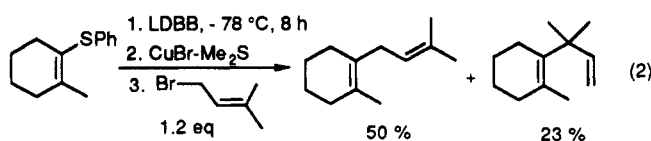


As can be seen from Scheme I, 1-lithio-2-methylcyclohexene (5) can be readily produced by the new procedure. This compound cannot be generated by the Bond process since the sulfonylhydrazone of ketone 1 decomposes to the isomeric 1-lithio-6-methylcyclohexene (4). The latter is also available, albeit by a slightly longer route, involving the methylation of 6 (itself available from cyclohexanone, or via other routes) by Trost's procedure,⁶ followed by reductive lithiation (Scheme I).

The reductive lithiation of vinyl phenyl sulfides (eq 1) with LDBB in THF occurs immediately at -78°C for seven- and eight-membered rings and in 2 h for unsubstituted cyclohexenyl sulfides; substituted six-membered rings require 4–8 h to form the vinylolithiums. Reduction with lithium 1-(dimethylamino)naphthalenide (LDMAN),^{12,13} which offers the advantage of an acid-extractable byproduct (DMAN), is very satisfactory for the production of cycloheptenyllithium ($1/2$ h reduction at -55°C yields 92% of cycloheptene-1-carboxaldehyde) but it requires 6–12 h at -60°C for six-membered rings and provides about 15% lower yields than LDBB; however, the reduction of substituted cyclohexenyl phenyl sulfides with this reagent is impractically slow.

As shown in Table I, attack of numerous electrophiles on the produced vinylolithiums results in good to excellent yields of desired products including allylic alcohols, vinylsilanes, and enals. Alkylation of 5 with 1-iodohexane proceeded in good yield but required 2.2 equiv of the alkylating agent due to the consumption of 1 equiv by the thiophenoxide ion; the products were easily separated by chromatography. In previous work on the methylation of an organolithium produced by reductive lithiation,¹² a heterocuprate¹⁴ was used to avoid the necessity of an extra equivalent of methyl iodide. In the present case 1-iodohexane was too unreactive to alkylate the heterocuprate formed by treatment of 5 with $\text{CuBr}-\text{Me}_2\text{S}$ at temperatures below the decomposition point of the cuprate. However, the heterocuprate reacted instantaneously with allylic bromides at -78°C (e.g. eq 2).



(11) Labiad, B. Villemin, D. *Synthesis* 1989, 143.

(12) Cohen, T.; Matz, J. R. *Synth. Commun.* 1980, 10, 311.

(13) For a description of the preparation and use of this reagent, see: Cohen, T.; Sherbine, J. P.; Hutchins, R. R.; Lin, M.-T. *Organomet. Synth.* 1986, 3, 361.

(14) Posner, G. H.; Whitten, C. E.; Sterling, J. J. *J. Am. Chem. Soc.* 1973, 95, 7788.

The heterocuprate was also extremely useful in providing exclusive 1,4 addition to enones,¹⁵ whereas 1,2 addition to enals and enones was readily achieved with the vinylolithium (Table I). The latter reaction leads to synthetically useful precursors for Nazarov¹⁶ rearrangements.

The brevity, low cost, and high yields obtained should make this procedure a particularly practical alternative to the Bond and Wulff processes for producing cyclohexenyl-, cycloheptenyl-, and cyclooctenyllithiums.¹⁷ It should be particularly suitable as an industrial process.

Acknowledgment. We thank the National Institutes of Health for financial support and Dr. Kasi Somayajula for recording the mass spectra.

Supplementary Material Available: Typical experimental procedures and spectral data for the products (6 pages). Ordering information is given on any current masthead page.

