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Convergent Cyclopentannelation Process

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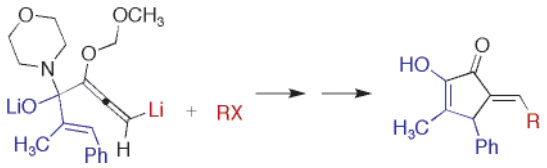
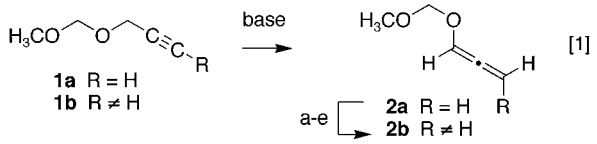
ABSTRACT



A triply convergent synthesis of α-methylene cyclopentenones has been demonstrated in which an intermediate C,O-dianion is formed and trapped on carbon by electrophiles.

A variant of the Nazarov reaction[1] in which one π electron pair is supplied by an allenyl ether has been a research interest of long standing in our group.[2] We have prepared the allenyl ethers according to Brandsma's excellent procedure[3] (eq 1) by isomerizing propargyl ethers **1** under basic conditions. In the case of **1a**, the isomerization to **2a** takes place in the presence of potassium *tert*-butoxide in 90% yield. In the case of **1b**, the isomerization requires the use of *n*-butyllithium as the base and inevitably leads to a mixture of allene and acetylene.



[1]

(a) *n*-BuLi, THF, -78 °C; (b) TMSCl, Et_3N; (c) *sec*-BuLi, THF, -78 °C; (d) R-X; (e) TBAF.

An alternative approach that leads to allenes **2b** exclusively takes place in three steps from **2a**. α-Lithiation of **2a** is followed by trapping of the resulting anion with trimethylsilyl chloride. With the α-carbon atom blocked, exposure to *sec*-butyllithium leads to the γ-lithiated allene ether that is then alkylated.[4] Desilylation leads to pure **2b**. Neither of the two approaches to **2b** is completely satisfactory. Since both terminal carbon atoms of the allene can be deprotonated, a more direct approach to **2b** would be through α,γ-allene dianion **4** (Scheme 1). Deprotonation of the γ-carbon atom would take place last; therefore, selective electrophilic trapping at that site might be possible. Every attempt to put this plan into practice failed. Although α,γ-dilithioallenes are known, it is apparently necessary to have stabilizing groups (e.g., R_3Si, SPh, Ph) at both ends of the allene.[5]

Consideration of this problem suggested the simple solution that is summarized by Scheme 1. Lithiation of **2a** leads to **3**, which adds to amide **5** to produce tetrahedral intermediate **6**. The γ-allenic protons in **6** are acidic, and exposure to

(1) (a) Jacobi, P. A.; Armacost, L. M.; Kravitz, J. I.; Martinelli, M. J.; Selnick, H. G. *Tetrahedron Lett.* **1988**, *29*, 6865. (b) Bender, J. A.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 7443. (c) Hashmi, A. S. K.; Bats, J. W.; Choi, J.-H.; Scharz, L. *Tetrahedron Lett.* **1998**, *39*, 7491. (d) Schultz-Fademrecht, C.; Tius, M. A.; Grimme, S.; Wibbeling, B.; Hoppe, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1532−1535. For a review of the Nazarov reaction, see: Habermas, K. L.; Denmark, S.; Jones, T. K. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1994; Vol. 45, pp 1−158.

(2) For an overview of our work in this area, see: Tius, M. A. *Acc. Chem. Res.* **2003**, in press, and references cited therein.

(3) Hoff, S.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 916−924.

(4) Tius, M. A.; Busch-Petersen, J.; Yamashita, M. *Tetrahedron Lett.* **1998**, *39*, 4219−4222.

