Development and Mechanism of an Enantioselective Bromocycloetherification Reaction via Lewis Base/ Chiral Brønsted Acid Cooperative Catalysis

SCOTT E. DENMARK,[1]* AND MATTHEW T. BURK[2]

[1]*Department of Chemistry, University of Illinois, Urbana-Champaign, Urbana, IL, USA*
[2]*Department of Chemistry, Yale University, New Haven, CT, USA*

ABSTRACT The development of a binary catalyst system for bromocycloetherification, consisting of an achiral Lewis base and a chiral Brønsted acid, is described in detail. The results of preliminary kinetic studies are also presented. *Chirality 26:344–355, 2014.*

KEY WORDS: enantioselective; halofunctionalization; Lewis base; cooperative catalysis

INTRODUCTION AND BACKGROUND

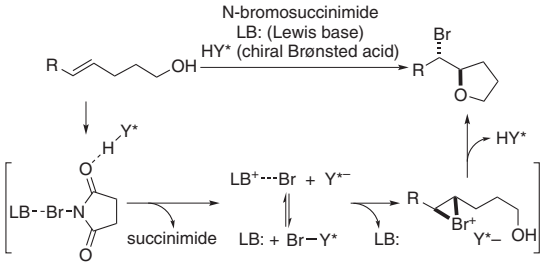
Bromocycloetherification of olefins[1–4] is an interesting and useful synthetic transformation, with proven application to the synthesis of biologically relevant molecules.[5–13] The bromo ether products can be valuable synthetic intermediates,[11] or natural product targets themselves.[9,10,12,13] Surprisingly, methods for the enantioselective synthesis of bromo ethers have only recently been reported.[14–16] The development of such methods presents a particular challenge, due in part to the propensity of the intermediate bromiranium ions to racemize by transfer between alkenes at rates competitive with nucleophilic capture.[17,18] Previous efforts in this laboratory[19] dealt with one potential strategy to overcome the racemization of haliranium ion intermediate. Specifically, these studies revealed a dramatic dependence of constitutional site selectivity (γ vs. δ-lactone) on the structure of the Lewis base in bromolactonization reactions. This behavior implied the continued association of the intermediate haliranium ion with the Lewis base catalyst. Thus, if the catalyst were chiral, this association would provide a mechanism for enantioselection via equilibrating diastereomeric bromiranium ions. As will be detailed below preliminary attempts to develop an enantioselective bromolactonization reaction were not promising. In view of successful, asymmetric bromolactonizations reported contemporaneously from other laboratories,[20–24] our attention shifted to the bromoetherification reactions. However, because the previous studies failed to provide evidence for association of the Lewis base in bromoetherifications, a different approach was sought, namely the ion pairing of the bromiranium ion with a chiral counterion.[21,22] Ion pairing of this type should in principle provide the same opportunity for stereocontrol that an associated chiral Lewis base does, except with the added advantage that the association of the haliranium ion with its counterion is guaranteed in nonpolar media by the principle of electroneutrality[25] and the force of Coulombic attraction.[26] Consequently, a chiral counterion should have the opportunity to influence the stereochemical course of every step of the reaction, regardless of any known or unknown racemization pathways. Such a chiral ion pair should arise as a natural consequence of catalysis by a sufficiently strong, chiral Brønsted acid or the combination of a chiral Brønsted acid and a Lewis base because the acid should protonate and replace the succinimide counterion (Scheme 1).

Related studies in these laboratories had demonstrated that Lewis base catalyzed seleno,[27] thio[28] and bromocycloetherification[19] are greatly accelerated by the addition of a *stoichiometric* amount of an achiral Brønsted acid. The pK_a and general applicability of chiral phosphoric acids made them attractive candidates for the development of an enantioselective bromocycloetherification process using a *catalytic* amount of a chiral Brønsted acid, potentially in conjunction with a Lewis base co-catalyst.[29–34] This line of research led to the development of an enantioselective bromocycloetherification reaction of 5-arylpentenols (**1a**, **1d-m**) cooperatively catalyzed by the combination of the versatile chiral phosphoric acid TRIP[35,36] (**2a**) and the achiral Lewis base Ph_3P=S, producing chiral tetrahydrofurans (**3a**, **3d-m**) and tetrahydropyrans (**4a, 4d-m**) (Fig. 1).[15,19] The development of this bromocycloetherification will be discussed here in full detail.

Furthermore, our attempts to develop an enantioselective bromolactonization of 5-aryl-4-pentenoic acids (**5a-b**), catalyzed by chiral Lewis basic sulfides (**6a-f**), and producing regrettably racemic bromolactones (**7a, 8a-b**), will be discussed in abbreviated detail.

Following the development of the chiral Brønsted acid/ achiral Lewis base cooperatively catalyzed enantioselective bromocycloetherification reaction, the novelty of the proposed mechanism made further investigation imperative. Additionally, the early results obtained in the absence of Ph_3P=S, the reactivity of unconjugated olefins in the absence of Ph_3P=S and the independent results from the Shi laboratory[16] raised questions about the true role of Ph_3P=S in this system. Therefore, after having demonstrated the scope of the cooperatively catalyzed bromocycloetherification reaction it was deemed necessary to explore the mechanism of the reaction. The determination of the kinetic equation for the reaction was judged to be an appropriate means of doing so.

Contract grant sponsor: National Institutes of Health; Contract grant number: GM R01-85235.
*Correspondence to: Scott E. Denmark, Department of Chemistry, University of Illinois, Urbana-Champaign, 245 Roger Adams Laboratory, 600 S. Mathews Avenue, Urbana, IL 61801, USA. E-mail: sdenmark@illinois.edu
Received for publication 31 July 2013; Accepted 13 September 2013
DOI: 10.1002/chir.22259
Published online 7 November 2013 in Wiley Online Library (wileyonlinelibrary.com).



Scheme 1. Hypothesized mechanism of Lewis base/Chiral Brønsted acid cooperative catalysis.

MATERIALS AND METHODS

General Experimental

All undeuterated reaction solvents were dried by percolation through neutral alumina in a solvent dispensing system. Toluene-d_8 was dried over 3Å molecular sieves. N-Bromosuccinimide (NBS) was recrystallized twice from hot water,[37] dried under vacuum at room temperature, stored at −20 °C, and protected from light. Phosphoric acid **2a** used in preparative experiments was prepared according to the procedure of Gong,[38] and was recrystallized from MeCN according to the procedure of List[35] whereas **2a** used for kinetic experiments was prepared by the procedure of List.[35] Other chiral acids were prepared by literature procedures (**2b-l**)[36,39–45] and were acid-washed according to the procedure of Ishihara,[46] or prepared without chromatography. The preparations of **1a-m**, **3a-m**, and **4a-m** (Table 4) were previously reported.[15] Procedures for the preparation of **6e-f** and **2h** are given in the Supporting Information.

Kinetic data was acquired by ^{19}F NMR using a Varian Unity Inova 600 NB spectrometer in a mixture of toluene and toluene-d_8. Spectra were manually phased, zero filled, Gaussian apodized, baseline corrected and integrated in MestReNova 7. Integral regions covered 42 Hz on either side of the peak centers. Concentrations were computed by integration relative to a fluorobenzene internal standard using an initial time point

