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Alkoxyamine-Mediated Radical Cyclizations

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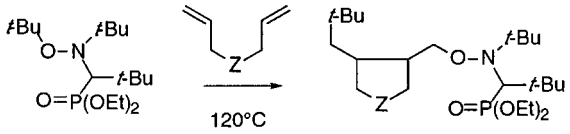
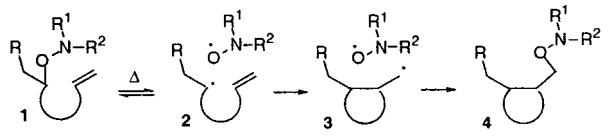
ABSTRACT



We present a new "conjunctive" radical cyclization process that involves the reaction of a 1,6-diene with the Tordo alkoxyamine, an agent originally developed for the radical polymerization of certain olefins through the "persistent radical effect".

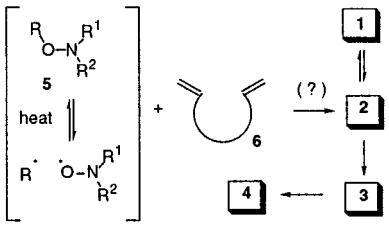
Recent work by Studer has established the feasibility of a noteworthy type of radical cyclization reaction triggered by the thermal dissociation of a *preformed* alkoxyamine, **1**, and leading to a cycloisomerization product, **4** (Scheme 1).[1] A

Scheme 1



possible extension of this interesting chemistry envisions that intermediates **1** might themselves arise through *bimolecular* addition of an appropriate alkoxyamine, **5**,[2] to a bis-olefinic substrate, **6**, as outlined in Scheme 2. A novel "conjunctive" radical cyclization reaction would thus materialize.

Scheme 2



The new chemistry offers a number of potential advantages relative to more traditional modes of radical C−C bond formation.[3] For instance, halogenated substrates and tin or silicon hydride reagents are no longer required, whereas the

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[§] Atofina SA, Centre de Recherche Rhône-Alpes.

(1) (a) Studer, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1108. (b) Studer, A. *Chem. Eur. J.* **2001**, *7*, 1159.

(2) Ciriano, M. V.; Korth, H.; van Scheppingen, W. B.; Mulder, P. *J. Am. Chem. Soc.* **1999**, *121*, 6375.

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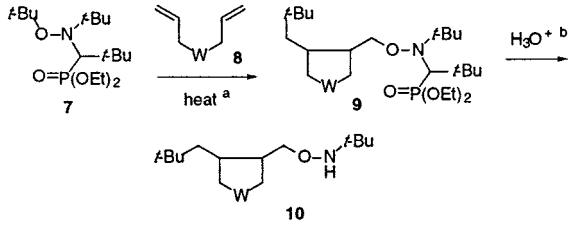
final termination step (cf. **3** → **4**) introduces useful oxygenated functionality, instead of simply reducing the ultimate radical intermediate **3** by the customary H-atom transfer event.

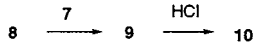
At the same time, the new process presents a number of potential difficulties, relative to the Studer cycloisomerization. First, little precedent is found in the literature for radical cyclization reactions initiated by the *bimolecular addition of a simple alkyl radical to a polyolefinic substrate*. The initial carbon radical would normally be produced by the interaction of an alkyl halide with a tin or silicon hydride and a radical initiator (AIBN, Et_3B, etc.). The rate of bimolecular addition of ordinary carbon radicals (barring species such as $Cl_3C^{\bullet}$,[4] enoyl,[5] or perfluoroalkyl[6] radicals) to unactivated olefins is generally slower than the rate of reduction of such radicals by the Sn/Si hydride present in the medium, or the rate of radical disproportionation. Such unfavorable relative rates normally preclude radical addition/cyclization sequences. Moreover, the initial addition step (**6** → **2**) is a bimolecular reaction, which would proceed faster at high concentrations. However, elevated concentrations may be detrimental to the success of the subsequent cyclization step, because of the possible occurrence of bimolecular side reactions of radicals **2**/**3**,[7] or even of the free nitroxyl radical itself.[8] Finally, the temperatures required to induce the reaction may be too high to ensure survival of various alkoxyamine-type intermediates (cf. **1**, **4**, and **5**), requiring careful tailoring of the physicochemical properties of the starting **5**.[9] We now describe the results of preliminary studies that illustrate the feasibility of the transformations outlined in Scheme 2 by the use of the Tordo alkoxyamine, **7**.[10]

Scheme 3



Compound **7** is a source of *tert*-butyl radicals. These species are especially problematic as initiators of radical cyclization reactions, because of particularly unfavorable relative rates of olefin addition vs rates of secondary reactions.[11] Yet, contrary to what one may anticipate, thermolysis of **7** in the presence of various bis-olefinic substrates resulted in formation of products **9** (Scheme 3). Representative examples are provided in Table 1.

