

Tandem Polar/Radical Crossover Sequences for the Formation of Fused and Bridged Bicyclic Nitrogen Heterocycles Involving Radical Ionic Chain Reactions. and Alkene Radical Cation Intermediates, Performed under **Reducing Conditions: Scope and Limitations**

David Crich,* Krishnakumar Ranganathan, Santhosh Neelamkavil, and Xianhai Huang

Contribution from the Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607-7061

Received April 15, 2003; E-mail: dcrich@uic.edu

Abstract: It is demonstrated that phosphorylated forms of β -nitro alcohols provide an excellent means of entry into β -(phosphatoxy)alkyl radicals on exposure to tributyltin hydride and AIBN in benzene at reflux. These radicals then undergo heterolytic cleavage of the phosphate group to yield alkene radical cation/ phosphate anion contact ion pairs which are trapped intramolecularly in a tandem polar/radical crossover sequence involving radical ionic chain reactions by allylic and propargylic amines. The substitution pattern of the alkene radical cation dictates the cyclization mode, and this may be engineered to form fused ring systems by an initial exo-mode nucleophilic cyclization or bridged bicyclic systems when the nucleophilic attack takes place in the endo-mode.

Introduction

Tandem sequences offer some of the most powerful and direct approaches to complex molecular frameworks;1 they have the potential to be especially so when two normally orthogonal modes of reactivity can be combined into one sequence. Murphy has called one set of such sequences tandem radical/polar crossover reactions and has demonstrated their utility in a number of concise alkaloid syntheses.² Alkene radical cations, delocalized, positively charged, open-shell intermediates (Scheme 1), are ideal triggers for tandem polar/radical crossover sequences, but this aspect of their chemistry has rarely been exploited, with the majority of preparative sequences focusing on their potential in cycloaddition reactions.³ One reason for the apparent exclusivity of polar/radical crossover sequences and alkene radical cations arises from the oxidizing conditions hitherto required to generate the open-shell intermediate. Thus, nucleophilic attack on the alkene radical cation generates the radical required for the tandem sequence, but under oxidizing conditions this is typically converted to the corresponding cation before it may be used to advantage in any radical process.⁴ The general underexploitation of alkene radical cations in synthesis, when compared to radicals themselves, can also be attributed

Scheme 1. Resonance Stabilization in Alkene Radical Cations

$$\stackrel{\oplus}{\xrightarrow{}}_{-/-} \stackrel{\bullet}{\xrightarrow{}} \stackrel{\bullet}{\xrightarrow{}}_{-/-} \stackrel{\oplus}{\xrightarrow{}} \stackrel{\bullet}{\xrightarrow{}} \stackrel{$$

Scheme 2. Fragmentation of the β -Acetoxy- α -methoxyethyl Radical in Water

$$\begin{array}{c} 0 \\ MeO \\ \cdot \\ 1 \end{array} \begin{array}{c} 0 \\ H_2O \\ \cdot \\ \oplus \end{array} \end{array} \begin{array}{c} 0 \\ H_2O \\ \cdot \\ \oplus \end{array} \end{array} \begin{array}{c} 0 \\ H_2O \\ \cdot \\ \oplus \end{array} \end{array} \begin{array}{c} 0 \\ H_2O \\ HO \end{array} \end{array} \begin{array}{c} MeO \\ HO \end{array}$$

in large part to the oxidizing conditions required for their generation from alkenes. In effect, the alkene precursor to the radical cation must be the HOMO of the substrate which clearly limits the range of compatible nucleophiles.

An alternative, nonoxidative means of generating alkene radical cations would clearly offer many advantages, including the potential to engineer tandem polar/radical crossover sequences which are the subject of this Article. The possibility of such an entry to alkene radical cations was first recognized by Gilbert and Norman, who suggested that the transformation of radical 1 to 2 in aqueous acid was best explained by an initial fragmentation to an alkene radical cation and an acetate anion followed by trapping with water (Scheme 2).⁵

Subsequently, it was recognized that a similar fragmentation could be used to rationalize the cleavage of DNA, by expulsion

^{(1) (}a) Malacria, M. Chem. Rev. 1996, 96, 289. (b) Ryu, I.; Sonoda, N.; Curran,

