The Generation and Trapping of Enantiopure Bromonium Ions†

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Enantiopure bromonium ions may be generated from enantiopure bromohydrins and derivatives. They can be trapped with an *in situ* nucleophile to give enantiomerically pure products.

The bromonium ion is a species of fundamental interest in organic chemistry.¹ It was first proposed by Roberts and Kimball in 1937 to account for the well-established stereochemistry of the addition of molecular bromine to olefins.² Milestones in the history of the bromonium ion include Winstein's experiment with 3-bromo-2-butanol to prove the existence of a cyclic symmetrical species,³ Olah's observation of a bromonium ion by NMR⁴ and Wynberg's stable bromonium ion of adamantlylideneadamantane,⁵ which was subsequently characterised crystallographically and studied by Brown.^{6,7} Herein we report a new milestone: the first generation and trapping of enantiopure bromonium ions to provide enantiomerically pure products.

During the course of our investigations, we observed that the attempted chlorination of (±)-bromophenethylalcohol **1**⁸ with thionyl chloride gave (±)-bromochloride **4**⁹ (Scheme 1), which was characterised by X-ray crystallography (Figure 1). The position of the chloride was also confirmed by the chlorine-induced isotopic shift method¹⁰ (see ESI). Evidently, a bromonium ion **3**[‡] must form by neighbouring group displacement¹¹ of the chlorosulphite group in intermediate **2** and is subsequently trapped in Markovnikov manner by chloride as a nucleophile. Since NGP of a bromide will proceed with inversion of stereochemistry at an adjoining stereocentre, and since ring-opening of the resulting cyclic bromonium ion is also expected to be stereospecific, this observation forms the basis for the successful formation and

trapping of enantiopure bromonium ions (*vide infra*).

Scheme 1. Reaction of alcohol **1** with thionyl chloride.

Figure 1. The molecular structure of **4-A**, the major occupancy molecule present in the crystals of bromo-chloride **4**.

Accordingly, we expected to be able to form enantiopure bromonium ions from enantiopure bromohydrins. Commercially available (1*S*,2*S*)-1-phenylpropylene oxide (**5**) was treated with 48% HBr¹² to give an inseparable 3:1 ratio of enantiopure diastereoisomers 1*R*,2*S*-**6** and 1*S*,2*S*-**7** (Scheme 2).¹³ The minor diastereoisomer **7** must arise from the partial intervention of a benzylic cation.¹⁴ However, the stereocentre at the homobenzylic position ensures that they retain their overall enantiomeric integrity. Alternatively, application of Jacobsen's highly efficient kinetic resolution procedure¹⁵ gave terminal 2*R*-epoxide **8**¹⁶ as essentially a single enantiomer (>98% ee) from racemic dodecane oxide. This was treated with HBr also, to give separable enantiopure bromohydrins 2*S*-**9** and 2*R*-**10**.¹⁷ We now sought to transform these bromohydrins into their enantiopure bromochlorides **11-14** via the intermediacy of enantiopure bromonium ions **A** and **B**. We elected to use neat thionyl chloride as an *in situ* activator, as above.¹⁸ Additionally, we prepared tosylates **15-18**, and Lepore's sulphonates¹⁹ **19-22**. We intended to activate these sulphonate substrates by the addition of titanium tetrachloride.²⁰ To generate authentic bromochlorides **13** and **14** of known configuration and regiochemistry, epoxide **8** was ring-opened with hydrochloric acid to give a mixture of separable enantiopure chlorohydrins (*S*)-**23** and (*R*)-**24**.²¹ Their regiochemistries were unambiguously identified on the basis of the chlorine isotopic shift method¹⁰ (see ESI). Appel bromination²² of each alcohol gave the individual enantiopure bromochlorides *S*-**13** ([α]_D -29) and *S*-**14** ([α]_D -32). A combination of DEPT NMR spectroscopy and the halide-induced

† Electronic Supplementary Information (ESI) available: Full experimental details and characterising data for compounds **4** and **6-24**, copies of ¹H and ¹³C NMR spectra for **13-22**, copies of ¹H NMR spectra of Mosher ester derivatives of **6,7,9,10,23** and **24**, chiral HPLC analysis of **11&12**, optical rotation measurements and ee calculations for **13** and **14**, copies of ¹³C NMR spectra showing halide-induced isotopic shifts for **4, 13, 14, 23** and **24**, and X-ray crystallographic details for **4** and **11**.
http://www.rsc.org/suppdata/xx/b0/b000000x/

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isotopic shift method¹⁰ unambiguously confirmed their identities (see ESI).

Scheme 2. Preparation of substrates and expected products via enantiopure bromonium ions **A** and **B**.

