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# Mechanistic Insight into the Dehydro-Diels–Alder Reaction of Styrene–Ynes

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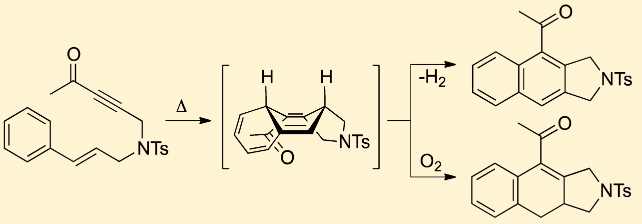
Ⓢ *Supporting Information*



**ABSTRACT:** The Diels–Alder reaction represents one of the most thoroughly studied and well-understood synthetic transformations for the assembly of six-membered rings. Although intramolecular dehydro-Diels–Alder (IMDDA) reactions have previously been employed for the preparation of naphthalene and dihydronaphthalene substrates, low yields and product mixtures have reduced the impact and scope of this reaction. Through the mechanistic studies described within, we have confirmed that the thermal IMDDA reaction of styrene–ynes produces a naphthalene product via loss of hydrogen gas from the initially formed cycloadduct, a tetraenyl intermediate. Alternatively, the dihydronaphthalene product is afforded from the same tetraenyl intermediate via a radical isomerization process. Moreover, we have identified conditions that can be used to achieve efficient, high-yielding, and selective IMDDA reactions of styrene–ynes to form either naphthalene or dihydronaphthalene products. The operational simplicity and retrosynthetic orthogonality of this method for the preparation of naphthalenes and dihydronaphthalenes makes this transformation appealing for the synthesis of medicinal and material targets. The mechanistic studies within may impact the development of other thermal transformations.

## ■ INTRODUCTION

Functionalized naphthalenes and their derivatives are valuable building blocks that serve as key structural components for various material, chemical, and biological applications. Naphthalenes are used as organic semiconductors in organic light-emitting diodes (OLEDs)[1] and liquid crystalline displays (LCDs).[2] They are also commonly incorporated into pharmaceuticals[3] and chiral reagents.[4] A classic example showcasing the importance of this motif is naproxen (**2**) and its derivatives. These COX-2 selective anti-inflammatory agents are obtained via an asymmetric hydrogenation of methoxynaphthenyl acrylic acid (**1**) in which high enantioselectivities were achieved by employing the chiral biaryl ligand (*R*)-BINAP (**3**), as depicted in Scheme 1.[5] Naphthalenes are present in a number of naturally occurring compounds,[6] one example being michellamine B (**4**), a compound that captured the attention of the research community because of its activity against HIV, as well as its unusual $C_2$-symmetric naphthylisoquinoline structure.[7] Naphthalenes possessing electron-donor and -acceptor groups also play an important role in bioimaging applications.[8] For example, dansyl, the structure represented in the box of the guanidinium-rich molecular transporter (MoTr) **5**, was used as a fluorescent probe to measure the cellular uptake efficiency of MoTr analogues.[9] Additionally, certain bacterial genetic codes have been expanded to include the nonnatural naphthalene- and benzo-fused heterocycle base pair d5SICS-dNaM (**6**).[10] By incorporating these nonnatural base pairs into bacterial DNA, nonnatural amino acids were created in vitro using the cellular machinery. These and other applications have revealed functionalized naphthalenes as desirable synthetic targets, but methods to access this valuable class of aromatic compounds have not kept up with the demand for new, diverse, and structurally complex naphthalene substrates.

Because naphthalene represents the most abundant component of coal tar,[11] it has been exploited in the industrial scale production of dyes, plastics, and insecticides, to name a few. Moreover, the methods by which naphthalene-containing compounds have conventionally been obtained are directed largely by an abundance of this feedstock. As an example, electrophilic aromatic substitution (EAS) reactions of naphthalene, such as Friedel–Crafts acylations and alkylations, halogenations, and nitrations, are commonly used protocols to prepare functionalized naphthalene-containing compounds.[12] While these methods have their place in the synthetic chemist's toolbox, alternative strategies that provide more complex naphthalene substructures not readily available using EAS and

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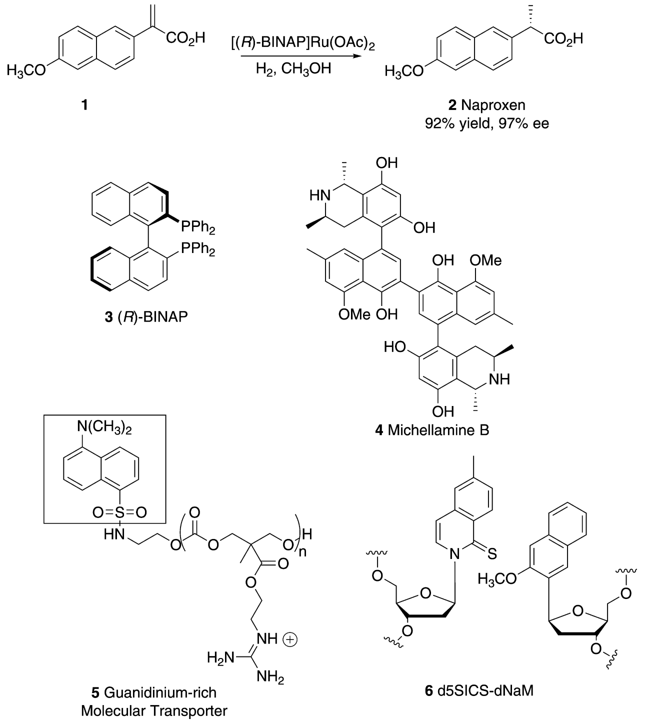
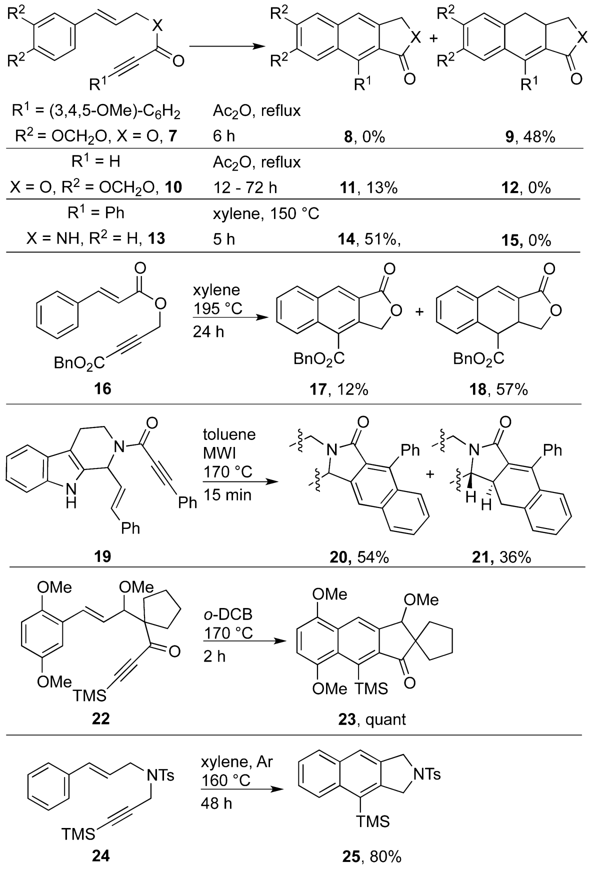
**Scheme 1. Biologically Relevant Naphthalene-Containing Compounds**



**Scheme 2. Previously Reported IMDDA Reactions of Styrene–Ynes**



other classical reactions are needed. Others have recognized the limitations imposed by these more classical approaches and have responded with new methods for naphthalene synthesis,[13] including transition-metal-catalyzed cross-coupling[14] and transition-metal-mediated reactions,[15] Diels–Alder reactions of benzyne[16] or *o*-quinodimethane derivatives,[17] phthalide annulations,[18] ring-closing metathesis,[19] and [2 + 2 + 2] cycloaddition reactions.[20] Also gaining widespread use is an acid-catalyzed benzannulation via [4 + 2] cycloaddition reaction of *o*-alkynyl(oxo)benzenes with alkynes discovered by Yamamoto.[21]

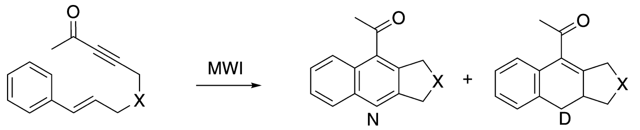
Intramolecular dehydro-Diels–Alder (IMDDA) reactions have previously been used for the construction of naphthalenes and other polycyclic aromatic hydrocarbons.[22] When aromatic products are preferred, IMDDA reactions are typically conducted with substrates containing two reactive triple bonds and one double bond. However, examples exist where aromatic products have been obtained from IMDDA precursors having *one* triple bond and *two* double bonds, a reaction that should afford the dihydroaromatic product. The formation of this product has in some cases been justified by the propensity of 1,4-cyclohexadiene derivatives to aromatize under oxidative conditions. Along similar lines, a potentially valuable IMDDA reaction for the preparation of aromatic hydrocarbons involves the reaction of styrene and an alkyne to afford a cycloadduct that aromatizes to give naphthalene derivatives. Despite the tendency for styrene polymerization, the feasibility of this reaction has been demonstrated, albeit with mixtures of products and/or low yields.[23]

Klemm was the first to report an IMDDA reaction where styrenyl alkynoate **7** was refluxed in acetic anhydride to provide *dihydro*naphthyl lactone **9** in 48% yield (Scheme 2).[24] When a similar IMDDA precursor **10** containing a terminal alkyne was used, only the naphthyl lactone **11** was obtained, but in 13% yield.[25] Cycloaddition of amide **13** gave naphthalene lactam **14** in 51% yield.[26] More recently, Chackalamannil effected an IMDDA reaction of alkynoate **16** to afford dihydronaphthofuranone **18** in 57% yield, along with naphthyl lactone **17**; the unusual position of the double bond in **18** was discussed.[27] Ruijter has reported an IMDDA reaction of styrene-functionalized *β*-carboline **19** that generated compounds **20** and **21** in a 1.5:1 ratio and 90% yield.[28] Interestingly, attempts to oxidize the product mixture to **20** using DDQ led to decomposition. Terashima reported the IMDDA reaction of alkynone **22**, which provided only **23** in quantitative yield.[29] Finally, Matsubara has reported an IMDDA reaction of silyl acetylene **24** that produced only the naphthalene product **25** in 80% yield; ten additional examples were reported.[30] While this nearly exhaustive listing of research in the area of IMDDA reactions of styrene–ynes provides precedent for this reaction,[31] its potential has not been realized due to harsh reaction conditions, long reaction times, mixtures of naphthalene and dihydronaphthalene compounds, and the inability to predict which product will be obtained.

