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A Secondary Amine Amide Organocatalyst for the Asymmetric Nitroaldol Reaction of α-Ketophosphonates

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The nitroaldol (Henry) reaction is a fundamental synthetic tool for the construction of nitrogen-containing compounds in the organic synthesis.[1] Transformation of Henry reaction adducts, such as reduction to amines or oxidation (i.e., Nef reaction) to carbonyl compounds, could yield a variety of useful synthetic intermediates.[2] Over the past several years, many efficient catalytic asymmetric versions of this reaction have been developed.[3] However, compared with the substantial progress made with aldehydes,[4] few efficient catalysts have been developed for the asymmetric nitroaldol reactions of ketones.[5] The only example using α-ketophosphonates as the acceptor was reported by Zhao's group.[5h] The products could be converted into optically active β-amino-α-hydroxy phosphonates, which are of significant biological activity intermediates, such as the inhibition of renin and HIV protease.[6]

To the best of our knowledge, chiral organocatalysts utilized in direct nitroaldol reactions mainly contain cinchona alkaloids derivatives, guanidine and thiourea to form the nitromethide intermediates.[3] Until now, no secondary amine has yet been reported as an efficient catalyst. Thus, the search for an effective catalyst system based on secondary amines is very interesting. However, the literature revealed that less steric hindered organic bases, such as triethylamine or diethylamine, could not be incorporated in the nitroaldol reactions of aryl-substituted α-ketophosphonates.[7a,b] The poor performance of the catalyst and extremely low yield was ascribed to the serious rearrangement of the aryl-substituted nitroaldol product (as well as potential C–C or C–P bond cleavages) initiated by the deprotonation of the product under the reaction conditions.[7c–e] Excitingly, during the course of our studies, it was found that secondary amines, such as diethylamine or piperidine, could efficiently promote the nitroaldol reaction of α-ketophosphonate **3a** in THF at 0 °C, to give the desired product in high yields (Table 1, entries 1–2). It might be that the appropriate solvent and low reaction temperature efficiently suppressed further transformation of the product. Encouraged by this result, we focussed on the development of an asymmetric version of the secondary amine catalyzed asymmetric nitroaldol reaction of α-ketophosphonate.

Accordingly, a series of excellent chiral secondary amine amides[8] **1a–g** (Figure 1) was synthesized and evaluated in the reaction of α-ketophosphonate **3a** with nitromethane using THF as the solvent at 0 °C (Table 1). The L-pipecolic acid derivative **1b** with a (*R*,*R*)-1,2-diphenylethylenediamine backbone was superior to L-proline-derived **1a** and gave the desired product **4a** in 54% yield with 56% *ee* (Table 1, entry 4 vs 3). Only 11% *ee* were obtained using (*R*,*R*)-1,2-diaminocyclohexane as chiral diamine backbone (Table 1, entry 5). Moreover, for the achiral ethylenediamine **1d** backbone, rather poor results were obtained (10% yield and 9% *ee*; Table 1, entry 6), which suggested that the chiral diamine backbone moiety is of great importance. Trace amounts of product with low enantioselectivity (35%) were obtained when two nitrogen hydrogen atoms of the piperidine moiety in catalyst **1b** were replaced by methyl groups (Table 1, entry 7). Furthermore, only 28% *ee* were obtained with **1f** derived from (*S*,*S*)-1,2-diphenylethylenediamine and L-pipecolic acid (Table 1, entry 8 vs 4), indicating that matched chirality between diamine and piperidine was very important for the high catalytic efficiency. When monoamide **1g** was synthesized to catalyze this reaction, mostly racemic product was obtained (Table 1, entry 9 vs 4), which implied that the cooperation of the C_2-symmetric two amino

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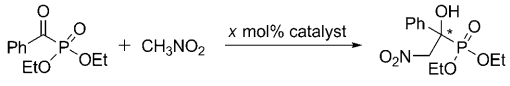
Table 1. Optimization of reaction conditions.