The diastereomeric mixture of enantiopure aryl bromohydrins **6** and **7** were treated with neat thionyl chloride at 65°C (Table 1, entry 1). In the event, the reaction proceeded smoothly to give enantiomerically pure bromochlorides **1S,2R-11** and **1R,2R-12** as a 3:1 mixture in excellent yield.^{††,23} Evidently, each diastereoisomer has proceeded through the enantiomerically pure bromonium ion **A**[‡] as expected with a signature inversion of stereochemistry at the 2-position. Subsequent Markovnikov trapping of the bromonium ion has occurred to give the two possible benzylic chloride diastereomers.^{**} To the best of our knowledge this constitutes the first time that an enantiopure bromonium ion[‡] has been generated and trapped to give enantiopure products. The mixture of tosylates (entry 2) and modified benzenesulphonates (entry 3) proved to be activated on treatment with titanium tetrachloride to give the bromochloride products in excellent yields, with complete enantiospecificity.^{††} Evidently, these proceed via enantiopure bromonium ion **A** also.[‡] Interestingly, using these sulphonates, the

NGP of the resident bromine on the Lewis acid-activated leaving group must be faster than any possible competing S_Ni process.²⁰

Table 1 Bromochlorides via enantiomerically pure bromonium ions^a

Entry	Substrate	Reagent	Product	%yield ^b	%ee
1	6&7 (73:23)	SOCl ₂	11&12 (76:24)	97	>98 ^c
2	15&16 (70:30)	TiCl ₄	11&12 (67:33)	100	>98 ^c
3	19&20 (65:35)	TiCl ₄	11&12 (86:14)	89	>98 ^c
4	9	SOCl ₂	13&14 (58:42)	57	77±5 ^d
5	10	SOCl ₂	13&14 (58:42)	53	68±5 ^d
6	17	TiCl ₄	13&14 (87:13)	95	100±5 ^d
7	18	TiCl ₄	13&14 (86:14)	87	103±5 ^d
8	21	TiCl ₄	13&14 (76:24)	92	104±5 ^d
9	22	TiCl ₄	13&14 (71:29)	95	103±5 ^d

^a See ESI for experimental conditions ^b After column chromatography.

^c Determined by chiral HPLC.^{††} ^d Determined by optical rotation.^{††}

Experiments using the *separable* alkyl bromohydrins **9** and **10**, and their sulphonate derivatives (entries 4-9) give unambiguous evidence for the formation of alkyl bromonium ion **B**. Firstly, when treated with thionyl chloride each of **9** and **10** gave the *same* product distribution of (inseparable) bromochlorides **13** and **14** implicating formation of a common intermediate, to wit, the bromonium ion **B**. Constant product distributions – within experimental error – were also observed in the cases of regioisomeric tosylates (entries 6 and 7) and benzenesulphonates (entries 8 and 9) showing that these also proceed through bromonium ion **B**. The difference in product distributions between the bromohydrin and sulphonate substrates can be largely attributed to the operating temperature (65°C versus -78°C respectively). The difference in product distributions between the tosylate and benzenesulphonate substrates should reflect a change in ion-pairing of the nascent bromonium ion **B** and the incoming chloride nucleophile as modified by the leaving Lewis acid-bound sulphonate.

Secondly, analysis of the enantiomeric composition of the various product mixtures of **13** and **14** proves to be entirely consistent with formation of enantiomerically pure bromonium ion **B**. Since NGP by a bromide will proceed with inversion at any adjoining stereocentre then each substrate **9**, **10**, **17**, **18**, **21** or **22** can only produce the *S*-configured bromonium ion **B**. Attack of the chloride nucleophile at the Markovnikov position will result in inversion and a *R*-configured chloride **13**, whereas attack at the terminal position will leave the bromide **14** as *S*-configured. For the sulphonate substrates **17**, **18**, **21** or **22** as activated by titanium tetrachloride (Table 1, entries 6-9), the bromochlorides **13** and **14** are produced with essentially complete enantiospecificity.^{††} Thus, the mapping of the stereochemical course of the reaction provides irrefutable evidence for the intermediacy of enantiopure bromonium ion **B**. Interestingly, when thionyl chloride was used (Table 1, entries 4 and 5) the bromochlorides **13** and **14** are formed with reduced enantiomeric purity. From the work of Brown,²³ it seems reasonable to suggest a competing pathway for formation of BrCl by direct attack of free chloride in solution on the bromonium ion. Re-addition of BrCl to the resulting olefin occurs without control of absolute stereochemistry and some leakage of enantiomeric purity occurs.

In conclusion, we have shown that enantiopure bromohydrins can be used to generate enantiopure bromonium ions. These may be trapped with a nucleophile to provide enantiomerically pure

bromine containing products. Since the bromonium ion precursors are generated from readily available enantiopure epoxides, these results open the door for the use of enantiopure bromonium ions in asymmetric synthesis. We regard this as a significant advance in the use of bromonium ions in synthetic organic chemistry.

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Notes and references

[‡] The exact structure of a “bromonium ion” of a styrene depends strongly on any substituents and on the solvent, and it is understood that a spectrum of ionic intermediates are possible, of which the cyclic bromonium ion and the open β -bromocarbocation are the extremes. See references 1a and 1b.

[§] The enantiomeric purity was assayed by Mosher ester formation and comparison with the Mosher ester of the racemic halohydrin prepared in identical fashion from racemic epoxide (see ESI).

^{††} The enantiomeric purity was assayed by chiral HPLC methods by reference to a racemic sample (see ESI).

^{**} A racemic sample of the major diastereomer **11** proved to be crystalline and the relative stereochemistry was confirmed by X-ray crystallography. Both diastereoisomers showed characteristic benzyl chloride fragments in their MS allowing the minor diastereoisomer to be assigned as **12** (see ESI).

^{††} The %ee was calculated on the basis of known specific rotations for enantiomerically pure *S*-**13** ($[\alpha]_D -29$) and *S*-**14** ($[\alpha]_D -32$). Since a mixture of *R*-**13** and *S*-**14** are obtained, the %ee can be calculated by [optical rotation of mixture/(0.01*((%**13***29)+(>%**14***-32)))] (see ESI).

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Graphical Abstract