Internal Lewis Acid Assisted Ureas: Tunable Hydrogen Bond Donor Catalysts

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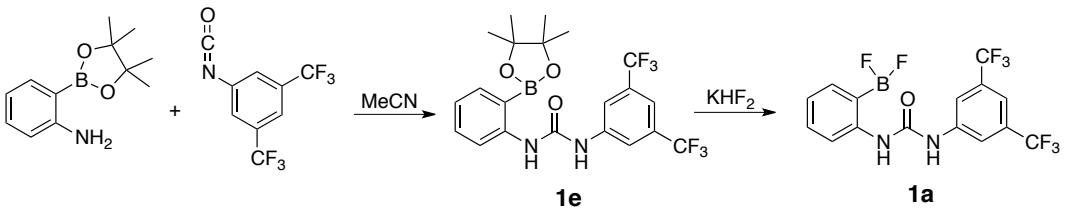
General Methods:

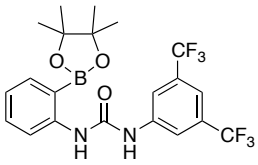
Benzene was freshly distilled from sodium, methanol was freshly distilled from calcium hydride, and acetone was distilled from calcium carbonate prior to use. Methylene chloride, tetrahydrofuran, toluene, acetonitrile, and ether were purified by passage through a bed of activated alumina.[1] Purification of reaction products was carried out by flash chromatography using Aldrich 60 Å (40 - 63 μm). Analytical thin layer chromatography was performed on Analtech Uniplate 250 μm silica gel plates. Visualization was accomplished with UV light and potassium permanganate or ceric ammonium molybdate stains followed by heating. Melting points (**mp**) were obtained on a Thermo Scientific Mel-temp apparatus and are uncorrected. Infrared spectra (**IR**) were obtained on a Perkin Elmer Spectrum 100R spectrophotometer. Infrared spectra for liquid products were obtained as a thin film on a NaCl disk, and spectra for solid products were collected by preparing a KBr pellet containing the title compound. Proton nuclear magnetic resonances (**^{1}H NMR**) were recorded in deuterated solvents on a Bruker Avance DPX 400 (400 MHz) spectrometer. Chemical shifts are reported in parts per million

(ppm, δ) using the solvent as internal standard ($CHCl_3$, δ 7.26; MeOH, δ 3.31; DMSO, δ 2.50) ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), or quartet (q). Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m) or broad (br). Coupling constants are reported in Hertz (Hz). Proton-decoupled carbon (**^{13}C-NMR**) spectra were recorded on a Bruker Avance DPX 400 (100 MHz) spectrometer and are reported in ppm using the solvent as an internal standard ($CDCl_3$ - δ 77.0; MeOD, δ 49.0; DMSO, δ 39.5). Proton decoupled fluorine (^{19}F NMR) spectra were recorded on a Bruker Avance DPX 400 spectrometer and are reported in ppm using $CF_3C_6H_5$ as an external standard (-63.72). Boron spectra (^{11}B-NMR) were recorded on a Bruker Avance DPX 500 spectrometer and are reported in ppm using BF_3•OEt_2 as an external standard (0.00). Electrospray mass spectra (**ESI-MS**) were obtained using a Bruker MicrOTOF Mass Spectrometer. Gas Chromatography (**GC**) analysis data were obtained on Agilent 6850 Series GC System with a 7673 Series Injector. An HP-1 capillary 30 m column was employed (19091Z-413E). Unless otherwise noted, all other commercially available reagents and solvents were purchased from Aldrich and used without further purification.

Procedures for the Preparation of Internal Lewis Acid Assisted Ureas:

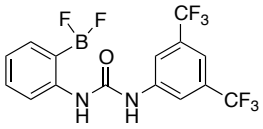
Preparation of boronate ureas 1a and 1e:





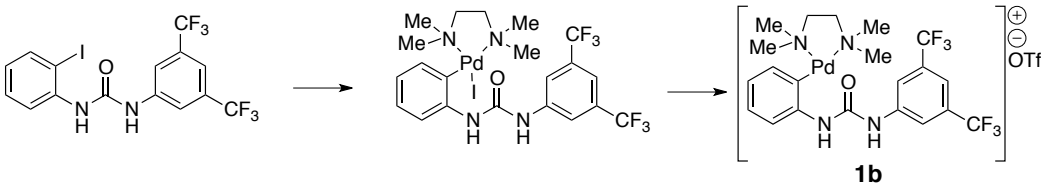
Synthesis of boronate urea pinacol ester 1e[2]: A flame-dried round bottom flask under N_2 was charged with 2-aminophenyl boronic acid pinacol ester (600 mg, 2.74 mmol) and acetonitrile (30 mL). Next, 3,5-bis-trifluoromethylphenyl isocyanate (0.474 mL, 2.74 mmol) was introduced to the reaction flask dropwise by syringe. Shortly after addition of the isocyanate, a white precipitate began to form and the reaction was allowed to stir at 23 °C for 4 h. The precipitate was isolated by vacuum filtration and washed with hexanes (2 x 20 mL) to afford boronoate urea pinacol ester **1e** as a white solid (1.08 g, 83%). R_f = 0.94 (4:4:1 ethyl acetate/hexanes/methanol);

mp 215.2 – 216.9 ºC; IR (NaBr) 3415, 3132, 2985, 1640, 1600, 1581, 1476, 1184, 1129, cm^{-1}; ^{1}H NMR (400 MHz, DMSO d_6) δ 9.93 (br s, 1H); 9.19 (br s, 1H); 8.16 (s, 2H); 7.69 (s, 1H); 7.52-7.50 (m, 1H); 7.42-7.34 (m, 2H); 7.08-7.04 (m, 1H); 1.24 (s, 12H); ^{13}C NMR (100 MHz, DMSO d_6) δ 154.0, 142.2, 141.7, 134.7, 131.2 (q, J = 33 Hz, $C$$CF_3$), 130.8, 123.8 (q, J = 271 Hz, CF_3), 123.4, 119.7, 119.4 (d, J = 6 Hz, CF_3), 155.61-155.5 (m), 83.0, 25.5 (the carbon bonded to boron was not seen due to broadening)[3]; ^{11}B NMR (160 MHz, DMSO d_6) δ 26.0 (br s); HRMS (ESI): Mass calculated for $C_{21}H_{21}BF_6N_2O_3$ $[M+H]^+$, 475.1622. Found $[M+H]^+$, 475.1614.

