## Homologous Mukaiyama Reactions via Trapping of the Nazarov Intermediate with Silyloxyalkenes

## ORGANIC LETTERS 2011 Vol. 13, No. 14 3584–3587

## Yen-Ku Wu, Robert McDonald,<sup>†</sup> and F. G. West\*

Department of Chemistry, University of Alberta, E3-43 Gunning-Lemieux Chemistry Centre, Edmonton, AB T6G 2G2, Canada

frederick.west@ualberta.ca

## Received April 27, 2011



Treatment of 1,4-pentadien-3-ones and silvloxyalkenes with  $BF_3 \cdot OEt_2$  at room temperature or lower initiates a domino process consisting of sequential  $4\pi$  electrocyclization and capture of the resulting cyclopentenyl cation by the electron-rich trap. The overall process furnishes 1,4-dicarbonyl products containing highly substituted cyclopentanones in good yields and with the establishment of up to five new stereocenters.

The Nazarov reaction as conventionally practiced entails the treatment of cross-conjugated 1,4-dien-3-ones with stoichiometric Lewis or Brønsted acid to effect an electrocyclic closure of the resulting pentadienyl cation, with termination by elimination to furnish cyclopentenone products.<sup>1</sup> There has been considerable recent interest in expanding the versatility of this well-established reaction, including the use of catalytic acid,<sup>2</sup> asymmetric induction,<sup>3</sup> unconventional pentadienyl cation precursors,<sup>4</sup> and

10.1021/ol201125h © 2011 American Chemical Society Published on Web 06/23/2011

interception of the cyclized intermediate with electrophiles<sup>5</sup> or nucleophiles.<sup>6</sup>

In this latter category, while a wide range of traps has been applied successfully, it is notable that relatively little is known about the effectiveness of olefins with enolate-like reactivity to intercept the Nazarov intermediate. An allenyl vinyl ketone was shown by Marx and Burnell to react with

 $<sup>^{\</sup>dagger} X\text{-ray}$  Crystallographic Lab, Department of Chemistry, University of Alberta.

Reviews: (a) Pellisier, H. Tetrahedron 2005, 61, 6479–6517.
 (b) Frontier, A. J.; Collison, C. Tetrahedron 2005, 61, 7577–7606.
 (c) Tius, M. A. Eur. J. Org. Chem. 2005, 2193–2206. (d) Nakanishi, W.; West, F. G. Curr. Opin. Drug Discov. 2009, 12, 732–751.

<sup>(2) (</sup>a) Vaidya, T.; Atesin, A. C.; Herrick, I. R.; Frontier, A. J.; Eisenberg, R. *Angew. Chem., Int. Ed.* **2010**, *49*, 3363–3366. (b) He, W.; Herrick., I. R.; Atesin, T. A.; Caruana, P. A.; Kellenberger, C. A.; Frontier, A. J. *J. Am. Chem. Soc.* **2008**, *130*, 1003–1011. (c) Amere, M.; Blanchet, J.; Lasne, M.-C.; Rouden, J. *Tetrahedron Lett.* **2008**, *49*, 2541–2545.

<sup>(3) (</sup>a) Walz, I.; Togni, A. Chem. Commun. 2008, 4315–4317.
(b) Banaag, A. R.; Tius, M. A. J. Org. Chem. 2008, 73, 8133–8141.
(c) Rueping, M.; Ieawsuwan, W. Adv. Synth. Catal. 2009, 351, 78–84.
(d) Yaji, K.; Shindo, M. Synlett 2009, 2524–2528. (e) Basak, A. K.; Shimada, N.; Bow, W. F.; Vicic, D. A.; Tius, M. A. J. Am. Chem. Soc. 2010, 130, 8266–8267. (f) Cao, P.; Deng, C.; Zhou, Y. Y.; Sun, X. L.; Zheng, J. C.; Xie, Z.; Tang, Y. Angew. Chem., Int. Ed. 2010, 49, 4463–4466. (g) Huang, J.; Leboef, D.; Frontier, A. J. J. Am. Chem. Soc. 2011, 133, 6307–6317.

