Auxiliary Induced ρ-Stereocontrol in Acetaloxyalkyl Radical Addition Reactions

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Radical-based C—C bond forming reactions offer a powerful alternative to their polar counterparts and, accordingly, occupy an increasingly prominent role in organic synthesis.[1] Whereas early work in this area had focused on issues related to chemoselectivity and regioselectivity, attention has now shifted to the control of acyclic stereochemistry.[2] Both substrate-[3] and auxiliary-derived[4] chirality have been used to control the stereochemical course of radical addition and substitution reactions. However, a general approach to the control of acyclic stereochemistry during radical reactions still remains an elusive goal. Toward this end, the development of a readily available and easily recoverable chiral auxiliary for α-hydroxyalkyl radicals would be particularly valuable ($1 \rightarrow 2 \rightarrow 3$ and 4).[5] We now report a conceptually simple solution to this problem wherein acetal-based chiral auxiliaries can be used to control

acyclic ρ-selectivity (see ref 2b for a description of this terminology) in addition reactions of hydroxyalkyl radical equivalents.
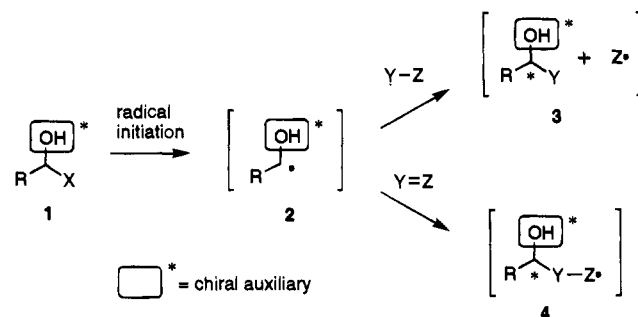
To test the general validity of our proposal, we prepared the diastereomeric carboxylic acids **5** and **6** from the known[6] tetrahydropyranyl (THP) ethers of (S)-methyl lactate. These were independently subjected to Barton's radical decarboxylation protocol[7] in the presence of methyl acrylate as a radical trap. Photolysis of the *diastereomeric* thiohydroxamate esters **7** and **8** led to the formation of *enantiomeric* radicals **9** and *ent*-**9** respectively, which could be trapped with methyl acrylate to give the *enantiomeric* addends **10** and *ent*-**10** in ca. 50% overall yield. (A minor amount of telomeric product resulting from double addition of **9**/*ent*-**9** to methyl acrylate was also formed.) The ρ-selectivity of these radical additions was best determined after reductive cleavage of the epimeric[8] 2-thiopyridyl ethers to afford **11** and *ent*-**11**. As expected for reactions passing through an early transition state, higher ρ-selectivities were observed at lower reaction temperatures (reaction temperature, diastereoselectivity: room temperature, 4/1; −20 °C, 6/1; −78 °C, 19/1). *These experiments clearly showed temperature dependent transmission of stereochemical information from the chiral acetal center to the developing C—C bond independent of the starting hydroxamate ester configuration.*
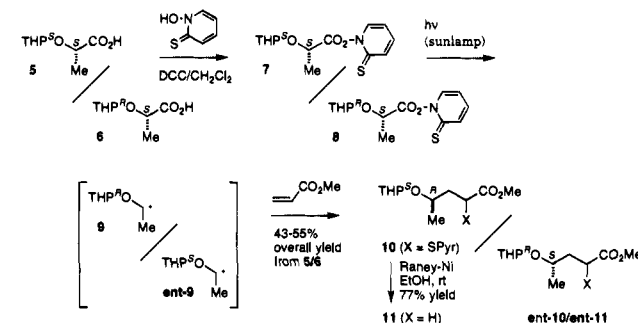
In order to see whether this acetal-mediated acyclic stereocontrol would extend to the use of carbohydrates as *recoverable* chiral auxiliaries,[9] the 2-deoxy-α-glucoside **12** was prepared by the addition of (S)-methyl lactate to tri-O-benzyl-D-glucal following Falck's procedure.[10] Subjection of the carboxylic acid **13** to the thiohydroxamate-mediated radical chemistry described above again resulted in the smooth formation of a chiral radical, **15**, which could be trapped with methyl acrylate to give **16** in

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(8) No β-selectivity was observed during the reaction of the distal radical with the starting thiohydroxamate ester (cf. ref 2b).

