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Mizoroki−Heck Cross-Coupling of Bromobenzenes with Styrenes: Another Example of Pd-Catalyzed Cross-Coupling with Potential Safety Hazards

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ABSTRACT: The potential safety hazards associated with the Mizoroki−Heck cross-coupling of bromobenzenes with styrenes were evaluated. The heat output from the reaction in various solvents was comparable in a variety of solvents; however, the rate of reaction was significantly faster in the presence of water. Thermal stability evaluation of the postreaction mixtures in DMSO and 3:1 DMSO/water by differential scanning calorimetry indicated that the onset temperatures of thermal decomposition were significantly lower than that of neat DMSO. Evaluation of the substrate scope revealed that the substitution pattern on the bromobenzene did not affect the heat output. The reaction rate of electron-deficient bromobenzenes was slower than that of the electron-rich bromobenzenes. In general, substituted styrenes afforded similar magnitudes of exotherms; however, the reaction rate of bromobenzene with 2-methylstyrene was significantly slower than the other studied styrenes. The predicted heat of reaction using the density functional theory method, B3LYP, was in good agreement with the experimental data. Such excellent agreement suggests that this calculation method can be used as a preliminary tool to predict heat of reaction and avoid exothermic reaction conditions. In many of the studied cases, the maximum temperature of a synthesis reaction was considerably higher than the solvent boiling point and thermal decomposition onset temperatures when the reaction was performed in DMSO or 3:1 DMSO/water. It is crucial to understand the thermal stability of the reaction mixture to design the process accordingly and ensure the reaction temperature is maintained below the onset temperature of decomposition to avoid potential runaway reactions.

KEYWORDS: *safety hazards, Mizoroki−Heck cross-coupling, reaction calorimetry, exotherm, bromobenzene, styrene*

INTRODUCTION

Since its discovery by Mizoroki[1] and Heck,[2] the Mizoroki−Heck cross-coupling[3] reaction has become an essential tool for synthetic chemists in academia and industry.[4] Over the years, this reaction has been extended to the coupling of pseudohalides such as triflates,[5] tosylates,[6] mesylates,[7] and aryl diazonium salts,[8] along with the generation of chiral centers with a high degree of enantiocontrol.[9] As a consequence, the Mizoroki−Heck cross-coupling presents itself as one of the most widely used Pd-catalyzed cross-coupling reactions as revealed in a survey of these reactions[10] and finds wide application in the large scale production of agrochemicals, hydrocarbons, pharmaceuticals, polymers, and other specialty chemicals.[11]

The potential safety hazards associated with Pd-catalyzed cross-couplings have recently become a growing concern in the chemistry community. Over the past several years, there have been multiple reports regarding the potential safety hazards associated with the Pd-catalyzed α-arylation,[12] the Sonagoshira cross-coupling,[13] and the Suzuki−Miyaura cross-coupling.[14] During our investigation of the Suzuki−Miyaura cross-coupling safety hazards,[14] we observed that the Mizoroki−Heck product **3** was favored over the Suzuki−Miyaura product **4** in a 4:1 ratio[15] when bromobenzene (**1**) was treated with pinacol *iso*-propenylboronate (**2**) in *N*,*N*-dimethylformamide (DMF) at 80 °C using 1,1′-bis(di-*tert*-butylphosphino)ferrocene palladium(II) dichloride [Pd(d*t*bpf)Cl_2 or Pd-118] as the catalyst in the presence of potassium carbonate (K_2CO_3) as the base (Scheme 1). It is also worth noting that a strong exotherm was observed during this reaction. A survey of literature revealed two papers reporting safety evaluations during process development and scale up of the Mizoroki−Heck cross-coupling.[16] In addition, Bossé et al. reported the use of isothermal and nonisothermal differential scanning calorimetry (DSC) for the characterization of the Heck-like exothermic reaction in solid films.[17] Blackmond and coworkers described the use of reaction calorimetry as a kinetic and stability screening tool of palladium catalysts in the Mizoroki−Heck cross-coupling.[18] However, to the best of our knowledge, no systematic evaluation of the potential safety hazards associated with the Mizoroki−Heck cross-coupling of bromobenzenes with styrenes has been disclosed in the literature. Herein, we present a comprehensive calorimetric study of the Pd-catalyzed cross-coupling of bromobenzenes with styrenes under a variety of solvent, base, and catalyst combinations that are frequently utilized in organic chemistry

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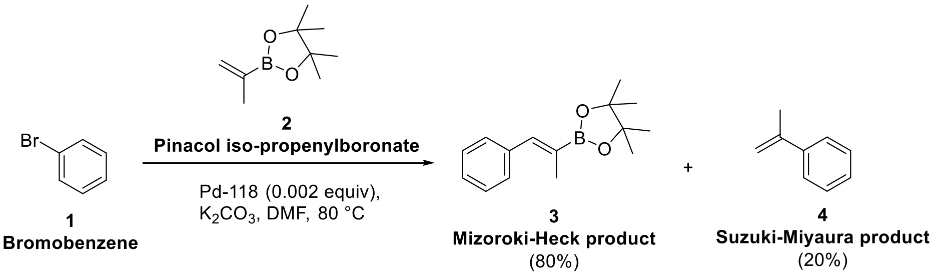
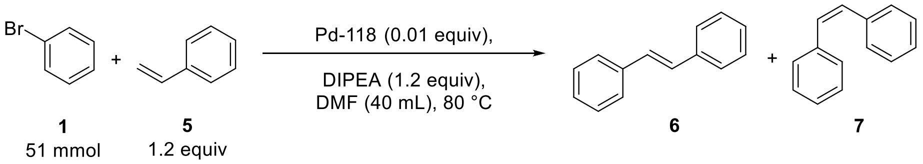
Scheme 1. Selectivity between the Mizoroki−Heck and the Suzuki−Miyaura Cross-Coupling



Scheme 2. Mizoroki−Heck Cross-Coupling of Bromobenzene with Styrene in the Presence of Pd-118 in DMF at 80 °C



laboratories and thereby gain a better understanding of the thermal profile of the Mizoroki−Heck cross-coupling reaction.

