behavior of the data. Note that the data at all four magnetic fields are superimposable, which indicates that the observed paramagnetism arises from $S = {}^1/_2$ centers. The solid line in Figure 1 represents the best fit using the EPR g values;[13] the amount of $S = {}^1/_2$ paramagnetism determined from this fit was 22% of the total copper in the sample. A similar result was obtained from a fit with the g values as a free parameter. Hence the vertical axis was scaled using the amount of $S = {}^1/_2$ paramagnetism determined from the first fit. Measurements on an independent sample gave essentially identical results, with the amount of $S = {}^1/_2$ paramagnetism equal to 24% of the total copper in this sample. Recent results[19] are beginning to converge on a figure near 25% for the amount of paramagnetic copper in samples of varying copper contents. Hence the data suggest that, at most, one copper out of four is paramagnetic in a subunit of the fully loaded enzyme.

The magnetization data of Figure 1 are presented in Figure 2 as μ_{eff}^2 ($g^2S(S + 1)$) versus temperature; the fit from Figure 1 is also shown as a solid line in Figure 2. This plot emphasizes the high-temperature, Curie law behavior of the data. The scattering of the data in Figure 2 about the horizontal theoretical line above 20 K provides strong evidence that no paramagnetic species is present other than the $S = {}^1/_2$ species assumed by the fit.[20] Hence we conclude (1) that the residual O_2 contribution has been satisfactorily removed from the protein data via subtraction of the buffer signal, and, more importantly (2), that no other paramagnetic state is significantly populated up to 200 K. Since the fits to the magnetization data from two independently prepared samples correspond to 23 ± 3% of the total copper, most of the copper in oxidized N_2O reductase is diamagnetic from 2 to 200 K. One possibility is that N_2O reductase contains antiferromagnetically coupled binuclear Cu(II) sites, similar to those found in hemocyanin or tyrosinase.[21] If this is the case, our data require that the splitting between the $S = 1$ state and the $S = 0$ ground state be 200 cm^{-1} or greater, which is consistent with the previous estimate from measurements of the EPR susceptibility.[11] Alternatively, some or, less likely, all of the diamagnetic copper may be Cu(I).

It is intriguing that nearly 25% of the copper in two independent preparations of oxidized N_2O reductase appears to be present as $S = {}^1/_2$ Cu(II). Recent EPR measurements on other N_2O reductases are consistent with this result.[22] A variety of spectroscopic evidence strongly indicates that N_2O reductase contains Cu_A-type sites,[10-13] which are paramagnetic and EPR detectable. Comparisons of the N_2O reductase sequence (inferred from translation of the structural gene) to cytochrome oxidase subunit II (cox II) sequences revealed significant homology between a 15-residue N_2O reductase sequence and the cox II sequences containing the putative Cu_A binding site.[7,10] Therefore it is highly probable that N_2O reductase contains two Cu_A-type sites out of a total of eight; in other words, all the paramagnetism may be accounted for by the Cu_A content. The remaining copper ions (*three per subunit*, if four are present in a fully loaded subunit) must be diamagnetic. Kroneck and co-workers have proposed that the Cu_A site is actually a binuclear, mixed-valent [Cu(II)···Cu(I)] site.[12,13,23] If so, the remaining copper could be present as antiferromagnetically coupled Cu(II) dimers. This is a plausible model for N_2O reductase. On the other hand, Chan and Malmström[24,25] have strongly challenged the binuclear model for Cu_A, arguing that a mononuclear $S = {}^1/_2$ model is more consistent with all the available data. In this case the diamagnetism of the "odd" copper could be rationalized in two ways. Each subunit might contain an isolated Cu(I) site, or a coupled binuclear site involving Cu(II) ions from each subunit might be formed. At this time it is not possible to exclude any of these models for the distribution of copper in oxidized N_2O reductase. Considered together with other data, the magnetization results establish that if antiferromagnetically coupled Cu(II) sites are present, the splitting between the singlet ground state and the triplet excited state ($E_{S=1} - E_{S=0}$) must be at least 200 cm^{-1}. This is similar to previous results obtained on other copper-containing oxidases that catalyze multielectron redox chemistry.[21]

Acknowledgment. This research was supported by the Cooperative State Research Service, U.S. Department of Agriculture, under Agreement 89-37280-4696 (to D.M.D.), the Deutsche Forschungsgemeinschaft and Fonds der Chemischen Industrie (W.G.Z.), and the National Institutes of Health (Grant GM-32394 to E.P.D.). We are very grateful to Professor Richard Frankel for his help and encouragement at the beginning of this study and to Dr. Chiou-Pirng Wang for her help in collecting and analyzing the data.