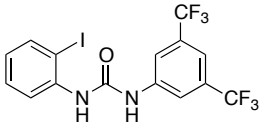


Synthesis of difluoroboryl urea 1a[4]: A flame-dried round bottom flask under N_2 was charged with boronate urea pinacol ester **1e** (2.18 g, 4.6 mmol) and MeOH (30 mL). Next, KHF_2 (4.5 M in water, 3.07 mL, 13.8 mmol) was introduced to the reaction flask dropwise by syringe. The resulting white, heterogenous mixture was heated to 50 °C resulting in a clear and colorless solution. After 2 h at 50 °C, the reaction was cooled to 23 °C and concentrated. The white solid was filtered and washed with water (3 x 50 mL) to afford the potassium trifluoroboryl urea salt. This salt (1.95 g, 4.3 mmol) was dissolved in ethyl acetate (15 mL) and extracted with water (2 x 5 mL). The organic layer was dried with sodium sulfate and concentrated to afford a white solid that was then dissolved in a minimal volume of boiling acetonitrile. The solution was allowed to cool to room temperature and then placed in an ice bath. The resulting precipitate was removed and the filtrate concentrated to afford difluoroboryl urea **6** (1.23 g, 3.11 mmol, 72%) as a white powder. R_f = 0.74 (4:4:1 ethyl acetate/hexanes/methanol); mp 205.3 – 205.9 ºC; IR (NaBr) 3628, 3345, 2986, 1741, 1671, 1585, 1479, 1187, 1128, cm^{-1}; ^{1}H NMR (400 MHz, DMSO d_6) δ 11.27 (br s, 1H); 10.65 (br s, 1H); 8.11 (s, 2H); 7.96 (s, 1H); 7.42-7.40 (m, 1H); 7.32-7.28 (m, 1H); 7.15-7.10 (m, 1H); 1.24; ^{13}C NMR (100 MHz, DMSO d_6) δ 154.5, 138.1, 137.4, 131.5, 131.2, 130.9, 130.6, 128.2, 124.7, 123.0, 123.0 (q, J = 267 Hz, CF_3), 118.4, 115.4; ^{11}B NMR (160 MHz, DMSO d_6) δ 3.63 (br s); ^{19}F NMR (376 MHz, DMSO d_6) δ –61.7 (s, 6F), -132.8 (s, 1F), -132.9 (s, 1F); HRMS (ESI): Mass calculated for $C_{21}H_{21}BF_6N_2O_3$ $[M+H]^+$, 419.0572. Found $[M+H]^+$, 419.0580.

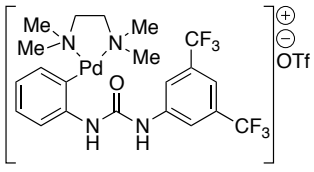
Preparation of palladacycle urea 1b:



1b



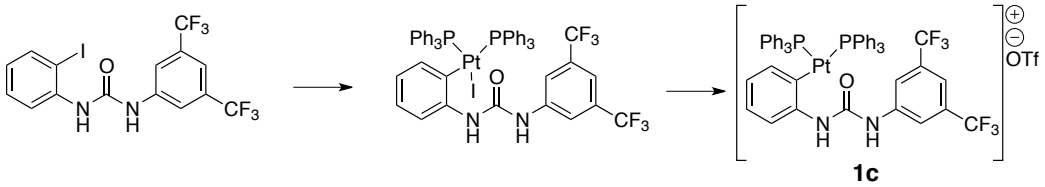
Synthesis of 1-(3,5-bis(trifluoromethyl)phenyl)-3-(2-iodophenyl)urea[5]: A 50 mL round-bottom flask equipped with a stir bar was charged with 2-iodoaniline (1.0 g, 4.6 mmoL) and 10 mL of diethyl ether. 3,5-Bis(trifluoromethyl)phenyl isocyanate (0.79 mL, 4.6 mmol) was added dropwise and a white precipitate formed. After 12 hr, the reaction mixture was concentrated under reduced pressure and then diluted with hexanes (10 mL). Vacuum filtration followed by rinsing with hexanes (3 x 1 mL) gave 1-(3,5-bis(trifluoromethyl)phenyl)-3-(2-iodophenyl)urea as a white solid (1.98 g, 91%); IR (film) 3319, 3046, 1649, 1585, 1538, 1469, 1436, 1384, 1298, 1279, 1176, 1135, 1123, 1015, 887, 846, 752, 698, 682 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 10.06 (s, 1H); 8.12 (s, 2H); 8.11 (s, 1H); 7.86 (dd, J = 7.9, 1.3 Hz, 1H); 7.80 (dd, J = 8.1, 1.3 Hz, 1H), 7.63 (s, 1H); 7.44-7.29 (m, 1H); 6.90 (dt, J = 1.4, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 152.4, 141.7, 139.2, 139.0, 130.8 (q, J = 32.6 Hz, CCF_3), 128.7, 126.0, 123.9, 123.3 (q, J = 272.7 Hz, CCF_3), 117.8, 114.5, 92.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.0 (s, 6F); HRMS (ESI): Mass calculated for $C_{15}H_9F_6IN_2ONa$ $[M+Na]^+$, 496.9556. Found $[M+Na]^+$, 496.9553.



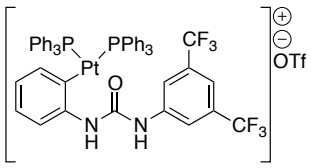
Synthesis of palladacycle urea 1b[5]: A 50 ml flame-dried round-bottom flask equipped with a stir bar was charged with bis(dibenzylideneacetone) palladium(0) (2.67 g, 4.64 mmol) and dry THF (20 mL) under an argon atmosphere. *N*,*N*,*N*',*N*'-tetramethylethylenediamine (TMEDA) (0.703 g, 0.907 mL, 6.05 mmol) was added and the reaction mixture stirred for 15 min. A color change from deep purple to orange-red was observed. A solution of 1-(3,5-bis(trifluoromethyl)phenyl)-3-(2-iodophenyl)urea (2.86 g, 6.0 mmol) (see above for preparation) in 10 mL dry THF was added in one portion and the reaction mixture turned dark green. After 3 h, the reaction mixture was concentrated under reduced pressure, and the resulting orange solid was dissolved in dichloromethane and filtered through