RESULTS AND DISCUSSION

Reaction Calorimetry Evaluation of the Mizoroki−Heck Cross-Coupling of Bromobenzene with Styrene. The Mizoroki−Heck cross-coupling of 51 mmol of bromobenzene with 1.2 equiv of styrene in 5 volumes of DMF at 80 °C using 0.01 equiv of Pd-118 as the catalyst in the presence of 1.2 equiv of *N*,*N*-diisopropylethylamine (DIPEA) as the base[19] (Scheme 2) was used as the model reaction for the initial reaction calorimetry evaluations. The thermal profile revealed a significant exotherm upon the addition of Pd-118 to a mixture of bromobenzene, styrene, and DIPEA in DMF at 80 °C.[20] The total heat output was calculated to be −10.77 kJ (−211.2 kJ/mol) over 44 min with a ΔT_{ad} of 99.4 °C, resulting in a maximum temperature of a synthesis reaction (MTSR) of 179.4 °C, which is considerably higher than the boiling point of the solvent, DMF (bp 152 °C). This heat profile suggests that in the absence of sufficient cooling, the system could suddenly boil and result in a runaway reaction. Although the thermal stability evaluation of the postreaction mixture by DSC indicated no exothermic decomposition up to 300 °C, it is essential for researchers to understand the thermal stability of their specific reaction mixtures (e.g., reactions performed in DMSO[14,21] or acetonitrile in the presence of a strong aqueous base[22]) and develop control strategies to conduct the reaction at a safe temperature[23] to ensure this exotherm does not trigger decomposition of the reaction mixture, possibly leading to uncontrollable temperature rise. Such a scenario could also cause pressure accumulation if the temperature reaches the solvent boiling point or if gaseous decomposition products are formed and result in runaway reaction.

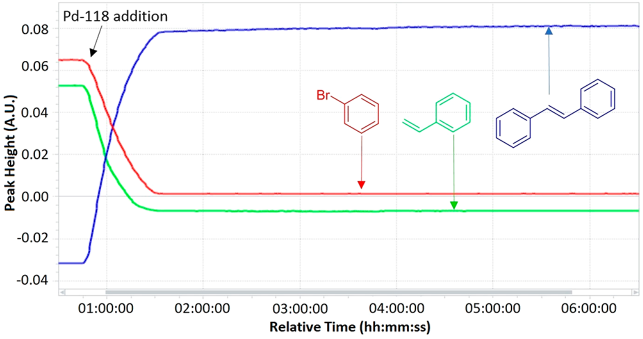


Figure 1. Reaction profile of the Mizoroki−Heck cross-coupling of bromobenzene with styrene in DMF at 80 °C.

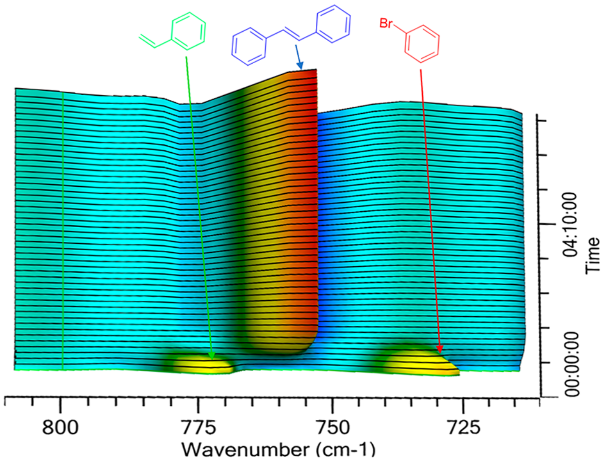


Figure 2. Three-dimensional plot of ReactIR monitoring of the Mizoroki−Heck cross-coupling of bromobenzene with styrene in DMF at 80 °C.

Reaction Kinetic Profiles. The reaction profile of the Mizoroki−Heck cross-coupling of bromobenzene with styrene in DMF at 80 °C using Pd-118 as the catalyst in the presence of DIPEA was monitored by *in situ* ReactIR analysis (Figures 1 and 2). Upon the addition of Pd-118 to the reaction mixture, the concentration of product **3** increased rapidly with the decrease in concentration of bromobenzene (**1**) and styrene (**5**), which also corresponded well with heat conversion. Prolonged stirring of the completed reaction at 80 °C did not result in decomposition of starting materials **1** and **5** or product **6**, as indicated by the ReactIR analysis. Unfortunately, the *cis* product **7** was not detected during this experiment, thus precluding any evaluation of its stability to the reaction conditions by ReactIR.

The reaction progress of the Mizoroki−Heck cross-coupling of bromobenzene (**1**) with styrene (**5**) using our standard reaction conditions (Scheme 2) was also monitored by quantitative in-process control (IPC) analysis by gas chromatography (GC),[24] which also correlated very well with the heat conversion and ReactIR profile during the course of reaction. Upon completion, the reaction afforded a 91% in-pot yield of **6** and a 4.5% in-pot yield of **7** to give a combined in-pot yield of 95.5% for the stilbene products. Prolonged stirring of the reaction mixture at 80 °C gave no indication of decomposition of starting materials or products (Figure 3), and the ratio of *trans* (**6**) and *cis* (**7**) stilbene products (~20:1) remained constant throughout the reaction (Figure 4).

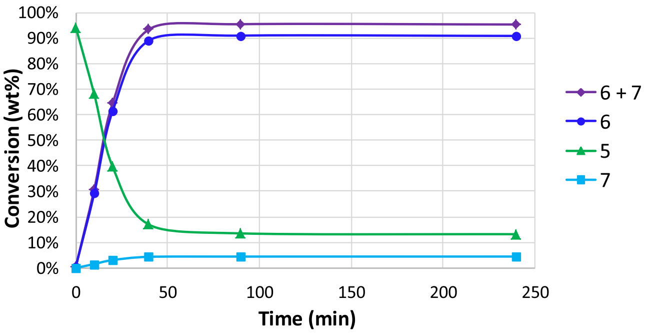


Figure 3. In-pot yield vs time profile of the Mizoroki−Heck cross-coupling of bromobenzene with styrene in DMF at 80 °C.

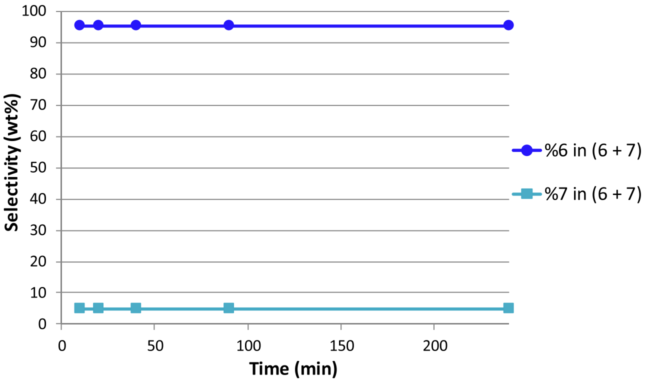
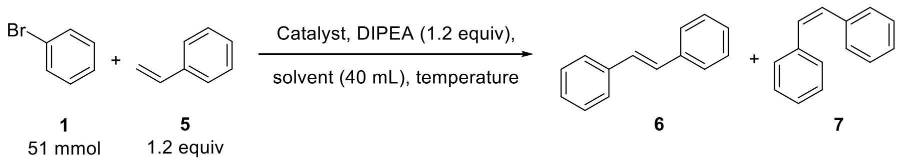


Figure 4. Selectivity of the Mizoroki−Heck cross-coupling of bromobenzene with styrene in DMF at 80 °C.

