

Process Safety Assessment of the Iron-Catalyzed Direct Olefin Diazidation for Expedient Synthesis of Vicinal Primary Diamines

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Supporting Material

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Part I: Iron-Catalyzed Indene Diazidation Reaction and Derivatization

A. General Information

General Procedures. All reactions were performed in oven-dried or flame-dried round-bottom flasks and vials. Stainless steel syringes and cannula were used to transfer air- and moisture-sensitive liquids. Flash chromatography was performed using silica gel 60 (230–400 mesh) from Sigma–Aldrich.

Materials. Commercial reagents were purchased from Sigma–Aldrich, Fluka, EM Science, and Lancaster and used as received. All solvents were used after being freshly distilled unless otherwise noted.

Instrumentation. Proton nuclear magnetic resonance (^1H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Bruker UltraShield–400 (400 MHz). Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to the NMR solvent residual peak (CHCl_3 δ 7.26). Chemical shifts for carbons are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the NMR solvent (CDCl_3 δ 77.0). Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz), and integration. The mass spectroscopic data were obtained at the Georgia State University mass spectrometry facility using a Micromass Platform II single quadrupole instrument.

Part II: Safety Assessment of the Iron-Catalyzed Direct Olefin Diazidation Reaction

D. Introduction to the Stability Data

A reactive chemical hazards assessment is the identification and quantification of dangerous energy release scenarios of a chemical process. This is typically accomplished by calculations and experimental testing.²

In many companies, a risk-consequence based approach is successfully applied to the testing strategy decision process. This approach balances the scale of operations (e.g., one-liter vessel in a R&D lab *vs.* a reactor in a plant) with the overall energy release potential.

A typical testing strategy is to screen first, and then apply. The term "screen" here means to apply less expensive, quicker turnaround, smaller scale, and less experimentally complicated tests. More sophisticated testing will be carried out if necessary.

Differential scanning calorimetry (DSC) is one of the most commonly applied thermal stability testing methodologies in reactive chemical hazards evaluation. In this study, the DSC was applied to assess the potential hazards of reagents, intermediates and final products in the iron-catalyzed olefin diazidation reaction.

It is also important to recognize that the overall energy release potential must contain two dimensions: thermodynamics (how much energy is released) and kinetics (how fast energy is released). The risk of the kinetics involves how "close" the process operates to a condition which would be hazardous. This concept has been explored in great details by Stoessel.^{2f}

Since the diazide compounds are sensitive to impact, we also carried out the Drop Weight Test (DWT) on some of the diazides and assessed any potential hazard during the powder manipulation in the process.

E. Results of the Stability Test

1. Materials and Methods

a. Differential Scanning Calorimetry (DSC)

The DSC measurements were performed in a Mettler 821e using 40 μL aluminum punctured crucibles under nitrogen atmosphere or 60 μL high pressure (gold-plated) steel crucibles under air atmosphere. All measurements were carried out at a heating rate of 5 K/min.

b. Mechanical Sensitivity: Impact

The Fall Hammer Test (Drop Hammer) designed to determine the sensitivity of potentially high explosive compounds was carried out in accordance to the UN Recommendation on the Transport of Dangerous Goods, Manual of Tests and Criteria–Test 3 (a) (ii) as well as EN 13631–4.

The limiting impact energy is determined as the lowest energy at which a flash, flame, or explosion is observed. The test is used to assess the sensitivity of the test material to drop-weight impact.

The determination of the sensitivity to impact stimuli is one of the most important characteristics of energetic materials such as the diazides, which can be heat and shock-sensitive and can explosively decompose with little input of external energy. This determination is necessary to evaluate their safety in handling, processing or transportation.

In this paper, all tested substances were analyzed by dropping 5 Kg from 0.80 m height, i.e., 400 Kg \times cm (40 Newton).

c. Quasi adiabatic Dewar experiment

The iron-catalyzed diazidation reactions were carried out in quasi-adiabatic glass Dewar in order to determine whether any runaway occurs.

2. Results & Discussion

First, compounds **L1**, **1b**, **1a**, TMSN_3 and $\text{Fe}(\text{OAc})_2$ are evaluated and the data are recorded and discussed as follows.

