Potential Safety Hazards Associated with Pd-Catalyzed Cross-Coupling Reactions

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Lilly

Why be Concerned with Process Safety?

Process Safety Begins in the Lab!

Why?

- Most reactive chemical incidents occur in research laboratories.
- Most incidents involving a chemical reaction could have been prevented, if the process hazards were understood beforehand.

Solution

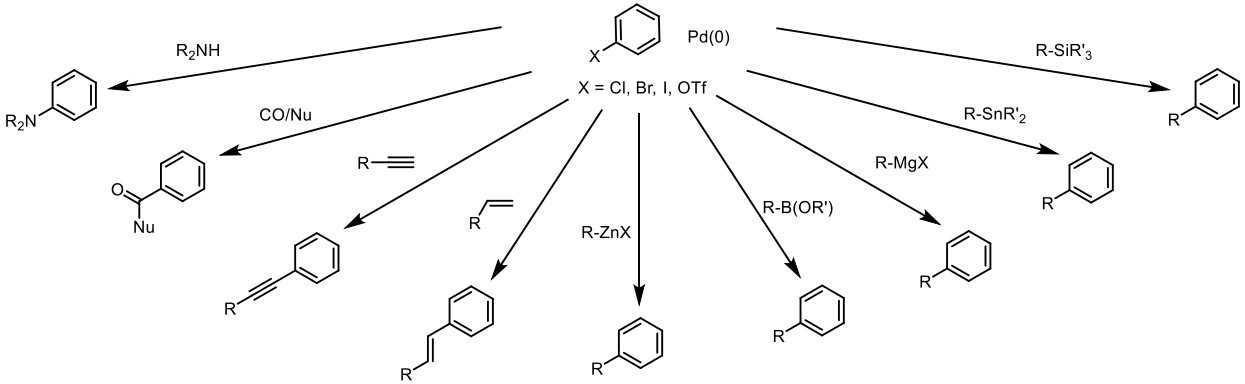
- Process safety should be considered early to avoid surprises during scale-up. Early identification of significant exotherms should be used to trigger the assessment of thermal hazard risks related to the process before scale-up.
- Personal safety should be considered always. A safe, well-controlled working environment in both the lab and plant is key to avoiding incidents during synthesis, safety studies and manufacturing.

The 12 Principles of Green Chemistry

- Prevent Waste
- Design Safer Chemicals and Products
- Design Less Hazardous Chemical Syntheses
- Use Safer Solvents/ Reaction Conditions
- Increase Energy Efficiency
- Use Renewable Feedstocks
- Design Chemicals and Products that Degrade After Use
- Minimize the Potential for Accidents
- Analyze in Real Time to Prevent Pollution
- Use Catalysts, Not Stoichiometric Reagents
- Maximize Atom Economy
- Avoid Chemical Derivatives

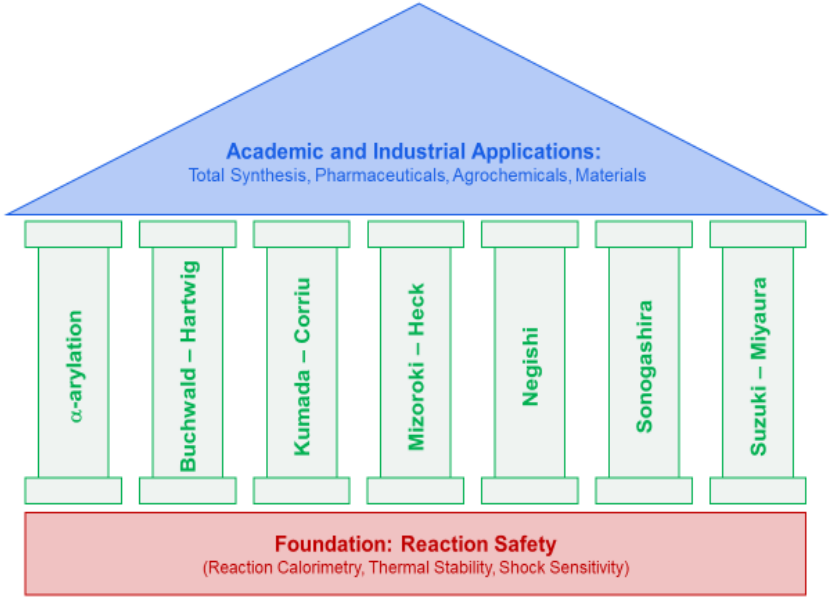
Courtesy of Mettler Toledo

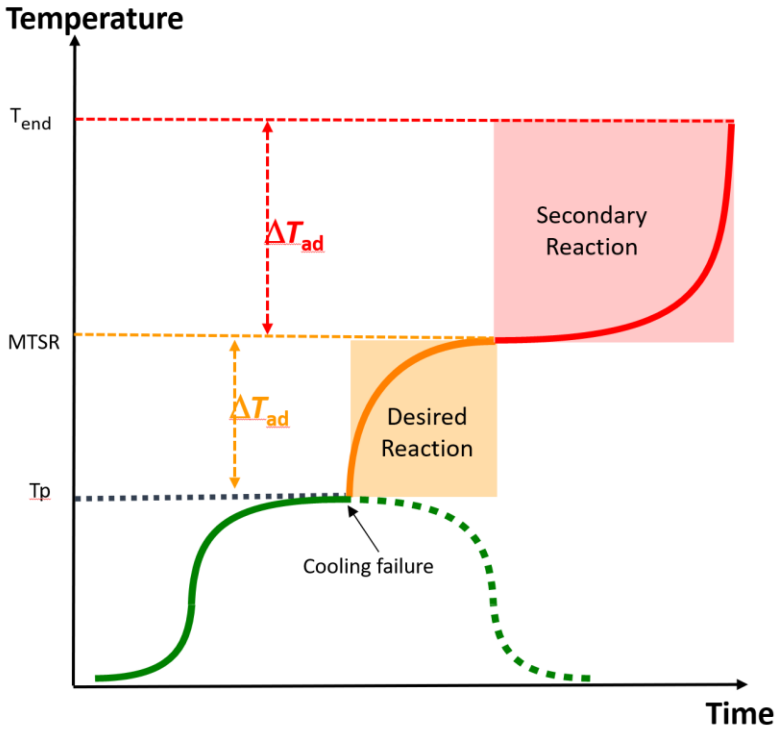
Pd-Catalyzed Cross-Couplings



- This class of reactions are exothermic.
- These reactions are frequently performed in an "*all in*" fashion that provides poor control over exotherm.
- The potential safety hazards associated with Pd-catalyzed cross-coupling reactions may remain largely underappreciated by many synthetic chemists.

Pd-Catalyzed Cross-Couplings Safety Hazards Examples

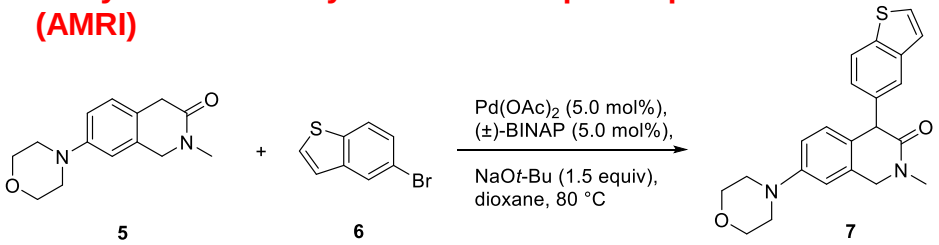


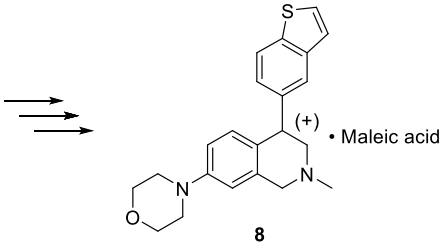


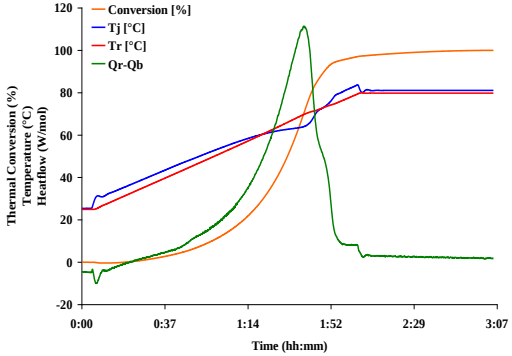
Org. Process Res. Dev. **2019**, *23*, 2608; *Stoessel, F. Basel, CH, WILEY-VCH Verlag GmbH & Co. KGaA*, 2008.

