Explorations into the Potential of Chiral Sulfonium Reagents to Effect Asymmetric Halonium Additions to Isolated Alkenes

Alexandria P. Brucks, Daniel S. Treitler, Shu-An Liu, Scott A. Snyder*

Department of Chemistry, Columbia University, Havemeyer Hall, 3000 Broadway, New York, NY 10027, USA
Fax +1(212)9321289; E-mail: sas2197@columbia.edu

Received: 17.04.2013; Accepted: 06.05.2013

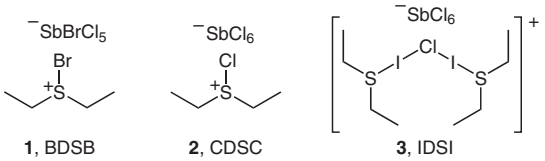
Dedicated to Prof. Scott E. Denmark on the occasion of his 60th birthday

Abstract: While methods for the racemic dihalogenation and halohydroxylation of alkenes have been known for decades, enantioselective variants of these processes remain elusive. Initial attempts were made to overcome this long-standing challenge by exploring the potential of chiral, crystalline, sulfur-derived halonium reagents to accomplish the asymmetric dichlorination and iodohydroxylation of 1,2-dihydronaphthalene. Asymmetric dichlorination of this substrate was achieved in 57% yield and 14% enantiomeric excess (ee), but asymmetric iodohydroxylation was much more successful, giving 67% yield and 63% ee. Thorough studies were made of these processes, including investigation of various chiral sulfide derivatives, their substrate scopes, and the reaction conditions.

Key words: chirality, halogenations, alkenes, enantioselectivity, hydroxylations

Although the racemic halogenation of alkenes has been studied and used productively for well over a century, enantioselective variants of this reaction remain largely undeveloped. To date, only a few procedures have provided any synthetically useful levels of optical activity, and these can be applied to only a very limited range of substrates.[1,2] A similar state of affairs exists in relation to halohydroxylation.[2d] The challenge of generating chirality from these particular reactions resides largely, if not entirely, in the known capability of chiral halonium ions to transfer racemically to unreacted alkenes before intermolecular attack by the terminating nucleophile (either a halide or water in these cases), thereby eliminating any opportunity to achieve enantioselectivity.[3] However, despite the absence of effective laboratory procedures for performing chiral variants of these reactions, the products of such processes are widely found in natural products and, moreover, might serve as useful handles for further functional manipulation if they could be formed with high chiral fidelity.

Here we describe our initial efforts to probe these reactions and to develop solutions that might have general applicability. Specifically, in our recent attempts to bring about a number of racemic halonium-induced cyclization processes involving alkenes, which had previously proven difficult to achieve, we found that reagents of the XDSX class (Figure 1)[4] were uniquely successful in effecting these reactions. We therefore wondered whether chiral variants of these materials might perform similar operations enantioselectively. We surmised that because chiral sulfides are widely used in asymmetric epoxidation reactions that take advantage of sulfur ylide chemistry,[5] similar replacement of the diethyl sulfide moiety of the XDSX reagents with chiral sulfides might permit effective asymmetric dihalogenations or halohydroxylations of simple isolated alkenes.



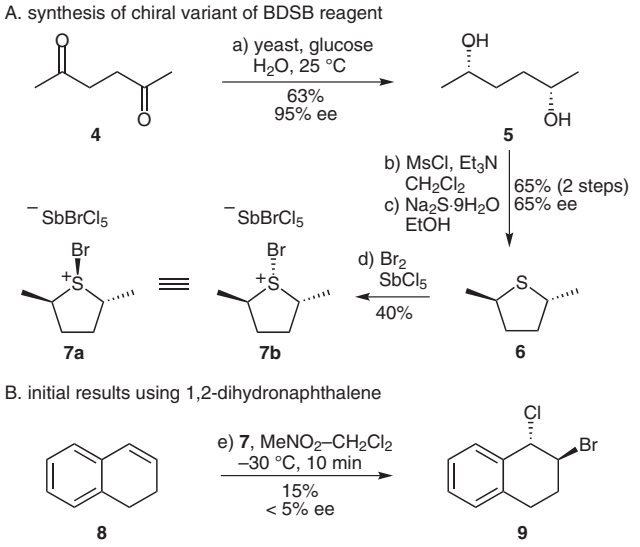
1, BDSB **2**, CDSC **3**, IDSI

Figure 1 The original XDSX reagents[4]

We began our explorations by using 1,2-dihydronaphthalene (**8**) in conjunction with the chiral sulfide (2*R*,5*R*)-2,5-dimethylthiolane [**6**; (2*R*,5*R*)-2,5-dimethyltetrahydrothiophene]. We selected this as our first chiral reagent on the basis of two main criteria: its ease of synthesis and its C_2-symmetry. The latter is important because a non-C_2-symmetric thiol will produce diastereomers once its halosulfonium salt is generated.[6] As shown in Scheme 1, the chiral sulfide was prepared from hexane-2,5-dione (**4**) by a yeast-mediated asymmetric reduction to give diol **5** in good yield and high enantioselectivity.[7] Significantly, this reduction could be performed on a large scale (over 30 g of diol **5** were prepared with 95% ee). Dimesylation of **5** and subsequent cyclization with sodium sulfide nonahydrate gave the desired thiolane **6**.[5d] Unfortunately, this material (**6**) possessed an ee of only 65%, suggesting that a loss of chirality occurred during the substitution step, probably as a result of an S_N1 process that competed with the desired S_N2 displacement. Despite this outcome, we elected to press on. Treatment of thiolane **6** with elemental bromine and antimony pentachloride gave the chiral bromosulfonium salt **7** as a crystalline solid in 40% yield. Because the enantiomeric purity of the synthesized bromosulfonium reagent **7** could not be determined directly, the compound was derivatized by hydrolysis to the sulfoxide, followed by reduction to the sulfide[8] to give thiolane **6**, whose ee could be remeasured and compared with data from the literature. Surprisingly, the recovered sulfide (**6**) had an ee of 97%, suggesting that crystalliza-

SYNTHESIS 2013, 45, 1886–1898
Advanced online publication: 13.06.2013
DOI: 10.1055/s-0033-1338865; Art ID: SS-2013-C0294-OP

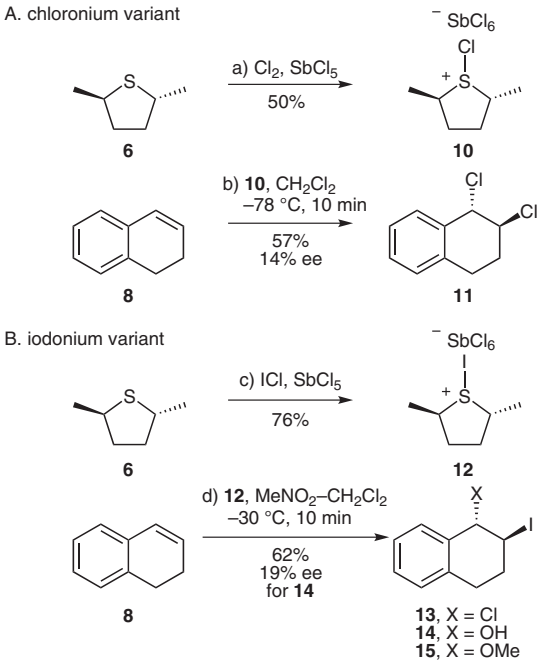
tion of the bromosulfonium salt **7** led to an increase in its enatiomeric excess.



Scheme 1 Synthesis of the chiral bromosulfonium salt **7** and its use in the chlorobromination of 1,2-dihydronaphthalene (**8**)

Treatment of 1,2-dihydronaphthalene (**8**) with 1.2 equivalents of bromosulfonium salt **7** resulted in the addition of bromine monochloride across the olefin to give the corresponding bromo chloro derivative **9** in 15% yield; in this reaction, the bromo(pentachloro)antimonate counterion acted as the source of the chlorine atom in the product. The low yield from this reaction probably reflects the instability of the product; furthermore, the resulting product was nearly racemic (< 5% ee). Because bromonium ions are readily transferred to unreacted alkenes, we decided to convert sulfide **6** into other halonium analogues in the hope of achieving superior outcomes.[3]

Pleasingly, upon changing the halogen to dichlorine, we obtained the chlorine derivative **10** quite smoothly (Scheme 2). In this case, reaction of 1,2-dihydronaphthalene (**8**) with the chloronium species resulted in a 57% yield of the *trans*-dichloride **11** with an observed ee of 14%.[9] Similarly, the chiral iodonium reagent **12** was also easily prepared, although its synthesis required the use of iodine monochloride rather than diiodine as the source of the iodine atoms. The crystal structure of reagent **12** was obtained, verifying the connectivity of the compound. The reaction of the iodonium compound **12** with 1,2-dihydronaphthalene (**8**) gave the iodine monochloride addition product **13**. This material was unstable, decomposing rapidly on silica gel. This outcome probably reflects the ease of chloride expulsion, a process that regenerated the iodonium intermediate and, ultimately, resulted in the formation of a number of decomposition products. However, by quenching the reaction directly with water, the more stable iodohydrin **14** could be formed from intermediate **13** in 62% yield and 19% ee. In this case, the initially installed chloro group is replaced, with retention of configuration, giving the *trans*-iodohydrin exclusively, thereby suggesting reformation of the iodonium intermediate. Having obtained these initial proof-of-principle results, we decided to probe the asymmetric dichlorination and iodohydrin formation processes further, first exploring the chloronium variant, as chiral dichlorides are much more prevalent in natural products.



Scheme 2 Synthesis of chiral chloronium and iodonium reagents and their use in halogenation reactions of 1,2-dihydronaphthalene (**8**)

Treatment of 1,2-dihydronaphthalene (**8**) with molecular chlorine gave the racemic dichloride **11** in a 95% yield as expected (Table 1, entry 1). Although our initial results showed that the reagent **10** worked quite well, we were concerned that the presence of the added antimony pentachloride might be detrimental to the efficiency and stereoselectivity of the reaction because of the ability of this salt to sequester the chloride anion, our intended nucleophile. We therefore performed our initial screenings by generating chiral reagents in situ from sulfide **6** and elemental chlorine without any added antimony pentachloride.[10] However, all of these efforts (entries 2–5) failed to afford any product and led only to recovery of the unreacted alkene substrate **8**. Interestingly, at low temperatures (entry 2) the thiolane was recovered as its sulfoxide after an aqueous quench. Yet upon warming (entry 3), the thiolane decomposed, confirming that the chlorosulfonium chloride had been produced in situ and that it probably decomposed before the reaction mixture reached a sufficiently high temperature to react with the alkene substrate.

