Published in final edited form as:
J Am Chem Soc. 2010 March 10; 132(9): 2880–2882. doi:10.1021/ja908814h.

Bifunctional Asymmetric Catalysis: Amplification of Brønsted Basicity Can Orthogonally Increase the Reactivity of a Chiral Brønsted Acid

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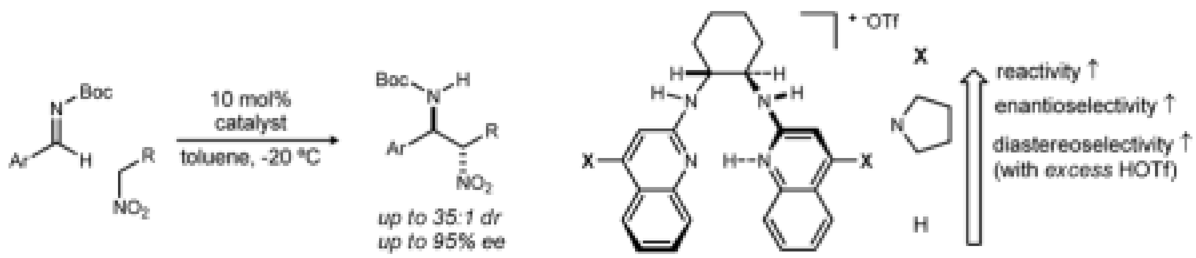
Abstract



The reactivity of a series of symmetrical chiral Brønsted acids (polar ionic hydrogen bond donors) follows the *counterintuitive* trend wherein the more Brønsted *basic* member is a more effective catalyst for the aza-Henry (nitro-Mannich) reaction. This new design element leads to a substantially more reactive catalyst for the aza-Henry reaction, and one that can promote the addition of a secondary nitroalkane. Additionally, when achiral Brønsted acid (TfOH) is used in slight excess to the neutral, chiral BisAMidine ligand, diastereoselection can be optimized to levels generally greater than 15:1 while enantioselection remains unchanged at generally >90% ee.

The development of small molecule catalysts that manage the key aspects of an asymmetric reaction has been tremendously successful, bringing stereochemically sophisticated organic compounds into hand in as little as a single operation from bench-stable reactants.[1] There are now numerous cases of small molecules that catalyze the reaction of two (or more) reactants in a highly diastereo- and enantioselective process, and these findings have illustrated that catalyst structural and functional complexity is not a prerequisite for high levels of stereoselection.[2] Despite this proliferation of examples, contributors often remain focused on a fraction of available catalyst motifs.[3] This is perhaps less intentional than it is necessary, as in *multi*functional catalysis, it remains difficult to manipulate reactivity independently of other stereocontrol factors;[4] the bond distances and angles that determine stereocontrol also impact overall reactivity.[5] We report here the finding that multifunctional catalysts **2** provide the opportunity to increase overall reactivity through manipulation of their Brønsted basicity[6] without detriment to stereocontrol. The behavior is suggestive of a semiorthogonal hierarchy among reactivity, diastereocontrol, and enantiocontrol that can be used to extend the scope of the enantioselective aza-Henry reaction,[7,8,9] a transformation that remains relatively limited

