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

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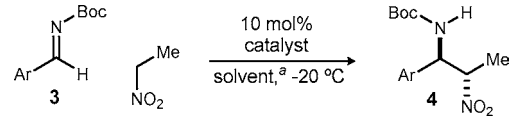
The development of small-molecule catalysts that manage the key aspects of an asymmetric reaction has been tremendously successful, bringing stereochemically sophisticated organic compounds into hand in as little as a single operation from bench-stable reactants.[1] There are now numerous cases of small 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 the available catalyst motifs.[3] This is perhaps less intentional than it is necessary, since in *multi*functional catalysis it remains difficult to manipulate the reactivity independently of other stereocontrol factors;[4] the bond distances and angles that determine stereocontrol also impact the overall reactivity.[5] We report here the finding that multifunctional catalysts **2** provide the opportunity to increase the 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,[7−9] a transformation that remains relatively limited 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.

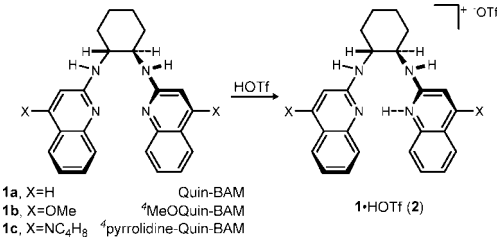
Chiral *b*is(*am*idine) (BAM) Brønsted acids [e.g., **1a**·HOTf (**2**)] are among the organocatalysts that have expanded the range of nonracemic *vic*-diamines available in two steps from nitroalkanes. With few exceptions, the enantioselective aza-Henry reaction remains generally limited to activated or unhindered nitroalkane pronucleophiles using warm reaction temperatures and relatively long reaction times. On the basis of the knowledge that Brønsted acidity is central to stereocontrol,[4] we prepared a range of electron-deficient ligands, but these failed to improve either the reactivity or stereocontrol. Instead, improvement in reaction rate and stereoselection was achieved through the preparation of ligands with *increased* Brønsted basicity. For 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 a sacrifice in selectivity (5:1 dr, 73% ee; Table 1, entry 4).[10] We next prepared four catalysts (**1b**, **2b**, **1c**,[11] and **2c**) expected to exhibit increased Brønsted basicity relative to their **1a**/**2a** counterparts. Although a direct comparison of **1b** should not be made because of its limited solubility under the reaction conditions, catalysts **2b** and **2c** provided a measurable improvement in the reaction rate.[13] The reactivity of **2c** was particularly striking, as complete conversion was reached within 24 h (1.5 equiv of $EtNO_2$), 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 the apparent rate, but selectivity for the salt was considerably greater at 7:1 dr, 90% ee (Table 1, entry 3).[13]

Table 1. Impact of Catalyst Brønsted Basicity and Protonation State on Reactivity and Stereoselection in the Aza-Henry Reaction[a]



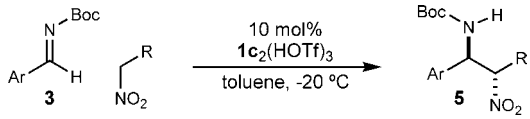
entry	catalyst	dr (anti/syn)[b]	ee (%)[b]	yield (%)[c]
	Ar = $^{p}ClC_6H_4$ (**3a**, **4a**)			
1[d]	**1a**·HOTf (**2a**)	8:1	87	29
2[d]	**1b**·HOTf (**2b**)	13:1	73	52
3	**1c**·HOTf (**2c**)	7:1	90	78
4	**1a**	5:1	73	47
5[d,e]	**1b**	3:1	58	51
6	**1c**	1:1	71	73
7	**1c**$_2$(HOTf)$_1$	4:1	91	76
8	**1c**$_2$(HOTf)$_3$	18:1	91	87
9	**1c**$_1$(HOTf)$_2$	16:1	86	42
10	**1c**$_1$(HOTf)$_3$	−	−	−[f]
	Ar = $^{p}MeOC_6H_4$ (**3b**, **4b**)			
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 = $^{3,4}(MeO)_2C_6H_3$ (**3c**, **4c**)			
16	**1c**	3:1	71	79
17	**1c**$_2$(HOTf)$_1$	5:1	87	88
18	**1c**·HOTf (**2c**)	12:1	89	80
19	**1c**$_2$(HOTf)$_3$	20:1	90	80

[a] Entries 1, 2, 4, and 5 were run neat in $EtNO_2$ (0.4 M), whereas all others were 1 M in toluene (based on imine) and used 1.5 equiv of $EtNO_2$. See the 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] Using nitroethane (56 equiv) as the solvent. [e] Catalyst **1b** was minimally soluble under these conditions. [f] Only imine hydrolysis was observed.



10.1021/ja908814h

Table 2. Scope of the Catalyzed Addition of Unactivated Nitroalkanes to Imines[a]



entry	Ar	R	3, 5	dr (anti/syn)[b]	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
19[g]	$^{p}ClC_6H_4$	Me_2	**s**	–	71	67

[a] All reactions employed 1.5 equiv of nitroalkane, were 1 M in imine, and used a 23−24 h reaction time. The absolute and relative configurations of **5a** were assigned by chemical correlation/X-ray analysis. The remaining stereochemical assignments were made by analogy. [b] Diastereomeric ratios were measured by GC, unless otherwise noted. Enantiomeric ratios were measured by HPLC using a chiral stationary phase. See the Supporting Information for complete details. [c] Isolated yields. [d] Using a 1:1 PBAM/HOTf ratio. [e] Approximated by ^{1}H NMR analysis. [f] Measured by HPLC. [g] Using **1c**·HOTf at 25 °C.

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, the aza-Henry product was formed in 1:1 dr and 71% ee (Table 1, entry 6). At substoichiometric triflic acid relative to ligand, both the dr and ee improved (4:1 dr, 91% ee; Table 1, entry 7). Beyond this, only the diastereoselection improved further [7:1 for **1c**(HOTf), 18:1 for **1c**$_2$(HOTf)$_3$, and 16:1 for **1c**(HOTf)$_2$; Table 1, entries 3, 8, and 9] while the enantioselection remained comparable. Higher degrees of catalyst protonation ultimately led to a drop in reactivity; the yield also suffered because of imine hydrolysis (Table 1, entries 9 and 10), a pathway not observed when a 2:3 or higher ratio of ligand to triflic acid was used. 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 and 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 were 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 h 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 equiv) in toluene, which reached 79% conversion after 2.5 h (6:1 dr, 94% ee), whereas reactions with **2c** and **1c** in neat nitroethane (56 equiv) after 26 h reached 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 did not occur with **1a** and **1a**·HOTf (**2a**), for which neat nitroethane provided the optimal rate and conversion.

In summary, a synergistic relationship between chiral bis(amidine) Brønsted basicity, its protonation state, and the 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 the 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.

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Supporting Information Available: 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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(12) For the only other report comparable to this level of reactivity and enantioselection, see ref 8b. Also see ref 8c for comparison.

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

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