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Formal Homologous Aldol Reactions: Interrupting the Nazarov Cyclization via Carboalkoxylation of Alkynes

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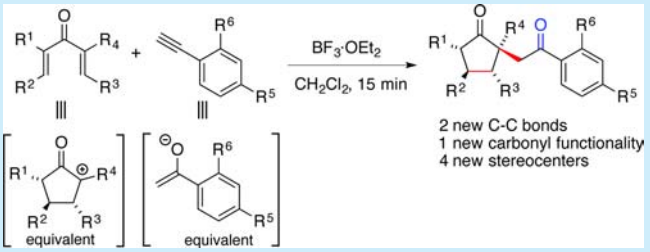
Supporting Information

ABSTRACT: Reactions between 1,4-pentadien-3-ones and aryl acetylenes in the presence of $BF_3{\cdot}OEt_2$ furnish α-phenacyl cyclopentanones via a domino electrocyclization/carboalkoxylation reaction sequence. The overall process underscores a new mode of interrupted Nazarov trapping, where two new carbon−carbon bonds are installed with concomitant formation of carbonyl functionality.

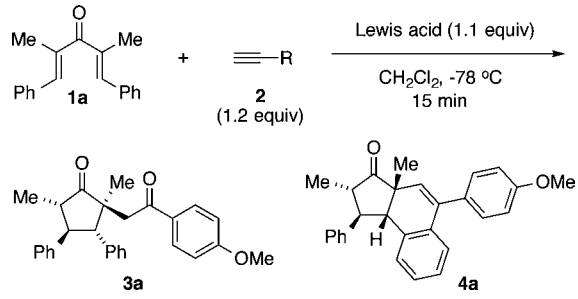


The Nazarov cyclization,[1] beyond its conventional practice in the synthesis of cyclopentanoid products, has recently been demonstrated to serve as a starting point for tandem or domino processes. The oxyallyl cation intermediate derived from the 4π-electrocyclization could be intercepted by intra- or intermolecular nucleophilic entities[2] or undergo a series of Wagner−Meerwein shifts or skeletal rearrangement,[3] where both processes allow expeditious formations of diverse elaborated carbocycles. In the prior approach, the use of carbon traps such as alkenes,[4] 1,3-dienes,[5] electron-rich olefins,[6] arenes,[7] heteroarenes,[8] and alkyl aluminum species[9] permitted facile installation of carbon fragments onto a pentacyclic framework, thus increasing the molecular complexity in a highly step-economical fashion.

While the survey of the carbon-based nucleophiles engaged in the "interrupted Nazarov" chemistry appears comprehensive (vide supra), it is noteworthy that the competence of alkynes to capture the Nazarov intermediate, to the best of our knowledge, remains unknown.[10] The relatively low nucleophilicity of alkyne in comparison with its alkene counterpart[11] was a potential concern for its application to cationic cascade reactions, especially for an intermolecular version. However, given ample precedents in the literature for bimolecular interception of carbon-based electrophiles with alkynes,[12] we set out to investigate the feasibility of trapping the cyclopentenyl cation with acetylene derivatives. Here we describe a novel domino process initiated by the Nazarov reaction, where the participation of aryl acetylene diverts the initial electrocyclization to a cationic carboalkoxylation (formal carbohydroxylation) sequence[13] furnishing α-quaternary α-phenacyl cyclopentanones.[14]

We commenced to examine the reaction between cross-conjugated ketone **1a** and selected alkynes **2** in the presence of $BF_3{\cdot}OEt_2$ (Table 1, entries 1−4). Preliminary experiments indicated that silyl and alkyl substituted alkynes were not compatible reaction partners, yielding intractable material with complete consumption of the starting dienone. Efforts then focused on aryl acetylenes since the nucleophilicity of the triple bond could be easily tuned by varying aromatic substituents. Though phenylacetylene (**2c**) was an incompetent trapping agent, we were delighted to find that 4-ethynyl anisole (**2d**) did permit the interception of the cyclized oxyallyl cation resulting in a type of interrupted Nazarov product, the structure of which

