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Achiral Counterion Control of Enantioselectivity in a Brønsted Acid-Catalyzed Iodolactonization

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Supporting Information

ABSTRACT: Highly enantioselective halolactonizations have been developed that employ a chiral proton catalyst–*N*-iodosuccinimide (NIS) reagent system in which the Brønsted acid is used at catalyst loadings as low as 1 mol %. An approach that modulates the *achiral* counterion (equimolar to the *neutral chiral ligand*–proton complex present at low catalyst loadings) to optimize the enantioselection is documented for the first time in this transformation. In this way, unsaturated carboxylic acids are converted to γ-lactones in high yields (up to 98% ee) using commercially available NIS.

The alkene halocarboxylation reaction was resistant to the application of proven approaches to enantioselective catalysis since its early realization, a shortcoming both unfortunate and notorious considering the practical value of the ester/lactone products.[1] Sporadic indications that enantioselective halogenative addition reactions (e.g., the alkene iodoacyloxylation outlined in Figure 1) are possible surfaced

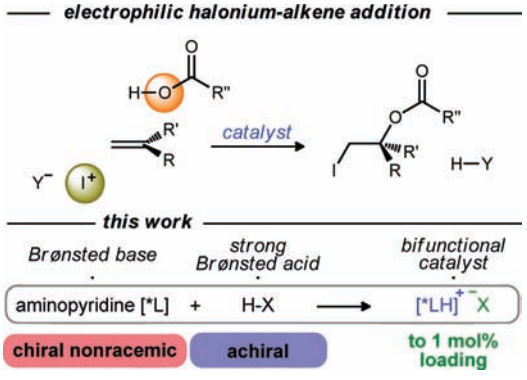

Figure 1. Overview of alkene haloacetoxylation using electrophilic halogen and the catalyst design used in this work.

in 2010, while careful mechanistic studies[2−4] outlined obstacles to significant, if not practically meaningful, enantioselectivity.[5−7] Within the broader topic of alkene halofunctionalization, the earliest strategies centered on Lewis base-promoted halogenation strategies, such as chiral amine[8,9] and phosphoramidite[10] methods for halolactonization and polyene cyclization, respectively. A strategically complementary strategy involves Lewis acid activation of the halogen donor: haloamination of a chalcone alkene[11] and enolsilane chlorination.[12] Other approaches have also been investigated: phase-transfer catalysis[13] for iodolactonization; thiocarbamate/amine-catalyzed bromolactonization[14] and aminobromination;[15] chiral amine-catalyzed chlorolactonization,[16] bromolactonization,[17] iodolactonization,[18,19] chloroamination,[20] and fluoroetherification;[21] and other transformations based on enantioselective alkene halogenation.[22−24]

Success with enantioselective iodolactonization has been limited to transformations with low enantioselection and/or regioselection.[8,13] The highest levels of enantioselection have been achieved using cryogens (−80 °C) and a noncommercial halogen source.[19] Our interest resided in a strategy of direct Brønsted acid halonium activation. Furthermore, the use of a polar ionic hydrogen-bond catalyst, if effective, might be optimized by manipulation of the *achiral* counterion rather than restructuring the chiral ligand to optimize the reactivity and enantioselectivity.[25] Bis(amidine) (BAM)-based protic acid complexes have been used extensively as bifunctional catalysts for nitroalkane addition reactions but not elsewhere.[26] The polar ionic hydrogen bond (BAM–H^+) formed from the neutral ligand provides an achiral counterion that can be used to modify the catalyst's reactivity directly (Figure 2).[27] We report the discovery of highly enantioselective, chiral proton-catalyzed iodolactonizations that illustrate the unique and helpful role of an achiral counterion. Furthermore, a new stilbenediamine-derived BAM provided a significant increase in enantioselection relative to the use of a cyclohexanediamine backbone.

