DOI: 10.1002/chem.200901377

Synthesis and Reactivity of Enantiomerically Enriched Thiiranium Ions

Scott E. Denmark* and Thomas Vogler[a]

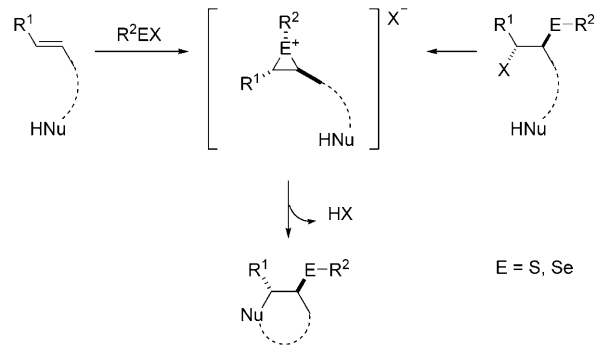
Abstract: Enantiomerically enriched thiiranium ion **5** has been prepared by silver-assisted ionization of chloro sulfide **4** at −20 °C. This thiiranium ion is configurationally stable in solution up to room temperature as demonstrated by the stereospecific capture of the ion by various oxygen- and nitrogen-based nucleophiles. Both isolated olefins and weak Lewis bases can promote the racemization of **5** but these processes can also be suppressed at low temperature. Capture of **5** by methanol is faster than the racemization processes.

Keywords: episulfonium ions · Lewis bases · nucleophiles · stereoselectivity · sulfur

Introduction

The stereoselective, electrophilic functionalization of prochiral olefins is a topic of great importance in organic chemistry. In particular, asymmetric epoxidations,[1] dihydroxylations[2] and hydroborations[3] are frequently used as reliable, chemo-, regio-, and stereoselective methods for the synthesis of complex molecules and useful building blocks. Whereas much effort has been devoted to the asymmetric transfer of oxygen, no examples of catalytic, enantioselective additions of the heavier chalcogenic reagents (S and Se) to unactivated olefins have been reported.[4] In the context of our ongoing program on Lewis base activation of Lewis acids,[5] preliminary mechanistic and preparative studies toward the ultimate goal of developing catalytic, enantioselective chalcogenofunctionalizations have been described.[6,7]

The common mechanistic feature of these reactions is the formation of thiiranium and seleniranium ions followed by trapping with a pendant nucleophile to eventually give configurationally defined products (Scheme 1).[8,9] In fact, the formation of -iranium ions has also been suggested in a various other transformations in organic synthesis.[9] Mechanistically, stereochemically defined, -iranium ions have often been proposed as intermediates in nucleophilic substitutions at carbon next to chalcogen atoms that proceed with retention of configuration. In these reactions, anchimeric assistance of the chalcogenic donors is believed to initially form an -iranium ion (inversion) which is followed by another invertive nucleophilic trapping thus leading to an overall accelerated retentive substitution.[10] Additionally, the synthesis of heterocycles via thiiranium ions generated upon displacement of a leaving group with neighboring-group participation by a sulfanyl group has been intensively studied.[11] Site-selective ring opening of a thiiranium ion with a pendant nucleophile (Scheme 1) can be used for the formation of five- and six-membered heterocycles. Similarly, seleniranium ions have been proposed to explain the stereochemical outcome after the dehydration of β-hydroxy selenides with subsequent nucleophile trapping.[12,13] Many other studies have postulated the intermediacy of thiiranium and seleniranium ions in reactions that employ stable precursors by analysis of the reaction rate and the structure of the products formed.[9,14,15] To achieve our goal of developing a catalytic,



Scheme 1. Electrophilic chalcogeno functionalization of unactivated olefins.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200901377.

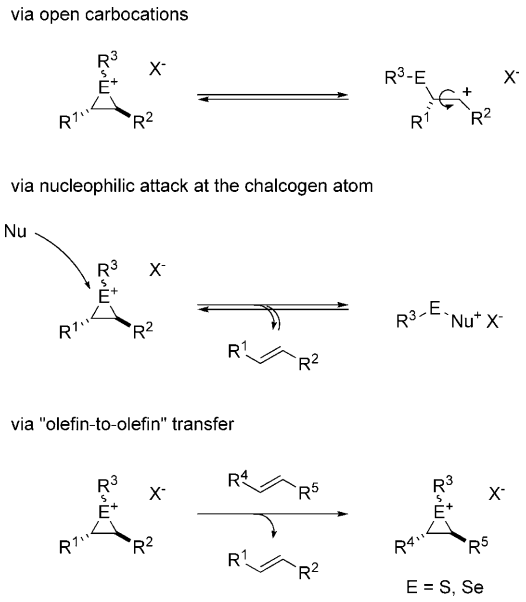
enantioselective chalcogenofunctionalization, a knowledge of the kinetic competence and configurational stability of the intermediate -iranium ions is essential.

