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Brønsted Acid-Catalyzed Direct Substitution of 2-Ethoxytetrahydrofuran with Trifluoroborate Salts

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Abstract: Metal-free transformations of organotrifluoroborates are advantageous since they avoid the use of frequently expensive and sensitive transition metals. Lewis acid-catalyzed reactions involving potassium trifluoroborate salts have emerged as an alternative to metal-catalyzed protocols. However, the drawbacks to these methods are that they rely on the generation of unstable boron dihalide species, thereby resulting in low functional group tolerance. Recently, we discovered that in the presence of a Brønsted acid, trifluoroborate salts react rapidly with in situ generated oxocarbenium ions. Here, we report Brønsted acid-catalyzed direct substitution of 2-ethoxytetrahydrofuran using potassium trifluoroborate salts. The reaction occurs when tetrafluoroboric acid is used as a catalyst to afford functionalized furans in moderate to excellent yields. A variety of alkenyl- and alkynyltrifluoroborate salts readily participate in this transformation.

Keywords: Brønsted acid; alkynylation; alkenylation; organotrifluoroborates; metal-free; catalysis; tetrahydrofuran (THF); ether; oxocarbenium

1. Introduction

Ethers are an important functional group in organic chemistry as they are present in pharmaceutical agents and bioactive compounds [1]. More specifically, dialkyl ethers such as tetrahydrofurans (THF) and tetrahydropyrans (THP), present as either sugar-derived units or simpler units, account for a large percentage of ethers in bioactive agents. Several methodologies have been developed for the construction of THP rings towards the synthesis of natural products [2]. More recently, THF rings have been increasingly observed in the structures of new bioactive compounds, specifically macrolides, potentially due to their smaller molecular weight and less complex structures as compared to their THP counterparts [3].

Herein, we report a transition metal-free methodology for the synthesis of 2-akenyl and 2-alkynyl tetrahydrofurans. Direct substitution at the 2-position of 2-ethoxytetrahydrofuran occurs in the presence of a Brønsted acid catalyst. Recently, our group has discovered that Brønsted acid-catalyzed reactions of benzhydryl alcohols [4] and acetals/ketals [5] with organotrifluoroborates proceed with excellent functional group tolerance. Previously, organotrifluoroborate salts have been shown to act as shelf-stable equivalents of boronic acids [6]. Trifluoroborates are attractive reagents due to their relative nontoxic nature and straightforward preparation [7–10]. Recently, metal-free transformations involving organotrifluoroborates have emerged as an alternative to metal-catalyzed protocols [11]. More specifically, their Lewis acid-catalyzed reactions with stabilized carbocations such as iminium [12] and oxocarbenium ions [13–16] have been explored. However, the drawbacks to these methods are that they rely on the generation of unstable boron dihalide species thereby resulting in low functional group tolerance.

The number of methodologies for the preparation of C-glycosides has increased tremendously over the past several decades due their presence in natural products and enzymatically stable analogs of pharmaceutical importance [17–26]. In particular, the synthesis of 2-alkenyl and 2-alkynyl tetrahydrofuran products has been relatively well explored. Notably, the treatment of 2-benzenesulphonyl cyclic ethers with organozinc reagents produced alkynylated products [27,28]. Moreover, intermolecular substitution of halides and intramolecular rearrangements using alkynyl stannanes have been reported [29,30]. Additionally, alkynylated furan derivatives were prepared using acetylenic triflones [31,32]. Furthermore, 2-alkynyl oxacycles were synthesized using cyclic and acyclic carbonates in the presence of a palladium catalyst [33]. More recently, boronic acid-catalyzed reaction for direct carbo- and heterocyclizations of free allylic alcohols has been developed [34].

