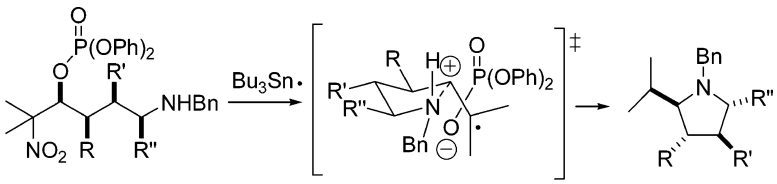
Article

Stereochemical Memory Effects in Alkene Radical Cation/Anion Contact Ion Pairs: Effect of Substituents, and Models for Diastereoselectivity

David Crich, and Krishnakumar Ranganathan

J. Am. Chem. Soc., **2005**, 127 (27), 9924-9929• DOI: 10.1021/ja051657t • Publication Date (Web): 15 June 2005



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 2 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

J|A|C|S
ARTICLES
Published on Web 06/15/2005

Stereochemical Memory Effects in Alkene Radical Cation/Anion Contact Ion Pairs: Effect of Substituents, and Models for Diastereoselectivity

David Crich* and Krishnakumar Ranganathan

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

Received March 15, 2005; E-mail: Dcrich@uic.edu

Abstract: A series of 12 stereochemically defined 2,*m*-dimethyl- and 2,*m*,*n*-trimethyl-6-benzylamino-2-nitro-3-(diphenylphosphatoxy)hexanes have been synthesized and their cyclization reactions leading to di- and trisubstituted *N*-benzyl pyrrolidines examined in the presence of tributyltin hydride and azoisobutyronitrile in benzene at reflux. The cyclizations are interpreted in terms of generation of an alkyl radical by abstraction of the nitro group with a stannyl radical. The phosphate leaving group is then expelled in a heterolytic cleavage to give a contact alkene radical cation/phosphate anion pair. For the majority of the examples studied, the cyclizations are best understood in terms of nucleophilic attack by the amine on the opposite face of the alkene radical cation to the one shielded by the leaving group, within the confines of the initial contact ion pair, resulting in overall cyclization with inversion of configuration. Dependent on the relative stereochemistry of the substituents, the cyclization is envisaged as taking place through either chair-like or twist-boat-like transition states with the maximum number of substituents pseudo-equatorial. The model breaks down when cyclization on the initial contact ion pair would engender significant destabilizing steric interactions, especially ^{1,3}A strain in the alkene radical cation. In these cases a fully equilibrated Beckwith−Houk-type transition state provides a satisfactory model. Interesting examples of matching and mismatching in the Corey-type oxazaborolidine-mediated reduction of alkyl (methyl-1-nitroethyl) ketones by a β-methyl group in the alkyl chain are reported, and the mismatching is attributed to a developing *syn*-pentane interaction in the transition state.

Introduction

The existence of stereochemical memory effects arising from nucleophilic attack on carbocations within the confines of contact ion pairs in classical solvolysis reactions is widely recognized and appreciated.[1,2] Similarly, the existence of memory effects in free radical reactions has been amply demonstrated in recent years.[3,4] The classical generation of alkene radical cations by one-electron oxidation of the corresponding alkenes,[5] however, has hitherto precluded the possibility of such a phenomenon in alkene radical cation chemistry. The demonstration that β-(phosphatoxy)alkyl radicals[6] undergo diastereoselective rearrangement in nonpolar solvents by a heterolytic fragmentation to an alkene radical cation/anion contact ion pair, followed by the open-shell equivalent of internal return,[7] raised the possibility that stereochemical memory effects in the nucleophilic substitution of these fascinating reactive intermediates might finally be realized. We describe an extensive series of investigations designed to test this hypothesis and derive a stereochemical model accounting for the effect of single and multiple substituents in the cyclization of γ-amino alkene radical cations within the confines of a contact radical ion pair.[8] The model has predictive value and should find application in synthetic schemes employing these intermediates.

