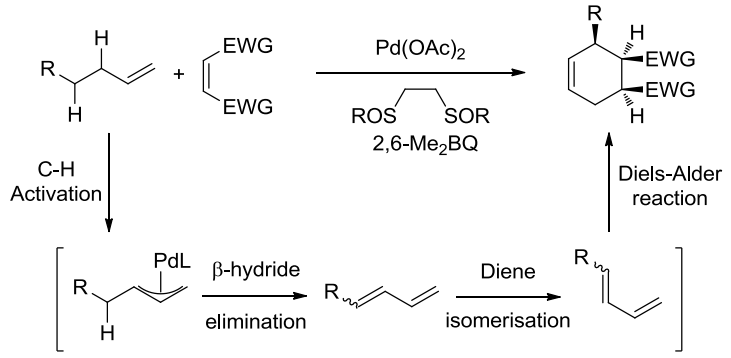
Dehydrogenative Diels-Alder Reactions – Literature Presentation 240112

The Diels-Alder reaction is one of the most fundamental and powerful complexity-generating reactions in organic chemistry. It is widely employed to form both carbocyclic and heterocyclic frameworks for the construction of complex organic molecules, allowing the formation of up to 4 stereogenic centres with complete control of stereochemistry. One limitation for the reaction can be the availability of appropriate dienes for the reaction, and in 2011 the groups of White (Illinois) and Matsubara (Kyoto) published dehydrogenative Diels-Alder reactions, that allowed the formation of complex carbocyclic frameworks from starting materials not usually associated with a Diels-Alder reaction.

Allylic C-H activation as a route to Diels-Alder reactions[1]

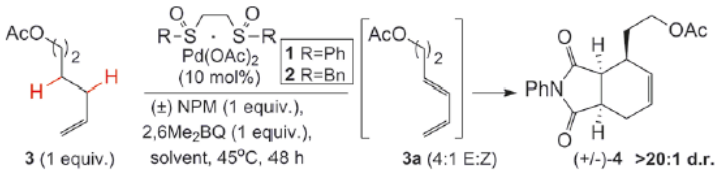
White *et al*. proposed a C-H activation route to terminal dienes utilising Pd(II)/sulfoxide catalysis. The number of commercially available terminal olefins far outnumbers the number of commerically available terminal dienes (>1600:120), and thus should provide a simple route to a variety of substituted cyclohexanes. The reaction is presumed to proceed *via* allylic C-H activation to a π-allyl complex which (in the absence of a suitable nucleophile) undergoes β-hydride elimination to the s-*trans* diene which isomerises to the s-*cis* diene to undergo the Diels-Alder reaction with an electron-deficient dienophile (**Scheme 1**).



Scheme 1 - *General reaction for the dehydrogenative Diels-Alder reaction*

Whilst 1,4-benzoquinone is normally used as a standard oxidant for these allylic C-H activation processes, White *et al*. employed 2,6-dimethyl-1,4-benzoquinone as the oxidant in this process to both prevent Diels-Alder reaction of the diene with the benzoquinone, and to prevent functionalization of the intermediate π-allyl species with acetate counterion. The allylic C-H activation of the γ-acetoxyolefin **3** in the absence of a dienophile was found to afford the diene **3a** in a 4:1 ration of E:Z isomers. Addition of N-phenylmaleimide to the reaction mixture in dioxane utilising catalyst **2** afforded 33% of the desired product **4** as a single diastereomer (>20:1 dr). Switching solvent to dichloroethane and the addition of p-nitrobenzoic acid (ostensibly to aid Pd(0)→Pd(II) catalyst reoxidation) resulted in an increase of yield of cycloadduct **5** of 74% (**Table 1**). It was found to be important to maintain a low concentration of diene throughout the reaction, to prevent polymerisation and other decomposition pathways. As such, when the reaction was carried out in the absence of dienophile, only 35% of diene **3a** was isolated.

