# Intramolecular Prins Reactions of Vinylcyclopropanes with Aldehydes and Ketones: A New Synthesis of Semicyclic Conjugated Dienes

Yinghui Liu, Nabi A. Magomedov*

Department of Chemistry, University of Rochester, Rochester, New York 14627-0216, USA
Fax +1(585)2760205; E-mail: magomedov@chem.rochester.edu

*Received 25 August 2005*

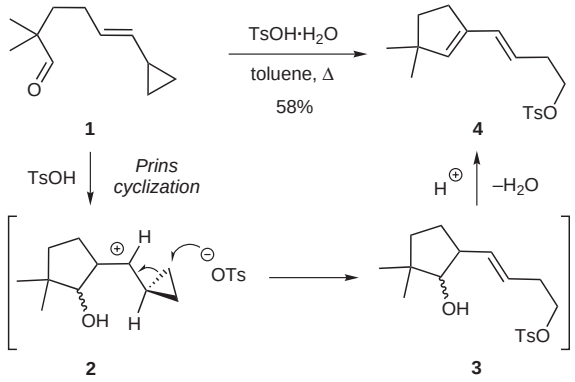
**Abstract:** Carbonyl compounds bearing pendant vinylcyclopropanes react with sulfonic acids to produce semicyclic conjugated dienes. These functionalized dienes can be readily elaborated into complex polycyclic compounds.

**Key words:** vinylcyclopropane, cyclizations, ring opening, eliminations, conjugated diene

Conjugated dienes are important building blocks for organic synthesis. In particular, semicyclic dienes, in which one of the olefins is endocyclic, are useful starting materials for the rapid assembly of complex polycyclic architectures.[1,2] Herein we demonstrate a new synthesis of semicyclic conjugated dienes proceeding through a one-pot sequence of an acid-mediated Prins cyclization of a vinylcyclopropane onto a carbonyl group, nucleophilic ring opening of the cyclopropane ring, and a regioselective dehydration reaction.

In the course of our investigation of acid-catalyzed intramolecular reactions of imines with nucleophilic alkenes,[3] we serendipitously discovered that aldehyde **1** reacted with *p*-toluenesulfonic acid in refluxing toluene to produce conjugated diene **4** in 58% yield as the only isolable product (Scheme 1).

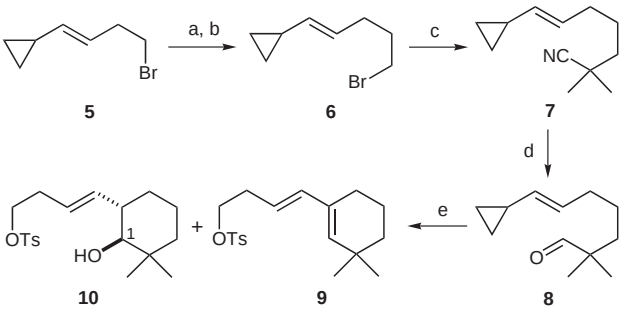
Presumably, the reaction commences with a nucleophilic attack of the electron-rich alkene onto the acid-activated carbonyl to generate cyclopropylcarbenium ion **2**.[4] This intermediate then undergoes cyclopropane ring opening with tosylate followed by dehydration of the resulting alcohol **3** to furnish the final diene. Notably, while sulfonic acids were found to result in clean reactions,[5] other protic acids such as trifluoroacetic acid or hydrobromic acid produced complex mixtures of products.




**Scheme 1**

An attractive feature of the diene products of type **4** is the presence of a strategically positioned leaving group, which can be used as a handle to introduce a dienophile moiety for subsequent cycloaddition chemistry. Realizing that this operationally simple synthesis of functionalized dienes may serve as a useful method for the preparation of complex compounds, we decided to explore it in more detail.

The utility of this cyclization for the preparation of vinylcyclohexenes was examined as outlined in Scheme 2. Aldehyde **8**, prepared from bromide **5**[6] using standard chemistry, cleanly reacted with *p*-toluenesulfonic acid to furnish the mixture of the expected diene **9** and alcohol **10** in 42% and 55% yields, respectively. Interestingly, when **10** was resubmitted to the reaction conditions, no dehydration was observed. This indicated that *trans*-**10** was not the precursor of **9**. Presumably diene **9** was produced from the diastereomer of **10** in which the vinyl and hydroxy groups are in the *cis* arrangement.