## ■ RESULTS AND DISCUSSION

Recently, an unexpected IMDDA reaction between the styrene and alkyne of **26** was observed during our studies directed toward capturing a diradical intermediate of a thermal intramolecular [2 + 2] cycloaddition reaction.[32] When comparing the IMDDA reaction of styrene–yne **26** to previously reported examples, we were intrigued by (1) the short reaction time, (2) high yield, (3) operational simplicity of the "thermal only" reaction conditions, and (4) complete selectivity for the formation of the aromatic product. Investigation into the scope and limitations of the IMDDA reaction of styrene−ynes began by making variations to the alkyne terminus and ultimately showed selective formation of a number of naphthalene products in high yield.[33] Further studies involving the addition of heteroatoms to the styrene−yne tether resulted in very different product mixtures. For example, replacing the all carbon tether of **26** with heteroatom-containing tethers **28** (X = O) and **30** (X = NTs) and subjecting these styrene−ynes to our standard microwave irradiation (MWI) reaction conditions afforded naphthalenes **29a** and **31a** in low yield. Additionally, dihydronaphthalenes **29b** and **31b** were obtained in 15% and 56% yields, respectively (entries 2 and 3, Table 1). Notably, for styrene−yne **30** containing a tosylamide tether, the dihydronaphthalene product **31b** was formed as the major product.

Table 1. IMDDA Reaction of Styrene−Ynes with Heteroatom Tethers

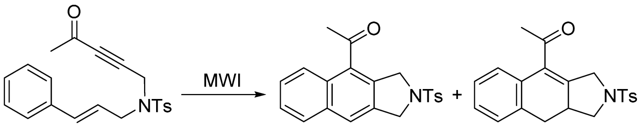


| entry | styrene−yne | conditions | N (%) | D (%) |
|---|---|---|---|---|
| 1 | **26**, X = $CH_2$ | DCE, 180 °C, 0.06 M, 30 min | **27a**, 100 | **27b**, 0 |
| 2 | **28**, X = O | DCE, 180 °C, 0.06 M, 30 min | **29a**, 28 | **29b**, 15 |
| 3 | **30**, X = NTs | DCE, 180 °C, 0.06 M, 10 min | **31a**, 30 | **31b**, 56 |
| 4 | **30** | DCE, 180 °C, 0.06 M, 60 min | 38 | 8 |
| 5 | **30** | *o*-DCB, 120 °C, 0.06 M, 15 min | 7 | 53 |
| 6 | **30** | *o*-DCB, 225 °C, 0.06 M, 1 min | 48 | 33 |
| 7 | **30** | *o*-DCB, 180 °C, 0.50 M, 1 min | 16 | 60 |

**Concentration, Temperature, and Atmosphere Studies.** To further explore this result, styrene−yne **30** was subjected to reaction conditions that involved changing the temperature, concentration, and atmosphere. Among the various experiments that were performed, four key results have emerged to alter our thoughts regarding this reaction. Prolonging microwave irradiation of **30** for 60 min at 180 °C in DCE afforded less dihydronaphthalene **31b** when compared to an example that was irradiated for 10 min (compare entries 3 and 4, Table 1, 8% vs 56%); however, the increase in naphthalene **31a** was not proportionate (38% vs 30%). This data confirms that under extended reaction times, dihydronaphthalene **31b** is not transforming to naphthalene **31a**. Lowering the temperature of the reaction from 180 to 120 °C afforded a higher ratio of **31b** to **31a** of 7.6:1 vs 1.9:1 (compare entries 3 and 5, Table 1); the mass balance for entry 5 was recovered starting material (34%). Increasing the reaction temperature to 225 °C resulted in a reversal of selectivity, giving a 1:1.5 ratio of **31b**:**31a** (entry 6). Thus, lower temperatures favor formation of dihydronaphthalene **31b**, and higher reaction temperatures produce more naphthalene **31a**. Increasing the reaction concentration from 0.06 to 0.50 M resulted in a 3.8:1 mixture of the dihydronaphthalene **31b** and naphthalene **31a** products (entry 7). As discussed in further detail below, this data combined with the temperature studies suggests the possibility that two different reaction mechanisms are operating to produce the two products. Irradiating styrene−yne **30** at 180 °C in DCE either under air or after degassing the reaction mixture with argon both generated a 1.9:1 mixture of dihydronaphthalene **31b** to naphthalene **31a** in as little as 2 min (see Table S1 (Supporting Information) for a complete listing of experimental conditions employed). While these conditions did not ensure rigorous exclusion of oxygen, this experiment indicates that performing the reaction in the presence or absence of oxygen has no effect on the product selectivity or the rate of reaction for the time scale that was measured. This data strongly suggests that molecular oxygen is not functioning as an adventitious oxidant of dihydronaphthalene **31b** to naphthalene **31a**. These thought-provoking results support the need for a more thorough understanding of the mechanism of product formation in this reaction prior to embarking on further scope and limitation studies. A discussion of the results from these mechanistic investigations is provided herein.

**Solvent Studies.** The IMDDA reaction of **30** was carried out at a constant temperature of 180 °C in solvents of increasing dielectric constant ranging from *o*-DCB ($\varepsilon = 9.93$) to water ($\varepsilon = 80.10$). Regardless of the solvent employed, each reaction was complete within 1 min. While there are some outlying results, the dielectric constant of the solvent appears to correlate well with the selectivity of the reaction, with product ratios of **31a**:**31b** ranging from 1:1.2 to 1:10 as the dielectric constant of the solvent increases (entries 1−4 and 8, Table 2).[34] A control experiment was performed where **30** was irradiated in DMF-$d_7$ and still yielded the same ratio of **31a**:**31b**, but with no deuterium incorporation (see the Supporting Information). One outlier in the solvent data was nitrobenzene ($PhNO_2$), which afforded exclusively naphthalene **31a** in 84% yield. We attribute this result to $PhNO_2$ functioning as a dehydrogenating agent,[35] and this is supported by the fact that as little as 8 equiv of $PhNO_2$ resulted in selective naphthalene formation (see Table S2, Supporting Information). Thus, solvent does play a significant role in the selectivity afforded by the IMDDA reaction for the formation of naphthalene or dihydronaphthalene products.

Table 2. Effect of Solvent on Product Selectivity



**30** **31a** **31b**

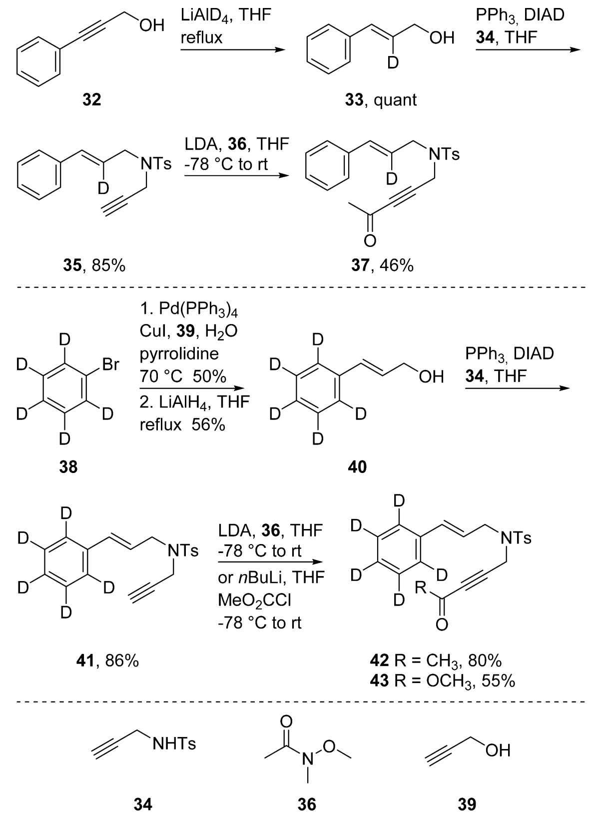
| entry[a] | solvent | tan δ | dielectric constant | **31a**:**31b**[b] |
|---|---|---|---|---|
| 1 | *o*-DCB | 0.28 | 9.93 | 1:1.2 |
| 2 | DCE | 0.127 | 10.36 | 1:1.8 |
| 3 | MEK | 0.079 | 18.50 | 1:2.6 |
| 4 | *i*PrOH | 0.799 | 20.18 | 1:4.4 |
| 5 | $EtNO_2$ |  | 28.06 | 1:1 |
| 6 | NMP | 0.275 | 32.20 | 1:3 |
| 7 | $PhNO_2$ | 0.589 | 34.82 | 1:0 |
| 8 | DMF | 0.161 | 36.71 | 1:10 |
| 9 | $H_2O$ | 0.123 | 80.10 | 1:2 |

[a] Irradiated reaction mixture (0.06 M) at 180 °C for 1 min. [b] Ratio of products determined by $^1H$ NMR spectroscopy.

**Isotopic-Labeling Experiments.** Next, experiments involving the IMDDA reaction of isotopically labeled precursors were performed to elucidate the mechanism(s) by which the naphthalene **31a** and the dihydronaphthalene **31b** products are formed. Three IMDDA precursors were prepared, one with deuterium incorporated into the double bond of the diene and the other two with deuteriums incorporated at all remaining positions of the aryl ring of the diene.

**Synthetic Protocols.** The monodeuterated alkynone **37** was prepared as follows. Reduction of 3-phenyl-2-propyn-1-ol (**32**) using lithium aluminum deuteride afforded monodeuterated cinnamyl alcohol **33** in quantitative yield; the *E*-configuration was inferred from $^1$H NMR spectroscopy (Scheme 3). Subjecting **33** to the Mitsunobu reaction conditions of triphenylphosphine, diisopropyl azodicarboxylate, and 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**34**) gave styrene−yne **35** in 85% yield.[36] *N*-Methoxy-*N*-methylacetamide (**36**) was then employed to acylate the lithium acetylide of **35**, providing 46% yield of alkynone **37**.[37]

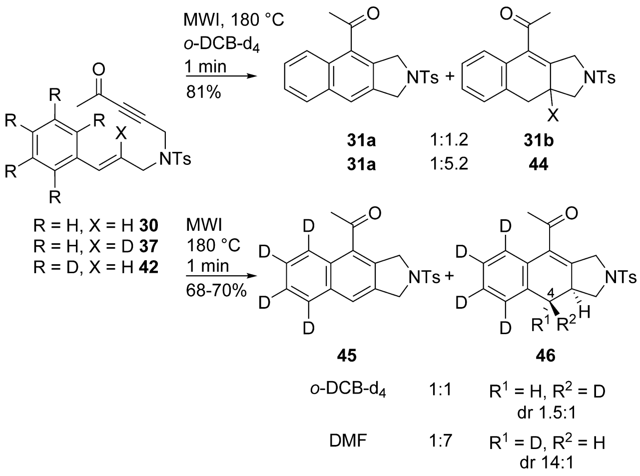
**Scheme 3. Synthesis of Isotopically Labeled Styrene−Ynes**



The pentadeuterated substrates **42** and **43** were prepared in a similar manner as **37**; however, the synthesis began by a Sonogashira cross-coupling reaction of bromobenzene-$d_5$ (**38**) with propargyl alcohol (**39**) in the presence of tetrakis(triphenylphosphine)palladium(0), copper(I) iodide, and pyrrolidine to generate 50% yield of 3-(phenyl-$d_5$)prop-2-yn-1-ol (Scheme 3). Subsequent reduction of the alkyne using lithium aluminum hydride produced cinnamyl alcohol **40** in 56% yield. Mitsunobu reaction conditions were utilized for the conversion of **40** to styrene−yne **41** in 86% yield. Finally, to the lithium acetylide of **41** was added either *N*-methoxy-*N*-methylacetamide (**36**) or methyl chloroformate, producing alkynone **42** and alkynoate **43** in 80 or 55% yield, respectively.