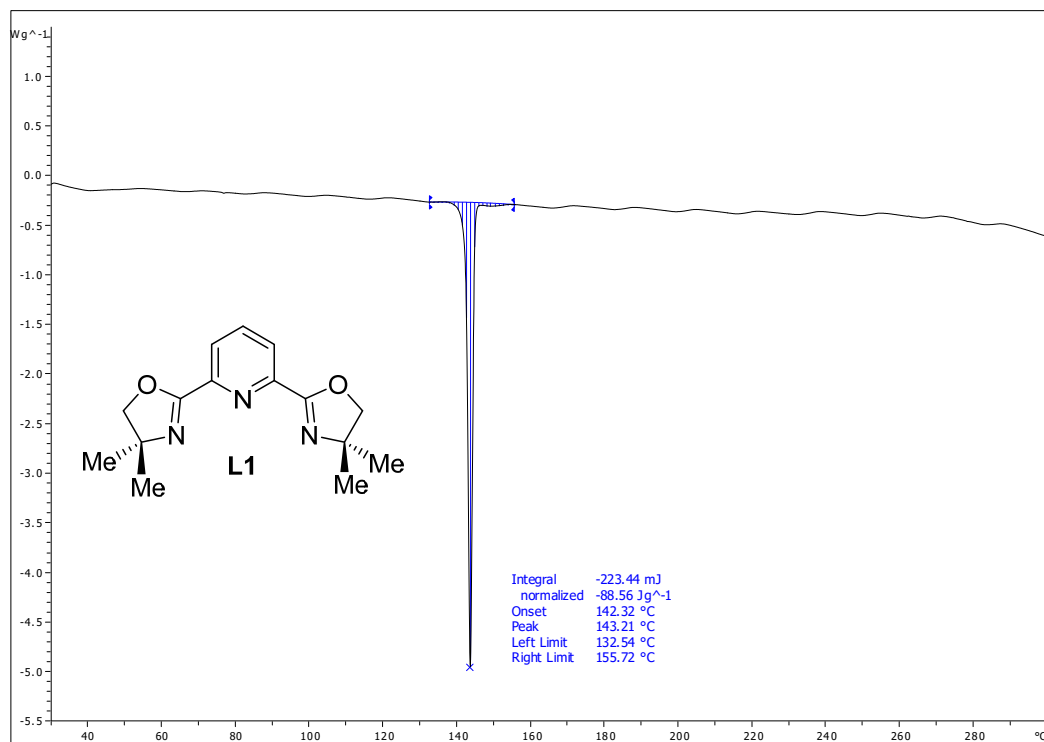


Figure S1. DSC Heating Curve of Ligand **L1** in Aluminum Pan

The ligand **L1** is very stable toward the DSC (heating rate = 5K/min), no decomposition is detected up to 300 $^{\circ}\text{C}$. Its melting point is 143 $^{\circ}\text{C}$ with a sharp peak ($\Delta H = -88.6 \text{ J/g}$) denoting the high purity of this compound (**Figure S1**).

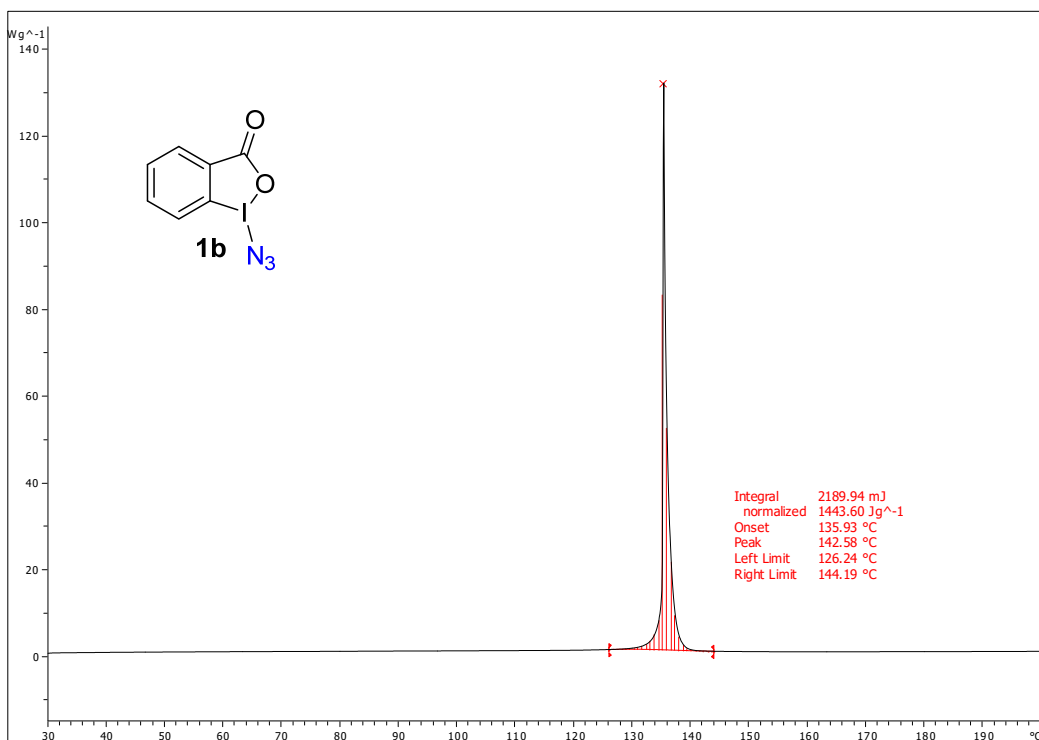


Figure S2. DSC Heating Curve of Azidation Reagent **1b** in Gold Plated Steel Pan

On the contrary, the azidation reagent **1b** shows a strong decomposition at 126 °C with high enthalpy ($\Delta H = 1444 \text{ J/g}$; 417 kJ/mol) indicating a violent decomposition (**Figure S2**).

When the experiment is carried out with a heating rate of 3K/min, the decomposition is anticipated at 118 °C. This decomposition would not be a problem in the diazidation reaction, which proceeds at room temperature (about 100 °C lower than its decomposition temperature).

1b originated a very strong detonation in the hummer test (DWT). Its impact-sensitivity may cause serious problems in the case of handling, grinding and charging into a reactor or simply a fallen-down storage drum in a warehouse.

The potential hazard with **1b** requires to modify the diazidation procedure to generate **1b** *in situ* from TMSN₃ and its precursor **1a**, which is more stable (see below).

