Development of a continuous photochemical bromination/alkylation sequence en route to AMG 423.

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Supporting Information – Table Of Contents

Methods And Materials.

Photochemical reactions were conducted under an ambient atmosphere while all other transformations where conducted under a nitrogen atmosphere using anhydrous solvents. All commercially obtained reagents were used as received. A kit from Sigma-Aldrich for a LED micro photochemical reactor[1] was used as received for reaction development and the equipment for photoNMR experiments was purchased from Goldstone Scientific[2]. Experiments for reaction screening and kinetics were conducted in 1-dram vials or NMR tubes. Other batch experiment work was conducted in Metter-Toledo EasyMax© reactors. Plug flow reactors for laboratory scale experiment were constructed from ⅛" ID, ¼" OD PFA tubing. ^{1}H NMR spectra were

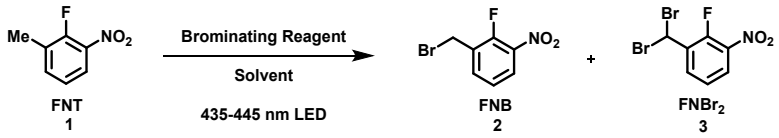
recorded on Bruker spectrometers (at 400 MHz for ^{1}H observation) and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra were recorded on Bruker Spectrometers (at 100 MHz for ^{13}C observation). Data for ^{13}C NMR spectra are reported in terms of chemical shift. PhotoNMR experiments were conducted by placing the fiber optic cable into an insert in a sealed NMR tube (photoNMR sampling device-5mm, cat# NE-396-5-Br, New Era Enterprises, Inc., Vineland, New Jersey, USA) and using a spectrometer as described here. The HTS NMR instrument has several components. The magnet is a high temperature superconducting (HTS) magnet (MR 9T4-54, iron-yoke NMR magnet) supplied by HTS-110 (Lower Hutt, New Zealand) and operating at 9.40 T (400.32 MHz for ^{1}H observation). The magnet always operates in the driven mode with current regulated by a high-stability power supply (Danfysik System 8500 model 854, Taastrup, Denmark). The cooling of the magnet is achieved by a Cryomech PT807 (Syracuse, NY, USA) pulse-tube cooler with a Cryomech CP2800 helium compressor. An air-cooled chiller (Huber Unichiller 040T, Offenburg, Germany) provides water cooling to the power supply. The shims used in the HTS magnet are passive ferromagnetic shims instead of the typical active superconducting shims found in standard commercial cryogen-bath magnets. The NMR console is an AVANCE III HD NMR (Bruker BioSpin, Billerica, MA, USA). The probe is a 5 mm Bruker multinuclear broadband fluorine observe (BBFO) (^{1}H on outer coil, inner coil tunable from ^{109}Ag – ^{19}F, coil length 24 mm). Additionally, the conventional NMR system was fitted with a BCU-II preconditioner to cool the incoming sample temperature control gas, allowing operation at, below or above room temperature. The shimstack is a Bruker orthogonal shim system-3 (BOSS3) with 38 shims. Additional information on this NMR system can be found in previous publications with details of electrical requirements and foot-print of the instrument.[3,4]

The reaction was carried out in sealed NMR tube (photoNMR sampling device-5mm, cat# NE-396-5-Br, New Era Enterprises, Inc., Vineland, New Jersey, USA) at 80 °C. Two alternating measurements were acquired over a period of up to 1 hr. These were a 1D ^{1}H NMR (400.32 MHz for ^{1}H observation) and a 1D ^{19}F NMR with inverse gated ^{1}H decoupling (376.64 MHz for ^{19}F observation). Chemical shift references are assigned to the residual solvent peak to 1.94 ppm for acetonitrile-d_3 for ^{1}H, the internal instrument default chemical shift reference to $CFCl_3$ liquid at 0.00 ppm for ^{19}F. The probe was matched, tuned and shimmed to the solvent selected in the sample after temperature equilibration. Topspin (version 3.6.2, Bruker Biospin, Billerica, MA, USA) was set to acquire in automation multiple spectra using the command multizg.The processing of the data was performed with Mnova (version 14) software package (Mestrelab Research, SL, Santiago de Compostela, Spain).

Optimization Conditions For Bromination.

General Experimental - A 10 mL volumetric flask is charged with **1** (822 mg, 5.30 mmol, 1 equiv.) followed by the addition of 6 mL of acetonitrile. Then *N*-bromosuccinimide (1.18 g, 6.63 mmol, 1.25 equiv. (or appropriate amount)) and appropriate additive were charged to the volumetric flask followed by the appropriate amount of acetonitrile to bring the final volume to 10 mL (530 mM concentration with respect to **1**). Using 1-dram vials 2.8 mL of this solution is dispensed into the vial and the vial is then placed in a water bath heated to 80 °C and irradiated (vials are ~3 cm from the light source, see picture below) for the appropriate time to furnish a

mixture of **1**, **2,** and **3** with the assay yield determined by calibrated HPLC. Assay yields vary from 100% mass balance due to variations in sample and preparation.

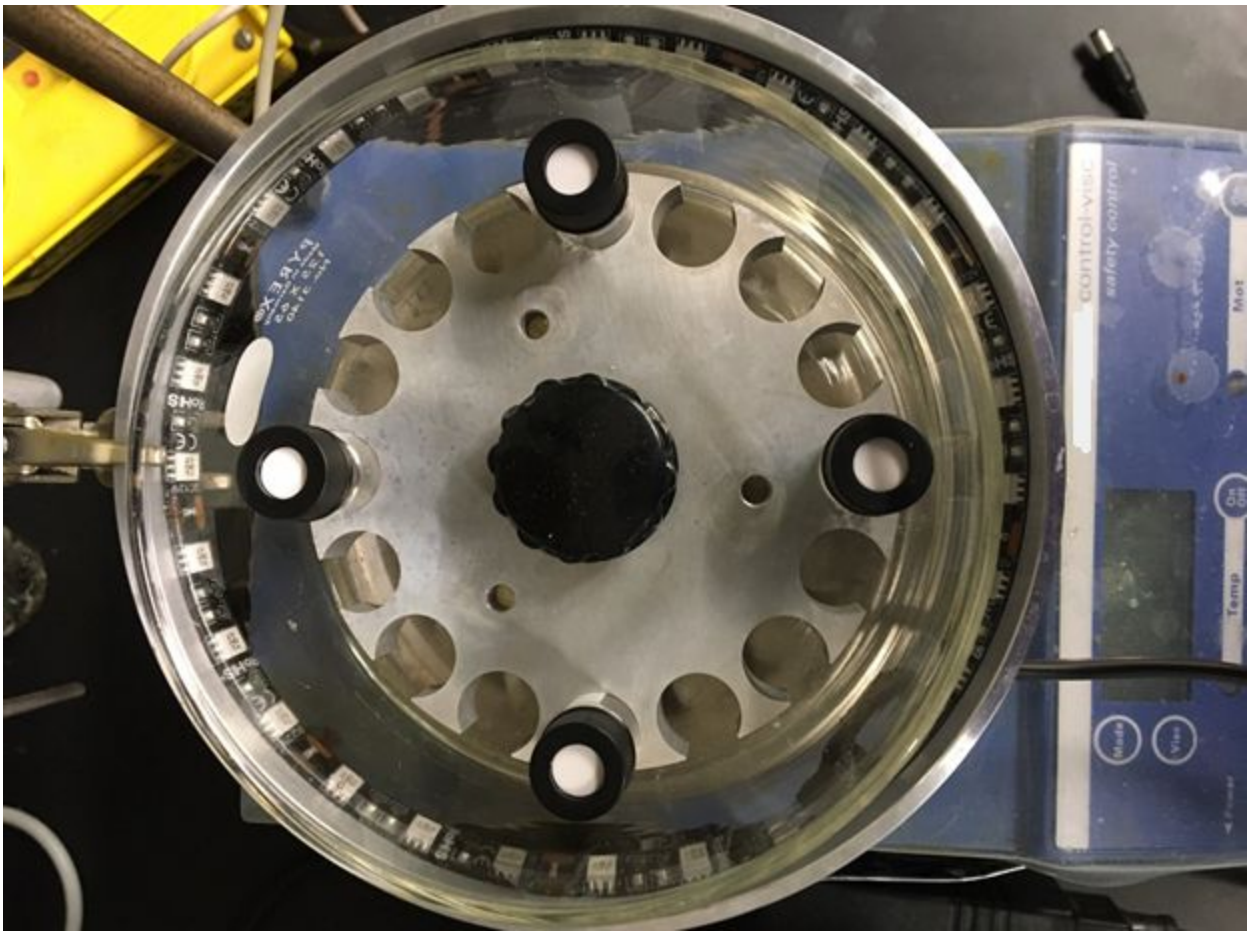


FNT 1 | FNB 2 | $FNBr_2$ 3

Table S1. Optimization Conditions For Bromination

Entry	Solvent (0.530 M)	Brominating Reagent (Equiv)	Temperature[a]	Time (minutes)	Additive (Equiv)	Yield 2 (FNB)[b]	Yield 3 ($FNBr_2$)[b]	Yield 1 (FNT)[b]
1	CH_3CN	NBS (1.0)	25-30 °C	360	None	75	6	14
2	CH_3CN	NBS (1.25)	25-30 °C	360	None	78	9	8
3	CH_3CN	NBS (1.50)	25-30 °C	360	None	75	15	2
4	CH_3CN[c]	NBS (1.50)	25-30 °C	360	None	0	0	100
5	CH_3CN:AcOH (1:1)	NBS (1.0)	25-30 °C	180	None	79	10	9
6	CH_3CN:AcOH (1:1)	NBS (1.25)	25-30 °C	180	None	73	21	2
7	CH_3CN:AcOH (1:1)	NBS (1.50)	25-30 °C	180	None	53	41	0
8	CH_3CN	Bromine (1.25)	25-30 °C	360	None	<1	0	99
9	CH_3CN	NBS (1.0)	25-30 °C	180	Bromine (0.25)	80	6	19
10	CH_3CN	DBDMH (0.6)[d]	25-30 °C	360	None	81	7	13
11	CH_3CN:AcOH (1:1)	DBDMH (0.6)[d]	25-30 °C	180	None	81	13	6
12	CH_3CN:TFA (1:1)	NBS (1.25)	25-30 °C	180	None	68	22	3
13	CH_3CN	NBS (1.25)	25-30 °C	60	TFA (1.0)	80	18	2
14	CH_3CN	NBS (1.25)	25-30 °C	60	TFA (5.0)	76	20	2
15	CH_3CN	NBS (1.25)	25-30 °C	60	AcOH (1.0)	54	2	43
16	CH_3CN	NBS (1.25)	25-30 °C	60	AcOH (5.0)	68	3	27
17	CH_3CN	NBS (1.25)	40 °C	25	TFA (1.0)	81	18	2
18	CH_3CN	NBS (1.25)	60 °C	15	TFA (1.0)	78	19	3
19	CH_3CN	NBS (1.25)	80 °C	10	TFA (1.0)	83	22	4
20	CH_3CN	NBS (1.25)	80 °C	15	TFA (0.25)	83	18	5

[a]Reactions conducted close to room temperature had slight variations due to heat output from LEDs. [b]Assay yields determined by HPLC. [c]Control experiment ran without exposure to 435-445 nm LED light. [d]DBDMH = 1,3-Dibromo-5,5-dimethylhydantoin



Picture of reaction set up for conduction bromination reactions in vials.

Continuous Process For Production Of PIPN HBr.

Experimental - A 2L Schott bottle is charged with acetonitrile (1087 mL) followed by the addition of **1** (100 g, 647 mmol, 1 equiv.), *N*-bromosuccinimide (144 g, 806 mmol, 1.25 equiv.) and tri-fluoroacetic acid (18.4 g, 12.0 mL, 161 mmol, 0.25 equiv.).

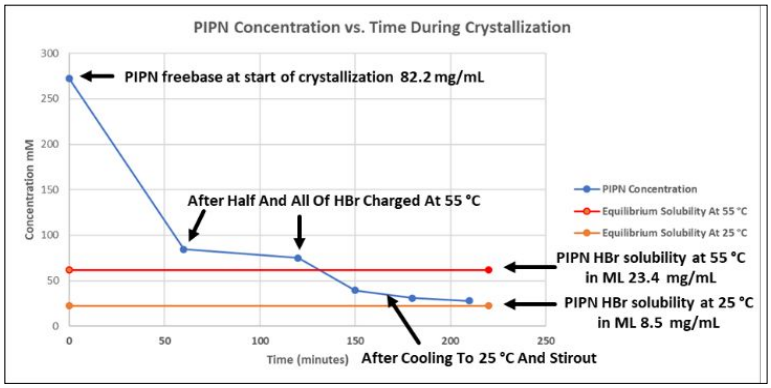
A second 250 mL Schott bottle is charged with methanol (100 mL) followed by the addition diethyl phosphite (33.2 mL, 258 mmol, 0.4 equiv.) and DIPEA (73 mL, 419 mmol, 0.65 equiv).

A third Schott bottle was charged with methanol (300 mL) followed by 5 (144 g, 648 mmol, 1 equiv.) and DIPEA (281 mL, 1611 mmol, 2.5 equiv). The mixture was filtered through a pad of Celite and then washed with methanol (170 mL). The combined filtrate was transferred back to the Schott bottle.

The acetonitrile solution of 1, *N*-bromosuccinimide, and trifluoroacetic acid was then pumped though a coiled tube PFR (⅛" ID, ¼" OD PFA tubing) irradi-ated under 435-445 nm LEDs (in this case a stack of 4 LEDs was used to cover the length of the PFR at a distance of 3 cm) and submerged in a thermostated water bath maintained at 77 °C at a rate of 2.9 mL/min (total residence time of 20 minutes). This stream was then joined together with the stream of diethyl

phosphite and DIPEA in methanol pumped at 0.46 mL/min at a T-mixer joint. The outgoing combined stream was then pumped though a coiled tube PFR sub-merged in a thermostated water bath maintained at 50 °C at a rate of 3.36 mL/min (total residence time of 13 minutes). Finally, this stream was then joined together with the stream of 5 and DIPEA in methanol pumped at 1.65 mL/min at a T-mixer joint. The outgoing combined stream was then pumped though a coiled tube PFR submerged in a thermostated water bath maintained at 60 °C at a rate of 5.01 mL/min (total res-idence time of 12.5 minutes). The resulting crude steam of PIPN was collected in a Schott bottle at 25 °C.

A seed bed of **6** was then prepared by charging a 1L jacketed reactor with acetonitrile (80 mL) and 6 (1.4 g) and heating the batch to 55 °C. To the seed bed was then added simultaneously 590 mL of the crude PIPN solution (concentration 82.2 mg/mL of crude PIPN, 48.5 g, 163 mmol) at a rate of 300 mL/h and concentrated HBr (48 wt/wt%, 45.6 mL, 408 mmol, 2.5 equiv. relative to crude PIPN) at a rate of 22.8 mL/h. The batch was then cooled to 25 °C over 30 minutes followed by and addition stir out at 25 °C for 1 hour. The mixture was then filtered, and the cake washed with 3 x 100 mL acetonitrile washings at 55 °C. After drying, 50.7 g of **6** was obtained as a white solid for an overall 82% yield.



Picture of crystallization set up and solubility data from crystallization.

Reaction data for on-line HPLC monitoring could be captured by equipping a in-line flow cell for HPLC sampling. An example of data collected is shown below for monitoring the reaction stream after exiting the second PFR.

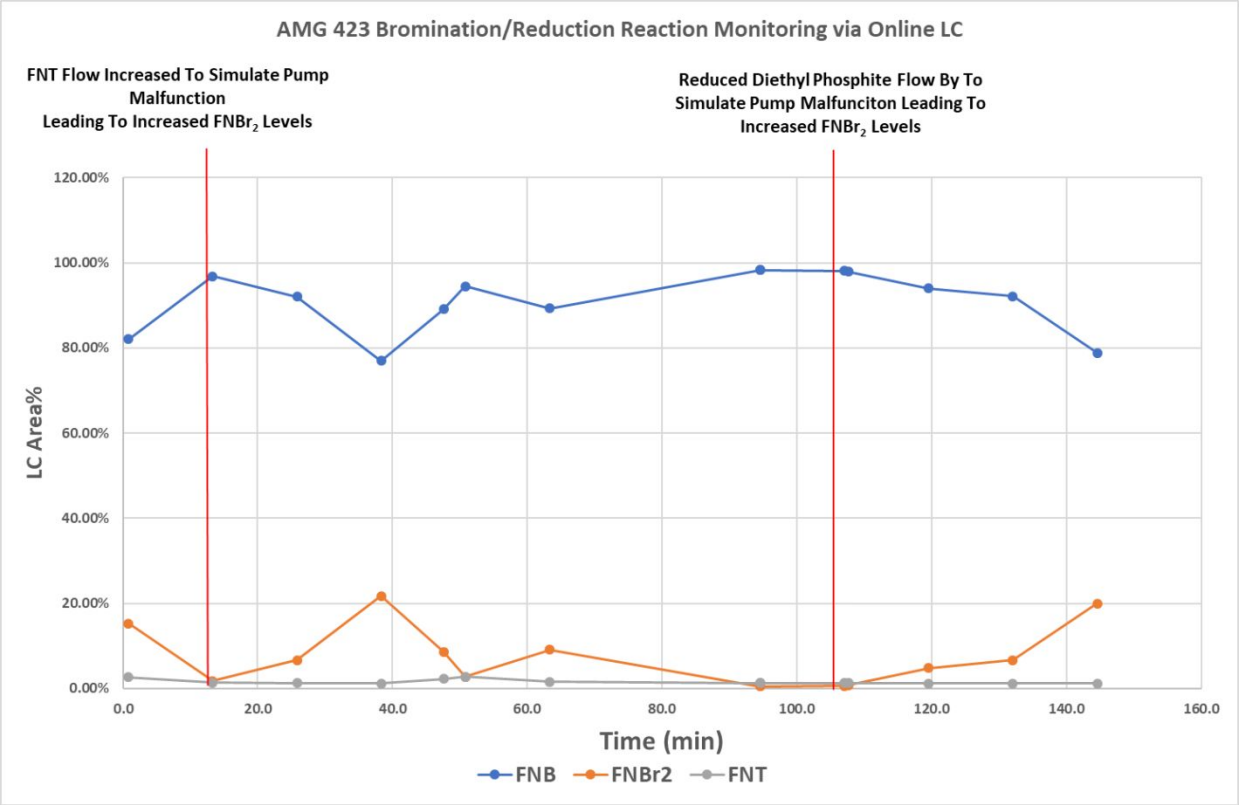


Figure S1. On-Line HPLC Data

Table S2. HPLC Area% Data For On-Line HPLC

Time (min)	FNB (Area%)	$FNBr_2$ (Area%)	FNT (Area%)
0.8	82.04%	15.28%	2.68%
13.3	96.80%	1.77%	1.43%
25.8	92.02%	6.71%	1.27%
38.3	77.02%	21.74%	1.24%
47.6	89.12%	8.60%	2.28%
50.8	94.49%	2.78%	2.74%
63.3	89.28%	9.09%	1.63%
94.5	98.26%	0.48%	1.26%
94.6	98.27%	0.47%	1.26%
107.1	98.11%	0.60%	1.29%
107.7	97.89%	0.83%	1.29%
119.5	94.01%	4.81%	1.18%
132.1	92.13%	6.70%	1.17%
144.6	78.88%	19.95%	1.17%

Control And Kinetic Experiments

General Experimental - A 10 mL volumetric flask is charged with **1** (822 mg, 5.30 mmol, 1 equiv.) followed by the addition of 6 mL of d_3-acetonitilre. Then *N*-bromosuccinimide (1.18 g, 6.63 mmol, 1.25 equiv. (or appropriate amount)) and appropriate additive were charged to the volumetric flask followed by the appropriate amount of d_3-acetonitilre to bring the final volume to 10 mL (530 mM concentration with respect to **1**). Then 0.5 mL of this solution is dispensed into separate NMR tubes and then placed in a water bath heated to 80 °C and irradiated for the appropriate time to furnish a mixture of **1**, **2,** and **3** with the assay yield determined by NMR.

