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Dehydrogenative Diels–Alder Reaction

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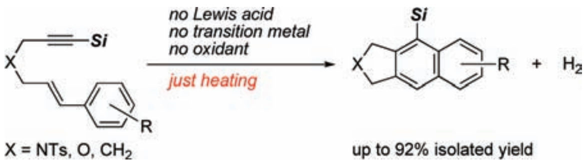
ABSTRACT



The dehydrogenative cycloaddition of dieneynes, which possess a diene in the form of a styrene moiety and a dienophile in the form of an alkyne moiety, produces naphthalene derivatives when heated. It was found that a key requirement of this process is the presence of a silyl group attached to the alkyne moiety, which forces a dehydrogenation reaction to occur.

The Diels–Alder reaction is undoubtedly one of the most fundamental and useful reactions available to organic chemists. It is used widely to form carbocyclic and heterocyclic frameworks as precursors for constructing complex organic molecules such as natural products.[1–3] Therefore, the quest to discover new variants of the Diels–Alder reaction remains important.[4–7] Herein, we report a dehydrogenative Diels–Alder reaction. Compounds that possess a diene in the form of a styrene moiety and a dienophile in the form of an alkyne moiety facilitate the production of naphthalene derivatives through the Diels–Alder reaction and a *retro*-Diels–Alder reaction that occurs via dehydrogenation. It was found that a key requirement of this process is the presence of a silyl group attached to the alkyne moiety, which forces a dehydrogenation reaction to occur.

We evaluated the reaction of **1a** in DMF at 160 °C for 48 h under an Ar atmosphere. The reaction afforded **2a** in 22% yield (Table 1, entry 1). While 77% of unreacted **1a** was recovered, the formation of byproducts such as cycloadduct **2a′** that were produced via the Diels–Alder reaction and subsequent aromatization was not observed. Microwave irradiation at 200 °C did not promote the occurrence of the reaction (entry 2). A 34% yield of **2a** was achieved without using a solvent (entry 3). We then assumed that, in other types of medium, the reaction might occur more efficiently.[8] Therefore, we examined the effect of the type of solvent on the reaction. When xylene was used as the reaction medium, the desired cycloadduct **2a** was obtained in 80% yield (entry 4). We also found that

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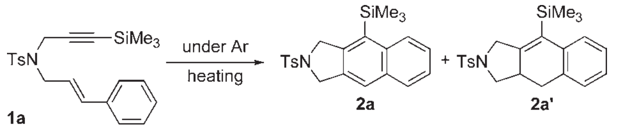
10.1021/ol202283d

polar solvents retarded the reaction (entries 5–8). Thus, xylene was the best solvent for the reaction. To further elucidate the factors that affect the reaction rate, the reaction temperature and time were also evaluated. We found that a reaction temperature of 160 °C was essential for achieving a good yield of **2a**; a lower yield was observed when the reaction was carried out at 130 °C (entry 9). The reaction time was also examined, and the results indicated that the yields of **2a** increased gradually from 22% to 80% when the reaction time was prolonged from 12 to 48 h (entries 4, 10, and 11). It was found that the reaction under air resulted in the decomposition of **1a** (entry 12).[9]

Table 1. Dehydrogenative Diels–Alder Reaction of **1a**[a]