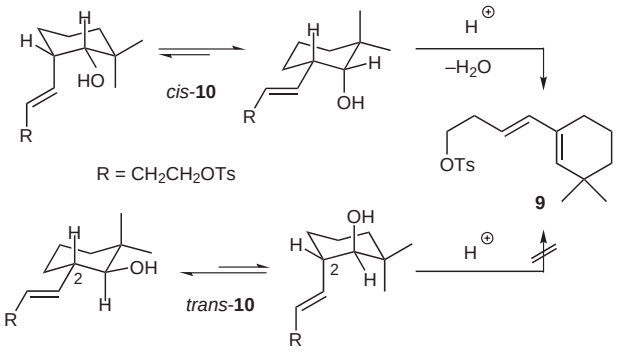



**Scheme 2** *Reagents and conditions*: a) Mg, $Et_2O$, then $(CH_2O)_n$, 78%; b) $PPh_3$, $Br_2$, pyridine, 85%; c) LDA/$Me_2CHCN$, 78%; d) DIBAL-H, 84%; e) TsOH, PhMe, 110 °C, 30 min.

These results can be rationalized on the basis of conformational analysis of the diastereomeric homoallylic alcohols formed upon Prins cyclization of **8** (Scheme 3).

Each of the diastereomeric cyclohexanols can exist in two chair conformations. One of the conformers of *cis*-**10** bears a hydroxy group antiperiplanar to the allylic proton, thereby satisfying the stereoelectronic requirement for an

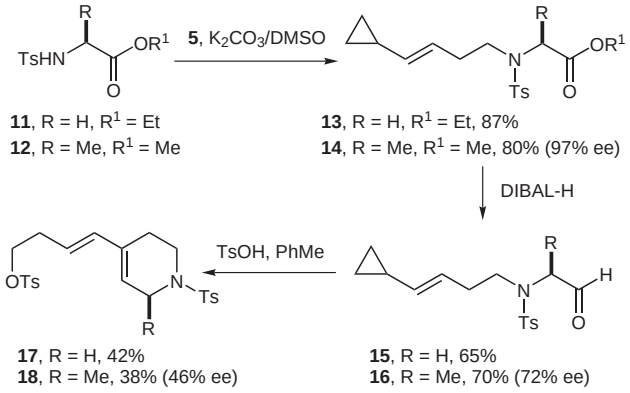
***SYNLETT*** 2005, No. 20, pp 3075–3078
Advanced online publication: 28.11.2005
DOI: 10.1055/s-2005-922752; Art ID: S08005ST




**Scheme 3**

E2 elimination reaction.[7] In contrast, *trans*-**10** cannot attain a chair conformation with the antiperiplanar arrangement of the hydroxy group and allylic hydrogen at C-2 and, as a consequence, survives under the reaction conditions.

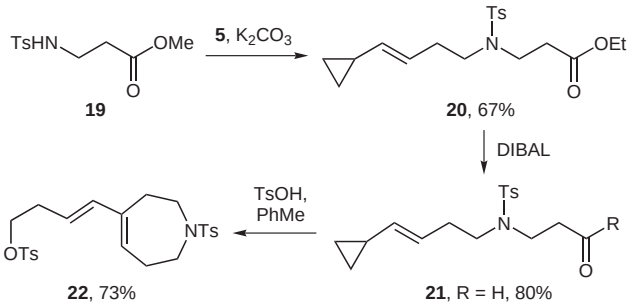
We then applied this strategy for the preparation of heterocyclic dienes, which could be of use for the synthesis of polycyclic nitrogen heterocycles. The substrate aldehydes **15** and **16** were readily prepared from α-amino acid derivatives **11** and **12** as outlined in Scheme 4.



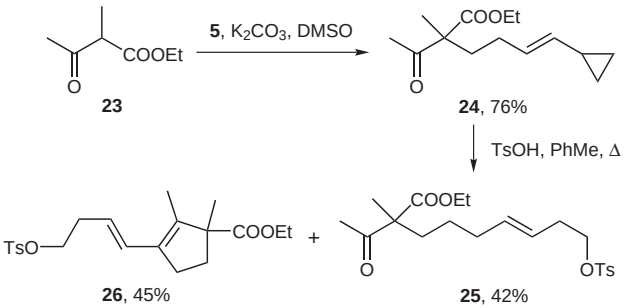

**Scheme 4**

Treatment of these aldehydes with *p*-toluenesulfonic acid in refluxing toluene produced the corresponding piperidine derivatives **17** and **18** in moderate yields. The reaction of the chiral non-racemic alanine derivative **16** was of particular interest, because enolizable α-amino aldehydes are exceptionally prone to racemization.[8] The cyclization of **16** (72% ee) occurred with partial racemization producing diene **18** with 46% ee. The formation of chiral non-racemic **18** suggests that the rate of the cyclization of **16** is faster than the rate of racemization. The reaction of β-amino acid derivative **21** was more efficient than reactions of substrates derived from the α-amino acids, producing azepane **22** in 73% isolated yield (Scheme 5).