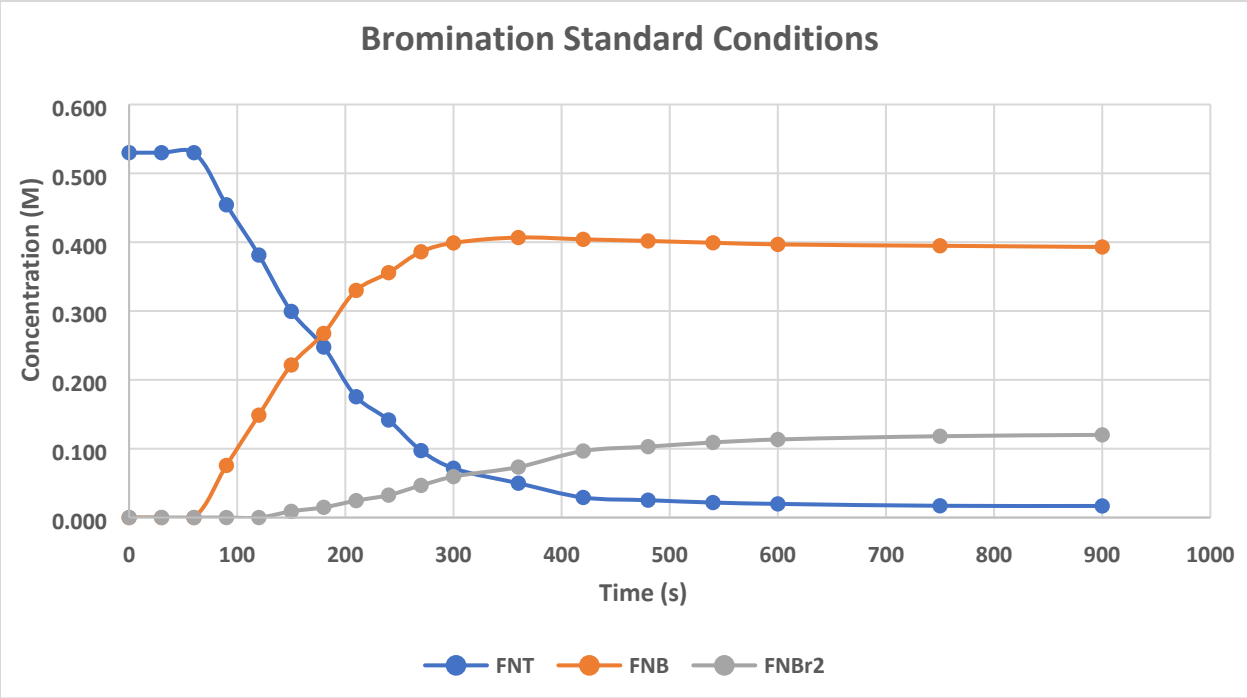


Figure S2. Standard Bromination Conditions

Experiment	[FNT **1**] (mM)	[NBS] (mM)	[TFA] (mM)
Standard Conditions	530	663	133

Table S3. Concentrations Under Standard Bromination Conditions

Time (s)	FNT Concentration (M)	FNB Concentration (M)	$FNBr_2$ Concentration (M)
0	0.530	0.000	0.000
30	0.530	0.000	0.000
60	0.530	0.000	0.000
90	0.454	0.076	0.000
120	0.381	0.149	0.000
150	0.299	0.222	0.009
180	0.248	0.267	0.015
210	0.175	0.330	0.025

240	0.142	0.356	0.033
270	0.097	0.386	0.047
300	0.072	0.399	0.059
360	0.050	0.407	0.073
420	0.029	0.404	0.097
480	0.025	0.402	0.103
540	0.022	0.399	0.109
600	0.020	0.397	0.113
750	0.017	0.395	0.118
900	0.017	0.393	0.120

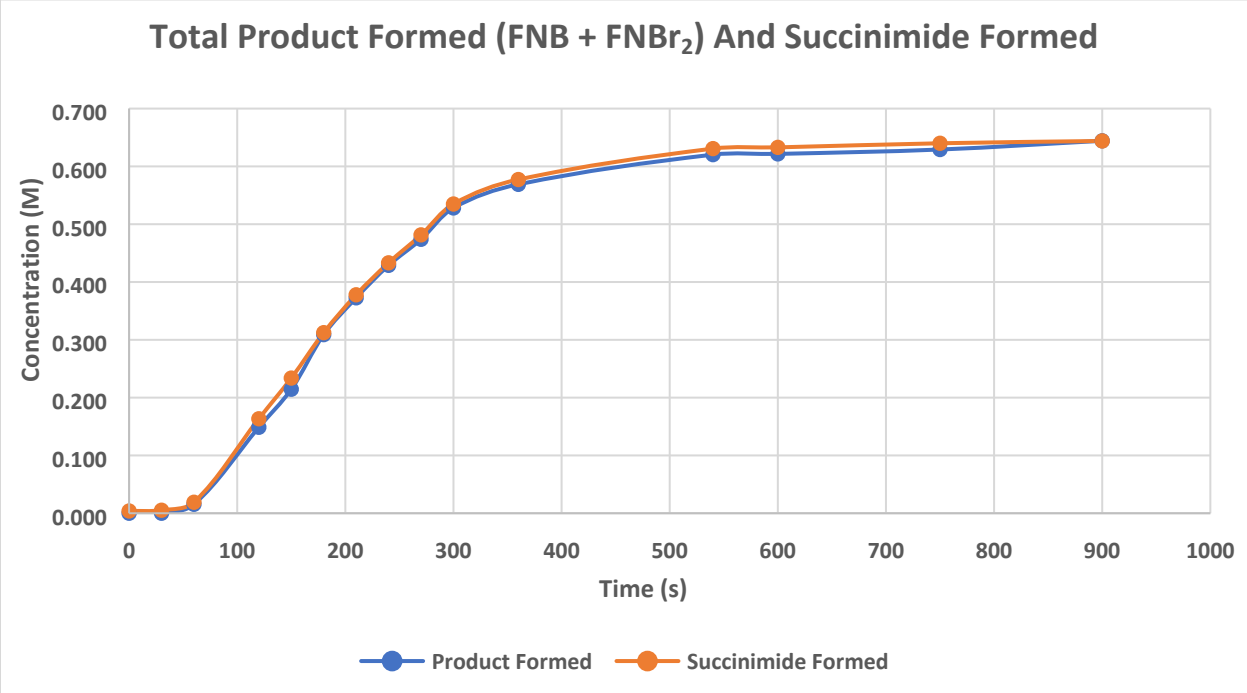


Figure S3. Product And Succinimide Formed Under Standard Conditions

Experiment	[FNT **1**] (mM)	[NBS] (mM)	[TFA] (mM)
Standard Conditions	530	663	133

Table S4. Product And Succinimide Concentrations Formed Under Standard Conditions

Time (s)	Total Product Formed (M)	Succinimide Formed (M)
0	0.000	0.004
30	0.000	0.005
60	0.015	0.019
120	0.149	0.163
150	0.215	0.234
180	0.309	0.312

210	0.373	0.378
240	0.429	0.433
270	0.474	0.482
300	0.528	0.535
360	0.569	0.577
540	0.620	0.631
600	0.622	0.633
750	0.629	0.640
900	0.644	0.644

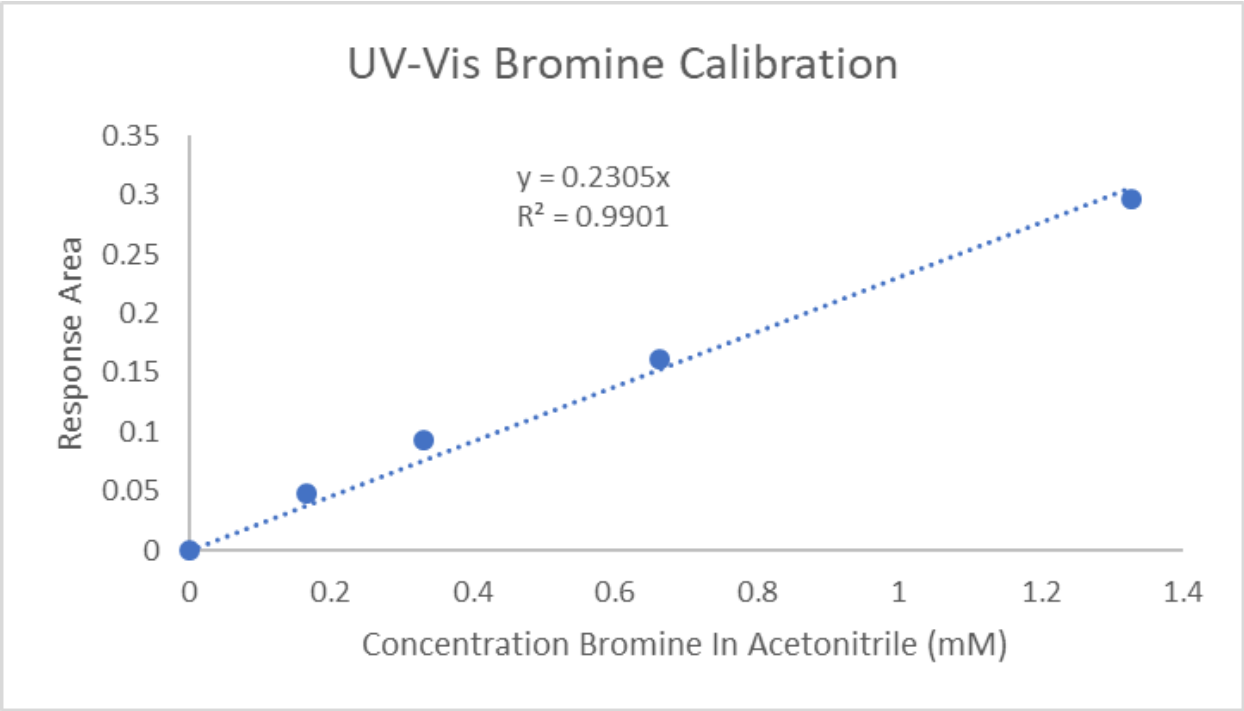


Figure S4. UV-Vis Calibration Curve For Bromine Assay

Table S5. Bromine Calibration Solutions In Acetonitrile

Bromine Concentration (mM)	UV Response At 395 nm
1.326575308	0.29637
0.663287654	0.16099
0.331643827	0.092756
0.165821914	0.048348
0	0

Experimental For Measuring Bromine Concentration - A 10 mL volumetric flask is charged with *N*-bromosuccinimide (1.18 g, 6.63 mmol) and 6 mL of d_3-acetonitilre. Then trifluoroacetic acid (0.100 mL, 1.33 mmol) was charged to the volumetric flask followed by the appropriate amount of d_3-acetonitilre to bring the final volume to 10 mL. Then 0.5 mL of this solution is

dispensed into separate NMR tubes, placed in a water bath heated to 80 °C, and irradiated for the appropriate time after which samples were diluted with acetonitrile and assayed by UV-Vis from bromine content.

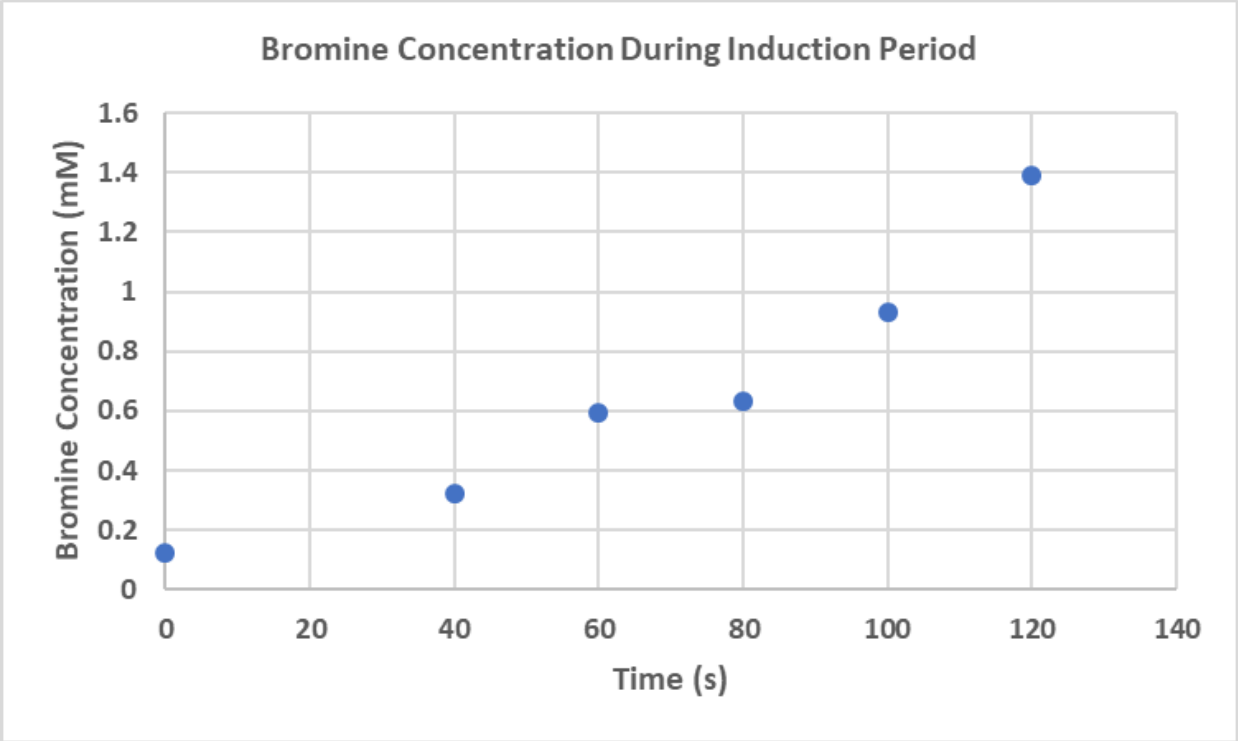


Figure S5. Bromine Concentration During Induction Period

Experiment	[FNT **1**] (mM)	[NBS] (mM)	[TFA] (mM)
Measuring Bromine During Induction	N/A	663	133

Table S6. Bromine Assay During Induction Period

Time (s)	Bromine Concentration (mM)	UV Response At 395 nm
0	0.124283297	0.0286473
40	0.321483731	0.074102
60	0.595305857	0.137218
80	0.629796095	0.145168
100	0.931019523	0.2146
120	1.392190889	0.3209

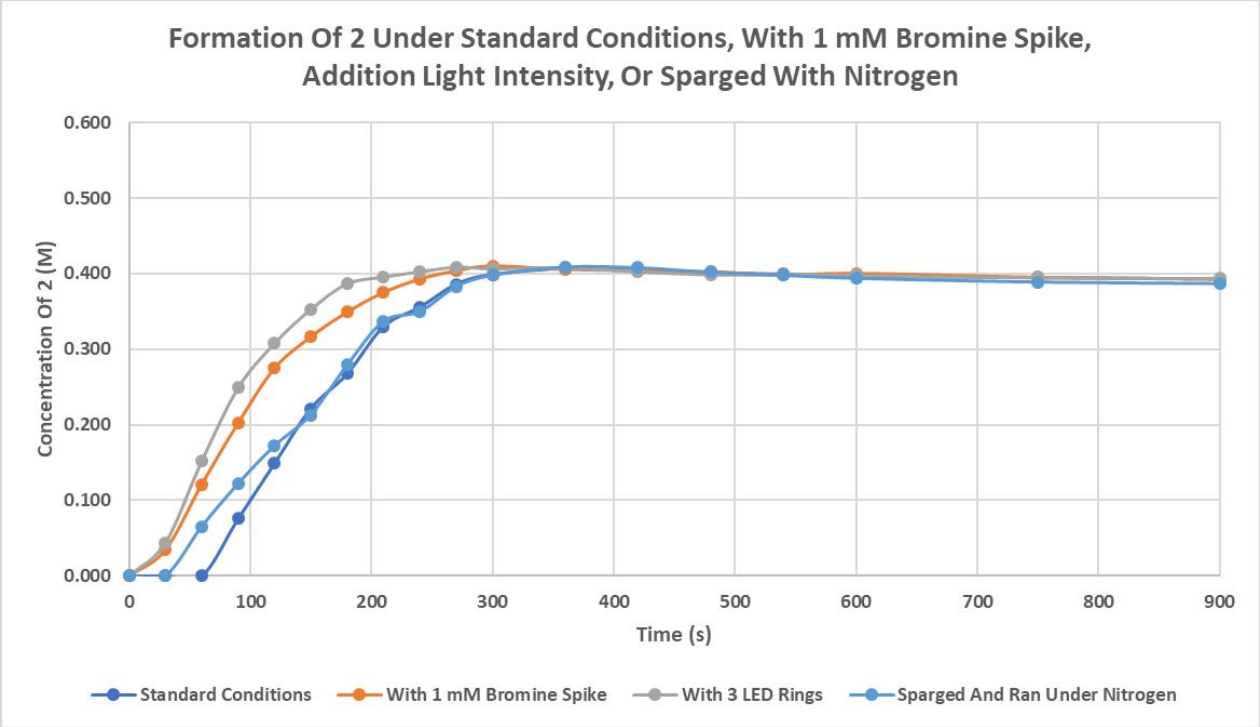


Figure S6. Comparison Of Standard Conditions With 1 mM Bromine Spike And High Light Intensity

Experiment	[FNT **1**] (mM)	[NBS] (mM)	[TFA] (mM)
Standard Conditions	530	663	133
With 1 mM Bromine Spike	530	663	133
With 3 LED Rings Instead Of 1	530	663	133
Sparged And Ran Under Nitrogen	530	663	133

Table S7. FNB Concentrations For Standard Conditions, 1mM Spike, Higher Light Intensity, Or Sparged With Nitrogen

Time (s)	Standard Conditions FNB Concentration (M)	1 mM Bromine Spike FNB Concentration (M)	With 3 LED Rings FNB Concentration (M)	Sparged And Ran Under Nitrogen FNB Concentration (M)
0	0.000	0.000	0.000	0.000
30	0.000	0.035	0.044	0.000
60	0.000	0.121	0.152	0.065
90	0.076	0.202	0.249	0.122
120	0.149	0.275	0.308	0.172
150	0.222	0.316	0.353	0.213
180	0.267	0.349	0.387	0.279
210	0.330	0.375	0.396	0.337
240	0.356	0.393	0.403	0.35
270	0.386	0.404	0.409	0.383

300	0.399	0.410	0.407	0.398
360	0.407	0.406	0.408	0.409
420	0.404	0.404	0.403	0.408
480	0.402	0.403	0.399	0.402
540	0.399	0.398	0.399	0.398
600	0.397	0.400	0.398	0.394
750	0.395	0.395	0.395	0.389
900	0.393	0.393	0.394	0.387

Experimental For "On-Off" Procedure - A 10 mL volumetric flask is charged with **1** (822 mg, 5.30 mmol, 1 equiv.) followed by the addition of 6 mL of d_3-acetonitilre. Then *N*-bromosuccinimide (1.18 g, 6.63 mmol, 1.25 equiv.) and trifluoroacetic acid (0.100 mL, 1.33 mmol, 0.25 equiv.) were charged to the volumetric flask followed by the appropriate amount of d_3-acetonitilre to bring the final volume to 10 mL (530 mM concentration with respect to **1**). Then 0.5 mL of this solution is dispensed into separate NMR tubes and then placed in a water bath heated to 80 °C and irradiated for the appropriate time to furnish a mixture of **1**, **2,** and **3** with the assay yield determined by NMR.

