Highly Efficient Ion-Tagged Catalyst for the Enantioselective Michael Addition of Aldehydes to Nitroalkenes

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Abstract: The ion-tagged diphenylprolinol silyl ether **6** very efficiently catalyzes the asymmetric Michael addition of aliphatic aldehydes to nitroalkenes with *ee* of up to > 99.5% at low catalyst loadings (0.25–5 mol%) and using only a slight excess of aldehydes (1.2–2 equiv.). This new organocatalyst can be used with the same outstanding efficiency in a wide variety of solvents and reaction conditions.

Keywords: asymmetric organocatalysis; ion-tagged diphenylprolinol; Michael addition; nitro compounds; synthetic methods
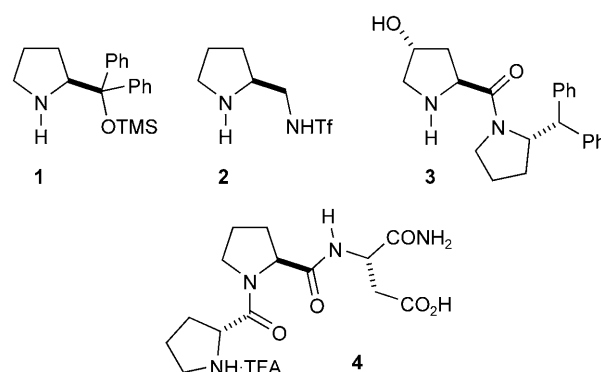

Figure 1. Selected organocatalysts for the Michael additions of aliphatic aldehydes to nitroalkenes.

Since the pioneering studies of Barbas on the organo-catalytic asymmetric Michael addition of aliphatic aldehydes to nitroalkenes,[1] many different catalysts and synthetic protocols have been developed and proposed.[2–5] In particular, *O*-TMS-protected diphenylprolinol (**1**; TMS = trimethylsilyl),[6] pyrrolidinesulfonamide **2** (Tf = trifluoromethanesulfonyl)[7] and *trans*-4-hydroxyprolylamide **3**[8] (Figure 1) act as effective organocatalysts for this class of reactions, affording almost complete enantioselectivities.

The only drawback of the use of these organocatalysts is the need to employ high catalyst loadings (5–20 mol%) and large excesses of donor aldehydes (up to 10 equiv.) to achieve high conversions in reasonable reaction times. This problem was recently addressed by Ma for long-chain water-insoluble aldehydes with a very efficient protocol using 0.5–2 mol% of **1** and 1.5–2 equiv. of aldehydes, in water as the solvent and in the presence of 5–20 mol% of benzoic acid as additive.[9] Finally, the tripeptide H-D-Pro-Pro-Asp-NH₂ (**4**), recently proposed by Wennemers, is able to efficiently catalyze the Michael additions of

aldehydes to nitroalkenes using 1 mol% catalyst loading and 3 equiv. of carbonyl compounds.[10]