Heat of Reaction Calculation. First-principles methods to calculate thermodynamic parameters have been routinely used for reaction design in chemical processes.[25] We used the B3LYP method to calculate the heat of reaction for the Mizoroki−Heck cross-coupling of bromobenzene with styrene in DMF at 80 °C using Pd-118 as the catalyst in the presence of DIPEA. Geometry optimization was performed to generate the structures of all reactants and products using the B3LYP/LAV3P* method. The B3LYP/CCPVDZ+ solution phase energy was calculated for all molecules involved in the reaction based on optimized structures in an implicit PBF solvation model with DMF as solvent. Frequency calculations were also performed using the same method to generate relevant thermodynamic quantities, including zero-point energy, thermal energy, and enthalpy at 353.15 K and 1 atm. All calculations were performed with Jaguar software in Maestro (Schrodinger Inc.). The enthalpy change for the reaction with DIPEA as base was −212.32 kJ/mol, in close agreement with the experimental data of −211.2 kJ/mol. The close agreement suggests that the density functional theory (DFT) method can be used as a preliminary tool to predict heat of reaction and avoid exothermic reaction conditions.

Effect of Key Parameters. Similar magnitudes of exothermic behaviors were observed when the reaction was performed in a variety of solvents (Table 1, Figure 5); however, the reaction rate was faster in solvent mixtures containing water[26] and reached complete conversion in 15 min in 7:1 DMF/water (entry 2) and 19 min in 3:1 DMF/water (entry 3) at 70 °C, compared to 44 min in anhydrous DMF at 80 °C (entry 1). The ΔT_{ad} values of the reactions in aqueous systems (79.5 °C for 7:1 DMF/water and 60.1 °C for 3:1 DMF/water) were lower than those under anhydrous conditions due to the increased heat capacity inherent with the presence of water (entries 2 and 3). The fast reaction rate observed in the aqueous system poses significant challenges for effective heat removal from the reaction system in an "all-in" batch mode reaction. In this case, control strategies such as controlled addition of reactants and/or continuous flow processes should be considered to mitigate safety risks associated with the exotherm. Surprisingly, the reaction in dimethyl sulfoxide (DMSO, entry 4) was much slower compared to those in DMF (entry 1), *N*,*N*-dimethylacetamide

Table 1. Effect of Critical Process Parameters on the Mizoroki−Heck Coupling of Bromobenzene with Styrene



entry	catalyst (equiv)	base	solvent	temp (°C)	time (min)	GC (% AUC) 1	6	7	ΔH (kJ)	ΔH (kJ/mol)	ΔT_{ad} (°C)	MTSR (°C)
1	Pd-118 (0.01)	DIPEA	DMF	80	44	ND	95.5	4.5	−10.77	−211.2	99.4	179.4
2	Pd-118 (0.01)	DIPEA	7:1 DMF/water	70	15	ND	95.3	4.7	−10.23	−200.6	79.5	149.5
3	Pd-118 (0.01)	DIPEA	3:1 DMF/water	70	19	ND	95.2	4.8	−10.31	−202.2	60.1	130.1
4	Pd-118 (0.01)	DIPEA	DMSO	80	170	ND	95.5	4.5	−10.44	−204.7	93.9	173.9
5	Pd-118 (0.01)	DIPEA	3:1 DMSO/water	70	28	ND	94.5	5.5	−11.00	−215.7	74.3	144.3
6	Pd-118 (0.01)	DIPEA	DMAc	80	70	ND	95.6	4.4	−11.02	−216.1	97.7	177.7
7	Pd-118 (0.01)	DIPEA	NMP	80	54	ND	95.8	4.2	−10.48	−205.5	91.0	171.0
8	Pd-118 (0.01)	K_2CO_3	3:1 DMF/water	70	27	ND	95.2	4.8	−10.88	−213.3	63.2	133.2
9	Pd(dppf)Cl_2 (0.1)	DIPEA	3:1 DMF/water	80	72	ND	93.9	6.1	−11.09	−217.5	72.6	152.6

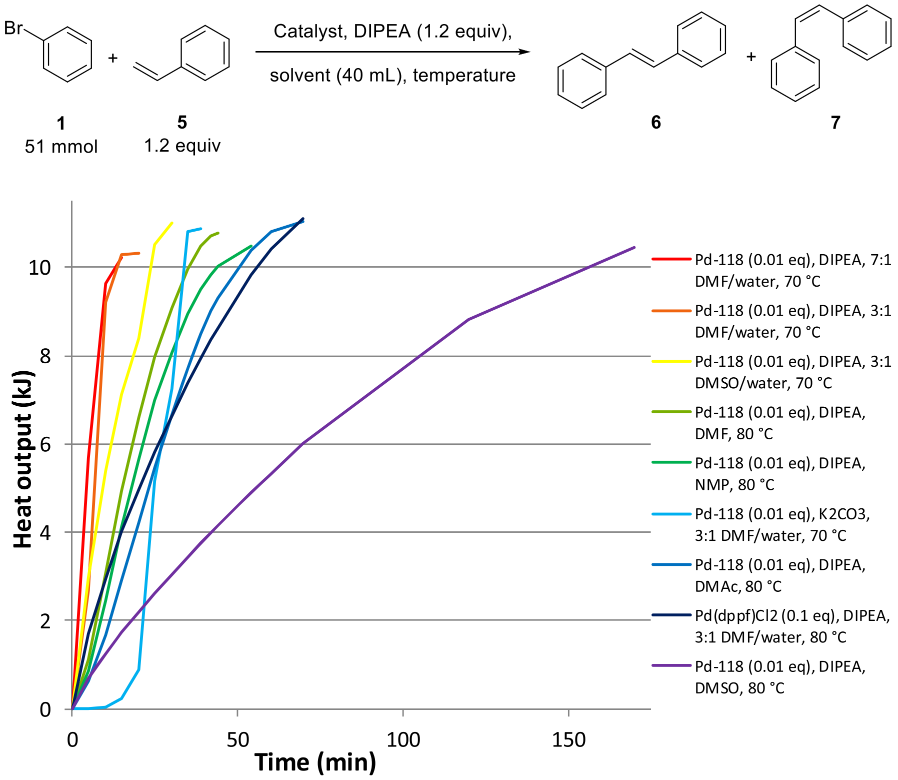


Figure 5. Heat profiles of the critical process parameter effect on the Mizoroki−Heck cross-coupling of bromobenzene with styrene.

