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Combined Computational and Experimental Studies of the Mechanism and Scope of the Retro-Nazarov Reaction

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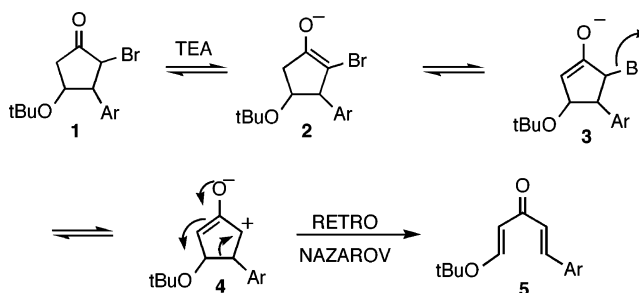
Abstract: Density functional theory calculations (B3LYP/6-31+G*) demonstrate that conjugating and electron-donating substituents at carbons three and four of a cyclopentenyl oxyallylic cation should have a rate-accelerating effect on the retro-Nazarov reactions of these species. The retro-Nazarov reaction of these intermediates is predicted to exhibit significant torquoselectivity when carbon three is substituted with a methoxy and a methyl group. Experimental studies show that oxyallylic cations can undergo effective retro-Nazarov reactions when two alkyl and one aryl/vinyl groups are on carbons three and four. An equal number of alkyl substituents or a single aryl substituent is not effective in promoting the reaction. Interestingly, a single alkoxy substituent at carbon three is sufficient for the retro-Nazarov reaction to occur. The methodology developed was used in a total synthesis of the natural product turmerone.

We recently reported the first examples of the retro-Nazarov reaction in which 3-aryl-2-bromo-4-*tert*-butoxy-cyclopentanones underwent ring opening upon treatment with base.¹ This reaction presumably occurred through the mechanism depicted in Scheme 1. The putative oxyallylic cation intermediate **4** underwent unimolecular retroelectrocyclization faster than potential bimolecular reactions such as elimination or nucleophilic attack. However, this intermediate is both kinetically and thermodynamically biased toward ring opening by virtue of its substitution pattern. Both the alkoxy and aryl (or vinyl) groups should weaken the bond to be cleaved and provide a driving force for opening through conjugative stabilization in the product.

As part of our effort to explore the scope of the reaction, we embarked on a computational study of the key mechanistic steps in the hope of gleaning some information about substituent effects in the process. This information would provide the basis for further experimental work. In this article, we report the results of a density functional theory (DFT) study of the barriers associated with ring opening of various cyclopentenyl oxyallylic cations and report studies that define the present experimental limits of the reaction.

Energies for oxyallylic cations, transition states, and ring-opened dienones were computed with Gaussian 98,² using Becke's three-parameter hybrid functional³ (B3LYP) with a 6-31+G* basis set. A restricted approach was used for all geometry optimizations, energy evaluations, and frequency analyses of the reactants. All stationary structures were identified as minima or transition structures by computing analytic vibrational frequencies, which were also used to compute zero-

Scheme 1



point vibrational energies (ZPVE). All absolute energies and geometries are given in the Supporting Information.

All of the reactions are computed to be exothermic (Table 1). As expected, substitution adjacent to the C³–C⁴ bond with atoms bearing lone pairs of electrons lowers the barrier significantly (relative to parent **6**, $\Delta H_0^\ddagger = 14.9$ kcal mol⁻¹) with the acceleration being greatest for the amino (**17**, $\Delta H_0^\ddagger = 4.2$ kcal mol⁻¹) and methoxy (**7**, $\Delta H_0^\ddagger = 4.6$ kcal mol⁻¹) groups

- (2) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision x.x; Gaussian, Inc.: Pittsburgh, PA, 1998.
- (3) (a) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098–3100. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. The Lee–Yang–Parr nonlocal correlation functional: (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
- (4) Kalle, E. A.; Houk, K. N. *J. Org. Chem.* **1989**, *54*, 6006.

[†] University of Missouri-Columbia.

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(1) Harmata, M.; Lee, D. R. *J. Am. Chem. Soc.* **2002**, *124*, 14328–14329.

