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BBDFA: A Practical Reagent for Trifluoromethylation of Allylic and Benzylic Alcohols on Preparative Scale

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ABSTRACT: We report a safe and readily prepared reagent [1,1′-biphenyl]-4-yl 2-bromo-2,2-difluoroacetate (BBDFA) for Cu-catalyzed trifluoromethylation of allylic or benzylic alcohols. An operationally simple and column-chromatography-free process to prepare BBDFA was developed and demonstrated on >100 g scale. Detailed reaction calorimetry and thermal analysis of the deoxytrifluoromethylation were performed using cinnamyl alcohol as a model substrate, demonstrating that the reactions could be safely implemented on preparative scale.

KEYWORDS: *trifluoromethylation, RC1 calorimetry, thermal stability, process safety, copper catalysis*

INTRODUCTION

Fluorination of organic molecules is an important strategy in the pharmaceutical and agrochemical industries, as incorporation of fluorinated groups typically modulates pharmacodynamic, pharmacokinetic, distribution, metabolism, and toxicity profiles.[1] As such, >30% of marketed drugs contain at least one fluorine atom. One of the most common fluorinated functional groups exploited in drug discovery is the trifluoromethyl group, which can (1) block metabolic oxidation, (2) alter lipophilicity and permeability profiles, (3) adjust the pK_a of vicinal functional groups, (4) perturb conformational dynamics, and (5) reduce the electron density of nearby π-systems.[2] As such, strategies for introducing trifluoromethyl groups from simple and ubiquitous functional groups are highly desirable. However, many current trifluoromethylation reactions require specialized/functionalized substrates and/or expensive or unsafe reagents[3] to access this important functional group,[4] which limit their utility for large-scale preparation.

Current methods to convert alcohols into trifluoromethanes unfortunately require four-step synthetic sequences that lead to low overall yields and generate large quantities of waste. Further, the sequences require the use of strong nucleophilic reagents (TMS−CF_3), oxidants, and reductants that limit the scope of accessible molecules (Figure 1a).[5,6] Thus, despite the potential significance of this reaction, the efficient conversion of alcohols to trifluoromethanes on large scale remains challenging.

An alternate strategy via nucleophilic substitution exploits halodifluoroacetate-derived reagents, which are prepared in two steps from 1,1-difluoro-2,2-dihaloethylene, or other readily available and inexpensive industrial byproducts,[7] to selectively convert activated electrophiles to trifluoromethanes. This strategy, pioneered by Chen and co-workers,[8] relies on in situ conversion of a difluorocarbene intermediate[9] and fluoride to an active Cu-CF_3 species, only generating CO_2 and halogen salts as byproducts (Figure 1b). However, application of this strategy for the conversion of activated alcohols to trifluoromethanes historically required isolation and purification of the intermediate bromodifluoroacetate esters and the use of stoichiometric Cu salts, which are undesirable for large-scale applications from the standpoints of operational simplicity and waste disposal.[10] In recent years, catalytic variants of this strategy have been developed, although these reactions still required isolation and purification of the intermediate ester to remove byproducts (Figure 1b).[11] To overcome this necessary isolation step and provide a one-pot deoxytrifluoromethylation reaction, phenyl bromodifluoroacetate (PhBDFA) was introduced as a deoxytrifluoromethylation reagent, enabling the direct conversion of alcohols to trifluoromethanes under Cu-catalyzed conditions (Figure 1c).[12] Beneficial aspects of this catalytic variant include fewer synthetic steps (1 vs 4), mild reaction temperatures, and a short reaction time. Though this process converted a variety of benzyl, allyl, and propargyl alcohols into the corresponding trifluoromethanes, the liquid physical state of PhBDFA limits its isolation and purification in a practical manner on large scale. Furthermore, process safety characterization for the Cu-catalyzed step remains unaddressed (Figure 2a). To further explore the large-scale feasibility of this catalytic deoxytrifluoromethylation process, we present a new, stable, and crystalline biphenyl bromodifluoroacetate (BBDFA) reagent and related process safety data to ensure its applicability on preparative scale (Figure 2b) using the conversion of cinnamyl alcohol to cinnamyl−CF_3 as a model reaction.

RESULTS AND DISCUSSION

Preparation of BBDFA. In the search for a bromodifluoroacetate reagent amenable to large scale synthesis via the disclosed deoxytrifluoromethylation protocol, we surveyed a variety of bromodifluoroacetate reagents reported previously[12] and selected the 4-phenylphenol analog BBDFA for

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Org. Process Res. Dev. XXXX, XXX, XXX−XXX