Table 2. DSC Results of Postreaction Mixtures in DMSO and 3:1 DMSO/Water

	exotherm 1			exotherm 2			exotherm 3				
solvent	onset (°C)	ΔH (J/g)	ΔT_{ad} (°C)	onset (°C)	ΔH (J/g)	ΔT_{ad} (°C)	onset (°C)	ΔH (J/g)	ΔT_{ad} (°C)	total ΔH (J/g)	total ΔT_{ad} (°C)
DMSO	89.2	−36.3	21.3	196.9	−483.6	284.0	275.4	−66.5	39.1	−586.4	344.4
3:1 DMSO/water	52.1	−148.3	68.9	235.8	−356.7	165.8	292.9	−45.7	21.2	−550.7	255.9

(DMAc, entry 6), and *N*-methyl-2-pyrrolidone (NMP, entry 7) and required a total of 170 min to afford complete conversion. Here again, water proved to be advantageous by significantly increasing reaction rate, and when 3:1 DMSO/water was employed as solvent, the reaction was completed in only 28 min at 70 °C (entry 5).

The use of potassium carbonate (K_2CO_3) as the base achieved reaction completion over 27 min at 70 °C in the presence of 0.01 equiv of Pd-118 as the catalyst in 3:1 DMF/water, generating a comparable ΔH of −10.88 kJ (−213.3 kJ/mol) and ΔT_{ad} of 63.2 °C (entry 8). Upon switching the catalyst to 0.01 equiv of 1,1′-bis(diphenylphosphino)ferrocene palladium(II) dichloride [Pd(dppf)Cl_2] and 1.2 equiv of DIPEA, the reaction afforded only a trace of desired product when bromobenzene was treated with styrene at 80 °C in DMF for 18 h. Increasing the catalyst loading to 0.1 equiv did not significantly improve conversion. Full conversion was observed after 72 min at 80 °C when water was introduced as a cosolvent (3:1 DMF/water) for reaction of bromobenzene with styrene in the presence of 0.1 equiv of Pd(dppf)Cl_2 and 1.2 equiv of DIPEA. Although the rate of this reaction was significantly slower than that using Pd-118 under the same reaction conditions, the ΔH of −11.09 kJ (−217.5 kJ/mol) and ΔT_{ad} of 72.6 °C (entry 9) were comparable to those from the reaction using Pd-118 (entry 3).

Thermal Stability Evaluation of Reaction Mixtures in DMSO. It is well-documented in the literature that the onset temperature of DMSO thermal decomposition is significantly affected by the components in the reaction matrix.[14,21] Compared to the 276.2 °C of pure DMSO decomposition onset temperature, DSC analysis of the postreaction mixture in DMSO (Table 1, entry 4) exhibited three exothermic decomposition events with onset temperatures of 89.1, 196.9, and 275.4 °C, respectively. These exothermic events afforded combined ΔH of −586.4 J/g and ΔT_{ad} of 344.4 °C (Table 2 and Figure 6). Similarly, DSC analysis of the postreaction mixture in 3:1 DMSO/water (Table 1, entry 5) also exhibited three exothermic decomposition events with onset temperatures of 52.1, 235.8, and 292.9 °C, respectively, affording combined ΔH of −550.7 J/g and ΔT_{ad} of 255.9 °C (Table 2 and Figure 6). These data suggest that without effective heat removal, the exotherm from the desired reaction of such reactions could potentially trigger the decomposition of DMSO to result in runaway scenarios. It therefore behooves researchers to fully study the thermal stability of their specific reaction mixtures and develop appropriate control strategies to conduct their reactions at safe temperatures.[23]

Effect of Substitution on Bromobenzene. A variety of substituted bromobenzenes ranging from electron-deficient to electron-rich systems were evaluated to study the scope of this exothermic behavior (Table 3 and Figure 7). All the reactions

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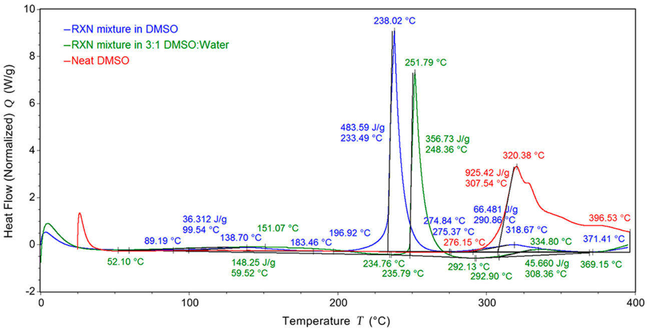


Figure 6. DSC profile of DMSO reaction mixtures in DMSO and 3:1 DMSO/water.

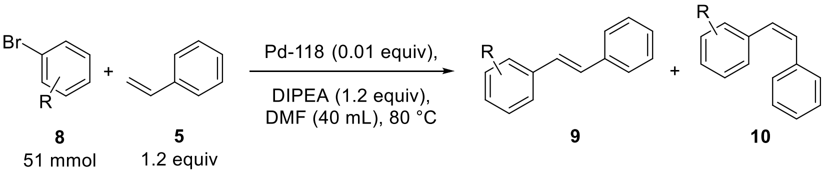
were performed at 80 °C in DMF in the presence of Pd-118 as the catalyst and DIPEA as the base. All evaluated substrates produced similar levels of exotherms with the heat of reaction ranging from −200.8 kJ/mol for 2-bromotoluene (entry 3) to −215.7 kJ/mol for 2-bromoanisole (entry 2) and 4-bromoacetophenone (entry 11). It is worth noting that both heat conversion and GC analysis supported that the reaction progressed faster with the electron-rich substrates compared to electron-deficient substrates. Electron-rich substrates achieved reaction completion with reaction times ranging from 39 min for 2-bromotoluene (entry 3) to 85 min for 2-bromoanisole (entry 2), while substrates with strong electron-withdrawing groups such as 2-bromobenzotrifluoride (entry 4), 3-bromobenzotrifluoride (entry 7), 3-bromobenzonitrile (entry 8), and 4-bromobenzotrifluoride (entry 12) required >170 min to reach reaction completion. The mechanism of the Mizoroki–Heck reaction is a well-studied, albeit much debated subject.[27] Recent studies have indicated that the mechanism is highly catalyst, ligand, base, and solvent dependent.[28] Our results indicate that the rate of reaction under the investigated conditions is faster with electron-rich bromobenzenes. It is also worthwhile to note that the level of the *cis* product **9** was consistent for all of the substrates, ranging from 1.1% for 4-bromoacetophenone (entry 11) to 6.5% for 4-bromoanisole (entry 9).