Initial attempts to effect the transformation focused on δ-unsaturated acid **3** and investigated both the free base (**1**) and the triflic acid salt (**1**·HOTf) of the selected BAM catalyst (eq 1 in Figure 2). Low levels of enantioselection were observed with the free base (19% ee), while slightly higher levels were observed using the triflic acid salt (46% ee). Evidence of ligand iodination at the 3 and 3′ positions was observed, as expected, but control reactions with this derivative revealed essentially identical behavior as the protocol implemented here, which employs the des(iodo) ligand as the reagent for operational convenience. Therefore, all of the reactions were prepared with an excess of *N*-iodosuccinimide (NIS) equivalent to the catalyst loading to account for bis(iodination) of the ligand.

The effect of the counterion on the reactivity and selectivity was examined by the use of different achiral Brønsted acid sources, focusing on those providing a range of steric and

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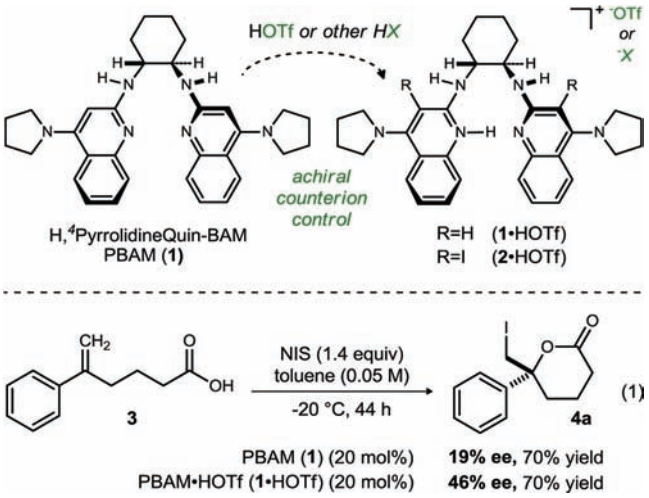
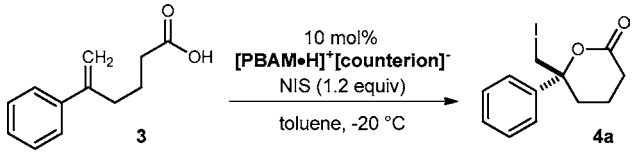
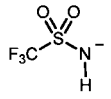
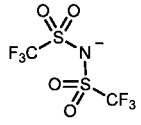
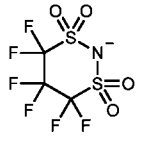


Figure 2. Enantioselective iodolactonization: initial experiments to explore the relationship between catalyst composition and stereoselection.

electronic variation (Table 1). Sulfonic acids generally increased the enantioselection with acid strength (Table 1, entries 1–5). The enantiomers of camphorsulfonate provided essentially identical outcomes (29% ee; Table 1, entries 2 and 3). The selectivity trend may illustrate the need for a more dissociated counterion, favoring a more electrophilic catalyst form.[28–30] This effect was not entirely additive, as the nonafluoric sulfonic acid salt behaved similarly to triflic acid (Table 1, entry 6). We also considered that the carboxylic acid substrate may be a more competitive counterion for the BAM catalyst (resulting in a less selective catalyst) when less acidic sulfonates are employed, a hypothesis advanced by others as an interaction critical to high enantioselection.[14,15]

Table 1. Iodolactonization Catalyzed by a Chiral Proton Complex: Effect of the Achiral Counterion on the Enantioselectivity[a]



entry	counterion	ee (%)[b]	yield (%)[c]	entry	counterion	ee (%)[b]	yield (%)[c]
1	$^{p}TolSO_3^-$	20	90	6	$CF_3(CF_2)_3SO_3^-$	49	45
2[d]	RSO_3^-	29	41	7		24	95
3[e]	RSO_3^-	29	35	8		84	90
4	FSO_3^-	40	35				
5	$F_3CSO_3^-$	53	87	9		82	74

[a]All reactions were performed on a 0.10 mmol scale (0.1 M) using 1 equiv of the carboxylic acid and a standard 22 h reaction time. The absolute configuration of **4** has been assigned (see ref 19). [b]Enantiomeric ratios were measured using HPLC with a chiral stationary phase. See the Supporting Information (SI) for details. [c]Isolated yields. [d]RSO_3^- = (−)-camphorsulfonate. [e]RSO_3^- = (+)-camphorsulfonate.