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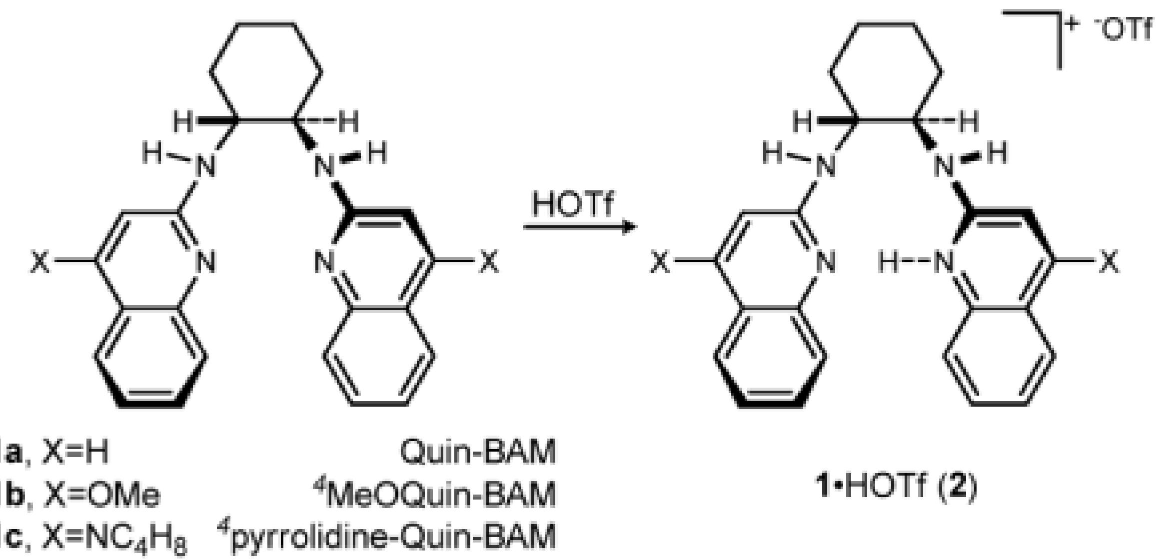
beyond nitroethane. In essence, the orthogonality (or priority) described in this study for an ostensibly symmetrical catalyst achieves the same goal as modularity in unsymmetrical ligand design.

Chiral *B*is(*AM*idine) Brønsted acids (e.g. **1a**·HOTf (**2**)) are among the organocatalysts that have expanded the range of nonracemic *vic*-diamines available in two steps from nitroalkanes. With few exceptions, the enantioselective aza-Henry reaction remains generally limited to activated or unhindered nitroalkane pronucleophiles, and warm reaction temperatures at relatively long reaction times. Based on the knowledge that Brønsted acidity is central to stereocontrol,[4] we prepared a range of electron deficient ligands, but these failed to improve either reactivity or stereocontrol. Instead, improvement of reaction rate and stereoselection was achieved through the preparation of ligands with *increased* Brønsted basicity. Using the addition of nitroethane to imine **3** as a representative example, chiral proton complex **2a** provides secondary amine **4** in 8:1 dr, 87% ee, and 29% yield after 5 days at −20 °C (Table 1, entry 1). Under otherwise identical conditions, its free base (**1a**) provides slightly improved conversion (47% yield) but with sacrifice of selectivity (5:1 dr, 73% ee, Table 1, entry 4).[10] We next prepared four catalysts (**1b**, **2b**, **1c**,[11] **2c**) expected to exhibit increased Brønsted basicity relative to their **1a**/**2a** counterparts. Although a direct comparison of **1b** should not be made due to its limited solubility under the reaction conditions, catalysts **2b** and **2c** provided a measurable improvement in reaction rate.[13] The reactivity of **2c** was particularly striking, as complete conversion was reached within 24 hours (1.5 equivalents $EtNO_2$), whereas **1a** and **2a** provided only 1–2% conversion (GC) under otherwise identical conditions.[13] Reactivity of **2c** and its free base (**1c**) were comparable as judged by apparent rate, but selectivity for the salt was considerably greater at 7:1 dr, 90% ee (Table 1, entry 3).[13]



The increased reactivity associated with **2c** enabled a systematic probe of the effect of triflic acid on catalyst selectivity. In the absence of triflic acid, aza-Henry product is formed in 1:1 dr and 71% ee (Table 1, entry 6). At substoichiometric triflic acid relative to ligand, both dr and ee improve to 4:1 dr, 91% ee (Table 1, entry 7). Beyond this, only diastereoselection improves further: 7:1 for **1c**(HOTf), 18:1 for $\mathbf{1c}_2(HOTf)_3$, 16:1 for $\mathbf{1c}(HOTf)_2$ (Table 1, entries 3,8,9) as enantioselection remains comparable. Higher degrees of catalyst protonation ultimately lead to a drop in reactivity; yield also suffers due to imine hydrolysis (Table 1, entries 9–10), a pathway not observed when using a 2:3 or higher ratio of ligand to triflic acid. We examined the behavior of two additional substrates using a range of ligand protonation states analogous to those just described (Table 1, entries 11–15 & 16–19). These studies further established catalyst **1c**$_2$(HOTf)$_3$ as the superior agent.