Table 1. Conjunctive Radical Cyclization of Substrates **8** with Alkoxyamine **7**



entry	W	react. time[c]	yield of **9**[d]	yield of **10**[d]	cis/trans ratio[e]
a	CH_2	60	25	99	69:31
b	O	40	23	83	70:30
c	$C(COOEt)_2$	30	51	90	85:15
d	N-Cbz	65	29	83	60:40
e	$N\text{-}SO_2C_6H_4\text{-}4\text{-}Br$	30	42	74	66:33

[a] 4 M in *t*-BuOH, 120 °C. [b] 4 M HCl, dioxane, rt. [c] Hours. [d] Chromatographed yields. [e] Determined by 1-D and 2-D ^1H NMR.

The interaction of **7** with substrates **8** was examined under a range of experimental conditions. Best results were obtained when equimolar amounts of **7** and **8**, as a 4 M solution in *t*-BuOH, were heated in a screw-cap tube at 120 °C, under argon, for several hours. The use of a protonic solvent (*t*-BuOH) in these reactions is believed to facilitate dissociation of alkoxyamine intermediates through H-bonding.[12]

The relative configuration of the stereogenic carbon bearing the phosphoryl group in **9** is not controllable,

(3) For an excellent review of radical addition/cyclization processes see: Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 4, Chapter 4.1, pp 715ff (radical additions) and Chapter 4.2, pp 779ff (radical cyclizations).

(4) (a) Brace, N. O. *J. Org. Chem.* **1967**, *32*, 2711. Recent examples: (b) Barks, J. M.; Gilbert, B. C.; Parsons, A. F.; Upeandran, B. *Tetrahedron Lett.* **2001**, *42*, 3137. Related processes: (c) Miyabe, H.; Fujii, K.; Goto, T.; Naito, T. *Org. Lett.* **2000**, *2*, 4071. (d) Sibi, M. P.; Rhéault, T. R.; Miyabe, H.; Patil, K.; Jasperse, C. P. *C. R. Acad. Sci. Paris, Chem.* **2001**, *4*, 581.

(5) (a) Brace, N. O. *J. Am. Chem. Soc.* **1964**, *86*, 523. Recent examples: (b) Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Synlett* **2002**, 674. (c) Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K.; Omoto, K.; Fujimoto, H. *J. Org. Chem.* **2001**, *66*, 7776. (d) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K.; Omoto, K.; Fujimoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 11041 and references therein. See also ref 6.

(6) Yorimitsu, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 853.

(7) For example: disproportionation, recombination, etc.

(8) For an example of disproportionation of nitroxyl radicals see: (a) Griller, D.; Perkins, M. J. *J. Am. Chem. Soc.* **1980**, *102*, 1354. For the reactivity of nitroxides see, for example: (b) Beckwith, A. L. J.; Bowry, V. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1992**, *114*, 4983. (c) Bowry, V. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1992**, *114*, 4992. (d) Aldabbagh, F.; Busfield, W. K.; Jenkins, I. D.; Thang, S. H. *Tetrahedron Lett.* **2000**, *41*, 3673.

(9) The precise dissociation temperature depends on the nature of R: (a) Le Mercier, C.; Lutz, J. F.; Marque, S.; Le Moigne, F.; Tordo, P.; Lacroix-Desmazes, P.; Boutevin, B.; Couturier, J. L.; Guerret, O.; Martschke, R.; Sobek, J.; Fischer, H. *ACS Symp. Ser.* **2000**, *768*, 108. (b) Marque, S.; Le Mercier, C.; Tordo, P.; Fischer, H. *Macromolecules* **2000**, *33*, 4403. (c) Goto, A.; Kwak, Y.; Yoshikawa, C.; Tsujii, Y.; Sugiura, Y.; Fukuda, T. *Macromolecules* **2002**, *35*, 3520. See also ref 8.

(10) Le Mercier, C. Dissertation, University of Provence, Aix-Marseille I, France, 2000.

