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Thermodynamic Control of Isomerizations of Bicyclic Radicals: Interplay of Ring Strain and Radical Stabilization

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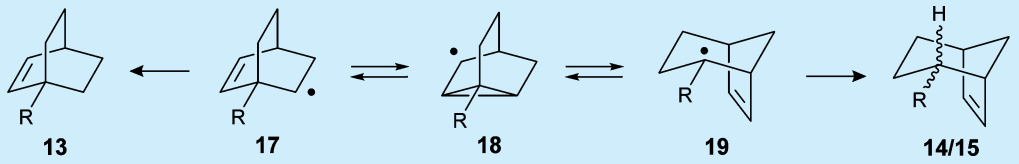
Supporting Information



ABSTRACT: The rearrangements of 4-substituted bicyclo[2.2.2]oct-5-en-2-yl radicals, generated from the corresponding Diels–Alder adducts with phenylseleno acrylates by radical-induced reductive deselenocarbonylations, give the 2-substituted bicyclo[3.2.1]oct-6-en-2-yl radicals with some substituents, e.g., alkoxy and phenyl, but not for silyloxymethyl or benzyl substituents. Theoretical calculations with DFT give the thermodynamics of these reactions and the origins of these processes.

Recently, we reported the development of phenylseleno acrylate **1** as an "ethylene equivalent" in Diels–Alder reactions.[1] Thus, heating **1** with various dienes **2** gave the expected cycloadducts **3**, which could be reduced cleanly using tris(trimethylsilyl)silane **4**, the Chatgilialoglu reagent,[2] to give the desired formal cycloadducts of ethylene **5** (Figure 1).

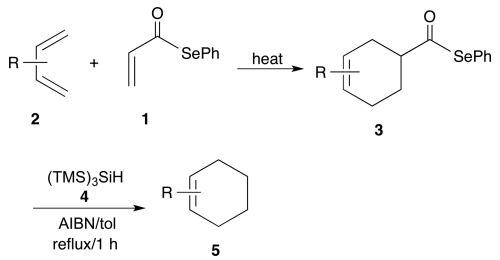
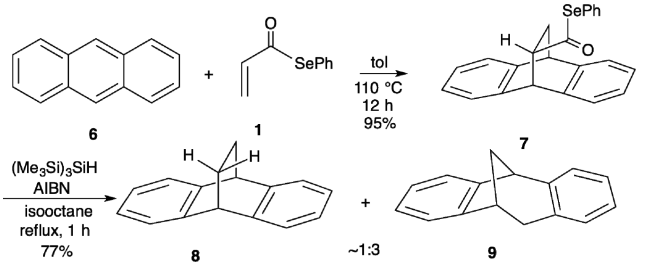


Figure 1. Use of **1** as an ethylene equivalent in Diels–Alder reactions.

The majority of substrates were reduced under the normal conditions without any rearrangement of the generated radicals.[3] However, we reported that the adduct **7**, prepared by the Diels–Alder reaction of anthracene **6** with the dienophile **1**, underwent significant rearrangement to give a 1:3 mixture of the expected dibenzobicyclo[2.2.2]octane product **8** and the rearranged dibenzobicyclo[3.2.1]octane product **9** (Scheme 1).[1] This was attributed to the well-known homoallyl–cyclopropyl carbinyl radical rearrangement pathway leading to a more stable radical.[4] This specific transformation is also known as a neophyl rearrangement.[5] We now report that this rearrangement is general and proceeds for all systems in which the radical in the new bicyclo[3.2.1]octyl ring system is more stable than the radical in the original bicyclo[2.2.2]octyl ring system. We observe an interesting result, namely that a secondary bicyclo[2.2.2]oct-5-en-2-yl radical is more stable than a tertiary bicyclo[3.2.1]oct-6-en-2-yl radical. Theoretical

Scheme 1. Rearrangement of Anthracene Adduct 7



calculations show the interplay of ring strain and relative stabilities of these substituted radical systems.