Triflylamine counterions, expected to have similar electronic character but larger size relative to triflate, were next evaluated. The triflamide counterion provided an active but less selective catalyst (24% ee; Table 1, entry 7). Although relatively dissociated, the counterion may still be critical in defining the size and shape of the substrate binding pocket. Indeed, triflimidic acid provided a substantial increase in enantioselection to 84% ee (Table 1, entry 8). Use of a fluorinated cyclic triflimide provided similar results (82% ee; Table 1, entry 9). The response of enantioselection to counterions with varying electronic and steric character suggests that the role of the achiral counterion, despite its presence down to 1 mol % (see below), is not simply to provide a resting state for the catalyst but instead to affect the catalyst reactivity and structure directly as it interacts with the substrate.[31] Encouraged by these results, we sought further increases in selectivity by examining other reaction parameters (Table 2).

Decreasing the catalyst loading from 10 to 5 mol % (Table 2, entry 2) did not dramatically influence the enantioselection, but increased selectivity with a longer reaction time was observed when the reaction mixture was diluted (Table 2, entry 3). Among a range of ligands surveyed, increased reactivity and selectivity were achieved when a stilbenediamine backbone (StilbPBAM, **5**) was used instead of the cyclohexanediamine backbone to support the aminoquinoline donors (Table 2, entries 4–6), while the counterion trend seen for PBAM (**1**) was maintained. In a direct comparison, the StilbPBAM·$HNTf_2$ catalyst delivered the adduct in 89% yield with 95% ee after only 2.5 h (Table 2, entry 6). This increased selectivity may be due to the smaller dihedral angle characteristic of the stilbenediamine backbone[32] relative to the cyclohexanediamine, leading to a smaller cavity for presentation of the polar ionic hydrogen bond. Furthermore, diluting the reaction to 0.05 M (Table 2, entry 7) and lowering the catalyst loading to 5 mol % (Table 2, entry 8) gave the adduct in 96 and 97% ee, respectively. With longer reaction times, we were able to decrease the catalyst loading to 2 mol % (Table 2, entry 9) and 1 mol % (Table 2, entry 10) with minimal effect on the yield, a trend not observed with the initial BAM ligand, PBAM.[33]

A combination of 5 mol % catalyst loading and 24 h was defined as the most general set of reaction parameters with which to examine a variety of unsaturated carboxylic acids (Table 3). The sterically demanding 2-naphthalene analogue gave the desired lactone (Table 3, **4b**) with 96% ee in 99% yield. Substrates with *p*- and *m*-methyl substitution gave the adducts with 96% ee (Table 3, **4c**) and 97% ee (Table 3, **4d**), respectively, while maintaining high levels of conversion and yield. Unfortunately, an *o*-methyl group (Table 3, **4e**) stymied the reaction, leading to less than 10% yield of the desired adduct. It is interesting to note that this rate difference was not observed when 4-dimethylaminopyridine was used to prepare *rac*-**4e**, a reaction that was complete within 40 min at room temperature. Aryl rings with halogen substitutions also performed well in the reaction for both the *p*-fluoro (98% ee, 96% yield; Table 3, **4f**) and *p*-chloro (97% ee, 91% yield; Table 3, **4h**) analogues. Moving the halogens to the meta position did

