Pergamon

Tetrahedron Letters 43 (2002) 351–353

TETRAHEDRON LETTERS

# Highly stereoselective Friedel–Crafts alkylations of unactivated benzenes by episulfonium ion cyclizations

Bruce P. Branchaud* and Heather S. Blanchette†

*Department of Chemistry, University of Oregon, Eugene, OR 97403-1253, USA*

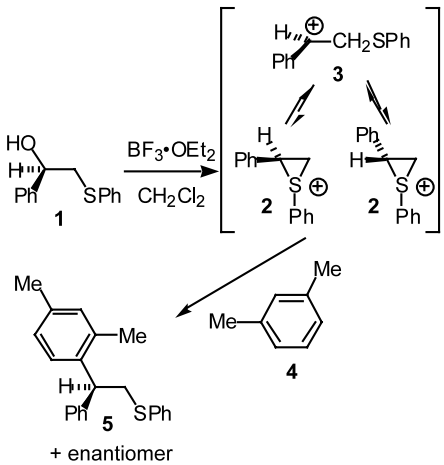
Received 8 November 2001; accepted 14 November 2001

**Abstract**—Intermolecular additions of highly enantiomerically enriched episulfonium ions onto activated benzene rings are known to accomplish chiral Friedel–Crafts alkylations. Unactivated benzenes are either unreactive or can give low stereoselectivities. Intramolecular cyclizations should be faster than intermolecular additions; thus, cyclization reactions should be able to avoid undesired episulfonium ion racemization. The work reported here tests that hypothesis and demonstrates that cyclizations of enantiomerically enriched episulfonium ions onto unactivated benzene rings are highly stereoselective. 

There have been numerous applications of racemic episulfonium ions in organic synthesis.[1] In the mid 1990s Toshimitsu and co-workers published a series of papers on some reactions of highly enantiomerically enriched episulfonium ions. Those reactions included reactions with nitriles,[2,3] sulfonamides,[4,5] silyl enol ethers[6] and substituted benzene rings.[7]

With the exception of Toshimitsu's work, the reaction of highly enantiomerically enriched episulfonium ions with aromatic compounds has not been studied previously. Such stereoselective Friedel–Crafts alkylations could be useful in asymmetric organic synthesis, faithfully transferring the chirality of alcohol chirality centers into new chirality centers next to an aromatic ring. Many important natural products and synthetic compounds have a chirality center next to an aromatic ring. Well-developed technology for stereoselective Friedel–Crafts reactions would provide a new strategy for the synthesis of such stereocenters.

Toshimitsu's work on stereoselective Friedel–Crafts alkylations examined intermolecular reactions of some simple chiral episulfonium ions with substituted benzenes.[7] Benzene or *t*-butylbenzene did not react, whereas mesitylene, *m*-xylene, anisole, phenol and *N*,*N*-dimethylaniline did react. Apparently activation by at least two electron-donating alkyl groups is necessary for a successful reaction. Even though mesitylene and *m*-xylene did react, the stereoselectivity of their reactions varied with reaction conditions. For example, the reaction of **1** with *m*-xylene **4** using $BF_3{\cdot}OEt_2$ in $CH_2Cl_2$ for 20 h at 0°C gave a 74% yield of **5** with 68% stereospecificity[8] (Scheme 1). Lowering the temperature to −20°C gave a lower 50% yield of **5** with an improved 91% stereospecificity. Lowering the temperature to −40°C gave a very low 9% yield of **5** with a much improved 99% stereospecificity. The results indicate that higher temperatures promote the partial racemization of episulfonium ions **2**, presumably by reversible ring opening of the chiral episulfonium ions **2** to gener-




**Scheme 1.** Toshimitsu's stereoselective episulfonium ion intermolecular electrophilic aromatic substitution reactions.

* Corresponding author. Tel.: (541) 346-4627; fax: (541) 346-4645; e-mail: bbranch@oregon.uoregon.edu

† Present Address: Shionogi Bioresearch Corp., 45 Hartwell Avenue, Lexington, MA 02173, USA.

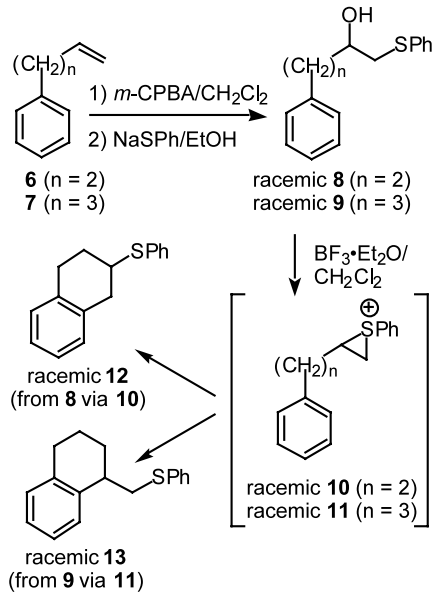
0040-4039/02/$ - see front matter 
PII: S0040-4039(01)02173-6

ate an achiral carbocation intermediate **3** which can recyclize to form either enantiomer of **2**.