<sup>(4)</sup> Recent examples:(a) Grant, T. N.; West, F. G. J. Am. Chem. Soc. **2006**, *128*, 9348–9349. (b) Lemiere, G.; Gandon, V.; Cariou, K.; Hours, A.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. J. Am. Chem. Soc. **2009**, *131*, 2993–3006. (c) Rieder, C. J.; Winberg, K. J.; West, F. G. J. Am. Chem. Soc. **2009**, *131*, 7504–7505. (d) Shimada, N.; Ashburn, B. O.; Basak, A. K.; Bow, W. F.; Vicic, D. A.; Tius, M. A. Chem. Commun. **2010**, 3774–3775. (e) Bow, W. F.; Basak, A. K.; Jow, W. F.; Wicic, D. A.; Tius, M. A. Org. Lett. **2010**, *12*, 440–443. (f) Wu, Y. K.; West, F. G. J. Org. Chem. **2010**, *75*, 5410–5413. (g) Spencer, W. T., III; Levin, M. D.; Frontier, A. J. Org. Lett. **2011**, *13*, 414–417.

<sup>(5) (</sup>a) Janka, M.; He, W.; Haedicke, I. E.; Fronczek, F. R.; Frontier, A. J.; Eisenberg, R. J. Am. Chem. Soc. **2006**, 128, 5312–5313. (b) Fujiwara, M.; Kawatsura, M.; Hayase, S.; Nanjo, M.; Itoh, T. Adv. Synth. Catal. **2009**, 351, 123–128. (c) Nie, J.; Zhu, H.-W.; Cui, H.-F.; Hua, M.-Q.; Ma, J.-A. Org. Lett. **2007**, 9, 3053–3056.

<sup>(6) (</sup>a) Marx, V. M.; Cameron, T. S.; Burnell, D. J. *Tetrahedron Lett.* **2009**, *50*, 7213–7216. (b) Rieder, C. J.; Fradette, R. J.; West, F. G. *Heterocycles* **2010**, *80*, 1413–1427. (c) Scadeng, O.; Ferguson, M. J.; West, F. G. Org. Lett. **2011**, *13*, 114–117. (d) Marx, V. M.; Lefort, F. M.; Burnell, D. J. Adv. Synth. Catal. **2011**, *353*, 64–68. For a recent review, see:(e) Grant, T. N.; Rieder, C. J.; West, F. G. Chem. Commun. **2009**, 5676–5688.

<sup>(7)</sup> Marx, V. M.; Burnell, D. J. J. Am. Chem. Soc. 2010, 132, 1685–1689.

several enol ethers and a silvl enol ether, providing 1, 4-dicarbonyl adducts and in some cases formal [3 + 2]cycloadducts.<sup>7</sup> This result stands in contrast to the earlier observation that vinvl sulfides primarily undergo 3 + 2trapping.<sup>8</sup> An important distinction in these cases is the relative nucleophilicity of the traps, with enol derivatives lying further to the extreme on the  $\pi$ -nucleophilicity scale than vinyl sulfides.9 Moreover, allenyl ketones appear to undergo very rapid Nazarov cyclization, and the cyclized intermediate is expected to be longer-lived due to its greater conjugative stabilization. With this in mind, we examined Lewis acid treatment of simple 1,4-dien-3-one substrates in the presence of silvloxyalkenes as a more appropriate comparison to the vinyl sulfide results. If trapping were successful, this tranformation would offer the potential for establishing up to four stereocenters around the cyclopentanone ring, and possibly a fifth one adjacent to the exocyclic carbonyl. Such a process would be homologous with the well-established Mukaiyama addition,<sup>10</sup> since attack by the enol nucleophile would take place  $\alpha$  to the cyclopentanone carbonyl, and would result in versatile 1, 4-dicarbonyl products.<sup>11</sup> Here we describe our preliminary results, consisting of the efficient and regioselective trapping of the Nazarov intermediate derived from a structurally diverse set of dienone substrates using silvl enol ethers, silvl ketene acetals, and mixed ketene S,O-acetals.

The possibility of competing Mukaiyama Michael addition to the Lewis acid-activated dienones was a concern, and so initial studies utilized dibenzylidenepentanone 1a (Scheme 1), previously demonstrated to undergo rapid electrocyclization even at low temperature.<sup>12</sup> In the event, treatment of 1a with 1.1 equiv of BF<sub>3</sub>·OEt<sub>2</sub> in the presence of silyl ketene acetal 2a at -78 °C provided adduct 3a as a single diastereomer in 78% yield. The structural assignment of 3a was unambiguously determined by X-ray diffraction analysis. The absence of any Mukaiyama Michael addition products with the highly nucleophilic 2a was especially encouraging. The relative stereochemistry of 3a indicated that 2a approached exclusively anti to the  $\beta$ -phenyl substitution as shown in transition state (A) to generate a quaternary stereocenter, and a highly stereoselective protonation of intermediate B furnished a densely substituted cyclopentanone 3a.