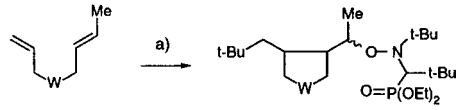
(11) The rate constants (M^{-1} s^{-1}) for the disproportionation of the *tert*-butyl radical to isobutene and isobutane (H-atom transfer) or for its recombination to 2,2,3,3-tetramethylbutane are about 10^9-10^{10}, whereas the rate constant for its addition to olefins is in the range of 10 to 10^5: (a) Fischer, H.; Schuh, H. *Int. J. Chem. Kinet.* **1976**, *8*, 341. (b) Fischer, H.; Schuh, H. *Helv. Chim. Acta* **1978**, *61*, 7, 2463. (c) Fischer, H.; Munger, K. *Int. J. Chem. Kinet.* **1985**, *17*, 809. (d) Fischer, H.; Rubin, H. *Helv. Chim. Acta* **1996**, *79*, 1670.

(12) Cf.: Marque, S.; Fischer, H.; Baier, E.; Studer, A. *J. Org. Chem.* **2001**, *66*, 1146, as well as refs 1. Conduct of the reaction in nonpolar solvents such as toluene, as well as in the neat state, produced unsatisfactory results, while higher boiling tertiary alcohols, such as triethyl carbinol, provided the same results as *tert*-butyl alcohol. Polar aprotic solvents such as NMP were also satisfactory.

resulting in formation of mixtures of four diastereomers of the products. This greatly complicated the spectroscopic determination of cis−trans diastereomeric ratios. Efforts to remove that undesired chirality by reductive cleavage of the N−O bond in **9** with various agents[13] were unfruitful. Fortunately, treatment of **9** with aqueous 4 M HCl resulted in efficient formation of hydroxylamines **10**, through hydrolytic loss of diethyl phosphite and of pivalaldehyde. Compounds **10** produced greatly simplified spectra that permitted facile determination of the diastereomeric ratios reported in Table 1. As expected, the cis-product was dominant in all cases.[14]

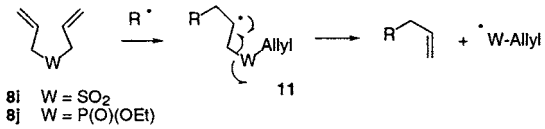
Substrates **8f**−**h** (Scheme 4) present an issue of regioselectivity during the initial radical addition step. In all cases

Scheme 4



the *t*-Bu radical underwent addition selectively to the least encumbered olefin, resulting in exclusive formation of product regioisomers **9f**−**h** (mixtures of diastereomers). On the other hand, we were unable to induce cyclization of substrates **8i**,**j** wherein W = SO_2 or P(O)(OEt). We attribute this failure to facile fragmentation of intermediate **11** formed in the initial radical addition step (Scheme 5).[15]

Scheme 5



In conclusion, we have devised a novel conjunctive radical cyclization technique that involves the merger of a molecule of alkoxyamine with a bis-olefinic substrate. A "green" aspect of the new chemistry is the suppression of any requirement for halogen-containing substrates and for Sn/Si hydride reagents. Our results demonstrate that alkoxyamine-based methodology circumvents the difficulties posed even by particularly unfavorable permutations of stabilized radical/unactivated substrate. This augurs well for further development of the technique into a synthetically useful method.

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Supporting Information Available: Experimental procedures and spectral characterization data for all new compounds described in the paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) SmI_2, hydrogenolysis, Zn/AcOH. Dissolving metal reduction gave ambiguous results.

(14) (a) Ryu, I.; Kurihara, A.; Muraoka, H.; Tsunoi, S.; Kambe, N.; Sonoda, N. *J. Org. Chem.* **1994**, *59*, 7570. (b) Beckwith, A. L. J.; Blair, I.; Phillipou, G. *J. Am. Chem. Soc.* **1974**, *96*, 1613. (c) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925. (d) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959. (e) Broeker, J. L.; Houk, K. N. *J. Org. Chem.* **1991**, *56*, 3651. (f) Beckwith, A. L. J.; Zimmermann, J. *J. Org. Chem.* **1991**, *56*, 5791.

(15) When W = SO_2, the unimolecular rate constant for this reaction is approximately equal to 10^6 s^{-1} at 25 °C: (a) Wagner, P. J.; Sedon, J. S.; Lindstrom, M. J. *J. Am. Chem. Soc.* **1978**, *100*, 2579. (b) Serra, A. C.; M. Da Silva Correa, C. M.; Vieira, M. A. M. S. A.; Gomes, M. A. *Tetrahedron* **1990**, *46*, 3061. At the temperature of our experiments (120 °C), the fragmentation may become so fast that the lifetime of intermediate **11** is too short to permit further cyclization. For an interesting synthetic application of this property see: (c) Mouriès, V.; Delouvrié, B.; Lacôte, E.; Fensterbank, L.; Malacria, M. *Eur. J. Org. Chem.* **2002**, 1776.