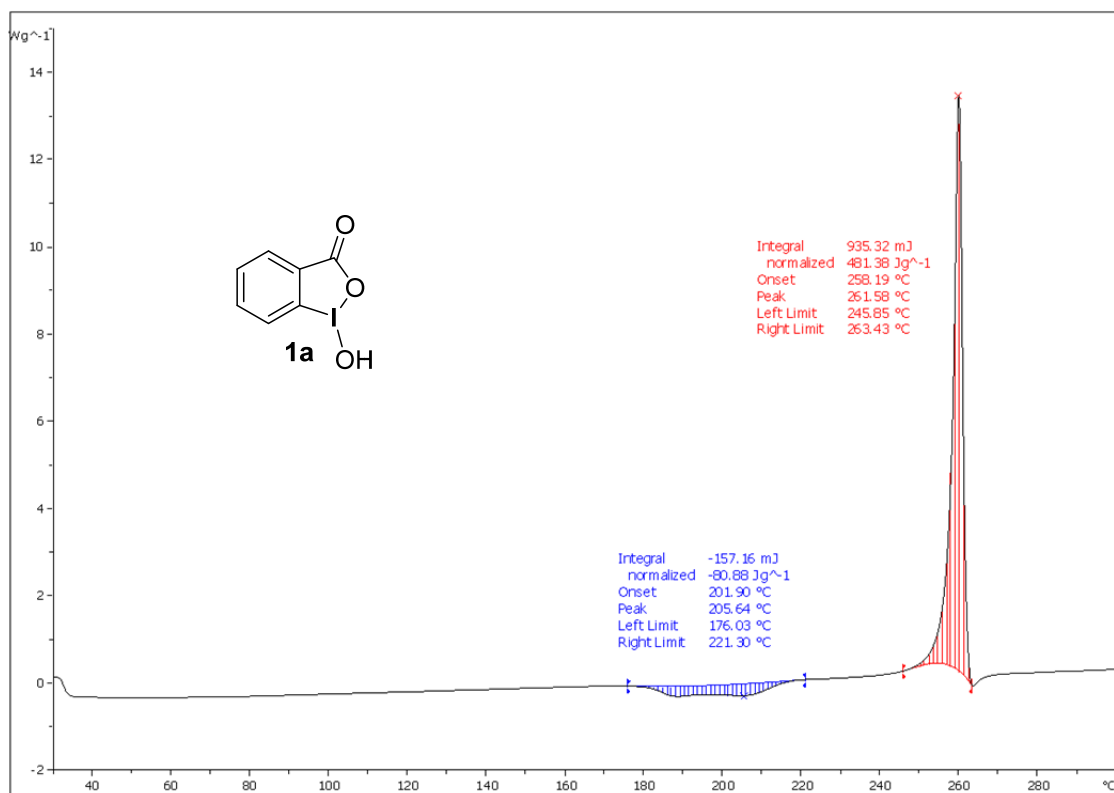


Figure S3. DSC Heating Curve of **1a** in Aluminum Pan

1a, the precursor of **1b**, is much more stable. An endothermic melting is detected in the range of 175 °C–220 °C followed by the decomposition starting above 245 °C (**Figure S3**). No positive result was recorded in the hummer test (DWT) of **1a**.

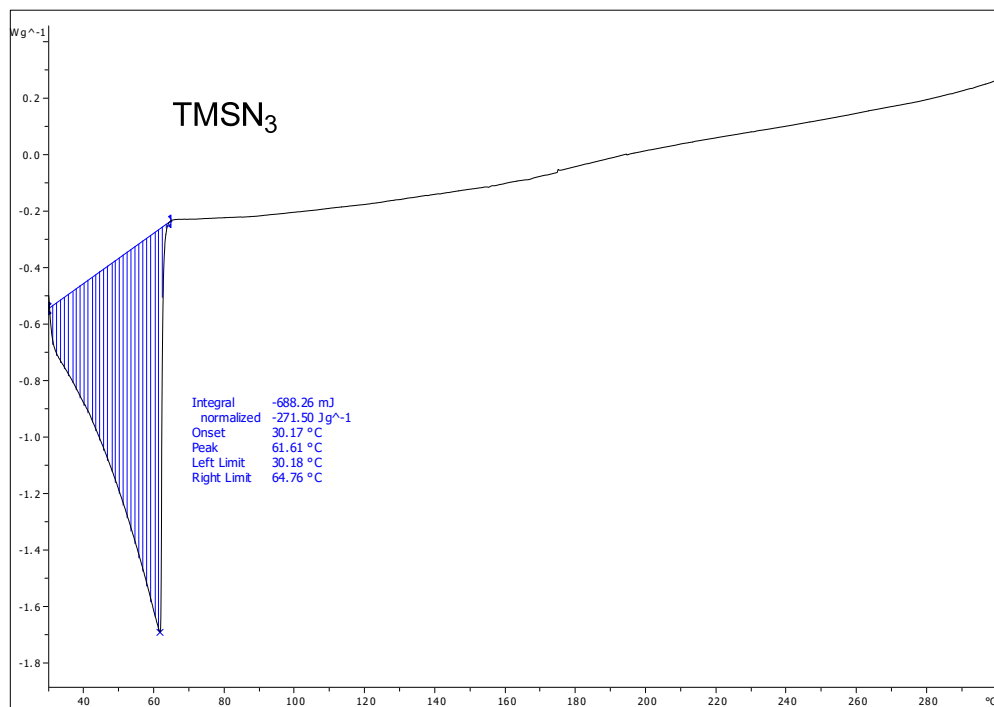


Figure S4. DSC Heating Curve of TMSN₃ in Aluminum Pan

Trimethylsilyl azide (TMSN₃) is liquid which starts to evaporate at room temperature without triggering any decomposition (**Figure S4**).