The substrates for the radical rearrangement studies were all prepared by the Diels–Alder reaction of the freshly prepared 1-substituted 1,3-cyclohexadienes **10**[6] with the phenylseleno acrylate **1**, which were carried out in refluxing toluene for 14 h (Table 1). The cycloadducts were obtained in yields of 55–97% as mixtures of endo and exo isomers **11** and **12**. In all cases, the endo isomers **11** were the major products, with the endo/exo ratio varying from 3.3–8 to 1.[7]

With the Diels–Alder products **11** and **12** in hand, we next examined their reductive decarbonylation to produce the reduced products. A mixture of the endo and exo esters was treated with tris(trimethylsilyl)silane and AIBN in refluxing benzene for several hours to give the reduction products (Table 2). The reduction of the parent unsubstituted compound **11a**/**12a** gave predominately the expected bicyclo[2.2.2]octene **13a**, with very little rearranged products (>20:1). However, the behavior of the substituted analogues was quite different. Reduction of the 4-methoxy esters **11b**/**12b** afforded only a minor amount of the unrearranged product **13b** and gave

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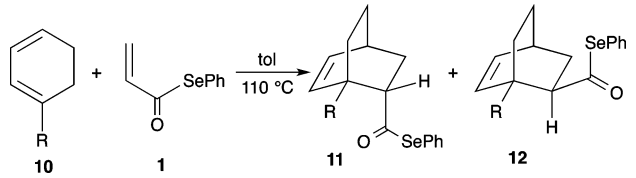
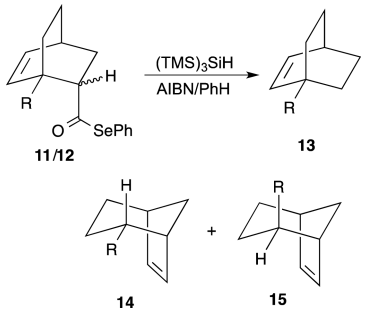
Table 1. Diels–Alder Reaction of 1-Substituted Dienes 10 and Phenylseleno Acrylate 1



entry	compd	R	yield (%)	ratio **11**:**12**[a]
1	**a**	H	97	8:1
2	**b**	OMe	87	5.1:1
3	**c**	OTBS	76	3.4:1
4	**d**	Ph	66	4.4:1
5	**e**	CH_2OTBS	83	3.3:1
6	**f**	CH_2Ph	88	4.1:1

[a]The ratios of all products were determined by careful integration of the appropriate peaks in the ^1H NMR spectra.[7]

Table 2. Reduction of Bicyclo[2.2.2]oct-2-enyl-5-selenophenyl Esters 11 and 12



entry	compd	R	ratio **13**:**14** + **15**	ratio **14**:**15**[a]
1	**a**	H	>20:1	NA
2	**b**	OCH_3	1:5.6	2.6:1
3	**c**	OTBS	1:2.5	2.5:1
4	**d**	Ph	1:10	2.4:1
5	**e**	CH_2OTBS	7:1	2.9:1
6	**f**	CH_2Ph	7:1	3.8:1

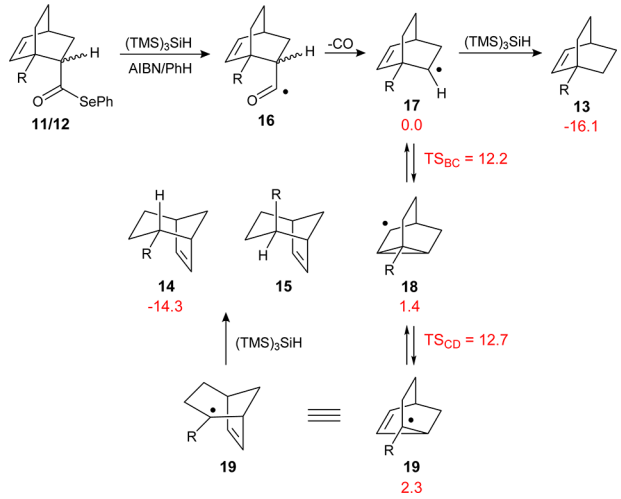
[a]The ratios of all products were determined by careful integration of the appropriate peaks in the ^1H NMR spectra.[8]

mainly the rearranged 2-methoxybicyclo[3.2.1]oct-6-enes **14b** and **15b**, with the ratio of unrearranged to rearranged product being 1:5.6.[8]

The proposed mechanism for the reduction is shown in Scheme 2. Treatment of the selenophenyl esters **11** and **12** with tris(trimethylsilyl)silane generates the acyl radicals **16**, which undergo decarbonylation to give the secondary radicals **17**.[9] Reduction of **17** by the silane affords the unrearranged bicyclo[2.2.2]octene product **13**. However, in competition with this reduction, the radical **17** can rearrange via the cyclopropyl carbinyl radical **18** to give the bicyclo[3.2.1]oct-6-en-2-yl radical **19**. Reduction of this radical by the silane gives a mixture of the equatorial and axial products **14** and **15**.

