Supporting Information

N-Heterocyclic Carbene and Chiral Brønsted Acid Cooperative Catalysis for a Highly Enantioselective [4+2] Annulation

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1. General Considerations

Commercial reagents were purchased from Aldrich, Alfa and TCI, and were used as received unless otherwise indicated. Dichloromethane was degassed with argon and passed through two columns of neutral alumina. Anhydrous THF, toluene and cyclohexane were purchased from Aldrich and used as received. All catalytic reactions were carried out under N₂ with oven-dried vials. Thin layer chromatography was performed on SiliCycle® 250 um, 60A plates. Column chromatography was performed on *SiliCycle®SilicaFlash*® P60, 40-63 um, 60A. Visualization was accomplished with UV light (254 nm) or DNP (Dinitrophenylhydrazine).

¹H, ¹³C and ¹⁹F NMR spectra were recorded on a Bruker 500 Hz (125 Hz) spectrometer at ambient temperature. All NMR spectra are referenced to TMS or the residual solvent signal. Data for ¹H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (Hz), integration. Data for ¹³C NMR are reported as follows: chemical shift (δ ppm). Data for ¹⁹F NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (Hz), integration. Data for ¹³C NMR are reported as follows: chemical shift (δ ppm). Data for ¹⁹F NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (Hz), integration. Several spectra had very complex coupling and deconvolution was not possible.

High resolution mass spectra (HRMS) were obtained from Columbia University Mass Spectrometry Facility on a JOEL JMSHX110HF mass spectrometer using FAB+ ionization model. Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FI-IR spectrometer. HPLC spectra were obtained on an Agilent 1100 series system. Optical rotation was obtained with an Autopol-III automatic polarimeter.

Ketones besides perfluoroethyl or perfluoropropyl phenones¹ were purchased from Aldrich and used as received. 2-(bromomethyl)benzaldehydes,² and chiral phosphoric acids ³ are known. The triazolium salts **4-5** were prepared according to our previous procedure.⁴

2. General Procedures for the Asymmetric [4+2] Annulation:

To an oven-dried 5 mL vial with a magnetic stir bar, aldehyde 1 (0.10 mmol), ketone 2 (0.20 mmol), triazolium salt **5a** (9.3 mg, 0.020 mmol), chiral phosphoric acid **6d** (6.8 mg, 0.010 mmol), KOAc (19.6 mg, 0.40 mmol) were added before being transferred to an argon-filled glovebox. 1.0 mL of dry cyclohexane was added. The vial was tightly capped and removed from the glovebox. The reaction was vigorously stirred at room temperature. After 12h, the mixture was concentrated and the residue was subjected to flash silica gel chromatography (hexane: ether = 20:1) to yield lactone product.

3. Characterization Data of New Compounds:



Prepared according to the general procedure: 19.9 mg, 68% yield, 95% ee, $R_f = 0.33$ (10:1 hex:EtOAc); $[\alpha]^{20}_D = +87.8^\circ$ (c = 0.014 g/ml, CHCl₃); HPLC analysis – Chiracel IC column, 80:20 hexanes/isopropanol, 1.0 mL/min. Minor: 5.36 min, major: 6.14 min; ¹H NMR (500 MHz, CDCl₃) δ 7.98 (dd, J = 7.8, 1.3 Hz, 1H), 7.56 – 7.42 (m, 3H), 7.35 – 7.25 (m, 5H), 3.83 (d, J = 16.3 Hz, 1H), 3.69 (d, J = 16.3 Hz, 1H). Data matches literature report.²



Prepared according to the general procedure: 21.4 mg, 69% yield, 91% ee, $R_f = 0.36$ (10:1 hex:EtOAc); $[\alpha]^{20}{}_D = +90.9^{\circ}$ (c = 0.017 g/ml, CHCl₃). HPLC analysis: Chiracel IC column, 85:15 hexanes/iso-propanol, 1.0 mL/min. Minor: 5.80 min, major: 6.25 min; ¹H NMR (500 MHz, CDCl₃) δ 7.97 (dd, J = 7.8, 1.3 Hz, 1H), 7.56 – 7.45 (m, 3H), 7.35 – 7.25 (m, 2H), 7.06 – 6.93 (m, 2H), 3.84 (d, J = 16.3 Hz, 1H), 3.64 (d, J = 16.4 Hz, 1H). Data matches literature report.²



