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Chiral Proton Catalysis: Enantioselective Brønsted Acid Catalyzed Additions of Nitroacetic Acid Derivatives as Glycine Equivalents

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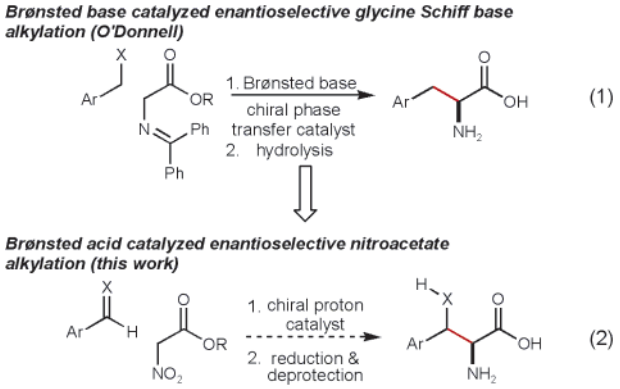
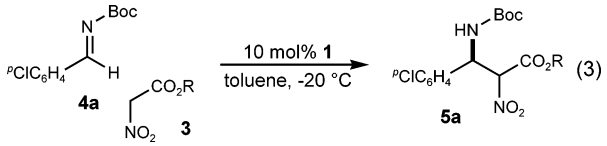
O'Donnell first reported in 1978 on the use of glycine Schiff base derivatives to synthesize α-amino acids (eq 1).[1] The two-step procedure involves base-mediated deprotonation and alkylation using phase transfer catalysis, followed by Schiff base hydrolysis and ester deprotection to reveal the α-amino acid. In the intervening years, this approach has succumbed to enantioselective catalysis[2] and has been exploited along innumerable synthetic lines to produce a collection of reliable, straightforward amino acid syntheses.[1] Nitroacetic acid derivatives have also been used as masked amino acids in a variety of transformations,[3] but their use in enantioselective transformations is presently limited to only two recent cases[4] that produce non-epimerizable nitroacetate derivatives. By analogy to the O'Donnell reaction, we now demonstrate the use of unsubstituted nitroacetic acid derivatives in combination with chiral proton catalysis[5] to effect diastereo- and enantioselective addition reactions (eq 2).[6] Key to the success of this approach was the identification of a catalyst (**2**) that (a) is a highly effective general base for the nitroalkane substrate, but (b) is a less effective base toward the product, while (c) providing high *anti*-diastereoselection. The resulting α,*β*-diamino acid adducts are protected orthogonally, allowing the underlying amino acid to be revealed with a high degree of chemoselectivity.[7]



We first examined commercially available α-nitro ethyl acetate as a nucleophile in the chiral proton catalyzed enantioselective aza-Henry reaction using conditions optimal for nitromethane pronucleophiles.[5,8] Using a single equivalent of nitroacetate **3b**, imine **4a**, and 10 mol% of H,Quin-BAM·HOTf (**1**), several solvents provided comparable levels of enantioselectivity (e.g., dichloromethane, toluene, diethyl ether), but toluene was chosen for further studies. The similar levels of enantioselectivity between nitroethane and α-nitro ethyl acetate (82% ee (17:1 dr)[5] vs. 80% ee) were not paralleled by diastereoselection, which was uncharacteristically low (1−2:1). This behavior extends to alternative ester protecting groups, including methyl, benzyl, and *tert*-butyl (Table 1, entries 1−4).[9] In all cases examined, encouraging levels of enantioselection contrasted low levels of diastereoselection. Al-

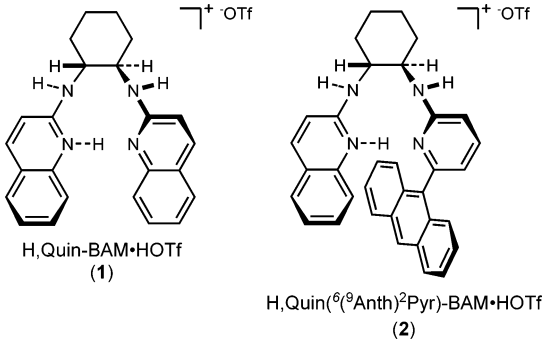
Table 1. Chiral Proton Catalyzed Additions of Nitroacetic Acid Esters[a]



entry	R		dr[b]	%ee[b] *cis*	%ee[b] *trans*	yield (%)[c]
1	Me	**a**	1:1	82	nd	70
2	Et	**b**	1:1	80	80	75
3	Bn	**c**	1:1	71	nd	80
4	^{t}Bu	**d**	2:1	84	84	80

[a] All reactions were 0.3 M in substrate and proceeded to complete conversion. [b] Diastereomer and enantiomer ratios were measured using chiral stationary phase HPLC. See Supporting Information for complete details. [c] Isolated yield.

though continuous monitoring of one reaction by ^{1}H NMR revealed a constant 1:1 dr throughout the time course, we hypothesized that the ligand may be used to influence diastereoselection.