 ^{(1) (}a) Matacha, M. Centa, Rev. 1996, 96, 209, 209, (b) Ryd, L., Solidda, N., Curlan, D. P. Chem. Rev. 1996, 96, 177.
 (2) (a) Bashir, N.; Patro, B.; Murphy, J. A. Adv. Free Radical Chem. 1999, 2, 123. (b) Murphy, J. A. In Radicals in Organic Synthesis; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, p 298.
 (3) (a) Hintz, S.; Heidbreder, A.; Mattay, J. In Topics in Current Chemistry;

Mattay, J., Ed.; Springer: Berlin, 1996; Vol. 177, p 77. (b) Bauld, N. L.; Bellville, D. J.; Harirchian, B.; Lorenz, K. T.; Pabon, R. A.; Reynolds, D. W.; Wirth, D. D.; Chiou, H.-S.; Marsh, B. K. Acc. Chem. Res. 1987, 20, 371. (c) Schmittel, M.; Burghart, A. Angew. Chem., Int. Ed. Engl. 1997, 36, 2550.

⁽⁴⁾ Of course, it is certainly possible to take advantage of this second oxidation as illustrated by Moeller's recent synthesis of nemorensic acid: Liu, B.; Duan, S.; Sutterer, A. C.; Moeller, K. D. J. Am. Chem. Soc. 2002, 124, 10101

⁽⁵⁾ Gilbert, B. C.; Larkin, J. P.; Norman, R. O. C. J. Chem. Soc., Perkin Trans. 2 **1972**, 794.

Scheme 3. General Mechanism Relating the β -(Phosphatoxy)alkyl Radical and Alkene Radical Cations



of a 3'-O-phosphate, following hydrogen atom abstraction from the C4' under conditions of ionizing radiation.⁶ In the intervening years, much indirect evidence has been advanced in support of the radical ionic fragmentation of radicals with good leaving groups β - to the radical⁷ culminating in the direct observation of certain radical cations by the time-resolved laser flash photolysis technique in polar solvents.^{8,9} Strong kinetic evidence has been advanced that supports the intermediacy of alkene radical cations in the rearrangements of β -(phosphatoxy)alkyl^{8,10} and, probably, β -(acyloxy)alkyl radicals^{8,10d,11} even in nonpolar media such as benzene. A model has been put forward to unify all of the various rearrangement and fragmentation reactions of β -(phosphatoxy)alkyl and related radicals in which the first step is radical ionic fragmentation to an alkene radical cation/anion contact ion pair (Scheme 3).8b,12 The subsequent evolution of this contact ion pair to either fragmentation or rearrangement products, or indeed back to the starting radical, is a function of substituent and solvent which leaves considerable room for the synthetic chemist to maneuver. Indeed, this model underpins all of our current thinking in the area, including the design of the systems presented below.

On the basis of the above analysis, we have designed a number of systems in which a built-in allylamine traps an alkene radical cation, generated by the fragmentation approach, with the formation of a first ring. In the second leg of this tandem polar/radical crossover sequence, a radical cyclization closes the final ring. This is followed by hydrogen abstraction from a stannane which completes the product formation and regenerates a stannyl radical. The complete sequence may therefore be termed a radical ionic chain reaction. We describe here the

- (6) (a) von Sonntag, C. The Chemical Basis of Radiation Biology; Taylor and Francis: London, 1987. (b) von Sonntag, C.; Hagen, U.; Schon-Bopp, A.; Schulte-Frohlinde, D. In Advances in Radiation Biology; Lett, J. T., Adler, H. Eds: Academic Press: New York 1981: Vol. 9, n. 109
- H., Eds.; Academic Press: New York, 1981; Vol. 9, p 109.
 (7) (a) Beckwith, A. L. J.; Crich, D.; Duggan, P. J.; Yao, Q. Chem. Rev. 1997, 97, 3273. (b) Gugger, A.; Batra, R.; Rzadek, P.; Rist, G.; Giese, B. J. Am. Chem. Soc. 1997, 119, 8740.
- (8) (a) Whitted, P. O.; Horner, J. H.; Newcomb, M.; Huang, X.; Crich, D. Org. Lett. **1999**, *1*, 153. (b) Newcomb, M.; Horner, J. H.; Whitted, P. O.; Crich, D.; Huang, X.; Yao, Q.; Zipse, H. J. Am. Chem. Soc. **1999**, *121*, 10685.
- (9) The highly delocalized alkene radical cation of 1,1-dimethoxyethene could be observed directly by ESR spectroscopy following generation by a fragmentation approach: Behrens, G.; Bothe, E.; Koltzenberg, G.; Schulte-Frohlinde, D. J. Chem. Soc., Perkin Trans. 2 1980, 883.
- Inaginetiation applicate. Journals, G., Joure, J., Koltzcholig, G., Schule-Frohlinde, D. J. Chem. Soc., Perkin Trans. 2. 1980, 883.
 (10) (a) Crich, D.; Yao, Q. J. Am. Chem. Soc. 1993, 115, 1165. (b) Crich, D.; Yao, Q.; Filzen, G. F. J. Am. Chem. Soc. 1995, 117, 11455. (c) Koch, A.; Lamberth, C.; Wetterich, F.; Giese, B. J. Org. Chem. 1993, 58, 1083. (d) Crich, D. In Radicals in Organic Synthesis; Renaud, P., Sibi, M., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, p 188.
- Wiley-VCH: Weinheim, 2001; Vol. 2, p 188.
 (11) (a) Surzur, J.-M.; Teissier, P. C. R. Acad. Sci. Fr. Ser. C 1967, 264, 1981.
 (b) Tanner, D. D.; Law, F. C. J. Am. Chem. Soc. 1969, 91, 7535.
- (12) A closely related scheme was also advanced earlier by Sprecher: Sprecher, M. Chemtracts: Org. Chem. 1994, 7, 115.