(18) Data collection, analysis, and curve fitting were carried out as described previously. See: (a) Day, E. P.; Kent, T. A.; Lindahl, P. A.; Münck, E.; Orme-Johnson, W. H.; Roder, H.; Roy, A. *Biophys. J.* **1987**, *52*, 837-853. (b) Hendrich, M. P.; Pearce, L. L.; Que, L., Jr.; Chasteen, N. D.; Day, E. P. *J. Am. Chem. Soc.* **1991**, *113*, 3039-3044.

(19) We independently determined the amount of EPR-detectable copper in the first sample of N_2O reductase and obtained a result that is fully consistent with the measurements reported here. The results reported in ref 11 suggest that 20-30% of the copper in resting *Pseudomonas stutzeri* N_2O reductase is EPR detectable; results reported in ref 22 are also consistent with an $S = {}^1/_2$ content of 20-25% for other N_2O reductases.

(20) For example, a similar fit to the raw data *before* subtracting the matched control gave a reasonable fit when viewed as shown in Figure 1 (with an 18% increase in the amount of "$S = {}^1/_2$" species), but when viewed as in Figure 2, decreased systematically with increasing temperature above 20 K, ending 100% below the theoretical line at 200 K. This dramatic and systematic deviation was caused by the presence of $S = 1$ oxygen that had not been subtracted from the data.

(21) Solomon, E. I.; Penfield, K. W.; Wilcox, D. E. *Struct. Bonding (Berlin)* **1983**, *53*, 1-57.

(22) (a) SooHoo, C. K.; Hollocher, T. C.; Kolodziej, A. F.; Orme-Johnson, W. H.; Bunker, G. *J. Biol. Chem.* **1991**, *266*, 2210-2218. (b) Zhang, C.-S.; Hollocher, T. C.; Kolodziej, A. F.; Orme-Johnson, W. H. *J. Biol. Chem.* **1991**, *266*, 2199-2202.

(23) Kroneck, P. M. H.; Antholine, W. A.; Riester, J.; Zumft, W. G. *FEBS Lett.* **1989**, *248*, 212-213.

(24) Li, P. M.; Malmström, B. G.; Chan, S. I. *FEBS Lett.* **1989**, *248*, 210-211.

(25) Malmström, B. G. *Arch. Biochem. Biophys.* **1990**, *280*, 233-241.

Aerobic Conversion of Organic Halides to Alcohols. An Oxygenative Radical Cyclization

Eiichi Nakamura,* Tsuyoshi Inubushi, Satoshi Aoki, and Daisuke Machii

Department of Chemistry, Tokyo Institute of Technology Meguro, Tokyo 152, Japan

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Reductive cleavage of a carbon-halogen bond by a tin hydride reagent generates a carbon radical, and the subsequent synthetic sequence generally ends with the formation of a carbon-hydrogen bond.[1,2] We report a unique tin hydride mediated reaction that aerobically converts a carbon-halogen bond to a synthetically valuable carbon-oxygen bond. A striking *synergetic action of molecular oxygen and a tin hydride* at low temperatures (0-20 °C) effects an efficient conversion of an organic halide to the corresponding alcohol under neutral conditions through oxygenation of an intermediate radical[3] (Scheme I). The reaction tolerates a wide range of functional groups, thus complementing the classical conditions employed for this standard, yet sometimes nontrivial transformation.[4] The radical nature of the reaction

(1) Pereyre, M.; Quintard, J. P.; Rahm, A. *Tin in Organic Synthesis*; Butterworth: London, 1987. Neumann, W. P. *Synthesis* **1987**, 665. Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: Oxford, 1987.

(2) For important exceptions: Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1989**, *111*, 6265 and references therein. See also: Kraus, G. A.; Landgrebe, K. *Tetrahedron* **1985**, *41*, 4039.

(3) Cf.: Porter, N. A. In *Free Radicals in Biology*; Pryor, W. A., Ed.; Academic Press: New York, 1980; Vol. IV, pp 261-294.