**IMDDA Reactions with Deuterated Substrates.** Deuterated styrene−ynes were also subjected to thermal conditions to further our understanding of the mechanism of the IMDDA reaction. First, heating styrene−yne-$d_1$ **37** at 180 °C for 1 min in *o*-DCB-$d_4$ generated naphthalene **31a** and dihydronaphthalene-$d_1$ **44** in 81% yield and in a 1:5.2 ratio, as determined by $^1$H NMR spectroscopy (Scheme 4). This represents a significant change in the product ratio when compared to heating of the nondeuterated precursor **30** and is interpreted as a large primary kinetic isotope effect. In an additional experiment, heating of styrene−yne-$d_5$ **42** for 1 min at 180 °C in *o*-DCB-$d_4$ resulted in a 1:1 mixture of naphthalene **45** and dihydronaphthalene **46** in 68% yield. Naphthalene **45** was separated from **46** by HPLC, and characterization of **46** by $^1$H NMR and COSY spectroscopy showed the presence of two diastereomers in a 1.5:1 ratio resulting from deuterium incorporation at the 4-position of the dihydronaphthalene, which was indicative of deuterium atom transfer from the aryl ring. Incorporation of a deuterium atom at the 4-position of the dihydronaphthalene altered the $^1$H NMR spectrum of **46**, allowing for the diastereomeric ratio to be distinguished. For example, the doublet of doublets and apparent triplet found at $\delta$ 2.82 and 2.51, representative of the two protons at the 4-position of **31b** (Figure 1A), each changed upon deuterium incorporation in **46** and became two doublets ($H_d$ and $H_e$) integrating for 0.69 and 0.47 protons, respectively. The coupling constants of $H_d$ and $H_e$ were reflective of coupling only to the neighboring proton ($H_c$) and not germinal coupling (Figure 1B). Additional smaller resonances at $\delta$ 2.89, 2.86, 2.81, 2.80, and 2.54, which were similar to the resonances observed for **31b**, were also noted in the $^1$H NMR spectrum of **46**.

**Scheme 4. Deuterium-Labeling Studies**



As expected, heating **42** in DMF under the same reaction conditions resulted in a 70% combined yield of **45** and **46** in a 1:7 ratio; however, dihydronaphthalene **46** was now generated with a much greater diastereoselectivity of 14:1 for the opposite diastereomer (Scheme 4). This change in diastereoselectivity was also obvious from the $^1$H NMR spectrum of **46**, in which the doublet at $\delta$ 2.50 ($H_e$) was now much more prominent in comparison to the doublet at $\delta$ 2.80 ($H_d$), with integrations of 0.95 and 0.07, respectively (Figure 1C).

**Crossover Experiment.** Incorporation of a deuterium atom at the 4-position of dihydronaphthalene **46** could arise via either an inter- or intramolecular transfer mechanism. To

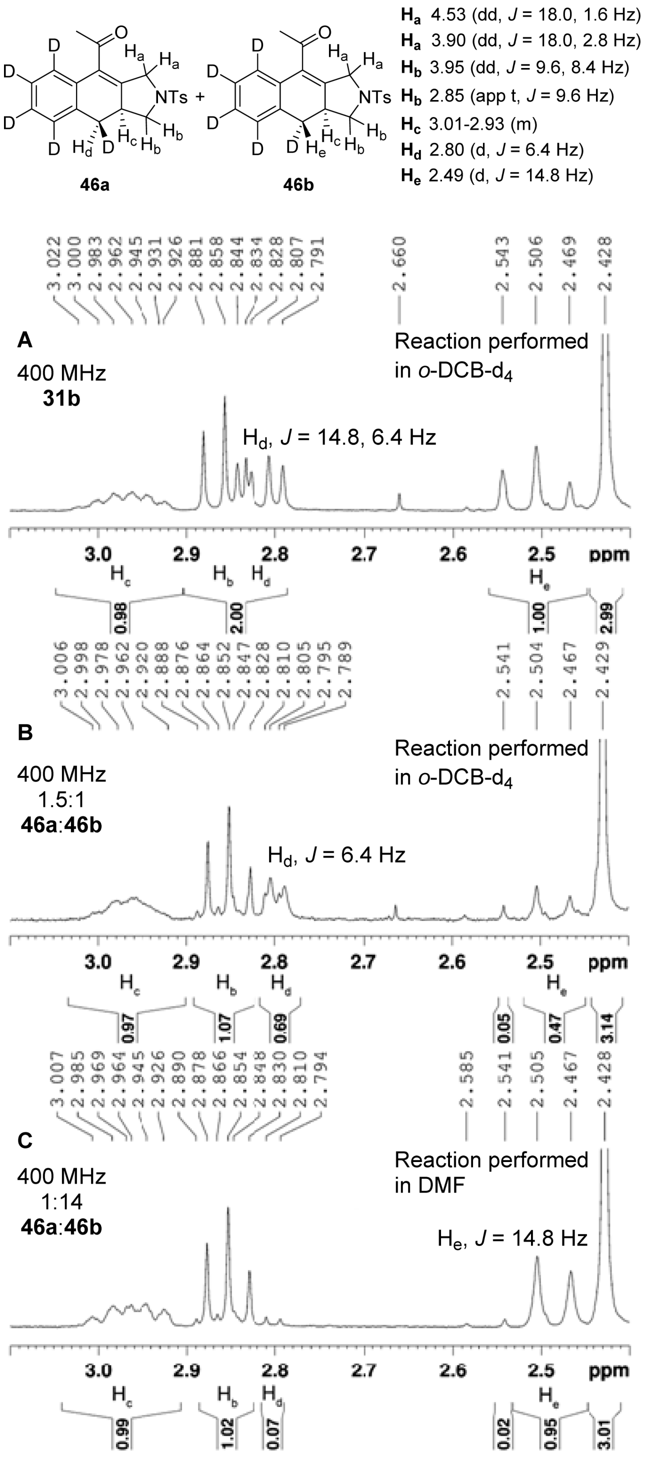
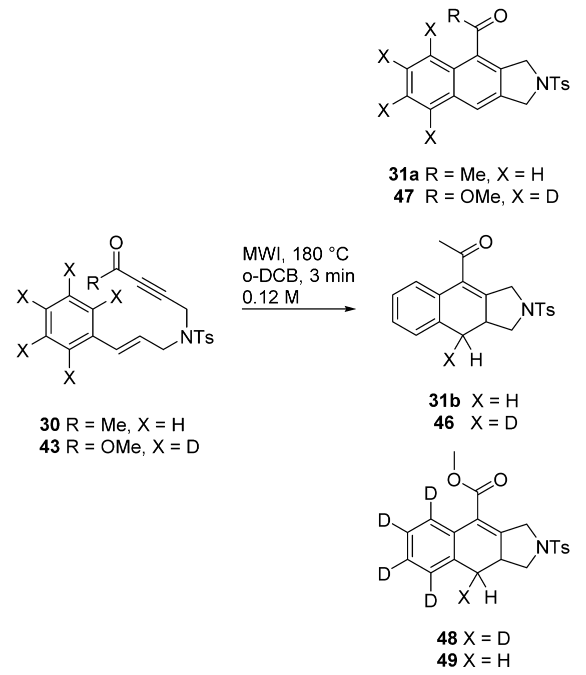


**Figure 1.** $^1$H NMR analysis of deuterium atom transfer in dihydronaphthalene **46**.

**Scheme 5. Crossover Experiment**

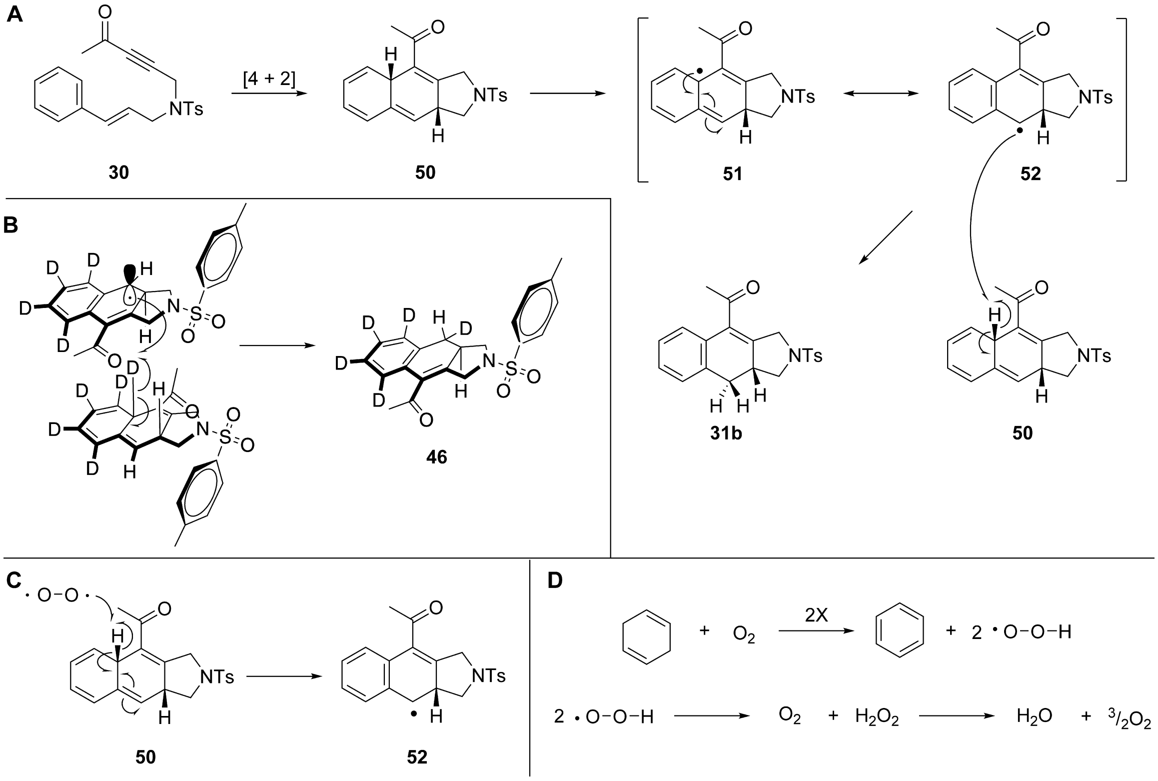


determine which mechanism was operative, a crossover experiment was performed employing alkynone **30** and alkynoate **43**, containing deuterated and nondeuterated aryl groups, respectively, to test for intermolecular hydrogen/deuterium atom transfer. If crossover were to occur, six total products would be expected (Scheme 5). Heating a 1:1 mixture of **30** and **43** for 3 min at 180 °C in *o*-DCB afforded a mixture of six compounds that were separated as four peaks by HPLC. Characterization by ESI-MS revealed two of the isolated chromatogram peaks as naphthalenes **31a** and **47**, while analysis of the remaining two chromatogram peaks showed a mixture of dihydronaphthalenes **31b** and **46** in one peak, in addition to a mixture of **48** and **49** in the other peak. The $(M+H)^+$ ions of the deuterated products **46** and **48** were observed with relative intensities of greater than 55%, thus differentiating these peaks from those that result from the natural abundance of carbon-13 for **31b** and **49** (see Supporting Information). The observation of all possible crossover products indicated that transfer of hydrogen or deuterium to the 4-position of the dihydronaphthalene was taking place via an intermolecular process.