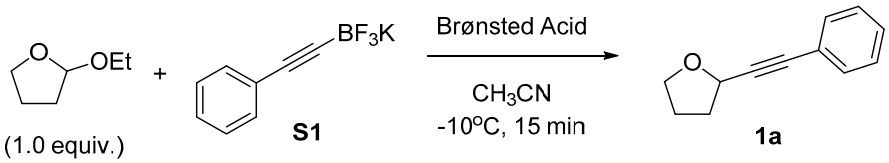
Additional methods for the synthesis of 2-alkenyl and 2-alkynyl tetrahydrofurans include the addition of tetrahydrofuranyl and tetrahydropyranyl α-oxy radicals to (*E*)-styryl sulfimide derivatives [35], terminal alkynes [36,37], alkynyl bromides [38,39], cinnamic acid derivatives [40], ethynylbenziodoxolones [41] and β-bromostyrenes [42]. Alcohols have also proven to be suitable reagents towards the synthesis of the cyclic ether products, in the presence of palladium and gold catalysts [43–46]. Diastereoselective zinc-catalyzed alkynylation of α-bromo oxocarbenium ions to synthesize *trans*-α-alkynyl-β-halo pyran and furan derivatives is known [47]. Lastly, C-H functionalization of THF derivatives has been achieved using organotrifluoroborates and trityl ions [48]. While a range of methodologies exists for the preparation of 2-alkenyl and 2-alkynyl tetrahydrofurans, the necessity to use stoichiometric amounts of a Lewis acid, expensive metal catalysts and sensitive reagents hinder the practicality of these approaches.

As a result, our efforts were focused on the development of an operationally simple protocol for the direct substitution of 2-ethoxytetrahydrofuran at the 2-position.

2. Results and Discussion

Previously, we discovered that tetrafluoroboric acid (HBF_4) is an effective catalyst for the reactions of trifluoroborate salts [4,5]. To investigate the efficiency of the HBF_4 as a Brønsted acid-catalyst towards the substitution of 2-ethoxytetrahydrofuran, we first looked at using unsubstituted potassium phenylacetylenetrifluoroborate salt (**S1**) as a model substrate (Table 1).

Table 1. Optimization of conditions for the synthesis of tetrahydrofuran **1a**.



Entry	BF_3K (Equiv.)	Brønsted Acid	Brønsted Acid (Equiv.)	Yield (%)
1	1.1	$HBF_4 \cdot OEt_2$	1.1	75
2	1.1	CF_3COOH	1.1	trace
3	1.5	$HBF_4 \cdot OEt_2$	1.5	92

We found that the substitution was achieved with 75% yield of the desired product **1a** when a slight excess of 1.1 equivalents of both the organotrifluoroborate (**S1**) and HBF_4 acid catalyst were used (Table 1, entry 1). Attempts to use an alternative acid such as trifluoroacetic acid, which has a pK_a similar to that of HBF_4, only resulted in trace amounts of product formation (Table 1, entry 2). Our previous studies indicated that increasing the amounts of trifluoroborate salt and $HBF_4 \cdot OEt_2$ to 1.5 equivalents resulted in a higher yield for the alkynylation of ketals [5]. We then looked to apply these reaction conditions to the direct functionalization of 2-ethoxytetrahydrofuran. To our delight, product **1a** was obtained in an excellent 92% yield (Table 1, entry 3). Other reaction conditions, such as

reaction temperature and solvent, were not directly explored since both conditions were already extensively studied in our previously described set of novel Brønsted acid-catalyzed reactions [4,5].

With the developed reaction conditions in hand, the scope of potassium alkynyltrifluoroborate salts was explored (Figure 1). We found that neutral naphthylacetylenetrifluoroborate salt afforded product **1b** in virtually quantitative yield. Electron-rich *p*-butyl and *p*-methoxy substituted derivatives of phenylacetylenetrifluoroborate salt produced the desired products **1c** and **1d** in 93% and 78% yields, respectively. Notably, a scaled-up reaction afforded 0.18 g of **1c** in essentially identical yield to the small-scale synthesis. The developed reaction conditions were also tolerant to electron-deficient groups of phenylacetylenetrifluoroborate salts such as fluoro, dichloro and trifluoromethyl substituents. Substituted furans **1e**–**1g** were obtained in good to excellent yields. In addition to phenylacetylenetrifluoroborates, hexynyltrifluoroborate salt reacted with 2-ethoxytetrahydrofuran to afford product **1h** in 64% yield.