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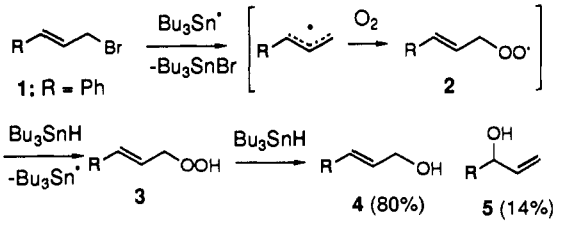
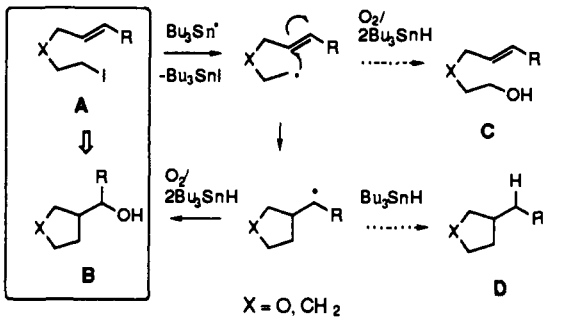
Scheme I



Scheme II



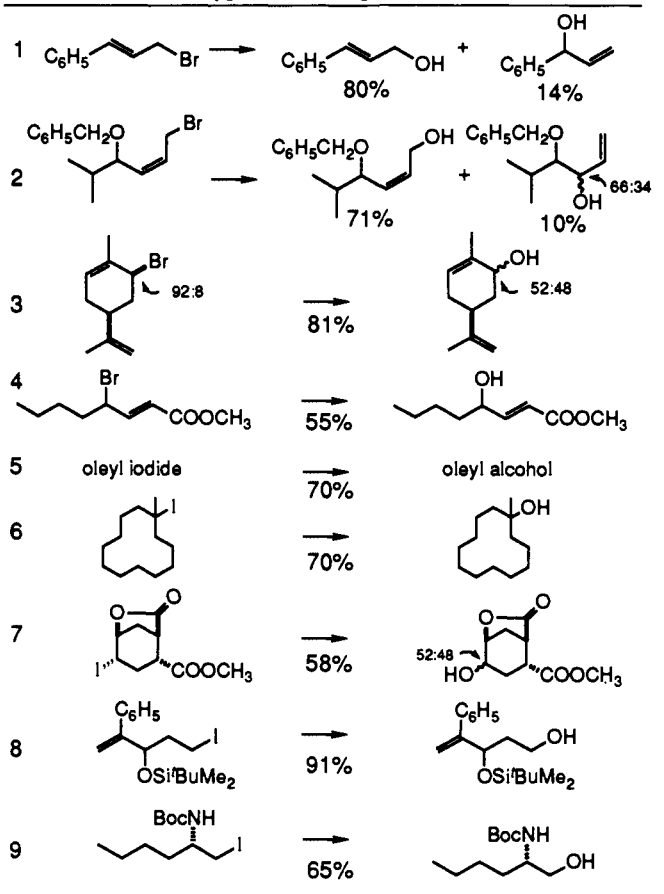
permits a new oxygenative radical cyclization of an olefinic iodide (Scheme II) with incorporation of a hydroxy group at the cyclization terminus.

Aerobic conversion of (*E*)-cinnamyl bromide (**1**) to cinnamyl alcohol (**4**) illustrates the simplicity and effectiveness of the reaction. Dry air was bubbled (120 mL/min) at 0 °C into a solution of **1** (1.97 g, 10.0 mmol) in 43 mL of toluene, to which Bu_3SnH (6.11 g, 21.0 mmol) was added dropwise. After air was bubbled in at 15–20 °C for 24 h, 0.1 g of $NaBH_4$ in 1 mL of ethanol was added (to ensure reduction of **3**). Purification of the crude product[5] on silica gel yielded cinnamyl alcohol (**4**, 1.075 g, 80%) and its regioisomer **5** (0.18 g, 14%). Less than 1% of simple reduction products (phenylpropenes) was detected in the crude mixture.

Detailed studies of the reaction for **1** and some representative substrates provided the following generalizations. (1) A small amount of the hydroperoxide **3** may be formed as a side product. The use of less than the stoichiometric 2 equiv of Bu_3SnH increases **3**, indicating the peroxy radical **2**[6] as an intermediate.[7] These observations coupled with the observed cyclization (Scheme II) indicate that the reaction involves an oxygen-initiated[8] radical chain, shown in Scheme I. (2) Under the present conditions, simple reduction products barely form from allylic bromides and form in 10–30% yield from alkyl iodides.[9] (3) With reactive halides, the tin hydride is selectively consumed by the halide-to-alcohol conversion rather than by molecular oxygen.[10] The halide/oxygen selectivity erodes with less reactive alkyl and aryl halides.[11] (4) In line with our previous observations,[12] ultrasound irradiation was found to be beneficial for reactions of allylic halides.

