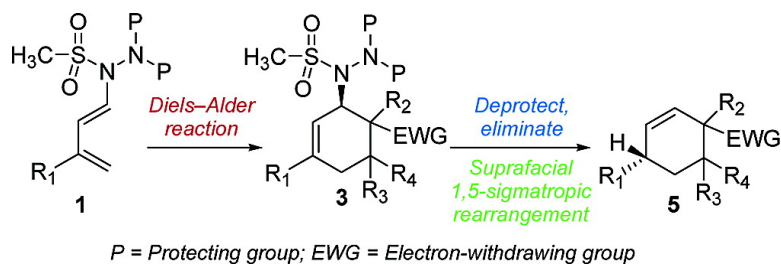


Design, Synthesis, and Reactivity of 1-Hydrazinodienes for Use in Organic Synthesis

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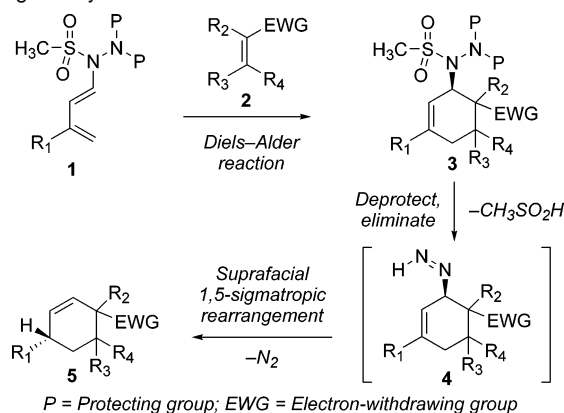
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Since its initial report in 1928,¹ the Diels–Alder reaction has provided the foundation for some of the most impressive achievements in the area of natural product synthesis, and much is known about the factors controlling the regioselectivities and stereochemical outcomes of inter- and intramolecular [4+2] cycloadditions.² Our laboratory was inspired to contribute a new modification to this well-studied process when we encountered the general structural type **5** in the course of a natural product synthesis (Scheme 1). In

Scheme 1. A New Type of Hydrazine-Substituted Diene for Use in Organic Synthesis

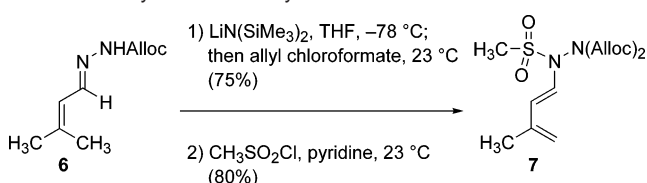


principle, this compound could originate from the Diels–Alder reaction of a 1-hydrazinodiene **1** and a suitable dienophile **2** to form cycloadduct **3**. In a subsequent step, liberation of a primary amino group through cleavage of the two nitrogen-bound protecting groups might then trigger loss of methanesulfinic acid to provide allylic diazene **4**. Several impressive literature examples demonstrate that allylic diazenes undergo smooth, suprafacial 1,5-sigmatropic rearrangements of hydrogen with loss of dinitrogen in diverse molecular contexts.³ Allylic diazene **4** is expected to undergo the desired nitrogen extrusion reaction with alkene transposition. A useful aspect of this rearrangement step is that a six-membered ring possessing a 1,2-stereochemical relationship may be stereospecifically transformed into a six-membered ring having a 1,4-stereochemical relationship.

