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Nitrone Cycloadditions of 1,2-Cyclohexadiene

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Supporting Information

ABSTRACT: We report the first 1,3-dipolar cycloadditions of 1,2-cyclohexadiene, a rarely exploited strained allene. 1,2-Cyclohexadiene is generated in situ under mild conditions and trapped with nitrones to give isoxazolidine products in synthetically useful yields. The reactions occur regioselectively and exhibit a notable endo preference, thus resulting in the controlled formation of two new bonds and two stereogenic centers. DFT calculations of stepwise and concerted reaction pathways are used to rationalize the observed selectivities. Moreover, the strategic manipulation of nitrone cycloadducts demonstrates the utility of this methodology for the assembly of compounds bearing multiple heterocyclic units. These studies showcase the exploitation of a traditionally avoided reactive intermediate in chemical synthesis.

The synthesis of heterocycles and natural product scaffolds remains a vital area of study.[1,2] One approach to construct such important compounds involves the use of strained intermediates such as benzyne, hetarynes, and cyclic alkynes (**1**–**6**, Figure 1).[3] Although initially viewed as undesirably reactive species several decades ago, these intermediates can now be used to prepare medicinally privileged scaffolds and stereochemically complex natural products.[3,4] Likewise, our understanding of the structure and reactivity of arynes and cyclic alkynes has evolved considerably.[3,4]

A less well-studied class of highly strained intermediates is cyclic allenes, such as 1,2-cyclohexadiene (**7**, Figure 1). 1,2-Cyclohexadiene (**7**) was first reported by Wittig in 1966[5] but has seen little synthetic use since, especially compared with its aryne and alkyne counterparts. Seminal efforts include theoretical studies[6] and the two C–C bond forming reactions: [2 + 2][6a,c,7] and [4 + 2][6a,d,7c–e,8] cycloadditions to form products such as **8** and **9**, respectively. These transformations hint at the potential utility of **7** as a versatile synthetic building block, but no other cycloadditions involving **7** have been reported.

We now report the first dipolar cycloadditions of 1,2-cyclohexadiene, which allow for a facile entryway to isoxazolidine products (Figure 1, **7** + **10** → **11**). The resulting products contain significant sp^3-character[9] and are obtained with high regio- and diastereoselectivities. Computational studies suggest that stepwise and concerted reaction pathways are operative in the cycloadditions and predict the observed selectivity trends.

We initiated our study toward the trapping of 1,2-cyclohexadiene (**7**) by first accessing a suitable precursor that could allow for allene generation in situ. Encouraged by Guitián's synthesis of a trimethylsilyltriflate precursor to **7**,[7e] which was used in Diels–Alder cycloadditions, we prepared the new

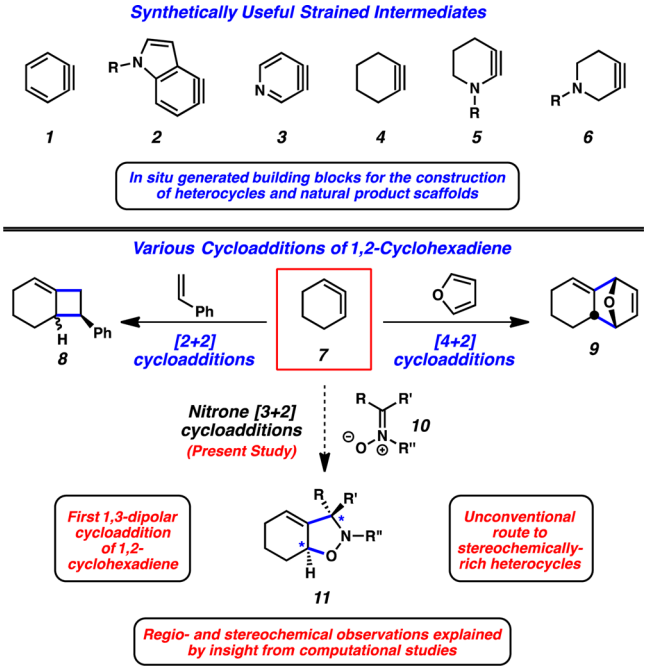

Figure 1. Strained intermediates **1**–**6**, known cycloadditions of 1,2-cyclohexadiene (**7**), and nitrone cycloadditions of **7** described in the present study.