Table I illustrates representative examples of the halide-to-alcohol conversions (with 0.2–1 M halide at 0–20 °C), which provided further generalizations. (1) Though the stereoselectivity

Table I. Reductive Oxygenation of Organic Halides[a]



[a] The reactions were carried out in toluene at 0–20 °C with 2.1–2.5 equiv of Bu_3SnH. Yield (except for entry 2, GC and NMR) are based on pure isolated material. See Table I in supplement material for details.

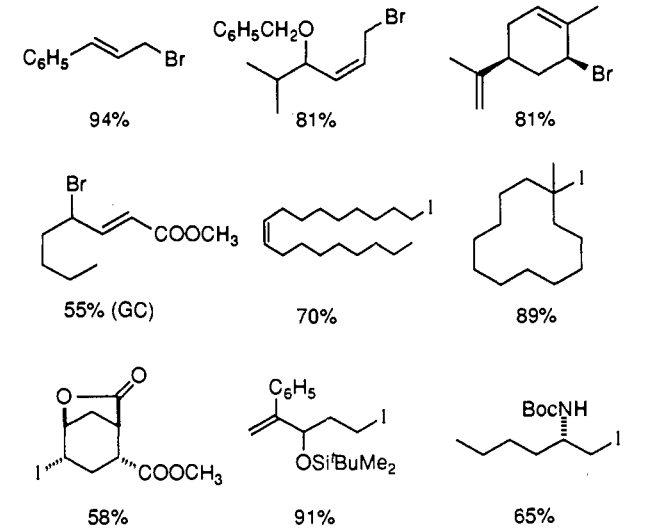


Figure 1. Reductive oxygenation of organic halides. The numbers below the structures refer to the isolated yield (except as otherwise noted) of the corresponding alcohol. See the supplement material for detailed data.

(4) Hutchings, R. O.; Taffer, I. M. *J. Org. Chem.* **1983**, *48*, 1360 and references therein.

(5) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140. See the supplementary material.

(6) Cf.: Porter, N. A. *Acc. Chem. Res.* **1986**, *19*, 262. Boyd, S.; Boyd, R. J.; Barclay, L. R. *J. Am. Chem. Soc.* **1990**, *112*, 5724.

(7) Cf.: Porter, N. A.; Wujek, J. S. *J. Org. Chem.* **1987**, *52*, 5085 and references therein.

(8) Under nitrogen, virtually no reaction takes place below room temperature.

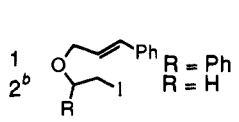
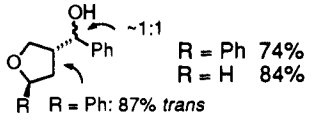
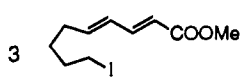
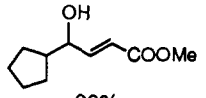
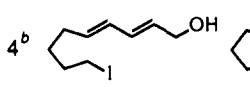
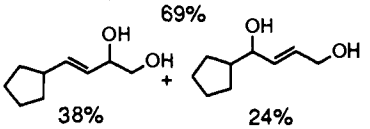
(9) Recovery and reduction account for the material balance. Slow mechanical addition of the hydride improves the oxygenation/reduction ratio.

(10) The solubility of oxygen in toluene is very low (8.3×10^{-3} M at 20 °C) (Battino, R.; Rettich, T. R.; Tominaga, T. *J. Phys. Chem. Ref. Data* **1983**, *12*, 163), while the reaction of $Bu_3Sn^•$ with molecular oxygen is very rapid (Maillard, B.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 5095).

(11) $Bu_3Sn^•$ reacts with an alkyl bromide more than an order of magnitude more slowly than with an iodide: Ingold, K. U.; Lusztyk, J.; Scaiano, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 343.

(12) Nakamura, E.; Machii, D.; Inubushi, T. *J. Am. Chem. Soc.* **1989**, *111*, 6849.

