

Synthesis of Unique Scaffolds via Diels–Alder Cycloadditions of Tetrasubstituted Cyclohexadienes

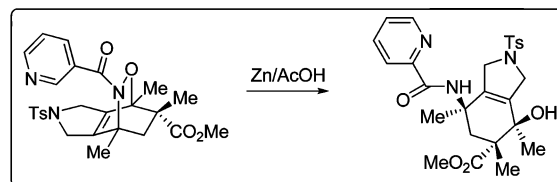
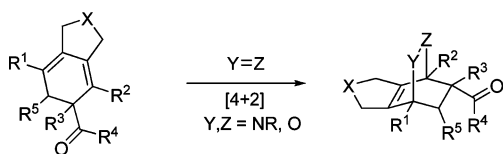
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ABSTRACT



Diels–Alder cycloadditions of highly substituted cyclohexadienes derived from rhodium-mediated $[2 + 2 + 2]$ cyclizations are reported. Reactive heterodienophiles, including singlet oxygen ($^1\text{O}_2$), 4-substituted-1,2,4-triazoline-3,5-diones (TADs), and aryl- and acylnitroso compounds were employed, yielding novel heterocyclic products.

Reactivity in Diels–Alder (DA) cycloadditions of cyclohexadienes is strongly influenced by steric constraints, often requiring forceful conditions or catalysis to promote the desired annulation.^{1,2} Unactivated, highly substituted cyclohexadienes, which can be accessed via transition-metal-catalyzed $[2 + 2 + 2]$ cyclizations, are relatively unreactive in intermolecular cycloadditions.^{2b,3}

Previously, we reported the rhodium-mediated intramolecular $[2 + 2 + 2]$ cyclizations of tethered diyne–enone substrates to produce cyclohexadiene systems which were subsequently aromatized with DDQ, giving highly substituted benzene rings.⁴ Other groups have also reported the use of $[2 + 2 + 2]$ cyclizations to generate cyclohexadienes with

quaternized allylic centers which cannot aromatize.⁵ We became interested in the reactivity of these highly substituted, electronically unactivated diene systems in DA cycloadditions, particularly with heterodienophiles, as this would allow the creation of unique, densely functionalized scaffolds.

The preparation of three model substrates **4a–c** was straightforward employing methodology we previously reported (Scheme 1).⁴ Diynyl esters **1a** and **1b**, prepared from sequential $\text{S}_\text{N}2$ displacements of 1,4-dibromobutyne,^{4,6} were subjected to Weinreb amidations followed by isopropenyl Grignard additions to give enediynes **3a** and **3b**. The desired $[2 + 2 + 2]$ cyclizations were achieved under Rh(I)-catalyzed, microwave-promoted conditions to give racemic cyclohexadienes **4a** and **4b** in 90% and 91% yields, respectively.⁴ Pyrrolidine substrate **4c** was easily prepared from $[2 + 2 + 2]$ cyclization of diyne **5**⁷ with excess methyl methacrylate **6**.^{5b}

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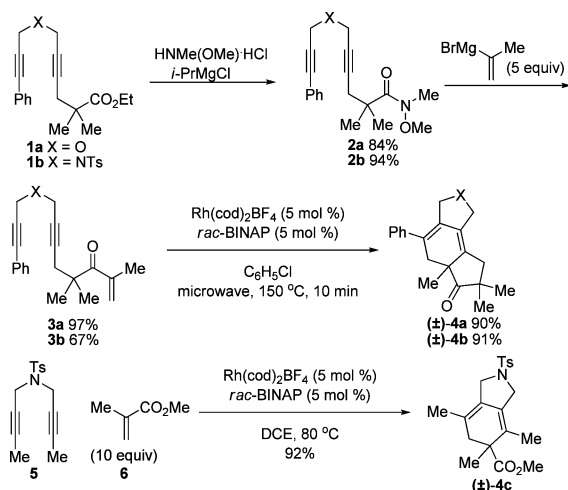
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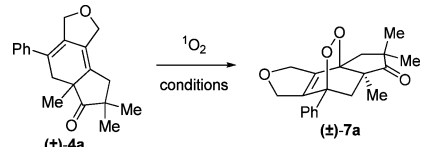
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Scheme 1. Synthesis of Model Cyclohexadiene Substrates



With the tetrasubstituted cyclohexadienes in hand, we turned to the cycloadditions of highly substituted cyclohexadiene **4a**. We began with singlet oxygen ($^1\text{O}_2$), generated in situ via photochemical excitation,⁸ or degradation of the 1:1 ozone/(PhO)₃P adduct.⁹ Successful cycloaddition of **4a** with $^1\text{O}_2$ would produce an endoperoxide, an intriguing class of compounds that display antimalarial and other therapeutic properties.¹⁰

