

A Highly Active 4-Siloxyproline Catalyst for Asymmetric Synthesis

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Abstract: *trans*-4-*tert*-Butyldimethylsiloxy-L-proline displays a greater catalytic activity than the parent proline without compromising the enantioselectivity, which widens the substrate scope in the α -aminoxylation of carbonyl compounds, as well as *O*-nitroso-aldol/Michael, and Mannich reactions.

Keywords: asymmetric synthesis; Mannich reaction; organic catalysis; oxidation; proline

Organic catalyst-mediated asymmetric reactions^[1] represent a rapidly developing field of research and numerous impressive results have appeared recently following the discovery of the proline-catalyzed aldol reaction, which is the intermolecular variant of the Hajos–Parrish–Eder–Sauer–Wiechert reaction,^[2] reported by List, Lerner and Barbas in 2000.^[3] Among several organic catalysts developed for asymmetric reactions, proline has occupied a central role. It has been successfully employed not only in the aldol,^[3,4] but also in Mannich,^[5] Michael,^[6] α -amination,^[7] and α -aminoxylation^[8] reactions. Several modifications of proline catalyst such as the substitution of the carboxylic acid moiety of proline with an amide or tetrazole function have been performed to improve the enantioselectivity and reactivity. Substituted proline amides have been employed in the aldol reaction to improve the enantioselectivity,^[9] while 5-pyrrolidin-2-yltetrazole was found to be a more reactive organic catalyst than proline in aldol,^[10] α -aminoxylation^[11] and *O*-nitroso-aldol/Michael^[12] reactions as reported by Yamamoto et al. and in the Mannich reaction by Ley et al.^[13]

During our study of proline-catalyzed α -aminoxylations of aldehydes,^[8g] the reproducibility of the reaction was poor, especially at low catalyst loading, owing to the poor solubility of proline in the organic solvent. After intensive investigations, reproducible results were obtained using ultrasound irradiation of a DMF suspension of proline.^[8g] This solubility problem prompted us

to find a more soluble catalyst, which led us to try *trans*-4-*tert*-butyldimethylsiloxy-L-proline (**1**), easily prepared from commercially available *trans*-4-hydroxy-L-proline in large quantities^[14] (Figure 1). The proline catalyst **1** not only provides reproducible results, but also accelerates the reaction dramatically with a reduced amount of the catalyst, promoting reactions that cannot be catalyzed by proline itself. As the catalyst **1** possesses a higher reactivity than the parent proline, its superiority to proline will be discussed in this paper.

First of all, the reactivity of the catalyst **1** was investigated in the α -aminoxylation of cyclohexanone in the presence of 30 mol % of the catalyst [Eq. (1)]. The increase in the solubility of **1** in organic solvents greatly widens the choice of possible reaction medium (Table 1). For instance, the reaction scarcely proceeded in CH₂Cl₂ and THF in the presence of proline owing to its poor solubility, while these solvents can be employed in the reaction with **1**, affording the product in moderate yield (entries 1 and 2), although DMF is the solvent of choice in this reaction. Moreover, use of **1** can reduce the reaction time dramatically: while it takes 60 minutes for the disappearance of nitrosobenzene catalyzed by 30 mol % of proline, the reaction was completed within *one minute* in the presence of **1** (entry 6). The catalyst loading can be reduced in the case of **1**: when the amount of catalyst was reduced to 10 mol %, 15 minutes was enough in the case of **1**, while slow addition of nitrosobenzene over 5.5 h is necessary in the case of proline (entry 7). Even in the presence of 5 mol % of catalyst **1**, reproducible results have been obtained, while the reaction scarcely proceeded with the same amount of proline as catalyst (entry 8). As for the enantioselectivity, excellent selectivity can be achieved with both proline and **1**.

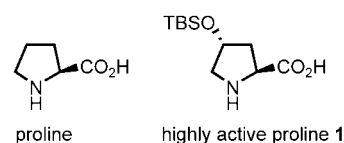


Figure 1.