Table 1. A Brief Survey of Lewis Acids and Alkynes[a]



entry	alkyne	R	Lewis acid	product(s)	yield (%)[b]
1	**2a**	$SiMe_3$	$BF_3{\cdot}OEt_2$	–	n/a
2	**2b**	^{n}Bu	$BF_3{\cdot}OEt_2$	–	n/a
3	**2c**	Ph	$BF_3{\cdot}OEt_2$	–	n/a
4	**2d**	PMP[c]	$BF_3{\cdot}OEt_2$	**3a**	97
5	**2d**	PMP[c]	$AlCl_3$	**3a**	92
6	**2d**	PMP[c]	$FeCl_3$	**3a**	85
7[d]	**2d**	PMP[c]	$TiCl_4$	**3a**	7
8	**2d**	PMP[c]	$SnCl_4$	**3a** + **4a**	91 (3:2)

[a]Standard procedure: To a stirred solution of **1a** and alkyne (1.2 equiv) in CH_2Cl_2 (0.2 M in **1a**) at −78 °C was added Lewis acid (1.1 equiv). After 15 min, the reaction mixture was quenched with sat. aq $NaHCO_3$, followed by extraction with CH_2Cl_2, drying over $MgSO_4$, and chromatographic purification. [b]Isolated yield. [c]PMP = 4-MeOPh. [d]Complex product mixture.

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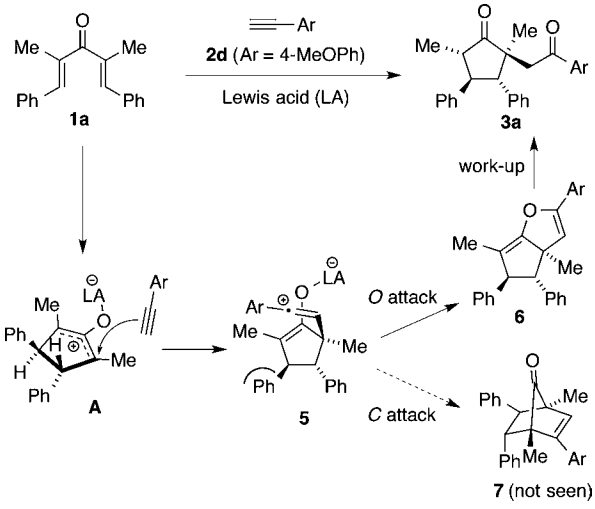
was fully characterized (see Supporting Information) and assigned as α-phenacyl cyclopentanone **3a**. The mechanism for the formation of **3a** merits some discussion (Scheme 1). Upon

Scheme 1. Proposed Mechanism

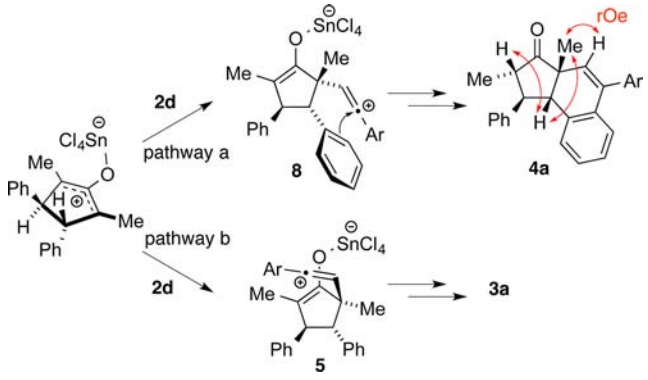


generation of the Nazarov cyclopentenyl cation intermediate, **2d** will then approach *anti* to the adjacent phenyl group as shown in the transition state (**A**) in accord with relative stereochemistry of final product **3a**. Attack of the resulting vinyl cation **5** by internal oxygen[15] would give strained dihydrofuran **6**, which would be hydrolyzed to **3a** during aqueous workup. The overall transformation highlights use of a simple alkyne as a nucleophilic enol surrogate. Notably, we did not observe any bridged bicyclic compound **7** via formal [3 + 2] cycloaddtion of **2d** with the oxyallyl cation;[16] presumably the preferential bonding between the sp^2 cation and the oxygen end of the ambident enolate nucleophile is guided by the kinetic control.[17] Also, nonbonded repulsion exerted by β' phenyl substitution (see **5**) may hamper the *C*-vinylation pathway.[16a]