Given these negative results, coupled with the conditions involved in our initial successful reaction, we concluded that the antimonate counterion is indeed critical in ensuring the stability of the chlorosulfonium intermediate and in leading to enantioselectivity. In line with this hypothesis, the in situ generation of reagent **10** afforded the prod-

Table 1 Initial Exploration of Asymmetric Dichlorination by Treatment of 1,2-Dihydronaphthalene (**8**) with Dichlorine and Chiral Thiolane **6**

Entry	Additive(s) (equiv)	Solvent	Temp (°C)	Yield (%)	ee (%)
1	none	CH_2Cl_2	–78	95	0
2	**6** (1.2)	CH_2Cl_2	–78	0	–
3	**6** (1.2)	CH_2Cl_2	–78 to 25	0	–
4	**6** (1.2)	MeCN	–40	0	–
5	**6** (1.2)	$EtNO_2$	–78	0	–
6	**6** + $SbCl_5$ (1.2)	CH_2Cl_2	0	50	10
7	**6** + $SbCl_5$ (1.2)	CH_2Cl_2	–78	35	18
8	**6** + $SbCl_5$ (2.0)	CH_2Cl_2	–78	35	24
9	**6** + $SbCl_5$ (3.0)	CH_2Cl_2	–78	35	30
10	**6** + $SbCl_5$ (1.2)	$EtNO_2$	–78 to 0	10	41
11	**6** + $SbCl_5$ (1.2)	hexane	–78 to 0	15	8
12	**6** + $SbCl_5$ (1.2)	toluene	–78 to 0	20	20
13	**10** (1.2)[a]	CH_2Cl_2	–78	57	14

[a] No Cl_2 was used.

uct in a yield and enantioselectivity that were similar to those initially observed (Table 1, entries 6 and 13). The temperature for the reaction appeared to play a small role in the chiral selectivity, as lower reaction temperatures resulted in slightly higher ee values (entries 6 and 7), but at the expense of yield. Additionally, the use of an excess of reagent **10** also resulted in higher ee values (entries 7–9). Finally, more polar solvents produced higher enantioselectivities, but again at the expense of lower yields (entries 10–12). The optimal enantioselectivity overall was 41% ee, but the low yield (10%) observed under these conditions discouraged us from pursuing this particular transformation any further.

Turning next to the formation of the iodohydrin, we chose the isolated crystalline *S*-iodo derivative **12** as our starting point because the results discussed above highlighted the importance of the antimonate component. As in the case of the chlorosulfonium reagent **10**, when the overall number of equivalents of **12** was increased, the enantioselectivity of the reaction also increased (Table 2, entries 1–5). Here, 2.2 equivalents of *S*-iodo compound **12** gave the best results, with a 73% yield and 35% ee (entry 4). This outcome could be interpreted as suggesting that aggregation of two or more molecules of the *S*-iodo derivative **12** in solution generates an initiator that is more selective than the isolated monomeric **12**.[11] Addition of water to the mixture at the same time as the iodonium source was unfavorable, yielding the product with low or no enantioselectivity (entries 6 and 7). In this case, product **14** was probably formed from achiral IOH generated in situ, which then added racemically across the alkene.[12] The reaction temperature had a marked effect (entries 8 and 9), and nonpolar solvents significantly decreased the yield of the reaction (entries 10 and 11). A solvent mixture of acetonitrile and dichloromethane allowed the temperature to be reduced further without freezing (entries 11–13). At –78 °C, the reaction was slow and recovered unreacted alkene was the major by-product (entry 13); warming slowly to –20 °C afforded the best results, giving 74% yield and 53% ee (entry 14). The addition of molecular sieves did not affect the yield or the ee (entry 15).

Having completed our initial explorations, we next examined the effects of various substituents on the thiolane to see if improved enantioselectivities might be achieved under our optimized conditions for iodohydroxylation. We began by varying the substituents on the core thiolane ring system, bearing in mind that our previous investigations on BDSB and related achiral reagents had shown that alcohols, amines, alkenes, alkynes, and electron-rich aromatic rings could not be present.[4]

As shown in Figure 2, our initial targets were a range of thiolanes substituted in the C2 and C5 positions with simple hydrocarbons of varying steric bulk (**12**, **16**–**19**). In all cases, the syntheses of these new thiolanes commenced with cyclization of the corresponding asymmetric diol precursors **26** (Scheme 3). Although the subsequent dimesylation and sodium sulfide nonahydrate-induced cyclization reactions occurred smoothly with sterically undemanding substituents such as methyl or ethyl,[5g] larger groups proved to be significantly more challenging, re-

Table 2 Initial Exploration of Chiral Iodosulfonium Reagent **12** for the Synthesis of Iodohydrin **14** from 1,2-Dihydronaphthalene (**8**) with Subsequent Quenching by Water at 25 °C for One Hour

Entry	**12** (equiv)	Solvent	Time (min)	Temp (°C)	Yield (%)	ee (%)
1	1.0	MeCN	10	–20	62	19
2	1.4	MeCN	10	–20	59	32
3	1.8	MeCN	10	–20	81	34
4	2.2	MeCN	10	–20	73	35
5	3.5	MeCN	10	–20	79	38
6	2.2	MeCN	10	–20	51[a]	3[a]
7	2.2	MeCN	10	–20	67[b]	0[b]
8	2.2	MeCN	10	0	59	31
9	2.2	MeCN	30	–40	71	40
10	2.2	CH_2Cl_2	10	–20	0	–
11	2.2	MeCN–CH_2Cl_2 (3:1)	10	–20	69	46
12	2.2	MeCN–CH_2Cl_2 (3:1)	10	–20	25	49
13	2.2	MeCN–CH_2Cl_2 (1:1)	120	–78	56	23
14	2.2	MeCN–CH_2Cl_2 (1:1)	60	–78 to –20	74	53
15	2.2	MeCN–CH_2Cl_2 (1:1)	60	–78 to –20	67	51[c]

[a] H_2O (2.0 equiv) was added.
[b] H_2O (10 equiv) was added.
[c] Powdered 3-Å MS (50 mg) were added.

quiring elevated temperatures and longer reaction times to achieve success, but at the price of the formation of numerous byproducts. As a result of these observations, we hypothesized that the cyclized thiolanes **27** (R = *i*-Pr, *t*-Bu) might have become racemized during the dimesylation and cyclization reactions as a result of competing S_N1 reaction pathways. Indeed, Connon and co-workers recently synthesized both the isopropyl and *tert*-butyl derivatives of **27** by using the same chemistry, obtaining the desired products in 18% and 43% ee, respectively.[13] However, it is worth noting that the enantiopurity of the diaryl thiolane derivative of **27**, as measured by HPLC, was 94% ee, so that the racemization processes might well be substrate-specific. Most significantly, irrespective of the chiral purity of the sulfide precursor, these synthesized thiolanes could be transformed into the corresponding isolable chiral iodonium reagents **16**–**19** in moderate to good yields by reaction with iodine monochloride and antimony pentachloride.

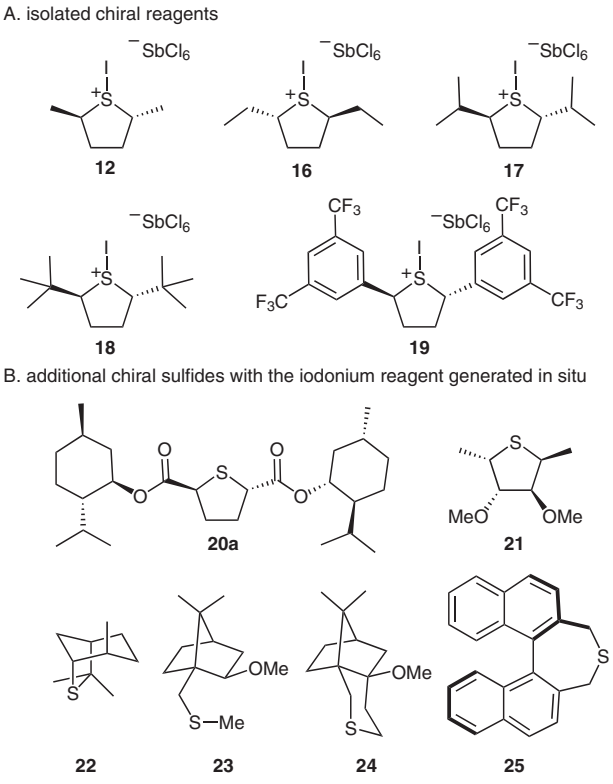
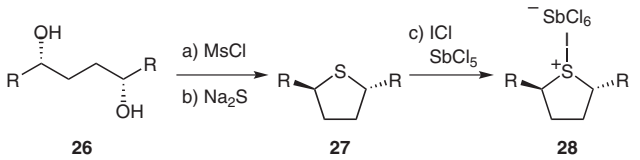
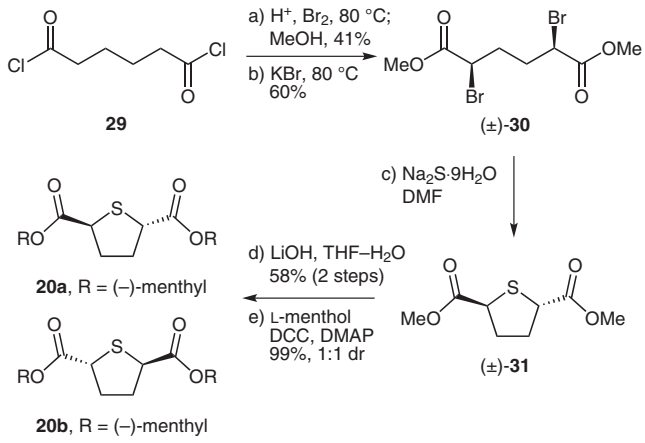


Figure 2 Structures of synthesized chiral sulfides



Scheme 3 Synthesis of thiolane derivatives and the corresponding chiral reagents

In addition to these ligands, we also prepared several more-complex C_2-symmetric derivatives, including the L-menthyl esters **20a** and **20b** and the D-mannitol-derived compound **21** (Figure 2). As shown in Scheme 4, the preparation of **20a** and **20b** began from adipoyl dichloride (**29**), which was subjected to α-bromination,[14] methyl ester formation, and equilibration with potassium bromide[15] to give the known compound **30** smoothly. Subsequent cyclization with sodium sulfide nonahydrate in *N*,*N*-dimethylformamide gave the racemic thiolane diester **31**. Hydrolysis and esterification with L-(–)-menthol then gave the separable diastereomers **20a** and **20b**. Sulfide **21** (Figure 2), a material bearing additional chiral centers along its backbone,[5g,h,16] was synthesized in five steps from a commercially available derivative of D-mannitol.



Scheme 4 Synthesis of di-L-(–)-menthyl thiolane-2,5-dicarboxylates[14,15]

Finally, there are a vast number of known chiral sulfides that can effect asymmetric epoxidation reactions.[5] On this basis, chiral sulfides **22**–**25** (Figure 2) were synthesized by procedures described in the literature.[5a,e,j,17] Because these materials lack C_2 symmetry, the potential exists for generating two diastereomers at the sulfur atom upon formation of the halonium ion, a design feature that would be explored further if these compounds proved to be effective in initial studies. However, with these sulfides, as well as thiolanes **20a**, **20b**, and **21**, attempts to obtain crystalline forms of the respective iodonium reagents failed or gave poor yields. As a result, we opted to generate the chiral iodonium reagents in situ for all our studies with these sulfides.

Each of these newly synthesized sulfides was then tested in the iodohydrin-formation reaction with 1,2-dihydronaphthalene (**8**), and the results of these studies are given in Table 3. Pleasingly, the reaction process itself could be quenched with either water or methanol to give the alcohol **14** or the methyl ether **15**, respectively (entries 1 and 2). Significantly, the diethyl iodosulfonium derivative **16** gave the desired iodohydrin in 67% yield and 63% ee (entry 3); in this case, because the enantiomer of the sulfate was utilized, the opposite enantiomer of iodohydrin was obtained.