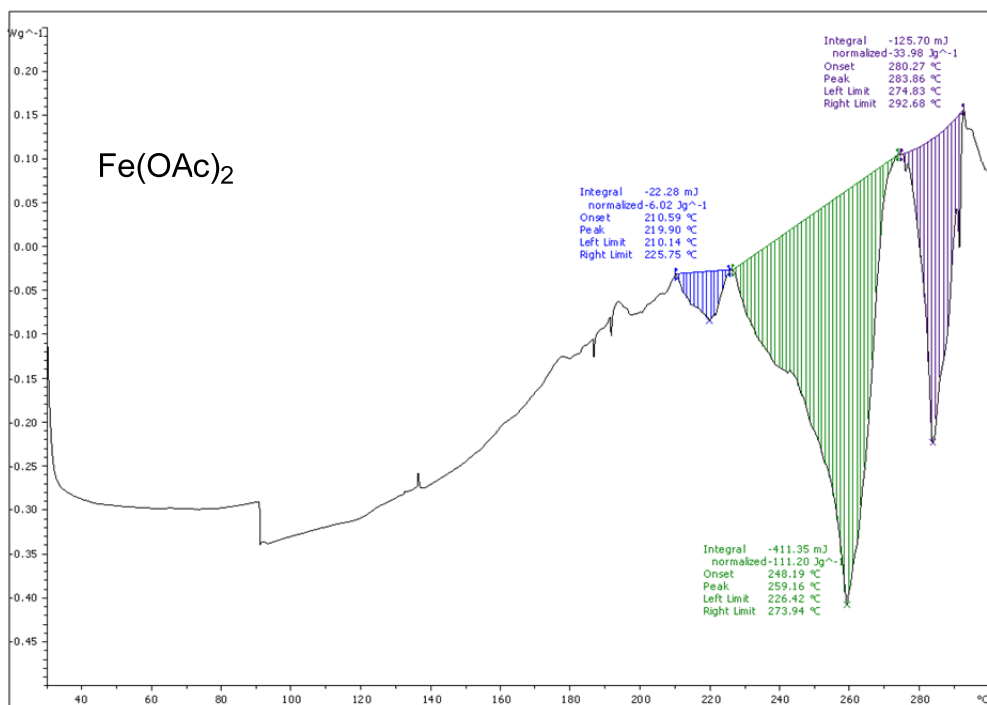


Figure S5. DSC Heating Curve of Fe(OAc)₂ in Aluminum Pan

Fe(OAc)₂ does not decompose exothermally up to 300°C. Only endothermic events are detected (Figure S5).

Secondly, the thermal stability of several diazides (**3**, **6**, **7**, **8**, and **9**) and a diaminium salt **4** were also assessed. The thermodynamic data (decomposition energy and temperature) are summarized in Table S1.

Table S1. DSC Parameters of Diazides **6**, **8**, **3**, **7** and **9**

Sample	Figure	ΔH dec.		Decomposition Temperature		
		J / g	kJ / mol	Range (°C)	Onset (°C)	Peak (°C)
3	S6	1195	239	156–240	207	208
6	S7	773	273	161–262	199	224
7	S8	854	374	154–281	156	234
8	S9	966	362	142–236	169	196
9	S10	663	186	123–145	134	142

In general, all the diazide compounds decompose with a very high energy at high temperature (>120 °C), which is 100 °C higher than the diazidation reaction temperature and allows a comfortable operating margin in carrying out the reaction. The decomposition energies of different diazides are very similar within a range of 190–380 kJ/mol and their decomposition generates gaseous byproducts, which can be approved by the detection of weight-loss at the end of the tests.

All the diazide compounds tested are liquid at room temperature except **8**, which starts to melt at 56 °C. However, its melting point is much lower than its decomposition temperature (140 °C).

Diazide compound **9** is the most reactive one. Its decomposition associates with a very sharp peak starting at the lowest temperature (about 120 °C). It is also unstable when exposed to light if it is transferred from a clear oil to a dark red colored oil within three days at room temperature.

These collected safety data prompt us to improve the work-up procedure¹ at the end of the diazidation reaction to avoid the isolation of the diazide product but reduce the crude product to the more stable diaminium salt directly.

Once the azido groups are reduced, the corresponding diamines become thermally stable and can be handled and isolated as *p*-toluenesulfonates safely. For example, diaminium ditosylate **4** does not decompose up to 300 °C. Only three endothermic events are detected at about 100 °C and above 280 °C, presumably due to loss of solvent or detosylation.

The thermal parameters for the diaminium salt **4** are summarized in **Table S2**.