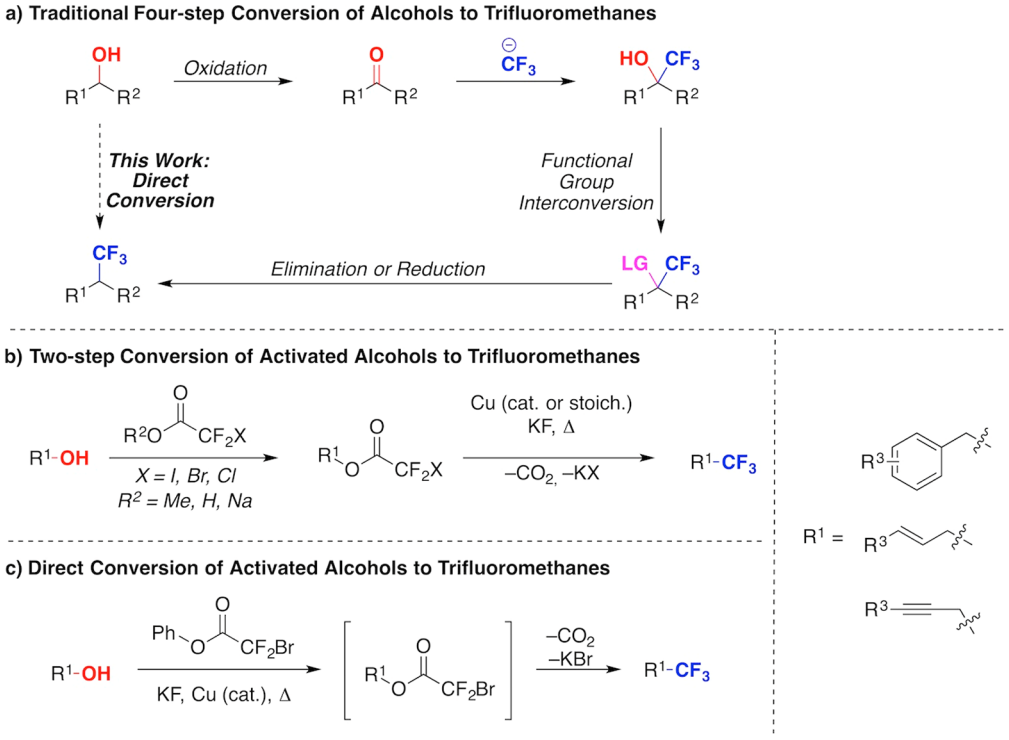


Figure 1. Functional group interconversion of alcohols to trifluoromethanes.

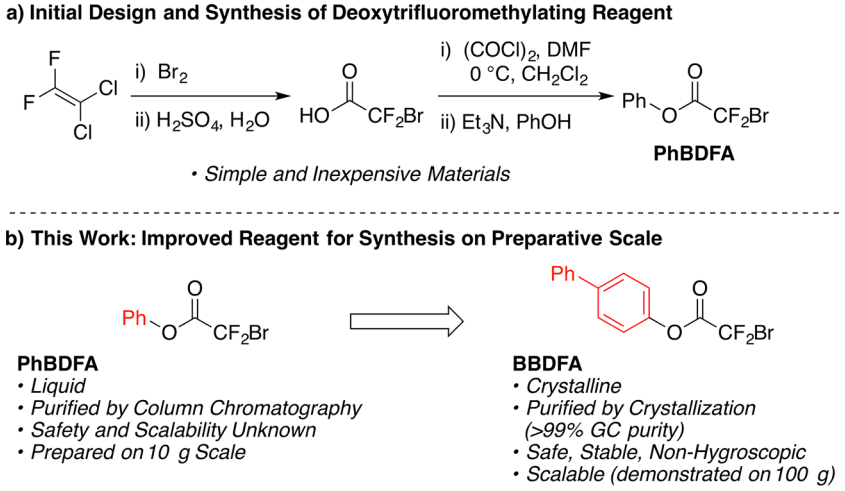
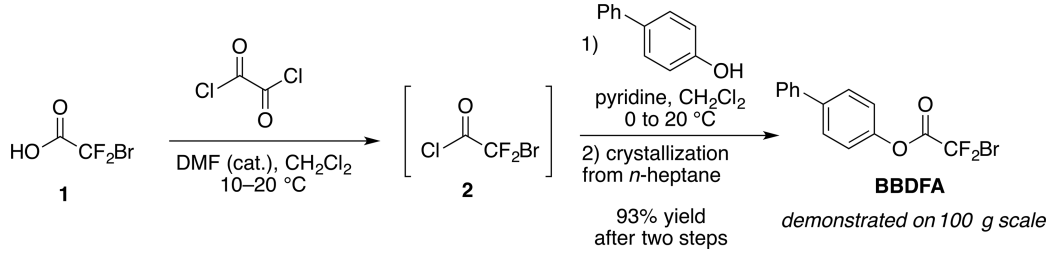


Figure 2. Design of new deoxytrifluoromethylating reagents

Scheme 1. Synthesis of BBDFA on 100 g Scale



further evaluation because of its comparable reactivity to PhBDFA and desirable solid form that enables isolation via crystallization. In the simple and practical sequence illustrated in Scheme 1, bromodifluoroacetic acid (**1**) was subjected to oxalyl chloride in the presence of a catalytic amount of DMF, and the resulting acid chloride **2** was reacted with 4-phenylphenol to afford the corresponding ester BBDFA. After aqueous workup, the product solution in toluene was solvent-switched to *n*-heptane, and the product was isolated as a white crystalline solid in 93% yield and 99.3% purity by GC