These conditions generally led to uniformly excellent diastereoselection, good to excellent enantioselection, and generally good isolated yield when applied to a range of aldimines (Table 2, entries 1–14). Favorable stereoselection could be obtained from a range of electronically and sterically diverse aldimines. Electron rich heterocycles such as furan and thiophene can be particularly good (Table 2, entries 10–12). Linear and branching unactivated nitroalkanes provided similarly high levels of stereoselection (Table 2, entries 15–18). Notably, a secondary nitroalkane such as 2-nitropropane provided enantioselection at a promising level at room temperature (Table 2, entry 19).[12]

We believe the diastereoselection observed with each catalyst to be kinetic in nature, as exposure of **5a** with 1:1.6 (*anti: syn*) dr (90% ee) to the reaction conditions returned material with 1:1.4 dr (92% ee) after 24 hours at −20 °C. Similarly, exposure of **5a** with 10.6:1 dr (93% ee) to the same conditions resulted in its recovery essentially unchanged (9.4:1 dr, 93% ee). Stereoselection as a function of conversion was also constant when examined.

These behaviors highlight the possibility that the selective catalyst is a conjugate acid of **1** throughout *all* cases in Table 1. In the case of free base catalysts **1a**–**c**, a chiral proton complex bearing a nitronate counterion might operate as a Lewis acid. In cases where the triflate salt is used (**2a**–**c**), the more selective triflate catalyst may be operative. Therefore, the excess acid relative to ligand in **1c**$_2$(HOTf)$_3$ ensures that the catalyst-bound imine is a triflate salt. Consistent with this picture is the finding that **1c**·HOTf (**2c**) catalyzes the addition of nitroethane (2 equivalents) in toluene, and reaches 79% conversion after 2.5 hours (6:1 dr, 94% ee), whereas reactions with **2c** and **1c** in neat nitroethane (56 equivalents) after 26 hours reach only 50% conversion (6:1 dr, 76% ee) and 74% conversion (1:1 dr, 53% ee), respectively.[13] This slowing of the reaction associated with the use of excess nitroethane does not occur with **1a** and **1a**·HOTf (**2a**), for which neat nitroethane provides optimal rate and conversion.

In summary, a synergistic relationship between chiral bis(amidine) Brønsted basicity, its protonation state, and overall efficiency in the stereoselective aza-Henry reaction has been uncovered. Furthermore, ligand **1c** provides *semiorthogonal* modulation of diastereoselection and enantioselection. Although a more precise image of stereoinduction remains too speculative at present, the counterintuitive finding that an *increase* in the Brønsted basicity of a chiral Brønsted acid catalyst can be used to independently manipulate a bifunctional catalyst's reactivity[6] may accelerate similar observations with complementary catalyst systems long before this mechanistic question is answered.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was initiated through funds provided by the NSF (CHE-0415811), and continued through support by NIH (GM-084333).

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10. Commercially available nitroalkanes often contain an inhibitor, and when distilled, these reagents quickly yellow with time. When distilled and used immediately, nitromethane produces the adduct with 0–10% ee. When not used immediately, adducts generated from nitromethane by **1a** exhibit variable ee, and as high as 30% ee.

