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Achiral Counterion Control of Enantioselectivity in a Brønsted Acid Catalyzed Iodolactonization

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Abstract

Highly enantioselective halolactonizations have been developed using a chiral proton catalyst 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 enantioselection is documented for the first time in this transformation. In this way, unsaturated carboxylic acids are converted to γ -lactones in high yield (up to 98% ee) using commercially available *N*-iodosuccinimide (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 surfaced in 2010 that enantioselective halogenative addition reactions (e.g. alkene iodoacyloxylation outlined in Figure 2) were possible while careful mechanistic studies^{2,3,4} outlined obstacles to significant, if not practically meaningful, enantioselectivity.^{5,6,7} Within the broader topic of alkene halofunctionalization, the earliest strategies centered on Lewis base-promoted halogenation strategies, such as chiral amine^{8,9} and phosphoramidite¹⁰ 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 catalysis¹³ for iodolactonization; thiocarbamate/amine catalyzed bromolactonization¹⁴ 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.^{22,23,24}

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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>.

Success with enantioselective iodolactonization has been limited to transformations with low enantioselection and/or regioselection.^{8,13} The highest levels of enantioselection are achieved using cryogenics ($-80\text{ }^{\circ}\text{C}$) and a non-commercial 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 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 directly modify the catalyst's reactivity (Figure 1).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 stilbene diamine derived BAM provided a significant increase in enantioselection relative to the use of a cyclohexane diamine 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. Low levels of enantioselection were observed with the free base (Figure 1, eq 1, 19% ee) while slightly higher levels were observed using the triflic acid salt (46% ee). Evidence of ligand iodination at the 3/3' 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 reactions were prepared with an excess of NIS equivalent to catalyst loading to account for bis(iodination) of the ligand.

The effect of the counterion on reactivity and selectivity was examined by use of different *achiral* Brønsted acid sources, focusing on those providing a range of steric and electronic variation (Table 1). Sulfonic acids generally increased enantioselection with acid strength (Table 1, entries 1–5). The enantiomers of camphorsulfonate provided essentially identical outcomes (29% ee, Table 1, entries 2–3). The selectivity trend may illustrate the need for a more dissociated counterion, favoring a more electrophilic catalyst form.^{28,29,30} This effect was not entirely additive, as the nonafluoric sulfonic acid salt behaved similarly to triflic acid (Table 1, entry 6). We have 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}

Triflylamine counterions were next evaluated, expecting similar electronic character, but larger size relative to triflate. 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% (*vide infra*), is not to simply provide a resting state for the catalyst, but instead to directly affect catalyst reactivity and structure as it interacts with the substrates.³¹ Encouraged by these results, we sought further increases in selectivity by examining other reaction parameters (Table 2).

Decreasing the catalyst loading from 10 mol% 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 was achieved when a stilbene-diamine backbone (StilbPBAM, **5**) was used instead of the cyclohexane diamine backbone to support the aminoquinoline donors (Table 2, entries 4–6), while maintaining the counterion trend seen for PBAM (**1**). In a direct comparison, the StilbPBAM•HNTf₂ catalyst delivered the adduct in 89% yield with 95% ee after only 2.5 hours (Table 2, entry 6). This increased selectivity may be due to the smaller dihedral angle characteristic of the stilbene diamine backbone,³² relative to the cyclohexane diamine, leading to a smaller cavity for presentation of the polar ionic hydrogen bond. Furthermore, dilution of 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 yield, a trend not observed with the initial BAM ligand, PBAM.³³

A combination of 5 mol% catalyst loading and 24 hours 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 analog gave the desired lactone (Table 3, **4b**) in 96% ee and 99% yield. Substrates with *para*- and *meta*-methyl substitution gave the adduct in 96% ee (Table 3, **4c**) and 97% ee (Table 3, **4d**), respectively, while maintaining high levels of conversion and yield. Unfortunately, an *ortho*-methyl group (Table 3, **4e**) stymied the reaction, leading to less than 10% of the desired adduct. It is interesting to note that this rate difference was not observed when using DMAP to prepare *rac*-**4e**, a reaction that is complete within 40 minutes at room temperature. Aryl rings with halogen substitutions also performed well in the reaction for both the *para*-fluoro (Table 3, **4f**, 98% ee, 96% yield) and *para*-chloro (Table 3, **4h**, 97% ee, 91% yield) analogs. Moving the halogens to the *meta*-position did 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 & 11). Further increase of the electron-deficiency of the aryl ring with a *para*-trifluoromethyl group (Table 3, **4j**) led to a drop in reactivity while maintaining the catalyst's high selectivity. The electron rich *para*-methoxy group (Table 3, **4k**) gave lower levels of enantioselection than expected when NIS was used (74% ee), but changing to DIH (1,3-diiodo-5,5-dimethylhydantoin) gave the adduct in 85% ee after only 2 hours of stirring. The *nor*-homolog (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-Dialkyl alkenes also performed well under these conditions. The *n*-butyl derivative (Table 3, **4m**) was isolated in 95% yield and 89% ee, while the more sterically demanding *iso*-propyl (Table 3, **4n**) was isolated in 86% yield and 81% ee. Unfortunately, 6-hexenoic acid was significantly less selective, resulting in the desired lactone (Table 3, **4o**) in only 33% ee.

