir bar was added the appropriate N-Boc spiropyrrrolidine (1 equiv), dry toluene (0.24 M) and activated Montmorillonite K10 (1 equiv by weight). The reaction mixture was heated to 110 ºC and stirred overnight. The reaction mixture was cooled to room temperature, filtered through a pad of celite, and the solvent removed under reduced pressure. No further purification was necessary.

**General Procedure for the Montmorillonite-promoted Synthesis of Spiropyrrrolidine-oxindoles:** Montmorillonite K10 was activated under vacuum at 200 ºC for 1 h. To an oven dried, Ar-purged 4-mL vial equipped with a stir bar was added activated montmorillonite K10 (1 equiv by weight) and NaBArF (22 mol %), and then dry CH$_2$Cl$_2$ (0.1 M). Crotylsilane (3 equiv) and N-Boc-iminooxindole (1 equiv) were then added to the solution. The reaction was monitored.
by TLC and when full consumption of the iminooxindole was observed, the reaction mixture was loaded directly onto a flash silica gel column and eluted using a gradient of DCM/EtOAc.

Procedure for montmorillonite-promoted synthesis of spirocarbamate 6:

![Chemical Reaction Diagram]

5-Fluoro-1-methyl-6'-(trimethylsilylmethyl)spiro[trans-indoline-3,4'-[1,3]oxazinane]-2,2'-dione (6): Montmorillonite K10 was activated under vacuum at 200 ºC for 1 h. Imine 4a (0.12 mmol, 32 mg), montmorillonite K10 (1 equiv by weight, 32 mg), NaBArF (0.024 mmol, 21 mg) were added to an Ar-purged flame dried 4-mL vial equipped with a stir bar. The reagents were then dissolved in dry CH₂Cl₂ (0.1 M, 1.2 mL). Next, allyltrimethylsilane (0.36 mmol, 57 µL) was added to the reaction mixture and allowed to stir at room temperature for 2 days until the imine was consumed. At this point the reaction was loaded on to a silica plug and was eluted with 10 mL of 70:30 DCM/EtOAc and concentrated in vacuo. The diastereomeric ratio was determined to be 60:40 based on analysis of the unpurified (filtered) reaction mixture using ¹H NMR spectroscopy. These spectral data match those reported previously in literature.³ trans-6 (major diastereomer): ¹H NMR (600 MHz, CDCl₃) δ 7.17 (dd, J = 7.5, 2.5, 1H), 7.08 (td, J = 8.7, 2.5, 1H), 6.83 (dd, J = 8.7, 4.0, 1H), 5.98 (s, 1H), 4.74 (dddd, J = 13.2, 11.1, 8.8, 1.4, 1H), 3.23 (s, 3H), 2.21 (dd, J = 13.2, 11.1 1H), 1.80 (d, J = 13.2, 1H), 1.23 (dd, J = 11.1, 4.1 1H), 0.96 (dd, J = 13.2, 8.8, 1H), 0.06 (s, 9H).

b. Full Optimization Table For Annulation Reaction:

Table S1. Optimization of conditions for spiropyrrrolidine 3a

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<td>DCM</td>
<td>5 d</td>
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a Reactions run with 20 mol % of catalyst unless otherwise noted. b Reaction performed with 22 mol % of counterion source. c Isolated yield. d The NH spiropyrrrolidine 4a was also isolated in 31% yield. e The NH spiropyrrrolidine 4a was also isolated in 8 % yield. f Reaction gave ~10 % yield of the free NH₂ crotylation S1. g Reaction performed in the presence 20 mol % indapbox. h Reaction performed with 10 mol % CuCl₂ and 11 mol % NaBArF. i Reaction performed with 1.0 equiv of montmorillonite K10
c. Characterization Data for Spiropyrrolidine Scaffolds