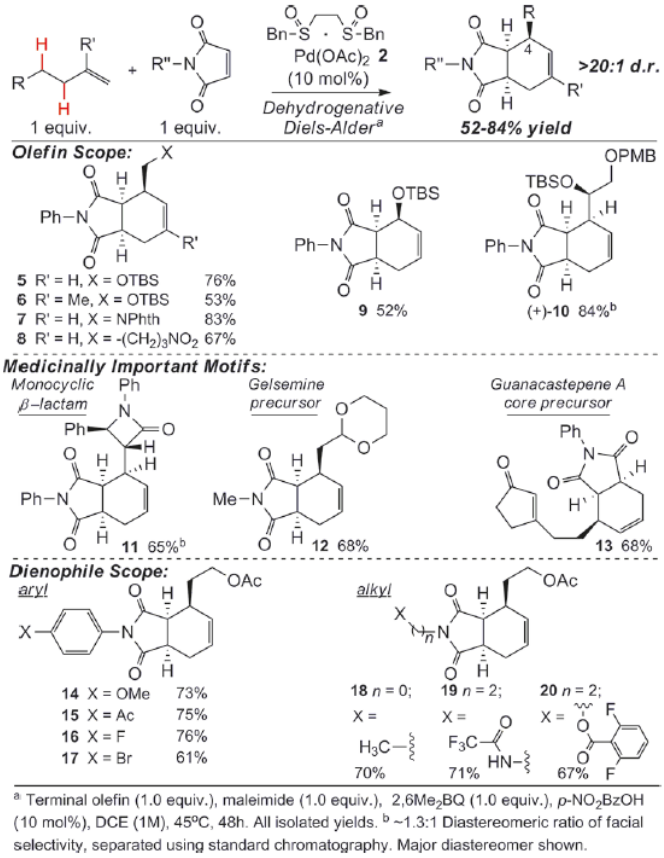
Table 1. Development of the Tandem Dehydrogenation/ Diels–Alder Reaction



entry	catalyst[a]	solvent	additive[f]	dienophile[e]	yield diene[b]	yield cycloadduct[c]
1	$Pd(OAc)_2$	dioxane	---	---	<1[d]	---
2	**1**	dioxane	---	---	6	---
3	**2**	dioxane	---	---	28	---
4	**2**	dioxane	---	NPM	<1[d]	33
5	**2**	DCE	---	NPM	<1[d]	52
6	**2**	DCE	*p*-NO_2BzOH	NPM	<1[d]	74
7	**2**	DCE	*p*-NO_2BzOH	---	35	---

[a] 10 mol% catalyst [b] Isolated after 24 hr as a 4:1 mixture of E/Z isomers along with rSM [c] isolated yield [d] Determined by GC analysis [e] NPM = N-phenylmaleimide (1.0 equiv.) [f] 10 mol%

The substrate scope for this reaction was probed for both the terminal olefin and the maleimide dienophile. Substituents on the olefin moiety could be varied from acetate **3**, to silyl protecting groups **5**, phthalimide protected amines **7**, benzyl ethers **10**, amides **11**, acetals **12** and enones **13** without a significant decrease in yield. 1,1-disubstituted olefins **6** were found to be less reactive dehydrogenation substrates, but still afforded the corresponding cycloadducts in synthetically useful yields. Olefin starting materials with pre-existing stereogenic centres were found to undergo the reaction without epimerisation, although the chiral substituent was found to display little control over diastereofacial selectivity, producing endo-adducts (**10** and **11**) with approximately 1:1 dr (Scheme 2).