<sup>(9)</sup> Mayr, H.; Kempf, B.; Ofial, A. R. Acc. Chem. Res. 2003, 36, 66-77.



The generality of this domino process with dienones **1a**-1e and a variety of oxygenated  $\pi$ -nucleophiles **2a**-2e was examined (Table 1). Not unexpectedly, dienone 1a offered a remarkable reaction profile, in which the intermolecular capture of the Nazarov intermediate with dimethyl ketene acetal **2b**, ketene *S*,*O*-acetal **2c** and silyl enol ethers  $2d-2e^{13}$  gave the corresponding ester 3b, thioester 3c, ketone 3d and aldehyde 3e/4e in good to excellent yields (entries 1-5). Among these adducts, thioester derivatives are particularly noteworthy due to the versatility in subsequent functional group manipulations.<sup>14</sup> Epimerization of cis-trans 4e to trans-trans 3e readily occurred in the presence of catalytic amount of base (eq 1). As in the case with 1a and 2a-2e, interrupted Nazarov reactions of dienone 1b and electron-rich alkenes 2b-2e proceeded in good yields and excellent diastereoselectivity (entries 6-8). Notably, contiguous quaternary centers can be efficiently created by employing  $\beta$ -disubstituted silvloxyalkenes as traps to the cyclopentenyl cations derived from symmetrical dienones 1a and 1b (entries 2, 5 and 6). In general, the higher reaction temperature was found to be crucial for Nazarov cyclizations of less reactive substrates 1b-1e in order to suppress the undesired Michael addition pathway.



To assess the potential for regiocontrol in the trapping process, unsymmetrically substituted dienones 1c and 1d were studied with several oxygenated alkenes. While

<sup>(10) (</sup>a) Modern Aldol Reactions; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004. (b) Mukaiyama, T.; Kobayashi, S. Org. React. **1994**, *46*, 1–103.

<sup>(11)</sup> For recent synthesis of 1,4-dicarbonyl substrates employing umpolung strategies, see: (a) Shen, Z. L.; Goh, K. K. K.; Cheong, H. L.; Wong, C. H. A.; Lai, Y. C.; Yang, Y. S.; Loh, T. P. J. Am. Chem. Soc. **2010**, 132, 15852–15855. (b) DeMartino, M. P.; Chen, K.; Baran, P. S. J. Am. Chem. Soc. **2008**, 130, 11546–11560. (c) Nahm, M. R.; Potnick, J. R.; White, P. S.; Johnson, J. S. J. Am. Chem. Soc. **2006**, 128, 2751–2756. (d) Mattson, A. E.; Bharadwaj, A. R.; Zuhl, A. M.; Scheidt, K. A. J. Org. Chem. **2006**, 71, 5715–5724. (e) Rossle, M.; Werner, T.; Baro, A.; Frey, W.; Christoffers, J. Angew. Chem., Int. Ed. **2004**, 43, 6547–6549. (f) Kerr, M. S.; de Alaniz, J. R.; Rovis, T. J. Am. Chem. Soc. **2002**, 124, 10298–10299.

<sup>(12)</sup> Giese, S.; West, F. G. Tetrahedron 2000, 56, 10221-10228.

<sup>(13)</sup> Use of alkyl enol ethers as trapping reagents gave intractable material within which neither homologous Mukaiyama adducts nor the simple cyclopentenones resulting from elimination could be detected.

<sup>(14) (</sup>a) Ley, S. V.; Woodward, P. R. *Tetrahedron Lett.* 1987, 28, 3019–3020. (b) Yamashita, Y.; Saito, S.; Ishitani, H.; Kobayashi, S. *J. Am. Chem. Soc.* 2003, 125, 3793–3798. (c) Prokopcova, H.; Kappe, C. O. *Angew. Chem., Int. Ed.* 2009, 48, 2276–2286.

