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Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.8b00001 • Publication Date (Web): 01 Feb 2018

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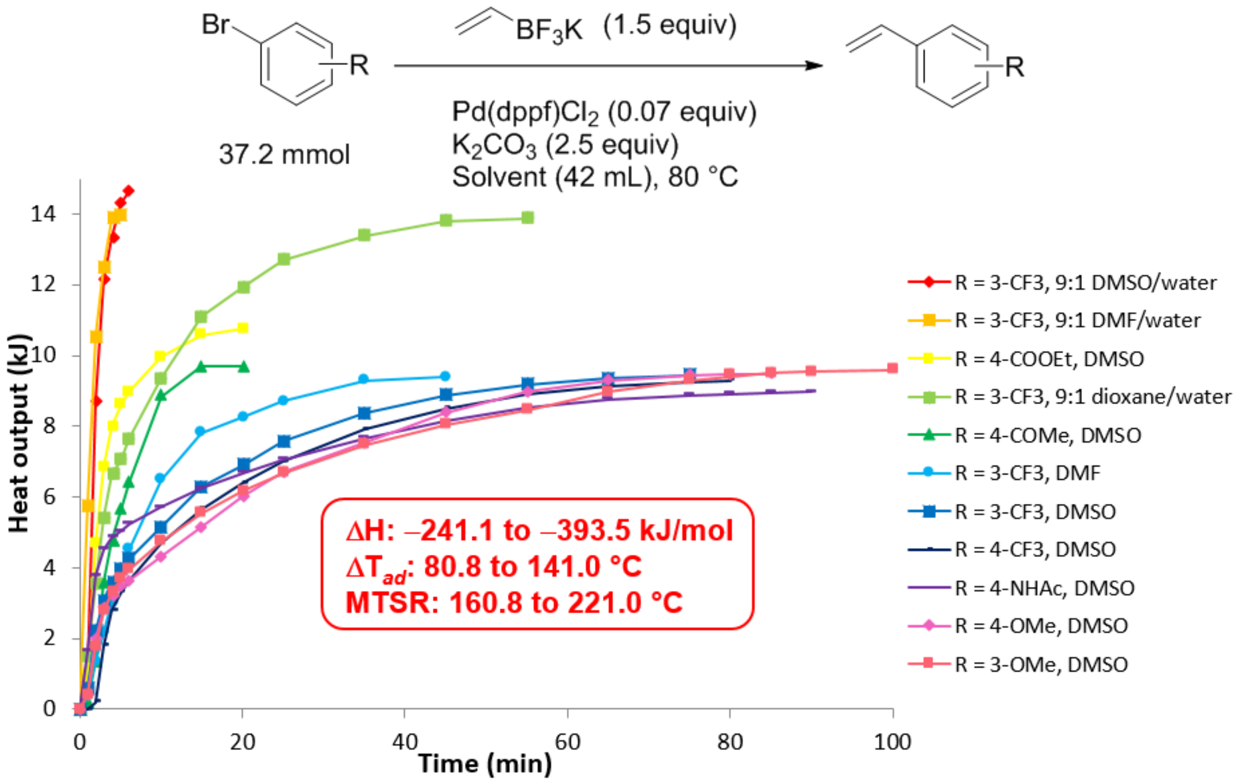
Evaluation of Potential Safety Hazards Associated with the Suzuki-Miyaura Cross-Coupling of Aryl Bromides with Vinylboron Species

Qiang Yang,[*,†] Belgin Canturk,[†] Kaitlyn Gray,[†] Elizabeth McCusker,[†] Min Sheng,[Ω] and Fangzheng Li[†]*

[†]Process Chemistry, Dow AgroSciences, 9330 Zionsville Rd., Indianapolis, IN 46268, USA

[Ω]Reactive Chemicals, Dow AgroSciences, Midland, MI 48667, USA

TOC:



ΔH: –241.1 to –393.5 kJ/mol
ΔT_{ad}: 80.8 to 141.0 °C
MTSR: 160.8 to 221.0 °C

ABSTRACT

The potential safety hazards associated with the Suzuki-Miyaura cross-coupling of aryl bromides with vinylboron species were evaluated. In the Suzuki-Miyaura cross-coupling of 1-bromo-3-(trifluoromethyl)benzene with potassium vinyltrifluoroborate in the presence of potassium carbonate (K_2CO_3) in 9:1 dimethyl sulfoxide (DMSO)/water at 80 °C, the thermal profile revealed a significant exotherm upon the addition of catalytic 1,1′-bis(diphenylphosphino)ferrocene palladium(II) dichloride [Pd(dppf)Cl_2]. Further investigations indicated that the exotherm was consistently higher and the reactions were faster in the studied aqueous systems compared to anhydrous conditions. Although under anhydrous conditions the exotherms were comparable among the studied cases, the rate of exotherm was highly dependent on the choice of aryl electrophile, solvent, base, catalyst, as well as vinylboron species. In many of the studied cases the maximum temperature of a synthesis reaction (MTSR) was considerably higher than the boiling point of the solvent and/or the onset temperature of the DMSO decomposition, indicating that in the absence of active cooling the system could quickly exceed the boiling point of the solvent or trigger the decomposition of the reaction mixture to result in a runaway reaction.

Keywords: safety hazards, Suzuki-Miyaura cross-coupling, reaction calorimetry, thermal decomposition, aryl bromide, vinylboron species.

INTRODUCTION

The Suzuki-Miyaura cross-coupling reaction is undeniably one of the most powerful reactions in modern organic synthesis for the construction of carbon-carbon bonds.[1] The development of new metal/ligand systems significantly broadened the scope of this reaction[2] and consequently it has found wide use both in academia and industry. The Suzuki-Miyaura cross-coupling has been frequently used in large scale production of active pharmaceutical ingredients[3] and agrochemicals.[4] The key advantages of this reaction include mild reaction conditions, relatively low toxicity of the boron byproducts, tolerance to a wide array of functional groups, and wide availability of organoboron species.[1]

The Suzuki-Miyaura cross-coupling reaction has been extensively used to access functionalized styrene derivatives via the reaction of nucleophilic vinylboron species with various aryl electrophiles, including aryl halides, pseudo halides, and diazonium salts.[5] Of the various vinylboron species, potassium vinyltrifluoroborate is the preferred reagent because it is easily prepared, atom economical, and stable for handling and storage.[5] Vinylation reactions involving potassium vinyltrifluoroborate are typically performed in protic solvents (e.g., water, ethanol, propanol) or a mixture of water and aprotic solvents (e.g., dioxane, tetrahydrofuran).[5,6] However, some recent reports disclosed that this reaction could also be performed in anhydrous aprotic solvents.[7] Frequently the reaction is conducted in an all-in fashion at elevated temperature, which provides poor control over potential reaction exotherms.

In a recent study, an unexpected exotherm was observed during the coupling of an aryl bromide with potassium vinyltrifluoroborate in the presence of Pd(dppf)Cl_2 and K_2CO_3 in a mixture of 9:1 DMSO/water at 80 °C. Potential safety hazards associated with the Pd-catalyzed α-arylation has been reported in the literature,[8] but to our knowledge, no evaluations of the potential safety hazards associated with the Suzuki-Miyaura cross-coupling of aryl bromides with vinylboron species has been disclosed in the public domain. This observation warranted further investigation into the potential safety hazards associated with the Suzuki-Miyaura cross-coupling of aryl bromides with vinylboron species in the presence of various bases, solvents, and catalysts to better understand the scope of this exothermic behavior.

RESULTS AND DISCUSSION

The reaction calorimetry was evaluated using a Mettler Toledo EasyMax 102 HF Cal.[9] The initial reaction calorimetry evaluations involved the Suzuki-Miyaura cross-coupling of 1-bromo-3-(trifluoromethyl)benzene with potassium vinyltrifluoroborate. These reactions were performed in five volumes of solvent relative to aryl bromide rather than more diluted for the convenience of work-up and product isolation, as removal of high boiling solvents such as DMSO, *N,N*-dimethylformamide (DMF), *N*-methyl-2-pyrrolidone (NMP), etc. on large scale can be problematic. For each experiment, a mixture of 37.2 mmol of aryl bromide, 1.5 equivalents of vinylboron species, and 2.5 equivalents of base in 42 mL of solvent was heated to 80 °C. To this mixture was added 0.07 equivalents of catalyst (unless otherwise stated) in one-portion, and the reaction was maintained at 80 °C until complete conversion was observed by GC analysis. It is worthwhile to note that no noticeable exotherms were observed prior to the addition of catalyst in any of the studied cases. The exothermic event was integrated to collect ΔH of the reaction, which was then used for the calculation of adiabatic temperature rise (ΔT_{ad}) and MTSR.