This scope improves upon the existing selection of enantioselective iodolactonization protocols, and utilizes commercially available *N*-iodosuccinimide (NIS) without additives to achieve this. While it is premature to advance a discrete model for which to rationalize trends of reactivity and selectivity, we note the following distinct behaviors. The electronic nature of the aromatic ring in **4a–k** had a significantly less effect on enantioselection as described elsewhere.^{14a,16a,19} And unlike the system described here, added acid either has no effect or lowers 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 was discovered using chiral proton catalysis. The achiral counterion of the polar ionic hydrogen bond can be used to optimize 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*-stilbene diamine-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 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 provide provocative historical context.²

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Enantioselective iodolactonization: initial experiments to explore relationship between catalyst composition and stereoselection.

Figure 2.

Overview of alkene haloacetoxylation using electrophilic halogen, and catalyst design used in this work.

Iodolactonization catalyzed by a chiral proton complex: effect of achiral counterions on enantioselectivity.

Table 1

entry	counterion	ee (%) ^b	yield (%) ^b	entry	counterion	ee (%) ^b	yield (%) ^c
1	<i>p</i> TolSO ₃ ⁻	20	90	6	CF ₃ (CF ₂) ₃ SO 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	9		82	74

^a All reactions were performed on a 0.10 mmol scale (0.1 M) using 1 equivalent of the carboxylic acid and a standard 22 h reaction time. Absolute configuration of **4** has been assigned (ref. 19).

^b Enantiomeric ratios were measured using HPLC with a chiral stationary phase.

^c Isolated yield.

^d RSO₃⁻ = (-)-camphorsulfonate

^e RSO₃⁻ = (+)-camphorsulfonate

Table 2

Optimization (ligand, catalyst loading, concentration) of the chiral proton-catalyzed iodolactonization.

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 equivalent of the carboxylic acid and a standard 22 h reaction time.

^b Isolated yield.

^c Enantiomeric ratios were measured using HPLC with a chiral stationary phase. See SI for details.

Table 3

Preliminary scope of the chiral proton-catalyzed enantioselective iodolactonization reaction.

entry	R	product	time (h)	yield (%) ^b	ee (%) ^c
1	C ₆ H ₅ (0.5 mmol scale)	4a	24	95	97
2	² Np	4b	24	96	96
3	<i>p</i> -MeC ₆ H ₄	4c	24	97	96
4	<i>m</i> -MeC ₆ H ₄	4d	24	91	97
5	<i>o</i> -MeC ₆ H ₄	4e	60	<10	-
6	<i>p</i> -FC ₆ H ₄	4f	24	96	98
7	<i>m</i> -FC ₆ H ₄	4g	12	27	96
8	<i>m</i> -FC ₆ H ₄	4g	48	52	96
9	<i>p</i> -ClC ₆ H ₄	4h	24	91	97
10	<i>m</i> -ClC ₆ H ₄	4i	12	29	95
11	<i>m</i> -ClC ₆ H ₄	4i	48	51	97
12	<i>p</i> -F ₃ CC ₆ H ₄	4j	48	26	96
13	<i>p</i> -F ₃ CC ₆ H ₄ (10 mol% 5 •HNTf ₂)	4j	48	42	96
14	<i>p</i> -MeOC ₆ H ₄ ^d	4k	2	84	85
15	C ₆ H ₅ ^e	4l	24	99	67
16	<i>n</i> -Bu	4m	12	95	89
17	<i>i</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 equivalent of the carboxylic acid, 5 mol% catalyst, and 1.1 equiv NIS in toluene (0.05 M) at -20 °C for 24 h.

^b Isolated yield.

^c Enantiomeric ratios were measured using chiral stationary phase HPLC. See SI for details.

^d1,3-diiodo-5,5-dimethylhydantoin (DIH) was used (0.06 mmol) instead of NIS. See SI for details.

^eThe pentenoic acid was used (forming a γ -lactone), rather than the hexenoic acid substrate **4a**.