α-Arylation Cross-Coupling

1. α-Arylation in the synthesis of a triple reuptake inhibitor (AMRI)

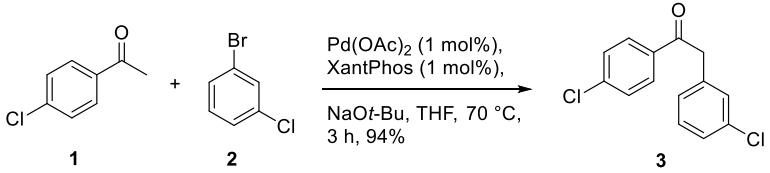


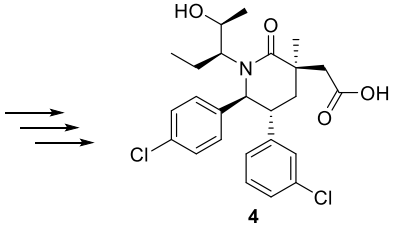




- A delayed exotherm was observed.
- ΔH = –221 kJ/mol, ΔT_{ad} = 62.0 °C, MTSR = 142.0 °C >> T_b!

2. α-Arylation in the synthesis of a MDM2/p53 inhibitor (Amgen)



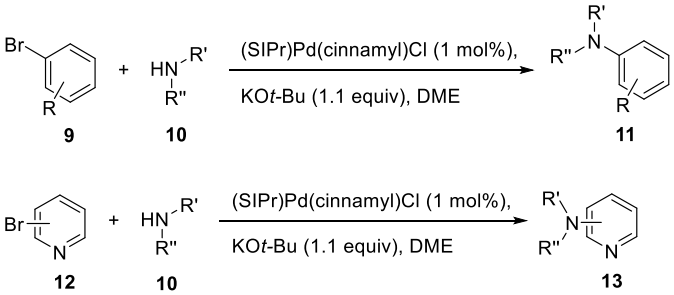


- Significant exotherms were observed upon heating during the scale-up of this reaction to 50 g and 200 g of **1**.
- The authors warned that proper engineering controls should be in place to control the exotherm before scaling up this reaction.

Org. Process Res. Dev. **2012**, *16*, 499; *J. Am. Chem. Soc.* **2012**, *134*, 12855.

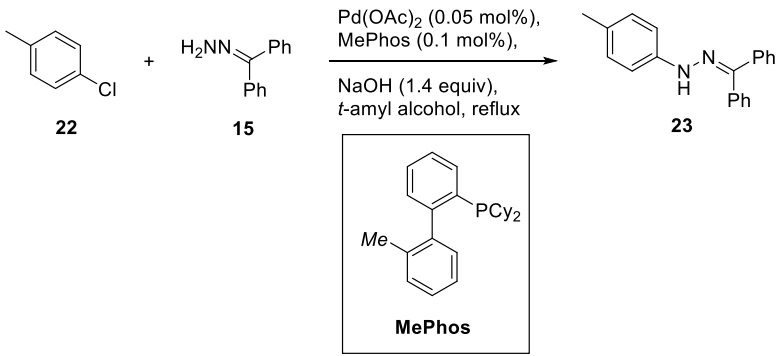
Buchwald–Hartwig Amination

1. Buchwald–Hartwig amination using (NHC)Pd(R-allyl)Cl



- Significant exotherms were observed during the development of a series of reactions utilizing (NHC)Pd(R-allyl)Cl catalysts.
- The researchers attributed this behavior to the exothermicity of the coupling reaction associated with the generation of the catalytically active species.
- Intense exotherm was also observed during the reactions involving the cross-coupling of 3-bromopyridine with morpholine or piperidine.

2. Buchwald–Hartwig amination in arylhydrazones synthesis (Rhodia)

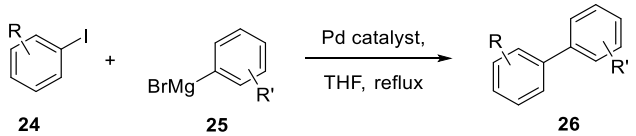


- RC1 evaluation of this reaction revealed a significant exotherm with a ΔH of –409 kJ/mol, which could potentially evaporate *ca.* 78% of the solvent.
- The researchers redesigned the process to prevent build-up of thermal potential by controlled addition of benzophenone hydrazine.

J. Am. Chem. Soc. **2006**, *128*, 4101; *Chem. Eur. J.* **2006**, *12*, 5142; *Org. Process Res. Dev.* **2004**, *8*, 1065; *Adv. Synth. Catal.* **2006**, *348*, 23.

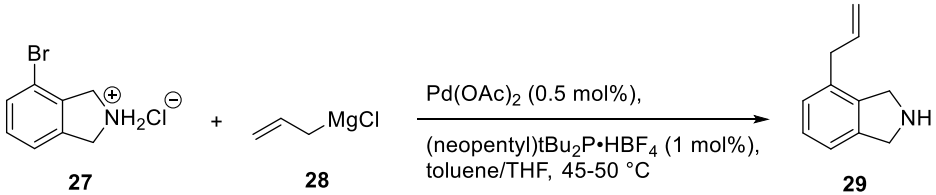
Kumada–Corriu Cross-Coupling

1. Kumada–Corriu cross-coupling of ArI with ArMgBr



- "An exothermic reaction occurred with deposition of magnesium salts" upon the addition of a solution of Grignard reagent to a warm solution of ArI and 0.1 mol% of $PdCl_2$ in THF.
- An exotherm was also observed in a control experiment in which a THF solution of Grignard reagent was added to a suspension of $PdCl_2$ in THF at reflux, along with the precipitation of black solids that the authors believed to be palladium metal.

2. Kumada–Corriu cross-coupling for 4-allylisoindoline (Merck)

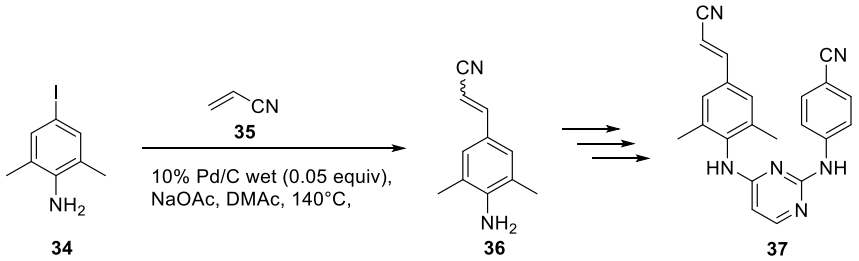


- An exotherm and off-gassing of propene were observed during the addition of a solution of allylmagnesium chloride (**28**) in THF to a mixture of **27**, 0.5 mol% of $Pd(OAc)_2$ and 1 mol% of (neopentyl)(*t*-Bu)$_2$P•HBF_4 in toluene.
- The neutralization reaction contributed to this exothermic behavior, but it is reasonable to postulate that the exotherm was also partially caused by the Kumada–Corriu cross-coupling reaction.

