Utilizing Biocatalysis and an Unprecedented Sulfolane-mediated Reductive Acetal Opening to Access Nemtabrutinib from Cyrene

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ABSTRACT: The chiral building block 5-amino-2-hydroxymethyltetrahydropyran **1a** has been previously synthesized through a cumbersome 9-step synthesis from tri-*O*-acetyl-D-glucal, which renders access to nemtabrutinib (**2**), a BTK inhibitor currently being evaluated for the treatment of various hematologic malignancies, inefficient and wasteful. Herein, we describe the development of a protecting group-free, 2-step synthesis of **1a** from Cyrene™, a biorenewable feedstock. The improved synthesis involves a biocatalytic transamination reaction of Cyrene™ to install the desired amine-stereocenter in a single step with high diastereoselectivity. The enzymatic reaction is followed by a stereo-retentive reductive acetal opening reaction of the chiral cyrene amine intermediate **3a** to furnish **1a**. A mechanistic investigation of the acetal opening reaction is also described which uncovered unprecedented reaction conditions for the *in-situ* generation of diborane mediated by the sulfolane co-solvent. The streamlined synthesis of **1a** from Cyrene™ resulted in a > 27% yield improvement and a significant reduction in the environmental impact of the synthesis.

INTRODUCTION

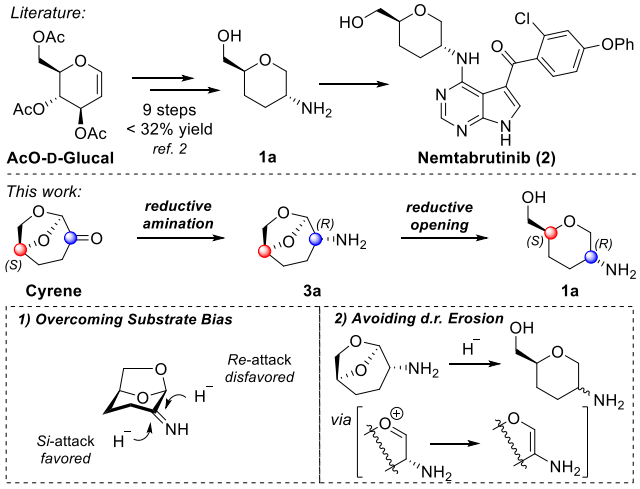
5-Amino-2-hydroxymethyltetrahydropyrans, such as compound **1a** (Scheme 1), are sought after building blocks for the synthesis of biologically active compounds used for the treatment of cancer, bacterial infections and neurodegenerative diseases.[1] Despite its close resemblance to readily available D-glucosamine, the synthesis of **1a** and its derivatives are rather lengthy, rendering structure-activity relationship (SAR) studies as well as large-scale synthesis of biologically active compounds containing **1a** cumbersome. For example, **1a** can be accessed from tri-*O*-acetyl-D-glucal utilizing an Overman rearrangement to install the key amine stereocenter.[2,3] Nevertheless, the synthesis requires 9 linear steps and numerous protecting group modifications, several of which utilize hazardous reaction solvents such as dichloromethane or 1,2-dichlorobenzene.[2a] As such, the reported synthesis to **1a** is not only inefficient but also misses our current standards for sustainability.[4]