Background

Several thiiranium and seleniranium ions have been independently synthesized and structurally analyzed as racemates. Thiiranium ions can be generated by the addition of sulfenium cations to olefins[16–18] or by S-alkylation of the corresponding thiiranes.[19] Additionally, halide abstraction from β-chloro sulfides with silver salts can form these reactive intermediates.[7] Seleniranium ions have been similarly formed via electrophilic addition of selenenyl cations to the corresponding olefins[20,21] or halide abstraction from the corresponding chloro selenides.[7,20] However, no examples of the independent synthesis of enantiomerically enriched -iranium ions are on record. Therefore, the absolute configurational stability of these hyper-reactive intermediates has never been directly established.

A priori, a number of mechanisms can be formulated that could lead to erosion of configurational integrity of enantiomerically enriched thiiranium and seleniranium ions (Scheme 2). For example, these species might not be intrinsically configurationally stable and could racemize via open carbocation intermediates before nucleophilic attack. The epimerization of a sterically encumbered, *cis*-substituted thiiranium ion to the more stable *trans*-isomer has been reported to occur via this pathway.[18] Alternatively, nucleophilic attack not at carbon but at the sulfenium or selenenium ion center could produce sulfenyl or selenenyl transfer reagents.[13,22,23] Redelivery of the sulfenium or selenenium cations to the olefin would racemize the -iranium ions. The ratio of attack at the sulfur and the carbon atom of a thiiranium ion was reported to correlate roughly with the strength of the attacking nucleophile. With weak nucleophiles, greater amounts of the olefin and therefore attack at sulfur was confirmed experimentally.[24] Finally, the direct sulfenium and selenenium group transfer from thiiranium and seleniranium ions to alkenes has been demonstrated recently and this "olefin-to-olefin" transfer is as a possible racemization mechanism for enantiomerically enriched -iranium ions.[7] For in situ generated seleniranium ions, olefin-to-olefin transfer was instantaneous at −70 °C! Thus, these species (R^3E^+ = PhSe, *n*BuSe) are not configurationally stable in an absolute sense (the relative configurations were preserved). Remarkably, however, in the same study,[7] olefin-to-olefin transfer for in situ generated thiiranium ions proceeded much more slowly or was not observed at all. Therefore the critical question of configurational stability of enantiomerically enriched thiiranium ions can be addressed.

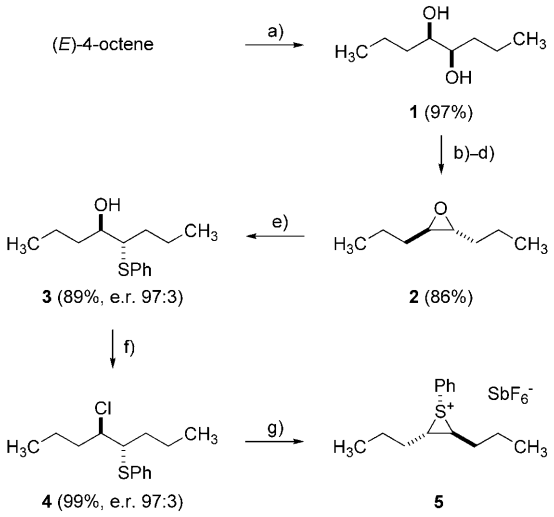
Pasquato and co-workers have shown that an in situ formed, chiral, nonracemic thiiranium ion can be trapped at low temperature with good enantioselectivity.[23] In this case, the proposed chiral thiiranium ion had been generated in situ by sulfenium ion transfer from an enantiomerically enriched thiosulfonium salt to an olefin with stoichiometric formation of a disulfide. These authors pointed out that the presence of the disulfide (Lewis base) might lead to partial racemization of the thiiranium ion before the attack of the nucleophile. Thus, to study the configurational stability of an enantiomerically enriched thiiranium ion required the synthesis of these hyper-reactive species in the absence of Lewis bases. We describe herein our studies on the generation, stability, and capture of enantiomerically enriched thiiranium ions. This study provides the boundary conditions needed to guide the development of a catalytic, enantioselective chalcogenofunctionalization reaction.[25]



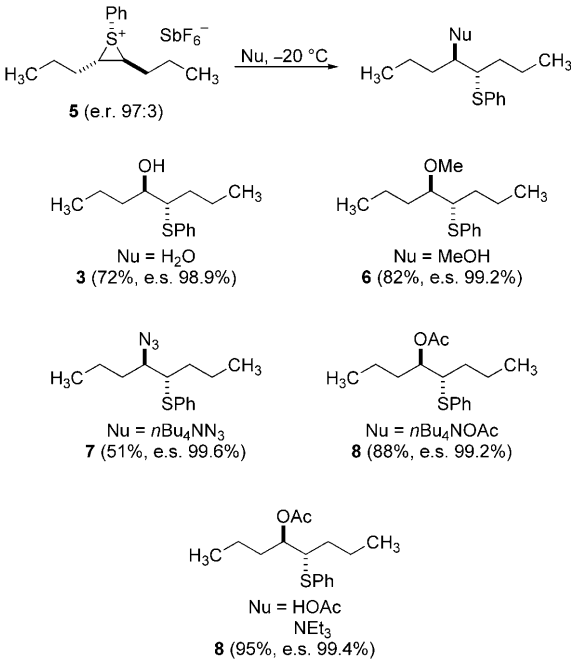
Scheme 2. Possible racemization mechanisms of enantiomerically enriched -iranium ions.

