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Nucleophilic Additions

Highly Efficient Catalytic System for Enantioselective Michael Addition of Aldehydes to Nitroalkenes in Water**

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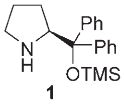
Since Betancort and Barbas reported the first organocatalytic asymmetric Michael addition of aldehydes to nitroalkenes,[1] a great effort has been devoted to the development of more selective and efficient catalytic systems for this synthetically useful transformation,[2–4] and significant progress has been made. Especially, the use of *o*-TMS-protected diphenylprolinol (**1**; TMS = trimethylsilyl)[3e] or pyrrolidine sulfonamide (**2**)[3d,h] as catalysts has given rise to excellent enantioselectivities in the reactions. However, for a long time, these reactions required a large excess of donor source (up to 10 equivalents of aldehyde) as well as high catalyst loadings (between 10 and 20 mol %), and they gave poor results when alkyl-substituted nitroalkenes were employed. These problems were efficiently solved by Palomo and co-workers by using the newly designed catalyst **3**.[3j] However, a loading of more than 5 mol % of this catalyst was still required in their experiments (although, at the time, this represented the lowest catalyst/substrate ratio employed in any enamine-based Michael addition with excellent enantioselectivity). While catalyst design has been the subject of several studies, little attention has been paid to exploring functionalized nitroalkene compounds as substrates.[3b,n] Such studies would be of immense benefit for expanding the scope of application of this reaction in organic synthesis. We recently found that β-nitroacrylate compounds are suitable acceptors for this reaction, the products of which are the precursors of biologically important β-amino acids[5] and β-lactams.[6] Accompanying this study, a more efficient catalytic system (which works in water and requires only 0.5–2 mol % of catalyst for the known substrates) was discovered. Herein, we disclose our results.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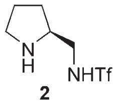
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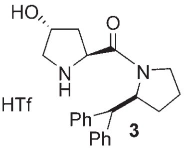
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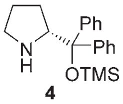
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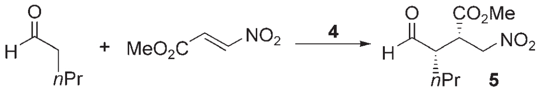
The required β-nitroacrylate compounds were easily accessible by the condensation of glyoxylic acid with nitromethane and subsequent esterification and elimination. Initially, we conducted our Michael addition under the conditions reported by Hayashi et al.[3e] We found that after 24 h, the desired adduct **5** and its epimer were produced with good diastereoselectivity and enantioselectivity (entry 1, Table 1). However, the conversion was incomplete, which prompted us to vary the reaction conditions. Changing the solvent to toluene led to a faster reaction, but the diastereoselectivity decreased significantly (entry 2, Table 1). Barbas and co-workers recently reported that water and brine were good media for organocatalytic reactions.[3k,7a] We were pleased to see that our reaction worked well in water to afford compound **5** with a high enantioselectivity (97 % *ee*) and good diastereoselectivity (entry 3, Table 1). Since it had been observed that the addition of some Brønsted acids could promote the formation of enamines, thereby accelerating amine-catalyzed reactions,[3a,8] we conducted the reaction in the presence of benzoic acid. When benzoic acid (100 mol %) was added, the reaction was greatly accelerated, although poor diastereoselectivity was observed (entry 4, Table 1). Interestingly, the selectivity was greatly improved by reducing the catalyst loading to 5 mol % and adding 50 mol % of

Table 1: Effect of the additive and the solvents on the Michael addition of *n*-pentanal to methyl 3-nitroacrylate (catalyzed by amine **4**).[a]



Entry	Solvent	Benzoic acid [mol %]	*t* [h]	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][d]
1	*n*-hexane	0	24	65[e]	95:5	94
2	toluene	0	24	80	67:33	94
3	water	0	22	67	91:9	97
4	water	100	1.5	91	53:47	> 99
5	water	50	2	90	97:3	> 99
6	water	50	1.5	88	64:36	> 99
7	water	25	4	82	98:2	> 99

[a] Reaction conditions: methyl 3-nitroacrylate (1 mmol), *n*-pentanal (2 mmol), 10 mol % **4** (5 mol % **4** was used for entries 5 and 7), 2 mL of solvent, 0 °C for 1 h, then RT for the indicated time. [b] Yield of isolated product. [c] Determined by means of ^{1}H NMR measurements performed on the crude product. [d] Determined by means of chiral-phase HPLC analysis of the *syn* product. [e] About 10 % of methyl 3-nitroacrylate was not consumed (determined by ^{1}H NMR spectroscopy).