Effect of Substitution on Styrene. Variation of the substitution on the styrene was also studied to determine the scope of this exothermic behavior (Table 4 and Figure 8). These studies were also performed at 80 °C in DMF in the presence of Pd-118 as the catalyst and DIPEA as the base. All of the studied substrates generated heat outputs comparable to that of styrene with ΔH ranging from −203.9 kJ/mol for 2-methylstyrene (entry 2) to −214.3 kJ/mol for 4-methylstyrene (entry 6). The ΔT_{ad} was also consistent across the studied substituted styrenes, ranging from 93.6 °C for 2-methylstyrene (entry 2) to 113.7 °C for 4-fluorostyrene (entry 8). Interestingly, 2-methylstyrene (entry 2) was the only substrate that progressed slowly compared to other analogues, requiring a total of 355 min to achieve reaction completion. The other investigated analogues needed only 34 min for 3-methylstyrene (entry 4) to 76 min for 2-chlorostyrene (entry 3). It is also worthwhile to point out that the level of *cis* products from 2-substituted styrenes was significantly higher compared to the other studied substrates, affording 43.5% with 2-methylstyrene (entry 2) and 10.8% with 2-chlorostyrene (entry 3), respectively.

■ CONCLUSIONS

The exotherm during the Mizoroki–Heck cross-coupling of bromobenzene with styrene in DMF at 80 °C using Pd-118 as the catalyst in the presence of DIPEA as the base was evaluated. The predicted heat of reaction using the DFT method, B3LYP, was in good agreement with the experimental data, suggesting that this theoretical calculation can be used as a preliminary tool to predict heat of reaction and avoid exothermic reaction conditions. Further investigations indicated that the exotherm was comparable in a variety of solvents, but the reaction progressed much faster in the presence of water compared to anhydrous conditions. Thermal stability evaluation of the postreaction mixtures in DMSO and 3:1 DMSO/water by DSC indicated that the exotherms from

Table 3. Mizoroki–Heck Cross-Coupling of Substituted Bromobenzenes with Styrene



entry	R	time (min)	GC (% AUC)[a] 8	9	10	ΔH (kJ)	ΔH (kJ/mol)	ΔT_{ad} (°C)	MTSR (°C)
1	H	44	ND	95.5	4.5	−10.77	−211.2	99.4	179.4
2	2-OMe	85	ND	95.5	4.5	−11.00	−215.7	96.3	176.3
3	2-Me	39	ND	97.0	3.0	−10.24	−200.8	95.2	175.2
4	2-CF_3	205	ND	96.7	3.3	−10.52	−206.3	97.7	177.7
5	3-OMe	42	ND	95.1	4.9	−10.96	−214.9	110.1	190.1
6	3-Me	48	ND	94.6	5.4	−10.90	−213.7	101.8	181.8
7	3-CF_3	172	ND	95.9	4.1	−10.94	−214.5	105.0	185.0
8	3-CN	183	ND	93.9	6.1	−10.82	−212.2	100.8	180.8
9	4-OMe	45	ND	93.5	6.5	−10.97	−215.1	95.8	175.8
10	4-*t*-Bu	63	ND	96.5	3.5	−10.77	−211.2	102.4	182.4
11	4-COMe	70	ND	98.9	1.1	−11.00	−215.7	95.6	175.6
12	4-CF_3	185	ND	97.5	2.5	−10.65	−208.8	112.0	192.0

[a] By GC analysis except for entries 8 and 11, which were analyzed by HPLC.

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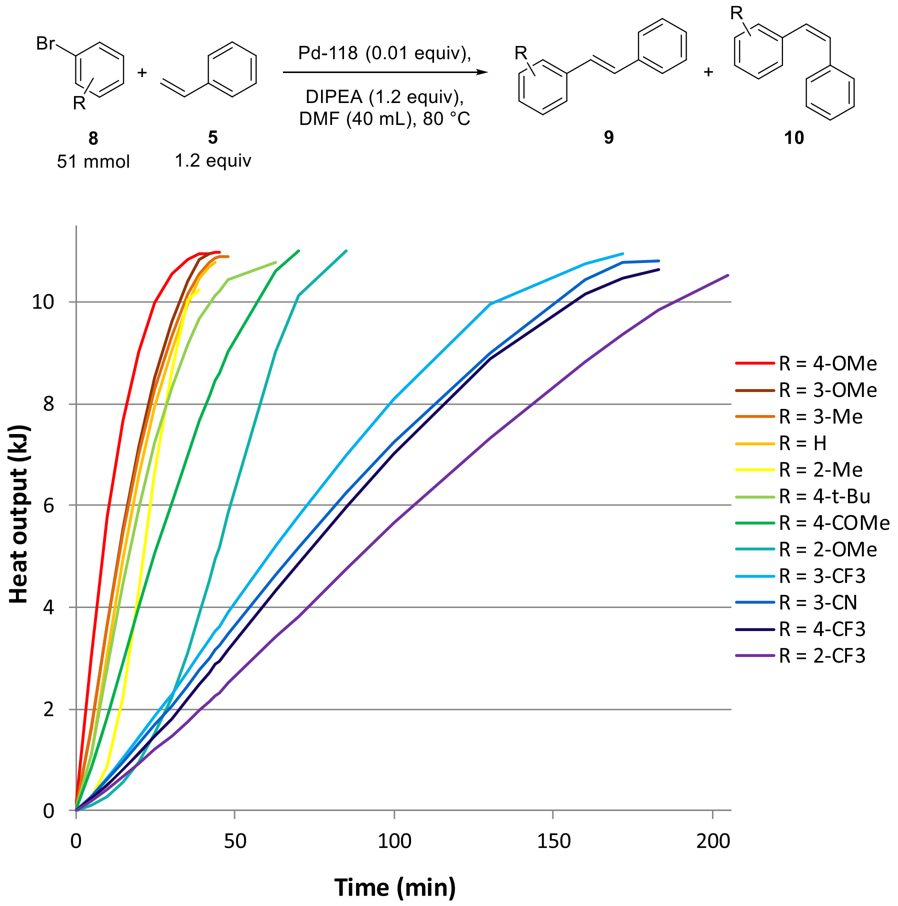
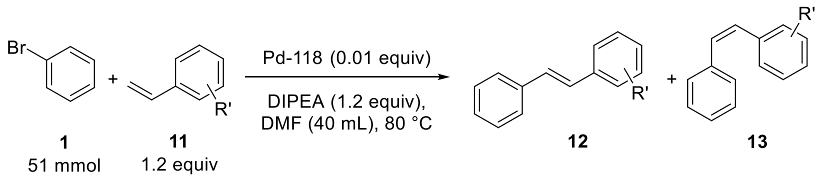


Figure 7. Heat profiles of the Mizoroki–Heck cross-coupling of substituted bromobenzenes with styrene.