The thermal profile revealed a significant exotherm upon the addition of $Pd(dppf)Cl_2$ to a mixture of 1-bromo-3-(trifluoromethyl)benzene, potassium vinyltrifluoroborate, and K_2CO_3 in 9:1 DMSO/water at 80 °C (Figure 1). The total heat output was calculated to be −14.67 kJ (−393.5 kJ/mol) over only 6 min with a ΔT_{ad} of 141.0 °C, resulting in a MTSR of 221.0 °C that is considerably higher than the boiling point of the solvent. This heat profile suggests that in the absence of sufficient cooling the system could quickly exceed the boiling point of the solvent and result in a runaway reaction. In comparison, the same reaction in anhydrous DMSO progressed relatively milder, generating a ΔH of −9.44 kJ (−253.8 kJ/mol) over 80 min and a ΔT_{ad} of 93.8 °C. This reaction started fast and decayed toward the end of reaction with 73% of the total heat released in the first 20 min of reaction (Figure 2).

Figure 1. Heat flow profile of the Suzuki-Miyaura cross-coupling of 1-bromo-3-(trifluoromethyl)benzene with potassium vinyltrifluoroborate in 9:1 DMSO/water.

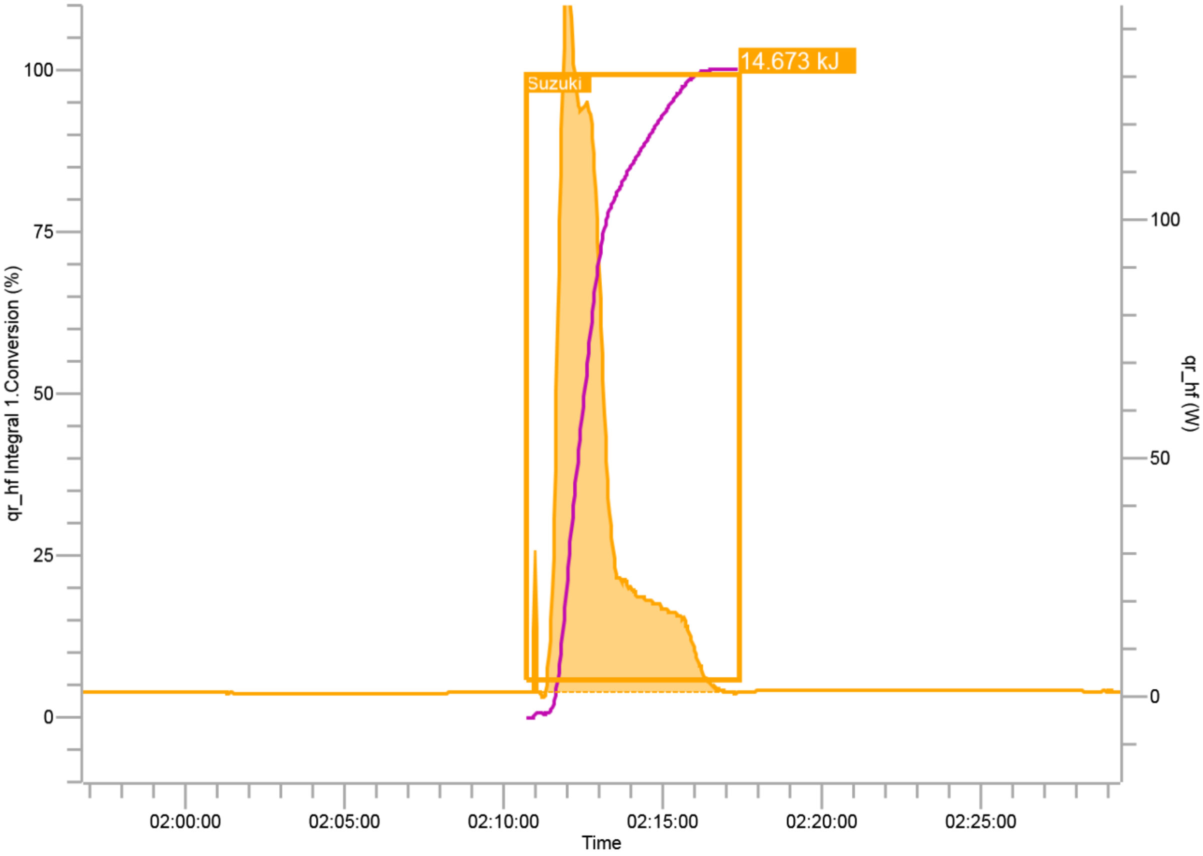
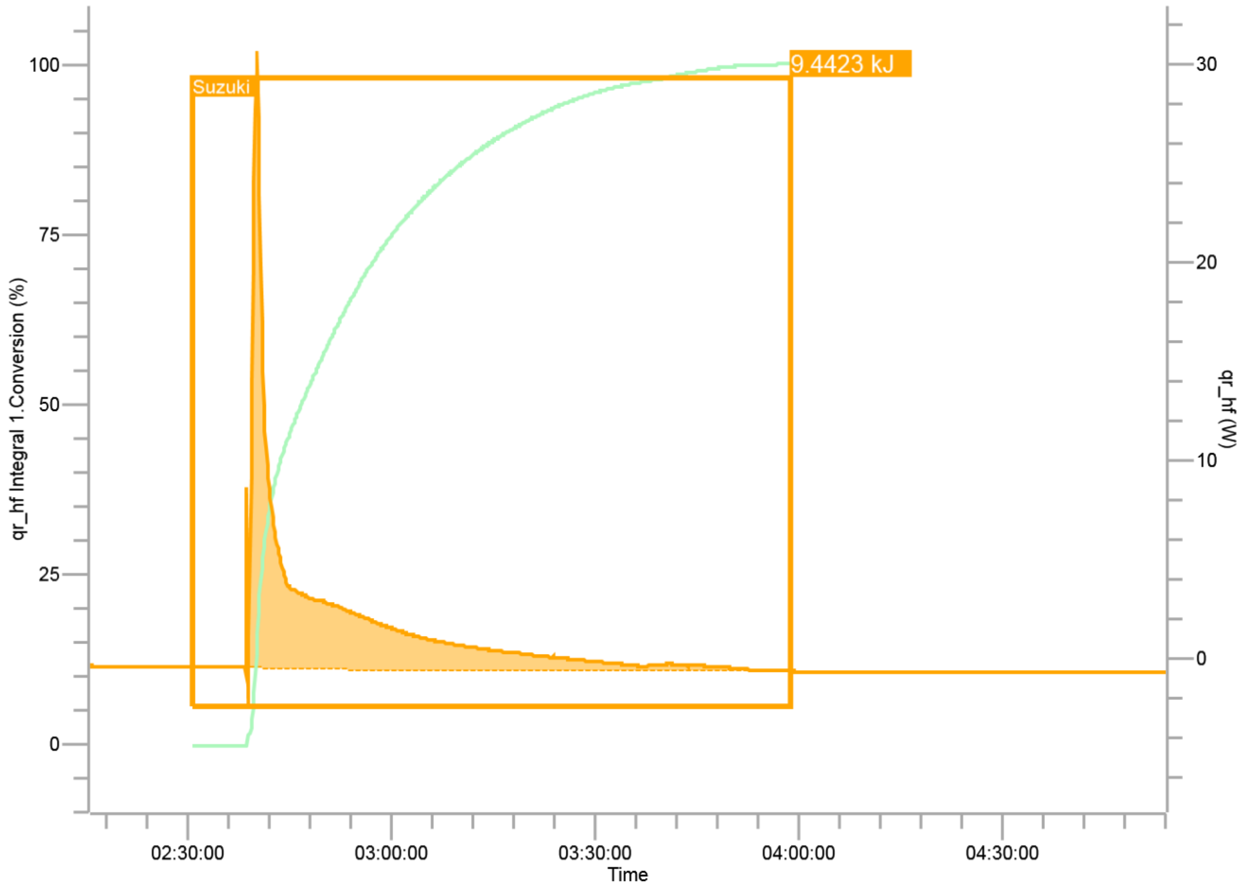


Figure 2. Heat flow profile of the Suzuki-Miyaura cross-coupling of 1-bromo-3-(trifluoromethyl)benzene with potassium vinyltrifluoroborate in anhydrous DMSO.