3a 4a

Entry[a]	X ([mol%])	Solvent [mL]	T [°C]	Yield [%][h]	*ee* [%][i]
1	Et_2NH (10)	0.1	0	76	0
2	piperidine (10)	0.1	0	80	0
3	**1a** (10)	0.1	0	40	11
4	**1b** (10)	0.1	0	54	56
5	**1c** (10)	0.1	0	43	11
6	**1d** (10)	0.1	0	10	9
7	**1e** (10)	0.1	0	trace	35
8	**1f** (10)	0.1	0	56	28
9	**1g** (10)	0.1	0	72	5
10[b]	**1b** (10)	0.1	0	47	66
11[c]	**1b** (10)	0.1	0	64	60
12[d]	**1b** (10)	0.1	0	68	63
13[d,e]	**1b** (10)	0.1	−20	54	65
14[d,e]	**1b** (5)	0.1	−20	52	66
15[d,f]	**1b** (5)	1.8	−20	38	78
16[d,f,g]	**1b** (5)	1.8	−20	66	84

[a] Unless noted otherwise, the reactions were carried out with **3a** (0.1 mmol), nitromethane (0.1 mL), 10 mol% catalyst in THF at 0°C for 24 h. [b] *t*BuOMe as solvent. [c] PhOMe as solvent. [d] *t*BuOMe/PhOMe (2/1) as solvent. [e] The reaction time was 48 h. [f] The reaction time was 80 h. [g] 0.3 mL nitromethane was used. [h] Isolated yield. [i] Determined by chiral HPLC.

amide units played a crucial role for the asymmetric induction.

A solvent survey revealed that *t*BuOMe showed higher *ee* while PhOMe provided higher yield (Table 1, entries 10–11).

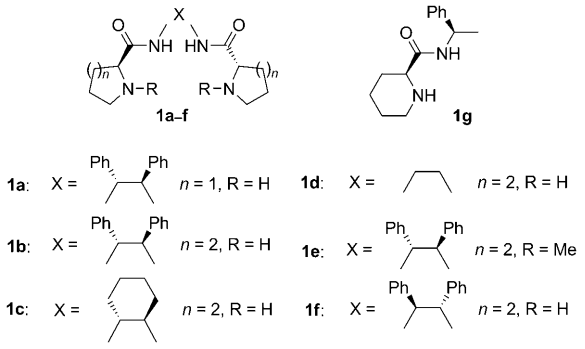


Figure 1. Catalysts evaluated in this study.

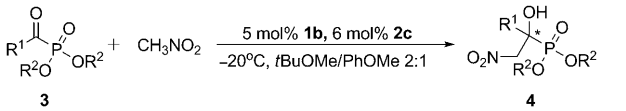
The best result could be obtained in a 2:1 mixture of *t*BuOMe and PhOMe (68% yield and 63% *ee*; Table 1, entry 12).[9] When the temperature was decreased to −20°C, the enantioselectivity was slightly increased to 65% *ee* (Table 1, entry 13). Furthermore, the catalyst loading could be reduced to 5 mol% without affecting the enantioselectivity (Table 1, entry 14). When the concentration of the substrate was decreased, the enantioselectivity was dramatically improved to 78% *ee* but the reactivity was further reduced (Table 1, entry 15). Fortunately, when the amount of nitromethane was increased, the reactivity and enantioselectivity were greatly improved (66% yield and 84% *ee*; Table 1, entry 16).

Table 2. Phenols screened in this reaction.

Entry[a]	Additive	pK_a[b]	Yield [%][c]	*ee* [%][d]
1	phenol (**2a**)	9.9	64	82
2	4-nitrophenol (**2b**)	7.14	76	88
3	2,4-dinitrophenol (**2c**)	4.01	83	96
4	2,4,6-trinitrophenol (**2d**)	1.02	88	80

[a] Unless noted otherwise, the reactions were carried out with 0.1 mmol α-ketophosphonate **3a**, 0.3 mL nitromethane, 5 mol% **1b**, 6 mol% additive and 1.8 mL *t*BuOMe/PhOMe (2/1) at −20°C for 80 h. [b] Relative pK_a[10] in water. [c] Isolated yield. [d] Determined by chiral HPLC.