Table 4. Mizoroki–Heck Coupling of Bromobenzene with Substituted Styrenes



entry	R′	time (min)	GC (% AUC) 1	GC (% AUC) 12	GC (% AUC) 13	ΔH (kJ)	ΔH (kJ/mol)	ΔT_{ad} (°C)	MTSR (°C)
1	H	44	ND	95.5	4.5	−10.77	−211.2	99.4	179.4
2	2-Me	355	ND	56.5	43.5	−10.40	−203.9	93.6	173.6
3	2-Cl	76	ND	89.2	10.8	−10.76	−211.0	99.0	179.0
4	3-Me	34	ND	95.4	4.6	−10.71	−210.0	95.4	175.4
5	3-Cl	38	ND	97.8	2.2	−10.80	−211.8	104.4	184.4
6	4-Me	43	ND	94.9	5.1	−10.93	−214.3	104.8	184.8
7	4-Cl	69	ND	97.4	2.6	−10.69	−209.6	99.9	179.9
8	4-F	50	ND	96.4	4.6	−10.88	−213.3	113.7	193.7

the desired reaction could potentially trigger the decomposition of DMSO to result in runaway scenarios. As expected, there was a strong substituent effect on the rate of the reaction for various bromobenzenes and styrenes, yet the magnitudes of the heat outputs were comparable across all of the studied substrates. It is crucial to understand the thermal stability of the reaction mixture and design control strategies accordingly, using methods such as controlled addition of reactants[15] or a continuous flow process,[29] to mitigate safety risk. Although only the Mizoroki–Heck cross-coupling of bromobenzenes with styrenes were studied in this work, precautions should be taken with all Mizoroki–Heck cross-coupling reactions.

■ EXPERIMENTAL SECTION

General. All reagents were commercially available and used as purchased without further purification. All reactions were carried out under N_2. 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

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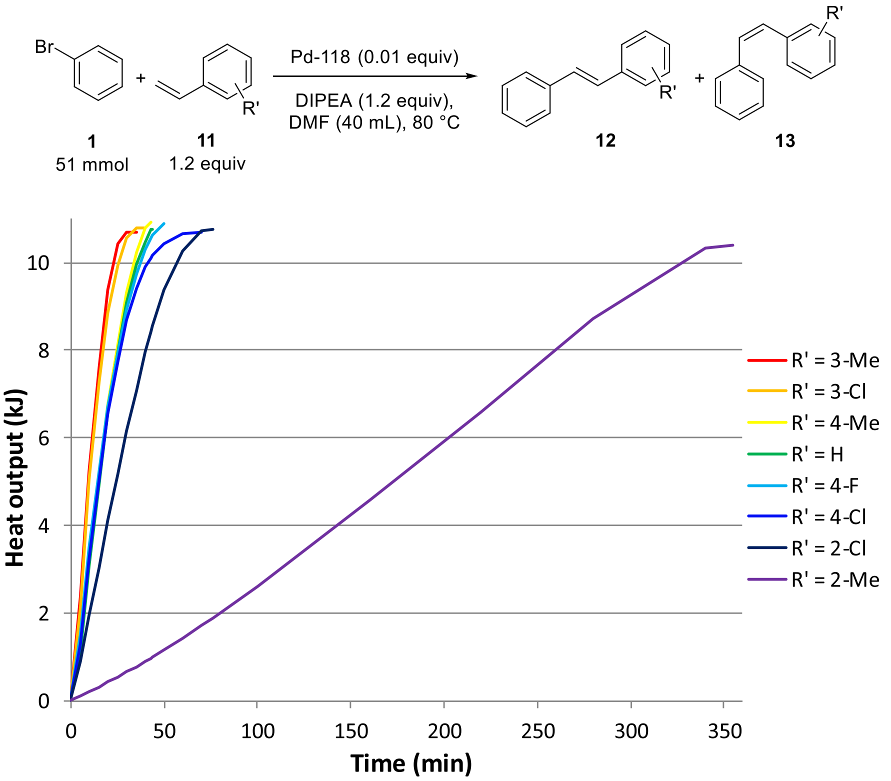

Figure 8. Heat profiles of the Mizoroki–Heck cross-coupling of bromobenzene with substituted styrene.

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: 1:25; 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. High-performance liquid chromatography (HPLC) analysis was performed on an Agilent 1260 using an Agilent Zorbax SB-Phenyl (150 × 4.6 mm) with a mobile phase A (water, adjusted to pH 2.5 with phosphoric acid) and B (acetonitrile) and detection at 254 nm; flow: 1.0 mL/min; column temperature: 40 °C; and gradient: 0 min: A = 76%, B = 24%; 2.25 min: A = 76%, B = 24%; 6 min: A = 66%, B = 34%; 10 min: A = 63%, B = 37%; 20 min: A = 5.3%, B = 94.7%; 23 min: A = 5.3%, B = 94.7%.

General Procedure for the Reaction Calorimetry Evaluation. 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 400 rpm) mixture of bromobenzene (50.1 mmol), styrene (1.2 equiv), and base (1.2 equiv) in solvent (40 mL) was heated to 77 °C (or 67 °C for reactions carried out at 70 °C). The virtual volume was recorded, followed by calibration to determine heat transfer coefficient (u) and heat capacity (cpr) with 15 min waiting time and ΔT_r 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 (or 70 °C) until complete conversion was observed by GC or HPLC analysis. The virtual volume was recorded, and a second calibration was performed to determine u and cpr with 15 min waiting time and ΔT_r 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 Q2500 DSC from TA Instruments was used for the constant heating rate tests in this study. A ~2 mg postreaction mixture sample was loaded into a gold-plated high-pressure crucible with nitrogen as the headspace. The sealed crucible was loaded onto the DSC and scanned from 0 to 400 °C at a heating rate of 10 °C/min. Upon completion of the scan, the sample was allowed to cool and rescanned at the same heating rate over the same temperature range. The sample container was weighed before and after the DSC tests to ensure sample mass loss is <10%.

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Notes

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REFERENCES

(1) (a) Mizoroki, T.; Mori, K.; Ozaki, A. Arylation of Olefin with Aryl Iodide Catalyzed by Palladium. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581. (b) Mori, K.; Mizoroki, T.; Ozaki, A. Arylation of Olefin with Iodobenzene Catalyzed by Palladium. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1505.

(2) (a) Heck, R. F. Acylation, methylation, and carboxyalkylation of olefins by Group VIII metal derivatives. *J. Am. Chem. Soc.* **1968**, *90*, 5518. (b) Dieck, H. A.; Heck, R. F. Organophosphinepalladium

complexes as catalysts for vinylic hydrogen substitution reactions. *J. Am. Chem. Soc.* **1974**, *96*, 1133.

