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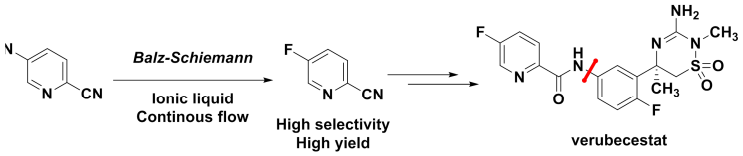

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An Improved Balz-Schiemann Reaction Enabled by Ionic Liquids and Continuous Processing

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KEYWORDS

Active Pharmaceutical Ingredient (API), Continuous Flow, Ionic Liquids (IL), Balz-Schiemann

ABSTRACT

A Balz-Schiemann reaction was developed to convert 2-cyano-5-aminopyridine to 2-cyano-5-fluoropyridine. The use of an ionic liquid (1-butyl-3-methylimidazolium tetrafluoroborate, $BMIMBF_4$) as a solvent was found to be critical in achieving high assay yields and high selectivity for the fluorination vs. protonation. A process was developed to recycle and reuse the ionic liquid enabling its cost-effective use as a solvent. Finally, the optimal conditions were demonstrated under as a continuous process to address process safety risks associated with diazonium intermediates and the product was used to access a key intermediate in the synthesis of β-amyloid cleaving enzyme 1 inhibitor, verubecestat.

INTRODUCTION

Verubecestat (**1**) is an inhibitor of the β-amyloid cleaving enzyme 1, and was recently evaluated for its potential to treat Alzheimer's disease.[1] Our laboratories disclosed a synthetic route to **1** that utilizes a copper-catalyzed C-N amidation reaction between 5-fluoro-picolinamide **2** and aryl bromide **3** to forge the aryl-nitrogen bond of **1** (Figure 1).[2] Commercial sources of **2** are prohibitively expensive for a commercial manufacturing process so we sought to identify a synthetic strategy to prepare **2** in a more cost efficient manner.

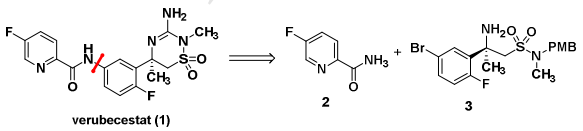


Figure 1: Synthesis of verubecestat (**1**) from 5-amino-2-cyanopyridine (**2**) and **3**.

Our efforts to identify new chemistry to **2** began from 2-cyano-5-aminopyridine. This starting material was readily available, and we reasoned the aryl amine could be readily converted to the aryl fluoride using Balz-Schiemann[3] conditions followed by amide hydrolysis (Figure 2). We established at the outset of this work that the most pressing challenges with this approach would be achieving acceptable levels of selectivity[4] during the Balz-Schiemann reaction and identifying a solution to address the handling of the intermediate diazonium salts upon scale up. Study of this transformation was initially performed in batch and was later optimized in flow.

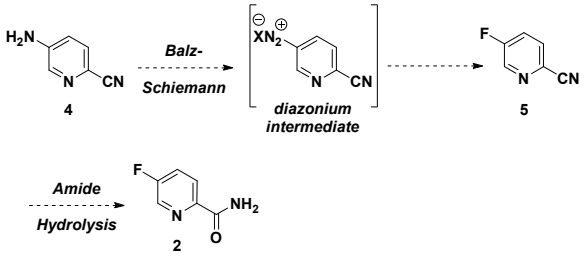


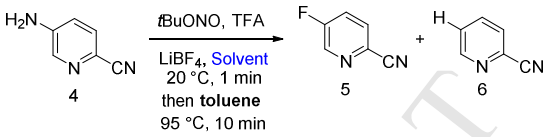
Figure 2: Proposed synthesis plan for the preparation of **2**.

RESULTS AND DISCUSSION

The Balz-Schiemann reaction involves initial conversion of an aryl amine to an intermediate diazonium salt followed by fluorination[5] to yield aryl fluorides. Our goal was to develop a through-process to directly convert **4** to **5**, overcoming any safety hazard related to the handling or isolation of diazonium salts.

We began evaluating this strategy by conducting a solvent screen of the initial diazotization reaction which revealed that MeCN gave the most favorable combination of yield and selectivity for the desired product relative to the reduced arene (Table 1). Under every reaction conditions, toluene was used to promote decomposition of the diazonium intermediate and fluorination. Alcohol solvents were also competent in the reaction showing a favorable balance between yield and selectivity. The solvent screen showed more highly substituted nitrile and alcohol solvents led to decreased levels of selectivity between **5** and **6**. Non-polar solvents such as toluene showed insufficient solvation of the starting material, precluding a single solvent composition for the diazotization and diazo decomposition transformations.

