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Enantioselective Bromocycloetherification by Lewis Base/Chiral Brønsted Acid Cooperative Catalysis

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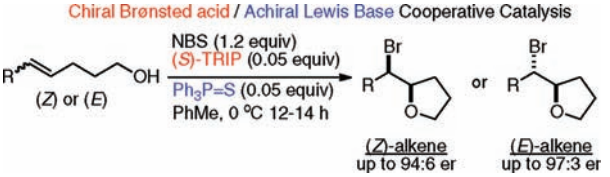
ABSTRACT



A binary catalyst system for the enantioselective bromocycloetherification of 5-arylpentenols is described. The combination of an achiral Lewis base and a chiral Brønsted acid affords good enantioselectivities for the cyclization of *Z* configured 5-arylpentenols to form bromomethyltetrahydrofurans. The constitutional site selectivity is highly dependent upon the aromatic substituent and the configuration of the double bond.

Bromocycloetherification of olefins is a valuable synthetic transformation, with proven application to the synthesis of biologically relevant molecules.[1] The bromo ether products can be useful synthetic intermediates[1a] or natural product targets themselves.[1b,c,h,i] Surprisingly, methods for the enantioselective synthesis of bromo ethers are notably absent. The development of such methods presents a particular challenge, due in part to the propensity of the intermediate bromonium ions to racemize by transfer between alkenes at rates competitive with nucleophilic capture.[2] One strategy to address this problem is the use of a chiral catalyst that remains associated with the intermediate bromonium ion until its ultimate irreversible capture. In this scenario, the catalyst is able to effect stereocontrol even with bromonium ion exchange, because the transition state structures for capture are diastereomeric. In addition, such a catalyst might also slow the exchange process by steric encumbrance or by reducing the coordinative unsaturation of the bromine atom.

In the related bromolactonization and bromosulfonamidocylization reactions, several chiral catalysts containing Lewis basic nitrogen functional groups are able to provide high enantioselectivity.[3,4] These successes have been ascribed in part to the formation of strong hydrogen bonds or tight ion pairs between the carboxylate and sulfonamide groups. However, these catalyst systems are not effective in enantioselective bromoetherification reactions.

Recent studies from these laboratories demonstrated that Lewis basic catalysts do indeed remain associated with the bromonium ion as reflected in the dependence of

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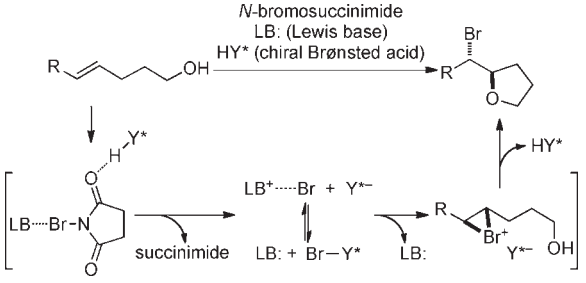
constitutional isomer ratios on catalyst structure.[5] Although this association was demonstrated for bromolactonizations, no evidence for association was found in bromoetherifications. The absence of a positive result was inconclusive in this case; however all of our attempts to develop a chiral Lewis base catalyst for bromoetherification failed to produce any level of enantioselectivity. Thus, another approach that would reduce such uncertainties was desired.

A catalyst that is ion paired with the bromonium ion is guaranteed by electroneutrality to remain associated (in low dielectric solvents) and to be carried through any olefin-to-olefin transfer. This concept was validated recently by the demonstration of moderate enantioselectivity in the opening of *meso* bromonium ions in the presence of a chiral sodium phosphate.[6] Moreover, related studies in these laboratories demonstrated that the rates of Lewis base catalyzed seleno-, thio-, and bromocycloetherification were greatly enhanced by the addition of Brønsted acids.[5,7] We hypothesized that, as a consequence of assisting in the Lewis base activation of the bromine source, the conjugate base of a sufficiently strong Brønsted acid would replace succinimide as the counterion of the bromonium intermediate (Scheme 1). If the Brønsted acid were chiral, it could influence the stereochemical course at every step of the mechanism, regardless of any known or as yet unknown racemization pathways. The pK_a and general applicability of BINOL-derived phosphoric acids made them attractive candidates to initiate this study.[8]

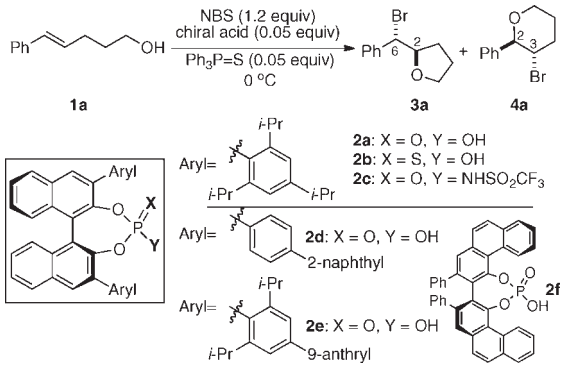
Scheme 1



The previous demonstration of Lewis base/Brønsted acid cocatalysis in bromoetherification involved the cyclization of pentenol **1a** in the presence of the Lewis base $Ph_3P{=}S$. Therefore, to test the potential of chiral Brønsted acids as cocatalysts with Lewis bases, **1a** was chosen as a representative substrate and a variety of chiral phosphoric acid derivatives (**2a**–**f**) were surveyed for their effect on bromocycloetherification in the presence of $Ph_3P{=}S$ (Table 1). Although the expected product of 6-*endo* cyclization (**4a**) was formed with negligible enantioselectivity, the product of anti-Markovnikov 5-*exo* cyclization (**3a**) was formed with higher enantioselectivity in all cases.[9]