J. Organomet. Chem. **1977**, *125*, 281; *Org. Process Res. Dev.* **2011**, *15*, 158.

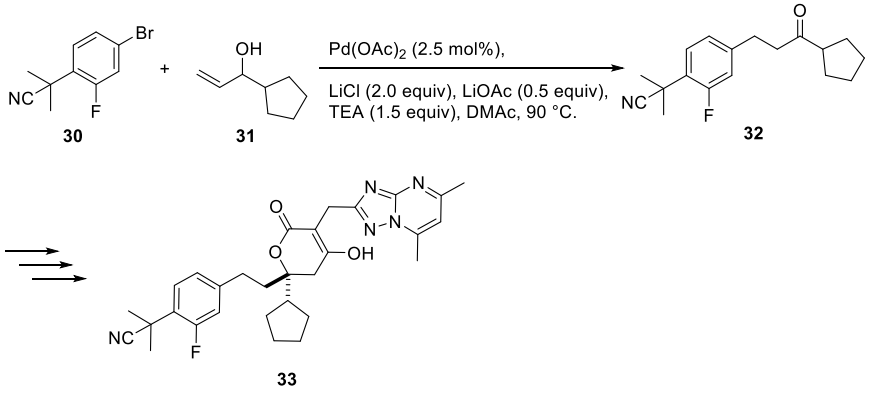
Mizoroki–Heck Cross-Coupling

1. Mizoroki–Heck cross-coupling in the synthesis of rilpivirine (J&J)



- The temperature spiked by 40 °C over 1 min when a mixture of **34**, **35**, 10 wt% Pd/C (wet, 0.05 eq), and NaOAc in DMAc was heated to 110 °C.
- RC1 revealed a ΔH of –191 kJ/mol, posing safety hazards for scale-up.
- A control strategy was developed to dose a solution of both coupling partners, **34** and **35**, in DMAc to a pre-heated suspension (140 °C) of Pd/C and NaOAc in DMAc.
- This process was safely performed in a 6000-L vessel affording 332.5 kg of the desired product **36** in 81% yield.

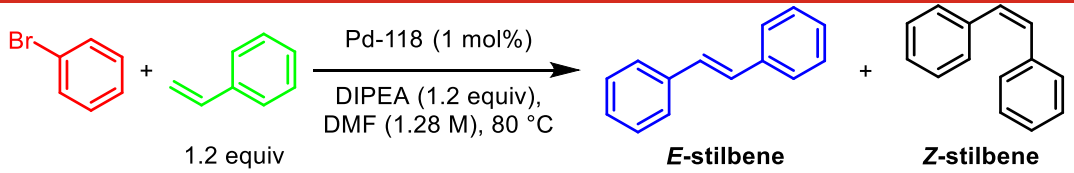
2. Mizoroki–Heck in a Hepatitis C Polymerase Inhibitor (Pfizer)

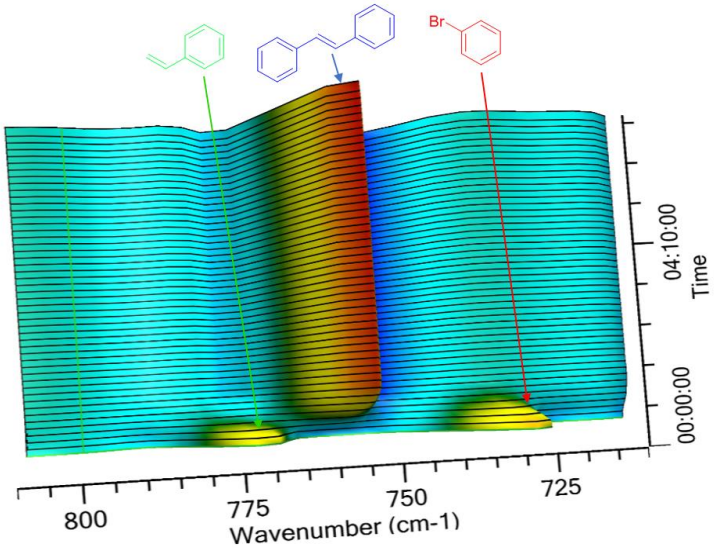


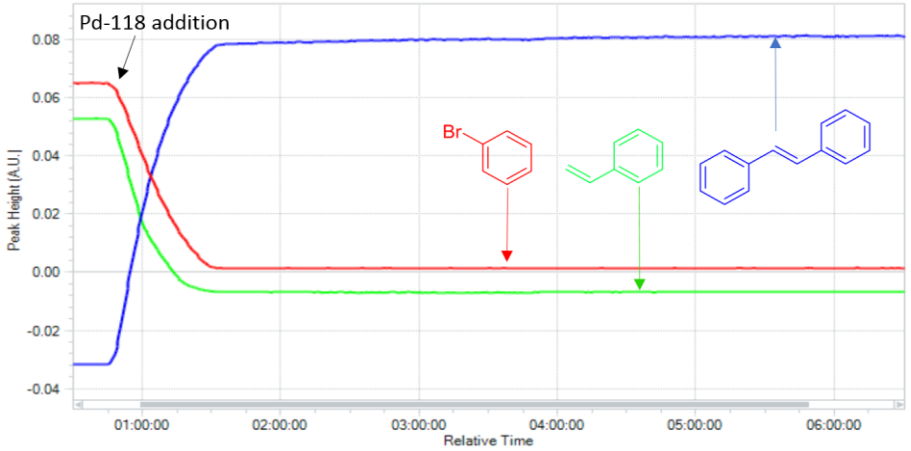
- RC1 evaluation revealed a ΔT_{ad} of 84 °C, which could potentially overwhelm the ability to remove heat in a pilot-plant setting.
- The safety hazard was mitigated by addition of TEA. LiOAc added to stabilize the catalyst system in the absence of adequate TEA.
- This reaction was safely performed on a 40-kg scale.

Org. Process Res. Dev. **2006**, *10*, 814, *Org. Process Res. Dev.* **2008**, *12*, 530.

Mizoroki–Heck Cross-Coupling



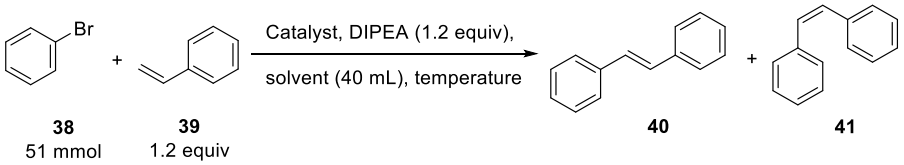


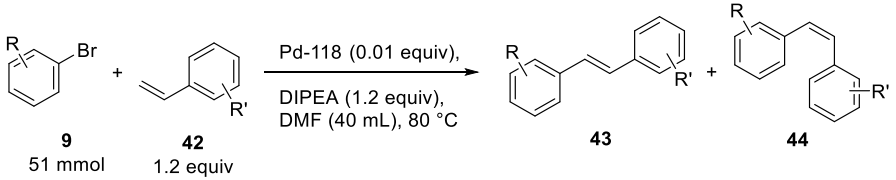


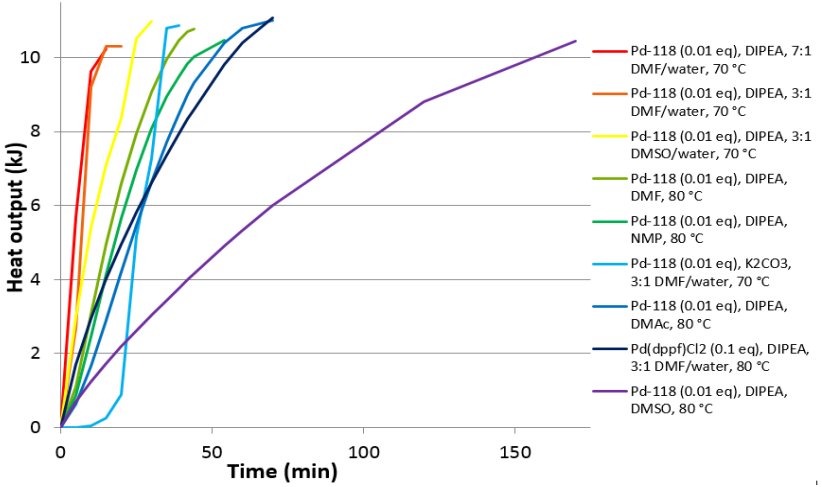
- Product did not decompose over prolonged time under the reaction conditions.

