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Efficient intermolecular 3+2 trapping of the Nazarov intermediate with vinyl sulfides

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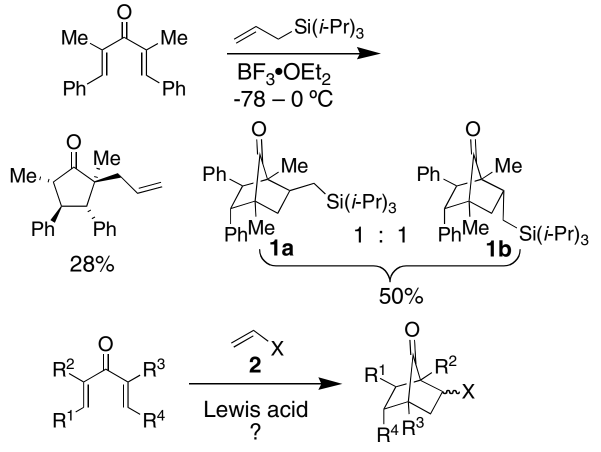
Abstract—Cross-conjugated 1,4-pentadien-3-ones undergo electrocyclization to 2-oxidocyclopentenyl cations upon treatment with $BF_3{\cdot}OEt_2$. When these reactions are carried out in the presence of electron-rich vinyl sulfides, nucleophilic trapping followed by ring-closure furnishes bridged bicyclic products that can be viewed as formal 3+2 cycloadducts. This process results in three new carbon–carbon bonds and establishes up to five new stereocenters.

The Nazarov cyclization offers a convenient entry to substituted cyclopentenones via electrocyclization of cross-conjugated dienone precursors.[1] A flurry of recent activity in this area has focused on new approaches for stereocontrol,[2] or on interception of the cyclopentenyl cation intermediate initially formed upon electrocyclization. The latter process, which we have termed the 'interrupted Nazarov reaction', can be carried out with a range of intra- and intermolecular traps. Nucleophilic attack at one end of the allyl cation by π nucleophiles,[3] amines,[4] halide[5] or hydride[6] results in substituted cyclopentanones,[7] while cycloaddition reaction with dienes or allylsilanes furnishes bridged bicyclic products.[8]

Intermolecular cycloaddition processes are especially appealing, as they permit the direct assembly of complicated, polycyclic products from simple, planar precursors. For example, interrupted Nazarov reaction using triisopropylallylsilane furnishes highly substituted bicyclo[2.2.1]heptanones **1**, in some cases with Lewis acid-dependent stereocontrol (Scheme 1).[8b] However, the trialkylsilyl group appended to the bicyclic product does not offer a convenient handle for further functionalization. This transformation is presumed to occur via a stepwise mechanism involving a stabilized β-silyl cation, which then undergoes attack by the enolate onto the cationic center, sometimes accompanied by lesser amounts of the simple allylation product resulting from desilylative elimination. We imagined that other electron-rich olefin traps **2** possessing suitable cation stabilizing groups (X) might also undergo this process. With the proper choice of X, competing pathways might be minimized, and a more versatile functional group might be introduced to the bicyclic product. Here we describe 3+2 trapping of the Nazarov intermediate with vinyl sulfides (X = SR)[9,10] to form sulfide-substituted bicyclo[2.2.1]heptanones.



Scheme 1.

Initial experiments were carried out with ethyl vinyl sulfide **2a** and dibenzylidenepentanone **3a** (Scheme 2). Optimal conditions were found to include the use of 4 equiv of the vinyl sulfide trap, and maintaining the reaction at −78 °C. Under these conditions, two

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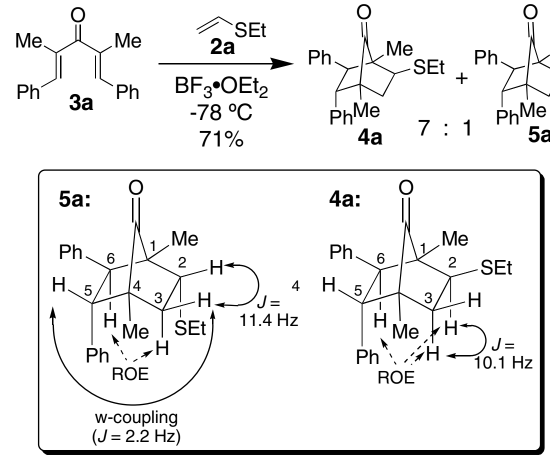


Scheme 2.