$MgSO_4$. The filtrate was concentrated under reduced pressure and the resulting residue was soaked in hexanes/diethyl ether (95:5, 300 mL) for 30 min and then filtered. The resulting orange solid was recrystallized from hot benzene to give pale yellow crystals suitable for X-ray crystallography (2.90 g, 91%); IR (film) 3331, 2975, 2890, 2842, 1696, 1618, 1559, 1507, 1474, 1436, 1385, 1278, 1178, 1131, 1178, 1131, 1033, 998, 954, 881, 849, 802, 750, 682 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 2H); 7.77 (s, 1H); 7.65 (s, 1H); 7.41-7.37 (m, 1H); 7.32 (dd, *J* = 7.9, 1.3 Hz, 1H); 7.24 (dd, *J* = 7.6, 1.4 Hz, 1H); 6.75-6.69 (m, 1H); 6.55 (dt, *J* = 7.4, 1.3 Hz, 1H); 2.86-2.47 (m, 4H); 2.74 (s, 3H); 2.72 (s, 3H); 2.40 (s, 3H); 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 141.3, 140.5, 137.0, 134.8, 131.5 (q, *J* = 33.0 Hz, CCF_3); 124.3, 123.7, 123.6 (q, *J* = 273 Hz, CCF_3), 123.3, 118.7, 115.0, 62.5, 58.7, 50.9, 50.4, 50.2, 49.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9 (s, 6F). This intermediate (1.0 g, 1.47 mmol) was placed in a 20 mL dry glass vial equipped with a stir bar and dissolved in acetone (5 mL) under an argon atmosphere. Thallium (I) triflate (0.52 g, 1.47 mmol) was added and a yellow precipitate immediately formed. The reaction mixture stirred under argon for 1.5 h and was subsequently filtered through Celite®, concentrated in vacuo to reveal a yellow powder and recrystallized in benzene/acetone (90:10) to give **1b** as yellow prisms suitable for X-ray crystallography (0.99 g, 94%) IR (film) 3276, 3121, 2925, 1603, 1567, 1466, 1385, 1279, 1172, 1135, 1028, 958, 889, 852, 804, 754, 682 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.1 (s, 1H); 9.95 (s, 1H); 7.91 (s, 2H); 7.61 (s, 1H); 7.15-7.05 (m, 1H); 7.05-6.90 (m, 3H); 2.89-2.82 (m, 2H); 2.81 (s, 6H); 2.67-2.60 (m, 2H); 2.46 (s, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 157.1, 140.3, 136.8, 134.9, 133.6 (q, *J* = 33.6 Hz, CCF_3); 127.0, 126.9, 125.3, 124.5 (q, J = 272 Hz, CCF_3), 123.6, 121.8 (q, *J* = 318 Hz, SCF_3), 119.3, 116.6, 66.8, 58.2, 51.7, 47.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9 (s, 6F); -78.3 (s, 3F).

Preparation of platinacycle urea 1c:

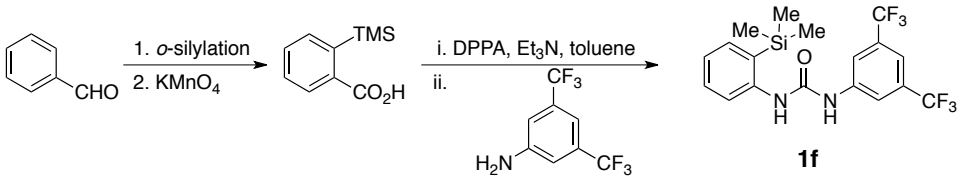


1c

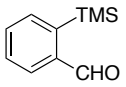


Synthesis of platinacycle 1c: Guided by the procedure of Rendina and coworkers,[6] a 150 mL flame-dried round-bottom flask equipped with a stir bar was charged with 1-(3,5-bis(trifluoromethyl)phenyl)-3-(2-iodophenyl) urea (0.206 g, 0.434 mmol) and dry toluene (60 mL) under a nitrogen atmosphere at 100 °C. Tetrakis(triphenylphosphine)platinum[7] (0.450 g, 0.362 mmol) was added, and a color change from yellow to yellow-orange was observed. After 18 h, the reaction mixture was removed from heat and concentrated under reduced pressure. The resulting yellow-orange solid was dissolved in methylene chloride and a yellow precipitate formed upon the addition of hexanes. The solid was filtered to give a light orange-yellow solid intermediate (0.417 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.64 (m, 3H); 7.54-7.28 (m, 31H); 6.90 (d, J =7.6 Hz, 1H); 6.67 (d, J = 8.0 Hz, 1H); 6.55 (t, J = 7.2 Hz, 1H); 6.14 (t, J = 7.4 Hz, 1H); 5.98 (s, 1H). The above intermediate (0.377 g, 0.315 mmol) was placed in a 50 mL flame-dried round-bottom flask equipped with a stir bar and dissolved in methylene chloride (20 mL) under an argon atmosphere. A solution of silver (I) triflate (0.0810 g, 0.315 mmol) in acetone (2 mL) was added and the reaction mixture was stirred in the dark at 23 °C for 19 h. The AgI precipitate was removed by filtration through a pad of Celite® and the filtrate was concentrated under reduced pressure. The resulting purple solid was recrystallized from hot isopropanol to give the product as pale yellow crystals suitable for X-ray crystallography (0.159 g, 39%) IR (film) 3424, 3059, 1643, 1593, 1435, 1379, 1279, 1029 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.92 (s, 1H); 9.78 (s, 1H); 7.73-7.72 (m, 6H); 7.24-7.05 (m, 28 H); 6.78 (t, J =7.8 Hz, 1H); 6.71-6.62 (m, 1H); 6.19 (t, J = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 138.1 (dd, J = 230.1, 6.5 Hz), 137.9, 135.3, 134.2, 134.0, 133.9, 131.3 (q, J = 33.4 Hz, CCF_3), 131.0 (dd, J = 56.4, 2.3 Hz), 130.6 , 129.8 (d, J = 47.0 Hz), 128.5 (d, J = 1.0 Hz), 128.4 (dd, J = 66.9, 2.3 Hz), 128.4, 122.6 (q, J = 274 Hz, CCF_3), 125.9, 124.2 (d, J = 4.8 Hz), 120.5 (q, J = 319 Hz, SCF_3), 120.2, 116.8 (d, J = 4.5 Hz) ^{19}F NMR (376 MHz, $CDCl_3$) δ –63.3 (s, 6F); –78.2 (s, 3F); ^{31}P NMR (170 MHz, $CDCl_3$) δ 24.6 (d, J = 16.9 Hz), 14.4 (d, J = 17.8 Hz).