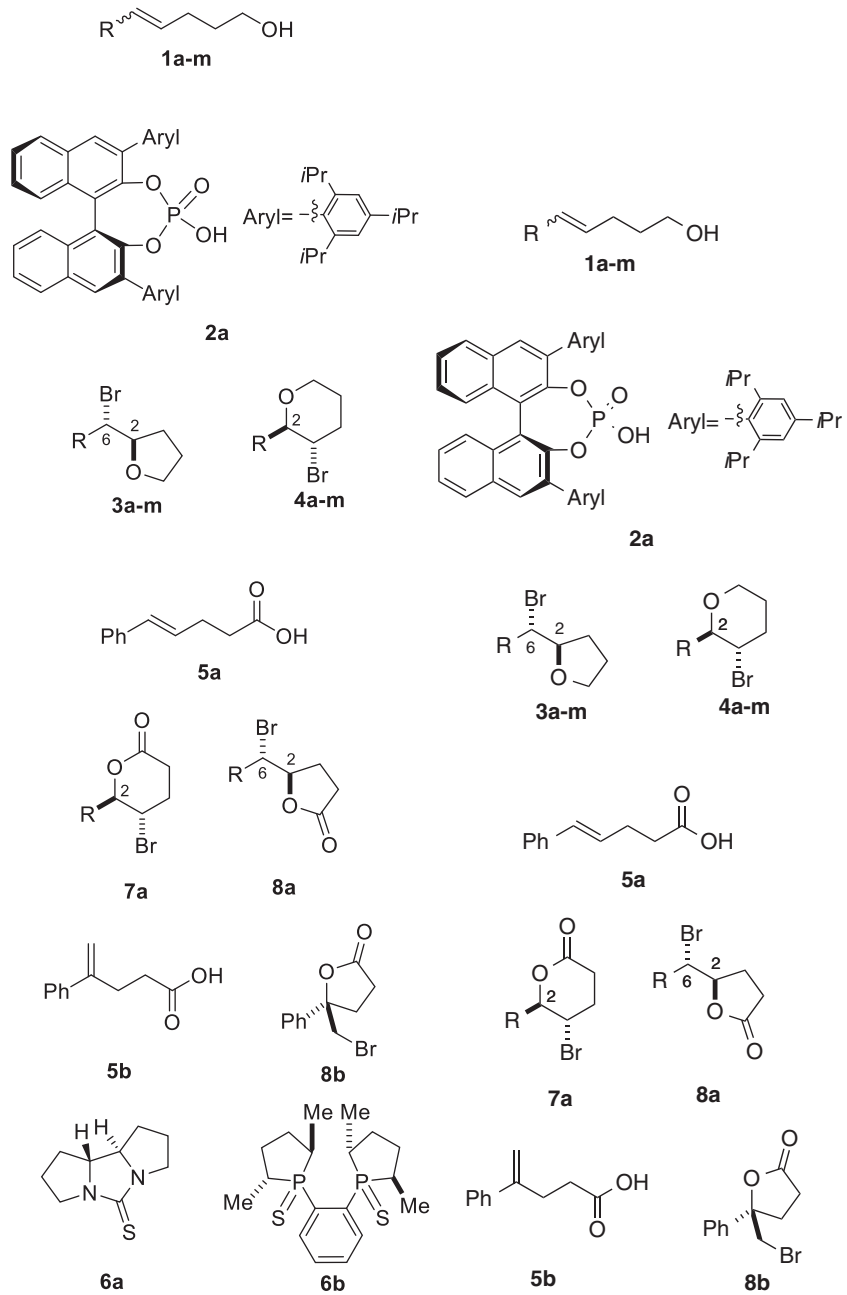


Fig. 1. Compound numbering scheme.

prior to catalyst addition to correct for the effects of incomplete relaxation and the volatility of the internal standard.

Preparative Procedures

Bromolactonization of 5a in the presence of 6a. Preparation of rel-(5R,6S)-5-bromotetrahydro-6-phenyl-2H-pyran-2-one (7a)[19] (Table 1, Entry 1). A 5-mL, flame-dried Schlenk flask, fitted with a septum and a magnetic stir bar, was charged with *N*-bromosuccinimide (21 mg, 0.12 mmol, 1.2 equiv). The flask was wrapped in Al-foil and then was evacuated and filled with argon. Dichloromethane (0.3 mL) was added via syringe. A solution of **5a** (17.6 mg in 0.4 mL, 0.1 mmol, 1.0 equiv) was added via a short cannula. A solution of **6a** in CH_2Cl_2 (0.9 mg in 50 μL, 0.1 M, 0.05 equiv, 0.005 mmol) was added rapidly via syringe, and the resulting solution was stirred for at room temperature for 5 min. Aq. $Na_2S_2O_3$ solution (1 mL) was added, and the resulting biphasic mixture was transferred to a 60-mL separatory funnel where it was diluted with sat. aq. $NaHCO_3$ solution (5 mL) and was extracted with EtOAc (5 mL, 2 x 2.5 mL). The combined organic extracts were dried over Na_2SO_4, decanted and concentrated in vacuo (23 °C, 10 mmHg). A 7.3:1 mixture of **7a** and **8a** was observed by ^{1}H NMR spectroscopy. The residue was purified by column chromatography (silica gel (1 g), Pasteur pipet., CH_2Cl_2), to provide 19.9 mg (78%) of a mixture of **7a** and **8a**.

Data for **7a/8a**: SFC: (5*R*,6*S*)/(5*S*,6*R*)-**7a**, t_R 5.0 min (38.1%); (5*S*,6*R*)/(5*R*,6*S*)-**7a**, t_R 5.5 min (38.7%); (5*R*,6*S*)/(5*S*,6*R*)-**8a**, t_R 6.3 min (11.7%); (5*S*,6*R*)/(5*R*,6*S*)-**8a**, t_R 7.2 min (11.4%) (Chiralpak OJ, 125 bar, 3 mL/min, 5% MeOH in CO_2).

Bromolactonization of 5b in the presence of 6e. Preparation of 5-(bromomethyl)dihydro-5-phenyl-2(3H)-furanone (8b) (Table 2, Entry 1)[21]. A 5-mL, flame-dried Schlenk flask, fitted with a septum and a magnetic stir bar, was charged with *N*-bromosuccinimide (21 mg, 0.12 mmol, 1.2 equiv). The flask was wrapped in Al-foil and then was evacuated and filled with argon. Dichloromethane (3 mL) was added via syringe. A solution of **5b** (17.7 mg, 0.1 mmol, 1.0 equiv) and **6e** (2.5 mg, 0.05 equiv, 0.005 mmol) in CH_2Cl_2 (1.0 mL) was added via a short cannula, and the resulting solution was stirred for at room temperature for 5 min. Aq. $Na_2S_2O_3$ solution (2 mL) was added, and the resulting biphasic mixture was transferred to a 60-mL separatory funnel where it was extracted with CH_2Cl_2 (2 × 2 mL). The combined organic extracts were washed with $NaHCO_3$ (2 × 2 mL), dried over $MgSO_4$, filtered and concentrated in vacuo (23 °C, 10 mmHg). The residue was purified by column chromatography (silica gel (1 g), Pasteur pipet, hexane/EtOAc, 4:1), to provide 26 mg (99%) of **8b**. The spectroscopic data were in accordance with those described in the literature.[21]

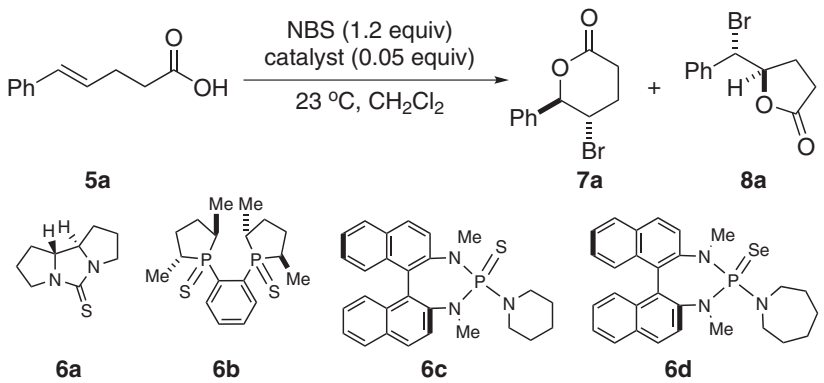
Data for **8b**: SFC: (*S*)/(*R*)-**8b**, t_R 4.38 min (49.9%); (*S*)/(*R*)-**8b**, t_R 4.90 min (50.1%); (Chiralpak AD, 125 bar, 3 mL/min, 5% MeOH in CO_2).