Results

Synthesis of an enantiomerically enriched thiiranium ion: Thiiranium ions have been prepared previously by halide ion abstraction of β-chloro sulfides with silver hexafluoroantimonate, albeit only in racemic form.[7] Thus, preparation of the specific enantiomerically enriched thiiranium ion for this study was envisioned by using a chiral, nonracemic β-chloro sulfide derived from (*E*)-4-octene (Scheme 3). (4*R*,5*R*)-Octane-4,5-diol (**1**) was readily obtained by asymmetric dihydroxylation of (*E*)-4-octene in excellent yield and was converted into epoxide **2** by the known three-step procedure reported for its enantiomer.[26] Ring opening of **2** with thiophenol under basic conditions gave the desired hydroxy sulfide **3** with a high enantiomeric ratio (e.r. 97:3). The instability of the chloro sulfide **4** to purification required that a clean and mild method for its synthesis be devised without the need for purification. Treatment of **3** with thionyl chloride (1.5 equiv) and DMF (0.05 equiv) gave the *anti*-chloro sulfide **4** in excellent yield.[10,27] (2*S*,3*S*)-2,3-Dipropyl-1-phe-



Scheme 3. Synthesis of enantiomerically enriched thiiranium ion **5**. a) $K_2OsO_4{\cdot}2H_2O$, $(DHQD)_2PHAL$, $[K_3Fe(CN)_6]$, $MeSO_2NH_2$, K_2CO_3, *t*BuOH, H_2O, RT; b) $(CH_3O)_3CH$, PPTS, CH_2Cl_2, RT; c) AcBr, CH_2Cl_2, RT; d) NaOH, MeOH, Et_2O, RT; e) PhSH, NaOH, MeOH, 60 °C; f) $SOCl_2$, DMF (0.05 equiv), CH_2Cl_2, RT; g) $AgSbF_6$, CH_2Cl_2, −40 → 0 °C.



Scheme 4. Reaction of enantiomerically enriched thiiranium ion **5** with various nucleophiles.

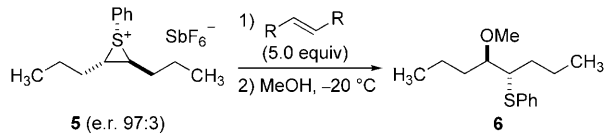
nylthiiranium hexafluoroantimonate (**5**) was prepared under anhydrous conditions by treatment of **4** with silver hexafluoroantimonate. The precipitated silver salts could be easily removed by filtration to afford a homogeneous solution of the thiiranium ion **5** in dichloromethane. The No-D NMR spectroscopic data[28] of **5** were in accordance with those described in the literature.[7] By this procedure, the isolation of the in situ generated thiiranium ion **5** was possible which was used immediately because of its instability at temperatures above −20 °C.

Reaction of enantiomerically enriched thiiranium ion 5 with nucleophiles: No analytical method is available to directly and accurately monitor the configurational stability of a hyper-reactive thiiranium ion. Therefore, **5** was combined with oxygen- and nitrogen-based nucleophiles and the enantiomeric composition of the products was determined by chiral stationary phase, supercritical fluid chromatographic (CSP-SFC) analysis. Nucleophiles were chosen that could mimic catalytic sulfenyl functionalizations and would provide homogeneous reaction mixtures (Scheme 4).[29] By using this approach, the stability of thiiranium ion intermediate **5** under various conditions could be easily deduced by comparison of the enantiomeric composition of the chloro sulfide precursor **4** and the capture products. A solution of thiiranium ion **5** (prepared as described above) hydrolyzed at −20 °C and the resulting hydroxy sulfide **3** was obtained with excellent enantiospecificity (e.s.).[30] Unfortunately, the results were not reproducible, so a slightly modified protocol that formed the thiiranium ion **5** at lower temperatures was developed which gave more reliable results. To this end, chloro sulfide **4** (e.r. 97:3) could be converted quantitatively into thiiranium ion **5**, and **3** could be obtained with excellent enantiospecificity after hydrolysis at −20 °C. The temperature at which the nucleophile was added was not a critical factor as similar results were also obtained at 0 °C or RT, further demonstrating the intrinsic configurational stability of **5**. Other oxygen- and nitrogen-based nucleophiles were tested next to examine if the stereospecific capture of enantiomerically enriched thiiranium ion **5** is limited to water. The reaction of **5** with methanol afforded methoxy sulfide **6** in good yields with complete enantiospecificity. Tetrabutylammonium azide gave the thio azide **7** without erosion of configurational integrity in moderate yield. Carboxylic acids and their salts were also used as trapping reagents to afford acetoxy sulfide **8** in excellent yield with stereospecific capture. No-D NMR spectroscopic analysis of the reaction of **5** with acetic acid showed an equilibrium mixture of thiiranium ion **5** and acetate **8**. Therefore, triethylamine was charged into the mixture 15 min after the addition of acetic acid to drive the reaction to completion.