In addition to the desired heat of reaction, potential causes of the exotherm can be attributed to the polymerization of the desired styrene products,[10] decomposition of potassium vinyltrifluoroborate under the reaction conditions, and/or decomposition of components of the reaction mixture. Quantitative In-Process Control (IPC) analysis by GC[11] correlated very well with the heat conversion during the course of the reaction and afforded >90% in-pot yield at reaction completion, indicating that the product was stable during the reaction. This was further supported by *in-situ* ReactIR analysis as shown in Figures 3 and 4. The product concentration increased rapidly with the decrease of the starting material upon the addition of catalyst, Pd(dppf)Cl$_2$, and also corresponded well with the heat conversion. Further stirring of the reaction mixture under the reaction conditions for a prolonged time after reaction completion did not show decrease of the product concentration, confirming that polymerization of the desired styrene product did not occur under the reaction conditions. Unfortunately, the signals of potassium vinyltrifluoroborate were buried under other signals, thus precluding monitoring the fate of potassium vinyltrifluoroborate by ReactIR. No noticeable heat was observed in a control experiment in which Pd(dppf)Cl$_2$ was added to a mixture of potassium vinyltrifluoroborate and K$_2$CO$_3$ in DMSO at 80 °C (in the absence of aryl bromide), indicating little of the observed exotherm was contributed by the decomposition of potassium vinlytrifluoroborate even if decomposition occurred during the reaction.

Figure 3. Reaction profile of the Suzuki-Miyaura cross-coupling of 1-bromo-3-(trifluoromethyl)benzene with potassium vinyltrifluoroborate in anhydrous DMSO at 80 °C.

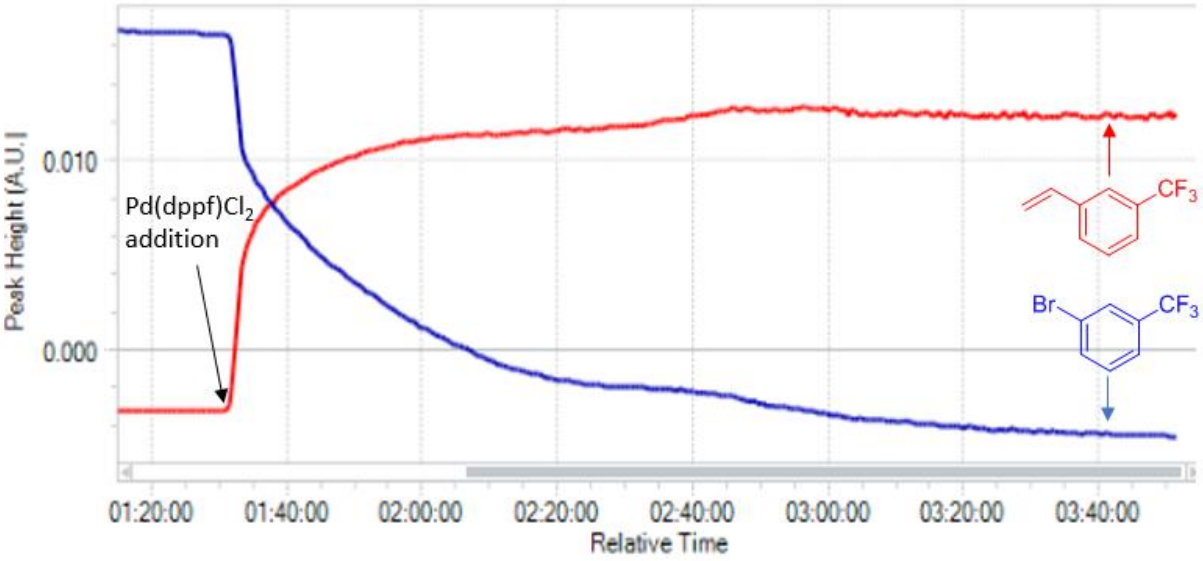
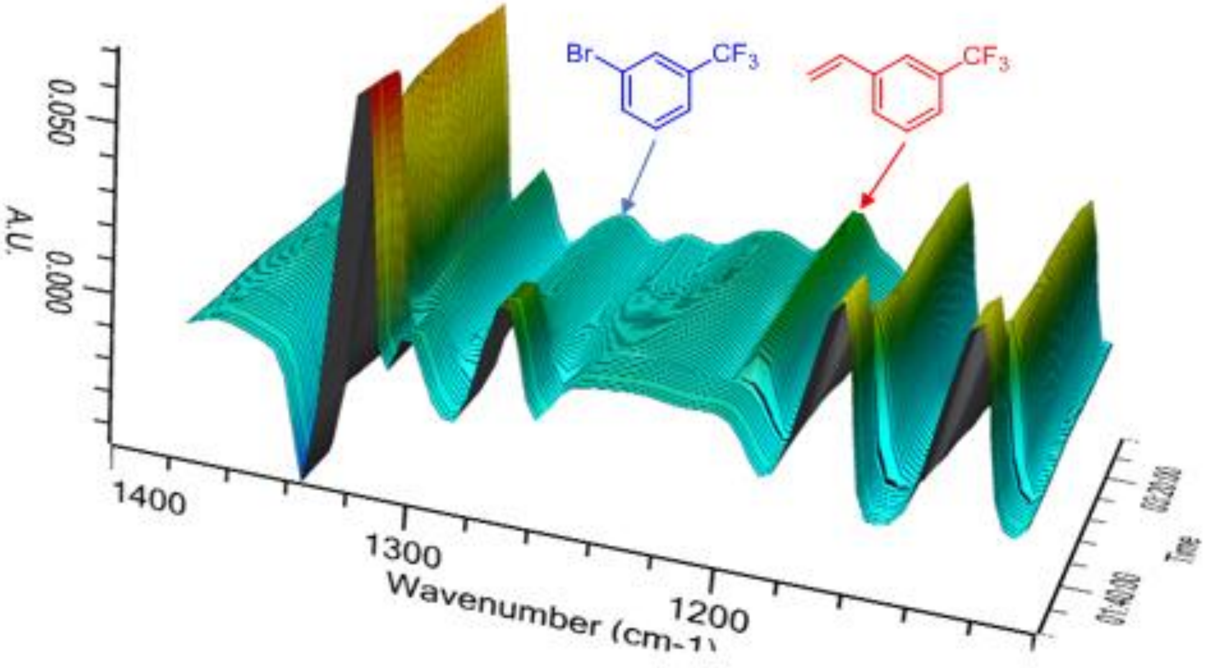


Figure 4. Three-dimensional plot of ReactIR monitoring of the Suzuki-Miyaura cross-coupling of 1-bromo-3-(trifluoromethyl)benzene with potassium vinyltrifluoroborate in anhydrous DMSO at 80 °C.

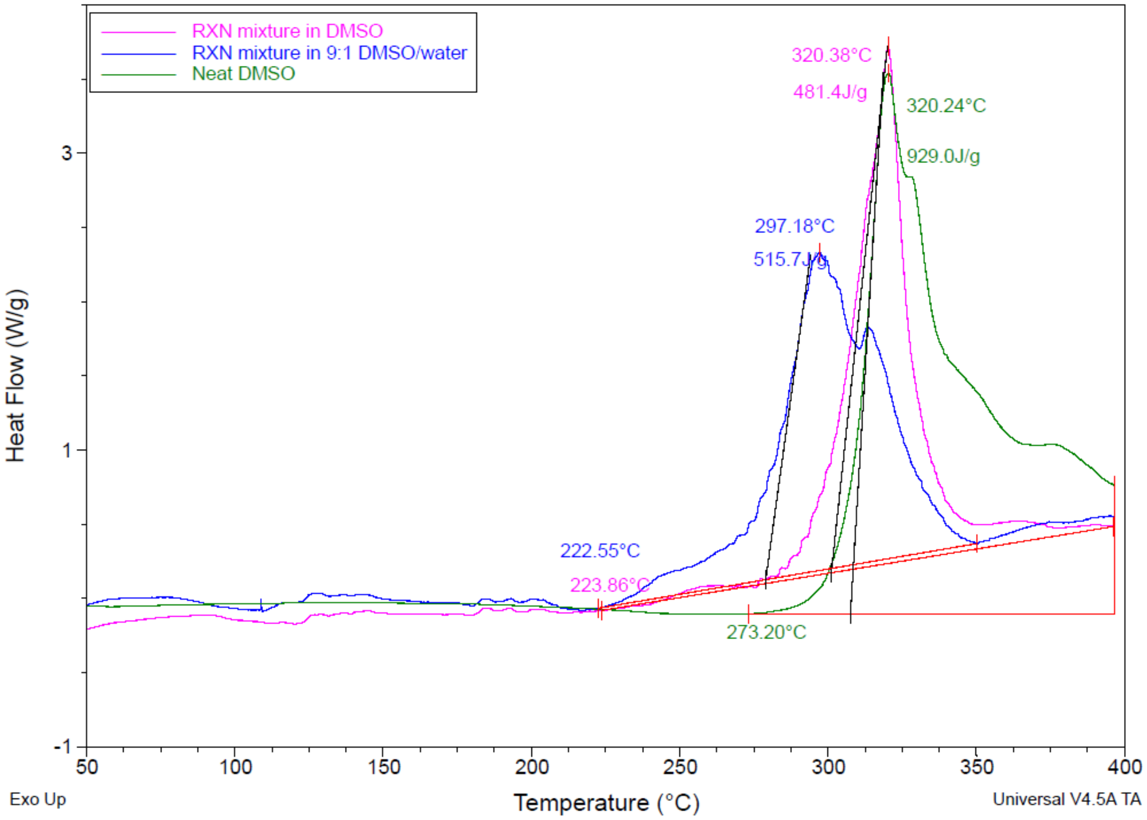


It is a good safety practice to understand the thermal decomposition behavior of a reaction mixture prior to scale-up and develop control strategies to ensure that the reaction is conducted at a safe temperature (e.g., 100 °C below the detected onset temperature of the thermal decomposition[12]). Decomposition events are generally characterized with differential scanning calorimetry (DSC), thermal screening unit (Tsu), accelerating rate calorimetry (ARC), and/or vent sizing package (VSP).

