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On the Absolute Configurational Stability of Bromonium and Chloronium Ions

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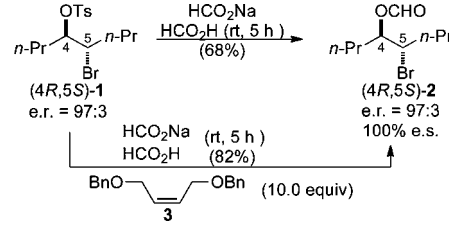
Electrophilic halofunctionalizations of olefins, in which electrophilic halonium ions are generated from olefins and opened by nucleophiles,[1] are among the oldest and simplest organic transformations. Despite the versatility of these reactions,[2] only a few examples of practical enantioselective variants have been reported, even fewer of which require substoichiometric amounts of chiral promoter.[3] Several recent syntheses of chlorosulfolipids in racemic form,[4] as well as the synthesis of (−)-napyradiomycin A1, which featured a stoichiometric enantioselective chlorination,[3c] serve to highlight the need for practical, catalytic enantioselective methods for halofunctionalization of olefins. The paucity of such methods can be ascribed in part to a lack of understanding of the factors that influence the configurational stability of the intermediate halonium ions.

Previous studies on adamantylidene adamantane bromonium ion and pentenyl glycosides have demonstrated that bromine exchange between bromonium ions and olefins can be rapid,[5] a process analogous to the olefin-to-olefin transfer process for thiiranium and seleniranium ions recently reported from these laboratories.[6] In addition, the absolute configurational stability of bromonium ions has been demonstrated recently in the absence of olefins;[7] however no studies are extant under conditions where olefin-to-olefin transfer might be observed. This is a critical issue, because under conditions for catalytic transformations, unreacted starting alkene is present in excess of the reactive intermediate until the end of the reaction. Much to our surprise, the absolute configurational stability of chloronium ions has never been demonstrated under any conditions, although their relative configurational stability has been established in classic studies by Lucas and Winstein.[8]

As part of a general program to develop enantioselective halofunctionalization of isolated alkenes, we felt it prudent to establish the configurational stability of bromonium and chloronium ions under conditions where racemization could be competitive with intermolecular trapping by representative nucleophiles. For these studies, enantiomerically enriched, C_2 symmetric bromonium and chloronium ions were generated by anchimerically assisted ionization of enantiomerically enriched β-halo sulfonates in strongly ionizing media.[9]

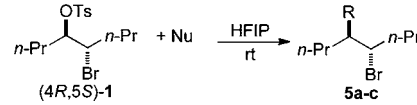
The solvolysis of enantiomerically enriched (4*R*,5*S*)-**1**[10] in formic acid (containing 13 equiv of sodium formate) provided (4*R*,5*S*)-**2** with complete retention of configuration and with perfect enantiospecificity (e.s.),[11] even in the presence of a large excess of olefin **3** (Scheme 1). Although these results were encouraging, it was deemed desirable to demonstrate bromonium ion formation and trapping in the presence of subsolvent quantities of nucleophile and to provide for a degenerate bromine exchange. Hexafluoroisopropanol (HFIP) was selected to provide a strong ionizing medium of low nucleophilicity,[12] capable of dissolving both nucleophilic salts and significant quantities of (*E*)-4-octene (**4**). Thus, treatment of (4*R*,5*S*)-**1** with a solution of a nucleophile in HFIP yielded **5a**−**c** in good yield and high enantiospecificity (Table 1). The slight erosion of enantiomeric purity observed when trapping with azide ion indicates the intervention of a minor racemization pathway, possibly arising from a small proportion of nucleophilic attack at bromine to generate BrN_3, by analogy to what has been observed in the presence of bromide ion.[9d,e]

Scheme 1



When **4** was introduced into the acetolysis of (4*R*,5*S*)-**1**, acetate (4*R*,5*S*)-**5a** was produced with lower enantiospecificity. The attenuation of enantiospecificity increased with increasing concentration of **4** (red diamonds, Figure 1). Contrary to expectation, the degree of erosion of the enantiospecificity was not ameliorated by employing a large excess of NaOAc (blue diamonds).[13]