Nitrogen-substituted 1,3-butadienes are useful, reactive species that often exhibit excellent behavior in normal electron-demand Diels–Alder reactions.⁴ However, 1-hydrazinodienes of the type **1** have not, to the best of our knowledge, been reported in the literature. Our synthesis of diene **7** commenced with hydrazone **6**, the product of a simple condensation between 3-methyl-2-butenal and monoallyloxycarbonyl (Alloc) hydrazine⁵ (Scheme 2). Introduction of the second Alloc group, followed by nitrogen sulfonylation with in situ diene formation, provided exclusively (*E*)-hydrazinodiene **7** in excellent yield.⁶

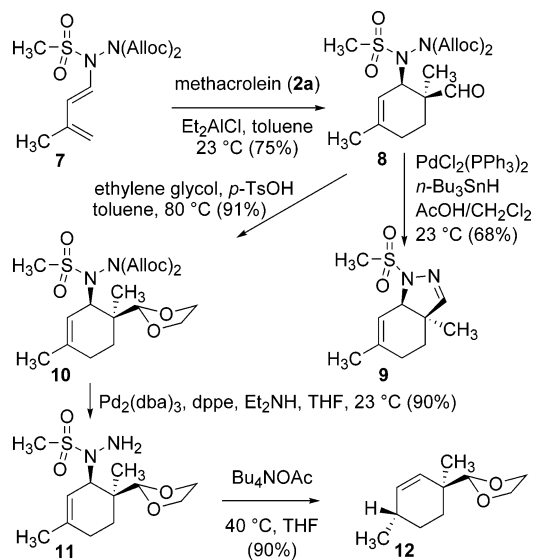
At the outset of this project, we were concerned that the types of groups that might enable an eventual allylic diazene formation

Scheme 2. Synthesis of 1-Hydrazinodiene **7**



would also significantly retard the reactivity of **7** as a diene in Diels–Alder reactions. The donor capacity of the diene nitrogen atom is, in fact, significantly tempered by the electron-withdrawing methanesulfonyl and imide groupings. Under strictly thermal conditions, compound **7** did not undergo cycloaddition with our model dienophile methacrolein. However, in the presence of a Lewis acid, such as scandium(III) triflate or diethylaluminum chloride, hydrazinodiene **7** reacted cleanly with methacrolein to provide cycloadduct **8** (Scheme 3).

Scheme 3. [4+2] Cycloaddition of 1-Hydrazinodiene **7** to Methacrolein and Subsequent 1,5-Sigmatropic Rearrangement



Having shown that 1-hydrazinodiene **7** is capable of undergoing Diels–Alder reactions, we turned to the second key transformation: the suprafacial, allylic diazene rearrangement. Removal of the Alloc groups from cycloadduct **8** resulted in the formation of heterocycle **9**. This finding necessitated an initial protection of the aldehyde in the form of a 1,3-dioxolane acetal **10**. When the necessary Alloc cleavage⁸ was performed in the context of compound **10**, hydrazine **11** could be isolated as a stable white solid.⁹ In the presence of tetrabutylammonium acetate at 40 °C, compound **11** smoothly rearranged to cyclohexene **12** in excellent yield.

Table 1. Dienophile Scope for the Diels–Alder/1,5-Sigmatropic Rearrangement Process

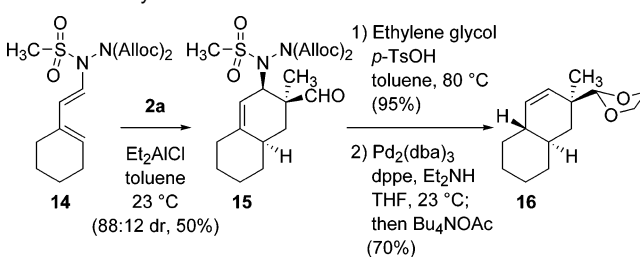
12a-f: X = CH(-OCH₂CH₂O-); 13a-b: X = CO₂Et

Dienophile	Sc(OTf) ₃ (mol%) ^a	dr (endo:exo) ^b	Yield 8 (%) ^c	Yield 12(13) (%)
2a	10	83:17 (92:8) ^d	89 ^e (81) ^{d,e}	62 ^f
2b	10	25:75	65	60 ^f
2c	10	30:70	45	55 ^f
2d	10	7:93	72	68 ^e
2e	10	33:67	47	54 ^f
2f	10	20:80	66	57 ^f
2g	30	5:95	76	49 ^g
2h	30	10:90	30	13 ^g