Table S2. DSC Parameters of Diaminium Salts **4**

Diaminium Salts	Figure	Thermic Event.		Temperature			Mass lost at the end of DSC
		J / g	J/ mol	Range (°C)	Onset (°C)	Peak (°C)	
4	S11	-141	-0.286	46–109	86	98	14%
		-88	-0.179	249–294	281	282	

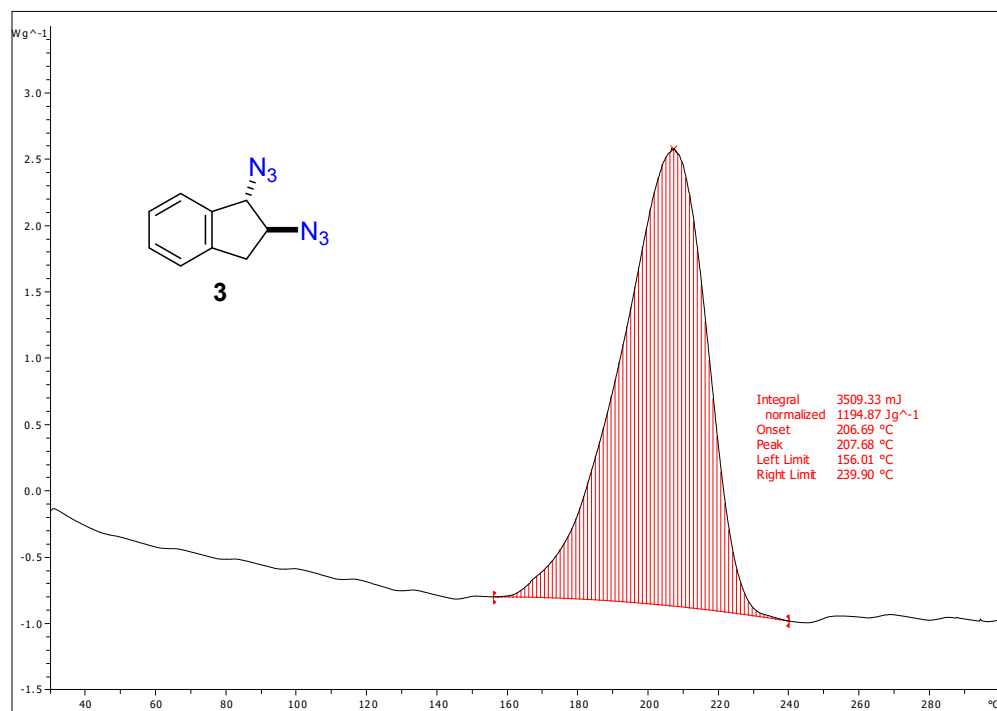


Figure S6. DSC Heating Curve of Diazide **3** in Aluminum Pan

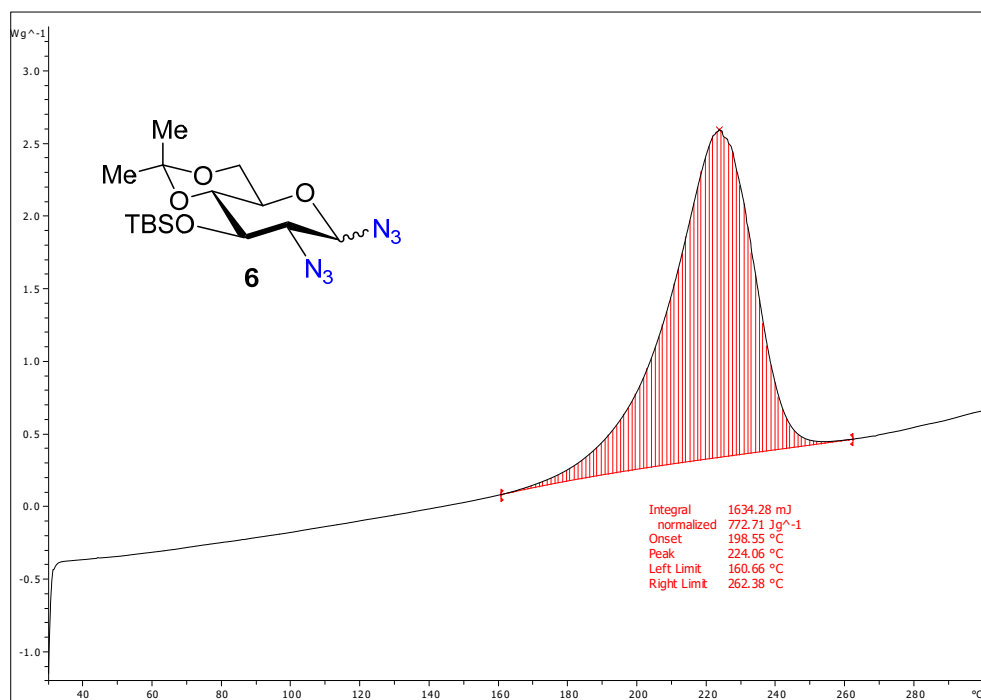


Figure S7. DSC Heating Curve of Diazide **6** in Aluminum Pan

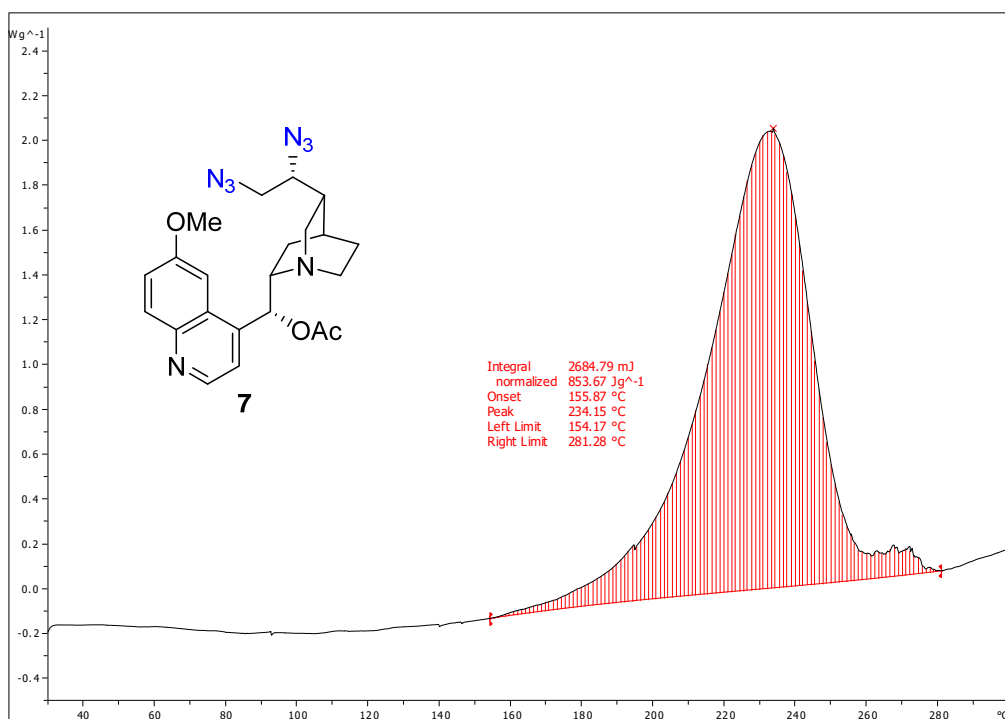


Figure S8. DSC Heating Curve of Diazide **7** in Aluminum Pan

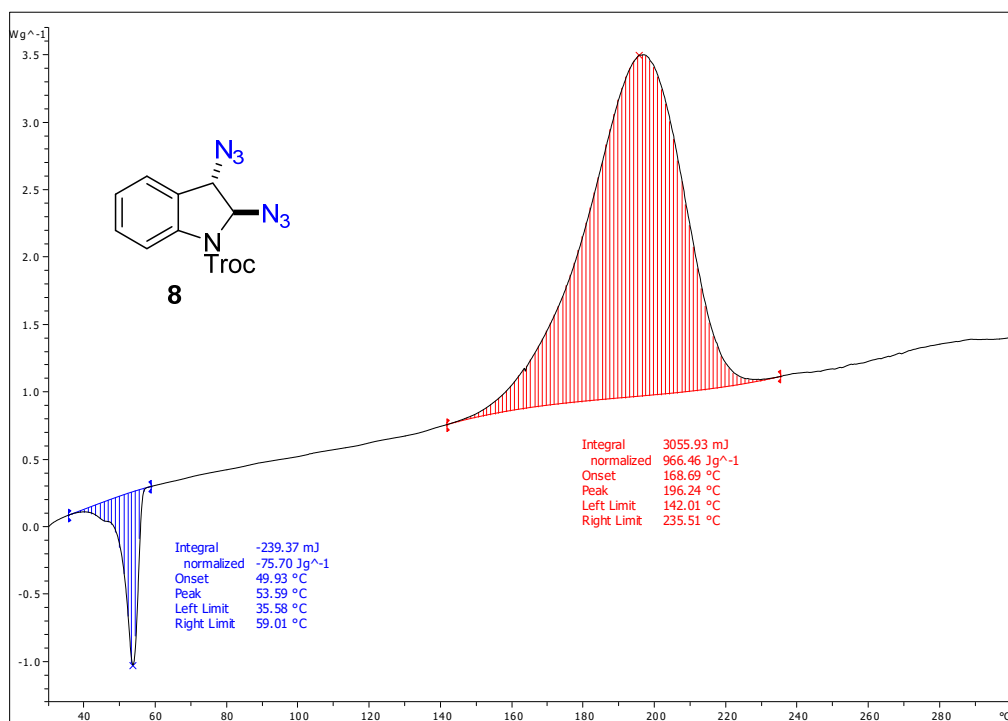


Figure S9. DSC Heating Curve of Diazide **8** in Aluminum Pan

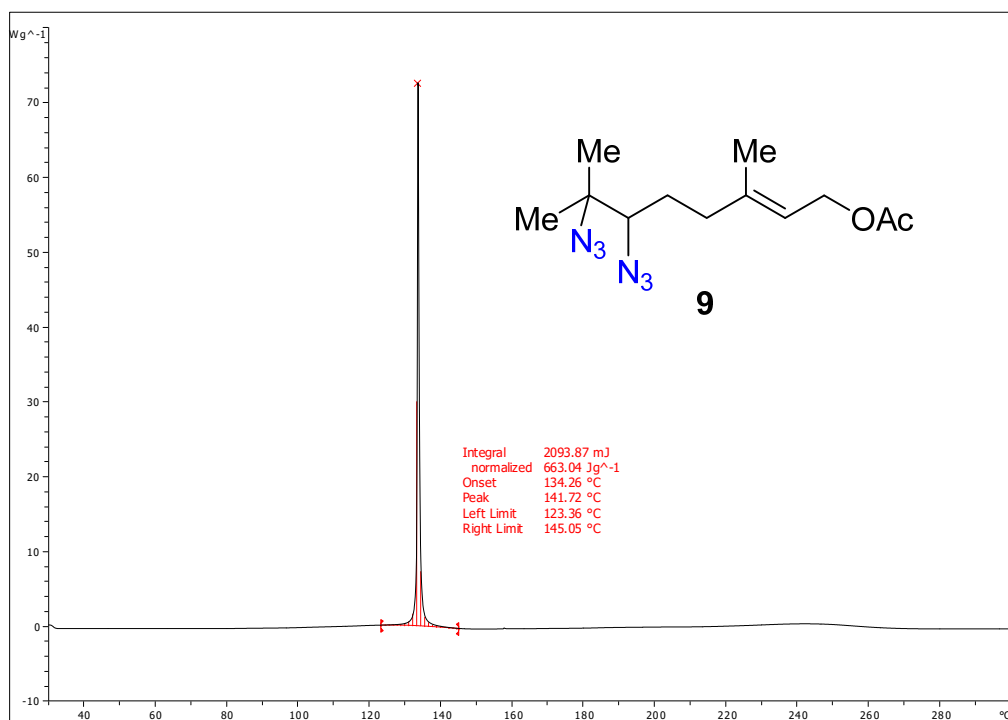


Figure S10. DSC Heating Curve of Diazide **9** in Aluminum Pan

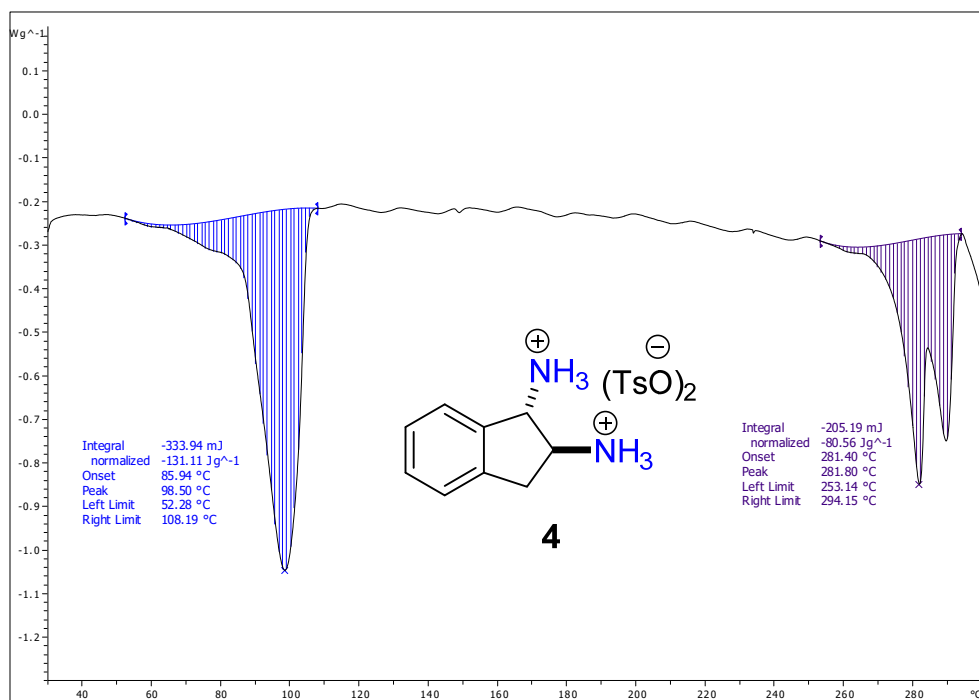


Figure S11. DSC Heating Curve of Diamino Tosylate **4** in Aluminum Pan