triethylsilyltriflate species **12**,[10] which proved more readily accessible and could be obtained in gram quantities.[11] We initially surveyed the reaction of silyltriflate **12** with 5 equiv of commercially available nitrone **13** using different fluoride sources at ambient temperature (Table 1). Although the use of TBAF gave low yields of cycloadduct **14** (entry 1), KF/18-crown-6 gave more promising results (entry 2). Additionally, the use of CsF cleanly gave product **14** in modest yield, although the remainder of the mass was unreacted silyl triflate **12** (entry 3). In all cases, it should be noted that **14** was formed regioselectively and in approximately 9:1 dr, with the major product being the endo isomer (**14a**). For practical reasons, we elected to further pursue the use of CsF and ultimately found that the reaction proceeded smoothly at elevated temperatures and higher concentration (entries 4 and 5) to give cycloadduct **14** in 4 h (entry 5; compared with 3 d for entry 3). Finally, to probe the necessary stoichiometry, we tested the cycloaddition using just 1 equiv of nitrone **13**. We were delighted to find that cycloadduct **14** could be formed in comparable yields under these conditions (entry 6).

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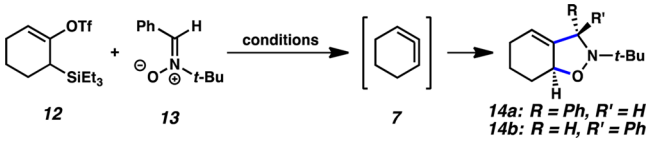
Table 1. Optimization of Nitrone Cycloaddition



entry	conditions	temp (°C)	concn (M)	equiv of **13**	yield, % (**14a**/**14b** dr)[a]
1	TBAF, THF	23	0.025	5.0	35 (10.8:1)
2	KF, 18-crown-6, CH_3CN	23	0.025	5.0	77 (12.1:1)
3	CsF, CH_3CN	23	0.025	5.0	41 (13.5:1)
4	CsF, CH_3CN	80	0.025	5.0	90 (9.5:1)
5	CsF, CH_3CN	80	0.1	5.0	92 (9.3:1)
6	CsF, CH_3CN	80	0.1	1.0	84 (8.5:1)

[a]Yields and diastereomeric ratios were determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an external standard.

Having identified suitable reaction conditions, we assessed the scope of the methodology by varying the nitrone component and evaluating isolated yields and diastereoselectivities (Figure 2). All

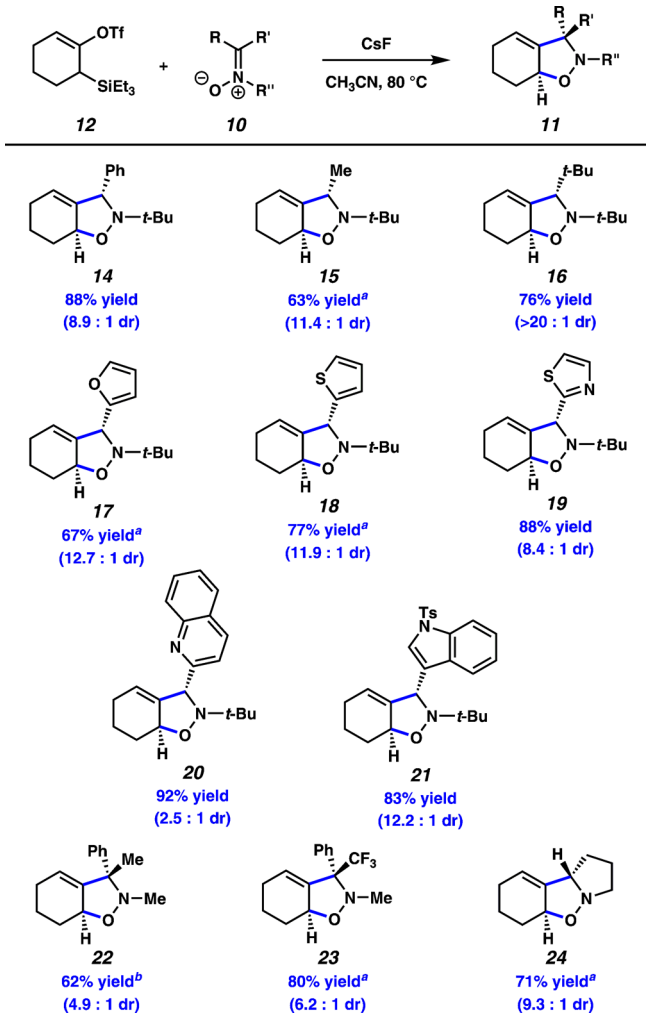


Figure 2. Scope of reaction methodology. Major diastereomer is shown. Conditions unless otherwise stated are silyl triflate (1.0 equiv), nitrone (1.0 equiv), CsF (5.0 equiv), and CH_3CN (0.1 M) at 80 °C. The yields reflect the average of two isolation experiments. [a]Nitrone (2.0 equiv) was used. [b]Nitrone (2.0 equiv) and THF (0.1 M) at 60 °C were used.