We recently showed that inserting an ion-tagged side chain in the skeleton of known ligands and organocatalysts may result in the production of more efficient catalytic species.[11] In particular, the ion-tagged *cis*-hydroxyproline derivative **5** [NTf₂ = bis(trifluoromethanesulfonyl)imide] (Figure 2) is one of the most efficient organocatalysts so far reported for the enantioselective cross-aldol reaction of ketones and aldehydes.[11c] Besides conferring to the molecule well-defined solubility profiles, the ion-tagged side chain can actively participate in the stabilization of charged
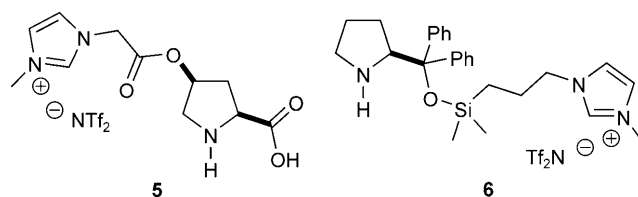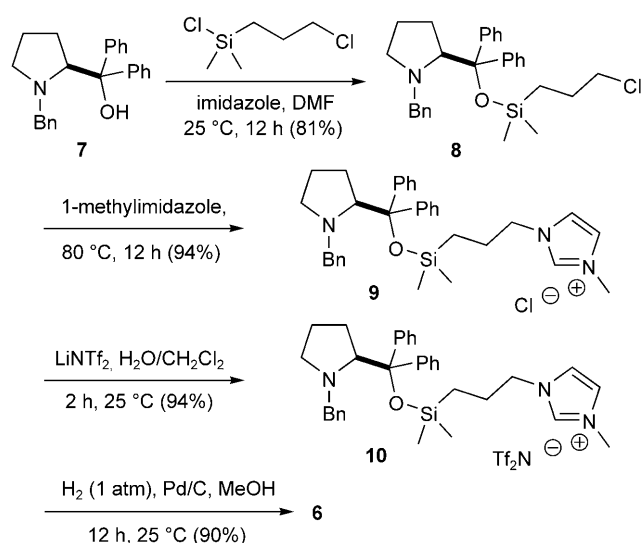

Figure 2. Ion-tagged organocatalysts.

transition states,[12] thus resulting in a faster reaction.[13]

Here we wish to report that the ion-tagged organocatalyst **6**, easily derived from *N*-benzyldiphenylprolinol **7**,[14] is a highly efficient organocatalyst for the enantioselective Michael addition of aldehydes to nitroalkenes, giving good yields and excellent enantioselectivities at 1 mol% catalyst loading, using only a small excess of donor aldehyde (1.2–2 equiv.) and in a variety of solvents, ranging from water to typical organic solvents and ionic liquids.

The synthesis of **6** proceeded in high yields using operationally simple procedures (Scheme 1).

Scheme 1. Synthesis of ion-tagged catalyst **6**.

Table 1. Solvent screening in the addition of propanal to (*E*)-β-nitrostyrene catalysed by **6** (5 mol%).[a]

Entry	Solvent	*t* [min]	Yield [%][b]	*ee* [%][c]	*syn/anti*[d]
1	[bmim][NTf$_2$][e]	15	95	99	85:15
2	[bmpy][NTf$_2$][f]	15	95	99	85:15
3	CH$_2$Cl$_2$	15	96	99	84:16
4	CHCl$_3$	15	96	99	72:28
5	H$_2$O	15	94	99	88:12
6	neat	30	97	99	86:14
7	CH$_3$CN	30	98	99	80:20
8	*n*-hexane	45	99	99	77:23
9	*c*-hexane	45	98	99	84:16
10	Et$_2$O	45	97	99	85:15
11	THF	45	96	99	82:18
12	*t*-BuOMe	45	99	99	85:15
13	EtOAc	90	99	99	84:16
14	MeOH	90	98	99	92:8
15	EtOH	90	97	99	84:16
16	acetone	90	98	99	86:14

[a] *Reaction conditions:* nitrostyrene (0.5 mmol), propanal (5 mmol), 5 mol% **6**, 0.5 mL of solvent, 25°C for the specified time.
[b] Yield of isolated product.
[c] The *ee* was determined by HPLC analysis (Chiralpak IC column). The absolute configuration was assigned by comparison of the optical rotation with that of the known products.
[d] Determined by HPLC on crude reaction mixture.
[e] bmim = 1-butyl-3-methyl imidazolium.
[f] bmpy = 1-butyl-1-methyl pyrrolidinium.

The choice of Tf$_2$N as counter-ion was dictated by its stability towards hydrolysis, a property not shared by the commonly use BF$_4$ or PF$_6$ anions. The latter produce traces amounts of fluoride anions in the presence of water,[15] that catalyze the desilylation of **6**.