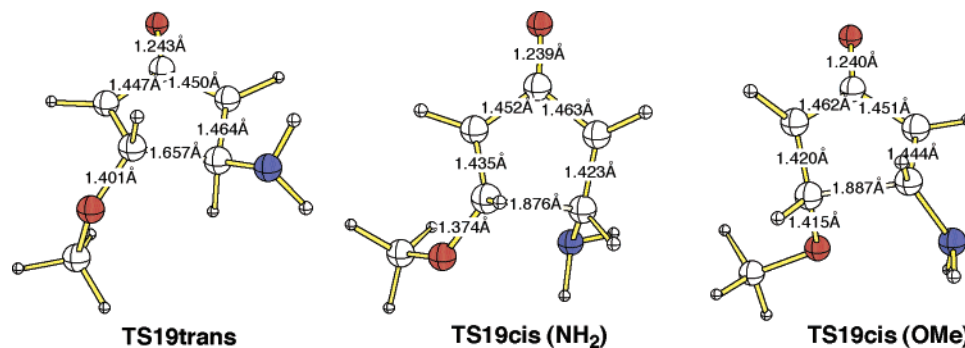


Figure 1. Transition structure for the ring opening of **19** (cis and trans forms).

Table 1. Relative (Including ZPVEs, to Starting Material in kcal mol⁻¹) at B3LYP/6-31+G*

Species	TS	Product
R ¹ = R ² = R ³ = H; R ⁴ = –(6)	14.9	–26.4
R ¹ = OMe, R ² = R ³ = H; R ⁴ = –(7)	4.6	–36.6
R ¹ = OMe, R ² = OMe, R ³ = H; R ⁴ = –(8 ^a)	0.0 ^b	–45.1
R ¹ = OMe, R ² = OMe, R ³ = CH ₃ ; R ⁴ = –(9)	2.1	–34.3
R ¹ = OMe, R ² = H, R ³ = H; R ⁴ = H (10)	2.7	–25.0
R ¹ = OMe, R ² = H, R ³ = H; R ⁴ = Li (11)	3.7	–27.3
R ¹ = vinyl, R ² = H, R ³ = H; R ⁴ = –(12)	10.5	–31.7
R ¹ = OMe, R ² = H, R ³ = Cl; R ⁴ = –(13)	7.6	–27.5
R ¹ = Me ₂ , R ² = H, R ³ = H; R ⁴ = –(14)	13.9	–30.9
R ¹ = Me/OMe, R ² = H, R ³ = H; R ⁴ = –(15)	4.9	–34.0
R ¹ = OMe/Me, R ² = H, R ³ = H; R ⁴ = –(16)	14.4	–34.8
R ¹ = NH ₂ , R ² = R ³ = H; R ⁴ = –(17)	4.2	–39.9
R ¹ = SH, R ² = R ³ = H; R ⁴ = –(18)	9.6	–32.3
R ¹ = OMe, R ² = NH ₂ , R ³ = H; R ⁴ = –(19c)	11.5 ^b	–42.0 ^b
	7.6 ^c	–42.3 ^c
R ¹ = OMe, R ² = NH ₂ , R ³ = H; R ⁴ = –(19t)	0.0 ^d	–50.6
R ¹ = –(CH ₂) ₃ – = R ² , R ³ = H; R ⁴ = –(20)	10.4	–29.5
R ¹ = –(CH ₂) ₄ – = R ² , R ³ = H; R ⁴ = –(21)	9.8	–17.1
R ¹ = –(CH ₂) ₅ – = R ² , R ³ = H; R ⁴ = (22)	11.5	–24.7

^a *trans*. ^b NH₂ group inside. ^c OMe group inside. ^d The transition structure is associated with a negligible barrier that disappears when ZPVE corrections are applied, i.e., the model reaction is practically barrierless.

and smallest for the thiol group (**18**, $\Delta H_0^\ddagger = 9.6$ kcal mol⁻¹). This trend correlates with the exothermicity of the reaction for these substituents ($\Delta_R H_0 = -26.4$, -39.9 , -36.6 , and -32.3 kcal mol⁻¹, respectively). When two methoxy groups straddle the breaking bond, ring opening should proceed highly exothermically ($\Delta_R H_0 = -45.1$ kcal mol⁻¹) without a barrier (**8**). Geminal dialkyl substitution at C⁴ provides for some acceleration, but not much, and ring opening of a species such as **14** is not expected to be significantly faster than **6** ($\Delta\Delta H_0^\ddagger = 1.0$ kcal mol⁻¹). Vinyl substitution (**12**) is expected to have a more substantial impact on ring opening, but not so important as an alkoxy group.