The thermal decomposition of DMSO has been a growing concern in the chemistry community.[13] While pure DMSO exhibits an exothermic thermal decomposition with an onset temperature of 273 °C by DSC analysis (Figure 5), the decomposition of DMSO in a reaction mixture frequently occurs at a much lower onset temperature. This thermal decomposition can be autocatalytic in the presence of acids, bases, and/or halogenated organic compounds.[14]

Initial evaluation of the stability of the post-reaction mixtures in DMSO and 9:1 DMSO/water was performed using DSC. The thermograms of the post-reaction mixtures along with the thermogram of neat DMSO are shown in Figure 5. In both experiments, significantly lower onset temperatures (~223 °C) were detected compared to that of neat DMSO (273 °C). In the case of the reaction mixture in 9:1 DMSO/water, the peak temperature representing the main DMSO decomposition reaction was shifted to a much lower temperature, which was likely caused by the presence of water in combination with a weak base (K_2CO_3).

Figure 5. DSC analysis of the post-reaction mixtures of the Suzuki-Miyaura cross-coupling of 1-bromo-3-(trifluoromethyl)benzene with potassium vinyltrifluoroborate.



Further thermal decomposition evaluations were performed using ARC to enable detection of the slow initial decomposition and/or other minor exothermic events. Two independent exothermic events were detected for the reaction mixtures in anhydrous DMSO and 9:1 DMSO/water (Figure 6). According to the onset temperature, mass ratio, and total released energy, the small exothermic events (around 150 °C) in both reaction mixtures were consistent with the polymerization of the styrene product. The major exothermic events recorded by ARC were comparable for the reaction mixtures in anhydrous DMSO and 9:1 DMSO/water, with a detected onset at 190.7 °C and 196.0 °C, respectively (Figure 6). Both ARC tests were terminated because the maximum cut-off pressure was reached and both tests had a significant cool down pressure, confirming that the DMSO decomposition resulted in significant amount of gas (Figure 7).

For the reaction in 9:1 DMSO/water, the reaction mixture could self-heat to as high as its MTSR of 221 °C, which would be much higher than the onset temperature of the DMSO decomposition. With insufficient cooling and fast reaction rate, a close-to-adiabatic condition would result, and the decomposition of DMSO would most likely promote a runaway reaction. Although the MTSR of the reaction in anhydrous DMSO (173.8 °C) is below the solvent boiling point and the onset temperature of the DMSO decomposition, if this temperature is reached it will induce the heat release from the polymerization of the styrene product, which in turn will further increase the temperature of the reaction mixture to potentially trigger the decomposition of DMSO.

Figure 6. ARC heat rate vs. temperature profile of the post-reaction mixture of the Suzuki-Miyaura cross-coupling of 1-bromo-3-(trifluoromethyl)benzene with potassium vinyltrifluoroborate.

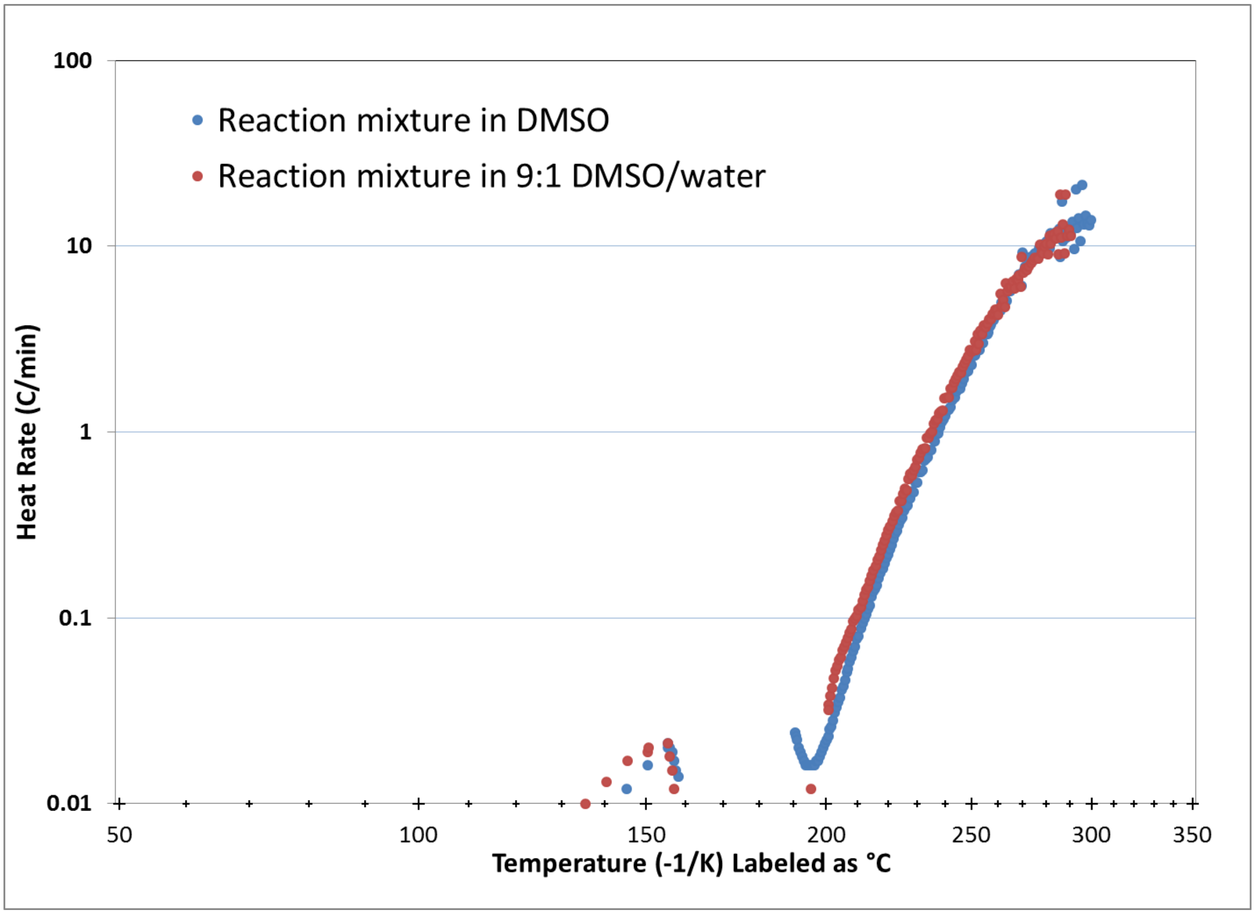
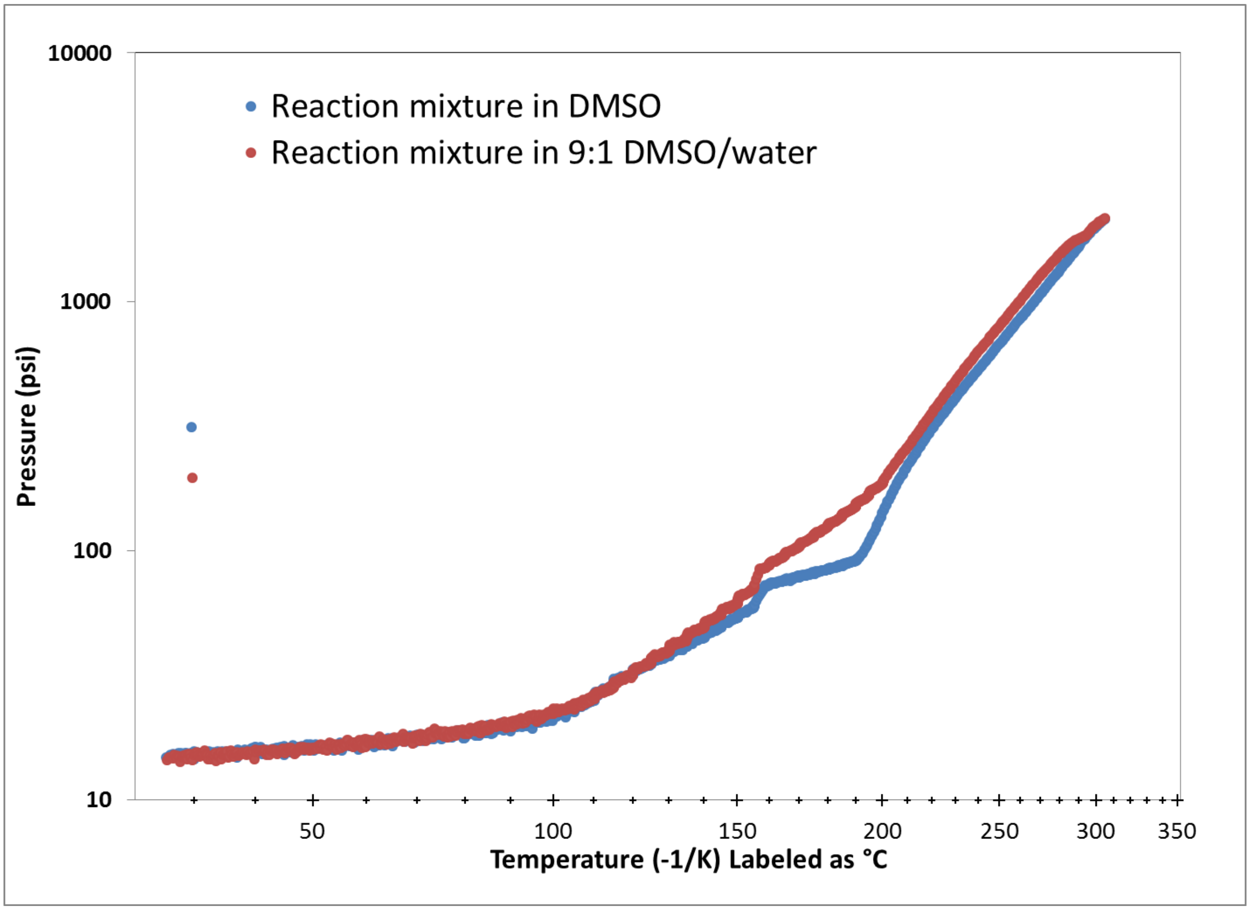


