

Conjugate Addition-Initiated Nazarov Cyclization

Joshua L. Brooks, Patrick A. Caruana, and Alison J. Frontier*

Department of Chemistry, University of Rochester, Rochester, New York 14627, United States

Supporting Information

ABSTRACT: A reaction sequence involving the 1,6-conjugate addition of a nucleophile to a dienyl diketone followed by Nazarov cyclization is described. Several nucleophiles are identified as competent initiators for the sequence. A different reaction outcome is observed when catalytic amounts of nucleophile are employed, involving elimination of the nucleophile after the electrocyclozation.

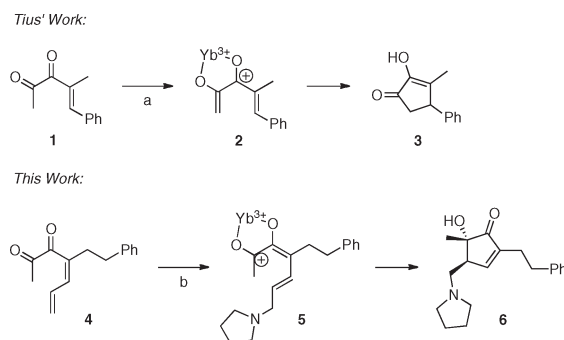
The classical Nazarov cyclization involves Lewis acid-promoted generation of a pentadienyl cation from a divinyl ketone, which undergoes conrotatory 4π electrocyclozation to deliver cyclopentenone derivatives.¹ Recent advances in catalysis² and capture of the oxyallyl cation intermediate³ have increased the synthetic utility of the reaction. It is also possible to generate the reactive pentadienyl cation using methods other than Lewis acid activation, including protonation of enol ethers,⁴ oxidation,⁵ and cyclopropanation.⁶ In this communication, the development of a 4π electrocyclozation initiated by 1,6-conjugate addition of a nucleophile to a dienyl diketone is described. The two-step sequence is catalyzed by Lewis acids, is stereoselective, and affords high yields of α -hydroxycyclopentenones.

Tius has described the Nazarov cyclization of diketones of type **1** using $\text{Yb}(\text{OTf})_3$ and pyrrolidine as a base, which gives diosphenol **3** (Scheme 1).^{7,8} We found that treatment of dienyl diketone **4** under similar reaction conditions resulted in a different cyclization, giving α -hydroxycyclopentenone **6**, with incorporation of the pyrrolidine base (see Figure 1). Further exploration of this interesting diastereoselective reaction was warranted.

Studies began with catalyst evaluation (Table 1). Although the reaction did occur in the absence of an acidic promoter, the rate was much slower (24 h vs 15 min), and no diastereoselectivity was observed (entry 1). Using 10 mol % of a protic or Lewis acid, full conversion was achieved in 15 min with very high diastereoselectivity (entries 2–5, and 6). In general, Lewis acidic transition metal complexes (entries 2–5) gave better chemical yields than the protic acid (TFA, entry 6).

At lower catalyst loading (2.5 mol %), yields decreased, and $\text{Y}(\text{OTf})_3$ was found to be more effective than $\text{Cu}(\text{OTf})_2$ (entries 7 and 8). Experimentation with solvents revealed that CH_2Cl_2 gave the best selectivity (entry 10), while THF produced the highest chemical yield (entry 11). The reaction was further optimized by the addition of Et_3N and LiCl (entry 12), which are thought to improve catalyst solubility.⁹

Efforts were then made to identify other viable nucleophiles for the reaction. Primary amines and cyclic and acyclic secondary amines did initiate the cyclization (**8a–8e**; Scheme 2). $\text{Cu}(\text{OTf})_2$

Scheme 1. Two Cyclization Pathways of Unsaturated α -Diketones^a

^a Reagents and conditions: a) $\text{Yb}(\text{OTf})_3$ (catalytic), pyrrolidine (1 equiv), DMSO, rt, 63%. b) $\text{Yb}(\text{OTf})_3$ (10 mol %), pyrrolidine (1 equiv), DMSO, rt, 83%.