Table 1: Diazotization solvent screen.[a]



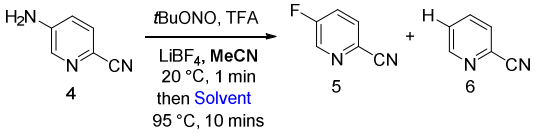
Entry	Solvent	5 (%)[b]	6 (%)	5/6
1	MeCN	69.7	3.6	19.4
2	*i*PrCN	58.5	4.7	12.4
3	PhCN	61.6	4.5	13.7
4	*n*BuOAc	72.1	11.4	6.3
5	MeOH	31.9	4.2	7.6
6	EtOH	52.9	5.5	9.6
7	*i*PrOH	63.9	8.6	7.4
8	AmOH	24.7	4.5	5.5
9	TFE[c]	69.3	6.7	10.3
10	HFIP	36.0	9.4	3.8
11	MTBE	6.5	ND	-
12	*i*PrNO$_2$	32.2	14.7	2.2
13	Pyridine	ND	15.7	-
14	Lutidine	ND	16.3	-

[a] *t*BuONO (0.600 mmol) added to solution of amino-2-cyanopyridine (0.500 mmol), $LiBF_4$ (4.50 mmol), and TFA (0.500 mmol) in solvent (5 mL total volume) at 20 °C. After 1 min, 200 µL was transferred and added to a mixture of toluene (1 mL) and $LiBF_4$ (0.169 g) and heated at 95 °C for 10 min. [b]Assay yield determined using HPLC. [c]Thermal decomposition run in trifluorotoluene rather than toluene.

While the preliminary selectivities shown in Table 1 were encouraging, additional optimization was necessary to meet the strict purity specification established for **5**. Unsurprisingly, **5** and **6** displayed similar solubilities in all solvents evaluated, limiting our capacity to remove **6** by crystallization. To further optimize our reaction a screen was conducted to evaluate the impact of co-solvent on the conversion of the intermediate diazonium salt to **5** (Table 2). We used MeCN for the initial diazotization reaction and varied the solvent used for the diazonium decomposition step. The solvent chosen for the diazonium decomposition showed minimal impact to both yield and selectivity with minor improvements to yield observed when trifluorotoluene was employed. The diazonium decomposition was complete in 10 minutes at 95 °C. Decreasing the temperature of the

reaction resulted in longer reaction times without improving the yield or selectivity. We next considered the possibility that the ratio of solvents used in the diazonium decomposition might influence the reaction outcome. To that end, changing the ratio of MeCN: toluene from 1:5 to 1:10 by doubling the volume of toluene used afforded a 70% yield with an improvement to selectivity to nearly 26:1 (Table 2, Entry 12). While the influence of concentration on selectivity was an exciting development this result presented a new challenge to our reaction design. Using flow chemistry for diazonium formation followed by diazonium decomposition in batch would not be suitable for our system as the constantly changing composition of solvent would result in deleterious selectivity changes over time.

Table 2: Diazonium decomposition solvent screen.[a]



Entry	Solvent	5[b] (%)	6 (%)	5/6
1	trifluorotoluene	71.9	4.0	18.0
2	toluene	69.7	3.6	19.4
3	1,2-difluorobenzene	73.3	5.4	13.6
4	1,4-difluorobenzene	70.4	6.8	10.4
5	fluorobenzene	36.3	4.8	7.6
6	HFIP	20.1	3.4	5.9
7	MeCN	13.4	8.6	1.6
8	THF	ND	94.2	-
9	Dioxane	13.2	77.1	0.2
10	DMF	ND	98.3	-
11	DMC	40.8	54.1	0.8
12	Toluene[c]	70.0	2.7	25.9