We recently became interested in the preparation of **1a** as a key building block for the synthesis of the reversible Bruton's tyrosine kinase inhibitor nemtabrutinib (**2**), currently being evaluated for the treatment of various fatal hematologic malignancies including chronic lymphocytic leukemia (CLL) and Richter's Transformation.[5] To enable efficient access to **2**, a shorter and more streamlined synthesis of the key building block **1a** was highly desirable. Seeking to minimize functional group manipulations and avoid the use of protecting groups, we were attracted to Cyrene™ (dihydrolevoglucosenone) as a potential starting material given that it already contains the requisite C2-stereocenter (red) and a ketone functional group (blue) that could be leveraged for further elaboration (Scheme 1). Cyrene™ itself has recently been put forward as a non-toxic biorenewable alternative to dipolar aprotic solvents, as it is readily obtained through a two-step process from cellulosic waste.[6] Hence, the use of Cyrene™ as a starting material was highly desirable to render the synthesis of **1a** and the active pharmaceutical ingredient (API) **2** more sustainable.[7] To this end, we envisioned that a diastereoselective reductive amination of the ketone followed by reduction of the bicyclic acetal could provide access to **1a** from Cyrene™ in a more efficient manner.[8] However, a number of challenges with this approach became apparent (Scheme 1). For example, to furnish the desired diastereomer we would have to overcome the thermodynamic and kinetic preference for a *si*-attack of the reductant in the reductive amination. Furthermore, even if cyrene amine **3a** could be accessed efficiently, erosion of the diastereomeric ratio (d.r.) *via* the formation of a putative enamine intermediate during the reductive acetal opening would need to be avoided.

Herein, we describe the development of a protecting group-free process to synthesize key building block **1a** in two steps from Cyrene™, a sustainable feedstock material, through an enzyme-catalyzed transamination followed by a reductive acetal opening. Additionally, we demonstrate through mechanistic

studies that this reductive acetal opening proceeds *via* an unprecedented *in-situ* formation of diborane as the active reductant, which is mediated by the reaction solvent sulfolane.

Scheme 1. Synthetic Approaches to Key Fragment 1a of Nemtabrutinib



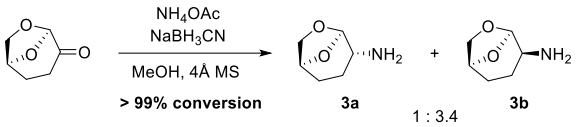
RESULTS AND DISCUSSION

Reductive amination. To initiate the synthetic route development of **1a**, we first focused our efforts on the reductive amination step. Upon subjecting Cyrene™ to standard reductive amination conditions (NH_4OAc, $NaBH_3CN$ in MeOH), we found that the undesired *cis*-diastereomer **3b** was preferentially formed in a 3.4:1 ratio confirming our hypothesis of a more facile hydride attack from the less hindered face of the bicyclic system (Table 1A).[9] We next explored if an appropriate catalyst system could be identified to overcome the substrate bias of Cyrene™. While asymmetric transition metal-catalyzed reductive amination reactions have been reported in the literature,[10] we sought to pursue an enzyme-catalyzed transamination as a more benign and environmentally friendly approach.[11] Moreover, amine transaminases (ATAs) are a well-studied class of enzyme catalysts that can convert prochiral ketone substrates into chiral amines in the presence of an amine donor.[12]

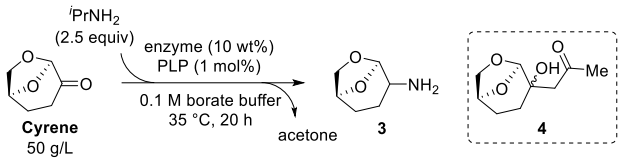
An initial screen of a panel of transaminase enzymes at 10 wt% enzyme loading and with isopropylamine as the amine donor showed several enzymes giving high conversion despite the moderate excess of isopropylamine used, suggesting a thermodynamically favorable transamination reaction.[13] However, most enzymes with high activity against Cyrene™ either formed undesired **3b** in good selectivity (Table 1B, Entry 2) or were unselective, such as transaminases previously developed for the synthesis of sitagliptin[14] (CDX-017, Entry 1) and vernakalant[15] (ATA-303, Entry 3).[16] To our delight, ATA-426[17] provided the desired *trans*-diastereomer **3a** with excellent 17:1 selectivity at 57% conversion (Entry 4) which could be further increased to 71% with 20 wt% enzyme loading (Entry 5). The reaction conversion could be further improved by maintaining the reaction pH above 7.5 to avoid unproductive protonation of isopropylamine (Entry 6). Performing the transamination with ATA-426 on gram scale, however, exacerbated an undesired aldol reaction between Cyrene™ and the acetone by-product forming 10% of side product **4**. Implementation of acetone removal *via* nitrogen sweep and gentle vacuum during the reaction was required to reduce the formation of **4** and improve the conversion to 94 % and the yield of **3a** and **3b** to 91% with a d.r. of 24:1 (Entry 7),[18] effectively yielding **3a** in a single step from Cyrene™, as opposed to the previously reported 4-step synthesis from Levogluocosenone.[19]