Table II. Oxygenative Radical Cyclization[a]

entry	halide	product (%)
1	 R = Ph, R = H	 ~1:1; R = Ph 74%, R = H 84%
2[b]		R = Ph: 87% *trans*
3		 69%
4[b]		 38% + 24%

[a] Dry air was bubbled for 5-24 h into a mixture of an iodide and Bu_3SnH in 0.2 M toluene at 0 °C (12 °C in entries 2 and 4). [b] Under ultrasound irradiation.

of the alcohol formation is low (entries 3 and 7), steric hindrance at the carbon bearing the halide atom poses little problem. For instance, conversion of a tertiary halide to a tertiary alcohol can be achieved in excellent yield (cf. entry 6). (2) While the regiochemistry of the hydroxylation is yet to be solved,[13] the olefin geometry of the allylic halide is maintained (>99%, cf. entries 1, 2, and 4). This is an advantage of the low-temperature conditions: the oxygenation of the 100% *Z*-allylic halide in entry 2 at 95 °C proceeded with loss of the stereochemistry (61% *E*-allylic alcohol).[14] (3) The present reaction tolerates a wide range of functional groups. Figure 1 illustrates the examples of the conversion of an iodo lactone and a Boc-protected β-iodo amine to the corresponding alcohols without affecting the neighboring functional groups.

The aerobic conversion of halides to alcohols provides an especially powerful synthetic strategy for intramolecular radical cyclization (Scheme II). Thus, bubbling air into a mixture of Bu_3SnH (2.1-2.5 equiv) and an olefinic iodide (**A**) at 0-12 °C gave the cyclization product **B** in good yield (Table II). Despite the presence of several competitive reaction pathways, the reaction gave the cyclization product as a single predominant product, together with small amounts (5-20%) of the uncyclized product **C** and/or reduced product **D**. Unlike the conventional *reductive* cyclization (**A** → **D**),[15] which generates one ring at the expense at two functional groups (halogen and olefin), the present *oxygenative* cyclization (**A** → **B**) generates a ring *and* a hydroxy group.[16,17] In light of this functional group economy, good chemoselectivity (cf. Figure 1), and procedural simplicity, the present reaction will add to the versatility of radical-based ring formation strategies.

Acknowledgment. We thank Y. Imanishi for some experiments and gratefully acknowledge the Yamanouchi Award in Synthetic Organic Chemistry, Japan, and the Sound Technology Promotion Foundation for financial support.

Supplementary Material Available: A detailed version of Table I, experimental details, and characterization of the compounds in the tables (12 pages). Ordering information is given on any current masthead page.

(13) Regioisomers such as **4** and **5** arise either from oxygen trapping at two allylic termini or from rearrangement of the peroxy radical **2**; cf.: Porter, N. A.; Kaplan, J. K.; Dussault, P. H. *J. Am. Chem. Soc.* **1990**, *112*, 1266.

(14) The activation energy of allyl radical isomerization is only 15.7 kcal/mol: Korth, H.-G.; Trill, H.; Sustmann, R. *J. Am. Chem. Soc.* **1981**, *103*, 4483. We thank Prof. T. Cohen for drawing our attention to this reference. See also: Feller, D.; Davidson, E. R.; Borden, W. T. *J. Am. Chem. Soc.* **1984**, *106*, 2513.

(15) (a) Reviews: Curran, D. P. *Synthesis* **1988**, 417, 489. Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. Thebtaranonth, C.; Thebtaranonth, Y. *Tetrahedron* **1990**, *46*, 1385. Giese, B., Ed. *Selectivity and Synthetic Applications of Radical Reactions*; *Tetrahedron Symposia-in-Print, number 22* **1985**, *41*, 3887. (b) Stork, G. In *Current Trends in Organic Synthesis*; Nozaki, H., Ed.; Pergamon Press: Oxford, England, 1983. Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564.

(16) An equivalent two-step sequence based on conventional radical cyclizations: Jolly, R. S.; Livinghouse, T. *J. Am. Chem. Soc.* **1988**, *110*, 7536. Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.* **1988**, *110*, 4796.

(17) (a) Porter, N. A.; Funk, M. O. *J. Org. Chem.* **1975**, *40*, 3614. Corey, E. J.; Shih, C.; Shih, N. Y.; Shimoji, K. *Tetrahedron Lett.* **1984**, *25*, 5013. (b) Radical oxygenation of organomercurials: Hill, C. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 870.

Asymmetric Synthesis of Lactones with High Enantioselectivity by Intramolecular Carbon-Hydrogen Insertion Reactions of Alkyl Diazoacetates Catalyzed by Chiral Rhodium(II) Carboxamides

Michael P. Doyle,* Arjan van Oeveren, Larry J. Westrum, Marina N. Protopopova,[‡] and Thomas W. Clayton, Jr.

