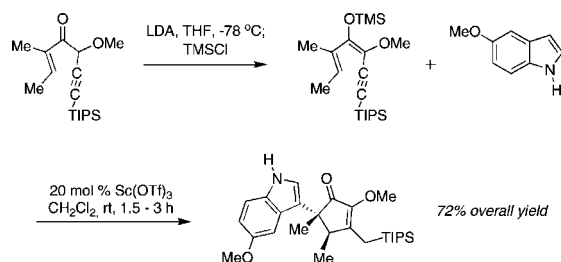


Interrupting the Nazarov Cyclization with
Indoles[§]Ashok K. Basak[†] and Marcus A. Tius^{*,†,‡}Department of Chemistry, 2545 The Mall, University of Hawaii, Honolulu, Hawaii 96822,
and The Cancer Research Center of Hawaii, 1236 Lauhala Street,
Honolulu, Hawaii 96813

tius@gold.chem.hawaii.edu

Received July 12, 2008

ABSTRACT



A carbon-terminated interrupted Nazarov reaction is described. The trimethylsilyl enol ethers derived from propargyl vinyl ketones undergo selective proton transfer at the distal acetylenic carbon atom to provide allenyl vinyl ketones as transient intermediates. In the presence of indoles, a cascade of reactions is initiated that converts the initially formed pentadienyl cations to cyclopentenones bearing a quaternary α carbon atom.

Allenyl vinyl ketones undergo a particularly rapid Nazarov cyclization.^{1–3} A few years ago, we reported a cascade process that involved the isomerization of propargyl vinyl

ketones such as **3** (Scheme 1) on silica gel in the presence of a primary or secondary amine.⁴ Ketones **3** are easily prepared from the addition of propargyllithium nucleophile

[§] Dedicated to Professor E. J. Corey on the occasion of his 80th birthday.
[†] Department of Chemistry.

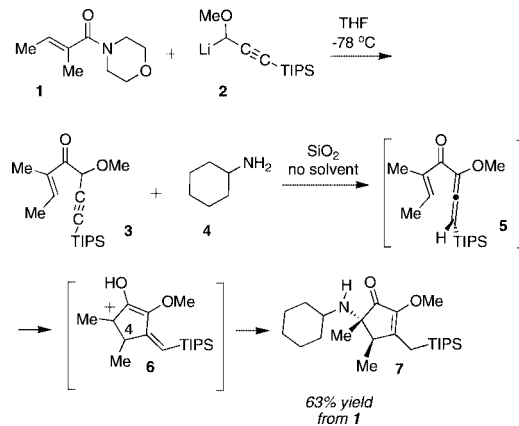
[‡] The Cancer Research Center of Hawaii.

(1) (a) Tius, M. A. *Acc. Chem. Res.* **2003**, *36*, 284–290. (b) Tius, M.; Kwok, C.-K.; Gu, X.-q.; Zhao, C. *Synth. Commun.* **1994**, *24*, 871–885. (c) Hashmi, A. S. K.; Bats, J. W.; Choi, J.-H.; Schwarz, L. *Tetrahedron Lett.* **1998**, *39*, 7491–7494.

(2) For reviews of the Nazarov reaction, see: (a) Habermas, K. L.; Denmark, S.; Jones, T. K. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons, Inc.: New York, 1994; Vol. 45, pp 1–158. (b) Harmata, M. *Chemtracts* **2004**, *17*, 416–435. (c) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577–7606. (d) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479–6517. (e) Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193–2206.

(3) For recent examples of the Nazarov reaction, see: (a) Li, W.-D. Z.; Wang, Y.-Q. *Org. Lett.* **2003**, *5*, 2931–2934. (b) Liang, G.; Trauner, D. *J. Am. Chem. Soc.* **2004**, *126*, 9544–9545. (c) Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A. *J. Org. Chem.* **2005**, *70*, 4542–4545. (d) Waters, S. P.; Tian, Y.; Li, Y.-M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 13514–13515. (e) Janka, M.; He, W.; Haedicke, I. E.; Fronczek, F. R.; Frontier, A. J.; Eisenberg, R. *J. Am. Chem. Soc.* **2006**, *128*, 5312–5313. (f) Grant, T. N.; West, F. G. *J. Am. Chem. Soc.* **2006**, *128*, 9348–9349. (g) He, W.; Huang, J.; Sun, X.; Frontier, A. J. *J. Am. Chem. Soc.* **2008**, *130*, 300–308. (h) Williams, D. R.; Robinson, L. A.; Nevill, C. R.; Reddy, J. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 915–918. (i) Rueping, M.; Ieawsuwan, W.; Antonchick, A. P.; Nachtsheim, B. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2097–2100.

