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Chemoselective Cyclizations of Divinyl Ketones to Cyclohexenones Mediated by Lewis Acid and Base

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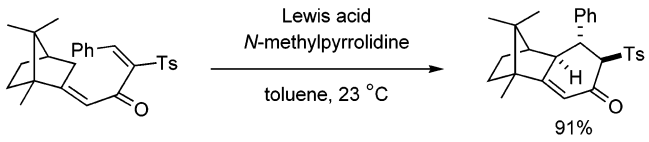
ABSTRACT



Chemoselective cyclizations of divinyl ketones to cyclohexenones mediated by a sterically demanding Lewis acid and an amine base have been accomplished under mild reaction conditions. The extension of this methodology to the synthesis of eight-membered rings is also demonstrated.

Divinyl ketones are valuable building blocks for organic synthesis. These substrates have been utilized in Diels−Alder reactions,[1] Michael reactions,[2] and conjugate addition reactions to prepare various ring systems.[3] The characteristic reaction of divinyl ketones is their acid-catalyzed Nazarov cyclization leading to cyclopentenones.[4] Although it was postulated that cyclizations of divinyl ketones could potentially produce cyclohexenones,[5] this viewpoint was not demonstrated experimentally.[6] In this paper, we describe *direct* cyclizations of divinyl ketones that result in chemoselective formation of cyclohexenones under mild reaction conditions.

Recently, we demonstrated the ring expansion reactions of cyclobutenones to cyclohexenones that involved the facile cyclization of intermediate 3-oxidohexatrienes bearing a strategically positioned electron-withdrawing group.[7] We realized that the key hexatriene intermediates could alternatively be generated by γ-enolization of the readily available divinyl ketones (**1**) (Scheme 1). Although generation of extended enolates from α,β-unsaturated carbonyl compounds was typically accomplished by reactions with strong bases,[8] we believed that enolization of a complex of **1** with a Lewis acid could be achieved under milder conditions using a tertiary amine base.[9] For the desired cyclization to occur,

(1) (a) Winkler, J. D.; Kim, H. S.; Kim, S.; Ando, K.; Houk, K. N. *J. Org. Chem.* **1997**, *62*, 2957−2962. (b) Jung, M. E.; McCombs, C. A.; Takeda, Y.; Pan, Y.-G. *J. Am. Chem. Soc.* **1981**, *103*, 6677−6685. (c) Nazarov, I. N.; Kuvarzina, M. V. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1948**, 599−609.

(2) (a) Britten-Kelly, M.; Willis, B. J.; Barton, D. H. R. *Synthesis* **1980**, 27−29. (b) Hamanaka, N.; Nakai, H.; Kurono, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2327−2329. (c) de Jongh, H. A. P.; Wynberg, H. *Tetrahedron* **1964**, *20*, 2553−2573.

(3) (a) Dunn, P. J.; Graham, A. B.; Grigg, R.; Higginson, P.; Thornton-Pett, M. *Tetrahedron* **2002**, *58*, 7727−7733. (b) Kuehne, M. E.; Bornmann, W. G.; Earley, W. G.; Marko, I. *J. Org. Chem.* **1986**, *51*, 2913−2927. (c) Snider, B. B.; Harvey, T. C. *Tetrahedron Lett.* **1995**, *36*, 4587−4590.

(4) Nazarov, I. N.; Zaretskaya, I. I.; Sorkina, T. I. *Zh. Obsh. Khim.* **1960**, *30*, 746−754. For a review, see: Habermas, K. L.; Denmark, S. E.; Jones, T. K. *Org. React.* **1994**, *45*, 1−158.

(5) Magnus, P. *Nouv. J. Chem.* **1978**, *2*, 555−557 and references therein.

(6) Divinyl ketones were indirectly converted to cyclohexenones under harsh reaction conditions: (a) Torok, D. S.; Scott, W. J. *Tetrahedron Lett.* **1993**, *34*, 3067−3070. (b) Fehr, C.; Galindo, J.; Guntern, O. *Tetrahedron Lett.* **1990**, *31*, 4021−4024.

(7) Magomedov, N. A.; Ruggiero, P. L.; Tang, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1624−1625.

(8) For example: Saito, S.; Nagahara, T.; Shiozawa, M.; Nakadai, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 6200−6210.