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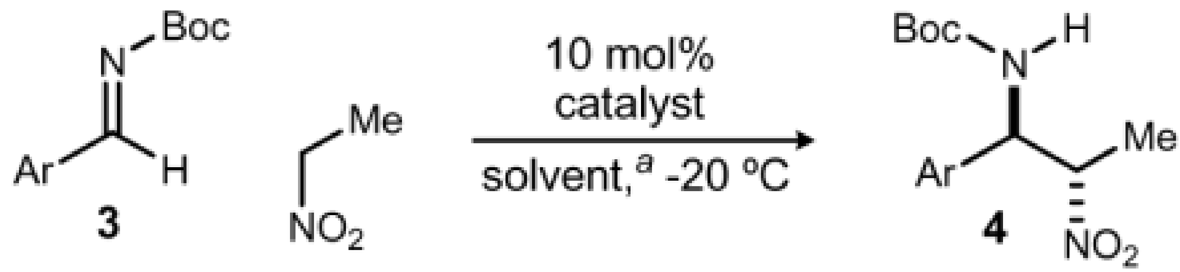
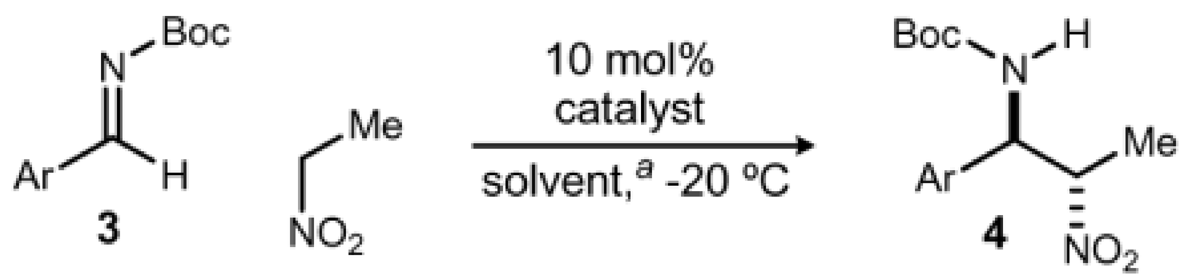
13. See Supporting Information for additional data tables and a chart of product formation vs. time for several catalysts.

Table 1

Impact of Catalyst Brønsted Basicity and Protonation State on Reactivity and Stereoselection in the aza-Henry Reaction[a]



	entry	catalyst	dr[b] (*anti:syn*)	ee[b] (%)	yield[c] (%)
Ar=^{p}ClC$_6$H$_4$ **a**	1[d]	**1a**·HOTf (**2a**)	8:1	87	29
	2[d]	**1b**·HOTf (**2b**)	13:1	73	52
	3	**1c**·HOTf (**2c**)	7:1	90	78
	4[d]	**1a**	5:1	73	47
	5[de]	**1b**	3:1	58	51
	6	**1c**	1:1	71	73
	7	**1c**$_2$(HOTf)$_1$	4:1	91	76
	8	**1c**$_2$(HOTf)$_3$	18:1	91	87
	9	**1c**$_1$(HOTf)$_2$	16:1	86	42
	10	**1c**$_1$(HOTf)$_3$	-	-	-[f]
Ar=^{p}MeOC$_6$H$_4$ **b**	11	**1c**	11:1	70	91
	12	**1c**$_2$(HOTf)$_1$	19:1	88	92
	13	**1c**·HOTf (**2c**)	20:1	87	76
	14	**1c**$_2$(HOTf)$_3$	24:1	88	84
	15	**1c**$_1$(HOTf)$_2$	23:1	90	63
Ar=^{3,4}(MeO)$_2$C$_6$H$_3$ **c**	16	**1c**	3:1	71	79



entry	catalyst	dr[b] (*anti:syn*)	ee[b] (%)	yield[c] (%)
17	$\mathbf{1c}_2(\mathrm{HOTf})_1$	5:1	87	88
18	**1c**·HOTf (**2c**)	12:1	89	80
19	$\mathbf{1c}_2(\mathrm{HOTf})_3$	20:1	90	80

[a] Entries 1,2,4,5 run neat in $EtNO_2$ (0.4 M), whereas all others were 1 M in toluene (based on imine) and used 1.5 equiv. $EtNO_2$. See Supporting Information for further details.

[b] Diastereomeric ratios were determined by GC analysis of the crude reaction mixture, and confirmed during HPLC determination of dr/ee using a chiral stationary phase.

[c] Isolated yield.

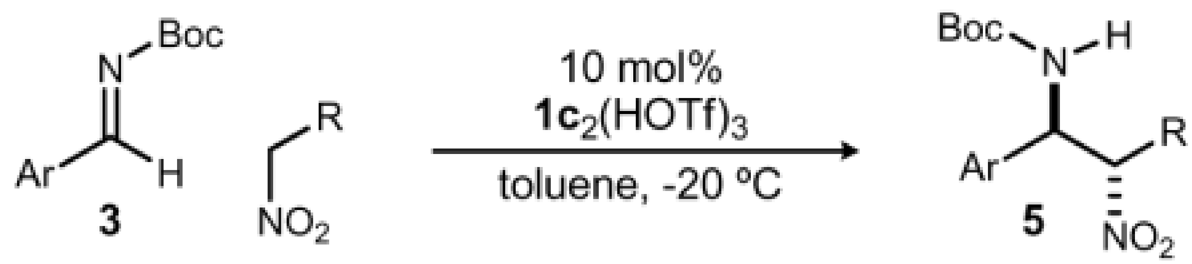
[d] Nitroethane used as solvent (56 equivalents).