reactions were performed using CsF at 80 °C and either 1 or 2 equiv of the nitrone trapping agent, as indicated.[12] In addition to the parent experiment, which gave **14** in 88% yield and roughly 9:1 dr, we were delighted to find that nitrones derived from acetaldehyde and pivaldehyde could be employed to give products **15** and **16**, respectively. Nitrones derived from aldehydes bearing heterocycles were also tested. As shown by the formation of products **17**−**21**, furan, thiophene, thiazole, quinoline,[13] and indole heterocycles are tolerated in this methodology. Finally, several nitrones prepared from ketone or cyclic amine precursors were tested, resulting in isoxazolidines **22**−**24**.[14]

DFT calculations were performed to assess mechanistic aspects of the 1,2-cyclohexadiene/nitrone cycloaddition.[15] We investigated both the regio- and diastereoselectivity of the cycloaddition. Although Diels−Alder and (2 + 2) cycloadditions of 1,2-cyclohexadiene (**7**) have been studied computationally, no reports of (3 + 2) cycloadditions of **7** are available. We assessed pathways that could lead to either of two possible constitutional isomers, in addition to all possible stereoisomers, as summarized in Figure 3. Cycloaddition via pathway A would give

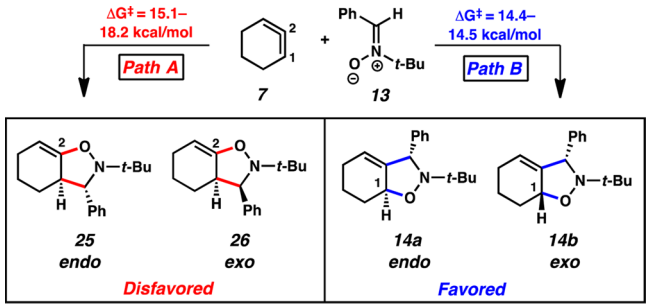


Figure 3. DFT calculations (B3LYP/6-31G*) were used to examine regioselectivites and diastereoselectivities.

diastereomers **25** and **26**, whereas pathway B would furnish **14a** and **14b**. Previous reports with linear allenes indicate the plausibility of both pathways. However, consistent with our experimental results, computations show that pathway A is disfavored for the reaction of **7** and nitrone **13**.[16] The lower energy pathway involves attack of the central allene carbon (C2) on the nitrone, with attack of the nitrone oxygen on C1 (pathway B).

To explain the observed diastereoselectivities, we compared the possible transition states for the formation of both endo and exo products **14a** and **14b** (Figure 4). First examining a concerted reaction mechanism, we found that the activation energy for the endo reaction is 14.5 kcal/mol (**TS1**), which presents a plausible pathway for the formation of **14a**. A concerted exo transition state could not be explicitly located; instead diradical transition state **TS2** always resulted, suggesting the concerted exo reaction is higher in energy. As we do observe exo product **14b**, we proceeded to examine the stepwise mechanism through **TS2**. We found that diradical **27** can be formed via initial formation of the C−C bond; an intrinsic reaction coordinate scan and a nonzero S^2 value confirms the diradical nature of this process. From diradical **27**, cyclization furnishes **14a** or **14b** (via **TS3a** or **TS3b**); the formation of **14a** is favored by 1.2 kcal/mol, which correlates to the observed 10:1 ratio of products. Therefore, we propose that both stepwise and concerted mechanisms for cycloaddition are in competition, a phenomenon we have previously observed in our studies on