Table 1. The solvent effect in α -aminoxylation of cyclohexanone catalyzed by proline and the highly active proline **1**.^[a]

Entry	Solvent	Catalyst [mol %]	Proline			1		
			Time [min]	Yield [%] ^[b]	ee [%] ^[c]	Time [min]	Yield [%] ^[b]	ee [%] ^[c]
1	THF	30	60	<5	nd ^[d]	2	67	>99
2	CH ₂ Cl ₂	30	60	11	>99	15	58	>99
3	CH ₃ CN	30	60	26	>99	15	65	>99
4	CH ₃ NO ₂	30	60	34	>99	15	50	>99
5	DMSO	30	60	31	>99	1	68	>99
6	DMF	30	60	37	>99	1	78	>99
7	DMF	10	330 ^[e]	77	>99	15 ^[f]	76	>99
8	DMF	5	330 ^[e]	<5	nd ^[d]	90 ^[g]	73	>99

^[a] Unless otherwise shown, reactions were conducted with a catalytic amount of catalyst, 1.0 equiv. nitrosobenzene, and 2.0 equivs. cyclohexanone at room temperature, and nitrosobenzene was added in one portion.

^[b] Yield of isolated product.

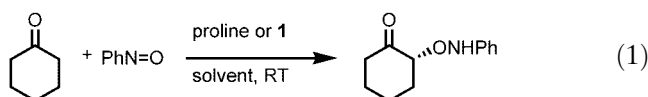
^[c] Determined by chiral HPLC with a Chiralpak AD-H column.

^[d] Not determined.

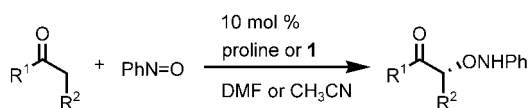
^[e] Slow addition of nitrosobenzene over 5.5 h.

^[f] Slow addition of nitrosobenzene over 15 minutes.

^[g] Slow addition of nitrosobenzene over 90 minutes.

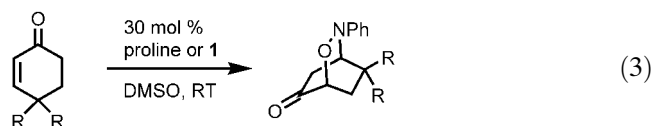


The results of other ketones and aldehydes in the presence of 10 mol % of proline and **1** are summarized in Table 2 [Eq. (2)]. In the reactions of 4,4-dimethylcyclohexanone and tetrahydrothiopyran-4-one, in which slow addition (24 h) of nitrosobenzene is essential, the reaction time was reduced dramatically to 2 h (entries 2 and 3). Catalyst **1** is effective when proline does not yield any product: no desired product was obtained from cycloheptanone and diethyl ketone in the presence of proline,^[8c, g] while **1** promoted the reactions effectively, producing the desired products in moderate yield with excellent enantioselectivity (entries 4 and 5). The higher reactivity of **1** was found not only in the α -aminoxylation of ketones but also in that of aldehydes: the reaction of phenylacetaldehyde with nitrosobenzene was completed within 2 h using 10 mol % of **1**, while the product was isolated in less than 5% yield in the presence of proline, although the reaction time was much longer (24 h) (entry 6). Two hours are enough for the reaction of 3-phenylpropanal catalyzed by **1**, which is in marked contrast to 24 h for the same reaction catalyzed by proline (entry 7).

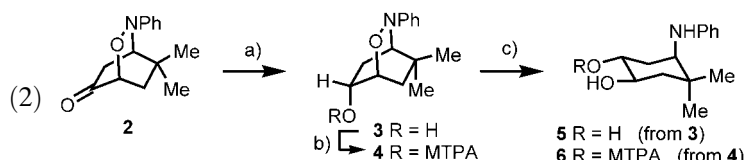


During the investigation of α -aminoxylation, we encountered the *O*-nitroso-aldol/Michael reaction, which was recently reported by Yamamoto et al.^[12]: when

