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Organocatalytic Highly Enantioselective Nitroaldol Reaction of α-Ketophosphonates and Nitromethane†

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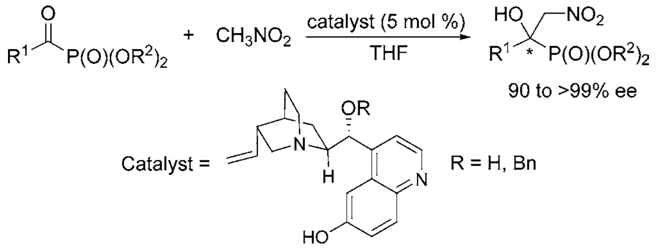
ABSTRACT



The first organocatalytic highly enantioselective nitroaldol reaction of α-ketophosphonates and nitromethane has been realized by using cupreine (2) or 9-*O*-benzylcupreine (3) as the catalyst. Both catalysts are highly reactive and highly enantioselective. α-Hydroxy-*β*-nitrophosphonates have been synthesized in good yields and excellent enantioselectivities (≥90% ee) at a low catalyst loading (5 mol %). These nitroaldol products may be reduced to the biologically significant *β*-amino-α-hydroxyphosphonates with complete retention of the stereochemistry.

As close analogues of α-hydroxy-*β*-amino acids, which are highly biological active substances,[1] *β*-amino-α-hydroxyphosphonic acid derivatives have received considerable interest in recent years.[2,3] Several methods have been developed for obtaining these compounds in optically active form;[2,4] however, only one enantioselective method has been reported so far,[5] in which the desired *β*-amino-α-hydroxyphosphonates were obtained in moderate to excellent ee values (32−95%) via the Sharpless asymmetric aminohydroxylation of vinyl phosphonates.[5]

Perekalin and co-workers reported in 1978 that racemic *β*-amino-α-hydroxyphosphonates may be readily obtained via the reduction of the nitro group of α-hydroxy-*β*-nitrophosphonates,[6] which, in turn, may be synthesized from α-ketophosphonates by using a nitroaldol reaction (Henry reaction) of α-ketophosphonates.[7] On the basis of these reports, we reasoned that a novel enantioselective synthesis

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† Dedicated to Professor David F. Wiemer.

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(2) (a) Mikołajczyk, M.; Drabowicz, J.; Łyżwa, P. In *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Juaristi, E., Soloshonok, V. A., Eds.; John Wiley: Hoboken, 2005; Chapter 12, pp 261−276. (b) Palacios, F.; Alonso, C.; de los Santos, J. In *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Juaristi, E., Soloshonok, V. A., Eds.; John Wiley: Hoboken, 2005; Chapter 13, pp 277−318.

(3) For a review on naturally occurring *β*-amino-α-hydroxyphosphonic acid derivatives, see: Mastałerz, P.; Kafarski, P. In *Aminophosphonic and Aminophosphinic Acids-Chemistry and Biological Activity*; Kukhar, V. P., Hudson, H. R., Eds.; John Wiley: Chichester, 2000; pp 1−31.

(4) For a review, see: Kukhar, V. P. In *Aminophosphonic and Aminophosphinic Acids-Chemistry and Biological Activity*; Kukhar, V. P., Hudson, H. R., Eds.; John Wiley: Chichester, 2000; pp 127−172.

(5) (a) Cravotto, G.; Giovenzana, G. B.; Pagliarin, R.; Palmisano, G.; Sisti, M. *Tetrahedron: Asymmetry* **1998**, *9*, 745−748. (b) Thomas, A. A.; Sharpless, K. B. *J. Org. Chem.* **1999**, *64*, 8379−8385.

