A diastereo- and enantioselective synthesis of α-substituted *anti*-α,β-diaminophosphonic acid derivatives†

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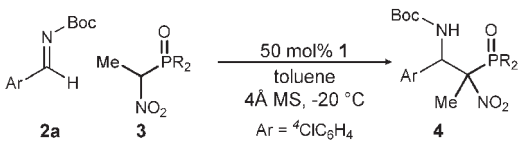
Highly diastereo- and enantioselective additions of α-nitrophosphonates to imines catalyzed by a chiral Brønsted acid are described.

As structural and functional surrogates for α-amino acids, α-amino phosphonic acids have been explored widely as tools for the study and manipulation of disease pathways.[1] More recently, this functionality has surfaced within biologically active natural products such as K-26.[2] α,β-Diamino acids have attracted interest for similar reasons.[3] Accordingly, these attributes have stimulated the development of methods for the synthesis of these functional motifs, but few possess the brevity of carbon–carbon bond-forming reactions to create the α-substituted amino phosphonic acid or *vic*-diamine substructures.[4–6] We would like to report the direct synthesis of α,β-diamino phosphonic acids using a bifunctional catalyst that activates both reactants. As an additional challenge, we targeted α-*substituted* α-amino phosphonic acids, as these required the development of a strategy to control diastereoselection between two hindered reactants. Similar substitutions to create non-proteinogenic tertiary (α-substituted) α-amino acids have been explored in the development of enzyme inhibitors, helix-inducing peptide monomers, and robust analogs of natural amino acids.[7,8]

As an approach to α-substituted α,β-diamino acids, the use of α-substituted nitro *acetates*[9–12] is not complicated by post addition epimerization, but demands a catalyst effective in activating this hindered pronucleophile. Additionally, only high levels of kinetically controlled diastereo- and enantioselection can render this approach as practical as it is straightforward. Enantioselective additions of nitroalkane derivatives have proliferated in recent years as a result of a variety of new catalyst systems.[13] We recently disclosed a bifunctional catalyst that could deliver epimerizable α-nitro esters with high diastereo- and enantioselection.[14] In this context, the use of α-nitro phosphonates appeared to be a straightforward extension to provide the α-aminophosphonic acid derivatives.[1,15,16] However, we immediately faced several obstacles that prevented the extension of these and other principles outlined in the literature: (1) the possible activating effect a phosphonate group might provide was overcome by the steric demands of the phosphonate group in the addition transition state, and (2) our initial survey of achiral base and acid catalysts revealed a complete absence of substrate-controlled diastereoselection. The latter aspect highlighted the need for a chiral reagent to impart high levels of diastereoselection. We describe here how these obstacles can be overcome using bifunctional catalyst **1**, leading in two steps (addition/reduction) to α-substituted-α,β-diamino phosphonic acids in diastereo- and enantiomerically enriched form. These transformations constitute the first fully stereocontrolled additions of α-nitro phosphonates to azomethines.

Initial experiments clearly indicated that substituted nitrophosphonates **3** were considerably less reactive than nitroethane, requiring 5 days to reach 72% conversion

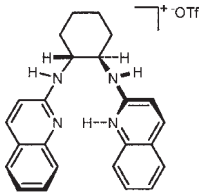
Table 1 Chiral proton catalyzed additions of α-nitrophosphonates to azomethines: effect of phosphonate ester size[a]



2a **3** **4**

Entry	R		*t*/d	Conv.[a] (%)	dr[b]	%ee[b]
1	OEt	**3a**	5	72	4 : 1	65
2[c]	OEt	**3a**	2	90	1 : 1	0
3	OBn	**3b**	7	70	2 : 1	63
4	O^{i}Pr	**3c**	8	68	4 : 1	80
5	OCHEt$_2$	**3d**	12	87	3 : 1	84
6	OCH^{i}Pr$_2$	**3e**	7	32	12 : 1	88

[a] All reactions were 0.1 M in substrate. Conversions were approximated by ^{31}P NMR. [b] Diastereomer ratios were measured by ^{31}P NMR and corroborated by HPLC. Enantiomer ratios were measured using chiral stationary phase HPLC. See ESI† for complete details. [c] The free base of **1** was used.