[e] Catalyst **1b** is minimally soluble under these conditions.

[f] Only imine hydrolysis observed.

Table 2

Scope of the Catalyzed Addition of Unactivated Nitroalkanes to Imines[a]



entry	Ar	R		dr[b] (*anti:syn*)	ee[b] (%)	yield[c] (%)
1	$^{p}ClC_6H_4$	Me	**a**	18:1	91	87
2	$^{p}MeOC_6H_4$	Me	**b**	24:1	88	84
3	$^{3,4}(MeO)_2C_6H_3$	Me	**c**	20:1	90	80
4	^{2}Np	Me	**d**	16:1	82	84
5	$^{p}MeC_6H_4$	Me	**e**	28:1	89	100
6	$^{o}MeC_6H_4$	Me	**f**	11:1	90	66
7	^{1}Np	Me	**g**	8:1	87	97
8	$^{p}FC_6H_4$	Me	**h**	26:1	93	66
9	$^{p}MeO_2CC_6H_4$	Me	**i**	12:1	91	63
10	$^{2}C_4H_3O$	Me	**j**	19:1	87	90
11	$^{2}C_4H_3S$	Me	**k**	20:1	95	100
12	$^{3}C_4H_3S$	Me	**l**	35:1	91	92
13	$^{p}PhSC_6H_4$	Me	**m**	20:1[e]	89	80
14	$^{p}AllylOC_6H_4$	Me	**n**	28:1	89	91
15[d]	$^{p}ClC_6H_4$	Et	**o**	20:1[f]	91	86
16[d]	$^{p}ClC_6H_4$	^{n}Pr	**p**	23:1[f]	89	89
17[d]	$^{p}ClC_6H_4$	^{i}Pr	**q**	7:1[e]	88	61
18[d]	$^{p}ClC_6H_4$	$CH_2C_6H_{11}$	**r**	13:1[e]	89	85

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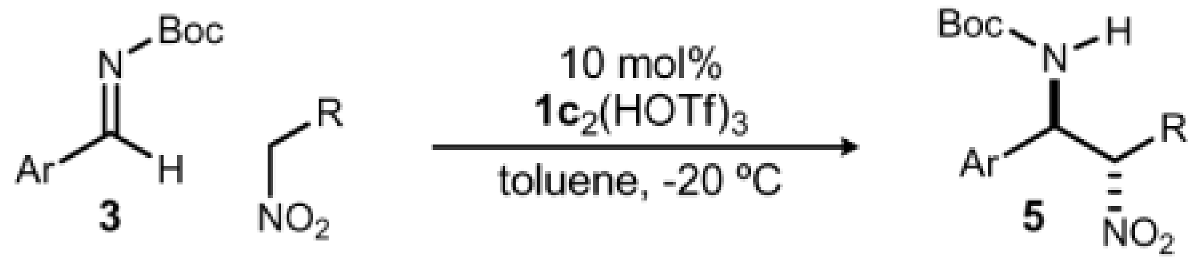

entry	Ar	R		dr[b] (*anti:syn*)	ee[b] (%)	yield[c] (%)
19[g]	$^{p}ClC_6H_4$	Me_2	**s**	-	71	67

[a]All reactions employed 1.5 equivalents of nitroalkane, were 1 M in imine, and reflect a 23–24 hour reaction time. Absolute and relative configuration of **5a** assigned by chemical correlation/X-ray. The remaining stereochemical assignments are made by analogy.

[b]Diastereomer ratios measured by GC unless otherwise noted. Enantiomer ratios measured by HPLC using a chiral stationary phase. See Supporting Information for complete details.

[c]Isolated yields.

[d]A 1:1 ratio of PBAM:HOTf was used.

[e]Approximated by ^{1}H NMR.

[f]Measured by HPLC.

[g]Use of **1c**·HOTf at 25 °C.