(1) (a) Winstein, S.; Clippinger, E.; Fainberg, A. H.; Heck, R.; Robinson, G. C. *J. Am. Chem. Soc*. **1956**, *78*, 328. (b) Raber, D. J.; Harris, J. M.; Schleyer, P. v. R. In *Ions and Ion Pairs in Organic Reactions*; Szwarc, M., Ed.; Wiley: New York, 1974; Vol. 2, p 247. (c) Richard, J. P.; Amyes, T. L.; Toteva, M. M.; Tsuji, Y. *Adv. Phys. Org. Chem.* **2004**, *39*, 1.

(2) For a recent example from our own laboratory, see: Crich, D.; Chandrasekera, N. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5386.

(3) For recent examples, see: (a) Buckmelter, A. J.; Powers, J. P.; Rychnovsky, S. D. *J. Am. Chem. Soc*. **1998**, *120*, 5589. (b) Buckmelter, A. J.; Kim, A. I.; Rychnovsky, S. D. *J. Am. Chem. Soc*. **2000**, *122*, 9386. (c) Dalgard, J. E.; Rychnovsky, S. D. *Org. Lett.* **2004**, *6*, 2713. (d) Rychnovsky, S. D.; Hata, T.; Kim, A. I.; Buckmelter, A. J. *Org. Lett*. **2001**, *3*, 807. (e) Sauer, S.; Schumacher, A.; Barbosa, F. G. B. *Tetrahedron Lett.* **1998**, *39*, 685. (f) Giese, B.; Wettstein, P.; Stahelin, C.; Barbosa, F.; Neuberger, M.; Zehnder, M.; Wessig, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 2586.

(4) For a recent review on stereochemical memory effects in synthesis, see: Zhao, H.; Hsu, D. C.; Carlier, P. R. *Synthesis* **2005**, 1.

(5) For reviews, see: (a) Schmittel, M.; Burghart, A. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2550. (b) Hintz, S.; Heidbreder, A.; Mattay, J. In *Topics in Current Chemistry*; Mattay, J., Ed.; Springer: Berlin, 1996; Vol. 177, p 77. (c) 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.

(6) (a) Beckwith, A. L. J.; Crich, D.; Duggan, P. J.; Yao, Q. *Chem. Rev.* **1997**, *97*, 3273. (b) Crich, D. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, p 188.

(7) (a) Newcomb, M.; Horner, J. H.; Whitted, P. O.; Crich, D.; Huang, X.; Yao, Q.; Zipse, H. *J. Am. Chem. Soc*. **1999**, *121*, 10685. (b) Whitted, P. O.; Horner, J. H.; Newcomb, M.; Huang, X.; Crich, D. *Org. Lett*. **1999**, *1*, 153. (c) Bales, B. C.; Horner, J. H.; Huang, X.; Newcomb, M.; Crich, D.; Greenberg, M. M. *J. Am. Chem. Soc.* **2001**, *123*, 3623. (d) Newcomb, M.; Miranda, N.; Huang, X.; Crich, D. *J. Am. Chem. Soc.* **2000**, *122*, 6128. (e) Bagnol, L.; Horner, J. H.; Newcomb, M. *Org. Lett.* **2003**, *5*, 5055. (f) Horner, J. H.; Bagnol, L.; Newcomb, M. *J. Am. Chem. Soc.* **2004**, *126*, 14979. (g) Wang, Y.; Grimme, S.; Zipse, H. *J. Phys. Chem. A* **2004**, *108*, 2324.

(8) For a preliminary communication, see: Crich, D.; Ranganathan, K. *J. Am. Chem. Soc*. **2002**, *124*, 12422.