Table 3 Effects of Various Chiral Thiolanes and Quench Reagents in Iodohydroxylation Reactions of 1,2-Dihydronaphthalene (**8**)

Entry	Chiral initiator	ROH quench	Yield (%)	ee (%)
1	**12**	H_2O	74	53
2	**12**	MeOH	67	33
3	**16**[a]	H_2O	67	–63
4	**17**	MeOH	59	18
5	**18**	MeOH	64	2
6	**19**[b]	H_2O	75	13
7	**20a**[c]	H_2O	15	0
8	**21**[a,c]	H_2O	53	–24
9	**22**[c]	H_2O	33	0
10	**23**[c]	H_2O	52	2
11	**24**[c]	H_2O	80	1
12	**25**[c]	H_2O	58	5

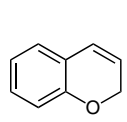
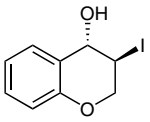
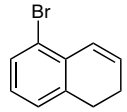
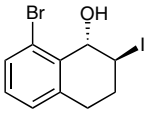
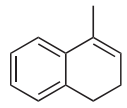
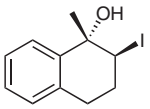
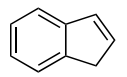
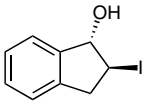
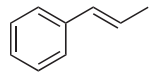
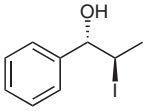
[a] The enantiomer of the chiral reagent was used.
[b] The diaryl thiolane precursor of **19** was recovered in 93% ee after the reaction.
[c] The chiral reagent was prepared in situ.

Intriguingly, the use of sterically larger groups in the C2 and C5 positions led to significantly reduced enantioselectivities (entries 4–6). Note that the diaryl thiolane precursor of **19** was recovered after the reaction with 93% ee, suggesting that no erosion of thiolane chirality occurred under the conditions of the reaction. With the remaining C_2-symmetric sulfides, in situ generation of the menthol ester halonium derivative of **20a** gave only a 15% yield of racemic iodohydrin (entry 7), whereas additional substitution on the backbone in thiolane **21** gave the product in 24% ee and a reasonable 53% yield (entry 8). Finally, the reagents formed in situ from the remaining non-C_2-symmetric chiral sulfides **22**–**25** all gave reasonable yields but poor enantioselectivities (entries 9–12), possibly as a result of the existence of two diastereomers of the iodosulfonium reagent.

Our concluding studies sought to explore the generality of the process with several slightly modified substrates. As

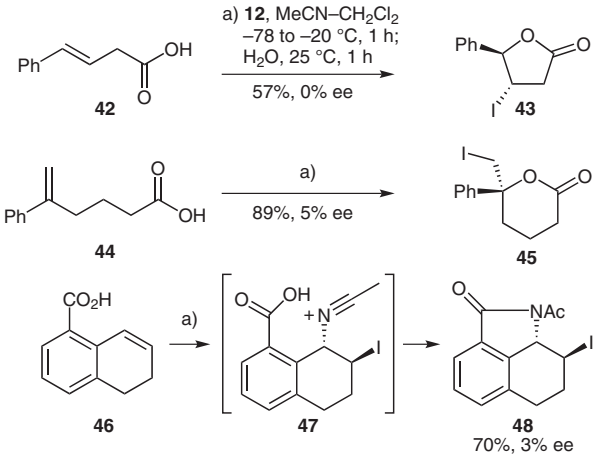
shown in Table 4, we examined the modification of the electronic and steric properties of the neighboring aromatic ring. We surmised that adding an additional resonating electron-donating group might stabilize the iodonium ion, providing more time for the external nucleophile to attack before any enantioselectivity-eroding iodonium transfer. However, as shown in entry 1, even though the iodohydrin product was formed in a superior yield (80%), the ee was only 21%. Increasing the steric bulk and adding an electron-withdrawing bromine to the ring gave 50% yield and 5% ee (entry 2). Use of the trisubstituted alkene **36** or indene (**38**) led mainly to decomposition under these conditions (entries 3 and 4), whereas cyclic substrates produced higher yields than the acyclic *trans*-β-methylstyrene (**40**; entry 5). Unfortunately, these results were not globally encouraging in that the developed reagents, while effective for some alkenes, did not appear to be especially general in terms of chiral selectivity, even for closely related materials.

Table 4 Substrate Scope for the Optimized Iodohydrin Formation with 2.2 Equivalents of **12**

Entry	Starting material	Product	Yield (%)	ee (%)
1	 **32**	 **33**	80	21
2	 **34**	 **35**	50	5
3	 **36**	 **37**	5	7
4	 **38**	 **39**	5	–
5	 **40**	 **41**	8	–

On the basis of some recent successes in the field of asymmetric iodolactonization,[1] we wanted to see if our chiral iodonium reagents might cyclize one of the known substrates from these studies asymmetrically. As shown in Scheme 5, treatment of carboxylic acid **42** with chiral iodosulfonium reagent **12** gave the racemic 5-*endo* lactone **43** in 57% yield.[18] Similarly, the combination of compound **44** with chiral reagent **12** gave an 89% yield of the 6-*exo* lactone **45**, though only a trace of enantioselectivity was observed.[19]

Given these results, we decided to explore a substrate that combined the structural characteristics of 1,2-dihydronaphthalene (**8**) with an intramolecular lactonization process, arriving at carboxylic acid **46**. Treatment of this material with 2.2 equivalents of **12** did not afford the expected 5-*exo* lactone, but instead gave imide **48** in 70% yield. This unexpected product was probably formed through a Ritter reaction in which a molecule of acetonitrile opened the iodonium via intermediate **47**.[20] Therefore, although all the iodolactonization substrates gave good yields of products with our chiral reagents, none, unfortunately, reacted with a useful degree of enantioselectivity.



Scheme 5 Attempts at asymmetric iodolactonization reactions

In conclusion, we have developed a moderately successful protocol for the asymmetric dichlorination and iodohydroxylation of 1,2-dihydronaphthalene (**8**), albeit one that appears to be substrate-specific. Indeed, the necessary conditions were not broadly amenable to alternative substrates, even those possessing seemingly minor modifications. Although the reagents that we prepared are capable of forming chiral halonium intermediates, as demonstrated by the fact that some optical activity was observed in nearly all cases, the rate of nucleophile attack to terminate the reaction may vary greatly and, in some cases, might be slower than that of halonium transfer to the unreacted alkene starting material. As a result, the overall enantioselectivities achieved might reflect significant losses of the initial chiral information imparted by the reagents. Further studies of more complex chiral sulfides of the types explored here, as well as entirely new classes of reagents, are currently underway in the hope of identifying reagents with greater power and generality in these important processes.

All reactions were carried out under argon in dry solvents under anhydrous conditions, unless otherwise noted. CH_2Cl_2, benzene, toluene, Et_2O, and THF were dried by passing the commercially available pre-dried, oxygen-free solvents through columns of activated alumina. $MeNO_2$ and MeCN were stored over 3-Å MS. Et_3N was distilled from KOH.

Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by TLC on 0.25-mm silica gel plates (60F-254; Merck) by using UV radiation and/or I_2 on silica as visualizing agents and development by aq phosphomolybdic acid and cerium sulfate or a soln of $KMnO_4$ in aq $NaHCO_3$ with heating. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography.

NMR spectra were recorded on Bruker DRX-400 and 500 AS-CEND instruments with the residual nondeuterated solvents as the internal references. IR spectra were recorded on a Nicolet Avatar 370 DTGS series FTIR spectrometer. High-resolution mass spectra were recorded at the Columbia University Mass Spectral Core facility on a JOEL HX110 mass spectrometer by using FAB and EI techniques. All ee values were determined by HPLC on Daicel CHIRALCEL OD or CHIRALPAK AD-H columns.

(2*S*,5*S*)-Hexanediol (**5**),[7] isothiocineole (**22**),[5h] thio ether **23**,[5a] thiepane **25**,[5i] dibromo diester **30**,[14,15] 2*H*-chromene (**32**),[21] 4-methyl-1,2-dihydronaphthalene (**36**),[22] (3*E*)-4-phenylbut-3-enoic acid (**42**),[18b] and 5-phenylhex-5-enoic acid (**44**)[19] were prepared according to the procedures described in the literature.

(2*R*,5*R*)-2,5-Dimethyltetrahydrothiophene (6); Typical Procedure

MsCl (7.83 mL, 101 mmol, 4.0 equiv) was added dropwise to a soln of diol **5** (3.00 g, 25.3 mmol, 1.0 equiv) and Et_3N (21.2 mL, 152 mmol, 6.0 equiv) in CH_2Cl_2 (50 mL) at –20 °C. The soln was then allowed to warm to 0 °C over 1 h before the reaction was quenched with 1 M aq HCl (100 mL). The mixture was extracted with CH_2Cl_2 (3 × 100 mL), and the organic layers were combined, washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated to give the desired bismesylated intermediate as a viscous oil that was used immediately without further purification.

Next, powdered $Na_2S{\cdot}9H_2O$ (12.2 g, 50.6 mmol, 2.0 equiv) was dissolved in EtOH (200 proof, 80 mL) and the soln was cooled to 0 °C. The crude bismesylate (25.3 mmol assumed, 1.0 equiv) was added and the mixture was stirred at 0 °C for 4 h. The mixture was warmed slowly to 25 °C over 4 h and then stirred at 25 °C for an additional 36 h. The reaction was then quenched with H_2O (150 mL), and the mixture was extracted with pentane (4 × 150 mL). The organic layers were combined, washed sequentially with H_2O (3 × 100 mL) and brine (2 × 100 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by vacuum distillation (≤120 °C, 100 Torr) to give the (2*R*,5*R*)-2,5-dimethyltetrahydrothiophene as a colorless liquid; yield: 2.70 mL (65%; 65% ee, contaminated with pentane); $[\alpha]_D^{23}$ +109.1 (*c* = 1.74, Et_2O). The spectral properties of the compound matched those reported in the literature.[5d]

(2*R*,5*R*)-1-Bromo-2,5-dimethyltetrahydrothiophenium Bromo(pentachloro)antimonate (7)

Thiolane **6** (0.26 g, 2.2 mmol, 1.0 equiv) and a 1.0 M soln of $SbCl_5$ in CH_2Cl_2 (2.64 mL, 2.64 mmol, 1.2 equiv) were added sequentially to a soln of Br_2 (0.124 mL, 2.42 mmol, 1.1 equiv) in CH_2Cl_2 (2.0 mL) at –30 °C, and the mixture was stirred for 15 min at –30 °C. The soln was then warmed gently until all the precipitates dissolved (35 °C), cooled slowly to 25 °C, and then further cooled to –20 °C for 12 h. The supernatant was decanted and the resulting crystals were washed with cold CH_2Cl_2 (2 × 1 mL) and dried under vacuum to give a yellow crystalline solid; yield: 0.52 g (40%).

***trans*-2-Bromo-1-Chloro-1,2,3,4-tetrahydronaphthalene (9)**

A soln of thiophenium derivative **7** (26 mg, 0.46 mmol, 1.2 equiv) in $MeNO_2$ (0.15 mL) was added to a soln of 1,2-dihydronaphthalene (**8**, 5.0 mg, 0.038 mmol, 1.0 mmol) in CH_2Cl_2 (0.6 mL) at –30 °C, and the soln was stirred at –30 °C for 10 min. The reaction was quenched by sequential addition of 5% aq Na_2SO_3 (1 mL) and sat. aq $NaHCO_3$ (1 mL). The heterogeneous mixture was stirred vigorously at 25 °C for 20 min, then poured into H_2O (2 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, dried ($MgSO_4$), filtered, concentrated, and purified by column chromatography [silica gel, hexanes–CH_2Cl_2 (9:1)] to give a white crystalline solid; yield: 2 mg (15%; contaminated with ~10% of an unknown impurity); mp 66–68 °C; R_f = 0.30 (silica gel, hexanes–CH_2Cl_2, 4:1).