Configurational stability of enantiomerically enriched thiiranium ion 5: The effect of olefins: Although the configurational stability of stoichiometrically generated thiiranium ion **5** has been demonstrated, it was essential to establish the configurational stability of **5** under a variety of pseudo catalytic reaction conditions. Specifically, under circumstances that form the thiiranium ion from an alkene in very small quantities, the presence of a large excess of the olefin can provide a racemization pathway by olefin to olefin transfer.[7] To test this hypothesis, thiiranium ion **5** was combined with (*E*)-4-octene at various temperatures followed by methanolysis.[31] Treatment of **5** with (*E*)-4-octene (5.0 equiv) at 0 °C for 15 min followed by addition of metha-

nol afforded racemic methoxy sulfide **6** (Table 1, entry 1). However, treatment of **5** with (*E*)-4-octene at −10 °C or −20 °C for prolonged reaction times afforded (after quench) the methanolysis product with little or no racemization (entries 2 and 3).

Table 1. Racemization of enantiomerically enriched thiiranium ion **5** by olefin-to-olefin transfer.



5 (e.r. 97:3) **6**

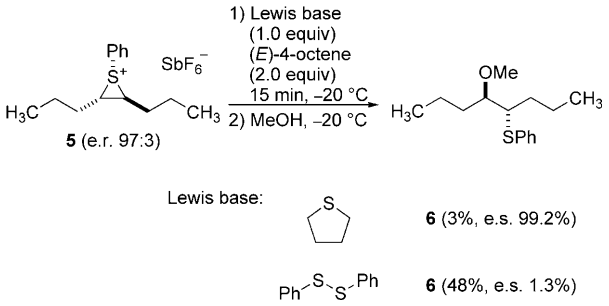
Entry	R	*T* [°C]	*t* [min]	Yield [%][a]	e.r.[b]	e.s. [%][c]
1	nC_3H_7	0	15	45	50:50	0.6
2	nC_3H_7	−10	60	53	94:4	97.3
3	nC_3H_7	−20	60	74	97:3	99.2
4	Bn	0	60	29	91:9	87.2

[a] Isolated yield of chromatographically homogeneous material. [b] Determined by CSP-SFC. [c] Calculated enantiospecificity.

As was demonstrated in the foregoing study, the rate of olefin-to-olefin transfer is strongly dependent on the choice of thiiranium ion and olefin.[7] Sulfenium group transfer from racemic thiiranium ion **5** to (*E*)-1,4-diphenyl-2-butene is not observed by ^{1}H NMR spectroscopic analysis.[7] Indeed, treatment of enantiomerically enriched **5** with *trans*-1,4-diphenyl-2-butene lead to only partial racemization even at 0 °C for 60 min (entry 4). The capture product **6** was isolated under these conditions in moderate yield with lower enantiospecificity.

Configurational stability of enantiomerically enriched thiiranium ion 5: The effect of Lewis bases and olefins: Pasquato's proposal that nucleophilic attack of Lewis bases at the sulfenium ion center could produce sulfenyl or selenenyl transfer reagents and therefore racemize thiiranium ions was studied next in more detail.[23] In these experiments, thiiranium ion **5** was combined with various Lewis bases in the presence of (*E*)-4-octene at −20 °C where no direct sulfenyl group transfer occurred (compare Table 1, entry 3). A stoichiometric amount of the Lewis base was used for these studies to obtain unambiguous results.[32] As anticipated, few Lewis bases were compatible with the hyper-reactive thiiranium ions. The desired trapping product **6** could not be detected with Lewis bases such as $(Me_3N)_2P{=}Se$, triethylamine or trimethylamine-*N*-oxide, even at lower temperatures (−50 °C). With tetrahydrothiophene, methoxy sulfide **6** was isolated in low yield but with excellent enantiospecificity (Scheme 5). In stark contrast, the reaction of thiiranium ion **5** with diphenyl disulfide and (*E*)-4-octene for 15 min at −20 °C followed by the addition of methanol gave racemic **6** in moderate yield. The interpretation of these disparate results is discussed below.

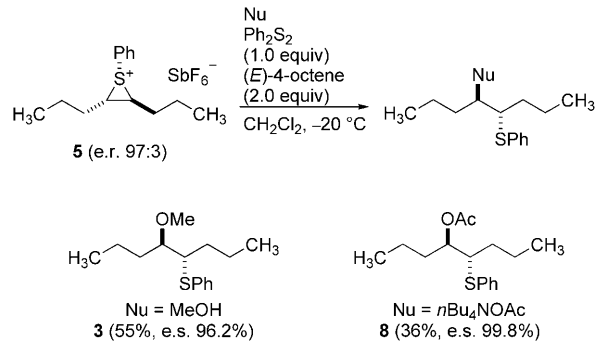
Competition experiments: These experiments were conducted to determine the relative rates of racemization of **5** in the



5 (e.r. 97:3)

Scheme 5. Reaction of enantiomerically enriched thiiranium ion **5** with Lewis bases and octene.