^a Standard reaction conditions: 1-hydrazinodiene **7** (0.5 mmol), Sc(OTf)₃, 3 equiv of dienophile, 150 mg/mmol 4 Å MS, 0.2 M CH₂Cl₂. ^b The diastereomeric ratio was determined by ¹H NMR. ^c Isolated yields of the major isomer. ^d Diethylaluminum chloride catalyzed reaction: 20 mol % Et₂AlCl, 2 equiv of dienophile, 0.2 M toluene. ^e Isolated yield of both diastereomers. ^f Isolated yield after three steps (dioxolane formation, Alloc deprotection, and Bu₄NOAc mediated elimination/diazene rearrangement). ^g Isolated yield after two steps (Alloc deprotection and NaOAc mediated elimination/diazene rearrangement).

The Diels–Alder reaction with 1-hydrazinodiene **7** and the subsequent rearrangement proved to be successful with a wide range of substituted aldehydes, including a number of β-substituted aldehydes (**2b–2d**) (Table 1). Simple ketones, such as methyl vinyl ketone (**2f**), were also excellent substrates for the Diels–Alder reaction. Reactions with α-substituted dienophiles, such as methacrolein, gave *endo* cycloadducts,¹⁰ while all α-unsubstituted dienophiles gave *exo* products.^{11,12} Although simple α,β-unsaturated esters employed in this process were not effective dienophiles, doubly activated dienophiles, such as diethyl maleate (**2g**) and diethyl fumarate (**2h**), were successfully activated with scandium(III) triflate. The observation that the products of the reactions of diene **7** with maleate **2g** and fumarate **2h** (**13a** and **13b**) are diastereoisomers suggests that these cycloadditions are concerted, stereospecific processes. Regardless of the substitution pattern, all of the Diels–Alder adducts underwent smooth deprotection and rearrangement to the desired olefins.¹³

The chemistry of 1-hydrazinodienes also provides efficient access to constitutionally and stereochemically complex decalin architectures, such as **16** (Scheme 4). A diethylaluminum chloride catalyzed Diels–Alder reaction between 1-hydrazinodiene **14** and methacrolein (**2a**) yields cycloadduct **15** in good yield with excellent

Scheme 4. Synthesis of *trans*-Fused Decalin **16**

stereoselectivity. Conversion of aldehyde **15** to a dioxolane, followed by one-pot deprotection and rearrangement, yields the desired decalin **16** in excellent yield.

In summary, we developed a new type of 1,3-diene that undergoes efficient Diels–Alder reactions with a range of electron-deficient alkenes and enables a subsequent reductive transposition of the initial [4+2] cycloadduct. The suprafacial nature of the latter transformation enables a 1,3-transfer of stereochemistry to a new position on the six-membered ring system. We anticipate that this chemistry could provide an alternative way of perceiving and utilizing the Diels–Alder reaction in the planning and execution of organic syntheses. Efforts to expand the family of 1-hydrazinodienes, achieve enantioselective cycloadditions, and evaluate the reactivities of these compounds with heterodienophiles are underway.

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Supporting Information Available: Complete experimental procedures and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- Mono-Alloc hydrazine was synthesized in two steps from *tert*-butyl carbazate. See the Supporting Information for details.
- Hydrazinodiene **7** can be stored, in pure form, for extended periods of time at temperatures <0 °C.
- For a review, see: Guibé, F. *Tetrahedron* **1998**, *54*, 2967–3042.
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- Sulfonylhydrazine **11** was stable to elimination, even when subjected to flash chromatography.
- The relative stereochemistry was determined from nOe experiments on heterocycle **9a**. See Supporting Information for experimental details.
- The relative stereochemistry was determined via an X-ray crystallographic analysis of **8d**.
- We are currently investigating the nature of the diastereoselectivity for 1-hydrazinodienes in Diels–Alder reactions.
- Cycloadducts **8g** and **8h** did not require protection of the esters prior to Alloc deprotection.

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