With organocatalyst **6** in our hands, we started testing the simple addition of propanal to nitrostyrene as the model reaction in different solvents, using 5 mol% catalyst loading in the presence of 10 equiv. of aldehyde (Table 1). The catalytic system displayed an outstanding activity in all the solvents examined, but especially in ionic liquids (entries 1 and 2), in halogenated solvents (entries 3 and 4) and in water (entry 5), where reactions were complete after 15 min. Moreover, in all the solvents examined, enantioselectivities were invariably high (99% *ee*) and good diastereoselectivities in favour of *syn* isomers were obtained. On the basis of the results obtained in Table 1, we chose CH$_2$Cl$_2$ and water as benchmark solvents. Using CH$_2$Cl$_2$ we optimized the reaction conditions in terms of catalyst loading and excess of aldehyde (Table 2).

Excellent levels of reaction efficiency and enantioselectivity were obtained in all conditions tested. In almost every case, decreasing the reaction temperature from 25°C to 0°C had a negligible impact on enantioselectivity and only a small effect on the diastereomeric ratio, but the reaction times needed to achieve complete conversion became notably longer (entries 1, 3, 5 and 7).

We were delighted to observe that catalyst loading can be decreased to 1 mol% in the presence of only 1.2 equiv. of aldehyde to achieve a quantitative conversion to the desired product in only 1.5 h (entry 8); the same reaction was also scaled up to 5 mmol, maintaining the same level of efficiency and enantiocontrol (entry 9). Decreasing the reaction temperature from 25°C to 0°C had in this last case a beneficial effect both on enantioselectivity (>99% *ee*) and on diastereoselectivity (*syn/anti* 93:7, entry 10). To confirm the efficiency of **6**, we performed some more reactions lowering further the catalyst loading (entries 11–13). In these cases, the presence of 10 equiv. of benzoic

Table 2. Screening of reaction conditions in the addition of propanal to (E)-β-nitrostyrene catalysed by **6** in CH₂Cl₂.[a]

Entry	Propanal [equiv.]	**6** [mol%]	T [°C]	t [h]	Yield [%][b]	ee [%][c]	anti/ syn[d]
1	10	5	0	1.5	97	99	92:8
2	2	5	25	0.5	98	99	88:12
3	2	5	0	3	97	99	90:10
4	10	1	25	1.5	98	99	86:14
5	10	1	0	8	96	99	90:10
6	2	1	25	1	98	99	86:14
7	2	1	0	4	94	99	90:10
8	1.2	1	25	1.5	98	99	86:14
9[e]	1.2	1	25	1.5	97	99	89:11
10	1.2	1	0	6	99	>99	93:7
11[f,g]	2	0.5	25	1.5	99	>99	95:5
12[f,g]	2	0.25	25	4	88	>99.5	96:4
13[f,h]	2	0.1	25	6	35	>99.5	96:4

[a] *Reaction conditions:* nitrostyrene (0.5 mmol), propanal (0.6–5 mmol), 0.1–5 mol% **6**, 0.5 mL of CH₂Cl₂, 0°C or room temperature for the specified time.
[b] Yield of isolated product.
[c] The *ee* was determined by HPLC analysis (Chiralpak IC column).
[d] Determined by HPLC on crude reaction mixture.
[e] The reaction was carried out on a 5 mmol scale.
[f] Reaction with 10 equiv. of benzoic acid with respect to **6**.
[g] The reaction was carried out on a 1 mmol scale.
[h] The reaction was carried out on a 2.5 mmol scale.