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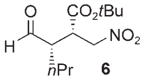
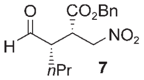
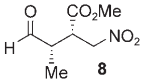
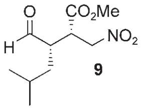
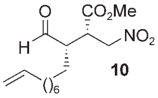
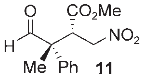
benzoic acid (entry 5, Table 1), whereas simply reducing the amount of benzoic acid still gave poor diastereomeric ratios (entry 6, Table 1). These results indicated that high catalyst loadings, which lead to quick conversion, could decrease the overall diastereoselectivity. This phenomenon has also been observed in some organocatalytic reactions.[9] Since using 5 mol% of catalyst **4** and 25 mol% of benzoic acid slowed down the reaction (entries 5 and 7, Table 1), we decided to use a ratio of 1:10 for the catalyst and the additive in the subsequent studies.

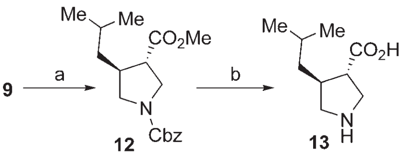
Using the optimized reaction conditions we examined a number of β-nitroacrylate and aldehyde compounds (Table 2). In most cases, good yields and excellent diastereo- and enantioselectivities were observed. When 2-phenylpropanal was used, the diastereoselectivity dropped dramatically. Noteworthy is that the *tert*-butyl and benzyl ester moieties in **6** and **7** can be cleaved by acid treatment and hydrogenolysis, respectively, to furnish the corresponding acids in a specific manner, and that the olefinic double bond in **10** can be further modified to afford molecules of higher complexity.

Table 2: Enantioselective Michael addition of aldehydes to 3-nitroacrylates.[a]

Entry	Product	*t* [h]	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][d]
1	 **6**	6	90	97:3	>99
2	 **7**	2	86	98:2	>99
3	 **8**	7	74	97:3	98
4	 **9**	2.5	83	98:2	>99
5	 **10**	2	81	96:4	>99
6	 **11**	15	81	81:19	96

[a] Reaction conditions: 3-nitroacrylate (1 mmol), aldehyde (2 mmol), 5 mol% **4**, 50 mol% benzoic acid, 2 mL of water, 0 °C for 1 h, then RT for the indicated time. [b] Yield of isolated product. [c] Determined by means of ^{1}H NMR measurements performed on the crude product. [d] Determined by means of chiral-phase HPLC analysis of the *syn* product.

To demonstrate the utility of our reaction, adduct **9** was transformed into the known amino acid **13**[10] by means of a four-step procedure (Scheme 1). Hydrogenation of **9**, followed by protection with benzyl chloroformate, provided pyrrolidine **12**, which was then subjected to deprotection to afford **13** (with an overall yield of 48%). The analytical data obtained for this compound were identical to the reported values, which confirms the stereochemistry of adduct **9**. Two routes for assembling this conformationally restricted analogue of the anticonvulsant pregabalin have been disclosed to date[10]—our route being shorter and more convenient.



Scheme 1. Synthesis of amino acid **13**. Reagents and conditions: a) $Pd(OH)_2$, H_2, MeOH; then benzyl chloroformate, Et_3N, DMAP, CH_2Cl_2, 54%; b) aq. LiOH, MeOH, THF; then Pd/C, H_2, MeOH, 90%.

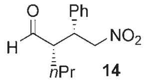
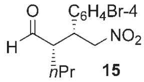
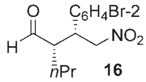
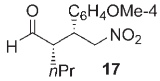
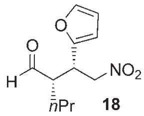
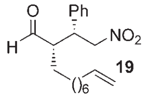
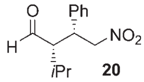
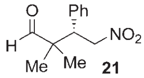
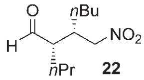
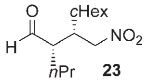
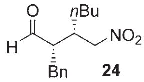
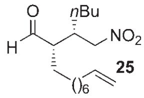
The excellent performance of our procedure in Michael additions of aldehydes to β-nitroacrylate compounds also encouraged us to check if it could provide improved results when simple aryl- and alkyl-substituted nitroalkenes were employed. Gratifyingly, for aryl nitroalkenes, excellent results were obtained by using only 1 mol% of the catalyst in less than 12 h (entries 1–6, 8, and 9, Table 3). Further reduction of the catalyst loading still gave satisfactory results (entry 7, Table 3). To our knowledge, these results represent the lowest suitable catalyst loadings reported to date for Michael additions and for several other organocatalyst-mediated reactions.[11]

Reaction of β-nitrostyrene with 2-methylpropanal produced adduct **21** (with 97% yield and 92% *ee*), although a prolonged reaction time and increased catalyst loading were required (entry 10, Table 3). This is—to date—the highest *ee* value achieved for this Michael adduct, thus providing further evidence of the excellent asymmetric induction ability of *o*-TMS-protected diphenylprolinol **4** and its enantiomer **1**.