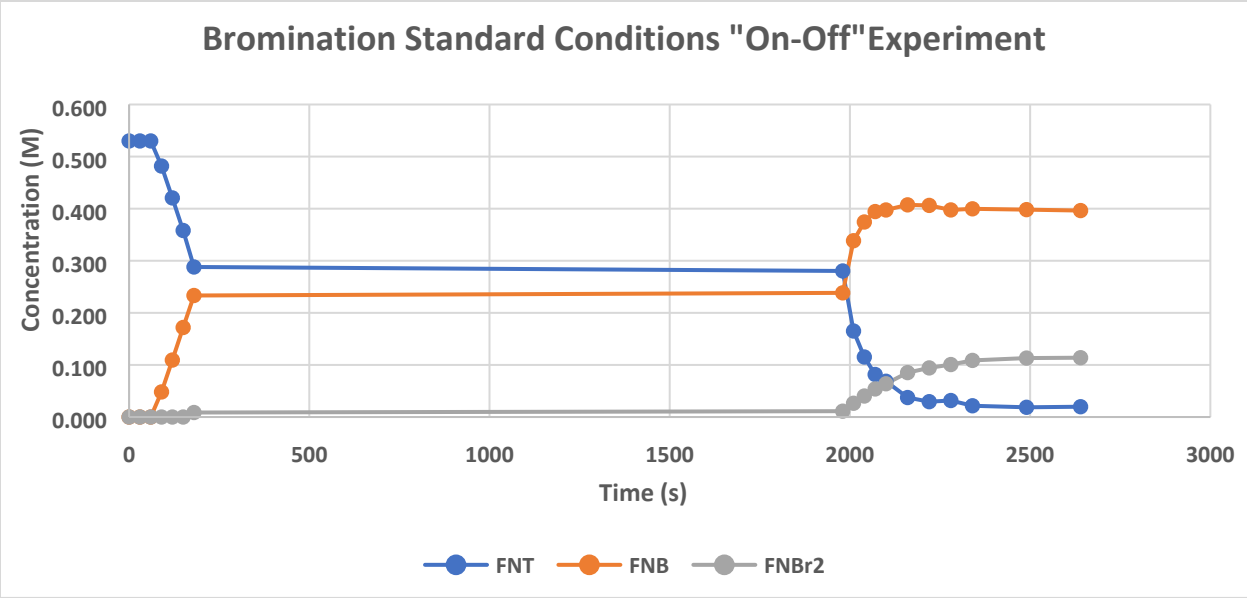


Figure S7. "On-Off" Experiment Under Standard Conditions

Experiment	[FNT **1**] (mM)	[NBS] (mM)	[TFA] (mM)
Standard Conditions	530	663	133

Table S8. Concentrations Under "On-Off" Conditions

Time (s)	FNT Concentration	FNB Concentration	$FNBr_2$ Concentration
0	0.530	0.000	0.000
30	0.530	0.000	0.000

60	0.530	0.000	0.000
90	0.482	0.048	0.000
120	0.421	0.109	0.000
150	0.358	0.172	0.000
180 (Light Turned Off)	0.288	0.233	0.009
1980 (Light Turned Back On)	0.280	0.238	0.011
2010	0.165	0.338	0.026
2040	0.115	0.374	0.040
2070	0.082	0.394	0.054
2100	0.069	0.398	0.064
2160	0.037	0.407	0.085
2220	0.029	0.406	0.094
2280	0.032	0.398	0.101
2340	0.022	0.400	0.109
2490	0.019	0.398	0.113
2640	0.020	0.396	0.114

Experimental For NBS Stability With TFA - A 10 mL volumetric flask is charged with *N*-bromosuccinimide (1.18 g, 6.63 mmol) and 6 mL of d_3-acetonitilre. Then trifluoroacetic acid (0.100 mL, 1.33 mmol) was charged to the volumetric flask followed by the appropriate amount of d_3-acetonitilre to bring the final volume to 10 mL. Then 0.5 mL of this solution is dispensed into a NMR tube, placed in the NMR spectrometer heated to 80 °C, and irradiated using the fiber optic set up. The concentration is monitored by NMR using the known starting concentration of NBS as the starting value.

Experimental For NBS Stability Without TFA - A 10 mL volumetric flask is charged with *N*-bromosuccinimide (1.18 g, 6.63 mmol) and the appropriate amount of d_3-acetonitilre to bring the final volume to 10 mL. Then 0.5 mL of this solution is dispensed into a NMR tube, placed in the NMR spectrometer heated to 80 °C, and irradiated using the fiber optic set up. The concentration is monitored by NMR using the known starting concentration of NBS as the starting value.

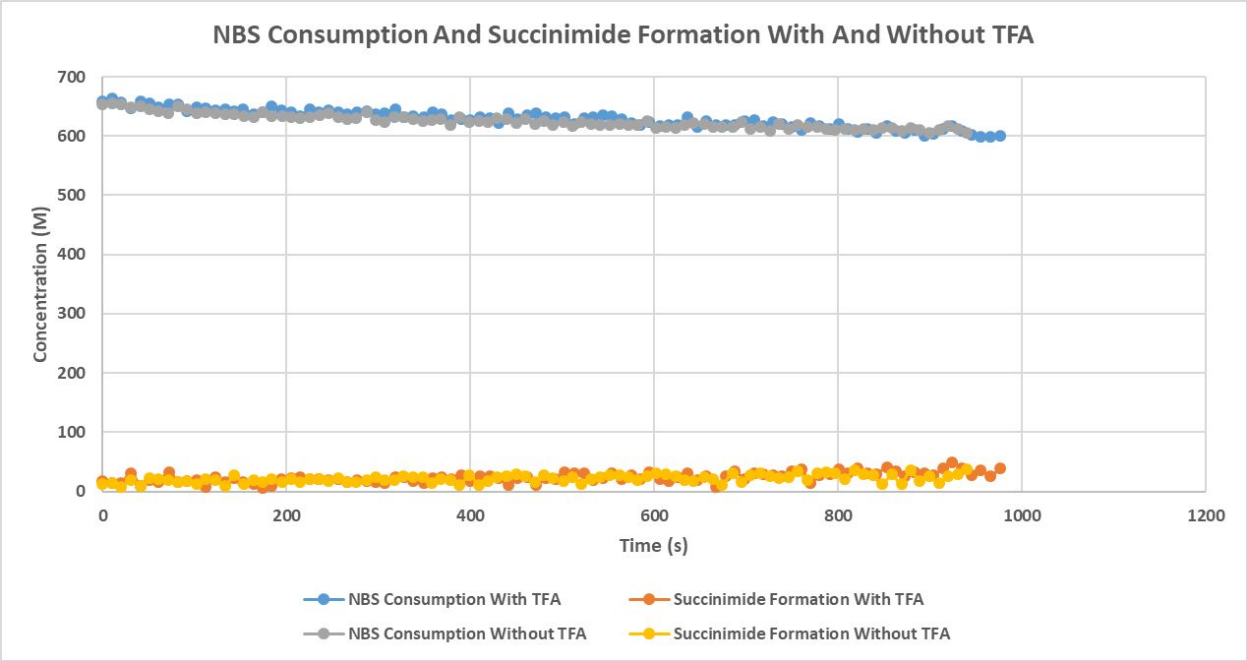


Figure S8. NBS Consumption And Succinimide Formation With And Without TFA

Experiment	[FNT **1**] (mM)	[NBS] (mM)	[TFA] (mM)
With TFA	N/A	663	133
Without TFA	N/A	663	N/A

Table S9. Concentration Of NBS And Succinimide With TFA

Time (s)	NBS Concentration (mM)	Succinimide Concentration (mM)
0	658.838	16.936
10	663.645	14.017
20	656.35	13.597
31	646.377	31.666
41	658.002	8.996
51	654.78	19.742
61	648.56	16.762
72	653.325	32.297
82	653.698	15.76
92	642.036	16.805
102	648.889	20.05
112	647.187	7.201
123	643.177	24.351
133	644.952	16.023
143	641.08	21.986
153	644.917	15.311
164	636.763	12.22

174	640.47	6.504
184	650.363	9.434
194	644.356	20.767
205	640.483	23.209
215	633.143	24.378
225	644.949	20.484
235	639.522	21.363
246	643.612	18.832
256	640.959	21.663
266	637.332	16.689
277	640.954	19.947
287	641.351	17.338
297	636.399	16.05
307	638.021	14.647
318	645.138	24.545
328	632.708	24.588
338	632.83	17.737
349	631.61	13.522
359	640.622	22.508
369	637.083	23.605
379	627.453	20.667
390	628.965	26.892
400	626.124	18.264
410	632.434	25.921
421	629.819	25.643
431	621.884	22.515
441	638.14	10.26
451	628.309	22.586
462	634.883	24.882
472	638.226	10.579
482	631.12	22.83
493	630.537	21.291
503	632.025	32.785
513	620.228	30.238
524	629.826	31.004
534	632.177	18.649
544	634.531	22.169
554	632.826	30.475
565	628.606	21.559
575	621.383	28.278
585	618.183	20.702

595	623.537	31.923
606	617.2	20.867
616	618.722	18.348
626	617.943	23.676
636	632.108	30.252
647	616.123	19.34
657	625.164	25.396
667	618.873	7.288
678	617.803	26.181
688	618.229	33.952
698	625.176	21.661
709	627.143	31.455
719	617.6	29.642
729	624.015	27.487
739	619.76	26.635
750	615.671	34.062
760	610.853	37
770	621.19	14.303
780	617.485	28.404
791	612.731	28.564
801	621.087	36.818
811	612.372	31.075
821	606.303	39.551
832	612.675	31.237
842	605.802	29.539
853	616.907	40.589
863	608.131	34.284
873	605.946	26.521
883	609.925	32.787
894	601.091	31.413
904	603.771	27.991
914	611.458	38.699
924	616.778	49.478
935	608.469	38.705
945	602.3	28.049
955	599.262	35.988
966	599.448	25.658
976	600.926	39.333

Table S10. Concentration Of NBS And Succinimide Without TFA

Time (s)	NBS Concentration (mM)	Succinimide Concentration (mM)

0	652.964	12.542
10	654.934	14.29
20	654.098	8.419
31	648.597	19.818
41	650.381	9.985
51	644.705	21.987
61	642.477	20.534
71	637.976	19.604
82	650.339	15.514
92	644.838	17.274
102	638.395	11.996
112	640.246	20.464
123	638.614	18.497
133	637.705	9.347
143	636.247	27.117
154	633.906	13.251
164	631.123	19.471
174	640.571	15.764
184	632.971	20.178
195	632.884	16.061
205	632.486	21.281
215	630.063	16.343
225	631.948	21.249
236	634.413	20.191
246	638.21	17.289
256	631.664	22.97
266	628.187	15.824
276	630.446	15.472
287	640.419	18.953
297	626.685	24.552
307	624.296	19.001
317	631.324	19.971
327	631.119	26.715
338	628.228	25.052
348	625.314	23.956
358	626.788	13.665
368	629.228	20.436
378	619.096	19.006
388	631.55	10.183
399	623.758	28.332
409	625.401	11.215

419	624.344	18.403
429	629.982	24.708
439	629.17	25.119
450	622.521	28.77
460	627.785	26.088
470	620.602	15.65
480	624.471	27.718
490	618.421	21.815
501	623.549	17.551
511	616.623	23.93
521	623.093	11.891
531	621.045	20.155
541	618.127	24.673
552	618.937	27.3
562	619.505	27.648
572	619.436	24.144
582	618.529	19.879
592	625.432	25.219
602	613.507	31.028
613	615.65	29.373
623	613.3	25.583
633	618.483	18.774
643	622.08	18.28
654	620.476	24.326
664	616.098	21.237
674	615.014	11.739
685	615.776	30.512
695	623.745	15.636
705	612.033	28.045
715	615.371	30.122
726	608.883	25.802
736	620.457	22.677
746	612.224	24.83
756	619.013	34.27
767	614.847	20.038
777	614.735	30.294
787	612.664	33.013
797	609.878	30.735
807	611.923	21.754
818	610.677	35.072
828	612.137	29.388

838	610.513	27.988
848	613.203	12.848
859	614.476	28.454
869	609.444	13.322
879	614.038	35.394
889	611.043	17.84
899	605.685	25.714
910	610.33	13.985
920	616.39	26.617
930	611.843	28.784
940	606.095	38.34

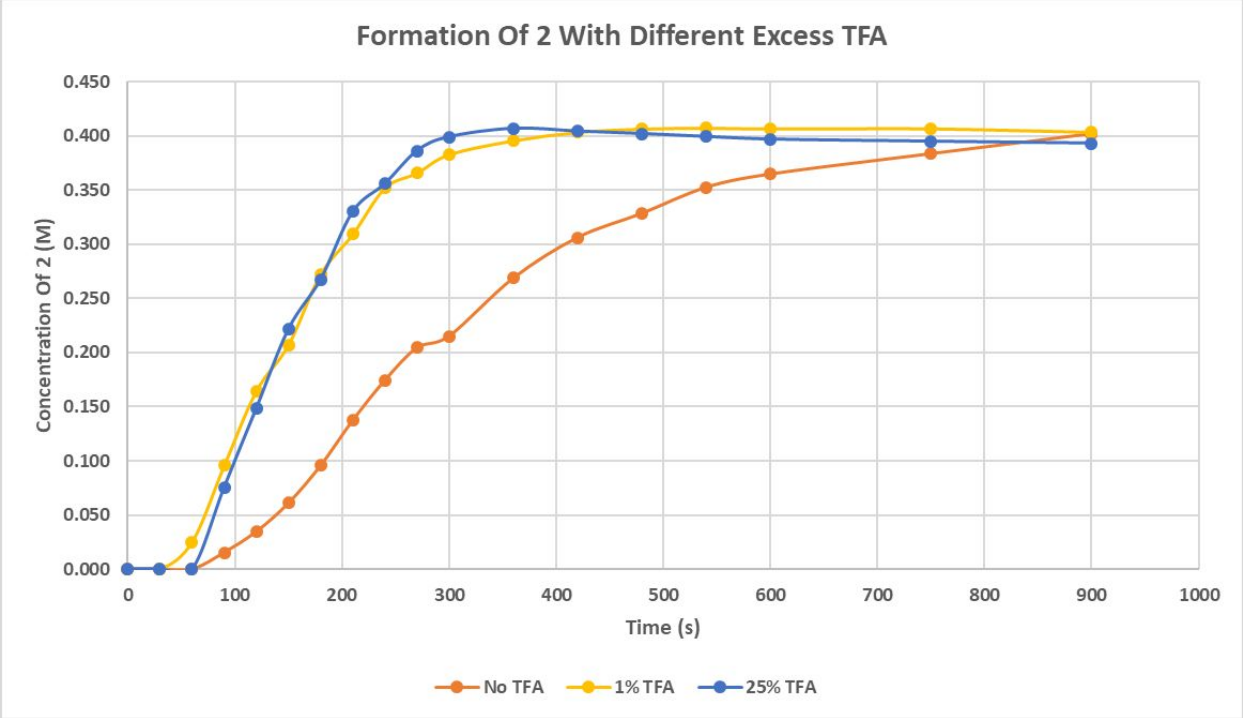


Figure S9. Reactions With Varying TFA Concentration

Experiment	[FNT **1**] (mM)	[NBS] (mM)	[TFA] (mM)
No TFA	530	663	N/A
1% TFA	530	663	5.3
25% TFA	530	663	133

Table S11. Concentration Of FNB With Varying TFA

Time (s)	No TFA FNB Concentration (M)	1% TFA FNB Concentration (M)	25% TFA FNB Concentration (M)

0	0.000	0.000	0.000
30	0.000	0.000	0.000
60	0.000	0.025	0.000
90	0.015	0.096	0.076
120	0.035	0.164	0.149
150	0.061	0.207	0.222
180	0.096	0.272	0.267
210	0.137	0.309	0.330
240	0.174	0.352	0.356
270	0.204	0.366	0.386
300	0.215	0.383	0.399
360	0.269	0.396	0.407
420	0.306	0.403	0.404
480	0.328	0.407	0.402
540	0.352	0.407	0.399
600	0.365	0.407	0.397
750	0.383	0.407	0.395
900	0.402	0.404	0.393

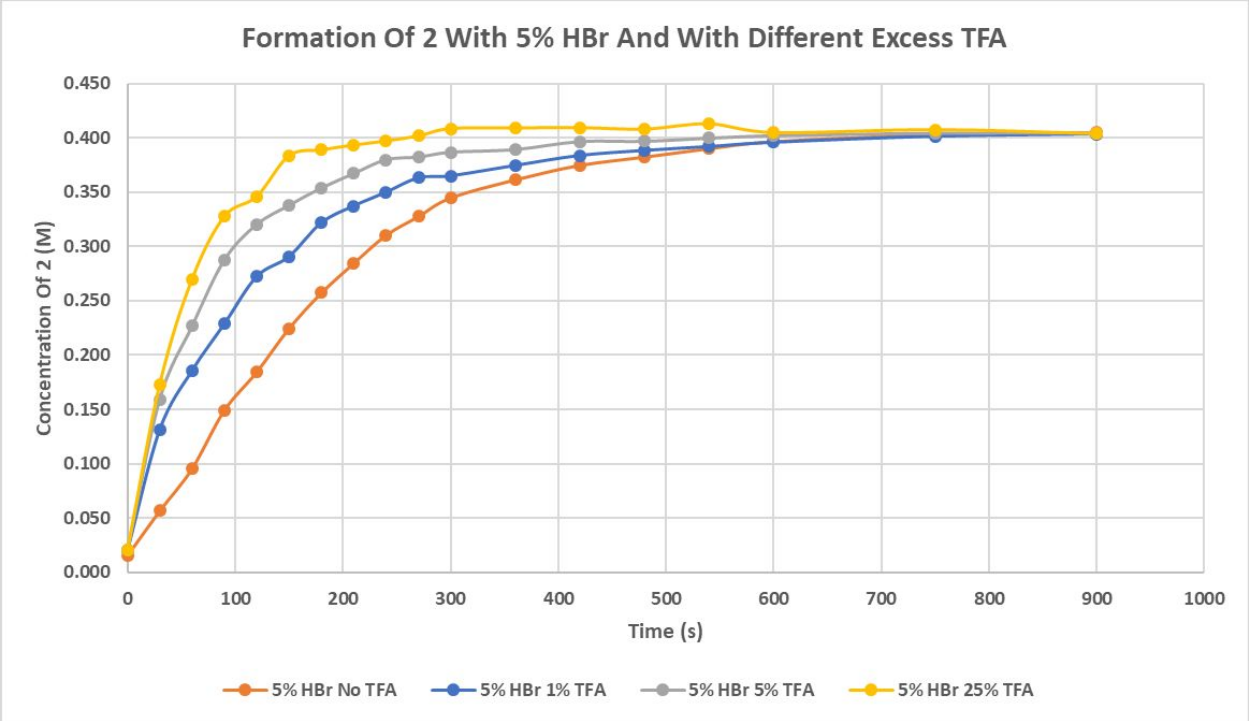


Figure S10. Reactions With Varying TFA Concentration And 5% HBr

Experiment	[FNT **1**] (mM)	[NBS] (mM)	[TFA] (mM)
No TFA, 5% HBr	530	663	N/A

1% TFA, 5% HBr	530	663	5.3
5% TFA, 5% HBr	530	663	26.6
25% TFA, 5% HBr	530	663	133

Table S12. Concentration Of FNB With Varying TFA And 5% HBr

Time (s)	5% HBr, No TFA FNB Concentration (M)	5% HBr, 1% TFA FNB Concentration (M)	5% HBr, 1% TFA FNB Concentration (M)	5% HBr, 25% TFA FNB Concentration (M)
0	0.015	0.020	0.020	0.020
30	0.057	0.132	0.159	0.173
60	0.096	0.186	0.227	0.270
90	0.149	0.229	0.288	0.328
120	0.184	0.272	0.320	0.346
150	0.225	0.291	0.338	0.383
180	0.257	0.322	0.354	0.389
210	0.285	0.337	0.367	0.393
240	0.310	0.350	0.380	0.397
270	0.328	0.363	0.382	0.402
300	0.345	0.365	0.387	0.408
360	0.361	0.374	0.389	0.409
420	0.375	0.384	0.397	0.409
480	0.382	0.388	0.397	0.408
540	0.390	0.392	0.400	0.413
600	0.397	0.396	0.402	0.405
750	0.403	0.401	0.404	0.407
900	0.405	0.403	0.404	0.404

Reaction Progress Kinetic Analysis (RPKA) And Variable Time Normalization Analysis (VTNA) For PhotoNMR Experiments.

Experimental Design was conducted as described by Blackmond.[5,6] Variable Time Normalization Analysis (VTNA) was conducted as described by Bures.[7,8,9] Initial rate calculations were conducted after the induction period and started from ~90-120 s depending upon the reaction.

Sample Preparation

For all photoNMR experiments the following preparation and set up was used (using the standard reactions as an example). Amounts of reagents are adjusted as described in the tables below. The time = 0 sample in MeCN-d_3 was used to conduct shimming at 80 ^{o}C with the light source off prior to collecting data.

A 10 mL volumetric flask is charged with **1** (822 mg, 5.30 mmol, 1 equiv.) followed by the addition of 6 mL of d_3-acetonitilre. Then *N*-bromosuccinimide (1.18 g, 6.63 mmol, 1.25 equiv. (or appropriate amount)) and appropriate additive were charged to the volumetric flask followed by the appropriate amount of d_3-acetonitilre to bring the final volume to 10 mL (530 mM concentration with respect to **1**). Then 0.5 mL of this solution is dispensed into a photoNMR tube (see Methods And Materials section for exact model) and then placed in the NMR (see Methods And Materials section for instrument specifications) heated to 80 °C and irradiated for the appropriate time (see Methods And Materials section for light source specifications) using the 445 nm light source head set at 500 on the current controller to furnish a mixture of **1**, **2,** and **3**.