(15) Kende first reported the preparation of a vinylcuprate by a Bond type reaction by using *tert*-butyllithium in order to avoid the use of TMEDA: Kende, A. S.; Jungheim, L. N. *Tetrahedron Lett.* 1980, 21, 3849. However, surprisingly, Heathcock appears to have been successful in preparing a vinylolithium for Cu^{I} -induced conjugate addition by the use of *n*-butyllithium in THF rather than in a solvent containing TMEDA: Hoagland, S.; Morita, Y.; Bai, D. L.; Märki, H.-P.; Kees, K.; Brown, L.; Heathcock, C. H. *J. Org. Chem.* 1988, 53, 4730.

(16) Santelli-Rouvier, C.; Santelli, M. *Synthesis* 1983, 429.

(17) Lithium di-*tert*-butylbiphenylide is prepared as follows. To an oven-dried three-neck round-bottom flask, equipped with a glass stirring bar, rubber septum, and argon inlet, is added THF (7 mL) and di-*tert*-butylbiphenyl (DBB, 0.85 g, 3.2 mmol). Lithium ribbon is prepared by scraping the dark oxide coating off the surface while it is immersed in mineral oil. The metal is dipped in pentane, in order to remove the oil, and then weighed (24 mg, 3.4 mmol) in a tared beaker containing mineral oil. The metal is cut into small very shiny pieces while immersed in mineral oil. The small lithium pieces are dipped again in pentane and quickly added to the THF/DBB mixture while the flask is rapidly being purged with argon. The mixture is cooled to 0°C and vigorously stirred for 4–5 h. The dark green-blue color of the radical anion appears within 10 min and formation is complete in 4–5 h. This procedure produces a 0.45 M solution of radical anion. A typical reductive lithiation procedure follows. To a solution of LDBB (5.25 mL of a 0.40 M solution in THF, 2.1 mmol) at -78°C , 1-(phenylthio)-1-cyclohexene (0.190 g, 1.00 mmol) in THF (4 mL) is slowly added via syringe pump over a 0.50-h period. The deep blue-green reaction mixture is stirred at -78°C for 2 h, during which time the color slowly changes to red. Cyclohexanecarboxaldehyde (0.133 mL, 0.123 g, 1.10 mmol) in THF (2 mL) is added dropwise until the mixture turns yellow. The reaction is quenched at -78°C with brine, and the mixture is warmed to room temperature. Following extraction with ether (3×20 mL), the combined organic layer is washed with 10% NaOH (3×10 mL, or at least until all of the thiophenol is removed) and brine. The organic layer is dried (MgSO_4), and the solvent is removed by rotary evaporation. Radial chromatography with hexane is used to recover DBB from the reaction mixture, followed by 5% ethyl acetate/hexane to give a 79% yield of 1-(1'-cyclohexenyl)-1-cyclohexylmethanol.

Oxidative Cyclization of δ,ϵ - and ϵ,ζ -Unsaturated Enol Silyl Ethers

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Summary: Oxidative cyclization of δ,ϵ - and ϵ,ζ -unsaturated enol silyl ethers of aryl ketones with cupric triflate and cuprous oxide or ceric ammonium nitrate and sodium bicarbonate in acetonitrile provides tricyclic ketones stereoselectively.

We have recently described oxidative free-radical cyclizations which are initiated by oxidation of a β -dicarbonyl

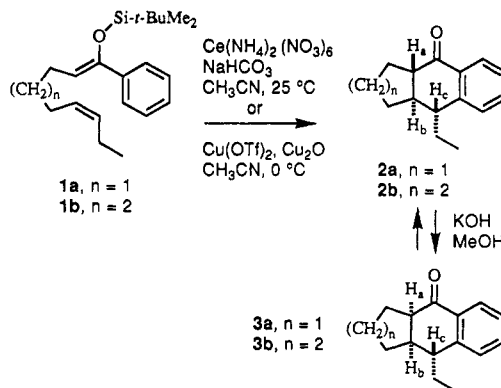
compound with $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$.¹ The scope of this reaction would be extended if the reaction could be initiated