**tert-butyl** (3R,3'S,4'R,5'S)-5-fluoro-5'-(2-methoxy-2-oxoethyl)-4'-(4-methoxyphenyl)dimethylsilyl)-1,3'-dimethyl-2-oxospir[ol[3'R,2'S'-pyrrolidin]-1'-carboxylate (3a): The general procedure for the preparation of spiropyrrolidine-oxindoles was followed using 0.0278 g of iminoxindole 1a and 0.083 g of enantioenriched crotylsilane (S)-2 (>95% ee). The reaction was monitored by TLC and stopped after 24 h to give product 3a as a single stereoisomer as judged by \(^1\)H NMR spectroscopy and with 96% ee based on HPLC. The reaction mixture was purified to afford 3a a yellow oil (0.0451 g, 79%). \([\alpha]_D^{23} -53.2^\circ\) (c 0.40, CHCl\(_3\)). Enantiomeric excess was determined using HPLC with a Daicel CHIRALPAK® AD-H column (5% IPA/hexanes), 1.0 mL/min. \(t_R\) (major) = 23.2 min, \(t_R\) (minor) = 8.9 min. 96% ee. \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.47 – 7.42 (m, 2H), 6.92 (dd, \(J = 8.7, 2.2, 1\)H), 6.91 – 6.87 (m, 2H), 6.63 (dd, \(J = 8.5, 4.0, 1\)H), 6.60 (dd, \(J = 7.8, 2.2, 1\)H), 4.54 (ddd, \(J = 10.4, 6.3, 1.8, 1\)H), 3.79 (s, 3H), 3.65 (s, 3H), 3.00 (s, 3H), 2.73 (dd, \(J = 15.6, 6.3, 1\)H), 2.61 (dd, \(J = 15.6, 1.8, 1\)H), 2.14 (dq, \(J = 13.0, 6.7, 1\)H), 1.74 (dd, \(J = 13.0, 10.4, 1\)H), 0.92 (s, 9H), 0.54 (d, \(J = 6.7, 3\)H), 0.39 (s, 3H), 0.37 (s, 3H); \(^13\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 176.0, 172.6, 161.7, 159.6, 145.9, 140.7, 133.7, 132.4, 127.4, 114.4 (d, \(J_{CFC} = 23.5\) Hz), 114.0, 109.9 (d, \(J_{CFC} = 24.5\) Hz), 108.3 (d, \(J_{CFC} = 7.9\) Hz), 72.6, 59.4, 55.2, 51.7, 48.4, 41.5, 35.9, 28.3, 27.9, 26.2, 13.4, -2.8, -3.5; FT IR (neat): 2954, 2372, 2335, 2161, 1708, 1617, 1459 cm\(^{-1}\); LRMS (ESI) \(m/z\) [M + H]\(^+\) caleld for C\(_{30}\)H\(_{40}\)FN\(_2\)O\(_6\)Si, 571.26; found 571.4.