Table 1. Intermolecular Trapping of Nazarov Intermediate with Electron-Rich Oxygen-Substituted Alkenes<sup>a</sup>



entry	dienone	$\mathbb{R}^1$	$\mathbb{R}^2$	$\mathbb{R}^3$	$\mathbb{R}^4$	alkene	$\mathbb{R}^5$	$\mathbb{R}^{6}$	$\mathbb{R}^7$	$temp(^{\circ}C)$	products (yield $\%$ ) <sup>b</sup>
1	1a	Me	Ph	Ph	Me	2a	Н	OMe	TBS	-78	<b>3a</b> (78)
2	1a	Me	Ph	Ph	Me	<b>2b</b>	Me	OMe	TMS	-78	<b>3b</b> (87)
3	1a	Me	Ph	Ph	Me	<b>2c</b>	Н	St-Bu	TBS	-78	<b>3c</b> (98)
4	1a	Me	Ph	Ph	Me	2d	Н	Ph	TBS	-78	<b>3d</b> (78)
5	1a	Me	Ph	Ph	Me	2e	Me	Н	TMS	-78	<b>3e</b> (44)/ <b>4e</b> (19)
6	1b	Me	Me	Me	Me	<b>2b</b>	Me	OMe	TMS	$\mathbf{rt}$	<b>3f</b> (59)
7	1b	Me	Me	Me	Me	2c	Н	St-Bu	TBS	0	<b>3g</b> (64)
8	1b	Me	Me	Me	Me	2d	Н	Ph	TBS	0	<b>3h</b> (66)
9	1c	Me	Ph	Ph	Η	2a	Н	OMe	TBS	0	<b>5i</b> (67)
10	1c	Me	Ph	Ph	Н	<b>2</b> e	Н	St-Bu	TBS	0	<b>3j</b> (71)
11	1c	Me	Ph	Ph	Н	2d	Н	Ph	TBS	0	<b>3k</b> (66)
12	1d	Me	Н	$(CH_2)_3$		2c	Н	St-Bu	TBS	0	<b>31/51</b> (67; 7:1) <sup>c</sup>
13	1d	Me	Н	$(CH_2)_3$		2d	Н	Ph	TBS	0	<b>3m/4m</b> (66; 30:1) <sup>d</sup>
14	1e	$(CH_{2})_{3}$		$(CH_2)_3$		<b>2c</b>	Н	St-Bu	TBS	$\mathbf{rt}$	<b>3n/5n</b> (78; 3:1) <sup>c</sup>
15	1e	$(CH_2)_3$		$(CH_2)_3$		<b>2d</b>	Н	Ph	TBS	$\mathbf{rt}$	<b>6</b> $(62)^e$

<sup>*a*</sup> Standard procedure:  $BF_3 \cdot OEt_2$  (1.1 equiv) was added to a solution of dienone 1 and electron-rich olefin 2 (2 equiv) in  $CH_2Cl_2$  (0.05 M in 1) at the indicated temperature. After 15 min, the reaction was quenched with sat. aq NaHCO<sub>3</sub>, followed by extraction, drying (MgSO<sub>4</sub>) and chromatographic purification. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> Inseparable mixture; the ratio was determined by integration of <sup>1</sup>H NMR signals. <sup>*d*</sup> Minor product could not be isolated in pure form but was tentatively assigned as **4m**. <sup>*e*</sup> A mixture of two diastereomers (ratio ca. 20:1) was obtained. The minor product was inferred to be isomeric at the carbinol carbon.

conjugate addition of silyl ketene acetal 2a to the less substituted terminus of 1c gave only 1,5-keto ester 5i under various conditions (entry 9), complete regioselective capture of the Nazarov intermediate derived from 1c was observed in the use of less nucleophilic traps 2c and 2d, providing substituted cyclopentanones 3j and 3k respectively in good yields and with complete selectivity for attack at the less substituted end of the cyclopentenyl cation (entries 10 and 11). In the case of cyclopentenylcontaining substrate 1d, the bicyclic cationic intermediate underwent selective attack by 2c at the bridgehead carbon to furnish 3l, along with minor amounts of 1,4-adduct 5l(entry 12). On the other hand, 1d reacted smoothly with 2din the presence of BF<sub>3</sub>·OEt<sub>2</sub> to afford 3m (entry 13).

The high regioselectivity seen with 1c,d is rationalized as shown in Scheme 2. In the case of differentially substituted cyclopentenyl cation **C**, selective attack at the less substituted end may result from greater accessibility as well as the incipient generation of the more substituted enolate **D** rather than **D**'. On the other hand, selective attack at the bridgehead carbon of bicyclic cation **E** may be attributed to the reduced strain experienced by enolate **F** relative to **F**'.<sup>15</sup> Apart from the observed regioselectivity, both cases displayed complete facial diastereoselectivity: with **C** the nucleophile approaches opposite the bulky phenyl group, while with **E** attack occurs exclusively from the convex face.