(3) (a) de Meijere, A.; Meyer, F. E. Fine Feathers Make Fine Birds: The Heck Reaction in Modern Garb. *Angew. Chem., Int. Ed. Engl.* **1995**, *33*, 2379. (b) Whitcombe, N. J.; Hii, K.; Gibson, S. Advances in the Heck chemistry of aryl bromides and chlorides. *Tetrahedron* **2001**, *57*, 7449. (c) Littke, A.; Fu, G. Palladium-Catalyzed Coupling Reactions of Aryl Chlorides. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176. (d) Jagtap, S. Heck Reaction—State of the Art. *Catalysts* **2017**, *7*, 267.

(4) Beletskaya, I. P.; Cheprakov, A. V. The Heck Reaction as a Sharpening Stone of Palladium Catalysis. *Chem. Rev.* **2000**, *100*, 3009.

(5) Jutand, A.; Mosleh, A. Rate and Mechanism of Oxidative Addition of Aryl Triflates to Zerovalent Palladium Complexes. Evidence for the Formation of Cationic (σ-Aryl)palladium Complexes. *Organometallics* **1995**, *14*, 1810.

(6) Fu, X.; Zhang, S.; Yin, J.; McAllister, T. L.; Jiang, S. A.; Tann, C.-H.; Thiruvengadam, T. K.; Zhang, F. First examples of a tosylate in the palladium-catalyzed Heck cross coupling reaction. *Tetrahedron Lett.* **2002**, *43*, 573.

(7) Hansen, A. L.; Skrydstrup, T. Regioselective Heck Couplings of α,β-Unsaturated Tosylates and Mesylates with Electron-Rich Olefins. *Org. Lett.* **2005**, *7*, 5585.

(8) Kikukawa, K.; Matsuda, T. Reaction of diazonium salts with transition metals, I. Arylation of olefins with arenediazonium salts catalyzed by zero valent palladium. *Chem. Lett.* **1977**, *6*, 159.

(9) (a) Ozawa, F.; Kubo, A.; Hayashi, T. Catalytic asymmetric arylation of 2,3-dihydrofuran with aryl triflates. *J. Am. Chem. Soc.* **1991**, *113*, 1417. (b) Dounay, A. B.; Overman, L. E. The asymmetric intramolecular Heck reaction in natural product total synthesis. *Chem. Rev.* **2003**, *103*, 2945. (c) McCartney, D.; Guiry, P. J. The asymmetric Heck and related reactions. *Chem. Soc. Rev.* **2011**, *40*, 5122.

(10) Colacot, T. J. The 2010 Nobel Prize in Chemistry: Palladium-Catalysed Cross-Coupling. *Platinum Met. Rev.* **2011**, *55*, 84.

(11) (a) Beller, M.; Zapf, A.; Mägerlein, W. Efficient Synthesis of Fine Chemicals and Organic Building Blocks Applying Palladium-Catalyzed Coupling Reactions. *Chem. Eng. Technol.* **2001**, *24*, 575. (b) de Vries, J. G. The Heck reaction in the production of fine chemicals. *Can. J. Chem.* **2001**, *79*, 1086. (c) Prashad, M. Palladium-Catalyzed Heck Arylations in the Synthesis of Active Pharmaceutical Ingredients. *Top. Organomet. Chem.* **2004**, *6*, 181. (d) Farina, V. High-Turnover Palladium Catalysts in Cross-Coupling and Heck Chemistry: A Critical Overview. *Adv. Synth. Catal.* **2004**, *346*, 1553. (e) Hansen, M. M.; Kallman, N. J.; Koenig, T. M.; Linder, R. J.; Richey, R. N.; Rizzo, J. R.; Ward, J. A.; Yu, H.; Zhang, T. Y.; Mitchell, D. Double Heck Route to a Dibenzoxepine and Convergent Suzuki Cross-Coupling Strategy for the Synthesis of an MR Antagonist. *Org. Process Res. Dev.* **2017**, *21*, 208.

(12) (a) Yang, Q.; Ulysse, L. G.; McLaws, M. D.; Keefe, D. K.; Haney, B. P.; Guzzo, P. R.; Liu, S. Initial Process Development and Scale-Up of the Synthesis of a triple reuptake inhibitor ALB109780. *Org. Process Res. Dev.* **2012**, *16*, 499. (b) Venkatraman, S.; Tweedie, S.; McLaws, M.; Lathbury, D. Continuous Flow Chemistry of Metal Mediated Carboxylation and α-Arylation Reactions. *ACS Symp. Ser.* **2014**, *1181*, 441.

(13) (a) Brown Ripin, D. H.; Bourassa, D. E.; Brandt, T.; Castaldi, M. J.; Frost, H. N.; Hawkins, J.; Johnson, P. J.; Massett, S. S.; Neumann, K.; Phillips, J.; Raggon, J. W.; Rose, P. R.; Rutherford, J. L.; Sitter, B.; Stewart, A. M., III; Vetelino, M. G.; Wei, L. Evaluation of Kilogram-Scale Sonagashira, Suzuki, and Heck Coupling Routes to Oncology Candidate CP-724,714. *Org. Process Res. Dev.* **2005**, *9*, 440. (b) Houpis, I. N.; Shilds, D.; Nettekoven, U.; Schnyder, A.; Bappert, E.; Weerts, K.; Canters, M.; Vermuelen, W. Utilization of Sequential Palladium-Catalyzed Cross-Coupling Reactions in the Stereospecific Synthesis of Trisubstituted Olefins. *Org. Process Res. Dev.* **2009**, *13*, 598.

(14) Yang, Q.; Canturk, B.; Gray, K.; McCusker, E.; Sheng, M.; Li, F. Evaluation of Potential Safety Hazards Associated with the Suzuki—Miyaura Cross-Coupling of Aryl Bromides with Vinylboron Species. *Org. Process Res. Dev.* **2018**, *22*, 351.

(15) Hunt, A. R.; Stewart, S. K.; Whiting, A. Heck versus Suzuki palladium catalysed cross-coupling of a vinylboronate ester with aryl halides. *Tetrahedron Lett.* **1993**, *34*, 3599.

(16) (a) Camp, D.; Matthews, C. F.; Neville, S. T.; Rouns, M.; Scott, R. W.; Truong, Y. Development of a Synthetic Process towards a Hepatitis C Polymerase Inhibitor. *Org. Process Res. Dev.* **2006**, *10*, 814. (b) Schils, D.; Stappers, F.; Solberghe, G.; Heck, R. V.; Coppens, M.; Van den Heuvel, D.; Van der Donck, P.; Callewaert, T.; Meeussen, F.; De Bie, E.; Eersels, K.; Schouteden, E. Ligandless Heck Coupling between a Halogenated Aniline and Acrylonitrile Catalyzed by Pd/C: Development and Optimization of an Industrial-Scale Heck Process for the Production of a Pharmaceutical Intermediate. *Org. Process Res. Dev.* **2008**, *12*, 530.

