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The Retro-Nazarov Reaction

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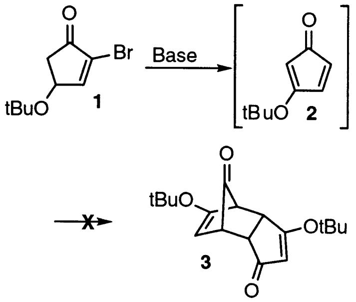
We recently reported the conversion of various 2-bromocyclopentenones into the corresponding cyclopentadienones by treatment with triethylamine in refluxing trifluoroethanol (TFE).[1] In an effort to expand the scope of the reaction, we treated bromoenone **1** under typical reaction conditions for cyclopentadienone formation.[2] We anticipated that the cyclopentadienone formed would dimerize to produce **3**, a compound rich in orthogonal functionality and one which we viewed as a candidate for a useful molecular scaffold.

The reaction of **1** with triethylamine in refluxing TFE gave a product which was clearly not **3**, by simple ^{1}H NMR analysis, in low yield. Two molecules of trifluoroethanol had been incorporated into the product. The *tert*-butoxy group remained, and an isolated trans alkene was also present ($J = 11.9$ Hz). We assigned the structure of this compound as the vinylogous ester **9**. Its formation could be rationalized according to the mechanism shown in Scheme 1.



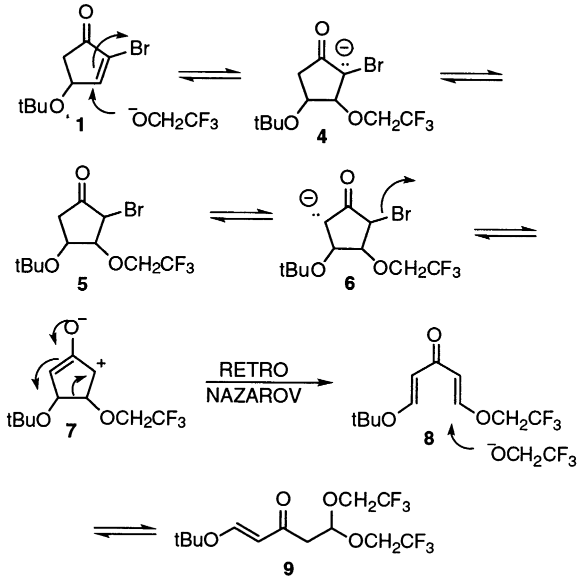
(1)

Conjugate addition of trifluoroethoxide to **1** followed by protonation and a second deprotonation would give rise to the enolate **6**. In a polar medium, this species could lose bromide to form the oxyallylic cation **7**. In the presence of base, this compound might be expected to simply lose a proton to afford an enone. Another possibility is a retro-electrocyclization. This would afford the dienone **8**. Under the reaction conditions, this dienone appears to be sufficiently electrophilic to add another molecule of trifluoroethanol via conjugate addition. The overall process from enone to dienone is a retro-Nazarov reaction and appears to be unknown, save for some examples in which substituted cyclopentenyl cations have been shown to open to pentadienyl cations.[3,4]

Although extensive optimization on this particular process has not been performed, we have been able to demonstrate that the yield could be improved to 56% yield upon heating **1** in the presence of DBU in TFE. Attempts to perform the reaction shown in eq 1 in acetonitrile have resulted in decomposition or recovery of starting material.

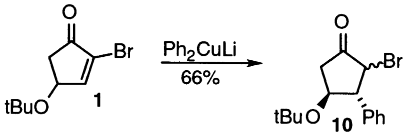
In an effort to establish a broader scope for this reaction, we decided to pursue a two-step retro-Nazarov process in which carbon nucleophiles were added to **1** and the adducts subsequently treated with base in TFE to afford dienones.

Scheme 1



Although conjugate addition protocols have thus far only given only moderate yields of the retro-Nazarov precursors, they provided sufficient material to complete a preliminary study and demonstrate that the process is more than a laboratory curiosity.

Conjugate addition of diphenylcuprate to **1** afforded **10** in 66% yield (eq 2). This compound was used to evaluate reaction conditions in the retro-Nazarov reaction. The results are summarized in Table 1. All reactions were conducted for 1 h using 1.1 equiv of base under the conditions indicated.



(2)

It appears that trifluoroethanol and hexafluoro-2-propanol are among the best solvents for this reaction, suggesting that both a polar and a protic environment are needed for the reaction to proceed (Table 1, entries 4, 5). However, there appeared to be a base dependence on the success of the reaction, at least in ethyl acetate (Table 1, entries 2, 7, 11, 15). Using tetramethylpiperidine as base gave reasonable yields of product in ethyl acetate and even resulted in the formation of low yields of product in THF, a solvent in which other attempts at the reaction, using different bases, had failed. Attempts to conduct the reaction in ether in the presence of lithium perchlorate were successful, however, with the Lewis acidity of the lithium ion probably playing a role in the success of the reaction.