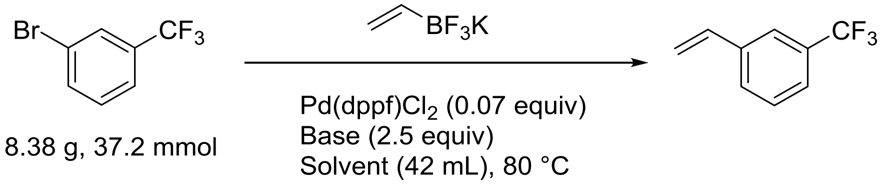
Figure 7. ARC pressure vs. temperature profile of the post-reaction mixture of the Suzuki-Miyaura cross-coupling of 1-bromo-3-(trifluoromethyl)benzene with potassium vinyltrifluoroborate.



The effect of key parameters on the reaction heat profile was also evaluated (Table 1 and Figure 8). The reactions conducted in DMF solvent systems followed the same trends as those in anhydrous DMSO as well as 9:1 DMSO/water, generating a ΔH of −9.39 kJ (−252.4 kJ/mol) over 46 min and a ΔT_{ad} of 100.6 °C in anhydrous DMF (Entry 4), and a ΔH of −13.96 kJ (−375.3 kJ/mol) over 5 min and a ΔT_{ad} of 138.6 °C in 9:1 DMF/water (Entry 2). In both cases, the MTSR (180.6 °C in anhydrous DMF and 218.6 °C in 9:1 DMF/water) exceeded the boiling point of the solvent and would result in runaway reaction without a sufficient cooling mechanism. The heat profile of this reaction system at 80 °C in 9:1 dioxane/water, a frequently used solvent for the Suzuki-Miyaura cross-coupling, revealed a ΔH of −13.87 kJ (−372.8 kJ/mol) over 55 min and a

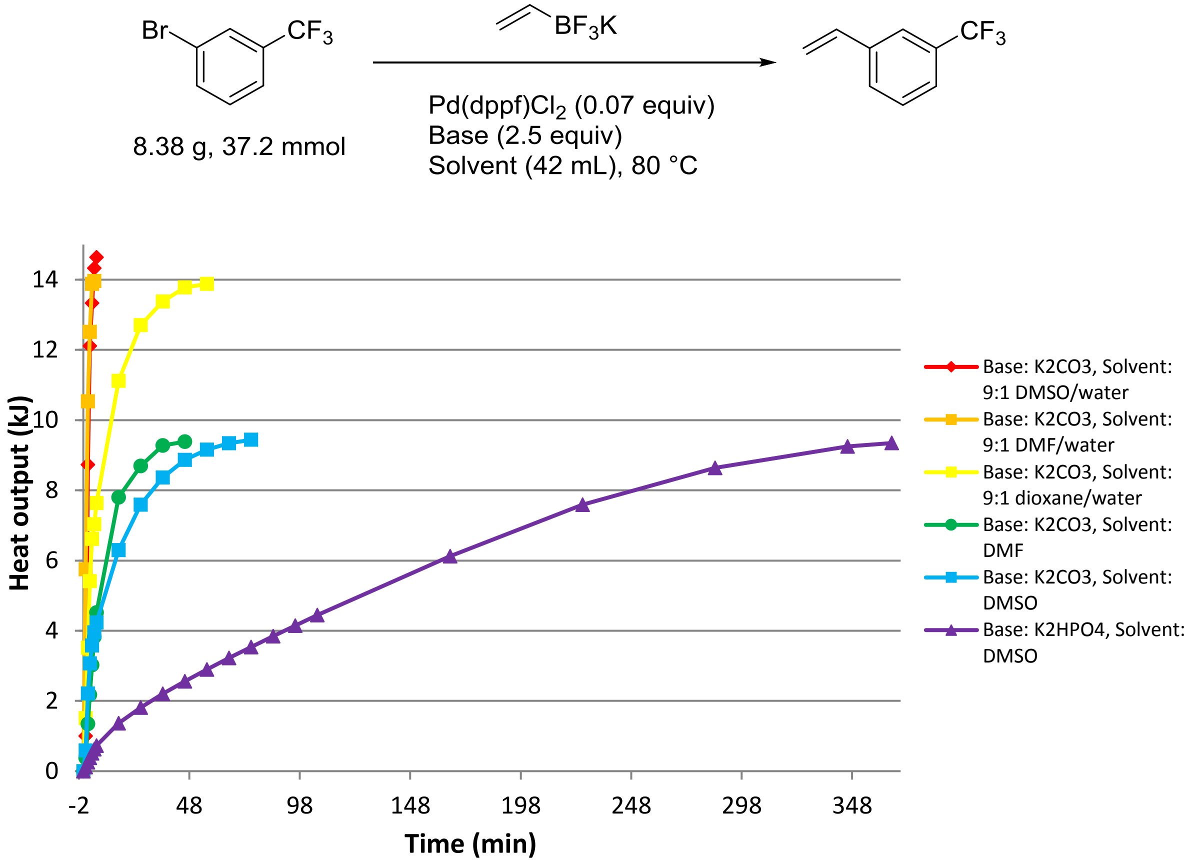
ΔT_{ad} of 131.5 °C (Entry 3). This exotherm resulted in a MTSR of 211.5 °C that poses a potential runaway hazard without active cooling during the reaction, especially given that the boiling point of dioxane is only 101 °C. The use of a relatively weaker base, potassium hydrogen phosphate (K_2HPO_4), caused the reaction to progress at a much slower rate compared to K_2CO_3, but generated a comparable ΔH of −9.35 kJ (−251.3 kJ/mol) over 365 min and ΔT_{ad} of 93.3 °C in anhydrous DMSO (Entry 6).

Table 1. Effect of base and solvent on the heat profile of the Suzuki-Miyaura cross-coupling of 1-bromo-3-(trifluoromethyl)benzene with potassium vinyltrifluoroborate.