Table 3. Addition of propanal to (E)-β-nitrostyrene catalysed by **6** (1 mol%) in water, with and without benzoic acid.[a]

Entry	Benzoic acid [mol%]	t [h]	Yield [%][b]	ee [%][c]	syn/ anti[d]
1	0	2	98	99	93:7
2	10	1	97	99	90:10

[a] *Reaction conditions:* nitrostyrene (0.5 mmol), propanal (1 mmol), 1 mol% **6**, 1 mL of H₂O, benzoic acid (0-0.05 mmol), 25°C for the specified time.
[b] Yield of isolated product.
[c] The *ee* was determined by HPLC analysis (Chiralpak IC column).
[d] Determined by HPLC on crude reaction mixture

acid with respect to **6** allowed us to achieve good conversions in reasonable reaction times.[9] Astonishing results were obtained when the catalyst was used at 0.5 and 0.25 mol%, with excellent conversions and enhanced selectivities after a few hours. When the catalyst was used at 0.1 mol% a 35% yield was obtained after 6 h, with improved values of enantio- and diastereoselectivity. These are, to the best of our knowledge, the smallest catalyst loadings ever employed successfully for this Michael reaction.

Finally, the model reaction was also examined using water as the solvent (Table 3). With 1 mol% of **6** and 2 equiv, of aldehyde a slower reaction occurred with respect to CH₂Cl₂, but the use of water slightly improved the diastereomeric ratio. The reaction became much faster in the presence of benzoic acid, while maintaining a high level of stereoselectivity.

CH₂Cl₂ and H₂O as solvents were selected also for expanding the scope of the reaction. As depicted in Table 4, excellent results were obtained for a wide range of aliphatic aldehydes and different substituted nitroalkenes.

By inspection of Table 4, some general trends can be derived. First of all, CH₂Cl₂ is a much better solvent compared to water for reactions of propanal with aromatic nitroalkenes (entries 1 and 2). On the other hand, water is a better reaction medium when

less reactive aliphatic nitroalkenes or longer chain aldehydes are used (entries 3–14). This behaviour can be ascribed to the rapid solubility decrease of aldehydes in water when the molecular weight increases. Indeed, at 20°C the solubility of propanal in water is much higher (22.9 mass%) compared to butanal (7.44), 2-methylpropanal (5.62), 4-methylpentanal (2.02) and pentanal (1.43).[16] These values possibly represent the ability of aldehydes to generate with water liquid-liquid biphasic systems, where faster reactions occur in a highly concentrated organic phase. Second, when sterically hindered nitroalkenes or aldehydes are used (entries 3, 8, 12–14), the presence of an acid additive is necessary to ensure high conversions. Moreover, the use of water and addition of benzoic acid generally afforded better enantio- and diastereomeric ratios. Finally, an increased catalyst loading was necessary for the less reactive aliphatic nitroalkene (entries 3, 8 and 12) and 2-methylpropanal (entry 14). This last reaction proved once more the great efficiency of **6**, since a quantitative yield of product was recovered after 22 h using 5 mol% of catalyst and without the addition of benzoic acid. Albeit with moderate enantioselectivity, these are to date the mildest reaction conditions used for the synthesis of this Michael adduct.

In summary, we have developed a new efficient ion-tagged organocatalyst for the asymmetric Michael addition of aldehydes to nitroalkenes, which displays remarkable features. Not only does it give excellent enantioselectivities and very good diastereoselectivities in a wide range of reaction media, ranging from water to organic solvents, but it displays enhanced reactivity compared to the known organocatalysts reported for this Michael reaction, also when used at 0.25–1 mol% and in the presence of only a slight excess of donor aldehyde (1.2–2 equiv.). Further studies to expand the catalyst scope and to elucidate reaction mechanism are in progress.

