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Nitrone Cycloadditions of 1,2-Cyclohexadiene

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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 1966⁵ but has seen little synthetic use since, especially compared with its aryne and alkyne counterparts. Seminal efforts include theoretical studies⁶ 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.

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Notes

The authors declare no competing financial interest.

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)

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 sp³-character⁹ 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 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 nitrene **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 nitrene **13**. We were delighted to find that cycloadduct **14** could be formed in comparable yields under these conditions (entry 6).

Having identified suitable reaction conditions, we assessed the scope of the methodology by varying the nitrene component and evaluating isolated yields and diastereoselectivities (Figure 2). All reactions were performed using CsF at 80 °C and either 1 or 2 equiv of the nitrene 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 nitrenes derived from acetaldehyde and pivaldehyde could be employed to give products **15** and **16**, respectively. Nitrenes 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 nitrenes 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/nitrene 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 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 nitrene **13**.¹⁶ The lower energy pathway involves attack

of the central allene carbon (C2) on the nitron, with attack of the nitron 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 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–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 known²⁰ and explain the facility of these reactions with 1,2-cyclohexadiene.

The nitron 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 synthesized via a nitron cycloaddition from **12**. Next, palladium-catalyzed Suzuki–Miyaura cross-coupling²¹ 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**. Nitron cycloaddition with **31** furnished isoxazolidine **32**. Subsequent N–O bond cleavage,²² followed by S_NAr cyclization²³ 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 nitrono 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. In 2013, 15 of the top 20 small molecule pharmaceuticals contained heterocycles. For discussions, see: Vitaku E, Smith BR, Smith DT, Njardarson JT. accessed December 13, 2015 <http://njardarson.lab.arizona.edu/sites/njardarson.lab.arizona.edu/files/Top%20US%20Pharmaceutical%20Products%20of%202013.pdf> McGraith NA, Brichacek M, Njardarson JT. *J Chem Educ.* 2010; 87:1348–1349.
2. Heterocycles are also prevalent motifs in agrochemicals and materials chemistry; see: Dinges J, Lamberth C. *Bioactive Heterocyclic Compounds Classes: Agrochemicals.* Wiley-VCH Weinheim 2012 Gilchrist TL. *J Chem Soc, Perkin Trans 1.* 1999:2849–2866.
3. For reviews of arynes and hetarynes, see: Pellissier H, Santelli M. *Tetrahedron.* 2003; 59:701–730. Wenk HH, Winkler M, Sander W. *Angew Chem, Int Ed.* 2003; 42:502–528. Sanz R. *Org Prep Proced Int.* 2008; 40:215–291. Bronner SM, Goetz AE, Garg NK. *Synlett.* 2011:2599–2604. Tadross PM, Stoltz BM. *Chem Rev.* 2012; 112:3550–3557. [PubMed: 22443517] Gampe CM, Carreira EM. *Angew Chem, Int Ed.* 2012; 51:3766–3778. Bhunia A, Yetra SR, Biju AT. *Chem Soc Rev.* 2012; 41:3140–3152. [PubMed: 22278415] Yoshida H, Takaki K. *Synlett.* 2012; 23:1725–1732. Dubrovskiy AV, Markina NA, Larock RC. *Org Biomol Chem.* 2013; 11:191–218. [PubMed: 23132413] Wu C, Shi F. *Asian J Org Chem.* 2013; 2:116–125. Hoffmann RW, Suzuki K. *Angew Chem, Int Ed.* 2013; 52:2655–2656. Goetz AE, Garg NK. *J Org Chem.* 2014; 79:846–851. [PubMed: 24410270] Goetz AE, Shah TK, Garg NK. *Chem Commun.* 2015; 51:34–45.
4. For select recent studies of cyclic alkynes, see: Tlais SF, Danheiser RL. *J Am Chem Soc.* 2014; 136:15489–15492. [PubMed: 25328003] Medina JM, McMahon TC, Jiménez-Osés G, Houk KN, Garg NK. *J Am Chem Soc.* 2014; 136:14706–14709. [PubMed: 25283710] McMahon TC, Medina JM, Yang YF, Simmons BJ, Houk KN, Garg NK. *J Am Chem Soc.* 2015; 137:4082–4085. [PubMed: 25768436]
5. Wittig G, Fritze P. *Angew Chem, Int Ed Engl.* 1966; 5:846.
6. (a) Bottini AT, Hilton LL, Plott J. *Tetrahedron.* 1975; 31:1997–2001. (b) Schmidt MW, Angus RO, Johnson RP. *J Am Chem Soc.* 1982; 104:6838–6839. (c) Wentrup C, Gross G, Maquestiau A, Flammang R. *Angew Chem, Int Ed Engl.* 1983; 22:542–543. (d) Nendel M, Tolbert LM, Herring