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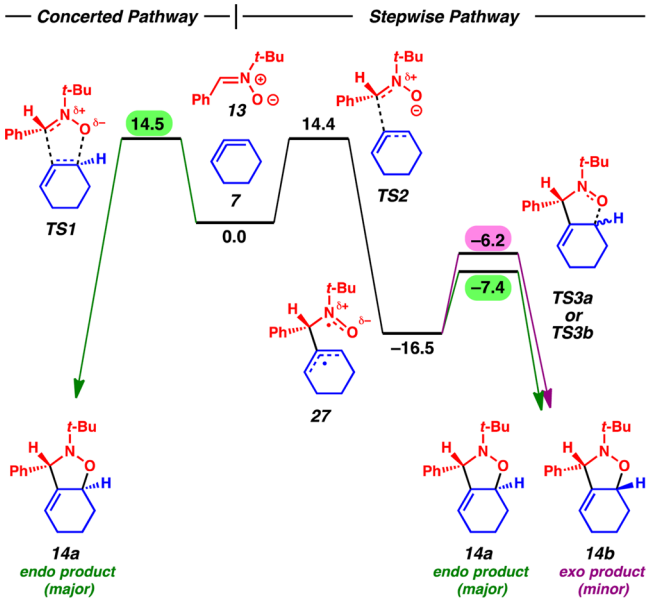

Figure 4. DFT calculations (B3LYP/6-31G*) of concerted and stepwise mechanistic pathways.

Diels–Alder reactions with allenes,[17,18] which are known to be very reactive and form relatively stable allylic radical intermediates.

Regardless of the reaction mechanism, the 1,3-dipolar cycloaddition of 1,2-cyclohexadiene occurs quickly with mild heating. The low ~15 kcal/mol barriers for these reactions, compared with the >30 kcal/mol barriers for cycloaddition with linear allenes,[17,18] can be attributed to the predistortion of **7** into geometries near those of the transition states for cycloadditions. The optimized structures of 1,2-cyclohexadiene (**7**) and **TS1** (concerted pathway) are shown in Figure 5. Of note, the C1–

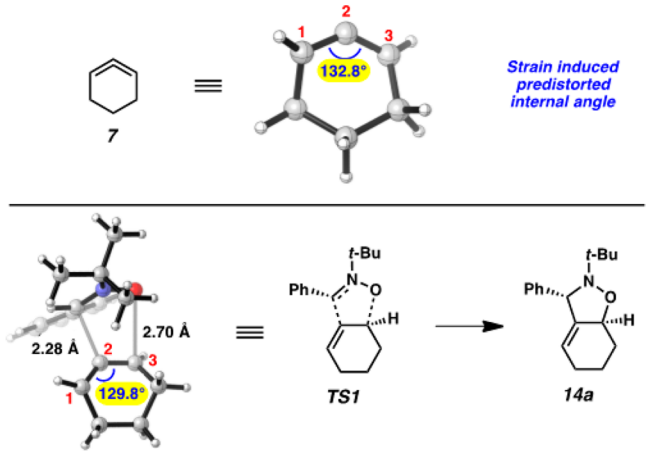

Figure 5. Comparison of C2 internal angle for **7** and **TS1**.

C2–C3 angle is nearly identical in both cases (132.8° vs 129.8°).[19] Thus, only 3° contraction is necessary to reach the transition state geometry. In contrast, linear allenes must bend by more than 30° in order to reach their optimal transition state geometries (see SI for details). Examples of distortion-accelerated reactions are known[20] and explain the facility of these reactions with 1,2-cyclohexadiene.

The nitrone cycloaddition of 1,2-cyclohexadiene (**7**), when used sequentially with other transformations, provides new and unique strategies for preparing compounds bearing multiple heterocyclic units (Figure 6). For example, isoxazolidine **28** was

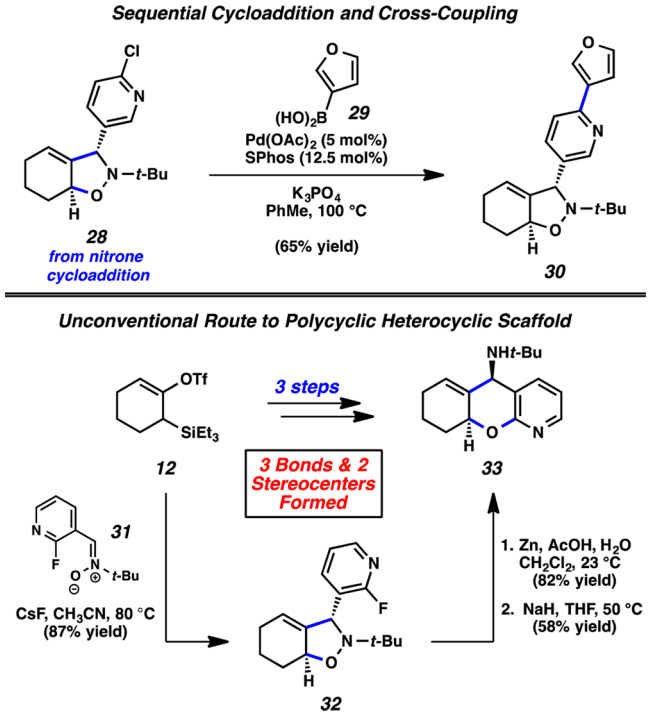

Figure 6. Strategic manipulation of nitrone cycloadducts.

