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Enantioselective Halocyclization Using Reagents Tailored for Chiral Anion Phase-Transfer Catalysis

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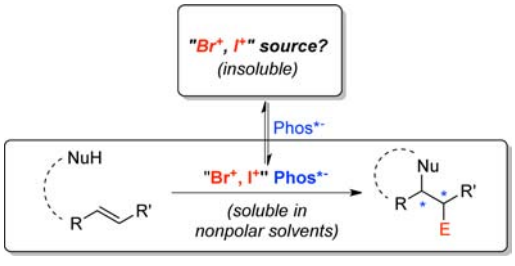
Supporting Information

ABSTRACT: A chiral anion phase-transfer system for enantioselective halogenation is described. Highly insoluble, ionic reagents were developed as electrophilic bromine and iodine sources, and application of this system to *o*-anilidostyrenes afforded halogenated 4*H*-3,1-benzoxazines with excellent yield and enantioselectivity.

The enantioselective synthesis of halogenated compounds is an important target for the synthetic community.[1] In particular, electrophilic halogenation of alkenes offers direct access to bifunctionalized molecules with the concomitant formation of up to two stereocenters. There are, however, only a limited number of approaches for the induction of enantioselectivity in this class of electrophilic addition reactions, especially in a catalytic sense.[2] In addition to transition metal-catalyzed alkene halogenations,[3] organocatalytic methods have recently been reported using modified cinchona alkaloids,[4] aminourea[5] and bis(amidine) derivatives,[6] C_3-symmetric imidazoline derivatives,[7] and phosphoric acids[8] as catalysts. While high enantioselectivities can been achieved, low temperatures and/or high catalyst loading are often required to overcome the uncatalyzed background reaction.

Very recently, our laboratories reported an enantioselective fluorocyclization of olefins using *chiral anion phase-transfer catalysis*,[9] (Scheme 1) by taking advantage of the low solubility of the cationic fluorinating reagent Selectfluor in nonpolar solvents. Exchange of the tetrafluoroborate anions from the reagent with lipophilic chiral phosphate anions brings the active electrophile into solution as a chiral ion pair, resulting in efficient, chemo- and enantioselective fluorination of the substrate at or near room temperature. Notably, due to the insoluble nature of the fluorinating reagent, nonselective background reaction is minimal. We hypothesized that other electrophilic functionalization reactions should be amenable to chiral anion phase-transfer catalysis, thereby extending the applicability of the concept to a general approach for catalysis. Toward this goal, novel electrophilic reagents needed to be developed where insolubility, normally detrimental, is a required feature. We report herein the synthesis of a new brominating reagent (**1d**) for use in anionic phase-transfer bromination, as well as an analogous reagent (**5d**) for iodination.

Scheme 1. Application of Chiral Anion Phase Transfer Catalysis to Bromo- And Iodocyclization[a]



[a]Phos*$^-$ = chiral phosphate anion, E = Br or I.

Given the lack of methods for enantioselective synthesis of 4*H*-3,1-benzoxazines,[10] we chose the 6-*exo*-trig cyclization of amide **3a** to examine the utility of the cationic brominating reagents in chiral anion phase-transfer catalysis. (Bis)amine-halonium reagents have long been known and employed as electrophilic halonium sources in reactions with alkenes;[11] however, attempts to use the known oligomeric DABCO-bromine complex or bis(*sym*-collidine)bromine(I) hexafluorophosphate under chiral anion phase-transfer conditions resulted in rapid conversion to **4a** with poor enantioselectivity, reflecting a significant amount of uncatalyzed background reaction (Table 1, entries 1 and 2).[12]

The lack of success using these monocationic reagents led us to consider the monoalkylated-DABCO scaffold as a starting point, in analogy to Selectfluor, for the generation of more highly charged reagents for phase-transfer bromination. To that end, treatment of monoalkyl DABCO tetrafluoroborates with elemental bromine in the presence of $AgBF_4$ resulted in the formation of tricationic brominating reagents **1**, which could be isolated by precipitation (Figure 1). These brominating reagents could be stored in an airtight vial at −20 °C for at least a month without deterioration. Moreover, **1a** was found to mediate the bromocyclization of amide **3a** almost instantaneously under homogeneous conditions in acetonitrile. In contrast, **1a** was insoluble in organic solvents of low or moderate polarity, including hexanes, toluene, and dichloromethane, and exposure of amide **3a** to **1a** in toluene did not result in significant formation of the cyclized product. Encouragingly, when **3a** was combined with **1a** in the presence of chiral phosphoric acid **2a** (10 mol %) and Na_2CO_3, desired product was obtained in moderate enantioselectivity (Table 1, entry 3).