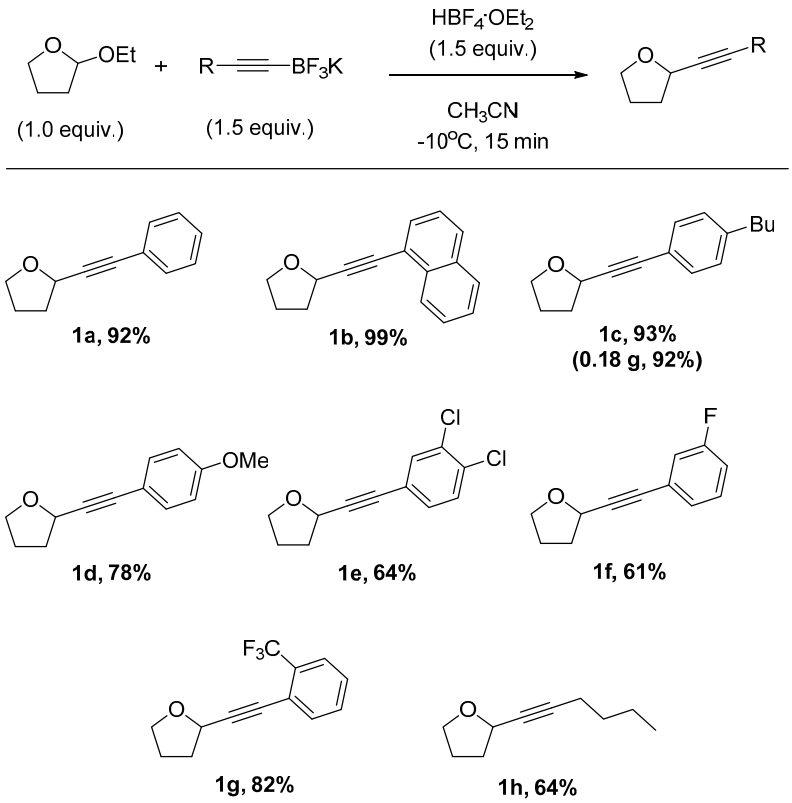


Figure 1. Reactions of potassium alkynyltrifluoroborate salts with 2-ethoxytetrahydrofuran.

We then discovered that potassium *trans*-styryltrifluoroborate salt and its derivatives reacted well under the developed reaction conditions to afford the alkenylated products in moderate to good yields (Figure 2). The reaction of unsubstituted potassium *trans*-styryltrifluoroborate salt with the starting material afforded product **2a** in 74% yield. The effect of aromatic substituents was then explored. It was found that potassium 2-(3-fluorophenyl)vinyltrifluoroborate and potassium (*E*)-trifluoro(4-(trifluoromethyl)styryl)borate reacted similarly to the unsubstituted *trans*-styryltrifluoroborate salt and the desired products **2b** and **2c** were formed in 78% yield. In contrast, electron-rich *trans*-styryltrifluoroborate salt derivative containing a methyl group in the *para*-position resulted in a modest 54% yield of **2d**. In addition, reaction of 2-ethoxytetrahydrofuran with potassium (*E*)-4-phenylstyryltrifluoroborate salt afforded product **2e** in 72% yield. Potassium trifluoro(1*H*-inden-2-yl)borate also participated in the reaction. Product **2f** was obtained in 79% yield. Detailed experimental procedures and characterization can be found in the supporting information file.