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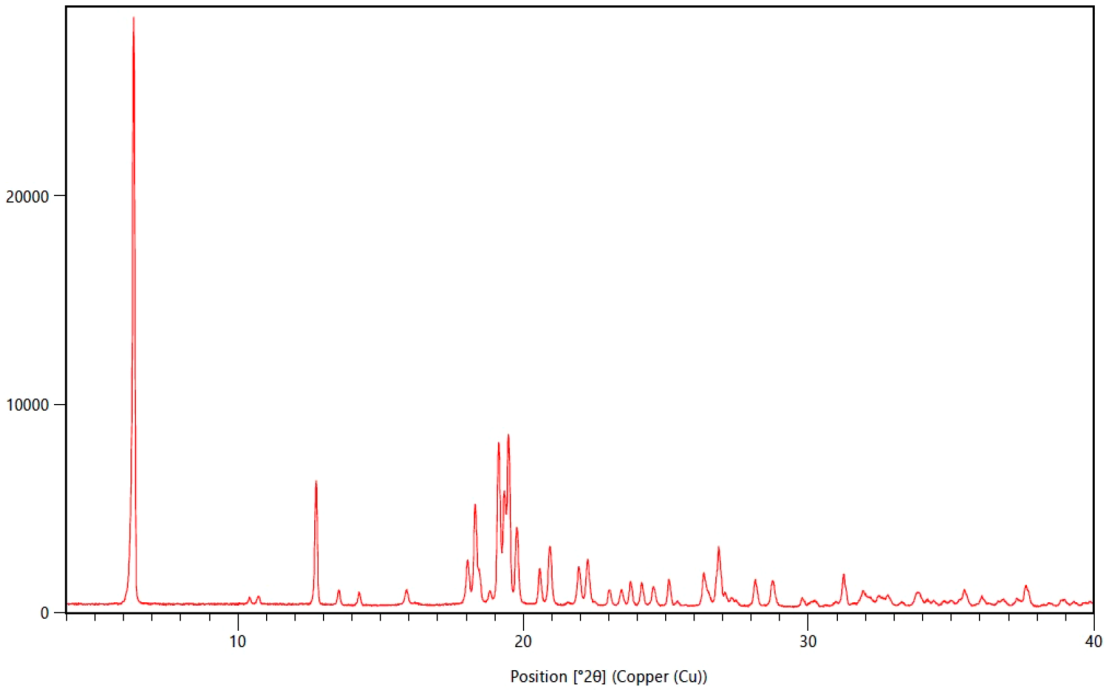

Figure 3. PXRD of crystalline BBDFA.

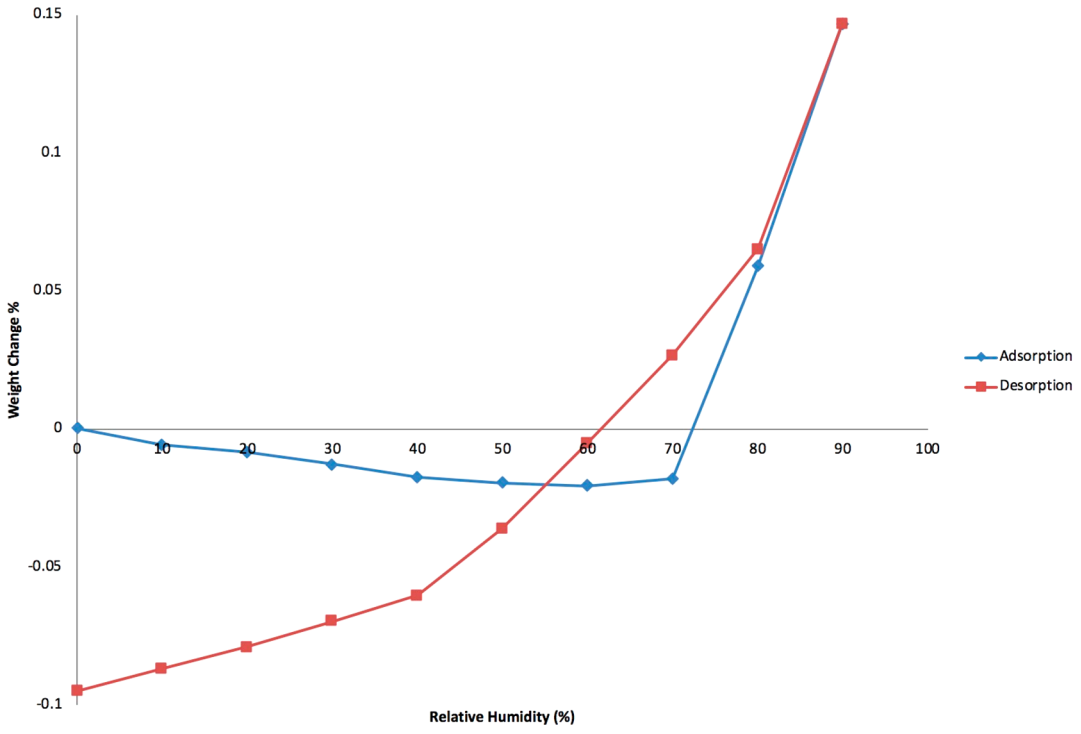

Figure 4. DVS analysis of crystalline BBDFA.

analysis. The powder X-ray diffraction (PXRD) pattern of the isolated crystalline BBDFA is illustrated in Figure 3. Dynamic vapor sorption (DVS) data showed the BBDFA absorbed up to only 0.15% (w/w) water at approximately 90% relative humidity. Therefore, this material is deemed nonhygroscopic and can be weighed and stored on the bench without special handling requirements (Figure 4).