Overall, some of the best results appeared to come from work involving TFE as solvent and TEA as base. We looked at several

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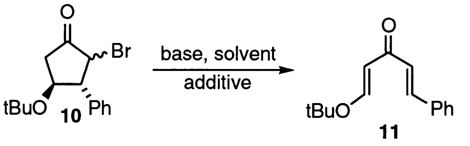
Table 1. Evaluation of the Retro-Nazarov Reaction of **10** under Various Conditions To Afford **11**



entry	base[a]	solvent	*T* °C	yield (%)
1	TEA	THF	reflux	NR
2	TEA	EtOAc	reflux	0
3	TEA	ether[b]	rt	53
4	TEA	CF_3CH_2OH	reflux	65
5	TEA	$(CF_3)_2CHOH$	reflux	54
6	DIEA	THF	reflux	NR
7	DIEA	EtOAc	reflux	NR
8	DIEA	ether[b]	rt	NR
9	DIEA	$(CF_3)_2CHOH$	reflux	56
10	DIPA	THF	reflux	NR
11	DIPA	EtOAc	reflux	1
12	DIPA	ether[b]	rt	30
13	DIPA	$(CF_3)_2CHOH$	reflux	59
14	TMP	THF	reflux	12
15	TMP	EtOAc	reflux	50
16	TMP	ether[b]	rt	44
17	TMP	$(CF_3)_2CHOH$	reflux	59

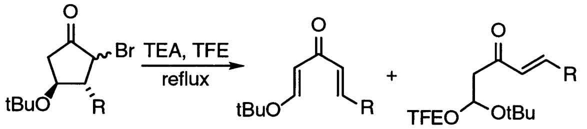
[a] TEA = triethylamine, DIPA = diisopropylamine, TMP = tetramethylpiperidine, DIEA = diisopropylethylamine. [b] Containing 1 equiv of $LiClO_4$.

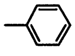
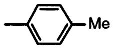
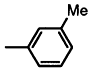
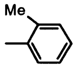
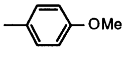
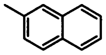
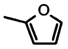
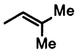
variables including reaction time and equivalents of base and found that, for the most part, yields did not change significantly as a function of these variables. We therefore chose to examine several other substrates using refluxing trifluoroethanol in the presence of 1.1 equiv of triethylamine as the standard reaction conditions for the reaction. The results are summarized in Table 2.

We decided to use substrates which would lead to dienones that contained additional unsaturation, in anticipation of the driving force for ring-opening that such structural features would provide. Reactions were conducted using 1.1 equiv of base in trifluoroethanol (ca. 0.04 M) at reflux for 1 h. At this stage, yields for the ring-opening are moderate. All of the reactions were accompanied by the appearance of 9−12% of a side product resulting from conjugate addition of trifluoroethanol to the primary dienone product. These side products were characterized by ^{1}H NMR spectra, which suggest that no vinylogous ester exists in the molecule. In particular, all of these side products displayed ^{1}H NMR which indicated the presence of a trans alkene ($J \approx 16$ Hz) with chemical shifts characteristic of an enone, not a vinylogous ester. Further, each side product showed a signal as a doublet of doublets near 5.5 ppm, indicative of an acetal, which was also a stereogenic center. Signals for the methylene protons α to the ketone functionality in these side products were doublets of doublets, indicative of their diastereotopic relationship.

In summary, we have established, to the best of our knowledge, the first examples of the retro-Nazarov reaction to produce dienones. Further optimization of the reaction, computational exploration of the potential energy surface associated with the process,[5] and exploration of the scope of the reaction, particularly with respect to substituents and developing applications, are in progress. Details will be reported in due course.

Table 2. Retro-Nazarov Reactions of a Series of Bromoketones



Entry	Educt, R		Dienone, (%)	Enone, (%)
1	**10**,		**11**, 65	**12**, 9
2	**13**,		**14**, 52	**15**, 9
3	**16**,		**17**, 59	**18**, 10
4	**19**,		**20**, 60	**21**, 10
5	**22**,		**23**, 59	**24**, 8
6	**25**,		**26**, 65	**27**, 8
7	**28**,		**29**, 60	**30**, 7
8	**31**,		**32**, 54	**33**, 8
9	**34**,		**35**, 42	**36**, 8
10	**37**,		**38**, 69	**39**, 12

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Supporting Information Available: Experimental procedures and copies of the proton and carbon spectra of the starting materials and products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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