[a] *t*BuONO (0.600 mmol) added to solution of amino-2-cyanopyridine (0.500 mmol), $LiBF_4$ (4.50 mmol), and TFA (0.500 mmol) in MeCN (5 mL total volume) at 20 °C. After 1 min, 200 µL was transferred and added to a mixture of solvent (1 mL) and $LiBF_4$ (0.169 g) and heated at 95 °C for 10 min. [b]Assay yield determined using HPLC [c]*t*BuONO (0.600 mmol) added to solution of amino-2-cyanopyridine (0.500 mmol), $LiBF_4$ (4.50 mmol), and TFA (0.500 mmol) in MeCN (5 mL total volume) at 20 °C. After 1 min, 200 µL was transferred and added to a mixture of toluene (2 mL) and $LiBF_4$ (0.169 g) and heated at 95 °C for 10 min

Additional reaction optimization revealed that the concentration of **4** was able to be increased from 0.1 to 0.5 M with only limited effect on the reaction outcome. Changes to TFA stoichiometry had minimal impact on reaction performance, as did additives such as $LiPF_6$, nitrosonium salts, 12-crown-4, nBu$_4$NBF$_4$, and HF·pyridine. The mass balance of the reaction was made up of by-products formed through nucleophilic substitution of the diazonium salt. Weak anions such as trifluoroacetate participated in S_NAr replacement of the diazonium salt as did the water formed during nitrite decomposition to yield the hydroxylated aromatic ring.

The highly electrophilic nature of the intermediate rendered it susceptible to multiple non-productive side reactions even in the presence of poor nucleophiles. A Ritter reaction with the MeCN solvent was a prominent side reaction in addition to dimerization of pyridine rings, and hydration of the nitrile across all the products formed. To address this, we considered strategies aimed at increasing the fluoride concentration but were limited by the poor solubility of most fluoride sources in our desired solvents. Given this limitation we shifted our investigation to imidazolium-based ionic liquids with fluorous counter-ions postulating these solvents could address the solubility limitations of fluoride salts.[6] Running the diazonium decomposition reaction in 1-butyl-3-methylimidazolium tetrafluoroborate (BMIMBF$_4$) led to an improved yield (84%) with excellent selectivity (40:1) (Figure 3).

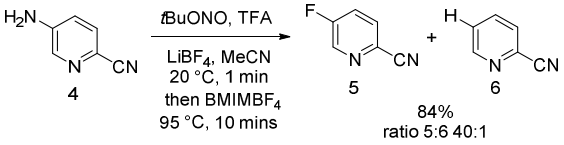
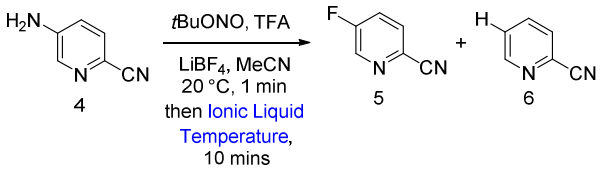


Figure 3: Improved yield and selectivity imparted by ionic liquid as a solvent for diazonium decomposition.

A solvent screen of ionic liquids showed a general improvement in yield without sacrificing selectivity. (Table 3).[7] ILs with the PF_6 counterion tended to produce slightly higher levels of reduced arene **5** than their tetrafluoroborate counterparts, and a slight reduction in selectivity was observed when incorporating SbF_6 anion (Entry 5). The PF_6 anion increased the hydrolysis of the cyano group to amide **2**, likely due to the tendency to form acidic by-products from the PF_6 group.[8] Similarly, use of MIM·H_2SO_4 leads to very high levels of **2** (>50%, entry 13). 1,3 substituted ionic liquids gave higher yields than analogous ionic liquids with incorporation of a methyl group at the 2-position (entries 9-12), and benzyl substitution also decreased yield (entry 8). A brief

examination of pyridinium and pyrrolidinium salts was not promising (entries 14-16).

Table 3: Ionic liquid solvent screen.[a]



Entry	Ionic Liquid	Counter-Ion	Temp. (°C)	5 (%)[b]	6 (%)	5/6
1	EMIM	BF_4	95	85.2	2.5	34.4
2	EMIM	PF_6	95	92.1[b]	3.1	29.8[b]
3	BMIM	BF_4	95	83.7	2.1	39.9
4	BMIM	PF_6	95	68.1	25.7	2.7
5	BMIM	SbF_6	95	85.0	4.1	20.6
6	OMIM	BF_4	95	93.1	3.5	26.8
7	OMIM	PF_6	95	89.0[b]	5.7	15.5[b]
8	BnMIM	PF_6	130	68.2	ND	ND
9	EDMIM	BF_4	130	71.6	2.5	29.1
10	BDMIM	BF_4	95	84.8	5.3	16.1
11	BDMIM	PF_6	95	70.4	9.6	7.3
12	BDMIM	PF_6	130	78.9	5.9	13.3
13	MIM	H_2SO_4	95	64.2[b]	2.6	25.1[c]
14	*N*-Butyl-4-methyl pyridinium	BF_4	130	77.5	7.0	11.0
15	*N*-Ethyl pyridinium	BF_4	95	76.4	2.6	29.0
16	*N*-Butyl-*N*-methyl pyrrolidinium	BF_4	130	65.8	5.6	11.7