Table 3. Substrate scope for the enantioselective nitroaldol reaction of α-ketophosphonates with nitromethane.



3 4

Entry[a]	R^1	R^2	Product	Yield [%][b,c]	*ee* [%][d]
1	Ph	Me	**4a**	86	94
2		Et	**4b**	83	96
3		*i*Pr	**4c**	73	92
4	4-F-Ph	Et	**4d**	88	99
5		Me	**4e**	90	99
6	4-Cl-Ph	Et	**4f**	93	96(*R*)[e]
7		Me	**4g**	90	97
8	4-Br-Ph	Et	**4h**	92	91
9	4-Me-Ph	Et	**4i**	73	98
10		Me	**4j**	76	92
11	4-MeO-Ph	Et	**4k**	67	95
12		Me	**4l**	68	93
13	4-*t*Bu-Ph	Et	**4m**	85	97
14		Me	**4n**	78	92
15	2-Cl-Ph	Et	**4o**	88	91
16		Me	**4p**	86	90
17	2-Br-Ph	Et	**4q**	80	91
18		Me	**4r**	81	90
19	2-Me-Ph	Et	**4s**	81	96
20		Me	**4t**	83	93
21	2-MeO-4-OMe-Ph	Et	**4u**	66	84
22		Me	**4v**	73	86
23	2-thienyl	Et	**4w**	54	88
24	$PhCH_2$	Et	**4x**	95	99
25	Me	Et	**4y**	90	91
26		Me	**4z**	90	84

[a] Unless noted otherwise, the reactions were carried out with 0.1 mmol α-ketophosphonate **3**, 0.3 mL nitromethane, 5 mol% **1b**, 6 mol% **2c** and 1.8 mL *t*BuOMe/PhOMe (2/1) at −20°C for 1–4.5 days. [b] Isolated yield. [c] For detailed reaction time, see Supporting Information. [d] Determined by chiral HPLC. [e] Determined by X-ray diffraction analysis.[11]

To further optimize the results, some achiral additives were screened. Phenols were found to be positive effect to the reaction (for details, see Supporting Information). When 2,4-dinitrophenol (**2c**) was used as additive, both the yield and enantioselectivity were improved drastically (83% yield and 96% *ee*; Table 2, entry 3). The slightly less acidic phenol (**2a**) or 4-nitrophenol (**2b**) gave lower yields and *ee* (Table 2, entries 1, 2 vs 3), while the stronger acidic 2,4,6-trinitrophenol (**2d**) exhibited high reactivity and low enantioselectivity (80% *ee*; Table 2, entry 4 vs 3). Extensive screening showed that the optimal reaction conditions were 5 mol% organocatalyst **1b**, 0.1 mmol α-ketophosphonate **3a**, 0.3 mL nitromethane in 1.8 mL *tert*-butyl methyl ether together with anisole (2:1 ratio), 6 mol% **2c** as additive at −20°C. Additionally, this process was tolerant to air and moisture.

Under the optimized reaction conditions, a wide range of α-ketophosphonates were investigated (Table 3). Aryl-substituted α-ketophosphonates with varying ester alkyl groups, such as Me, Et and *i*Pr, were found to be tolerable in this reaction and good results were obtained (Table 3, entries 1–3). Also, benzoylphosphonates with different substituents on the aromatic ring could give the desired nitroaldol products in good to excellent results. Substrates with either electron-donating, such as methyl, methoxyl and *tert*-butyl substituents or electron-withdrawing including halogen substituents, reacted smoothly with nitromethane to give moderate to high yields with excellent enantioselectivities (Table 3, entries 4–20). Moreover, the disubstituted aromatic, heteroaromatic and aliphatic α-ketophosphonates could also be converted to the desired products with good to excellent enantioselectivities (Table 3, entries 21–26). In addition, the absolute configuration of product **4f** was determined to be *R* through X-ray diffraction analysis.[11]

