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Diastereoselectivity in the Cyclization of Alkene Radical Cations Generated under Non-Oxidizing Conditions: Contact Ion Pairs and Memory Effects

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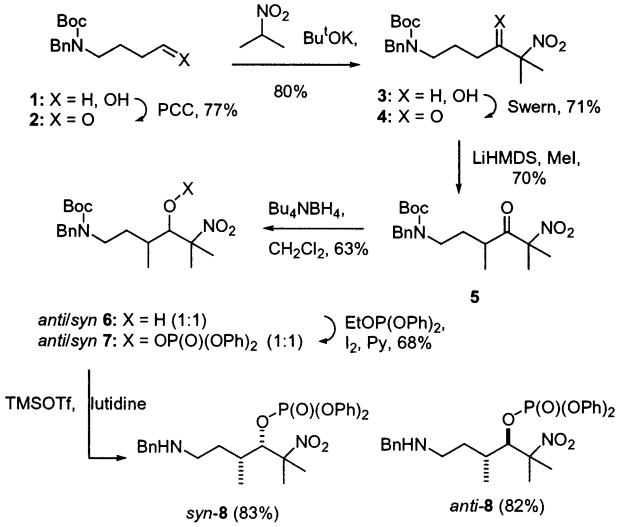
Appropriately substituted β-(phosphatoxy)alkyl radicals suffer radical ionic fragmentation to highly organized contact ion pairs comprised of alkene radical cations and phosphate anions.[1−3] In the absence of nucleophiles, in nonpolar solvents, recombination occurs on a time scale competitive with reorganization within the contact ion pair, as repeatedly demonstrated by stereochemical and isotopic labeling studies, to give either the initial[4] or the rearranged radical.[5,6] When a suitable nucleophile is included, the ion pair may be trapped, leading to the formation of heterocycles[7,8] and, through radical/polar crossover processes, to alkaloid-like skeleta.[9,10] Although the alkene radical cations undergoing nucleophilic attack in these processes are formally planar and achiral, their association with the anion in a contact ion pair raises the possibility of enantio- and diastereoselective reactions that exhibit memory[11] of the stereogenicity of the precursor radical provided that trapping takes place before equilibration of the various possible ion pairs. The potential for such stereoselective reactions marks a significant difference between the present fragmentation approach to alkene radical cations, aside from the non-oxidizing conditions, and the more classical entries[12,13] involving one-electron oxidation of alkenes. Here, we reduce the concept to practice and illustrate the dependence of the diastereoselectivity on substitution.

We first investigated the effect of a stereogenic center adjacent to the alkene radical cation. A suitable substrate was assembled from the known alcohol **1** as set out in Scheme 1. In this sequence, reduction of the ketone **5** produced a 1/1 *anti*/*syn* mixture of the nitro-aldol **6** which was conveniently separated at the level of the phosphates **7**, whose stereochemistry was assigned on the basis of coupling constant and NOE data. The individual isomers were then deprotected by exposure to TMSOTf and lutidine to give the amines **8**. These were then cyclized individually with tributyltin hydride and AIBN in benzene at reflux, giving in both cases a predominance of *trans*-*N*-benzyl-3-methyl-2-isopropylpyrrolidine **9** over the *cis*-isomer **10** (Scheme 2).[14]

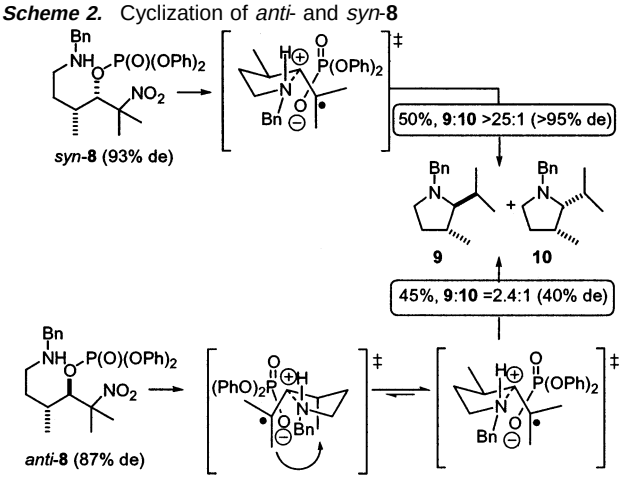
Two further pairs of diastereomeric substrates, with backbone substituents β- and γ- to the site of reaction, were prepared by unambiguous, stereocontrolled routes[15] and subjected to the cyclization conditions. The tin hydride-mediated cyclizations of both *anti*- and *syn*-**11** were highly diastereoselective and gave the pyrrolidines **12** and **13**, respectively, that is, both with effective inversion of configuration at carbon (Scheme 3).