successful implementation of this general scheme in the formation of a number of fused and bicyclic heterocyclic amines.

Results and Discussion

In the planning of radical chain reactions, knowledge of the kinetics of the individual steps and of their competitors is extremely advantageous.¹³ The same will evidently be true in the design of radical ionic chain reactions, and, accordingly, we open this discussion with a consideration of the relevant, available data. The rate constants of immediate interest are those concerning the (i) fragmentation of β -(phosphatoxy)alkyl radicals to alkene radical cations,^{7,8,14} (ii) addition of nucleophiles to alkene radical cations,^{7b,14c,15} and (iii) recombination within contact ion pairs, that is, the competing rearrangement reactions.^{7,8,16} The situation, however, is complex, with different kinetic methods often yielding disparate results because of their probing the radical cation at different stages of solvation.¹⁷ Nevertheless, it is evident from the available literature that fragmentations are accelerated in more polar solvents and that nucleophilic attack patterns reflect those of closed-shell systems.

Initial experiments with allyl alcohol as an intermolecular nucleophile trapping a fragmentation generated β , β -dimethylstyrene radical cation/diphenyl phosphate anion pair revealed that high concentrations of the nucleophile were required to out compete recombination leading to the rearrangement product.^{18,19} We therefore focused on the considerably more nucleophilic allylamines²⁰ and targeted intramolecular systems as these typically permit the assembly of more complex systems.

In designing the desired sequences, we determined that a suitable radical precursor compatible with the presence of a nucleophile was required. The radical precursor must furthermore be consistent with, and preferentially stabilize, the adjacent leaving group. In an earlier tandem system with a built-in alcohol as a nucleophile, we overcame this problem by employing a C-H bond as a radical precursor and by making double usage of the oxygen, first as an alkoxyl radical to bring about 1,5-hydrogen abstraction, thereby generating desired radical, and,