**Mechanism for the Formation of Dihydronaphthalene.** As a result of our mechanistic studies, we postulate that dihydronaphthalene formation occurs via an initial [4 + 2] cycloaddition reaction of **30** to produce the tetraene **50** (Scheme 6A). In turn, the tris-allylic hydrogen atom is abstracted to afford a carbon-centered radical, depicted as the two resonance structures **51** and **52**. Next, **52** abstracts a hydrogen atom from another equivalent of **50** to give dihydronaphthalene **31b**, along with an additional radical **51**/**52** which will propagate the reaction. The intermolecular hydrogen atom abstraction proposed is supported by both the crossover experiment (Scheme 5), as well as the concentration studies, which demonstrated that increasing the concentration of the IMDDA reaction provided larger amounts of the dihydronaphthalene substrate compared to naphthalene (entries 3 and 7, Table 1). Additionally, the diastereoselectivity that is observed for reaction of the deuterated substrate **42** in DMF also supports the intermolecular hydrogen atom transfer mechanism (Scheme 6B).[38]

In order to initiate the radical process proposed for the formation of dihydronaphthalene **31b**, hydrogen atom abstraction must occur. It is possible that the tris-allylic C−H bond of **50** is spontaneously broken at the temperatures that we perform the reaction (120−180 °C).[39] However, we propose that triplet oxygen initiates the radical reaction by abstraction of the tris-allylic hydrogen atom from **50** (Scheme 6C). This hypothesis is supported by the work of Hendry et al., who used

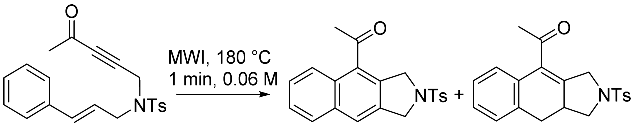
Scheme 6. Proposed Mechanism for Dihydronaphthalene Formation: (A) Intramolecular Deuterium Atom Abstraction To Produce Dihydronaphthalene; (B) Proposed Mechanism to Explain the Diastereoselectivity Observed when the IMDDA Reaction of 42 Is Performed in DMF; (C) Initiation of the Radical Reaction by Triplet Oxygen; (D) Hendry's Mechanism for Dehydrogenation of 1,4-Cyclohexadiene by Triplet Oxygen



kinetic data and quantitative water analysis to reveal that only substoichiometric amounts of oxygen were required for the thermal dehydrogenation of 1,4-cyclohexadiene to benzene (Scheme 6D).[40] When we performed the IMDDA reaction in the presence or absence of oxygen, the same product selectivity for naphthalene **31a** and dihydronaphthalene **31b** was observed; this data is supported by Hendry's results, which indicated that stoichiometric quantities of oxygen are not necessary to achieve oxidation.

Attempts were also made to trap the postulated radical intermediates. Utilization of standard IMDDA reaction conditions, along with 1,4-cyclohexadiene (10 equiv), afforded a similar yield and 1:1.2 ratio of **31a** and **31b** when compared to reaction mixtures in which 1,4-cyclohexadiene was not present (Scheme 7). No byproducts resulting from trapping of radical or biradical intermediates were observed. Increasing the concentration of 1,4-cyclohexadiene (88 equiv) led to problems reaching the reaction's target temperature. Alternatively, heating of **30** in DCE at 180 °C for 2 min in the presence of excess (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO, 1.5 equiv) resulted in a 52% yield of **31a**; **31b** and the TEMPO-trapped products were not detected. The increase in yield of **31a** from 30% in the absence of TEMPO to 52% in the presence of TEMPO may be explained by TEMPO acting as an oxidant during the reaction.[41] The overall lower yield of the reaction and the lack of dihydronaphthalene product observed is attributed to decomposition of dihydronaphthalene under the reaction conditions and is evidenced by tosyl and unresolved aliphatic impurities observed in the $^1$H NMR spectrum of the crude reaction mixture.

Scheme 7. IMDDA Reactions in the Presence of Radical-Trapping Agents



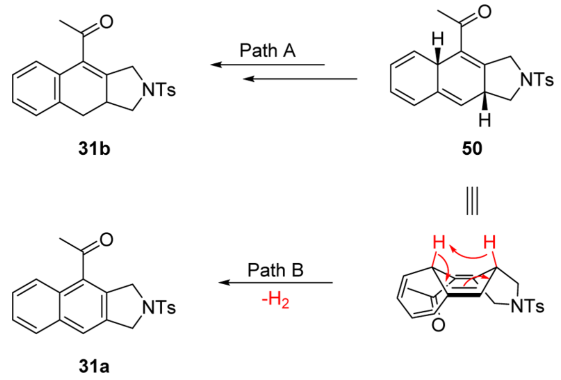
30 31a 31b

| | 31a | | 31b |
|---|---|---|---|
| *o*-DCB-d$_4$, CHD (10 equiv) | 33% | 1:1.2 | 39% |
| DCE, TEMPO (1.5 equiv) | 52% | | 0% |

**Mechanism for the Formation of Naphthalene.** The data above presents compelling support for the mechanism of formation of dihydronaphthalene; however, this data does not provide a satisfying explanation for how the naphthalene product is generated, aside from evidence strongly suggesting that the naphthalene is not produced directly from dihydronaphthalene (entries 3 and 4, Table 1). The lack of evidence for oxidation of dihydronaphthalene to naphthalene, along with the large primary kinetic isotope effect observed (Scheme 4), implies that the naphthalene and dihydronaphthalene products are being formed by diverging mechanistic pathways. One possible pathway by which the naphthalene could be formed is a concerted elimination of hydrogen gas via the same tetraene intermediate **50**, a process that was originally proposed by Matsubara (Scheme 8).[30]

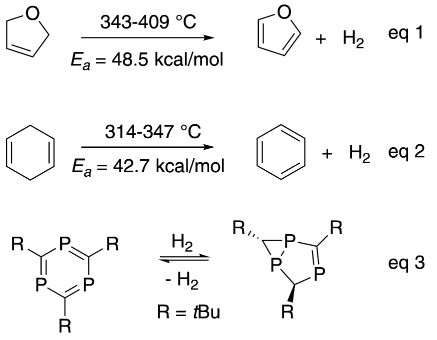
Woodward–Hoffmann state that atom transfers via a concerted unimolecular process are allowed when m = 4*q* + 2, where *m* is the number of *π* electrons and *q* is an integer.[42] Several reactions demonstrating unimolecular elimination of $H_2$ have been reported that have established a similar mechanism

**Scheme 8. Proposed Mechanism for Generation of Naphthalene via Concerted Loss of $H_2$**



to what we suggest for the formation of the naphthalene **31a**. One such example was published by Wellington and Walters, where thermal decomposition of 2,5-dihydrofuran showed production of both furan and $H_2$ in equal amounts (eq 1, Scheme 9).[43] Similar reports that were published independently by Ellis and Frey or Benson and Shaw demonstrated a related unimolecular elimination of $H_2$ for 1,4-cyclohexadiene in the generation of benzene (eq 2).[44] Recently, a triphosphabenzene was reduced under 4 atm of hydrogen pressure via a reversible 1,4-$H_2$ addition (eq 3).[45]

**Scheme 9. Unimolecular Elimination Reactions**



To test the hypothesis that the tetraene intermediate **50** would undergo a concerted unimolecular elimination of $H_2$ to generate naphthalene **31a**, we performed several IMDDA reactions with the goal of detecting $H_2$. We previously established that conventional heating and microwave irradiation conditions provided nearly identical results for the IMDDA reaction, and we envisioned that $H_2$ could potentially be observed by $^1H$ NMR spectroscopy if the IMDDA reaction was conducted in a sealed NMR tube using conventional heating. After heating styrene−yne **30** in *o*-DCB-$d_4$ at 180 °C for 2 min, a $^1H$ NMR spectrum of the reaction mixture was acquired which showed the presence of a new singlet at $\delta$ 4.73 that was not attributed to the products **31a** or **31b**; this resonance was assumed to correspond to $H_2$ that was formed during the reaction (Figure 2). To confirm that this resonance was $H_2$, additional $H_2$ was bubbled through the reaction mixture and an increase in the integration value for the resonance at $\delta$ 4.73 from 0.05 to 0.09 was observed, indicating that this resonance was correctly identified as $H_2$. Argon was also bubbled through the reaction mixture which resulted in the disappearance of this resonance from the $^1H$ NMR spectrum. This information supports our hypothesis that $H_2$ was being produced during the reaction; however, only the quantity of $H_2$ in solution could be determined using this approach.

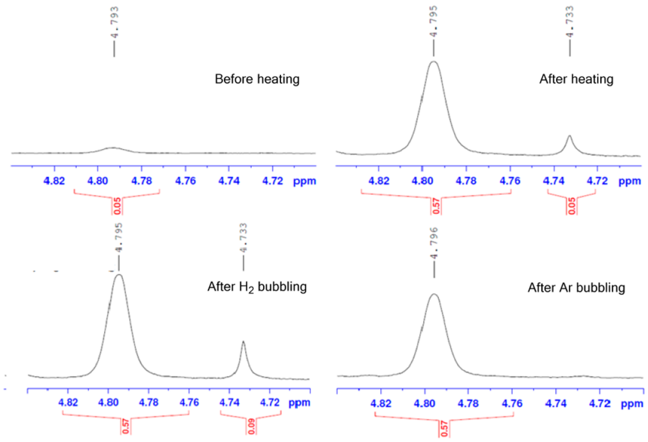


**Figure 2.** Detection of hydrogen gas by $^1H$ NMR spectroscopy.

In order to quantify the amount of $H_2$ gas that was produced during the IMDDA reaction, gas chromatography (GC) was utilized to examine the headspace of the reaction. For the GC experiments, styrene−yne **30** was irradiated for 1 min at 180 °C in *o*-DCB (see the Supporting Information). Based upon the average 80% yield and 1:1.2 ratio of naphthalene **31a** and dihydronaphthalene **31b** products typically generated for these IMDDA reactions, the theoretical yield of $H_2$ was calculated (see Supporting Information). Overall, a 39−48% yield of $H_2$ was determined by GC for these experiments. These results indicate that a substantial amount of $H_2$ is produced during the IMDDA reaction, and that the original hypothesis in which the naphthalene product is formed via intramolecular concerted elimination of $H_2$ from tetraene intermediate **50** is supported (Scheme 8).

With experimental evidence in hand supporting diverging reaction mechanisms for the formation of naphthalene and dihydronaphthalene products, further mechanistic insight was gained through quantum chemical calculations.[46] Both the direct expulsion of $H_2$ and hydrogen atom abstraction by triplet oxygen, affording the naphthalene and dihydronaphthalene products, respectively, were examined for tetraene **50**. The results from these calculations predict the hydrogen atom abstraction process to be more favorable by 9.8 kcal/mol (Figure 3). This data correlates with the 2-fold preference for formation of the dihydronaphthalene over the naphthalene product at 180 °C (entry 3, Table 1). Likewise, at lower temperatures an 8-fold preference for the dihydronaphthalene was observed (120 °C, entry 5, Table 1), whereas at higher temperatures the opposite product selectivity was afforded (225 °C, entry 6, Table 1).