Safety Assessment of BBDFA. The thermal stability of BBDFA was investigated using differential scanning calorimetry (DSC, Figure 5). The reagent showed good thermal stability with endothermic melting starting at 75 °C and the major exothermic decomposition event with an onset temperature of 325 °C and energy release of 285 J/g. The introduction of a thermal runaway event is unlikely if a 100 °C safety margin from the handling temperature to the onset temperature of the exothermic event can be established. Given the high onset temperature of the thermal decomposition and

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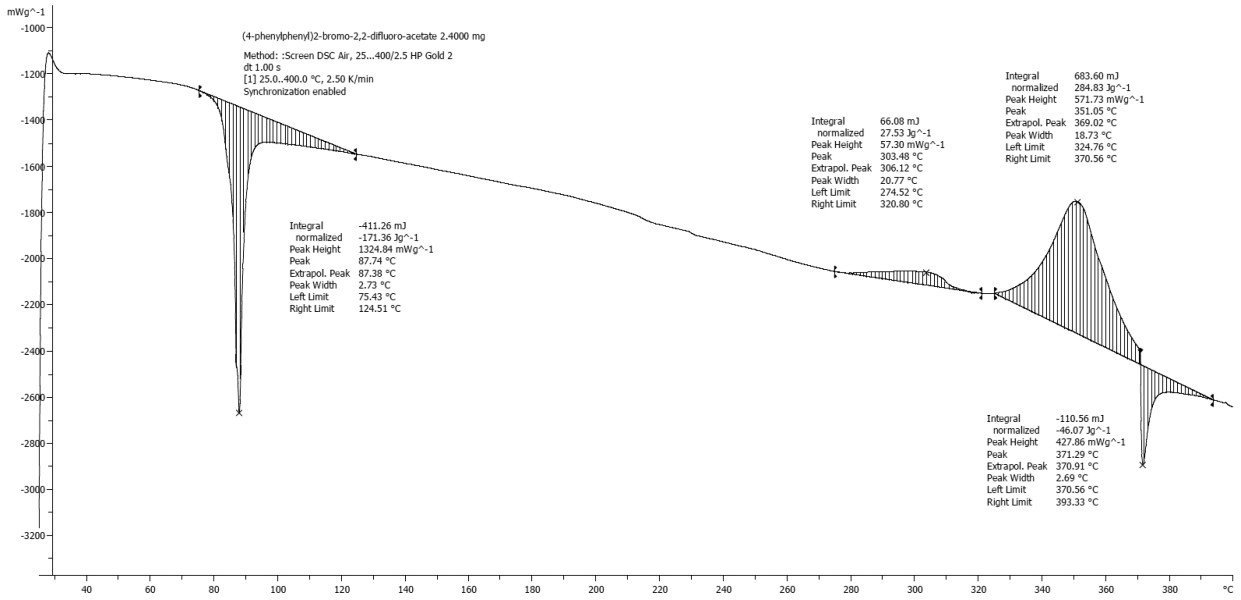
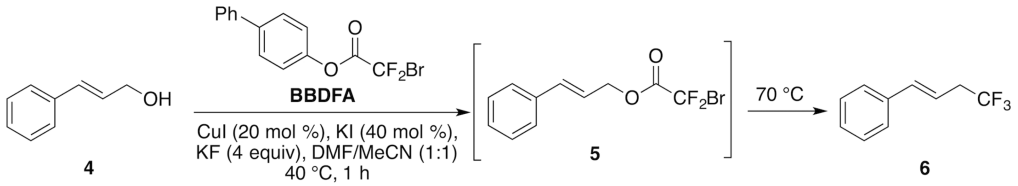


Figure 5. DSC curve (range: 25−400 °C) of BBDFA.

Table 1. Key Parameters for RC1 Experiment[a]



stage	operation	total enthalpy of reaction (kJ/mol)	total adiabatic temp rise (K)[a]	reaction temp (°C)	MTSR (°C)[b]
1	first dose of BBDFA (0.67 equiv)	10.4	3.6	25	28.6
2	second dose of BBDFA (0.67 equiv)	−3.5	−1.1	25	23.9
3	third dose of BBDFA (0.67 equiv)	−16.8	−5.0	25	20
4	formation of active ester at 40 °C	2.1	0.6	40	40.6
5	reaction at 70 °C	132	38.9	70	108.9
6	addition of water	56	4.7	20	24.7

[a]Total adiabatic temperature rise (ΔT_{ad}): Adiabatic temperature rise of the synthesis reaction (temperature increase under adiabatic conditions in case of cooling failure). [b]MTSR: Maximum temperature of the synthesis reaction (max temperature attainable under adiabatic conditions after cooling failure; Reaction Temperature + Total Adiabatic Temperature Rise).

very low hygroscopicity, BBDFA is considered as a safe reagent for storage, shipping, and routine handling.