- (13) (a) Ingold, K. U.; Griller, D. Acc. Chem. Res. 1980, 13, 317. (b) Newcomb, M. Tetrahedron 1993, 49, 1151. (c) Newcomb, M. In Radicals in Organic Synthesis; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, p 317.
- (14) (a) Koltzenburg, G.; Behrens, G.; Schulte-Frohlinde, D. J. Am. Chem. Soc. 1982, 104, 7311. (b) Cozens, F. L.; O'Neill, M.; Bogdanova, R.; Schepp, N. J. Am. Chem. Soc. 1997, 119, 10652. (c) Horner, J. H.; Taxil, E.; Newcomb, M. J. Am. Chem. Soc. 2002, 124, 5402.
- N. J. Am. Chem. Soc. 1997, 119, 1052. (c) Holida, J. H., Taxii, E., Newcomb, M. J. Am. Chem. Soc. 2002, 124, 5402.
 (15) (a) Johnston, L. J.; Schepp, N. P. J. Am. Chem. Soc. 1993, 115, 6564. (b) Johnston, L. J.; Schepp, N. P. Pure Appl. Chem. 1995, 67, 71. (c) Johnston, L. J.; Schepp, N. P. Adv. Electron-Transfer Chem. 1996, 5, 41.
 (16) (a) Crich, D.; Jiao, X.-Y. J. Am. Chem. Soc. 1996, 118, 6666. (b) Choi, Chem. 1996, 118, 6666.
- (16) (a) Crich, D.; Jiao, X.-Y. J. Am. Chem. Soc. 1996, 118, 6666. (b) Choi, S.-Y.; Crich, D.; Horner, J. H.; Huang, X.; Newcomb, M.; Whitted, P. O. Tetrahedron 1999, 59, 3317.
- (17) For example, time-resolved LFP studies of alkene radical cations generated according to Scheme 3 using a nanosecond laser only detect the diffusively free radical cation and so are unable to provide data on the rates of formation of contact ion pairs or of their trapping. This situation arises because diffusion out of the contact ion pair is expected to be faster than the nanosecond time scale of the instrument: Arnold, B. R.; Noukakis, D.; Farid, S.; Goodman, J. L.; Gould, I. R. J. Am. Chem. Soc. 1995, 117, 4399. For a discussion, see ref 14c.
- (18) This is not surprising given that the bimolecular rate constant for the addition of methanol to the $\beta_{\beta}\beta$ -dimethylstyrene radical cation is only 2 × 10⁵ M⁻¹ s⁻¹ (at 20 °C in trifluoroethanol),^{15a} whereas the unimolecular rate constant for β -(phosphatoxy)alkyl rearrangement of the β -(diphenylphosphatoxy)- β -phenyl- α , α -dimethyl radical, that is, the rearrangement proceeding via the same contact ion pair, is 1.2 × 10⁶ s⁻¹ in benzene and 1.8 × 10⁷ s⁻¹ in acetonitrile (both at 20 °C).^{16b}
- (19) For the use of allyl alcohol as a probe for alkene radical cations, see: Giese, B.; Beyrich-Graf, X.; Burger, J.; Kesselheim, C.; Senn, M.; Schafer, T. Angew. Chem., Int. Ed. Engl. 1993, 32, 1742.
- (20) The bimolecular rate constant for the addition of butylamine to the *p*-methoxystyrene radical cation in acetonitrile at 20 °C is much faster at $2.1 \times 10^9 \text{ M}^{-1} \text{ s}^{-1.15b}$









second, as a nucleophile to capture the ensuing alkene radical cation. A parallel scheme with a nitrogen nucleophile would make use of hydrogen atom abstraction by an aminium radical cation as, in the Hoffmann-Loeffler-Freytag reaction, unfortunately this leaves the amine in the form of an ammonium salt and, so, incapable of taking part in a subsequent nucleophilic reaction step.²¹ A suitable solution to the problem was found in the shape of nitroalkanes which react nicely with stannyl radicals, especially when tertiary.²² The use of a nitro group as a radical precursor additionally permits the rapid assembly of β -nitro alcohols by the Henry reaction, and the strongly electronwithdrawing nature of the nitro group stabilizes the β -nitrophosphates by retarding any premature solvolysis. In a test case, 2-nitropropane was condensed with benzaldehyde, and the product converted to the diphenyl phosphate 3, which was stable to silica gel chromatography. On treatment with tributyltin hydride²³ in 3:1 mixture of benzene and allyl alcohol at reflux, smooth conversion to a 1/10 trans/cis-mixture of 2,2,4-trimethyl-3-phenyltetrahydrofuran (4) was observed (Scheme 4), and it is apparent that the system generates the same alkene radical cation as was obtained previously by the decarboxylative approach.24,25

An intramolecular test involved the synthesis of the phosphorylated nitro acid 9, as set out in Scheme 5, now taking advantage of the ability of nitronate anions to participate in conjugate additions. Especially noteworthy here is the predominance of the Michael addition over any competing β -elimination

⁽²³⁾ In this chemistry, tributyl- and triphenyltin hydride may be used interchangeably. Triphenyltin hydride has the obvious advantage of not obscuring the upfield region of the ¹H NMR spectrum, which facilitates interpretation of spectra of crude reaction mixtures.



(25) For preliminary communications, see: (a) Crich, D.; Ranganathan, K.; Huang, X. Org. Lett. 2001, 3, 1917. (b) Crich, D.; Neelamkavil, S. Org. Lett. 2002, 4, 2573.



Figure 1. Transition states for the formation of 16.