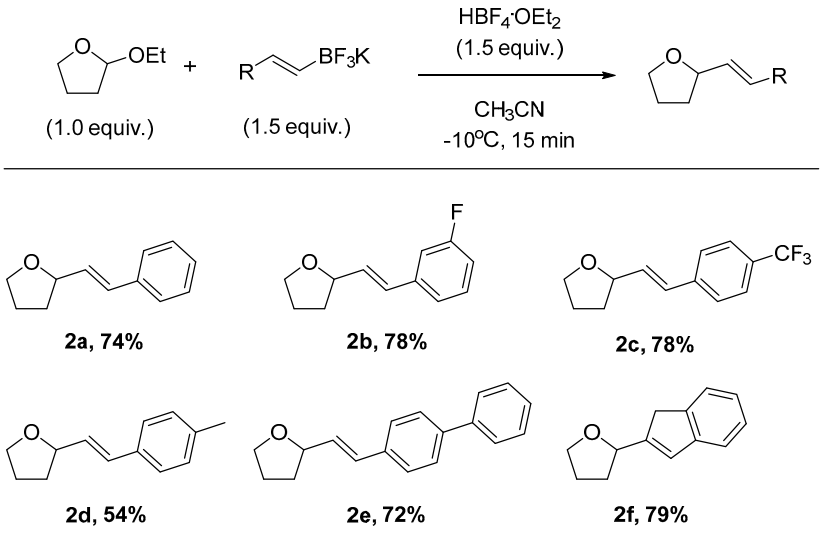
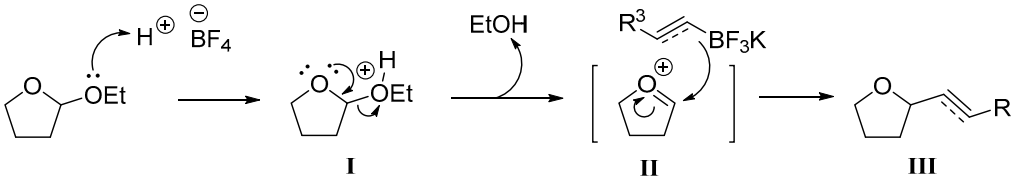


Figure 2. Reactions of potassium *trans*-styryltrifluoroborate salts with 2-ethoxytetrahydrofuran.

We propose that the protonation of 2-ethoxytetrahydrofuran leads to the elimination of ethanol (**I**) and the formation of 5-membered-ring oxocarbenium ion intermediate (**II**) (Scheme 1). The nucleophilic trifluoroborate salt then reacts at the 2-position generating the desired product (**III**). Furthermore, we propose that the ethanol produced from the generation of the oxocarbenium ion acts as a sequestering agent of the boron trifluoride byproduct. This in situ generation of ethanol is advantageous since previously, MacMillian and co-workers used hydrofluoric acid in order to sequester the boron trifluoride byproduct produced from the conjugate addition of organotrifluoroborates to activated enals [49].



Scheme 1. Proposed mechanistic pathway for the preparation of 2-alkenyl and 2-alkynyl tetrahydrofurans.

3. Experimental Section

3.1. General Synthetic Methods

All reactions were set up in two-dram glass vials at room temperature under air. Unless otherwise noted, all reagents were obtained from Sigma-Aldrich (Oakville, ON, Canada or Milwaukee, WI, USA) and used without further purification. Potassium trifluoroborate salts were synthesized according to published procedures [4,5,16,50,51]. Reaction progress was monitored via thin layer chromatography (TLC) on silica gel (60 Å) with visualization using ultraviolet light (254 nm) and by staining with phosphomolybdic acid (PMA). NMR characterization data was collected at 25 °C on an Oxford AS400 NMR as solutions in deuterated solvents ($CDCl_3$ and DMSO-d_6 were obtained from Cambridge Isotope Laboratories, Inc., Andover, MA, USA). ^{1}H and ^{19}F-NMR spectra were collected at 400 and 376 MHz, respectively, while ^{13}C $\{^{1}H\}$ and ^{11}B NMR spectra were collected at 100 and 128 MHz, respectively. Chemical shifts are expressed in ppm values. NMR spectra were processed with ACD/NMR Processor Academic Edition software (Version 12.01, Advanced Chemistry Development, Inc.). FT-IR spectra were recorded on a Bruker ALPHA-P spectrometer using a platinum ATR with a diamond ATR crystal. Spectra are reported in terms of frequency of absorption (cm^{-1}) and only partial data is provided.

IR spectra were processed with OPUS Spectroscopy software (Version 7.5, Bruker Optik, GmbH). Automated flash chromatography was conducted using a Biotage Isolera flash chromatography system using silica gel (60 Å, low acidity, obtained from SiliCycle, Quebec City, QC, Canada) and reagent grade solvents. Structures were drawn with ChemBioDraw Ultra software (Version 14.0.0.117, CambridgeSoft Corporation).