Table 1. Synthesis of 3a using Transaminase Enzymes

A: Substrate-Controlled Reductive Amination



B: Catalyst-Controlled Transamination



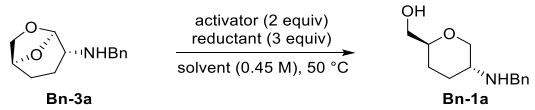
Entry[a]	Enzyme [wt%]	Conversion [%]	**3a:3b** d.r.	**4** [%]
1	CDX-017 (10)	72	1 : 1	n.d.
2	ATA-234 (10)	86	1 : 7	n.d.
3	ATA-303 (10)	95	2 : 1	n.d.
4	ATA-426 (10)	57	17 : 1	n.d.
5	ATA-426 (20)	71	17 : 1	n.d.
6[b]	ATA-426 (20)	87 (75)[d]	23 : 1	10.1
7[b,c]	**ATA-426 (20)**	**94 (91)[d]**	**24 : 1**	**2.6**

[a] Unless otherwise noted, the reactions were performed on 25 mg scale using an aqueous 0.1 M sodium tetraborate buffer at pH 9.5 and conditions as indicated above. [b] Reaction was performed on 4 g scale at 45 °C with 2.2 equiv $^{i}PrNH_2$. pH was maintained above 7.7. [c] N_2 sweep and vacuum were applied. [d] Combined assay yield for **3a** and **3b** was determined by ^1H NMR using an internal standard. PLP (co-factor) = pyridoxal-5′-phosphate.

Reductive acetal opening. With a method in hand to access **3a** in high diastereoselectivity, we next sought to identify reductive conditions to access **1a**. While conditions for the reductive opening of bicyclic acetals have been reported in the literature,[20] there remains a paucity of examples containing basic amine functional groups. Hence, to overcome the unproductive formation of amine-Lewis acid complexes, we opted to subject our benzyl-protected model substrate **Bn-3a**[16] to an excess of various oxophilic Lewis acids in the presence of 1 M BH_3·THF complex in acetonitrile at 50 °C for 8 h (Table 2, Entry 1–3).

Lewis acids such as BF_3·OEt_2, $TiCl_4$, and $AlCl_3$ yielded **Bn-1a** in moderate yields without significant d.r. erosion (Entries 1–3). Interestingly, trifluoroacetic acid (TFA) also proved to be an effective promoter for the acetal opening, resulting in the formation of **Bn-1a** without erosion of the d.r. in 78% yield (Entry 4). When increasing the equivalents of TFA from 2 to 3, full conversion was achieved improving the yield of **Bn-1a** to 95%.[16] Due to safety concerns associated with handling and storage of BH_3·THF,[21] we next sought to explore safer alternatives. However, more stable borane reductants such as BH_3·Py were found to be unreactive (Entry 5).

Table 2. Reductive Acetal Opening Condition Screening[a]



Bn-3a Bn-1a

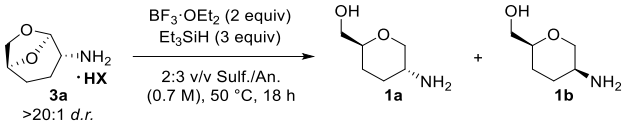
Entry	Reductant	Activator	Solvent	**Bn-1a** [%]
1	BH_3·THF	BF_3·OEt_2	MeCN	48
2	BH_3·THF	$TiCl_4$	MeCN	52
3	BH_3·THF	$AlCl_3$	MeCN	67
4	BH_3·THF	TFA	MeCN	78
5	BH_3·Py	TFA	MeCN	0
6	Et_3SiH	BF_3·OEt_2	MeCN	37
7	Et_3SiH	BF_3·OEt_2	DCM	9
8	Et_3SiH	BF_3·OEt_2	THF	0
9	Et_3SiH	BF_3·OEt_2	Sulfolane	83
10	Et_3SiH	BF_3·OEt_2	Anisole	< 1
11	Et_3SiH	BF_3·OEt_2	Sulf./An.[b]	73
12[c]	**Et_3SiH**	**BF_3·OEt_2**	**Sulf./An.**[b]	**84**
13	Et_3SiH	TFA	Sulfolane	0