Predicting selectivity for the formation of the dihydronaphthalene or naphthalene product may also be possible from the calculated through-space distance between the flagpole hydrogens of the corresponding tetraene intermediates. For example, for the tetraene intermediate with the all-carbon tether, **53**, the $H_a$−$H_b$ distance was calculated to be 3.05 Å. By comparison, this distance for tetraene **50**, containing a tosylamide tether, was 3.63 Å, representing a difference of nearly 0.6 Å. These calculated distances correlate well with our experimental observations for product selectivity, where a shorter calculated distance between the hydrogen atoms affords the naphthalene

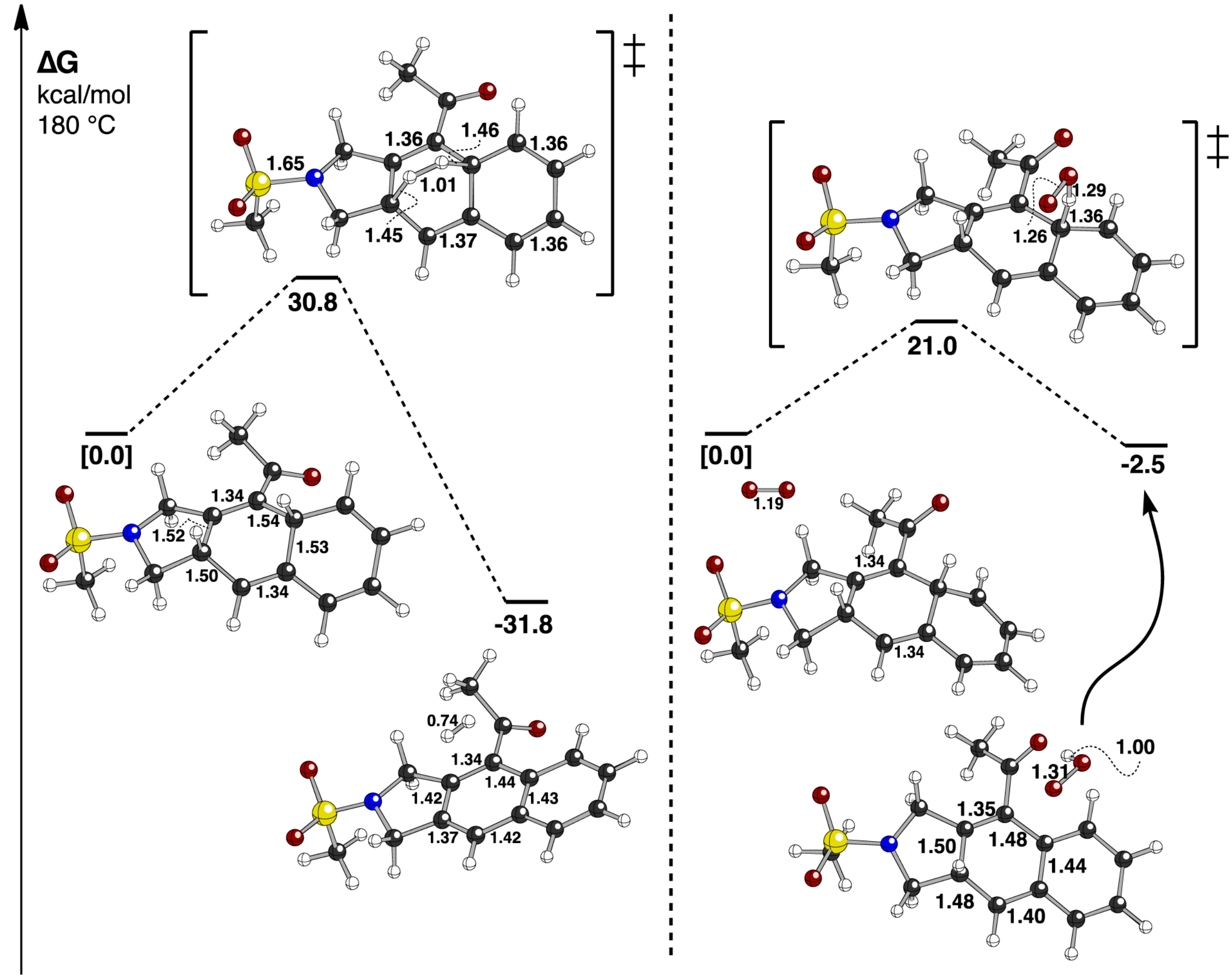
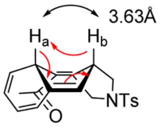
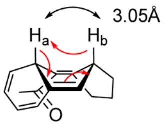


**Figure 3.** Direct $H_2$ expulsion and hydrogen abstraction by $^3O_2$, modeled with SMD(DCE)-UM06-2*X*/6-31+G(d,p) at 180 °C. Relative free energies are shown in kcal/mol and selected distances are shown in angstroms. A mesyl group was used in place of a tosyl group to simplify the calculations.

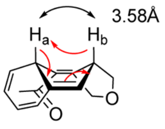
product selectively, and a longer distance favors dihydronaphthalene formation. For example, an IMDDA reaction of the all-carbon tether precursor **26** afforded the naphthalene product in **27a** quantitative yield, whereas reaction of the tosylamide tether-containing substrate **30** produced the dihydronaphthalene **31b** in 56% yield and the naphthalene **31a** in 30% yield when reacted under identical conditions (entries 1 and 3, Table 1). It is interesting to note that for the latter case, we can alter this product ratio to further favor dihydronaphthalene formation by lowering the reaction temperature (entry 5, Table 1). For the ether tether **54**, the $H_a$-$H_b$ calculated distance is 3.58 Å and the dihydronaphthalene was afforded in 15% yield and the naphthalene in 28% yield (entry 2, Table 1). To help explain this anomalous 1:2 ratio, we suspect that decomposition of the dihydronaphthalene **29b** during the longer reaction time may be skewing this data, as suggested by the low yields.



**50**



**53**



**54**

## ■ CONCLUSIONS

In summary, the naphthalene and dihydronaphthalene product distribution afforded from the IMDDA reaction of styrene–ynes is attributed to mechanistic divergence. Compelling evidence, such as the isotopic labeling and hydrogen gas detection experiments provided herein, supports the premise that both products are obtained from a common intermediate. An understanding of the mechanisms of formation of each of these products can potentially allow for better control of product selectivity during the IMDDA reaction through tuning of the reaction substrates and conditions. While previous examples of thermal IMDDA reactions have been reported with variable results, this represents the first systematic study of the mechanism of the IMDDA reaction of styrene–ynes for the production of both naphthalene and dihydronaphthalene products. Furthermore, we expect that these mechanistic studies, along with the operational simplicity and synthetic orthogonality of this approach, will transform the IMDDA reaction into a synthetically useful alternative for the preparation of naphthalene and dihydronaphthalenes, as well as other previously inaccessible aromatic compounds. Finally, the removal of hydrogen gas from IMDDA adducts to form aromatic compounds offers an environmentally benign alternative to typical oxidation protocols.[47]

## ■ EXPERIMENTAL SECTION

**General Experimental Methods.** Dichloromethane (DCM) and tetrahydrofuran (THF) were dried by passing through alumina, and triethylamine was freshly distilled from $CaH_2$ prior to use. $^1H$ and $^{13}C$ NMR spectra were referenced to residual chloroform (7.26 ppm for $^1H$ NMR spectroscopy, 77.16 ppm for $^{13}C$ NMR spectroscopy), 1,2-dichlorobenzene (7.14 ppm for $^1H$ NMR spectroscopy), or *N,N*-dimethylformamide (8.38 ppm for $^1H$ NMR spectroscopy). Chemical shifts are reported in ppm; multiplicities are indicated by s (singlet), b s (broad singlet), d (doublet), t (triplet), q (quartet), p (pentet), and m (multiplet). In experiments where yields were determined by $^1H$ NMR spectroscopy, *p*-dimethoxybenzene was used as an internal standard. A standard solution of *p*-dimethoxybenzene (20 mg) in *o*-DCB-$d_4$ (0.5 mL) was prepared so that quantities of *p*-dimethoxybenzene could be accurately added to the reaction mixtures. All microwave-mediated reactions were conducted in either a Biotage Initiator Exp microwave synthesizer or in an Anton-Paar Monowave 300 microwave synthesizer. The temperature of reactions in the Monowave 300 was monitored internally by a ruby sensor probe, unless otherwise specified. The microwave parameters were set to variable power, constant temperature, stirring on, and a fixed hold time. Styrene-yne **30**, naphthalene **31a**, and dihydronaphthalene **31b** were prepared and characterized according to procedures previously reported by our laboratory.[14i] See the Supporting Information for additional general methods and details.

**General Microwave Irradiation Procedure.** To a microwave irradiation vial were added styrene–yne and the reaction solvent (0.06 M). The solution was irradiated at 180 °C for 1 min, followed by concentration of the reaction mixture under high vacuum. The crude material was purified by silica gel column chromatography to yield the naphthalene and/or dihydronaphthalene as a solid. Mixtures of naphthalene and dihydronaphthalene products were separated for characterization by HPLC. Experiments conducted under argon involved initial degassing of the starting solution by bubbling with argon through the septum of the microwave irradiation vial for 30 min prior to irradiation.

**1-(2-Tosyl-2,3-dihydro-1*H*-benzo[*f*]isoindol-4-yl)ethan-1-one (31a).** Compound **31a** was prepared from **30** according to the general microwave procedure. Characterization data is consistent with previously reported literature data.[14i] $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.85–7.79 (m, 4H), 7.70 (s, 1H), 7.54–7.47 (m, 2H), 7.32 (d, $J$ = 8.2 Hz, 2H), 4.73 (s, 2H), 4.70 (s, 2H), 2.66 (s, 3H), 2.39 (s, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 204.1, 144.1, 134.9, 133.8, 133.6, 133.3, 133.0, 130.1 (2C), 129.1, 128.7, 127.9 (2C), 127.4, 126.6, 124.8, 123.8, 53.0, 52.9, 32.1, 21.7.

**1-(2-Tosyl-2,3,9,9a-tetrahydro-1*H*-benzo[*f*]isoindol-4-yl)-ethan-1-one (31b).** Compound **31b** was prepared from **30** according to the general microwave procedure. Characterization data is consistent with previously reported literature data.[14i] $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.75 (d, $J$ = 8.2 Hz, 2H), 7.34 (d, $J$ = 8.2 Hz, 2H), 7.24–7.16 (m, 3H), 7.09 (d, $J$ = 6.9 Hz, 1H), 4.53 (dd, $J$ = 18.0, 1.6 Hz, 1H), 3.95 (dd, $J$ = 9.4, 8.2 Hz, 1H), 3.90 (dd, $J$ = 18.0, 2.8 Hz, 1H), 3.02–2.93 (m, 1H), 2.86 (app t, $J$ = 9.2 Hz, 1H), 2.82 (dd, $J$ = 14.8, 6.4 Hz, 1H), 2.51 (app t, $J$ = 14.8 Hz, 1H), 2.44 (s, 3H), 2.34 (s, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 200.9, 148.1, 144.0, 134.7, 133.1, 132.1 (2C), 130.0 (2C), 128.2, 128.1, 128.0 (2C), 127.3, 125.8, 53.1, 51.8, 40.2, 32.4, 30.2, 21.7.