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of β-amino-α-hydroxyphosphonates may be developed if the nitroaldol reaction is made enantioselective.[8]

According to the reported procedure,[7a,b] the nitroaldol reaction of α-ketophosphonates and nitromethane is catalyzed by an organic base, such as triethylamine or diethylamine. In principle, this reaction may be made enantioselective if an enantioenriched amine is used as the catalyst. Nevertheless, the original reaction conditions are not suitable for this purpose because the reaction is limited to alkyl-substituted α-ketophosphonates only.[7a,b] Because of our continued interest in the asymmetric synthesis of α-substituted phosphonate derivatives,[9] recently we reinvestigated this nitroaldol reaction and developed the first general organocatalytic nitroaldol reaction of α-ketophosphonates and nitromethane by using steric hindered bases, such as DABCO or quinuclidine, as the catalyst.[10]

Because quinuclidine is a good catalyst for the nitroaldol reaction of α-ketophosphonates and nitromethane, it is quite reasonable to hypothesize that its optically active congeners, such as quinine or quinidine,[11] are also good catalysts. On the basis of this assumption and inspired by the recent success in the quinine derivative catalyzed highly enantioselective nitroaldol reaction of α-keto esters and nitromethane reported by Deng and co-workers,[11a] we studied the nitroaldol reaction of α-ketophosphonates and nitromethane with some quinine derivatives as the catalysts. Herein, we wish to report the preliminary results of the first highly enantioselective synthesis of α-hydroxy-β-nitrophosphonates via a quinine derivative catalyzed nitroaldol reaction of α-ketophosphonates and nitromethane.

By using diethyl benzoylphosphonate (**4a**) as the substrate, we first screened some readily available quinine derivatives (**1**−**3**, Figure 1)[11a] as the catalysts. The results are summarized in Table 1.

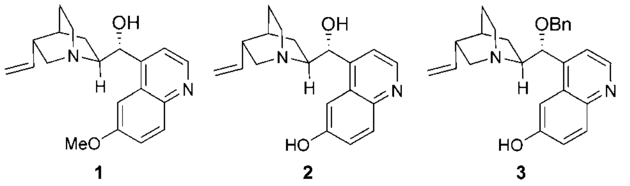
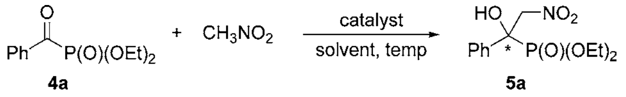


Figure 1. Catalysts screened for the nitroaldol reaction.

Table 1. Catalyst Screening and Reaction Condition Optimization[a]



entry	catalyst	solvent	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	**1**[d]	THF	rt	28	74	33
2	**2**[d]	THF	rt	10	85	94
3	**2**	THF	rt	15	81	92
4	**2**	CH_2Cl_2	rt	15	63	93
5	**2**	dioxiane	rt	19	48	93
6	**2**	toluene	rt	17	73	92
7	**2**	DMSO	rt	8	82	55
8	**2**	THF	0	28	71	97
9	**3**	THF	rt	14	80	98
10	**3**	THF	0	28	65	96

[a] Unless otherwise specified, all reactions were carried out with diethyl benzoylphosphonate (**4a**, 0.25 mmol), nitromethane (0.2 mL), and the catalyst (0.0125 mmol, 5 mol %) in the specified solvent (0.2 mL). [b] Yield of isolated product. [c] Determined by HPLC analysis with a Chiralcel OJ-H column; the absolute configuration of the major enantiomer was not determined. [d] With 0.025 mmol (10 mol %) of catalyst.

As shown in Table 1, with 10 mol % loading of quinine (**1**) in THF, the reaction of **4a** and nitromethane gave the desired product in 74% yield after 28 h at room temperature (entry 1); however, the enantioselectivity was very poor (33% ee). In contrast, the C6′-OH derivative **2** (cupreine) proved to be a very good catalyst[12] for this reaction, as an excellent ee value of 94% of the product was obtained under similar conditions (entry 2). The catalyst loading may be further reduced to 5 mol %, with an only slightly lower ee value of the product (92%, entry 3). Further screening of the solvents (entries 4−7) revealed that THF is the best one in terms of both reactivity and enantioselectivity. The ee value of the product may be further improved to 97% by lowering the reaction temperature to 0 °C (entry 8). A similar result was also obtained for the O-benzylated catalyst **3** (9-*O*-benzylcupreine) under these conditions (entry 9). Nevertheless, lowering the reaction temperature did not improve the enantioselectivity in this case (entry 10). It is interesting to note that these catalysts are much more reactive than their core, quinuclidine, because similar yields of the product were obtained with much less catalyst loading (20 mol % loading is required for quinuclidine).[10] Apparently, the increased steric hindrance around the nitrogen atom of these optically active catalysts prevents them from being poisoned by the nitroaldol product **5a**.[10]