(1) (a) Snider, B. B.; Mohan, R. M.; Kates, S. A. *J. Org. Chem.* 1985, 50, 3659. (b) Snider, B. B.; Mohan, R. M.; Kates, S. A. *Tetrahedron Lett.* 1987, 28, 841. (c) Mohan, R.; Kates, S. A.; Dombroski, M.; Snider, B. B. *Ibid.* 1987, 28, 845. (d) Dombroski, M. A.; Kates, S. A.; Snider, B. B. *J. Am. Chem. Soc.* 1990, 112, 2759. (e) Kates, S. A.; Dombroski, M. A.; Snider, B. B. *J. Org. Chem.* 1990, 55, 2427.

by oxidation of a monocarbonyl compound. Oxidative cyclization of ϵ,ζ -unsaturated ketones will probably not be practical, since intermolecular oxidative additions of ketones to alkenes are successful² only when a large excess of ketone is used to preclude further oxidation of the product. Oxidative cyclization of δ,ϵ - and ϵ,ζ -unsaturated enolates or enol ethers did appear to be viable since the oxidative coupling of enolates or enol ethers with copper(II)³⁻⁵ or cerium(IV)^{6,7} can be carried out without further oxidation of the product diketones. We expected that conditions could be developed in which intramolecular addition of an enol radical, or cation radical, prepared by oxidation of an enol ether, to an alkene would be faster than intermolecular coupling with a second enol ether. These cyclizations should be very distinct from the palladium(II)-mediated cyclizations of unsaturated enol silyl ethers studied by Saegusa⁸ and Kende.⁹

We have found that oxidative cyclization of δ,ϵ - and ϵ,ζ -unsaturated enol silyl ethers can be carried out with either copper(II) or cerium(IV).¹⁰ Treatment of enol silyl ether **1a**^{11,12} with 2 equiv of $\text{Cu}(\text{OTf})_2$ and excess Cu_2O in CH_3CN at 0 °C, as described by Kobayashi for the oxidative coupling of trimethylsilyl enol ethers,⁴ gives 90% of a 20:1 mixture of **2a** and **3a**. Similarly, treatment of **1a** with 2 equiv of ceric ammonium nitrate and excess NaHCO_3 in acetonitrile at 25 °C⁶ gives 73% of a 20:1 mixture of **2a** and **3a**.

The stereochemistry of **2a** is assigned based on $J_{\text{H}_a,\text{H}_b} = 13.3$ Hz and $J_{\text{H}_b,\text{H}_c} = 10.7$ Hz, which require that H_a , H_b , and H_c are all axial. Equilibration of **2a** with KOH in MeOH gives a 7.7:1 mixture of **3a** and **2a**, thereby establishing the stereochemistry of the minor product **3a** as



successful, providing a complex mixture containing 42% of a 4.3:1 mixture of **2b** and **3b** and 2% of the unsaturated α -nitrooxy ketone. The stereochemistry of **2b** is assigned based on $J_{\text{H}_a,\text{H}_c} = 10.4$ Hz, indicating that H_b and H_c are axial. Equilibration of **2a** with KOH in MeOH provides a 2.5:1 mixture of **3b** and **2b**. MM2¹⁵ calculations suggest that **3b**¹⁶ is more stable by 1.3 kcal/mol.

Oxidative cyclization of **4**¹¹ with cupric triflate provides 90% of a 3.2:1 mixture of **5** and **6**. Oxidative cyclization with ceric ammonium nitrate provides 75% of a similar mixture of **5** and **6**. The stereochemistry of **5** and **6** follow from the coupling constants and the absence of significant epimerization on treatment with KOH in MeOH.¹⁸

Reaction mixtures are more complex with a terminal alkene. Oxidative cyclization of **7**¹¹ with cupric triflate gives 13% of **8**,¹⁹ 7% of tricyclic ketone **11**,²⁰ and 7% of recovered ketone. Oxidative cyclization of **7** with ceric ammonium nitrate is more efficient giving 30% of **8**, 15% of equatorial nitrate **9**, 29% of axial nitrate **10**, 3% of tricyclic ketone **11**, and 1% of the acyclic α -nitrooxy ketone.

