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Role of 2-Oxonia Cope Rearrangements in Prins Cyclization Reactions

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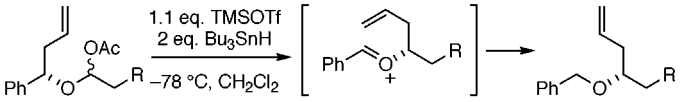
ABSTRACT

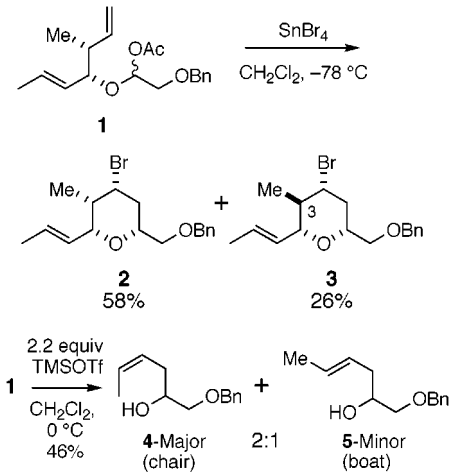


The 2-oxonia Cope rearrangement is undetectable in typical Prins cyclization reactions. We have investigated the Cope rearrangement in a Prins cyclization reaction using a competitive reduction of the oxocarbenium ion intermediate, and a racemization reaction mediated by the rearrangement. In our unactivated substrate, the 2-oxonia Cope rearrangement was much faster than Prins cyclization. An enantioselective allyl transfer reaction also was developed using a 2-oxonia Cope rearrangement.

The 2-oxonia Cope rearrangement has been invoked as a competitive pathway in Prins cyclizations and related transformations.[1,2] Direct evidence for the 2-oxonia Cope rearrangement as a side reaction in Prins cyclizations comes from Speckamp's work. He found products arising from the 2-oxonia Cope rearrangement in attempted Prins cyclizations of vinyl silanes.[3] The rearrangement also was implicated in a synthesis of *cis*- and *trans*-2,6-disubstituted tetrahydropyrans.[4] More recently Roush found exchange products arising from 2-oxonia Cope rearrangements in Prins cyclization reactions, once again with vinyl silane substrates.[5] The 2-oxonia Cope rearrangement also has been invoked to explain allyl transfer reactions developed by Nokami[6] and by Loh.[7] In this communication we demonstrate that 2-oxonia Cope rearrangements are faster than Prins cyclizations in simple substrates and use this rearrangement in an enantioselective allyl transfer reaction.

Our attention was drawn to the 2-oxonia Cope rearrangement by an unexpected epimerization in a Prins cyclization, Scheme 1. The α-acetoxy ether **1**, a possible precursor to ratjadone,[8] was cyclized with $SnBr_4$ to produce the expected

Scheme 1. Unexpected C3 Epimerization in a Prins Cyclization



(1) (a) Brown, M. J.; Harrison, T.; Herrinton, P. M.; Hopkins, M. H.; Hutchinson, K. D.; Mishra, P.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5365−5378. (b) Gasparski, C. M.; Herrinton, P. M.; Overman, L. E.; Wolfe, J. P. *Tetrahedron Lett.* **2000**, *41*, 9431−9435.

(2) Al-Mutairi, E. H.; Crosby, S. R.; Darzi, J.; Hughes, R. A.; Simpson, T. J.; Smith, R. W.; Willis, C. L.; Harding, J. R.; King, C. D. *Chem. Commun.* **2001**, 835−836. This paper includes an example (e.g., **13** to **17**) where a 2-oxonia Cope rearrangement is implicated. We thank Professor Willis for bringing it to our attention.

(3) (a) Lolkema, L. D. M.; Hiemstra, H.; Semeyn, C.; Speckamp, W. N. *Tetrahedron* **1994**, *50*, 7115−7128. (b) Lolkema, L. D. M.; Semeyn, C.; Ashek, L.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1994**, *50*, 7129−7140.

(4) (a) Semeyn, C.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3426−3427. (b) Huang, H. B.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9836−9837.

(5) Roush, W. R.; Dilley, G. J. *Synlett* **2001**, 955−959.

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product **2** in 58% yield. It was accompanied by 26% of product **3**, epimeric at C3. The configuration at C3 had been established in **1**, and epimerization was completely unexpected.