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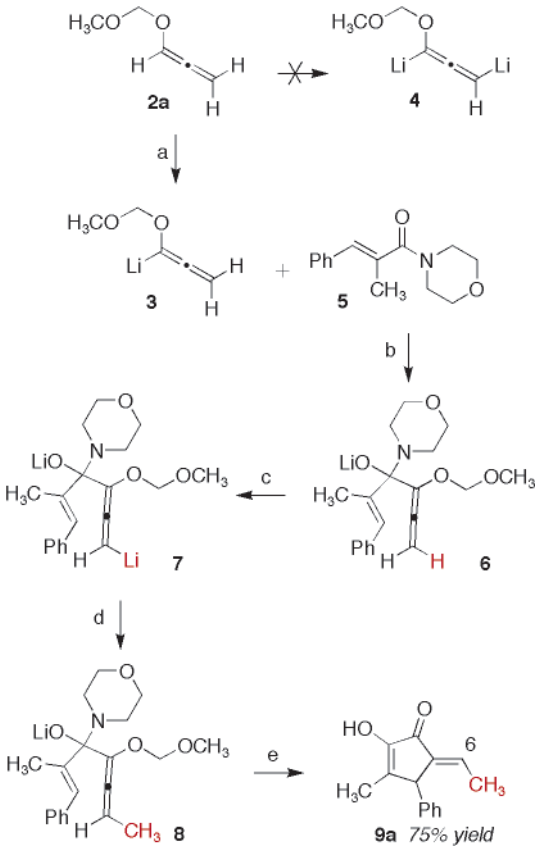
Scheme 1[a]



[a] Reaction conditions: (a) 1.2 equiv of *n*-BuLi, THF, −78 °C, 20 min; (b) 1.0 equiv of **5**, −78 °C, 30 min; (c) 1.7 equiv of *sec*-BuLi, −78 °C, 20 min; (d) 3.0 equiv of MeI, −78 °C for 30 min and then −40 °C for 30 min; (e) aqueous HCl.

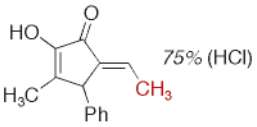
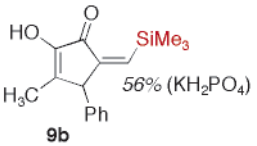
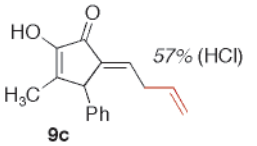
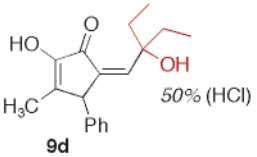
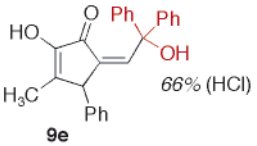
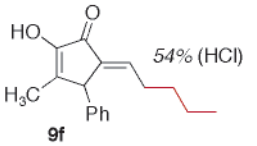
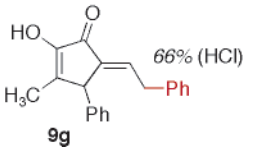
sec-butyllithium leads to *O*,*C*-dianion **7**. Whereas the *C*,*C*-dianion **4** apparently cannot be formed, **7** is a readily accessible intermediate. Exposure of **7** to iodomethane, followed by quenching the reaction with 5% HCl in ethanol gave **9a** in 75% overall yield.

The cyclization leading to **9a** is a triply convergent process involving an allene, a morpholino amide, and an electrophile. As such, it may be useful for application to the synthesis of diverse small-molecule libraries.[6] At a minimum, this modification to our method has the potential to simplify the preparation of α-methylene cyclopentenones substituted at C6. We had also postulated that the approach that is outlined in Scheme 1 would lend itself to the preparation of α-methylene cyclopentenones that incorporate functionality at C6 that is not compatible with the conditions for α-lithiation of allenyl ethers. This proved to be the case.

(5) (a) Leroux, Y.; Mantione, R. *Tetrahedron Lett.* **1971**, *12*, 591−592. (b) Eisch, J. J.; Behrooz, M.; Galle, J. E. *Tetrahedron Lett.* **1984**, *25*, 4851−4854. (c) Pang, Y.; Petrich, S. S.; Young, V. G., Jr.; Gordon, M. S.; Barton, T. J. *J. Am. Chem. Soc.* **1993**, *115*, 2534−2536. (d) Seyferth, D.; Langer, P.; Döring, M. *Organometallics* **1995**, *14*, 4457−4459. See also: Reich, H. J.; Holladay, J. E.; Walker, T. G.; Thompson, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 9769−9780.