A preliminary study on the mechanism of this direct nitroaldol reaction of α-ketophosphonate has been investigated by theoretical calculations. As shown in Figure 2 for the two transition states, one of the piperidine moiety is protonated by the acidic additive **2c**, which activates the α-ketophosphonate via hydrogen bonding; the other deprotonates the hydrogen atom from nitromethane to protonate itself, which stabilizes the nitromethide by an intermolecular hydrogen bond.[12] According to the computational results, the energy of **TS1** is lower than that of **TS2** by ≈3.7 kcal mol^{-1}. Furthermore, the hydrogen bond between the carbonyl group of the substrate and the piperidine moiety of the catalyst **1b** in **TS1** is shorter than that in **TS2** (1.588 vs 1.791 Å), which elongates the carbonyl bond of the substrate in **TS1** (1.287 vs 1.285 Å).[9] A hydrogen bond is observed between the phosphorus oxygen and the amide moiety in **TS1**, which greatly contributes to the stability of the transition state. Therefore, **TS1** is evidently the favorable transition state which leads to the formation of major *R* product, which is in accordance with the experimental results.

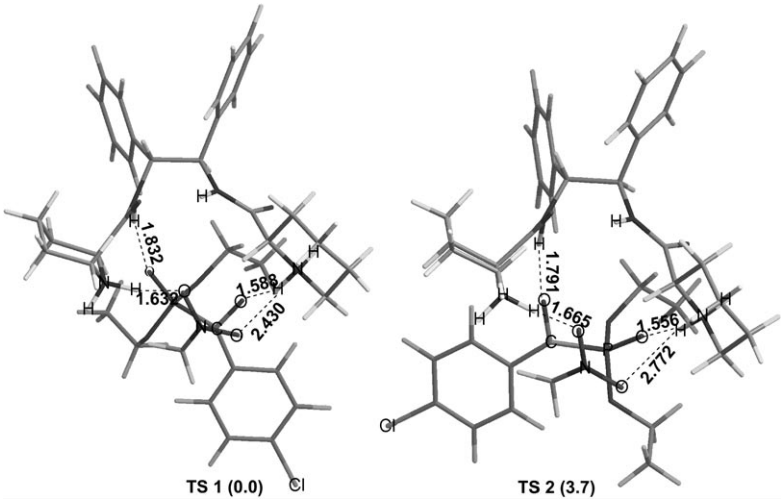


Figure 2. The calculated transition state of Henry reaction of *para*-chlorophenyl α-ketophosphonate **3f** with nitromethane catalyzed by **1b**–**2c**. The geometries were optimized at the level of HF/3-21g*. The relative energies [kcal mol^{-1}] are with HF/3-21 g* in brackets. **TS1** favored (*R*)-product, **TS2** favored (*S*)-product.

In conclusion, we have developed an efficient secondary amine amide catalyst system for the asymmetric nitroaldol reaction of α-ketophosphonates under mild conditions. In the presence of 5 mol% organocatalyst **1b**, excellent enantioselectivities (up to 99% *ee*) and moderate to high yields were achieved for most substrates. Additionally, a theoretical study on the transition states revealed that this secondary amine amide catalyst could be involved in hydrogen-bond interactions, which is important for the reactivity and enantioselectivity of this reaction.

Experimental Section

Typical experimental procedure: A solution of catalyst **1b** (2.17 mg, 5 mol%) and nitromethane (0.3 mL) in *t*BuOMe and PhOMe (1.8 mL, 2:1 ratio) was stirred for 10 min at ambient temperature. After it was cooled to −20°C, α-ketophosphonate **3a** (24 μL, 0.1 mmol) and **2c** (1.2 mg, 6 mol%) were added successively. The mixture was stirred at −20°C for 80 h and quenched with satd. NH_4Cl (2 mL). The aqueous layer was extracted with ethyl acetate (10 mL × 2). The combined organic layers were washed with satd. $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography by using EtOAc/PE to afford **4a** as a white solid.

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Keywords: aldol reaction · amides · amines · Henry reaction · organocatalysis

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[11] CCDC 698885 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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