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Chiral Proton Catalysis: A Catalytic Enantioselective Direct Aza-Henry Reaction

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Enzymes, nucleic acids, and other chiral biopolymers are charged with the responsibility to sustain life. To fulfill this mandate, a straightforward strategy is necessary to effect the basic chemical reactions that synthesize organic molecules, often in enantiomerically enriched form. The proton (H^+) is arguably the most common Lewis acid found in Nature and exists in two forms classified by the type of hydrogen bond that results: polar covalent and polar ionic (Scheme 1).[1] It is therefore not surprising that this functionality is believed to play a key role by both activating and orienting substrates for chemical reaction within, for example, a peptide cavity.[2] Nonenzymatic, synthetically useful *enantioselective* transformations utilizing polar covalent hydrogen bonds (eq 1, RXH is an enantiomerically pure catalyst) have recently emerged,[3,4] whereas the analogous use of a polar ionic hydrogen bond (eq 2) has remained elusive.[5,6] The latter was generally believed unattainable through the use of chiral small-molecule ligands for two reasons. First, the spherical nature of the proton's empty 1s orbital challenges the typical sensibilities regarding the design of a stereoisomerically discrete coordination complex. Second, this same feature has led to the perception that the nucleus is substantially more promiscuous than most other Lewis acids, leading to the kinetic argument that attempts to implement the chiral complex would succumb to achiral catalysis by solvent-coordinated Brønsted acid (eq 2).[7]

We report here a highly enantioselective chiral proton-catalyzed aza-Henry reaction (eq 3).[8,9] Neither Brønsted base additive or preactivation of the nucleophile is necessary. The success of this new Lewis acid catalyst demonstrates that intervention of the achiral solvent catalyst pathway (eq 2) can be minimized or avoided entirely.[10]

Guided by the prejudices outlined above, we assumed that a potentially bidentate ligand would be an important design element.[11] The **B**is**AM**idine ligand in **1** (**HQuin-BAM**) was therefore synthesized as a single enantiomer from commercially available (+)-*trans*-cyclohexane diamine and 2-chloroquinoline in 86% yield using palladium catalysis.[12] Formation of the corresponding 1:1 Brønsted acid salt (**1**) was then accomplished by the addition of trifluoromethane sulfonic acid, delivering a white crystalline bench-stable solid.

An initial screen of aldimine electrophiles revealed that *tert*-butoxy carbonyl (Boc) Schiff bases provide the necessary combination of reactivity and enantioselection. Less than 5% of the β-amino nitroalkane **3a** is formed at −20 °C after 5 days. When the same reaction is executed in the presence of 10 mol % HQuin-BAM catalyst **1**, secondary amine **3a** is formed in 60% ee and 57% yield (Table 1, entry 1). Subsequent samarium(II) iodide reduction provided in 92% yield the *R*-enantiomer of the derived Boc-protected *vic*-diamine reported previously.[13] This degree of rate acceleration concomitant with enantioselection illustrates the central role of the proton; addition of 10 mol % HQuin-BAM alone also failed to accelerate the aza-Henry reaction beyond the (slow) background rate. Enantioselection and reactivity were further

Scheme 1

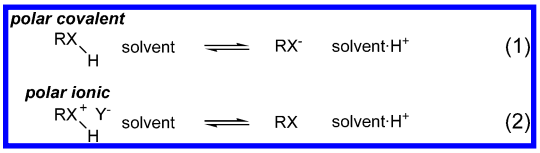
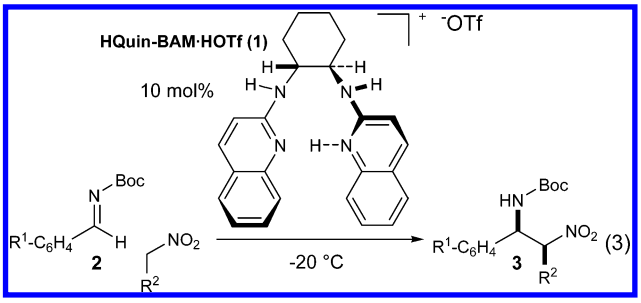


Table 1. Chiral Proton-Catalyzed Aza-Henry Reactions[a]



entry	R^1	R^2		% yield[c]	dr[b]	% ee[b]
1	H	H	**3a**	57	–	60
2	*p*-NO_2	H	**3b**	61	–	82
3	*m*-NO_2	H	**3c**	65	–	95
4	H	CH_3	**3d**	69	14:1	59
5	*p*-CF_3O	CH_3	**3e**	53	19:1	81
6	*p*-Cl	CH_3	**3f**	59	17:1	82
7	*m*-NO_2	CH_3	**3g**	51	11:1	89
8	*o*-NO_2	CH_3	**3h**	62	7:1	82
9	*p*-CF_3	CH_3	**3i**	50	19:1	84
10	*p*-NO_2	CH_3	**3j**	60	7:1	90

[a] All reactions were 0.25 M in substrate. Absolute and relative configuration for **3a** and **3d** assigned by chemical correlation (see Supporting Information). Remaining products assigned by analogy. [b] Diastereomeric ratios determined by GC. Enantiomeric excess determined by HPLC using a chiral stationary phase. [c] Isolated yield after chromatography.

improved by implementation of more electrophilic aldimine derivatives **2b**−**c**, delivering secondary amines **3b** and **3c** in 82 and 95% ee, respectively (Table 1, entries 2−3).

The opportunity to simultaneously control absolute and relative stereochemistry was afforded by the use of nitroethane as the pronucleophile. Benzaldehyde Schiff base **2d** delivered the derived secondary amine in 59% ee (Table 1, entry 4). Assignment of the product as the *cis*-diastereomer and (*R*)-absolute configuration at the benzylic carbon was made after reduction and Boc-deprotection to the *cis vic*-diamine.[14] Further improvement in enantioselection was made possible again through the use of electron-deficient Schiff bases. *p*-Trifluoromethoxy- and *p*-chloro-benzaldehyde Schiff bases **2e** and **2f** furnished their aza-Henry products in 81 and 82% ee, respectively, and with high (17−19:1) diastereoselectivity (Table 1, entries 5−6). Nitrobenzaldehyde derivatives provided the secondary amines in 82−90% ee (Table 1, entries 7, 8, 10). Finally, the

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p-trifluoromethyl benzaldimine furnished the aza-Henry adduct as a 19:1 mixture of *cis:trans* diastereomers **3i** affording the *cis*-isomer in 84% ee.

Speculation about the exact nature of the stereochemical-determining catalyst−substrate complex would be premature at this time. However, it is clear from these initial experiments that the proton plays a key role in both substrate activation and orientation leading to asymmetric induction. To this point, the pseudo-C_2-symmetric coordination complex **1** has provided an effective prospecting tool,[15] and determination of the actual reactive intermediate remains the subject of investigation.

In conclusion, we have demonstrated the use of a chiral proton (a polar ionic hydrogen bond) alone as both the means of activation (function) and control (structure) of absolute and relative stereochemistry. That the small-molecule BAM ligand effectively sequesters the proton from solvent without reliance on an enveloping peptidic superstructure suggests that chiral proton coordination complexes may ultimately find broad application in enantioselective Lewis acid catalysis. The ease with which a Brønsted acid can be removed from the final reaction via a base wash, coupled with its significantly lower cost and toxicity compared to traditional Lewis acid complexes, should further stimulate the development of new Brønsted acid-catalyzed reactions.[16]

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Supporting Information Available: General experimental procedures and analytical data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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