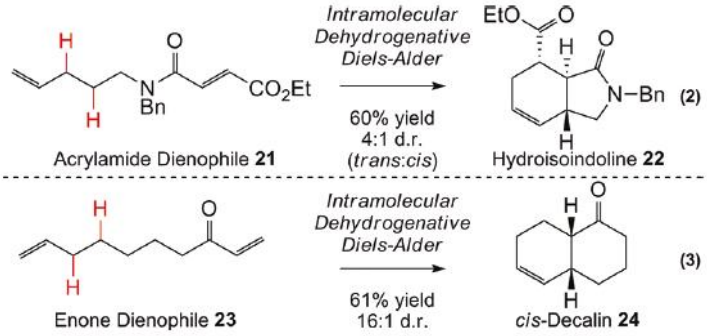


Scheme 2 - *Substrate scope for the dehydrogenative Diels-Alder reaction*

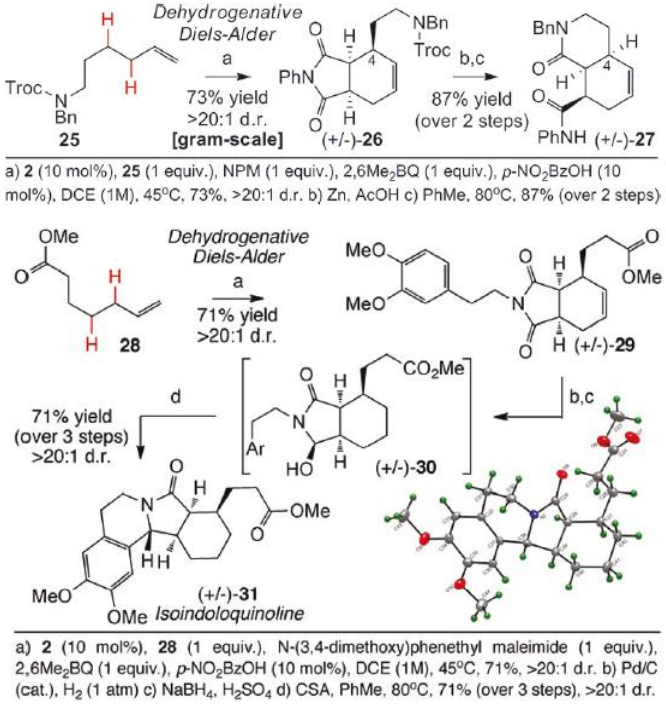
The maleimide substrate was found to tolerate both electron-rich and electron-deficient protecting groups, including a variety of aryl groups **14-17**, alkyl groups **18**, and functionalised ethyl substituents **19** and **20**, which present a handle for further functionalization

Other dienophiles were found to be less reactive than maleimides in the dehydrogenative Diels-Alder reaction, a common limitation found in non-Lewis acid catalysed Diels-Alder reactions of unactivated dienes under mild conditions. However, intramolecular dehydrogenative Diels-Alder reactions of tethered alkenes and dienophiles saw a significant rate enhancement allowing the use

of acrylamide **21** and enone **23** to provide expedient access to isoindoline **22** and *cis*-decalin **24** in good yield and good to excellent dr (**Scheme 3**).



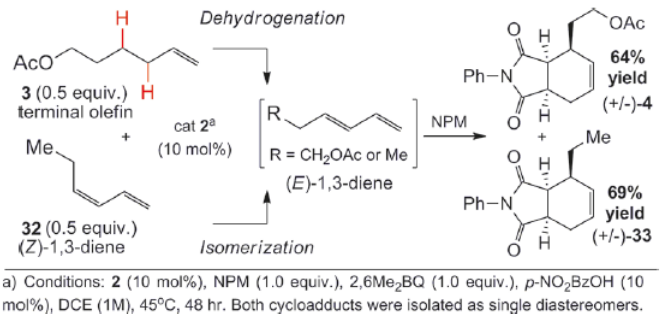
Scheme 3 - *Other dienophiles in the dehydrogenative DIels-Alder*



Scheme 4 - *Application to biologically active products*

This methodology was applied to a variety of medicinally and biologically important compounds, from the monocyclic β-lactam **11** (known to be useful against Gram-negative bacteria), as well as the Gelsemine precursor **12** (an analgesic and antianxiolytic), and **13** , a precursor to Guanacastepene A, an active antibiotic against methicillin- and vancomycin-resistant bacteria (Scheme 2). Furthermore, this methodology was also applied to the synthesis to substituted hydroisoquinolone **27** and also to the isoindoloquinone structure **31**, found in several alkaloids including jamtine, which displays significant antihyperglycemic activity (**Scheme 4**).