[a] *t*BuONO (2.40 mmol) added to solution of amino-2-cyanopyridine (2.00 mmol), $LiBF_4$ (18.0 mmol), and TFA (2.00 mmol) in MeCN (5 mL total volume) at 20 °C. After 1 min, 50 µL was transferred and added to a mixture of ionic liquid (0.5 mL) and $LiBF_4$ (0.500 g) and heated for 10 min. [b]Assay yield determined using HPLC. [c]Combined yield of picolinamide **2** and picolinonitrile **5**.

Though the use of ionic liquids as solvent for this reaction provided a favorable outcome with respect to yield and selectivity, the isolation of product was not some trivial endeavor as ionic liquids are non-volatile and excellent solvents for organic compounds. Gratifyingly, we found that isolation of **5** from $BMIMBF_4$ *via* extraction using a co-solvent mixture of toluene and ethyl acetate (6.7:1) was effective. We were also pleased to observe that the extractive workup resulted in an improved ratio between **5** and **6** after the extraction (>70:1) with simultaneous removal of impurities resulting from side reactions between MeCN and the diazonium salt intermediate **(**Figure 4a). Analysis of the residual ionic liquid showed an enrichment of the reduced arene **6**. After solvent removal the isolated yield of **5** was 77%.

We next sought to develop a protocol to purify and recycle the ionic liquid to render its use cost-effective on scale.[9] The boiling point of **6** and **5** are 230 and 240 °C respectively. These compounds can be distilled from $BMIMBF_4$ along with water and MeCN used in the process to purify the ionic liquid to a suitable point for reuse (Figure 4b). Application of this methodology demonstrated effective removal of product from the reaction mixture via vacuum distillation at temperatures below 175 °C. At distillation temperatures exceeding 180 °C, decomposition products were generated, and they

remained in the ionic liquid. The purified ionic liquid was successfully recycled in the reaction for seven reaction cycles (Figure 5). First, the diazotization was run in MeCN followed by thermal decomposition in $BMIMBF_4$. Then, product was isolated *via* three extractions with organic solvent, and the ionic liquid was purified by distillation at 150 °C under vacuum. The reaction was subsequently repeated for 7 cycles, where the average isolated yield across the 7 reactions was 74% with a selectivity of 66:1 for **5** over **6**.

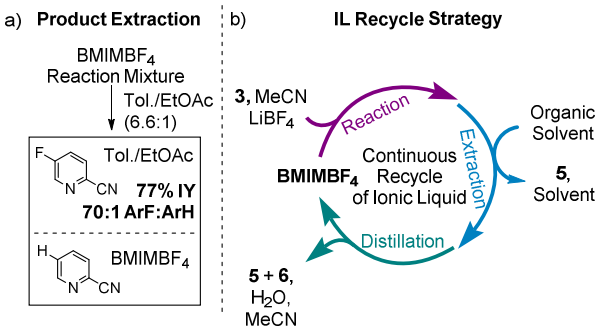


Figure 4: Scheme for ionic liquid reuse including a) Selective extraction of product from $BMIMBF_4$. b) Strategy for recycle of ionic liquid.