Prepared according to the general procedure: 18.1 mg, 55% yield; 83% ee, $R_f = 0.34$ (10:1 hex:EtOAc); $[\alpha]^{20}_D = +75.6^\circ$ (c = 0.016 g/ml, CHCl₃); HPLC analysis – Chiracel IC column, 85:15 hexanes/isopropanol, 1.0 mL/min. Minor: 5.68 min, major: 5.99 min; 1 H NMR (500 MHz, CDCl₃): δ 7.26 (dd, J =5.8, 2.9 Hz, 1H), 7.22-7.11 (m, 5H), 6.75-6.72 (m, 3H), 5.07 (s, 1H), 3.80 (dt, J = 11.2, 4.9 Hz, 1H), 3.34 (ddd, J = 11.1, 10.0, 4.1 Hz, 1H), 3.08 (ddd, J = 15.5, 10.1, 5.2 Hz, 1H), 2.91 (dt, J = 15.6, 4.3 Hz, 1H), 2.53-2.31 (m, 2H), 0.83 (t, J = 7.2 Hz, 3H. Data matches literature report.²



Prepared according to the general procedure: 21.1 mg, 68% yield; 87% ee, $R_f = 0.33$ (10:1 hex:EtOAc); $[\alpha]^{20}_D = +72.0^\circ$ (c = 0.014 g/ml, CHCl₃); HPLC analysis – Chiracel IC column, 85:15 hexanes/isopropanol, 1.0 mL/min. Minor: 5.66 min, major: 6.29 min; ¹H NMR (500 MHz, CDCl₃) δ 7.98 (dd, J = 7.9, 1.3 Hz, 1H), 7.52 (td, J = 7.6, 1.3 Hz, 1H), 7.35 – 7.22 (m, 5H), 7.01 (m, 1H), 3.84 (d, J = 16.3 Hz, 1H), 3.63 (d, J = 16.4 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 162.7 (d, J = 246 Hz), 161.9, 136.1 (d, J = 7.1Hz), 134.9, 134.8, 130.5, 130.4 (d, J = 8.1 Hz), 128.3, 127.9, 124.2, 123.0 (q, J = 282 Hz), 122.8 (d, J = 2.6 Hz), 116.7 (d, J = 20.9 Hz), 114.6 (d, J = 23.8 Hz) 82.7 (q, J = 30.7 Hz), 31.1 (d, J = 1.5 Hz); ¹⁹F NMR (471 HZ, CDCl₃) δ -78.6 (s), -110.3 (m); IR (NaCl, neat) 1742, 1594, 1445, 1280, 1185, 1115, 1073, 749, 729, 708 cm⁻¹; HRMS (ESI⁺) calcd for C₁₆H₁₁O₂F₄ as [M+H]⁺, 311.0695. Found 311.0696.



Prepared according to the general procedure: 21.6 mg, 63% yield; 87% ee, Rf = 0.41 (10:1 hex:EtOAc); $[\alpha]^{20}_{D} = +75.1^{\circ}$ (c = 0.011 g/ml, CHCl₃); HPLC analysis – Chiracel IC column, 85:15 hexanes/isopropanol, 1.0 mL/min. Minor: 5.09 min, major: 5.39 min; ¹H NMR (500 MHz, CDCl₃) δ 7.95 (dd, J = 7.8, 1.2 Hz, 1H), 7.50 – 7.44 (m, 3H), 7.33-7.24 (m, 4H), 7.22 (d, J = 7.6 Hz, 1H), 3.93 (d, J = 16.2 Hz, 1H), 3.66 (d, J = 16.2 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 162.1, 135.3, 134.6, 133.5, 130.2, 129.5, 128.7, 128.1, 127.9, 126.9, 124.4, 118.8 (qt, J = 287, 35.8 Hz), 111.3 (tq, J = 264, 35.6 Hz), 83.8 (t, J = 24.9 Hz), 31.4; ¹⁹F NMR (471 MHZ, CDCl₃) δ -76.8 (s), -120.1, 121.5 (ABq, $J_{AB} = 280.0$ Hz); IR (NaCl, neat) 1740, 1451, 1219, 1190, 1151, 1116, 1076, 745, 731, 716 cm⁻¹; HRMS (ESI⁺) calcd for C₁₇H₁₂O₂F₅ as [M+H]⁺, 343. 0575. Found 343. 0761.