Department of Chemistry, Trinity University
San Antonio, Texas 78212

Received August 5, 1991

The catalytic uses of rhodium(II) carboxylates and rhodium(II) carboxamides for intramolecular carbon-hydrogen insertion reactions of diazo esters and diazo ketones has made possible the synthesis of γ-lactones and cyclopentanones with high regio- and diastereoselectivity and in moderate to high yield.[1-3] With few exceptions,[4,5] these reactions exhibit an overwhelming preference for five-membered-ring formation and, where insertion can occur at more than one C-H bond, conformational preferences as well as electronic influences appear to govern regioselection.[6] In contrast, copper catalysts have not shown similar suitability for carbon-hydrogen insertion reactions,[7] and dirhodium(II) compounds are now recognized to be the catalysts of choice for these transformations.

We have recently reported that chiral dirhodium(II) carboxamides are remarkably effective catalysts for asymmetric intramolecular cyclopropanation reactions of allyl diazoacetates.[8] The design of these catalysts, in particular dirhodium(II) tetrakis-[methyl 2-pyrrolidone-5(*S*)-carboxylate], $Rh_2(5S\text{-MEPY})_4$, and its enantiomeric form, $Rh_2(5R\text{-MEPY})_4$, with their cis orientation for the two nitrogen donor atoms on each rhodium,[9] is particularly suitable for highly enantioselective intramolecular transformations. For comparison, chiral dirhodium(II) carboxylates, whose architecture places the chiral center perpendicular to the rhodium-carbene bond axis, have recently been reported to catalyze in-

[‡] Visiting research associate: N. D. Zelinsky Institute of Organic Chemistry, Moscow, USSR.

(1) (a) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919. (b) Maas, G. *Top. Curr. Chem.* **1987**, *137*, 75. (c) Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765.

(2) (a) Wenkert, E.; Davis, L. L.; Mylari, B. L.; Solomon, M. F.; da Silva, R. R.; Shulman, S.; Warnet, R. J.; Ceccherelli, P.; Curini, M.; Pellicciari, R. *J. Org. Chem.* **1982**, *47*, 3242. (b) Taber, D. F.; Ruckle, R. E., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7686. (c) Monteiro, J. J. *Tetrahedron Lett.* **1987**, *28*, 3459. (d) Corbel, B.; Hernot, D.; Haelters, J.-P.; Sturtz, G. *Tetrahedron Lett.* **1987**, *28*, 6605. (e) Sonawane, H. R.; Bellur, N. S.; Ahuja, J. R.; Kulkarni, D. G. *J. Org. Chem.* **1991**, *56*, 1434.

(3) Doyle, M. P.; Bagheri, V.; Pearson, M. M.; Edwards, J. D. *Tetrahedron Lett.* **1989**, *30*, 7001.

(4) (a) Cane, D. E.; Thomas, P. J. *J. Am. Chem. Soc.* **1984**, *106*, 5295. (b) Lee, E.; Jung, K. W.; Kim, Y. S. *Tetrahedron Lett.* **1990**, *31*, 1023.

(5) (a) Brown, P.; Southgate, R. *Tetrahedron Lett.* **1986**, *27*, 247. (b) Doyle, M. P.; Taunton, J.; Pho, H. Q. *Tetrahedron Lett.* **1989**, *30*, 5397.

(6) (a) Doyle, M. P.; Pieters, R. J.; Taunton, J.; Pho, H. Q.; Padwa, A.; Hertzog, D. L.; Precedo, L. *J. Org. Chem.* **1991**, *56*, 820. (b) Adams, J.; Poupart, M.-A.; Grenier, L. *Tetrahedron Lett.* **1989**, *30*, 1753. (c) Adams, J.; Poupart, M.-A.; Grenier, L.; Schaller, C.; Quimet, N.; Frenette, R. *Tetrahedron Lett.* **1989**, *30*, 1749.

(7) (a) Burke, S. D.; Greico, P. A. *Org. React. (N.Y.)* **1979**, *26*, 361. (b) Taber, D. F.; Saleh, S. A.; Korsmeyer, R. W. *J. Org. Chem.* **1980**, *45*, 4699.

(8) Doyle, M. P.; Pieters, R. J.; Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Müller, P. *J. Am. Chem. Soc.* **1991**, *113*, 1423.

(9) Doyle, M. P.; Brandes, B. D.; Kazala, A. P.; Pieters, R. J.; Jarstfer, M. B.; Watkins, L. M.; Eagle, C. T. *Tetrahedron Lett.* **1990**, *31*, 6613.

0002-7863/91/1513-8982$02.50/0