The cis and trans substitution pattern in, for example, **19** also makes quite a difference (Figure 1) owing to the much earlier nature of the TS for the trans pathway. In accord with Hammond's postulate, **TS19t** is much less developed (early transition structure) compared to **TS19c**, as evident from the considerable difference in bond lengths for the two transition structures. Note in particular the key central bond distance of the breaking bond that is significantly more lengthened (by 0.219

Å) in **TS19c**, leading to an appreciable barrier. Alternatively, one may look at either conrotation of **19c** as having a higher barrier due to untoward steric and stereoelectronic effects.⁴ The reverse reactions are equally different as the two electronegative heteroatoms get into each other's way in the cis approach when viewed from the product side. One other important point is that conrotation of **19c** demands the inward rotation of either the methoxy or amino group. Our calculations suggest that rotation to place the methoxy group inside is favored substantially kinetically and to a slight extent thermodynamically.

Interestingly, but as expected in the context of work by the Houk group,⁴ the retro-Nazarov reaction is expected to be torquoselective. As illustrated in Scheme 2, while the formation of both **15p** and **16p** is favored to essentially the same extent thermodynamically ($\Delta\Delta_R H_0 = 0.8$ kcal mol⁻¹), the barriers for the two processes differ considerably (4.9 vs 14.4 kcal mol⁻¹), and selective formation of **15p** is anticipated. As found for *cis*- and *trans*-**19**, the decisive difference in the transition structures leading to torquoselectivity traces back to their varying stages of development toward the respective product. **TS15** occurs earlier on the PES, as evident from the 0.050 Å shorter breaking central bond; all structural parameters of this TS are closer to the starting material than for the competing **TS16**.

With respect to our latest experimental work in this area, it is the ring openings of **6**, **7**, **12**, and **14** that are most relevant. Except for **7**, these oxyallylic species are expected to undergo ring opening at a relatively slow rate and thus be more subject to side reactions. To examine this, we set out to determine the minimum substitution requirements adjacent to the C³–C⁴ bond for the oxyallylic cation intermediate in the ring-opening process.