Calculation of Concentration

The concentration of each species was calculated *via* absolute integration relative to the known concentration of FNT **1** at t_0 using ^{19}F spectroscopy.

Reaction conditions for RPKA are describe below (Table 12 and 13).

Table S13. Starting Concentrations For RPKA Experiments

Experiment	[FNT **1**] (mM)	[NBS] (mM)	[TFA] (mM)		
Standard - TFA	530	663	133		
Diff. XS [FNT] - TFA	265	663	133	[FNT]% change	50
Diff. XS [NBS] - TFA	530	331	133	[NBS]% change	50
Dif XS - [TFA] – 5 mol%	530	663	27	[TFA]% change	25
Diff. XS [TFA] – 1 mol%	530	663	5	[TFA]% change	5
Standard – No TFA	530	663	0		
Diff. XS [FNT] – No TFA	265	663	0	[FNT]% change	50
Diff. XS [NBS] – No TFA	530	331	0	[NBS]% change	50

Table S14. Mass Of Components In RPKA Experiments From Table 12 In MeCN-d_3 (5 mL)

Experiment	[FNT **1**] (mg)	[NBS] (mg)	[TFA] (mL)
Standard - TFA	411	590	0.051
Diff. XS [FNT] - TFA	206	590	0.051
Diff. XS [NBS] - TFA	411	295	0.051
Dif XS - [TFA] – 5 mol%	411	590	0.010
Diff. XS [TFA] – 1 mol%	411	590	0.002
Standard – No TFA	411	590	0
Diff. XS [FNT] – No TFA	206	590	0
Diff. XS [NBS] – No TFA	411	295	0

Standard Reaction Profile - TFA

Experiment	[FNT **1**] (mM)	[NBS] (mM)	[TFA] (mM)
Standard - TFA	530	663	133

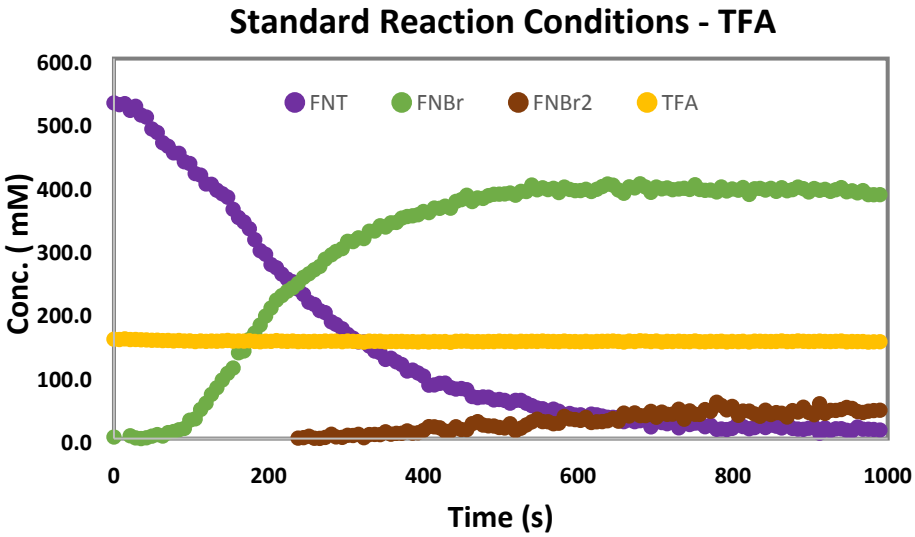


Figure S11. Reaction Progress Data For Standard Reaction Conditions

Table S15. ^{19}F NMR Reaction Progress Data For Standard Reaction Conditions

Time	FNT (mM)	FNBr (mM)	$FNBr_2$ (mM)	TFA (mM)
0	530.0	2.5		156.9
7	527.2	-1.9		156.4
14	528.9	-1.4		157.5
21	518.2	4.5		156.4
28	524.7	1.1		156.5
35	510.9	0.0		156.0

42	507.6	1.3		155.8
49	488.9	3.8		155.2
56	483.3	6.3		155.3
63	467.1	4.0		154.7
70	461.5	9.4		154.9
77	451.2	11.1		154.2
84	450.4	13.9		154.9
91	437.1	16.1		154.1
98	434.3	29.0		154.3
105	418.4	31.2		153.2
112	416.0	45.9		154.1
119	402.1	55.9		153.5
126	401.5	69.8		154.0
133	392.2	80.3		153.7
140	386.6	92.5		154.3
147	381.2	103.0		155.0
154	362.0	111.4		153.9
161	349.1	135.5		154.2
168	342.0	138.4		153.9
175	331.3	156.7		154.5
182	314.1	166.6		153.4
189	296.7	179.4		152.9
196	290.9	193.5		153.8
203	274.8	206.2		153.5
210	269.8	218.6		154.7
217	259.7	225.7		153.9
224	251.9	232.6		153.5
231	247.6	238.0		154.0
238	236.0	245.1	0.8	153.1
245	227.5	254.6	1.5	153.5
252	215.3	260.2	3.7	153.1
259	211.8	266.6	0.5	153.6
266	202.1	271.8	0.3	153.2
273	198.9	283.2	1.8	154.0
281	184.3	290.2	6.9	153.7
287	180.4	295.4	2.7	153.9
295	173.4	300.0	1.9	153.0
302	164.6	311.5	5.2	154.0
309	158.6	311.0	4.9	153.5
316	152.6	317.0	6.7	153.2
323	152.6	315.8	1.4	152.4
330	146.1	327.4	6.4	153.9
337	138.2	327.8	6.6	153.5
344	135.4	336.0	6.2	153.7
351	125.0	334.0	10.7	152.7
358	126.8	340.7	7.0	153.3
365	121.2	341.3	8.3	153.2
372	116.9	348.1	8.4	153.5
379	106.7	350.6	12.1	152.9
386	108.1	351.8	8.7	153.1

393	103.6	353.5	9.2	152.6
400	98.7	358.6	12.9	153.4
407	84.4	356.8	18.9	152.5
414	84.7	364.0	18.6	153.3
421	87.2	363.6	17.0	152.9
428	87.6	367.0	11.7	153.3
435	80.6	363.8	12.0	152.0
442	78.2	374.5	18.7	153.6
449	79.1	377.3	14.3	153.7
456	77.2	384.2	14.1	153.8
463	66.4	374.3	23.6	152.9
470	64.6	380.0	26.8	153.2
477	65.8	379.2	21.4	152.9
484	65.4	383.6	20.1	153.4
491	61.1	385.7	19.9	153.2
498	61.8	385.9	17.5	153.9
505	60.3	386.3	16.8	153.2
512	56.0	387.8	23.4	153.6
519	60.3	384.3	12.5	152.7
526	60.3	390.4	16.4	153.7
533	55.9	390.1	21.6	153.3
540	52.1	400.4	26.5	153.7
547	48.3	392.9	30.6	153.4
554	47.1	396.0	26.8	154.0
561	43.3	393.1	26.6	153.4
568	46.5	395.2	23.5	153.4
575	43.1	388.5	24.3	153.1
582	37.9	397.1	35.1	154.0
589	39.6	393.4	31.0	153.2
596	37.2	391.5	30.0	153.2
603	37.6	391.6	28.8	152.8
610	30.8	393.6	33.5	153.6
617	38.6	390.2	25.4	152.8
624	37.5	393.6	26.6	153.4
631	35.6	397.9	26.8	153.6
638	33.6	402.0	28.2	153.7
645	33.6	400.1	31.6	154.0
652	33.6	392.5	27.5	153.4
659	26.7	387.4	40.3	152.4
666	29.5	397.5	35.7	153.9
673	26.7	395.8	40.6	153.2
680	28.3	402.3	36.3	154.5
687	29.3	397.2	36.3	154.0
694	18.5	388.8	43.0	153.2
701	27.1	397.2	33.7	154.0
708	25.3	394.3	41.8	152.6
715	23.5	395.8	38.3	153.5
722	26.0	393.0	38.6	153.2
730	17.0	394.1	46.4	153.7
737	30.2	395.2	30.6	153.3

744	22.2	393.4	43.7	153.1
751	24.5	400.8	38.4	154.1
757	24.5	393.3	38.2	153.0
764	18.7	392.0	45.8	152.9
771	21.2	392.4	43.1	153.5
779	14.6	389.4	57.4	153.2
785	15.2	397.3	52.3	153.7
792	14.2	391.0	45.3	152.7
799	16.2	394.1	50.8	153.4
807	24.8	392.2	36.7	153.0
813	19.0	396.4	43.5	153.6
821	15.6	385.5	43.4	152.6
828	17.4	394.5	38.9	153.8
835	23.3	395.0	35.2	153.7
842	17.5	392.4	44.8	153.4
849	21.4	395.1	38.0	153.3
856	19.6	390.4	41.0	153.4
863	16.8	396.1	40.0	154.2
870	24.6	391.3	34.1	153.2
877	16.2	393.1	44.2	153.3
884	15.1	397.1	41.9	154.2
891	14.6	394.6	49.6	153.6
898	16.4	389.4	41.3	153.3
905	18.1	394.8	37.7	153.4
912	8.5	392.0	55.0	153.9
919	16.8	393.5	39.8	153.4
926	12.7	390.4	44.6	153.2
933	15.5	393.0	44.5	153.6
940	15.6	396.3	45.9	154.0
947	13.1	389.7	49.2	152.9
954	12.4	391.3	47.6	153.3
961	18.3	388.0	42.7	153.2
968	14.8	391.5	41.2	153.2
975	14.8	385.2	43.2	152.4
982	14.4	385.0	44.2	152.8
990	13.5	385.1	44.8	153.0

Diff. XS [FNT] - TFA

Experiment	[FNT **1**] (mM)	[NBS] (mM)	[TFA] (mM)
Standard - TFA	530	663	133
Diff. XS [FNT] - TFA	265	663	133

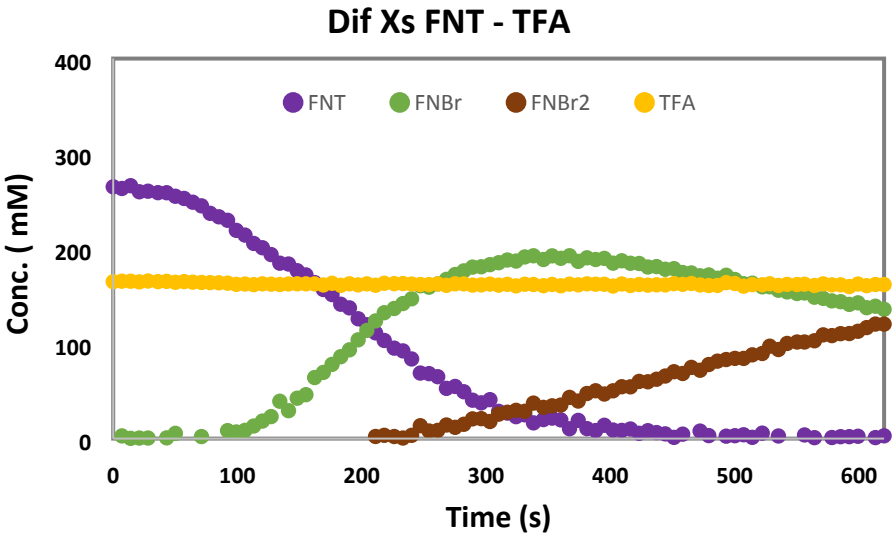


Figure S12. Reaction Progress Data For Diff. XS [FNT] - TFA

Table S16. 19F NMR Reaction Progress Data For Diff. XS [FNT] - TFA

Time (s)	FNT (mM)	FNBr (mM)	$FNBr_2$ (mM)	TFA (mM)
0	265.0	0.0		165.1
7	263.3	2.8		165.7
14	266.2	0.2		165.7
21	259.8	0.6		164.9
28	260.4	0.6		165.9
36	258.9	-2.9		165.2
43	258.8	0.8		165.5
50	255.1	5.5		164.5
57	252.8	0.0		165.2
64	248.8	-0.3		164.7
71	245.0	2.1		164.4
78	237.1	-3.7		164.2
85	233.4	-3.7		164.0
92	229.8	8.4		163.6
99	219.2	7.0		162.3
106	214.2	8.7		162.7
113	205.4	13.2		162.0
120	200.9	18.4		162.9
127	193.7	23.2		162.5
134	184.6	39.3		162.1
141	183.7	29.4		162.8
148	176.7	42.5		162.9
155	172.3	46.2		162.9
162	164.2	64.3		162.9

169	156.9	69.6		161.7
176	151.5	78.1		163.5
183	141.4	86.2		161.3
190	137.6	93.4		162.9
197	126.1	103.9		161.8
204	119.8	113.9		162.9
211	111.3	123.9	2.2	161.4
218	103.3	132.5	3.5	163.5
226	95.2	137.0	2.2	163.1
233	92.3	142.1	0.6	163.2
240	83.8	147.1	3.4	162.7
247	69.0	160.8	13.6	162.2
254	68.4	159.4	8.0	162.1
261	65.1	162.8	8.6	162.8
268	52.9	167.6	14.3	161.3
275	54.9	172.7	11.8	162.9
282	49.3	176.5	15.1	162.9
289	40.4	180.5	20.8	161.5
296	37.6	180.9	21.0	161.8
303	41.0	183.1	18.0	162.6
310	28.7	185.1	25.7	161.5
317	26.9	188.0	27.7	162.4
324	23.1	186.9	29.7	160.7
331	25.0	191.2	28.7	162.5
338	16.5	192.4	37.4	162.2
346	20.0	188.5	32.9	160.9
353	21.6	192.3	34.5	162.3
360	19.7	189.7	35.3	160.8
367	10.4	192.5	43.4	162.6
374	19.2	186.5	39.5	161.9
381	10.5	190.3	47.4	162.9
388	8.4	188.5	50.4	162.5
395	14.0	189.7	46.9	162.4
402	9.0	184.7	50.3	160.6
409	8.6	187.2	54.6	162.8
416	10.1	184.5	54.5	161.1
423	5.6	184.3	60.2	162.2
430	8.3	180.6	59.8	161.5
437	6.3	181.1	62.5	161.8
444	5.0	178.3	65.9	161.8
451	1.3	178.9	70.4	163.1
458	4.7	174.8	68.5	162.4
465	-0.3	174.3	74.9	163.3
472	7.9	171.3	71.9	161.7
479	3.1	172.2	78.0	161.1
486	-2.8	168.8	81.5	161.2
493	2.6	171.9	83.2	164.2

500	3.0	167.4	84.4	163.2
507	4.0	163.0	84.4	160.4
514	1.3	163.6	88.2	162.1
522	5.7	159.8	89.6	161.9
528	-5.9	159.8	97.2	163.0
535	2.7	156.2	93.7	161.2
542	-1.9	154.4	100.2	162.3
550	-2.5	152.7	101.7	162.2
556	3.8	153.3	101.7	162.5
564	1.0	148.8	103.0	161.1
571	-3.3	147.6	109.2	162.9
578	1.1	145.0	108.4	161.8
585	2.0	144.1	110.4	161.8
592	2.0	141.2	110.6	160.0
599	2.4	142.9	113.0	162.7
606	-0.7	137.8	116.8	160.9
613	1.0	139.3	120.5	162.2
620	2.9	136.1	120.5	162.2
627	1.6	133.0	123.8	162.1
634	-0.7	132.2	124.9	160.7
641	-1.8	132.0	127.4	163.0
648	0.3	127.4	127.5	161.8

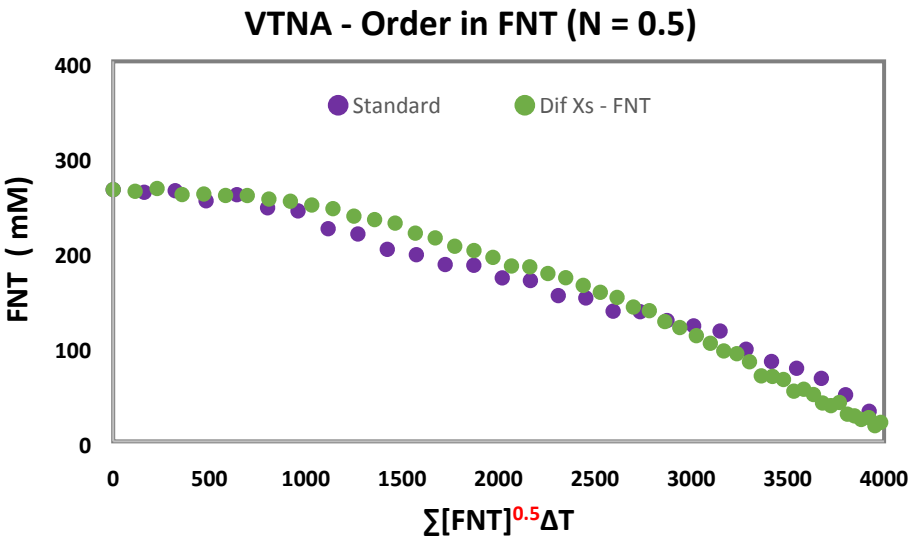


Figure S13. VTNA Of Diff. XS [FNT] - TFA

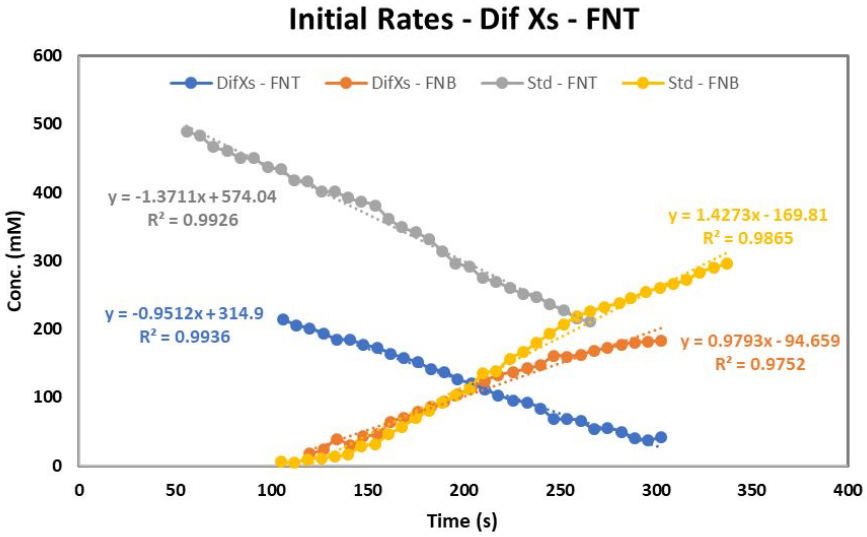


Figure S14. Initial Rates For Diff. XS [FNT] - TFA

Diff. XS [NBS] - TFA

Experiment	[FNT **1**] (mM)	[NBS] (mM)	[TFA] (mM)
Standard - TFA	530	663	133
Diff. XS [NBS] - TFA	530	331	133