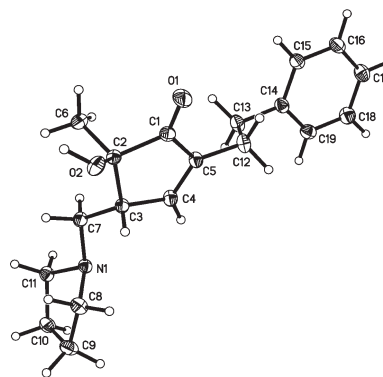
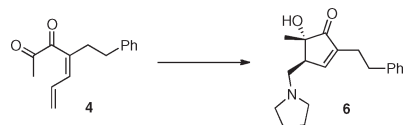


Figure 1. ORTEP drawing of **6**.

was also effective for these reactions, but yields were lower. Malonate derivatives also participated as nucleophiles, allowing for the installation of a versatile carbon-based handle (**8f–8i**). Addition of malonate did not occur when $\text{Cu}(\text{OTf})_2$ was used as catalyst. In all of these reactions, only one diastereoisomer was detected. The more complex diketone **7** also underwent smooth cyclization to give pyrrolidine adduct **9**, as a 1:1 mixture of diastereomers relative to the remote stereocenter (see Supporting Information [SI]). The stereochemistry of compounds **6** and **8c** was assigned using X-ray crystallographic data, and in other cases the syn

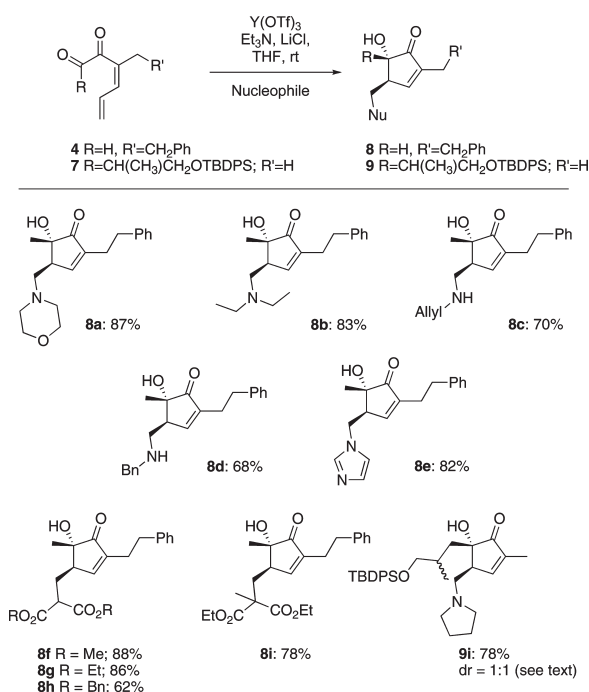
Received: June 18, 2011

Published: July 22, 2011

Table 1. Optimization of the Pyrrolidine-Initiated Cyclization^a

entry	catalyst	solvent	dr	yield (%)
1 ^b	--	DMSO	1:1	68
2	Cu(OTf) ₂ (10 mol %)	DMSO	>20:1	99
3	Sc(OTf) ₃ (10 mol %)	DMSO	3:1	87
4	Yb(OTf) ₃ (10 mol %)	DMSO	>20:1	83
5	Y(OTf) ₃ (10 mol %)	DMSO	>20:1	99
6	TFA (10 mol %)	DMSO	>20:1	74
7	Cu(OTf) ₂ (2.5 mol %)	DMSO	4:1	54
8	Y(OTf) ₃ (2.5 mol %)	DMSO	15:1	68
9	Y(OTf) ₃ (1 mol %)	DMF	9:1	81
10	Y(OTf) ₃ (1 mol %)	CH ₂ Cl ₂	>20:1	71
11	Y(OTf) ₃ (1 mol %)	THF	9:1	89
12 ^c	Y(OTf) ₃ (1 mol %)	THF	>20:1	99

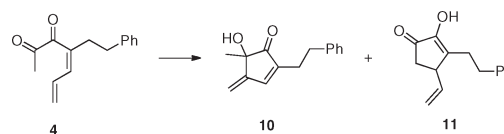
^a Reaction conditions: **4** (1 equiv), pyrrolidine (1.2 equiv), catalyst as listed. All reactions were conducted at 0.1 M for 15 min at rt except where otherwise noted. ^b The reaction required 24 h for completion. ^c With Et₃N (1 equiv) and LiCl (2 equiv).