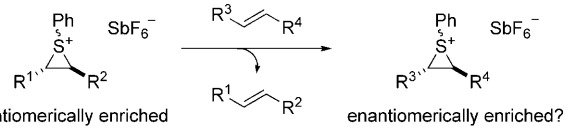
presence of diphenyl disulfide versus trapping of **5** by a nucleophile. Therefore, **5** was treated with a preformed solution of diphenyl disulfide, (*E*)-4-octene and a trapping nucleophile in dichloromethane at −20 °C (Scheme 6). The ring opened products from reaction with methanol (4.0 equiv) or tetrabutylammonium acetate (1.0 equiv) were formed stereospecifically under these conditions. Although racemization occurs within 15 min under these conditions without the nucleophile (compare Scheme 5) the *intermolecular* capture occurs faster!



5 (e.r. 97:3)

Scheme 6. Competition experiments with methanol and tetrabutylammonium acetate.

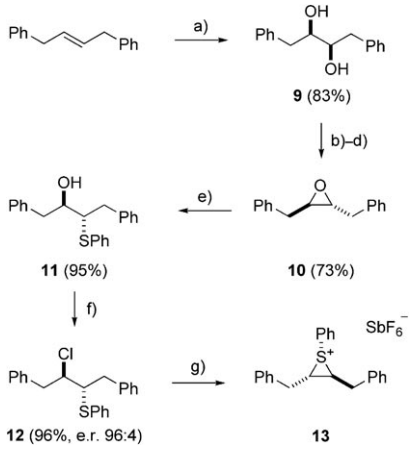
Investigation of the mechanism of "olefin-to-olefin" transfer: Even though olefin-to-olefin transfer is a viable racemization pathway for a thiiranium ions under certain conditions, the mechanism of this process is unclear. Two limiting scenarios can be envisioned, a dissociative pathway in which a phenylsulfenium cation departs unassisted from the thiiranium ion and is captured by another olefin, and an associative pathway in which a second olefin assists in the removal of the phenylsulfenium ion. These pathways can be differentiated by the use of a chiral, nonracemic thiiranium ion in combination with an alkene. Capture of the alkene transfer product with a nucleophile and analysis of its enantiomeric composition can distinguish the pathways (Scheme 7). If the capture product is enantiomerically enriched, then the transfer must be, at least in part, associative. If the capture product is racemic, then the dissociative pathway is likely opera-



Scheme 7. Plan for the transfer experiment.

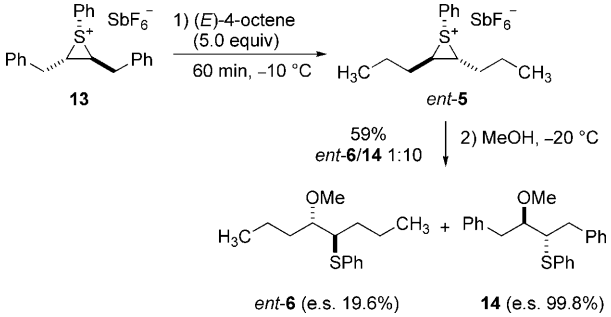
tive.[33] Thus, the enantiomerically enriched thiiranium ion derived from 1,4-diphenyl-2-butene was synthesized and the olefin-to-olefin transfer to (*E*)-4-octene was studied. Since, the reverse reaction is slow (compare Table 1, entry 4) this transfer should give valuable insights.[7]

The synthesis of the target thiiranium ion **13** was achieved via a route similar to that for the (*E*)-4-octene derivative **5**. Asymmetric dihydroxylation of (*E*)-1,4-diphenyl-2-butene afforded diol **9** which was converted to epoxide **10** in three steps (Scheme 8).[34] Opening of **10** with basic thiophenol gave hydroxy sulfide **11** in excellent yield. The corresponding chloro derivative **12** (e.r. 96:4) was obtained in nearly quantitative yield by treatment with thionyl chloride. Conversion of **12** to the enantiomerically enriched thiiranium ion **13** was achieved by chloride abstraction with silver hexafluoroantimonate following to the modified temperature profile described above.



Scheme 8. Synthesis of enantiomerically enriched thiiranium ion **13**. a) $K_2OsO_4{\cdot}2H_2O$, $(DHQD)_2PHAL$, $[K_3Fe(CN)_6]$, $MeSO_2NH_2$, K_2CO_3, *t*BuOH, H_2O, RT; b) $(CH_3O)_3CCH_3$, PTSA, CH_2Cl_2, RT; c) TMSCl, CH_2Cl_2, RT; d) K_2CO_3, MeOH, RT; e) PhSH, NaOH, MeOH, 60 °C; f) $SOCl_2$, DMF (0.05 equiv), CH_2Cl_2, RT; g) $AgSbF_6$, CH_2Cl_2, −40 → 0 °C.

Next, the sulfenyl group transfer conditions were carefully optimized. The transfer from thiiranium ion **13** to (*E*)-4-octene did not proceed at temperatures lower than −20 °C and was slow at 0 °C. However, racemization of the transfer thiiranium-ion **5** occurred rapidly a 0 °C (compare Table 1, entry 1). Therefore, the reaction had to be performed between −20 and −10 °C where the transfer process was very slow. To this end, the experiment was performed at −10 °C for 60 min by using an excess of (*E*)-4-octene followed by methanolysis (Scheme 9). The trapping products *ent*-**6** and **14** were isolated as a 1:10 mixture in a combined yield of 59 % which could be readily analyzed via CSP-SFC. Gratifyingly, the transfer product *ent*-**6** was slightly enantiomerically enriched (e.s. 19.6 %). Capture of the thiiranium ion **13** afforded methoxy sulfide **14** with an enantiospecificity of 99.8 %.