As **3a** is ordinarily a minor product, it was fortunate that the most enantioselective catalyst (**2a**, entry 1) also altered the isomer ratio, increasing the proportion of **3a**, albeit to only a 48:52 mixture. Modifying the acidic functional group (entries 2–3) or the chiral moieties (entries 4–6) reduced selectivities and, in some cases, rates (entries 2, 5). Only modestly reduced selectivities were observed at higher concentration (entry 7). More substantial reductions in enantioselectivity occurred when solvents more polar than toluene were used (entries 8–9).

Table 1. Optimization of Bromocycloetherification Conditions



entry	cat.	solvent	concn (M)	t (h)	**3a:4a**[a]	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** vs HC(2) of **4a**. [b] Yield after chromatography; all reactions run on 0.1 mmol of substrate.

To better understand the selectivity of this cyclization and determine its potential utility, a series of substrates were chosen to evaluate the effects of sterically and electronically diverse aryl groups, as well as olefin configuration. The effect of electronic perturbations was strong, particularly among the (*E*)-configured substrates. A moderately more electron-rich aryl group unsurprisingly reduced the proportion of 5-*exo* cyclization (entry 2),

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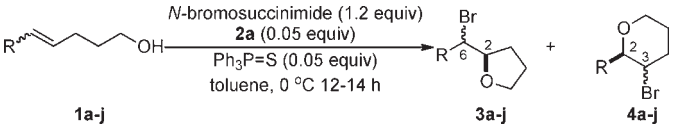
(9) Control experiments showed that, in the absence of $Ph_3P{=}S$ and the presence of 10 mol% of **2a**, the cyclization of **1a** was incomplete after 24 h (0.025 M, toluene, 0 °C). The **3a:4a** ratio and the er of **3a** were unchanged. The exact extent of conversion showed a strong dependence on the batch of catalyst used. No batch dependence was observed in the presence of $Ph_3P{=}S$.

Table 2. Scope of Bromocycloetherification[a]



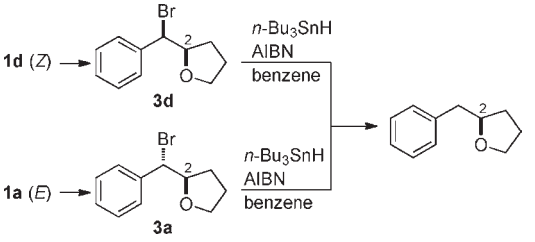
entry	R	products	3/4[b]	er (3)[c]	yield (3), %[d]	er (4)	yield (4), %
1	(*E*)-C_6H_5	**3a**, **4a**	45:55	93:7	77[e,f]	58:42	
2	(*E*)-4-$CH_3C_6H_4$	**3b**, **4b**	37:63	97:3	28	65:35	67
3	(*E*)-4-$CF_3C_6H_4$	**3c**, **4c**	86:14	85:15	43	65:35	12[e]
4	(*Z*)-C_6H_5	**3d**	>95:5	91:9	77	n/d	
5	(*Z*)-2-naphthyl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

[a] All reactions run at 0.025 M on 1.0 mmol of substrate. [b] Determined by ^{1}H NMR integration of signals for HC(6) of **3** vs HC(2) of **4**. [c] Determined by CSP-SFC. [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 homogeneous material.

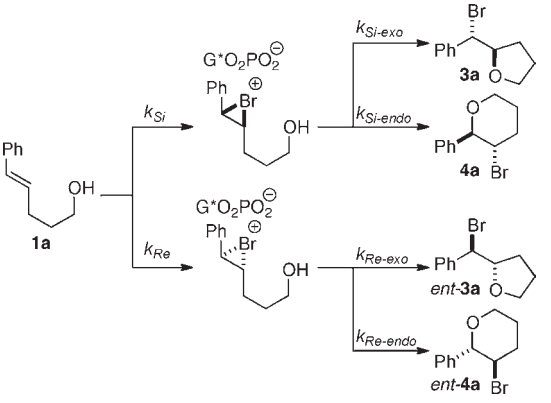
although enantioselectivity increased. Conversely, substitution with an electron-withdrawing group favored the formation of *exo* cyclized product **3c** but with reduced enantioselectivity (entry 3). More encouragingly, the cyclization of (*Z*)-configured olefins occurred with uniformly high *exo* selectivity (entries 4−10). Enantioselectivity was only slightly reduced compared to (*E*)-configured alkenes (entries 1 and 4, 2 and 8), and varying the steric demands of the substrate (entries 5−8) had no clearly discernible effect. Electron-withdrawing groups again reduced enantioselectivity (entries 9−10). The absolute configuration of the (*Z*)-olefin derived products was established by single crystal X-ray diffraction analysis of **3e**[10] and was then correlated with that of the (*E*)-olefin derived products by reductive dehalogenation of **3a** and **3d**. The resulting samples of 2-benzyltetrahydropyran were of identical configuration judged by optical rotation and CSP-SFC analysis (Scheme 2). The configurations of **4a**−**j** are assumed based on this information.