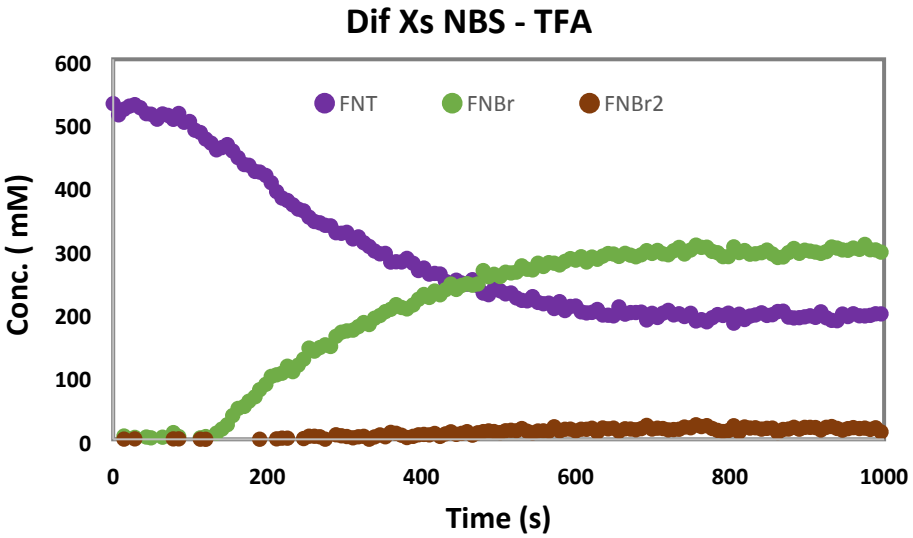


Figure S15. Reaction Progress Data For Diff. XS [NBS] - TFA

Table S17. ^{19}F NMR Reaction Progress Data For Diff. XS [NBS] - TFA

Time (s)	FNT (mM)	FNBr (mM)	$FNBr_2$ (mM)
0	530.0	-2.1	
7	512.3	-0.6	
14	521.1	5.2	
21	526.1	-4.5	
28	528.4	3.0	
35	523.6	-1.1	
43	514.2	3.6	
49	513.3	2.4	
57	505.5	-0.2	
64	513.7	3.4	
71	511.5	-2.4	
78	505.2	10.6	
85	514.5	4.3	
92	500.6	-10.7	
99	501.8	-2.2	
106	488.1	-6.7	
113	484.4	2.3	
120	474.1	4.3	
127	467.6	-0.4	
134	457.1	9.8	
141	460.6	16.2	
148	465.3	23.1	
155	455.2	37.5	
162	444.8	48.8	
170	433.8	52.0	
176	432.7	60.1	
184	423.0	67.2	
190	422.0	78.3	
198	416.6	86.9	
205	405.2	99.3	
212	391.1	101.9	
219	381.0	104.4	
226	377.1	115.4	
233	370.2	106.9	
240	363.5	117.1	
247	360.7	126.6	1.2
254	350.8	144.0	4.9
261	343.9	139.3	4.9
268	341.9	144.9	4.0
275	337.9	149.2	0.2
282	337.0	146.6	-0.9
289	326.2	162.6	7.2
296	325.3	169.1	5.6
303	326.8	171.2	4.4
311	316.4	172.4	2.4

318	319.6	177.9	4.0
325	310.5	184.4	4.7
332	304.5	181.3	0.2
339	297.4	191.2	3.8
346	292.9	195.5	7.0
353	293.5	201.6	4.0
360	279.8	205.3	11.0
367	280.4	212.6	9.5
374	280.0	208.2	6.5
381	285.7	205.9	2.8
389	277.9	212.2	4.7
396	266.5	221.2	7.1
403	270.4	228.7	7.8
410	260.8	224.0	7.0
417	262.0	234.1	9.3
424	261.0	228.2	4.6
431	249.5	236.1	8.6
438	243.1	245.1	11.8
445	251.2	236.7	7.8
452	246.8	242.9	9.4
459	245.0	245.7	12.1
466	252.0	243.4	6.6
473	242.6	245.4	10.3
480	230.9	266.4	12.2
487	228.4	256.8	13.3
494	237.9	260.6	12.3
502	234.5	257.1	10.6
509	229.7	263.9	13.5
516	231.0	262.7	14.3
523	223.3	264.0	13.4
530	219.4	273.9	17.0
537	218.7	268.5	12.8
544	225.3	267.5	10.3
551	216.2	278.0	13.2
558	214.0	272.9	13.4
565	215.0	278.9	12.7
572	206.5	278.1	19.8
579	217.4	275.3	13.2
586	203.3	280.9	15.9
593	209.8	285.3	16.1
600	210.4	282.9	13.1
607	201.3	288.2	15.9
614	199.6	279.9	15.8
621	200.4	287.8	17.5
628	205.0	284.3	11.3
635	196.3	289.3	18.0
642	195.9	293.3	16.6

649	194.9	292.5	17.7
656	209.1	288.8	12.6
664	197.7	293.6	16.7
671	200.1	290.7	16.3
678	200.2	288.2	15.0
685	200.8	291.4	16.9
692	188.5	297.9	22.0
699	198.9	293.5	16.2
706	192.4	298.2	17.6
713	199.1	292.9	17.0
720	203.6	291.4	14.9
727	196.5	297.7	15.4
734	198.2	303.0	15.9
741	193.9	292.6	19.4
749	199.0	298.9	18.3
756	186.9	306.6	23.0
763	188.9	303.1	20.1
770	185.6	303.4	21.6
777	192.0	296.7	17.1
784	197.0	294.6	14.1
791	195.6	288.4	12.2
798	199.2	288.5	13.7
805	183.4	303.9	21.4
812	197.5	294.9	11.5
819	189.2	298.1	19.5
826	194.6	292.3	17.8
833	196.3	293.0	18.2
841	199.7	294.7	16.1
848	195.6	298.8	17.3
855	196.7	292.7	17.7
862	201.8	287.1	10.7
869	202.3	288.0	15.5
876	193.0	294.8	16.2
883	191.6	301.3	19.0
890	192.1	293.7	16.0
897	193.4	298.6	18.9
904	195.0	297.1	18.9
911	192.6	295.6	18.6
918	201.3	293.6	14.7
925	191.9	296.4	19.0
932	187.8	303.6	20.2
939	187.3	301.9	17.2
946	197.8	299.0	14.5
953	193.8	298.5	16.8
960	198.2	302.0	18.5
968	195.0	300.0	17.0
975	194.8	307.7	17.7

982	195.7	299.4	15.7
989	198.2	299.1	18.2
996	198.0	295.6	11.6
1003	197.5	296.9	19.7
1010	195.4	302.4	18.3
1017	196.0	293.7	19.0
1024	194.1	304.6	18.7
1031	197.7	4.8	17.6
1154	193.2	282.2	14.7

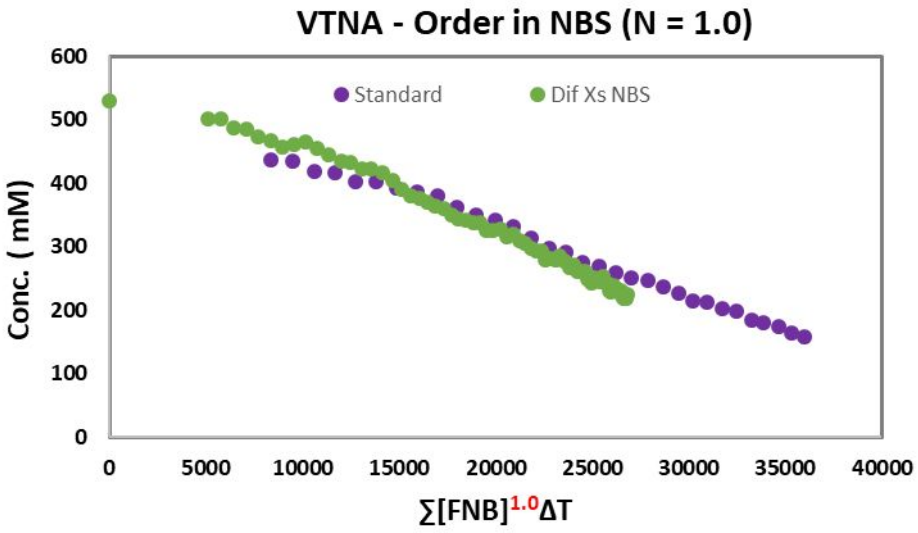


Figure S16. VTNA Of Diff. XS [FNT] – TFA

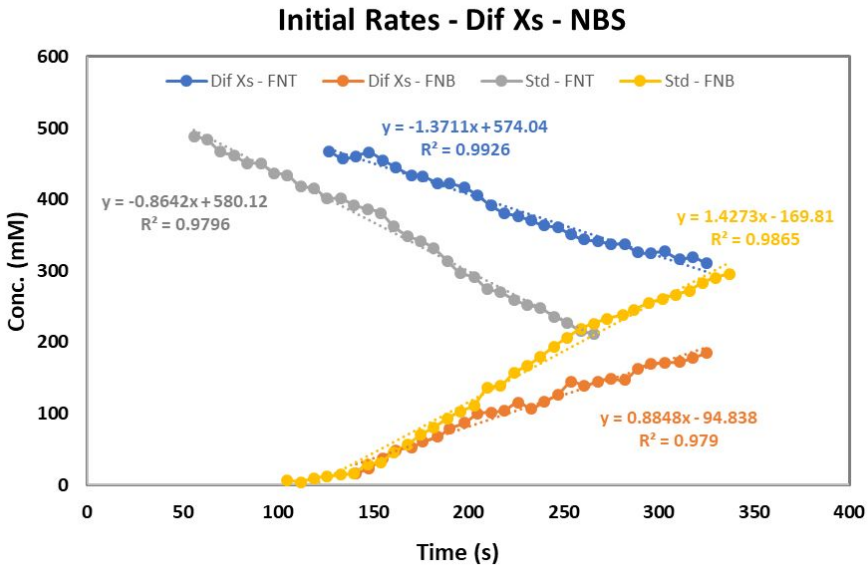


Figure S17. Initial Rates For Diff. XS [FNT] - TFA

Diff. XS [TFA] – 5 mol%

Experiment	[FNT **1**] (mM)	[NBS] (mM)	[TFA] (mM)
Standard - TFA	530	663	133
Dif XS - [TFA] – 5 mol%	530	663	27

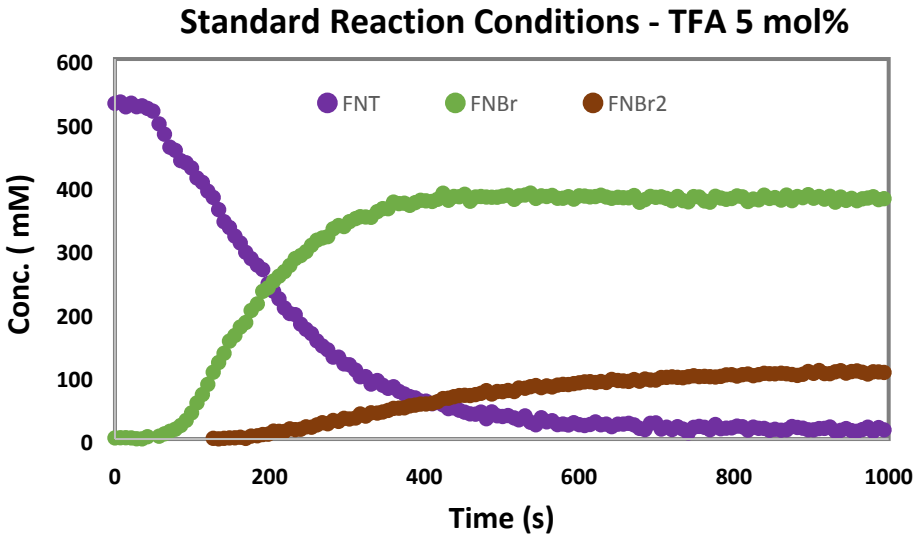


Figure S18. Reaction Progress Data For Diff. XS [TFA] – 5 mol%

Table S18. ^{19}F NMR Reaction Progress Data For Diff. XS [TFA] – 5 mol%

Time (s)	FNT (mM)	FNB (mM)	$FNBr_2$ (mM)
0	530.0	1.8	
7	532.2	2.1	
14	524.5	2.1	
21	530.2	1.8	
28	524.7	0.5	
35	526.1	0.3	
42	522.1	3.7	
49	517.7	-3.2	
57	497.6	4.5	
64	481.3	8.2	
71	460.8	12.2	
78	455.8	15.5	
85	439.6	21.4	
92	436.2	29.5	
99	428.0	41.3	
106	412.2	57.0	
113	405.2	70.3	

120	391.4	86.3	
127	381.5	105.5	1.1
134	362.2	120.8	0.3
141	343.2	135.4	1.2
148	334.0	154.6	1.8
155	320.5	163.5	1.9
162	309.6	176.8	2.8
169	294.9	184.0	1.0
176	284.9	203.0	4.7
184	274.6	213.4	5.1
191	267.6	233.2	7.1
198	245.5	239.0	7.7
205	233.3	249.5	12.5
212	221.4	257.2	12.2
219	207.0	264.4	11.9
226	198.2	274.0	16.1
233	196.4	285.0	14.8
240	181.4	289.7	15.5
247	173.3	295.9	19.3
254	166.4	305.9	18.7
261	155.0	314.0	22.3
268	147.0	317.4	25.8
275	140.9	319.5	24.1
282	129.3	331.9	29.3
289	129.3	337.1	27.9
296	118.6	335.5	32.7
303	117.3	343.2	31.7
311	108.8	348.0	33.2
317	98.4	351.1	39.6
324	98.5	350.6	36.2
331	86.8	350.1	41.4
339	92.4	359.0	41.0
346	85.0	363.8	42.7
353	80.1	363.7	45.2
360	82.6	374.1	48.4
367	75.3	371.7	48.8
374	71.1	372.4	49.3
381	67.0	369.0	52.3
388	65.0	373.2	53.5
395	59.9	377.0	55.2
402	59.9	376.1	55.3
410	55.7	375.1	56.5
417	57.7	378.5	59.0
424	54.0	388.1	63.9
431	48.0	377.0	64.5
438	49.3	383.0	66.9
445	45.5	382.6	68.6

452	42.4	386.4	69.1
459	39.8	375.4	68.7
466	39.3	382.2	70.2
473	42.6	383.0	72.2
480	32.1	382.1	76.4
487	42.9	381.8	71.1
494	36.7	381.8	75.1
501	35.6	383.5	74.8
508	37.1	385.0	76.7
516	33.3	378.5	75.0
522	30.3	383.9	80.6
530	36.5	385.3	80.2
537	26.5	388.3	82.6
544	22.5	379.9	84.5
551	33.6	384.0	81.1
558	27.1	382.9	83.9
565	29.0	384.6	82.2
572	22.8	380.1	85.1
579	23.7	380.2	86.3
586	22.2	382.6	86.0
593	25.8	378.8	87.5
600	22.7	384.0	88.8
607	21.3	383.6	90.3
614	23.0	382.3	90.6
621	27.1	382.8	89.2
628	22.5	385.0	90.8
635	23.6	382.1	89.4
642	19.5	380.1	94.1
650	23.5	381.7	92.4
657	23.6	381.0	91.7
664	24.8	380.9	91.0
671	22.3	384.5	93.9
678	16.9	373.8	91.3
685	14.9	378.0	94.8
692	24.8	383.1	93.2
699	25.5	381.6	93.1
706	15.8	382.4	97.1
713	18.7	379.9	97.4
720	15.0	376.3	98.2
727	19.5	382.9	97.4
734	15.8	376.5	96.8
741	9.7	374.5	98.4
748	18.4	382.8	99.9
755	20.0	382.1	98.6
762	18.5	375.9	99.0
769	14.7	374.0	98.4
776	22.9	383.3	97.9

783	16.3	380.5	98.9
790	17.2	378.5	101.3
797	17.6	379.7	101.6
804	20.4	383.9	99.4
811	19.4	382.4	101.6
818	14.0	375.0	102.7
825	18.8	378.9	100.0
832	16.9	377.7	101.7
839	16.8	385.1	103.8
846	13.7	379.9	103.1
853	15.4	381.2	103.0
861	13.9	377.2	103.9
868	14.5	385.2	103.1
875	19.8	376.4	101.9
882	18.3	382.9	100.5
889	17.2	381.1	102.2
896	14.6	385.8	106.7
903	14.5	380.2	103.7
910	16.6	382.9	108.2
917	16.8	378.8	103.3
924	19.0	383.3	103.2
931	12.4	374.0	106.2
938	13.7	382.0	107.9
945	16.5	376.8	104.1
952	13.3	380.0	106.6
959	12.2	376.3	107.6
966	14.9	379.3	105.4
973	18.7	380.5	102.6
980	11.9	382.6	106.2
987	18.1	378.0	106.0
994	14.4	379.5	105.2
1001	14.5	379.1	104.1
1008	12.6	378.7	109.0
1015	14.1	379.9	105.3

Diff. XS [TFA] – 1 mol%

Experiment	[FNT **1**] (mM)	[NBS] (mM)	[TFA] (mM)
Standard - TFA	650	663	133
Dif XS - [TFA] – 1 mol%	650	663	5

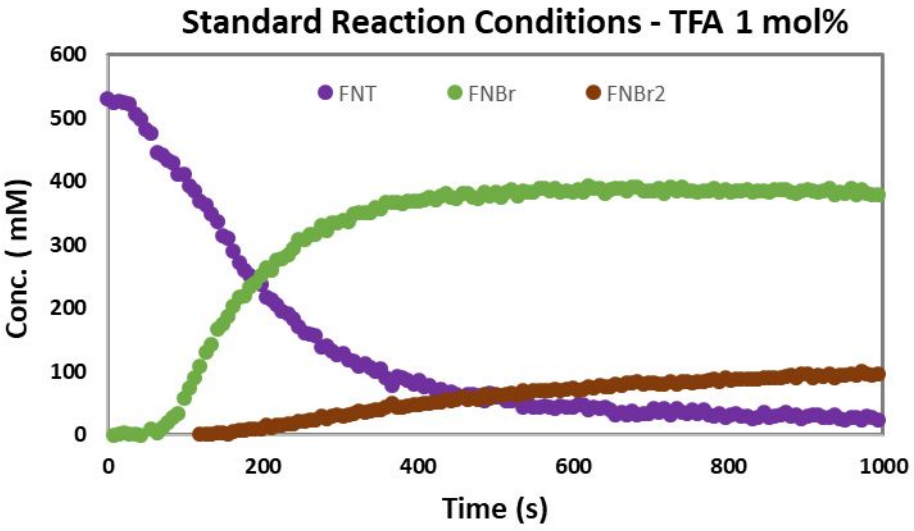


Figure S19. Reaction Progress Data For Diff. XS [TFA] – 1 mol%

Table S19. ^{19}F NMR Reaction Progress Data For Diff. XS [TFA] – 1 mol%

Time (s)	FNT (mM)	FNBr (mM)	$FNBr_2$ (mM)	TFA (mM)
0	530.0	-0.8	-3.1	3.6
7	525.1	0.5	-1.6	3.8
14	526.9	0.6	-1.8	3.6
21	524.1	4.3	-1.1	3.5
28	522.7	1.2	-2.3	3.8
35	507.5	2.3	-1.4	3.4
42	499.5	0.4	-2.5	3.4
49	483.3	-0.6	-3.4	3.6
56	475.6	10.3	-0.9	3.6
63	446.7	4.5	-3.3	3.3
70	441.9	10.7	-3.6	3.2
77	433.1	18.9	-3.7	3.7
84	430.0	28.6	-3.3	3.7
91	411.5	34.4	-4.5	3.4
98	411.1	57.6	-0.7	3.2
105	393.4	73.7	-1.0	3.8
112	385.4	89.9	-0.9	2.8
119	368.5	109.2	0.8	3.4
126	363.9	129.9	0.9	3.5
134	348.8	142.1	1.4	3.8
141	337.1	167.3	4.0	3.6
148	314.6	174.8	4.3	2.9
155	309.9	186.7	2.3	3.1
162	290.8	204.5	5.9	3.5
169	271.8	217.6	8.5	3.3
176	260.6	220.5	7.8	3.2
183	252.3	233.0	9.7	3.2
190	243.8	239.9	9.8	2.9

197	238.0	251.5	9.2	3.4
204	218.6	265.0	15.7	3.3
211	213.9	260.3	11.2	3.5
218	205.6	276.9	15.3	3.3
225	195.9	278.6	16.0	3.9
232	190.7	285.2	17.3	3.5
239	182.6	294.7	17.7	3.7
246	170.7	308.0	21.6	3.1
254	161.4	308.3	22.2	3.3
261	159.6	317.2	23.0	3.5
268	156.6	316.4	23.5	3.0
275	138.6	331.9	30.2	3.9
282	140.2	323.1	26.4	3.6
289	132.7	335.8	29.4	3.4
296	126.9	335.8	31.1	3.3
303	128.3	339.5	29.0	3.3
310	119.5	337.7	32.7	2.3
317	116.5	348.9	34.0	3.6
324	108.4	350.6	37.8	3.5
331	112.4	351.7	36.0	3.7
338	105.9	351.8	38.0	3.0
345	100.2	358.4	40.0	3.6
352	104.0	356.3	39.3	3.0
359	90.7	368.0	44.4	3.5
366	78.1	368.1	49.1	3.7
373	93.3	367.5	43.8	3.3
380	91.0	364.7	44.9	3.1
387	87.3	369.1	46.9	3.3
394	80.2	368.8	48.1	3.3
401	86.9	368.8	48.1	3.3
408	76.9	372.2	49.4	3.6
415	77.6	375.1	49.3	3.1
422	70.7	371.4	52.6	3.5
429	73.1	378.4	53.0	3.2
436	66.9	381.2	55.8	3.7
443	68.2	374.5	54.2	3.3
450	64.5	373.1	55.8	3.2
458	60.4	381.6	60.2	3.4
464	64.7	380.6	55.5	3.7
471	65.1	374.6	58.2	2.3
478	62.2	372.4	57.0	3.0
485	54.6	382.5	64.7	3.2
493	65.3	376.5	57.6	3.3
500	59.5	383.9	64.5	3.6
507	59.3	374.6	62.9	3.6
514	54.4	383.0	64.7	3.2
521	53.5	386.9	66.0	3.5
528	56.7	377.6	63.0	2.6
535	44.5	386.0	71.2	3.2
542	50.9	383.7	66.7	3.4