IR (film): 2917, 2854, 1456, 1218, 767, 572 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.34 (m, 1 H), 7.30–7.15 (m, 3 H), 5.68 (t, *J* = 2.0 Hz, 1 H), 4.97 (m, 1 H), 3.30 (ddd, *J* = 17.6, 12.0, 6.0 Hz, 1 H), 2.97 (dd, *J* = 17.6, 5.6 Hz, 1 H), 2.85 (m, 1 H), 2.23 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.4, 132.8, 131.2, 129.2, 128.9, 126.7, 51.5, 51.5, 25.1, 24.5.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{10}H_{10}BrCl$: 243.9654; found: 243.9658.

HPLC: OD column, 1.0 mL/min, hexanes, 30 °C, 270 nm; t_R (major) = 6.42 min, t_R (minor) = 6.98 min (5% ee).

(2*R*,5*R*)-1-Chloro-2,5-dimethyltetrahydrothiophenium Hexachloroantimonate (10)

Cl_2 gas from a standard lecture bottle was bubbled through CH_2Cl_2 (2.0 mL) at 25 °C for 10 min to produce a sat. soln of Cl_2 (~1 M, ~2 mmol, 1 equiv). This soln was cooled to –78 °C and thiolane **6** (0.23 g, 2.0 mmol, 1.0 equiv) and a 1.0 M soln of $SbCl_5$ in CH_2Cl_2 (2.40 mL, 2.40 mmol, 1.2 equiv) were added sequentially. The soln was stirred for 20 min at –78 °C then the cold bath was removed and the mixture was allowed to warm to 25 °C over 30 min. The mixture was then diluted with CH_2Cl_2 (5 mL), layered with hexanes (5 mL), and cooled to –20 °C for 16 h. The supernatant was decanted and the resulting crystals were washed with cold 1:1 hexanes–CH_2Cl_2 (2 × 1 mL) then dried under vacuum to give a white crystalline solid; yield: 0.244 g (50%).

***trans*-1,2-Dichloro-1,2,3,4-tetrahydronaphthalene (11): Typical Procedure**

Cl_2 gas (7.4 mg, 0.10 mmol, 0.90 equiv) was added from a syringe to a soln of **6** (15 mg, 0.13 mmol, 1.1 equiv) in CH_2Cl_2 (1.7 mL) at –78 °C. A 1.0 M soln of $SbCl_5$ in CH_2Cl_2 (0.10 mL, 0.10 mmol, 0.90 equiv) was added dropwise, and the mixture was stirred at 0 °C for 5 min. Next, a soln of 1,2-dihydronaphthalene (**8**; 15 mg, 0.12 mmol 1.0 equiv) in CH_2Cl_2 (0.3 mL) was added dropwise and the mixture was stirred for 15 min at 0 °C. The reaction was then quenched by sequential addition of 5% aq Na_2SO_3 (1 mL) and sat. aq $NaHCO_3$ (1 mL). The heterogeneous mixture was stirred vigorously at 25 °C for 20 min, poured into H_2O (2 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography [silica gel, hexanes–CH_2Cl_2 (9:1)] to give a colorless liquid: yield: 12 mg (35%). The spectral properties of the product matched those reported in the literature.[4b]

HPLC: OD column, 1.0 mL/min, hexanes–*i*-PrOH (250:1), 30 °C, 270 nm; t_R (major) = 7.32 min, t_R (minor) = 7.91 min.

Dichlorination of 1,2-dihydronaphthalene (**8**) by using **12** (Table 1, entry 13) was performed by the same procedure as that used to synthesize **9**.

(2*S*,5*S*)-1-Iodo-2,5-dimethyltetrahydrothiophenium Hexachloroantimonate (12); Typical Procedure

ICl (1.42 mL, 28.4 mmol, 1.0 equiv) and a 1.0 M soln of $SbCl_5$ in CH_2Cl_2 (29.5 mL, 29.5 mmol, 1.1 equiv) were added sequentially to a soln of thiolane **6** (3.30 g, 28.4 mmol, 1.0 equiv) in DCE (370 mL) at –25 °C, and the mixture was stirred at –25 °C for 30 min. The

mixture was then allowed to warm to 25 °C, layered with hexanes (600 mL), and cooled to –20 °C for 1 week. The supernatant was decanted and the resulting crystals were washed with cold CH_2Cl_2 (2 × 10 mL) then dried under vacuum to give an orange crystalline solid; yield: 12.4 g (76%).

***trans*-2-Iodo-1,2,3,4-tetrahydronaphthalen-1-ol (14); Typical Procedure Using a Preformed Chiral Iodonium Reagent**

A soln of 1,2-dihydronaphthalene (**8**, 5.0 mg, 0.038 mmol, 1.0 equiv) in MeCN (0.2 mL) and CH_2Cl_2 (0.5 mL) was cooled to –78 °C then treated with a soln of chiral reagent **12** (48 mg, 0.084 mmol, 2.2 equiv) in MeCN (0.3 mL) added slowly down the side of the flask. The mixture was allowed to warm slowly to –20 °C over 1 h, and the reaction was then quenched by sequential and rapid addition of MeCN (1.0 mL) and H_2O (1.0 mL). The cold bath was removed, and the resulting soln was stirred at 25 °C for 1 h. 5% aq Na_2SO_3 (1 mL) and sat. aq $NaHCO_3$ (1 mL) were added and the heterogeneous mixture was stirred vigorously at 25 °C for 20 min, then poured into H_2O (2 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography [silica gel, hexanes–EtOAc (9:1 to 7:3)] to give a white crystalline solid; yield: 8 mg (74%); R_f = 0.46 (silica gel, hexanes–EtOAc, 7:3).

IR (film): 3243 (br), 2903, 1419, 1203, 979, 774, 741 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.52 (m, 1 H), 7.30–7.24 (m, 2 H), 7.14 (m, 1 H), 5.03 (t, *J* = 5.6 Hz, 1 H), 4.52 (td, *J* = 6.8, 3.2 Hz, 1 H), 2.94 (t, *J* = 6.4 Hz, 2 H), 2.54–2.45 (m, 2 H), 2.36 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.2, 135.1, 128.7, 128.5, 128.1, 126.7, 75.1, 36.0, 30.8, 29.3.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{10}H_{11}IO$: 273.9855; found: 273.9858.

HPLC: OD column, 1.0 mL/min, hexane–*i*-PrOH (50:1), 30 °C, 263 nm; t_R (major) = 9.62 min, t_R (minor) = 11.98 min (53% ee).

The absolute configuration of **14** was determined by Mosher's ester analysis.[23] This reaction was performed separately with both the *R*- and the *S*-enantiomers of Mosher's acid [3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid], and the major diastereomer produced in each case was characterized by means of ^1H NMR spectroscopy.

Specifically, a soln of Mosher's acid (39.8 mg, 0.17 mmol, 2.0 equiv) in hexane (2.3 mL) at 25 °C was sequentially treated with DMF (4.5 μL, 0.058 mmol, 1.0 equiv) and oxalyl chloride (25 μL, 0.29 mmol, 5.0 equiv). The mixture was then stirred at 25 °C for 1 h, filtered through Celite, rinsed with hexanes (2 × 1 mL), and concentrated.

A soln of the resulting acid chloride (0.17 mmol assumed) and iodohydrin **14** (16 mg, 0.058 mmol, 1.0 equiv) in CH_2Cl_2 (0.12 mL) was cooled to 0 °C, and DMAP (0.07 mg, 0.0006 mmol, 0.01 equiv) and Et_3N (40 μL, 0.29 mmol, 5.0 equiv) were added sequentially. The mixture was allowed to warm slowly to 25 °C over 2 h and then the reaction was quenched with 1 M aq HCl (1 mL). The mixture was extracted with CH_2Cl_2 (3 × 5 mL), and the organic layers were combined, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography [silica gel, hexanes–EtOAc (9:1)] to give the appropriate diastereomeric ester as a white crystalline solid.

***trans*-2-Iodo-1,2,3,4-tetrahydronaphthalen-1-yl (2*R*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate**

Yield: 5.0 mg (17%).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 7.5 Hz, 2 H), 7.41–7.28 (m, 5 H), 7.22 (t, *J* = 7.0 Hz, 1 H), 7.17 (d, *J* = 7.5 Hz, 1 H), 6.41 (d, *J* = 3.0 Hz, 1 H), 4.60 (q, *J* = 3.5 Hz, 1 H), 3.49 (s, 3 H), 3.01 (dt, *J* = 17.0, 6.0 Hz, 1 H), 2.83 (dq, *J* = 17.5, 3.0 Hz, 1 H), 2.08–1.93 (m, 2 H).

***trans*-2-Iodo-1,2,3,4-tetrahydronaphthalen-1-yl (2*S*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate**

Yield: 5.6 mg (20%).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 7.0 Hz, 2 H), 7.41–7.34 (m, 3 H), 7.26 (m, 1 H), 7.19–7.12 (m, 3 H), 6.40 (d, *J* = 3.5 Hz, 1 H), 4.68 (q, *J* = 4.0 Hz, 1 H), 3.49 (s, 3 H), 3.01 (dt, *J* = 17.0, 8.0 Hz, 1 H), 2.85 (dt, *J* = 17.5, 4.5 Hz, 1 H), 2.15 (quint, *J* = 4.5 Hz, 2 H).

***trans*-2-Iodo-1-methoxy-1,2,3,4-tetrahydronaphthalene (15)**

Prepared by the procedure used to synthesize **14**, but with quenching by MeOH instead of H_2O.

Colorless liquid; yield: 7.3 mg (67%); R_f = 0.52 (silica gel, hexanes–EtOAc, 19:1).

IR (film): 2924, 2818, 1455, 1203, 1070, 768, 746 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.18 (m, 3 H), 7.14 (d, *J* = 6.8 Hz, 1 H), 4.75 (m, 1 H), 4.57 (d, *J* = 3.6 Hz, 1 H), 3.50 (s, 3 H), 2.97 (dq, *J* = 16.8, 5.6 Hz, 1 H), 2.85 (dq, *J* = 17.2, 3.6 Hz, 1 H), 2.29 (m, 1 H), 2.10 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.7, 133.0, 130.4, 129.1, 128.5, 126.3, 83.0, 57.3, 29.4, 27.9, 27.8.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{11}H_{13}IO$: 288.0011; found: 288.0000.

HPLC: AD-H column, 1.0 mL/min, hexane–*i*-PrOH (99:1), 30 °C, 263 nm; t_R (major) = 7.81 min, t_R (minor) = 8.62 min (33% ee).

(2*S*,5*S*)-2,5-Diethyltetrahydrothiophene

Prepared by the procedure used to synthesize **6**. The cyclization with $Na_2S{\cdot}9H_2O$ was performed at 25 °C for 22 h.

Colorless liquid; yield: 0.28 g (75%, contaminated with pentane); $[\alpha]_D^{23}$ –38.4 (*c* = 0.65, $CHCl_3$); R_f = 0.62 (silica gel, hexanes–CH_2Cl_2, 9:1).