With these promising results, we sought to optimize the structure of the brominating reagent. To increase the phase-

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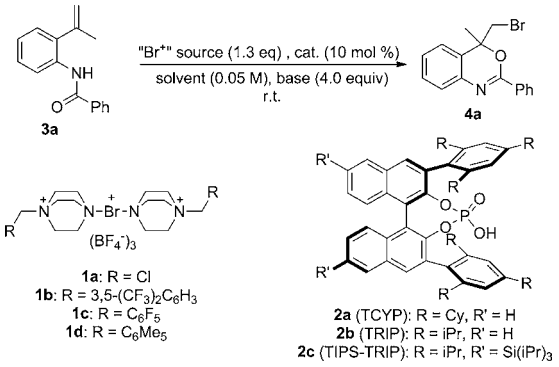
Table 1. Optimization of Enantioselective Bromocyclization



entry	"Br+"	cat.	solv	base	time	conv.[a]	ee[b]
1	DABCO·2Br$_2$	**2a**	toluene	Na_2CO_3	0.5 h	100%	39%
2	(coll)$_2$Br$^+$PF$_6^-$	**2a**	toluene	Na_2CO_3	0.5 h	100%	1%
3	**1a**	**2a**	toluene	Na_2CO_3	24 h	82%	59%
4	**1b**	**2a**	toluene	Na_2CO_3	24 h	67%	70%
5	**1c**	**2a**	toluene	Na_2CO_3	24 h	30%	20%
6	**1d**	**2a**	toluene	Na_2CO_3	24 h	67%	83%
7	**1d**	**2a**	*p*-xylene	Na_2CO_3	16 h	62%	86%
8	**1d**	**2a**	xyl/hex (1:1)[c]	Na_2CO_3	16 h	90%	89%
9	**1d**	**2a**	hexanes	Na_2CO_3	16 h	21%	60%
10	**1d**	**2b**	xyl/hex (1:1)[c]	Na_2CO_3	17 h	90%	89%
11	**1d**	**2c**	xyl/hex (1:1)[c]	Na_2CO_3	17 h	90%	91%
12	**1d**	**2c**	xyl/hex (1:1)[c]	Na_2CO_3[d]	17 h	100%	90%
13	**1d**	**2c**	xyl/hex (1:1)[c]	Na_3PO_4[d]	17 h	100%	92%
14	**1d**[e]	**2c**[f]	xyl/hex (1:1)[c,g]	Na_3PO_4[d]	4 h	100%[h]	94%

[a]Estimated from ^{1}H NMR of the crude product. [b]Determined by chiral HPLC. [c]*p*-Xylene and hexanes. [d]Finely ground and dried overnight. [e]Reprecipitated from $MeNO_2$. [f]5 mol %. [g]0.025 M. [h]82% isolated yield.

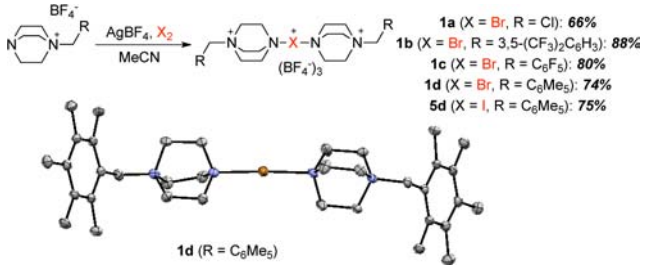


Figure 1. Synthesis of cationic halogenating reagents and ORTEP diagram of **1d** (ellipsoids at 50% probability level, counterions and H's omitted for clarity).

transfer efficiency and electrophilicity of the brominating reagent, we synthesized the more lipophilic and electron-deficient reagent **1b**. Indeed, treatment of **3a** with **1b** resulted in product formation in improved enantioselectivity. While a further increase in electron-deficiency (**1c**) was detrimental, the use of more lipophilic reagent **1d** afforded **4a** with increase in enantioselectivity to 83% ee (Table 1, entries 3−6). A decrease in the polarity of the solvent to 1:1 *p*-xylene/hexanes resulted in better conversion and enantioselectivity (entries 7, 8). While commercially available TRIP (**2b**) catalyzed the reaction with nearly identical efficiency and selectivity, a more highly lipophilic phosphoric acid with 6,6′-TIPS substituents (**2c**, TIPS-TRIP) resulted in further improvements (entries 10, 11). Use of **1d** reprecipitated from nitromethane (see Supporting Information) shortened reaction time without affecting enantioselectivity, and optimization of base and concentration improved enantioselectivity to 94% ee in 82% isolated yield with no loss in enantioselectivity observed when catalyst loading was decreased to 5 mol % (entry 12−14).