3,3-dimethyl-2-cyclohexen-1-one was treated with **1**, the *O*-nitroso-aldol/Michael adduct was isolated in 76% yield with >99% ee [Eq. (3)]. The regiochemistry was determined by an X-ray crystallographic analysis^[15] of amino diol **5**, synthesized by reduction of the carbonyl group and reductive cleavage of the N–O bond, as shown in Scheme 1, and the absolute stereochemistry was determined by the modified Mosher method^[16] with the MTPA ester **6**. Proline can promote the reaction, but the yield of the product is synthetically unsatisfactory (Table 3, entry 1). The same high reactivity of **1** was observed in the reaction of cyclohexen-1,4-dione monoethylene ketal, in which a moderate yield was obtained in the presence of **1**, in contrast to the low yield under catalysis by proline (entry 2).




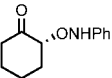

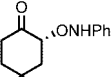

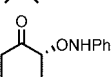

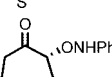

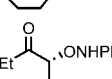

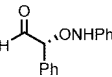

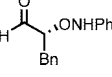
Catalyst **1** is effective not only in the α -aminoxylation of carbonyl compounds, but also in the Mannich reaction. Although proline is an effective catalyst in the three-



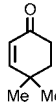
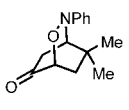
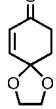
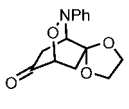
a) NaBH₄; b) MTPACl, Et₃N, cat DMAP; c) Pd/C, H₂.

Scheme 1. Determination of absolute and relative stereochemistry of **2**.

Table 2. The comparison between proline and highly active proline **1** in α -aminoxylation.

Entry	Substrate	Product	Proline			1		
			Time [h]	Yield [%] ^[a]	Ee [%] ^[b]	Time [h]	Yield [%] ^[a]	Ee [%] ^[b]
1 ^[c]			5.5 ^[d]	77	> 99	0.25 ^[d]	76	> 99
2 ^[c]			24 ^[d]	84	> 99	2 ^[d]	74	> 99
3 ^[c]			24 ^[d]	69	> 99	2 ^[d]	68	> 99
4 ^[c]			24 ^[d]	< 5	nd ^[f]	2 ^[d]	45	> 99
5 ^[e]			24 ^[d]	< 5	nd ^[f]	1 ^[d]	50	> 99
6 ^[g]			24	< 5	nd ^[f]	2	50	99
7 ^[g]			24	67	98	2	76	98

^[a] Yield of isolated product.^[b] Determined by chiral HPLC analysis.^[c] Reactions were conducted with 10 mol % catalyst, 1.0 equiv. nitrosobenzene, and 2.0 equivs. ketone in DMF at 0 °C with slow addition of nitrosobenzene.^[d] Addition time of nitrosobenzene.^[e] Reactions were conducted with 10 mol % catalyst, 1.0 equiv. nitrosobenzene, and 10.0 equivs. ketone in DMF at 0 °C with slow addition of nitrosobenzene.^[f] Not determined.^[g] Reactions were conducted with 10 mol % catalyst, 1.0 equiv. nitrosobenzene, and 3.0 equivs. aldehyde in CH₃CN at 0 °C, and nitrosobenzene was added in one portion.**Table 3.** The comparison between proline and highly active proline **1** in the *O*-nitroso-aldol/Michael reaction.^[a]

Entry	Enone	Product	Proline			1		
			Time [h]	Yield [%] ^[b]	ee [%] ^[c]	Time [h]	Yield [%] ^[b]	Ee [%] ^[c]
1			3	27	> 99	0.5	76	> 99
2			6	25	> 99	6	56	> 99

^[a] Reactions were conducted with 30 mol % catalyst, 2.5 equivs. nitrosobenzene, and 1.0 equiv. ketone in DMSO at room temperature.^[b] Yield of isolated product.^[c] Determined by chiral HPLC with a Chiralpak AD-H column.