Table 1. Cycloaddition of $^1\text{O}_2$ with Cyclohexadiene **4a**



entry	conditions ^a (equiv of (PhO) ₃ P)	yield ^b (%)	dr ^c
1	A (10)	25	17:1
2	A (5)	21	>20:1
3	A (2)	36	>20:1
4	B	37(30) ^d	13:1

^a Conditions: (A) (PhO)₃P, O₃, DCM, −70 to 0 °C, 1.5 h; (B) Rose Bengal (1 mol %), O₂ (1 atm), *hν*, EtOH, 0–10 °C, 7 h. ^b Isolated yields. ^c Determined by NMR. ^d Percentage of (±)-**4a** recovered.

Both methods of $^1\text{O}_2$ generation produced endoperoxide cycloadduct **7a** in modest yield (Table 1).¹¹ The high diastereoselectivity was unexpected considering the small size and limited steric bias of the dienophile.¹² The relative

configuration was determined by NOE studies,¹³ with the major stereoisomer resulting from $^1\text{O}_2$ addition to the face opposite the angular methyl group. Although the ozone–phosphite adduct reaction underwent complete conversion (entry 1), several other products were also formed. These byproducts were reduced by lowering the amount of (PhO)₃P used and ensuring all exogenous ozone was purged (entry 3). The photochemical reaction was limited by low conversion of **4a** even after extended reaction times (entry 4), though the yield and dr remained comparable to the ozone–phosphite procedure.

The singlet oxygen cycloaddition was then extended to cyclohexadienes **4b** and **4c** (Table 2, entries 1 and 2),

Table 2. Cycloaddition of Dienes **4b–d** with $^1\text{O}_2$ ^a

entry	substrate	product	yield (%) ^b	dr ^c
1	(±)- 4b	(±)- 7b	40	10:1
2	(±)- 4c	(±)- 7c	48	>20:1
3	(±)- 4d	(±)- 7d (19%) + (±)- 7e (14%)		

^a Conditions: (PhO)₃P (2 equiv), O₃, −70 to 0 °C, 1.5 h. ^b Isolated yield. ^c Determined by NMR.

yielding endoperoxides **7b** and **7c**. The high diastereoselectivity of **7c** likely results from the unfavorable electronic repulsion that would exist between the angular ester group and the approaching oxygen dienophile in leading to the other diastereomer. Aromatizable cyclohexadiene **4d** (entry 3) could also be trapped with $^1\text{O}_2$ at low temperature, yielding diastereomeric endoperoxides **7d** and **7e** in a 4:3 ratio.¹⁴ The low selectivity was attributed to the equatorial orientation of the ester group in **4d**, which reduces competition between addition to the two faces of the diene.

With these promising results in hand, reactive nitrogen-containing heterodienophiles were screened with cyclohexadiene **4c**, which is easily prepared in large quantities. These included 1,2,4-triazoline-1,4-diones (TADs) **9** (Table 3, entries 1 and 2),¹⁵ aryl nitroso **10** (entries 3–6),^{16,17} and acyl nitroso compounds **11** (entries 7–9), which are generated

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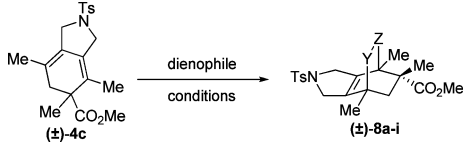
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(13) See the Supporting Information for details on NOE studies.

(14) The structures of **7d** and **7e** were confirmed after O–O bond cleavage. See the Supporting Information for complete details.

in situ by hydroxamic acid oxidation¹⁸ and have been extensively used by Miller and co-workers to prepare a variety of biologically active compounds.^{18a–c,e}

Table 3. Dienophile Screening with Cyclohexadiene **4c**

					
entry	dienophile	conditions ^a	product	yield (%) ^b	isomer ratio ^c
1	9a R = Me	A	(±)- 8a	74	>20:1 ^d
2	9b R = Ph	A	(±)- 8b	69	>20:1 ^d
3	10a X ¹ = H X ² = H	B	(±)- 8c	82	15:1
4	10b X ¹ = Br X ² = H	B	(±)- 8d	87	6:1
5	10c X ¹ = H X ² = Br	B	(±)- 8e	52	3.5:1 ^e (10:1) ^d
6	10d X ¹ = Cl X ² = H	B	(±)- 8f	73	5:1
7	11a R =	C	(±)- 8g	70	8:1
8	11b R = BnO	D	(±)- 8h	72	17:1
9	11c R = ^t BuO	D	(±)- 8i	64	10:1