H,Quin-BAM·HOTf (**1**)

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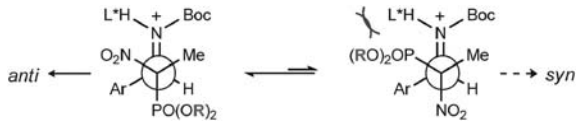


Fig. 1 Effect of phosphonate ester size on putative diastereomeric transition state arrangements.

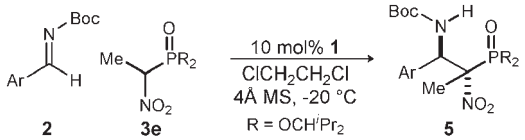
(Table 1, entry 1). And although the free base of **1** shortened the reaction time significantly (5 → 2 d), the addition product was delivered as a 1 : 1 ratio of diastereomers, both as racemates (Table 1, entry 2). The chiral Brønsted acid did improve diastereoselection to a modest level (4 : 1) while providing the major diastereomer in 65% ee and the minor diastereomer in 11% ee.

The consistently absent (achiral catalysts, *e.g.* Et_3N, $^{i}Pr_2NEt$: 1 : 1 dr) or low diastereoselection in these experiments may be due to a combination of effects. Comparison was first made to the diastereoselective additions of nitroethane (with **2a**: 17 : 1, 82% ee), using **1**. We hypothesized that the addition of a diethyl phosphonate group to nitroethane to give **3a** provides an additional hydrogen bond acceptor that abrogates the high diastereoselection. We therefore considered diastereomeric transition state arrangements shown in Fig. 1 and tactics to manage this possible competition. Phosphonate ester size would be used to minimize a potential catalyst-phosphonate hydrogen bond by increasing the associated energetic cost. A catalyst–nitro hydrogen bond, however, would be affected much less by a change in phosphonate ester size. The phosphonate ester size could also improve diastereoselection by providing better differentiation of the three groups attached to the nucleophilic carbon (methyl/nitro/phosphonate).

Small changes in phosphonate ester size (Table 1, entries 1–4) provided only improvement to enantioselection (65–84% ee) while maintaining some diastereoselection at the 2–4 : 1 level. Fortunately, further branching of the ester led to significant improvement in diastereoselection to 12 : 1 (Table 1, entry 5), but substantial attenuation of rate. With regard to reactivity, our comparisons were made using 50 mol% catalyst loadings in an attempt to separate catalyst reactivity from turnover. Control experiments throughout these studies also established that there was no detectable product formation at room temperature or below when using larger phosphonate esters (**3d**, **3e**) in the absence of catalyst. Low conversion at long reaction times did mitigate our enthusiasm of substantial catalyst-induced dual stereoselection. However, we moved forward due to the unparalleled simplicity with which these enantioenriched α,α-disubstituted α-amino phosphonic acid precursors could be produced.

In order to improve overall rate, we developed a protocol that employs dichloroethane solvent, slightly higher substrate concentration (0.67 M), 10 mol% catalyst loading, and a standard reaction time to produce the desired adducts in good isolated yield (Table 2). Dichloroethane provided for greater homogeneity at higher concentration. Electron rich aldimines can be particularly good substrates, leading to the *anti*-adducts **5** diastereo- and enantioselectively (Table 2, entries 3–7). Cocrystallization of **5i** and *ent*-**5h** led to assignment of relative

Table 2 Chiral proton catalyzed additions of nitrophosphonates to azomethines[a]