Oxidative cyclization of enol ethers derived from dialkyl ketones proceed in lower yield. Oxidative cyclization of **12** with ceric ammonium nitrate affords 20% of **13** and 2% of **14**.

(15) Molecular mechanics calculations were carried out with MODEL version KS 2.94 provided by Prof. Kosta Steliou, University of Montreal.

(16) Calculations suggest that the cis isomers **3a** and **3b** are more stable in the conformation with an axial ethyl group to avoid steric interactions between the ethyl group and the outside rings. All couplings to H_a , H_b , and H_c in **3a** and **3b** are small as would be expected for this conformer since there are no axial-axial couplings. The ethyl group in the trans isomers **2a** and **2b** must be equatorial. Steric repulsion is calculated to be minimized if the ethyl group is anti to H_c . This analysis is confirmed by the unusually small coupling of 3.6–3.8 Hz between H_c and the CH_2 group and the absorption of the methyl group in the ¹³C NMR spectra upfield at δ 8.1 and 7.6 in **2a** and **2b** due to two gauche butane interactions. The methyl groups absorb at δ 12.3 and 12.8 in **3a** and **3b**.

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(18) In **5**, $J_{\text{H}_a,\text{H}_b} = 13.6$ Hz and $J_{\text{H}_a,\text{H}_c} = 8.7$ Hz requiring that all three hydrogens are pseudoaxial. Equilibration with KOH in methanol gives $\approx 10\%$ of a third stereoisomer which is calculated to be less stable than **5** by 0.5 kcal/mol. In **6**, $J_{\text{H}_a,\text{H}_b} = 8.2$ Hz and $J_{\text{H}_a,\text{H}_c} = 5.5$ Hz, indicating that the ring fusion is cis. Equilibration gives none of the fourth stereoisomer which is calculated to be less stable than **6** by 2.7 kcal/mol.

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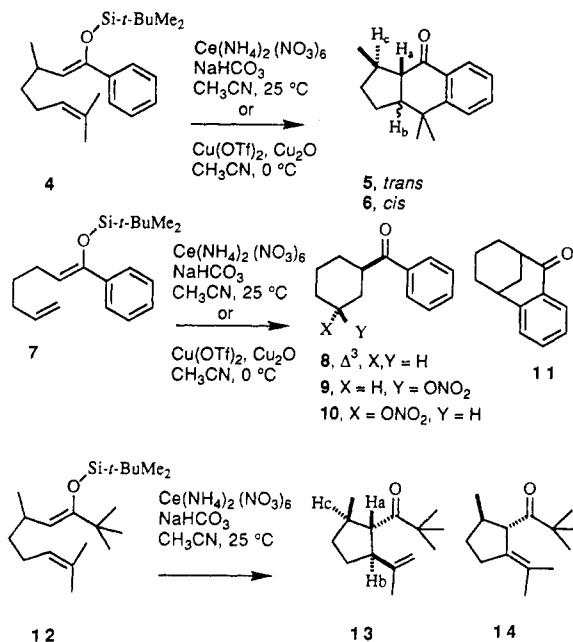
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(11) Enol silyl ethers were prepared from the ketone by the procedure of Mander.¹³ The ketone precursors to **1a**, **1b**, **4**, and **12** were prepared by the addition of phenylmagnesium bromide or methyllithium to the aldehyde followed by Jones oxidation. The ketone precursor to **7** was prepared by addition of 5-hexenylmagnesium bromide to benzonitrile.¹⁴

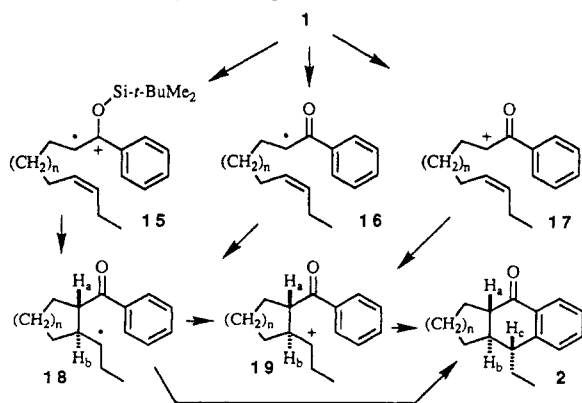
(12) No cyclic products could be obtained from oxidation of the enolate corresponding to **1a** with cupric triflate. Oxidation of the trimethylsilyl enol ether gave **2a** in low yield.