Prepared according to the general procedure: 30.2 mg, 77% yield; 90% ee, Rf = 0.43 (10:1 hex:EtOAc); $[\alpha]^{20}{}_{D} = 107.3$ (c = 0.015 g/ml, CHCl₃); HPLC analysis – Chiracel IC column, 85:15 hexanes/iso-propanol, 1.0 mL/min. Minor: 4.69 min, major: 4.91 min; ¹H NMR (500 MHz, Chloroform-*d*) δ 7.96 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.51 – 7.44 (m, 3H), 7.33 – 7.25 (m, 5H), 7.21 (d, *J* = 7.6 Hz, 1H), 3.95 (d, *J* = 16.2 Hz, 1H), 3.67 (d, *J* = 16.2 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 162.0, 135.2, 134.6, 133.5, 130.2, 129.4, 128.6, 128.1, 127.9, 127.1, 124.4, 118.8 (m), 116.3 (m), 113.9 (m), 111.9 (m), 109.9 (m), 107.8 (m), 84.7 (t, *J* = 25.3 Hz), 31.7; ¹⁹F NMR (471 MHz, CDCl₃) δ -79.9 (t, *J* = 11.3 Hz, 3F), -116.1 – -118.4 (m, 2F), -120.5 (ddd, *J* = 289.6, 12.5, 4.7 Hz, 1F), -122.9 (ddd, *J* = 289.2, 12.5, 3.0 Hz, 1F); IR (NaCl, neat) 1741, 1461, 1450, 1340, 1226, 1125, 1074, 745, 730, 716, cm⁻¹; HRMS (ESI⁺) calcd for C₁₈H₁₂O₂F₇ as [M+H]⁺, 393. 0726. Found 393. 0718.



Prepared according to the general procedure: 18.6 mg, 57% yield; 90% ee, $R_f = 0.33$ (10:1 hex:EtOAc); $[\alpha]^{20}_D = +112.9^\circ$ (c = 0.018 g/ml, CHCl₃); HPLC analysis – Chiracel IC column, 85:15 hexanes/isopropanol, 1.0 mL/min. Minor: 6.06 min, major: 7.05 min; ¹H NMR (500 MHz, CDCl₃) δ 7.93 (d, J = 8.8Hz, 1H), 7.54 – 7.50 (m, 3H), 7.40-7.33 (m, 3H), 7.32 – 7.29 (m, 2H), 3.83 (d, J = 16.4, 1H), 3.68 (d, J =16.4 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 161.5, 141.1, 137.0, 133.1, 131.9, 129.7, 128.9, 128.7, 127.9, 126.9, 122.8, 123.1 (d, J = 282 Hz), 83.2 (d, J = 30.6 Hz), 31.0; ¹⁹F NMR (471 MHz, Chloroformd) δ -78.7 (s); IR (NaCl, neat) 1736, 1600, 1270, 1185, 1168, 1095, 1074, 765, 720, 683 cm⁻¹; HRMS (ESI⁺) calcd for C₁₆H₁₁O₂F₃Cl as [M+H]⁺, 327. 0400. Found 327.0397.



Prepared according to the general procedure: 24.3 mg, 66% yield; 77% ee, $R_f = 0.41$ (10:1 hex:EtOAc); $[\alpha]^{20}_D = +93.1^{\circ}$ (c = 0.019 g/ml, CHCl₃); HPLC analysis – Chiracel IC column, 85:15 hexanes/isopropanol, 1.0 mL/min. Minor: 8.15 min, major: 11.11 min; ¹H NMR (500 MHz, CDCl₃) δ 8.03 (d, J = 8.0 Hz, 1H), 7.58 – 7.50 (m, 4H), 7.48 – 7.40 (m, 4H), 7.36 – 7.28 (d, J = 7.4 Hz, 3H), 3.89 (d, J = 16.2 Hz, 1H), 3.75 (d, J = 16.3 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): 162.3, 147.4, 139.1, 135.8, 133.5, 130.9, 129.6, 129.1, 128.8, 128.7, 127.2, 127.0, 126.9, 126.3, 123.3 (d, J = 282 Hz), 123.0, 83.2 (d, J = 30.4 Hz), 31.3; ¹⁹F NMR (471 MHz, CDCl₃) δ -78.7 (s); IR (NaCl, neat) 2923, 1737, 1611, 1450, 1271, 1238, 1169, 1130, 1073, 758, 740, 721, 695 cm⁻¹; HRMS (ESI⁺) calcd for C₂₂H₁₆O₂F₃ as [M+H]⁺, 369.1102. Found 369.1100.