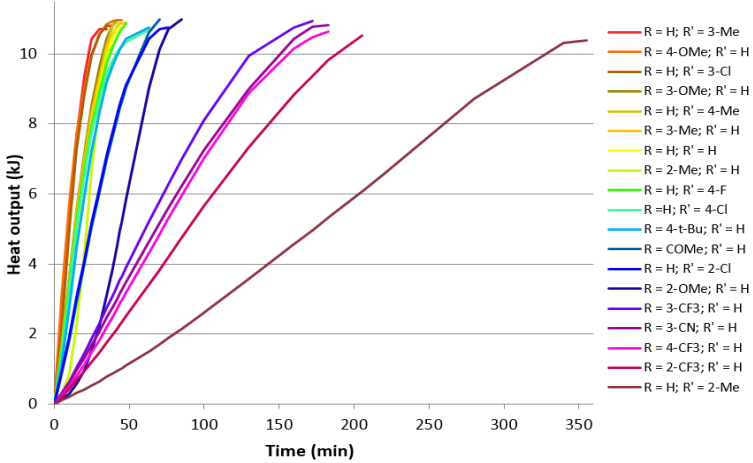
Org. Process Res. Dev. **2019**, *23*, 2148.

Mizoroki–Heck Cross-Coupling



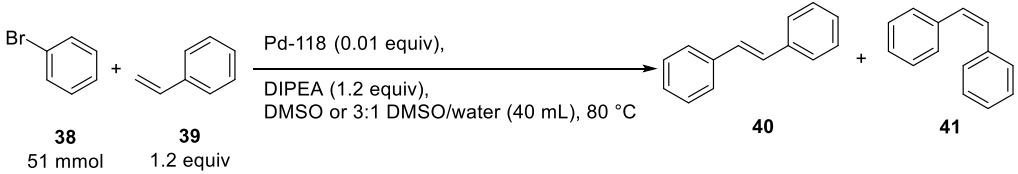


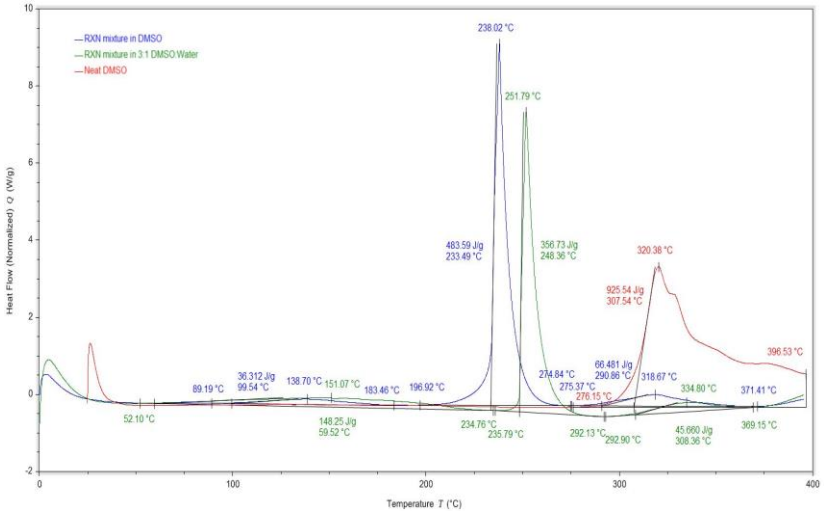




Org. Process Res. Dev. **2019**, *23*, 2148.

DSC Analysis of Reaction Mixture in DMSO





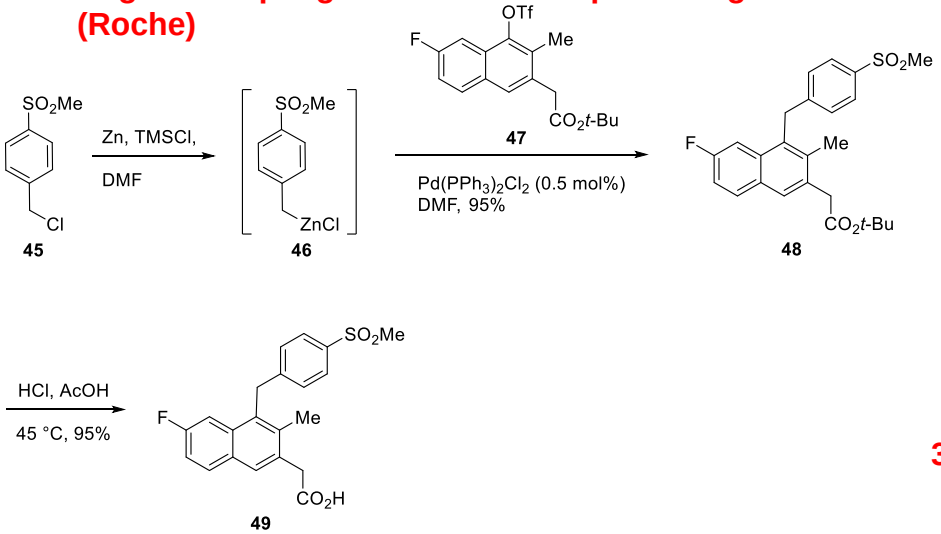
This data suggests that without effective heat removal, the exotherm from the desired reaction of such reactions could potentially trigger the decomposition of DMSO to result in runaway scenarios.

Solvent	Exotherm 1			Exotherm 2			Exotherm 3			Total ΔH (J/g)	Total ΔT_{ad} (°C)
	Onset (°C)	ΔH (J/g)	ΔT_{ad} (°C)	Onset (°C)	ΔH (J/g)	ΔT_{ad} (°C)	Onset (°C)	ΔH (J/g)	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

Org. Process Res. Dev. **2019**, *23*, 2148.

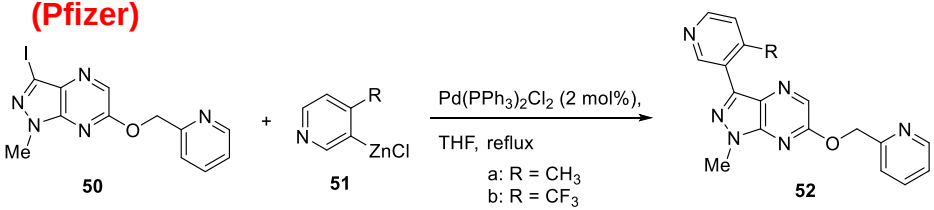
Negishi Cross-Coupling

1. Negishi coupling in a CRTH2 receptor antagonist (Roche)



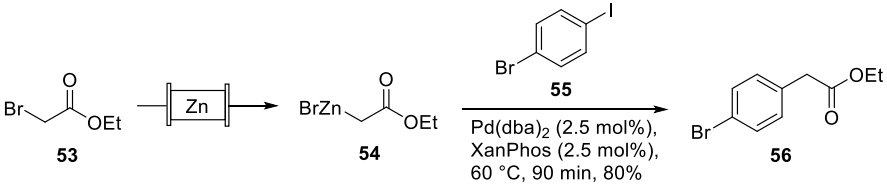
- A ~30 °C temperature rise over ~10 min was observed once the reaction was initiated at 60–65 °C.
- Controlled addition of either **46** or **47** to a preheated reaction mixture, or continuous flow conditions were proposed to control the exotherm.

2. Negishi coupling in mGluR5 negative allosteric modulators (Pfizer)



- A substantial exotherm was observed that brought the reaction temperature from 50 °C to reflux (66 °C) over 5 min despite maintaining the jacket temperature at 55 °C .
- A controlled addition process was developed to avoid accumulation of reactive chemicals.