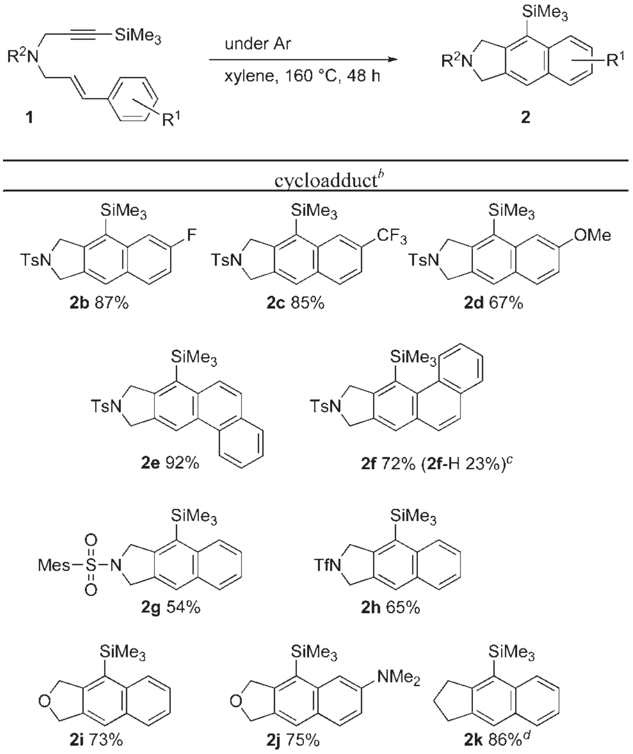


entry	solvent	temp (°C)	time (h)	yield (%) 2a	yield (%) 2a′
1	DMF	160	48	22	<1
2	DMF	200[b]	1	8	<1
3	–	160	48	34	<1
4	xylene	160	48	80 (78)[c]	<1
5	1,4-dioxane	160	48	18	<1
6	MeCN	100	48	<1	<1
7	AcOEt	100	48	<1	<1
8	H_2O	100	48	<1	<1
9	xylene	130	48	3	<1
10	xylene	160	12	22	<1
11	xylene	160	24	56	<1
12	xylene	160[d]	48	<1	<1

[a] All reactions were carried out using **1** (0.2 mmol) in 1.6 mL of solvent under an Ar atmosphere unless otherwise noted. [b] Microwave irradiation. [c] Isolated yield. [d] Reaction was carried out under air.

Even though it was necessary to carry out the reaction at a high temperature and for a long period of time to bring about its completion, we believed that this was reasonable in terms of producing polycyclic aromatic compounds without yielding byproducts considering that the constituents of the reaction were a styrene moiety and an alkyne. We therefore further examined the details of this type of cycloaddition to demonstrate its synthetic utility. We first examined various dieneynes **1** that possessed various functional groups; the results for these dieneynes are summarized in Scheme 1. The reactions of fluoro- and trifluoro-substituted dieneynes **1b** and **1c** afforded correspondingly substituted cycloadducts **2b** and **2c** in 87% and 85% isolated yields, respectively. Methoxy-substituted **1d** also produced cycloadduct **2d** in 67% yield. Dieneyne **1e**, which contained a naphthyl ring, participated in the reaction and afforded polyaromatic cycloadduct **2e** in 92% yield. The reaction of **1f**, which possessed a 2-naphthyl component, produced **2f** in 72% yield along with protodesilylated cycloadducts **2f**-H in 23% yield. The molecular structure of **2f** was confirmed by carrying out X-ray crystal structure analysis (Figure 1).

Scheme 1. Scope of Dehydrogenative Diels–Alder Reaction[a]



[a] All reactions were carried out using **1** (0.2 mmol) in 1.6 mL of xylene (160 °C) under an Ar atmosphere for 48 h unless otherwise noted. [b] Isolated yields. [c] **2f**-H; Protodesilylated cycloadduct. [d] Reaction temperature: 250 °C (neat).

Figure 1. ORTEP drawing of **2f**.

The effects of the presence of a tether group were also examined. Not only a tosyl group but also mesitylsulfonyl and trifluoromethanesulfonyl groups remained intact under the reaction conditions to afford the corresponding cycloadducts **2g** and **2h**. The ether tether **1i** also reacted to give the desired product **2i** in 73% yield. The expected cycloadduct **2k** was not obtained through the reaction of carbon-tethered dieneyne **1k** under the standard conditions used thus far. However, the desired product **2k** was obtained in 86% yield at an elevated reaction temperature

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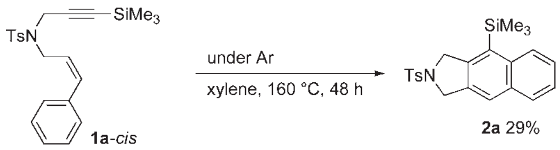
[9] The reaction of **1a** in both the presence and absence of radical initiator azobisisobutyronitrile (5 mol %) under the standard conditions provided cycloadduct **2a** in the same yields (78%).

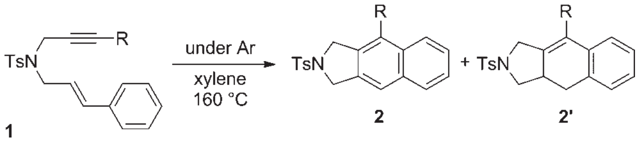
of 250 °C. The effects of double bond geometry on the reaction were evaluated using the *cis* form of **1a**. The low yield of **2a** (29%) suggested that a double bond *trans*-configuration geometry was essential for the cycloaddition to occur (Scheme 2).