^a Conditions: (A) **9a,b** (1.1 equiv), DCM, 0 °C; (B) **10a–d** (2.0 equiv), DCM, 0 °C; (C) **11a** (1.5 equiv), NaIO₄ (1.6 equiv), BnEt₃NCl (1.6 equiv), DCM, 0 °C; (D) **11b,c** (1.5 equiv), Bu₄NIO₄ (1.5 equiv), DCM, 0 °C.
^b Isolated yield. ^c Determined by NMR, identity of minor product unknown unless otherwise noted. ^d Diastereomeric ratio. ^e Regioisomeric ratio.

The resulting racemic heterocyclic cycloadducts **8a–i** were produced in yields ranging from 64 to 87% and isomeric ratios of up to >20:1 (Table 3). The diastereoselectivities of

the cycloadditions were analogous to those of ¹O₂ additions, in which the major diastereomer resulted from dienophile addition to the face away from the ester group. This was supported by NOE studies¹³ and, for the triazoline dienophiles, confirmed by X-ray crystal structure analysis of PTAD cycloadduct **8b** (Figure 1). The para-substituted arylnitroso

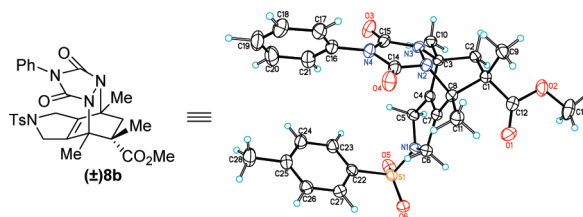
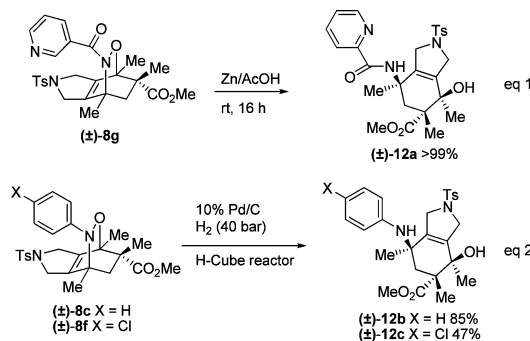


Figure 1. ORTEP diagram of cycloadduct (±)-**8b**.

compounds **10a,b,d** and acylnitroso precursors **11a–c** exhibited good regioselectivity in favor of the bulkier *N*-substituted group adding remote to the ester-containing quaternary center.¹⁹ Introduction of an ortho bromine substituent (**10c**, Table 3, entry 5) reduced both the reactivity and regioselectivity.

While acylnitroso adducts **8g–i** are stable in solution for several days, arylnitroso adducts **8c,d,f** undergo 10–25% cycloreversion to **4c** within 24 h in CDCl₃.²⁰ In order to address this instability, reductive cleavage of the N–O bond of **8g** with Zn/AcOH²¹ was carried out (Scheme 2, eq 1),

Scheme 2. N–O Bond Cleavage of Nitroso Cycloadducts



producing amido alcohol **12a** in excellent yield. The comparatively electron rich N–O bond of arylnitroso cycloadduct **8c** was resistant to these and other reductive conditions, including SmI₂,²² Na/SiO₂,²³ and Pd/C–H₂ (1 atm),²⁴ leading only to recovery of a mixture of cycloadduct and cyclor-

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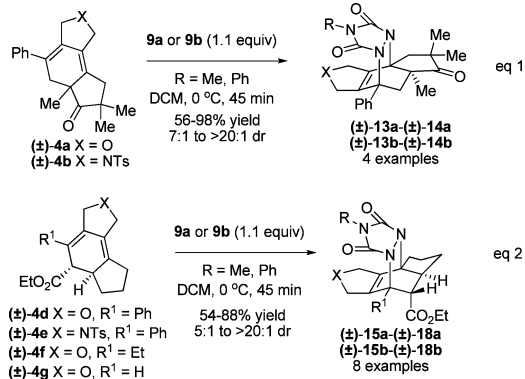
(19) See the Supporting Information for details of regioselectivity determination.

(20) Cycloadduct **10e** was more stable in solution, possibly due to the bulky *o*-Br substituent forcing the aromatic ring to rotate out of the plane of the N–O bond, slowing the cycloreversion.