(6) Jang, W. B.; Hu, H.; Lieberman, M. M.; Morgan, J. A.; Stergiades, I. A.; Clark, D. S.; Tius, M. A. *J. Comb. Chem.* **2001**, *3*, 346−353.

Table 1. α-Hydroxy Cyclopentenones[a]

Conditions	Product/Yield (quench)
3.0 equiv MeI; -78 °C, 30 min; -40 °C, 30 min.	 75% (HCl) **9a**
2.0 equiv TMSCl (1/1 v/v with Et_3N); -78 °C, 15 min.	 56% (KH_2PO_4) **9b**
6.0 equiv $BrCH_2CH{=}CH_2$, 1.1 equiv HMPA; -78 °C, 30 min; -30 °C, 1.5 h.	 57% (HCl) **9c**
6.0 equiv 3-pentanone; -78 °C, 30 min; -30 °C, 30 min.	 50% (HCl) **9d**
6.0 equiv benzophenone; -78 °C, 30 min; -30 °C, 30 min.	 66% (HCl) **9e**
6.0 equiv *n*-BuI, 3.0 equiv HMPA; -78 °C, 1 h; -30 °C, 2.5 h.	 54% (HCl) **9f**
5.0 equiv $PhCH_2Br$; -78 °C, 2 h; -30 °C, 30 min.	 66% (HCl) **9g**

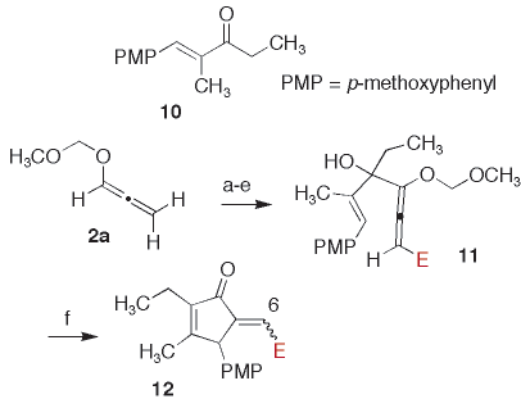
[a] Yields calculated from the corresponding amides.

Table 1 summarizes the results that were obtained with various electrophiles. Product yields varied from moderate to good; in all cases, a negligible (<5%) amount of cyclic product unsubstituted at C6 was isolated from the reaction mixtures. In the case of allyl bromide and *n*-butyl iodide, we found it necessary to add HMPA in order to accelerate the alkylation reaction that was slow at −30 °C. The yield of **9f** through the triply convergent procedure (54%; see Table 1) is comparable to the yield of **9f** from allene **2b** (R = *n*-Bu; 61%). When alkyl halides were used as electrophiles, quenching the reaction with aqueous KH_2PO_4 catalyzed the cyclization and generally led to a mixture of the (*E*)- and (*Z*)-isomers at the exocyclic double bond. Treatment of this mixture with aqueous HCl led to isomerization of the (*E*)- and (*Z*)-isomer. The reaction could also be quenched with aqueous HCl, in which case only the (*E*)-isomers were isolated. When ketones were used as electrophiles, no

isomerization of the exocyclic double bond was observed[7] even when the reactions were quenched with HCl (see **9d** and **9e**). This may be an indication that the rate of acid-catalyzed isomerization of the exocyclic double bond is diminished by electronic deactivation by the allylic hydroxyl group. Alternatively, the sterically favored isomer may be the (*Z*)-isomer in these cases. The (*E*)-isomer may be disfavored by destabilizing interactions of the sterically demanding C6 substituent with the C4 phenyl group.[8] When trimethylsilyl chloride was used as the electrophile, it was necessary to quench the reaction with KH_2PO_4 since protiodesilylation of **9b** took place rapidly in the presence of HCl. Under these conditions, the (*Z*)-isomer **9b** was isolated as the sole reaction product.