Table 1. Solvolytic Substitution with (4*R*,5*S*)-**1**[a]



Nu	R	product	yield (%)	er[b]	e.s. (%)
NaOAc[c]	OAc	(4*R*,5*S*)-**5a**	79	97:3	100
MeOH[d]	OCH_3	(4*S*,5*R*)-**5b**	80	97:3	100
n-Bu_4NN_3[c]	N_3	(4*R*,5*S*)-**5c**	80	95:5	96

[a] All reactions were run at 0.1 M substrate concentration. [b] Determined by CSP-GC analysis. [c] 2.0 equiv. [d] 10.0 equiv.

Substitution of NaOAc with *n*-Bu_4NOAc afforded increased enantiospecificity in the presence of **4** (red circles, Figure 1). Interestingly, and in contrast to NaOAc, increasing the amount of *n*-Bu_4NOAc led to further enhancement in the enantiospecificity (blue circles), consistent with increased trapping rate due to a less coordinated and hence more nucleophilic anion.[14]

Previous studies on the olefin-to-olefin transfer in group 16 iranium ions revealed a dramatically slower rate for thiiranium ions compared

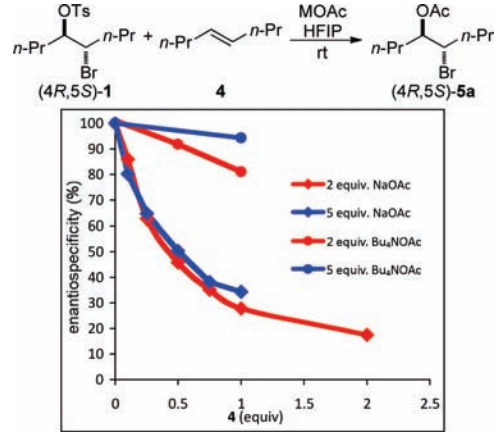


Figure 1. Effects of added olefin, acetate concentration, and counterion identity on the enantiospecificity of acetolysis.

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to seleniranium ions.[6a] Accordingly, we hypothesized that a similar reduction in olefin-to-olefin transfer rate might be observed upon moving from bromonium ions to chloronium ions. This hypothesis was contingent upon the expectation that enantioenriched chloronium ions could be generated and trapped enantiospecifically even in the absence of olefin-to-olefin transfer.

Encouragingly, the solvolysis of β-chloro triflate (4*R*,5*S*)-**8**[10] in buffered formic acid was found to proceed with high diastereospecificity and complete enantiospecificity. The solvolysis of *rel*-(4*R*,5*R*)-**8** also proceeded with high diastereospecificity (Scheme 2). The enantiospecificity was preserved in the presence of an excess of **3**. Acetolysis of (4*R*,5*S*)-**8** with NaOAc in HFIP resulted in a complex mixture of products; however modest yields of **10a** were obtained when *n*-Bu_4NOAc was used as the nucleophile in HFIP/CH_2Cl_2 (Table 2). Presumably, the low *chemical* stability of 1,2-dialkylchloronium ions dictates the use of more reactive nucleophiles to trap them before low energy decomposition pathways can intervene.[9c] Most gratifyingly, no enantiomeric erosion was observed even in the presence of added **4**.