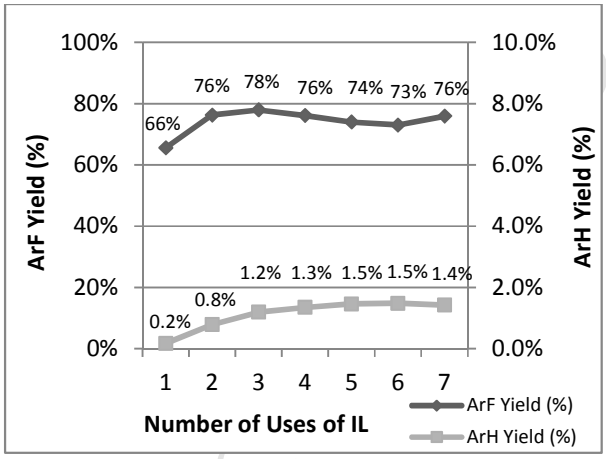


Figure 5: Performance of recycled ionic liquid in 7 reactions

With an optimized reaction in place, as well as a protocol to recycle the ionic liquid solvent, we next turned our attention to addressing the hazardous nature of the reaction. We considered flow chemistry[10] to be one possible solution to this challenge as the dye industry, as well as the broader synthetic community, has used continuous operations to address safety concerns surrounding build-up and isolation of these high energy intermediate diazonium salts.[11,12,13] Use of the diazonium salts formed *in situ* have been applied to a number of different reactions[14] including the Balz-Schiemann reaction.[15,16]

We developed a procedure to run both the diazotization and diazonium decomposition continuously since maintaining the ratio of the two solvents was shown to impact the reaction profile (Figure 6). The reactor setup consists of a t-mixer to combine *tert*-butyl nitrate with a solution of **4**, $LiBF_4$ and TFA in MeCN, followed by a PFA loop to age the reaction mixture for 1 minute at room temperature. Upon exiting the first reactor, $BMIMBF_4$ and $LiBF_4$ were combined with the reaction stream using a second t-mixer. The resulting solution was pushed into a PFA reactor heated to 95 °C to yield the desired product after a 10 minutes residence time. To minimize the impact of gas evolution (N_2) on residence time, the entire reactor was pressurized to 100 psi with the aid of a back-pressure regulator. It is worth noting that we observed slightly diminished levels of selectivity when running the reaction under continuous conditions but the work up procedure enabled an upgrade to selectivity as described earlier.

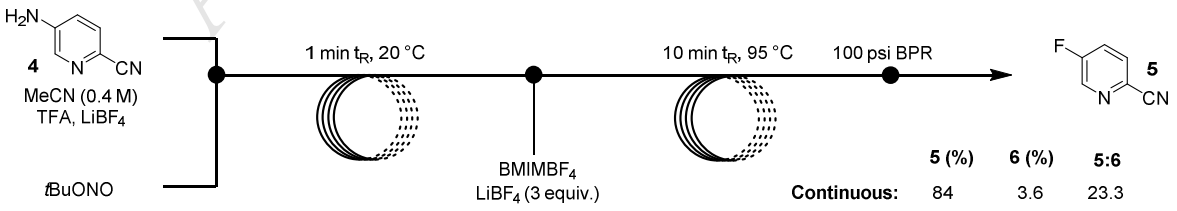


Figure 6: Continuous flow synthesis of **5**.

Finally, **5** was converted to **2** using hydrolysis conditions described by Shimizu and co-workers (Figure 7).[17,18] The 2-step procedure to convert 2-cyano-5-aminopyridine to 5-fluoro-2-pyridinecarboxamide proceeded in 79% overall yield.

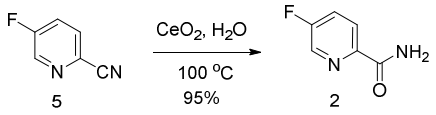


Figure 7: Hydration of **5**.

CONCLUSION

The use of an ionic liquid as solvent enabled improvements to yield and selectivity for the conversion of **4** to **5**. The purity of the Balz-Schiemann adduct could be further enhanced through an extractive process which lowered the levels of the reduced arene **6**. The extraction was followed by a distillation to purify and recycle the ionic liquid. The robust performance of the recovered ionic liquid was demonstrated for 7 iterations with negligible impact to the reaction profile. Finally, the reaction was demonstrated under continuous flow conditions to address process safety concerns related to build-up of unstable diazonium salts.

EXPERIMENTAL

General Remarks: Solvents, reagents and starting materials were purchased from commercial sources and used as received. Reactions were analyzed using an Agilent 1100 Series HPLC and quantified through calibration curves developed for 2-cyano-5-fluoropyridine, 2-cyanopyridine, and 5-fluoropicolinamide. A C18 reversed-phase analytical column (Ascentis Express C18, 10 cm x 4.6 mm, 2.7 μm particle size) was used for separations with mobile phases A (water + 0.1% H_3PO_4) and B (MeCN) flowing at a rate of 1.25 mL/min. 2 μL of sample was injected, and the following gradient was applied: hold at 90:10 ratio of A to B for 1 min then linearly increase to 95% B from 10% B over 6 min. Hold at 5:95 A to B for 3 min. ^{1}H-NMR was collected on a Bruker 500 MHz spectrometer, and chemical shifts (δ) are expressed in part per million. Spectra were obtained using MeCN-d_3 as solvent with MTBE used as an external standard.