Scheme 9. Partial sulfenyl group transfer from **13** to (*E*)-4-octene followed by methanolysis.

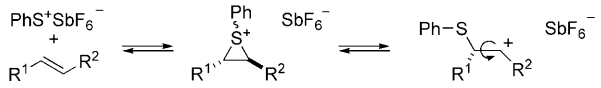
Discussion

The results above represent a significant contribution for the understanding of the chemistry of chiral thiiranium ions. Several important questions will be discussed:

1) can chiral, nonracemic thiiranium ions be independently synthesized and are they intrinsically configurationally stable;
2) does trapping of thiiranium ions by nucleophiles occur at the carbon or the sulfur atom;
3) could the racemization of thiiranium ion by sulfenyl group transfer to olefins occur under catalytic reaction conditions and
4) does the sulfenyl group transfer from thiiranium ions to olefins proceed via an associative or dissociative transition process?

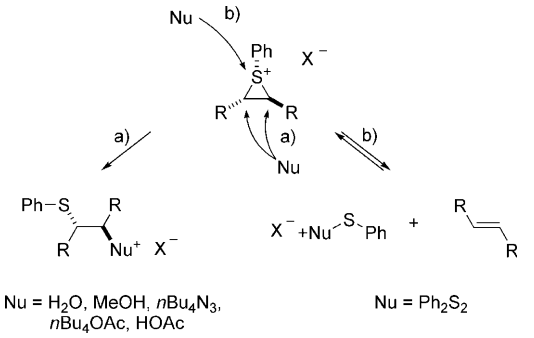
Configurational stability of enantiomerically enriched thiiranium ion 5 and trapping with nucleophiles: The synthesis of enantiomerically enriched thiiranium ion **5** required the preparation of ((4*S*,5*R*)-5-chlorooctan-4-yl)(phenyl)sulfane (**4**) as a precursor. The preparation of **4** was designed to make use of the well established substitution of β-hydroxy sulfides by chloride with retention of configuration by anchimeric assistance of the sulfide to form a thiiranium ion.[10, 27] The required β-hydroxy sulfide **3** was prepared with high enantiomeric enrichment by thiolate opening of the corresponding epoxide. The conversion of the chloro sulfide **4** to (2*S*,3*S*)-2,3-dipropyl-1-phenylthiiranium hexafluoroantimonate (**5**) with silver hexafluoroantimonate followed by trapping with water gave product **3** enantiospecifically (Scheme 4). This result clearly shows that both the synthesis of thiiranium ion **5** and its interception occur without erosion of configurational integrity. Therefore, thiiranium ion **5**

is configurationally stable under the reaction conditions. This observation rules out a number of possible intrinsic racemization mechanisms such as double epimerization by reversible opening of the thiiranium ion to a carbocation intermediate followed by C–C bond rotation. Additionally, reversible dissociation of a thiiranium ion into the corresponding olefin and a sulfenyl cation also does not occur (Scheme 10).



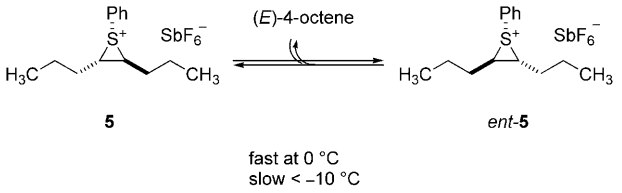
Scheme 10. Reversible opening of a thiiranium ion.

The second critical issue in this study is the ability to stereospecifically capture the enantiomerically enriched thiiranium ion with nucleophiles. Thiiranium ions possess four electrophilic positions.[14] Invertive attack at either of the ring carbons (Scheme 11, pathway a) should lead stereospecifically to product formation. To simplify the test system a symmetrically substituted thiiranium ion was utilized. This strategy has two advantages, attack at either carbon leads to the same product and the sulfur atom is not stereogenic. However, nucleophilic attack could also occur at the sulfur atom resulting in formation of the olefin and a sulfenyl transfer reagent (pathway b).[23,24] Redelivery of the sulfenyl group to the olefin from the other face would ultimately racemize the thiiranium ion. The final possibility, attack at the *exo*-carbon to eject a thiirane is rare and has never been observed with S-phenyl substituted thiiranium ions.[35] To investigate if attack at sulfur occurs, some common nucleophiles were combined with the enantiomerically enriched thiiranium ion **5**. The corresponding ring opened products **3**, **6**, **7** and **8** were isolated after stereospecific trapping with water, methanol, azide, acetic acid, and acetate respectively. All of the O- and N-reagents employed attacked irreversibly at carbon and hence could be used in electrophilic sulfenyl cyclofunctionalizations as pendant nucleophiles.



Scheme 11. Site-selective attack of nucleophiles at S-phenyl substituted thiiranium ions.