The problems in loss of stereoselectivity and low yields in the examples described above can be attributed to the intermolecular nature of the reactions. When unactivated arenes are used, the episulfonium ion will have more time to remain unreacted, and will thus have more of an opportunity to racemize. An intramolecular reaction should not suffer as much from this problem since the episulfonium ion and the arene will be in close proximity to react efficiently, thus suppressing racemization. We decided to examine the stereospecificity of the cyclization of the phenyl episulfonium ion onto unactivated benzene rings to see if the intramolecularity of the reaction would make it highly stereoselective.

Racemic samples of hydroxysulfides **8** and **9**, and cyclization products **12** and **13** were needed to calibrate the chiral HPLC analyses used in these studies. Racemic hydroxysulfides **8** and **9**, and cyclization products **12** and **13** were prepared as shown in Scheme 2.

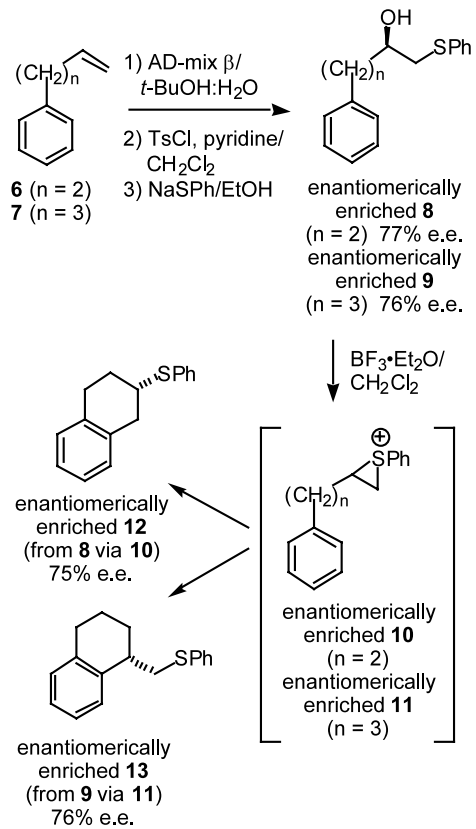
Following a literature procedure,[9] commercially available 4-phenyl-1-butene **6** was epoxidized with *meta*-chloroperoxybenzoic acid. The epoxide was treated with NaSPh (formed by the reaction of PhSSPh with $NaBH_4$ in absolute EtOH) for 19 h at room temperature to produce racemic **8** in 94% isolated yield after purification by radial chromatography.[10] Treatment of racemic **8** with $BF_3{\cdot}Et_2O$ in $CH_2Cl_2$ at 0°C followed by warming to room temperature with stirring for 16 h led to racemic **12** in 63% isolated yield after purification by radial chromatography.[11]




**Scheme 2.** Preparation of racemic standards to calibrate chiral HPLC analyses.

Following a literature procedure,[12] 5-phenyl-1-pentene **7** was prepared by the condensation of the Grignard reagent of β-phenylethyl bromide with allyl bromide. Following a literature procedure,[13] **7** was epoxidized with *meta*-chloroperoxybenzoic acid. The epoxide was treated with NaSPh in absolute EtOH for 16 h at room temperature to produce racemic **9** in 97% isolated yield after purification by radial chromatography.[14] Treatment of racemic **9** with $BF_3{\cdot}Et_2O$ in $CH_2Cl_2$ at 0°C followed by warming to room temperature with stirring for 23 h led to racemic **13** in 40% isolated yield after purification by radial chromatography.[15] This reaction was not optimized, and proceeded in much lower yield than that of enantiomerically enriched **9** (see below), but it provided enough pure material to calibrate the chiral HPLC analyses.

Enantiomerically enriched hydroxysulfide **8** was prepared by Sharpless asymmetric dihydroxylation of **6** using AD-mix-β, monotosylation of the resulting diol, then reaction of the tosylate with NaSPh (Scheme 3) to provide enantiomerically enriched **8** in 57% isolated overall yield, after radial chromatography of **8**, for three steps from **6**.[10,16] Sharpless asymmetric dihydroxylation of **6** using AD-mix-β has been reported to proceed in 84% enantiomeric excess (e.e.).[17] We did not determine the e.e. of the diol produced from Sharpless asymmetric dihydroxylation of **6**. Enantiomerically enriched **8** was found to have 77% e.e. by chiral HPLC analysis.[18] Treatment of enantiomerically enriched **8**




**Scheme 3.** Preparation of enantiomerically enriched hydoxysulfides and their episulfonium ion cyclizations.

(77% e.e.) with $BF_3{\cdot}Et_2O$ in $CH_2Cl_2$ at 0°C followed by warming to room temperature with stirring for 16 h led to enantiomerically enriched **12**, in 35% isolated yield after radial chromatography.[11] Enantiomerically enriched **12** was found to have 75% e.e. by chiral HPLC analysis.[18] Thus, this reaction proceeded with 97% stereospecificity.[8] Although this reaction proceeded in lower yield than the racemic one, the stereospecificity for the cyclization reaction is high.