synthesized via a nitrone cycloaddition from **12**. Next, palladium-catalyzed Suzuki–Miyaura cross-coupling[21] with boronic acid **29** afforded product **30** in 65% yield. Of note, **30** contains three distinct heterocycles (i.e., a furan, pyridine, and isoxazolidine). In another example, we questioned if silyltriflate **12** could be used as a building block for the assembly of polycyclic fused heterocycles, such as **33**. Nitrone cycloaddition with **31** furnished isoxazolidine **32**. Subsequent N–O bond cleavage,[22] followed by S_NAr cyclization[23] gave tricycle **33**. The conversion of **12** to **33** allows for the facile construction of three new bonds and two stereogenic centers. Moreover, the two synthetic applications shown in Figure 6 showcase how the unusual intermediate cyclohexadiene (**7**), despite its high reactivity, can be used to access varying types of polycyclic heterocycles in a controlled way.

In summary, we have discovered the first 1,3-dipolar cycloadditions of 1,2-cyclohexadiene. The transformation involves in situ generation of the strained intermediate under mild conditions, and trapping with nitrones to give isoxazolidine products in synthetically useful yields. The reactions occur regioselectively, with a notable endo preference, thus resulting in the controlled formation of two new bonds and two stereogenic centers. DFT calculations suggest that stepwise and concerted reaction pathways are operative in the cycloadditions and predict the observed selectivity trends. Moreover, the strategic manipulation of nitrone cycloadducts demonstrates the utility of this methodology for the assembly of compounds bearing multiple heterocyclic units. These studies are expected to prompt the further exploitation of traditionally avoided reactive intermediates in chemical synthesis.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b13304.

Detailed experimental and computational procedures, compound characterization, Cartesian coordinates, electronic energies, entropies, enthalpies, Gibbs free energies, and lowest frequencies of the calculated structures (PDF)

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Notes

The authors declare no competing financial interest.

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(9) Another attractive aspect of using 1,2-cyclohexadiene (**7**) as a synthetic intermediate is the potential to access sp^3-rich heterocycles, especially in comparison to benzyne cycloadducts. The synthesis of sp^3-rich heterocycles is a current priority area in medicinal chemistry; see (a) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752–6756. (b) Ritchie, T. J.; Macdonald, S. J. F. *Drug Discovery Today* **2009**, *14*, 1011–1020. (c) Lovering, F. *MedChemComm* **2013**, *4*, 515–519.

(10) Our efforts to prepare the known trimethylsilyl counterpart of **12** were thwarted by complications associated with the synthesis and purification of 2-(trimethylsilyl)cyclohexanone.

(11) See Supporting Information for the synthesis of silyltriflate **12**.

(12) In some cases, improved yields were obtained using 2 equiv of the nitrone trapping agent. Optimal conditions used for each substrate are indicated.

(13) The modest dr observed in the formation of **20** is currently not well understood.

(14) We also explored the use of nitrones bearing chiral auxiliaries. Use of Vasella's mannose-derived nitrones led to modest dr, whereas the use of phenethylamine derivatives gave the corresponding cycloadducts in 1.5:1 dr. For Vasella's mannose derivative, see: Vasella, A. *Helv. Chim. Acta* **1977**, *60*, 1273–1295.

(15) All geometries were optimized using the density functional B3LYP with a 6-31G(d) basis set. Free energies were then determined using B3LYP single point calculations with the D3 correction (with no Becke–Johnson damping) to account for dispersion, in conjunction with the larger 6-311+G(d,p) basis set. The conductor-like polarizable continuum model (CPCM) for acetonitrile was used to simulate implicit solvent. Minima and transition states were located and verified with 0 and 1 imaginary frequencies, respectively.

(16) Stepwise and concerted reaction mechanisms were evaluated; see the Supporting Information for details.

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