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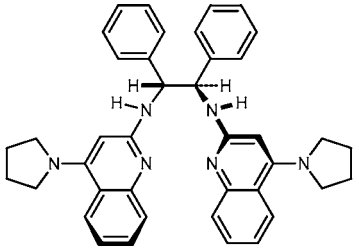
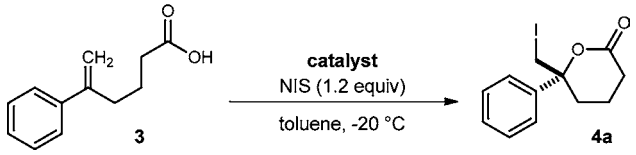
Table 2. Optimization (Ligand, Catalyst Loading, Concentration) of the Chiral Proton-Catalyzed Iodolactonization[a]



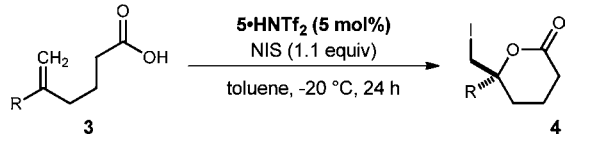
StilbPBAM (**5**)



entry	catalyst	loading (mol%)	toluene (M)	time (h)	yield (%)[b]	ee (%)[c]
1	**1**•HNTf$_2$	10	0.1	22	90	84
2	**1**•HNTf$_2$	5	0.1	46	84	82
3	**1**•HNTf$_2$	10	0.05	46	83	89
4	**5**	10	0.1	22	99	57
5	**5**•HOTf	10	0.1	23	95	87
6	**5**•HNTf$_2$	10	0.1	2.5	89	95
7	**5**•HNTf$_2$	10	0.05	4	98	96
8	**5**•HNTf$_2$	5	0.05	6	99	97
9	**5**•HNTf$_2$	2	0.05	36	95	98
10	**5**•HNTf$_2$	1	0.05	72	79	97

[a]All reactions were performed on a 0.10 mmol scale (0.1 M) using 1 equiv of the carboxylic acid and a standard 22 h reaction time. [b]Isolated yields. [c]Enantiomeric ratios were measured using HPLC with a chiral stationary phase. See the SI for details.

Table 3. Preliminary Scope of the Chiral Proton-Catalyzed Enantioselective Iodolactonization Reaction[a]



entry	R	product	time (h)	yield (%)[b]	ee (%)[c]
1	C_6H_5 (0.5 mmol scale)	**4a**	24	95	97
2	^{2}Np	**4b**	24	96	96
3	^{p}MeC$_6$H$_4$	**4c**	24	97	96
4	^{m}MeC$_6$H$_4$	**4d**	24	91	97
5	^{o}MeC$_6$H$_4$	**4e**	60	<10	-
6	^{p}FC$_6$H$_4$	**4f**	24	96	98
7	^{m}FC$_6$H$_4$	**4g**	12	27	96
8	^{m}FC$_6$H$_4$	**4g**	48	52	96
9	^{p}ClC$_6$H$_4$	**4h**	24	91	97
10	^{m}ClC$_6$H$_4$	**4i**	12	29	95
11	^{m}ClC$_6$H$_4$	**4i**	48	51	97
12	^{p}F$_3$CC$_6$H$_4$	**4j**	48	26	96
13	^{p}F$_3$CC$_6$H$_4$ (10 mol% **5**•HNTf$_2$)	**4j**	48	42	96
14	^{p}MeOC$_6$H$_4$[d]	**4k**	2	84	85
15	C_6H_5[e]	**4l**	24	99	67
16	^{n}Bu	**4m**	12	95	89
17	^{i}Pr	**4n**	48	86	81
18	H	**4o**	24	25	33

[a]All reactions were performed on a 0.10 mmol scale using 1 equiv of the carboxylic acid, 5 mol % catalyst, and 1.1 equiv of NIS in toluene (0.05 M) at −20 °C for 24 h, unless otherwise noted. [b]Isolated yields. [c]Enantiomeric ratios were measured using HPLC with a chiral stationary phase. See the SI for details. [d]DIH (0.06 mmol) was used instead of NIS. See the SI for details. [e]The pentenoic acid (which forms a γ-lactone) was used rather than hexenoic acid substrate **4a**.