Scheme 1



J. Am. Chem. Soc. **2005**, *127*, 12472–12473.

2 to morpholino enamides like **1**. Exposure of **3** to a small excess of cyclohexylamine **4** and dry silica gel in the absence of solvent led to a single diastereoisomer of **7** in 63% overall yield from enamide **1**. Cyclohexylamine performs two functions in this process. It catalyzes the isomerization of **3** to allenyl vinyl ketone **5**, and it acts as a nucleophile to intercept cation **6**. This is an example of an interrupted Nazarov process, a reaction type that has been extensively developed and refined in recent years through the efforts of the West group.^{5,6}

We questioned whether the intermediate cyclic cation **6** could be intercepted by carbon nucleophiles in addition to amines. Such a process, if successful, would greatly increase the versatility as well as the synthetic utility of the reaction. We chose indole as the first carbon nucleophile with which to probe this issue for reasons of convenience and reactivity. We surmised that the reaction of indole with cation **6** would be rapid. It is important to recognize that **6** is generated from **3** in an *irreversible* process; therefore, it must be trapped before proton loss takes place. This places some restrictions on the types of nucleophiles that can be used.

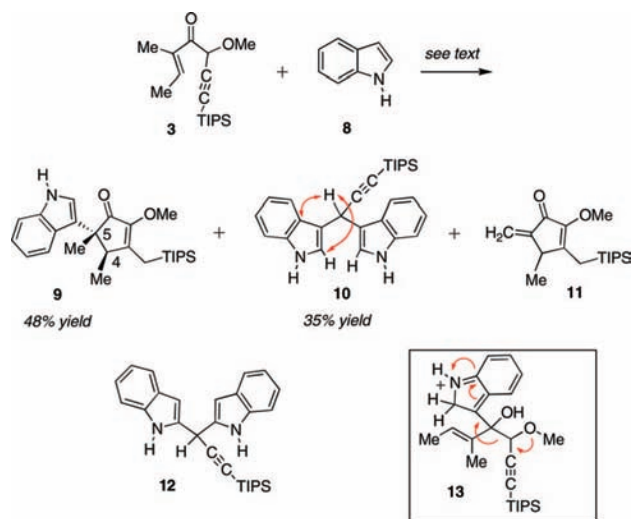
Simply agitating a mixture of ketone **3**, indole **8**, and silica gel led to no reaction. It is not surprising that the conditions that had proven to be successful for amines failed since indole is not basic enough to catalyze the first step, isomerization of **3** to **5**. In earlier work, we had observed that in the absence of an external nucleophile some Lewis acids were effective in catalyzing the conversion of **3** to **11** (Scheme 2) in solution, suggesting that **5** had been formed

observed with 20 mol % of Sc(OTf)₃ in acetonitrile with 1.25 equiv of indole. Under these conditions, the anticipated product **9** was formed in 48% overall yield from **1**. The stereochemistry of **9** is controlled by nucleophilic attack of indole *trans* to the C4 methyl group in cyclic cation **6** (see Scheme 1). The stereochemical assignment of **9** was made on the basis of NOE experiments. Irradiation of the C4 methyl group in the ¹H NMR spectrum of **9** led to enhancement of the signal due to the C5 methyl group, indicating that the two methyl groups are *cis*. Irradiation of the C4 methine led to enhancement only of the signal due to the C4 methyl group. However, the reaction leading to **9** was very slow, requiring several days for the complete consumption of **3**, and led to a large amount of byproduct **10** as well as smaller amounts of cross-conjugated cyclopentenone **11**.