(9) (a) Lehnert, W. *Tetrahedron Lett.* **1970**, 4723−4724. (b) Mukaiyama, T.; Inoue, T. *Chem. Lett.* **1976**, 559−562. (c) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120−6123. (d) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099−3111. (e) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566−1568. (f) Rathke, M. W.; Cowan, P. J. *J. Org. Chem.* **1985**, *50*, 2622−2624. (g) Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram B. *J. Am. Chem. Soc.* **1989**, *111*, 3441−3442. (h) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894−902.

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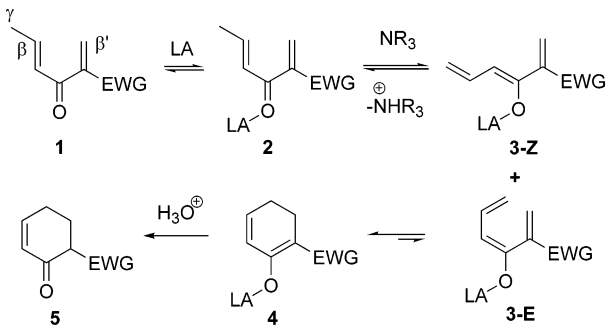
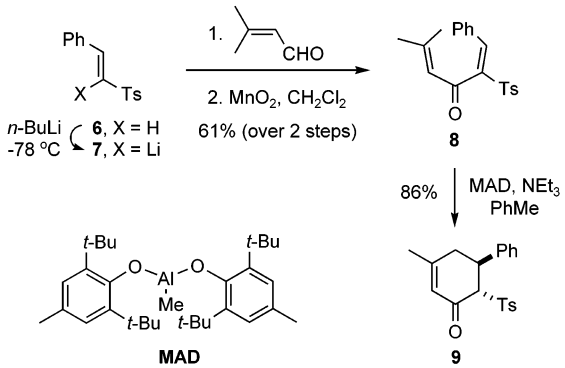
Scheme 1. Proposed Cyclization of Divinyl Ketones to Cyclohexenones



enolization of complex **2** had to produce the *E*-enolate **3-E**. Hence, a study aimed at identification of a competent Lewis acid/base combination was a logical point of departure.

The initial experiments demonstrated that activation of dienone **8** with a range of oxophilic Lewis acids, such as $Mg(ClO_4)_2$, $LiClO_4$, $TiCl_2(O\text{-}i\text{-}Pr)_2$, $Zn(OTf)_2$, $Sc(OTf)_3$, or $AlCl_3$, followed by addition of triethylamine returned the starting material unchanged. Use of trimethylaluminum, however, produced the desired cyclohexenone **9**, albeit in poor yield.[10] During their studies of vinylogous aldol reactions, Yamamoto and co-workers utilized an ATPH/LDA system for the stereoselective generation of *E*-dienolates from α,*β*-unsaturated carbonyl compounds.[8,11] We reasoned that a sterically demanding aluminum Lewis acid might increase the population of the productive *E*-enolate and result in a faster and more efficient cyclization reaction. We were pleased to find that treatment of **8** with MAD (2.0 equiv) and NEt_3 (1.1 equiv) in toluene at room temperature furnished **9** in 86% isolated yield (Scheme 2).[12] Toluene was

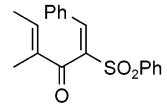
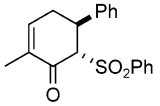
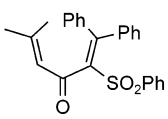
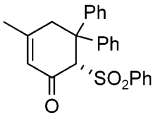
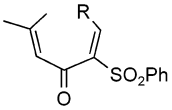
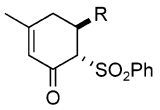
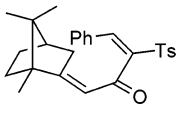
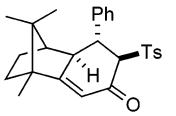
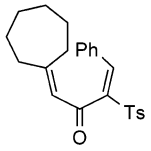
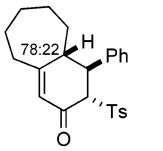
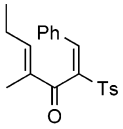
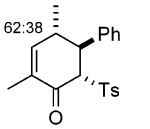
Scheme 2. Cyclization of **8** Mediated by MAD/NEt_3



found to be the optimal solvent for this cyclization, as reactions in stronger coordinating solvents (THF, MeCN) resulted in poor reaction conversion. In addition to triethylamine, *N*-methylpyrrolidine was a competent base, whereas Hunig's base gave lower reaction conversion. Notably, no cyclization occurred in the absence of a base or in the presence of stronger bases, such as DBU and *N*,*N*′,*N*′,*N*′-tetramethylguanidine.