549	44.0	384.4	70.8	3.1
556	43.7	388.8	69.8	3.6
563	45.9	389.2	69.4	3.0
570	44.6	386.2	69.7	3.1
577	41.1	389.1	73.0	3.2
584	46.3	382.9	70.4	3.6
591	44.7	386.2	72.1	3.3
599	43.2	383.3	74.4	3.5
606	48.8	386.9	70.7	2.9
613	48.5	383.0	72.0	3.2
620	39.1	392.7	77.1	3.3
627	44.3	388.6	73.6	3.1
634	41.6	388.7	77.8	3.0
641	44.2	381.1	76.2	3.0
648	40.7	387.2	76.5	3.2
655	31.4	388.6	79.9	3.1
662	36.0	389.4	78.9	3.0
669	31.1	385.3	82.6	2.2
676	37.1	391.2	81.8	3.4
683	31.1	391.1	83.5	3.0
690	34.6	385.0	80.7	3.1
697	33.9	385.1	82.7	3.2
704	41.2	384.6	81.5	3.0
711	36.0	389.8	80.4	3.4
718	42.5	381.5	79.6	3.2
726	31.8	391.5	85.0	2.8
733	41.7	384.9	79.8	2.8
740	35.4	391.2	85.2	3.5
747	33.6	385.8	83.6	3.2
754	39.0	384.5	81.8	2.9
761	34.8	384.4	85.2	3.3
768	39.1	385.4	83.8	2.6
775	32.7	386.2	85.8	3.2
782	28.9	389.1	88.3	3.0
789	34.8	382.5	84.4	3.2
796	27.2	387.6	90.7	3.0
803	32.0	384.0	86.5	3.2
810	32.9	385.8	88.1	2.6
817	30.2	385.5	88.8	3.3
824	30.4	387.8	88.9	3.5
831	26.5	383.1	89.1	3.0
838	28.2	386.5	89.0	3.4
846	35.1	385.5	89.5	3.5
853	28.4	383.8	90.8	3.6
860	30.4	387.5	90.0	3.3
867	32.7	387.9	89.4	3.1
874	35.7	387.0	91.7	2.4
881	29.2	383.9	93.5	3.3
888	31.5	382.2	91.3	3.2
895	26.0	386.4	96.5	3.1

902	29.2	387.0	96.0	2.3
909	32.1	384.7	91.2	3.3
916	31.8	384.2	93.6	2.7
923	27.8	386.4	92.4	3.2
930	28.0	389.8	97.0	2.9
937	30.8	379.1	91.2	3.4
944	26.3	383.6	93.9	3.0
951	24.7	382.0	95.0	3.1
958	27.1	388.6	95.5	3.3
965	27.4	380.4	94.4	2.9
972	24.4	387.3	99.6	2.3
979	28.9	381.9	96.8	3.4
986	28.5	379.1	94.6	3.1
993	24.2	378.9	97.3	3.5
1000	21.2	385.1	97.0	3.4
1008	17.8	383.4	101.3	2.9
1015	20.3	386.6	99.2	2.5
1022	32.4	383.1	96.1	3.3
1029	22.2	383.0	100.2	3.0
1036	28.6	383.0	96.1	2.9
1043	24.1	384.2	98.9	2.3
1050	21.6	380.9	100.6	2.6
1057	19.8	385.0	100.9	2.8
1064	27.1	381.9	98.6	2.9
1071	24.3	386.4	102.9	2.7
1078	23.7	379.8	99.5	3.1
1085	25.5	384.4	98.4	3.0
1092	19.7	387.7	104.0	2.8
1099	25.8	383.6	100.4	2.9
1106	25.5	379.3	96.9	3.3
1113	18.9	387.3	104.7	2.2
1120	31.8	384.2	99.0	2.5
1127	22.8	388.0	100.8	3.3
1134	25.1	384.3	102.0	3.1
1142	25.3	382.4	101.1	2.4
1149	30.2	383.0	100.9	3.1
1156	21.6	381.7	101.8	2.8
1163	23.2	376.9	101.7	3.0
1170	28.5	384.0	100.8	3.1
1177	29.5	385.7	101.6	3.2
1184	22.3	383.4	102.6	2.6
1191	27.6	378.8	101.9	3.5
1198	20.8	385.0	104.6	2.7
1205	22.5	390.1	105.4	2.9
1212	26.3	382.9	100.9	3.2
1219	18.3	386.4	104.5	3.3
1227	24.1	381.2	103.4	3.0
1234	26.9	388.0	104.3	2.4
1241	25.8	378.6	103.0	3.1
1248	30.2	387.9	105.5	1.3

1255	26.6	381.5	102.9	3.2
1262	22.9	385.5	105.6	3.2
1269	23.1	378.3	101.9	2.8
1276	23.0	383.9	102.3	3.3
1283	19.1	382.0	106.1	2.8
1290	27.5	383.4	105.8	3.1
1297	30.7	376.9	105.6	-2.6
1304	18.1	384.0	108.0	3.5
1311	24.3	378.3	105.5	2.9
1318	26.3	378.9	101.9	3.0
1325	20.8	379.5	103.2	3.0
1332	27.8	381.2	105.4	3.1
1339	25.2	379.6	102.9	3.2
1346	19.9	381.6	106.4	3.1
1354	28.3	376.4	104.7	3.1
1361	23.7	382.1	106.2	3.2
1368	24.4	381.4	108.6	2.5
1375	23.1	378.7	104.1	2.9
1382	24.5	378.3	106.6	2.6
1389	20.8	377.9	107.4	2.8
1396	26.4	378.5	105.6	3.2

Standard – No TFA

Experiment	[FNT **1**] (mM)	[NBS] (mM)	[TFA] (mM)
Standard – No TFA	530	663	0

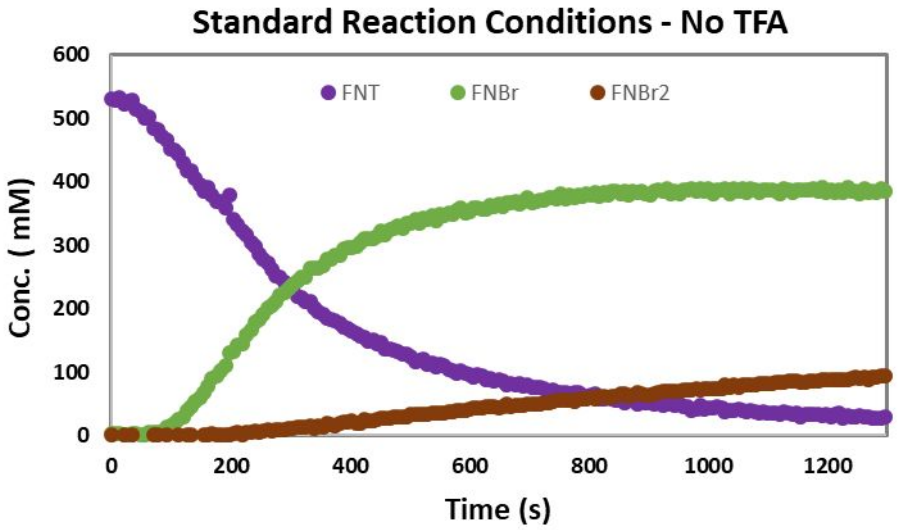


Figure S20. Reaction Progress Data For Standard – No TFA

Table S20. ^{19}F NMR Reaction Progress Data For Standard – No TFA

Time (s)	FNT (mM)	FNB (mM)	$FNBr_2$ (mM)
0	530.0	4.0	0.4
7	529.1	2.0	-0.4
14	532.6	3.2	-0.6
21	522.4	2.0	0.6
28	525.5	1.4	-0.2
35	528.2	3.3	0.4
42	513.7	3.4	-0.6
49	509.4	0.9	-0.6
56	500.8	1.7	-2.1
63	501.8	5.3	-0.4
71	484.3	5.8	0.3
78	483.0	4.9	0.1
85	472.0	4.5	-0.4
92	466.5	12.4	1.1
99	450.7	14.2	-0.1
106	449.0	18.6	-0.3
113	442.8	25.5	0.9
120	428.7	30.1	-0.5
127	417.6	38.6	0.2
134	416.8	45.3	0.6
141	406.1	54.1	-0.3
148	395.7	59.8	-0.2
155	385.0	68.4	0.5
162	390.7	78.0	0.6
169	379.0	90.7	3.6
176	369.4	93.3	1.4
183	368.7	101.1	1.5
191	357.9	110.2	1.2
198	379.7	130.3	1.9
205	340.6	131.6	2.2
212	332.6	142.6	4.3
220	322.6	145.3	1.8
227	316.1	158.8	4.1
234	303.7	167.3	4.7
241	298.3	178.7	6.3
248	285.0	182.2	5.6
255	278.2	191.2	6.6
262	271.1	200.7	8.7
269	260.9	205.3	6.2

276	251.1	211.9	9.6
283	249.1	221.6	8.6
290	240.5	225.5	8.8
297	233.3	230.5	11.3
304	230.4	237.3	10.6
311	220.0	243.8	12.2
318	217.8	249.6	12.8
325	210.7	250.4	12.5
333	210.6	264.2	15.0
340	201.4	263.8	11.3
347	195.3	264.0	14.7
354	190.8	267.0	13.0
361	185.1	277.9	20.0
368	181.9	278.1	17.6
375	181.2	283.8	16.0
382	176.1	283.1	18.9
389	170.7	293.6	21.6
396	169.7	296.9	20.7
403	165.5	295.6	23.8
410	161.3	298.2	20.1
417	156.9	303.5	19.6
424	153.8	310.7	24.9
431	149.5	310.9	24.1
438	151.2	311.1	24.1
445	144.0	314.2	24.8
452	147.2	322.0	26.5
459	136.7	316.7	28.1
466	136.5	324.5	28.1
474	134.9	326.0	29.2
480	133.3	330.7	29.0
488	129.2	326.7	29.3
495	128.4	333.6	29.4
502	123.6	334.3	32.7
509	116.6	340.0	34.2
516	117.2	334.0	32.6
523	119.8	342.4	34.0
530	112.3	340.1	32.4
537	113.8	345.6	34.7
544	107.6	339.3	35.5
551	111.7	348.3	35.5
558	109.2	347.2	36.2

565	105.0	349.8	37.3
572	101.9	347.8	37.2
579	97.6	354.4	39.2
586	102.3	358.1	38.6
593	98.6	351.1	38.5
600	95.5	352.5	40.6
607	91.0	359.4	43.1
614	95.0	358.5	42.8
621	93.7	355.8	42.5
628	87.0	356.6	44.8
635	89.6	363.5	45.2
642	85.0	360.9	45.7
649	87.7	364.8	43.3
656	85.5	360.6	44.6
663	80.6	367.5	48.5
670	81.7	366.2	46.2
677	80.1	369.3	47.5
684	82.7	363.8	47.9
691	78.3	369.0	48.4
698	79.3	374.5	49.4
705	75.4	366.6	49.7
712	75.0	368.2	49.3
719	76.1	371.8	50.5
726	74.3	370.6	52.3
733	68.2	375.4	51.6
740	71.2	375.3	53.7
747	68.4	373.5	54.6
754	68.4	381.2	55.2
762	67.9	373.3	55.9
769	65.7	379.7	55.4
776	67.2	375.4	53.2
783	68.0	379.3	57.1
790	62.9	376.7	57.4
797	61.1	381.3	57.4
804	63.1	379.6	59.1
811	65.2	382.6	57.0
818	58.3	377.3	61.7
825	58.3	383.4	60.8
832	58.9	378.9	60.5
839	57.9	384.7	62.6
846	55.1	385.2	62.2

853	56.5	381.6	65.2
860	51.4	385.5	64.8
867	57.8	378.6	62.0
874	55.2	385.3	64.5
882	50.4	382.7	67.5
889	53.7	384.3	65.7
895	52.3	381.3	64.3
903	52.3	378.7	62.7
910	49.5	384.9	66.6
917	51.6	387.1	68.5
924	48.4	384.4	70.5
931	49.7	388.7	68.8
938	51.6	380.9	70.0
945	48.2	384.6	70.6
952	48.9	380.9	69.7
959	44.8	386.6	71.7
966	45.9	387.9	72.0
973	38.9	388.8	71.4
980	42.0	385.2	74.6
987	46.9	388.4	72.4
994	41.1	385.4	74.7
1001	43.1	388.2	73.6
1008	44.1	381.6	74.5
1015	45.3	387.4	73.6
1023	43.7	386.1	74.3
1029	37.1	388.3	79.1
1037	38.7	381.2	74.8
1044	39.6	389.6	80.2
1051	41.1	385.7	76.5
1058	38.7	389.4	80.5
1065	38.3	382.4	78.9
1072	39.9	388.2	79.0
1079	36.4	387.6	80.6
1086	36.2	383.5	81.4
1093	37.3	386.5	81.4
1100	35.8	386.2	81.7
1107	35.9	387.7	81.9
1114	36.0	385.9	83.5
1121	32.8	380.8	84.2
1128	36.4	388.3	83.3
1135	36.4	386.5	85.4

1142	33.1	382.9	85.1
1149	35.5	386.5	85.5
1156	30.1	386.9	83.8
1163	33.8	387.4	84.8
1170	34.0	387.6	86.3
1177	33.5	388.3	85.5
1185	33.3	385.2	86.7
1191	31.1	391.5	88.3
1199	33.0	383.7	87.9
1206	29.9	386.1	87.8
1213	33.0	383.7	88.4
1220	34.6	387.0	88.8
1227	28.2	382.2	88.2
1234	31.8	390.1	88.6
1241	30.1	384.3	89.1
1248	30.1	385.9	90.9
1255	31.5	381.8	89.3
1262	29.1	388.3	92.6
1269	29.4	382.6	88.3
1276	27.8	385.8	92.2
1283	26.8	382.9	91.6
1290	28.1	388.5	93.2
1297	28.4	385.8	93.7
1304	26.4	387.0	92.9
1311	24.1	379.2	94.2
1318	27.7	384.7	95.1
1325	24.8	383.1	93.6
1332	26.8	384.5	94.3
1339	27.5	380.3	95.2
1346	26.9	387.0	96.2
1353	27.1	387.7	94.8
1360	25.8	385.0	96.4
1367	25.6	384.4	96.5
1374	21.4	384.6	96.3
1381	23.8	387.1	99.0
1389	26.7	382.5	97.8
1395	22.3	384.7	97.8
1403	25.8	380.6	95.3
1410	22.1	388.6	100.3
1417	22.4	383.5	95.8
1424	19.7	382.4	100.4

1431	25.2	379.9	98.8
1438	22.3	386.4	100.0
1445	20.4	381.6	102.2
1452	20.2	383.9	98.0
1459	18.3	382.7	101.8
1466	21.2	385.9	100.9
1473	20.5	381.8	99.9
1480	16.7	382.8	104.1
1487	20.8	380.6	103.4
1495	21.9	394.9	104.5
1502	23.2	380.8	102.8
1509	21.4	380.8	102.7
1516	19.6	383.6	106.2
1523	20.8	375.4	102.4
1530	21.3	381.2	102.3
1537	18.9	384.2	105.1
1544	19.3	379.6	102.5

Diff. XS [FNT] – No TFA

Experiment	[FNT **1**] (mM)	[NBS] (mM)	[TFA] (mM)
Standard – No TFA	530	663	0
Diff. XS [FNT] – No TFA	265	663	0

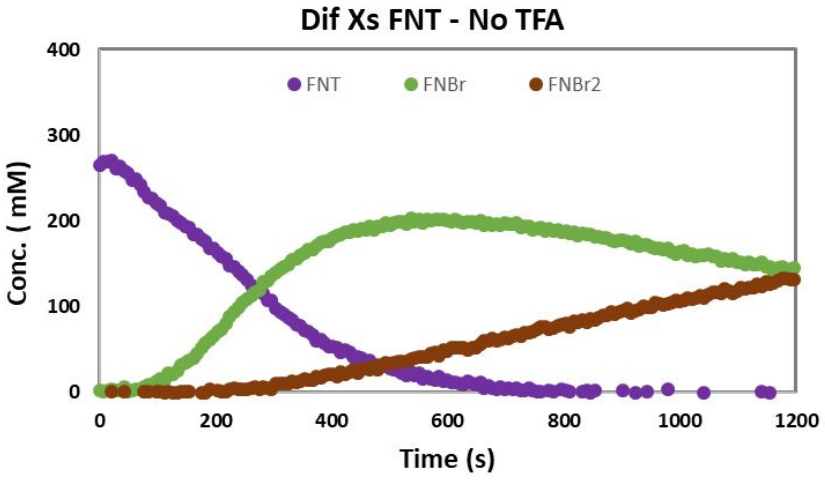


Figure S21. Reaction Progress Data For Diff. XS [FNT] – No TFA

Table S21. ^{19}F NMR Reaction Progress Data For Diff. XS [FNT] – No TFA

Time (s)	FNT (mM)	FNB (mM)	$FNBr_2$ (mM)

0	265.0	2.2	-1.0
7	269.3	1.5	-2.6
14	269.9	2.5	-1.3
21	271.3	3.3	0.6
28	261.2	3.0	-2.2
35	263.9	3.0	-0.1
42	258.1	6.2	1.6
49	255.9	1.1	-2.0
56	247.6	2.4	-1.6
63	248.7	3.7	-1.4
70	242.6	3.9	-0.4
77	234.5	6.2	0.9
84	228.1	8.8	1.2
91	226.5	9.2	-2.2
98	221.0	12.8	0.8
105	218.7	16.2	1.4
112	209.7	14.0	0.2
119	208.8	23.0	1.7
126	206.3	21.5	0.4
134	200.7	25.6	0.2
141	197.8	32.0	1.6
148	193.5	35.2	1.0
155	191.9	37.6	1.0
162	183.8	40.1	-3.2
169	184.1	45.5	-1.4
176	179.2	52.0	0.3
183	175.9	57.8	0.4
190	168.7	62.0	3.3
197	168.8	66.1	-0.2
204	162.8	70.7	1.9
211	158.5	74.3	1.4
218	155.8	81.3	1.0
225	147.4	88.4	3.9
232	146.5	94.0	4.6
240	141.7	99.8	4.4
247	136.8	105.2	4.1
254	131.3	109.2	4.1
261	125.1	112.7	5.5
268	120.0	117.7	6.4
275	119.0	120.2	4.2
282	115.5	129.7	6.9

289	108.0	130.5	5.6
296	107.1	136.6	4.1
304	98.4	140.3	11.0
311	94.5	144.3	10.2
318	90.8	146.9	11.2
325	87.7	149.4	10.1
332	85.2	154.8	12.7
339	79.8	156.1	11.9
346	77.4	159.8	13.5
353	73.2	163.5	15.4
360	70.6	166.7	15.2
367	67.4	167.5	14.8
374	60.6	171.2	18.8
381	61.8	174.5	17.2
388	58.0	175.8	19.8
395	53.7	176.8	22.0
402	54.0	180.2	21.0
409	52.1	182.5	19.0
416	47.6	183.9	24.6
423	49.9	186.7	22.0
431	47.3	187.2	24.0
438	42.0	189.6	26.2
445	41.4	188.4	22.2
452	40.4	191.0	26.3
459	36.4	189.7	28.1
466	37.6	193.4	27.3
473	31.2	189.9	30.4
480	31.6	193.6	27.2
487	31.5	193.7	31.8
494	30.6	198.1	35.3
501	27.9	194.6	33.4
508	26.8	198.0	35.4
515	25.7	199.5	35.6
522	23.1	199.4	36.6
529	19.9	197.2	35.9
536	23.9	202.7	38.5
543	20.5	199.1	40.8
550	22.2	201.4	42.3
557	16.6	198.2	41.7
564	19.0	201.8	42.2
571	16.4	200.4	45.1