Scheme 2. Effects of Double Bond Geometry on Reaction



We next examined effects of substituents on alkynes to gain insight into how the cycloaddition proceeds selectively to provide dehydrogenated cycloadduct **2** with a silyl-substituent. The results of this investigation are summarized in Table 2. We found that substituents such as H, Ph, and CO$_2$Et produce cycloadducts **2′** as major products and that desirable dehydrogenated cycloadducts **2** were obtained as minor products (entries 1, 5, and 6). Dehydrogenated cycloadducts **2** were not obtained as a major product even with prolonged reaction time (entries 2 and 7). At an elevated reaction temperature of 250 °C, **1l** was decomposed (entry 3). It is worth pointing out that the reaction of methyl-substituted dieneyne **1m** did not provide dehydrogenated cycloadduct **2m** or cycloadduct **2m′** (entry 4). On the other hand, the reaction of dieneyne **1p**, which possessed a bulky triisopropylsilyl group, resulted in the formation of the dehydrogenated cycloadduct **2p** in 13% yield (entry 8). In addition, dimethylphenylsilyl-substituted dieneyne **1q** also afforded **2q** as the sole product in 63% yield (entry 9). To further evaluate this dehydrogenative Diels–Alder reaction, we examined it with respect to the participation of dieneyne **4** (Scheme 3). The reaction of **4** under optimized reaction conditions produced Diels–Alder cycloadduct **5″** in 68% yield. Not even a trace amount of isomerized product **5′** or dehydrogenated cycloadduct **5** was observed. Thus, the aromatic moiety that was present in dieneyne **1** was also critical for carrying out the dehydrogenative Diels–Alder reaction.

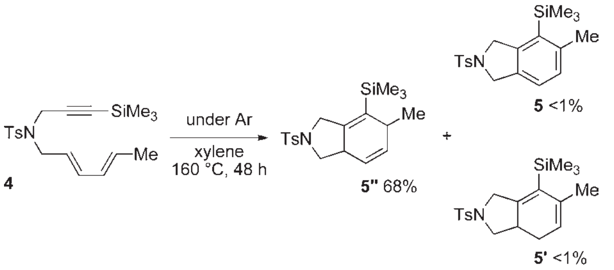
Table 2. Evaluation of Silyl-Substituent Effects[a]



entry	1	R	time (h)	yield (%) 2	2′
1	**1l**	H	48	6	37
2	**1l**	H	96	11	66
3	**1l**	H	48	<1[b]	<1
4	**1m**	Me	48	<1	<1
5	**1n**	Ph	48	14	56
6	**1o**	CO$_2$Et	48	29	65
7	**1o**	CO$_2$Et	96	35	59
8	**1p**	Si*i*Pr$_3$	48	13	<1
9	**1q**	SiMe$_2$Ph	48	63	<1
10	**1a**	SiMe$_3$	48	80	<1

[a] All reactions were carried out using **1** (0.2 mmol) in 1.6 mL of solvent under an Ar atmosphere. [b] Reaction temperature: 250 °C (neat).

Scheme 3. Reaction of Dieneyne **4**



While the mechanism of this reaction has not been elucidated completely, we propose the following reaction pathway based on the results that we observed (Scheme 4). The interaction between a styrene moiety and an alkyne moiety of dieneyne **1** to give cycloadduct **2″** is initiated by the Diels–Alder reaction.[10] In the case of dieneyne **1** with an alkylsilane group (*e.g.*, R = SiMe$_3$), the dehydrogenative *retro*-Diels–Alder reaction of **2″** will proceed owing to a potent thermodynamic driving force that originates from the simultaneous dual aromatization; this will result in the production of polyaromatic cycloadducts with higher thermodynamic stability (path A).[11] We also presume that the intermediate cycloadduct **2″** has a 1,4-cyclohexadine moiety with a strained boat conformation that originated from its benzannulated structure and steric repulsive effects due to its bulky trimethylsilyl group. Accordingly, two hydrogen atoms are in spatial proximity, and thus, a facile dehydrogenative *retro*-Diels–Alder reaction may proceed under the reaction conditions.[12] For dieneynes **1** with another terminal substituent such as H, Ph, and COOEt, cycloadduct **2′** is produced via the isomerization of **2″**, which is converted gradually to **2** under the reaction conditions (path B).