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Mechanistically, the tandem cyclizations of 1, 4, and 7 are complex. Two one-electron oxidations, two cyclizations, and loss of the silyl group must occur. Some information about the order of these steps can be inferred from the products isolated. Reaction of the metal with the enol silyl ether could give 15 by a one-electron oxidation, 16 by a one-electron oxidation and loss of the silyl group, or 17 by two one-electron oxidations and loss of the silyl group. Formation and cyclization of a free enol radical such as 16 is unlikely since Curran and Chang have shown that cyclization of the enol radical which would be generated from 7 gives a 3:1 mixture of 5-exo and 6-endo products²¹ while cyclization of 7 gives only 6-endo products. Formation of an enol cation such as 17 is unlikely since cyclization of enol cations leads preferentially to the 6-endo product²² while only 5-exo products are obtained from 1a. The formation of cation radicals has been proposed as the first step in photoinduced desilylation of enol silyl ethers.²³ The exclusive formation of 6-endo products from 7 and 5-exo products from 1a is consistent with the expected behavior of a very electrophilic cation radical such as 15.



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If the cation radical 15 forms and cyclizes to give 18, similar products should be obtained from oxidation of enol silyl ethers with aminium salt which are known to oxidize electron-rich double bonds to cation radicals.²⁴ As expected, oxidation of 4 with 2 equiv of tris(*p*-bromophenyl)aminium hexachloroantimonate²⁴ and sodium carbonate affords 41% of a 2.5:1 mixture of 5 and 6. This procedure is of limited synthetic utility since 2 equiv of the aminium cation are consumed in the oxidative cyclization and purification of the product is difficult.

Good yields of 2a are obtained with either oxidation protocol; much better yields of 2b are obtained with copper(II) than with ceric(IV). The lower yield of 2b obtained with Ce(IV) may be due to side reactions of the intermediate cation radical, such as formation of the α -nitroxy ketone, which are competitive with a slow 6-exo cyclization leading to 2b, but not with a fast 5-exo cyclization leading to 2a.

Cyclization to form the tetralone ring can occur at either the cation or radical oxidation state. Cyclization of 4-phenylbutyl radicals to give, after oxidation, tetralins is well known.^{1b,2a} Oxidation to cation 19 followed by Friedel-Crafts alkylation is also possible.^{1c} The lower yields of products formed from 7 may result from problems with the termination rather than oxidation or cyclization steps. Cyclization to give 11 will be slow since this can only occur in the conformation with an axial benzoyl group. Cupric triflate oxidizes radicals more rapidly than cupric acetate and gives predominantly oxidative substitution rather than oxidative elimination products.²⁵ Ceric ion also rapidly oxidizes radicals to cations.²⁶ Therefore the cyclohexyl cation will be formed which can lose a proton to give 8, or react with nitrate to give 9 or 10. Other products which could not be characterized are probably derived from the cationic intermediate. The low yield of products from 12 could be due to side reactions of the cyclized tertiary cation or to differences in the rate of oxidation of aliphatic and aromatic enol silyl ethers.

These results demonstrate that oxidative cyclization of δ,ϵ - and ϵ,ζ -unsaturated enol silyl ethers can proceed in high yield with excellent stereocontrol in favorable cases providing an efficient route to polycyclic compounds. Further studies of the scope and mechanism of this reaction are in progress.

Acknowledgment. We are grateful to the National Science Foundation (CHE-8721312) for generous financial support.

Supplementary Material Available: Representative procedures and spectral data for 1a, 2a,b, 3a,b, 4-14 (8 pages). Ordering information is given on any current masthead page.

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