There are three broad categories of the cyclopentannelation, differing in the α,β-unsaturated electrophilic component. The morpholino amides lead to α-hydroxy cyclopentenones, whereas nitriles lead to α-amino cyclopentenones[9] and ketones to α-alkyl (or aryl) cyclopentenones. Our goal was to determine whether what was successful in the case of morpholino amides would also work in the other two categories. When we used enone **10** as the electrophile, the intermediate alcohol **11** was isolated and then cyclized in a separate step (Scheme 2). The cyclization could be effected

Scheme 2[a]



[a] Reaction conditions: (a) 1.2 equiv of *n*-BuLi, THF, −78 °C, 20 min; (b) 1.0 equiv of **10**, −78 °C, 30 min; (c) 1.7 equiv of *sec*-BuLi, −78 °C, 20 min; (d) E^+ (see Table 2); (e) aqueous $NaHCO_3$; (f) $FeCl_3$, CH_2Cl_2.

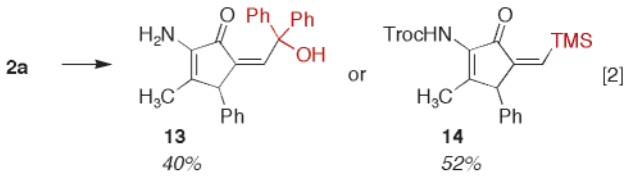
either by trifluoroacetic anhydride/2,6-lutidine or $FeCl_3$. The yields of products were in all cases moderate or good (Table 2).[10] As in the cases described in Table 1, exposure of the

Table 2. α-Ethyl Cyclopentenones[a]

Conditions	Product/Yield (quench)
3.0 equiv MeI; -78 °C, 30 min; -30 °C, 30 min.	*E*/*Z* ≈ 1/1 **12a** *79%* (0.6 equiv $FeCl_3$)
2.0 equiv TMSCl (1/1 v/v with Et_3N); -78 °C, 15 min.	*E*/*Z* ≈ 2/1 **12b** *65%* (0.6 equiv $FeCl_3$)
6.0 equiv $BrCH_2CH{=}CH_2$; 1.1 equiv HMPA; -78 °C to -30 °C, 1 h; - 30 °C, 1.5 h.	*E*/*Z* ≈ 3/2 **12c** *63%* (0.6 equiv $FeCl_3$)
6.0 equiv EtOCOCN; -78 °C, 2 h; -30 °C, 30 min.	only *E* **12d** *55%* (0.6 equiv $FeCl_3$)
6.0 equiv *n*BuI; 3.0 equiv HMPA; -78 °C, 1 h; -30 °C, 2.5 h.	*E*/*Z* ≈ 1/1 **12e** *67%* (0.6 equiv $FeCl_3$)
5.0 equiv $PhCH_2Br$; -78 °C, 2 h; -30 °C, 30 min.	*E*/*Z* ≈ 1/1 **12f** *73%* (0.6 equiv $FeCl_3$)

[a] Yields calculated from the corresponding amides.

cyclic products to HCl led to isomerization of the exocyclic double bond.



The triply convergent strategy also works in the case of α,β-unsaturated nitriles (eq 2). Addition of **3** to α-methylcinnamonitrile followed by γ-deprotonation of the intermediate, trapping of the dianion with either benzophenone or trimethylsilyl chloride, and cyclization led to (*Z*)-products **13** (KH_2PO_4 quench) or **14** ($FeCl_3$ quench).[11] The choice of electrophiles appears to be limited, since the deprotonated imine function in the intermediate dianion is a reactive

(7) Stereochemistry of the exocyclic double bond was assigned on the basis of comparison of the ^{1}H NMR chemical shift of the vinyl proton at C6. The vinyl proton of the (*E*)-isomers appears up to 1.2 ppm downfield of where it appears in the spectra of the (*Z*)-isomers. In cases in which a single isomer was isolated, stereochemistry was assigned by analogy, or, in the case of **9d** and **12d**, by NOE.