Enantiomerically enriched hydroxysulfide **9** was prepared by Sharpless asymmetric dihydroxylation of **7** using AD-mix-β, monotosylation of the resulting diol, then reaction of the tosylate with NaSPh (Scheme 3) to provide enantiomerically enriched **9** in 12% isolated overall yield, after radial chromatography of **9**, for three steps from **7**.[14] Enantiomerically enriched **9** was found to have 76% e.e. by chiral HPLC analysis.[18] Treatment of enantiomerically enriched **9** (76% e.e.) with $BF_3{\cdot}Et_2O$ in $CH_2Cl_2$ at 0°C followed by warming to room temperature with stirring for 16 h led to enantiomerically enriched **13** in 98% isolated yield after radial chromatography.[15] Enantiomerically enriched **13** was found to have 76% e.e. by chiral HPLC analysis.[18] Thus, this reaction proceeded with $\sim$100% stereospecificity.[8] This reaction proceeded in high chemical yield and high stereospecificity.

These results demonstrate that cyclizations of phenyl episulfonium ions onto unactivated (or lightly activated) benzene rings can be highly stereoselective (97–100% stereospecificity).[8] Since it is easy to prepare β-hydroxysulfides from epoxides or vicinal diols, the results also illustrate how episulfonium ion chemistry can be used to convert the products of contemporary asymmetric epoxidation and dihydroxylation reactions into more complex chiral enantiomerically enriched products.

## Acknowledgements

This work was supported by the National Science Foundation and the Elsa U. Pardee Foundation for Cancer Research.

## References

1. Harring, S. R.; Edstrom, E. D.; Livinghouse, T. *Adv. Heterocyclic Nat. Prod. Synth.* **1992**, *2*, 299–376.
2. Toshimitsu, A.; Hirosawa, C.; Tanimoto, S. *Tetrahedron Lett.* **1991**, *32*, 4317–4320.
3. Toshimitsu, A.; Hirosawa, C.; Tamao, K. *Tetrahedron* **1994**, *50*, 8997–9008.
4. Toshimitsu, A.; Abe, H.; Hirosawa, C.; Tanimoto, S. *J. Chem. Soc., Chem. Commun.* **1992**, 284–285.
5. Toshimitsu, A.; Abe, H.; Hirosawa, C.; Tamao, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3465–3471.
6. Toshimitsu, A.; Hirosawa, C.; Tanimoto, S. *Chem. Lett.* **1992**, 239–242.
7. Toshimitsu, A.; Hirosawa, C.; Tamao, K. *Synlett* **1996**, 465–467.
8. Stereospecificity is defined in Ref. 7 as follows: stereospecificity = [(% enantiomeric excess of product/% enantiomeric excess of reactant)×100].
9. Elings, J. A.; Downing, R. S.; Sheldon, R. A. *Eur. J. Org. Chem.* **1999**, *4*, 837–846.
10. Compound **8** is a known compound but has not been previously used for episulfonium ion cyclizations. See: (a) Hosomi, A.; Ogata, K.; Hoashi, K.; Kora, S.; Tominaga, Y. *Chem. Pharm. Bull.* **1988**, *36*, 3736–3738; (b) Takeda, T.; Furukawa, H.; Fujimori, M.; Suzuki, K.; Fujiwara, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1863–1869.
11. Compound **12** is a known compound but has not been prepared previously using episulfonium ion cyclizations. See: (a) Reich, H. J.; Peake, S. L. *J. Am. Chem. Soc.* **1978**, *100*, 4888–4889; (b) Eisenbraun, E. J.; Bansal, R. C.; Hertzler, D. V.; Duncan, W. P.; Flanagan, P. W. K.; Manning, M. C. *J. Org. Chem.* **1970**, *35*, 1265–1271.
12. Sih, N.; Pines, H. *J. Org. Chem.* **1965**, *30*, 1462–1466.
13. Adamczyk, M.; Johnson, D. D.; Reddy, R. E. *Tetrahedron* **1999**, *55*, 63–88.
14. The *S* enantiomer of **9** is a known compound. See: Fujisawa, T.; Itoh, T.; Nakai, M.; Sato, T. *Tetrahedron Lett.* **1985**, *26*, 771–774.
15. Compound **13** is a new compound and was characterized by $^1$H NMR, $^{13}$C NMR and IR.
16. The vicinal diol prepared by Sharpless asymmetric dihydroxylation of **6** using AD-mix-β is known (see Ref. 17). The *S* enantiomer of the monotosylate derived from the vicinal diol is a known compound. See: Klunder, J. M.; Onami, T.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 1295–1304.
17. Wang, Z.-M.; Zhang, X.-L.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 2267–2270.
18. All chiral HPLC analyses for **8**, **9**, **12**, and **13** were run using a Chiracel OD-H column from Daicel Chemical Industries with 10–20% *i*-propyl alcohol/hexanes as solvent with UV–vis spectrophotometric detection of peaks. In each case, the corresponding racemic compounds, prepared as shown in Scheme 2, were used as calibration standards.