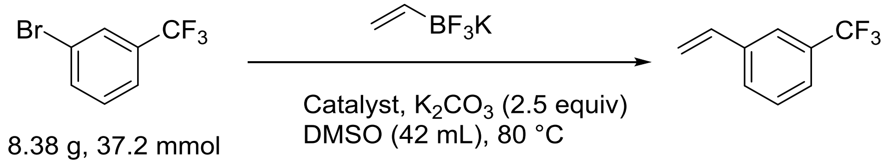
Entry	Base	Solvent	Time (min)	Conversion (% by GC)	ΔH (kJ)	ΔH (kJ/mol)	ΔT_{ad} (°C)	MTSR (°C)
1	K_2CO_3	DMSO/water	6	98.7	–14.64	–393.5	141.0	221.0
2	K_2CO_3	DMF/water	5	>99.9	–13.96	–375.3	138.6	218.6
3	K_2CO_3	Dioxane/water	55	99.1	–13.87	–372.8	131.5	211.5
4	K_2CO_3	DMF	46	98.8	–9.39	–252.4	100.6	180.6
5	K_2CO_3	DMSO	80	98.7	–9.44	–253.8	93.8	173.8
6	K_2HPO_4	DMSO	365	99.1	–9.35	–251.3	93.3	173.3

Figure 8. Effect of base and solvent on the heat profile of the Suzuki-Miyaura cross-coupling of 1-bromo-3-(trifluoromethyl)benzene with potassium vinyltrifluoroborate.



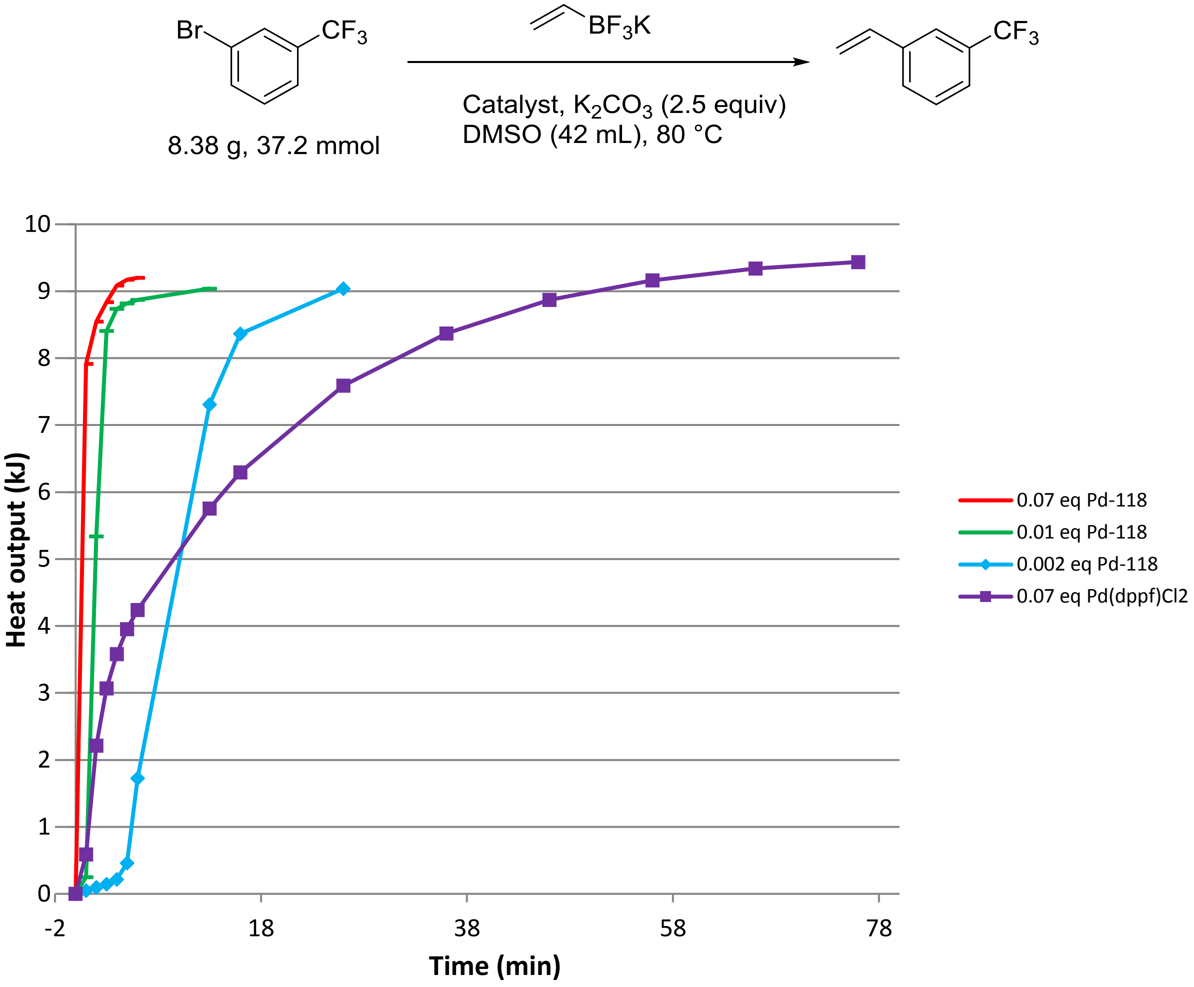
Moreover, upon switching to a more active catalyst, 1,1′-bis(di-*tert*-butylphosphino)ferrocene palladium(II) dichloride [Pd(dtbpf)Cl_2 or Pd-118], we observed complete conversion to the desired styrene product in only 6 min (Figure 9) when the reaction was performed in anhydrous DMSO at 80 °C with a ΔH of −9.22 kJ (−247.8 kJ/mol) and a ΔT_{ad} of 93.3 °C (Table 2, Entry 2). When the Pd-118 loading was reduced to 0.01 equivalents, the reaction rate was marginally reduced, but a similar exotherm was produced [ΔH: −9.04 kJ (−243.0 kJ/mol), ΔT_{ad}: 93.2 °C] (Table 2, Entry 3) affording complete conversion in 13 min. However, it is worthwhile to note that 93% of the total heat was released within the first 3 min of the reaction, which was comparable to the 96% heat conversion in the same timeframe when 0.07 equivalents of Pd-118 was used (Figure 9). Slow reaction initiation was observed when the Pd-118 loading was further reduced to 0.002 equivalents; however, the reaction ramped up drastically upon initiation to give 87% heat conversion within 11 min, achieving reaction completion in a total of 26 min (Figure 9). The ΔH [−9.04 kJ (−243.0 kJ/mol)] and ΔT_{ad} 98.4 °C of this reaction (Table 2, Entry 4) were comparable with those with Pd(dppf)Cl_2 and Pd-118 under anhydrous conditions. The reaction using tetrakis(triphenylphosphine)palladium(0) [Pd(PPh_3)$_4$] as the catalyst was very slow at 80 °C achieving only 4.1% conversion after 80 min, and reached 95.4% conversion after stirring at 100 °C for 17 h with no integrable exotherm (Table 2, Entry 5).

Table 2. Effect of catalyst on the heat profile of the Suzuki-Miyaura cross-coupling of 1-bromo-3-(trifluoromethyl)benzene with potassium vinyltrifluoroborate.



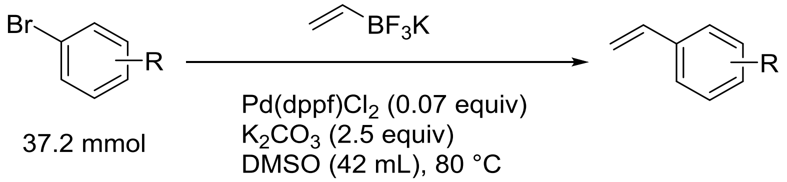
Entry	Catalyst	Loading (equiv)	Temperature (°C)	Time (min)	Conversion (% by GC)	ΔH (kJ)	ΔH (kJ/mol)	ΔT_{ad} (°C)	MTSR (°C)
1	Pd(dppf)Cl_2	0.07	80	80	98.7	−9.44	−253.8	93.8	173.8
2	Pd-118	0.07	80	6	99.8	−9.22	−247.8	93.3	173.3
3	Pd-118	0.01	80	13	>99.9	−9.04	−243.0	93.2	173.2
4	Pd-118	0.002	80	26	99.6	−9.04	−243.0	98.4	178.4
5	Pd(PPh_3)$_4$	0.07	100	17 h	95.4	ND	ND	ND	ND

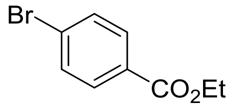
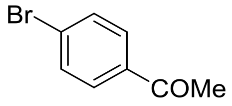
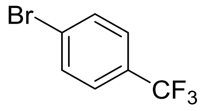
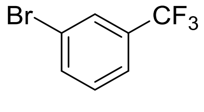
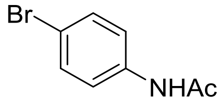
Figure 9. Effect of catalyst on the heat profile of the Suzuki-Miyaura cross-coupling of 1-bromo-3-(trifluoromethyl)benzene with potassium vinyltrifluoroborate.