**methyl** 2-((3R,3'S,4'R,5'S)-5-fluoro-4'-(4-methoxyphenyl)dimethylsilyl)-1,3'-dimethyl-2-oxospir[ol[3'R,2'S'-pyrrolidin]-5'-y]acetate (4a): The general procedure for the deprotection of N-Boc-spiropyrrolidines was followed using 0.045 g of spiropyrrolidine 3a and 0.045 g of montmorillonite K10, and spiropyrrolidine was obtained as a yellow oil (0.0335 g, 90%) as a single stereoisomer as judged by \(^1\)H NMR spectroscopy, and 95% ee based on HPLC. \([\alpha]_D^{23} -17.4^\circ\) (c 0.40, CHCl\(_3\)). Enantiomeric excess was determined using HPLC with a Daicel CHIRALPAK® OD-H column (10% IPA/hexanes), 1.0 mL/min. \(t_R\) (major) = 6.0 min, \(t_R\) (minor) = 8.4 min. 95% ee. \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.45 – 7.42 (m, 2H), 6.87 (m, 2H), 6.63 (dd, \(J = 8.6, 2.2, 1\)H), 6.95 (d, \(J = 8.6\) Hz, 3H), 6.89 (dd, \(J = 7.6, 2.4\) Hz, 1H), 6.65 (dd, \(J = 7.6, 3.9\) Hz, 1H), 3.93 (ddd, \(J = 10.5, 9.5, 2.1\) Hz, 1H), 3.82 (s, 3H), 3.60 (s, 3H), 3.10 (s, 3H), 2.86 (dd, \(J = 16.1, 10.5\) Hz, 1H), 2.29 (dd, \(J = 16.1, 2.1\) Hz, 1H), 2.22 (dq, \(J = 13.2, 6.8\) Hz, 1H), 1.70 (dd, \(J = 12.5, 9.5\) Hz, 1H), 0.62 (d, \(J = 6.8\) Hz, 3H), 0.39 (s, 3H), 0.37 (s, 3H); \(^13\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 173.6, 160.7, 159.4 (d, \(J_{CFC} = 24.1\) Hz), 139.7, 135.2, 127.7, 115.0 (d, \(J_{CFC} = 23.4\) Hz), 113.8, 110.9, 110.7, 108.3 (d, \(J_{CFC} = 23.5\) Hz), 114.0, 109.9 (d, \(J_{CFC} = 24.5\) Hz), 108.3 (d, \(J_{CFC} = 7.9\) Hz), 72.6, 59.4, 55.2, 51.7, 48.4, 41.5, 35.9, 28.3, 27.9, 26.2, 13.4, -2.8, -3.5; FT IR (neat): 2954, 2372, 2335, 2161, 1708, 1459 cm\(^{-1}\); LRMS (ESI) \(m/z\) [M + H]\(^+\) caleld for C\(_{30}\)H\(_{40}\)FN\(_2\)O\(_6\)Si, 571.26; found 571.4.
$J_{FCCC} = 7.8$ Hz), 72.8, 57.9, 55.0, 51.5, 49.5, 42.4, 36.8, 26.1, 13.6, −0.01, −3.5, −3.6; FT IR (neat): 3436, 2946, 2164, 1719, 1577, 1497, 1454 cm$^{-1}$; LRMS (ESI) $m/z$ [M + H]$^+$ cale for C$_{25}$H$_{32}$FN$_2$O$_4$Si, 471.21; found 471.4.

methyl 2-((3R,3'S,4'R,5'S)-4'-(4-methoxyphenyl)dimethylsilyl)-1,3'-dimethyl-2-oxospiro[indoline-3,2'-pyrrolidin]-5'-yl)acetate (4b): The general procedure for the synthesis of N-Boc-protected spiropyrolidines was followed using 0.037 g of iminooxindole 1b, and 0.124 g of enantioenriched crotylsilane (S)-2 (>95% ee). The reaction was monitored by TLC and stopped after 24 h to give spiropyrolidine 3b as a single stereoisomer as judged by $^1$H NMR spectroscopy. The reaction mixture was purified by flash chromatography (SiO$_2$, DCM/EtOAc) and product 3b (0.0546 g, 80%) was confirmed by LRMS and $^1$H NMR spectroscopy and directly deprotected. Following the general procedure for the deprotection of spiropyrolidines, 0.0546 g of 3b was heated in the presence of 0.037 g of montmorillonite K10. The reaction was monitored by TLC, and when complete (24 h) the mixture was filtered through a pad of celite using 10% MeOH/DCM. The solvent was removed in vacuo to afford spiropyrolidine 4b as a yellow oil (0.038 g, 85%), which was determined to be a single stereoisomer as judged by $^1$H NMR spectroscopy and with 99% ee based on HPLC. [α]$_D^{23}$ $-$31.9° (c 0.41, CHCl$_3$). Enantiomeric excess was determined using HPLC with a Daicel CHIRALPAK® AD-H column (5% IPA/hexanes), 1.0 mL/min. $t_R$ (major) = 12.6 min, $t_R$ (minor) = 4.7 min. 99% ee. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.46 (d, $J$ = 8.5 Hz, 2H), 7.24 (td, $J$ = 7.8, 1.3 Hz, 1H), 7.14 (dd, $J$ = 7.5, 1.3 Hz, 1H), 7.02 (td, $J$ = 7.5, 1.0 Hz, 1H), 6.92 (d, $J$ = 8.5 Hz, 2H), 6.74 (d, $J$ = 7.8 Hz, 1H), 4.01–3.90 (m, 1H), 3.82 (s, 3H), 3.59 (s, 3H), 3.11 (s, 3H), 2.86 (dd, $J$ = 16.1, 10.5 Hz, 1H), 2.39–2.20 (m, 2H), 1.73 (dd, $J$ = 12.6, 9.6 Hz, 1H), 0.63 (d, $J$ = 6.7 Hz, 3H), 0.39 (s, 3H), 0.37 (s, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 173.9, 161.1, 143.9, 135.4, 135.0, 129.9, 125.7, 123.5, 123.1, 117.7, 114.2, 108.5, 72.7, 64.5, 55.3, 52.1, 49.4, 37.1, 26.4, 19.3, 13.8, −3.2, −3.8; FT IR (neat): 3336, 2956, 2524, 2148, 1980, 1704, 1592, 1502, 1349, 1276, 1157 cm$^{-1}$; LRMS (ESI) $m/z$ [M + H]$^+$ cale for C$_{25}$H$_{33}$N$_2$O$_4$Si, 453.22; found 453.3.