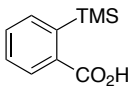
Preparation of silicate urea 1f:



1f

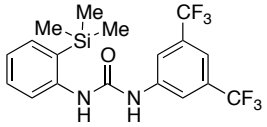


Synthesis of 2-(trimethylsilyl)benzaldehyde: This compound was prepared as previously reported by Comins and Brown.[8] A flame-dried round bottom flask under N_2 was charged with trimethylethylenediamine (0.79 mL, 6.1 mmol) and THF (15 mL) . The solution was cooled to –20 °C and *n*-butyl lithium (1.53 M in hexanes, 3.8 mL, 5.8 mmol) was added dropwise over 15 min. Next, freshly distilled benzaldehyde (0.57 mL, 5.6 mmol) was added and the solution turned light yellow. The reaction was allowed to stir for 15 min at –20 °C and then a second portion of *n*-butyl lithium (1.53 M in hexanes, 11.4 mL, 17.4 mmol) was added to the solution and the reaction was allowed to stir for 18 h at –20 °C. Next, the reaction was cooled to –40 °C and freshly distilled TMSCl (4.3 mL, 34 mmol) was added dropwise. The reaction was stirred for 30 min at –40 °C and then warmed to 23 °C. At this time, the reaction was judged to be complete by thin layer chromatography and was diluted with diethyl ether (40 mL) and poured into 10% HCl (40 mL). The aqueous layer was extracted with diethyl ether (2 x 40 mL) and the combined organic extracts were washed with brine (40 mL), dried over Mg_2SO_4, filtered and concentrated to afford a crude oil. Purification by flash column chromatography on silica gel (2% to 5% ether/hexanes) yielded 2-(trimethylsilyl)benzaldehyde as a pale yellow oil (0.740 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H); 7.94-7.91 (m, 1H); 7.75-7.73 (m, 1H); 7.60-7.57 (m, 2H); 0.38 (s, 9H).



Synthesis of 2-(trimethylsilyl)benzoic acid: This compound was prepared as previously reported by Schultz and Antoulinakis.[9] A round bottom flask under N_2 containing 2-(trimethylsilyl)benzaldehyde (0.740 g, 4.16 mmol) was charged with acetone (11 mL) and water (1.8 mL). The resulting solution was cooled to 0 °C and potassium permanganate (0.789 g, 4.99 mmol) was added. The reaction was allowed to stir for 5 min at 0 °C and then warmed to 23 °C. After 1.5 h, the reaction was concentrated under reduced pressure. A solution of saturated NaS_2O_3 was added and the resulting mixture was filtered through a pad of Celite® washing with saturated NaS_2O_3 (3 x 10 mL) and dichloromethane (3 x

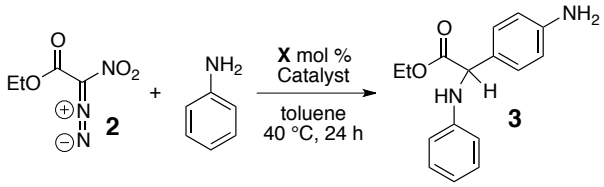
10 mL). The filtrate was then acidified with 10% HCl and extracted with dichloromethane (3 x 30 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated to afford the product as a white solid (0.533 g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.99 (br s, 1H); 7.94 (dd, J = 7.6, 1.2 Hz, 1H); 7.66 (dd, J = 7.2, 1.2 Hz, 1H); 7.56 (td, J = 7.6, 1.6 Hz, 1H); 7.49 (td, J = 7.6, 1.6 Hz, 1H); 0.28 (s, 9 H).



Synthesis of silicate urea 1f: Following the procedure reported by Capson and Poulter,[10] a flame-dried round bottom flask under N_2 was charged with 2-(trimethylsilyl)benzoic acid (0.200 mg, 1.03 mmol) and toluene (4 mL). Freshly distilled triethylamine (0.140 mL, 1.0 mmol) was added followed by diphenylphosphorylazide (DPPA) (0.220 mL, 1.03 mmol). The reaction was heated to 80 °C for 2 h and reaction progress was monitored by thin layer chromatography to ensure consumption of the benzoic acid. Next, 3,5-bis(trifluoromethyl)aniline (0.177 mL, 1.13 mmol) was added dropwise by syringe. The reaction was stirred at 80 °C for 3 h and concentrated. The crude yellow oil was taken up in diethyl ether and extracted with 1M NaOH (2 x 10 ml). The organic layer was dried over Mg_2SO_4, filtered and concentrated. The resulting light brown solid was recrystallized from ethyl acetate and hexanes to afford the product as a fluffy white solid (0.220 g, 51%). R_f = 0.47 (20:80 ethyl acetate/hexanes); mp 213.4 – 213.8 ºC; IR (KBr) 3329, 3116, 2963, 1649, 1579, 1520, 1476, 1185, 1128 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 2H); 7.65 (dd, J = 7.2, 1.2 Hz, 1H); 7.55-7.52 (m, 2H); 7.45-7.38 (m, 2H); 6.57 (br s, 1H); 6.34 (br s, 1H); ^{13}C NMR (100 MHz, DMSO d6) δ 154.2, 142.7, 142.5, 136.5, 135.0, 131.2 (q, J = 32 Hz, CCF^3), 130.1, 128.3, 126.9, 123.8 (q, J = 271 Hz), 118.2, 114.5, 0.0; HRMS (ESI): Mass calculated for $C_{18}H_{18}F_6N_2OSiNa$ $[M+Na]^+$, 443.0985. Found $[M+Na]^+$, 443.0964.