With optimized reaction conditions in hand, we explored the substrate scope of our bromination reaction (Table 2). We were pleased to find good tolerance for substituents of varying steric bulk at the α position of the styrenyl system. Potentially problematic functional groups including a silyl ether (**4e**), an unprotected alcohol (**4f**), and a tertiary amine (**4o**) did not significantly impact the reactions. Notably, a substrate with a pyridyl backbone gave desired product in excellent yield and enantioselectivity (**4n**). Electron-withdrawing (**4q**) and electron-donating (**4r**) substitution at the *para* position, as well as *ortho* substitution (**4p**) of the benzamide aryl were tolerated. A slight modification of reaction conditions also afforded benzoxazine **4s** with *t*-butyl substitution at the 2-position. Gratifyingly, heteroarylamides (**3t**−**3v**) were also suitable substrates under standard reaction conditions. These examples, all run at room temperature without precaution to exclude air and moisture, demonstrate the mildness and operational simplicity of the reaction conditions.

We next explored substrates bearing substitution at both the α and the β positions of the styrenyl system. In the event, subjection of these substrates to standard reaction conditions furnished desired products in excellent yields and enantioselectivities. In all cases, only one diastereomer was observed in the ^{1}H NMR of the crude product. Notably, substituents of varying steric and electronic properties were tolerated (**4g**−**4i**). For example, enantioenriched *gem*-bromochloro adduct **4h** was formed in 88% yield and 96% ee from the corresponding vinyl chloride. Cyclic substrates, including conjugated (**4k**) and

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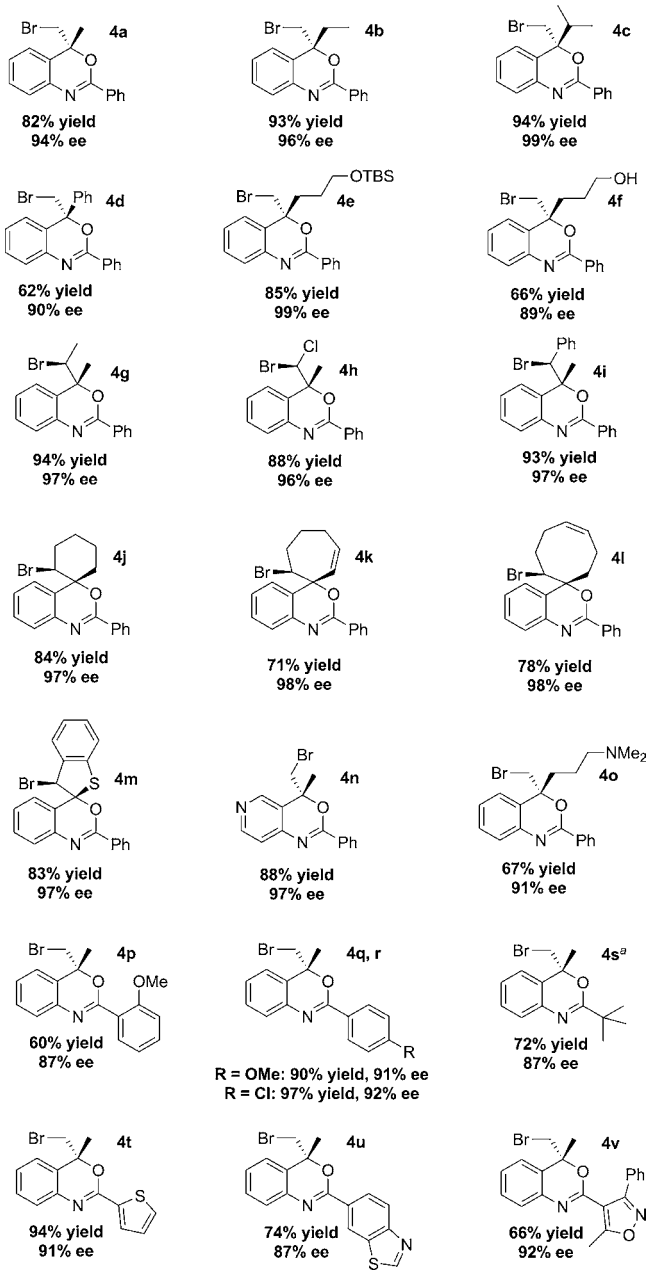
Table 2. Scope of Enantioselective Bromocyclization