methyl 2-((3R,3'S,4'R,5'S)-5-methoxy-4'-(4-methoxyphenyl)dimethylsilyl)-1,3'-dimethyl-2-oxospiro[indoline-3,2'-pyrrolidin]-5'-yl)acetate (4c): The general procedure for the synthesis of N-Boc-protected spiropyrolidines was followed using 0.087 g of iminooxindole 1c, and 0.262 g of enantioenriched crotylsilane (S)-2 (>95% ee). The reaction was monitored by TLC and after 24 h the reaction mixture was purified by column chromatography (SiO$_2$, DCM/EtOAc) to afford spiropyrolidine 3c (0.140 g, 88%) as a single stereoisomer as determined by $^1$H NMR spectroscopy. Product was confirmed by LRMS and $^1$H NMR spectroscopy and directly...
deprotected. Following the general procedure for the deprotection of spiropyrrolidines, 0.140 g of 3c was heated in the presence of 0.140 g of montmorillonite K10. The reaction was monitored by TLC. After 48 h the reaction was not complete and was filtered through a pad of celite using 10% MeOH/DCM. The mixture was purified via column chromatography (SiO$_2$, DCM/EtOAc) to afford spiropyrrolidine 4c as a yellow oil (0.076 g, 66%), which was a single stereoisomer as judged by $^1$H NMR spectroscopy. [$\alpha$]$_D^{23}$ $-$60.0° (c 0.40, CHCl$_3$). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.47 (d, $J$ = 7.6 Hz, 2H), 6.96 (d, $J$ = 7.6 Hz, 2H), 6.79 (dd, $J$ = 8.4, 2.5 Hz, 1H), 6.75 (d, $J$ = 2.5 Hz, 1H), 6.68 (d, $J$ = 8.4 Hz, 1H), 4.01 – 3.92 (m, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 3.58 (s, 3H), 3.10 (s, 3H), 2.81 (dd, $J$ = 16.0, 10.0 Hz, 1H), 2.37 – 2.26 (m, 2H), 1.66 (dd, $J$ = 12.3, 10.0 Hz, 1H), 0.68 (d, $J$ = 6.8 Hz, 3H), 0.42 (s, 3H), 0.40 (s, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 178.8, 173.7, 160.7, 156.3, 137.1, 135.2, 134.8, 127.6, 113.8, 113.0, 110.0, 108.3, 76.8, 72.9, 64.4, 58.2, 55.7, 55.0, 51.6, 49.6, 42.1, 37.0, 26.0, 13.8, –3.4, –3.7; FT IR (neat): 2952, 2929, 2165, 2046, 1704, 1500, 1353 cm$^{-1}$; LRMS (ESI) m/z [M + H]$^+$ calcd for C$_{26}$H$_{35}$N$_2$O$_3$Si 487.23; found 483.3.