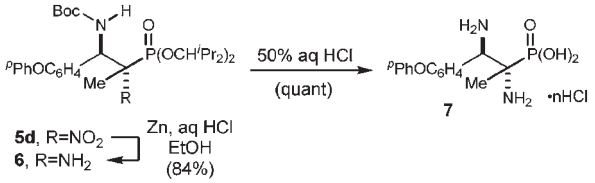
Entry	Ar		Yield (%)	dr[b]	%ee[b]
1	4-ClC_6H_4	**a**	49	9 : 1	88
2	3,4-$Me_2OC_6H_3$	**b**	68	2 : 1	67
3	4-$MeOC_6H_4$	**c**	84	6 : 1	99
4	4-$PhOC_6H_4$	**d**	74	7 : 1	99
5	4-$AllyloxyC_6H_4$	**e**	78	8 : 1	99
6	4-MeO-3-MeC_6H_3	**f**	75	6 : 1	85
7	4-MeO-3-BrC_6H_3	**g**	71	5 : 1	83
8	4-$MeSC_6H_4$	**h**	86	15 : 1	99
9	4-$PhSC_6H_4$	**i**	69	12 : 1	99
10	4-PhC_6H_4	**j**	46	10 : 1	88
11	C_6H_5	**k**	54	5 : 1	82
12	2-Np	**l**	50	9 : 1	88
13	4-$AcOC_6H_4$	**m**	48	6 : 1	97

[a] All reactions were 0.67 M in substrate. Conversions (7 d) were approximated by ^{31}P NMR: entry 1, 57%; 2, 96%; 3, 93%; 4, 95%; 5, 99%; 6, 92%; 7, 92%; 8, 92%; 9, 94%; 10, 77%; 11, 62%; 12, 67%; 13, 62%. [b] Diastereomer ratios were measured by ^{31}P NMR and corroborated by HPLC. Enantiomer ratios were measured using chiral stationary phase HPLC. See ESI.†

and absolute configuration by X-ray crystallography (see ESI†).[17] The *anti*-diastereoselection is consistent across three nitroalkane addition classes (nitroalkane,[18] nitroester,[14] and nitrophosphonate), but opposite that of α-substituted nitroesters[14b] using this catalyst class.[14c] Diastereoselection was generally high (Table 2, entries 3–13) in the range of 5–15 : 1, with one exception at 2 : 1 dr for disubstituted aldimine **2b**. This substrate also provided the lowest enantioselection (67%), whereas the remaining examples ranged from 83%–99% ee (Table 2, entries 3–13).

Investigations of less electron rich aldimines led to a noticeable loss of reactivity (*ca.* 20% lower yield), but virtually identical selectivity, when paired with catalyst **1** (Table 2, entries 1, 10–13). Insofar as bifunctional catalyst **1** is providing both Lewis acid activation of the Schiff base, and functions as a general base[19] for pronucleophile (**3**) activation as well, we have not successfully deconvoluted the catalyst's roles to determine the primary reason for this slightly lower reactivity.

We unmasked nitro phosphonates **5** to their underlying amino phosphonic acid functionality in a representative example (Scheme 1). Phosphonate **5d** was reduced to the corres-



Scheme 1 Conversion of α-nitrophosphonates to α-amino phosphonates and α-amino phosphonic acids.

ponding α-amino phosphonate in 84% yield using zinc powder in HCl/ethanol[9] with retention of configuration and without Boc deprotection. Additionally, warming of this α-amino phosphonate in 50% aq HCl cleanly forms the fully deprotected α,β-diamino phosphonic acid.

In summary, we have developed the first stereocontrolled additions of α-nitrophosphonates to imines as a concise route to α-substituted α,β-diamino phosphonic acids. Key to this development is the identification of sterically large phosphonate ester **3e** as a pivotal design element in our use of a chiral catalyst to achieve simultaneously high diastereo- and enantioselection in the synthesis of the tertiary nitrophosphonate products.[20] The Lewis acidity of these catalysts is clearly important (the free base is nonselective) for stereocontrol, but the catalyst efficacy is not compromised by the use of sterically large nitrophosphonate **3e**. These *anti*-diastereoselective additions are—for reasons not yet clear—stereocomplementary to similar additions of α-nitro esters which provide *syn*-adducts. Studies are underway to further examine our hypothesis that control of phosphonate hydrogen bonding is the key to high diastereoselection.

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