- LE, Islam MN, Houk KN. *J Org Chem.* 1999; 64:976–983. [PubMed: 11674172] (e) Hänninen MM, Peuronen A, Tuononen HM. *Chem - Eur J.* 2009; 15:7287–7291. [PubMed: 19551788]
7. (a) Moore WR, Moser WR. *J Org Chem.* 1970; 35:908–912. (b) Bottini AT, Corson FP, Fitzgerald R, Frost KA II. *Tetrahedron.* 1972; 28:4883–4904. (c) Christl M, Schreck M. *Angew Chem, Int Ed Engl.* 1987; 26:449–451. (d) Christl M, Fischer H, Arnone M, Engels B. *Chem - Eur J.* 2009; 15:11266–11272. [PubMed: 19746463] (e) Quintana I, Peña D, Pérez D, Guitián E. *Eur J Org Chem.* 2009; 5519–5524
8. (a) Balci M, Jones WM. *J Am Chem Soc.* 1980; 102:7607–7608. (b) Tolbert LM, Islam MN, Johnson RP, Loisel PM, Shakespeare WC. *J Am Chem Soc.* 1990; 112:6416–6417.
9. Another attractive aspect of using 1,2-cyclohexadiene (**7**) as a synthetic intermediate is the potential to access sp³-rich heterocycles, especially in comparison to benzyne cycloadducts. The synthesis of sp³-rich heterocycles is a current priority area in medicinal chemistry; see Lovering F, Bikker J, Humblet C. *J Med Chem.* 2009; 52:6752–6756. [PubMed: 19827778] Ritchie TJ, Macdonald SJF. *Drug Discovery Today.* 2009; 14:1011–1020. [PubMed: 19729075] 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 nitron 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.
17. Schmidt Y, Lam JK, Pham HV, Houk KN, Vanderwal CD. *J Am Chem Soc.* 2013; 135:7339–7348. [PubMed: 23634642]
18. Pham HV, Houk KN. *J Org Chem.* 2014; 79:8968–8976. [PubMed: 25216056]
19. The C1–C2–C3 angle in the diradical transition state (**TS2**) is very similar as well (i.e., 129.5°).
20. For examples of distortion-accelerated reactions, see: Gordon CG, Mackey JL, Jewett JC, Sletten EM, Houk KN, Bertozzi CR. *J Am Chem Soc.* 2012; 134:9199–9208. [PubMed: 22553995] Lopez SA, Houk KN. *J Org Chem.* 2013; 78:1778–1783. [PubMed: 22764840] Hong X, Liang Y, Griffith AK, Lambert TH, Houk KN. *Chem Sci.* 2014; 5:471–475.
21. Billingsley K, Buchwald SL. *J Am Chem Soc.* 2007; 129:3358–3366. [PubMed: 17326639]
22. Swift PA, Stagnito ML, Mullen GB, Palmer GC, Ceorgiev VS. *Eur J Med Chem.* 1988; 23:465–471.
23. Saitton S, Kihlberg J, Luthman K. *Tetrahedron.* 2004; 60:6113–6120.