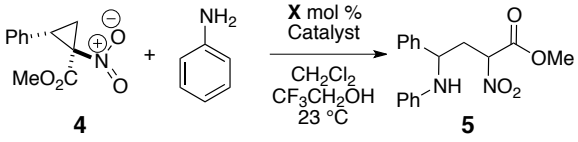
Procedures for the Internal Lewis Acid Assisted Urea Catalyzed Reactions:

Reaction A - activation of ethyl nitrodiazoacetate:



The previously published procedure was followed.[11] A dry, screw-capped reaction vial equipped with a magnetic stir bar was charged with ethyl nitrodiazoacetate (30.0 mg, 0.189 mmol) and toluene (189 μL). The reaction was fitted with cap and septum and placed under a positive pressure of argon. Catalyst (0.038 mmol, 20 mol %) was added followed immediately by aniline (172 μL, 1.89 mmol) and the reaction was allowed to stir at 40 ºC for 24 h. The reaction was immediately purified by flash column chromatography with basic alumina (20:80 diethyl ether/hexanes to 100% diethyl ether) yielding the product as a light yellow oil. R_f = 0.81 (100% diethyl ether); FTIR (film) 3051, 2982, 1731, 1604, 1507, 1266, 1178, 1023, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27-7.25 (m, 2H); 7.14-7.10 (m, 2H); 6.71-6.64 (m, 3H); 6.58-6.56 (m, 2H); 4.95 (d, J = 6.4 Hz, 1H); 4.82 (d, J = 6.0 Hz, 1H); 4.27-4.19 (m, 1H); 4.17-4.09 (m, 1H); 3.7 (br s, 2H); 1.21 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 146.4, 146.3, 129.2, 128.3, 127.4, 117.9, 115.3, 113.4, 61.6, 60.3, 14.1; HRMS (ESI): Mass calculated for $C_{16}H_{18}N_2O_2$ $[M+Na]^+$, 293.1260. Found $[M+Na]^+$, 293.1263.

Reaction B - activation of *trans*-methyl 1-nitro-2-phenylcyclopropane carboxylate:



The previously published procedure was followed.[4] A dry, screw-capped reaction vial equipped with a magnetic stir bar was charged with (±)-*trans*-methyl 1-nitro-2-phenylcyclopropane carboxylate (38 mg, 0.170 mmol) and the catalyst (0.0170 mmol, 10 mol %). The reaction was fitted with a cap and septum and put under a positive pressure of N_2. Methylene chloride (0.340 mL) was added followed by aniline (23.2 μL, 0.255 mmol) and 2,2,2-trifluoroethanol (12.2 μL, 0.170 mmol). The reaction was allowed to stir for 48 hr. Purification by silica gel flash column chromatography (5:95 ethyl acetate/hexanes to 20:80 ethyl acetate/hexanes) yielded the product

(1:1 dr) as a light yellow solid. R_f = 0.19 (20:80 ethyl acetate/hexanes). Characterization data was identical to that reported in the literature. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of two diastereomers) δ 7.39-7.26 (m, 10H); 7.14-7.09 (m, 4H); 6.71 (t, *J* = 8 Hz, 2H); 6.58-6.55 (m, 4H); 5.44 (dd, *J* = 8.0, 4.0 Hz, 1H); 5.13 (dd, J = 8.0, 4.0 Hz, 1H); 4.56-4.48 (m, 2H); 4.03-4.01 (m, 2H); 3.83 (s, 3H), 3.80 (s, 3H); 2.91-2.65 (m, 2H); 2.63-2.55 (m, 2H).

Rate Study Comparisons

The method of initial rates was used to determine k_{obs} for catalysts **1a-1f** by monitoring product formation in **Reaction A** (activation of nitrodiazoesters) and **Reaction B** (activation of nitrocyclopropane) using an internal standard (0.17 equiv of duroquinone) and ^{1}H NMR. The concentration of the product was plotted against time to provide the initial rate.

$$rate = \frac{[product]}{time\ (s)}$$

For each catalyst loading, k_{obs} was calculated as shown below.

$$k_{\mathrm{obs}} = \frac{rate}{[catalyst]}$$

Multiple catalyst loadings allowed the order of the reaction to be determined according to:

$$rate = k_{\mathrm{obs}}[catalyst]^{order}$$

where the concentrations of the starting substrates were kept sufficiently high enough to be considered constant during the initial reaction period studied and are included in k_{obs} (Figure 1). By plotting the natural log of the rate versus the natural log of catalyst concentration, orders for each reaction were determined by sampling different catalyst loadings (Figure 2 and 3**)**. The results are tabulated in Tables 1 and 2.

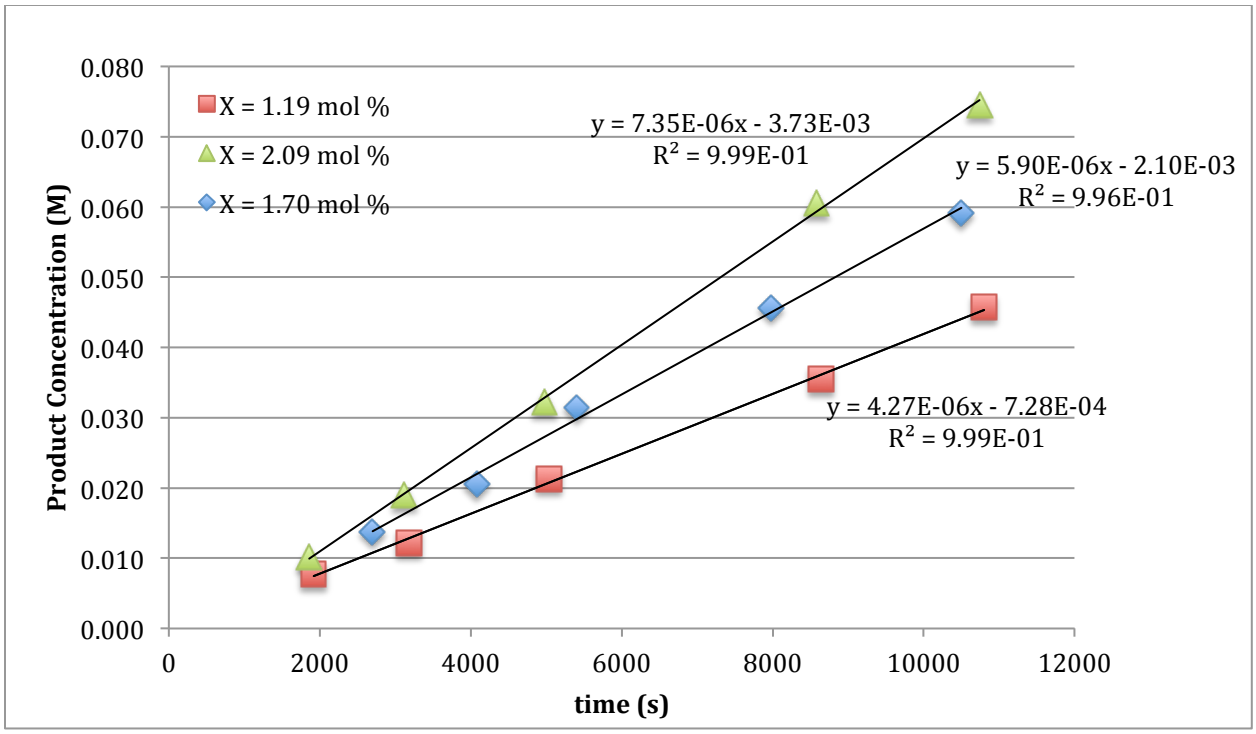


Figure 1. Representative rate plots for Reaction B with catalyst **1a** at three loadings (X).