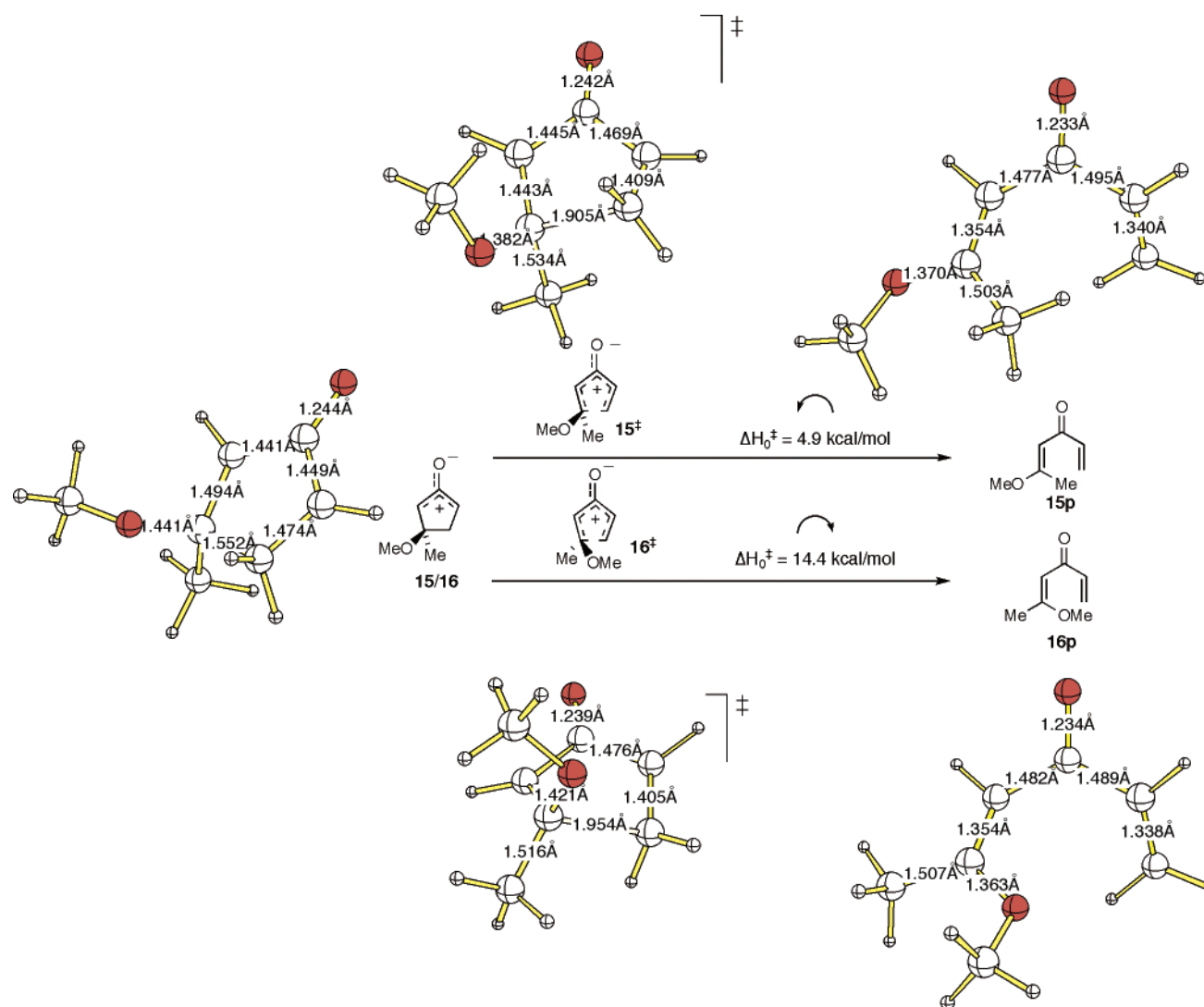
We began by removing the alkoxy group and testing a system that was rather heavily substituted, but possessed only two alkyl and one aryl substituent adjacent to the breaking bond. The synthesis of the substrate and subsequent manipulations are shown in Scheme 3. The reaction of enone **23**⁵ with *p*-tolyl cuprate afforded bromoketone **24** in 92% yield. This was heated in refluxing trifluoroethanol (TFE) for 1.5 h in the presence of excess triethylamine and afforded the dienone **25** in 77% yield. Subsequent treatment with an organocopper species derived from methylmagnesium chloride and cuprous iodide gave the natural product turmerone **26** in 73% yield.⁶

The general substitution pattern present in **24** was effective in promoting retro-Nazarov reaction in other cases. These results

(5) Paquette, L. A.; Tae, J.; Arrington, M. P.; Sadoun, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 2742.

(6) Motoyoshiya, J.; Miyajima, M.; Hirakawa, K.; Kakurai, T. *J. Org. Chem.* **1985**, *50*, 1326.

Scheme 2



Scheme 3

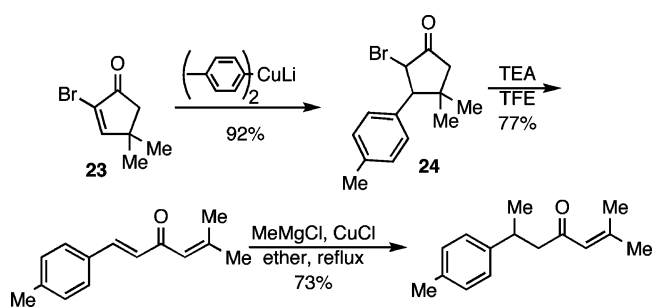
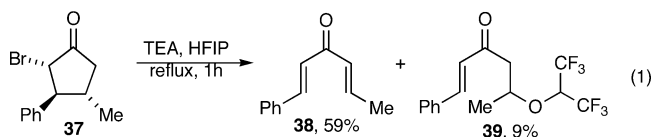