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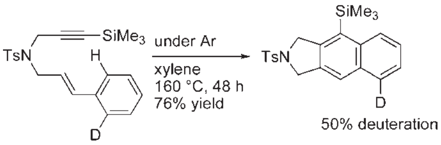
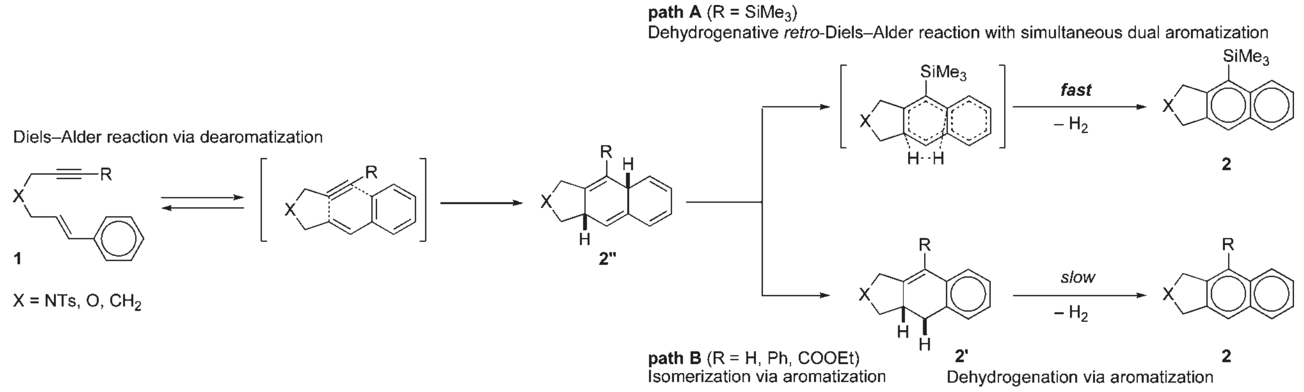
[11] For detailed energy profiles of the reactions and corresponding molecular structures, see Supporting Information.

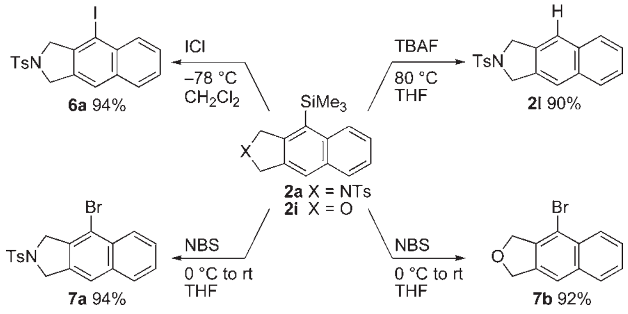
[12] The reaction of deuterium-labeled dieneyne **1a** produced **2a** with 50% deuterium labeling (*vide infra*). Therefore, the H/D kinetic isotope effect was not observed.



Scheme 4. Plausible Reaction Pathways



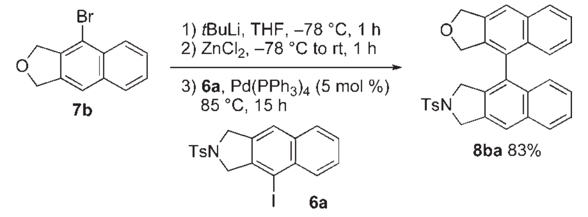
Scheme 5. Utility of Silyl Group for Transformation of **2**



Additional experiments were performed to show the silyl group on the cycloadducts **2** obtained through the dehydrogenative Diels–Alder reaction can be utilized for further chemical transformation (Scheme 5). For example, the halogenation of **2a** with iodine chloride or NBS produced **6a** or **7a**, respectively, both in 94% yields. The treatment of **2a** with TBAF afforded **2l** in 90% yield. Furthermore, Negishi cross coupling of **7b** and **6a**, which were synthesized from **2i** and **2a**, respectively, also resulted in the production of binaphthyl compound **8ba** in 83% yield (Scheme 6).

In summary, we have developed a dehydrogenative Diels–Alder reaction through which we can use dieneynes to produce polyaromatic cycloadducts. A silyl substituent on an alkyne moiety directs the reaction toward producing dehydrogenated cycloadducts in a selective manner. Aside from the challenge of linking a styrene as a conjugated diene with an alkyne via dearomatization and dehydrogenation, the process is simple; that is, it does not require the addition of a Lewis acid, transition metal, or oxidant. Further efforts to expand the scope of this type of chemistry and its applications for synthesizing complex molecules are now in progress.

Scheme 6. Cross-Coupling To Form Binaphthyl Frameworks



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Supporting Information Available. Experimental procedures, analytical data of new compounds. CIF file of **2a**, **2b**, **2d**, and **2f**. Computational results, energies and Cartesian coordinates of stationary points, full citations of Gaussian 03 program. This material is available free of charge via the Internet at http://pubs.acs.org.

Note Added after ASAP Publication. The graphic in table 2 has been corrected along with a production error involving the graphic in Table 1. The revised version reposted September 13, 2011.