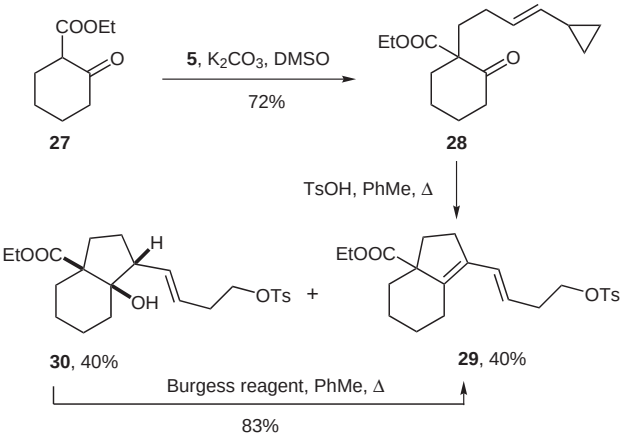
The use of ketones as carbonyl components in this reaction would significantly expand the scope of the process. Although Oshima found that ketones were not reactive in the intermolecular reactions of vinylcyclopropanes with ketones,[4] we hoped that under our conditions the intramolecular variant of this reaction might be successful. When the methyl ketone **21** (R = Me) was reacted with *p*-toluenesulfonic acid, a complex mixture of products was produced containing no desired diene. However, the derivatives of β-ketoesters possessing more electrophilic carbonyl groups were reasonably reactive (Scheme 6 and Scheme 7).




**Scheme 5**




**Scheme 6**

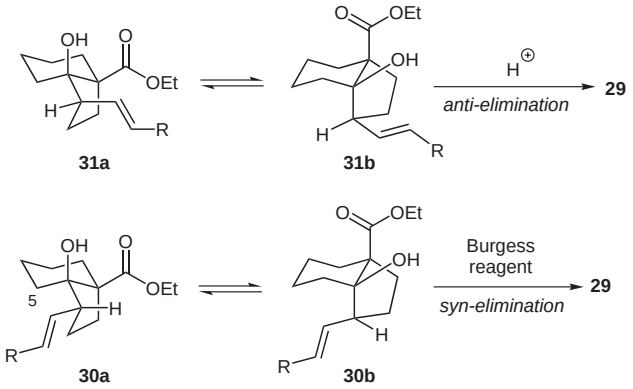



**Scheme 7**

Thus, cyclization of **24** yielded the desired diene **26** in addition to acyclic compound **25**. Evidently, **25** results from the direct reaction of vinylcyclopropane with sulfonic acid. In case of the less reactive carbonyl compounds, this process appears to compete with the cyclization reaction.

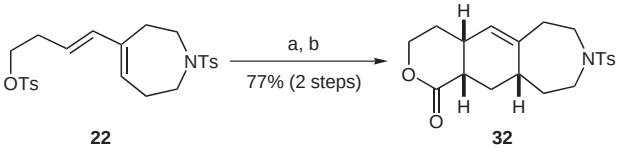
The cyclohexanone derivative **28** was more reactive in the cyclization process, producing an equimolar mixture of bicyclic diene **29** and alcohol **30** (Scheme 7).

Interestingly, while alcohol **30** failed to undergo dehydration to **29** when resubmitted to the reaction conditions, this transformation was readily accomplished by treatment with the Burgess reagent. These observations can be rationalized by the conformational analysis outlined in Scheme 8. The sterically favored nucleophilic attack of the alkene onto the activated ketone carbonyl can produce two diastereomeric *cis*-hydrindanes **30** and **31** (R = $CH_2CH_2OTs$). The *cis*-hydrindane system is conformationally flexible, thereby enabling the two diastereomeric alcohols to exist as a pair of conformers.[9] Compound **31** can attain a conformation with the antiperiplanar arrangement between the leaving group and allylic hydrogen (**31b**), and, as a consequence, readily forms diene **29** under acidic catalysis. This stereoelectronic requirement for an E2-like elimination reaction cannot be satisfied for isomer **30**.[10] Interestingly, although an axial OH group in conformer **30a** is antiperiplanar to the C-5 proton on the cyclohexane ring, no cyclohexene formation is observed under these reaction conditions. Evidently, the reaction conditions are sufficiently mild such that only regioselective dehydration involving elimination of the activated allylic proton occurs. Transformation of **30** to **29** was instead affected by reaction with the Burgess reagent via a *syn*-elimination mechanism.[11]