Table 2. Retro-Nazarov Reaction of Selected Bromoketones

entry	reactant	R	product	yield (%)
1	27	phenyl	28	91
2	29	<i>p</i> -methoxy phenyl	30	65
3	31	vinyl	32	82
4	33	2-methylpropenyl	34	75
6	35	methyl	36	low

are summarized in Table 2. It is anticipated that geminal dialkyl substitution flanking the breaking bond coupled with an aryl or alkenyl substituent on the adjacent carbon will be generally useful for the retro-Nazarov reaction. However, three alkyl groups are not sufficient to allow efficient reaction to occur (Table 2, entry 6).

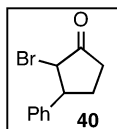
Removing a single alkyl group also allowed the reaction to proceed. Treatment of **37** with triethylamine in refluxing hexafluoroisopropanol (HFIP) gave the dienone **38** in 59% yield along with a small amount (9%) of **39** (eq 1).⁷ The stereochem-



istry of **37** was inferred from its synthesis, which involved addition of diphenylcuprate to the corresponding bromoenone. Data for this compound (see Supporting Information) indicated a single isomer was present. Conrotatory ring opening of an

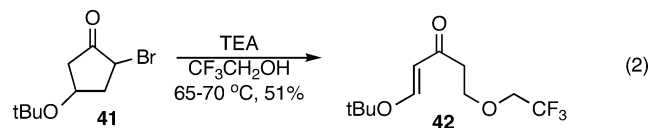
(7) When this reaction was conducted in trifluoroethanol in triethylamine, **38** and the corresponding Michael adduct were produced in a 1:1 ratio (crude NMR) in a combined yield of 60%.

oxyallylic cation generated from **37** would thus be expected to produce **38** as the all *E* isomer, as shown.

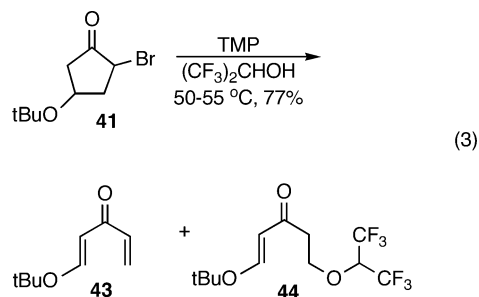


However, removal of the remaining methyl group completely stopped retro-Nazarov ring opening. Bromoketone **40** gave only elimination product upon treatment with base under standard reaction conditions. No other reaction conditions afforded retro-Nazarov product.

Finally, the reaction of **41** with triethylamine in trifluoroethanol afforded the retro-Nazarov product **42** in 51% yield (eq 2). This compound arose from retro-Nazarov reaction and



subsequent Michael addition of trifluoroethanol to the resulting dienone. The yield of this reaction could be improved through the use of tetramethylpiperidine as base, which produced **42** in 61% yield. In the best case to date for this reaction, heating **41** in the presence of TMP in HFIP afforded both **43** and **44** in a 2:1 ratio in a combined yield of 77% (eq 3). Other reaction conditions afforded slightly different ratios of products, but it is clear that a single alkoxy substituent is sufficient to enable the retro-Nazarov reaction.



In summary, we have computed transition structures and reaction energies for the retro-Nazarov reaction of a variety of cyclopentenyl oxyallylic cations. Our experimental findings give greater meaning to the computations and suggest that reactions with computed gas-phase barriers of near 10 kcal/mol will not proceed effectively along the retro-Nazarov pathway. The results shown in Scheme 2 are especially interesting in this context, as we anticipate that high torquoselectivity should be observed in the retro-Nazarov reaction given the relatively large energy difference between the two conrotations. Efforts to study this are in progress and will be reported in due course.

Acknowledgment. This work was supported by the National Science Foundation, to whom we are grateful.

Supporting Information Available: *x,y,z*-Coordinates and absolute energies for all computed species, experimental procedures, and copies of ¹H and ¹³C NMR. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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