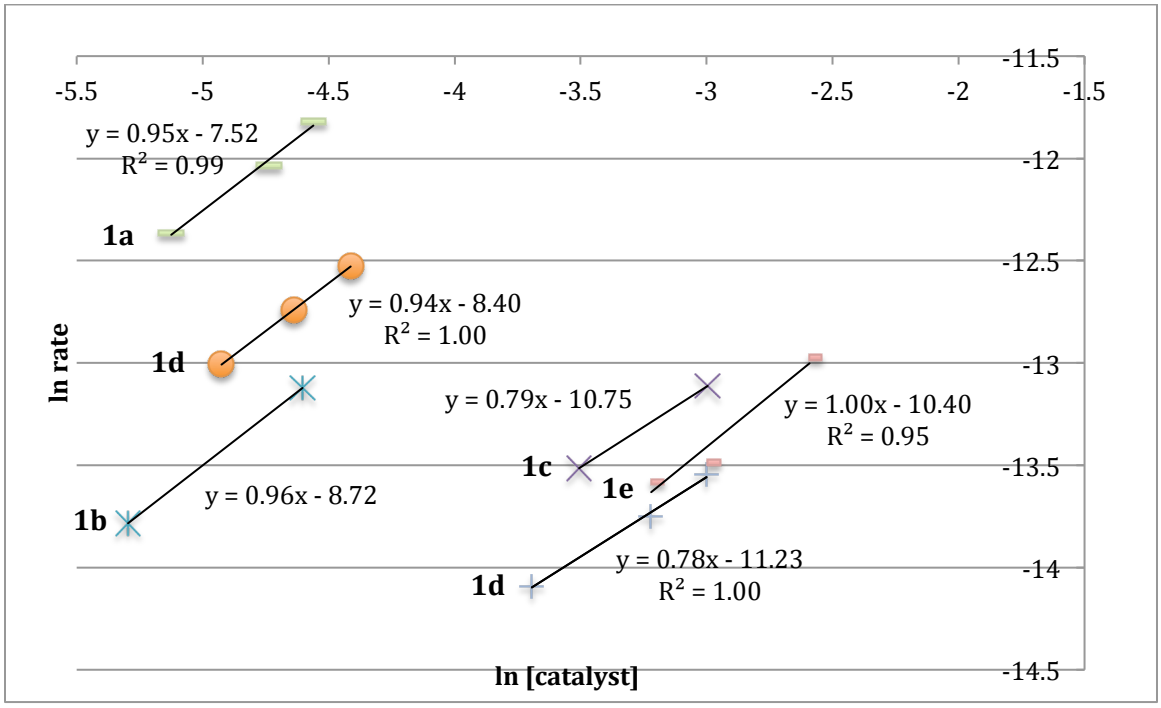


Figure 2. Representative observed reaction orders for catalysts **1a-1f** in Reaction A.

Table 1. Tabulated Rate Data for Reaction A (activation of nitrodiazoacetate)

Catalyst	Rate	[catalyst]	k_{obs} (s^{-1})	average k_{obs} (s^{-1})
1a	5.33E-06	0.05232	1.02E-04	9.2E-05
	7.53E-06	0.07848	9.59E-05	
	9.71E-06	0.10486	9.26E-05	
	1.21E-05	0.15701	7.71E-05	
1b	3.92E-06	0.10467	3.74E-05	3.6E-05
	5.43E-06	0.15700	3.46E-05	
1c	4.44E-06	0.15708	2.83E-05	2.8E-06
	2.98E-06	0.10467	2.85E-05	
1d	1.55E-06	0.10486	1.48E-05	1.4E-05
	2.01E-06	0.15701	1.28E-05	
1e	9.41E-07	0.10486	8.97E-06	7.7E-06
	1.02E-06	0.15701	6.50E-06	
1f	1.19E-06	0.15718	7.54E-06	7.7E-06
	8.30E-07	0.10486	7.92E-06	

Table 2. Tabulated Rate Data for Reaction B (activation of a nitrocyclopropane)

Catalyst	Rate	[catalyst]	k_{obs} (s^{-1})	average k_{obs} (s^{-1})
1a	7.35E-06	0.010456	7.03E-04	7.0E-04
	4.27E-06	0.005948	7.17E-04	
	5.94E-06	0.00876	6.78E-04	
1b	1.03E-06	0.00501	2.06E-04	2.0E-04
	2.00E-06	0.010015	2.00E-04	
1c	2.02E-06	0.050002	4.04E-05	4.3E-05
	1.35E-06	0.030017	4.50E-05	
1d	3.63E-06	0.012124	2.99E-04	3.0E-04
	2.92E-06	0.009659	3.02E-04	
	2.25E-06	0.007261	3.09E-04	
1e	7.59E-07	0.024884	3.05E-05	2.8E-05
	1.07E-06	0.039857	2.67E-05	
	1.31E-06	0.049768	2.63E-05	
1f	1.39E-06	0.049950	2.78E-05	3.0E-05
	1.27E-06	0.039960	3.17E-05	
	2.32E-06	0.074925	3.10E-05	

Determination of pK_a

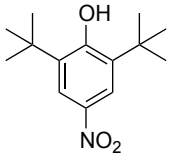
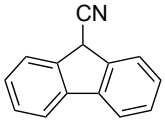
This method was adapted from those described in the literature.[12,13]

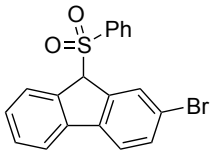
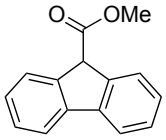
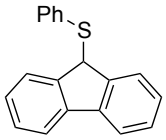
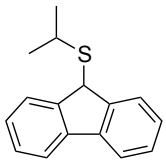
Preparation of DMSO: Due to the extreme water sensitivity for pK_a measurements, DMSO was freshly prepared before each run as follows: a flame-dried distillation apparatus attached to a trap filled with liquid N_2 was charged with 75 mL of commercial grade DMSO (>99.9%) via cannula. A small portion (1-2 mg) of triphenylmethane indicator was added. Next, small amounts of $NaNH_2$ (5-10 mg) were added successively until the solution turned deep red. Fractional distillation was performed at 50 mTorr at 50°C and the first 10 mL of distillate was disgarded. The DMSO was stored under argon until use (not more than 1 hour) and used for dissolution of the indicator, pK_a candidate, and dimsyl anion stock solution.