With some effort, we identified unsymmetrical Bis(AMidine) complex **2** as a catalyst for the highly *anti*-diastereoselective and enantioselective nitroacetate additions (Table 2). Using catalyst **2**, higher enantioselectivity is consistently observed, with **5a**−**c** representing typical observations (generally 10−20% ee higher). More importantly, diastereoselection is improved considerably, from essentially nonselective to levels of 7−11:1 for **5a**−**d** (Table 2, entries 1−8). Reduction of the adducts (without purification) and remeasurement of the stereoisomer ratios provided values consistent with essentially no drop in dr or ee for the α-amino ester products.[10] Use of sodium borohydride/cobalt(II) chloride is rather important in this context, as it effects reduction of the adducts without epimerization at the α-position. Alternatives that were investigated resulted in either lowering of the diastereomeric ratio or reduction of halogenated adducts. These issues are cleanly avoided in the protocol described here, and over two steps, high yields are consistently observed (>80%, Table 2). To determine initial scope

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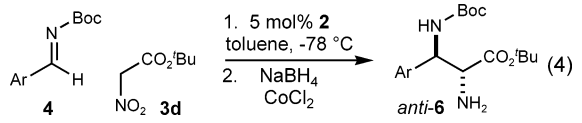
Table 2. Chiral Proton Catalyzed Additions of α-Nitroesters to Azomethines: Initial Scope[a]

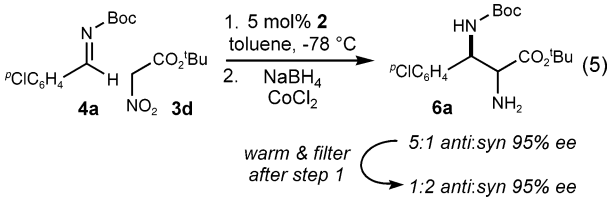


entry	Ar		catalyst	dr[b] (**5**)	dr[b] (**6**)	%ee[b] (**6**)	yield[c]
1	$^{p}ClC_6H_4$	**a**	**1**	1:2	1:2	84	80
2	$^{p}ClC_6H_4$	**a**	**2**	5:1	5:1	95	88
3	$^{p}AcOC_6H_4$	**b**	**1**	2.5:1	2.1:1	85	76
4	$^{p}AcOC_6H_4$	**b**	**2**	11:1	11:1	89	74
5	^{2}Np	**c**	**1**	4:1	4:1	78	69
6	^{2}Np	**c**	**2**	12:1	11:1	91	80
7	$^{p}FC_6H_4$	**d**	**1**	—[b]	1:1	67	80
8	$^{p}FC_6H_4$	**d**	**2**	—[b]	7:1	93	81
9	$^{p}CF_3C_6H_4$	**e**	**2**	7:1	7:1	88	83
10	$^{p}MeC_6H_4$	**f**	**2**	6:1	6:1	95	81
11	$^{m}PhOC_6H_4$	**g**	**2**	6:1	6:1	87	84
12	$^{m}ClC_6H_4$	**h**	**2**	10:1	10:1[d]	87	70
13	$^{p}MeO_2CC_6H_4$	**i**	**2**	8:1	8:1	95	84

[a] All reactions were 0.30 M in substrate and proceeded to complete conversion. [b] Diastereomer ratios were measured by ^{1}H NMR (a reliable measurement was not possible for the addition product for entries 7 and 8). Enantiomer ratios were measured using chiral stationary phase HPLC. See Supporting Information for complete details. [c] Isolated yield (two steps). [d] Measured by GC.

of the reaction, we further surveyed a collection of electronically diverse aldimines (Table 2, entries 9−13). Diastereoselection ranges from a minimum of 5:1 (Table 2, entry 2) to 12:1 for the 2-naphthyl adduct **5c** (Table 2, entry 6). Across these substrates, enantioselection is maintained simultaneously to a high degree (87−95% ee).

We are working to understand the mechanism of stereocontrol and activation, and although a complete picture is not yet at hand, it is evident that *anti*-diastereoselection here represents kinetic selectivity. For example, if addition product **5a** is allowed to stand in the presence of catalyst at room temperature, and then filtered through a pad of silica gel, *syn*-enriched **5**[11] is obtained. Analysis of the *syn*-diastereomer established its enantiomeric ratio to be identical to its *anti*-precursor, thereby indicating that the benzylic amine carbon possesses the same configuration in both diastereomers and with the same level of enantioselection. This post-addition epimerization further highlights the balance of catalyst **2**'s basicity: kinetic selectivity is achieved in part due to the ability of catalyst **2** to selectively deprotonate **3d** in mixtures of **3d** and **5a** (the precursor to **6a**).[12]



In summary, a diastereo- and enantioselective Brønsted acidic complement to the O'Donnell Schiff base alkylation strategy has been developed using chiral proton catalysis. Substituted glycines are produced with good enantioselection and in a single operation using unsymmetrical Bis(AMidine) complex **2**. The products are also orthogonally protected for subsequent amide bond formation. At present, this catalyst is uniquely able, in this reaction, to play the role of chiral Lewis acid and general base[13] while organizing both substrates for carbon−carbon bond formation. This embodiment establishes that the risk of post-addition epimerization can be averted when using a bifunctional catalyst of proper basicity and suggests that this strategy may be more broadly applicable to the straightforward enantioselective synthesis of epimerizable nonnatural amino acids from nitroacetic acid esters.

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Supporting Information Available: Preparation 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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