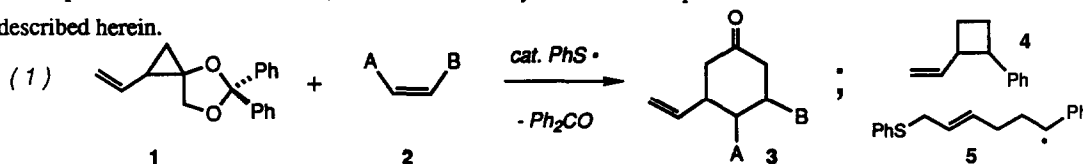


PHENYLTHIO RADICAL MEDIATED SYNTHESIS OF SUBSTITUTED 3-VINYLCYCLOHEXANONES.  
INTERRUPTION OF THE RING-OPENING POLYMERIZATION OF 1,3-DIOXOLAN-4-YL RADICALS.

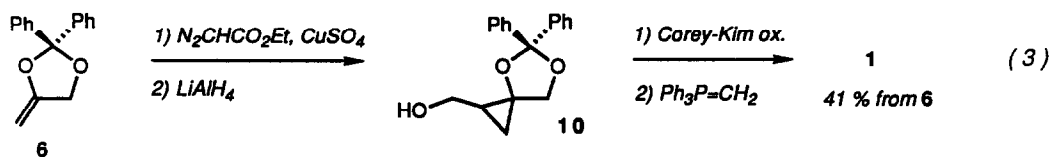
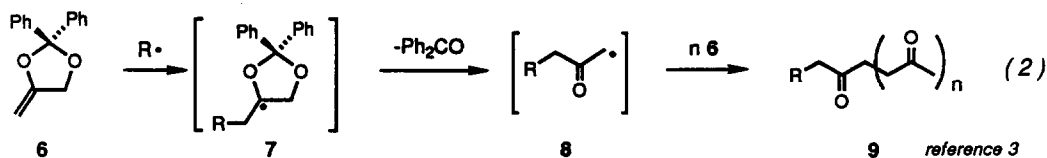
Ken S. Feldman\* and Antonio Kuok Keong Vong  
Department of Chemistry, The Pennsylvania State University,  
University Park, PA 16802

**Abstract:** Substituted 3-vinylcyclohexanones result from the radical mediated combination of functionalized alkenes with a vinylcyclopropyl-1,3-dioxolane reagent.

The phenylthio radical mediated combination of substituted vinylcyclopropanes with either functionalized alkenes or alkynes furnishes a broad spectrum of vinylcyclopentanoid products.<sup>1</sup> Attributes of this [3-atom + 2-atom] addition process include tolerance to a wide range of functionality, complete regioselectivity, and in favorable cases, moderate levels of stereoselectivity upon bond formation. Extension of this transformation to include four atom components might provide access, upon addition with appropriate olefinic partners, to an analogous collection of highly functionalized vinylcyclohexane products. We have developed a novel vinylcyclohexanone synthesis based on this strategy, which utilizes the vinylcyclopropyl 1,3-dioxolane species **1** as a precursor to the four atom component, eq (1). Preliminary experiments which probe the scope, limitations, mechanism, and stereochemistry of this multistep free radical mediated transformation are described herein.



Initial attempts to effect vinylcyclohexane synthesis by direct analogy with the successful vinylcyclopentane studies utilized the vinylcyclobutane **4** as a substrate. However, screening experiments with representative alkenes were not fruitful-presumably, an inability to generate the requisite bishomoallylic radical **5** under the reaction conditions thwarted this simple approach.<sup>2</sup> Therefore, an alternative strategy for generating a bishomoallylic radical related to **5** was developed, which ultimately resulted in the successful vinylcyclohexanone synthesis described in eq (1). This strategy relied on coupling successful vinylcyclopropane chemistry<sup>1</sup> with the ring opening polymerization chemistry of 1,3-dioxolan-4-yl radicals **7** recently reported by Endo,<sup>3</sup> eq (2). Use of the "modified" vinylcyclopropane **1** permits interruption of the dioxolane polymerization process, and allows interception of a key bishomoallylic radical (*vide infra*) by an alkene, leading to the desired vinylcyclohexanone product **3**.