b. Assessment of Safety Aspects in the Diazidation Step

The incompatibility of azide reagents with certain metals³ and chlorinated solvents⁴ constitute other hurdles in developing routes that involve azide-containing intermediates. Since Fe(OAc)₂ and CH₂Cl₂ are involved in our diazidation protocol, the thermal stability of the reacting mixture was also investigated. A blank diazidation reaction, i.e., without substrates and ligand, was performed in a quasi-adiabatic calorimeter glass Dewar. The concentration was double diluted from the published protocol¹ due to the volume of the vessel. Obviously, this does not affect the ΔH of reaction but only rises the observed adiabatic temperature ΔT_{ad} .

Experimental Procedures

In a glass Dewar equipped with a stirrer were added **1a** (5.0 g, 18.92 mmol, 1.2 equiv) and anhydrous CH₂Cl₂ (24.0 mL) at 25°C. A white suspension precipitates out. Subsequently, TMSN₃ (7.27 g, 8.4 mL, 63.1 mmol, 4.0 equiv) that was pre-cooled at 8 °C was added in one-shot and this process is slightly exothermic (experimental ΔT_{ad} = 4.1 °C).

In a second vial, Fe(OAc)₂ (137 mg, 0.788 mmol, 0.05 equiv) was suspended in CH₂Cl₂ (6.4 mL) and MeCN (1.6 mL) under N₂. This brownish suspension was added in one shot to the heterogeneous solution of **1a** and TMSN₃ in the glass Dewar. The reaction mixture turned to be dark brown and a slight increase of temperature was detected (experimental $\Delta T_{ad} = 3.2^\circ\text{C}$). This indicates that the iron catalyst promotes the formation of the azidation reagent **1b** and there is no risk of a runaway reaction, even add Fe(OAc)₂ to **1a** and TMSN₃ instantaneously.

Results and Discussions

The main parameters are summarized in Table S3 and the trend of the temperature along the experiment is depicted in Figure S12.