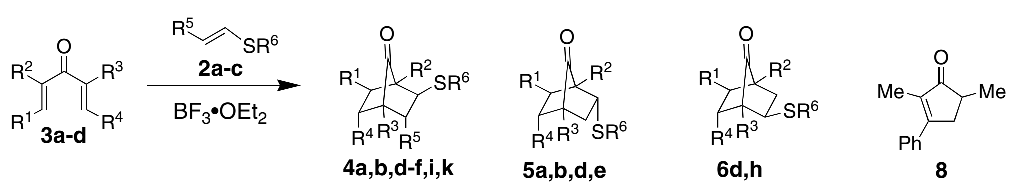
isomeric products were isolated in a 7:1 ratio and in 71% combined yield. Spectral data clearly indicated the presence of a strained ketone, but no alkenes. The structures of the two products were assigned as **4a** and **5a**, epimeric at the SEt-substituted carbon. For minor product **5a**, $H3_{(exo)}$ clearly showed a long-range W-coupling with H5, and a large vicinal coupling with H2. This established the relative configurations at C-2 and C-5. Standard conrotatory electrocyclization was assumed to install a trans relationship for the C-5 and C-6 phenyl groups. The observation of a TROESY correlation between H6 and $H3_{(endo)}$ provided confirmation for that stereochemical assignment. In the case of major product **4a**, $H3_{(endo)}$ displayed a large vicinal coupling to H2, indicating that the SEt group occupied the *exo* position on C-2. A TROESY correlation between H6 and both $H3_{(endo)}$ and H2 provided additional support for the stereochemical assignment. This compound proved to be crystalline, and X-ray diffraction analysis confirmed the structure to be as shown.[11]

Given the initial success with **2a** and **3a**, a range of dienones (**3a**–**d**) and vinyl sulfides (**2a**–**c**) were examined (Table 1). For **3a**,**b**, phenyl vinyl sulfide **2b** furnished similar results to those seen with **2a**. In contrast, β-substituted vinyl sulfide **2c** was significantly less effective at trapping the cationic intermediate, furnishing complex mixtures (entry 3) or relatively low yields (entries 6 and 9).

The effect of dienone substitution on the outcome of the reaction was also quite profound. Trisubstituted dienone **3b** was efficiently trapped by **2a**,**b**, although a third isomeric adduct was seen in those cases. Cyclic substrate **3c** gave only low yields of 3+2 adduct, with opposite regioselectivity for **2b** and **2c**. Furthermore, *i*-Pr substituted dienone **3d** failed to give any adduct with **2a** and only minor amounts of 3+2 adduct with **2b**. Control experiments indicate destructive consumption of **2a** in the presence of $BF_3{\cdot}OEt_2$, resulting in the recovery of substrates whose cyclization is sluggish (entries 7 and 10).

The regio- and stereoselectivity of the trapping reactions merits some discussion. The 3+2 reaction is presumed to proceed by a stepwise mechanism, with initial nucleophilic attack by the β-carbon of the vinyl sulfide on one terminus of the 2-oxidocyclopentenyl cation. Ring closure would then ensue via enolate attack of the thionium ion. In the cases employing tetrasubstituted dienone **3a** (entries 1 and 2), *endo* disposition of the C-4

Table 1. Intermolecular trapping of Nazarov intermediate with vinyl sulfides[a]