not influence the selectivity (**4g** and **4i**), but a significant effect on conversion was observed, even with an extended reaction time (48 h; Table 3, entries 8 and 11). A further increase in the electron deficiency of the aryl ring using a *p*-trifluoromethyl group (Table 3, **4j**) led to a drop in reactivity while maintaining the catalyst's high selectivity. The electron rich *p*-methoxy group (Table 3, **4k**) gave lower levels of enantioselection than expected when NIS was used (74% ee), but changing to 1,3-diiodo-5,5-dimethylhydantoin (DIH) gave the adduct in 85% ee after only 2 h of stirring. The *nor*-homologue (Table 3, **4l**) was more reactive than its parent compound, leading to the desired lactone in high yield but with lower enantioselection (67% ee). 1,1-Dialkylalkenes also performed well under these conditions. The *n*-butyl derivative (Table 3, **4m**) was isolated in 95% yield with 89% ee, while the more sterically demanding isopropyl derivative (Table 3, **4n**) was isolated in 86% yield with 81% ee. Unfortunately, 6-hexenoic acid was significantly less selective, affording the desired lactone (Table 3, **4o**) with only 33% ee.

This scope improves upon the existing selection of enantioselective iodolactonization protocols and utilizes commercially available NIS without additives to achieve this. While it is premature to advance a discrete model to rationalize the observed trends of reactivity and selectivity, we note the following distinct behaviors. The electronic nature of the aromatic ring in **4a**−**k** had a significantly smaller effect on the enantioselection, as described elsewhere.[14a,16a,19] Moreover, unlike the system described here, added acid either has no effect or lowers the enantioselectivity.[8,16,27] Our current mechanistic hypothesis invokes a bifunctional role for the catalyst: Brønsted acid activation of the NIS and Brønsted base activation of the carboxylic acid.

In summary, a distinctive hydrogen-bond-catalyzed enantioselective iodolactonization using chiral proton catalysis was discovered. The achiral counterion of the polar ionic hydrogen bond can be used to optimize the enantioselection, offering an innovative tool for the study of electrophilic halonium ion-initiated reactions. To the best of our knowledge, there is no precedent for this effect, and its observation here suggests that the triflimide counterion is not exchanged for other potential counterions present in larger amounts, particularly carboxylate and succinimide. A *trans*-stilbenediamine-derived bis(amidine) ligand was identified to achieve levels of enantioselection up to 98% ee. The success of this approach contributes to the small but growing number of methods that form boundaries for

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longstanding mechanistic hypotheses related to reactions involving putative halonium−alkene complexes. Insofar as the reagents described here may be viewed as chiral pyridines, the findings (up to 4.8% ee) and conclusions of Brown's pioneering work[2] provide a provocative historical context.

■ ASSOCIATED CONTENT

Supporting Information

Complete preparatory and analytical data for all new compounds. 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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(27) An interesting complementary strategy using substoichiometric *achiral neutral* Brønsted base and chiral (Brønsted acid) counterion as cocatalysts for enantioselective bromoetherification just appeared. See: Denmark, S. E.; Burk, M. T. *Org. Lett.* **2012**, *14*, 256.
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(30) However, we have demonstrated in this bifunctional catalyst class that the catalyst basicity (rather than its acidity) can be the dominant determinant of the reactivity. See ref 26f.
(31) The enantioselectivity and reactivity are optimal at Tf_2NH:**5** = 1:1, with Tf_2NH:**5** = 2:1 delivering the product as the racemate. See the SI for details.
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(33) Lower catalyst loadings and more dilute conditions may favor catalyst monomers or lower oligomers of the catalyst, leading to a more selective catalyst. We have not observed a nonlinear effect in this system to date. However, this does not preclude the possibility of dimers or oligomers. See the SI for details.