**Scheme 8**

Finally, we briefly examined the synthetic utility of the diene products for the preparation of polycyclic compounds. The cycloaddition reactions of unactivated semicyclic dienes sometimes suffer from poor reactivity and low regioselectivity.[12] However, employing the primary alkyl tosylate as a point of attachment of a dienophile followed by intramolecular cycloaddition would address the issues of reactivity and regioselectivity.[13] With this in mind, tosylate **22** was reacted with potassium acrylate (Scheme 9). Subsequent heating of the resulting ester to 150 °C cleanly produced tricycle **32** in 77% overall yield. The efficiency of this cycloaddition reaction is noteworthy because ester-tethered intramolecular Diels–Alder cycloadditions are often problematic due to the unfavorable conformation of the ester moiety.[14]




**Scheme 9** *Reagents and conditions*: a) potassium acrylate, DMF, 100 °C, 30 min; b) toluene, 150 °C, 17 h.

In summary, we have demonstrated the synthesis of semicyclic dienes involving sulfonic acid-mediated intramolecular Prins reactions of vinylcyclopropanes with aldehydes and ketones followed by regioselective dehydration reactions. The products of these reactions bear a primary alkyl sulfonate group, which can be employed to introduce an internal dienophile for the preparation of complex polycyclic compounds by cycloaddition chemistry.

**Representative Procedure; Synthesis of 22**

To a solution of 84 mg (0.26 mmol) of aldehyde **21** (R = H) in 50 mL of toluene was added 46 mg (0.24 mmol) of *p*-toluenesulfonic acid monohydrate. The reaction mixture was refluxed for 30 min, after which time TLC indicated complete consumption of starting aldehyde. The reaction mixture was cooled down to r.t., and washed with 10 mL of sat. aq $NaHCO_3$. The organic layer was separated, dried over $MgSO_4$, and concentrated in vacuo. The residue was flash-chromatographed over silica gel (EtOAc–hexane, 1:2) to provide 83 mg (73%) of diene **22** as thick colorless oil. IR (neat): 2924, 1597, 1452, 1358, 1336, 1174, 1159, 1095 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 2.34–2.45 (m, 6 H), 2.42 (s, 3 H), 2.45 (s, 3 H), 3.25–3.29 (m, 4 H), 4.02 (t, *J* = 6.6 Hz, 2 H), 5.33 (dt, *J* = 15.7, 6.9 Hz, 1 H), 5.70 (t, *J* = 6.2 Hz, 1 H), 5.97 (d, *J* = 15.7 Hz, 1 H), 7.90 (d, *J* = 8.2 Hz, 2 H), 7.33 (d, *J* = 8.2 Hz, 2 H), 7.65 (d, *J* = 8.2 Hz, 2 H), 7.77 (d, *J* = 8.2 Hz, 2 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 21.6, 21.7, 28.4, 28.6, 32.3, 46.8, 47.5, 69.9, 121.1, 127.2, 127.9, 129.8, 129.9, 130.6, 133.1, 135.8, 136.8, 140.1, 143.4, 144.9. HRMS (EI): *m/z* calcd for $C_{24}H_{29}NO_5S_2$ [$M^+$]: 475.1487; found: 475.1485.

**Synthesis of 32**

To a solution of 67 mg of diene **22** (0.14 mmol) in 2 mL of dry DMF was added 77 mg (0.70 mmol) of potassium acrylate. The mixture was heated at 100 °C for half an hour, after which time TLC indicated complete consumption of starting tosylate. The reaction mixture was cooled down to r.t., diluted with 10 mL of a 1:1 mixture of EtOAc and hexane, and washed with four 3-mL portions of $H_2O$. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was dissolved in 2 mL of toluene, hydroquinone (1 mg) was added, and the mixture was heated at 150 °C in a sealed tube for 17 h. The reaction mixture was cooled down to r.t., concentrated in vacuo, and the residue was flash-chromatographed over silica gel (EtOAc–hexane 1:1, then 2:1) to provide 40 mg (77% yield) of tricycle **32** as thick colorless oil. IR (neat): 2960, 2920, 2852, 1724, 1259, 1157, 1091 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.58–1.76 (m, 3 H), 1.82–1.93 (m, 2 H), 2.00 (ddd, *J* = 12.9, 4.5, 4.5 Hz, 1 H), 2.33–2.58 (m, 4 H), 2.42 (s, 3 H), 2.79 (ddd, *J* = 10.9, 6.8, 4.1 Hz, 1 H), 3.10 (ddd, *J* = 11.2, 10.3, 3.2 Hz, 1 H), 3.21 (ddd, *J* = 12.8, 10.8, 2.0 Hz, 1 H), 3.26–3.35 (m, 2 H), 4.24 (ddd, *J* = 11.2, 10.3, 3.2 Hz, 1 H), 4.37 (ddd, *J* = 11.2, 4.1, 4.1 Hz, 1 H), 5.32 (s, 1 H), 7.30 (d, *J* = 8.2 Hz, 2 H), 7.64 (d, *J* = 8.2 Hz, 2 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 21.7, 27.9, 32.0, 32.9, 33.9, 37.1, 38.0, 39.6, 47.7, 48.2, 68.8, 125.5, 127.3, 129.9, 136.1, 141.8, 143.4, 173.9. HRMS (EI): *m/z* calcd for $C_{20}H_{25}NO_4S$ [$M^+$]: 375.1504; found: 375.1501.