3.2. General Procedure for the Synthesis of Alkynyl Potassium Organotrifluoroborate Salts

Potassium alkynyltrifluoroborate salts were prepared according to known procedures [4,5,16,51]. To a solution of the indicated terminal alkyne (1.0 equiv.) in dry THF at −70 °C under argon atmosphere was added *n*-BuLi (1.0 equiv.) dropwise, and the solution was stirred for 1 h at this temperature. Trimethylborate (1.5 equiv.) was added dropwise at −60 °C. The solution was stirred at this temperature for 2 h. A saturated aqueous solution of KHF_2 (6.0 equiv.) was added at −20 °C. The mixture was allowed to stir for 1 h at −20 °C and for 1 h at room temperature. The solvent was removed under reduced pressure, and the resulting solid was placed under vacuum overnight to remove any remaining water. The solid was washed several times with hot acetone (4 × 10 mL), which was collected and concentrated to a volume of ~10 mL. The product was precipitated with diethyl ether (30 mL) and cooled to 4 °C to complete precipitation. The crystalline trifluoroborate salt was collected by gravity filtration.

3.3. General Procedure for the Synthesis of Alkenyl Potassium Organotrifluoroborate Salts

Potassium alkenyltrifluoroborate salts were prepared according to a procedure modified from Molander and coworkers [50]. To a solution of the indicated boronic acid (1.0 equiv.) in Et_2O (6 mL) was added KHF_2 (2.8 equiv.), followed by H_2O (2.7 mL) over a period of 30 min. After stirring at rt for 3 h, the solvent was removed under reduced pressure, and the resulting solid was placed under vacuum overnight to remove any remaining water. The solid was washed several times with hot acetone (4 × 10 mL), which was collected and concentrated to a volume of ~10 mL. The product was precipitated with diethyl ether (30 mL) and cooled to 4 °C to complete precipitation. The crystalline trifluoroborate salt was collected by gravity filtration.

3.4. General Procedure for the Synthesis of Tetrahydrofurans

In a two-dram vial containing a stir bar, the indicated potassium trifluoroborate salt (1.5 equiv.) was added at room temperature followed by the addition of anhydrous acetonitrile (C = 0.1 M). 2-ethoxytetrahydrofuran (1.0 equiv.) was then added to the solution, and the solution was stirred at −10 °C for 5 min. $HBF_4{\cdot}OEt_2$ (1.5 equiv.) was added to the stirring solution at −10°C. The solution was stirred at this temperature for 15 min. The reaction was quenched with water and extracted with 20 mL of ethyl acetate. The organic layer was washed with water (3 × 15 mL) followed by brine (1 × 10 mL). The organic layer was dried with $MgSO_4$ and concentrated. The crude product was purified by flash chromatography and concentrated. In the cases where a CH_3CN/hexanes extraction was required, the product was solubilized in 5 mL of acetonitrile and 1 mL of hexanes was added forming a bi-layer. The two layers were thoroughly mixed and cooled to 0 °C in an ice bath to promote separation. The bottom acetonitrile layer was then removed and the extraction was performed again on the same hexanes layer. The acetonitrile extractions were then concentrated to afford the product.

4. Conclusions

In summary, a novel methodology for the alkenyl- and alkynylation of tetrahydrofuran has been developed. The reaction occurs rapidly between 2-ethoxytetrahydrofuran and a variety of alkenyl- and alkynyltrifluoroborate salts to yield the desired products in moderate to excellent yields. The reaction proceeds under mild Brønsted acid-catalyzed conditions within fifteen minutes. Further investigation into the scope of this reaction and its application towards bioactive compounds is currently ongoing.

Supplementary Materials: The following are available online at www.mdpi.com/2073-4344/6/7/94/s1.

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Author Contributions: K.F. and Y.B. conceived and designed the experiments; K.F. performed the experiments; K.F. and Y.B. analyzed the data; K.F. and Y.B wrote the paper.

Conflicts of Interest: The authors declare no conflict of interest.

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