Other metal halide Lewis acids (MCl_n) were surveyed in an attempt to divert the putative vinyl cation intermediate **5** via chloride transfer[12c,d] (Table 1, entries 5−8). In the event, aluminum chloride and ferric chloride both were found to be effective promoters, providing **3a** in good yields. On the other hand, titanium(IV) chloride, which has previously been shown to deliver chloride in the Nazarov cyclization,[18] produced a complex product mixture, in which **3a** could be isolated in only 7% yield. When tin(IV) chloride was employed, a single diastereomer of tricyclic product **4a**, an apparent interrupted Nazarov product possessing only one keto functionality, was formed along with regular product **3a**.

Structural assignment of **4a** was based on a series of spectral analyses (^{1}H NMR, DEPT, COSY, HMBC, HSQC, TROESY, and HRMS). In addition, a notable spectroscopic feature of **4a** is the appearance of a long-range coupling between the vinyl proton and the benzylic proton adjacent to the α-quartenary center. Compound **4a** may arise from an intramolecular Friedel−Crafts reaction of cationic intermediate **8** originating via alkyne attack from the same face as the neighboring β-phenyl substitution (Scheme 2, pathway a).[19] The distinctive reaction courses of diastereomeric reactive intermediates **8** and **5** leading to the formation of **4a** and **3a** respectively are obscure. From both mechanistic and synthetic viewpoints, this

Scheme 2. Competing Pathways with $SnCl_4$



unusual result seen only with $SnCl_4$ merits further investigation.[20]

In order to probe the scope of this domino electrocyclization/carboalkoxylation reaction sequence, various dienones along with alkynes were subjected to the optimized conditions noted above. The influence of increasing steric hindrance around the triple bond on the overall process was first tested. To our delight, a reaction using alkyne trap **2e** with an additional *ortho* methyl group proceeded smoothly, thus allowing potential variation of substitution pattern at this position (Table 2, entry 2). To ascertain the importance of the *para* substitution (R^5 of **2**), the electronic nature of the aryl alkyne was altered by replacing the methoxy group with methyl, a weaker electron-donating group. Although the yield of reaction involving **2f** is clearly lower (entry 3), it demonstrated that a simple *para* alkyl substituent could provide sufficient stabilization to the presumed vinyl cation **5**, facilitating the alkylative alkoxylation transformation. Symmetrical dienones **1b**,**c** reacted with alkynes to give the corresponding adducts **3d**−**g** in moderate to good yields (entries 4−7). Bearing in mind that alkyne is a relatively small nucleophile, the regioselectivity of the trapping event for unsymmetrical dienones was an issue to be addressed. With dienone substrates **1d** and **1e**,[21] regioselective capture of the oxyallyls with **2e** furnished single diastereomers **3h** and **3i** respectively.[22]

While the Nazarov cyclization was readily interrupted by 4-ethynyl anisole (**2d**) showcasing a novel trapping pathway, it is of interest to compare the reactivity of its partially saturated analogue 4-vinyl anisole (**9**) under the same reaction conditions. Interestingly, the $BF_3{\cdot}OEt_2$-mediated reaction of **1a** with **9** furnished aryl-substituted bicyclo[2.2.1]heptanone **10** as a single diastereomer (Scheme 3).[23] The structure of **10**, a crystalline solid, was unambiguously determined by X-ray diffraction analysis. The formation of a bridged [3 + 2] adduct could be accounted for by a stepwise mechanism, where addition by vinyl anisole *syn* to the neighboring phenyl group on the 2-oxidocyclopentenyl cation (TS **B** → **11**) was followed by a highly stereoselective ring closure via enolate carbon attack on the benzylic cation (**11** → **10**). This result is analogous to previous interrupted Nazarov studies involving allylsilanes and vinyl sulfides;[16] hence, the abnormal reactivity seen with an alkyne trap is particularly intriguing. However, the origin of reversal in facial selectivity (TS **A** versus **B**) is not apparent at this moment and demands further computational investigations.