The most plausible mechanism for the epimerization invokes a 2-oxonia Cope rearrangement, Figure 1. Oxocarbenium ion **6** could rearrange to **7** via a chair transition state. Both **6** and **7** would cyclize to the expected product **2**.[9] Product **3** could arise by a 2-oxonia Cope rearrangement in a boat transition state to produce the oxocarbenium ion **8**. Cyclization of **8** from a chair transition state would produce **3**, the C3 epimer. A 2-oxonia Cope rearrangement from a chair transition state (e.g., **6** to **7**) leads to the expected product **2**. Epimerization at C3 requires a boat transition state in the Cope rearrangement. Nokami's crotyl transfer reactions proceed with good stereochemical fidelity and suggest that such a boat transition state is unexpected.[6] Further evidence of the intermediacy of **8** in the formation of **3** comes from the treatment of **1** with TMSOTf (Scheme 1.) The *E*-alkene **5** was produced as a minor product, along with *Z*-alkene **4**. Both presumably arise from hydrolysis of the oxocarbenium ions **8** and **7**. We conclude that the 2-oxonia Cope rearrangement plays an important role in this unusual Prins cyclization.

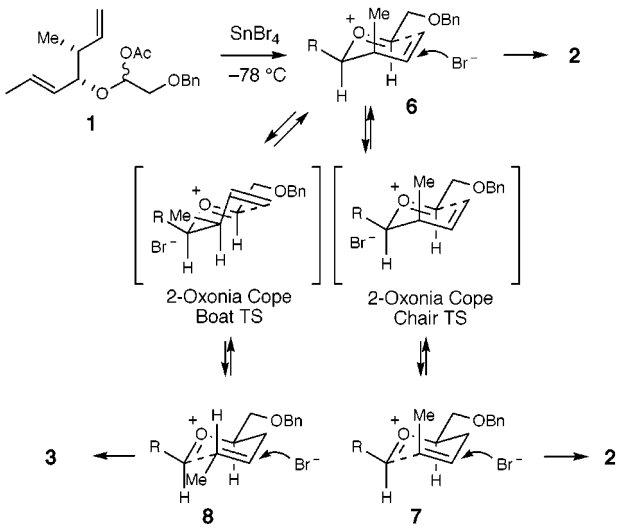


Figure 1. The chair and boat 2-oxonia Cope rearrangements that lead to tetrahydropyran **2** and its C3 epimer **3**.

Does the 2-oxonia Cope rearrangement compete with the Prins cyclization with a typical substrate? This question is difficult to answer because the 2-oxonia Cope rearrangement is usually undetectable by product analysis. Figure 2 shows a typical Prins cyclization substrate **9**. Oxocarbenium ion **10** can rearrange via a chair transition state to **11**, or cyclize to **12**. Compound **11**, however, also cyclizes to **12**. The 2-oxonia Cope rearrangement with a chair transition state does not affect the outcome of a Prins cyclization and in most cases can be ignored.[9]

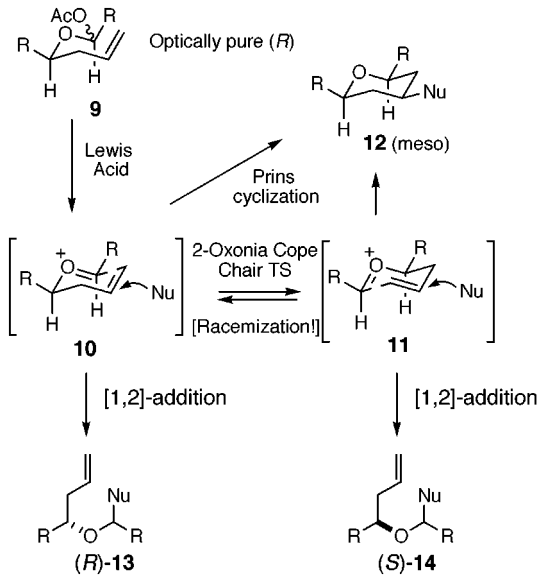


Figure 2. Racemization test for a 2-oxonia Cope rearrangement in a Prins cyclization reaction.

Figure 2 outlines a test for the 2-oxonia Cope rearrangement in a Prins cyclization substrate. If we add a nucleophile to the Prins cyclization reaction, it could add to the oxocarbenium ions **10** and **11** in competition with the Prins cyclization. If the two alkyl groups are not equivalent, two different compounds, **13** and **14**, would be produced. Producing both **13** and **14** would be good evidence for a 2-oxonia Cope rearrangement, but it would be difficult to analyze the relative rate of the reactions, as **13** and **14** could be formed as a kinetic or a thermodynamic mixture. A more sensitive test uses optically pure **9**. In this case, **13** and **14** are enantiomers, and the 2-oxonia Cope rearrangement mediates racemization of the substrate. Racemization is a one-way process, and so a thermodynamic (racemic) mixture of **13** and **14** can be easily distinguished from a kinetic (optically active) mixture. Racemization of the side products would be good evidence for the 2-oxonia Cope rearrangement competing with the Prins cyclization.