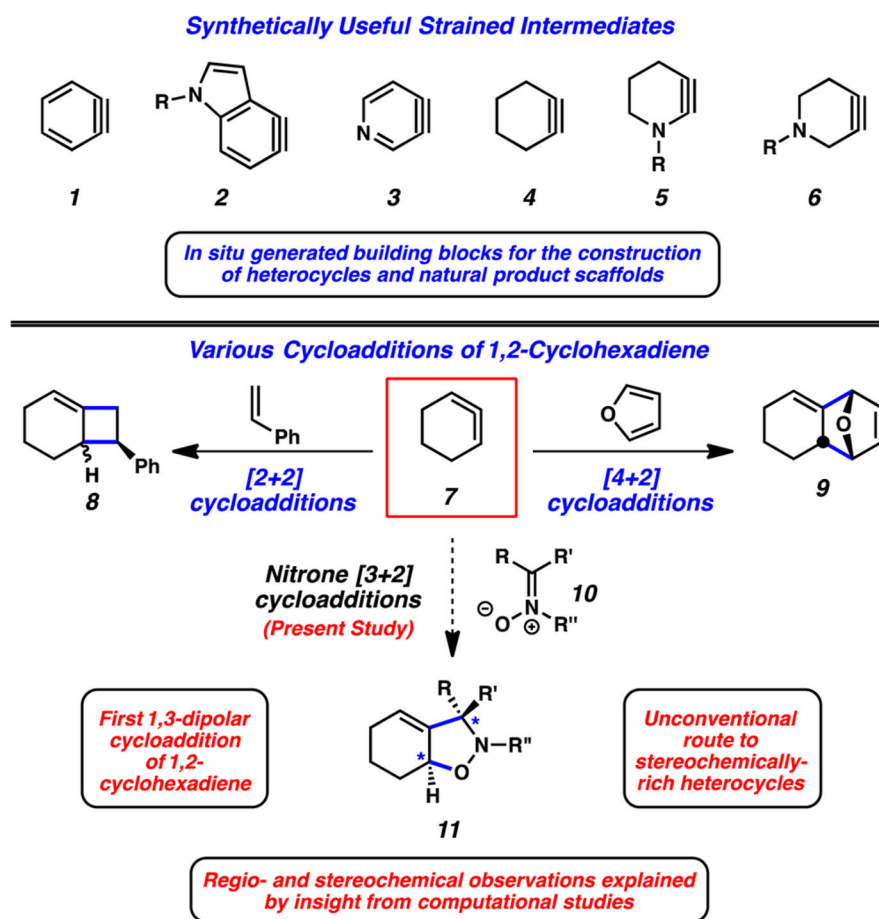
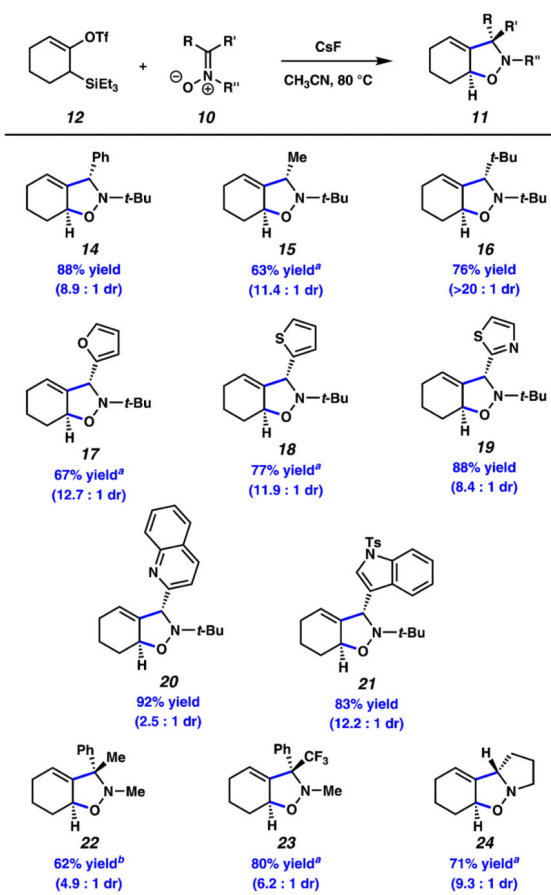


Figure 1. Strained intermediates 1–6, known cycloadditions of 1,2-cyclohexadiene (7), and nitron cycloadditions of 7 described in the present study.