Having established conditions for this cyclization reaction, we investigated the scope of the process (Table 1). Substrates

Table 1. Cyclizations of Divinyl Ketones to Cyclohexenones[a]

entry	substrate	product		t, °C	yield,[b] %
1			(**10**)	60	76
2			(**11**)	60	74
3			(**12**)	23	91 (R = *t*-Bu)
4			(**13**)	23	0[c] (R = *n*-Bu)
5[d]			(**14**)	23	91
6			(**15**)[e]	23	77
7			(**16**)[e]	60	92

[a] See the Supporting Information for detailed experimental procedures. [b] Isolated yields. [c] The substrate was isomerized to the corresponding allylic sulfone. [d] *N*-Methylpyrrolidine was utilized as a base. [e] Stereochemistry was established by X-ray crystallographic analysis.

bearing a substituent at the α-position to the carbonyl were well tolerated and cyclized to the corresponding cyclohexenones at 60 °C (entries 1 and 7). The reaction in entry 2 produced a cyclohexenone bearing a quaternary carbon center. In addition to aromatic groups, the *β*′-carbon of **1** could bear a tertiary alkyl group (entry 3). However, the isomeric substrate possessing a primary alkyl did not form cyclohexenone (**13**) (entry 4), but rather underwent rearrangement to the corresponding allylic sulfone.

The stereochemistry of the process (entries 5−7) was of particular interest because it could provide insights into the mechanism of the cyclization step, which could be viewed

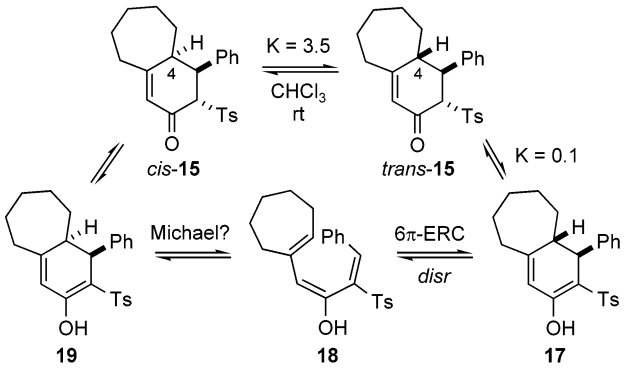
(10) Friedel−Crafts acylation of alkenes with *β*,*γ*-unsaturated acid chlorides produces, among other products, cyclohexenones. The formation of cyclohexenones was rationalized by electrocyclization of intermediate aluminum trienolates: Faure, R.; Pommier, A.; Pons, J. M.; Rajzmann, M.; Santelli, M. *Tetrahedron* **1992**, *48*, 8419−8430.

(11) ATPH is aluminum tris(2,6-diphenylphenoxide).

(12) (a) Starowieyski, K. B.; Pasynkiewicz, S.; Skowronska-Ptasinska, M. *J. Organomet. Chem.* **1975**, *90*, C43−C44. (b) Maruoka, K.; Itoh, T.; Sakurai, M.; Nonoshita, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 3588−3597. For a review, see: Saito, S.; Yamamoto, H. *J. Chem. Soc., Chem. Commun.* **1997**, 1585−1592.

as either a 6π-electrocyclic ring closure or an intramolecular Michael reaction.[13] Cyclization of the camphor-derived enone furnished a single diastereomer of the product (entry 5), whose stereochemistry was consistent with a disrotatory 6π-electrocyclization involving the exo face of the intermediate enolate.[7] The reaction in entry 6 appeared to be more complicated and produced a mixture of two diastereomers in a 78:22 ratio. Apparently, the observed product ratio reflects the thermodynamic stability of the two diastereomers, as a sample of pure *trans*-**15** gives rise to the same ratio of isomers upon standing in chloroform for 3 days at room temperature (Scheme 3).[14] A reasonable mechanism for