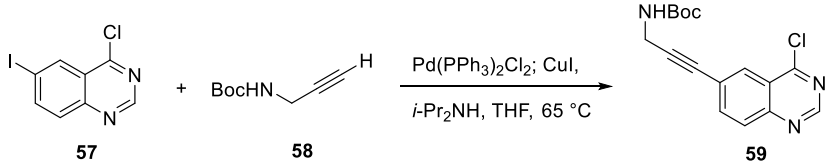
3. On-demand synthesis of organozinc halides

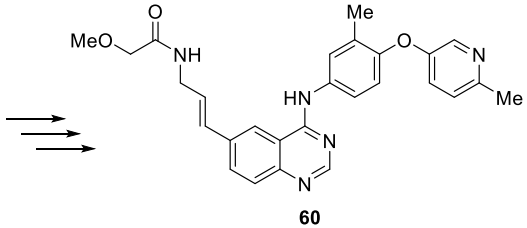


Org. Process Res. Dev. **2013**, *17*, 651; *Org. Process Res. Dev.* **2014**, *18*, 1145; *Nat. Protoc.* **2018**, *13*, 324.

Sonogashira Cross-Coupling

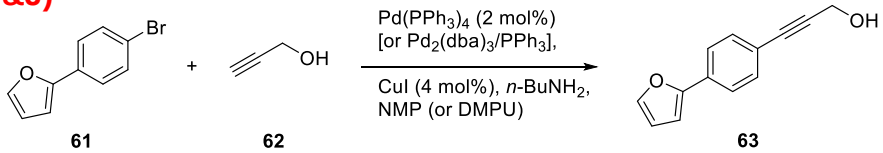
1. Sonogashira cross-coupling in an oncology candidate

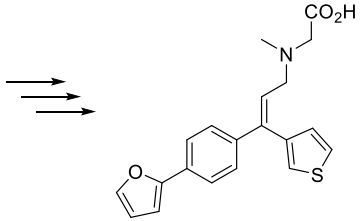




- An exothermic behavior was reported during the Sonogashira cross-coupling of aryl iodide **57** with alkyne **58**.
- The rate of heat generation was controlled by lowering the copper and palladium catalyst loadings.
- The reaction was successfully scaled up to prepare 5.7 kg of **59**.

2. Unexpected exotherm during the coupling of 61 and 62 (J&J)

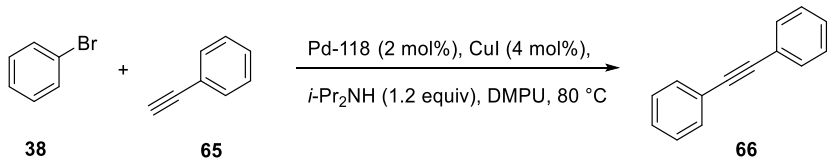


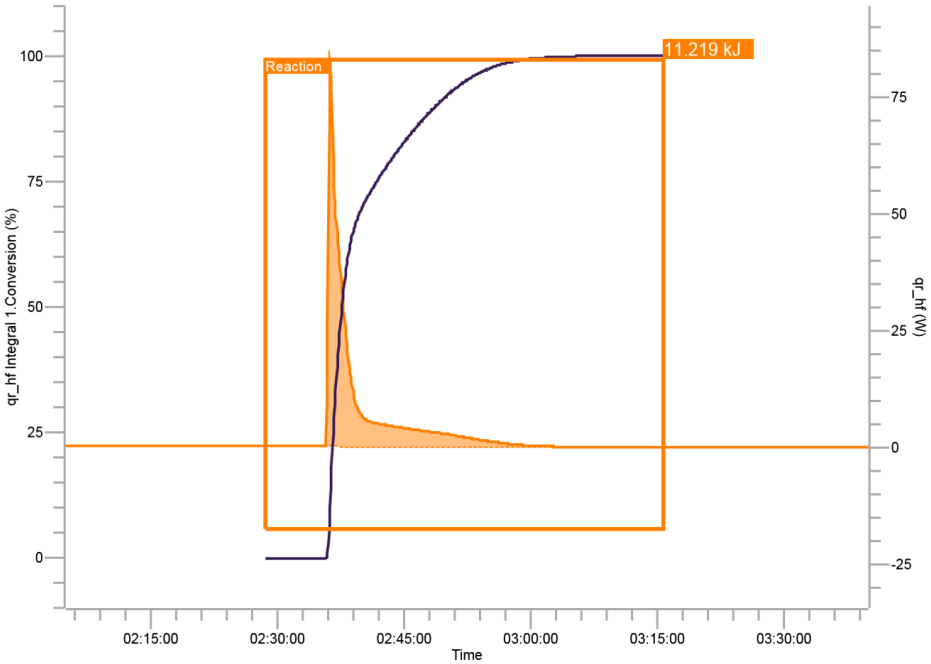


- An abrupt temperature rise to 145 °C was observed, along with visible formation of dark polymeric material when the reaction was heated to 70 °C.
- The authors concluded that the exotherm was probably caused by the polymerization of the propargyl species in the presence of CuI.

Org. Process Res. Dev. **2005**, *9*, 440; *Org. Process Res. Dev.* **2009**, *13*, 598.

Sonogashira Cross-Coupling

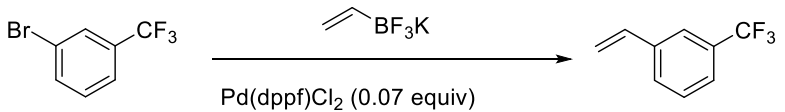




- The thermal profile revealed a significant exotherm upon the addition of the catalysts. The total heat output was calculated to be –217.6 kJ/mol with a ΔT_{ad} of 118.4 °C, resulting in a MTSR of 198.4 °C.
- The reaction rate initiated dramatically upon the addition of the catalysts, reaching 73% heat conversion in 5 min, and slowly decayed to reach complete conversion over a total of 40 min.
- No polymerization or decomposition of the starting materials or product was observed.
- The exotherm poses potential safety hazards when components of the reaction mixture decomposes at a temperature lower than the MTSR.

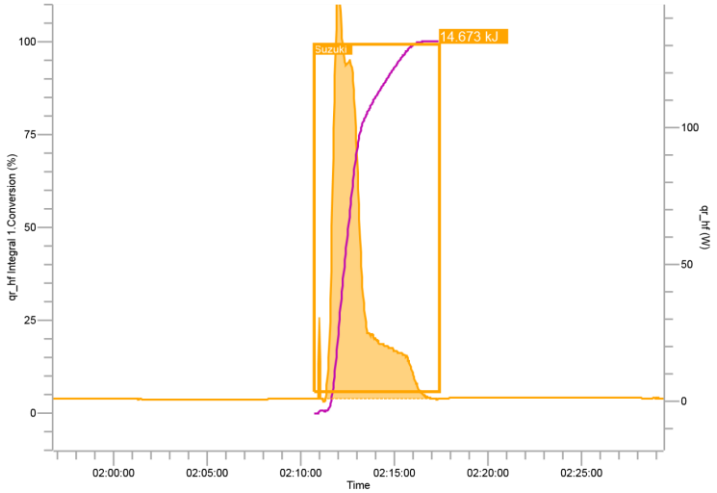
Org. Process Res. Dev. **2019**, *23*, 2608.

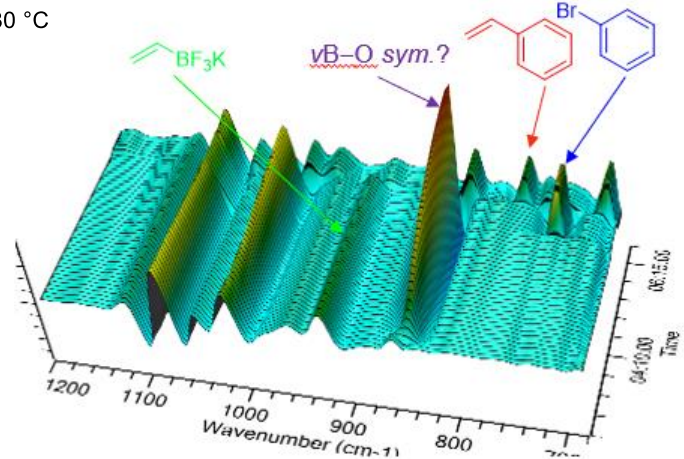
Suzuki–Miyaura Cross-Coupling in DMSO/water



8.38 g, 37.2 mmol

$Pd(dppf)Cl_2$ (0.07 equiv)
K_2CO_3 (2.5 equiv)
DMSO/water (9:1, 42 mL), 80 °C



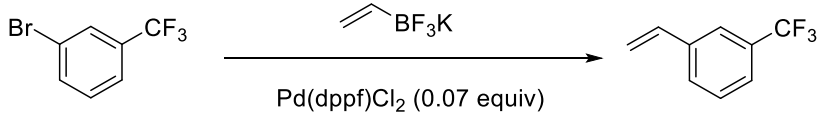


- Heat was released in 5 min
- ΔH = –14.67 kJ (–393.5 kJ/mol), ΔT_{ad} = 141.0 °C
- MTSR = 221.0 °C, >> solvent boiling point and decomposition onset!