(S)-3-(4-fluorophenyl)-6-phenyl-3-(trifluoromethyl)isochroman-1-one

Prepared according to the general procedure: 27.5 mg, 71% yield; 93% ee, Rf = 0.40 (10:1 hex:EtOAc); $[\alpha]^{20}{}_{\rm D}$ = +103.5° (c = 0.014 g/ml, CHCl₃); HPLC analysis – Chiracel IC column, 85:15 hexanes/isopropanol, 1.0 mL/min. Minor: 7.05 min, major: 8.85 min; ¹H NMR (500 MHz, CDCl₃) δ 8.03 (d, *J* = 8.1 Hz, 1H), 7.58 – 7.51 (m, 5H), 7.49 – 7.39 (m, 4H), 7.02 (t, *J* = 8.6 Hz, 2H), 3.89 (d, *J* = 16.3 Hz, 1H), 3.70 (d, *J* = 16.3 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 163.2 (d, *J* = 249 Hz), 162.1, 147.6, 139.0, 135.6, 131.0, 129.4 (d, *J* = 3.3 Hz), 129.2 (d, *J* = 8.7 Hz), 129.1, 128.8, 127.3, 127.0, 126.3, 123.1 (d, *J* = 282 Hz), 122.8, 116.0 (d, *J* = 21.7 Hz), 82.8 (d, *J* = 30.5 Hz), 31.3; ¹⁹F NMR (471 MHz, CDCl₃) δ -78.9 (s), -110.5 (tt, *J* = 8.4, 5.0 Hz); IR (NaCl, neat) 1739, 1611, 1512, 1239, 1171, 1073, 988, 836, 745, 697 cm⁻¹; HRMS (ESI⁺) calcd for C₂₂H₁₅O₂F₄ as [M+H]⁺, 387.1008. Found 387.1002.



Prepared according to the general procedure: 29.8 mg, 81% yield; 86% ee, $R_f = 0.43$ (10:1 hex:EtOAc); $[\alpha]^{20}_D = +118.0^\circ$ (c = 0.028 g/ml, CHCl₃); HPLC analysis – Chiracel IC column, 85:15 hexanes/isopropanol, 1.0 mL/min. Minor: 7.27 min, major: 8.35 min; ¹H NMR (500 MHz, CDCl₃) δ 8.21 (d, J = 1.9Hz, 1H), 7.72 (dd, J = 7.9, 2.0 Hz, 1H), 7.58 – 7.48 (m, 4H), 7.41 (t, J = 7.5 Hz, 2H), 7.38 – 7.28 (m, 5H), 3.86 (d, J = 16.3 Hz, 1H), 3.73 (d, J = 16.3 Hz, 1H); δ ¹³C NMR (125 MHz, CDCl₃) δ 162.4, 141.3, 138.9, 134.0, 133.5, 133.1, 129.6, 129.0, 128.8, 128.7, 128.4, 128.1, 127.1, 126.9, 124.7, 123.3 (d, J = 282 Hz), 83.0 (d, J = 30.4 Hz), 30.8; ¹⁹F NMR (471 MHz, CDCl₃) δ -78.8 (s); IR (NaCl, neat) 2924, 1742, 1451, 1306, 1221, 1169, 1073, 760, 745, 702 cm⁻¹; HRMS (ESI⁺) calcd for C₂₂H₁₆O₂F₃ as [M+H]⁺, 369.1102. Found 369.1100.

References:

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- (2) Janssen-Müller, D.; Singha, S.; Olyschläger, T.; Daniliuc, C. G.; Glorius, F. Org. Lett. 2016, 18, 4444.
- (3) Momiyama, N.; Nishimoto, H.; Terada, M. Org. Lett. 2011, 13, 2126.
- (4) (a) Kerr, M. S.; Rovis, T. J. Am. Chem. Soc. 2004, 126, 8876. (b) He, M.; Struble, J. R.; Bode, J. W. J. Am. Chem. Soc. 2006, 128, 8418.