We have demonstrated the first example of intermolecular capture of the Nazarov intermediate with alkyne species,

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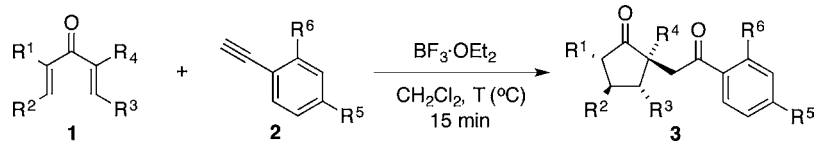
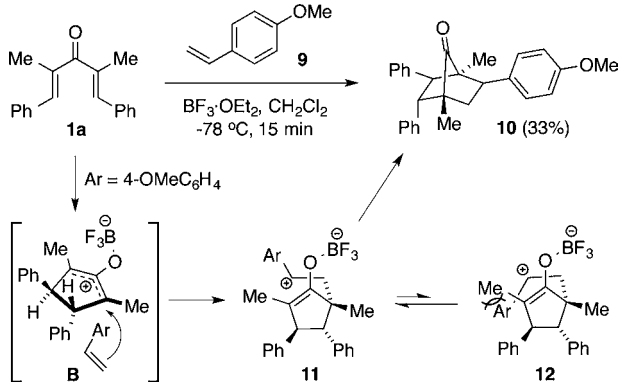
Table 2. Intermolecular Trapping of Nazarov Intermediates with Terminal Alkynes[a]



entry	dienone	R^1	R^2	R^3	R^4	alkyne	R^5	R^6	temp (°C)	product	yield (%)[b]
1	**1a**	Me	Ph	Ph	Me	**2d**	OMe	H	−78	**3a**	97
2	**1a**	Me	Ph	Ph	Me	**2e**	OMe	Me	−78	**3b**	95
3	**1a**	Me	Ph	Ph	Me	**2f**	Me	H	−78	**3c**	62
4	**1b**	Me	4-Cl-Ph	4-Cl-Ph	Me	**2d**	OMe	H	−40	**3d**	92
5	**1b**	Me	4-Cl-Ph	4-Cl-Ph	Me	**2e**	OMe	Me	−40	**3e**	84
6	**1b**	Me	4-Cl-Ph	4-Cl-Ph	Me	**2f**	Me	H	−40	**3f**	61
7	**1c**	Me	^{i}Pr	^{i}Pr	Me	**2f**	Me	H	−12	**3g**	30
8	**1d**	Me	^{t}Bu	Ph	Me	**2e**	OMe	Me	−40	**3h**	32
9	**1e**	^{n}Bu	Ph	Ph	Me	**2e**	OMe	Me	−78	**3i**	62

[a]Standard procedure: To a stirred solution of **1** and alkyne **2** (1.2 equiv) in CH_2Cl_2 (0.2 M in **1a**) at the indicated temperature was added BF_3·OEt_2 (1.1 equiv). After 15 min, the reaction mixture was quenched with sat. aq $NaHCO_3$, followed by extraction with CH_2Cl_2, drying over $MgSO_4$, and chromatographic purification. [b]Isolated yield.

Scheme 3. Formal [3 + 2] Cycloaddition of 4-Vinylanisole 9 with the Nazarov Intermediate[a]



[a]Compound **10** is the only identifiable product in the crude mixture. For comparison purposes, the reaction conditions have not been optimized for this substrate.

providing access to highly substituted α-phenacyl cyclopentanones in good yields. The transformation entails the cationic carboalkoxylation of aryl acetylene with the oxyallyl in a highly stereo- and regioselective manner. In one case, intramolecular arene trapping of the Kucherov vinyl cation intermediate derived from the interrupted Nazarov process was observed as a minor reaction pathway when $SnCl_4$ was used to activate the dienone substrate. Further studies to optimize this intriguing process, and to better understand the factors governing facial selectivity, are underway and will be described in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure and characterization data for **3a−i**, **4a**, and **10**, and X-ray crystallographic data for **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For recent reviews, see: (a) West, F. G.; Scadeng, O.; Wu, Y.-K.; Fradette, R. J.; Joy, S. In *Comprehensive Organic Synthesis*, 2nd ed.; Molander, G. A., Knochel, P., Eds.; Elsevier: Oxford, 2014; Vol. *5*, pp 827−866. (b) Tius, M. A. *Chem. Soc. Rev.* **2014**, *43*, 2979−3002. (c) Spencer, W. T.; Vaidya, T.; Frontier, A. J. *Eur. J. Org. Chem.* **2013**, 3621−3633. (d) Shimada, N.; Stewart, C.; Tius, M. A. *Tetrahedron* **2011**, *67*, 5851−5870. (e) Vaidya, T.; Eisenberg, R.; Frontier, A. J. *ChemCatChem* **2011**, *3*, 1531−1548. (f) Nakanishi, W.; West, F. G. *Curr. Opin. Drug Discovery Dev.* **2009**, *12*, 732−751.