Reaction Calorimetry of the Deoxytrifluoromethylation Reaction. We commenced our studies on understanding the process safety profile of the desired deoxytrifluoromethylation reaction through reaction calorimetry (RC1) and other potential undesired thermal events through differential reaction calorimetry (DSC) studies.

The key reaction and safety parameters for the reaction calorimetry experiment conducted in RC1 on 10 g scale were summarized in Table 1. The reaction was set up by premixing all components at 25 °C except for BBDFA, which was added in three portions over the course of approximately 30 min. The heat flow was measured during the addition (Figure 6). Only the addition of the first portion (0.67 equiv, relative to **4**) was exothermic with a total enthalpy of 10.4 kJ/mol that translated to a very minor adiabatic temperature rise (ΔT_{ad}) of 3.6 °C (Table 1, entry 1). The addition of the subsequent two portions were slightly endothermic (Table 1, entries 2−3). After the addition of BBDFA, the reaction mixture was heated to 40 °C over 30 min. The formation of the ester intermediate **5** was slightly exothermic with an inconsequential ΔT_{ad} (Table 1, entry 4). After the complete conversion of the starting alcohol was confirmed by HPLC analysis, the reaction mixture was heated to 70 °C over 45 min. The formation of the trifluoromethylated product **6** from the ester intermediate **5** at 70 °C was exothermic with a total enthalpy of reaction of 132 kJ/mol that translated to a total adiabatic temp rise of 38.9 °C (Table 1, entry 5; Figure 7). The reaction was complete after approximately 1 h at 70 °C based on the heat flow data. In the event of cooling failure, the maximum temperature of the synthesis reaction (MTSR),[13] which is the maximum temperature attainable under adiabatic conditions after cooling failure, would be 108.9 °C, which would exceed the bp of MeCN (82 °C) but be below the bp of DMF (156 °C). In addition, the release of CO_2 as a byproduct was measured by a gas flow meter. The maximum gas flow rate observed throughout the course of the reaction was 22 mL/min, of which approximately 10 mL/min was contributed by the baseline N_2 flow, which indicated a mild reaction slowly releasing CO_2 from BBDFA.

After the complete disappearance of ester **5** by HPLC analysis, the reaction was diluted with *n*-heptane and then

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Org. Process Res. Dev. XXXX, XXX, XXX−XXX