Optimization of the bromocycloetherification of 1b in the absence of Ph_3=S. bromocycloetherification of 1b in the presence of 2a (Table 6, Entry 1). A 10-mL, oven-dried Schlenk flask, fitted with a septum and a magnetic stir bar, wrapped in Al-foil, under Ar, was charged with *N*-bromosuccinimide (22 mg, 0.12 mmol, 1.2 equiv). The flask was then evacuated and filled with argon. Toluene (3.2 mL) was added via syringe and then the flask was cooled to 0 °C (thermostated H_2O/ethylene glycol bath). A solution of **1b** (16.0 mg, 0.1 mmol, 1.0 equiv) in toluene (0.6 mL) was added via short cannula. A solution of **2a** (7.5 mg, 0.01 mmol, 0.1 equiv) in toluene (0.2 mL) was added via syringe. The reaction mixture was stirred at 0 °C for 39 h. Chilled (ca. 0 °C) aq. $Na_2S_2O_3$ solution (1 mL) was added, followed by chilled sat. aq. $NaHCO_3$ solution (1 mL). The resulting biphasic mixture was stirred at 0 °C for 10 min, after which it was allowed to warm to room temperature while stirring vigorously. The colorless biphasic mixture was transferred to a 60-mL separatory funnel where it was diluted with H_2O (5 mL) and was extracted with Et_2O (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo (23 °C, 6 mmHg). The residue was purified by column chromatography (silica gel (4.5 g), 1 cm diam., 10 cm length, hexane/EtOAc, 19:1) to provide 23.9 mg (89%) of **3b**. Spectral data matched those previously reported.[19] SFC: (2*S*,6*R*)-**3b**, t_R 6.7 min (15.5%); (2*R*,6*S*)-**3b**, t_R 7.8 min (84.5%) (Chiralcel OD, 200 bar, 1.5 mL/min, 2% MeOH in CO_2)

General Procedure for Kinetic Studies

Determination of the partial order in 1l for bromocyclization of 1l by ^{19}F NMR. (0.025 M, replicate 1). An oven-dried, 5-mm NMR tube, fitted with a septum and wrapped in Al foil was charged with NBS

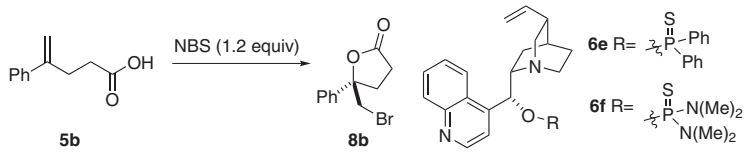
TABLE 1. Attempted Enantioselective Bromolactonization of 5a



entry	catalyst	**7a**:**8a**	er (**7a**)[b]	er (**8a**)[b]	yield, %[a]
1	**6a**	7.3:1	50:50	51:49	78
2	**6b**	20:1	50:50	53:47	73
3	**6c**	4.9:1	50:50	50:50	82
4	**6d**	7.5:1	51:49	53:47	66

[a]Determined by CSP-HPLC analysis.
[b]Yield of chromatographically homogenous material.

TABLE 2. Attempted Enantioselective Bromolactonization of 5b



entry	catalyst	mol %	solvent	T, °C	er[a]	yield, %[b]
1	**6e**	5	CH_2Cl_2	23	50:50	98
2	**6e**	10	toluene/$CHCl_3$ 2:1	−75	50:50	4
3	**6f**	5	CH_2Cl_2	23	51:49	88
4	**6f**	10	toluene/$CHCl_3$ 2:1	−75	54:46	91

[a]Determined by CSP-HPLC analysis.
[b]Yield of chromatographically homogenous material.

(3.72 mg, 0.021 mmol). The septum was removed and tube was then brought in to an Ar filled glove box, where the septum was replaced. The tube removed from the glove box and was charged with toluene-d_8 (0.1 mL), a stock solution of **1l** and fluorobenzene in dry toluene (1:1 molar ratio, 216.6 M, 81 μL, 0.017 mmol) and toluene (494 μL). The tube was agitated in a vortex mixer until homogenous by visual inspection. The tube was inserted into the NMR spectrometer and shimmed. An initial time point was acquired (64 scans, at=1, pw=8.25, d1=2.77). The tube was ejected from the spectrometer. A stock solution of Ph_3P=S and **2a** (8.76 mM, 25 μL, 0.000219 mmol) was added. The tube was rapidly inverted three times and was reinserted into the spectrometer. An arrayed acquisition was begun (nt=8, d1=2.77, at=1, pad=array of zeroes).

RESULTS

Initial Efforts with Chiral Lewis Bases

In view of the foregoing studies from these laboratories on halocyclization,[19] the initial efforts toward the development of enantioselective bromocyclization reactions were focused on the use of chiral Lewis bases. In particular, these efforts were directed toward bromolactonization, as our previous work demonstrated the involvement of achiral sulfur-containing Lewis bases in the cyclization step of bromolactonization, implying that these classes of compound were suitable for the development of enantioselective catalysts. Thioureas, phosphine sulfides, thiophosphoramides, and selenophosphoramides showed a promising ability to effect the ratio of *endo* to *exo* cyclization in the bromolactonization of **5a**. Accordingly, the sulfide catalysts **6a-d** were tested under the conditions established in the previous study (Table 1).[19] Although catalysts **6a** and **6c-d** were able to alter the ratio of **7a** to **8a**, no enantioselectivity was observed. Catalysts **6c-d** were previously optimized for analogous thio-[28] and seleno-[27] cycloetherifications, so their failure in this transformation was particularly disappointing.

Inspired by the pioneering work of Yeung on bromolactonization,[21,22,47] catalysts **6e-f** were prepared and tested in a series of bromolactonization reactions (Table 2). No significant enantioselectivity was observed in any case. The absence of enantioselectivity observed with these catalysts suggested that a different approach would be required, although the recent development of a bromoaminocyclization catalyzed by a monofunctional chiral selenide[48] shows that the general approach may be viable, albeit quite difficult to implement

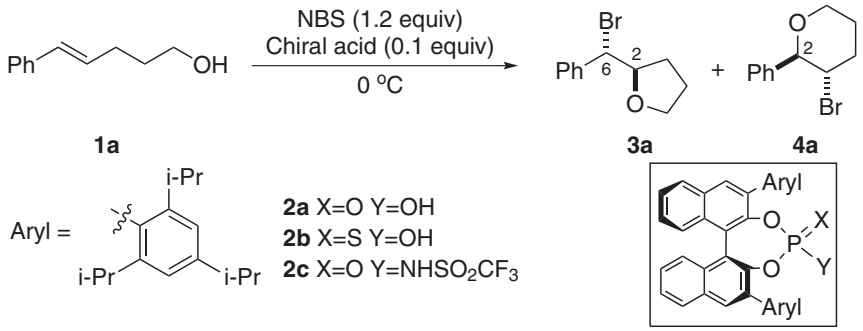
Chiral Phosphoric Acid Catalysis

On the basis of the broad applicability of **2a**, the potential of **2b** to act as a Lewis base, and general knowledge of the chiral Brønsted acid catalysis literature, catalysts **2a-c** seemed to provide the best chances for inducing enantioselectivity. Gratifyingly, **2a-c** (Table 3, entries 1–3) catalyzed the enantioselective bromocycloetherification of **1a** to provide the *exo* cyclization product **3a** with moderate to high enantioselectivity and the *endo* cyclization product **4a** with low enantioselectivity. With achiral Lewis bases, **3a** is a minor product in the cyclization of **1a**.[19] It is therefore fortunate that **2a-b** substantially increase the proportion of **3a** formed, albeit to only ca. 1:1 mixtures. Contrary to what had been hypothesized based on its potential to provide an internal Lewis base to assist in activation of the NBS, **2a** (entry 1) catalyzed the cyclization in higher yield and selectivity than the thio analog **2b** (entry 2). Triflimide **2c** (entry 3) catalyzed the cyclization in higher conversion, however the site and enantioselectivity was again lower and the absolute sense of enantioselectivity was inverted (entry 3). Lower enantio- and site selectivities were also observed when the reaction was run at higher concentrations (entries 4–5) or when the cyclizations were run in $CHCl_3$ (entry 6), $PhCF_3$ (entry 7), Et_2O (entry 8), hexane (entry 9), or MeCN (entry 10). From this initial survey, it appeared that a Lewis base was not required for this transformation.

Chiral Brønsted Acid/Achiral Lewis Base Cooperative Catalysis

Unfortunately, a serious problem was encountered while attempting to extend the results described above. Subsequent batches of **2a** catalyzed the cyclization of **1a** in substantially lower conversion and site selectivity and slightly lower enantioselectivity. The cause of this discrepancy was not firmly established because unfortunately the original batch had been expended before the problem was noticed. Multiple batches of **2a** prepared from different batches of the diol precursor exhibited similar behavior, so the new, inferior result appeared to be the reproducible one. It was hypothesized that the original material contained some co-catalytic impurity, possibly some sort of Lewis base. It was found that the addition of catalytic amounts of Ph_3P=S restored catalyst

TABLE 3. Optimization of Chiral Phosphoric Acid Catalyzed Bromocycloetherification



entry	catalyst	solvent	conc., M	time, h	**4a:3a**[a]	er (**4a**)[b]	er (**3a**)[b]	yield, %[c]
1	**2a**	toluene	0.025	24	48:52	62:38	95:5	64
2	**2b**	toluene	0.025	24	56:44	59:41	94:6	40
3	**2c**	toluene	0.025	13	87:13	48:52	28:72	78
4	**2a**	toluene	0.05	24	61:39	58:42	92:8	39
5	**2a**	toluene	0.1	24	72:28	55:45	88:12	48
6	**2a**	$CHCl_3$	0.025	24	89:11	51:49	86:14	59
7	**2a**	$PhCF_3$	0.025	24	73:27	52:48	74:26	82
8	**2a**	hexane	0.025	24	80:20	51:49	81:19	37
9	**2a**	Et_2O	0.025	25	98:2	50:50	51:49	57
10	**2a**	MeCN	0.025	1	98:2	50:50	51:49	75

[a]Determined by integration of ^{1}H NMR signals for HC(6).
[b]Determined by CSP-SFC analysis.
[c]Yield of chromatographically homogenous material.

activity and site selectivity (Table 4). The optimal conditions (entry 1) gave higher conversion than the original conditions in shorter reaction times using only half as much **2a**.