- A mixture of potassium vinyltrifluoroborate, bromobenzene, and K_2CO_3 in 9:1 DMF/water was heated at 80 C for ~160 min
- A new peak at ~ 850 cm^{-1} consistent with the B-O symmetric stretching vibration was observed prior to the addition of catalyst.

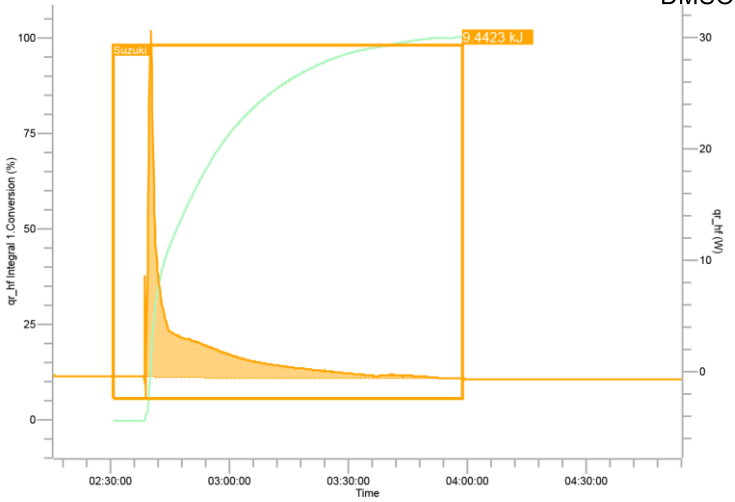
Org. Process Res. Dev. **2018**, *22*, 351.

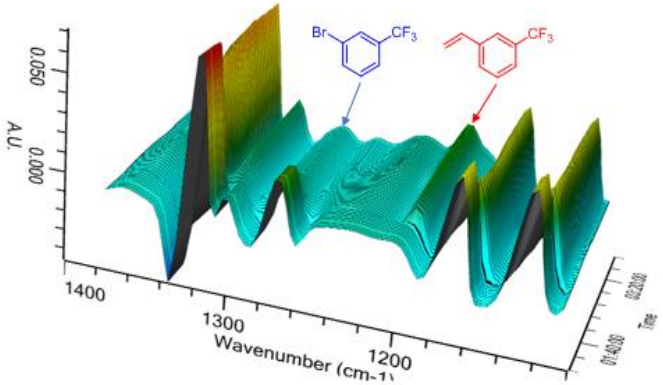
Suzuki–Miyaura Cross-Coupling in Anhydrous DMSO



8.38 g, 37.2 mmol

$Pd(dppf)Cl_2$ (0.07 equiv)
K_2CO_3 (2.5 equiv)
DMSO (42 mL), 80 °C



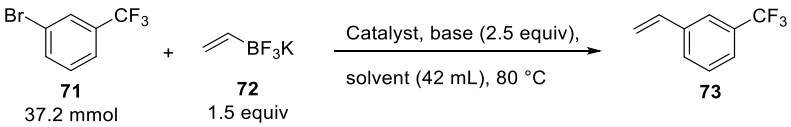


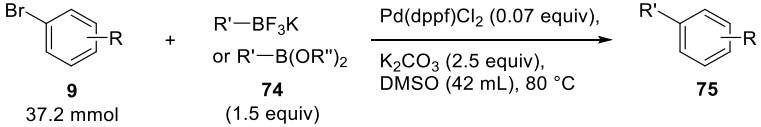
- Reaction achieved completion in 80 min
- ΔH = –9.44 kJ (–253.8 kJ/mol), ΔT_{ad} = 93.8 °C
- Heat profile revealed 73% of the total heat released in the first 20 min

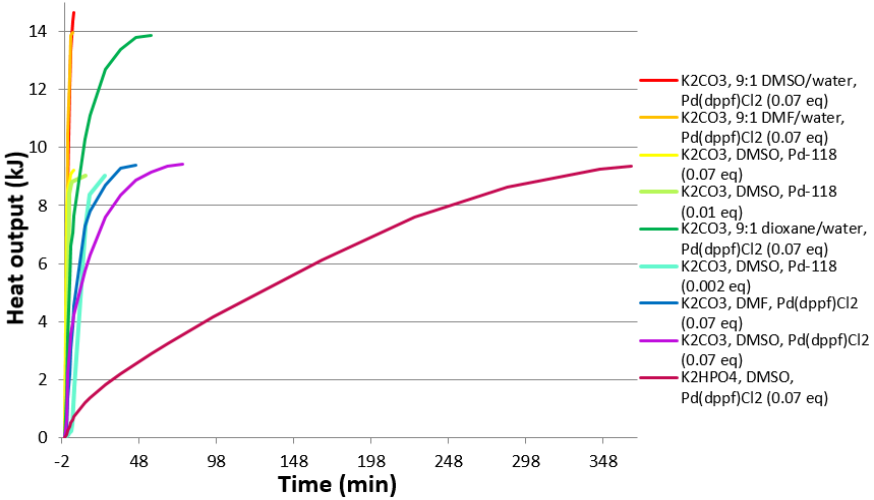
- Quantitative IPC analysis by GC afforded >90% in-pot yield at reaction completion
- The product concentration corresponded well with the heat conversion
- Product did not decompose over prolonged time under the reaction condition

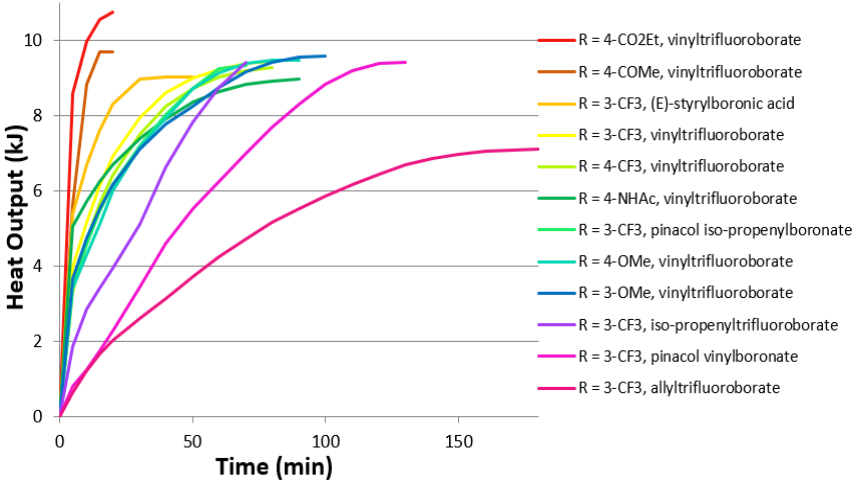
Org. Process Res. Dev. **2018**, *22*, 351.