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version product **4c**. By increasing the H₂ pressure to 40 bar using an H-Cube hydrogenation reactor, the desired N–O cleavage was achieved for **8c** and **8f**, yielding stable amino alcohols **12b** and **12c**, respectively (Scheme 2, eq 2). Aryl bromide cycloadducts **8d** and **8e** underwent dehalogenation in addition to N–O bond cleavage under these conditions, yielding only **12b**.

Scheme 3. Cycloadditions of Cyclohexadienes **4a,b,d–g** with TADs **9a** and **9b**^a



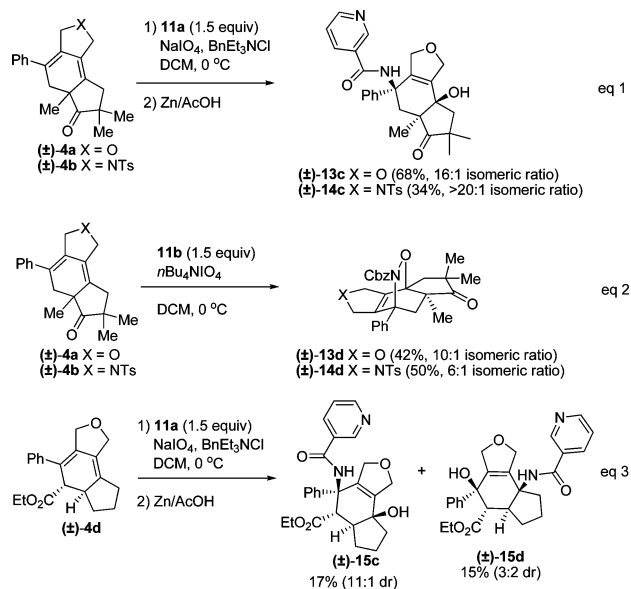
^a See the Supporting Information for complete reaction details and compound characterization

The reactivity of racemic tricyclic cyclohexadienes with select heterodienophiles from Table 3 was also investigated (Schemes 3 and 4). Substrates **4a** and **4b** underwent cycloadditions with TADs **9a** and **9b** (Scheme 3, eq 1), providing four novel heterocyclic cycloadducts, **13a–14b**, in good to excellent yields and high diastereoselectivities. Aromatizable cyclohexadienes **4d–g** were also successfully trapped with **9a** and **9b**, yielding cycloadducts **15a–18a** and **15b–18b**, respectively, also in good yields and diastereoselectivities (Scheme 3, eq 2).

Acynitroso dienophiles also underwent cycloadditions with **4a** and **4b** (Scheme 4, eqs 1 and 2). Subsequent N–O cleavage of the pyridinyl-containing cycloadducts yielded amido alcohols **13c** and **14c**. (Scheme 4, eq 1). Low regio- and diastereoselectivities were observed in the analogous cycloaddition of aromatizable cyclohexadiene **4d** with **11a** (Scheme 4, eq 3), similar to what was observed for the cycloaddition of **4d** with ¹O₂.

Overall, the regio- and diastereoselectivities of all cycloadducts derived from tricyclic cyclohexadienes were consistent with previous observations. For nonaromatizable tricyclic dienes **4a** and **4b** (Scheme 3, eq 1 and Scheme 4, eqs 1 and 2), major products resulted from approach of the dienophile from the face opposite the angular methyl group

Scheme 4. Acynitroso Cycloadditions of Cyclohexadienes **4a,b,d**^a



^a See the Supporting Information for complete reaction details and compound characterization.

with the more sterically demanding *N*-substituted portion of the unsymmetrical acynitroso dienophiles adding away from the Me-bearing quaternary center. Aromatizable cyclohexadienes **4d–g** (Scheme 3, eq 2) formed TAD cycloadducts in which the dienophile added to the face opposite the ethyl ester.

In conclusion, cycloadditions of highly substituted, unactivated cyclohexadienes were achieved using several classes of heterodienophiles under mild conditions. The substrates are easily prepared by Rh(I)-catalyzed [2 + 2 + 2] cyclizations previously reported.⁴ The resulting novel heterocyclic cycloadducts were generally isolated in good yields and high selectivities. Future work is focused on diversification of the cycloadducts. Development of an asymmetric version of the [2 + 2 + 2] cyclization as well as studies to better understand the origin of selectivity in these cycloadditions are also being investigated and will be reported in due course.

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Supporting Information Available: Full experimental procedures, characterization data, and copies of ¹H and ¹³C spectra of all new products, and X-ray crystallographic data for **8b** and **15b** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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