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Enantioselective Cyclization of Alkene Radical Cations

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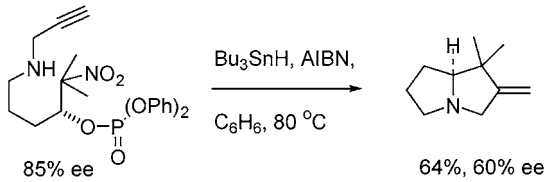
ABSTRACT



Enantiomerically enriched *β*-(diphenylphosphatoxy)nitroalkanes undergo radical ionic fragmentation, induced by tributyltin hydride and AIBN in benzene at reflux, to give alkene radical cations in contact radical ion pairs. These contact ion pairs are trapped intramolecularly by amines to give pyrrolidines and piperidines with significant enantioselectivity (∼60% ee), indicative of cyclization competing effectively with equilibration within the ion pairs. Use of an intramolecular *N*-propargylamine as a nucleophile provides an enantiomerically enriched pyrrolizidine skeleton via a tandem polar/radical crossover sequence.

Alkene radical cations may be advantageously generated under reducing conditions by the radical ionic fragmentation of *β*-(phosphatoxy)alkyl radicals.[1−3] In nonpolar solvents, the contact radical ion pair generated on fragmentation undergoes rapid recombination to provide either a rearranged[4] or the initial[5] radical depending on the substituent pattern. Both of these processes take place with a high degree of retention of configuration at phosphorus, indicative of the short lifetimes of the contact radical ion pair. The incorporation of suitable nucleophiles, particularly allylamines, in the system enables trapping of the alkene radical cation in tandem polar/radical crossover reactions leading to the formation of numerous alkaloid skeletons and other heterocyclic systems.[6] If nucleophilic trapping of the alkene radical cation is to compete effectively with formation of the rearranged radical in nonpolar solvents, then it must necessarily take place at the level of the initial contact radical ion pair. This in turn implies a high degree of organization in the trapping reaction and raises the possibility of stereocontrolled additions, even though the alkene radical cation itself is planar and devoid of chirality. Indeed, we have observed high diastereoselectivity in the cyclization of a series of methyl substituted *β*-(phosphatoxy)alkyl radicals

(1) (a) Newcomb, M.; Horner, J. H.; Whitted, P. O.; Crich, D.; Huang, X.; Yao, Q.; Zipse, H. *J. Am. Chem. Soc*. **1999**, *121*, 10685−10694. (b) Whitted, P. O.; Horner, J. H.; Newcomb, M.; Huang, X.; Crich, D. *Org. Lett*. **1999**, *1*, 153−156. (c) Newcomb, M.; Miranda, N.; Huang, X.; Crich, D. *J. Am. Chem. Soc*. **2000**, *122*, 6128−6129.

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(3) For classical oxidative approaches to alkene radical cations from alkenes themselves, see: (a) Hintz, S.; Heidbreder, A.; Mattay, J. In *Topics in Current Chem*; 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*, 371−378. (c) Schmittel, M.; Burghart, A. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2550−2589.

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(6) (a) Crich, D.; Ranganathan, K.; Huang, H. *Org. Lett*. **2001**, *3*, 1917−1920. (b) Crich, D.; Neelamkavil, S. *Org. Lett*. **2002**, *4*, 2573−2575. (c) Crich, D.; Ranganathan, K.; Neelamkavil, S.; Huang, X. *J. Am. Chem. Soc*. **2003**, *125*, 7942−7947. (d) Crich, D.; Huang, X.; Newcomb, M. *J. Org. Chem*. **2000**, *65*, 523−529. (e) Sartillo-Piscil, F.; Vargas, M.; Anaya de Parrodi, C.; Quintero, L. *Tetrahedron Lett*. **2003**, *44*, 3919−3921.

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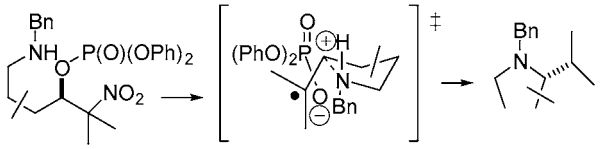
to pyrrolidines, which is consistent with this hypothesis.[7] These cyclizations were rationalized in terms of chairlike transition states, with the maximum number of pseudoequatorial substitutents, in which the nucleophilic amine attacks the alkene radical cation on the opposite face to the phosphate anion (Scheme 1).