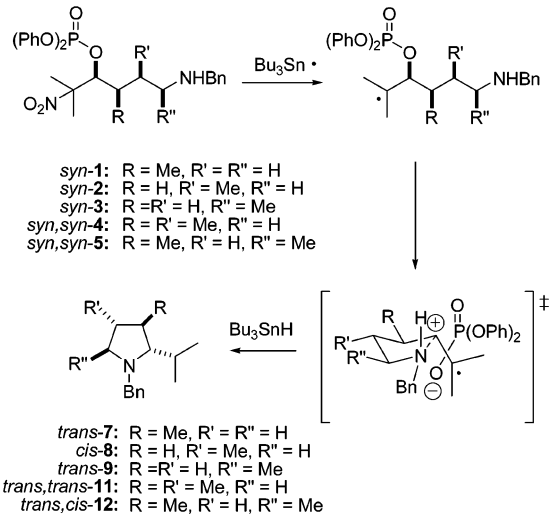
10.1021/ja051657t CCC: $30.25

Results and Discussion

Early stereochemical and isotopic labeling experiments from our laboratory on the β-(phosphatoxy)alkyl radical rearrangement,[9] when interpreted in terms of the ion pair mechanism for this rearrangement,[7] coupled with well-known nucleophilic attack[10] on alkene radical cations, lead directly to the conclusion that nucleophilic attack on fragmentation-derived alkene radical cations has the potential to exhibit stereochemical memory effects. In order for memory effects to be observed, it is necessary that the rate of nucleophilic attack on the contact ion pair be more rapid than the rate of memory-destroying solvation of the contact ion pair. The rate of attack of butylamine on the *p*-methoxystyrene radical cation has been determined to be 2.5×10^9 M^{-1} s^{-1} in acetonitrile at 25 °C,[10e,f] whereas Farid and co-workers find that radical cation/radical anion pairs solvate with estimated rate constants of 10^8-10^9 s^{-1} in dichloroethane at room temperature.[7f,11] These rate constants, and other considerations of a more practical nature, prompted us to focus on cyclization reactions with a view to increasing the effective molarity of the nucleophile and the rate of the trapping reaction.

Radical Ionic Cyclization and Assignment of Product Stereochemistry. A series of 12 substrates were prepared as described in full in the Supporting Information.[12] The radical ionic cascade reactions were conducted by heating a mixture of substrate (0.02 M), tributyltin hydride (1.5 molar equivalents), and azobisisobutyronitrile (AIBN, 0.3 molar equivalents) to reflux in benzene under nitrogen for 40 h with the periodic addition of further AIBN. The use of syringe pump techniques and lower reaction temperatures was investigated, but neither was found to support the radical ionic chain process. The basic products were isolated from the reaction mixture by extraction into dilute hydrochloric acid and re-extraction into ether following basification, with product ratios being determined by integration of the ^{1}H NMR spectra of the extracts before chromatographic separation.[13] The results obtained are reported in Table 1. As expected from previous studies on simpler systems, no evidence was found for the alternative formation of piperidines by 6-*endo* ring closure.[14,15]

Scheme 1. Transition State Model A: All Pseudo-equatorial



Stereochemical Models for Cyclization. Of the 12 cyclizations examined, 9 take place with moderate to high degrees of diastereoselectivity favoring the product with formal inversion of configuration (Table 1, entries 1, 3−7, 9, 11, and 12). These reactions are best understood in terms of fragmentation of the initial radical to a contact alkene radical cation/phosphate anion pair with the phosphate shielding the face of the molecule from which it has just departed. This ion pair undergoes rapid intramolecular nucleophilic attack by the amine in an *ipso*-5-*exo* manner on the face of the alkene radical opposite to the one shielded by the phosphate, before any scrambling of the ion pair. Among these nine examples, five may be accounted for by a chair-like transition state with all substituents pseudo-equatorial (Scheme 1), even if the selectivity is reduced, as in the case of *syn*-**3** (Table 1, entry 5).