Suzuki–Miyaura Cross-Coupling



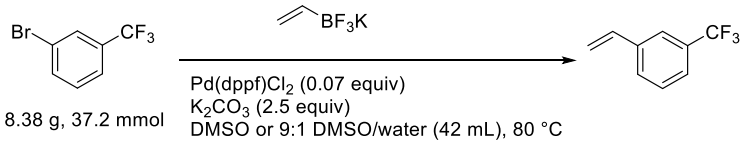




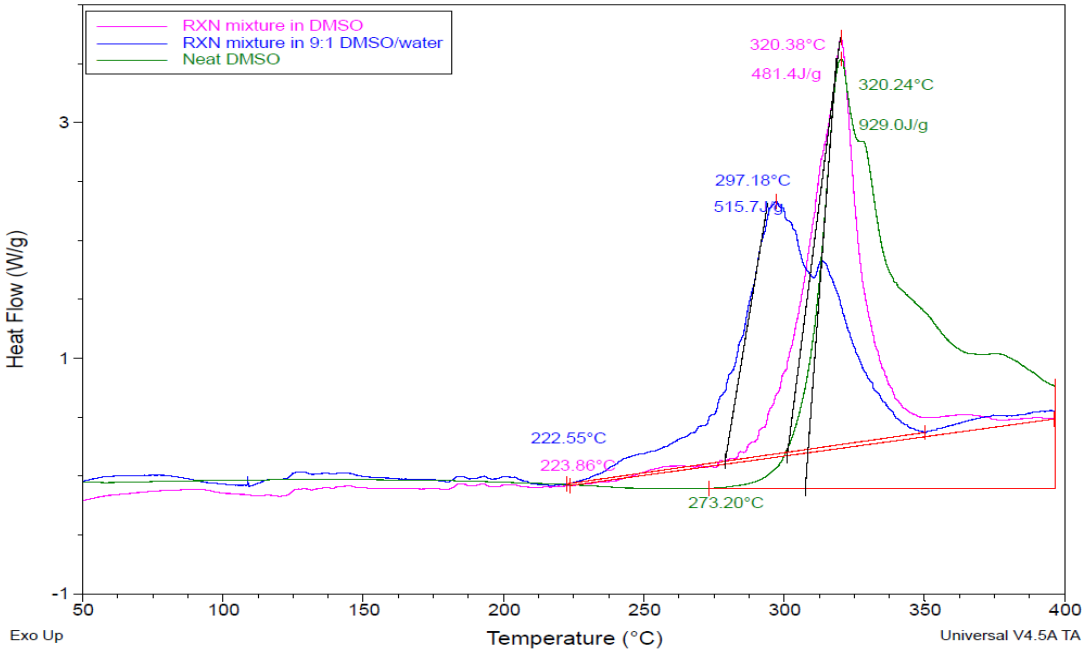


Org. Process Res. Dev. **2018**, *22*, 351.

DSC Analysis of Reaction Mixture in DMSO

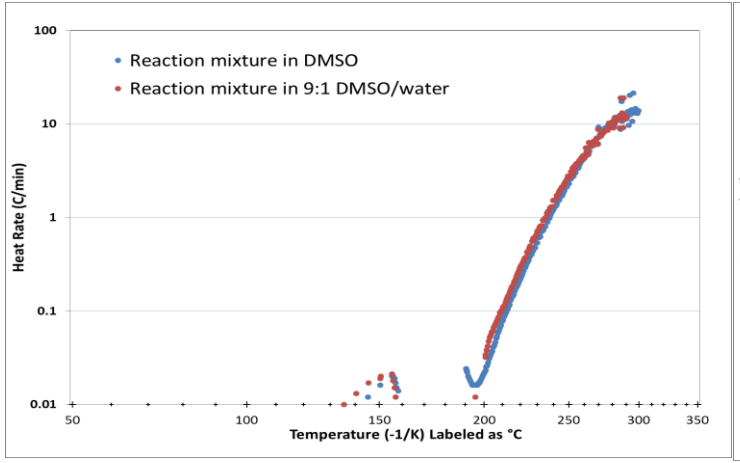


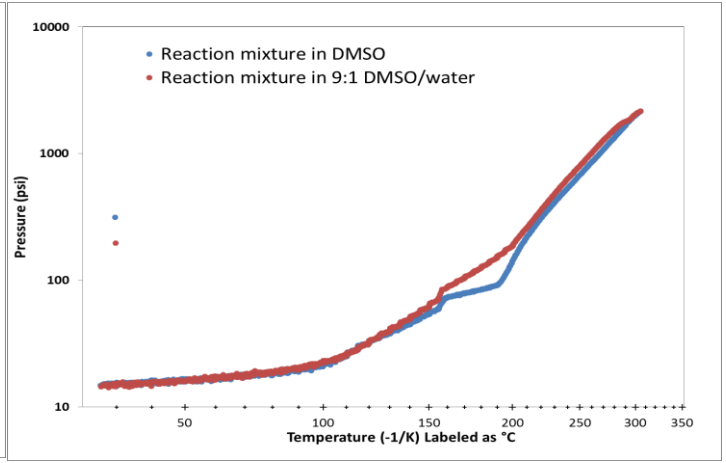
- In both experiments, significantly lower onset temperatures (~223 °C) were detected compared to that of neat DMSO (273 °C)
- In the case of 9:1 DMSO/water, the peak temperature representing the main DMSO decomposition reaction was shifted to a much lower temperature



Org. Process Res. Dev. **2018**, *22*, 351.

ARC Analysis of Reaction Mixture in DMSO



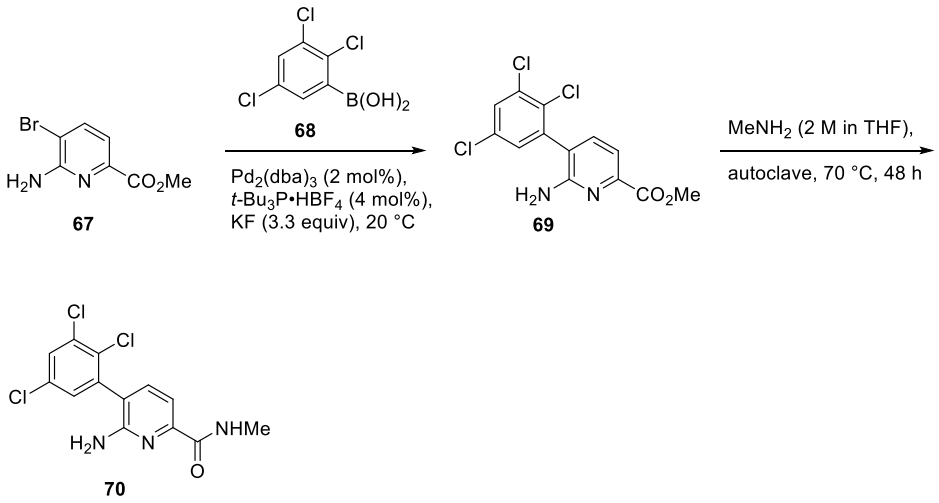


- The small exothermic events at ~150 °C were consistent with the polymerization of the styrene product.
- The major exothermic events were comparable for the reaction mixtures in DMSO and 9:1 DMSO/water (190.7 °C and 196.0 °C), respectively.
- Both ARC tests were terminated because the maximum cut-off pressure was reached and both tests had a significant cool down pressure.
- In case of cooling failure, the exotherm from the desired reaction would most likely trigger thermal decomposition of DMSO to result in a runaway scenario.

Org. Process Res. Dev. **2018**, *22*, 351.

Suzuki–Miyaura Cross-Coupling

Suzuki–Miyaura in a $Na_V1.8$ Sodium Channel Modulator (Pfizer)



- The coupling was exothermic enough that an ice-bath was required to moderate the temperature on 40–50 g scales.
- The safety risk was mitigated by the controlled addition of **68** in THF to a mixture of **67**, $Pd_2(dba)_3$, *t*-Bu_3P•HBF_4, and KF in THF at <30 °C on scale.

Org. Process Res. Dev. **2010**, *14*, 263.

Thermal Hazards of Propargyl Alcohol

ORGANIC PROCESS RESEARCH & DEVELOPMENT
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Thermal Hazards of Using Propargyl Alcohol with Strong Bases

Published as part of the Organic Process Research & Development joint virtual special issue "Process Safety from Bench to Pilot to Plant" in collaboration with ACS Chemical Health & Safety and Journal of Loss Prevention in the Process Industries.