 $\ensuremath{\textit{Scheme 6.}}$ Precursor Synthesis for a $\ensuremath{\textit{cine-exo}/exo}\xspace$ Mode Tandem Cyclization



from the nitronate. Treatment of the acid **9** with triphenyltin hydride and AIBN in benzene at reflux led to the isolation of the γ -lactone **10** in 90% yield by a process involving radical generation, fragmentation to the alkene radical cation, capture by the acid, and chain transfer with the stannane (Scheme 5).

An initial substrate for a tandem cyclization was prepared as outlined in Scheme 6, starting from the alcohol **11**, which was accessed by lithium aluminum hydride reduction of **8**.

Treatment of 15 with triphenyltin hydride and AIBN in benzene at reflux resulted in the formation of the pyrrolizidine 16 as a mixture of four diastereomers in the ratio of 2.7:1.6:1:1 and 85% overall yield (Table 1). After separation, the stereochemistry of the various isomers was assigned, as designated in Figure 1, by extensive NOE studies. The two major isomers (16a, 16b) have the phenyl group on the exo-surface of the bicyclic system and differ in the relative configurations of the two stereocenters formed in the final radical cyclization. As is typical in 5-hexenyl type cyclizations of benzylic radicals,²⁶ and indeed as is seen in the formation of 4 (Scheme 4), the major isomer has the *trans*-configuration about the newly formed C-Cbond. We propose therefore that the major isomer arises from a boatlike transition state (17a) that is a consequence of the preference of the phenyl group for the exo-surface and of the nascent C-C bond to be *trans*. The second major product arises from the chairlike transition state (17b), whereas the two minor products are the result of chair- and boatlike transition states with the phenyl on the more hindered endo-surface of the bicyclic system.

The formation of **16** may be viewed as a 5-*exo*-mode nucleophilic attack on the alkene radical cation derived from **15** followed by a 5-*exo*-radical cyclization, and we therefore categorize it as a 5-*exo*/5-*exo* tandem cyclization. We further denote this cyclization as having occurred with an effective *cine*-

⁽²¹⁾ Neutral aminyl radicals are insufficiently electrophilic to achieve rapid intramolecular hydrogen abstraction: Musa, O. M.; Horner, J. H.; Shahin, H.; Newcomb, M. J. Am. Chem. Soc. 1996, 118, 3862.

^{(22) (}a) Ono, N.; Miyake, H.; Kamimura, A.; Hamamoto, I.; Tamura, R.; Kaji, A. Tetrahedron **1985**, *41*, 4013. (b) Ono, N. The Nitro Group in Organic Synthesis; Wiley-VCH: New York, 2001.

 ^{(26) (}a) Walling, C.; Cioffari, A. J. Am. Chem. Soc. 1972, 94, 6064. (b) Taber,
 D. F.; Wang, Y.; Pahutski, T. F. J. Org. Chem. 2000, 65, 3861. (c) Miranda,
 L. D.; Zard, S. Z. Chemm Commun. 2001, 1068.

Table 1. Tandem Reactions for the Formation of Fused and Bicyclic Heterocycles



^{*a*} Overall displacement of the phosphate leaving group by the nucleophile. ^{*b*} Nucleophilic attack/radical cyclization. ^{*c*} Bonds formed by the nucleophilic attack are in bold blue, and those achieved by radical cyclization are in bold red. ^{*d*} No cyclization was observed.

substitution of the phosphate group.²⁷ The delocalized nature of the intermediate alkene radical cation in these cyclizations (Scheme 1) suggests reactions may be set up with either overall *cine-* or *ipso-*substitution of the original leaving group; indeed, this was demonstrated to be the case in our earlier work on capture with allyl alcohol.²⁴ In pursuing tandem cyclizations beyond the formation of **16** from **15**, we have generally found

it more convenient and straightforward to prepare substrates for the *ipso*-mode. Scheme 7 sets out very straightforward protocols

⁽²⁷⁾ It should be noted that Zipse has considered substitutions closely related to the ones employed here as concerted displacements accelerated by the adjacent radical rather than as dissociative mechanisms. The balance of the experimental evidence, however, favors the dissociative pathway, and the computations continue to move in this direction with each successive cycle of refinement: Zipse, H. Acc. Chem. Res. **1999**, *32*, 571.





for the preparation of 28 and 29, precursors to pyrrolizidine and indolizidine skeletons by 5-exo/5-exo and 6-exo/5-exo sequences, respectively, both of which employ the overall ipsosubstitution. The cyclizations of 28 and 29 both proceed in good yield (Table 1) and result in the formation of approximately 1:1 mixtures of diastereoisomers.