Scheme 2

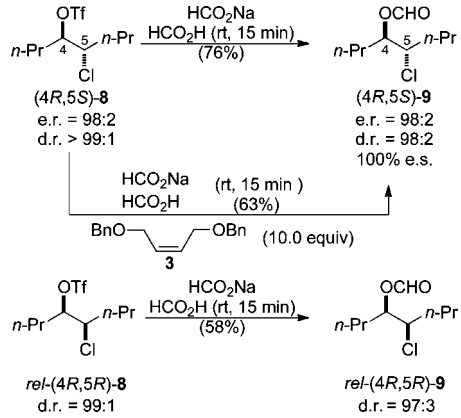
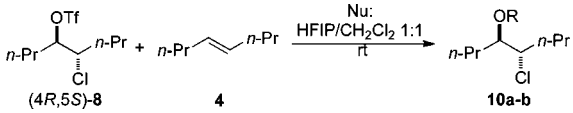


Table 2. Solvolytic Substitution with (4*R*,5*S*)-**8**[a]



product	R	Nu:	**4** (equiv)	yield (%)	er[b]	e.s. (%)
10a	Ac	*n*-Bu_4NOAc[c]	0.0	32	98:2	100
10a	Ac	*n*-Bu_4NOAc[c]	0.25	39	98:2	100
10a	Ac	*n*-Bu_4NOAc[c]	1.0	43	98:2	100
10b	Me	MeOH[d]	0.0	42	98:2	100

[a] All reactions were run at 0.1 M substrate concentration. [b] Determined by CSP-GC analysis. [c] 2.0 equiv. [d] 10.0 equiv.

This apparent inverse relationship between chemical and stereochemical stability can be explained by the degree to which positive charge is localized on the halogens in the halonium ions. The greater electronegativity of chlorine leads to less positive charge on chlorine and more on carbon,[9a] increasing the propensity of chloronium ions toward processes characteristic of carbocations, such as elimination and Wagner−Meerwein rearrangements. The likely associative mechanism of olefin-to-olefin transfer proposed by Brown proceeds via nucleophilic attack by the olefin at bromine following formation of a preassociation olefin π complex.[5a] This process should be favored by the greater positive charge on the less electronegative bromine.

In conclusion, we have demonstrated the enantiospecific generation and trapping of bromonium ions and have shown that racemization of bromonium ions via olefin-to-olefin transfer is competitive with *intermolecular* capture by anionic nucleophiles. While the relative rates do not exclude the possibility of a catalytic, enantioselective bromination process, they present an obstacle that must be surmounted by any successful catalyst system. In addition, we have demonstrated the first enantiospecific generation and trapping of chloronium ions. The stereochemical stability of these ions in the presence of olefins bodes well for invention of catalytic enantioselective electrophilic halogenation of olefins, the development of which will be the subject of future reports.

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Supporting Information Available: Full experimental procedures, analyses, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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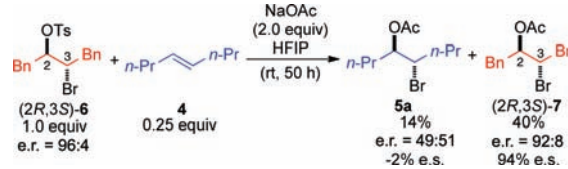
(10) The syntheses of enantiomerically enriched halo sulfonates **1**, **6**, and **8** are described in the Supporting Information.

(11) The term enantiospecificity [e.s. = ($ee_{product}/ee_{starting\ material}$) × 100%] provides a convenient method of describing the conservation of configurational purity for the reaction.

(12) Hexafluoroisopropanol has been used in classic studies of solvolysis mechanisms; see: Schadt, F. L.; Bentley, T. W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1976**, *98*, 7667–7674.

(13) The insensitivity of e.s. to the concentration of NaOAc can be interpreted as a sodium ion assisted ionization to a solvent separated ion pair which collapses to product. If dissociated ions are not formed, then the concentration of NaOAc is irrelevant. For detailed discussion of solvolysis reactions, see: Raber, D. J.; Harris, J. M.; Schleyer, P. v. R. In *Ions and Ion Pairs in Organic Reactions*; Szwarc, M., Ed.; John Wiley and Sons: New York, 1974; Vol. 2, Chapter 3.

(14) To determine if the bromonium ion transfer is associative or dissociative, acetolysis of (2*R*,3*S*)-**6**[10] was carried out in the presence of **4**. The crossover product **5a** was formed in 51:49 er. This outcome is ambiguous and cannot distinguish the pathways; see ref 5c.



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