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Direct Asymmetric α-Amination of Cyclic Ketones Catalyzed by Siloxyproline

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Dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday

Abstract: *trans-tert*-Butyldimethylsiloxy-L-proline displays greater catalytic activity and affords higher enantioselectivity than the parent proline in the α-amination reaction of carbonyl compounds with azodicarboxylate. A quantum mechanical calculation reveals the structure of the transition state. In the presence of a catalytic amount of siloxyproline and water (3–9 equiv), α-amino carbonyl derivatives, which are important synthetic intermediates, are obtained in good yield and with excellent enantioselectivity.

Keywords: amination · asymmetric synthesis · organocatalysis · proline · siloxyproline

Introduction

α-Amino ketones are important synthetic intermediates for the construction of biologically active products, and a wide variety of diastereo- and enantioselective methods for their preparation has been developed. One straightforward method is the electrophilic α amination of ketones.[1] As with the catalytic enantioselective α-amination reactions of carbonyl compounds, there have been several reports, such as the α-amination reaction of a silyl enol ether with azodicarboxylate in the presence of chiral metal catalysts,[2] as well as that of a β-ketoester with azodicarboxylate in the presence of a chiral Lewis acid.[3] In contrast to these reactions promoted by chiral Lewis acids, direct enantioselective synthesis was recently developed by the use of organocatalysis.[4] List[5] and Jørgensen and co-workers[6] independently reported in 2002 that aldehydes react with azodicarboxylate under proline catalysis to afford α-aminated aldehydes with excellent enantioselectivity.[7] In the same year, Jørgensen and co-workers also reported that ketones too react with azodicarboxylate to afford α-aminated ketones with high enantioselectivity.[8] The same group reported that diarylprolinol silyl ether is an effective catalyst for the α amination of aldehydes with azodicarboxylate.[9] These are practical and atom-economical methods without the preformation of silyl enol ethers. After this discovery, Bräse[10] and Barbas[11] and their co-workers expanded this reaction to α,α-disubstituted aldehydes to generate quaternary asymmetric centers in an enantioselective manner. Other organocatalysts also promote the α-amination reaction.[12] The reaction proceeds effectively in ionic liquids,[13] and this method was applied to the synthesis of (*S*,*S*)-ethambutol.[14] The β-isocupreidine- or alkaloid-mediated α amination of α-substituted α-cyanoacetate and β-dicarbonyl compounds for the asymmetric construction of quaternary stereocenters has also been reported.[15] Although proline-mediated α amination is an excellent reaction, a rather long reaction time is generally required. Pyrrolidinyltetrazole catalyst[16] was reported to be a more reactive catalyst than proline in the α amination of aldehydes, which was successfully applied to the total synthesis of BIRT-377, an LFA-1 antagonist, by Chowdari and Barbas.[17] Although Jørgensen and co-workers had already reported the α amination of ketones catalyzed by proline, the ketones examined are mostly acyclic species, cyclohexanone being the only cyclic ketone to be investigated; the

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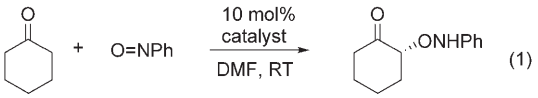
generality for cyclic ketones was not reported. Even though there are several organocatalyst-mediated α-amination reactions, there are limitations to the use of cyclic ketones as carbonyl substrates.

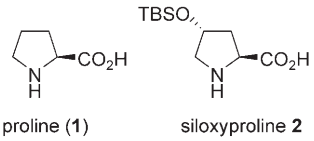
Our group developed a direct, asymmetric α aminoxylation of carbonyl compounds, in which nitrosobenzene was used as an electrophile to react with aldehydes and ketones, thus affording α-aminoxy carbonyl compounds with excellent enantioselectivity (Equation (1); DMF = *N*,*N*-dimethylformamide).[18,19] In our search for a reactive catalyst in the α aminoxylation of carbonyl compounds, we found that 4-*tert*-butyldimethylsiloxyproline, which is readily prepared from commercially available 4-hydroxyproline, is an effective catalyst that promotes the α aminoxylation in a much shorter reaction time than by using proline, without compromising the enantioselectivity.[20] The siloxyproline catalyst is also effective in the Mannich reaction with a smaller catalyst loading than for proline.[20] For the further application of this catalyst to other asymmetric reactions, we recently discovered that siloxyproline is an effective asymmetric catalyst in the aldol reaction in the presence of water, thus affording products with excellent diastereo- and enantioselectivities.[21] For the further application of the siloxyproline catalyst to other synthetically useful reactions, we found that it is an effective catalyst in the asymmetric α amination of cyclic ketones, which is reported herein. As for the reaction mechanism of proline-mediated α amination, there is controversy over the transition state. Moreover, rate acceleration and a nonlinear effect were observed.[22] To shed light on the reaction mechanism, a quantum mechanical calculation was performed, which is also reported in this paper.



proline (**1**)	5.5 h	77%	>99% *ee*
siloxyproline **2**	15 min	76%	>99% *ee*

Results and Discussion

The reaction of cyclohexanone and diethyl azodicarboxylate (DEAD) was chosen as a model reaction, which Jørgensen and co-workers reported to be promoted by proline in dichloroethane to afford the product in 67% yield and with 84% *ee* within 23 h.[8] When the reaction was performed in the same solvent in the presence of 10 mol% siloxyproline **2** (Scheme 1), the starting material disappeared within 1.5 h to afford the product in good yield with good enantioselectivity

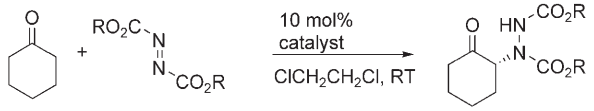


proline (**1**) siloxyproline **2**

Scheme 1. Organocatalysts examined in this study. TBS = *tert*-butyldimethylsilyl.