Configurational stability of an enantiomerically enriched thiiranium ion in the presence of olefins: The studies described above differ from catalytic, asymmetric reactions because only a small amount of the enriched thiiranium ion would be generated from the substrate in the latter case. Although an enantiomerically enriched thiiranium ion might have been generated initially, only racemic products would be isolated because of racemization of the intermediate. Therefore, it was important to learn if an excess of olefin could racemize the thiiranium ion by the olefin-to-olefin transfer demonstrated previously.[7] Indeed, this process turned out to be a rapid racemization pathway for enantiomerically enriched thiiranium ions (complete racemization within 15 min at 0 °C). Gratifyingly, the racemization could be suppressed at temperatures below −10 °C even after 1 h in the case studied herein (Scheme 12).

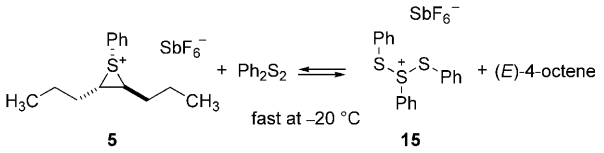


Scheme 12. Racemization of thiiranium ion **5** via "olefin-to-olefin" transfer

Therefore, the development of a catalytic enantioselective process should focus on low temperature protocols. In addition, the sulfenyl transfer equilibrium constant was shown to be strongly dependent on the structure of the olefins.[7] Transfer from the (*E*)-4-octene derived thiiranium ion **5** to (*E*)-1,4-diphenyl-2-butene gave no trapping product (Table 1, entry 4). The slight erosion of configurational purity of **6** in this case might also be attributed to partial decomposition of hyper-reactive intermediate **5** at 0 °C as reflected by the low yield.

Configurational stability of enantiomerically enriched thiiranium ion 5 in the presence of Lewis bases and an olefin: As indicated in Scheme 11, Lewis bases can also attack at the sulfur atom resulting in the formation of an achiral sulfenyl transfer agent that can lead to racemization of the thiiranium ion. Therefore, enantiomerically enriched **5** was first treated with a variety of Lewis bases at −20 °C where uncatalyzed olefin-to-olefin transfer did not take place. The corresponding trapping product **6** could not be isolated by using strong Lewis bases. This observation might be due to irreversible attack of the Lewis base at the carbon of the thiiranium ion **5** (Scheme 11, pathway a). However, treatment of **5** with tetrahydrothiophene gave a small amount of the methoxy sulfide **6** (Scheme 5). Racemization of the intermediate **5** did not occur in this case. Treatment of **5** with diphenyl disulfide resulted in the isolation of racemic methanolysis product **6** after 15 min at −20 °C in a significantly higher yield compared to the reaction with tetrahydrothio-

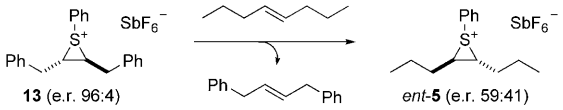
phene. These results are strong indicators that diphenyl disulfide attacks the thiiranium ion **5** at the sulfur atom at which point a dithiosulfonium salt **15** and (*E*)-4-octene are reversibly formed (Scheme 13). In fact, attack of disulfides at the sulfur atom of thiiranium ions is also supported by calculations and kinetic experiments.[17,36] In contrast, attack at the carbon atom has been shown with dimethyl disulfide.[37] These experimental results support Pasquato's proposal, that chiral, nonracemic thiiranium ions generated by enantiomerically enriched dithiosulfonium salts might racemize after formation.[23] However, racemization depends, of course, on the relative rates of attack at the sulfur or carbon atom of the thiiranium ion which led to the next mechanistic experiments.



Scheme 13. Racemization of thiiranium ion **5** catalyzed by diphenyl disulfide.

Competition experiments: Competition reactions were performed to investigate whether attack on a thiiranium ion at sulfur by diphenyl disulfide or at carbon by nucleophiles is faster. This factor is mechanistically relevant, since once formed, a chiral, nonracemic thiiranium ion must be intercepted faster than racemization occurs to observe asymmetric induction. In view of our ongoing efforts to develop enantioselective Lewis base catalysis of chalcogeno functionalizations, a Lewis base would always be present. These reactions were conducted as competition experiments wherein enantiomerically enriched **5** was treated with a preformed mixture of diphenyl disulfide, (*E*)-4-octene and tetrabutylammonium acetate or methanol (Scheme 6). Attenuated stereospecificities were anticipated in these inherently biased *intermolecular* cases. However, no erosion of configurational purity occurred! This striking result suggests that the intramolecular trapping of an in situ formed, enantiomerically enriched thiiranium ion might not be necessary to preserve enantioenrichment. Therefore, one could ultimately also envision *intermolecular* chalocogeno functionalizations.

Investigation of the "olefin-to-olefin" transfer mechanism: Because the "olefin-to-olefin" transfer process represents a viable racemization pathway, a mechanistic investigation was undertaken to gain more insight into its mechanism. No experimental precedent addresses the possibility of either a dissociative or an associative mechanism (Scheme 14). The preceding studies had already shown that enantiomerically enriched thiiranium ions are inherently configurationally stable at low temperatures and racemization via carbocation intermediates or dissociation of a sulfenyl cation does not readily occur (Scheme 10). An associative sulfenyl group transfer to an olefin seemed likely for this reason. In addition, computational studies by Radom and co-workers suggested an associative pathway.[38] Because the initially formed thiiranium ion is chiral and enantiomerically enriched, it can distinguish the enantiotopic faces of the added olefin thus leading to an enantiomerically enriched transfer product. The magnitude of the asymmetric induction, however, is not important.