By adjusting the substitution pattern on the alkene radical cation, it was thought possible to divert the initial nucleophilic cyclization to an endo-, rather than the hitherto employed exo-, mode. A test case for a 6-endo cyclization (44) was obtained from angelica lactone and benzylamine, as set out in Scheme 8. On heating to reflux in benzene with tributyltin hydride and AIBN, the piperidine 47 was obtained in 90% yield by the anticipated ipso-6-endo-process. It is instructive to compare the cyclizations of 15 and 44: both involve alkene radical cations doubly substituted at the proximal position; yet the nucleophilic attack in the first example takes place in the exo-mode, whereas in the latter case the endo-mode is highly favored. In the case of 15, it appears that the regioselectivity is determined by a combination of the trisubstituted nature of the alkene radical cation, which serves to retard the endo-mode attack, and the benzylic nature of the radical formed. Encouraged by the successful formation of the piperidine 47 from 44, we obtained two substrates for tandem cyclization (45 and 46) by similar routes (Scheme 8). The first of these provided the 1-aza-[3.2.1]bicyclooctane system 48 in good yield together with a minor amount of the piperidine 49 (Table 1) when exposed to the usual cyclization conditions. It is noteworthy that the slightly reduced yield in the formation of 48 is due to the follow-up radical cyclization, not to the initial nucleophilic attack.²⁸ This is readily understood in terms of the transition state for the radical cyclization which requires the allyl group to adopt a pseudoaxial position. The more interesting cyclization, though, is obviously that of 46 which leads to the formation of the 1-aza[4.2.1]bicyclononane skeleton 50 by means of a 7-endo nucleophilic cyclization followed up by the usual 5-exo radical ring closure: the slightly reduced yield here obviously reflects the slower nature of the 7-endo cyclization. Both bicyclic sysScheme 8. Precursor Synthesis for ipso-endo/exo-Mode Tandem Cyclizations Leading to Bridged Systems



tems (48 and 50) were formed as approximately 2:1 mixtures of diastereomers in the final radical step which remain unassigned because of difficulties in separation and the complexity of the spectra. The 1-azabicyclo[3.2.1]octane skeleton constitutes the nucleus of the 5,11-methanomorphanthridine (montanine) class of the Amaryllidaceae alkaloids²⁹ and of the novel Lycpodium alkaoid lyconadin A.30 Moreover, 1-azabicyclo-[3.2.1] octane derivatives have been found to be potent muscarinic agonists with antipsycotic-like activity³¹ and to be dopamine transporter inhibitors.^{32,33} The 1-azabicyclo[4.2.1]nonane skeleton constitutes the nucleus of the Iboga alkaloids such as catharanthine.34 Additionally, certain medicinally useful vinblastine-type (vincorine) alkaloids also embody this skeleton.35 The basic tandem cyclizations of 45 and 46 (Table 1) coupled with their ready preparation therefore provide novel entries into valuable classes of molecules with the potential to afford new substitution patterns for medicinal chemistry research.

- (29) Martin, S. F. In The Alkaloids; Brossi, A., Ed.; Academic Press: San Diego, 1987; Vol. 30, p 252. Kobayashi, J.; Hirasawa, Y.; Yoshida, N.; Morita, H. J. Am. Chem. Soc.
- (30)**2001**, 123, 5901.
- (31)Sauerberg, P.; Jeppesen, L.; Olesen, P. H.; Rasmussen, T.; Swedberg, M. D. B.; Sheardown, M. J.; Fink-Jensen, A.; Thomsen, C.; Thogersen, H.; Rimvall, K.; Ward, J. S.; Calligaro, D. O.; Delapp, N. W.; Bymaster, F. P.; Shannon, H. E. J. Med. Chem. 1998, 41, 4378.
- Tamiz, A. P.; Smith, M. P.; Enyedy, I.; Flippen-Anderson, J.; Zhang, M.; Johnson, K. M.; Kozikowski, A. P. Bioorg. Med. Chem. Lett. 2000, 10, (32)1681.
- (33) Indeed, Scifinder Scholar locates >2000 substances containing the 1-azabicyclo[3.2.1]octane nucleus with the majority in the medicinal and patent literature, suggesting that this may be an example of a "privileged structure": (a) Ariens, E. J.; Beld, A. J.; Rodrigues de Miranda, J. F.; Simonis, A. M. In *The Receptors: A Comprehensive Treatise*; O'Brien, R. D., Ed.; Plenum: New York, 1979; Vol. 1, pp 33. (b) Evans, B. E.: Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. J. Med. Chem. 1988, 31, 2235.
 (34) Popik, P.; Skolnick, P. Alkaloids 1999, 52, 197.
 (35) Atta-Ur-Rahman; Iqbal, I.; Nasir, H. Stud. Nat. Prod. Chem. 1994, 14, 805.