(89%, 85% *ee*; Table 1, entry 2). When the same reaction was carried out in the presence of proline for 1.5 h, a low yield (31%) with the same optical purity (85% *ee*) was obtained (Table 1, entry 1). Next, dibenzyl azodicarboxylate (DBAD) was employed instead of DEAD, and excellent enantioselectivity was attained in the reaction of siloxyproline, whereas lower yield and enantioselectivity were obtained in the case of proline (Table 1, entries 3 and 4). Thus, siloxyproline was found to be a more reactive catalyst than proline, and not only yield but also enantioselectivity were increased in the reaction of DBAD when siloxyproline was employed.

Table 1. α-Amination reaction of cyclohexanone and DEAD or DBAD catalyzed by proline (**1**) or siloxyproline **2**.[a]



Entry	Catalyst	R	*t* [h]	Yield[b] [%]	*ee*[c] [%]
1	**1**	Et	1.5	31	85
2	**2**	Et	1.5	89	85
3	**1**	Bn	3.0	50	75
4	**2**	Bn	3.0	86	94

[a] The reaction was performed with cyclohexanone (0.75 mmol) and DEAD (0.5 mmol) or DBAD (0.5 mmol) in the presence of the catalyst (0.05 mmol) in dichloroethane (1 mL). [b] Yield of isolated product. [c] Yield determined before purification by HPLC on a chiral phase (Chiralpak IA).

As excellent results were obtained in the reaction of cyclohexanone with DBAD catalyzed by siloxyproline **2**, the reaction was applied to 4,4-dimethylcyclohexanone, but an unsatisfactory result was obtained. When the reaction was performed in the presence of proline for 2 h, the yield was 49%, and, to our surprise, a nearly racemic product was obtained (Table 2, entry 1). Even when siloxyproline was employed, the enantioselectivity was 46% (Table 2, entry 2). As inferior results were obtained, the reaction was investigated in detail, and the results are summarized in Table 2. Upon lowering the temperature to 0°C, the enantioselectivity was increased to 79% (Table 2, entry 3). In our previous study of the asymmetric aldol reaction in the presence of

Abstract in Japanese:

我々は、4-シロキシプロリンが、カルボニル化合物とジベンジルアゾジカルボキシラートとのα-アミノ化反応において、プロリンよりも高い触媒活性、高度な不斉識別能を有する、優れた有機触媒である事を見出した。すなわち触媒量のシロキシプロリン存在下、少量の水 (3–9 当量) を加え反応を行う事により、良好な収率、かつ非常に高い不斉収率で、合成化学的に重要なα-アミノカルボニル化合物が得られる。また反応のメカニズムを計算化学により明らかにした。

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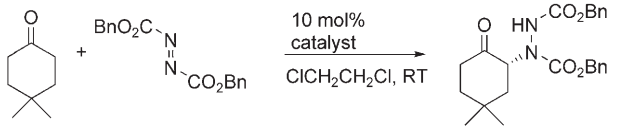
Table 2. Effect of water in the α-amination reaction of 4,4-dimethylcyclohexanone and DBAD catalyzed by proline (**1**) or siloxyproline **2**.[a]



Entry	Catalyst	Water [equiv]	T [°C]	t [h]	Yield[b] [%]	ee[c] [%]
1	**1**	0	23	2	49	5
2	**2**	0	23	2	92	46
3	**2**	0	0	5	95	79
4	**2**	9	23	8	88	87
5	**2**	1	0	20	92	86
6	**2**	3	0	20	91	88
7	**2**	9	0	20	89	91
8	**2**	18	0	20	88	87

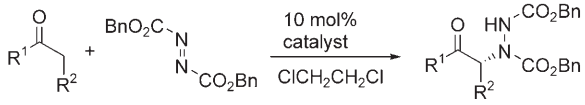
[a] The reaction was performed with cyclohexanone (0.75 mmol) and DBAD (0.5 mmol) in the presence of the catalyst (0.05 mmol) in dichloroethane (1 mL). [b] Yield of isolated product. [c] Yield determined before purification by HPLC on a chiral phase (Chiralcel OD-H).