The vinylcyclopropyldioxolane **1** was prepared from the alkenyldioxolane **6**<sup>3</sup> as shown in eq (3). Immediate methylenation of the very sensitive aldehyde formed by oxidation of alcohol **10** was critical for successful preparation of the substrate **1**. The phenylthio radical catalyzed addition of alkenes **2** to the vinylcyclopropane **1** proceeded with equal facility either in benzene (15 mM, 5eq. alkene, sealed tube) at 135°C, or in refluxing chlorobenzene<sup>4</sup> (Table). The product vinylcyclohexanones **3** were chromatographically isolated and their stereochemistry was ascertained by an analysis of coupling constants and DNOE data.<sup>5</sup>

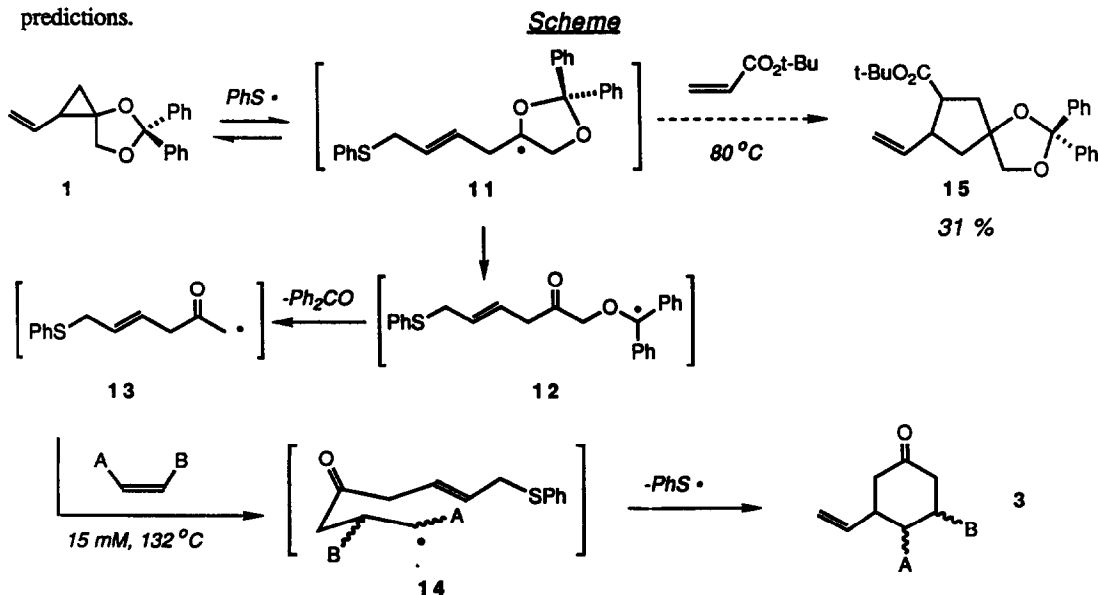
**Table** Vinylcyclohexanones formed from the addition of alkenes **2** to reagent **1**.

alkene	vinylcyclohexanone products <sup>a</sup>		yield <sup>b</sup>
a) <b>2a</b> R = CH <sub>3</sub> b) <b>2b</b> R = t-Bu c) <b>2c</b> R = 1-adamantyl		<b>3a</b> 1.1 : 1 <b>3b</b> <b>3c</b> 1.9 : 1 <b>3d</b> <b>3e</b> 1.8 : 1 <b>3f</b>	46 % 51 % 50 %
d) <b>2d</b> R = OBU e) <b>2e</b> R = OCOT-Bu f) <b>2f</b> R = Ph g) <b>2g</b> R = SO <sub>2</sub> Ph		<b>3g</b> 2.2 : 1 <b>3h</b> <b>3i</b> 1.4 : 1 <b>3j</b> <b>3k</b> 1.1 : 1 <b>3l</b> <b>3m</b> 2.7 : 1 <b>3n</b>	46 % 48 % 52 % 42 %
h) <b>2h</b>		<b>3o</b> 13 : 1 <b>3p</b> 1 <b>3q</b> 5 : 1 <b>3r</b> 13	36 %
i) <b>2i</b>		<b>3s</b> 1.6 : 1 <b>3t</b>	17 %

a) All reactions were run under the conditions described in footnote 4. b) All yields refer to isolated, chromatographically and spectroscopically pure material.<sup>5</sup>

An examination of the results reported in the Table reveal several notable characteristics of this transformation. The reaction appears tolerant of electron deficient, electron rich and conjugated alkenes, and works with either mono- or 1,2-disubstituted olefinic addends. Unfortunately, only moderate yields were obtained with all alkenes, although no other characterizable compounds could be isolated from the reactions. Furthermore, stereoselectivity is negligible in many cases and does not appear responsive to the steric bulk of the alkenyl substituent (compare entries *a, b, c, f*).<sup>6a</sup> Nevertheless, the ease of synthesis of substrate **1**, and the ready conversion to functionalized vinylcyclohexanones which might otherwise be difficult to prepare in a concise manner, suggests that this chemistry may find application in the synthesis of appropriately functionalized natural products.