The production of constitutional isomers of different composition provides a few intriguing clues about the reaction mechanism. First, the effect of electron-donating and -withdrawing groups on site selectivity (Table 2, entries 2−3) shows the dependence expected from altering the degree of charge stabilization at the benzylic carbon of a bromonium ion intermediate. The increased amount of the tetrahydrofuran isomer observed in the presence of **2a** (Table 1, entry 1) shows that the chiral acid is present in the final cyclization step and is not merely controlling the initial bromine delivery. The differences in enantioselectivity between **3a** and **4a** are striking and are visible to varying degrees in all of the catalysts surveyed. A number of explanations are possible given the limited data;

Scheme 2



Scheme 3

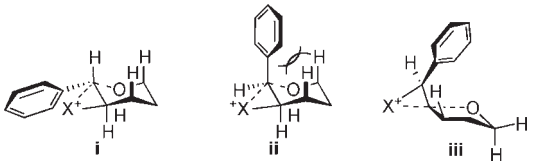


(10) The crystallographic coordinates of **3e** have been deposited with the Cambridge Crystallographic Data Centre; Deposition No. 831569. These data can be obtained free of charge via from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; via www.ccdc.cam.ac.uk/conts/retrieving.html or deposit@ccdc.cam.ac.uk.

however it should be noted that the presence of the chiral counterion means that all four product-generating transition state structures are unequal in energy and therefore *a priori* the enantiomeric composition of **3** and **4** need not be equal (Scheme 3). For example if $k_{Re-endo}/k_{Re-exo} > k_{Si-endo}/k_{Si-exo}$ then kinetic resolution would occur, increasing the er of **3a** at the expense of lower er of **4a** and a lower ratio of **3a:4a**.[11] Any background reaction would also produce mostly racemic **4a**.

The greater proportion of exo cyclization of *Z* alkenes compared to *E* alkenes is a property of the substrate, independent of the selectivity of the catalyst system. This phenomenon has been observed in many different electrophile-initiated olefin cyclization reactions[3b,5,12] and epoxide opening reactions.[13] The transition structure for 6-*endo* cyclization of *Z* alkenes, **ii**, experiences unfavorable 1,3-diaxial interactions that are absent in the 5-*exo* cyclization transition structure **iii** as well as in the 6-*endo* transition structure for *E* alkenes (Scheme 4).

Scheme 4



The racemization of bromonium ions by olefin-to-olefin transfer is not important in the current catalyst system. A 4-fold increase in reaction concentration led to a negligible decrease in the enantiomeric composition of **3a** (93:7 to 90:10). This drop suggests that olefin-to-olefin transfer may be occurring to some extent, but either it is substantially slower than cyclization at 0.1 M or the equilibrium ratio of bromonium ions is favorably high. All other experiments were conducted at 0.025 M, where associative transfer should be 16 times slower, and the erosion of enantioselectivity should be negligible.

Comparing the absolute configurations of the (*E*)- and (*Z*)-derived products offers a clue about the origin of enantioselection. 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*). 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 catalyst system consistently delivers Br^+ to the C(4)-*Si* face, regardless of whether that face is also C(5)-*Si* or C(5)-*Re* (Figure 1). We hypothesize that this outcome reflects which substituent on the double bond dominates the chiral recognition 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[14] (Figure 1).

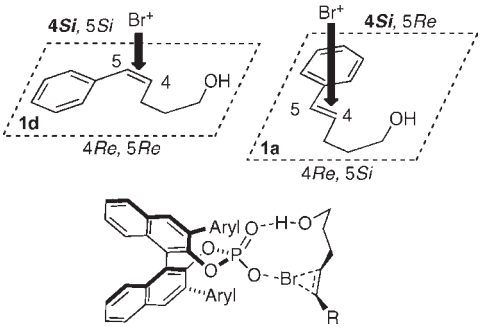


Figure 1. Absolute sense of enantioselectivity and postulated substrate−catalyst interaction.

In conclusion, an enantioselective bromocycloetherification of 5-arylpentenols has been developed using a chiral Brønsted acid and an achiral Lewis base to provide good yield and enantiomeric induction. High site selectivity was achieved by a combination of substrate and catalyst control. Further studies to expand the scope, improve the selectivity, and understand the mechanism of this transformation are ongoing.[15]

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Supporting Information Available. Full experimental procedures, analyses, characterization data, and crystallographic data for **3e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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