component Mannich reaction of aldehydes, *p*-anisidine and ketones [Eq. (4)],^[5a, b] there is a limitation: the reaction can be successfully applied to reactive, electron-de-

ficient aldehydes, while electron-rich aldehydes are poor substrates.^[17] In the presence of 5 mol % of the catalyst, proline scarcely promotes the reaction of alde-

Table 4. The comparison between proline and highly active proline **1** in Mannich reaction.^[a]

Entry	RCHO	Proline			1		
		Time [h]	Yield [%]	ee [%] ^[b]	Time [h]	Yield [%]	ee [%] ^[b]
1	benzaldehyde	20	<5	nd ^[c]	20	63	96 ^[d]
2	2-naphthaldehyde	24	<5	nd ^[c]	24	62	93 ^[e]
3	<i>p</i> -anisaldehyde	20	<5	nd ^[c]	20	55	90 ^[d]
4	3,4-dimethoxybenzaldehyde	20	<5	nd ^[c]	20	48	98 ^[d]

^[a] Reactions were conducted with 5 mol % of catalyst in DMF at -20°C .

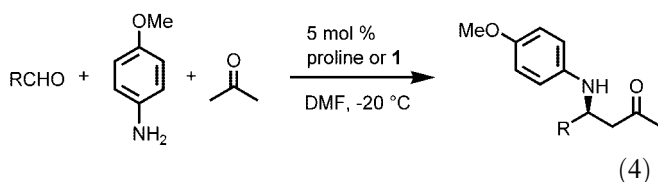
^[b] Isolated yield.

^[c] Not determined.

^[d] Determined by chiral HPLC analysis of the *anti*-1,3-aminosilyl ether derived from the Mannich adduct by the following procedure: (1) reduction with NaBH_4 , (2) silylation with TBSOTf and 2,6-lutidine, (3) separation of the *anti*- from the *syn*-isomer.

^[e] Determined by chiral HPLC analysis.

hydres such as benzaldehyde, 2-naphthaldehyde, *p*-anisaldehyde, and 3,4-dimethoxybenzaldehyde, which can be catalyzed by **1**, producing the Mannich adducts in moderate yields with excellent enantioselectivity (Table 4).



In summary, we have demonstrated that subtle modification of proline increases the activity and that 4-*tert*-butyldimethylsilyloxyproline (**1**) displays a greater catalytic activity without compromising on enantioselectivity, thus widening the substrate scope in α -aminoxylation of carbonyl compounds as well as the *O*-nitroso aldol/Michael, and Mannich reactions. There are several noteworthy features in this reaction: (1) excellent enantioselectivity can be achieved with **1**, (2) **1** can catalyze reactions that proline does not promote, (3) the loading of the catalyst can be reduced with reproducible results, (4) most organic solvents can be employed as a reaction medium owing to its increased solubility in organic solvents, and (5) **1** can be easily prepared in large quantities from *trans*-4-hydroxyproline, both enantiomers of which are commercially available. As proline is a widely used organic catalyst, **1** with the above mentioned superior features will be an indispensable new catalyst in asymmetric synthesis.

Experimental Section

Typical Experiment (Table 2, Entry 1)

To a DMF solution (1.0 mL) of cyclohexanone (124.5 μL , 1.2 mmol) and catalyst **1** (14.9 mg, 0.06 mmol) was added a

DMF solution (0.5 mL) of nitrosobenzene (64.2 mg, 0.6 mmol) over 15 minutes at room temperature. The reaction was quenched with pH 7 phosphate buffer solution, the organic materials were extracted with ethyl acetate three times and the combined organic materials were washed with brine three times, dried over anhydrous Na_2SO_4 , and concentrated under vacuum after filtration. Purification by silica gel column chromatography (ethyl acetate:hexane, 1:20–1:5) gave α -anilinoxycyclohexanone; yield: 93.4 mg (0.455 mmol, 76%). The enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (40:1 hexane:2-propanol), 1.0 mL/min; major enantiomer $t_r=34.3$ min, minor enantiomer $t_r=28.1$ min. The absolute stereochemistry was determined after conversion to (*R*)-2-hydroxycyclohexanone.^[8e, g]

Acknowledgements

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