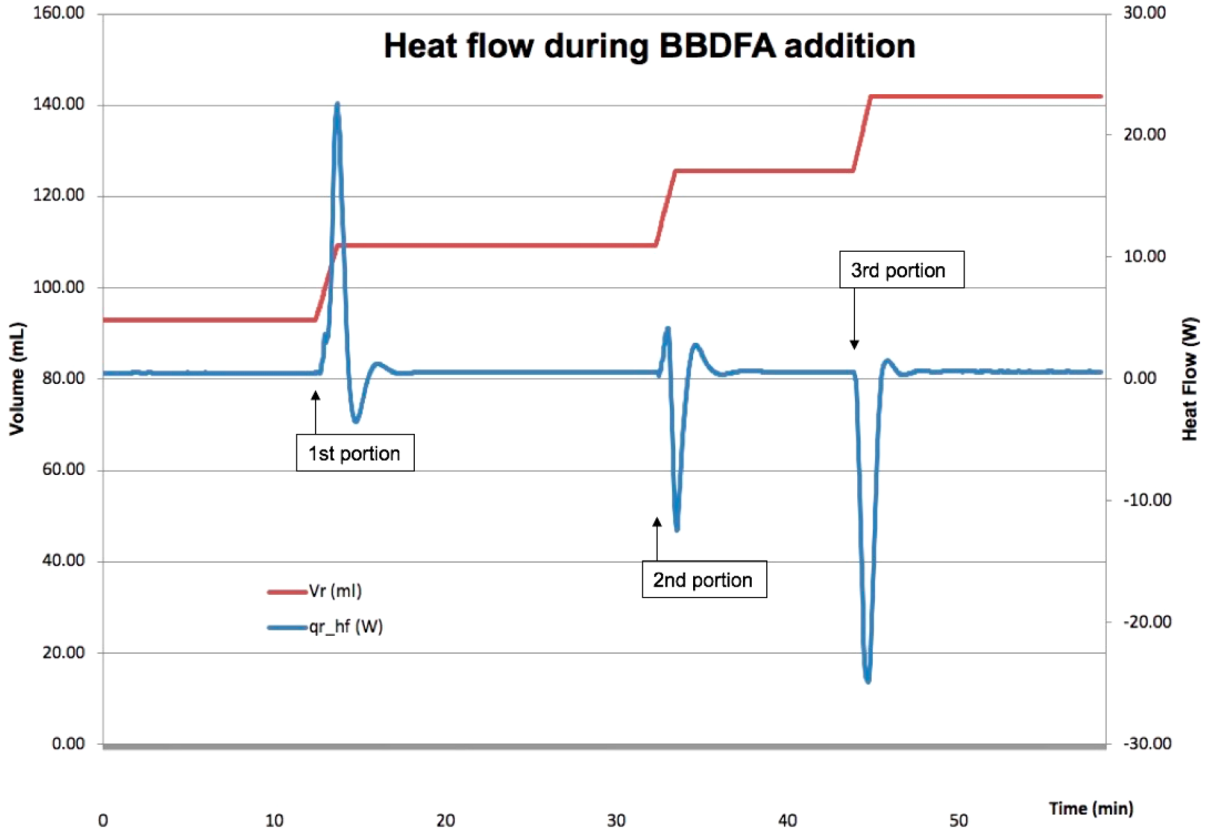

Figure 6. Heat flow during BBDFA addition.

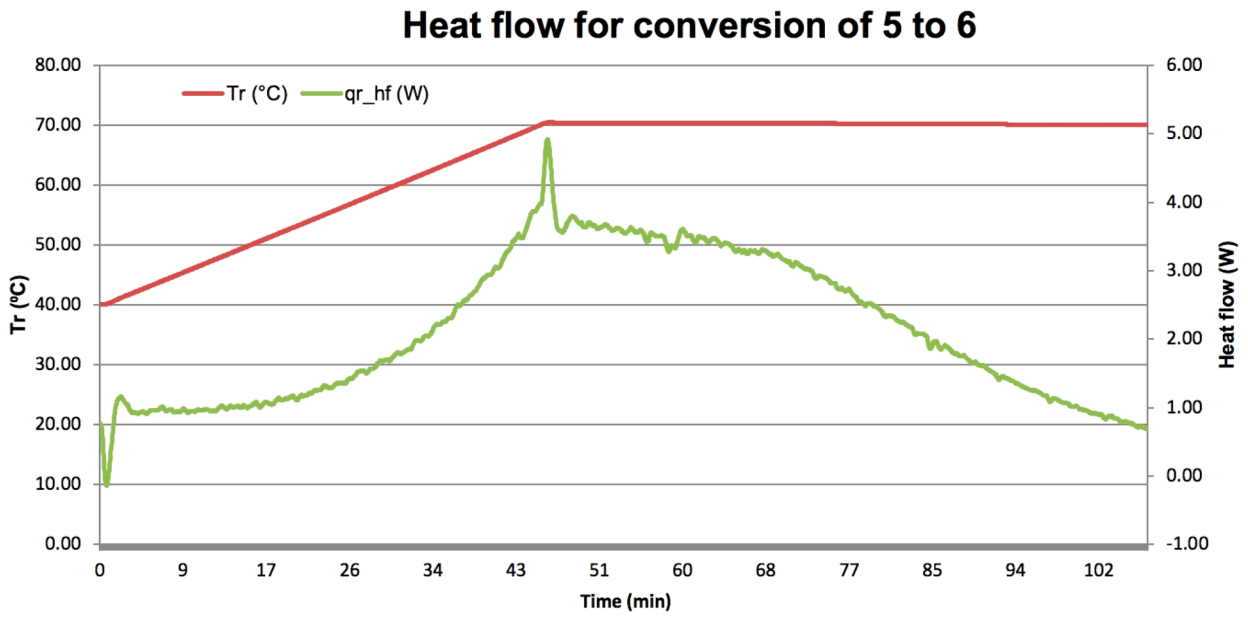

Figure 7. Heat flow for the conversion of intermediate **5** to product **6**.

water was added over 30 min. The addition of water was exothermic, with a total enthalpy of 56 kJ/mol and a total adiabatic temp rise of 4.7 °C (Table 1, entry 6). No noticeable accumulation was observed, with the heat flow returning back to baseline after 22% of the total water was added.

Thermal Stability of the Reaction Mixture. The thermal stability of the reaction mixture was next studied by DSC to understand if any undesired thermal decomposition might occur (Figure 8). The DSC analysis was conducted in gold-plated high-pressure crucibles that are rated up to 220 bar. The crucible was heated from 25 to 400 °C at a scan rate of 2.5 °C/min. The first exothermic event was observed at an onset temperature of 59.6 °C with a total heat release of 251.43 J/g, consistent with the heat release of the desired transformation from intermediate **5** to product **6** observed in the RC1 experiment mentioned above. The second exothermic event was observed at an onset temperature of 186.4 °C with a minor heat release of 35.23 J/g, which could be characterized as an