**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 CH₃CN (0.1 M) at 80 °C. The yields reflect the average of two isolation experiments. ^aNitrone (2.0 equiv) was used. ^bNitrone (2.0 equiv) and THF (0.1 M) at 60 °C were used.

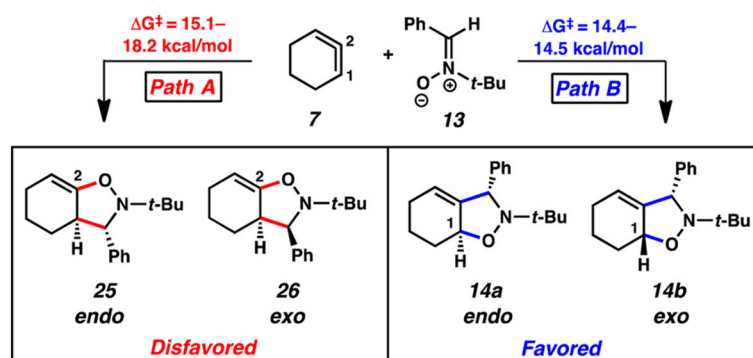


Figure 3. DFT calculations (B3LYP/6-31G*) were used to examine regioselectivities and diastereoselectivities.

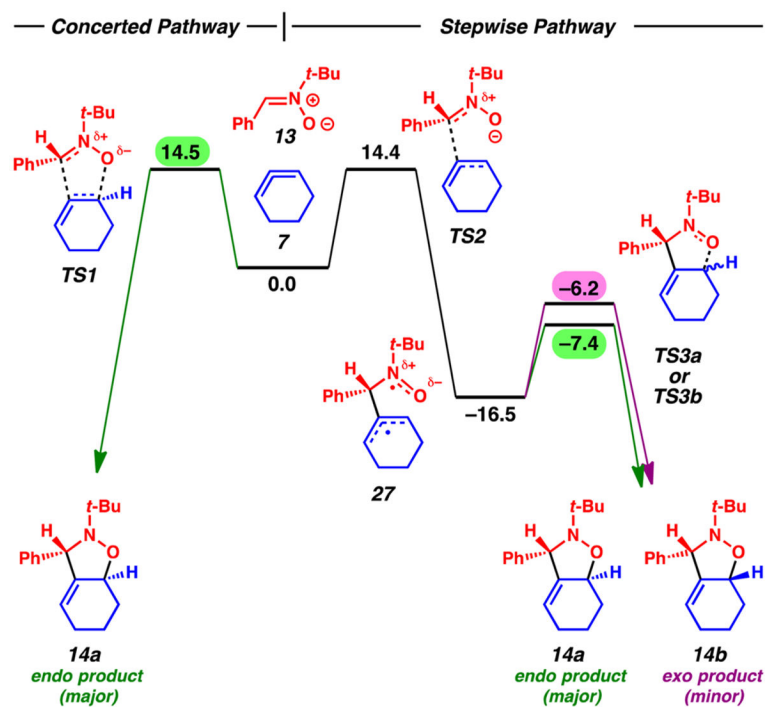


Figure 4. DFT calculations (B3LYP/6-31G*) of concerted and stepwise mechanistic pathways.