A cross-over experiment was also conducted to explain why a 4:1 E:Z mixture of diene isomers was able to furnish cycloadduct in >20:1 dr (**Scheme 5**). 0.5 eq. of olefin **3** and 0.5 eq of (Z)-1,3-hexadiene **32** were employed in the reaction, and furnished cycloadducts **4** and **33** in 64% and 69% yields respectively, both in >20:1 dr. Reaction of pure **32** also resulted in formation of cycloadduct **32** in

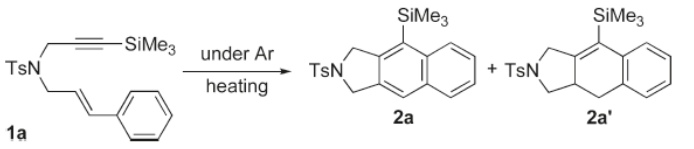


Scheme 5 - *Crossover experiment*

>20:1 dr, suggesting that the diene isomerisation to the (E)-diene was promoted by Pd(II). In the absence of $Pd(OAc)_2$ the diene was recovered unreacted. These results suggest a Pd(II) catalysed diene isomerisation that funnels both (E)- and (Z)- dienes to the desired cycloadduct *in situ.*

Diels-Alder reaction followed by dehydrogenative aromatisation[2]

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



entry	solvent	temp (°C)	time (h)	yield (%) 2a	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

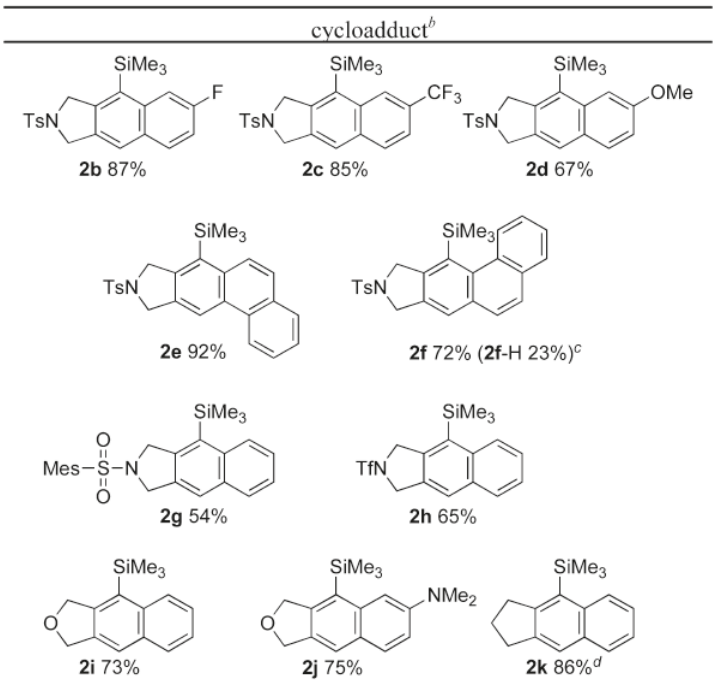
[a] All reactions were carried out using **1** (0.2 mmol) in 1.6 mL of solvent under an Ar atmosphere unless otherwise noted. [b] Microwave irradiation. [c] Isolated yield. [d] Reaction was carried out under air.

bond geometry was essential in allowing effective cyclisation, with the *cis*-styrene *cis*-**1a** only forming cycloadduct **2a** in 29% yield, as opposed to 80% for *trans*-**1a**.