The four remaining examples of inversion (Table 1, entries 4, 6, 11, and 12) all proceed with predominant inversion of configuration but through transition states that necessarily include pseudo-axial substituents if a chair-like conformation is invoked. This leads to the hypothesis of competing twist-boat-like transition states in these cases (Scheme 2).[17]

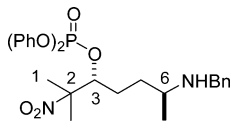
The other extreme, retention of configuration, is represented by entries 2 and 8, and to a lesser extent by entry 10, in Table 1. These systems all share the *anti* configuration between the departing phosphate and the methyl group at the vicinal stereogenic center and cyclize with predominant retention of configuration. We view these reactions in terms of the transition state for cyclization of the initial contact ion pair, with attack

(9) (a) Crich, D.; Yao, Q. *Tetrahedron Lett.* **1993**, *34*, 5677. (b) Crich, D.; Yao, Q. *J. Am. Chem. Soc.* **1994**, *116*, 2631. (c) Crich, D.; Yao, Q.; Filzen, G. F. *J. Am. Chem. Soc.* **1995**, *117*, 11455. (d) Crich, D.; Sartillo-Piscil, F.; Quintero-Cortes, L.; Wink, D. J. *J. Org. Chem.* **2002**, *67*, 3360. (e) Crich, D.; Huang, W. *J. Am. Chem. Soc.* **2001**, *123*, 9239.

(10) (a) Mihelcic, J.; Moeller, K. D. *J. Am. Chem. Soc.* **2004**, *126*, 9106. (b) Duan, S.; Moeller, K. D. *Org. Lett.* **2001**, *3*, 2685. (c) Giese, B.; Beyrich-Graf, X.; Burger, J.; Kesselheim, C.; Senn, M.; Schafer, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1742. (d) Crich, D.; Huang, X.; Newcomb, M. *J. Org. Chem.* **2000**, *65*, 523. (e) Johnston, L. J.; Schepp, N. P. *J. Am. Chem. Soc.* **1993**, *115*, 6564. (f) Johnston, L. J.; Schepp, N. P. *Adv. Electron-Transfer Chem.* **1996**, *5*, 41.

(11) Arnold, B. R.; Noukakis, D.; Farid, S.; Goodman, J. L.; Gould, I. R. *J. Am. Chem. Soc.* **1995**, *117*, 4399.

(12) In this paper, nitrophosphates and their precursors are numbered as indicated. The *N*-benzyl group is considered part of the extended zigzag conformation backbone, and all methyl groups are considered substituents. For purposes of consistency throughout the paper, this system is applied even to compounds **3**, **5**, and **6**, which would be more correctly shown with the methyl group as part of the backbone and the amine as a substituent.



anti

(13) No significant difference was observed on the product ratios, whether determined on the crude reaction mixtures or following the extractive workup.

(14) Crich, D.; Ranganathan, K.; Neelamkavil, S.; Huang, X. *J. Am. Chem. Soc.* **2003**, *125*, 7942.

(15) The isolated yields for these cyclizations, as reported in Table 1, are typical for reactions of this type.[14] As the focus of this study was the stereoselectivity of the ring closure, no attempt was made to isolate and characterize products arising from other reaction pathways. In previous work, we have identified a number of competing decomposition pathways for the alkene radical cation, including overall reduction to the corresponding alkene[7] and CC bond cleavage.[14]

(16) In the trisubstituted pyrrolidines **11**−**13**, the first stereochemical descriptor refers to the relationship between the isopropyl group on the 2-position and the next substituent around the ring. The second stereochemical descriptor applies to the relationship between the two methyl groups; thus, for example, *cis*,*trans*-**11** refers to 2,3-*cis*-3,4-*trans*-1-benzyl-2-isopropyl-3,4-dimethylpyrrolidine.

(17) It should be noted, however, that 1,3-diaxial interactions are less important in chair-like transition states with their longer partial bonds than in actual chair form rings, which leaves open the possibility that these cyclizations may occur through the chair-like transition states.

(18) In this scheme, *anti*,*anti*-**6** and *trans*,*cis*-**13**, and the associated transition states, are represented as their enantiomers for ease of comparison.