The prevalence of the rearranged products **14b**/**15b** is not surprising since intermediate **19b**, leading to the bicyclo[3.2.1]-octene product, has a radical adjacent to a methoxy group. In contrast, intermediate **17b**, leading to the bicyclo[2.2.2]octene product, has a simple secondary radical (Scheme 2). As expected, the more substituted radical is more stable. In a like manner, the 4-silyloxy analogue **11c**/**12c**, upon similar

Scheme 2. Proposed Mechanism of Reduction of Selenophenyl Esters[a]



[a]Relative computed Gibbs free energies for the parent compound (R = H) are given in red.

treatment, gave the rearranged products **14c** and **15c** as the major products in a 2.5:1 ratio with the unrearranged product **13c**. Again, the stability of the intermediate radical leading to the rearranged product would be expected to be greater than that of the unrearranged product. The 4-phenyl analogue **11d**/**12d** behaved similarly and afforded the rearranged products **14d** and **15d** in a 10:1 ratio with the unrearranged product **13d**. Here the bicyclo[3.2.1]octenyl radical **19d** is tertiary and benzylic and, therefore, is much more stable than the secondary homobenzylic radical in **17d**. On the basis of these foregoing results, the reduction of the 4-silyloxymethyl analogue **11e**/**12e** seems surprising, since in this case the unrearranged product **13e** predominated, formed in a 7:1 ratio with the rearranged products **14e** and **15e**. This implied that the bicyclo[2.2.2]-octenyl intermediate leading to **13e**, containing a secondary radical, is more stable than the rearranged bicyclo[3.2.1]octenyl intermediate with a tertiary radical. We also reduced the 4-benzyl analogue **11f**/**12f**, and the unrearranged product **13f** was formed preferentially over the rearranged products **14f** and **15f**, again in a ratio of 7:1.

To further investigate these varying product ratios, we performed density functional calculations at the M06-2X/6-311G(d,p)//B3LYP/6-31G(d) level of theory using the Gaussian09 program.[10] Activation free energies for the homoallyl–cyclopropyl carbinyl radical rearrangement of **17a**–**18a** and **18a**–**19a** were also computed.

Figure 2 shows the relative energies of radicals, transition states for rearrangement, and products for the parent system (R = H). The bicyclo[2.2.2]octene, **13a**, is 1.8 kcal/mol more stable than the bicyclo[3.2.1]octene **14a**. The corresponding radicals **17a** and **19a** differ in energy by 2.3 kcal/mol in the same direction. This results from the greater strain of the bicyclo[3.2.1] skeleton. The low activation barriers for $\mathbf{TS}_{17-18}$ and $\mathbf{TS}_{18-19}$ are consistent with the proposed equilibrium between radical species **17** and **19**.

Table 3 shows the computed energy differences between substituted radical species **17** and **19**, along with the corresponding equilibrium ratios from these energies. The energy differences are in good accord with the expected energies of radical stabilization by these substituents.[11]

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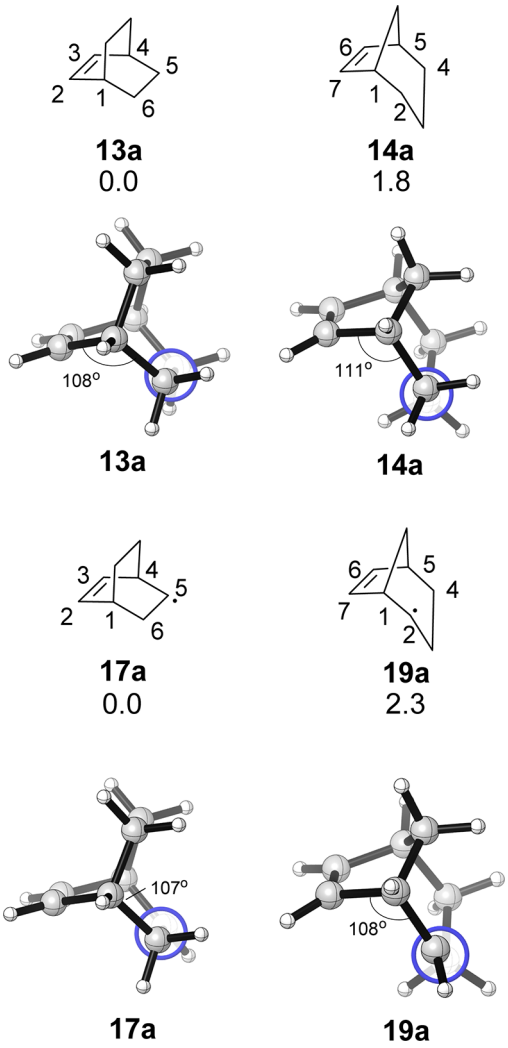

Figure 2. Structures of bicyclo[2.2.2]oct-2-ene **13a**, bicyclo[3.2.1]oct-6-ene **14a**, and their radicals **17a** and **19a**, with relative M06-2X/6-311G(d,p)//B3LYP/6-31G(d) Gibbs free energies in kcal/mol.