**Irradiation of 30 in DMF-$d_7$.** To a G4 Anton-Paar microwave irradiation vial were added styrene–yne **30** (0.020 g, 0.054 mmol) and DMF-$d_7$ (0.91 mL). The solution was irradiated at 180 °C for 1 min, turning the reaction mixture orange in color. The reaction mixture was then concentrated under high vacuum and the crude material purified by silica gel flash column chromatography (1.5 cm, 20% ethyl acetate/hexanes) to yield the title compounds as a white solid and as a 1:10 mixture of **31a** and **31b** (0.015 g, 75%). These products were separated for characterization by HPLC, utilizing 10% ethyl acetate/hexanes as the eluent and a flow rate of 4 mL/min. The HPLC retention time of naphthalene **31a** was 34.2 min and the retention time of dihydronaphthalene **31b** was 38.2 min. An $^1H$ NMR spectrum of the dihydronaphthalene product **31b** showed no deuterium incorporation (Figure S1, Supporting Information).

**Irradiation of 30 in the Presence of 1,4-Cyclohexadiene.** To an NMR tube were added styrene–yne **30** (0.013 g, 0.036 mmol), *o*-DCB-$d_4$ (0.55 mL), and a solution of *p*-dimethoxybenzene in *o*-DCB-$d_4$ (50 $\mu$L, 0.002 g) as an internal standard. A $^1H$ NMR spectrum of the solution was obtained, followed by transfer of the solution to a G4 Anton-Paar microwave irradiation vial and addition of 1,4-cyclohexadiene (34 $\mu$L, 0.36 mmol). The solution was then irradiated at 180 °C for 1 min, turning the reaction mixture light brown in color. The reaction mixture was then transferred to an NMR tube, and a $^1H$ NMR spectrum was obtained showing conversion of the starting material **30** to products **31a** and **31b** as a 1:1.2 mixture in 81% combined yield (Supporting Information).

**Irradiation of 30 in the Presence of TEMPO.** To a 0.5–2 mL Biotage microwave irradiation vial were added styrene–yne **30** (0.022 g, 0.060 mmol), DCE (1.0 mL), and (2,2,6,6-tetramethylpiperidin-1-yl)oxy (0.014 g, 0.090 mmol). The solution was then irradiated at 180 °C for 1 min, turning the reaction mixture dark brown in color. The reaction mixture was concentrated under reduced pressure and the crude material purified by silica gel flash column chromatography (10% ethyl acetate–hexanes) to yield **31a** as a light yellow solid (0.011 g, 52%).

**Conventional Heating and Hydrogen Detection by $^1H$ NMR Spectroscopy.** To a screw-cap NMR tube were added styrene–yne **30** (0.013 g, 0.036 mmol), *o*-DCB-$d_4$ (0.55 mL), and a solution of *p*-dimethoxybenzene in *o*-DCB-$d_4$ (50 $\mu$L, 0.002 g) as an internal standard via pipet. The cap was screwed onto the NMR tube, and an $^1H$ NMR spectrum of the starting solution was obtained. The solution was then heated at 180 °C for 2 min in an oil bath, turning the reaction mixture brown in color. A $^1H$ NMR spectrum of the reaction mixture was obtained showing conversion of the starting material **30** to the products **31a** and **31b** as a 1:1.2 mixture in 86% combined yield (Supporting Information).

The $^1H$ NMR spectrum of the products also showed the presence of hydrogen gas ($H_2$) in solution as a singlet integrating for 0.06H at 4.73 ppm (Supporting Information), which indicated a 11:1 ratio of **31a**:$H_2$. To confirm that this resonance corresponded to $H_2$, $H_2$ was bubbled through the reaction mixture and another $^1H$ NMR spectrum was obtained which showed an increase in the integration value from 0.06 to 0.10H, representing a 6:1 ratio of **31a**:$H_2$ (Supporting Information). Argon was then bubbled through the reaction mixture, and the resonance corresponding to $H_2$ disappeared (see Figure 2 manuscript).

***(E)*-3-Phenylprop-2-en-2-*d*-1-ol (33).** To a flame-dried, two-neck, 100 mL round-bottomed flask equipped with a condenser and a septum under an atmosphere of argon was added lithium aluminum deuteride (0.877 g, 20.9 mmol). The round-bottomed flask was evacuated and refilled with argon (3×), and THF (35 mL) was added via syringe with stirring. 3-Phenyl-2-propyn-1-ol (**32**) (2.0 mL, 16 mmol) in THF (5 mL) was then added slowly dropwise via syringe, and bubbling occurred along with a color change from dark to light gray. The reaction mixture was heated to reflux in an oil bath for 5 h, turning the reaction mixture brown, followed by cooling to rt then 0 °C in an ice bath. To quench the reaction, water was added *slowly* dropwise and vigorous bubbling occurred. Once bubbling had ceased and the reaction mixture had become white in color, diethyl ether was added, and the aqueous layer was separated. The aqueous layer was then extracted with diethyl ether (2×), and the combined organic layers were washed with brine, dried over magnesium sulfate, gravity filtered, and concentrated under reduced pressure to yield the title compound as a clear oil (2.23 g, quant). The crude material was carried on without purification. Analytical TLC on silica gel: $R_f$ = 0.4 (40% ethyl acetate/hexanes). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.39 (d, $J$ = 7.5 Hz, 2H), 7.32 (t, $J$ = 7.5 Hz, 2H), 7.26 (t, $J$ = 7.5 Hz, 1H), 6.61 (s, 1H), 4.32 (s, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 136.8, 131.2, 128.7 (2C), 128.3 (t, $J$ = 24.0 Hz, 1C), 127.8 (2C), 126.6, 63.8. IR (film): 3338, 3080, 3059, 2919, 2863, 1600, 1493, 1449 $cm^{-1}$. HRMS (ESI): *m/z* calcd for $C_9H_8DO$ $[M - H]^+$ 134.0722, found 134.0711.

**4-Methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (34).** Synthesized according to the procedure reported by Gilbertson.[48]

**(*E*)-4-Methyl-*N*-(3-phenylallyl-2-*d*)-*N*-(prop-2-yn-1-yl)benzenesulfonamide (35).** To a flame-dried, two-neck, 100 mL round-bottomed flask equipped with an argon inlet adapter and a septum were added (*E*)-3-phenylprop-2-en-2-*d*-1-ol (**33**) (1.00 g, 7.40 mmol), 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**34**) (1.55 g, 7.40 mmol), and triphenylphosphine (1.94 g, 7.40 mmol). The round-bottomed flask was evacuated and refilled with argon (3×), and THF (69 mL) was added via syringe with stirring. Diisopropyl azodicarboxylate (1.46 mL, 7.40 mmol) was added dropwise via syringe, and the reaction mixture turned bright yellow in color. The reaction mixture was stirred at rt for 20 h and was then concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (5 cm column, 5−15% ethyl acetate/hexanes) to yield the title compound as a white solid (2.04 g, 85%). Analytical TLC on silica gel: $R_f$ = 0.5 (25% ethyl acetate/hexanes). Mp: 74−75 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.77 (d, *J* = 8.1 Hz, 2H), 7.35−7.26 (m, 7H), 6.56 (s, 1H), 4.13 (d, *J* = 2.4 Hz, 2H), 3.99 (s, 2H), 2.44 (s, 3H), 2.04 (t, *J* = 2.4 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 143.7, 136.2 (2C), 134.9, 129.6 (2C), 128.7 (2C), 128.2, 127.9 (2C), 126.7 (2C), 122.7 (t, *J* = 24.0 Hz, 1C), 76.8, 74.0, 48.6, 36.0, 21.7. IR (film): 3026, 2921, 2119, 1598, 1495, 1348, 1162 cm$^{-1}$. HRMS (ESI): *m*/*z* calcd for $C_{19}H_{19}DO_2NS$ [M + H]$^+$ 327.1278, found 327.1269.

**(*E*)-4-Methyl-*N*-(4-oxopent-2-yn-1-yl)-*N*-(3-phenylallyl-2-*d*)-benzenesulfonamide (37).** To a flame-dried, two-neck, 15 mL round-bottomed flask equipped with an argon inlet adapter and a septum was added styrene−yne **35** (0.112 g, 0.34 mmol) in THF (7.8 mL). The solution was cooled to −78 °C in a dry ice−acetone bath, and then lithium diisopropylamide (0.17 mL of a 2.0 M solution in THF/heptane/ethylbenzene, 0.34 mmol) was added slowly dropwise via syringe, turning the reaction mixture dark purple. The reaction mixture was stirred at −78 °C for 1 h and became green in color. *N*-Methoxy-*N*-methylacetamide (**36**) (33 $\mu$L, 0.31 mmol) was subsequently added via syringe, and the reaction mixture turned light purple. The reaction mixture was stirred at −78 °C for 15 min and at rt for 1.5 h. Over time, the color became a dark brown. The reaction mixture was poured into brine, and satd aq ammonium chloride was added. The aqueous layer was separated and extracted with ethyl acetate (2×), and the combined organic layers were washed with brine, dried over magnesium sulfate, gravity filtered, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (2.5 cm column, 15% ethyl acetate/hexanes) to yield the title compound as a light yellow solid (0.052 g, 46%). Analytical TLC on silica gel, $R_f$ = 0.3 (25% ethyl acetate/hexanes). Mp: 93−94 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.76 (d, *J* = 8.0 Hz, 2H), 7.35−7.24 (m, 7H), 6.55 (s, 1H), 4.27 (s, 2H), 3.99 (s, 2H), 2.43 (s, 3H), 2.10 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 183.3, 144.2, 135.9, 135.7, 135.4, 129.9 (2C), 128.8 (2C), 128.4, 127.9 (2C), 126.7 (2C), 122.2 (t, *J* = 24.0 Hz, 1C), 84.9, 84.4, 49.3, 36.2, 32.4, 21.6. IR (film): 3026, 2921, 2210, 1679, 1597, 1495, 1350, 1163 cm$^{-1}$. HRMS (ESI): *m*/*z* calcd for $C_{21}H_{21}DO_3NS$ [M + H]$^+$ 369.1374, found 369.1383.

**(*E*)-3-(Phenyl-*d*$_5$)prop-2-en-1-ol (40).** To a flame-dried, two-neck, 50 mL round-bottomed flask equipped with an argon inlet adapter and a septum were added bromobenzene-*d*$_5$ (**38**) (1.30 mL, 12.3 mmol) and water (62 mL). Propargyl alcohol (**39**) (1.1 mL, 19 mmol), pyrrolidine (1.52 mL, 18.5 mmol), tetrakis(triphenylphosphine)palladium(0) (0.071 g, 0.062 mmol), and copper(I) iodide (0.023 g, 0.12 mmol) were added sequentially. The reaction mixture was stirred at 70 °C for 1 h, turning the reaction mixture from yellow to light green. The reaction mixture was then cooled to rt, and diethyl ether was added. The aqueous layer was separated and extracted with diethyl ether (2×), and the combined organic layers were washed with water and brine, dried over magnesium sulfate, gravity filtered, and concentrated under reduced pressure. The crude material was filtered through a pad of silica gel with diethyl ether washings and then was placed under high vacuum to yield 3-(phenyl-*d*$_5$)prop-2-yn-1-ol as a yellow oil (0.844 g, 50%). Characterization data is consistent with previously reported literature data.[49] Analytical TLC on silica gel: $R_f$ = 0.3 (20% ethyl acetate/hexanes). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 4.51 (s, 2H), 1.64 (b s, 1H).