Table S3. Calorimetric Parameters for the Mixing of Diazidation Reagents

Operation	Reaction Mass (g)	Heat Capacity (J/g·K)	Experimental Adiabatic ΔT (°C)	Corrected Adiabatic ΔT (°C)	Reaction Heat (J)	Heat for Reaction Mass (J/g)	Heat for 2b (J/g)
TMSN ₃ addition to 1a in CH ₂ Cl ₂	44.2	1.31	4.1	5.1	237	5.36	12.540
Fe(OAc) ₂ suspension addition to 1a +TMSN ₃ in CH ₂ Cl ₂	54.1	1.50	3.2	4.0	255	4.71	13.492

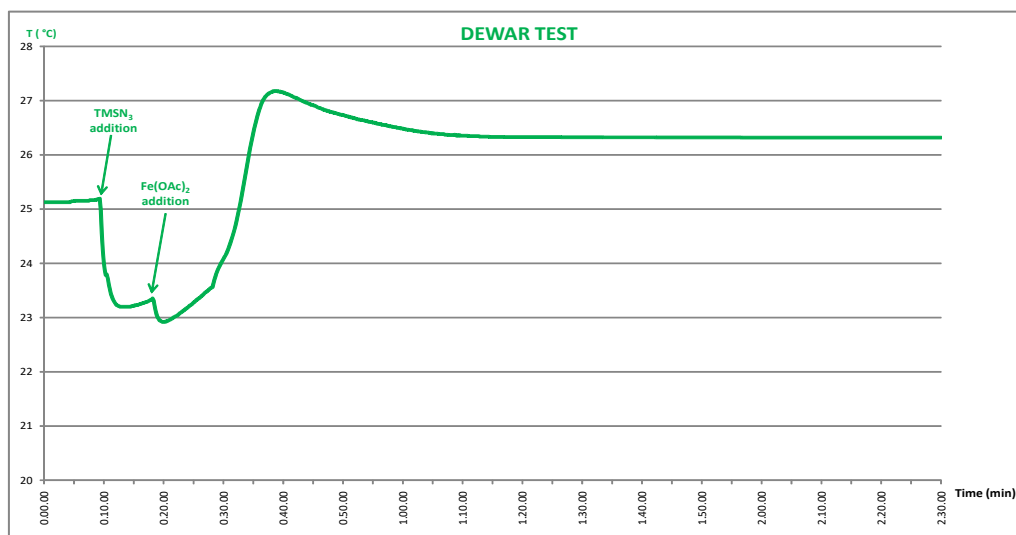


Figure S12. Temperature Trend of the “Blank Reaction”

A sample of the above obtained reaction mixture was dried under a nitrogen stream and subjected to DSC test (**Figure S13**). Its profile is very similar to that of **1a** with the decomposition temperature about 20 °C lower, indicating that the iodo-azido derivative **1b** was formed only in a small amount.

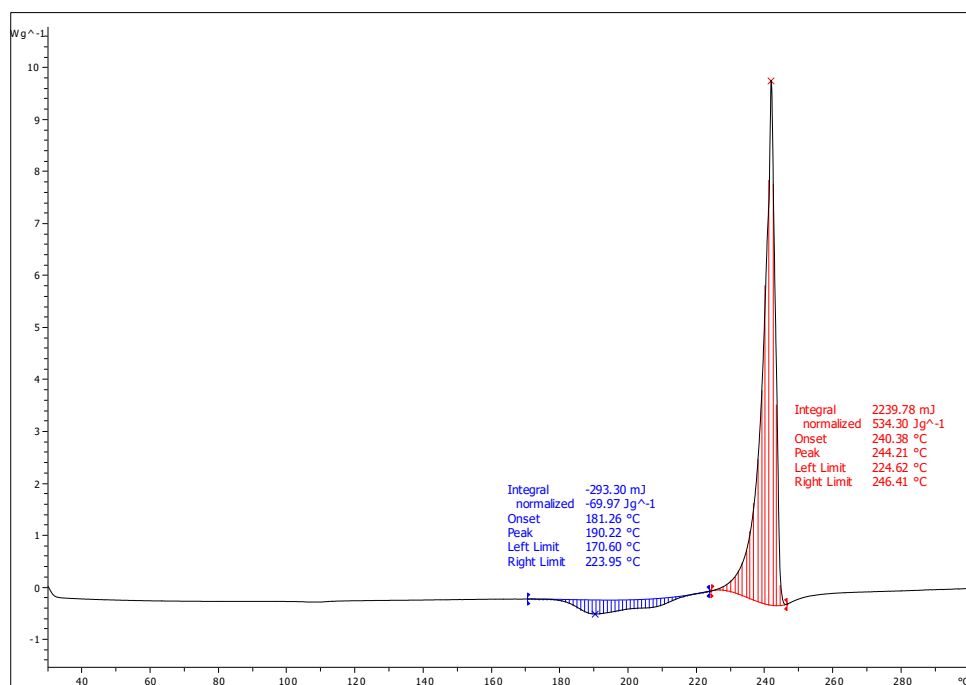


Figure S13. Dewar Test: Reaction Mixture after the Mixing of the Diazidation Reagents in
Aluminum Pan

The data presented above ensure that this diazidation protocol is thermally safe. In order to establish the operating parameters of diazidation reaction of any olefins under safe conditions, the ΔH should be evaluated for each substrate.

References

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