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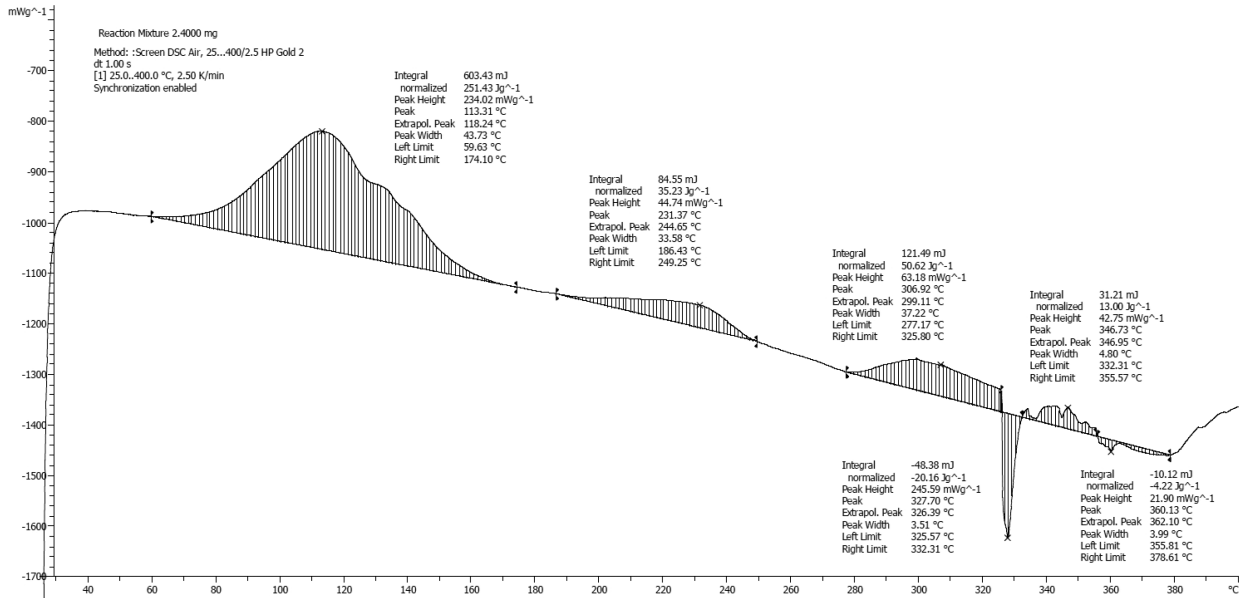

Figure 8. DSC curve of the reaction mixture

undesired thermal event. When applying the safety margin of 100 °C from the onset temperature, running the reaction at 70 °C is considered safe.

A suggestion for assessment criteria by Stoessel[13] for the severity of a runaway reaction is presented in Table 2. This assessment was based on the study that, for any adiabatic temperature rise of over 200 °C, the temperature increase as a function of time under adiabatic conditions or cooling failure becomes very sharp. This results in a violent reaction that could potentially lead to a thermal explosion. Based on a maximum adiabatic temperature rise of 38.9 °C for the trifluoromethylation reaction, the severity of a runaway scenario is deemed to be low.

Table 2. Assessment Criteria for the Severity of a Runaway Reaction

severity (simplified)	severity (extended)	ΔT_{ad}
high	catastrophic	>400 °C
	critical	200–400 °C
medium	medium	50–100 °C
low	negligible	<50 °C and no pressure

Criticality Class: 1 or 2. Based on all the collected safety assessment data, the one-pot deoxytrifluoromethylation using BBDFA can be assigned to a criticality class 1 or 2 following the systematic approach developed by Gygax[14] and Stoessel[13] (Table 3). For applications beyond preparative scale, it is recommended to further evaluate the reaction mixture by accelerating reaction calorimetry (ARC) to determine $T_{D,24}$[15] and perform in-depth material compatibility evaluation.

CONCLUSION

In summary, we developed a large-scale preparation, isolation, and purification of a new crystalline deoxytrifluoromethylating reagent, BBDFA. The reagent itself is safe, thermally stable, and stable to storage under ambient conditions. BBDFA efficiently and directly converts activated alcohols to trifluoromethanes on >10 g scale. Detailed reaction calorimetry and thermal analysis of the deoxytrifluoromethylation reaction of cinnamyl alcohol allowed the process to be safely implemented on preparative scale. The delivery of the trifluoroethane product from readily accessible alcohols complements preparations from alkenes,[16] allyl halides,[17] or allyl silanes,[18] which have not yet been demonstrated on such scale. We envision that, with appropriate adjustments/optimization, the scope of this process should match that of previously reported small-scale reactions.[12]

Table 3. Process Parameters for Criticality Class Definition: Trifluoromethylation Reaction Using BBDFA

parameter	value	comments
Tp	70 °C	process defined
ΔT_{ad}	38.9 °C	from reaction calorimetry, worst case for the batch process
MTSR	108.9 °C	from reaction calorimetry, worst case for the batch process
MTT	156 °C	bp of DMF
Thermal decomposition onset temperature	186.4 °C	DSC on reaction mixture

EXPERIMENTAL SECTION

General Information. All reactions were performed under a nitrogen atmosphere unless otherwise stated. All reagents and solvents were used as received from commercial suppliers without further purification unless otherwise specified. KF was stored and weighted in a nitrogen-filled glovebox because of its hygroscopic nature. Reaction calorimetry was conducted on a Mettler Toledo RC1e RTCal reaction calorimeter equipped with an HFCal reaction calorimeter module. Differential scanning calorimetry (DSC) analysis was conducted on the Mettler Toledo DSC 1 STAR^e System using high-pressure gold-plated crucibles. Dynamic vapor sorption (DVS) data were collected at 25 °C over a range of 0% to 90% relative humidity using a TA Q5000SA vapor sorption analyzer. NMR spectra were recorded on a Bruker 300 MHz instrument at ambient temperature. Melting points were measured by DSC and reported as the onset temperature.