Scheme 2. Scope of the Cyclization^a

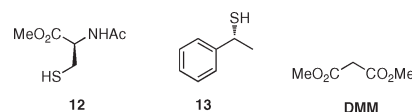
^a Reaction conditions: a) **4**, Y(OTf)₃ (1 mol %), Et₃N (1 equiv), LiCl (2 equiv), amine or malonate nucleophile (1.2 equiv), THF, rt; b) **7**, Cu(OTf)₂ (10 mol %), pyrrolidine (1 equiv), DMSO, rt.

relationship between the α-methyl and β-methylene was detected by measurement of the NOE (see SI).

By employing DMAP as the nucleophile, it was possible to achieve a different reaction outcome, obtaining dienone **10**

Table 2. Formation of Dienone **10^a**

entry	nucleophile	product (ratio 10:11)	base ^b	time (h)	yield (%)
1	DMAP (10 mol %)	10 only	—	48	45
2	DMAP (1 equiv)	10 only	—	48	75
3	<i>i</i> -PrMe ₂ N (10 mol %)	1:1	—	48	45
4	<i>N</i> -methyl-morpholine (10 mol %)	1:1	—	48	55
5 ^{c,d}	12 (10 mol %)	10 only	<i>t</i> -BuOK	1	93
6 ^{c,d}	13 (10 mol %)	10 only	<i>t</i> -BuOK	1	82
7	DMM (1 mol %)	10 only	Et ₃ N	8	64
8	DMM (1 mol %)	1:1	NaH	1	94
9	DMM (1 mol %)	10 only	DBU	1	50
10	DMM (1 mol %)	10 only	—	—	—
	DABCO	1	82	—	—



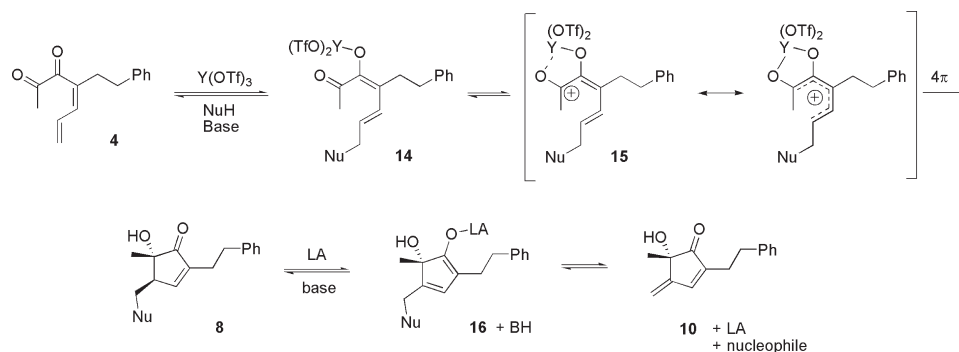
^a Reaction conditions: **4**, Y(OTf)₃ (1 mol %), LiCl (2 equiv), THF (0.1 M), at rt unless otherwise stated. ^b Ratio of base:nucleophile was 1:1. ^c Thiol premixed with base, −78 °C then **4**. ^d No Lewis acid present. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DABCO = 1,4-diazabicyclo[2.2.2]octane.

instead of enones **8** (Table 2, entries 1 and 2). A stoichiometric amount was required for complete conversion (entry 2). Other nucleophiles known to be effective in the Morita–Baylis–Hillman reaction were also tested.¹⁰ The tertiary amines *N,N*-dimethylisopropylamine and *N*-methylmorpholine gave a 1:1 mixture of **10** and **11** in moderate yield (entries 3 and 4), while DBU and DABCO did not catalyze the reaction. Tertiary phosphines were also ineffective. Thiols **12** and **13**, which are effective in the Rauhut–Currier reaction,¹¹ did catalyze the cyclization, allowing complete conversion to **10** in 1 h. Interestingly, we found that catalytic amounts of dimethyl malonate (DMM) in the presence of base also led to formation of product **10**. The most effective base for the DMM-catalyzed process was DABCO (cf. entries 6–9, Table 2).