Table 1. Radical−Ionic Cascade Reactions[16]

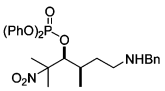
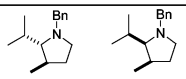
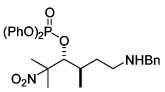
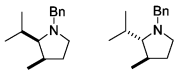
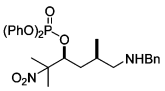
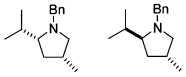
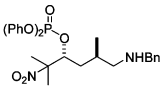
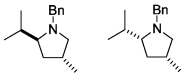
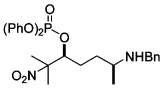
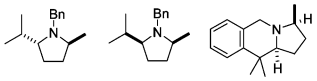
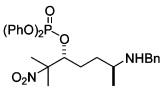
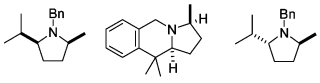
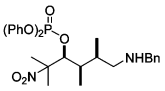
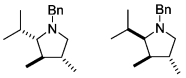
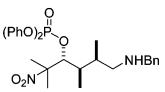
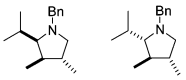
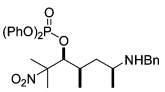
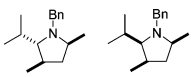
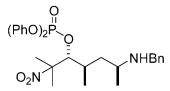
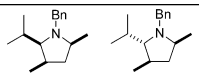
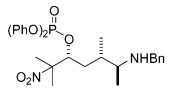
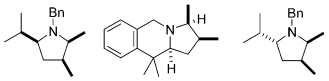
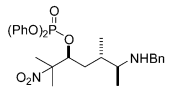
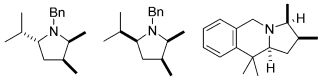
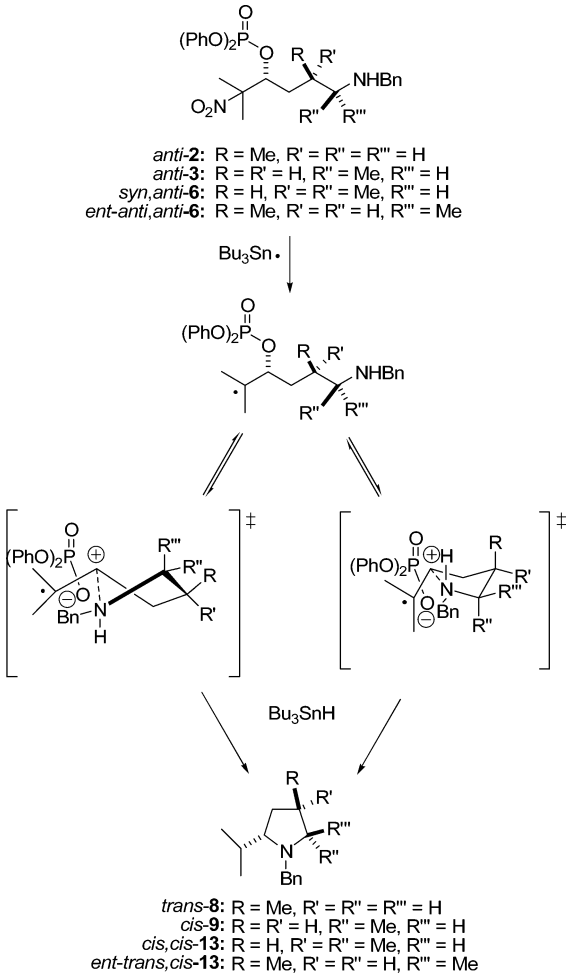
Entry	Substrate	Products, ratio	% Yield	% de	Major Mode[a]
1	 *syn*-**1**, 93% de	 *trans*-**7**, *cis*-**7** >25:1	50,	>95	inv.
2	 *anti*-**1**, 87% de	 *cis*-**7**, *trans*-**7** 1:2.4	45	40	ret.
3	 *syn*-**2**, 94% de	 *cis*-**8**, *trans*-**8** 13:1	56	86	inv
4	 *anti*-**2**, 87% de	 *trans*-**8**, *cis*-**8** 18:1	52	89	inv
5	 *syn*-**3**, 88% de	 *trans*-**9**, *cis*-**9**, **10** (*cis*-) 13:3:1	52	53	inv
6	 *anti*-**3**, 92% de	 *cis*-**9**, **10** (*cis*-), *trans*-**9** 4.2:1.7:1.0	51	71	inv
7	 *syn*,*syn*-**4**, 85% de	 *trans*,*trans*-**11**, *cis*,*trans*-**11** 16:1	38	88	inv
8	 *anti*,*syn*-**4**, 100% de	 *cis*,*trans*-**11**, *trans*,*trans*-**11** 1:1.7	49	26	ret
9	 *syn*,*syn*-**5**, 91% de	 *trans*,*cis*-**12**, *cis*,*cis*-**12** >29:1	49	>93	inv