Derek B. Brown,* Ayman D. Allian, and Ying Chen

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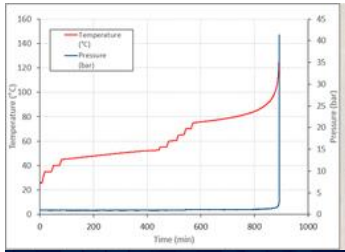
ABSTRACT: Thermal hazard screening of a reaction mixture that involves the use of propargyl alcohol as the reactant/solvent along with potassium hydroxide as catalyst resulted in catastrophic thermal decomposition that ruptured an accelerating rate calorimeter (ARC) test cell. Due to this critical hazard, scale-up of the chemistry was not advisible. In order to enable scale-up, further investigations into solvent and base combinations were carried out. New optimum conditions enabled the synthesis of the desired product in a safe manner. The main purpose of this manuscript is to alert the scientific community to the thermal hazards of this compound.

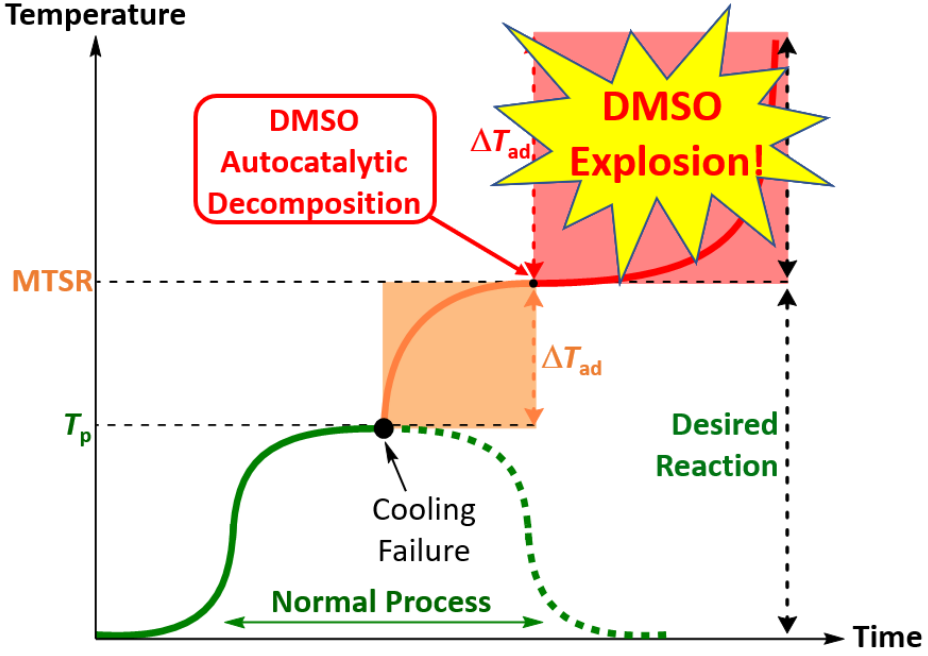
KEYWORDS: *propargyl alcohol, thermal hazards, process safety, DSC, ARC*



Org. Process Res. Dev. **2021**, *25*, 1932.

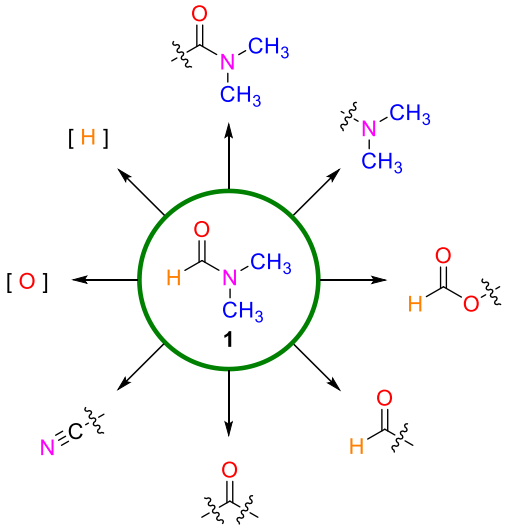
DMSO is Incompatible with a Variety of Substances…

- Bases
- Acids
- Halides
- Metals and metal ions
- Electrophiles
- Oxidants
- Reductants
- **Almost any substances in DMSO will lower the onset temperature and increase the severity of DMSO decomposition.**



Org. Process Res. Dev. **2020**, *24*, 916–939.

N,N-Dimethylformamide (DMF)

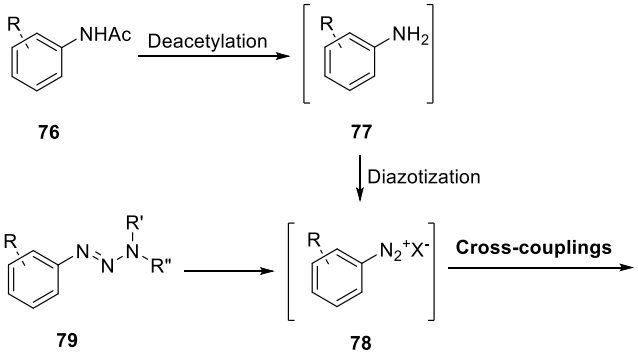


- DMF is widely used as a polar aprotic solvent in synthetic organic chemistry to effect a broad range of chemical reactions
- DMF has found broad applications in a wide variety of chemical transformations
- DMF is incompatible with a wide variety of chemicals such as bases, acids, halogenated reagents, oxidants, and reductants, etc.

Org. Process Res. Dev. **2020**, *24*, 1586–1601.

Thermal and Shock Stability Hazards of Aryldiazonium Salts

- Aryldiazonium salts have been frequently used as coupling partners in a number of Pd-catalyzed cross-coupling reactions.
- Isolation of an aryldiazonium salt as a solid presents significant safety hazards due to the inherent instability of this class of chemicals.
- Generating the aryldiazonium salts *in situ* from anilines is an apparent method to avoid the handling of solid aryldiazonium salts and has been successfully demonstrated on scale over the years.
- Continuous flow technology has been frequently used to prepare aryldiazonium salts *in situ* to mitigate the potential safety risks.
- Acetanilides (acetylated anilines), and aryl triazenes have been used as *in situ* precursors for aryldiazonium salts.
- The potential safety hazards associated with the triazene moiety (>N–N=N–) have been well-documented in the literature.



Org. Process Res. Dev. **2014**, *18*, 1786.

Summary

- The potential safety hazards associated with Pd-catalyzed cross-coupling reactions may remain largely underappreciated by many synthetic chemists.
- The safety risks posed by the highly exothermic nature of this chemistry are magnified because the reactions have been frequently conducted and developed such that all the reagents are added into the reaction vessel prior to heating.
- Aryldiazonium salts present significant safety hazards due to the inherent instability of this class of chemicals.
- Safety hazards associated with the thermal decomposition of DMSO and DMF have been well documented and continuing to be reported.
- The exotherm from the desired Pd-catalyzed cross-coupling may trigger the decomposition of other involved reactive chemicals such as aryldiazonium salts, propargyl species, DMSO, or DMF to result in potential runaway scenarios or other severe incidents.

Please fully evaluate potential safety hazards of your reactions and develop control strategies

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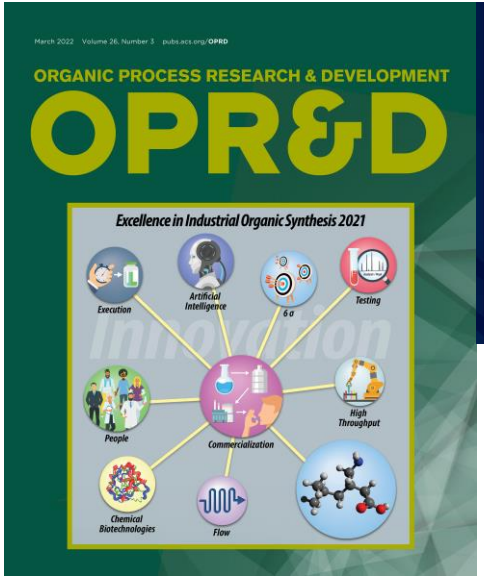

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