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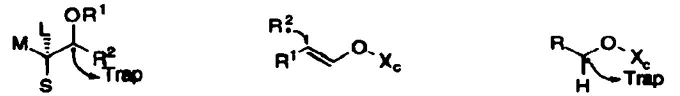
Group Transfer Addition Reactions of Selenomalononitriles to Chiral Enol Ethers. Asymmetric Radical Addition and Selenium Transfer Reactions

Dennis P. Curran,* Steven J. Geib, and Lung Huang Kuo
Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, USA

Summary: *Group transfer addition reactions of alkyl phenylselenomalononitriles to enol ethers derived from trans-2-phenylcyclohexanol and 8-phenylmenthol occur cleanly, and moderate to excellent stereoselection is observed in both the radical addition and phenylselenium transfer steps.*

Over the past few years, the features of several types of asymmetric radical reactions have begun to emerge.[1] Such reactions are generally classified as under substrate control (stereocontrol element permanently attached to substrate) or chiral auxiliary control (stereocontrol element temporarily attached to substrate), and they involve the reactions of chiral radicals with achiral traps or of achiral radicals with chiral traps (often alkenes). Early work focusing on the reactions of chiral, π-conjugated radicals and alkenes has quickly been expanded to include asymmetric reactions of heteroatom-substituted radicals and alkenes.[1] In the oxygen series (Figure 1), it has been shown that substrate controlled reactions of α-oxy radicals follow a Felkin-Anh model.[2] Further exploring asymmetric radical reactions involving oxygen substituents, we now report the first examples of good selectivity in chiral auxiliary controlled radical additions to enol ethers and in group transfer reactions of the resulting α-oxy radicals.

Figure 1. Classification of Asymmetric Radical Reactions with Oxygen Substituents



substrate control
α-oxy radicals follow
a Felkin-Ahn model
(reference 2)

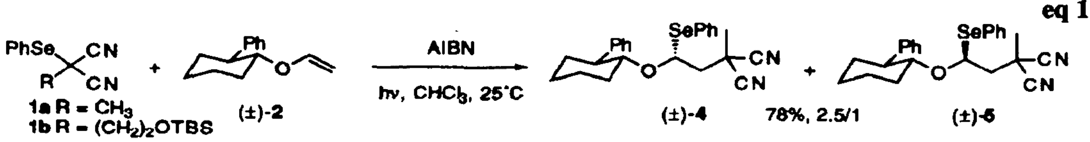
chiral auxiliary control
enol ethers
(this work)

chiral auxiliary control
α-oxy radicals
(this work)

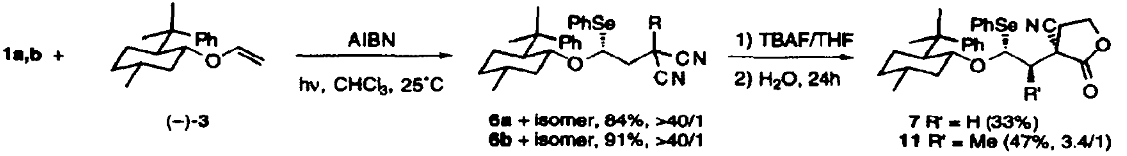
To provide a parallel between radical reactions and related ionic and pericyclic reactions, we selected the popular 8-phenylmenthol[3,4] and 2-phenylcyclohexanol[3,4d] auxiliaries for study. To probe reactions of the chiral radicals, we conducted group transfer additions[5] of methyl phenylselenomalononitrile (**1a**) to readily available enol ethers **2** and **3**.[6] Addition of the methyl malononitrile radical to **2** or **3** generates a chiral radical that can abstract a phenylselenium group from the starting reagent **1a** to provide a pair of diastereomeric products (eqs 1a,b).[5]

A 25°C chloroform solution of **1a** (1 equiv), racemic enol ether **2** (1 equiv), and AIBN (10%) was irradiated with a sunlamp for 1.5 h (eq 1a). Concentration and purification of the crude product by flash chromatography provided a mixture of racemic adducts **4** and **5** in 78% yield. Analysis of the product by ^{1}H NMR spectroscopy and GC (both before and after purification) showed a 2.5/1 mixture of diastereomers. The major isomer **4** was separated from the mixture by fractional crystallization, and its structure was solved by x-ray crystallography. This crystal structure is shown in Figure 2. Neither the pure major product **4** nor an enriched sample of the minor product **5** were interconverted when they were resubjected to reaction conditions. This suggests that the observed diastereoselectivity results from a kinetically controlled selenium transfer reaction to a chiral radical.