Table 1. (Continued)

Entry	Substrate	Products, ratio	% Yield	% de	Major Mode[a]
10	 *anti*,*syn*-**5**, 100% de	 *cis*,*cis*-**12**, *trans*,*cis*-**12** 1:1.1	40	5	ret
11	 *syn*,*anti*-**6**, 100% de	 *cis*,*cis*-**13**, **14** (*cis*,*cis*), *trans*,*cis*-**13** 7.0:2.5:1.0	56	81	inv
12	 *anti*,*anti*-**6**, 100% de	 *trans*,*cis*-**13**, *cis*,*cis*-**13**, **14** (*cis*,*cis*) 13:2.8:1.0	55	55	inv

[a] Inv and ret refer to overall inversion and retention of configuration, respectively, at the site of substitution.

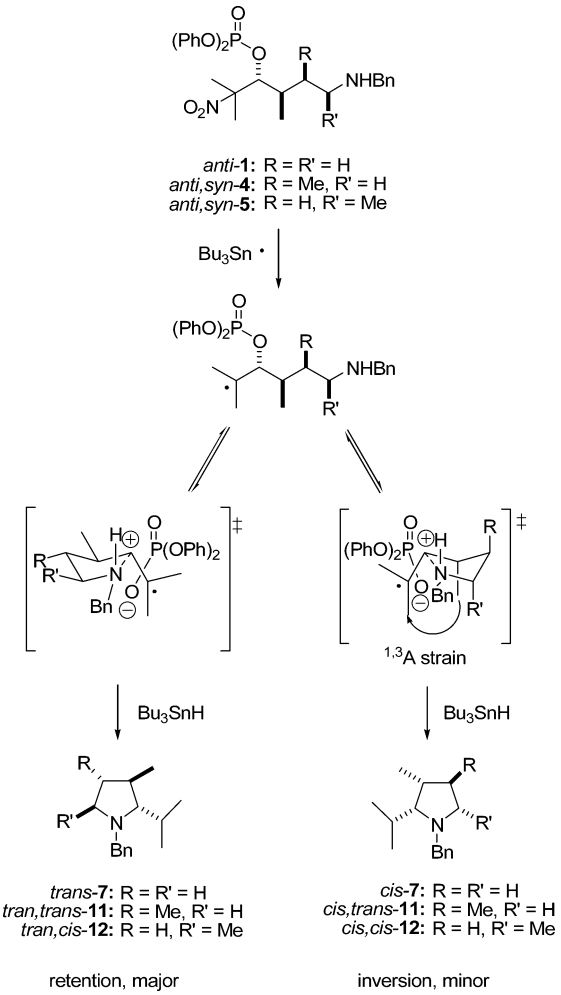
Scheme 2. Transition State Model B: Twist-Boats[18]



of the amine opposite to the face shielded by the phosphate, suffering from ^{1,3}A strain in the alkene radical cation moiety. This retards the initial cyclization to the extent that the migration of the phosphate between the faces of the alkene radical cation and conformational inversion of the skeleton lead to a second chair-like transition state for ring closure, resulting in overall retention of configuration (Scheme 3).