To understand the scope of this novel enantioselective nitroaldol reaction, we studied reaction of various α-ketophosphonate substrates with nitromethane, using **2** or **3** as

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[8] For a recent review on the asymmetric nitroaldol reactions, see: Palomo, C.; Oiarbide, M.; Mielgo, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5442−5444.

[9] (a) Samanta, S.; Zhao, C.-G. *J. Am. Chem. Soc.* **2006**, *128*, 7442−7443. (b) Dodda, R.; Zhao, C.-G. *Org. Lett.* **2006**, *8*, 4911−4914. (c) Dodda, R.; Zhao, C.-*G. Org. Lett.* **2007**, *9*, 165−167.

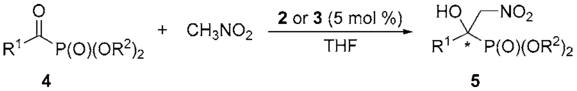
[10] Samanta, S.; Zhao, C.-G. *J. Mol. Catal. A: Chem.*, submitted.

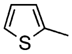
[11] For examples of alkaloid-catalyzed asymmetric nitroaldol reactions, see: (a) Li, H.; Wang, B.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 732−733. (b) Marcelli, T.; van der Haas, R. N. S.; van Maarseveen, J. H.; Hiemstra, H. *Synlett* **2005**, 2817−2819. (c) Misumi, Y.; Bulman, R. A.; Matsumoto, K. *Heterocycles* **2002**, *56*, 599−605. For an example of phase-transfer catalysis, see: Corey, E. J.; Zang, F. Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 1931−1934. For a review, see: Ooi, T.; Maruoka, K. *Acc. Chem. Res.* **2004**, *37*, 526−533.

[12] The C6′-OH has been shown to be essential for achieving high enantioselectivity in other reactions, too. For examples, see: (a) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906−9907. (b) Li, H.; Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 105−108. (c) Liu, X.; Li, H.; Deng, L. *Org. Lett.* **2005**, *7*, 167−169. (d) Li, H.; Song, J.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2005**, *127*, 8948−8949. (e) Ref 11a.

the catalyst. On the basis of our screening (Table 1), further reactions were conducted at 0 °C for catalyst **2** and at room temperature for catalyst **3**. The results are compiled in Table 2.

Table 2. Enantioselective Nitroaldol Reaction with Catalysts **2** and **3**[a]



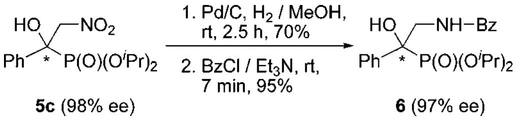
entry	R¹	R²	**4/5**	time (h)[b]	yield (%)[b,c]	ee (%)[b,d]
1	Ph	Et	**a**	28 (14)	71 (80)	97 (98)[e]
2	Ph	Me	**b**	20 (12)	72 (78)	94 (95)
3	Ph	^{i}Pr	**c**	32 (13)	77 (79)	98 (95)[e]
4	4-FC_6H_4	Me	**d**	16 (8)	83 (80)	96 (95)
5	4-FC_6H_4	Et	**e**	17 (9)	81 (84)	95 (93)
6	4-FC_6H_4	^{i}Pr	**f**	18 (16)	91 (79)	>99 (95)
7	3-FC_6H_4	Et	**g**	14 (11)	93 (82)	96 (96)[e]
8	4-ClC_6H_4	Me	**h**	12 (11)	86 (80)	93 (90)
9	4-ClC_6H_4	Et	**i**	14 (9)	84 (82)	93 (90)[f]
10	4-ClC_6H_4	^{i}Pr	**j**	16 (10)	83 (78)	99 (98)
11	4-BrC_6H_4	Et	**k**	13 (10)	91 (77)	94 (91)[e]
12	4-MeC_6H_4	Me	**l**	31 (16)	75 (72)	91 (97)
13	4-MeC_6H_4	Et	**m**	32 (18)	72 (76)	99 (96)
14	4-$MeOC_6H_4$	Et	**n**	48 (24)	61 (60)	98 (96)[e]
15		Et	**o**	26 (18)	76 (73)	93 (90)[e]
16	Me	Et	**p**	10 (8)	81 (79)	95 (95)
17	Me	^{i}Pr	**q**	10 (8)	80 (84)	98 (97)[g]
18	Et	Et	**r**	9 (9)	87 (79)	91 (90)[g]
19	$PhCH_2$	Et	**s**	8 (9)	81 (78)	97 (93)[g]
20	$PhCH_2CH_2$	Et	**t**	10 (9)	78 (75)	94 (96)[e]