methyl 2-((3R,3'S,4'R,5'S)-5-chloro-4'-(4-methoxyphenyl)dimethylsilyl)-1,3'-dimethyl-2-oxospiro[indoline-3,2'-pyrrolidin]-5'-yl)acetate (4d): The general procedure for the synthesis of N-Boc-protected spiropyrrolidines was followed using 0.088 g of iminoxindole 1d, and 0.262 g of enantioenriched crotylsilane (S)-2 (>95% ee). The reaction was monitored by TLC and after 24h the reaction mixture was purified via flash chromatography (SiO$_2$, DCM/EtOAc) to afford spiropyrrolidine 3d (0.140 g, 81%) as a single diastereomer as judged by $^1$H NMR spectroscopy. Product was confirmed by LRMS and $^1$H NMR spectroscopy and then directly deprotected to access the NH compound. Following the general procedure for the deprotection of spiropyrrolidines, 0.334 g of 3d was heated in the presence of 0.34 g of montmorillonite K10. The reaction was monitored by TLC, and when complete (24 h) the mixture was filtered through a pad of celite using 10% MeOH/DCM. The solvent was removed in vacuo to afford spiropyrrolidine 4d as a brown oil (0.027 g, 99%), which was a single stereoisomer as judged by $^1$H NMR spectroscopy. [$\alpha$]$_D^{23}$ $-$44.8° (c 0.38, CHCl$_3$). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.11 (d, $J$ = 8.1 Hz, 2H), 6.86 (d, $J$ = 8.2 Hz, 1H), 6.78 (s, 1H), 6.58 (d, $J$ = 8.1 Hz, 2H), 6.32 (d, $J$ = 8.2 Hz, 1H), 3.62 - 3.56 (m, 1H), 3.47 (s, 3H), 3.25 (s, 3H), 2.75 (s, 3H), 2.49 (dd, $J$ = 15.6, 10.0 Hz, 1H), 2.20 (bs, 1H), 1.93 (d, $J$ = 15.6 Hz, 1H), 1.90 (dd, $J$ = 12.8, 6.7 Hz, 1H), 1.35 (dd, $J$ = 10.0, 2.6 Hz, 1H), 0.27 (d, $J$ = 6.7 Hz, 3H), 0.05 (s, 3H), 0.03 (s, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 179.0, 173.4, 160.7, 142.5, 135.2, 133.1, 128.5, 128.04, 127.97, 123.2, 113.8, 108.6, 72.7, 57.8, 55.0, 51.4, 49.5, 42.8, 36.7, 26.0, 13.6, –3.49, –3.52; FT IR (neat): 3403, 2952, 2215, 2046, 1710, 1608, 1245 cm$^{-1}$; LRMS (ESI) m/z [M + H]$^+$ calcd for C$_{25}$H$_{32}$ClN$_2$O$_4$Si 487.18; found 487.2.
methyl 2-((3R,3'S,4'R,5'S)-4'-(4-methoxyphenyl)dimethylsilyl)-3'-methyl-2-oxo-1-phenylspiro[indoline-3,2'-pyrrolidin]-5'-yl)acetate (4e): The general procedure for the synthesis of Boc-protected spiropyrrolidines was followed using 0.064 g of iminoxindole 1e, and 0.174 g of enantioenriched crotylsilane (S)-2 (>95% ee). The reaction was monitored by TLC and after 24h the reaction mixture was purified via flash chromatography (SiO$_2$, DCM/EtOAc) to afford spiropyrrolidine 3e (0.108 g, 88%) as a single stereoisomer as determined by $^1$H NMR spectroscopy. Product was confirmed by LRMS and $^1$H NMR spectroscopy and then directly deprotected to access the NH compound. Following the general procedure for the deprotection of spiropyrrolidines, 0.140 g of 3e was heated in the presence of 0.108 g of montmorillonite K10. The reaction was monitored by TLC, and when complete the mixture was filtered through a pad of celite using 10% MeOH/DCM. The solvent was removed in vacuo to afford spiropyrrolidine 4e as a yellow oil (0.072 g, 80%), which was a single stereoisomer as judged by $^1$H NMR spectroscopy.