Entry	Dienone	R^1	R^2	R^3	R^4	Vinyl sulfide	R^5	R^6	Solvent	Temp (°C)/time (h)	$BF_3{\cdot}OEt_2$ (equiv)	Products (yield)[b]
1	**3a**	Ph	Me	Me	Ph	**2a**	H	Et	CH_2Cl_2	−78/0.5	1.0	**4a** (62), **5a** (9)
2	**3a**	Ph	Me	Me	Ph	**2b**	H	Ph	CH_2Cl_2	−78/0.5	1.0	**4b** (70), **5b** (9)
3	**3a**	Ph	Me	Me	Ph	**2c**	Ph	Ph	CH_2Cl_2	−78/0.25	1.0	—[c]
4	**3b**	Ph	Me	Me	H	**2a**	H	Et	$PhCH_3$	−78/0.25 → 23/10	1.5	**4d** (33), **5d** (13), **6d** (10)
5	**3b**	Ph	Me	Me	H	**2b**	H	Ph	$PhCH_3$	−78/2	1.5	**4e** (37), **5e** (37)[d]
6	**3b**	Ph	Me	Me	H	**2c**	Ph	Ph	$PhCH_3$	−78/0.25 → −45/1	1.2	**4f** (38), **8** (30)
7	**3c**	$(CH_2)_4$		Me	H	**2a**	H	Et	$PhCH_3$	−78/2	2.0	—[e]
8	**3c**	$(CH_2)_4$		Me	H	**2b**	H	Ph	$PhCH_3$	−78/0.25 → 23/1	2.0	**6h** (37)
9	**3c**	$(CH_2)_4$		Me	H	**2c**	Ph	Ph	$PhCH_3$	−78/0.25 → 23/2	2.0	**4i** (24)
10	**3d**	*i*-Pr	Me	Me	*i*-Pr	**2a**	H	Et	$PhCH_3$	−78/0.5	2.0	—[e]
11	**3d**	*i*-Pr	Me	Me	*i*-Pr	**2b**	H	Ph	$PhCH_3$	23/10	2.0	**4k** (32)

[a] Standard procedure: dienone **3** and vinyl sulfide **2** (4 equiv) were dissolved in the solvent (0.01 M in **3**) at the indicated temperature, then $BF_3{\cdot}OEt_2$ was added dropwise and the reaction was stirred until consumption of **3** was apparent (TLC). The reaction was quenched by the addition of satd aq $NaHCO_3$, followed by extraction, drying ($MgSO_4$) and chromatographic purification.

[b] All yields indicate isolated, homogeneous material after chromatographic separation.

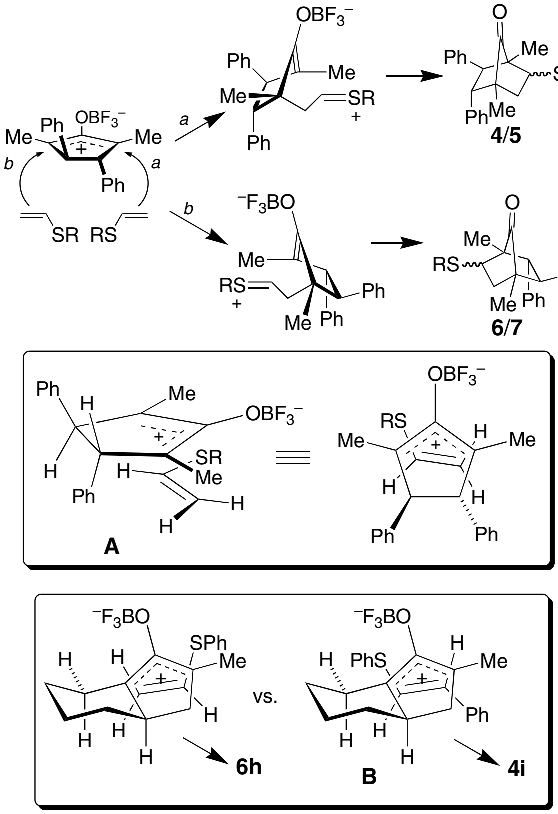
[c] Dienone **3a** was consumed to give a complex mixture of inseparable and uncharacterizable products.