4. ¹H, ¹³C & ¹⁹F NMR Spectra





























5. HPLC Spectra



#	Time	Area	Height	Width	Area%	Symmetry
1	5.332	122.3	19.8	0.0941	50.064	0.868
2	6.111	122	17.3	0.1105	49.936	0.898
L <u> </u>	0.111	122	17.3	0.1100	43.330	



#	Time	Area	Height	Width	Area%	Symmetry
1	5.356	10.2	1.7	0.0953	2.501	0.868
2	6.138	397.9	55.3	0.112	97.499	0.887



	#	Time	Area	Height	Width	Area%	Symmetry
[1	5.822	348.4	50.4	0.1067	49.925	0.859
[2	6.275	349.5	46.4	0.1158	50.075	0.866



#	Time	Area	Height	Width	Area%	Symmetry
1	5.803	5	6.1E-1	0.1372	4.310	0.742
2	6.248	112	14.4	0.1299	95.690	0.843



	#	Time	Area	Height	Width	Area%	Symmetry
[1	5.937	115.9	17.5	0.1106	49.993	0.93
[2	6.3	115.9	15.8	0.1225	50.007	0.888



#	Time	Area	Height	Width	Area%	Symmetry
1	5.683	7.9	1.2	0.104	8.458	0.884
2	5.994	85.4	11.8	0.1105	91.542	0.871



#	Time	Area	Height	Width	Area%	Symmetry
1	5.771	23.3	3.4	0.1061	50.166	0.844
2	6.217	23.2	3.1	0.1139	49.834	0.883

3d:



#	Time	Area	Height	Width	Area%	Symmetry
1	5.66	5.4	5.4E-1	0.1664	6.629	1.067
2	6.287	76	9.8	0.1294	93.371	7.82E-5



#	Time	Area	Height	Width	Area%	Symmetry
1	5.086	27.1	4.5	0.0929	49.280	0.823
2	5.387	27.9	4.3	0.0989	50.720	0.874



#	Time	Area	Height	Width	Area%	Symmetry
1	5.092	6.4	8.8E-1	0.1208	6.372	0.688
2	5.392	93.8	14	0.1116	93.628	0.826



		1	1000	mongine		1100.0	ojimiotij
[1	4.693	26.1	4.5	0.089	49.179	0.838
[2	4.913	27	4.5	0.0926	50.821	0.863



	i ime	Area	Height	Wiath	Area%	Symmetry
1	4.691	5	8.1E-1	0.1028	5.155	0.809
2	4.912	92.5	15.4	0.0921	94.845	0.835



#	Time	Area	Height	Width	Area%	Symmetry
1	6.061	587.2	77.6	0.1142	50.010	0.816
2	7.05	586.9	65.1	0.1371	49.990	0.836



	#	Time	Area	Height	Width	Area%	Symmetry
Γ	1	6.062	39.4	5.3	0.1139	5.052	0.837
	2	7.051	740.3	81.9	0.1374	94.948	0.83



_	#	Time	Area	Height	Width	Area%	Symmetry
	1	8.155	396.6	36.2	0.1677	50.219	0.879
	2	11.114	393.1	25.3	0.2391	49.781	0.945



#	Time	Area	Height	Width	Area%	Symmetry
1	8.152	78.5	7.2	0.1669	11.296	0.898
2	11.113	616.6	39.6	0.2397	88.704	0.933



#	Time	Area	Height	Width	Area%	Symmetry
1	7.044	61.1	6.7	0.1426	49.893	0.9
2	8.835	61.3	5.1	0.1855	50.107	0.904



#	Time	Area	Height	Width	Area%	Symmetry
1	7.054	18.5	2	0.1423	3.260	0.904
2	8.853	547.6	45.6	0.1863	96.740	0.912



_	#	Time	Area	Height	Width	Area%	Symmetry
	1	7.278	536	57	0.1457	50.054	0.891
	2	8.352	534.9	47.5	0.1753	49.946	0.942



#	Time	Area	Height	Width	Area%	Symmetry
1	7.273	28.4	3.1	0.1437	7.178	0.882
2	8.347	367.1	32.8	0.1725	92.822	0.953