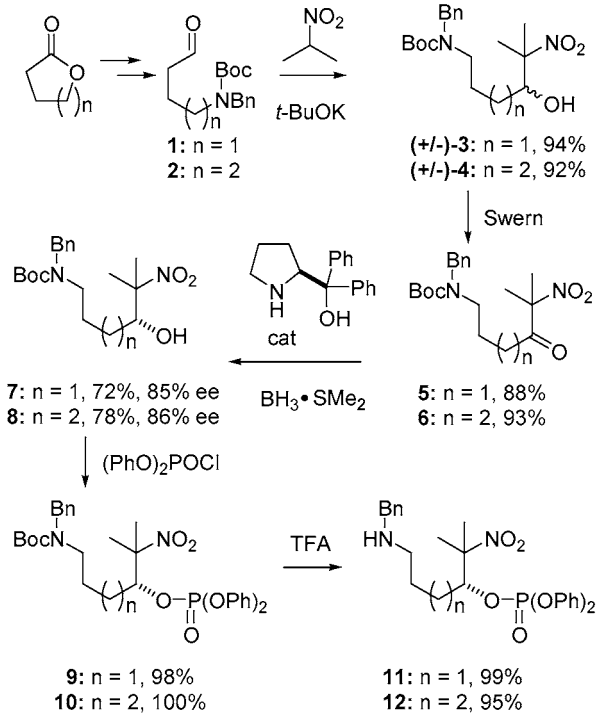
Scheme 1. Diastereoselective Formation of Pyrrolidines



In this communication, we show, with enantiomerically enriched β-nitrophosphate radical cation precursors, that the concept may be extended to enantiomerically controlled cyclizations of alkene radical cations, and that the conformational influence of the methyl groups in Scheme 1 was not a major stereodetermining factor. Additionally, we show that the sequence is readily extended to the formation of piperidines, i.e., that stereocontrol is not significantly eroded by the formation of six- rather than five-membered rings, and to tandem polar/radical crossover sequences.

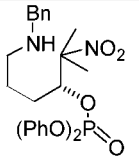
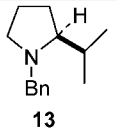
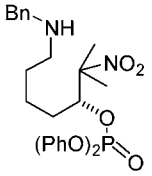
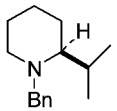
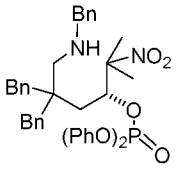
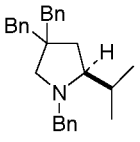
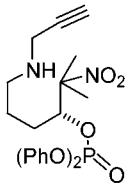
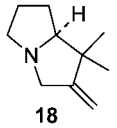
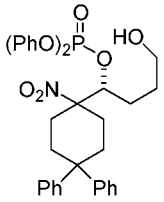
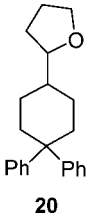
As previously, the precursors of choice to the β-(phosphatoxy)alkyl radicals were the readily assembled, stable tertiary β-nitrophosphates.[6,7] This required the asymmetric synthesis of these substances, for which we have employed the Corey oxazaborolidine reduction of α,α-disubstituted-α-nitroketones developed in this laboratory.[8] The absolute configurations of all nitro alcohols prepared were assigned following the standard Corey model,[9] as rigorously established previously.[8,10] The synthesis of pyrrolidine and piperidine precursors **11** and **12** (Scheme 2) was otherwise straightforward and proceeded from readily available materials.