IR (film): 2939, 1275, 1266, 767, 750 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.36–3.28 (m, 2 H), 2.23–2.14 (m, 2 H), 1.71–1.60 (m, 2 H), 1.60–1.48 (m, 4 H), 0.95 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.4 (2 C), 36.9 (2 C), 30.6 (2 C), 13.4 (2 C).

HRMS: no molecular-ion peak was observed.

(2*S*,5*S*)-2,5-Diethyl-1-iodotetrahydrothiophenium Hexachloroantimonate (16)

Prepared by the procedure used to synthesize **12**.

Orange crystalline solid; yield: 0.58 g (70%).

(2*R*,5*R*)-2,5-Diisopropyltetrahydrothiophene

Prepared by the procedure used to synthesize **6**. The cyclization with $Na_2S{\cdot}9H_2O$ was performed at 25 °C for 7 d.

Colorless liquid; yield: 0.60 g (50%, contaminated with pentane). The spectral properties matched those reported in the data.[13]

(2*R*,5*R*)-1-Iodo-2,5-diisopropyltetrahydrothiophenium Hexachloroantimonate (17)

Prepared by the procedure used to synthesize **12**.

Orange crystalline solid; yield: 0.15 g (48%).

(2*R*,5*R*)-2,5-Di-*tert*-butyltetrahydrothiophene

Prepared by the procedure used to synthesize **6**. The cyclization with $Na_2S{\cdot}9H_2O$ was performed in DMF at 50 °C for 24 h. The concentrated crude reaction mixture was purified by column chromatography [silica gel, hexanes–CH_2Cl_2 (9:1)] to give a white crystalline solid; yield: 0.040 g (12%). The spectral properties matched those reported in the literature.[13]

(2*R*,5*R*)-2,5-Di-*tert*-butyl-1-iodotetrahydrothiophenium Hexachloroantimonate (18)
Prepared by the procedure used to synthesize **12**.

Yellow–orange crystalline solid; yield: 0.11 g (38%).

(1*R*,4*R*)-1,4-Bis[3,5-bis(trifluoromethyl)phenyl]butane-1,4-diol
Prepared by adaptations of procedures reported in the literature.[24]

MeNHOMe·HCl (4.10 g, 42.0 mmol, 3.0 equiv) was azeotroped with toluene, sealed under argon, and cooled to 0 °C. CH_2Cl_2 (32.6 mL) and Et_3N (7.8 mL, 56 mmol, 4.0 equiv) were then added sequentially at 0 °C. The resulting suspension was stirred for 10 min at 0 °C. Next, a soln of succinyl chloride (1.54 mL, 14.0 mmol, 1.0 equiv) in CH_2Cl_2 (10.7 mL) was added at 0 °C and the soln was allowed to warm to 25 °C over 3 h. The reaction was then quenched with H_2O (10 mL), and the mixture was extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated to afford the crude bis-Weinreb amide, a portion of which was used in the next operation.

A soln of 1-bromo-3,5-bis(trifluoromethyl)benzene (0.75 mL, 4.5 mmol, 3.0 equiv) was dissolved in Et_2O (5.0 mL) and the soln was cooled to –78 °C. A 1.6 M soln of BuLi in Et_2O, (2.8 mL, 4.5 mmol, 3.0 equiv) was added dropwise, and the mixture was stirred for 1 h at –78 °C to give the required aryllithium species.

In a separate flask, a suspension of the crude bis-Weinreb amide (0.31 g, 1.5 mmol, 1.0 equiv) in Et_2O (5.0 mL) was cooled to –78 °C, and the soln of the aryllithium was added at –78 °C. The mixture was allowed to warm to 25 °C over 3 h and then was stirred for an additional 1 h at 25 °C. The reaction was quenched with 1 M aq HCl (10 mL), and the mixture was extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by dissolving it in hot EtOAc (4 mL), cooling the soln to 25 °C, layering it with hexanes (1 mL), and cooling the mixture to –20 °C for 12 h. The supernatant was decanted and the crystals were washed with cold hexanes (2 × 1 mL) and dried under vacuum to afford the diaryl ketone intermediate as a shiny orange–yellow crystalline solid; yield: 0.40 g (53%, 2 steps).

Next, diphenyl[(2*S*)-pyrrolidin-2-yl]methanol (7.7 mg, 0.030 mmol, 0.15 equiv) was azeotroped with toluene (1.0 mL), sealed under argon, and dissolved in THF (0.3 mL). $B(OMe)_3$ (4.5 μL, 0.040 mmol, 0.20 equiv) was added at 25 °C and the mixture was stirred at 25 °C for 1 h before $BH_3·Me_2S$ (42 μL, 0.44 mmol, 2.2 equiv) was added. The resulting mixture was stirred at 25 °C for 10 min then THF (0.5 mL) was added, followed by a portion of the solid diaryl ketone (0.10 g, 0.20 mmol, 1.0 equiv) prepared above. The mixture was heated to 40 °C for 30 min then cooled to 25 °C. The reaction was quenched with 1 M aq HCl (4 mL), and the mixture was extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography [silica gel, hexanes–EtOAc (9:1 to 1:1)] to give the diaryl diol as a white crystalline solid; yield: 0.080 g (78%); mp 86–95 °C; R_f = 0.53 (silica gel, hexanes–EtOAc, 7:3).

IR (film): 3384 (br), 3283 (br), 2927, 1275, 1167, 1122, 898, 682 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.03 (s, 4 H), 7.90 (s, 2 H), 5.08–4.97 (m, 2 H), 4.90 (br d, J = 18.4 Hz, 2 H), 2.05–1.94 (m, 3 H), 1.85 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 150.6, 150.6, 131.9 (q, J = 32.6 Hz, 4 C), 127.3 (4 C), 124.6 (q, J = 270.3 Hz, 4 C), 121.4 (t, J = 3.6 Hz, 2 C), 72.8, 72.6, 36.4, 36.3.

HRMS: no molecular ion peak was observed.

(2*S*,5*S*)-2,5-Bis[3,5-bis(trifluoromethyl)phenyl]tetrahydrothiophene
The diaryl thiolane was prepared by the procedure used to synthesize **6**. The cyclization with $Na_2S·9H_2O$ was performed at 25 °C for 30 min.

White crystalline solid; yield: 0.068 g (53%); mp 86–89 °C; R_f = 0.27 (silica gel, hexanes–CH_2Cl_2, 9:1).

IR (film): 2934, 2859, 1376, 1275, 1123, 681 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.93 (s, 4 H), 7.80 (s, 2 H), 5.02–4.96 (m, 2 H), 2.77–2.67 (m, 2 H), 2.21–2.09 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.5 (2 C), 132.0 (q, J = 33.2 Hz, 4 C), 128.0 (4 C), 123.2 (q, J = 271.1 Hz, 4 C), 121.6 (quint, J = 3.8 Hz, 2 C), 53.6 (2 C), 41.2 (2 C).

HRMS (FAB): m/z $[M – H]^+$ calcd for $C_{20}H_{11}F_{12}S$: 511.0390; found: 511.0373.

HPLC: OD column, 1.0 mL/min, hexane–*i*-PrOH (50:1), 30 °C, 200 nm; t_R (major) = 4.11 min, t_R (minor) = 4.63 min (94% ee).

(2*S*,5*S*)-2,5-Bis[3,5-bis(trifluoromethyl)phenyl]-1-iodotetrahydrothiophenium Hexachloroantimonate (19)
Prepared by the procedure used to synthesize **12**.

Yellow crystalline solid; yield: 0.17 g (92%).

Di-L-menthyl Tetrahydrothiophene-2,5-dicarboxylate (20a and 20b)
Dibromo diester (±)-**30** (17.2 g, 51.8 mmol, 1.0 equiv) was dissolved in DMF (200 mL) and the soln was cooled to –40 °C. Powdered $Na_2S·9H_2O$ (18.7 g, 77.7 mmol, 1.5 equiv) was then added in a single portion and the mixture was allowed to warm to 0 °C over 4 h. The reaction was quenched with sat. aq NH_4Cl (200 mL), and the mixture was poured into H_2O (100 mL) and extracted with Et_2O (3 × 200 mL). The organic layers were combined, washed with H_2O (3 × 200 mL), dried ($MgSO_4$), filtered, and concentrated to give the crude diester (±)-**31** as a yellow viscous oil; yield: 9.9 g. The spectral properties of the product matched those reported in the literature.[25]

Next, the crude diester **31** (51.8 mmol assumed) was dissolved in a mixture of THF (520 mL) and H_2O (173 mL), and the mixture was cooled to 0 °C. Solid LiOH (6.20 g, 259 mmol, 5.0 equiv) was added and the mixture was stirred at 0 °C for 1 h. The cold bath was then removed and the mixture was stirred at 25 °C for an additional 1 h then cooled to 0 °C. The reaction was quenched by slow addition of 3 M aq HCl (300 mL), and the mixture was extracted with EtOAc (4 × 200 mL). The organic layers were combined, washed with acidic brine (200 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by crystallization from hot EtOAc (80 mL) to give the racemic diacid derivative as a white crystalline solid; yield: 6.57 g (72%, 2 steps).

A portion of the diacid (3.53 g, 20.0 mmol, 1.0 equiv) together with L-menthol (7.81 g, 50.0 mmol, 2.5 equiv) and DMAP (0.24 g, 2.0 mmol, 0.1 equiv) were dissolved in CH_2Cl_2 (40 mL) and MeCN (40 mL), and the soln was cooled to 0 °C. A soln of DCC (9.08 g, 44.0 mmol, 2.2 equiv) in CH_2Cl_2 (20 mL) was added slowly at 0 °C and the mixture was stirred at 0 °C for 1 h. The cold bath was then removed and the soln was warmed to 25 °C then stirred for an additional 1 h. The mixture was diluted with hexanes (100 mL), and the resulting mixture was stirred for a further 1 h. The solid that separated was removed by filtration and rinsed with 1:1 hexanes–CH_2Cl_2 (3 × 40 mL). The organic phases were combined and concentrated to afford a crude mixture of **20a** and **20b**; yield: 9.35 g (99%, 1:1 dr). Recrystallization from hot hexanes (200 mL) gave the more polar diastereomer **20b** as a white crystalline solid; yield: 3.67 g (41%). The supernatant was concentrated and the residue was recrystallized from PrOH (100 mL) to afford give the less polar diastereomer **20a** as a white crystalline solid; yield: 4.45 g (49%).

The diastereomeric relationship between compounds **20a** and **20b** was established by means of crystallographic analysis.

20a
Mp 89–92 °C; R_f = 0.53 (silica gel, hexanes–EtOAc, 4:1).

IR (film): 2954, 2870, 1730, 1456, 1199, 1162 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.65 (td, *J* = 11.2, 4.4 Hz, 2 H), 4.02–3.98 (m, 2 H), 2.42–2.21 (m, 4 H), 2.03–1.90 (m, 4 H), 1.72–1.63 (m, 4 H), 1.55–1.35 (m, 4 H), 1.11–0.93 (m, 4 H), 0.89 (d, *J* = 6.8 Hz, 12 H), 0.87 (m, 2 H), 0.75 (d, *J* = 6.8 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4 (2 C), 75.2 (2 C), 49.0 (2 C), 47.1 (2 C), 40.8 (2 C), 34.2 (2 C), 32.9 (2 C), 31.4 (2 C), 26.0 (2 C), 23.3 (2 C), 22.0 (2 C), 20.8 (2 C), 16.1 (2 C).

HRMS (FAB): *m/z* $[M - H]^+$ calcd for $C_{26}H_{43}O_4S$: 451.2882; found: 451.2883.