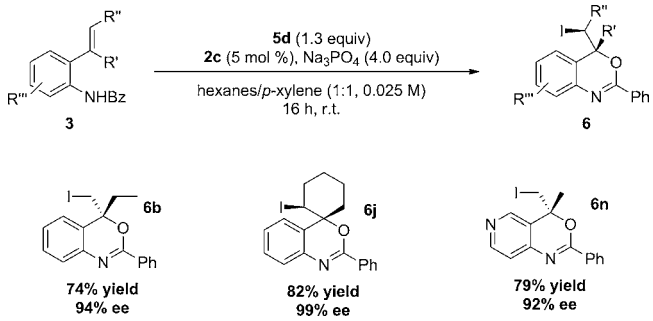


[a]Conditions: **1d** (1.3 equiv), TIPS-TRIP (5 mol %), Na_3PO_4 (4.0 equiv), *p*-xylene/hexanes (1:1, 0.025 M), 4 h, rt. Relative and absolute stereochemistry assigned by analogy to that of **4l**, determined by X-ray crystallography. Yields after chromatographic purification and enantioselectivities determined by chiral HPLC. [b]1.5 equiv **1d** in mesitylene/hexanes (1:1).

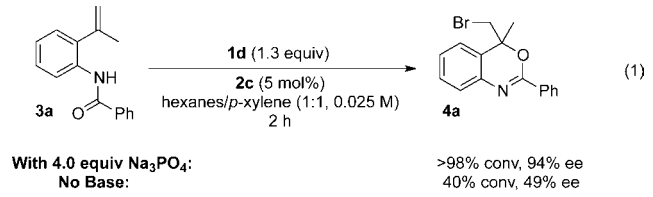
remote dienes (**4l**), afforded desired product with excellent chemo- and enantioselectivity. Similarly, benzothiophene substituted substrate **3m** provided dearomatized product in excellent yield and enantioselectivity. These results highlight the extraordinary tolerance of this catalyst system for substitution on the alkene moiety.

We speculated that enantioselective iodination might also be achieved through an analogous reagent. Thus, we prepared iodination reagent **5d** as a further test of the robustness and generality of the anionic phase-transfer approach. Through a procedure nearly identical to the one used in the preparation of **1d**, reagent **5d** was obtained as an off-white solid of similar stability. We were pleased to find that treatment of **3b**, **3j**, and **3n** with **5d** (in place of **1d**) for 16 h without otherwise modifying reaction conditions furnished the corresponding iodinated products **6b**, **6j**, and **6n** in similarly high yields and enantioselectivities (Scheme 2).

Scheme 2. Enantioselective Electrophilic Iodocyclization



To provide some evidence that the reaction is proceeding through the proposed anionic phase-transfer process, we subjected **3a** to optimized reaction conditions but in the absence of base, which is required for the formation and regeneration of the chiral phosphate anion. After 2 h reaction time, the product was obtained in moderate conversion. The enantioselectivity observed, however, was greatly diminished (eq 1). On the other hand, use of base alone without **2c** did not



(1)

result in rate acceleration. Thus, the observed rate and enantioselectivity enhancement in the presence of base cannot be attributed to deprotonation of the amide substrate. These experiments strongly suggest that the chiral phosphate *anion* is the active catalytic species in our optimized system (and not the phosphoric *acid*). Moreover, a nonlinear effect study (see Supporting Information) showed significant deviation from linearity. This study, combined with the observation that monoalkyl DABCO-derived reagents provide products with increased enantioselectivity, suggests that the occurrence of highly charged intermediates may be advantageous for enantioinduction in chiral phosphate phase-transfer catalysis.

In summary, an anionic phase-transfer protocol for enantioselective bromination was developed and applied to the 6-*exo*-trig bromocyclization of styrenyl amides. To realize this system, an insoluble cationic brominating reagent was developed, with optimal results delivered with 6,6′-silyl substituted TRIP phosphoric acid as an anionic phase-transfer precatalyst. Enantioselective iodination was achieved with an analogous cationic iodinating reagent. The resulting methods furnished a broad range of enantioenriched 4*H*-3,1-benzoxazines under mild and operationally simple reaction conditions. The highly insoluble nature of the halogenating reagents in nonpolar solvents effectively suppressed the noncatalyzed background reaction and led to halocyclization reactions with excellent enantioselectivity, even at low catalyst loading. For

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example, reaction of cyclohexenyl substrate **3j** with **1d** with catalyst loading reduced of 0.1 mol % afforded the desired product in 87% yield and 90−93% ee.[13] These methods extend the utility of the chiral anion phase-transfer approach and serve as a starting point for the design of other reagents for use in this paradigm.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data for new compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(13) Freshly dried and powdered base and vigorous stirring was required to achieve high enantioselectivities with 0.1 mol % catalyst loading. The reported range represents results obtained from 4 experiments.

■ NOTE ADDED AFTER ASAP PUBLICATION

This paper was published ASAP on July 25, 2012. Due to a production error, Table 2 was incorrect. The revised version was posted on July 26, 2012.