Scheme 2. Synthesis of Enantiomerically Enriched Radical Precursors



Treatment of **11** with tributyltin hydride and AIBN in benzene at reflux resulted in the isolation of pyrrolidine **13** in 43% yield and 61% ee (Table 1). Taking into account the 85% ee of the substrate, it is readily calculated that **13** with 71% ee would be obtained if enantiomerically pure **11** were used in this cyclization. The absolute configuration of **13** was assigned following hydrogenolysis and reaction with

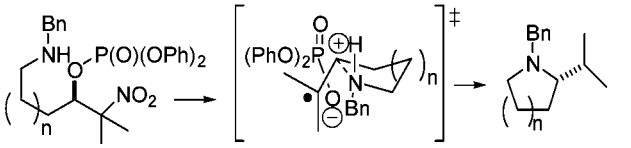
Table 1. Enantioselective Alkene Radical Cation Cyclizations

substrate (%ee)	product	yield	%ee[a]
 **11** (85)	 **13**	43%	61 (71)
 **12** (86)	 **14**	41%	60 (70)
 **15** (79)	 **16**	44%	60 (76)
 **17** (85)	 **18**	64%	60 (71)
 **19** (94)	 **20**	25%	0

[a] Actual ee (ee predicated on enantiomerically pure substrate).

tosyl chloride when (*S*)-(−)-2-isopropyl-1-tosylpyrrolidine was obtained, whose specific rotation conformed to the literature value.[11] The absolute configuration of **13** is consistent with the model set out in Scheme 3, in which

Scheme 3. Enantioselective Formation of Heterocycles

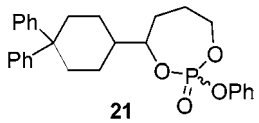


nucleophilic attack occurs within the initial contact radical ion pair and on the face of the alkene radical cation opposite to that shielded by the departing phosphate group. The cyclization of the next higher homologue **12** provided **14** in very similar enantiomeric excess (Table 1) thereby demonstrating the extension of the model to the formation of piperidines.

A further substrate **15**, prepared analogously to **11** and **12** from 3,3-dibenzyl-4-(*N*-Boc-benzylamino)butanal, resulted in the formation of pyrrolidine **16** in 60% ee (Table 1). The corrected ee values for **13**, **14**, and **16** (Table 1) are very similar, which suggests comparable rates of cyclization in the three cases. This is indicative of a very rapid attack on the contact radical ion pair, which allows little room for acceleration by the presence of a quaternary center or, indeed, rate erosion due to the extra degree of freedom in **12**.[12]

Hydrogenolysis of **9** cleanly removed the benzyl group, which was replaced with a propargyl moiety. After cleavage of the carbamate in the standard manner, this conveniently afforded substrate **17** for a tandem polar radical crossover reaction[6] with the formation of pyrrolizidine **18** (Table 1).

Finally, we turned our attention to alcohols as nucleophile and the formation of tetrahydrofurans. Substrate **19** was prepared as described in Supporting Information, with the key step being oxazaboroline-catalyzed reduction of a nitro ketone much like that in Scheme 2, and subjected to tin hydride reduction under the standard conditions. Tetrahydrofuran **20** was isolated in 25% yield from this reaction but was unfortunately found to be racemic (Table 1). This observation is entirely consistent with the model, alcohols being less nucleophilic than amines and unable to trap the initial contact radical ion pair before equilibration. An additional complication in the alcohol series was the formation of byproducts (**21**) arising from cyclization of the nucleophile onto phosphorus. This problem, which was exacerbated by the inclusion of a quaternary center, discouraged us from further work with the alcohols for the time being.[13]



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Supporting Information Available: Complete experimental details and characterization data, including details of assignment of configuration, for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Crich, D.; Ranganathan, K.; Rumthao, S.; Shirai, M. *J. Org. Chem.* **2003**, *68*, 2034−2037.

(9) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1987−2012.

(10) Enantioselectivities of radical precurosors and of products were assigned by GC and/or HPLC, as appropriate, over chiral stationary phases that demonstrated baseline resolution of the corresponding racemic materials.

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(12) Typical contact radical ion pairs escape to solvent-separated ion pairs in dichlorobenzene with rate constants of $\sim 10^9$ s^{-1} at room temperature (Arnold, B. R.; Noukakis, D.; Farid, S.; Goodman, J. L.; Gould, I. R. *J. Am. Chem. Soc.* **1995**, *117*, 4399−4400). Given that equilibration with the solvent-separated ion pair is the stereorandomizing event, it can be estimated that the nucleophilic cyclizations under investigation have rate constants of $\geq 10^9$ s^{-1}.

(13) There are indications,[4e,7b] however, of diastereoselective attack of alcohols on alkene radical cations in similarly generated radical ionic contact ion pairs when the counterion is the weaker nucleofuge, diethyl phosphate.