The structure of **10** was proven as follows. The ESI mass spectrum indicated a molecular ion at *m/z* 427 (M⁺ + H), while the ¹³C NMR spectrum indicated a symmetrical structure and eight aromatic carbon atoms. The ¹H NMR spectrum (500 MHz, CDCl₃) showed the presence of indole and TIPS in a ratio of 2 to 1, as well as the absence of indole C3 protons. The ¹H NMR spectrum also revealed the presence of a deshielded singlet at 5.60 ppm that integrated for one proton. The methine proton at 5.60 ppm showed the three-bond correlations with the indole carbon atoms that are indicated by the red arrows in Scheme 2. In the HSQC spectrum, the indole C2 proton at 7.06 ppm showed a strong correlation with the indole C2 carbon atom at 122.5 ppm. The data support structure **10** and exclude structure **12** for the byproduct.⁷ The mechanism that rationalizes the formation of **10** from **3** is not obvious, but it can probably be thought of as a reverse benzoin condensation that is initiated by nucleophilic attack of indole at the carbonyl carbon atom of **3**. Cleavage of the carbon–carbon bond could take place through **13**, following protonation at C2 of the indole. It remains to be seen whether this process is general.

We were never successful in completely eliminating **10** from the reactions of **3**. A faster reaction was desirable for this reason and also to make the method more practical for synthesis. Since allenyl vinyl ketones once formed undergo very fast cyclization, we modified our reaction conditions to ensure the rapid generation of the allene. Accordingly,

Scheme 2



as an intermediate. A series of Lewis acids (Sc(OTf)₃, Cu(OTf)₂, TMSOTf, BF₃·Et₂O, silica gel) and solvents (CH₃CN, CH₂Cl₂, THF, PhH, EtOAc, DMF, DMSO) were screened in the reaction of **3** with **8**. The best results were

(4) (a) Dhoro, F.; Tius, M. A. *J. Am. Chem. Soc.* **2005**, *127*, 12472–12473. (b) Dhoro, F.; Kristensen, T. E.; Stockmann, V.; Yap, G. P. A.; Tius, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 7256–7257.

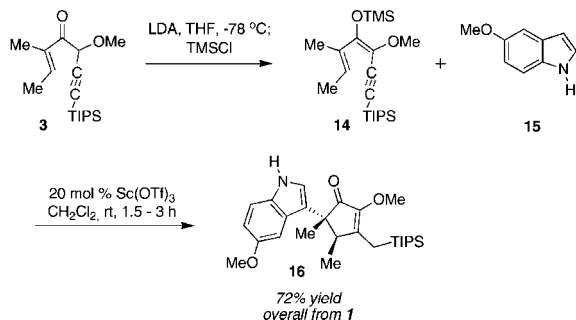
(5) (a) Song, D.; Rostami, A.; West, F. G. *J. Am. Chem. Soc.* **2007**, *129*, 12019–12022. (b) Grant, T. N.; West, F. G. *Org. Lett.* **2007**, *9*, 3789–3792. (c) Mahmoud, B.; West, F. G. *Tetrahedron Lett.* **2007**, *48*, 5091–5094. (d) Rostami, A.; Wang, Y.; Arif, A. M.; McDonald, R.; West, F. G. *Org. Lett.* **2007**, *9*, 703–706. (e) Giese, S.; Mazzola, R. D., Jr.; Amann, C. M.; Arif, A. M.; West, F. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 6546–6549. (f) White, T. D.; West, F. G. *Tetrahedron Lett.* **2005**, *46*, 5629–5632. (g) Browder, C. C.; Marmsäter, F. P.; West, F. G. *Can. J. Chem.* **2004**, *82*, 375–385. (h) Yungai, A.; West, F. G. *Tetrahedron Lett.* **2004**, *45*, 5445–5448. (i) Wang, Y.; Schill, B. D.; Arif, A. M.; West, F. G. *Org. Lett.* **2003**, *5*, 2747–2750. (j) Browder, C. C.; Marmsäter, F. P.; West, F. G. *Org. Lett.* **2001**, *3*, 3033–3035. (k) Giese, S.; Kastrup, L.; Stiens, D.; West, F. G. *Angew. Chem., Int. Ed.* **2000**, *39*, 1970–1973. (l) Giese, S.; West, F. G. *Tetrahedron* **2000**, *56*, 10221–10228.

(6) Rieder, C. J.; Fradette, R. J.; West, F. G. *Chem. Commun.* **2008**, 1572–1574. This recent paper by the West group describes the capture of pentadienyl carbocations by electron-rich aromatics and is conceptually related to the present work.