Several additional catalysts were prepared, and the effects of solvent, concentration and catalyst were evaluated under the new conditions (Table 4). In all cases, furan **3a** was formed with higher enantioselectivity than pyran **4a**. Phosphoric acid **2a** continued to be the optimal catalyst (entry 1). Substantially lower enantio- and site selectivities were observed when catalysts with alternative acidic groups (entries 2–3), alternative 3,3-aryl groups (entries 4–5) and an alternative chiral scaffold (entry 6) were used. Curiously, the absolute sense of enantioselectivity induced by **2c** was inverted compared to the previous result (entry 3 vs. Table 3 entry 3), making it the same as that observed with **2a-b** and **2d-f**. Increasing the reaction concentration (entry 7) or using solvents other than toluene (entries 8–9) gave inferior enantioselectivity.

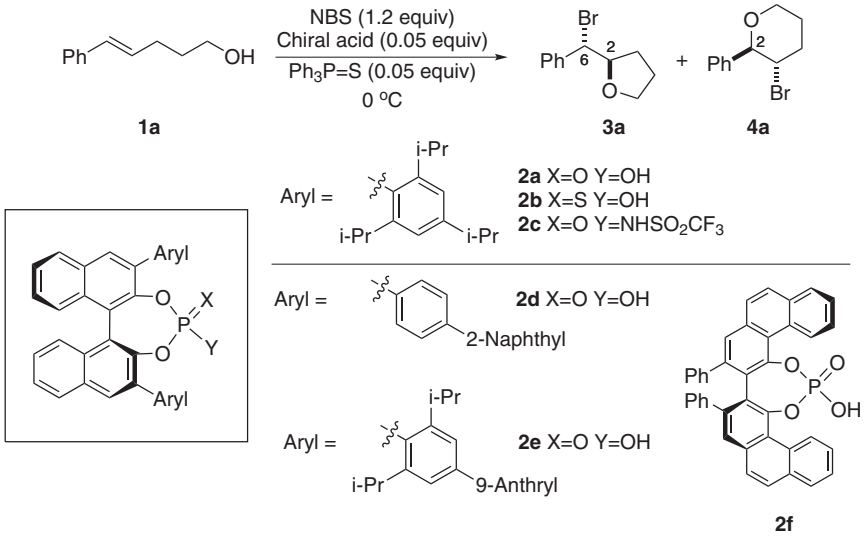
A series of substrates, exhibiting variations in olefin configuration as well as sterically and electronically diverse aryl groups, were prepared and subjected to the cyclization conditions in order to obtain a better understanding of the selectivity of this cyclization and explore its potential utility (Table 5). Altering the electronic properties of the aryl group strongly affected the selectivity of the cyclization, particularly among (*E*)-configured substrates. Inclusion of a moderately electron donating group (CH_3) in the 4-position of the phenyl ring unsurprisingly reduced the proportion of 5-*exo* cyclization (entry 2), although enantioselectivity increased. Conversely, the introduction of an electron-withdrawing group (CF_3) increased the proportion of *exo* cyclized product **3f** but with lower enantioselectivity (entry 3). Cyclization of a substrate with a strongly electron donating substituent (4-CH_3O) on the phenyl ring resulted in a 5-*exo* product that was too unstable to isolate or characterize (data not shown).

The cyclization of substrates containing (*Z*)-configured olefins occurred with uniformly high *exo* selectivity (entries 4–10). These cyclizations proceeded with only slightly lower enantioselectivity than those of (*E*)-configured olefins (entries 1 and 4, 2 and 8), and minimal differences were seen among substrates with varied steric demands (entries 5–8). Lower enantio-selectivity was again observed in the cyclizations of electron-poor substrates (entries 9–10).

The enantioselectivities observed in the cyclization of unconjugated olefins **1b-c** were significantly lower (Table 6, entry 1). This outcome is partially due to the higher intrinsic reactivity of **1b-c**, which leads to a substantial rate of cyclization in the absence of acid. When Ph_3P=S was omitted, enantioselectivity improved (entries 2–3), although not to the level observed with conjugated olefins. This modification came at the cost of greatly extended reaction times and, in the case of **1c**, low conversion. Several additional catalysts were prepared and tested in the cyclization of **1b-c**. Cyclization of **1c** proceeded in modestly higher enantioselectivity when catalyzed by **2g** than when catalyzed by **2a** (entry 5), however no difference was observed in the cyclization of **1b** (entry 4).

Single crystal, X-ray diffraction analysis of **3h** established the absolute configuration of the (*Z*)-olefin derived products. The absolute configurations of (*E*) and (*Z*)-olefin derived products were correlated by reductive dehalogenation of **3a** and **3g**. The 2-benzyltetrahydrofuran samples produced were judged to be of identical configuration by optical rotation ($[\alpha]_D^{24}$ -1.9 and −5.5) and CSP-SFC analysis (t_R 3.707 and 3.714 min)

TABLE 4. Optimization of Chiral Bronsted Acid/Achiral Lewis Base Cooperatively Catalyzed Bromocycloetherification



entry	cat.	solvent	conc., M	t, h	**3a**:**4a**	er (**3a**)	er (**4a**)	yield, %[b]
1	**2a**	toluene	0.025	9	48:52	93:7	57:43	83
2	**2b**	toluene	0.025	12	13:87	72:28	50:50	65
3	**2c**	toluene	0.025	12	12:88	75:25	49:51	85
4	**2d**	toluene	0.025	12	15:85	63:37	50:50	95
5	**2e**	toluene	0.025	35	26:74	77:23	49:51	31
6	**2f**	toluene	0.025	12	19:81	68:31	48:52	86
7	**2a**	toluene	0.1	12	39:61	90:10	54:46	84
8	**2a**	Et_2O	0.025	12	17:83	88:12	50:50	87
9	**2a**	$CHCl_3$	0.025	12	3:97	56:44	51:49	90

[a]Determined by ^{1}H NMR integration of signals for HC(6) of **3a** against HC(2) of **4a**.
[b]Yield after chromatography, all reactions run on 0.1 mmol substrate.

(Scheme 2). The configurations of **4a–m** were assigned on the basis of this information.

Kinetic Studies

The kinetic behavior of the cooperatively-catalyzed bromocycloetherification reaction was studied using the method of initial rates. *In situ* monitoring of the bromocycloetherification of **1l** using ^{19}F NMR spectroscopic analysis was chosen because this method provides good sensitivity, and a high sampling rate (Fig. 1). This method is also applicable to a substrate (**1l**) that was known to react productively and selectively. The solubility of NBS in toluene required that the reactions be carried out at 23 °C* and the concentrations of Ph_3P=S and **2a** were reduced by a factor of 4 to 0.31 mM (1.25 mol% at 25 mM **1l**) to allow a sufficient number of data points to be collected. Otherwise the conditions developed for the preparative reaction were used. To determine the partial order of the reaction in each readily soluble component (acid **2a**, Ph_3P=S, and olefin **1l**) five concentrations per component were chosen such that the data points spanned an order of magnitude, were evenly spaced on a logarithmic scale, and were centered around the baseline conditions (25 mM **1l**, 30 mM NBS, 0.31 mM Ph_3P=S, 0.31 mM **2a**). Because of the limited solubility of NBS in toluene, five concentrations were chosen such that they were evenly spaced on a logarithmic scale and spanned an order of magnitude from the baseline concentration (30 mM NBS) to 1/10th of the baseline concentration (3 mM NBS). Triplicate experiments were run for each concentration. Additional replicates were run as needed.