## Acknowledgment

We thank the University of Rochester for support of this work.

## References

(1) Fringuelli, F.; Taticchi, A. *Dienes in the Diels–Alder Reaction*; Wiley: New York, **1990**.
(2) For recent examples, see: (a) Mander, L. N.; McLachlan, M. M. *J. Am. Chem. Soc.* **2003**, *125*, 2400. (b) Barriault, L.; Thomas, J. D. O.; Clement, R. *J. Org. Chem.* **2003**, *68*, 2317. (c) Van Cauwenberge, G.; Gao, L.-J.; Van Haver, D.; Milanesio, M.; Viterbo, D.; De Clercq, P. J. *Org. Lett.* **2002**, *4*, 1579. (d) Jung, M. E.; Davidov, P. *Angew. Chem. Int. Ed.* **2002**, *41*, 4125. (e) Sestelo, J. P.; Real, M. M.; Sarandeses, L. A. *J. Org. Chem.* **2001**, *66*, 1395.
(3) Magomedov, N. A. *Org. Lett.* **2003**, *5*, 2509.
(4) Oshima recently reported intermolecular Prins-type reactions of vinylcyclopropanes with aldehydes mediated by a combination of $TiCl_4$ and *n*-$Bu_4NI$. See: Tsuritani, T.; Shinokubo, H.; Oshima, K. *Synlett* **2002**, 978.
(5) The use of methanesulfonic acid in the reaction with **1** produced the corresponding mesylate in 48% yield.
(6) Julia, S.; Julia, M.; Graffin, P. *Bull. Soc. Chim. Fr.* **1964**, 3218.
(7) (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, **1983**, 252. (b) Bartsch, R. A.; Zavada, J. *Chem. Rev.* **1980**, *80*, 453.
(8) Myers, A. G.; Zhong, B.; Movassaghi, M.; Kung, D. W.; Lanman, B. A.; Kwon, S. *Tetrahedron Lett.* **2000**, *41*, 1359.
(9) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, **1994**, 775.
(10) It is commonly accepted that acid-catalyzed dehydrations of tertiary alcohols occur via an E1 mechanism: (a) Banthorpe, D. V. *Elimination Reactions*; Elsevier: New York, **1963**, 145–156 . However, the reluctance of **30** to undergo the acid-catalyzed dehydration suggests that the presumed elimination **31** → **29** is unlikely to proceed through a free carbocationic intermediate. We suppose that the elimination step, which involves an intermediate oxonium species, lies on the carbocationic side of the E2 mechanistic spectrum with the tosylate anion serving as a weak base. It is well known that the weak base-mediated E2 processes display strong preference for *anti*-elimination: (b) Ford, W. T. *Acc. Chem. Res.* **1973**, *6*, 410.
(11) Burgess, E. M.; Penton, H. R. Jr.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.
(12) See, for example: (a) Markgraf, J. H.; Greeno, E. W.; Miller, M. D.; Zaks, W. J.; Lee, G. A. *Tetrahedron Lett.* **1983**, *24*, 241. (b) Tanis, S. P.; Abdallah, Y. M. *Synth. Commun.* **1986**, *16*, 251.
(13) (a) Ciganek, E. *Org. React.* **1984**, *32*, 1. (b) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183.
(14) (a) Saito, A.; Ito, H.; Taguchi, T. *Org. Lett.* **2002**, *4*, 4619. (b) Boeckman, R. K.; Demko, D. M. *J. Org. Chem.* **1982**, *47*, 1789. (c) Martin, S. F.; Williamson, S. A.; Gist, R. P.; Smith, K. M. *J. Org. Chem.* **1983**, *48*, 5170.