To a flame-dried, two-neck, 15 mL round-bottomed flask equipped with a condenser and a septum under an atmosphere of argon was added lithium aluminum hydride (0.164 g, 4.33 mmol). The round-bottomed flask was evacuated and refilled with argon (3×), and THF (7.2 mL) was added via syringe with stirring. 3-(Phenyl-*d*$_5$)prop-2-yn-1-ol (0.457 g, 3.33 mmol) in THF (1.1 mL) was then added slowly dropwise via syringe, and bubbling occurred. The reaction mixture was heated to reflux in an oil bath for 1 h, turning the reaction mixture from light gray to light brown, followed by cooling to rt then 0 °C in an ice bath. To quench the reaction, water was added *slowly* dropwise and vigorous bubbling occurred. Once bubbling had ceased and the reaction mixture had become white in color, diethyl ether was added and the aqueous layer was separated. The aqueous layer was then extracted with diethyl ether (4×), and the combined organic layers were washed with brine, dried over magnesium sulfate, gravity filtered, and concentrated under reduced pressure to yield the title compound as an amber oil (0.257 g, 56%). The crude material was carried on without purification. Analytical TLC on silica gel: $R_f$ = 0.2 (20% ethyl acetate/hexanes). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 6.63 (d, *J* = 15.9 Hz, 1H), 6.37 (dt, *J* = 15.9, 5.4 Hz, 1H), 4.33 (d, *J* = 5.4 Hz, 2H), 1.55 (b s, 1H).

**(*E*)-4-Methyl-*N*-(3-(phenyl-*d*$_5$)allyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide (41).** To a flame-dried, two-neck, 25 mL round-bottomed flask equipped with an argon inlet adapter and a septum were added (*E*)-3-(phenyl-*d*$_5$)prop-2-en-1-ol (**40**) (0.253 g, 1.82 mmol), 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**34**) (0.381 g, 1.82 mmol), and triphenylphosphine (0.478 g, 1.82 mmol). The round-bottomed flask was evacuated and refilled with argon (3×), and THF (17 mL) was added via syringe with stirring. Diisopropyl azodicarboxylate (0.36 mL, 1.8 mmol) was added dropwise via syringe, and the reaction mixture turned bright yellow in color. The reaction mixture was stirred at rt for 16 h and was then concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (2.5 cm column, 15% ethyl acetate/hexanes) to yield the title compound as an off-white solid (0.517 g, 86%). Analytical TLC on silica gel, $R_f$ = 0.5 (25% ethyl acetate/hexanes). Mp: 69−71 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.77 (dd, *J* = 8.4, 1.8 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 6.58 (td, *J* = 15.9, 1.2 Hz, 1H), 6.08 (dt, *J* = 15.9, 6.9 Hz, 1H), 4.13 (d, *J* = 2.4 Hz, 2H), 3.99 (dd, *J* = 6.9, 1.2 Hz, 2H), 2.44 (s, 3H), 2.04 (t, *J* = 1.2 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 143.7, 136.2, 136.1, 135.0, 129.6 (2C), 128.5−127.5 (m, 5C), 126.2 (t, *J* = 24.0 Hz, 2C), 123.0, 76.7, 73.9, 48.7, 36.0, 21.7. IR (film): 3289, 3034, 2923, 2276, 2118, 1598, 1494, 1346, 1161 cm$^{-1}$. HRMS (ESIMSMS): *m*/*z* calcd for $C_{19}H_{15}D_5O_2NS$ [M + H]$^+$ 331.1518, found 331.1529.

**(*E*)-4-Methyl-*N*-(4-oxopent-2-yn-1-yl)-*N*-(3-(phenyl-*d*$_5$)allyl)-benzenesulfonamide (42).** To a flame-dried, two-neck, 25 mL round-bottomed flask equipped with an argon inlet adapter and a septum was added styrene−yne **41** (0.200 g, 0.61 mmol) in THF (14 mL). The solution was cooled to −78 °C in a dry ice−acetone bath, and then lithium diisopropylamide (0.30 mL of a 2.0 M solution in THF/heptane/ethylbenzene, 0.61 mmol) was added slowly dropwise via syringe, turning the reaction mixture dark purple. The reaction mixture was stirred at −78 °C for 80 min and became light yellow. *N*-Methoxy-*N*-methylacetamide (**36**) (58 $\mu$L, 0.55 mmol) was subsequently added dropwise via syringe, and the reaction mixture was stirred at −78 °C for 15 min and at rt for 1 h. Over time, the reaction mixture turned reddish in color. Saturated aq ammonium chloride was added, and the aqueous layer was separated and extracted with ethyl acetate (2×). The combined organic layers were washed with brine, dried over magnesium sulfate, gravity filtered, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (2.5 cm column, 15% ethyl acetate/hexanes) to yield the title compound as a white solid (0.163 g, 80%). Analytical TLC on silica gel: $R_f$ = 0.3 (25% ethyl acetate/hexanes). Mp: 84−86 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.77 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 6.57 (d, *J* = 15.9 Hz, 1H), 6.08

(dt, *J* = 15.9, 6.9 Hz, 1H), 4.27 (s, 2H), 4.00 (dd, *J* = 6.9, 0.9 Hz, 2H), 2.44 (s, 3H), 2.10 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 183.3, 144.2, 135.8 (2C), 135.4, 129.9 (2C), 128.5−127.6 (m, 5C), 126.3 (t, *J* = 24.0 Hz, 2C), 122.5, 84.9, 84.4, 49.4, 36.2, 32.4, 21.6. IR (film): 3031, 2922, 2246, 2209, 1670, 1597, 1494, 1349, 1163 cm$^{-1}$. HRMS (ESIMSMS): *m*/*z* calcd for $C_{21}H_{17}D_5O_3NS$ $[M + H]^+$ 373.1622, found 373.1634.

**Methyl (*E*)-4-((4-Methyl-*N*-(3-(phenyl-*d*$_5$)allyl)phenyl)sulfonamido)but-2-ynoate (43).** To a flame-dried, two-neck, 5 mL round-bottomed flask equipped with an argon inlet adapter and a septum was added styrene−yne **41** (0.10 g, 0.30 mmol) in THF (1.5 mL). The solution was cooled to −78 °C in a dry ice−acetone bath, and then *n*-butyllithium (0.21 mL of a 1.6 M solution in hexanes, 0.33 mmol) was added slowly dropwise via syringe, turning the reaction mixture dark purple. The reaction mixture was stirred at −78 °C for 45 min and became light brown. Methyl chloroformate (30 μL, 0.39 mmol) was subsequently added dropwise via syringe, and the reaction mixture was stirred at −78 °C for 1 h, becoming darker brown over time. The reaction mixture was allowed to warm slowly to −10 °C, and satd aq ammonium chloride was added. The aqueous layer was separated and extracted with ethyl acetate (2×), and the combined organic layers were washed with brine, dried over magnesium sulfate, gravity filtered, and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (2.5 cm column, 10% ethyl acetate/hexanes) to yield the title compound as a clear oil (0.065 g, 55%). Analytical TLC on silica gel: $R_f$ = 0.3 (25% ethyl acetate/hexanes). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 6.58 (td, *J* = 16.0, 1.2 Hz, 1H), 6.07 (dt, *J* = 16.0, 6.8 Hz, 1H), 4.24 (s, 2H), 3.98 (dd, *J* = 6.8, 0.8 Hz, 2H), 3.71 (s, 3H), 2.44 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 153.2, 144.2, 135.9, 135.6 (2C), 129.9 (2C), 128.5−127.8 (m, 5C), 126.3 (t, *J* = 24.0 Hz, 2C), 122.6, 80.8 (2C), 52.9, 49.4, 36.1, 21.7. IR (film): 2954, 2240, 1717, 1597, 1435, 1258, 1162 cm$^{-1}$. HRMS (ESI) *m*/*z* calcd for $C_{21}H_{17}D_5O_4NS$ $[M + H]^+$ 389.1556, found 389.1583.

**1-(2-Tosyl-2,3,9,9a-tetrahydro-1*H*-benzo[*f*]isoindol-4-yl-9a-*d*)ethan-1-one (44).** To an NMR tube were added the styrene−yne **37** (0.013 g, 0.036 mmol), *o*-DCB-*d*$_4$ (0.60 mL), and a solution of *p*-dimethoxybenzene in *o*-DCB-*d*$_4$ (50 μL, 0.002 g) as an internal standard. A $^1$H NMR spectrum of the solution was obtained, followed by transfer of the solution to a G4 Anton-Paar microwave irradiation vial which was irradiated at 180 °C for 1 min, turning the reaction mixture brown in color. The reaction mixture was then transferred to an NMR tube, and a $^1$H NMR spectrum was obtained showing conversion of the starting material **37** to the products **31a** and **44** as a 1:5.2 mixture in 81% combined $^1$H NMR yield (Supporting Information). The reaction mixture was then concentrated under high vacuum, and a portion of the mixture was separated by HPLC for characterization, utilizing 10% ethyl acetate/hexanes as the eluent and a flow rate of 4 mL/min. The HPLC retention time of naphthalene **31a** was 33.9 min, and the retention time of dihydronaphthalene **44** was 38.2 min. Analytical TLC on silica gel: $R_f$ = 0.5 (35% ethyl acetate/hexanes). Mp: 154−156 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.26−7.18 (m, 3H), 7.09 (dd, *J* = 6.8, 2.0 Hz, 1H), 4.52 (d, *J* = 18.0 Hz, 1H), 3.94 (d, *J* = 9.6 Hz, 1H), 3.90 (d, *J* = 18.0 Hz, 1H), 2.86 (d, *J* = 9.6 Hz, 1H), 2.81 (d, *J* = 14.6 Hz, 1H), 2.51 (d, *J* = 14.6 Hz, 1H), 2.43 (s, 3H), 2.34 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 200.9, 147.9, 144.0, 134.7, 133.2 (2C), 132.2, 130.0 (2C), 128.3, 128.1, 128.0 (2C), 127.3, 125.8, 53.0, 51.8, 39.8 (t, *J* = 20 Hz, 1C), 32.4, 30.2, 21.7. IR (film): 3059, 2925, 2255, 1682, 1622, 1598, 1347, 1163 cm$^{-1}$. HRMS (ESI): *m*/*z* calcd for $C_{21}H_{21}DO_3NS$ $[M + H]^+$ 369.1383, found 369.1370.