$[^a]_D$^23 = 18.1$^\circ$ (c 0.39, CHCl$_3$). $^1$H NMR (600 MHz, CDCl$_3$) δ 7.56 – 7.46 (m, 2H), 7.44 (d, $J$ = 8.0 Hz, 2H), 7.38 (t, $J$ = 8.0 Hz, 1H), 7.34 (d, $J$ = 8.6 Hz, 2H), 7.26 (d, $J$ = 5.2 Hz, 1H), 7.19 (t, $J$ = 7.8 Hz, 1H), 7.08 (t, $J$ = 7.8 Hz, 1H), 6.92 (d, $J$ = 8.6 Hz, 2H), 6.77 (d, $J$ = 7.8 Hz, 1H), 4.03 – 3.92 (m, 1H), 3.82 (s, 3H), 3.57 (s, 3H), 2.84 – 2.74 (m, 2H), 2.25 (d, $J$ = 13.0, 6.7 Hz, 1H), 2.25 (d, $J$ = 6.7 Hz, 3H), 0.88 (s, 3H), 0.38 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 182.5, 177.2, 164.2, 147.3, 138.3, 138.0, 134.4, 133.0, 132.1, 131.7, 131.3, 129.9, 126.7, 126.4, 117.3, 112.6, 76.3, 61.3, 58.6, 55.0, 54.0, 46.3, 40.1, 17.2, 0.2, 0.00; FT IR (neat): 2954, 2892, 2385, 2524, 1997, 1724, 1592, 1500, 1612, 1463, 1369, 1276, 1247, 1180, 1126, 1047, 910 cm$^{-1}$; LRMS (ESI) m/z [M + H]$^+$ calcd for C$_{30}$H$_{35}$N$_2$O$_4$Si, 515.23; found 515.3.

methyl 2-((3R,3'S,4'R,5'S)-1-benzyl-4'-(4-methoxyphenyl)dimethylsilyl)-3'-methyl-2-oxo-1-phenylspiro[indoline-3,2'-pyrrolidin]-5'-yl)acetate (4f): The general procedure for the synthesis of Boc-protected spiropyrrolidines was followed using 0.0124 g of iminoxindole 1f, and 0.040 g of enantioenriched crotylsilane (S)-2. The reaction was monitored by TLC and after 24h the reaction mixture was purified via flash chromatography (SiO$_2$, DCM/EtOAc) to afford spiropyrrolidine 3f (0.0153 g, 53%) as a single stereoisomer as determined by $^1$H NMR spectroscopy. Product was confirmed by LRMS and $^1$H NMR. Following the general procedure for the deprotection of spiropyrrolidines, 0.0153 g of 3f was heated in the presence of 0.015 g of montmorillonite K10. The reaction was monitored by TLC, and when complete (24h) the mixture was filtered through a pad of celite using 10% MeOH/DCM. The solvent was removed in vacuo to afford spiropyrrolidine 4f as a yellow oil (0.0098 g, 93%), which was a single...
stereoisomer as judged by \(^1\)H NMR spectroscopy. \([\alpha]_D^{23}\) -32.0° (c 0.40, CHCl\(_3\)). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.47 (d, \(J = 8.6\) Hz, 2H), 7.32-7.22 (m, 5H), 7.17 – 7.07 (m, 2H), 6.99 (t, \(J = 8.0\) Hz, 1H), 6.92 (d, \(J = 8.6\) Hz, 2H), 6.63 (d, \(J = 7.7\) Hz, 1H), 5.10 (d, \(J = 15.6\) Hz, 1H), 4.52 (d, \(J = 15.6\) Hz, 1H), 3.98 (td, \(J = 12.6, 9.7\) Hz, 1H), 0.69 (d, \(J = 6.8\) Hz, 3H), 0.40 (s, 3H), 0.40 (s, 3H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 183.0, 177.1, 164.1, 146.8, 139.6, 138.7, 134.6, 132.13, 132.10, 131.6, 130.9, 126.1, 123.0, 117.2, 112.2, 75.9, 61.2, 58.5, 54.9, 53.1, 47.3, 46.4, 40.3, 17.5, 0.03, 0.00; FT IR (neat): 2958, 2524, 2362, 2335, 2159, 1712, 1592, 1502 cm\(^{-1}\); LRMS (ESI) \(m/z\) [M + H]\(^+\) calcld for C\(_{31}\)H\(_{37}\)N\(_2\)O\(_4\)Si, 529.72; found 529.5.