20b
Mp 116–129 °C; R_f = 0.50 (silica gel, hexanes–EtOAc, 4:1).

IR (film): 2953, 2868, 1730, 1453, 1177, 750 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.72–4.63 (m, 2 H), 3.94 (t, *J* = 6.0 Hz, 2 H), 2.56–2.47 (m, 2 H), 2.16–2.05 (m, 2 H), 2.03–1.81 (m, 4 H), 1.73–1.63 (m, 4 H), 1.60–1.32 (m, 4 H), 1.15–0.94 (m, 4 H), 0.95–0.80 (m, 14 H), 0.75 (d, *J* = 7.2 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6 (2 C), 75.3, 75.1, 49.2, 49.1, 47.1, 46.8, 40.7, 40.4, 34.2 (2 C), 32.9, 32.8, 31.4, 31.4, 26.2, 26.0, 23.4, 23.3, 22.0 (2 C), 20.8, 20.8, 16.3, 16.1.

HRMS (FAB): *m/z* $[M - H]^+$ calcd for $C_{26}H_{43}O_4S$: 451.2882; found: 451.2899.

(2*R*,3*R*,4*R*,5*R*)-3,4-Dimethoxyhexane-2,5-diol
Prepared by a procedure adapted from that of Yamamoto and co-workers.[26]

A soln of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (2.50 g, 9.53 mmol, 1.0 equiv) in THF (2.0 mL) was added slowly to a stirred suspension of NaH (60% dispersion in mineral oil, 1.28 g, 38.1 mmol, 4.0 equiv) in THF (6.5 mL) at 0 °C, and the resulting suspension was stirred at 0 °C for 30 min. MeI (1.78 mL, 28.6 mmol, 3.0 equiv) was added dropwise, and the mixture was stirred at 25 °C for 1 h, then cooled to 0 °C. The reaction was quenched by slow addition of H_2O (10 mL), and the mixture was extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated to afford the crude dimethylated mannitol derivative.

Without further purification, the crude intermediate (9.53 mmol assumed) was dissolved in 70% aq AcOH (25 mL), and the mixture was heated at 40 °C for 2 h. The mixture was then cooled to 25 °C and concentrated directly by co-evaporation with toluene (6 × 25 mL) to remove all the AcOH and H_2O. The resulting crude tetraol (9.53 mmol assumed) was dissolved in dry pyridine (28 mL), and the soln was cooled to 0 °C, treated with TsCl (4.09 g, 21.4 mmol, 2.25 equiv), and stirred at 0 °C for 4 h. The reaction was then quenched by addition of H_2O (3 mL), and the mixture was directly concentrated by co-evaporation with toluene (3 × 10 mL) to remove any residual pyridine. The crude product was dissolved in CH_2Cl_2 (10 mL), and the soln was washed with H_2O (2 × 10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography [silica gel, hexanes–EtOAc (7:3 to 1:4)] to give the bis-tosylate intermediate as a yellow amorphous solid; yield: 3.0 g (61%, 3 steps).

Finally, the bis-tosylate (3.0 g, 5.78 mmol, 1.0 equiv) was dissolved in THF (27 mL) and the soln was cooled to 0 °C. Solid $LiAlH_4$ (0.548 g, 14.5 mmol, 2.5 equiv) was added in five separate portions over 30 min. The resulting slurry was stirred at 25 °C for 12 h then cooled to 0 °C. The reaction was quenched by slow addition of H_2O (10 drops), and the resulting suspension was filtered through Celite, which was rinsed with MeOH (5 mL). The filtrate was concentrated and the residue was purified by column chromatography [silica gel, CH_2Cl_2–MeOH, (9:1)] to give the dimethoxyhexanediol product as a white crystalline solid; yield: 0.044 g (27%, 4 steps); R_f = 0.58 [silica gel, CH_2Cl_2–MeOH (9:1)].

IR (film): 3443 (br), 3378 (br), 2969, 2839, 1111, 1028 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.07 (t, *J* = 5.2 Hz, 2 H), 3.50 (s, 6 H), 3.32–3.28 (m, 2 H), 2.98 (br s, 2 H), 1.26 (d, *J* = 6.4 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 83.2 (2 C), 66.8 (2 C), 58.7 (2 C), 19.9 (2 C).

HRMS (FAB): *m/z* $[M + H]^+$ calcd for $C_8H_{19}O_4$: 179.1283; found: 179.1293.

(2*S*,3*S*,4*S*,5*S*)-3,4-Dimethoxy-2,5-dimethyltetrahydrothiophene (21)
Prepared by the procedure used to synthesize **6**. The cyclization with $Na_2S·9H_2O$ was performed at 50 °C for 24 h.

Light-yellow volatile oil; yield: 11.5 mg (13%); $[\alpha]_D^{23}$ –48.3 (*c* = 0.44, $CHCl_3$); R_f = 0.81 (silica gel, hexanes–EtOAc, 4:1).

IR (film): 2934, 1451, 1121, 752, 474 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.74–3.70 (m, 2 H), 3.64–3.55 (m, 2 H), 3.43 (s, 6 H), 1.27 (d, *J* = 6.8 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 86.0 (2 C), 58.3 (2 C), 40.6 (2 C), 16.6 (2 C).

HRMS: no molecular-ion peak was observed.

6-Methoxy-11,11-dimethyl-3-thiatricyclo[6.2.1.0^{1,6}]undecane (24)
MeI (31 μL, 0.50 mmol, 2.0 equiv) and NaH (60% dispersion in mineral oil, 0.081 g, 2.5 mmol, 10 equiv) were added sequentially to a soln of 11,11-dimethyl-3-thiatricyclo[6.2.1.0^{1,6}]undecan-6-ol[5e] (0.053 g, 0.25 mmol, 1.0 equiv) in DMF (2 ml) at 25 °C. The suspension was stirred at 25 °C for 4 h then the reaction was quenched with EtOH (0.5 mL) and H_2O (2 mL). The mixture was extracted with Et_2O (4 × 10 mL), and the organic layers were combined, washed with brine (4 × 30 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography [hexanes–EtOAc (1:0 to 9:1)] to give a yellow viscous oil; yield: 0.026 g (47%); R_f = 0.65 (silica gel, hexanes–EtOAc, 9:1).

IR (film): 2924, 1451, 1148, 1075, 799, 728 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.34 (d, *J* = 12.0, 1 H), 3.05 (s, 3 H), 2.98 (td, *J* = 12.0, 4.0, 1 H), 2.34 (m, 1 H), 2.27–2.19 (m, 2 H), 2.09 (dt, *J* = 14.6, 3.0, 1 H), 2.00–1.91 (m, 2 H), 1.75 (t, *J* = 4.6, 1 H), 1.69 (m, 1 H), 1.55 (m, 1 H), 1.02 (s, 3 H), 1.01 (m, 1 H), 0.91 (s, 3 H), 0.85 (d, *J* = 13.6, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 81.2, 51.8, 48.8, 46.3, 45.4, 38.7, 30.7, 28.2, 27.2, 26.7, 23.3, 22.3, 20.9.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{13}H_{22}OS$: 226.1398; found: 226.1391.

***trans*-2-Iodo-1,2,3,4-tetrahydronaphthalen-1-ol (14); Typical Procedure Using a Chiral Iodonium Reagent Generated In Situ (Table 3, Entry 8)**
A soln of chiral thiolane **21** (12 mg, 0.068 mmol, 2.2 equiv) in CH_2Cl_2 (0.2 mL) was cooled to –30 °C and treated sequentially by dropwise addition of ICl (3.4 μL, 0.068 mmol, 2.2 equiv) and a 1.0 M soln of $SbCl_5$ in CH_2Cl_2 (68 μL, 0.068 mmol, 2.2 equiv). The mixture was allowed to warm to 0 °C over 1 h, MeCN (0.3 mL) was added, and the soln was cooled to –78 °C. A soln of 1,2-dihydronaphthalene (**8**; 4.0 mg, 0.03 mmol, 1.0 equiv) in MeCN (0.1 mL) and CH_2Cl_2 (0.1 mL) was added at –78 °C, and the soln was allowed to warm to –20 °C over 1 h. The reaction was then quenched by addition of 5% aq Na_2SO_3 (1 mL) and sat. aq $NaHCO_3$ (1 mL). The heterogeneous mixture was stirred vigorously at 25 °C for 20 min, poured into H_2O (2 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, dried ($MgSO_4$), filtered, concentrat-

ed, and purified by column chromatography [silica gel, hexanes–CH_2Cl_2 (4:1)] to give a white crystalline solid; yield: 4 mg (53%).

***Trans*-3-Iodochroman-4-ol (33)**
Prepared by the procedure used to synthesize **14**.

White crystalline solid; yield: 9 mg (80%); mp 98–105 ° C; R_f = 0.47 (silica gel, hexanes–EtOAc, 7:3).

IR (film): 3344 (br), 2859, 1486, 1223, 1981, 757 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.37 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.26 (td, *J* = 7.8, 1.6 Hz, 1 H), 6.99 (td, *J* = 7.2, 0.8 Hz, 1 H), 6.89 (dd, *J* = 8.4, 1.2 Hz, 1 H), 5.00 (t, *J* = 5.2 Hz, 1 H), 4.45–4.39 (m, 2 H), 4.32 (m, 1 H), 2.43 (d, *J* = 5.2 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.3, 130.4, 129.2, 122.4, 120.7, 116.3, 70.2, 66.9, 28.0.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_9H_9IO_2$: 275.9647; found: 275.9640.

HPLC: AD-H column, 1.0 mL/min, hexane–*i*-PrOH (9:1), 30 °C, 280 nm; t_R (major) = 8.14 min, t_R (minor) = 7.68 min (21% ee).

5-Bromo-1,2-dihydronaphthalene (34)
Prepared by a procedure adapted from that of Voskoboynikov and co-workers.[27]

A 1.7 M soln of *t*-BuLi in pentane (8.8 mL, 15 mmol, 3.0 equiv) was added dropwise to a soln of 1,2,3,4-tetrahydro-1-naphthol (0.74 g, 5.0 mmol, 1.0 equiv) in hexanes (10 mL) at 0 °C and the mixture was heated at 40 °C for 1 h. The soln was then cooled to –78 °C and $BrCCl_2CCl_2Br$ (3.42 g, 10.5 mmol, 2.1 equiv) was added quickly in a single portion. The mixture was allowed to warm to 25 °C over 4 h then the reaction was quenched with sat. aq NH_4Cl (10 mL). The mixture was extracted with EtOAc (3 × 10 mL), and the organic layers were combined, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography [silica gel, hexanes–EtOAc (9:1 to 4:1)] to give 8-bromo-1,2,3,4-tetrahydro-1-naphthol as a light-brown crystalline solid; yield: 0.42 g (37%); mp 61–63 °C.

Next, a portion of the bromo alcohol (0.10 g, 0.44 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (2.2 mL), and the soln was cooled to 0 °C. MsCl (68 μL, 0.88 mml, 2.0 equiv) and Et_3N (0.245 mL, 1.76 mmol, 4.0 equiv) were added sequentially, and the resulting soln was allowed to warm to 25 °C over 1 h. DBU (0.329 mL, 2.20 mmol, 5.0 equiv) was then added and the soln was stirred at 25 °C for a further 1 h. The reaction was then quenched with 1 M aq HCl (3 mL), and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography [silica gel, hexanes–CH_2Cl_2 (9:1)] to give **34** as a colorless viscous oil; yield: 21 mg (23%); R_f = 0.90 (silica gel, hexanes–CH_2Cl_2, 9:1).