⁽²⁸⁾ For a related, rare, example of the cyclization of a 3-allylcyclohexyl radical leading to the formation of the bicyclo[3.2.1]octane type skeleton, see: Hart, D. J.; Tsai, Y. M. J. Org. Chem. **1982**, 47, 4403.

Scheme 9. Precursor Synthesis for *ipso-endo/exo-dig*-Mode Tandem Cyclizations



With a view for retaining more functionality in the tandem products, a sequence terminating in a 5-*exo-dig* radical cyclization was also pursued. The substrate (**61**) for this reaction, while potentially available by an obvious minor variation in Scheme 7, was obtained from commercially available 4-aminobutyral-dehyde diethylacetal as shown in Scheme 9. In this instance (Table 1), the product (**63**) was obtained as a 5.7/1 *E:Z* mixture of isomers, assigned by NOE measurements, with the major *E*-isomer arising with approach of the stannane to the more exposed side of the rapidly inverting vinyl radical.³⁶

A final substrate (**62**), intended to probe the limits of the system, was also obtained by the general pathway of Scheme 9. Unfortunately, when this compound was subjected to the standard cyclization conditions, a complex mixture was obtained from which no cyclized products, neither 4-*exo*/5-*exo* nor any other possible regioisomers, could be isolated (Table 1). We believe this failure to be the result of the slower nature of the 4-*exo* cyclization coupled with the possibility of C–C bond cleavage in the intermediate alkene radical cation (Scheme 10).^{3c,37}

As a final test of the nucleophilic trapping of fragmentation generated alkene radical cations, we prepared substrate **68** as shown in Scheme 11. Radical ionic fragmentation of this system would clearly push the limits as it involves fragmentation of strong, primary C–O by a stabilized, tertiary benzylic radical.

In the event, in benzene, no cyclization was observed, suggesting either no fragmentation or an equilibrium between the contact ion pair and the initial radical that favored the latter to such an extent that ring closure on the radical cation by the weakly nucleophilic alcohol was not kinetically competent. To overcome this, we conducted the reaction in a 1:1 mixture of benzene and acetonitrile and were rewarded by the isolation of 30% of the cyclized product **69** (Scheme 12). This dramatic

Scheme 10. Possible Cleavage Modes of a 4-Aminoalkene Radical Cation







Scheme 12. Formation of a Tetrahydropyran



solvent effect can obviously be understood in terms of stabilization of the contact ion pair in the more polar solvent, thereby bringing about a shift in the initial equilibrium which enables capture of the contact ion pair by the alcohol.³⁸

In summary, alkene radical cations derived from the fragmentation of β -(phosphatoxy)alkyl radicals provide for a very versatile series of tandem polar/radical crossover sequences involving radical ionic chain reactions and leading to a broad selection of fused and bridged nitrogen heterocycles. Nitroalkanes are ideal radical precursors in this system, permitting rapid assembly of the substrates by virtue of the rich chemistry of the nitro group and preventing premature displacement of the leaving group by their strongly electron-withdrawing nature. The substitution patterns can be engineered so as to favor nucleophilic attack on the radical cations in either the *exo-* or the *endo*cyclic modes.

Acknowledgment. We thank the NSF (CHE 9986200) for support of our work in this area.

Supporting Information Available: Complete experimental details and characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA035639S

⁽³⁶⁾ Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996.

⁽³⁷⁾ For the application of related fragmentations in synthesis, see: Aubele, D. L.; Floreancig, P. E. Org. Lett. 2002, 4, 3443.

⁽³⁸⁾ It is interesting to note that, although tributyltin hydride is not soluble in acetonitrile, and indeed partitioning between acetonitrile and hexanes is a favorite method for the removal of organotin byproducts from more polar products,³⁹ there is sufficient solubility in a hot 1/1 mixture of benzene and acetonitrile for chain reactions to proceed smoothly.

⁽³⁹⁾ Berge, J. M.; Roberts, S. M. Synthesis 1979, 471.