The cyclizations of *anti*- and *syn*-**14**, conducted in the standard manner with tributyltin hydride and AIBN in benzene at reflux, were both diastereoselective for the product arising from apparent backside attack on the parent phosphates (Scheme 4). Additionally, in this series, significant amounts of the tricyclic product **17**, whose stereochemistry was unambiguously assigned by NOE measurements, were isolated. The formation of considerable amounts of

Scheme 1. Preparation of *anti*- and *syn*-**8**



Scheme 2. Cyclization of *anti*- and *syn*-**8**



17 in these latter cyclizations presumably arises from the high degree of steric compression following nucleophilic ring closure according to the transition state for the formation of **15**, which results in a further oxidative radical cyclization onto the benzyl group. Product **17** is therefore a derivative of the *cis*-pyrrolidine **15** and has been incorporated as such in the de for the overall cyclization.

Of the six cyclizations presented, all but one conform to a simple model for formation of the major diastereomer. Thus, the initial radical, generated on reaction with tin hydride, undergoes fragmentation to a contact alkene radical cation/phosphate anion pair, wherein the anion shields the face of the radical cation from which it has just departed. Nucleophilic attack then takes place on the

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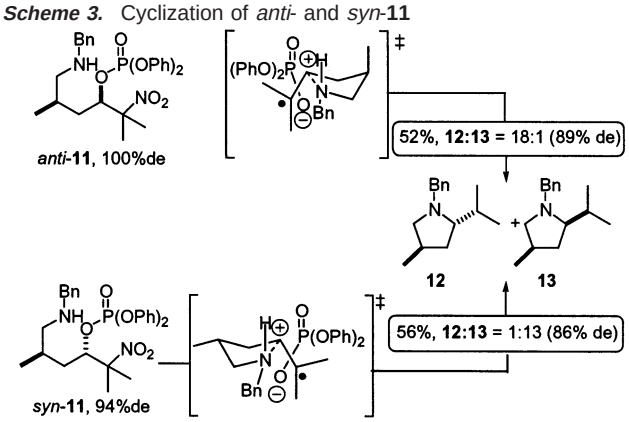
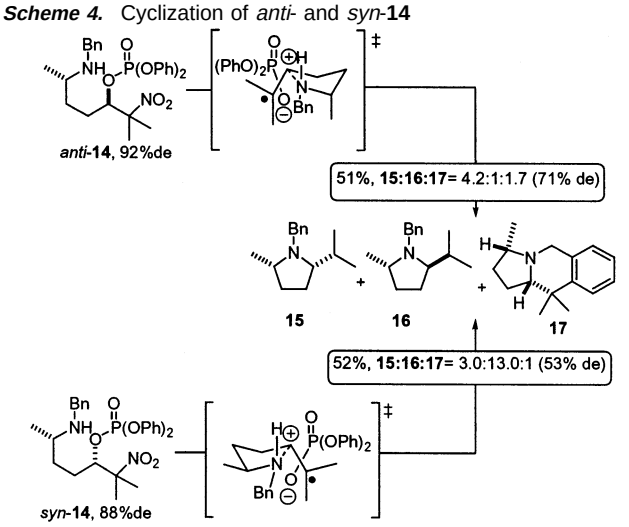
Scheme 3. Cyclization of *anti*- and *syn*-**11**



Scheme 4. Cyclization of *anti*- and *syn*-**14**



opposite face of the contact ion pair, resulting in cyclization with effective inversion of configuration at the site of the original C−O bond. These cyclizations may be rationalized by chairlike transition states with nucleophilic attack on the initial contact ion pair (Schemes 2−4). In three of these, all substituents are pseudoequatorial, and the chairlike model seems appropriate. In two examples, however (*anti*-**11** → **12** and *anti*-**14** → **15**), the methyl substituent is pseudoaxial, and it is possible that alternative twist boatlike transition states are favored in these cases. Indeed, the higher de for the cyclization of *anti*-**14** over that of *syn*-**14** strongly suggests that the chairlike transition state model cannot be the predominant one in this pair of diastereomers. Boatlike transition states are presumably not effective because of bowspit interactions with the pseudoaxial methyl group in the trisubstituted alkene radical cation. Cyclization of the initial contact ion pair arising from *anti*-**8** through a chairlike transition state would be strongly disfavored because of ^{1,3}A strain this would engender in the alkene radical cation (Scheme 2). This particular radical cation/anion pair therefore undergoes equilibration of the phosphate between the two faces of the system and eventually cyclizes via a transition state akin to that for *syn*-**8** → **9**.

The invocation of chairlike transition states in cyclizations, with the maximum number of substituents pseudoequatorial, resulting in the formation of five-membered rings, has been immensely popular since put forward by Beckwith[16] for 5-hexenyl radical cyclizations and legitimized computationally.[17,18] The present model for alkene radical cation cyclizations differs fundamentally from the Beckwith/Houk one for radical cyclizations as, with the exception of pervading steric interactions in the initial contact ion pair, it takes into account the configuration of the precursor to the reactive intermediate.

Although the chemistry described herein has been conducted with β-(phosphatoxy)alkyl radicals, we fully anticipate, given the close parallels in their known rearrangements,[19,20] that the corresponding β-(sulfatoxy)alkyl,[21] β-(nitroxy)alkyl,[21,22] β-(acyloxy)alkyl,[23] and β-halogenoalkyl radicals[24] will function analogously albeit on different time scales.

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

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