IR (film): 3054, 2935, 2829, 1552, 1442, 1012, 763 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 7.6 Hz, 1 H), 7.04 (d, *J* = 7.2 Hz, 1 H), 6.96 (t, *J* = 8.0 Hz, 1 H), 6.85 (dq, *J* = 10.0, 1.6 Hz, 1 H), 6.18 (dt, *J* = 9.2, 4.4 Hz, 1 H), 2.79 (t, *J* = 8.0 Hz, 2 H), 2.34–2.27 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.0, 133.0, 130.9, 130.7, 127.8, 126.7, 126.4, 121.9, 28.2, 22.8.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{10}H_9Br$: 207.9888; found: 207.9877.

***trans*-8-Bromo-2-iodo-1,2,3,4-tetrahydronaphthalen-1-ol (35)**
Prepared by the procedure used to synthesize **14**.

White crystalline solid; yield: 4 mg (50%); R_f = 0.42 (silica gel, hexanes–EtOAc, 7:3).

IR (film): 3289 (br), 2929, 2854, 1566, 1446, 1261, 768 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.47 (m, 1 H), 7.17–7.10 (m, 2 H), 5.31 (t, *J* = 3.2 Hz, 1 H), 4.72 (q, *J* = 2.8 Hz, 1 H), 3.09 (ddd, *J* = 17.6, 11.6, 5.6 Hz, 1 H), 2.86 (m, 1 H), 2.56 (d, *J* = 4.4 Hz, 1 H), 2.21 (m, 1 H), 2.06 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.3, 133.7, 131.0, 129.6, 128.6, 126.2, 72.7, 31.2, 27.8, 25.8.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{10}H_{10}BrIO$: 351.8960; found: 351.8972.

HPLC: AD-H column, 1.0 mL/min, hexane–*i*-PrOH (9:1), 30 °C, 220 nm; t_R (major) = 11.58 min, t_R (minor) = 10.80 min (5% ee).

***trans*-2-Iodo-1-methyl-1,2,3,4-tetrahydronaphthalen-1-ol (37)**
Prepared by the procedure used to synthesize **14**.

White crystalline solid; yield: 2 mg (5%); R_f = 0.57 (silica gel, hexanes–EtOAc, 4:1).

IR (film): 3353 (br), 2936, 2838, 1371, 1078, 899, 761 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.66 (m, 1 H), 7.26–7.17 (m, 2 H), 7.05 (m, 1 H), 4.69 (dd, *J* = 12.4, 3.6 Hz, 1 H), 3.01 (ddd, *J* = 17.2, 10.4, 7.2 Hz, 1 H), 2.84 (ddd, *J* = 17.2, 6.4, 2.8 Hz, 1 H), 2.62 (m, 1 H), 2.52 (m, 1 H), 2.19 (br s, 1 H), 1.68 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.2, 133.7, 128.4, 127.5, 126.6, 126.6, 73.0, 46.1, 33.5, 31.1, 30.8.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{11}H_{13}IO$: 288.0011; found: 288.0019.

HPLC: OD column, 1.0 mL/min, hexane–*i*-PrOH (9:1), 30 °C, 263 nm; t_R (major) = 13.81 min, t_R (minor) = 8.41 min (7% ee).

***trans*-2-Iodoindan-1-ol (39)**
Prepared by the procedure used to synthesize **14**.

White crystalline solid; yield: 2 mg (5%). The spectral properties matched those reported in the literature.[28]

2-Iodo-1-phenylpropan-1-ol (41)
Prepared by the procedure used to synthesize **14**.

White crystalline solid; yield: 7 mg (8%); R_f = 0.67 (silica gel, hexanes–EtOAc, 7:3).

IR (film): 3431 (br), 2969, 2922, 1451, 1165, 1014, 751, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.29 (m, 5 H), 4.96 (t, *J* = 3.2 Hz, 1 H), 4.53 (ddd, *J* = 14.0, 6.8, 3.6 Hz, 1 H), 2.35 (d, *J* = 3.2 Hz, 1 H), 1.74 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.7, 128.4 (2 C), 128.0, 126.4 (2 C), 78.5, 35.9, 21.2.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_9H_{11}IO$: 261.9855; found: 261.9845.

5-*endo*-4-Iodo-5-phenyldihydrofuran-2(3*H*)-one (43)
Prepared by the procedure used to synthesize **14**.

White crystalline solid; yield: 8 mg (57%). The spectral properties matched those reported in the literature.[18]

HPLC: AD-H column, 1.0 mL/min, hexane–*i*-PrOH (9:1), 30 °C, 260 nm; t_R (major) = 11.60 min, t_R (minor) = 9.87 min (0% ee).

6-*exo*-6-(Iodomethyl)-6-phenyltetrahydro-2*H*-pyran-2-one (45)
Prepared by the procedure used to synthesize **14**.

White crystalline solid; yield: 14 mg (89%). The spectral properties matched those reported in the literature.[19]

HPLC: OD column, 1.0 mL/min, hexane–*i*-PrOH (9:1), 30 °C, 260 nm; t_R (major) = 12.82 min, t_R (minor) = 9.88 min (5% ee).

5,6-Dihydronaphthalene-1-carboxylic Acid (46)
Prepared by a procedure adapted from that of Voskoboynikov and co-workers.[27]

A 1.7 M soln of *t*-BuLi in pentane (4.4 mL, 7.5 mmol, 2.5 equiv) was added dropwise to a soln of 1,2,3,4-tetrahydro-1-naphthol (0.45 g, 3.0 mmol, 1.0 equiv) in THF (12 mL) at 0 °C, and the resulting

soln was heated at 40 °C for 1 h. The mixture was then cooled to 0 °C and bubbled with CO_2 for 5 min. The reaction was quenched with 1 M aq HCl (10 mL) and the mixture was extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography [silica gel, hexanes–EtOAc (4:1 to 0:1)] to afford 1,2,3,4-tetrahydronaphthalene-1-carboxylic acid as a light-yellow crystalline solid; yield: 0.22 g (37%).

A portion of the newly synthesized carboxylic acid (0.145 g, 0.754 mmol, 1.0 equiv) was dissolved in MeOH (5.0 mL) at 25 °C and treated by addition of a 2.0 M soln of $TMSCHN_2$ in hexanes (2.26 mL, 4.52 mmol, 6.0 equiv) over 20 min. The mixture was stirred for an additional 5 min at 25 °C and then the reaction was quenched by dropwise addition of AcOH (0.2 mL). The mixture was concentrated directly to afford the desired crude methyl ester as a colorless viscous solid; yield: 0.161 g (99%).

The crude methyl ester (0.75 mmol assumed) was dissolved in CH_2Cl_2 (3.0 mL) and the soln was treated with Et_3N (0.523 mL, 3.75 mmol, 5.0 equiv). The resulting soln was cooled to –20 °C and MsCl (0.116 mL, 1.50 mmol, 2.0 equiv) was added dropwise over 5 min. The mixture was then warmed slowly to 25 °C over 1 h. DBU (0.561 mL, 3.75 mmol, 5.0 equiv) was added and the soln was stirred at 25 °C for a further 1 h. The reaction was then quenched with H_2O (20 mL) and the mixture was extracted with 1:1 hexanes–EtOAc (3 × 20 mL). The organic layers were combined, washed with 1 M aq HCl (2 × 5 mL) and sat. aq $NaHCO_3$ (5 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography [silica gel, hexanes–EtOAc (1:0 to 9:1)] to give methyl 5,6-dihydronaphthalene-1-carboxylate as a colorless viscous oil; yield: 0.026 g (18%).

Finally, the methyl ester (0.026 g, 0.14 mmol, 1.0 equiv) was dissolved in THF (2.0 mL) and H_2O (1.0 mL), and the soln was cooled to 0 °C. Solid LiOH (0.034 g, 1.4 mmol, 10 equiv) was added and the mixture was stirred vigorously at 25 °C for 2 d. The mixture was then cooled to 0 °C and the reaction was quenched with 1 M aq HCl (5 mL). The mixture was extracted with EtOAc (3 × 10 mL), and the organic layers were combined, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography [silica gel, hexanes–EtOAc (1:1)] to give acid **46** as a white crystalline solid; yield: 0.023 g (90%); R_f = 0.24 (silica gel, hexanes–EtOAc, 2:1).

IR (film): 2954 (br), 1680, 1456, 1274, 932, 752 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 8.0 Hz, 1 H), 7.50 (d, *J* = 10.0 Hz, 1 H), 7.31 (d, *J* = 7.2 Hz, 1 H), 7.18 (t, *J* = 7.6 Hz, 1 H), 6.26 (dt, *J* = 9.6, 4.4 Hz, 1 H), 2.83 (t, *J* = 8.0 Hz, 2 H), 2.34–2.27 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 137.2, 135.3, 132.3, 131.7, 129.5, 126.2, 125.4, 125.0, 28.3, 22.3.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{11}H_{10}O_2$: 174.0681; found: 174.0680.

***trans*-1-Acetyl-8-iodo-6,7,8,8a-tetrahydrobenzo[*cd*]indol-2(1*H*)-one (48)**

Prepared by the procedure used to synthesize **1**.

White crystalline solid; yield: 7 mg (70%); R_f = 0.31 (silica gel, hexanes–EtOAc, 3:1).

IR (film): 2934, 2854, 1734, 1716, 1253, 750 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 7.2 Hz, 1 H), 7.49 (t, *J* = 7.6 Hz, 1 H), 7.44 (d, *J* = 7.6 Hz, 1 H), 5.49 (d, *J* = 8.8 Hz, 1 H), 3.91 (td, *J* = 9.2, 5.2 Hz, 1 H), 3.08 (m, 1 H), 2.88 (m, 1 H), 2.76 (m, 1 H), 2.70 (s, 3 H), 4.56 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 168.3, 142.6, 135.2, 132.7, 130.1, 127.8, 122.7, 62.5, 36.7, 27.5, 26.2, 22.8.

HRMS (FAB): *m/z* $[M + H]^+$ calcd for $C_{13}H_{13}NIO_2$: 341.9991; found: 341.9987.

HPLC: AD-H column, 1.0 mL/min, hexane–*i*-PrOH (9:1), 30 °C, 240 nm; t_R (major) = 10.09 min, t_R (minor) = 13.61 min (3% ee).

Acknowledgment

We thank the NSF (CHE-0619638) for an X-ray diffractometer and Professor Gerard Parkin, Dr. Aaron Sattler, and Mr. Serge Ruccolo for crystallographic analysis of compounds **12** and **20a**. Financial support was provided by Columbia University, the NSF (CAREER Award CHE-0844593 and Predoctoral Fellowships to A.P.B. and D.S.T.), Ludwig-Maximilians-University-Munich (study stipend to S.A.L.), the ACS Petroleum Research Fund (47481-G), the Camille and Henry Dreyfus Foundation (New Faculty Award to S.A.S.), and generous gifts from Bristol-Myers Squibb, Eli Lilly, and Amgen.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) For recent reviews, see: (a) Chen, G.; Ma, S. *Angew. Chem. Int. Ed.* **2010**, *49*, 8306. (b) Castellanos, A.; Fletcher, S. P. *Chem. Eur. J.* **2011**, *17*, 5766. (c) Snyder, S. A.; Treitler, D. S.; Brucks, A. P. *Aldrichimica Acta* **2011**, *44*, 27. (d) Hennecke, U. *Chem. Asian J.* **2012**, *7*, 456. (e) Snyder, S. A.; Brucks, A. P. In *Asymmetric Synthesis II: More Methods and Applications;* Christmann, M.; Bräse, S., Eds.; Wiley–VCH*:* Weinheim, **2012**, Chap. 20. (f) Denmark, S. E.; Kuester, W. E.; Burk, M. T. *Angew. Chem. Int. Ed.* **2012**, *51*, 10938.