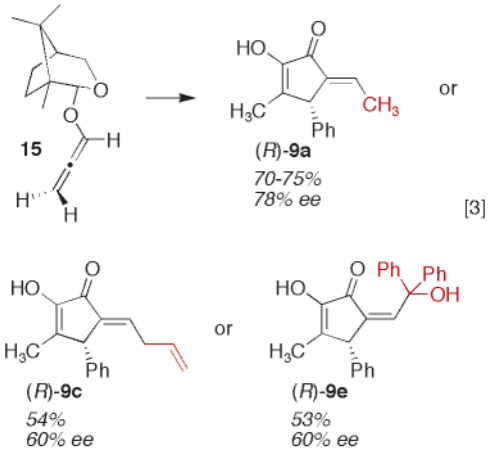
(8) In the case of **9d**, this hypothesis is supported by an MM2 calculation.

(9) Tius, M. A.; Chu, C. C.; Nieves-Colberg, R. *Tetrahedron Lett.* **2001**, *42*, 2419−2422.

(10) Dr. Oliver Weichold was the first person in our research group to prepare C6-substituted cyclopentenones through a variant of the process that is summarized in Scheme 2.

nucleophile. All attempts to use alkyl halides as electrophilic traps for the dianion led to complex mixtures of products.

We have recently described an asymmetric version of the cyclopentannelation reaction that makes use of allene **15**.[12] We were particularly interested in learning whether the asymmetric version of the cyclization would also be amenable to this new approach. The three preliminary experiments have led to gratifying results (eq 3). Cyclopentenone (*R*)-**9a** was obtained in 70−75% yield and in 78% ee. This represents a modest improvement over our earlier work that had led to (*R*)-**9a** in 67% yield and 70% ee.[12] Cyclopentenone (*R*)-**9c** was formed in 54% yield and 60% ee, whereas (*R*)-**9e** was formed in 53% yield and 60% ee.[13]



In conclusion, we have been successful in developing a very convenient procedure that leads to C6-substituted α-methylene cyclopentenones. The success of the method depends on being able to generate dianions such as **7** and to trap them with diverse electrophiles. The result is a triply convergent process[14] that combines α-lithioallene **3** with an α,*β*-unsaturated morpholino amide, ketone, or nitrile and with an electrophile. The respective products are α-hydroxy-, α-alkyl-, or α-aminocyclopentenones. Structures that cannot be prepared through our earlier method (**9b**, **9d**, **9e**, **12b**, **12d**, **13**, and **14**) are readily accessible. Significantly, this protocol is also successful in the asymmetric version of the cyclopentannelation (eq 4). These results extend the scope of the cyclopentannelation reaction, add to its versatility, and suggest applications to the synthesis of small-molecule libraries.

Acknowledgment. We thank the National Institutes of Health (GM57873) for generous support. We acknowledge Dr. Oliver Weichold for his early contribution to this project.

Supporting Information Available: General procedures for the synthesis of **9a**, **12a**, **14**, and (*R*)-**9a**; spectroscopic data for **9b**−**g**, **12a**−**f**, **13**, and **14**; and reproductions of ^{1}H NMR spectra of **9a**−**g**, **12a**−**f**, **13**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) It is usually necessary to protect the α-amino function in this series to prevent polymerization of the products from occurring. In the case of **13**, the polymerization through Michael addition to C6 by the amino function is sterically inhibited.

(12) Harrington, P. E.; Murai, T.; Chu, C.; Tius, M. A. *J. Am. Chem Soc.* **2002**, *124*, 10091−10100.

(13) Ee of (*R*)-**9e** was determined by Mosher analysis of the ^{1}H NMR spectrum because we were unable to resolve the enantiomers by chiral HPLC (Chiralcel OD column). To validate the Mosher method for our system, we measured the ee of (*R*)-**9a** by chiral HPLC (78%) and by Mosher's method (76%). (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519. (b) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549.

(14) Tius, M. A.; Gomez-Galeno, J.; Gu, X.-Q.; Zaidi, J. H. *J. Am. Chem. Soc.* **1991**, *113*, 5775−5783.