Preparation of the dimsyl anion stock solution: A flame-dried round bottom flask fitted with a stirbar was charged with 120 mg of KH in an argon atmosphere. Freshly prepared DMSO (10 mL) was added with vigorous stirring as H_2 evolved. The flask was evacuated and purged with Argon three times and kept under Argon until use. The resulting concentration of the dimsyl anion was found to be approximately 0.2 M.

Preparation of indicators: The following indicators of known pK_a were prepared according to literature procedures[12,13] as shown in Table 3.

Table 3. Indicators used to determine the pK_a of the catalysts.

Structure	pK_a	Name (abbreviation)
	7.3	2,6-di-*tert*-butyl-4-nitrophenol (DN-*t*-BuPH)
	8.3	9-cyanofluorene (CN-FH)

	9.6	2-bromo-9-(phenylsulfonyl)fluorene (2-Br-PhSO$_2$-FH)
	10.35	9-(carbomethoxy)fluorine (CO_2Me-FH)
	15.4	9-(phenylthio)fluorine (PhS-FH)
	16.9	9-(isopropylthio)fluorine (*i*-PrS-FH)

Preparation of indicator and pK_a candidate solutions: A solution with approximate concentration of 0.015 M was prepared as follows. Approximately 50 mg of the desired compound was added to a pre-weighed flask under an Argon environment, and the precise amount was determined gravimetrically. Next, freshly prepared DMSO was added, and the exact amount was determined gravimetrically. Argon was bubbled through the solution for 15 minutes before use.

Determination of pK_a: An oven-dried, quartz, spectrophotometric cell (d = 1 cm) equipped with a stir bar was fitted with a septum, flushed with Argon, and weighed. Approximately 0.05 mL of the freshly prepared dimsyl anion solution was added followed by approximately 3 mL of dry DMSO. Argon was rapidly bubbled through the solution for 15 minutes and the cell was weighed again. After the initial UV spectrum baseline was recorded, the UV spectra of sequential indicator additions (approximately 0.20 mL aliquots of the indicator stock solution) were determined until the UV spectral absorbance revealed a saturated indicator-anion state evidenced by a steady or falling (due to dilution) absorbance at an appropriate wavelength. The

solution was stirred and the precise amount of each aliquot was determined gravimetrically after each addition.

A Lambert-Beer's law plot was constructed from the indicator-anion concentration and the corresponding absorbance at an appropriate wavelength (A_λ). It was crucial to account for dilution from the indicator addition (assumed to be the same density as DMSO) during every concentration determination. From this relationship, the molar extinction coefficient (ε) could be calculated and the indicator-anion base (B^-) concentration in the cell could be determined at any future time during the experiment. An example plot is shown in Figure 3.

$$[B^-] = \frac{A_\lambda}{\epsilon}$$

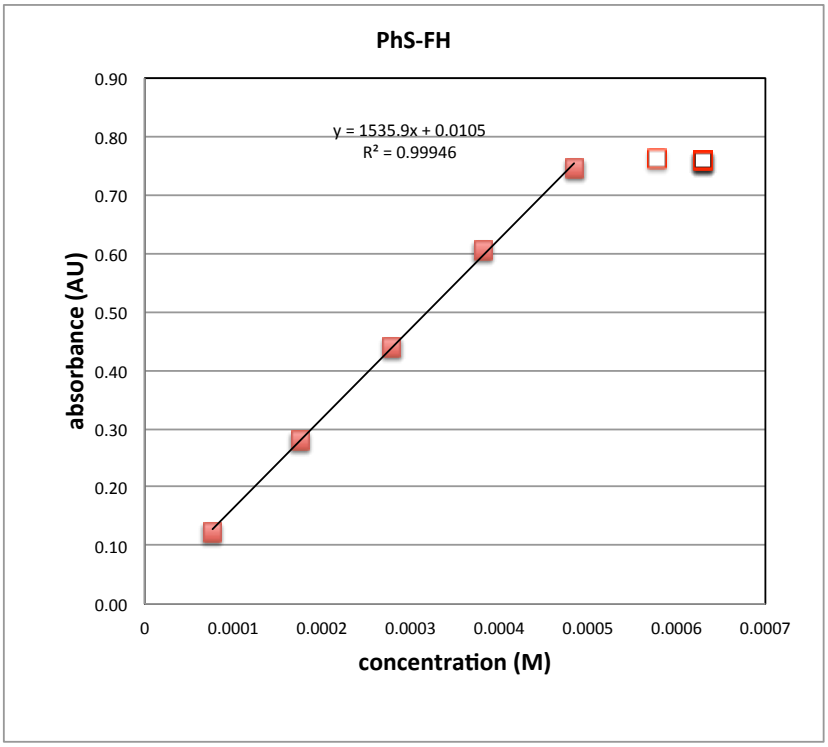


Figure 3. Beer-Lambert plot for PhS-FH indicator.

Since the total amount of indicator (HB) and indicator-anion (B^-) was known from the gravimetric measurements, the concentration of the indicator could be determined as follows:

$$[\mathrm{HB}] = [\mathrm{HB\ and}\ B^-] - [\mathrm{B}^-]$$

The solution was now ready for the pK_a determination as it contained *only* a known concentration of the base (indicator-anion) and a known concentration of the conjugate acid (indicator). An aliquot (approx. 0.020 mL) of the pK_a candidate stock solution (approx. 0.015 M) was added and the solution was stirred briefly. The precise addition amount was determined gravimetrically and a UV spectrum was recorded. Assuming an appropriate indicator had been selected having a pK_a within approx. 1.5 units of the candidate (trial-and-error), a meaningful acid-base equilibrium was observed! However, if the indicator was too strong (i.e. the pK_a was 1.5 or more units greater than the candidate) or too weak (i.e the pK_a was 1.5 or more units less than the candidate), the effect on the equilibrium was either too extreme or miniscule for meaningful measurements. The new acid-base equilibrium between the candidate (HA), the indicator-anion (B^-), the candidate-anion (A^-) and the indicator (HB) is shown below:

$$\mathrm{HA} + \mathrm{B}^- \rightleftharpoons \mathrm{A}^- + \mathrm{HB}$$

Using the Beer-Lambert relationship shown in equation (1), the new concentration of the indicator-anion was determined. Since the decrease of the indicator-anion concentration must correspond exactly with an increase in the indicator concentration, the new indicator concentration could be determined as follows:

$$[\mathrm{HB}] = [\mathrm{HB}]_{initial} + \Delta[\mathrm{B}^-]$$

Since the only proton source for the protonation of the indicator-anion (B^-) is the candidate (HA), the decrease in indicator-anion (B^-) corresponds with an increase of candidate-anion (A^-) as shown below:

$$[\mathrm{A}^-] = \Delta[\mathrm{B}^-]$$

Since the decrease of the indicator-anion (B^-) also corresponds exactly with a decrease of the candidate (HA), the concentration of the candidate can be determined as follows:

$$[\mathrm{HA}] = [\mathrm{HA}]_{initial} - \Delta[B^-]$$

When calculating the concentrations, it is essential to account for dilution due to the aliquot addition. Since all the concentrations are known, the equilibrium constant (K_{eq}) can be determined as follows:

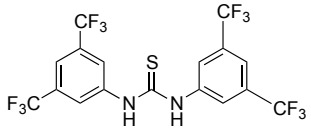
$$K_{eq} = \frac{[\mathrm{HB}][A^-]}{[\mathrm{HA}][\mathrm{B}^-]}$$

The pK_a of the candidate can then be calculated according to

$$\mathrm{p}K_a = \mathrm{p}K_{a(indicator)} - \log K_{eq}$$

This process was repeated with successive aliquots to furnish additional pK_a values. Typically, five pK_a values were determined during each run and the average and standard deviation were calculated. Each pK_a candidate was tested against at least two different indicators in at least three independent runs (freshly prepared DMSO in each case). The standard deviations of the dataset gave the associated error. To determine if our procedure was reliable and accurate, an initial test of a thiourea with known pK_a was performed with two different indicators and the results showed close agreement with the literature values (Table 4).

Table 4. Testing the pK_a of a thiourea against the literature value.

Compound	Indicator	pK_a (lit.)[13]	pK_a (experimental)	St. Dev.
	2-Br-9-PhS-FH	8.5 ± 0.1	8.54	0.09
	CN-FH		8.48	0.04
	CN-FH		8.58	0.11

Confident our methodology was sound, we proceeded to measure the pK_a of catalysts **1a, 1b, 1e** and **1f** using the above procedures. Unfortunately, for catalyst **1c,** treatment with the indicator

base resulted in a secondary UV absorption in the experimental range obfuscating the reference absorption and preventing data collection. A typical spreadsheet showing a pK_a calculation is shown in Figure 4 and the results are tabulated in Table 5.

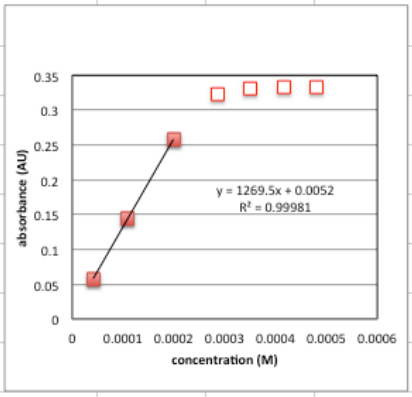
	name	pKa	mw	g	g dmso	mL	M
indicator	iPrS-FH	16.9	240.36	0.0383	13.304	12.0901	0.01318
catalyst	TMS	15.96	420.42	0.051	9.2752	8.4289	0.01439

empty cuvette (g)	11.8353

Cat 1f with *i*-PrS-FH indicator

Ext. Coeff. 1269.514626 0.005225465

	[species added] (M)	tot cuv mass	abs.	[ind] *(calculated)*	[Hind] *(calculated)*
indicator addition 0	0	14.9686		0	0
1	4.15115E-05	14.9785	0.057	4.07829E-05	7.28532E-07
2	0.000108051	14.9945	0.144	0.000109313	-1.26237E-06
3	0.000198857	15.0166	0.257	0.000198323	5.33837E-07
4	0.000287204	15.0384	0.323	0.000250312	3.68917E-05
5	0.000350885	15.0543	0.330	0.000255826	9.50592E-05
6	0.000415519	15.0706	0.333	0.000258189	0.00015733
7	0.000479114	15.0868	0.333	0.000258189	0.000220925



		[urea]	[urea-]	Keq	pKa
catalyst addition a	4.58856E-05	15.0972	0.279	0.000215653	0.000261933	4.17289E-06	4.17128E-05	12.14135781	15.81573274
b	0.000118958	15.1139	0.21	0.000161301	0.000313852	2.42051E-05	9.47533E-05	7.616844913	16.01822489
c	0.000178351	15.1276	0.163	0.000124279	0.000348897	4.76409E-05	0.00013071	7.702403261	16.01337375
d	0.000245809	15.1433	0.121	9.11959E-05	0.000379735	8.32254E-05	0.000162583	8.134376883	15.98967571
e	0.000310511	15.1585	0.093	6.91402E-05	0.000399636	0.000127033	0.000183478	8.348384107	15.97839758
								Avg.pKa	15.96
								Std. Dev.	0.08

Figure 4. Representative Spreadsheet Calculation of pK_a for catalyst **1f** with indicator *i*-PrS-FH.

Table 5. Results for the determination of the pK_a of catalysts **1**.

Catalyst	Indicator	pK_a (5 run average)	Stand. Dev.	Reported Value
1a	DN-*t*-BuPH	7.47	0.19	7.5 ± 0.2
	DN-*t*-BuPH	7.51	0.17	
	CN-FH	7.44	0.16	
1b	DN-*t*-BuPH	6.73	0.04	6.8 ± 0.5
	DN-*t*-BuPH	6.77	0.07	
	CN-FH	6.81	0.55	
1e	2-Br-$PhSO_2$-FH	9.49	0.02	9.49 ± 0.02
	2-Br-$PhSO_2$-FH	9.49	0.003	
	CO_2Me-FH	9.49	0.05	
1f	PhS-FH	15.98	0.04	15.96 ± 0.09
	PhS-FH	15.95	0.16	
	i-PrS-FH	15.96	0.08	

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Selected NMR spectra