The behavior of bicyclic dienone 1e in this domino sequence was also investigated (entries 14 and 15). The slow rate of electrocyclization in this case necessitated conducting the reactions at rt, and even so the adduct 3b was accompanied by significant amounts of Michael adduct 5n. The cis-anti-cis ring-fusion stereochemistry of 3n was confirmed by 2D-TROESY experiments, and is consistent with other trapping processes involving 1e.<sup>6a,16</sup> More intriguingly, 1e and 2d reacted under typical reaction conditions to provide an unusual product whose spectral data indicated the presence of a hydroxyl and two phenyl groups. The structure of this compound was tentatively assigned as 6, which is presumed to arise from a domino Nazarov electrocyclization/homologous Mukaiyama addition/Mukaiyama aldol process.<sup>17</sup> This unusual reactivity was observed only in this instance, and it merits further study.

Finally, (Z)-enol silvl ether **2f** was used to examine the question of stereocontrol at an exocyclic stereocenter (Scheme 3). Treatment of **1a** and **2f** under standard

<sup>(16)</sup> Giese, S.; Kastrup, L.; Stiends, D.; West, F. G. Angew. Chem., Int. Ed. 2000, 39, 1970–1973.

<sup>(17)</sup> For an elegant demonstration of the cascade Mukaiyama aldol reaction, see: (a) Albert, B. J.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 2747–2749. (b) Boxer, M. B.; Akakura, M.; Yamamoto, H. J. Am. Chem. Soc. **2008**, *130*, 1580–1582 and references therein.

<sup>(15)</sup> Similar selectivity is noted in ref 6b.

Scheme 2. Regioselective Trapping of Unsymmetrical Nazarov Intermediates



conditions furnished 30 and 40, each consisting of two diastereomers in a 3:2 ratio at the branched carbon on the side chain. The less stable 40 could easily be converted into 30 in the presence of base catalyst; however, no epimerization took place at the  $\alpha$  carbon on the side-chain. In contrast, use of unsymmetrical dienone 1c resulted trapping with complete regio- and diastereoselectivity to provide a single product **3p**, remarkably establishing five new stereocenters in a single transformation. Although it was not possible to ascertain the relative configuration at the exocyclic stereocenter using direct methods.<sup>18</sup> Baeyer-Villiger oxidation afforded the lactone 7 as a crystalline solid, whose analysis by X-ray diffraction allowed for rigorous assignment of all five stereocenters. The effect of the C-2 substituent on the stereochemical outcome of these cases is clearly profound, but the role it plays is difficult to discern. In the case of **3p**, there are two open transition states, T1 and T2, with relatively small anticipated steric demand. Of these two, T2 may derive additional stabilization through interactions of developing partial charges, and would lead to the relative configuration shown for 3p. Replacement of the C-2 hydrogen with methyl, as in 1a, will increase the steric demand in the open transition states corresponding to **T1** and **T2**, allowing other possible orientations to compete, and leading to the minimal selectivity observed.





The interrupted Nazarov reaction of silyloxyalkenes is general and efficient, providing access to highly substituteded carbocycles in good yields through what amounts to a homologous Mukaiyama addition. Excellent diastereofacial selectivity and regioselectivity were seen in the attack of the olefin traps on the cyclized intermediates, with the establishment of up to five new stereocenters. Potential application of this domino process to natural product synthesis and the use of other  $\pi$ -nucleophiles with enolate-type reactivity will be described in due course.

Acknowledgment. We thank NSERC for support of this work. Y.K.W. gratefully thanks the Alberta Innovates—Technology Futures for a PhD graduate scholarship.

Supporting Information Available. Experimental procedures and characterization data for 3a-h, 3j-p, 4e, 4m, 4o, 5i, 6 and 7, and X-ray crystallographic data for 3a and 7. This material is available free of charge via the Internet at http://pubs.acs.org.

<sup>(18)</sup> Matsumori, N.; Kaneno, D.; Murata, M.; Nakamura, H.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 866–876. This approach was used successfully by Marx and Burnell (ref 7), but in the case of **3**p, the observed  ${}^{3}J_{C,H}$  couplings fell in an intermediate range, precluding stereochemical assignment with confidence.