eq 1a

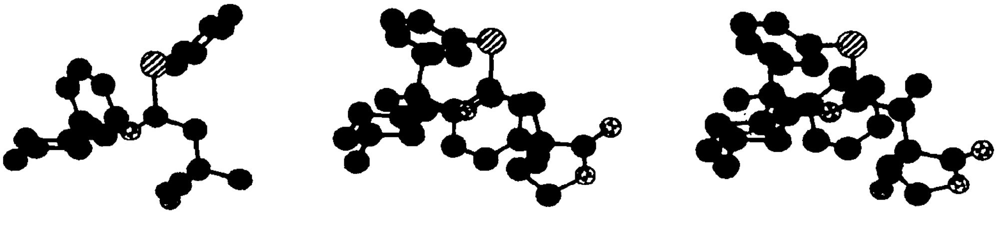


eq 1b



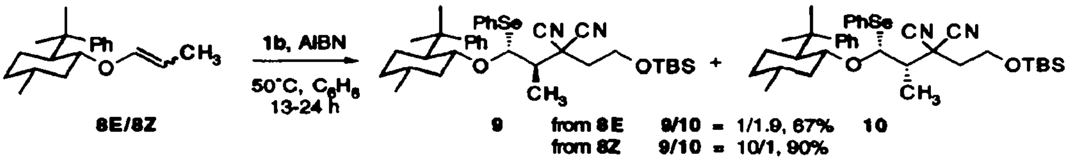
Considerably better selectivity was observed with (–)-8-phenylmenthol enol ether **3** (eq 1b). Sunlamp promoted addition of **1a** to **3** provided **6a** and its stereoisomer (not shown) in a ratio >40/1 in 84% yield. The major isomer **6a** was stable to the reaction conditions, and it was fully characterized. The minor isomer could not be isolated in pure form, and its structure assignment rests only on the appearance of very small peaks in the ^{1}H NMR spectrum of the mixture. The configurational assignment of **6a** proved quite difficult since it, and a number of related adducts, were all oils. Finally, we obtained a crystalline compound by adding selenomalononitrile **1b** to **3** to provide **6b** as a >40/1 mixture with its isomer in 91% yield. Desilylation of the **6b** with TBAF, followed by exposure of the product to water for 24 h, provided a single crystalline cyanolactone **7** (33% yield), whose structure was solved by x-ray crystallography (see Figure 2). Though the 8-phenylmenthol derivative is considerably more selective, both chiral auxiliaries favor formation of the same relative stereoisomer in the selenium transfer reaction.

Figure 2. Crystal Structures of 4 (left), 7 (middle), and 11 (right)



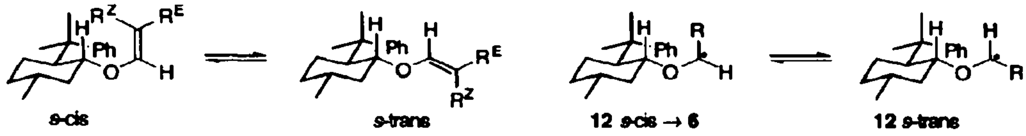
To probe stereoselective carbon-carbon bond-forming reactions, we prepared (–)-8-phenylmenthol derived enol ethers **8E** and **8Z**.[7] Addition of **1b** to **8E** proceeded to give only two of the four possible diastereoisomers (**9/10**) in a ratio of 1/1.9 in 67% yield. Addition to **8Z** provided the same two isomers (**9/10**) in 90% yield, but now the ratio was 10/1. Lactonization of **9** as before provided a 3.4/1 mixture of cyanolactones (47% yield).[8] The major lactone **11** (eq 1b) was crystalline, and its x-ray crystal structure is shown in Figure 2.[9]