(2) For a review, see: Grant, T. N.; Reider, C. J.; West, F. G. *Chem. Commun.* **2009**, 5676−5688.

(3) Recent examples: (a) Leboeuf, D.; Wright, C. M.; Frontier, A. J. *Chem.—Eur. J.* **2013**, *19*, 4835−4841. (b) Leboeuf, D.; Gandon, V.; Ciesielski, J.; Frontier, A. J. *J. Am. Chem. Soc.* **2012**, *134*, 6296−6308. (c) Huang, J.; Leboeuf, D.; Frontier, A. J. *J. Am. Chem. Soc.* **2011**, *133*, 6307−6317. (d) Chiu, P.; Li, S. *Org. Lett.* **2004**, *6*, 613−616. (e) Scadeng, O.; West, F. G. *Eur. J. Org. Chem.* **2014**, 1860−1865.

(4) Giese, S.; Mazzola, R. D., Jr.; Amann, C. M.; Arif, A. M.; West, F. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 6546−6549.

(5) (a) Wang, Y.; Schill, B.; West, F. G. *Org. Lett.* **2003**, *5*, 2747−2750. (b) Marx, V. M.; Stoddard, R. L.; Heverly-Coulson, G. S.; Burnell, D. J. *Chem.—Eur. J.* **2011**, *17*, 8098−8104.

(6) (a) Marx, V. M.; Burnell, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 1685−1689. (b) Wu, Y.-K.; McDonald, R.; West, F. G. *Org. Lett.* **2011**, *13*, 3584−3587.

(7) Recent examples: (a) Grant, T. N.; West, F. G. *Org. Lett.* **2007**, *9*, 3789−3792. (b) Kerr, D. J.; Miletic, M.; Chaplin, J. H.; White, J. M.; Flynn, B. L. *Org. Lett.* **2012**, *14*, 1732−1735. (c) Bonderoff, S. A.; Grant, T. N.; West, F. G.; Tremblay, M. *Org. Lett.* **2013**, *15*, 2888−2891.

(8) (a) Basak, A. K.; Tius, M. A. *Org. Lett.* **2008**, *10*, 4073−4076. (b) Rieder, C. J.; Fradette, R. J.; West, F. G. *Heterocycles* **2010**, *80*,