Comparison of entries 5 and 12 in Table 1 (*syn*-**3** and *anti*,*anti*-**6**), which differ only in the presence of the C-5 methyl group in *anti*,*anti*-**6**, is informative as both proceed with similar, reduced diastereoselectivity. Both also afford a minor hexahydropyrroloisoquinoline from the minor cyclization mode as discussed below. The implication is that both reactions proceed through similar transition states, with the role of the C-5 methyl group subordinate to that of the C-6 methyl group in the cyclization of *anti*,*syn*-**6**. In the above discussion, the cyclization of *syn*-**3** is assigned to model A, whereas that of *anti*,*anti*-**6** is placed under model B. Either, as discussed above, the effect of the axial methyl group in the chair-like transition state arising from *anti*,*anti*-**6** is minimal, or both cyclizations proceed through twist-boat-like transition states (Scheme 2) resulting from a minimization of steric interactions between the C-5 methyl and *N*-benzyl groups. Comparison between entries 6 and 11 of Table 1 (*anti*-**3** and *syn*,*anti*-**6**), again differing only in the presence of a methyl group at C-5, is also instructive as again the C-5 methyl group has only a minimal effect on the outcome of the cyclization. This lack of influence of the substituent at C-5 is again seen in a comparison of entries 3 and 4 in Table 1 (*syn*- and *anti*-**2**), and overall, we conclude that models A and B can reasonably be refined into a single model, most likely that of a chair-like transition state in which pseudo-axial substituents at C-5 are only minimally destabilizing. A chair-like transition state is ultimately favored over a common twist-boat-like transition state because of the problems arising in the initial transition state for the cyclization of *anti*-**1**, *anti*,*syn*-**4**, and *anti*,*syn*-**5** (Scheme 3, model C), which ultimately results in predominant cyclization with retention of configuration. As indicated, the problem here is one of ^{1,3}A strain in the alkene radical cation, which would be reduced in any twist-boat-like transition state.

Scheme 3. Transition State Model C: Retention of Configuration



Model C (Scheme 3) is akin to the Beckwith−Houk model[19] for the cyclization of substituted 5-hexenyl radicals with the main chain undergoing conformational equilibration before cyclization through the more stable transition state with the maximum number of substituents pseudo-equatorial. 5-*exo*-Alkyl radical cyclizations typically[20] have rate constants of 10^5-10^6 s^{-1}, but the nucleophilic cyclizations of amines onto alkene radical cations examined here are expected to be significantly faster. Intermolecular additions of butylamine to substituted styrene radical cations[10e,f] have rate constants of 10^9 M^{-1} s^{-1}, and it is reasonable to expect the present cyclizations to proceed with rate constants of at least 10^9 s^{-1}. It is therefore reasonable that cyclizations following models A and B (Schemes 1 and 2) take place before full scrambling of the geometry of the initial contact ion pair and, thus, before the system can sample the full range of conformations available to it. The fully equilibrated Beckwith−Houk-type model comes into play only when cyclization onto the initial contact ion pair is disfavored.

Formation of Pyrrolo[1,2-*b*]isoquinolines 10 and 14. Hexahydropyrrolo[1,2-*b*]isoquinolines are formed in 4 of the 12 cyclizations (Table 1, entries 5, 6, 11, and 12). In the case of *anti*-**3** (Table 1, entry 6), the pyrroloisoquinoline **10** arises from an oxidative cyclization of the major ring-closed radical,[21] whereas with *syn*-**3** the same pyrroloisoquinoline **10** is formed from the minor cyclization mode. In other words, while two stereoisomeric pyrroloisoquinolines are possible from *syn*- and *anti*-**3**, only one (**10**) is formed. The same scenario exists for the two isomers of susbstrate **6** when pyrroloisoquinoline **14** is formed from the major cyclization pathway in the cyclization of the *syn*,*anti*-isomer and from the minor pathway in the cyclization of the *anti*,*anti*-isomer. All four cases belong to radicals arising from model B (Scheme 2), twice as the major mode and twice as the minor mode. Obviously, in this system, with the *cis*-6-methyl group and 2-isopropyl radical, the pyrrolidine ring adopts a conformation in which the methyl group buttresses the *N*-benzyl moiety, forcing it closer to the isopropyl radical, thereby promoting the second cyclization. Presumably, in the corresponding *trans* series, the pyrrolidine ring adopts a conformation that allows for less compression between the methyl and benzyl groups.[22] The question arises as to why such a pyrroloisoquinoline was not formed in measurable amount in the cyclization of either *syn*,*syn*- or *anti*,*syn*-**5**, both of which have the requisite methyl group on the 5-position of the ring-closed radical. The answer must lie with the methyl group on the 3-position of the cyclized system, which may predispose the pyrrolidine ring to a conformation that minimizes the buttressing between the 5-methyl and *N*-benzyl groups. Alternatively, it is conceivable that the 3-methyl group impinges on the conformation of the vicinal isopropyl radical and prevents it from achieving the correct orbital alignment with the aromatic ring for cyclization.