**1-(2-Tosyl-2,3-dihydro-1*H*-benzo[*f*]isoindol-4-yl-5,6,7,8-*d*$_4$)ethan-1-one (45) and 1-(2-Tosyl-2,3,9,9a-tetrahydro-1*H*-benzo[*f*]isoindol-4-yl-5,6,7,8,9-*d*$_5$)ethan-1-one (46).** To an NMR tube were added styrene−yne **42** (0.013 g, 0.036 mmol), *o*-DCB-*d*$_4$ (0.60 mL), and a solution of *p*-dimethoxybenzene in *o*-DCB-*d*$_4$ (50 μL, 0.002 g) as an internal standard. A $^1$H NMR spectrum of the solution was obtained, followed by transfer of the solution to a G4 Anton-Paar microwave irradiation vial which was irradiated at 180 °C for 1 min. The reaction mixture was then transferred to an NMR tube, and a $^1$H NMR spectrum was obtained showing conversion of the starting material **42** to the products **45** and **46** as a 1:1 mixture in 70% combined $^1$H NMR yield (Supporting Information). The reaction mixture was then concentrated under high vacuum, and a portion of the mixture was separated by HPLC for characterization, utilizing 10% ethyl acetate/hexanes as the eluent and a flow rate of 4 mL/min. The HPLC retention time of naphthalene **45** was 35.0 min, and the retention time of dihydronaphthalene **46** was 38.8 min. Dihydronaphthalene **46** was formed as a 1.5:1 ratio of diastereomers, as evidenced by $^1$H NMR spectroscopy after chromatography (major diastereomer shown). The diastereomers were not separable by HPLC. 1-(2-Tosyl-2,3-dihydro-1*H*-benzo[*f*]isoindol-4-yl-5,6,7,8-*d*$_4$)ethan-1-one (**45**). Analytical TLC on silica gel: $R_f$ = 0.5 (35% ethyl acetate/hexanes). Mp: 134−136 °C. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.1 Hz, 2H), 7.72 (s, 1H), 7.33 (d, *J* = 8.1 Hz, 2H), 4.74 (s, 2H), 4.72 (s, 2H), 2.67 (s, 3H), 2.40 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 204.0, 144.1, 134.9, 133.7, 133.5, 133.3, 133.0, 130.1, 129.0 (2C), 128.3 (t, *J* = 24.3 Hz, 1C), 127.9 (2C), 126.9 (t, *J* = 24.3 Hz, 1C), 126.1 (t, *J* = 24.3 Hz, 1C), 124.3 (t, *J* = 24.3 Hz, 1C), 123.8, 53.0, 52.9, 32.1, 21.7. IR (film): 2926, 2258, 1685, 1597, 1461, 1346, 1163 cm$^{-1}$. HRMS (ESI): *m*/*z* calcd for $C_{21}H_{16}D_4O_3NS$ $[M + H]^+$ 370.1415, found 370.1404. 1-(2-Tosyl-2,3,9,9a-tetrahydro-1*H*-benzo[*f*]isoindol-4-yl-5,6,7,8,9-*d*$_5$)ethan-1-one (**46**). Analytical TLC on silica gel: $R_f$ = 0.5 (35% ethyl acetate/hexanes). Mp: 159−160 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 4.53 (dd, *J* = 18.0, 1.6 Hz, 1H), 3.95 (dd, *J* = 9.6, 8.4 Hz, 1H), 3.90 (dd, *J* = 18.0, 2.8 Hz, 1H), 3.01−2.93 (m, 1H), 2.85 (app t, *J* = 9.6 Hz, 1H), 2.80 (d, *J* = 6.4, 0.69H), 2.49 (d, *J* = 14.8 Hz, 0.47H), 2.43 (s, 3H), 2.34 (s, 3H).[50] $^{13}$C NMR (175 MHz, $CDCl_3$): δ 200.9, 148.1, 144.0, 134.5, 133.1 (2C), 132.0, 130.0 (2C), 128.0 (2C), 127.8−127.4 (m, 2C), 126.7 (t, *J* = 24.0 Hz, 1C), 125.4 (t, *J* = 24.0 Hz, 1C), 53.1, 51.8, 40.2, 32.0 (t, *J* = 19.3 Hz, 1C), 30.2, 21.7. IR (film): 2925, 2255, 1682, 1598, 1494, 1346, 1162 cm$^{-1}$. HRMS (ESI): *m*/*z* calcd for $C_{21}H_{17}D_5O_3NS$ $[M + H]^+$ 373.1634, found 373.1621.

**Irradiation of 42 in DMF.** To a G4 Anton-Paar microwave irradiation vial were added styrene−yne **42** (0.015 g, 0.040 mmol) and DMF (0.67 mL). The solution was irradiated at 180 °C for 1 min and became orange in color. The temperature of the reaction was monitored by IR sensor (no ruby sensor probe). The reaction mixture was then concentrated under high vacuum, and a $^1$H NMR spectrum of the crude material was obtained which showed a 1:7 mixture of **45** and **46**. Purification by silica gel flash column chromatography (10% ethyl acetate/hexanes) yielded the mixture as a white solid (0.013 g, 86%). The mixture was then separated by HPLC for characterization, utilizing 10% ethyl acetate/hexanes as the eluent and a flow rate of 4 mL/min. Dihydronaphthalene **46** was formed as a 14:1 ratio of diastereomers (major diastereomer shown), as evidenced by $^1$H NMR spectroscopy after chromatography (Supporting Information). The diastereomers were not separable by HPLC. 1-(2-Tosyl-2,3,9,9a-tetrahydro-1*H*-benzo[*f*]isoindol-4-yl-5,6,7,8,9-*d*$_5$)ethan-1-one (**46**). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 4.53 (dd, *J* = 18.0, 1.6 Hz, 1H), 3.95 (dd, *J* = 9.6, 8.8 Hz, 1H), 3.90 (dd, *J* = 18.0, 2.8 Hz, 1H), 3.00−2.90 (m, 1H), 2.85 (app t, *J* = 9.6 Hz, 1H), 2.80 (d, *J* = 6.4 Hz, 0.07H), 2.49 (d, *J* = 15.2 Hz, 0.95H), 2.43 (s, 3H), 2.34 (s, 3H).[51]

**Methyl 2-Tosyl-2,3-dihydro-1*H*-benzo[*f*]isoindole-4-carboxylate-5,6,7,8-*d*$_4$ (47) and Methyl 2-Tosyl-2,3,9,9a-tetrahydro-1*H*-benzo[*f*]isoindole-4-carboxylate-5,6,7,8,9-*d*$_5$ (48).** To a G4 Anton-Paar microwave irradiation vial were added styrene−yne **43** (0.022 g, 0.057 mmol) and *o*-DCB (0.95 mL). The solution was irradiated at 180 °C for 4 min and became orange/brown in color. The temperature in this experiment was monitored by IR sensor (no ruby sensor probe). The reaction mixture was then concentrated under high vacuum, and a $^1$H NMR spectrum of the crude material was obtained which showed a 1:1.1 mixture of **47** and **48** (Supporting Information). Purification by silica gel flash column chromatography (1.5 cm column, 10−15% ethyl acetate/hexanes) yielded the mixture as a white solid (0.013 g, 59%). The mixture was then separated by HPLC for characterization utilizing 10% ethyl acetate/hexanes as the eluent and a flow rate of 4 mL/min. Dihydronaphthalene **48** was formed as a 2.6:1

ratio of diastereomers, as evidenced by $^1$H and $^2$H NMR spectroscopy after chromatography. The diastereomers were not separable by HPLC. Methyl 2-tosyl-2,3-dihydro-1*H*-benzo[*f*]isoindole-4-carboxylate-5,6,7,8-$d_4$ (**47**). Analytical TLC on silica gel: $R_f$ = 0.2 (15% ethyl acetate/hexanes). HPLC retention time: 27.3 min. Mp: 193−195 °C. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.80 (d, $J$ = 8.1 Hz, 2H), 7.76 (s, 1H), 7.32 (d, $J$ = 8.1 Hz, 2H), 4.92 (s, 2H), 4.74 (d, $J$ = 0.9 Hz, 2H), 4.03 (s, 3H), 2.39 (s, 3H). $^{13}$C NMR (175 MHz, CDCl$_3$): $\delta$ 167.4, 144.0, 138.3, 134.6, 133.6, 133.4, 130.1, 128.1−127.8 (m, 3C), 127.3 (t, $J$ = 22.2 Hz, 1C), 126.1 (t, $J$ = 22.2 Hz, 1C), 125.7 (2C), 125.4 (t, $J$ = 22.2 Hz, 1C), 54.8, 52.9, 52.5, 21.7. IR (film): 2919, 1713, 1462, 1162 cm$^{-1}$. HRMS (ESI): $m/z$ calcd for $C_{21}H_{16}D_4O_4NS$ [M + H]$^+$ 386.1359, found 386.1379. Methyl 2-Tosyl-2,3,9,9a-tetrahydro-1*H*-benzo[*f*]isoindole-4-carboxylate-5,6,7,8,9-$d_5$ (**48**). Analytical TLC on silica gel, $R_f$ = 0.2 (15% ethyl acetate/hexanes). HPLC retention time: 28.7 min. Mp: 148−150 °C. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.76 (d, $J$ = 8.1 Hz, 2H), 7.35 (d, $J$ = 8.1 Hz, 2H), 4.68 (dd, $J$ = 18.6, 1.5 Hz, 1H), 4.07 (dd, $J$ = 18.6, 3.0 Hz, 1H), 3.99 (dd, $J$ = 9.3, 9.3 Hz, 1H), 3.86 (s, 3H), 3.07−2.94 (m, 1H), 2.83−2.75 (m, 1.9H), 2.52−2.42 (m, 3.4H). $^{13}$C NMR (175 MHz, CDCl$_3$): $\delta$ 166.2, 152.8, 144.1, 134.1, 132.8, 130.0 (2C), 128.0 (2C), 127.5−127.2 (m, 2C), 126.8−126.2 (m, 2C), 123.4, 53.4, 52.8, 52.0, 40.7, 31.6 (t, $J$ = 19.0 Hz, 1C), 21.7. IR (film): 2925, 2854, 1712, 1598, 1494, 664, 595 cm$^{-1}$. HRMS (ESI): $m/z$ calcd for $C_{21}H_{17}D_5O_4NS$ [M + H]$^+$ 389.1578, found 389.1574.

**Crossover Study.** To a G4 Anton-Parr microwave irradiation vial were added styrene−ynes **30** (6.6 mg, 0.018 mmol) and **43** (7.0 mg, 0.018 mmol) in *o*-DCB (0.3 mL). The solution was irradiated at 180 °C. After 1 min, the reaction of **30** was complete by TLC, but a significant amount of **43** remained. The reaction was irradiated for an additional 2 min until complete by TLC. After irradiation, the reaction mixture was orange/brown in color. The reaction mixture was then concentrated under high vacuum, and the crude brown oil was subjected to HPLC, utilizing 10% ethyl acetate/hexanes as the eluent and a flow rate of 4 mL/min. The HPLC chromatogram showed four major peaks with retention times of 27.284, 28.707, 34.210, and 38.200 min, which were collected and characterized by ESI-MS (Figure S2, Supporting Information). Characterization showed that all six potential compounds of the crossover experiment were present within the four HPLC peaks isolated. The data pertaining to which HPLC peaks contained which products, as well as comparison of found masses to calculated masses, are listed in Table S3 (Supporting Information).

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

X-ray crystallography data, computational data, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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(51) The resonances at 2.85, 2.80, and 2.49 ppm appear to be overlapping with peaks at 2.89, 2.87, and 2.54 ppm that are similar in chemical shift and coupling constant to those for the nondeuterated substrate **31b**.