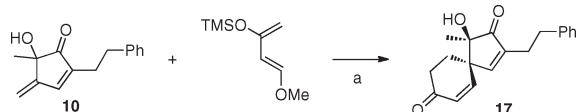
A proposed mechanism for the cyclization and subsequent elimination is presented in Scheme 3. The reaction begins with Lewis acid-promoted conjugate addition of the nucleophile to form intermediate **14**. Activation of the ketone carbonyl produces pentadienyl cation **15**, which undergoes 4π conrotatory cyclization to give products of type **8**. The high diastereoselectivity is thought to result from the conrotatory electrocyclic cyclization of pentadienyl cation **15**.¹² Thus, Lewis acidic Y(OTf)₃ is responsible for activation of first one carbonyl (for conjugate addition) and then the other (for electrocyclic cyclization). In the formation of compound **10**, intermediate **8** undergoes elimination through intermediate **16**.

The reactions with dimethylmalonate (DMM) as nucleophile warrant further comment. Products **8f**–**8i** are obtained using a

Scheme 3. Proposed Mechanism for Cyclization



Scheme 4. Cycloaddition of 10 with Danishefsky's Diene



Reaction conditions: a) toluene, 180 °C, sealed tube, 24 h, then TFA (10 mol %) 10 min, rt, 80%.

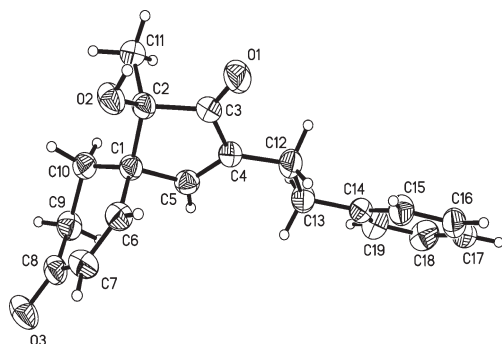


Figure 2. ORTEP drawing of 17.

stoichiometric amount of malonate (Scheme 2), while product **10** is obtained using catalytic DMM (Table 2, entry 9). A series of experiments were performed to better understand these observations. Subjection of **10** to DMM under the reaction conditions used in the Scheme 2 experiments gave **8f** as a 1:1 mixture of diastereomers, presumably via intermediate **16**. Also, if the reaction of **4** with DMM (Scheme 2) was run for a longer period, **8f** with dr = 1:1 was isolated. When **8f** (dr > 20:1) was resubjected to the Scheme 2 reaction conditions, complete epimerization was observed after 2 h (dr = 1:1). Finally, treatment of **8f** with 1 equiv of diethylmalonate under the usual reaction conditions led to a 1:1 mixture of **8f** and **8g**, as mixtures of diastereomers. These experiments indicate that, with malonate derivatives as nucleophiles, the formation of **10** from **8** is reversible under the reaction conditions, and this equilibrium between **8** and **10** lies in favor of **8**.

In the context of future application to natural product total synthesis, we were able to demonstrate that **10** is a useful building block for spirocycle formation. The Diels–Alder reaction of **10** with Danishefsky's diene provided **17** as a single diastereomer (Scheme 4), whose structure was confirmed by single crystal X-ray analysis (Figure 2).

In summary, a new method for the initiation of the Nazarov cyclization via conjugate addition to a dienyl diketone is described. The reaction efficiently proceeds to afford either the nucleophile adducts **8** or the elimination products **10**. Further investigation into substrate scope is underway, as well as the development of an enantioselective variant of this reaction sequence.

■ ASSOCIATED CONTENT

S Supporting Information. Experimental details and characterization data for all new compounds, X-ray crystal structures, and CIF file for **6**, **8c**, and **17**. This material is available free of charge via the Internet at <http://pubs.acs.org>

■ AUTHOR INFORMATION

Corresponding Author

frontier@chem.rochester.edu

■ ACKNOWLEDGMENT

We thank the National Institutes of Health (NIGMS R01 GM079364) and ARRA supplement (3R01GM079364-03S2) for funding this work. We are also grateful to Dr. William Brennessel for solving X-ray structures of **6**, **7c**, and **17**.