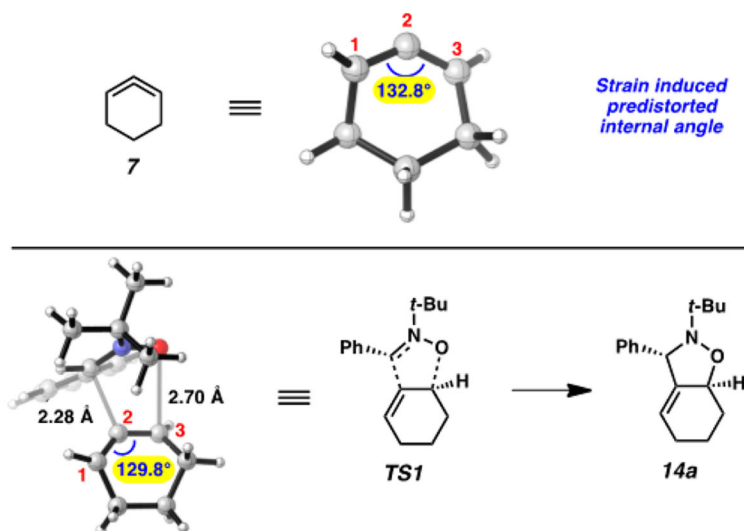


Figure 5.
Comparison of C2 internal angle for 7 and TS1.

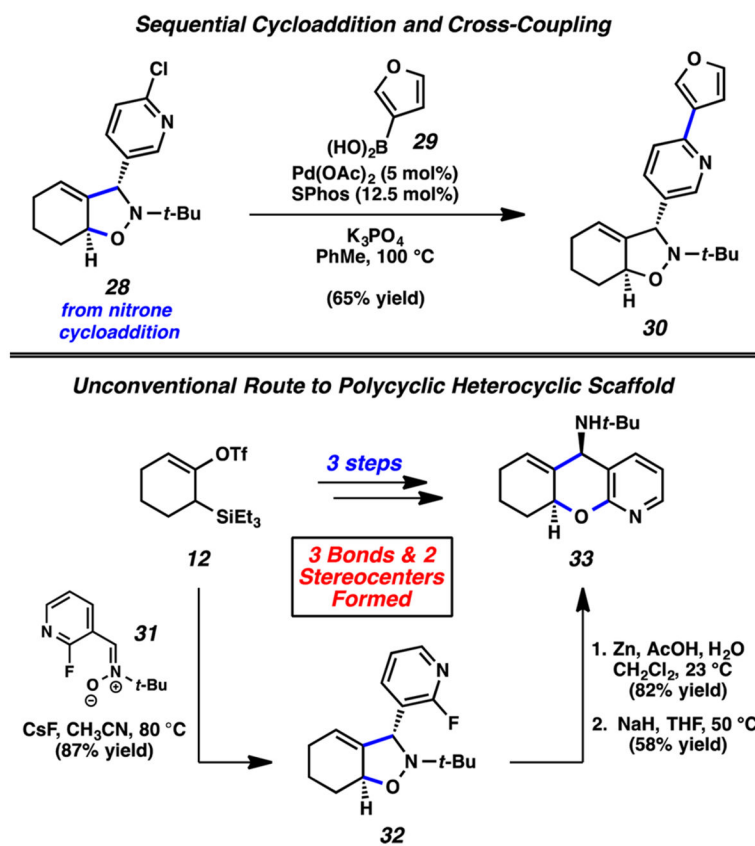


Figure 6.
Strategic manipulation of nitronium cycloadducts.

Table 1

Optimization of Nitron 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 ₃ CN	23	0.025	5.0	77 (12.1:1)
3	CsF, CH ₃ CN	23	0.025	5.0	41 (13.5:1)
4	CsF, CH ₃ CN	80	0.025	5.0	90 (9.5:1)
5	CsF, CH ₃ CN	80	0.1	5.0	92 (9.3:1)
6	CsF, CH ₃ CN	80	0.1	1.0	84 (8.5:1)

^aYields and diastereomeric ratios were determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as an external standard.