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61% yield. (Once again, a small quantity of telomer was isolated as well.) The ϱ-selectivity of this radical addition reaction at −78 °C was found to be 11/1 after removal of the thiopyridyl group to give **17**. To determine the absolute configuration of the newly formed stereocenter, **17** was subjected to acidic methanolysis to afford the known (*R*)-γ-lactone **18**[11] in 66% yield and the methyl 2-deoxyglucoside **19** (which could in theory be recycled) in 93% yield. *This experiment demonstrated that the D-sugar derived auxiliary leads to preferential addition to the si-face of radical* **15**. *As the antipodal series will likely be accessible via the "pseudo-enantiomeric" auxiliary derived from L-rhamnose,*[12] *these results translate into a general method for absolute ϱ-stereocontrol via acyclic acetaloxyalkyl radicals.*
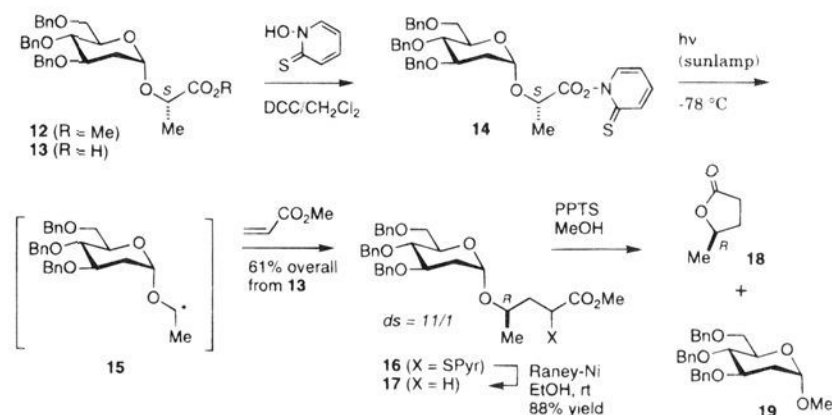
To elucidate the factors responsible for the observed asymmetric induction, energies and canonical partition functions (employing rigid rotor harmonic oscillator assumptions) were determined for both pyramidalized radicals corresponding to *ent-***9** and six transition structures (TS) corresponding to the addition of $CH_2=CH_2$ to both faces of *ent-***9** in three different torsional orientations.[13] Interestingly, while the "*re*-pyramidalized" radical was found to be 0.3 kcal/mol lower in energy than its "*si*-pyramidalized" counterpart, the situation was reversed in the transition structure region. The three separate TSs for addition to the *si*-face were found to be within 0.1 kcal/mol of

si-TS   **re-TS**
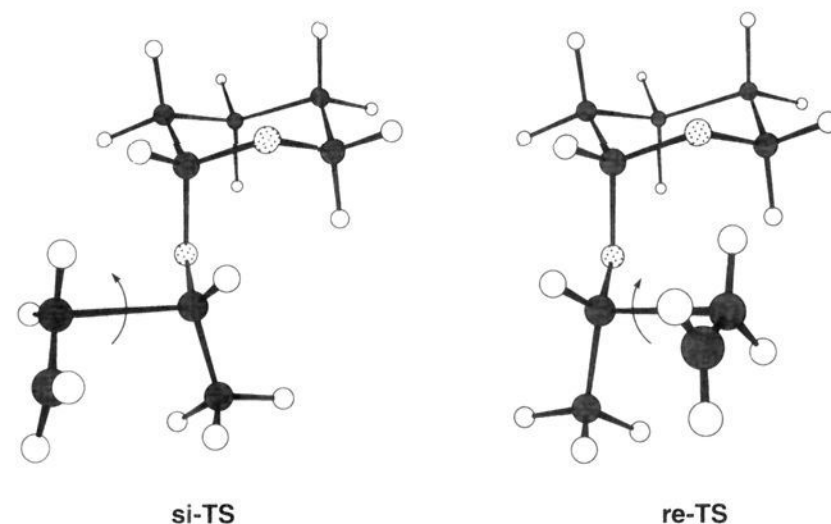
Figure 1. Calculated transition structures for the *si*- and *re*-addition of *ent-***9** to ethylene. In each case, only one of three torsional orientations about the developing C—C bond is shown.

each other while those for addition to the *re*-face were 0.2, 0.3, and 1.0 kcal/mol higher in energy than the lowest value for *si*-addition. Furthermore, the torsional motions in the *re*-TS are on average much more strongly hindered than those associated with the *si*-TS. (See Figure 1). As a result, entropic effects strongly favor (i.e., by a factor of 6) *si*-attack; yielding a net preference of 12/1 for the *(R,R)*-diastereomer at room temperature and 17/1 at −78 °C.[14] *These entropic effects are simply indicative of the greater probability of $CH_2=CH_2$ having an appropriate orientation for si-attack and suggest caution when one attempts to explain kinetic preferences in terms of enthalpic factors alone.*[15]

Supplementary Material Available: Experimental procedures and characterization data for compounds **10**−**12** and **16**−**19** (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

(11) Lactone **18** prepared from a 5.8/1 mixture of **17** plus its (*4S*)-diastereomer (i.e., 71% de) exhibited an $[\alpha]_D^{22}$ +21.3° (*c* 0.25, CH_2Cl_2) [Lit. $[\alpha]_D^{23}$ +30.1° (*c* 0.85, CH_2Cl_2): Mori, K. *Tetrahedron* **1975**, *31*, 3011] corrresponding to a 71% ee.

(12) Cf.: Charette, A. B.; Côté, B.; Marcoux, J.-F. *J. Am. Chem. Soc.* **1991**, *113*, 8166.

(13) Quantum mechanical calculations were performed at the Hartree−Fock level with a STO-3G basis set using the GAUSSIAN 92 Program Package, Revision A: Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. Gaussian Inc., Pittsburgh, PA (1992).

(14) The small values of the energetic differences between the transition states for the *si*-face and *re*-face additions suggest that the ϱ-selectivity for this reaction should be quite small (ds = 1.9/1) when a prequilibrium between the two radicals and only energetic effects are considered. The barrier for inversion of these pyramidalized radicals through a planar configuration is calculated to be on the order of 2.0 kcal/mol, thereby suggesting the validity of this preequilibrium assumption. For experimental support of this notion, see: Hoffmann, R.; Rückert, T.; Brückner, R. *Tetrahedron Lett.* **1993**, *34*, 297.

(15) For an alternative approach, see: Damm, W.; Giese, B.; Hartung, J.; Hasskerl, T.; Houk, K. N.; Hüter, O.; Zipse, H. *J. Am. Chem. Soc.* **1992**, *114*, 4067.