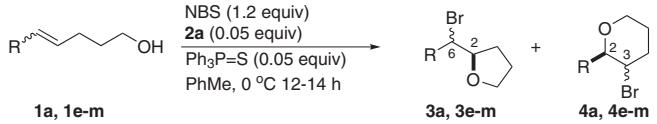
On the basis of the collected data (Fig. 2), the rate equation for the reaction was:

$$R = k_{obs}[NBS]^{1.07}[1\boldsymbol{l}]^{0.82}[Ph_3PS]^{1.47} \; where \; k_{obs} = k[2\boldsymbol{a}]^{1.02}$$

The two well-behaved components, NBS and **2a**, displayed clean first order behavior with respect to the concentrations of (1.07 ± 0.08 and 1.021 ± 0.005 respectively). However, fractional partial orders were obtained for Ph_3PS and **1l**. Such fractional orders in the kinetic data greatly complicate analysis of the reaction mechanism. The observed order of 0.82 in substrate could arise from a systematic error, partial

*TetramethylNBS was explored as an alternative, more soluble reagent, however the reaction rate was much lower and there was an induction period of ca. 8.5 min. The use of this reagent was judged to be a substantial alteration that was likely to affect the outcome of the study and was therefore not pursued further.

TABLE 5. Scope of Bromocycloetherification



entry	R	products	3:4[b]	er (3)[c]	yield (3), %[d]	er (4)	yield (4), %
1	(*E*)-C_6H_5	**3a**, **4a**	45:55	93:7	77[f]	58:42	
2	(*E*)-4-$CH_3C_6H_4$	**3e**, **4e**	37:63	97:3	28	65:35	67
3	(*E*)-4-$CF_3C_6H_4$	**3f, 4f**	86:14	85:15	43	65:35	12[e]
4	(*Z*)-C_6H_5	**3g**	>95:5	91:9	77	n/d	
5	(*Z*)-2-naphthyl	**3h**, **4h**	95:5	92:8	73	n/d	
6	(*Z*)-2-$CH_3C_6H_4$	**3i**, **4i**	94:6	94:6	86[f]	89:11	
7	(*Z*)-3-$CH_3C_6H_4$	**3j**	>95:5	92:8	86	n/d	
8	(*Z*)-4-$CH_3C_6H_4$	**3k**, **4k**	90:10	94:6	64	65:35	9
9	(*Z*)-4-FC_6H_4	**3l**, **4l**	95:5	90:10	78[f]	60:40	
10	(*Z*)-4-$CF_3OC_6H_4$	**3m**, **4m**	98:2	84:16	77[f,g]	n/d	

[a]All reactions run at 0.025 M on 1.0 mmol substrate.
[b]Determined by ^{1}H NMR integration of signals for HC(6) of **3** against HC(2) of **4**.
[c]Determined by CSP-SFC analysis.
[d]Yields of analytically pure material.
[e]Run at 23 °C for full conversion, selectivity at 0 °C was unchanged.
[f]Yield of both isomers.
[g]Yield of chromatographically homogenous material.

(ca. 40% at 25 mM **11**) contribution of a mechanism with an order of ½ or the beginning of a slow transition to a saturation kinetic regime. Attempts to determine whether saturation could be reached were stymied by the onset of radical *E/Z* isomerization at high olefin concentration.[†]

The origin of the fractional order (1.47) in Ph_3P=S is unclear however it may be due to experimental difficulties.[‡] At the lowest concentration of Ph_3P=S, 0.0988 mM, the reactions stalled before reaching 10% conversion, making it impossible to process the data in a manner consistent with the rest of the study. To construct the plot in Figure 2, the initial rate for that point was calculated from the first 5% conversion. The time/concentration plots for the low [Ph_3P=S] still show some curvature that is not present in the other data series which should increase the apparent order. At the highest concentration of Ph_3P=S examined (0.988 mM) only two data points could be acquired below 10% conversion because of the high reaction rate.

Several noteworthy phenomena were encountered in the analysis of this data. The first is that the reaction exhibits a transient phase or induction period. The length of this period depends on the reagent concentrations and is therefore unlikely to be due to incomplete mixing or other experimental artifacts. The most likely explanation is that it takes time for the concentrations of reactive intermediates to reach a steady state. The transient phase has been removed from the plotted data by basing the initial rate on the interval from 1 to 10% conversion, or in the case of the order in (*E*)-**11**, by removing the first acquired time point. Acquiring data with higher time resolution may allow mechanistic information to be extracted from this phase of the reaction, however this will require an entirely different method of reaction monitoring.

Under the conditions of this study, all reactions stalled at low conversion (typically ca. 30%) due to catalyst deactivation. As discussed above, at low Ph_3P=S concentration the reactions stalled before reaching 10% conversion. It is therefore likely that Ph_3P=S is the component of the catalyst system that is deactivated. The severity of catalyst deactivation is unfortunate because it makes numerical modeling of the reaction time course to resolve the origin of the observed fractional orders quite difficult.

DISCUSSION

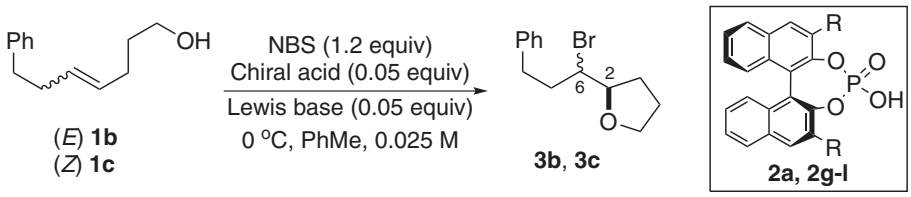
The development and subsequent mechanistic study of the enantioselective Lewis base/chiral Brønsted acid cooperatively catalyzed bromocycloetherification has provided insights in to the mechanism of this unique process and synthetically useful levels of enantioselectivity. These advances, their implications for future work in the field, and key unanswered questions will be discussed.

Optimization

Apart from the poor reproducibility of the results in Table 3, the trends observed during the optimization of the cooperatively catalyzed bromoetherification reaction (Table 4) are strikingly similar to those observed in the absence of Ph_3P=S (Table 3) with an intriguing difference. In both cases, phosphoric acid **2a** was the optimal catalyst. However, while all BINOL-derived catalysts surveyed in the presence of Ph_3P=S provided the same sense of enantioselectivity, suggesting that they exhibit a similar mechanism of enantioselection, the BINOL-derived triflimide **2c** provided the opposite sense of enantioselectivity when run in the *absence* of Ph_3P=S

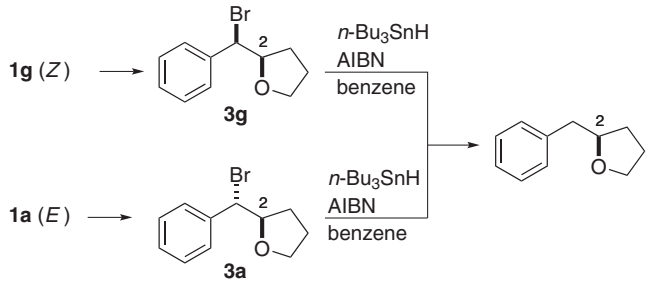
[†]The inclusion of 0.5 mol % of 2,6-di-*tert*-butyl-4-methoxyphenol as a radical inhibitor greatly reduced isomerization, however the resulting data was still not satisfactory.
[‡]The fractional order in Ph_3PS is not due to random error, multiple approaches to data analysis including nonlinear regression place an order of 1.0 outside of the 99% confidence limit.