[a] 0.225 mmol of **Bn-3a** was dissolved in a solvent (0.5 mL), the activator and reductant were added, and the mixture was heated to 50 °C for 8 h (Entry 1–4) or 18 h (Entry 5–12). After quenching with MeOH at 50 °C for 1–2 h, the assay yield was determined by HPLC analysis. [b] Sulf. = sulfolane, An. = anisole, 2:3 v/v sulfolane:anisole ratio used. [c] 5 equiv of Et_3SiH were used. TFA = trifluoroacetic acid.

Interestingly, we found that triethylsilane in the presence of BF_3·OEt_2 was capable of converting **Bn-3a** to **Bn-1a**, albeit in only 37% yield due to competing side reactions between the starting material and the solvent (Entry 6).[22] This observation prompted us to perform an exhaustive solvent screen for the triethylsilane/BF_3·OEt_2 reagent combination.[16] While dichloromethane (DCM) and THF, solvents commonly used for reductions with triethylsilane/BF_3·OEt_2,[20] proved to be ineffective (Entry 7–8), we found the five-membered sulfone solvent sulfolane to be uniquely effective in promoting the reductive opening of **Bn-3a** to **Bn-1a** (Entry 9). Due to the high melting point of sulfolane (27 °C), co-solvents were explored to simplify handling and mixing.[16] While not being suitable as the single reaction solvent (Entry 10), aromatic co-solvents, such as anisole, did not impact the reaction performance of sulfolane resulting in the formation of **Bn-1a** in up to 84% yield (Entry 11–12). Interestingly, in addition to sulfolane, the nature of the activator was also critical for the productive reduction, as TFA was shown to be completely ineffective when using triethylsilane as the reductant (Entry 13).

With optimized conditions in hand, we next investigated other derivatives of **3a** to establish if a protecting group-free synthesis of **1a** from Cyrene™ would be feasible. In this regard, the unprotected freebase **3a** performed comparably to the benzyl-protected derivative **Bn-3a** (Table 3, Entry 1). Nevertheless, we were interested in utilizing an ammonium salt of **3a** directly, given the ease of isolation and handling of these crystalline derivatives in comparison to the freebase. Hence, whilst a variety of salts of **3a** were competent in the reductive acetal opening, the TsOH salt performed best (Entries 2–5). Interestingly, a decrease in diastereoselectivity was observed for the HBr salt, suggesting that more nucleophilic counter anions could facilitate formation of a putative enamine intermediate en route to **1a**-**1b** mixtures (Entry 5).[23]

Table 3. Reductive Acetal Opening with Unprotected 3a[a]



Entry	Salt HX	**1a** [%]	**1a:1b** d.r.
1	None	85	>20:1
2	**TsOH**	**90**	**>20:1**
3	TfOH	64	>20:1
4	HCl	81	>20:1
5	HBr	68	10:1

[a] 0.664 mmol of **3a·HX** was suspended in 2:3 v/v sulfolane:anisole (1 mL), triethylsilane (3 equiv), and BF_3·OEt_2 (2 equiv) were added, and the mixture was heated to 50 °C for 18 h. Upon quench with MeOH at 50 °C for 1–2 h, the assay yield and d.r. were determined by ^{1}H NMR analysis. TsOH = *para*-toluenesulfonic acid. TfOH = Trifluoromethylsulfonic acid.