Table 3. Computed Radical Stabilities and Equilibrium Ratios of Bicyclic Compounds with Various Substituents

entry	R	$\Delta\Delta G_{17-19}$ (kcal/mol)	predicted ratio **17:19**	experimental ratio **13:14 + 15**
1	H	2.3	48:1	>20:1
2	OCH_3	−1.0	1:5	1:5.6
3	Ph	−6.7	$1:>8 \times 10^4$	1:10
4	CH_3	1.2	8:1	7:1[a]

[a]Experimental value for the CH_2OTBS and CH_2Ph substituents.

Comparing these computed ratios with those observed experimentally confirms our initial assumptions that radical-stabilizing substituents promote the ring rearrangement—methoxy and phenyl substituents favor formation of the bicyclo[3.2.1]octene system, while a methyl substituent, although also stabilizing, prefers to remain unrearranged as the [2.2.2] system.

Furthermore, in the rearranged 2-substituted bicyclo[3.2.1]-oct-6-ene products, the equatorial product **14** is always favored over the axial, **15**, and the ratio of **14**/**15** varies from a low of 2.3:1 to a high of 3.8:1. The radical is only slightly nonplanar, as shown in Figure 3, to minimize eclipsing between the bonds to

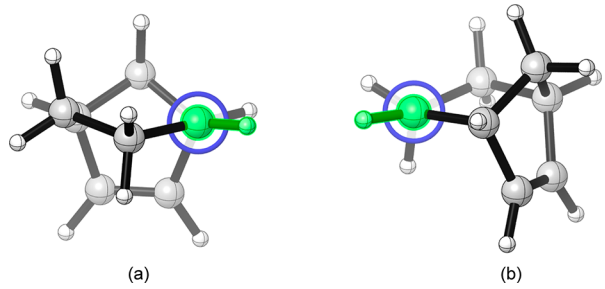

Figure 3. Newman projections for **19a**, viewing from (a) C2−C1 and (b) C2−C3.

the radical center and the attached carbon. Moreover, this preference is reinforced in the transition states in order to minimize eclipsing with the newly forming bond, a well-known phenomenon in C−C bond-forming reactions, sometimes referred to as torsional steering.[12] For instance, in Figure 3, hydrogen abstraction from silane will occur from the top of the radical center of **19a** to avoid torsional strain from eclipsing bonds. This favors formation of product **14** over **15**.

In conclusion, we have found that the in situ generated [2.2.2] radicals are generally more stable than the corresponding [3.2.1] rearrangement counterparts, but radical-stabilizing substituents can reverse this preference. The relative stabilities of these radicals control the product ratios, while torsional effects control the stereochemistry of hydrogen transfer from silane to the alkyl radicals.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03112.

Experimental methods, NMR spectra, and analytical data for all new products (PDF)

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Notes

The authors declare no competing financial interest.

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(6) Most of the 1-substituted 1,3-cyclohexadienes **10** were known. The new 1-silyloxymethyl diene **10e** was prepared by reduction of the known methyl 1,3-cyclohexadiene-1-carboxylate with DIBAL followed by silylation. Harding, K. E.; Strickland, J. B.; Pommerville, J. *J. Org. Chem.* **1988**, *53*, 4877. The new benzyl analogue **10f** was prepared by reaction of benzyl Grignard reagent with the known 1-(triflyloxy)-1,3-cyclohexadiene using $NiCl_2$(dppp) as catalyst. Corey, E. J.; Kigoshi, H. *Tetrahedron Lett.* **1991**, *32*, 5025.

(7) The mixture of isomers could not be separated, but the assignment of the stereochemistry of the two diastereomeric cycloadducts was made by NMR measurements since all of the exo isomers **12** showed an additional small coupling (J = 1.6−2.0 Hz) for the proton α to the carbonyl group due to W coupling which is not possible in the endo isomer **11**.

(8) The mixture of diastereomers could not be separated, but their stereochemistry was assigned by analysis of the crude NMR spectra. The proton α to the R group in **14** always exhibited a very large coupling constant (J = 9.0−12.0) due to the axial−axial coupling, whereas that large coupling was absent from the isomeric compounds **15**.

(9) The acyl radical **A** can also be reduced before decarbonylation, and indeed small amounts of aldehydes are occasionally isolated from these reductions.

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