■ REFERENCES

- (1) (a) Pellissier, 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**, 2005, 2193–2206. (d) Grant, T. N.; Rieder, C. J.; West, F. G. *Chem. Commun.* **2009**, 5676–5688. (e) Nakanishi, W.; West, F. G. *Curr. Opin. Drug Discovery Dev.* **2009**, 12, 732–751.
- (2) For a review on the catalytic Nazarov cyclization, see: Vaidya, T.; Frontier, A. J.; Eisenberg, R. *ChemCatChem* **2011** in press.
- (3) (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) Marx, V. M.; Burnell, D. J. *J. Am. Chem. Soc.* **2010**, 132, 1685–1689. (c) Rieder, C. J.; Fradette, R. J.; West, F. G. *Heterocycles* **2010**, 80, 1413–1427. (d) Scadeng, O.; Ferguson, M. J.; West, F. G. *Org. Lett.* **2010**, 13, 114–117. (e) Marx, V. M.; LeFort, F. M.; Burnell, D. J. *Adv. Synth. Catal.* **2011**, 353, 64–68.
- (4) (a) Prandi, C.; Deagostino, A.; Venturello, P.; Occhiato, E. G. *Org. Lett.* **2005**, 7, 4345–4348. (b) Wu, Y.-K.; West, F. G. *J. Org. Chem.* **2010**, 75, 5410–5413.
- (5) Spencer, W. T.; Levin, M. D.; Frontier, A. J. *Org. Lett.* **2010**, 13, 414–417.
- (6) Grant, T. N.; West, F. G. *J. Am. Chem. Soc.* **2006**, 128, 9348–9349.

(7) Batson, W. A.; Sethumadhavan, D.; Tius, M. A. *Org. Lett.* **2005**, 7, 2771–2774.

(8) For other examples of this type of Nazarov cyclization, see: (a) Muxfeldt, H.; Weigle, M.; Rheenen, V. V. *J. Org. Chem.* **1965**, 30, 3573–3574. (b) Weinreb, S. M.; Auerbach, J. *J. Am. Chem. Soc.* **1975**, 97, 2503–2506. (c) Uhrich, E. A.; Batson, W. A.; Tius, M. A. *Synthesis* **2006**, 2006, 2139–2142. (d) Williams, D. R.; Robinson, L. A.; Nevill, C. R.; Reddy, J. P. *Angew. Chem., Int. Ed.* **2007**, 46, 915–918. (e) Bow, W. F.; Basak, A. K.; Jolit, A.; Vicic, D. A.; Tius, M. A. *Org. Lett.* **2009**, 12, 440–443. (f) Basak, A. K.; Shimada, N.; Bow, W. F.; Vicic, D. A.; Tius, M. A. *J. Am. Chem. Soc.* **2010**, 132, 8266–8267. (g) Cai, Z.; Harmata, M. *Org. Lett.* **2010**, 12, 5668–5670.

(9) LiCl is known to aid in the solubility of copper (II) salts in THF: Tamura, M.; Kochi, J. *Synthesis* **1971**, 303.

(10) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, 103, 811–892.

(11) Aroyan, C. E.; Dermenci, A.; Miller, S. J. *J. Org. Chem.* **2010**, 75, 5784–5796.

(12) For examples of cyclopentannulations of intermediates like **15**, see ref 4a and (a) Denmark, S. E.; Habermas, K. L.; Hite, G. A. *Helv. Chim. Acta* **1988**, 71, 168–194. (b) Stone, G. B.; Liebeskind, L. S. *J. Org. Chem.* **1990**, 55, 4614–4622. (c) Paquette, L. A.; Morwick, T. M. *J. Am. Chem. Soc.* **1997**, 119, 1230–1241. (d) Paquette, L. A. *Eur. J. Org. Chem.* **1998**, 1709–1728. (e) Pujanauskis, B. G.; Bhanu Prasad, B. A.; Sarpong, R. *J. Am. Chem. Soc.* **2006**, 128, 6786–6787. (f) Zou, W. *Res.* **2004**, 339, 2475–2485. (g) Caddick, S.; Cheung, S.; Doyle, V. E.; Frost, L. M.; Soscia, M. G.; Delisser, V. M.; Williams, M. R. V.; Etheridge, Z. C.; Khan, S.; Hitchcock, P. B.; Pairaudeau, G.; Vile, S. *Tetrahedron* **2001**, 57, 6295–6303.