Mechanistic investigation. Since the combination of BF_3·OEt_2 and sulfolane as solvent was shown to be unique in promoting the reductive acetal opening of **3a·TsOH** when using triethylsilane as reductant, we sought to investigate the reaction mechanism of these newly identified reduction conditions. The reaction profile of the reductive opening in a mixture of 2:3 (v:v) sulfolane and anisole-d_8 obtained by ^{1}H and ^{19}F NMR spectroscopy analysis revealed an induction period of almost one hour during which formation of H_2 and Et_3SiF was observed (Figure 1).[24] Past the induction period, the onset of the productive reaction to form **1a·TsOH** coincided with a rapid increase of Et_3SiF.

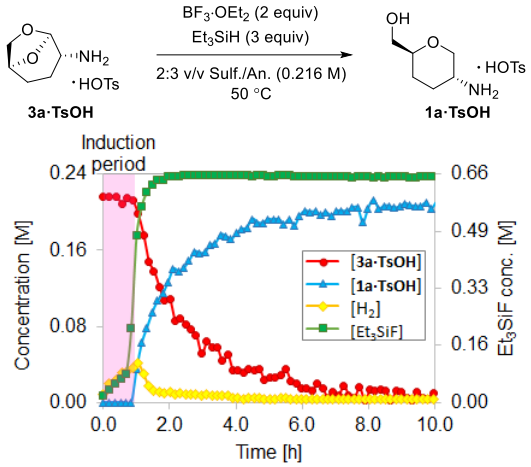


Figure 1. Concentration profiles monitored by ^{1}H and ^{19}F NMR spectroscopy for the reductive opening of **3a·TsOH**. [**3a·TsOH**]$_0$ = 0.216 M, BF_3·OEt_2 (2 equiv, 0.431 M), Et_3SiH (3 equiv, 0.656 M), sulfolane:anisole-d_8 (2:3), 50 °C. Octafluoronaphthalene (0.49 equiv) was used as an internal standard for quantitative ^{19}F NMR experiments.

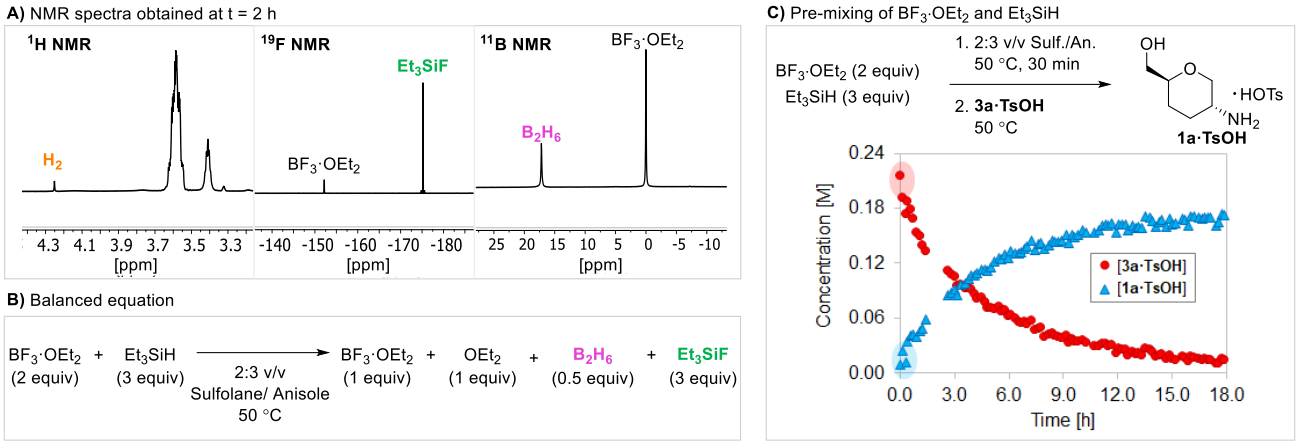


Figure 2. (A) $BF_3{\cdot}OEt_2$ (0.431 M) and Et_3SiH (0.656 M) in 2:3 v/v sulfolane:anisole-d_8 at 50 °C. (B) Balanced reaction for the formation of diborane under studied conditions. (C) Reaction profiles monitored by ^1H NMR spectroscopy for the reductive acetal opening of **3a·TsOH**, with a delayed addition of **3a·TsOH**. [**3a·TsOH**] = 0.216 M, [$BF_3{\cdot}OEt_2$] = 0.431 M, [Et_3SiH] = 0.656 M, 2:3 v/v sulfolane:anisole-d_8, 50 °C.