A variety of substituted aryl bromides ranging from electron-deficient to electron-rich systems were evaluated to study the scope of this exothermic behavior (Table 3 and Figure 10). All the reactions were performed at 80 °C in anhydrous DMSO in the presence of Pd(dppf)Cl_2 and K_2CO_3. Similar magnitude exothermic behaviors were observed in all evaluated substrates, with the heat of reaction ranging from –241.1 kJ/mol with 4-bromoacetanilide (entry 5) to –289 kJ/mol with ethyl 4-bromobenzoate (Entry 1). Both heat conversion and GC analysis supported that the reaction progressed faster with the electron-deficient substrates than with electron-rich substrates, with complete conversion ranging from 20 min with ethyl 4-bromobenzoate (Entry 1) and 4-bromoacetophenone (Entry 2) to 100 min with 1-bromo-3-methoxybenzene (Entry 7). The exothermic behavior of these substrates under aqueous conditions (i.e., 9:1 DMSO/water) was not studied, but it is reasonable to speculate that these reactions should progress faster with higher levels of heat generated than those under anhydrous conditions based on the observations described in Table 1.

Table 3. The Suzuki-Miyaura cross-coupling of substituted aryl bromides with potassium vinyltrifluoroborate.



Entry	ArBr	Time (min)	Conversion (% by GC)	ΔH (kJ)	ΔH (kJ/mol)	ΔT$_{ad}$ (°C)	MTSR (°C)
1		20	98.3	–10.75	–289.0	88.5	168.5
2		20	>99.9	–9.70	–260.8	80.8	160.8
3		80	98.8	–9.28	–249.5	89.2	169.2
4		80	98.7	–9.44	–253.8	93.8	173.8
5		90	>99.9	–8.97	–241.1	89.5	169.5

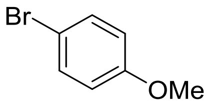
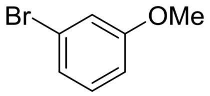
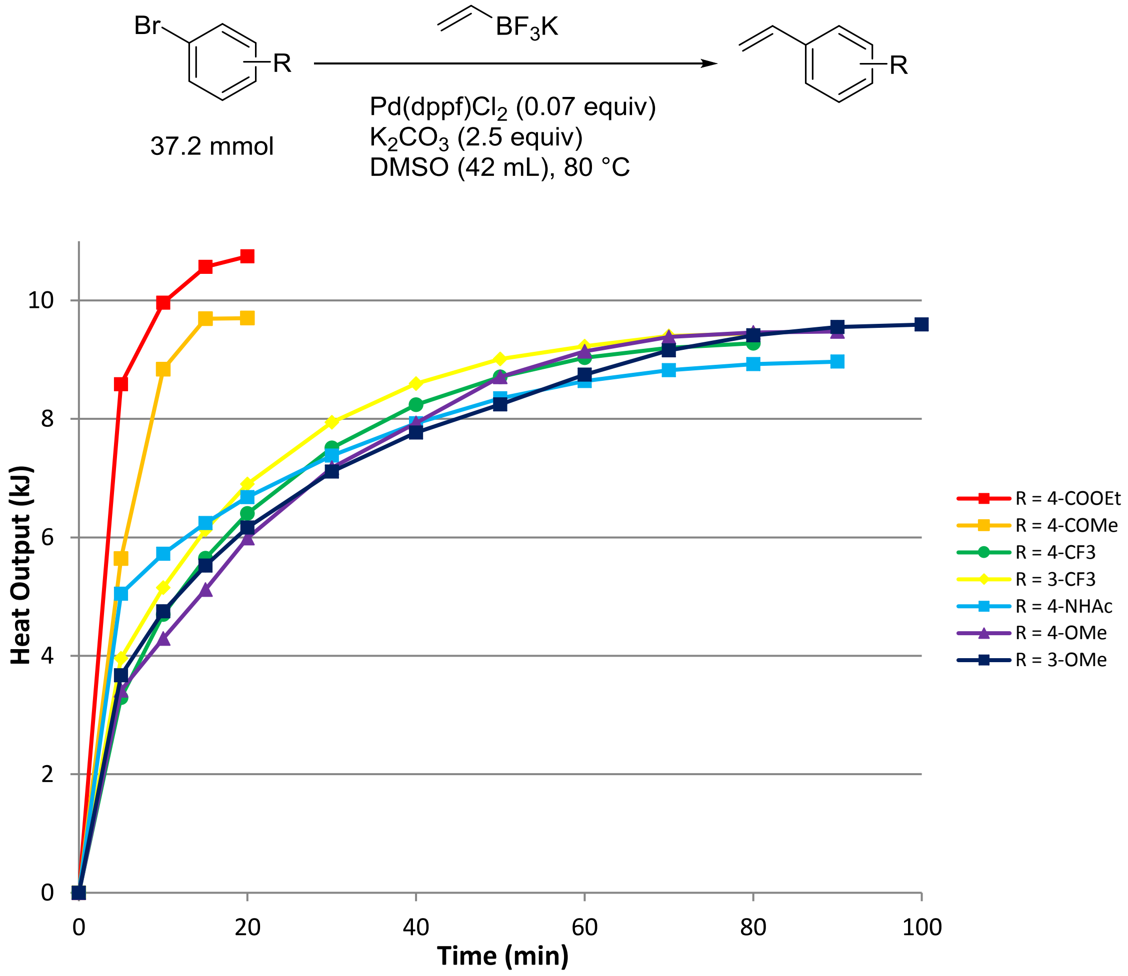
6		90	>99.9	−9.48	−254.8	111.0	190.0
7		100	>99.9	−9.59	−257.8	90.4	170.4

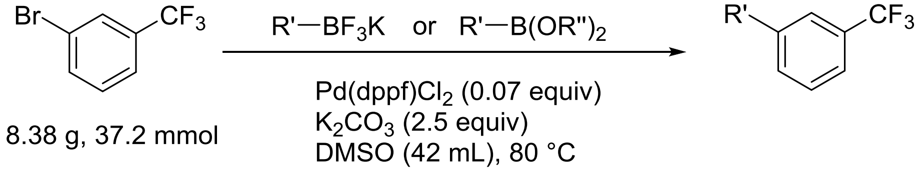
Figure 10. Heat profiles of the Suzuki-Miyaura cross-coupling of substituted aryl bromides with potassium vinyltrifluoroborate.



Variation of the vinylboron species was also explored to determine if the observed exotherm was specific to potassium vinyltrifluoroborate (Table 4 and Figure 11). The reaction of 1-bromo-

3-(trifluoromethyl)benzene with potassium *iso*-propenyltrifluoroborate generated a similar heat profile compared with potassium vinyltrifluorborate, giving a ΔH of −9.46 kJ (−259.1 kJ/mol) over 70 min and a ΔT_{ad} of 90.4 °C in anhydrous DMSO (Entry 2). It is worthwhile to note that the reactions with pinacol vinylboronate (entry 4) and *iso*-propenylboronate (entry 5) also produced similar heat profiles in anhydrous DMSO [−9.42 kJ (−253.2 kJ/mol) and −9.33 kJ (−250.8 kJ/mol), respectively] compared to those with potassium vinyltrifluoroborate. The ΔT_{ad} of 96.3 °C for pinacol vinylboronate and 94.2 °C for pinacol *iso*-propenylboronate were also comparable with the ΔT_{ad} using potassium vinyltrifluoroborate. The reaction time for pinacol vinylboronate was significantly longer than that of pinacol *iso*-propenylboronate (130 min vs. 70 min), which was suspected to be caused by poor mass transfer as a thick suspension was observed during the reaction with pinacol vinylboronate. The heat profile with (*E*)-styrylboronic acid in anhydrous DMSO was also comparable to other studied organoboron reagents under anhydrous conditions, with a ΔH of −9.04 kJ (−243.0 kJ/mol) and a ΔT_{ad} of 89.0 °C (Entry 6). Interestingly, when we switched to potassium allyltrifluoroborate, the reaction was much slower and milder, requiring 180 min to achieve completion with a ΔH of −7.1 kJ (−190.9 kJ/mol) and a ΔT_{ad} of 78.7 °C (Entry 3).

Table 4. The Suzuki-Miyaura cross-coupling of 1-bromo-3-(trifluoromethyl)benzene with various organoboron species.