(17) Bossé, F.; Das, P.; Belfiore, L. A. Annealing Effects on the Solid State Properties of Transition-Metal Coordination Complexes and Networks Based on Diene Polymers with Palladium Chloride. *J. Polym. Sci., Part B: Polym. Phys.* **1996**, *34*, 909.

(18) Blackmond, D. G.; Rosner, R.; Pfaltz, A. Comprehensive Kinetic Screening of Catalysts Using Reaction Calorimetry. *Org. Process Res. Dev.* **1999**, *3*, 275.

(19) The choice of amine can dramatically affect the fate of the reaction. For additional information, see: Singer, R. A. Commercial Development of Axitinib (AG-013736): Optimization of a Convergent Pd-Catalyzed Coupling Assembly and Solid Form Challenges. *Transition Metal-Catalyzed Couplings in Industry, Case Studies from the Pharmaceutical Industry*; Magano, J., Dunetz, J., Eds.; Wiley: 2013, p 165.

(20) While this addition sequence is optimal for our calorimetry studies, it will cause accumulation of reactive chemicals and thus should be avoided for scale-up.

(21) (a) Bollyn, M. DMSO Can Be More than a Solvent: Thermal Analysis of Its Chemical Interactions with Certain Chemicals at Different Process Stages. *Org. Process Res. Dev.* **2006**, *10*, 1299. (b) Wang, Z.; Richter, S. M.; Gates, B. D.; Grieme, T. A. Safety Concerns in a Pharmaceutical Manufacturing Process Using Dimethyl Sulfoxide (DMSO) as a Solvent. *Org. Process Res. Dev.* **2012**, *16*, 1994. (c) Wang, Z.; Richter, S. M.; Bellettini, J. R.; Pu, Y. M.; Hill, D. R. Safe Scale-Up of Pharmaceutical Manufacturing Processes with Dimethyl Sulfoxide as the Solvent and a Reactant or a Byproduct. *Org. Process Res. Dev.* **2014**, *18*, 1836. (d) Yang, Q.; Cabrera, P. J.; Li, X.; Sheng, M.; Wang, N. X. Safety Evaluation of the Copper-Mediated Cross-Coupling of 2-Bromopyridines with Ethyl Bromodifluoroacetate. *Org. Process Res. Dev.* **2018**, *22*, 1441.

(22) Wang, Z.; Richter, S. M.; Rozema, M. J.; Schellinger, A.; Smith, K.; Napolitano, J. G. Potential Safety Hazards Associated with Using Acetonitrile and a Strong Aqueous Base. *Org. Process Res. Dev.* **2017**, *21*, 1501.

(23) Butters, M.; Catterick, D.; Craig, A.; Curzons, A.; Dale, D.; Gillmore, A.; Green, S. P.; Marziano, I.; Sherlock, J.-P.; White, W. Critical Assessment of Pharmaceutical Processes-A Rationale for Changing the Synthetic Route. *Chem. Rev.* **2006**, *106*, 3002.

(24) Quantitative GC analysis was performed using acetophenone as an internal standard.

(25) (a) Curtiss, L. A.; Redfern, P. C.; Frurip, D. J. Theoretical Methods for Computing Enthalpies of Formation of Gaseous Compounds. *Rev. Comput. Chem.* **2007**, *15*, 147. (b) Boese, A. D.; Oren, M.; Atasoylu, O.; Martin, J. M. L. W3 theory: Robust computational thermochemistry in the kJ/mol accuracy range. *J. Chem. Phys.* **2004**, *120*, 4129.

(26) (a) Ryberg, P. Development of a Highly Efficient Regio- and Stereoselective Heck Reaction for the Large-Scale Manufacture of an $\alpha 4\beta 2$ NNR Agonist. *Transition Metal-Catalyzed Couplings in Industry, Case Studies from the Pharmaceutical Industry*; Magano, J., Dunetz, J., Eds.; Wiley: 2013, p 147. (b) Lipshutz, B. H. Applying the Hydrophobic Effect to Transition Metal-Catalyzed Couplings in Water at Room Temperature. *Transition Metal-Catalyzed Couplings in Industry, Case Studies from the Pharmaceutical Industry*; Magano, J., Dunetz, J., Eds.; Wiley: 2013, p 299.

(27) (a) Fitton, P.; Rick, E. A. The addition of aryl halides to tetrakis(triphenylphosphine)palladium(0). *J. Organomet. Chem.* **1971**, *28*, 287. (b) Knowles, J. P.; Whiting, A. The Heck−Mizoroki cross-coupling reaction: a mechanistic perspective. *Org. Biomol. Chem.* **2007**, *5*, 31. (c) Jutand, A. Mechanisms of the Mizoroki−Heck Reaction. *Mizoroki−Heck Reaction* **2009**, 1.

(28) Amatore, C.; Godin, B.; Jutand, A.; Lemaître, F. Rate and Mechanism of the Heck Reactions of Arylpalladium Complexes Ligated by a Bidentate P,P Ligand with an Electron-Rich Alkene (Isobutyl Vinyl Ether). *Organometallics* **2007**, *26*, 1757.

(29) (a) Liu, S.; Fukuyama, T.; Sato, M.; Ryu, I. Continuous Microflow Synthesis of Butyl Cinnamate by a Mizoroki−Heck Reaction Using a Low-Viscosity Ionic Liquid as the Recycling Reaction Medium. *Org. Process Res. Dev.* **2004**, *8*, 477. (b) Nikbin, N.; Ladlow, M.; Ley, S. V. Continuous Flow Ligand-Free Heck Reactions Using Monolithic Pd [0] Nanoparticles. *Org. Process Res. Dev.* **2007**, *11*, 458. (c) Fan, X.; Manchon, M. G.; Wilson, K.; Tennison, S.; Kozynchenko, A.; Lapkin, A. A.; Plucinski, P. K. Coupling of Heck and hydrogenation reactions in a continuous compact reactor. *J. Catal.* **2009**, *267*, 114. (d) Konda, V.; Rydfjord, J.; Sävmarker, J.; Larhed, M. Safe Palladium-Catalyzed Cross-Couplings with Microwave Heating Using Continuous-Flow Silicon Carbide Reactors. *Org. Process Res. Dev.* **2014**, *18*, 1413. (e) Cortés-Borda, D.; Kutonova, K. V.; Jamet, C.; Trusova, M. E.; Zammattio, F.; Truchet, C.; Rodriguez-Zubiri, M.; Felpin, F. Optimizing the Heck−Matsuda Reaction in Flow with a Constraint-Adapted Direct Search Algorithm. *Org. Process Res. Dev.* **2016**, *20*, 1979.

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