Scheme 3. Possible Mechanism for Epimerization of **15**

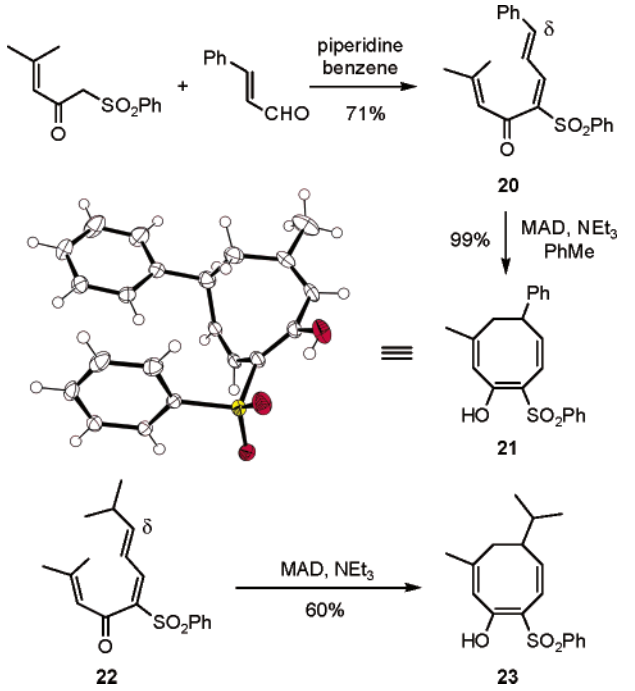


epimerization at C-4 of **15** involves the 6π-electrocyclic ring opening of enol **17**, which is in equilibrium with *trans*-**15**, followed by the ring closure of intermediate hexatriene **18**. However, transformation **18** → **19** cannot be explained by a thermal 6π-electrocyclization, which is a stereospecific disrotatory process.[15] The formation of *cis*-**15** presumably involves the addition of an extended enol to the electron-deficient double bond.

It should be noted that triethylamine significantly accelerates the interconversion of *cis*- and *trans*-**15**, which reach equilibrium distribution within 15 min at room temperature. In this particular case, the reaction probably proceeds via the ammonium enolate of **17**, as the 6π-electrocyclic ring opening of hexatrienes is known to be charge-accelerated.[16]

We imagined that the cyclization strategy outlined in Scheme 1 could be applied to the synthesis of other ring systems. We were delighted to discover that the reaction of sulfone **20** mediated by MAD (1.1 equiv) and NEt_3 (1.0 equiv) in toluene at room temperature afforded the cyclooctatriene **21** in 99% yield within 5 min (Scheme 4).

Scheme 4. Synthesis of Cyclooctane Derivatives



Moreover, the type of substitution at the δ-position was not limited to aromatic groups as demonstrated by the successful reaction of **22**. The formation of the eight-membered rings instead of the six-membered carbocycles provides indirect evidence for the importance of an electrocyclization pathway in the ring-forming step. Pericyclic reactions often choose to proceed through the symmetry-allowed transition states involving the longest conjugated chain.[17]

In summary, we demonstrated a new cyclization reaction of divinyl ketones that produces cyclohexenones. The insights gained in this study may be used for the synthesis of other ring systems, as we illustrated by the preparation of cyclooctane derivatives.

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Supporting Information Available: Experimental procedures, characterization data for new compounds, and X-ray data for *trans*-**15**, **16**, and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Aside from the stereochemical probe, it is hard to distinguish between the two mechanistic pathways because orbital interactions that favor Michael-type addition also enhance electrocyclization: Davies, I. W.; Marcoux, J.-F.; Kuethe, J. T.; Lankshear, M. D.; Taylor, J. D. O.; Tsou, N.; Dormer, P. G.; Hughes, D. L.; Houk, K. N.; Guner, V. *J. Org. Chem.* **2004**, *69*, 1298−1308.

(14) The same ratio of isomers was obtained when a sample of pure *trans*-**15** was submitted to the cyclization conditions.

(15) (a) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Academic Press: New York, 1970. (b) Okamura, W. H.; De Lera, A. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: New York, 1991; Vol. 5, pp 699−750.

(16) Evans, D. A.; Hart, D. J.; Koelsch, P. M. *J. Am. Chem. Soc.* **1978**, *100*, 4593−4594. See also: Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765−4766.

(17) See, for example: (a) Paquette, L. A.; Barrett, J. H. *J. Am. Chem. Soc.* **1966**, *88*, 2590−2591. (b) Goldstein, M. J.; Dai, S.-H. *J. Am. Chem. Soc.* **1973**, *95*, 933−935.