The 2-oxonia Cope rearrangement was evaluated as outlined in Scheme 2. Optically active **16**[10] was prepared as

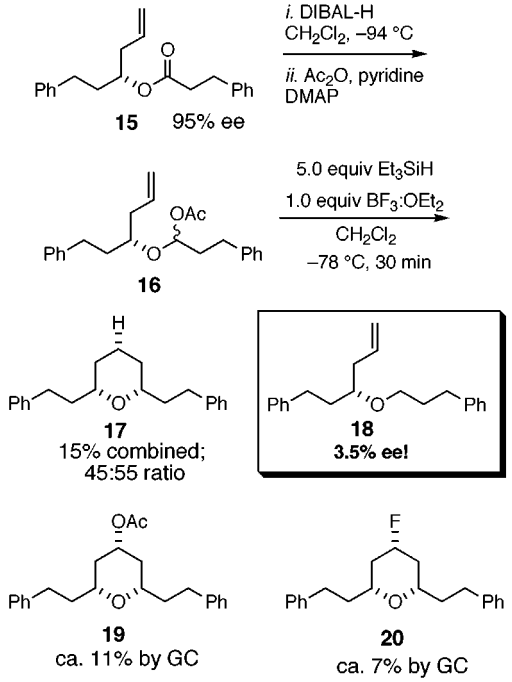
(6) (a) Nokami, J.; Yoshizane, K.; Matsuura, H.; Sumida, S.-i. *J. Am. Chem. Soc.* **1998**, *120*, 6609−6610. (b) Nokami, J.; Anthony, L.; Sumida, S.-I. *Chem. Eur. J.* **2000**, *6*, 2909−2913. (c) Nokami, J.; Ohga, M.; Nakamoto, H.; Matsubara, T.; Hussain, I.; Kataoka, K. *J. Am. Chem. Soc.* **2001**, *123*, 9168−9169.

(7) (a) Loh, T.-P.; Hu, Q.-Y.; Ma, L.-T. *J. Am. Chem. Soc.* **2001**, *123*, 2450−2451. (b) Loh, T.-P.; Tan, K.-T.; Hu, Q.-Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 2921−2922.

(8) (a) Gerth, K.; Schummer, D.; Hoefle, G.; Irschik, H.; Reichenbach, H. *J. Antibiot.* **1995**, *48*, 973−6. (b) Christmann, M.; Bhatt, U.; Quitschalle, M.; Claus, E.; Kalesse, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4364−4366. (c) Bhatt, U.; Christmann, M.; Quitschalle, M.; Claus, E.; Kalesse, M. *J. Org. Chem.* **2001**, *66*, 1885−1893. (d) Williams, D. R.; Ihle, D. C.; Plummer, S. V. *Org. Lett.* **2001**, *3*, 1383−1386.

(9) (a) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679−4686. (b) Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217−1219.

Scheme 2. Evidence for a 2-Oxonia Cope Rearrangement in a Typical Prins Cyclization from Racemization of a Side Product



a mixture of diastereomers and subjected to low-temperature Prins cyclization conditions. Triethylsilane was added as a nucleophile to compete with the cyclization. The expected cyclic products **19** and **20** were identified by GC and comparison with authentic standards.[11] Hydride addition products **17** and **18** were isolated as an inseparable mixture, and the optical purity of **18** was evaluated by HPLC on a Chiracel OD-H column. Trapping product **18** was nearly racemic, thus demonstrating that the 2-oxonia Cope rearrangement was fast under these conditions. Roughly comparable amounts of cyclic products and direct trapping product **18** were isolated, suggesting that the rates of formation of these products are roughly comparable and are much slower than the 2-oxonia Cope rearrangement.