A mechanistic proposal, which combines established vinylcyclopropane chemistry<sup>1,6b,c</sup> with the dioxolane chemistry described in eq (2), is shown in Scheme. Salient features of this proposal include 1) conversion of the homoallylic radical **12** into the desired bishomoallylic radical **13** via benzophenone extrusion, and 2) selectivity for alkene addition only to radical **13** under the defined experimental conditions.<sup>4</sup> Evidence consistent with this scheme was obtained by examining the products formed under alternative experimental conditions. Thus, reaction with methacrylate in refluxing benzene, rather than chlorobenzene, led to isolation of the vinylcyclopentane product **15**. In this instances, interception of radical intermediate **11** prior to successful generation of the bishomoallylic radical **13** accounts for formation of the cyclopentanoid products. Product stereochemistry is established during the cyclization of the substituted 6-heptenyl radical **14**. Without an equational "anchor" at another site along the carbon backbone, the minimal selectivity observed upon formation of the vinylcyclohexanone products is in accord with much experimental evidence<sup>7a-d</sup> and computational<sup>7e</sup> predictions.



In summary, we have developed a simple synthesis of substituted 3-vinylcyclohexanones which relies on a combination of functionalized alkenes with a vinylcyclopropyldioxolane reagent **1**. This transformation is believed to proceed through a multi-step mechanism featuring several free radical intermediates. Tolerance to a range of electronically dissimilar functional groups and complete regiochemical control of bond formation may ultimately provide convenient access to structurally related natural product targets.

**Acknowledgment:** We thank the National Institutes of Health (GM37681) and the National Science Foundation (CHE-8657016) for financial support.

## References

- 1) Feldman, K.S.; Romanelli, A.L.; Ruckle, R.E., Jr.; Miller, R.F. *J. Am. Chem. Soc.*, **1988**, *110*, 3300.
- 2) The much slower rate of cyclobutylcarbinyl radical isomerization ( $k=2.4 \times 10^3 \text{ s}^{-1} (60^\circ\text{C})$ ) vs. the corresponding cyclopropylcarbinyl case ( $k=1.4 \times 10^9 (70^\circ\text{C})$ ) is probably responsible for the lack of desired reactivity. See Beckwith, A.L.J.; Moad, G. *J. Chem. Soc., Perkin Trans. II*, **1980**, 1083, and references cited therein.
- 3) Hiraguri, Y.; Endo, T. *J. Am. Chem. Soc.*, **1987**, *109*, 3779.
- 4) A deoxygenated solution of  $\text{Ph}_2\text{S}_2$  (76 mg, 0.25 mmol) and AIBN (6 mg, 0.04 mmol) in 5 mL of chlorobenzene was added slowly via motor driven syringe to a refluxing, deoxygenated solution of vinylcyclopropane **1** (96 mg, 0.35 mmol) and t-Bu acrylate (222 mg, 1.74 mmol) in 24 mL of chlorobenzene under Ar with concomitant sunlamp irradiation. When TLC indicated consumption of substrate **1** (ca. 2 mL of  $\text{Ph}_2\text{S}_2$  solution added), the reaction solution was concentrated in vacuo, and the residue was purified by flash chromatography on  $\text{SiO}_2$  with  $\text{Et}_2\text{O}$ /hexane as eluent to afford mg (51%) of vinylcyclohexanones **3c/d** as a colorless oil. Samples of individual stereoisomers were obtained by HPLC chromatography on  $\text{SiO}_2$  with  $\text{Et}_2\text{O}$ /hexane as eluent.
- 5) All new compounds exhibited spectral data ( $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, IR, MS, HRMS and/or combustion analysis) fully consistent with the assigned structures. Coupling constants, and in some cases DNOE measurements, between the methine hydrogens adjacent to the vinyl and alkene-derived substituents, permitted unambiguous assignment of stereochemistry.
- 6) a) Feldman, K.S.; Fisher, T.E. *Tetrahedron*, **1989**, *45*, 2969. b) Feldman, K.S.; Simpson, R.E.; Parvez, M. *J. Am. Chem. Soc.*, **1986**, *108*, 1328. c) Feldman, K.S.; Simpson, R.E. *J. Am. Chem. Soc.*, **1989**, *111*, 4878.
- 7) a) Bachi, M.D.; Hoornaert, C. *Tetrahedron Lett.*, **1981**, *22*, 2689. b) Buchi, G.; Wuest, H. *J. Org. Chem.*, **1979**, *44*, 546. c) Bakuzis, P.; Campos, O.O.S.; Bakuzis, M.L.F. *J. Org. Chem.*, **1976**, *41*, 3261. d) Goltshalk, P.; Neckers, D.C. *J. Org. Chem.*, **1985**, *50*, 3498. e) Beckwith, A.L.J.; Schiesser, C.H. *Tetrahedron*, **1985**, *41*, 3925.

(Received in USA 1 November 1989)