Interestingly, quantitative ^{19}F NMR spectroscopy revealed that formation of Et_3SiF from Et_3SiH reached full conversion more rapidly than the reaction of **3a·TsOH** to **1a·TsOH** itself, suggesting that a different reductant may be responsible for the desired reductive acetal opening. This prompted us to further investigate the interaction between $BF_3{\cdot}OEt_2$ and Et_3SiH in the absence of **3a·TsOH**. By mixing $BF_3{\cdot}OEt_2$ and Et_3SiH at the reaction temperature (50 °C), formation of both H_2 and Et_3SiF was again observed during the induction period by ^1H and ^{19}F NMR, respectively (Figure 2A). After the initial induction period, ^{11}B NMR spectroscopy of the same mixture indicated the formation of a new boron signal around 17 ppm which was subsequently assigned to diborane utilizing NMR spectroscopy techniques such as ^1H, ^{11}B and $^{11}B\{^1H\}$ with both broadband and selective ^1H decoupling.[16, 25] Once **3a·TsOH** was spiked into a solution of $BF_3{\cdot}OEt_2$ and Et_3SiH that was pre-mixed in anisole-d_8:sulfolane (3:2) at 50 °C for 30 minutes, the immediate formation of **1a·TsOH** was observed confirming that diborane, formed from a reaction between $BF_3{\cdot}OEt_2$ and Et_3SiH (Figure 2B), is an active reductant in the acetal opening reaction (Figure 2C). However, it cannot be excluded that HBF_2 and H_2BF, intermediates en route to diborane, are also promoting the formation of **1a·TsOH**.[26, 27]

To obtain more insight into the mechanism governing the induction period, we found that the duration of the induction period increased with an increased water content in the reaction mixture (Figure 3A). With the observation of H_2 generation during the induction period (Figure 1), we thus concluded that residual water is quenched during the induction period *via* release of H_2 before an increase in diborane concentration can be observed. A linear correlation between the water content and the Et_3SiF concentration at the end of the induction period (Figure 3B) further suggested that an intermediate species generated from Et_3SiH and $BF_3{\cdot}OEt_2$ is reacting with the residual water before diborane formation is observed. While *in-situ* formation of diborane from the reaction of boron trichloride with silanes has been described in the literature,[28] the ability of silanes to react with boron trifluoride is, to the best of our knowledge, unknown. Thus, we next sought to further explore solvent effects of this transformation using NMR spectroscopy and computational methods.

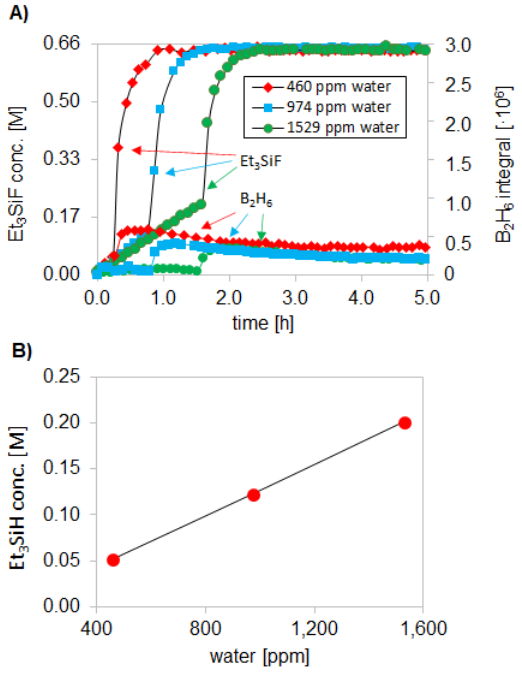


Figure 3. (A) Et_3SiF and B_2H_6 concentration profiles monitored by ^{11}B and ^{19}F NMR spectroscopy for the reaction of $BF_3{\cdot}OEt_2$ (0.431 M) with Et_3SiH (0.656 M) to probe the water effect (0, 0.1 and 0.2 equiv). (B) Linear correlation between water equivalents added and the concentration of Et_3SiF at the end of the induction period. Octafluoronaphthalene (0.49 equiv) was used as an internal standard for ^{19}F NMR.