(7) To the best of our knowledge, this type of bond cleavage followed by rearrangement has not been previously reported.

ketone **3** was converted to trimethylsilyl enol ether **14** by treatment with LDA at $-78\text{ }^{\circ}\text{C}$ followed by trimethylsilyl chloride (Scheme 3). Enol ether **14** was formed as a single

Scheme 3



geometrical isomer to the limits of detection by ^1H NMR, presumed to be *Z*.⁸ Exposure of **14** to a 25% molar excess of 5-methoxyindole **15** in dichloromethane with 20 mol %

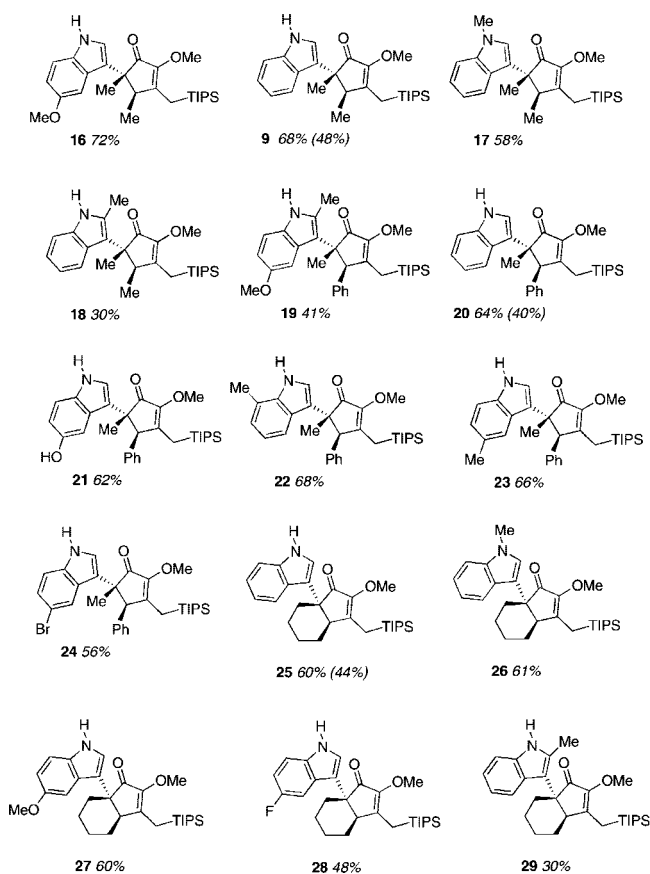
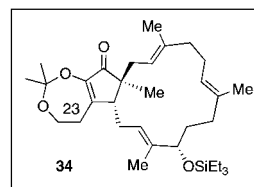
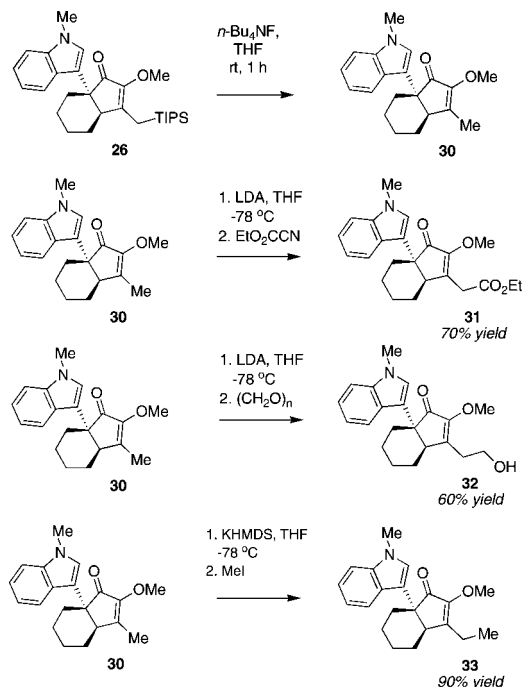


Figure 1. 3-Substituted indoles from the interrupted Nazarov reaction. Overall yields are reported for the three steps: nucleophilic addition of propargyllithium anion **2** to the enamide, formation of the silyl enol ether, and cyclization. Yields in parentheses refer to the overall yield for the two-step process proceeding through the propargyl vinyl ketone.