TABLE 6. Catalyst Survey for Bromocycloetherification of Unconjugated Olefins



entry	cat.	R	Lewis base	substrate	t, h	er[a]	yield, %[b]
1	**2a**	2,4,6-*i*-Pr$_3$(C$_6$H$_2$)	Ph$_3$P=S	**1b**	12	65:35	n/d
2	**2a**	2,4,6-*i*-Pr$_3$(C$_6$H$_2$)	-	**1b**	39	85:15	89
3	**2a**	2,4,6-*i*-Pr$_3$(C$_6$H$_2$)	-	**1c**	40	82:18	50
4	**2g**	2,4,6-Cy$_3$(C$_6$H$_2$)	-	**1b**	40	85:15	83
5	**2g**	2,4,6-Cy$_3$(C$_6$H$_2$)	-	**1c**	40	86:14	79
6	**2h**	2,4,6-Ph$_3$(C$_6$H$_2$)	-	**1b**	40	53:47	30
7	**2h**	2,4,6-Ph$_3$(C$_6$H$_2$)	-	**1c**	15	56:44	75
8	**2i**	2,4,6-Me$_3$(C$_6$H$_2$)	-	**1b**	40	68:32	65
9	**2i**	2,4,6-Me$_3$(C$_6$H$_2$)	-	**1c**	40	80:20	76
10	**2j**	4-CF$_3$C$_6$H$_4$	-	**1b**	40	61:39	59
11	**2j**	4-CF$_3$C$_6$H$_4$	-	**1c**	40	70:30	64
12	**2k**	3,5-(CF$_3$)$_2$C$_6$H$_4$	-	**1b**	40	63:37	82
13	**2k**	3,5-(CF$_3$)$_2$C$_6$H$_4$	-	**1c**	40	64:36	75
14	**2l**	9-anthryl	-	**1b**	12	72:28	87
15	**2l**	9-anthryl	-	**1c**	40	72:28	74

[a]Determined by CSP-SFC analysis.
[b]Yield after chromatography, all reactions run on 0.1 mmol substrate.



Scheme 2. Correlation of the absolute configuration of *E* and *Z* olefin derived bromotetrahydrofurans.

(Table 3, entry 3 vs. Table 4, entry 3). This reversal of selectivity suggests that Ph$_3$P=S free reactions catalyzed by **2c** are in some way mechanistically different than those catalyzed by **2a-b** as well as those catalyzed by **2c** in the presence of Ph$_3$P=S.

The catalyst survey undertaken for the bromocyclizations of *E* and *Z* unconjugated olefins **1b-c** (Table 6) highlights several salient points. First, there is no consistent relationship between reaction rate and any other parameter, such as olefin geometry, catalyst identity, or enantioselectivity. Second, the relationship between catalyst structure and enantioselectivity is sufficiently different between cyclizations of *E* and *Z* olefins to justify screening them separately in the future.

Scope

The scope of the cooperatively catalyzed bromocycloetherification includes a range of *E* (**1a**, **1e-f**) and *Z* (**1g-m**) substituted 5-arylpentenols. (Table 5) The reaction is tolerant of a variety of substituted aryl groups, although strongly electron withdrawing substituents led to reduced enantioselectivity. Very high site selectivity favoring the tetrahydrofuran isomer (**3g-m**) was observed in the cyclization of *Z*-configured olefins **1g-m**.

The bromocyclizations of *E* and *Z* unconjugated olefins **1b-c** (Table 6) highlight a limitation of achiral Lewis base/chiral Brønsted acid cooperative catalysis, that is the rate of reaction catalyzed purely by the achiral Lewis base must be negligible. Unfortunately, the unconjugated olefins **1b-c** do not satisfy this criterion; they cyclize in the presence of only Ph$_3$P=S and NBS, resulting in greatly reduced enantioselectivity in cooperatively catalyzed reactions. (Table 6, entry 1) Olefins **1b-c** also display elevated reactivity in the presence of only NBS and acid **2a** and under such conditions improved enantioselectivity is observed at the cost of longer reaction times and lower conversion. (Table 6, entries 2–3) A survey of additional catalysts identified **2g** as a more selective catalyst for the cyclization of *Z* olefin **1c** (Table 6, entry 5), although the enantioselectivity observed in the cyclization of **1b-c** remains lower that that obtained in the cooperatively catalyzed cyclizations of all but the most electron-poor conjugated olefins.

Site Selectivity

The ratio of constitutional isomers produced in the reaction provides additional information about the reaction mechanism. Most clearly, the effect of electron-donating and withdrawing groups on site selectivity (Table 5, entries 2–3) is consistent with altering the degree of charge stabilization

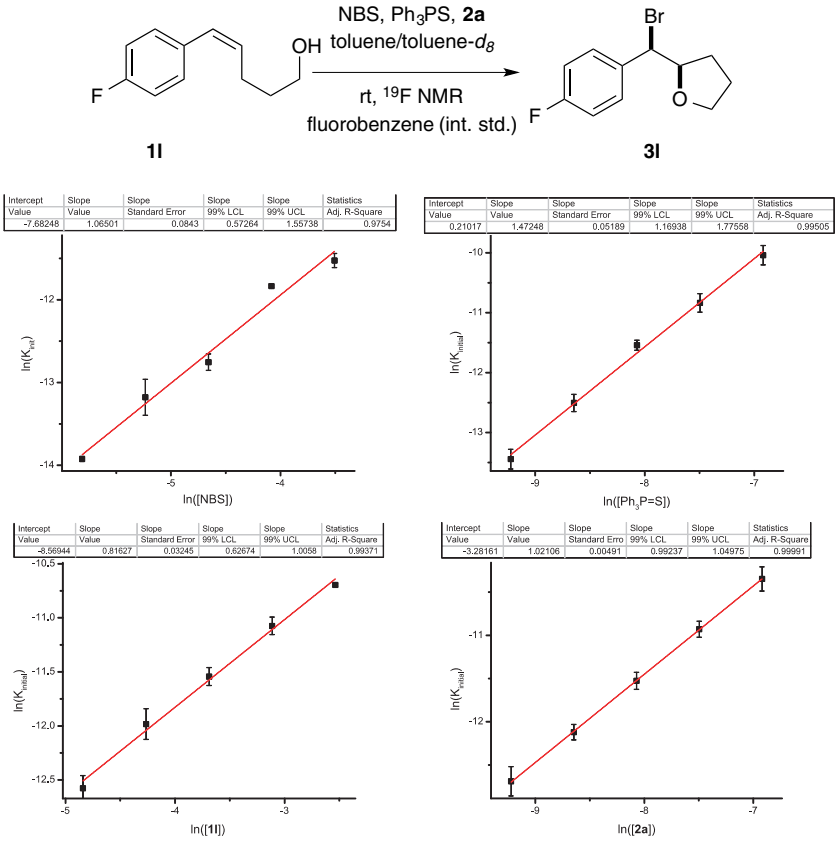


Fig. 2. Determination of partial orders in reaction components.

at the benzylic carbon of a bromiranium ion intermediate. The greater proportion of 5-*exo* cyclization observed in the presence of **2a** (Table 4, entry 1) indicates that the chiral acid must be present in the final cyclization step rather than simply providing stereocontrol in an initial, irreversible bromirenium ion delivery. This finding is consistent with the hypothesized intermediacy of a chiral ion pair. Conversely, the presence or absence of $Ph_3P{=}S$ in **2a** catalyzed cyclizations had negligible influence on the ratio of 5-*exo* to 6-*endo* cyclized products. Although it is tempting to suggest that $Ph_3P{=}S$ dissociates from the bromiranium ion prior to the cyclization step, a negative result is not conclusive in this case.

The *exo* and *endo* products **3a** and **4a** are produced with strikingly different levels of enantioselectivity, regardless of changes in catalyst structure or the presence or absence of $Ph_3P{=}S$. The available data is insufficient to distinguish all possible hypotheses; however the asymmetric environment produced by the chiral counterions renders all four product-generating transition states nonequivalent and therefore potentially unequal in energy. Therefore, the enantiomeric compositions of **3** and **4** are, in principle, expected to differ (Scheme 3). For example, if $k_{Re\text{–}endo}/k_{Re\text{–}exo} > k_{Si\text{–}endo}/k_{Si\text{–}exo}$ then an asymmetric transformation would occur, increasing the er of **3a** at the expense of lower er of **4a** and a lower ratio of **3a:4a**.[§] In other words, the minor enantiomer of the bromiranium ion undergoes mostly *endo* cyclization, while the major enantiomer undergoes both cyclization modes. Furthermore, as all cyclizations of **1a** in the absence of chiral acids were highly *endo* selective, any background reaction would also produce mostly **4a** in racemic form.

The racemization of bromiranium ions, or more precisely stereomutation of bromiranium phosphate ion pairs, by olefin-to-olefin transfer does occur in this catalyst system, however its contribution to the product composition at the optimal concentration (0.025 M) is small. A four-fold increase in reaction concentration led to a small decrease in the enantiomeric composition of **3a** (93:7 to 90:10) and a modest decrease in the proportion of *exo* cyclization (**3a:4a** 48:52 to 39:61). This result demonstrates that either olefin-to-olefin transfer is slower than but competitive with cyclization at 0.1 M, or the equilibrium ratio of bromiranium ions is favorably high.[¶] Under the optimal conditions of 0.025 M **1a**, associative transfer should be 16 times slower,[‖] and therefore the erosion of enantioselectivity should be negligible. A somewhat greater erosion of enantioselectivity was observed when Lewis base-free cyclizations were run at 0.1 M (95:5 to 88:12).