Consistent with the optimization results in Table 2, neither the generation of Et_3SiF and diborane nor the formation of **1a** was observed when the acetal opening reaction was performed in deuterated anisole or deuterated dichloromethane alone.[16] However, the formation of Et_3SiF and diborane was immediately restored in either solvent upon the addition of sulfolane (Figure 4A) suggesting that sulfolane is required to initiate the formation of diborane. This result was further corroborated by the strong dependence of the Et_3SiF reaction rate, a surrogate measure for diborane formation,[29] on the sulfolane concentration.[16]

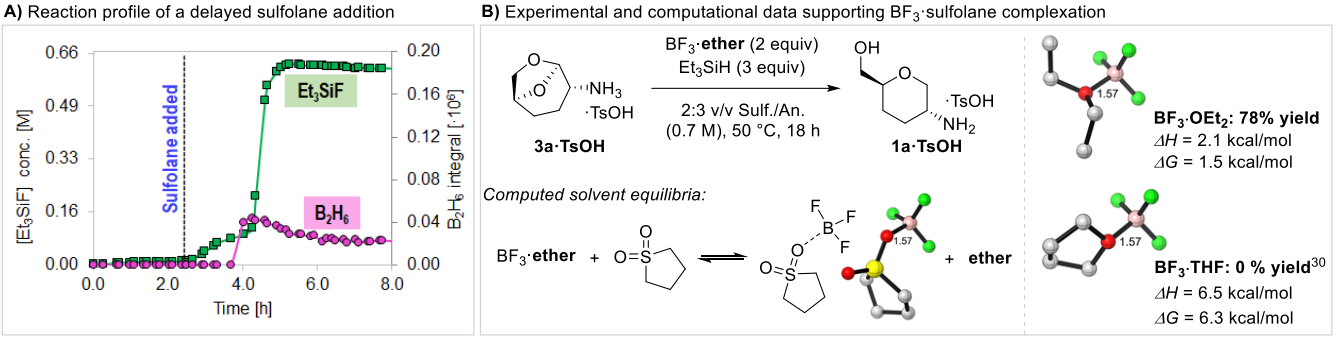


Figure 4. (A) Reaction profile monitored by ^{11}B and ^{19}F NMR spectroscopy for the reaction between $BF_3{\cdot}OEt_2$ (0.431 M) and Et_3SiH (0.656 M) with a late addition of sulfolane to trigger the reaction of BF_3 with Et_3SiH. (B) Computed reaction equilibria of different $BF_3{\cdot}$solvent complexes with sulfolane using M06-2X/6-311+G(d,p)/SMD(anisole)//M06-2X/6-31+G(d,p)/SMD(anisole). B···O distances shown in Å.

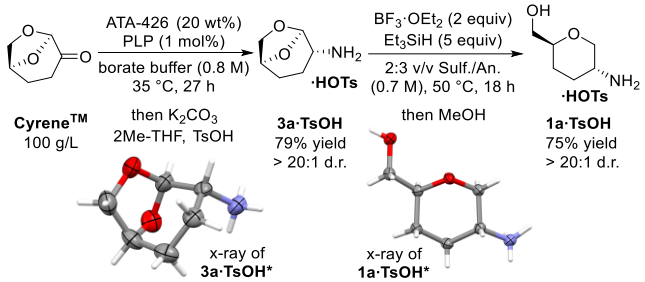
This novel reactivity was also observed with other sulfones. For example, non-cyclic dialkylsulfones and even Ph_2SO_2 promoted the reductive acetal opening to furnish **1a·TsOH** in acceptable yields.[16]