Conclusion and Predictions

Alkene radical cations generated by heterolytic fragmentation of β-(phosphatoxy)alkyl radicals can undergo highly diastereoselective cyclization reactions with suitably positioned amine groups. These cyclizations take place at the level of the initial contact ion pair with attack by the amine on the opposite face of the alkene radical cation to the one shielded by the just-departed phosphate group. Onto this fundamental model for overall inversion of stereochemistry are layered the conformational and torsional effects of the chain linking the alkene radical cation to the nucleophile. The more selective cyclizations are best described by chair-like transition states, although the possibility of twist-boat-like analogues cannot be excluded. A 1,2-*anti* relationship between the departing phosphate and a vicinal substituent is highly detrimental to this model, owing to ^{1,3}A strain in the alkene radical cation, and results in a more Beckwith−Houk-like equilibrated model. Substituents having a 1,3-relationship with the departing phosphate group have little influence on diastereoselectivity. The influence of substituents in 1,4-relationship with the departing phosphate and geminal

(19) (a) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073. (b) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925. (c) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959. (d) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996.

(20) (a) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151. (b) Newcomb, M. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, p 317. (c) Ingold, K. U.; Griller, D. *Acc. Chem. Res.* **1980**, *13*, 317.

(21) Current thinking suggests that the cyclohexadienyl radical resulting from the second cyclization is oxidized by the initiator AIBN: (a) Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Storey, J. M. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 95. (b) Engel, P. S.; Wu, W.-X. *J. Am. Chem. Soc.* **1989**, *111*, 1830. (c) Curran, D. P.; Yu, H.; Liu, H. *Tetrahedron* **1994**, *50*, 7343. (d) Curran, D. P.; Liu, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1377.

(22) Presumably, these oxidative cyclizations take place at the level of the pyrrolidinium ion arising from the first cyclization, suggesting that the configuration at nitrogen and possibly even the bulk of the associated phosphate anion must be taken into account in any model.

to the amine depends on configuration. When the configuration is 1,4-*anti* the influence is minimized, but in the 1,4-*syn*-system diastereoselectivity is considerably reduced. In systems with a substituent geminal to the amine, a second oxidative radical cyclization follows the initial nucleophilic attack on the alkene radical cation, leading to the formation of hexahydropyrrolo-[1,2-*b*]isoquinolines. Beckwith−Houk-type cyclic transition states for the cyclizations of free alkene radical cations generated by oxidation of alkenes have been discussed previously by Moeller;[10a,b] however, the memory effects that are the main focus of this paper have not been previously observed owing to the mode of generation of alkene radical cations from alkenes that has been most commonly employed in other laboratories.[5] The reactions described in this paper are conducted in refluxing benzene in order to ensure that the nitroalkane, a relatively poor radical precursor, participates in a sustainable radical chain reaction. Nevertheless, for the most part, the diastereoselectivities observed are significant. Accordingly, we anticipate that when more efficient radical precursors, compatible with the presence of the leaving group and of the nucleophilic amine, are located, reactions run at lower temperatures will give even higher selectivities.

Acknowledgment. We thank the National Science Foundation (CHE 9986200) for support of this work.

Supporting Information Available: Complete description of substrate preparation, full experimental details, and copies of spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JA051657T