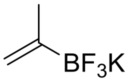
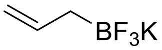
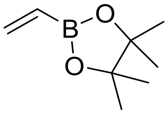
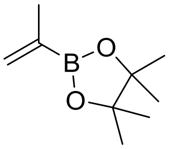
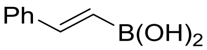
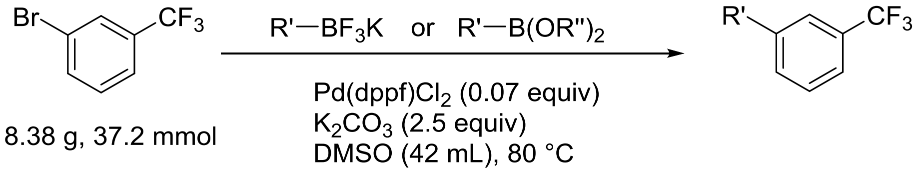
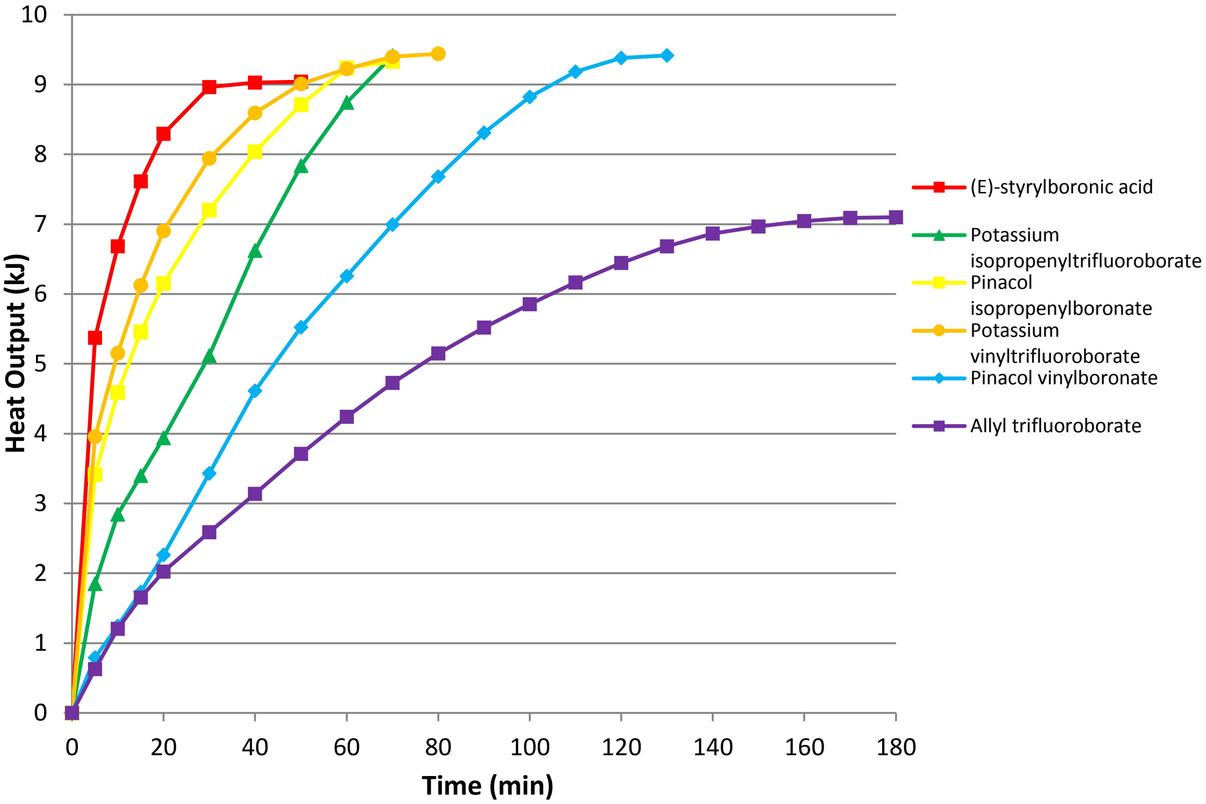
Entry	Borate	Time (min)	Conversion (% by GC)	ΔH (kJ)	ΔH (kJ/mol)	ΔT_{ad} (°C)	MTSR (°C)
1		80	98.7	−9.44	−253.8	93.8	173.8
2		70	>99.9	−9.64	−259.1	90.4	170.4
3		180	96.9	−7.10	−190.9	78.7	158.7
4		130	99.7	−9.42	−253.2	96.3	176.3
5		70	>99.9	−9.33	−250.8	94.2	174.2
6		50	98.7	−9.04	−243.0	89.0	169.0

Figure 11. Heat profiles of the Suzuki-Miyaura cross-coupling of 1-bromo-3-(trifluoromethyl)benzene with various organoboron species.





CONCLUSIONS

Significant exothermic events were observed during the Suzuki-Miyaura cross-coupling of aryl bromides with potassium vinyltrifluoroborate in the studied systems. The exotherm was more significant and much faster in aqueous systems compared to anhydrous conditions. This exotherm posed potential safety hazards as in many reaction systems, especially in the presence of water, the MTSR exceeded the boiling point of the solvent and/or the onset temperature of the decomposition of DMSO. The effects of key parameters such as solvent, catalyst, and base, etc. were evaluated, and it was found that these systems produced exotherms of comparable magnitude, but at different reaction rates. The scope studies revealed similar exotherms with different aryl bromides and various vinylboron species, with faster reactions occurring with electron-deficient aryl bromides. Researchers are encouraged to conduct safety evaluations and develop control strategies accordingly to mitigate potential safety risks prior to practicing similar chemistry, especially on large scale. Although only aryl bromides were studied in this work, similar precautions should be taken with the Suzuki-Miyaura cross-coupling of other aryl electrophiles.

EXPERIMENTAL SECTION

General: All reagents were commercially available and used as purchased without further purification. Reaction conversion and product formation were confirmed by spiking with an authentic sample of the desired product purchased from commercial suppliers and/or GCMS analysis. GC analysis was performed on an Agilent 6850 equipped with Agilent DB-WAX column (30 m × 320 μm × 0.5 μm, P/N 123−7033); Inlet 250 °C; FID, 250 °C; helium constant flow: 3 mL/min; hydrogen flow: 40 mL/min; air flow: 450 mL/min; nitrogen makeup: 30 mL/min; injection volume: 1 μL; split ratio: 25; temperature programming: 50 °C: 0 min, 30°C/min to 200 °C then 5 °C/min to 250 °C, hold 2 min; maximum column temperature: 250 °C.

General procedure for the reaction calorimetry evaluation by EasyMax HF Cal: The reaction calorimetry was evaluated using a Mettler-Toledo EasyMax 102 with HF Cal. All reactions were performed under a nitrogen blanket. For each experiment a stirred (at 300 rpm) mixture of aryl bromide (37.2 mmol), organoboron reagent (1.5 equiv), and base (2.5 equiv) in solvent (42 mL) was heated to 77 °C. The virtual volume was recorded, followed by calibration to determine heat transfer co-efficient (u) and heat capacity (cpr) with 15 min waiting time and ΔTr of 3 °C. The catalyst (see tables for specific catalyst and amount) was added in one-portion, and the reaction was heated at 80 °C until complete conversion was observed by GC analysis. The virtual volume was recorded, and a second calibration was performed to determine u and cpr with 15 min waiting time and ΔTr of 3 °C. The reaction was then cooled to 25 °C to complete the experiment. The exothermic event was integrated to determine ΔH, which was then used for the calculation of ΔT_{ad} and MTSR.

Procedure for DSC analysis: A Q2000 DSC from TA instruments was used for the constant heating rate tests in this study. A 1 mg sample was loaded into a glass capillary and then flame sealed with air as the headspace. During the flame sealing of the glass, the sample containing portion of the ampoule was cooled with liquid nitrogen. The sealed ampoule had a total internal volume of ~25 µL. The sealed ampoule can withstand pressures up to 3000 psi at 400 °C and therefore effectively prevents the escape of any tested chemical or the products from reaction.[15]

Procedure for ARC analysis: An ARC manufactured by Thermal Hazard Technology was used in this study. A 4.0 g sample was loaded into a standard Titanium ARC sphere with air as the headspace. The ARC experiment was performed with a Heat-Wait-Search (HWS) mode. A heat step of 5 °C, waiting time of 30 min and a detection threshold of 0.02 °C/min was utilized. The Phi factor calculated from mass and heat capacity was 2.04.[16]

AUTHOR INFORMATION

Corresponding Author

e-mail: qyang1@dow.com

Notes

The authors declare no competing financial interest.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

ACKNOWLEDGMENT

The authors thank Dr. Gregory T. Whiteker for helpful discussions during this investigation and Dr. Shawn Chen for assisting with the interpretation of ReactIR data. Dow AgroSciences is acknowledged for support of this work.

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