eq 2

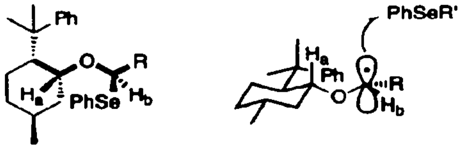


For the 8-phenylmenthol auxiliary, interpretation of the radical additions to the enol ether is relatively straightforward; however, the asymmetric selenium transfer reactions are less clear-cut. Spectroscopic and computational studies of related enol ethers suggest[7] that the E-8-phenylmenthol enol ether **8E** should exist as a mixture of s-trans and s-cis isomers (see Figure 3). There is probably a slight preference (<1 kcal/mol) for the s-trans isomer. In contrast, the Z-8-phenylmenthol ether **8Z** should have a significant preference for the s-trans isomer (>3 kcal/mol) due to the steric interactions between the Z-methyl group and the cyclohexyl ring in the s-cis isomer. Assuming that the front face of both isomers is exposed,[3,7] the observed stereoselectivities parallel the conformational analysis. E-Enol ether **8E** provides a low 1.9/1 selectivity in favor of **10**, the product resulting from front-side attack on the s-trans rotamer, while Z-enol ether **8Z** provides a significantly higher selectivity (10/1) in favor of **9**, again the product of attack on the s-trans rotamer.

Figure 3. Transition State Models for Addions (left) and Group Transfers (right)



3 R^E, R^Z = H; 8E R^E = Me, R^Z = H; 8Z R^E = H, R^Z = Me



The results of the selenium transfer reactions show a high degree of selectivity controlled by the chiral auxiliary; the adjacent stereocenter produced in the additions to **8E** and **8Z** does not seem to have any effect. Assuming an "enol ether-like" model **12** in Figure 3, the results suggest a highly selective reaction from the s-cis conformer. Applying the popular radical/alkene analogy, radical **12** is best modeled by enol ethers **3** or **8E**, suggesting that **12** s-trans should be slightly favored over **12** s-cis. However, the configurations of the major products **6**, **9** and **10** are not consistent with the analogy.[10,11] Recent calculations suggest that transition states of α-oxy radicals are significantly pyramidalized.[2d,e] This implies that a more "product-like" transition state model might be appropriate. Inspection of the three x-ray structures (Figure 2) shows that each exhibits a very similar conformation about the ether linkage, as summarized by **13** in Figure 3. The largest groups consistently adopt the ends of a "W" shape through the ether oxygen atom. The phenylselenium group is in a cis-1,3 orientation with respect to an axial cyclohexyl hydrogen (H_a) and the hydrogen (H_b) α-to the PhSe group is cis-1,3 to a cyclohexyl methylene group. This conformation suggests a transition state model **14** where the normally proposed "front-side" attack is now replaced by a "top-side" attack. Conformations like **13** and **14** may be preferred due to steric repulsions; however, it is worth considering that distances between the phenyl ring and the group R might also be appropriate for van der Waals attraction.[12]

In conclusion, additions of substituted malononitriles to E-8-phenylmenthol enol ethers occur with low selectivity (~1/2) while additions to the isomeric Z-enol ether occur in good selectivity (10/1) to provide the opposite product (due to the change in alkene stereochemistry). The subsequent selenium transfer reactions occur with high selectivity controlled by the 8-phenylmenthol auxiliary. The radical addition results are consistent with models based on the ground state conformations of the enol ethers. In contrast, the popular protocol of modeling asymmetric reactions of chiral radicals by related reactions of chiral alkenes does not satisfactorily reproduce the selenium transfer reactions, and a more product like model may prove useful.

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8. These isomers differ in configurations at the nitrile-bearing carbon.
9. Isomer **10** provided an E-alkene upon syn elimination, showing that it is a syn product. Its configuration then follows from the (presumed) selectivity of the selenium transfer step.
10. For example, nitrile oxide cycloadditions to alkenes often show a nice stereochemical parallel to reactions of related radicals (see reference 1a), but such cycloadditions to phenylmenthol enol ethers proceed with very low stereoselectivity. See: Boa, A. N.; Booth, S. E.; Dawkins, D. A.; Jenkins, P. R.; Fawcett, J.; Russell, D. R. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1277.
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