The reaction was found to tolerate both electron-poor (products **2b** and **2c**) and electron-rich styrene units (product **2d**), along with vinylnaphthalene moieties (products **2e** and **2f**) in the reaction (**Figure 1**). Interestingly, product **2f** was formed in 72% yield along with 23% of the protodesilylated producted **2f-**H. The effect of the tether group was also evaluated, with a variety of different N-protecting groups (Tosyl **2b-f**, mesitylsulfonyl **2g** and triflyl **2h**) remaining intact during the cyclisation. Ether tethers were also found to afford desired

The work of Matsubara *et al.* also allows Diels-Alder reactions to be carried out on substrates that were not previously utilised. However, this methodology results in the formation of substituted naphthalenes, which are useful in a wide variety of complex organic molecules and natural products.

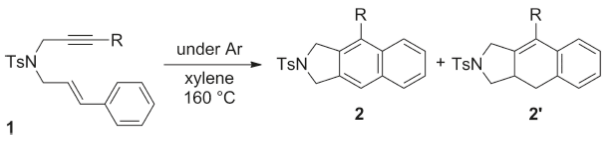
The reaction employs a TMS-alkyne unit tethered to a styrene moiety, which upon heating in xylene results in the formation of naphthalene frameworks, such as the conversion of **1a** to **2a** in 80% yield (**Table 1, Entry 4**). It was found that polar solvents retarded the reaction (**Entries 5-8**), and that it was necessary for the reaction to be carried out under argon to prevent decomposition of starting material **1a** (**Entry 12**). It was found that the double



[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 - *Exploration of reaction scope*

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



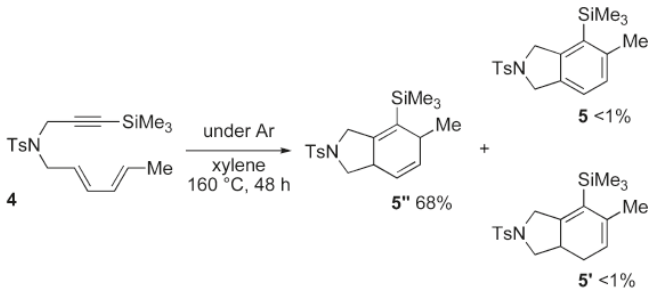
entry	1	R	time (h)	yield (%) 2	yield (%) 2′
1	**1l**	H	48	6	37
2	**1l**	H	96	11	66
3	**1l**	H	48	<1[b]	<1
4	**1m**	Me	48	<1	<1
5	**1n**	Ph	48	14	56
6	**1o**	CO_2Et	48	29	65
7	**1o**	CO_2Et	96	35	59
8	**1p**	$Si\textit{i}Pr_3$	48	13	<1
9	**1q**	$SiMe_2Ph$	48	63	<1
10	**1a**	$SiMe_3$	48	80	<1

cycloadducts **2i** and **2j** in good yields. Use of a carbon tether was found to be more problematic, with no cycloadduct **2k** formed under standard reaction conditions, but elevation of the reaction temperature to 250 °C resulted in formation of **2k** in 86% yield.

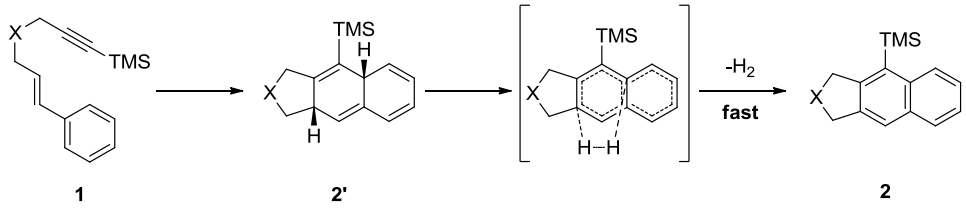
It was found that the presence of the silyl group on the alkyne moiety was important in the formation of the aromatic product **2**. Use of terminal alkynes, and alkynes substituted with alkyl, aryl or ester groups resulted in formation of the non-aromatised products **2'** as the major product (**Table 2**).