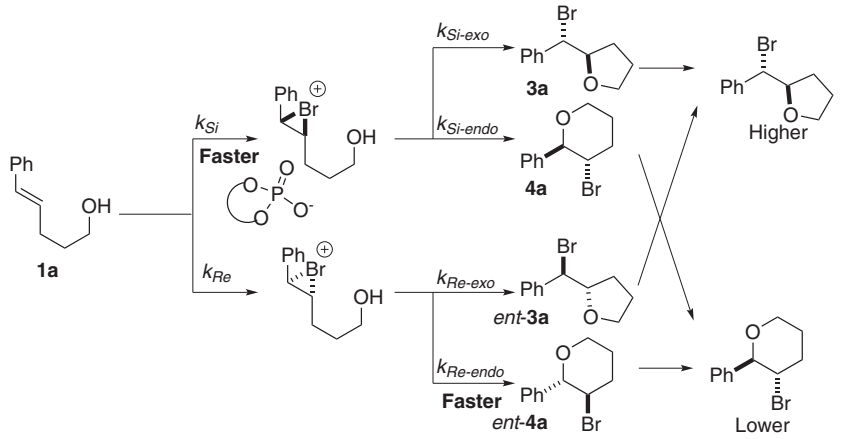
Origin of Enantioselectivity

The absolute configurations of the (*E*)- and (*Z*)-olefin derived products hold an important clue about the origin of

[§]This situation is analogous to the divergence of enantioselectivity for *cis* and *trans* epoxides seen in the Jacobsen epoxidation of (*Z*) alkenes.

[¶]In principle, the equilibrium ratio could be estimated by greatly increasing the reaction concentration. However, as discussed below, very high olefin concentrations promote radical processes that would likely complicate such an experiment.

[‖]This analysis makes the reasonable assumption that the associative bimolecular transfer is second order in olefin.



Scheme 3. Hidden asymmetric transformation of bromiranium ion intermediates

enantioselection. First, it is a critical point that the *Si* and *Re* designations for prochiral faces are defined with respect to a single trigonal carbon atom. Thus, an olefin with two prochiral, trigonal carbon atoms requires two such designations per face. Just as a molecule with two (*R*)-configured stereocenters is designated (*R*,*R*), the two trigonal carbons that constitute the (*Z*) olefin faces are (*Si*, *Si*) and (*Re*, *Re*) whereas the (*E*) olefin faces are (*Si*, *Re*) and (*Re*, *Si*). Therefore, the cyclization of (*E*) and (*Z*) isomers can be said to have the same (or opposite) sense of enantioselection only if one focuses on one trigonal carbon. This is not a consequence of nomenclature; rather the nomenclature is a consequence of the nature of the system. This catalyst system consistently delivers the bromirenium ion to the C(4)-*Si* face, regardless of whether that face is also C(5)-*Si* or C(5)-*Re* (Fig. 3). This outcome likely reflects which substituent on the double bond dominates the enantioface selection and that since the configuration of the tetrahydrofuran is conserved (Scheme 2, C(4) of **1**, C(2) of **3**), the dominant recognition feature is the tethered hydroxyl group. This sense of recognition is tentatively hypothesized to result from hydrogen bonding to the phosphate group, analogous to what is proposed in certain Mannich reactions (Fig. 3).[49,50]

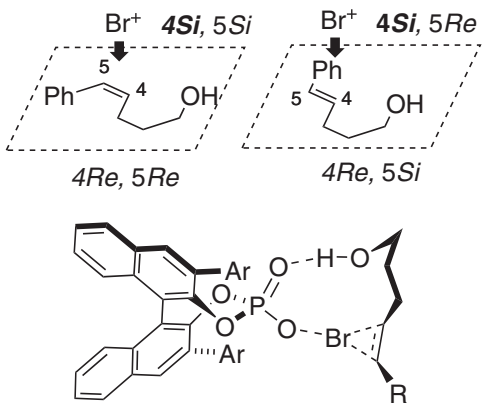


Fig. 3. Observed sense of enantioselectivity and postulated substrate-catalyst interaction

Kinetic Studies

The authors are keenly aware of the incomplete nature of the kinetic data presented here, however we believe that some conclusions may be drawn from this data despite its flaws. Furthermore, the nature of certain experimental difficulties provides additional insight into the behavior of the catalyst system.

Most importantly, the reaction displayed clean first order dependence on NBS and phosphoric acid **2a**. This behavior is consistent with the mechanism proposed in Scheme 1. Despite the lack of a definitive interpretation of the observed fractional orders in $Ph_3P{=}S$ and **1l** the existence of non-zero orders in $Ph_3P{=}S$ and **1l** is significant. The non-zero order in $Ph_3P{=}S$ demonstrates the intimate involvement of the phosphine sulfide in the catalytic cycle and supports the hypothesis that the two catalysts act cooperatively. The non-zero order in olefin **1l** excludes the possibility that the activation of NBS, or any step involving only the $Ph_3P{=}S$, NBS, and **2a**, is rate-determining. Rather, the rate determining step must be the formation of the bromiranium ion, nucleophilic opening of the bromiranium ion, or the subsequent proton transfer. All of these possibilities imply that one or more intermediates may be observable under appropriate conditions.

CONCLUSIONS

In conclusion, an enantioselective bromocycloetherification of 5-aryl-4-pentenols has been developed using a chiral Brønsted acid and an achiral Lewis base to provide good yield and enantioselectivity. High site selectivity was achieved by a combination of substrate and catalyst control. Cooperative catalysis was not applicable to more reactive, unconjugated 5-alkylpentenols due to the intervention of a purely Lewis base catalyzed pathway. However, 5-alkyl-4-pentenols could be cyclized productively in the absence of achiral Lewis bases, albeit with lower enantioselectivity.

The mechanism of enantioselective bromocycloetherification and the nature of the observed cooperative catalysis were explored by a ^{19}F NMR kinetic study. This study constitutes the first published attempt at a comprehensive kinetic analysis of an enantioselective bromocycloetherification reaction. The complete mechanism could not be elucidated due to the limitations of the experimental method chosen. Nevertheless, the

intimate involvement of $Ph_3P{=}S$ in the catalytic cycle was clearly demonstrated. Furthermore, no step prior to the entry of olefin **11** into the catalytic cycle can be rate determining. More definite conclusions will require reinvestigation of the system at lower temperature or the observation of a reactive intermediate.

ACKNOWLEDGMENT

We are grateful to the National Institutes of Health (R01 GM82535)) for financial support, and to Dr. D. Kalyani for assistance and helpful discussions. M.T.B. thanks the University of Illinois for a Seemon H. Pines Graduate Fellowship.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