Table 4. Scope of the Michael addition of aliphatic aldehydes to nitroalkenes catalysed by **6**.[a]

Entry	Product	Reaction conditions	t [h]	Yield [%][b]	ee [%][c]	syn/anti[d]
1	C6H4Br-4	A	1	97	99	86:14
		C	4	98	99	92:8
2	C6H4OMe-4	A	1	96	99	87:13
		C	4	96	99	91:9
3[e]	c-C6H11	A	24	28	98	78:22
		B	22	66	99	89:11
		C	24	89	99	78:22
4	Ph, Et	A	5	94	>99	87:13
		C	4	90	>99	92:8
		D	2	94	>99.5	94:6
		D[f]	3.5	84	>99.5	93:7
5	C6H4Br-4, Et	A	8	92	99	90:10
		C	4	86	>99	95:5
6	C6H4Br-2, Et	A	8	96	>99	88:12
		C	4	94	>99	96:4
7	C6H4OMe-4, Et	A	12	87	99	80:20
		C	4	92	99	92:8
8[e]	c-C6H11, Et	A	22	48	97	90:10
		B	22	65	95	85:15
		C	22	50	95	89:11
		D	22	81	97	79:21
9	Ph, n-Pr	A	6	94	>99	85:15
		C	4	99	>99.5	95:5
		D	2	98	>99.5	96:4
10	C6H4Br-4, n-Pr	A	6	95	>99	81:19
		C	4	99	>99.5	95:5
11	C6H4OMe-4, n-Pr	A	10	92	>99.5	83:17
		C	4	98	>99.5	93:7
12[e]	c-C6H11, n-Pr	A	24	43	>99	91:9
		B	24	98	>99.5	95:5
		C	24	54	>99	91:9
		D	9	99	>99.5	92:8
13	Ph, i-Pr	B	24	42	>99	92:8
		D	7	65	>99	98:2
14[g]	Ph	A	53	49	58	–
		C	22	99	76	–

[a] *Reaction conditions:* nitroalkene (0.25 mmol), aldehyde (0.5 mmol), 1 mol% **6** at room temperature for the specified time. **A**: 0.25 mL of CH$_2$Cl$_2$; **B**: benzoic acid (0.025 mmol), 0.25 mL of CH$_2$Cl$_2$; **C**: 0.5 mL of H$_2$O; **D**: benzoic acid (0.025 mmol), 0.5 mL of H$_2$O.
[b] Yield of isolated product.
[c] Determined by chiral HPLC analysis (Chiralpak IC column). The absolute configuration was assigned by comparison of the optical rotation with that of the known products.
[d] Determined by HPLC on crude reaction mixture.
[e] 2 mol% of **6**.
[f] The reaction was carried out on a 4-mmol scale using 1.2 equiv. of butanal.
[g] 5 mol% of **6**.

Experimental Section

Reaction in CH$_2$Cl$_2$ – Typical Procedure

The aldehyde (1.2–2 equiv.) was slowly added at 25 °C or at 0 °C to a solution of nitroalkene (0.25–5 mmol) and catalyst **6** (0.25–5 mol%) in CH$_2$Cl$_2$ (0.25–5 mL) in a screw-capped vial and the reaction mixture was stirred at the desired temperature until thin-layer chromatography (TLC) showed the disappearance of the starting nitroalkene. The solvent was evaporated at reduced pressure and the residue was purified by flash chromatography on silica eluting with cyclohexane/ethyl acetate, 9:1. The enantiometric excess was determined on the crude reaction mixture by high-performance liquid chromatography (HPLC) using a Chiralpak IC column.

Reaction in H$_2$O – Typical Procedure

The aldehyde (1.2–2 equiv.) was slowly added at room temperature to a suspension of nitroalkene (0.25–4 mmol) and catalyst **6** (1–5 mol%) in H$_2$O (0.5–8 mL) in a screw-capped vial and the reaction mixture was vigorously stirred at room temperature until thin-layer chromatography (TLC) showed the disappearance of the starting nitroalkene. The aqueous phase was extracted with CH$_2$Cl$_2$, the combined organic layers were dried (Na$_2$SO$_4$) and evaporated at reduced pressure. The residue was further purified by flash chromatography on silica eluting with cyclohexane/ethyl acetate 9:1. The enantiometric excess was determined on the crude reaction mixture by high-performance liquid chromatography (HPLC) using a Chiralpak IC column.

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