Replacement of the styrene moiety with a standard diene resulted in the formation of the standard Diels-Alder cycloadduct **5''** without a trace of either the isomerised product **5'** or the aromatised product **5** observed (**Scheme 1**).

Scheme 1 Reaction of Dieneyne **4**

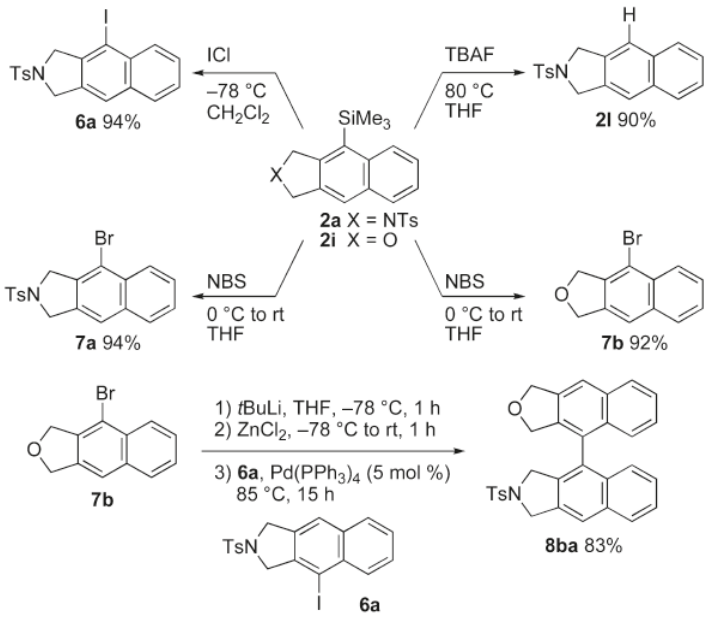


The proposed mechanism for this reaction involves initial Diels-Alder reaction between the alkyne and styrene moieties of dienyne **1**, to form cycloadduct **2''**. The intermediate cycloadduct **2''** is presumed to contain a strained 1,4-cyclohexadiene moiety in a strained boat conformation as a result of the benzannulated structure and the bulky trimethylsilyl group. As such, two hydrogen atoms are in spatial proximity and thus undergo a facile *retro*-Diels-Alder reaction (**Scheme 2**).



Scheme 2 - *Postulated mechanism for the dehydrogenative Diels-Alder of enynes **1***

The rearomatised products **2** can be utilised for further functionalization, resulting from standard manipulations of the silyl group (halogenations **6a, 7a, 7b**, protodesilylation **2l** etc.), and these can be further utilised in Negishi cross-couplings in the synthesis of binaphthyl frameworks **8ba** (**Scheme 3**).



Scheme 3 - *Synthetic manipulation of naphythyl products* **2**

Summary

Both of the above methods provide access to synthetically useful products *via* Diels-Alder reactions. White *et al.* have shown that Pd(II)/sulfoxide allylic C-H activation and dehydrogenation of terminal olefins provides a route to 1,3-dienes suitable for the Diels-Alder reaction, thus allowing the formation of complex molecular skeletons from topologically simple starting materials as a single diastereomer. If this can be expanded to a wider variety of olefin and dienophile starting materials then it should prove to be a very useful reaction. Matsubara *et al.* have also utilised dehydrogenation in Diels-Alder reactions, but in order to provide naphthyl-substituted products *via* dehydrogenative aromatisation. This process allows the formation of synthetically useful naphthalene products from simple starting materials without the use of any extra reagents.

References

1) *J. Am. Chem. Soc.*, **2011**, 14892
2) *Org. Lett.*, **2011**, 5390