Scheme 14. Results from the transfer experiment.

In this study, sulfenyl group transfer from an enantiomerically enriched thiiranium ion to an olefin is carried out followed by methanolysis and analysis of enantiomeric composition of the products. This experiment had to be designed and optimized carefully because two chiral, nonracemic thiiranium ions and two olefins would be present in the reaction mixture. In principle each of the two thiiranium ions could deliver sulfenyl cations to the olefins, hence four sulfenyl group transfers are possible. All of these transfers could ultimately lead to the racemization of the present thiiranium ions. The challenge was to find substrates and conditions, where only one of the four pathways occurred irreversibly. For this demanding experiment (2*S*,3*S*)-2,3-dibenzyl-1-phenylthiiranium hexafluoroantimonate (**13**) and (*E*)-4-octene were chosen as substrates for several reasons. The inverse, thermodynamically unfavorable sulfenyl group transfer from thiiranium ion **5** to (*E*)-1,4-diphenyl-2-butene does not lead to fast racemization even at 0 °C (Table 1, entry 4) and transfer from **5** to (*E*)-4-octene can be suppressed thermally (Table 1, entries 1–3).[7] Sulfenyl group transfer from **13** to its parent olefin (*E*)-1,4-diphenyl-2-butene was expected to have a similar temperature profile. The mandatory preservation of enantiomeric purity of both thiiranium ions before methanolysis seemed possible for these substrates.

The synthesis of (2*S*,3*S*)-2,3-dibenzyl-1-phenylthiiranium hexafluoroantimonate (**13**) was executed uneventfully in good overall yield. Critical to the success of the experiment was the development of conditions where the sulfenyl group transfers of **5** and **13** to their parent olefins and hence racemization of the thiiranium ions was thermally suppressed but wherein the transfer from **13** to (*E*)-4-octene could still occur occurred. Additionally, the reaction time was limited because of the competing decomposition of the thiiranium ions **5** and **13** above −20 °C. The experiment was performed at −10 °C, where **5** and **13** were still sufficiently stable for 1 h. Gratifyingly, the transfer product was isolated not as a racemate, but with slight enantiomeric enrichment in *ent*-**6** (Scheme 9). Thus, the olefin-to-olefin transfer afforded modest stereochemical induction which provides compelling

evidence that the exchange proceeded, at least partially, via an associative pathway.

Conclusions

The syntheses of two chiral, nonracemic thiiranium ions **5** and **13** have been reported and the absolute configurational stability of **5** has been investigated in detail. Several important conclusions can be drawn:

1) chiral, nonracemic thiiranium ions are configurationally stable;
2) trapping of these thiiranium ions by nucleophiles occurs stereospecifically;
3) thiiranium ions racemize readily via direct or disulfide induced olefin-to-olefin transfer and
4) sulfenyl group transfer from thiiranium ions to olefins proceeds (at least partially) via an associative pathway.

Furthermore, these results indicate that racemization occurs only with very weak Lewis bases such as diphenyl disulfide and intermolecular sulfenyl functionalizations may be possible. Therefore, the development of a Lewis base catalyzed sulfenyl functionalization reaction seems feasible.

Acknowledgements

We are grateful to the National Science Foundation (NSF CHE-0717989) for financial support. T.V. thanks the Alexander von Humboldt-Foundation for a Feodor Lynen Research Fellowship. We also thank Drs. William R. Collins and Matthew D. Cullen for helpful discussions and technical advice.

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[29] All reported yields of the caputure products are based on the starting chloro sulfide and therefore represent the yield over two steps

(formation of the thiiranium-ion and trapping). The lower yield for the azide capture product **7** may result from instability upon silica gel purification.

[30] The term enantiospecificity [e.s. $= (ee_{\text{product}}/ee_{\text{starting material}}) \times 100\,\%$] provides a convenient method of describing the conservation of configurational purity for the reaction. The corresponding β-chloro sulfide was used as the starting material for the calculation of all enantiospecificities presented.

[31] These experiments were conducted with purified solutions of thiiranium-ions that were free from the precipipated silver salts by filtration in order to avoid side reactions such as polymerization of the olefin. About 10–25 % of the material was lost in the cannula-filtration determined by ^{1}H NMR spectroscopic analysis with an internal standard. The lower yields seen in Table 1 are also attributable to the instability of the highly reactive thiiranium-ions at temperatures above −20 °C.

[32] A substoichiometric amount of Lewis base could rapidly and irreversibly add into the thiiranium ion. Analysis of the remaining, unreacted thiiranium-ion by methanolysis would consequently provide a wrong mechanistic picture.

[33] The formation of a racemic product is not unambiguous as an associative transfer may simply have no stereoinduction. However, the formation of even a slightly enantiomerically enriched transfer product must require an association with the thiiranium ion.

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Received: May 22, 2009
Revised: July 17, 2009
Published online: September 16, 2009