*[1,1′-Biphenyl]-4-yl 2-bromo-2,2-difluoroacetate (**BBDFA**).* Into a mixture of 2-bromo-2,2-difluoroacetic acid

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Org. Process Res. Dev. XXXX, XXX, XXX−XXX

(**2**) (308 g, 1.76 mol, 300 mol %) in CH_2Cl_2 (300 mL), DMF (13.0 g, 0.178 mol, 30 mol %) and oxalyl chloride (216 g, 1.71 mol, 290 mol %) were added sequentially below 20 °C. The reaction mixture was stirred for 2 h at 10−20 °C until complete conversion was confirmed by GC analysis. A mixture of [1,1′-biphenyl]-4-ol (100 g, 0.588 mol, 100 mol %), pyridine (139 g, 1.76 mol, 300 mol %), and CH_2Cl_2 (200 mL) was stirred at 0 °C for 10 min. The solution of **2** in CH_2Cl_2 was transferred into the solution of [1,1′-biphenyl]-4-ol in CH_2Cl_2 at 0 ± 5 °C, and the resulting reaction mixture was stirred at 20 ± 5 °C for 2 h until complete conversion was confirmed by GC analysis. The reaction mixture was then added to a mixture of water (1.00 L) and toluene (1.00 L) below 20 °C. The resulting upper organic layer was washed with water (1.00 L × 2) and brine (1.00 L × 3) sequentially until the pH reached 7. The organic phase was concentrated to approximately 3 mL/g under vacuum. Azeotropic distillation by feeding in anhydrous toluene (1.50 L × 3) was conducted until the residual water was below 500 ppm by Karl Fischer (KF) analysis. A solvent switch to *n*-heptane (0.500 L × 4) resulted in crystallization of the desired product, which was filtered and dried under vacuum at 50 °C to give BBDFA as a white solid (179 g, 93% yield, 99.3% purity by GC analysis); mp = 75 °C; ^{1}H, ^{13}C, and ^{19}F NMR spectra were in accord with characterization data published previously.[12]

Reaction Calorimetry Experiment Using RC1. A clean, dry nitrogen purged 500 mL RC1 reactor equipped with an HFCal calibration probe, RT Cal, and EL-Flow gas meter was charged with cinnamyl alcohol (10.0 g, 74.5 mmol, 1.00 equiv), CuI (2.84 g, 14.9 mmol, 20.0 mol %), KF (17.3 g, 298 mmol, 4.00 equiv), KI (3.09 g, 18.6 mmol, 40.0 mol %), DMF (37.3 mL), and MeCN (37.3 mL). BBDFA (48.8 g, 149 mmol, 2.00 equiv) was charged in three portions at 25 °C, and the reaction mixture was then heated to 40 °C over 30 min. The clean formation of the ester intermediate **5** was confirmed by HPLC analysis. The reaction mixture was then heated to 70 °C over 45 min and held for an additional 1 h until reaction completion was confirmed by HPLC analysis. After cooling to 20 °C, the reaction mixture was diluted with heptane (100 mL) and water (200 mL) sequentially to evaluate the exotherm upon quenching.

Trifluoromethylation on a Preparative Scale. *2-(2,2,2-Trifluoroethyl)naphthalene.* A mixture of 2-naphthalenemethanol (31.6 g, 200 mmol, 100 mol %), CuI (7.62 g, 40.0 mmol, 20.0 mol %), KF (46.5 g, 800 mmol, 4.00 equiv), KI (8.30 g, 50.0 mmol, 25.0 mol %), and BBDFA (131 g, 400 mmol, 2.00 equiv) in DMF (100 mL) and MeCN (100 mL) was sparged with nitrogen for 30 min at 25 °C. The reaction mixture was stirred at 70 °C for 15 h and cooled to 25 °C. 2-MeTHF (300 mL) was added, and the resulting mixture was sequentially washed with a 0.5 N NaOH solution (200 mL × 2), and then an aqueous solution (200 mL) of a 1:1 (v/v) mixture of 15 wt % brine and sat'd $NaHCO_3$. The organic layer was filtered, and the cake was rinsed with 2-MeTHF (100 mL). The combined filtrate was washed with 15 wt % brine (100 mL). An analytical sample of the desired product 2-(2,2,2-trifluoroethylnaphthalene) was purified by silica column chromatography using heptane (R_f = 0.45). The spectroscopic data (^{1}H, ^{13}C, and ^{19}F NMR) are consistent with a previous report in the literature.[11d] The product solution was then assayed by quantitative HPLC analysis using the purified analytical sample as the reference standard (22.7 g, 54% yield).

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Notes

The authors declare no competing financial interest.

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Org. Process Res. Dev. XXXX, XXX, XXX−XXX