2-Cyano-5-fluoropyridine (4, Representative procedure for batch screening): Amino-2-cyanopyridine (0.0600 g, 0.500 mmol, 0.1 M), $LiBF_4$ (0.422 g, 4.50 mmol), and TFA (38.6 μL, 0.500 mmol) were combined with MeCN to reach a total volume of 4.928 mL. The orange solution was transferred to a 6 mL scintillation vial equipped with a magnetic stir bar and temperature was controlled *via* a water batch held at 20 °C. *t*BuONO (71.5 μL, 0.600 mmol) was added to the rapidly stirred solution to form the diazonium salt, and after 1 minute, 200 μL was transferred and added to a 1 mL mixture of trifluorotoluene and $LiBF_4$ (0.169 g, 1.8 mmol) heated at 95 °C. After 10 minutes, the reaction mixture was removed from heat and diluted to 5 mL to make a homogeneous solution. The reaction was analyzed by HPLC as described above.

2-Cyano-5-fluoropyridine (5, Ionic Liquid Recycle): Amino-2-cyanopyridine (0.238 g, 2.00 mmol, 0.4 M), $LiBF_4$ (1.69 g, 18.0 mmol), and TFA (154 μL, 2.00 mmol) were combined with MeCN to reach a volume of 4.714 mL. The orange solution was transferred to a 6 mL scintillation vial equipped with a magnetic stir bar and temperature was controlled *via* a water batch held at 20 °C. *t*BuONO (286 μL, 2.40 mmol) was added to the rapidly stirred solution to form the diazonium salt, and after 1 minute, 50.0 μL was transferred and added to a mixture of $BMIMBF_4$ (0.5 mL) and $LiBF_4$ (0.500 g, 5.33 mmol) heated at 95 °C. After 10 minutes, the reaction mixture was removed from heat, and a 1 mL mixture of 6.6:1 toluene to ethyl acetate was added. A vortex mixer stirred the mixture for 30 seconds, and then the organic and ionic liquid phases were allowed to settle. The organic phase was collected, the extraction was repeated twice more, and the organic fractions were combined, diluted to 5 mL and analyzed by HPLC as described above. The vial containing ionic liquid was capped with a septum, placed under vacuum, and heated for 10 minutes at 150 °C to remove residual solvent and product. The ionic liquid was returned to 95 °C under an atmosphere of air, and freshly prepared diazonium solution was added. The cycle was repeated six times after the initial run.

2-Cyano-5-fluoropyridine (5, Continuous Flow): Plug-flow reactors were constructed from 1/16" PFA tubing (0.03" ID, Upchurch Scientific) and reagents and reaction streams were joined through connections with PEEK tee-mixers (0.04" ID, Upchurch Scientific). Pressure was regulated with a 100 psi backpressure regulator cartridge from Upchurch Scientific. Reagent streams were pumped with Harvard Apparatus PhD Ultra syringe pumps. A 20 μL (4.4 cm, 1 min t_R) segment of PFA air-cooled tubing was used as a reactor for diazonium formation, and a 2.2 mL (482 cm, 10 min t_R) coil of PFA tubing heated at 95 °C in an oil bath was used for the thermal dediazoniation. 5-Amino-2-cyanopyridine (0.238 g, 2.00 mmol, 0.4 M),

$LiBF_4$ (0.562 g, 6.00 mmol), and TFA (154 μL, 2.00 mmol) were combined in a 5 mL volumetric flask and MeCN was added to reach a total volume of 5 mL. The orange solution was transferred to an 8 mL stainless steel syringe and pumped at 18.92 μL/min. *t*BuONO (8.41 M) was added to a 2.5 mL glass syringe with luer lock adapter and pumped at 1.08 μL/min. A solution of $LiBF_4$ (1.00 g, 10.7 mmol) in $BMIMBF_4$ was made to 10 mL, added to a stainless-steel syringe, and pumped at 200 μL/min. After passing 5 residence volumes (1.10 mL) sample was collected for 2 minutes and 38 seconds (0.579 mL), diluted to 5 mL in MeCN, and analyzed by HPLC as described above.

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SUPPLEMENTARY MATERIAL

Supplementary data to this article can be found online.

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