[d] A third product was apparent in the crude mixture (ratio of **4e**:**5e**:unknown = 3.3:3.3:1). This product could not be obtained in pure form, but is assumed to be the regioisomer analogous to **6d**.

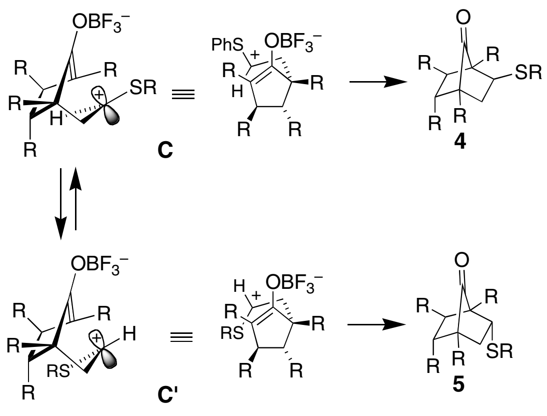
[e] Starting dienone was recovered even after extended reaction times.

phenyl substituent indicates preferential attack *syn* to the bulky phenyl (path a, Scheme 3). The alternative *anti* attack (path b) would lead to diastereomers **6** and **7**, which were not observed with that substrate. This result, which is analogous to the diastereofacial selectivity seen in the earlier allylsilane 3+2 trapping reactions,[8b] suggests reaction via a compact transition state (**A**),[12] with the unsubstituted end of the vinyl sulfide adjacent to the more sterically demanding *endo* phenyl. A similar rationale can be applied to results of the reaction of dienones **3b–d** with **2a**,**b** (entries 4–6, 9, 12).

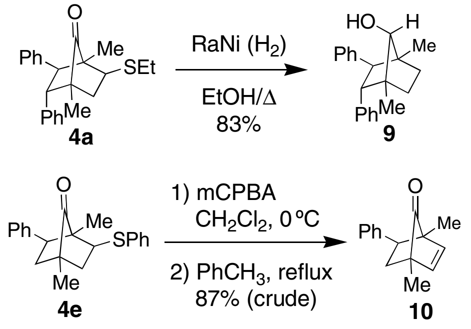
In the case of disubstituted vinyl sulfide **2c**, compact transition state **A** is precluded with **3a** due to unfavorable steric interactions between the *endo* C-4 phenyl group and the β substituent of vinyl sulfide. However, reaction with **3b**, which lacks a C-4 phenyl, is possible, albeit in lower yield together with the simple Nazarov cyclization product **8**. The reversal in regioselectivity seen for **3c** may result from the greater steric demand of the β-phenyl group of **2c** relative to the SPh group in compact transition state **B**.



Scheme 3.



Scheme 4.



Scheme 5.

The formation of epimers at C-1 is consistent with a stepwise mechanism. Following the initial nucleophilic attack of the 2-oxidocyclopentenyl cation, bond rotation can compete with cyclization (Scheme 4). The major *exo* product **4** may result from fast cyclization after trapping via the proposed compact transition state. However, complete randomization and preferential cyclization via transition state **C** rather than the sterically more demanding **C′** could also explain the predominant formation of **4** in most cases.

Finally, the selective modification of the sulfide moiety was examined (Scheme 5). Treatment of adduct **4a** with Raney nickel[13] furnished the desulfurized product **9** (with concomitant reduction of the bridging ketone) in 83% yield. Alternatively, oxidation and sulfoxide elimination[14] using adduct **4e** led to the sensitive alkene **10** in good yield.[15]

These results demonstrate that electron-rich heteroatom-substituted alkenes can function as effective traps in the interrupted Nazarov reaction. Bicyclo[2.2.1]heptanones are formed in a stepwise 3+2 cycloaddition, via a presumed compact transition state. The resulting sulfide group is amenable to further processing via either reductive or oxidative pathways. Further applications of this chemistry will be described elsewhere in due course.

Acknowledgments

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