methyl 2-((3R,4'R,5'S)-5-fluoro-1-methyl-2-oxo-4'-(trimethylsilyl)spiro[indoline-3,2'-pyrrolidin]-5'-yl)acetate (8): To an oven dried, Ar-purged 4-mL vial equipped with a stir bar was added activated 4 Å molecular sieves (10 mg), ScCl\(_3\) (3 mg and NaBArF (19.6 mg in dry CH\(_2\)Cl\(_2\) (0.1 M). This solution was stirred at room temperature for 0.5-1 h. Iminooxindole 1a (28 mg) and allylsilane 7 (56 mg) were then added to the solution. The reaction was monitored by TLC until full consumption of the iminooxindole was observed (19 h), then the reaction mixture was loaded directly onto a flash silica gel column and eluted using a gradient of DCM/EtOAc to afford the spiropyrrrolidine as a yellow oil (1.96 mg, 42%) as a single diastereomer as determined by \(^1\)H NMR spectroscopy. Product was confirmed by LRMS and \(^1\)H NMR spectroscopy. NOTE: No allylation was observed. Next, the general procedure for the deprotection of spiropyrrrolidines was followed using 1.96 mg of the spiropyrrrolidine and 19.6 mg of montmorillonite k10 to give compound 8 as a yellow oil (0.0154 g, 99%) after 24 h, which was a single diastereomer as judged by \(^1\)H NMR spectroscopy. \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.00 (dd, \(J = 7.7, 2.6\) Hz, 1H), 6.92 (td, \(J = 9.0, 2.6\) Hz, 1H), 6.66 (dd, \(J = 9.0, 4.0\) Hz, 1H), 3.85 (ddd, \(J = 12.6, 9.9, 2.7\) Hz, 1H), 3.63 (s, 3H), 3.11 (s, 3H), 2.70 (dd, \(J = 16.5, 9.9\) Hz, 1H), 2.64 (dd, \(J = 16.5, 2.7\) Hz, 1H), 2.24 (dd, \(J = 13.2, 7.2\) Hz, 1H), 1.87 – 1.76 (m, 1H), 1.71 (ddd, \(J = 13.8, 10.2, 7.2\) Hz, 1H), 1.66 (ddd, \(J = 13.5, 10.4, 7.1\) Hz, 1H), 0.05 (s, 9H); \(^13\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 180.6, 173.4, 159.5 (d, \(J_{FCC} = 241.2\) Hz), 139.4, 135.2, 114.7 (d, \(J_{FCCC} = 23.5\) Hz), 110.7 (d, \(J_{FCCC} = 24.7\) Hz), 108.4 (d, \(J_{FCCC} = 8.0\) Hz), 67.8, 58.9, 51.8, 42.4, 42.2, 32.0, 26.5, -2.3; FT IR (neat): 3366, 2960, 2178, 1715, 1826, 1493, 1475 cm\(^{-1}\); LRMS (ESI) \(m/z\) [M + H]\(^+\) calcld for C\(_{18}\)H\(_{26}\)FN\(_2\)O\(_3\)Si, 365.50; found 365.1.

e. Selected Characterization Data for Crotylation Side Products

During the course of this study, two crotylation side-products were identified under several of the Lewis acid-catalyzed conditions. Selected characterization data is provided below.
methyl \((S,E)-5-((R)-3-(\text{tert}-\text{butoxycarbonyl})\text{amino})-5\text{-fluoro-1-methyl-2-oxoindolin-3-yl})\text{hex-3-enoate (S1)}\): During the optimization study, this product was isolated as a colorless oil for several of the conditions. To an oven dried, Ar-purged 4-mL vial equipped with a stir bar was added activated 4 Å molecular sieves (10 mg), CuCl \(_2\) (2.7 mg) and NaBArF (19.6 mg) in dry CH\(_2\)Cl\(_2\) (0.1 M). This solution was stirred at room temperature for 0.5-1 h. The iminooxindole \(1\) (27.8 mg) and crotylsilane \((S)-2\) (83 mg) were then added to the solution at room temperature. The reaction was monitored by TLC until full consumption of the iminooxindole was observed (2 h), then the reaction mixture was loaded directly onto a flash silica gel column and eluted using a gradient of DCM/EtOAc to give annulation product \(3\) as the major product and crotylation product \(5\) as a minor product as a colorless oil (11 mg, 27%).