1413−1427. (c) Marx, V. M.; Lefort, F. M.; Burnell, D. J. *Adv. Synth. Catal.* **2011**, *353*, 64−68.
(9) Kwon, Y.; McDonald, R.; West, F. G. *Angew. Chem., Int. Ed.* **2013**, *52*, 8616−8619.
(10) (a) For tandem Knoevenagel condensation/Nazarov cyclization/Conia−ene sequence with alkynes, see: Liu, L.; Wei, L.; Lu, Y.; Zhang, J. *Chem.—Eur. J.* **2010**, *16*, 11813−11817. (b) Intramolecular alkyne trapping of a cyclopentenyl cation: Volkmann, R. A.; Andrews, G. C.; Johnson, W. S. *J. Am. Chem. Soc.* **1975**, *97*, 4777−4779.
(11) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66−77.
(12) Selected recent examples: (a) Yadav, V. K.; Sriramurthy, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 2669−2671. (b) Yadav, V. K.; Kumar, N. V.; Parvez, M. *Chem. Commun.* **2007**, 2281−2283. (c) Kabalka, G. W.; Yao, M.-L.; Borella, S.; Wu, Z.; Ju, Y.-H.; Quick, T. *J. Org. Chem.* **2008**, *73*, 2668−2673. (d) Miranda, P. O.; Diaz, D. D.; Padron, J. I.; Ramirez, M. A.; Martin, V. S. *J. Org. Chem.* **2005**, *70*, 57−62.
(13) Selected recent examples: (a) Suga, S.; Kageyama, Y.; Babu, G.; Itami, K.; Yoshida, J.-i. *Org. Lett.* **2004**, *6*, 2709−2711. (b) Jin, T.; Himuro, M.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 5893−5896. (c) Meyer, V. J.; Fu, L.; Marquardt, F.; Niggemann, M. *Adv. Synth. Catal.* **2013**, *355*, 1943−1947. (d) Kim, C.; Bae, H. J.; Lee, J. H.; Jeong, W.; Kim, H.; Sampath, V.; Rhee, Y. H. *J. Am. Chem. Soc.* **2009**, *131*, 14660−14661. (e) Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 12598−12599. (f) Chavre, S. N.; Choo, H.; Lee, J. K.; Pae, A. N.; Kim, Y.; Cho, Y. S. *J. Org. Chem.* **2008**, *73*, 7467−7471. (g) Gharpure, S. J.; Prasath, V. *J. Chem. Sci.* **2011**, *123*, 943−949.
(14) Recent synthetic studies toward this structural motif: (a) Rössle, M.; Werner, T.; Baro, A.; Frey, W.; Christoffers, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 6547−6549. (b) Moore, J. L.; Kerr, M. S.; Rovis, T. *Tetrahedron* **2006**, *62*, 11477−11482. (c) See also ref 6b.
(15) Bender, J. A.; Blize, A. E.; Browder, C. C.; Giese, S.; West, F. G. *J. Org. Chem.* **1998**, *63*, 2430−2431.
(16) (a) Giese, S.; Kastrup, L.; Stiens, D.; West, F. G. *Angew. Chem., Int. Ed.* **2000**, *39*, 1970−1973. (b) Mahmoud, B.; West, F. G. *Tetrahedron Lett.* **2007**, *48*, 5091−5094.
(17) Mayr, H.; Breugst, M.; Ofial, A. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 6470−6505.
(18) (a) White, T. D.; West, F. G. *Tetrahedron Lett.* **2005**, *46*, 5629−5632. (b) Marx, V. M.; Stanley, T.; Burnell, D. J. *Tetrahedron Lett.* **2009**, *50*, 7213−7216.
(19) Recent examples of a Friedel−Crafts reaction of vinyl cation derived from electrophilic activation of alkyne: (a) Xu, T.; Yang, Q.; Ye, W.; Jiang, Q.; Xu, Z.; Chen, J.; Yu, Z. *Chem.—Eur. J.* **2011**, *17*, 10547−10551. (b) Walkinshaw, A. J.; Xu, W.; Suero, M. G.; Gaunt, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 12532−12535. (c) Jin, T.; Uchiyama, J.; Himuro, M.; Yamamoto, Y. *Tetrahedron Lett.* **2011**, *52*, 2069−2071. (d) Hanessian, S.; Tremblay, M. *Org. Lett.* **2004**, *6*, 4683−4686. (e) Hinkle, R. J.; Lewis, S. E. *Org. Lett.* **2013**, *15*, 4070−4073. (f) Reddy, U. C.; Saikia, A. K. *Synlett* **2010**, 1027−1032. (g) Otani, T.; Kunimatsu, S.; Takahashi, T.; Nihei, H.; Saito, T. *Tetrahedron Lett.* **2009**, *50*, 3853−3856.
(20) In the context of interrupted Nazarov chemistry, the dependence of stereochemical outcomes on the Lewis acid applied was also noted in ref 16a.
(21) Scadeng, O.; Ferguson, M. J.; West, F. G. *Org. Lett.* **2011**, *13*, 114−117.
(22) The regiochemical assignment of **3h** was based on 2D HMBC data.
(23) Styrene derivatives have been used to trap the pentadienyl cation intermediate derived from allenyl vinyl ketones providing a [3 + 2] adduct (ref 6a). Notably, the facial selectivity seen there is opposite to the example described here.

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