Scheme 4



of Sc(OTf)_3 resulted in a fast (1.5–3 h) reaction that led to the desired product **16** in 72% overall yield from enamide **1**. Under these reaction conditions, *none* of the bisindole byproduct was observed in the product mixture, and neither was ketone **3**, indicating that protonation of **14** must occur exclusively or nearly so at the distal acetylenic carbon atom. This leads directly to the pentadienyl cation that cyclizes. In the absence of an external nucleophile, proton loss terminates the process and leads to **11**. Since the reaction is catalyzed by a proton, the role of Sc(OTf)_3 may be to activate some trace of water that is present, thereby converting it into a strong Bronsted acid.⁹ Since we did not go to extraordinary lengths to ensure rigorously anhydrous reaction conditions, this seems plausible. The fact that no reaction takes place when crushed 4 Å molecular sieves are added to the reaction mixture lends support to this hypothesis since the sieves would scavenge both water and Bronsted acids. The reaction of **14** with **15** can certainly be catalyzed by Bronsted acid since treatment with 20 mol % Tf_2NH also leads to product **16**. We did not screen Bronsted acids because the Sc(OTf)_3 -catalyzed process worked so well. Of the solvents we did screen (PhH, CH_3CN , CH_2Cl_2), reactions in dichloromethane at moderate concentration (ca. 0.35 M) were the cleanest.¹⁰

(8) The step that converts **3** to **14** does not lead to allenyl vinyl ketone, indicating that there is no competition with an alkyne–allene isomerization process.

(9) For a review, see: Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924–1942.

The scope of the reaction is indicated by the examples shown in Figure 1. Several trends are evident. Substitution of the indole by a methyl group at C2 is tolerated, but at the expense of efficiency, as can be seen by comparing the yields of **9** and **18** (68% and 30%, respectively). It also appears that electron-rich indoles function more effectively than indoles that are substituted with electron-withdrawing groups, as indicated by a comparison of the yields of **27** and **28** (60% and 48%, respectively). 5-Nitroindole did not participate in the reaction. 2-Phenylindole and 3-methylindole were also not effective in trapping the tertiary Nazarov cation, possibly for steric reasons. The yields that are reported in Figure 1 are overall for the three steps from the respective enamides.

To demonstrate some of the options to further functionalize the products, the reactions that are summarized in Scheme 4 were carried out. Rapid cleavage of the TIPS group from **26** took place with *n*-Bu₄NF in THF at room temperature (81% yield). Subsequent deprotonation of the methyl group in **30** with LDA at -78 °C was followed by trapping of the extended enolate anion with ethyl cyanofornate¹¹ or with paraformaldehyde, leading to ethyl ester **31** or alcohol **32** in 70% and 60% yield, respectively. Surprisingly, all attempts to trap the *lithium* enolate derived from **30** with alkyl halides failed, leading only to unreacted ketone. However, changing the base from LDA to KHMDS and treatment of the potassium enolate of **30** with iodomethane led to the desired product **33** in 90% yield. This is quite puzzling since a key

(10) The trimethylsilyl group is presumably lost after indole trapping but before workup. Workup with aqueous NaHCO₃ would be expected to preserve a trimethylsilyl enol ether (cf. **14**). Adventitious water may serve as the silylophilic.

(11) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425–5428.

(12) Berger, G. O.; Tius, M. A. *J. Org. Chem.* **2007**, *72*, 6473–6480.

step in our synthesis of (±)-terpestacin is alkylation of the *lithium* enolate derived from **34** with iodomethane.¹² This reaction takes place in high yield at C23 (terpestacin numbering) under conditions that are identical to those used for **30**. It may be the case that the lithium enolate derived from **30** is stabilized to a greater extent through bidentate chelation than the enolate of **34**, due to conformational constraints in **34** that are imposed by the acetonide ring and that are absent in the enolate of **30**.

In summary, the interrupted allenyl ether version of the Nazarov cyclization has been demonstrated to take place with indoles at C3. The reaction is reasonably efficient and subject to the constraints that the indole be electron-rich and not bear a C2 substituent larger than methyl. The reaction is stereospecific, generates a quaternary carbon atom in the five membered ring, and leads to a large increase in molecular complexity. It seems likely that other carbon nucleophiles in addition to indole can be utilized in this interrupted Nazarov reaction, suggesting broad utility in synthesis.

Acknowledgment. We thank the National Institutes of Health (GM57873) for generous support. We are indebted to Mr. Scott Birmingham and Boulder Scientific Company for a generous gift of scandium triflate.

Supporting Information Available: Experimental procedures for **14**, **16**, and **30–33**; ¹H and ¹³C NMR, HRMS, and IR data for **9**, **16–33**, and **10**; reproductions of ¹H and ¹³C NMR spectra for **9**, **16–33**, and **10**. Reproductions of HSQC and HMBC spectra of **10**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL801587U