\[ ^1H\text{ NMR (600 MHz, CDCl}_3\] δ 7.24 (dd, \(J = 5.9, 4.5\) Hz, 1H), 7.02 – 6.95 (m, 1H), 6.72 (dd, \(J = 8.4, 4.5\) Hz, 1H), 5.73 (dt, \(J = 15.1, 6.7\) Hz, 1H), 5.66 (dd, \(J = 15.1, 9.4\) Hz, 1H), 5.31 (bs, 1H), 3.70 (s, 3H), 3.19 (s, 3H), 3.14 – 3.07 (m, 2H), 2.81 – 2.42 (m, 1H), 1.25 (s, 9H), 0.80 (d, \(J = 6.9\) Hz, 3H); LRMS (ESI) \(m/z [M + H]^+\) calcld for C\(_{21}\)H\(_{28}\)N\(_2\)O\(_5\) 407.30; found 407.0.

methyl \((E)-5-(3\text{-amino-5-fluoro-1-methyl-2-oxoindolin-3-yl})\text{hex-3-enoate (S1)}\): To a flame dried 4 mL vial equipped with a stir bar was added 0.0278 g of iminooxindole \(1\), 1 mL of CH\(_2\)Cl\(_2\) (0.1M) 0.083 g of crotylsilane \((S)-2\). The reaction was cooled to -78 °C, and 0.017 mL of TfOH was added. This reaction was allowed to slowly warm up to – 60 °C in a cryocool. Upon completion (as determined by TLC), the reaction was placed directly on the silica, and eluted with DCM/EtOAc to give 0.003 g of S1. \(^1H\text{ NMR (400 MHz, CDCl}_3\) δ 7.33 (dd, \(J = 7.7, 2.6\) Hz, 1H), 7.10 (td, \(J = 8.8, 2.6\) Hz, 1H), 6.80 (dd, \(J = 8.8, 4.0\) Hz, 1H), 6.02 – 5.78 (m, 1H), 5.73 (bs, 2H), 5.54 (dd, \(J = 15.4, 9.6\) Hz, 1H), 3.66 (s, 3H), 3.15 (s, 3H), 3.06 (d, \(J = 6.6\) Hz, 2H), 2.99 – 2.86 (m, 1H), 0.86 (d, \(J = 6.9\) Hz, 5H); LRMS (ESI) \(m/z [M + H]^+\) calcld for C\(_{16}\)H\(_{20}\)FN\(_2\)O\(_3\), 307.15; found 307.3.

**f. nOe Experiments to Determine Relative Stereochemistry for spiropyrrolidine 3**

One dimensional nOe experiments were performed on \(N\)-Boc-protected annulation product \(3\) using a 400 MHz NMR spectrophotometer. Proton \(a\) was found to interact with both protons \(b\) and \(c\), indicating that they are on the same face of the pyrrolidine ring system. The reaction is highly stereoselective and the absolute stereochemistry was assigned based on the starting configuration of the crotylsilane, which has been previously demonstrated and attributed to an anti-\(S_E\) addition.
f. Selected HPLC Spectra

Racemic Standard for 3a:

Enantiomerically-enriched 3a (96% ee):
Racemic standard for 4a:

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Enantiomerically-enriched 4a (95% ee):

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Racemic standard for 4b:

Enantiomerically-enriched 4b (99% ee):
III. $^1$H and $^{13}$C NMR Spectra

3a, 600 MHz, CDCl$_3$
Electronic Supplementary Material (ESI) for Chemical Communications
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3a, 150 MHz, CDCl₃
4a, 600 MHz, CDCl₃
4a, 150 MHz, CDCl₃
4b, 400 MHz, CDCl₃
Electronic Supplementary Material (ESI) for Chemical Communications
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**4b**, 100 MHz, CDCl₃
Electronic Supplementary Material (ESI) for Chemical Communications
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4c, 600 MHz, CDCl₃
4d, 600 MHz, CDCl₃
4d, 150 MHz, CDCl₃
**4e, 600 MHz, CDCl₃**
Electronic Supplementary Material (ESI) for Chemical Communications
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$4e$, 150 MHz, CDCl$_3$
Electronic Supplementary Material (ESI) for Chemical Communications
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4f, 400 MHz, CDCl₃
4f, 100 MHz, CDCl₃
Electronic Supplementary Material (ESI) for Chemical Communications
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8, 600 MHz, CDCl₃
Electronic Supplementary Material (ESI) for Chemical Communications
This journal is © The Royal Society of Chemistry 2013
S1, 600 MHz, CDCl₃