LITERATURE CITED

1. Castellanos A, Fletcher SP. Current methods for asymmetric halogenation of olefins. Chem Eur J 2011;17:5766–5776.
2. Tan CK, Zhou L, Yeung YY. Organocatalytic Enantioselective Halolactonizations: Strategies of Halogen Activation. Synlett 2011;10:1335–1339.
3. Hennecke U. New Catalytic Approaches towards the Enantioselective Halogenation of Alkenes. Chem Asian J 2012;7:456–465.
4. Denmark SE, Kuester WE, Burk MT. Catalytic, Asymmetric Halofunctionalization of Alkenes- A Critical Perspective. Angew Chem Int Ed 2012;51:10938–10953.
5. Cardillo G, Orena M. Sterocontrolled cyclofunctionalizations of double bonds through heterocyclic intermediates. Tetrahedron 1990;46:3321–3408.
6. Montana AM, Batalla C, Barcia JA, Montana AM, Batalla C. Intramolecular Haloetherification and Transannular Hydroxycyclization of Alkenes. A Synthetic Methodology to Obtain Polycyclic Ethers and Amines. Curr Org Chem 2009;13:919–938.
7. Dowle MD, Davies DI. Synthesis and synthetic utility of halolactones. Chem Soc Rev 1979;8:171–197.
8. Ranganathan S, Muraleedharan KM, Vaish NK, Jayaraman N. Halo- and selenolactonisation: the two major strategies for cyclofunctionalisation. Tetrahedron 2004;60:5273–5308.
9. Gribble GW. The Diversity of Naturally Occurring Organohalogen Compounds. Chemosphere 2003;52:289.
10. Blunt JW, Copp BR, Munro MHG, Northcote PT, Prinsep MR. Marine natural products. Nat Prod Rep 2011;28:196.
11. Baskaran S, Islam I, Chandrasekaran S. A general approach to the synthesis of butanolides: synthesis of the sex pheromone of the Japanese beetle. J Org Chem 1990;55:891–895.
12. Broka CA, Lin YT. Synthetic studies on thyrsiferol. Elaboration of the bromotetrahydropyran ring. J Org Chem 1988;53:5876–5885.
13. Braddock DC, Bhuva R, Millan DS, Pérez-Fuertes Y, Roberts CA, Sheppard RN, Solanki S, Stokes ESE, White AJP. A biosynthetically-inspired synthesis of the tetrahydrofuran core of obtusallenes II and IV. Org Lett 2007;9:445–448.
14. Hennecke U, Müller CH, Fröhlich R. Enantioselective haloetherification by asymmetric opening of meso-halonium ions. Org Lett 2011;13: 860–863.
15. Denmark SE, Burk MT. Enantioselective Bromocycloetherification by Lewis Base/Chiral Brønsted Acid Cooperative Catalysis. Org Lett 2012;14:256–259.
16. Huang D, Wang H, Xue F, Guan H, Li L, Peng X, Shi Y. Enantioselective Bromocyclization of Olefins Catalyzed by Chiral Phosphoric Acid. Org Lett 2011;13:6350–6353.
17. Brown RS. Investigation of the early steps in electrophilic bromination through the study of the reaction with sterically encumbered olefins. Accounts Chem Res 1997;30:131–137.
18. Denmark SE, Burk MT, Hoover AJ. On the absolute configurational stability of bromonium and chloronium ions. J Am Chem Soc 2010;132:1232–1233.
19. Denmark SE, Burk MT. Lewis base catalysis of bromo- and iodolactonization, and cycloetherification. Proc Natl Acad Sci USA 2010;107:20655–20660.
20. Chen J, Zhou L, Tan CK, Yeung Y-Y. An Enantioselective Approach toward 3,4-Dihydroisocoumarin through the Bromocyclization of Styrene-type Carboxylic Acids. J Org Chem 2011;77:999–1009.
21. Zhou L, Tan CK, Jiang X, Chen F, Yeung Y-Y. Asymmetric bromolactonization using amino-thiocarbamate catalyst. J Am Chem Soc 2010;132:15474–15476.
22. Tan CK, Zhou L, Yeung Y-Y. Aminothiocarbamate-catalyzed asymmetric bromolactonization of 1,2-disubstituted olefinic acids. Org Lett 2011;13:2738–2741.
23. Murai K, Matsushita T, Nakamura A, Fukushima S, Shimura M, Fujioka H. Asymmetric Bromolactonization Catalyzed by a C3-Symmetric Chiral Trisimidazoline. Angew Chem Int Ed 2010;49:9174–9177.
24. Zhang W, Zheng S, Liu N, Werness JB, Guzei IA, Tang W. Enantioselective bromolactonization of conjugated (Z)-enynes. J Am Chem Soc 2010;132:3664–3665.
25. Pauling L. The Principles Determining the Structure of Complex Ionic Crystals. J Am Chem Soc 1929;51:1010–1026.
26. Coulomb C-A. Premier mémoire sur l'électricité et le magnétisme. Mém Acad R Sci Inst Fr 1785:569–577.
27. Denmark SE, Kalyani D, Collins WR. Preparative and mechanistic studies toward the rational development of catalytic, enantioselective selenoetherification reactions. J Am Chem Soc 2010;132:15752–15765.
28. Denmark SE, Kornfilt DJP, Vogler T. Catalytic Asymmetric Thiofunctionalization of Unactivated Alkenes. J Am Chem Soc 2011;133:15308–15311.
29. Akiyama T, Itoh J, Fuchibe K. Recent Progress in Chiral Brønsted Acid Catalysis. Adv Synth Catal 2006;348:999–1010.
30. Pihko PM. Recent Breakthroughs in Enantioselective Broensted Acid and Broensted Base Catalysis. ChemInform 2006;37:398–403.
31. Rueping M, Koenigs RM, Atodiresei I. Unifying metal and Brønsted acid catalysis–concepts, mechanisms, and classifications. Chem Eur J 2010;16:9350–9365.
32. Schenker S, Zamfir A, Freund M, Tsogoeva SB. Developments in Chiral Binaphthyl-Derived Brønsted/Lewis Acids and Hydrogen-Bond-Donor Organocatalysis. Eur J Org Chem 2011;2011:2209–2222.
33. Rueping M, Nachtsheim BJ, Ieawsuwan W, Atodiresei I. Modulating the Acidity-Highly Acidic Brønsted Acids in Asymmetric Catalysis. Angew Chem Int Ed 2011;50:6706–6720.
34. Christ P, Lindsay AG, Vormittag SS, Neudörfl J-M, Berkessel A, O'Donoghue AC. pKa values of chiral Brønsted acid catalysts: phosphoric acids/amides, sulfonyl/sulfuryl imides, and perfluorinated TADDOLs (TEFDDOLs). Chem Eur J 2011;17:8524–8528.
35. Klussmann M, Ratjen L, Hoffmann S, Wakchaure V, Goddard R, List B. Synthesis of TRIP and Analysis of Phosphate Salt Impurities. Synlett 2010;2010:2189–2192.
36. Cheng X, Goddard R, Buth G, List B. Direct Catalytic Asymmetric Three-Component Kabachnik–Fields Reaction. Angew Chem Int Ed 2008;47:5079–5081.
37. Amerego WLF, Chai CLL. Purification of Laboratory Chemicals. New York: Butterworth-Heinman; 2003.
38. Chen X-H, Zhang W-Q, Gong L-Z. Asymmetric Organocatalytic Three-Component 1,3-Dipolar Cycloaddition: Control of Stereochemistry via a Chiral Brønsted Acid Activated Dipole. J Am Chem Soc 2008;130:5652–5653.
39. Lu G, Birman VB. Dynamic Kinetic Resolution of Azlactones Catalyzed by Chiral Brønsted Acids. Org Lett 2010;13:356–358.
40. Cheon CH, Yamamoto H. A Brønsted Acid Catalyst for the Enantioselective Protonation Reaction. J Am Chem Soc 2008;130:9246–9247.
41. Nakashima D, Yamamoto H. Design of chiral N-triflyl phosphoramide as a strong chiral Brønsted acid and its application to asymmetric Diels-Alder reaction. J Am Chem Soc 2006;128:9626–9627.
42. Lacasse M-C, Poulard C, Charette AB. Iodomethylzinc Phosphates: Powerful Reagents for the Cyclopropanation of Alkenes. J Am Chem Soc 2005;127:12440–12441.

43. Desai AA, Huang L, Wulff WD, Rowland GB, Antilla JC. Gram-Scale Preparation of VAPOL Hydrogenphosphate: A Structurally Distinct Chiral Brønsted Acid. Synthesis 2010;2010:2106–2109.
44. Rauniyar V, Wang ZJ, Burks HE, Toste FD. Enantioselective Synthesis of Highly Substituted Furans by a Copper(II)-Catalyzed Cycloisomerization–Indole Addition Reaction. J Am Chem Soc 2011;133:8486–8489.
45. Akiyama T. Asymmetric-Synthesis Catalyst Based on Chiral Broensted Acid, Patent EP1623971A1, 2006.
46. Hatano M, Moriyama K, Maki T, Ishihara K. Which is the actual catalyst: chiral phosphoric Acid or chiral calcium phosphate? Angew Chem Int Ed Engl 2010;49:3823–3826.
47. Zhou L, Chen J, Tan CK, Yeung Y-Y. Enantioselective Bromoaminocyclization Using Amino-Thiocarbamate Catalysts. J Am Chem Soc 2011;133:9164–9167.
48. Chen F, Tan CK, Yeung Y-Y. C_2-Symmetric Cyclic Selenium-Catalyzed Enantioselective Bromoaminocyclization. J Am Chem Soc 2013;135:1232–1235.
49. Akiyama T, Itoh J, Yokota K, Fuchibe K. Enantioselective Mannich-type reaction catalyzed by a chiral Brønsted acid. Angew Chem Int Ed 2004;43:1566–1568.
50. Uraguchi D, Terada M. Chiral Brønsted acid-catalyzed direct Mannich reactions via electrophilic activation. J Am Chem Soc 2004;126: 5356–5357.