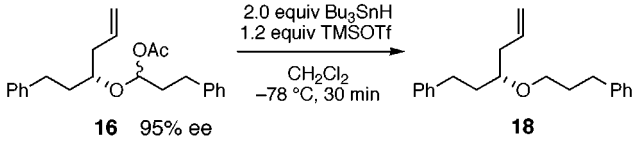
The rate of 2-oxonia Cope rearrangement is much faster than reduction by triethylsilane. The rate of the rearrangement can be evaluated qualitatively using a stronger reducing agent. Bu_3SnH is a much more nucleophilic in the reduction of stabilized carbenium ions than triethylsilane.[12] The results of the reduction of optically active **16** with Bu_3SnH at low temperature are shown in Table 1. Under these conditions, little or no Prins cyclization takes place. Even at high concentrations of Bu_3SnH, the reduction product **18** was isolated in only 47% ee. Lowering the concentration of the

(10) (a) Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **1993**, *115*, 7001−7002. (b) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467−8468. (c) Keck, G. E.; Krishnamurthy, D. *Org. Synth.* **1996**, *75*, 12−17. (d) Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **2000**, *65*, 191−198.

(11) Tetrahydropyrans **19** and **20** were prepared from racemic **15**. See Supporting Information for details.

(12) Mayr, H.; Patz, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938−957.

Table 1. Reduction the α-Acetoxy Ether **16** and Competitive Racemization in the Presence of Bu_3SnH



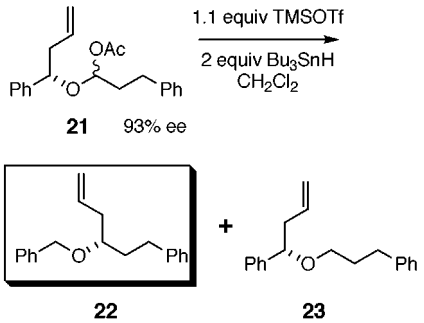
entry	[Bu_3SnH]	ee, %[a]	yield, %
1	0.4	47	88
2	0.2	38	91
3	0.1	31	92[b]
4	0.04	17	83[c]

[a] The ees were determined by HPLC analysis on a chiracel OD-H column. [b] Contains 1% of a cyclic alkene. [c] Contains 3% of a cyclic alkene.

trapping agent results in further racemization. At 0.04 M Bu_3SnH, **18** was isolated with just 17% ee. Qualitatively, these results show that 2-oxonia Cope rearrangements are much faster than typical Prins cyclizations.

Several examples of the 2-oxonia Cope rearrangement were identified in allyl migration reactions.[6] We became interested in enantioselective allyl transfer reactions. The initial investigation of an enantioselective allyl transfer mediated by the 2-oxonia Cope rearrangement is outlined in Table 2. In this case, the two oxocarbenium ions interconverted by the 2-oxonia Cope rearrangements are not enantiomers but are constitutional isomers. The oxocarbenium ion leading to **22** is more stable than that leading to **23** because of conjugation with the phenyl ring. This increased stability should favor formation of **22** and lead to an enantioselective allyl transfer reaction. Optically active

Table 2. Enantioselective 2-Oxonia Cope Rearrangement and Regioselective Reduction



entry	[Bu_3SnH]	temp, °C	**22**:**23**	yield, %	ee, %[a] (**22**)
1	0.044	−78	56:44	94	95[c]
2	0.015	−78	80:20	85	93[b]
3	0.007	−78	85:15	84	–
4	0.015	0	93:7	70	–

[a] The ees were determined with the alcohol after debenzylation (Na/NH_3). [b] The ee was determined by HPLC on a Chiracel OD-H column. [c] The ee was determined by GC on a β-cyclodextrin permethylated hydroxypropyl column (but without baseline separation.)

21 was prepared using standard methods[10] and subjected to reductive rearrangement conditions with Bu_3SnH. High concentrations of Bu_3SnH lead to 1:1 mixtures of **22** and **23**, but lower concentrations of the reducing agent produced **22** and **23** as >4:1 mixtures in good yield. The optical purity of **22** was identical to that of **21**. Under these conditions, the 2-oxonia Cope rearrangement proceeded with complete stereochemical fidelity. This allyl transfer reaction is an interesting alternative to enantioselective allylation reactions[13] and produces benzyl protected products directly.

(13) Roush, W. R. in *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I. and Heathcock, C. H., Ed.; Pergamon Press: New York, 1991; Vol. 2, pp 1−53.

Competitive reductions of the intermediate oxocarbenium ions demonstrate that the 2-oxonia Cope rearrangement is typically much faster than Prins cyclization. Although usually invisible, 2-oxonia Cope rearrangements can produce surprising stereochemical outcomes in Prins cyclizations.

Acknowledgment. The National Institutes of Health (CA-81635) and Sankyo Co., Ltd. provided financial support.

Supporting Information Available: Preparation and characterization of the compounds described in the paper are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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