578	14.2	202.4	46.4
585	18.6	201.4	43.6
592	12.8	201.3	49.7
599	14.1	201.2	48.3
606	12.2	199.7	51.8
613	11.3	201.6	52.0
621	10.8	199.2	52.0
627	9.7	198.3	52.6
635	13.5	199.5	49.3
642	10.0	199.7	51.9
649	9.8	198.2	52.1
656	11.8	201.0	55.8
663	5.2	195.7	59.9
670	7.2	198.4	60.3
677	5.3	195.8	63.3
684	4.0	196.9	60.7
691	6.7	195.1	61.4
698	3.4	198.0	64.7
705	5.9	196.6	63.5
712	3.7	196.0	65.7
719	4.6	197.4	67.6
726	2.1	192.9	66.0
733	2.5	193.9	69.4
740	5.7	193.9	70.0
747	2.6	189.3	71.2
754	1.6	191.5	73.8
761	1.7	192.8	76.9
768	-1.6	188.4	76.7
775	2.4	191.3	74.6
782	1.7	187.9	75.8
789	-1.3	190.4	78.5
796	3.6	187.6	79.2
803	1.9	189.0	80.4
810	0.9	186.3	76.4
817	-0.4	187.6	83.0
824	-0.1	183.1	82.1
831	0.6	185.3	84.8
839	1.9	184.5	82.6
845	0.2	183.9	86.1
853	2.8	181.4	84.8
860	-0.1	182.1	87.4

867	-0.5	180.6	89.5
874	-4.6	179.7	89.9
881	-3.1	177.7	93.9
888	-1.9	176.8	92.0
895	-0.6	178.0	94.6
902	2.2	177.6	95.5
909	-1.4	176.1	98.3
916	-1.0	174.3	92.5
923	0.3	175.8	96.1
930	-3.9	170.7	97.0
937	-2.8	171.7	100.3
944	0.7	172.0	99.6
951	-4.4	169.3	100.2
958	-1.9	168.2	105.0
965	-3.6	168.2	103.4
972	-0.9	166.7	102.3
979	3.3	167.6	103.2
986	-3.4	163.6	104.7
993	-3.2	162.1	107.0
1000	-1.5	164.1	106.6
1007	-0.9	165.2	107.1
1014	-1.6	160.8	110.5
1021	-2.3	161.6	108.3
1028	-4.4	158.8	109.9
1035	-0.4	160.7	112.4
1042	0.4	160.0	109.7
1049	-0.1	161.3	113.7
1056	-2.5	158.6	117.5
1063	-1.4	158.7	117.0
1070	-3.9	153.9	115.1
1077	-3.0	156.6	120.7
1084	-3.1	153.0	118.0
1091	-1.0	155.7	115.8
1098	-2.1	151.5	118.0
1105	-2.0	151.7	121.8
1112	-4.4	149.5	120.5
1119	-0.9	151.9	122.4
1126	-2.5	149.0	121.9
1133	-3.4	149.2	126.9
1141	0.6	152.0	123.4
1148	-4.7	147.1	129.3

1155	0.0	146.6	126.8
1161	-8.3	141.8	127.5
1169	-2.4	145.9	130.3
1176	-2.2	147.0	133.2
1183	-5.9	142.3	132.9
1190	-3.2	144.0	131.6
1197	-2.5	145.6	131.9
1204	-3.4	141.1	134.8
1211	-1.5	140.8	131.6
1218	-2.7	142.3	137.0
1225	-6.1	137.6	138.8
1232	-2.5	140.6	136.4
1239	-3.1	137.8	139.0
1246	-4.1	138.2	139.9
1253	-1.9	136.2	139.6
1260	-6.9	134.1	144.3
1267	-4.7	133.6	143.1
1274	-3.4	134.5	145.1
1281	-0.7	135.8	141.9
1288	-0.8	133.4	145.9
1295	0.8	132.9	144.9
1302	-5.0	130.9	146.4
1309	0.1	131.9	144.5
1316	-4.1	131.5	147.4
1323	-3.8	128.0	147.7
1330	-4.4	127.8	150.5
1337	-2.5	127.3	147.0
1344	-4.4	128.6	152.3
1351	-5.5	125.2	148.9
1358	-2.7	126.2	151.5
1365	-7.6	122.2	153.1

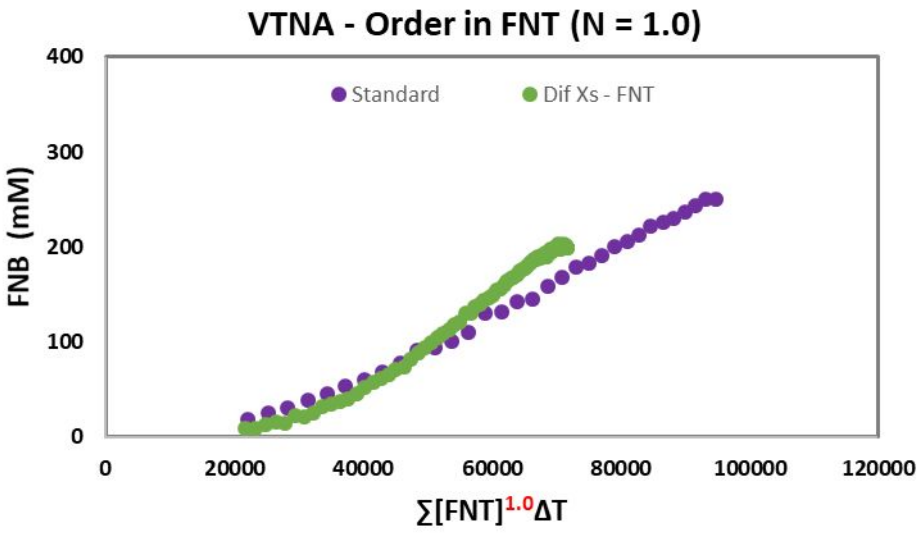


Figure S22. VTNA Of Diff. XS [FNT] – No TFA

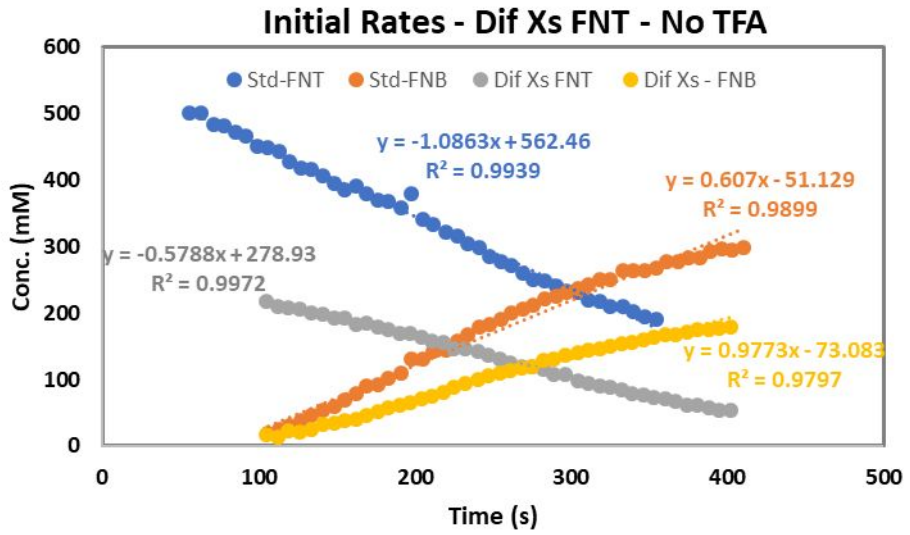


Figure S23. Initial Rates For Diff. XS [FNT] – No TFA

Diff. XS [NBS] -No TFA

Experiment	[FNT **1**] (mM)	[NBS] (mM)	[TFA] (mM)
Standard – No TFA	650	663	0
Diff. XS [NBS] – No TFA	650	331	0

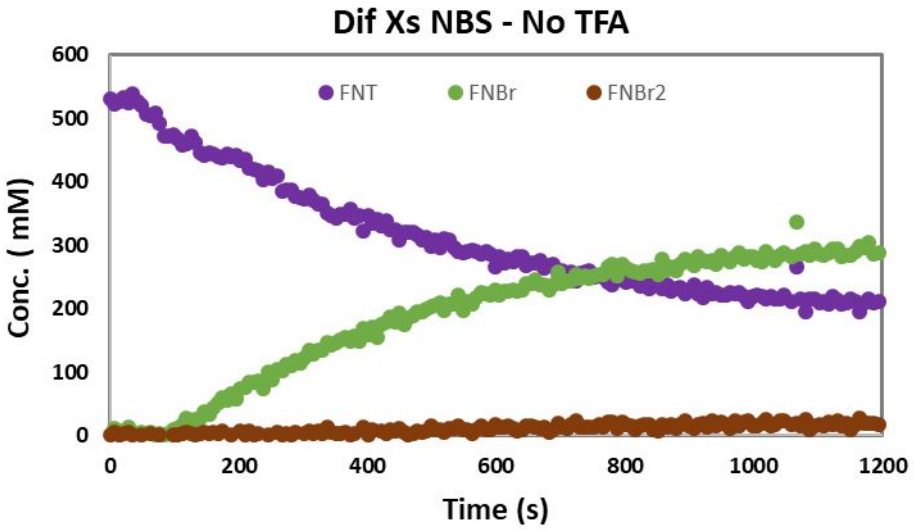


Figure S24. Reaction Progress Data For Diff. XS [NBS] – No TFA

Table S22. ^{19}F NMR Reaction Progress Data For Diff. XS [NBS] – No TFA

Time (s)	FNT (mM)	FNB (mM)	$FNBr_2$ (mM)
0	530.0	-2.2	1.6
7	521.3	11.5	5.4
14	526.6	0.7	0.5
21	532.2	7.5	3.6
28	523.4	12.1	5.6
35	539.3	2.8	1.4
42	525.8	2.1	-0.8
49	520.6	5.0	1.9
56	505.3	-3.8	-2.2
63	503.4	4.1	3.1
70	508.7	1.9	-0.1
77	491.9	2.3	0.3
84	472.8	1.4	-1.6
91	471.4	3.4	-2.9
98	473.9	9.6	1.3
105	466.7	10.3	1.1
112	457.0	17.3	3.4
119	459.0	28.1	5.0
126	470.8	23.9	2.3
133	462.0	25.3	1.2
140	445.4	26.7	3.7
147	441.1	36.9	4.2
154	446.2	33.6	1.9

161	443.7	43.3	4.0
168	438.7	50.6	3.1
175	438.3	59.5	6.2
182	444.3	55.5	-2.1
189	438.5	64.6	1.6
196	441.4	58.0	-2.5
203	434.1	73.3	6.7
210	435.0	76.5	0.2
217	420.9	83.9	6.5
225	419.3	82.9	0.1
231	416.5	86.1	2.0
239	402.1	73.8	-7.3
246	414.2	99.3	1.2
253	404.8	88.8	-3.2
260	408.3	103.4	4.2
267	385.4	102.7	1.8
274	386.8	111.1	2.1
281	386.7	110.2	1.4
288	376.6	117.9	4.7
295	374.9	114.9	-1.6
302	372.4	121.4	2.7
309	378.4	133.8	7.3
316	370.2	127.8	2.4
323	363.8	133.7	6.5
330	364.4	133.6	2.1
337	350.9	146.4	12.1
344	347.1	142.8	5.4
352	342.0	146.6	3.4
358	348.1	149.7	3.4
366	348.8	155.3	4.8
373	357.3	148.0	1.4
380	342.7	155.6	2.2
387	345.7	147.9	-1.1
394	321.9	167.8	12.1
401	346.0	159.0	1.0
408	334.7	170.3	9.5
415	341.3	155.2	-2.6
422	331.0	174.4	7.3
429	339.3	177.7	2.1
436	325.2	185.8	9.8
443	323.6	178.6	7.3

450	308.5	192.3	11.6
457	320.3	175.4	5.3
464	319.9	184.7	1.9
471	321.1	188.5	3.6
478	316.6	195.1	7.4
485	307.5	194.2	5.5
492	312.2	198.3	7.4
499	297.2	202.9	15.0
506	307.1	204.3	9.2
513	295.2	209.0	8.8
520	311.0	196.5	5.4
527	307.3	207.6	10.2
534	295.5	207.9	11.9
541	289.7	220.3	15.6
548	288.4	196.2	8.6
555	288.9	211.0	9.5
563	291.9	207.2	2.9
569	289.9	216.9	9.3
576	286.7	224.2	15.9
584	290.6	222.5	9.4
591	286.0	221.8	8.3
598	265.3	228.3	18.0
605	281.7	221.8	13.4
612	271.6	228.1	13.4
619	278.6	227.0	14.1
626	273.8	229.0	11.2
633	282.6	226.7	6.3
640	282.8	230.1	8.7
647	267.7	238.7	15.2
654	271.9	239.0	16.0
661	272.0	246.3	12.4
668	275.2	236.9	10.7
675	264.1	238.2	13.5
682	268.0	230.1	5.3
689	269.1	236.7	8.7
696	256.1	257.7	18.8
703	259.0	240.1	12.8
710	254.7	243.1	10.9
717	257.1	242.6	17.1
724	243.7	252.7	22.2
731	255.1	247.5	13.5

739	257.1	250.8	12.2
745	259.0	248.0	12.2
753	249.7	250.5	12.3
760	251.2	254.3	16.6
767	249.8	252.8	13.8
774	241.4	265.6	22.0
781	236.9	269.6	21.5
788	252.1	252.1	11.8
795	246.1	270.5	21.9
802	240.6	263.4	16.2
809	244.2	260.5	15.7
816	249.2	256.8	9.6
823	236.3	256.3	14.7
830	236.9	258.6	16.1
837	232.0	260.4	16.6
844	237.5	262.2	9.2
851	241.4	253.3	6.5
858	231.8	277.5	16.9
865	236.6	262.5	12.5
872	226.9	265.7	17.3
879	230.8	259.9	11.2
886	233.3	270.1	16.3
893	223.1	278.6	23.4
900	229.0	273.6	15.4
907	236.9	268.1	11.8
914	223.1	281.2	17.9
921	217.5	275.4	19.2
928	232.4	272.9	13.9
935	222.6	276.6	22.5
942	224.7	269.4	15.5
949	220.2	284.0	21.3
957	220.5	278.6	16.5
964	225.7	272.7	11.8
971	223.3	282.7	23.8
978	224.4	288.5	15.7
985	218.7	277.7	21.0
992	210.5	282.6	22.6
999	218.9	281.6	14.7
1006	221.1	275.7	15.3
1013	219.1	274.3	18.8
1020	215.2	289.2	24.3

1027	220.1	282.6	14.2
1034	216.1	275.2	17.4
1041	215.7	284.1	22.1
1048	220.3	286.9	22.4
1059	210.5	282.8	17.2
1066	264.7	337.0	18.5
1073	214.9	286.8	15.6
1080	195.8	289.3	25.2
1087	216.0	284.5	9.5
1094	215.4	293.9	15.6
1102	208.9	285.0	17.8
1108	211.4	283.1	14.8
1116	207.3	287.5	20.6
1123	219.1	294.6	16.4
1130	212.5	293.0	23.0
1137	207.0	282.4	14.4
1144	209.4	284.1	19.6
1151	215.6	284.3	9.8
1158	210.9	290.1	16.9
1165	194.7	298.1	27.8
1172	208.2	296.0	18.9
1179	215.9	303.4	18.9
1187	209.9	286.6	18.6
1194	210.1	288.4	16.9
1201	206.6	293.0	15.6
1208	212.9	292.5	16.4
1215	211.2	286.7	15.5
1222	189.2	298.0	31.1
1229	202.7	291.9	20.4
1236	209.6	294.7	21.8
1243	182.9	308.7	33.6
1250	204.2	293.6	17.7
1257	205.8	292.0	17.7
1264	193.5	302.3	31.9
1271	207.8	292.3	14.4
1278	193.2	291.6	23.0
1285	203.9	289.4	14.2
1292	203.7	294.3	25.7
1299	196.9	296.6	22.7
1306	211.8	299.1	17.7
1313	195.6	293.8	23.4

1320	196.0	301.3	26.0
1328	200.6	292.4	24.1
1335	201.9	297.7	29.0
1342	206.6	300.7	25.1
1349	205.3	294.3	18.2
1356	202.5	293.9	14.1
1363	195.3	287.8	22.1
1370	204.9	295.1	18.3
1377	205.1	293.6	15.5
1384	198.1	-0.6	20.8
1391	203.0	-0.8	17.1
1398	203.1	-0.5	19.1
1401	195.0	284.8	17.7
1408	186.0	280.4	15.1
1415	192.8	283.6	18.3
1422	192.9	281.2	11.1
1429	188.9	283.7	24.1
1436	192.8	282.4	17.0
1443	194.1	279.3	12.3
1450	192.5	284.9	21.6
1457	193.5	280.3	15.6
1464	191.8	282.3	19.8
1471	193.6	280.5	16.4
1478	193.5	283.1	19.2
1485	188.2	280.8	17.8
1492	186.3	287.1	23.1
1499	191.6	281.8	16.3
1506	196.8	284.1	17.6
1513	191.0	280.6	19.7
1520	190.7	284.1	18.9
1527	190.2	285.8	20.0
1534	190.9	284.4	17.0
1541	187.3	282.4	19.8
1549	192.1	286.8	19.3
1556	190.8	284.3	19.5
1563	198.5	284.5	15.1
1570	190.3	278.4	20.2
1577	190.4	282.4	19.1
1584	188.5	286.3	23.2
1591	188.2	287.6	21.4
1598	191.2	278.4	17.0

1605	184.5	287.6	24.7
1612	191.0	282.0	19.0
1619	192.6	285.3	22.2
1626	191.5	283.9	18.7
1633	191.9	283.7	18.2
1640	191.6	286.5	20.6
1647	187.8	279.7	20.7
1654	191.5	284.1	21.9
1661	197.5	279.3	15.1
1668	194.4	288.3	20.8
1675	188.1	282.3	20.8
1682	189.3	283.4	20.1
1689	188.3	284.2	19.3
1696	193.2	284.4	20.1
1703	190.7	285.1	21.5
1710	194.1	282.9	17.6
1718	189.3	284.2	22.0
1724	188.4	291.5	25.0
1732	188.2	284.8	20.6
1739	195.2	289.2	23.2
1746	192.6	284.0	20.6