(2) (a) Juliá, S.; Ginebreda, A. *Tetrahedron Lett.* **1979**, *23*, 2171. (b) Tanaka, Y.; Sakuraba, H.; Nakanishi, H. *J. Chem. Soc., Chem. Commun.* **1983**, 947. (c) Adam, W.; Mock-Knoblauch, C.; Saha-Möller, C. R.; Herderich, M. *J. Am. Chem. Soc.* **2000**, *122*, 9685. (d) Sakurada, I.; Yamasaki, S.; Göttlich, R.; Iida, T.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 1245. (e) El-Qisairi, A. K.; Qaseer, H. A.; Katsigras, G.; Lorenzi, P.; Trivedi, U.; Tracz, S.; Hartman, A.; Miller, J. A.; Henry, P. M. *Org. Lett.* **2003**, *5*, 439. (f) Snyder, S. A.; Tang, Z.-Y.; Gupta, R. *J. Am. Chem. Soc.* **2009**, *131*, 5744. (g) Nicolaou, K. C.; Simmons, N. L.; Ying, Y.; Heretsch, P. M.; Chen, J. S. *J. Am. Chem. Soc.* **2011**, *133*, 8134. For examples of asymmetric seleniranium and thiiranium ions see: (h) Denmark, S. E.; Voler, T. *Chem. Eur. J.* **2009**, *15*, 11737. (i) Denmark, S. E.; Kalyani, D.; Collins, W. R. *J. Am. Chem. Soc.* **2010**, *132*, 15752. (j) Denmark, S. E.; Kornfilt, D. J. P.; Vogler, T. *J. Am. Chem. Soc.* **2011**, *133*, 15308. (k) Denmark, S. E.; Burk, M. T. *Org. Lett.* **2012**, *14*, 256.

(3) For pioneering work on bromonium transfer, see: (a) Bellucci, G.; Bianchini, R.; Chiappe, C.; Marioni, F.; Ambrosetti, R.; Brown, R. S.; Slebocka-Tilk, H. *J. Am. Chem. Soc.* **1989**, *111*, 2640. (b) Bennet, A. J.; Brown, R. S.; McClung, R. E. D.; Klobukowski, M.; Aarts, G. H. M.; Santarsiero, B. D.; Bellucci, G.; Bianchini, R. *J. Am. Chem. Soc.* **1991**, *113*, 8532. (c) Brown, R. S.; Nagorski, R. W.; Bennet, A. J.; McClung, R. E. D.; Aarts, G. H. M.; Klobukowski, M.; McDonald, R.; Santarsiero, B. D. *J. Am. Chem. Soc.* **1994**, *116*, 2448. For additional critical studies, see: (d) Rodebaugh, R.; Fraser-Reid, B. *Tetrahedron* **1996**, *52*, 7663. (e) Chiappe, C.; De Rubertis, A.; Jaber, A.; Lenoir, D.; Wattenbach, C.; Pomelli, C. S. *J. Org. Chem.* **2002**, *67*, 7066. (f) Denmark, S. E.; Burk, M. T.; Hoover, A. J. *J. Am. Chem. Soc.* **2010**, *132*, 1232.

(4) (a) Snyder, S. A.; Treitler, D. S. *Angew. Chem. Int. Ed.* **2009**, *48*, 7899. (b) Snyder, S. A.; Treitler, D. S.; Brucks, A. P.

J. Am. Chem. Soc. **2010**, *132*, 14303. (c) Snyder, S. A.; Treitler, D. S.; Brucks, A. P.; Sattler, W. *J. Am. Chem. Soc.* **2011**, *133*, 15898. (d) Snyder, S. A.; Treitler, D. S. *Org. Synth.* **2011**, *88*, 54. (e) Snyder, S. A.; Brucks, A. P.; Treitler, D. S.; Moga, I. *J. Am. Chem. Soc.* **2012**, *134*, 17714. For additional applications of these reagents, see: (f) Snyder, S. A.; Wright, N. E.; Pflueger, J. J.; Breazzano, S. P. *Angew. Chem. Int. Ed.* **2011**, *50*, 8629. (g) Snyder, S. A.; Gollner, A.; Chiriac, M. I. *Nature (London)* **2011**, *474*, 461. (h) Lin, H.; Pochapsky, S. S.; Krauss, I. J. *Org. Lett.* **2011**, *13*, 1222. (i) Stefan, E.; Taylor, R. E. *Org. Lett.* **2012**, *14*, 3490. (j) Bonney, K. J.; Braddock, D. C. *J. Org. Chem.* **2012**, *77*, 9574; BDSB is currently available from Sigma-Aldrich as product number 751987.

(5) (a) Furukawa, N.; Sugihara, Y.; Fujihara, H. *J. Org. Chem.* **1989**, *54*, 4222. (b) Breau, L.; Durst, T. *Tetrahedron: Asymmetry* **1991**, *2*, 367. (c) Aggarwal, V. K.; Ford, J. G.; Thompson, A.; Jones, R. V. H.; Standen, M. C. H. *J. Am. Chem. Soc.* **1996**, *118*, 7004. (d) Julienne, K.; Metzner, P.; Henryon, V.; Greiner, A. *J. Org. Chem.* **1998**, *63*, 4532. (e) Aggarwal, V. K.; Ford, J. G.; Fonquerna, S.; Adams, H.; Jones, R. V. H.; Fieldhouse, R. *J. Am. Chem. Soc.* **1998**, *120*, 8328. (f) Aggarwal, V. K.; Angelaud, R.; Bihan, D.; Blackburn, P.; Fieldhouse, R.; Fonquerna, S. J.; Ford, G. D.; Hynd, G.; Jones, E.; Jones, R. V. H.; Jubault, P.; Palmer, M. J.; Ratcliffe, P. D.; Adams, H. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2604. (g) Zanardi, J.; Leriverend, C.; Aubert, D.; Julienne, K.; Metzner, P. *J. Org. Chem.* **2001**, *66*, 5620. (h) Bellenie, B. R.; Goodman, J. M. *Chem. Commun. (Cambridge)* **2004**, 1076. (i) Davoust, M.; Brière, J.-F.; Jaffrès, P.-A.; Metzner, P. *J. Org. Chem.* **2005**, *70*, 4166. (j) Illa, O.; Arshad, M.; Ros, A.; McGarrigle, E. M.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 1828.

(6) (a) Pfaltz, A.; Drury, W. J. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5723. (b) Mellah, M.; Voituriez, A.; Schulz, E. *Chem. Rev.* **2007**, *107*, 5133.

(7) Lieser, J. K. *Synth. Commun.* **1983**, *13*, 765.

(8) (a) Fujihara, H.; Akaishi, R.; Furukawa, N. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4451. (b) Olah, G. A.; Vankar, Y. D.; Fung, A. P. *Synthesis* **1979**, 59.

(9) The chlorodimethylsulfonium chloride reagent has been used previously for electrophilic aromatic substitution, see: Olah, G. A.; Ohannesian, L.; Arvanaghi, M. *Synthesis* **1986**, 868.

(10) Chlorosulfonium chloride derivatives are known to be unstable at room temperature as seen with the Swern reagent: Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(11) While this may be possible, the participation of a monomeric unit is more likely, as previously shown with related bromonium and iodonium reagents, see: (a) Neverov, A. A.; Brown, R. S. *J. Org. Chem.* **1998**, *63*, 5977. (b) Haas, J.; Piguel, S.; Wirth, T. *Org. Lett.* **2002**, *4*, 297. The presence of adventitious water could explain the ee values observed in entries 1–7 of Table 2.

(12) Masuda, H.; Takase, K.; Nishio, M.; Hasegawa, A.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* **1994**, *59*, 5550.

(13) Piccinini, A.; Kavanagh, S. A.; Connon, P. B.; Connon, S. J. *Org. Lett.* **2010**, *12*, 608.

(14) Lees, W. J.; Singh, R.; Whitesides, G. M. *J. Org. Chem.* **1991**, *56*, 7328.

(15) Yamamoto, Y.; Hoshino, J.; Fujimoto, Y.; Ohmoto, J.; Sawada, S. *Synthesis* **1993**, 298.

(16) In a similar system, a C_2-symmetrical cyclic selenium catalyst has been used to perform enantioselective bromoaminations, see: Chen, F.; Tan, C. K.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2013**, *135*, 1232.

(17) Foubelo, F.; Moreno, B.; Soler, T.; Yus, M. *Tetrahedron* **2005**, *61*, 9082.

(18) (a) Cambie, R. C.; Hayward, R. C.; Roberts, J. L.; Rutledge, P. S. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1864. (b) Garnier, J. M.; Robin, S.; Rousseau, G. *Eur. J. Org. Chem.* **2007**, 3281.

(19) For a pioneering recent example, see: Veitch, G. E.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2010**, *49*, 7332.

(20) Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045.

(21) (a) Boyd, D. R.; Sharma, N. D.; Bowers, N. I.; Boyle, R.; Harrison, J. S.; Lee, K.; Bugg, T. D. H.; Gibson, D. T. *Org. Biomol. Chem.* **2003**, *1*, 1298. (b) Varela, J. A.; González-Rodríguez, C.; Rubin, S. G.; Castedo, L.; Saá, C. *J. Am. Chem. Soc.* **2006**, *128*, 9576.

(22) Adamczyk, M.; Watt, D. S.; Netzel, D. A. *J. Org. Chem.* **1984**, *49*, 4226.

(23) Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nature Protoc.* **2007**, *2*, 2451.

(24) (a) Déziel, R.; Goulet, S.; Grenier, L.; Bordeleau, J.; Bernier, J. *J. Org. Chem.* **1993**, *58*, 3619. (b) Prasad, K. R. K.; Joshi, N. N. *J. Org. Chem.* **1996**, *61*, 3888. (c) Kumar, G. D. K.; Chavarria, G. E.; Charlton-Sevcik, A. K.; Arispe, W. M.; MacDonough, M. T.; Strecker, T. E.; Chen, S.-E.; Siim, B. G.; Chaplin, D. J.; Trawick, M. L.; Pinney, K. G. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1415.

(25) Terao, Y.; Aono, M.; Imai, N.; Achiwa, K. *Chem. Pharm. Bull.* **1987**, *35*, 1734.

(26) Hanaya, T.; Nakamura, Y.; Yamamoto, H. *Heterocycles* **2007**, *74*, 983.

(27) Izmer, V. V.; Lebedev, A. Y.; Nikulin, M. V.; Ryabov, A. N.; Asachenko, A. F.; Lygin, A. V.; Sorokin, D. A.; Voskoboynikov, A. Z. *Organometallics* **2006**, *25*, 1217.

(28) (a) Stavber, G.; Iskra, J.; Zupan, M.; Stavber, S. *Adv. Synth. Catal.* **2008**, *350*, 2921. (b) Pandit, P.; Gayen, K. S.; Khamarui, S.; Chatterjee, N.; Maiti, D. K. *Chem. Commun. (Cambridge)* **2011**, *47*, 6933.