[a] All reactions were carried out with α-ketophosphonate (**4**, 0.5 mmol), nitromethane (0.2 mL), and the catalyst (0.0125 mmol, 5 mol %) in THF (0.2 mL). The reactions with catalyst **2** were conducted at 0 °C, and the reactions with catalyst **3** were conducted at rt. [b]Data in parentheses are the results of catalyst **3**. [c]Yield of isolated product. [d]Unless otherwise specified, the enantioselectivities were determined by HPLC analyses with a Chiralpak AD-H column; the absolute configurations of the major enantiomers were not determined. [e]With a Chiralcel OJ-H column. [f]With a Chiralcel OD-H column. [g]With a Chiralpak AS column.

As shown in Table 2, with cupreine (**2**) as the catalyst, excellent enantioselectivities (≥91% ee) were obtained for both aryl-substituted (entries 1−15) and alkyl-substituted (entries 16−19) α-ketophosphonate substrates. As compared to the electron-donating group (entries 1−3 and 12−14), an electron-withdrawing group on the phenyl ring enhances the reaction rate (entries 4−11) but has no significant effects on the enantioselectivity. Alkyl-substituted α-ketophosphonates (entries 16−19) are also much more reactive than their aryl counterparts. In contrast to the electronic effects, the steric effects do have some influence on the enantioselectivity: the enantioselectivity normally increases slightly when the size of the ester alkyl group is increased, from the smaller Me and Et to the larger ^{i}Pr (entries 1−3, 4−6, 7−9, 16, and 17).

Similarly, excellent results were also obtained for catalyst **3** at room temperature (data inside the parentheses, ≥90% ee). With a few exceptions (entries 1, 2, 7, 12, 16, and 20), the enantioselectivities obtained are usually slightly inferior to those of catalyst **2**. However, because the reactions were carried out at room temperature, normally much shorter reaction times were required.

To show the usefulness of this reaction in the synthesis of enantioenriched *β*-amino-α-hydroxyphosphonates, the nitroaldol product **5c** was reduced to the corresponding *β*-amino-α-hydroxyphosphonate by following the reported procedure (eq 1; to facilitate the ee value determination, it was further converted to the benzoyl derivative **6**).[6] As is



(1)

evident from eq 1, the nitroaldol product may be reduced with complete retention of the stereochemistry.

In conclusion, we have developed the first organocatalytic highly enantioselective nitroaldol reaction of α-ketophosphonates and nitromethane by using cupreine (**2**) or 9-*O*-benzylcupreine (**3**) as the catalyst. α-Hydroxy-*β*-nitrophosphonates have been synthesized in good yields and excellent enantioselectivities (≥90% ee) at a low catalyst loading (5 mol %). These nitroaldol products may be reduced to *β*-amino-α-hydroxyphosphonates with complete retention of the stereochemistry.

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Supporting Information Available: Experimental procedures, NMR spectra for new compounds, and HPLC analysis data. This material is available free of charge via the Internet at http://pubs.acs.org.

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