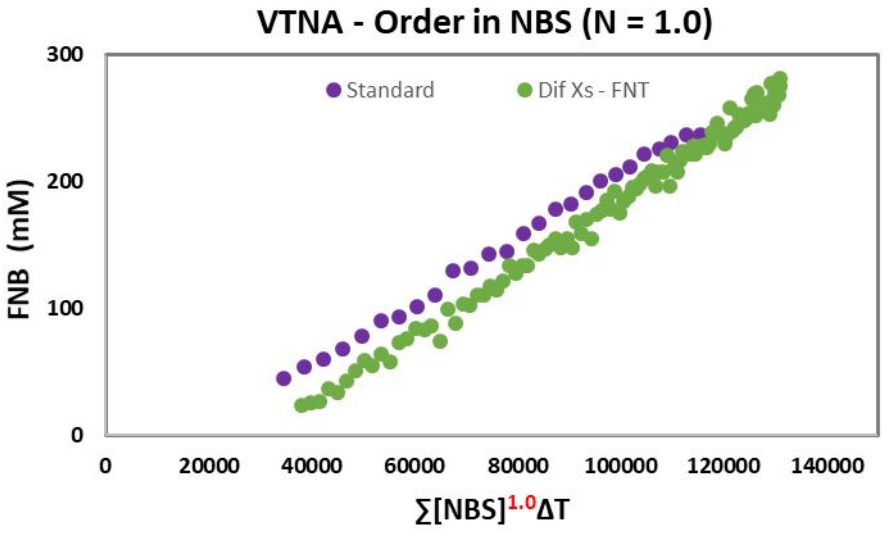


Figure S25. VTNA Of Diff. XS [NBS] – No TFA

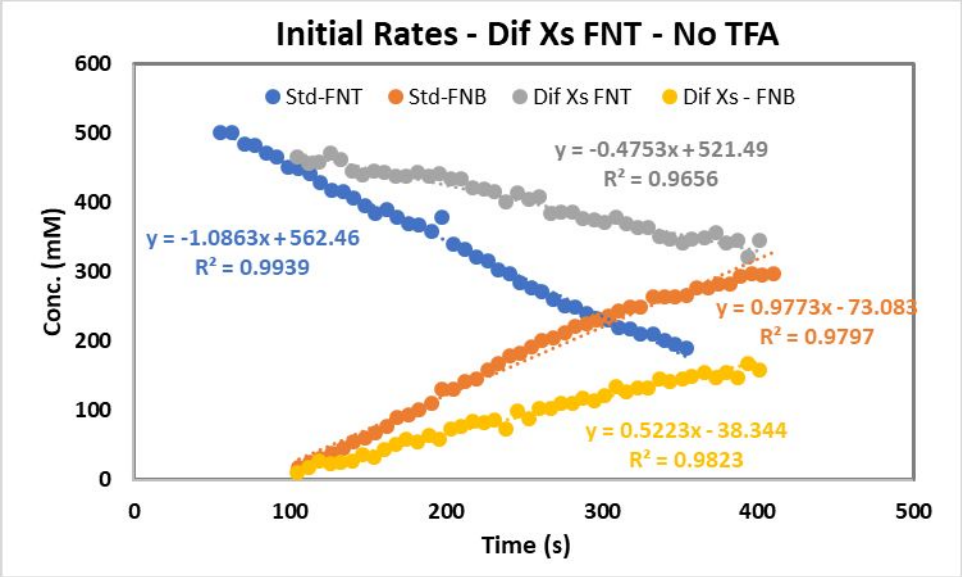
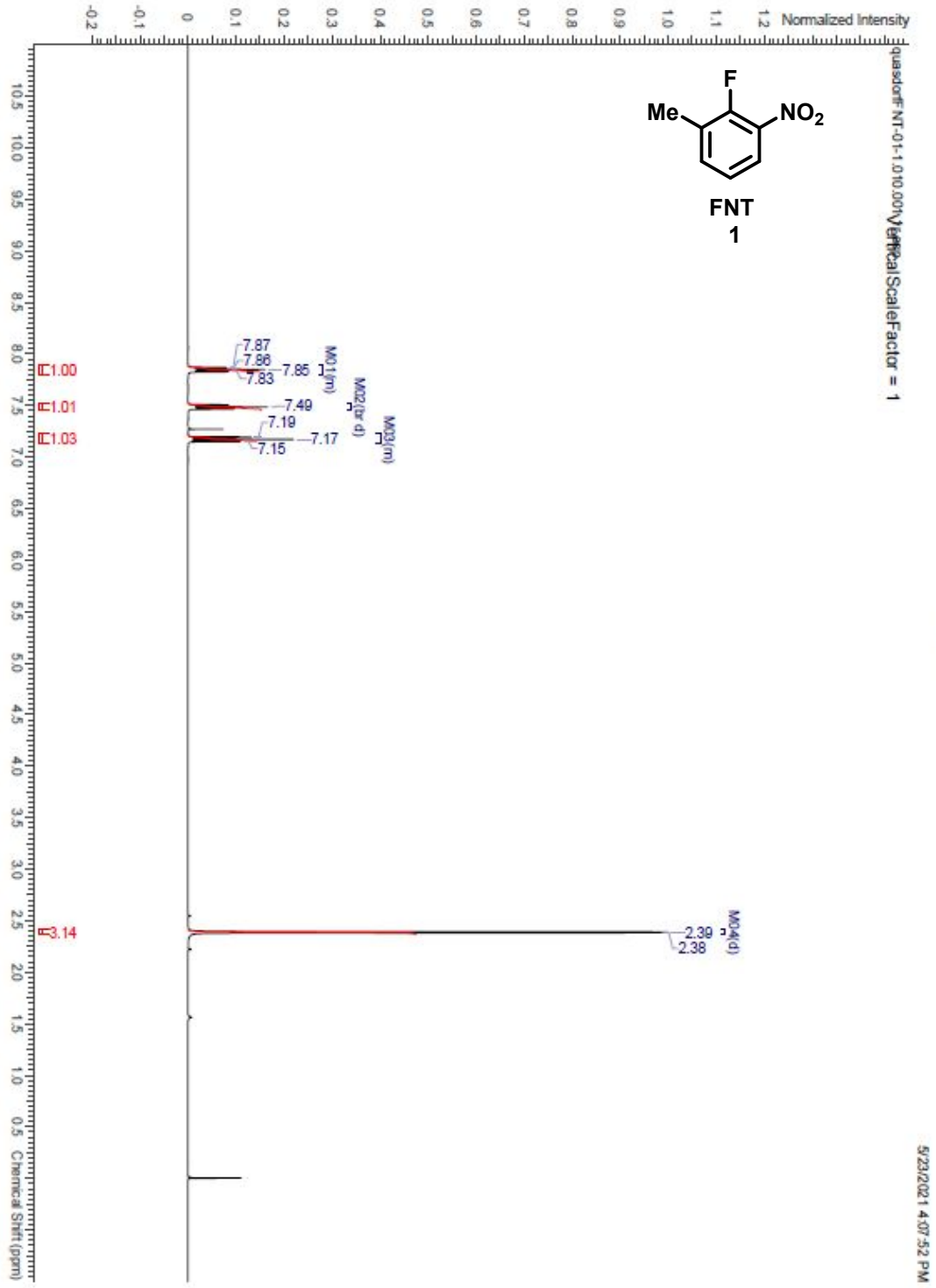


Figure S26. Initial Rates For Diff. XS [NBS] – No TFA

^{1}H NMR Spectra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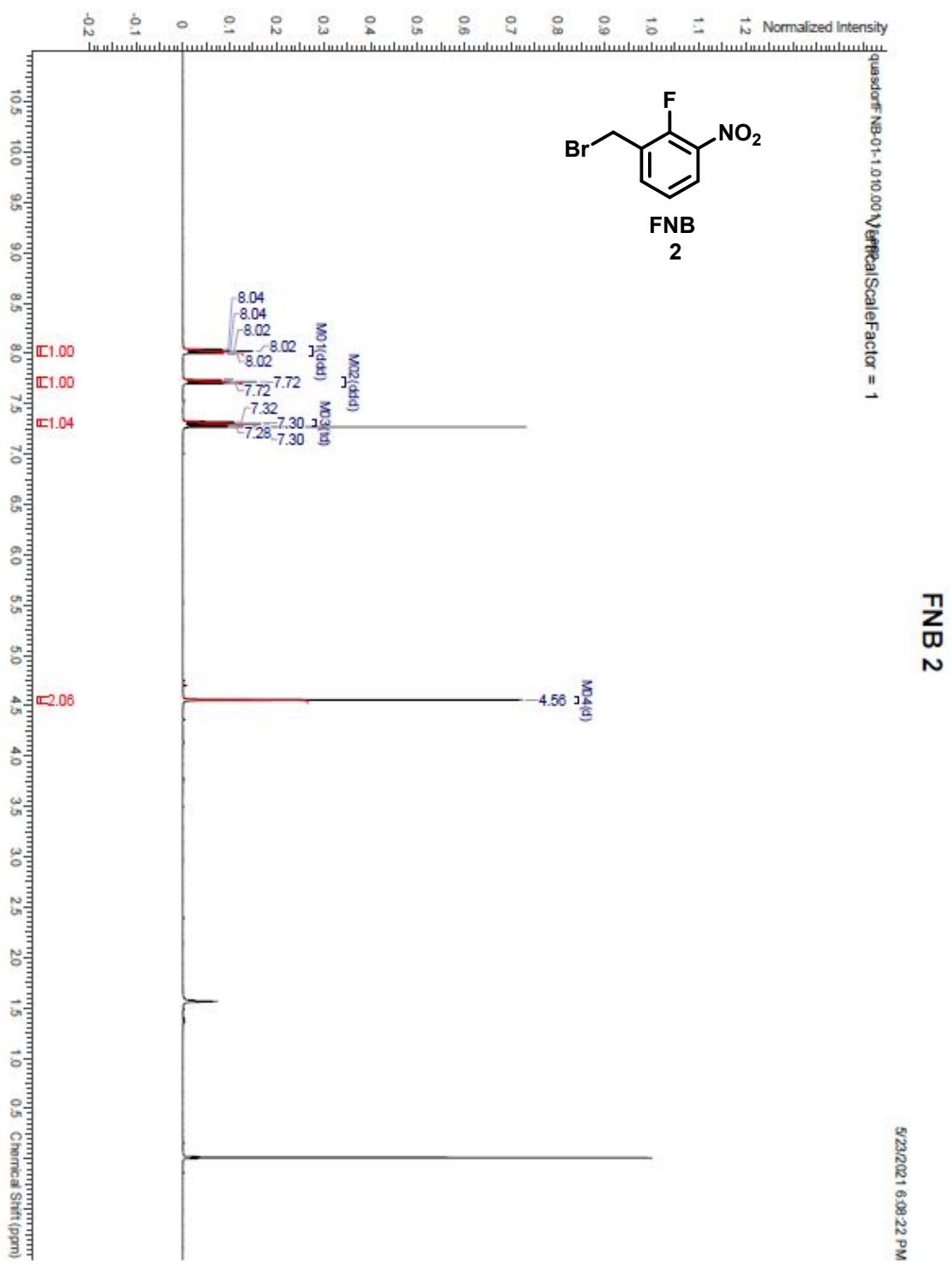
F
Me
NO2
FNT
1
FNT 1
7.87
7.86
7.85
7.83
7.49
7.19
7.17
7.15
2.39
2.38
M01(m)
M02(br d)
M03(m)
M04(d)
1.00
1.01
1.03
3.14
Chemical Shift (ppm)
5/23/2021 4:07:52 PM


Normalized Intensity
Chemical Shift (ppm)
F
NO2
Br
FNB
2
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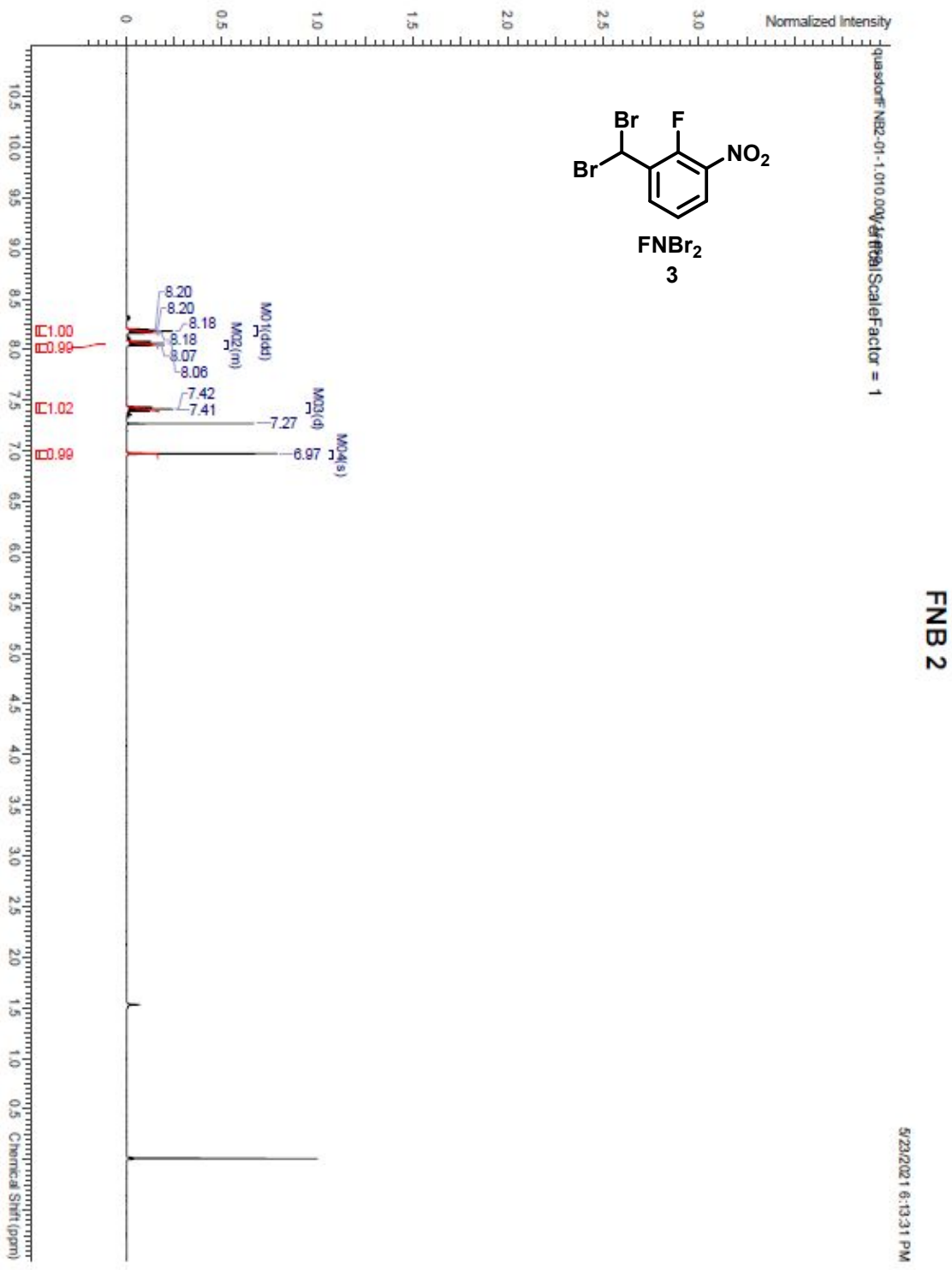
8.04
8.02
8.02
8.02
7.72
7.72
7.32
7.30
7.30
7.28
4.56
1.00
1.00
1.04
2.06
M01(ddd)
M02(ddd)
M03(td)
M04(d)
FNB 2
5/23/2021 6:09:22 PM


Normalized Intensity
Br
F
Br
NO2
FNBr2
3
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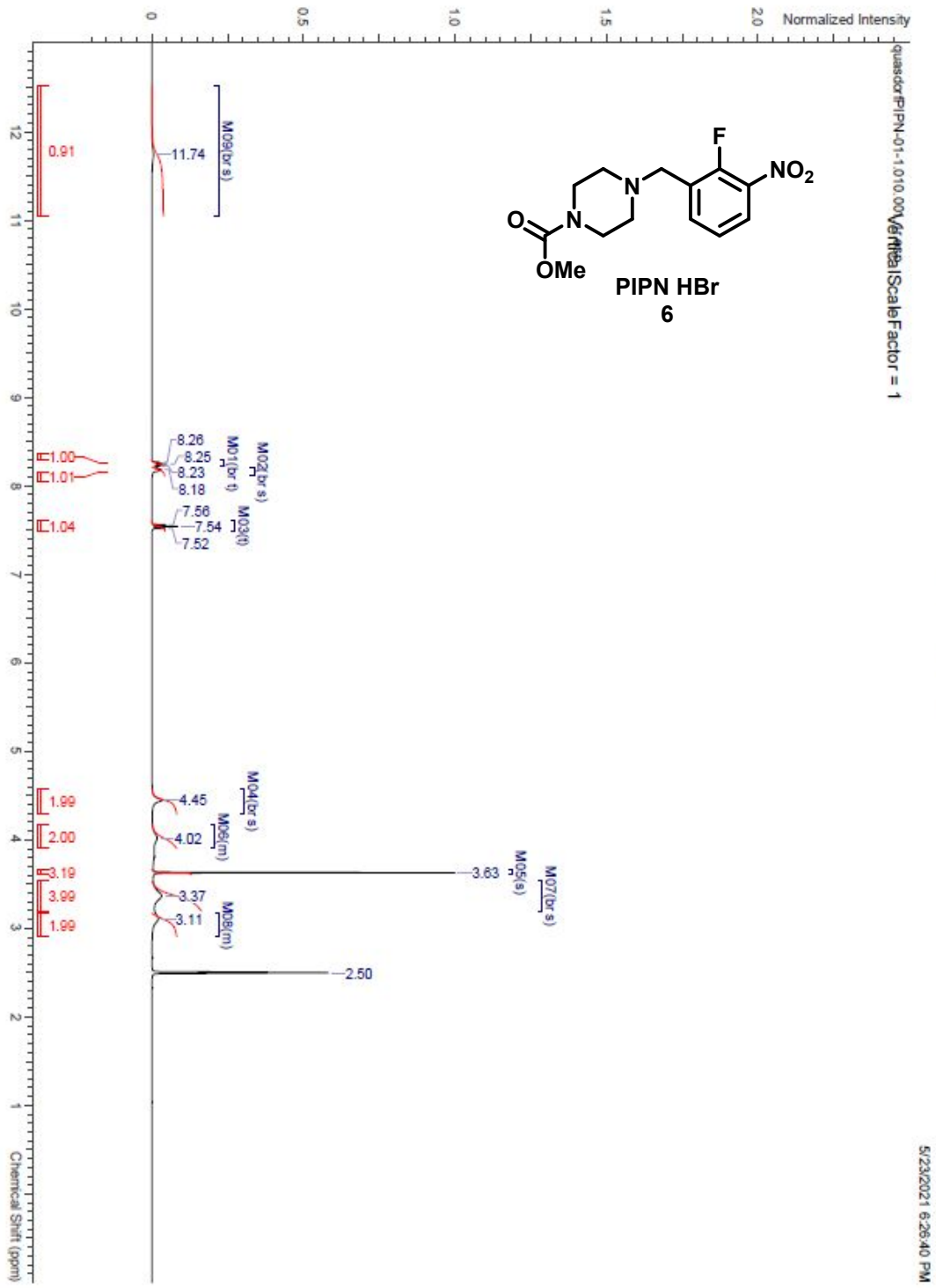
8.20
8.18
8.18
8.07
8.06
7.42
7.41
7.27
6.97
1.00
0.99
1.02
0.99
M01(ddd)
M02(m)
M03(d)
M04(s)
FNB 2
5/23/2021 6:13:31 PM
Chemical Shift (ppm)


PIPN HBr 6
5/23/2021 6:26:40 PM
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Normalized Intensity
Chemical Shift (ppm)
F
NO2
N
O
N
OMe
PIPN HBr
6
0.91
11.74
M09(br s)
1.00
1.01
8.26
8.25
8.23
8.18
M01(br t)
M02(br s)
1.04
7.56
7.54
7.52
M03(t)
1.99
2.00
4.45
4.02
M04(br s)
M06(m)
3.19
3.99
1.99
3.63
3.37
3.11
M05(s)
M07(br s)
M08(m)
2.50

[1] https://www.sigmaaldrich.com/catalog/product/aldrich/aldkit001?lang=en&region=US. Catalog number ALDKIT001.
[2] https://www.goldstonescientific.com/fiber-coupled-led-for-nmr-spectroscopy-includes-fiber-optic-cable/. In photoNMR experiments the 445 nm light source was used.
[3] Silva Elipe, M. V.; Donovan, N.; Krull, R.; Pooke, D.; Colson, K. L. Performance of New 400-MHz HTS Power-Driven Magnet NMR Technology on Typical Pharmaceutical API, Cinacalcet HCl. *Magn. Reson. Chem.* **2018**, *56* (9), 817–825. https://doi.org/10.1002/mrc.4740.
[4] Silva Elipe, M. V.; Donovan, N.; Krull, R.; Pooke, D.; Colson, K. L. Structure Elucidation Capabilities on Typical Pharmaceutical Drugs by New Nuclear Magnetic Resonance Technology: A 400 MHz High-Temperature Superconducting Power-Driven Magnet NMR System. *Instrum. Sci. Technol.* **2019**, *47* (2), 195–212. https://doi.org/10.1080/10739149.2018.1516226.
[5] Blackmond, D. G. Reaction Progress Kinetic Analysis: A Powerful Methodology for Mechanistic Studies of Complex Catalytic Reactions. *Angew. Chem. Int. Ed. Engl.* **2005**, *44* (28), 4302–4320. https://doi.org/10.1002/anie.200462544.
[6] Blackmond, D. G. Kinetic Profiling of Catalytic Organic Reactions as a Mechanistic Tool. *J. Am. Chem. Soc.* **2015**, *137* (34), 10852–10866. https://doi.org/10.1021/jacs.5b05841.
[7] Burés, J. A Simple Graphical Method to Determine the Order in Catalyst. *Angew. Chemie Int. Ed.* **2016**, *55* (6), 2028–2031. https://doi.org/10.1002/anie.201508983.
[8] Burés, J. What Is the Order of a Reaction? *Top. Catal.* **2017**, *60* (8), 631–633. https://doi.org/10.1007/s11244-017-0735-y.
[9] Nielsen, C. D.-T.; Burés, J. Visual Kinetic Analysis. *Chem. Sci.* **2019**, *10* (2), 348–353. https://doi.org/10.1039/C8SC04698K.