In the case of less-reactive alkyl nitroalkene compounds, a catalyst loading of 2 mol% was necessary to ensure complete conversion within 2–12 h. Variation of the aldehyde and alkyl nitroalkene species did not alter the excellent yield, diastereoselectivity, and enantioselectivity (entries 11–15, Table 3). To investigate the suitability of our system for multigram-scale synthesis, some reactions were carried out on a 10-mmol scale using a slight excess of aldehyde (entries 4 and 13, Table 3). In general, we obtained satisfactory results, although in one case both the diastereoselectivity and the enantioselectivity were slightly diminished (entries 3 and 4, Table 3). Thus, our procedure is quite promising for pharmaceutical and industrial applications.

In conclusion, we have developed a new procedure for the asymmetric Michael addition of aldehydes to nitroalkenes, which provides an excellent solution to the problems associated with this reaction. The diarylprolinol ether catalyst used herein is simple and easily accessible. These advantages make this procedure more suitable for practical use. Mechanistically, the progress may result from a combination of the excellent asymmetric induction ability of the *o*-TMS-protected diphenylprolinol compounds,[12] the quick formation of enamine species in the presence of benzoic acid, and the highly concentrated organic phase directed by the aqueous medium.[7] These observations may prepare the ground for the development of more effective conditions for other enamine-based reactions catalyzed by *o*-TMS-protected diphenylprolinol compounds. Investigations in this direction,

Table 3: Enantioselective Michael addition of aldehydes to aryl- and alkyl-substituted nitroalkenes.[a]

Entry	Product	Catalyst [mol%]	t [h]	Yield [%][b]	*syn/anti*[c]	*ee* [%][d]
1	 **14**	1	6	96	98:2	> 99
2	 **15**	1	13	87	96:4	> 99
3 4	 **16**	1 1	4 24	98 95[e]	95:5 92:8	> 99 > 99
5	 **17**	1	12	86	97:3	> 99
6 7	 **18**	1 0.5	2 6	95 96	98:2 98:2	> 99 > 99
8	 **19**	1	5	86	96:4	> 99
9	 **20**	1	7	96	97:3	> 99
10	 **21**	10	60	97	–	92
11	 **22**	2	2	83	94:6[f]	> 99
12 13	 **23**	2 2	12 44	88 78[e]	94:6[f] 94:6[f]	> 99 > 99
14	 **24**	2	2.5	81	96:4	> 99
15	 **25**	2	5	85	94:6[f]	> 99

[a] Reaction conditions: 3-nitroalkene (1 mmol), aldehyde (2 mmol), 0.5–2 mol% **4**, 5–20 mol% benzoic acid, 2 mL of water, 0 °C for 1 h, then room temperature for the indicated time. [b] Yield of isolated product. [c] Determined by means of ^{1}H NMR measurements performed on the crude product. [d] Determined by means of chiral-phase HPLC analysis of the *syn* product. [e] The reaction was carried out on a 10-mmol scale using 1.5 equivalents of aldehyde. [f] Determined by means of chiral-phase HPLC analysis after purification.

as well as studies on the application of the above results to the synthesis of more complex molecules, are currently under.

Experimental Section

Typical Procedure: *n*-Pentanal (213 μL, 2.0 mmol) was added to a suspension of catalyst **4** (16 mg, 0.05 mmol), methyl 3-nitroacrylate (131 mg, 1.0 mmol), and benzoic acid (61 mg, 0.5 mmol) in water (2.0 mL) at 0 °C. After 1 h at 0 °C, the reaction mixture was allowed to warm to room temperature and then stirred until methyl 3-nitroacrylate was consumed (the course of the reaction was monitored by means of thin-layer chromatography, TLC). The reaction was then quenched by adding saturated $NaHCO_3$, and the resultant mixture was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated. Purification by flash column chromatography (silica gel, petroleum ether/AcOEt) afforded the Michael adduct (195 mg, 90%) as a colorless oil. A ratio of 97:3 for the *syn* and *anti* isomers was determined by performing ^{1}H NMR measurements on the crude mixture. The *ee* value (> 99%) was measured by means of high-performance liquid chromatography (HPLC) on a chiral stationary phase: Chiralpak IC column, $\lambda = 214$ nm, EtOH/hexane 10:90, $t_R = 23.4$ min (major), 28.5 min (minor).

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