However, when $BF_3{\cdot}THF$ was used instead of $BF_3{\cdot}OEt_2$, diborane and product formation was not observed after 18 h (Figure 4B),[30] consistent with unsuccessful formation of **Bn-1a** in THF (Table 2, Entry 8). Computed reaction equilibria between $BF_3{\cdot}$solvent complexes (solvent = Et_2O, THF) and a $BF_3{\cdot}$sulfolane complex[31] showed that displacement of Et_2O by sulfolane, while endergonic, is more facile (ΔG = 1.5 kcal/mol) than displacement of THF by sulfolane (ΔG = 6.3 kcal/mol). We thus hypothesize that complexation of sulfolane to BF_3 is a key step to enable H-F exchange to form Et_3SiF and diborane. Further mechanistic analysis was convoluted by the fact that any measurable species in the acetal opening reaction (Et_3SiF, diborane) may result from multiple different transformations. For example, formation of diborane from BF_3 theoretically encompasses three H-F exchange reactions. Additionally, diborane generation *via* disproportionation of HBF_2 cannot be excluded.[32]

With suitable reaction conditions in hand, we were able to finalize the synthesis of **1a**. Upon completion of the transamination reaction, **3a** was first extracted into 2-methyl tetrahydrofuran using salting out principles,[33] and then crystallized as tosylate salt **3a·TsOH** in 79% yield and >20:1 d.r. (Scheme 2). Isolated **3a·TsOH** was subjected to the reductive acetal opening conditions using an excess of triethylsilane. After quenching any unreacted reducing reagent with methanol, **1a** was directly crystallized from the reaction mixture yielding **1a·TsOH** in 75% yield and 59% overall yield from Cyrene™. The absolute stereochemistry of both compounds was further corroborated by x-ray crystallography.[16]

The combination of a highly selective biocatalytic process with a unique reagent combination for the acetal opening step which bypasses direct handling of reactive and toxic borane-based reagents significantly reduced the number of synthetic steps and protecting group manipulations. The novel 2-step synthesis of **1a·TsOH** resulted in a > 27% yield improvement compared to the previously reported 9-step sequence,[2a] which subsequently led to a more than 94% reduction of the process mass intensity (PMI = 47), energy footprint and global warming potential (kg CO_2 equiv.) of raw materials used compared to the previous route to **1a**.[34]

Scheme 2. Two-Step Synthesis of 1a·TsOH



*TsOH excluded for clarity.

CONCLUSIONS

In summary, we have described the development of a protecting group-free, 2-step synthesis of 5-amino-2-hydroxymethyl-tetrahydropyran **1a** from biorenewable Cyrene™.

Installation of the desired amine stereocenter was achieved by employing a biocatalytic transamination in the first step. Transaminase ATA-426 was shown to be uniquely effective in overriding the substrate bias of Cyrene™ to form the desired amine **3a** which was isolated as a tosylate salt with high diastereoselectivity.

Conditions for the reductive acetal opening of intermediate **3a** were identified *via* screening of various Lewis acids and reductants, which resulted in the identification of a novel reagent combination to mediate the stereo-retentive opening of the amine-containing bicycle. Further mechanistic investigation revealed that the reagent combination of $BF_3{\cdot}OEt_2$ and Et_3SiH in sulfolane affects the *in-situ* generation of diborane which acts as the active reductant. The presence of weakly Lewis basic sulfolane was shown to be critical for diborane formation to occur.

Taken together, these features significantly reduced the overall environmental impact for the manufacture of the pharmaceutically relevant building block **1a**, rendering the synthesis of BTK-inhibitor nemtabrutinib (**2**) more efficient and sustainable.

ASSOCIATED CONTENT

Supporting Information

All experimental procedures, reaction optimizations, complete characterization (NMR, MS) for all new compounds, kinetic data and crystallographic data.

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Notes

The authors declare the following competing financial interest(s): A patent application has been filed directed to the work described herein.

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