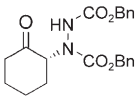
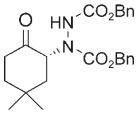
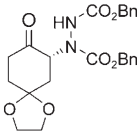
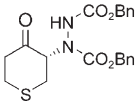
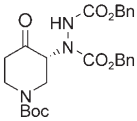
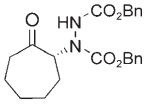
water,[21,23] water was found to increase the enantioselectivity. In several asymmetric aldol reactions with organocatalysis, the enantioselectivity was reported to increase in the presence of water.[24] Thus, we examined the effect of water in the present α-amination reaction. With the addition of 1 equivalent of water, the reaction was slowed and a longer reaction time was needed, but an excellent yield was obtained, and the enantioselectivity was increased to 86% (Table 2, entry 5). With the addition of 3 or 9 equivalents of water, excellent enantioselectivities (88 and 91% *ee*) were obtained (Table 2, entries 6 and 7). A slight decrease in enantioselectivity was observed with the addition of 18 equivalents of water (Table 2, entry 8). In the present α-amination reaction, water has a positive effect on the enantioselectivity despite retarding the reaction, and 3–9 equivalents of water gave excellent results.

As excellent results were obtained in the presence of water, the generality of the siloxyproline-mediated α-amination reaction was investigated in the absence and presence of water; the results are summarized in Table 3.

Excellent enantioselectivity (98% *ee*) was obtained in the reaction of cyclohexanone when 9 equivalents of water were employed at 0°C (Table 3, entry 3). Besides 4,4-dimethylcyclohexanone, other substituted cyclohexanones were also suitable substrates. Moreover, not only six-membered cyclic ketones but also seven-membered ketones such as cycloheptanone gave good results. For example, in the reaction of 1,4-cyclohexanedione monoethylene ketal, 1-*tert*-butoxycarbonyl-4-piperidone, and cycloheptanone, good enantioselectivity (≈80% *ee*) was obtained without water, but it increased to over 90% *ee* in the presence of 9 equivalents of water. Siloxyproline **2** gave a good result in the reaction of tetrahydrothiopyran-4-one, for which water did not have a positive effect on the enantioselectivity. One feature should be noted about racemization. Whereas α-aminated cyclohexanone did not racemize during purification, other α-aminated ketones were prone to racemization. During purification with column chromatography, there was partial racemization. For example, the enantioselectivity of the crude reaction mixture of the α-aminated product of 1-*tert*-butoxycarbonyl-4-piperidone was 84% (Table 3, entry 15), but it became 73% after rapid purification by silica-gel column chromatography. Thus, the determination of enantiomeric excess was conducted before purification by injecting the reaction mixture into the chiral

Table 3. α-Amination reaction of various cyclic ketones and DBAD catalyzed by proline (**1**) or siloxyproline **2**.[a]

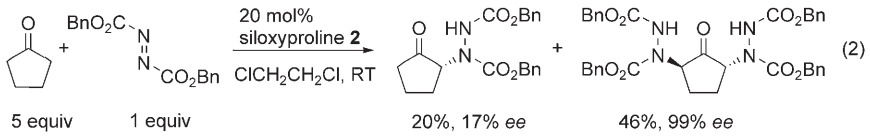


Entry	Product	Catalyst	Water [equiv]	T [°C]	t [h]	Yield[b] [%]	ee[c] [%]
1		**1**	0	23	3	50	75
2		**2**	0	23	3	86	94
3		**2**	9	0	3	89	98
4		**1**	0	23	2	49	5
5		**2**	0	0	5	95	79
6		**2**	9	0	20	91	91
7		**1**	0	23	2.5	34	57
8		**2**	0	23	2.5	92	84
9		**2**	9	23	9	91	91
10		**2**	9	0	48	81	96
11		**1**	0	23	2	32	69
12		**2**	0	23	2	83	91
13		**2**	9	23	48	72	89
14		**1**	0	23	2.5	28	54
15		**2**	0	23	2.5	92	84
16		**2**	9	23	9	91	91
17		**2**	9	0	48	81	96
18		**1**	0	23	10	9	72
19		**2**	0	23	10	81	85
20		**2**	9	23	12	89	65
21		**2**	9	0	54	73	95

[a] Reactions were conducted with catalyst (10 mol%), DBAD (1.0 equiv), and carbonyl compound (1.5 equiv) in dichloroethane. [b] Yield of isolated product. [c] Determined with the crude mixture before purification. Boc = *tert*-butoxycarbonyl.

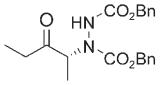
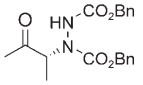
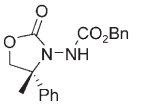
HPLC column. We also analyzed the enantioselectivity according to the reaction time, and it was found that excellent enantioselectivity was maintained from the beginning. The enantioselectivity did not change in the reaction in Table 2, entry 7, which indicates that racemization did not proceed during the reaction.

Cyclopentanone gave a different result. Even with an excess amount of cyclopentanone (5 equiv), α,α′-diaminated cyclopentanone was obtained in moderate yield in a nearly optically pure form [Eq. (2)].



Next, the reaction was applied to acyclic ketones. Proline is known to promote the α amination of acyclic ketones in good yield with excellent enantioselectivity,[8] but siloxyproline was also found to be effective; it afforded the α-aminated product in a shorter reaction time with excellent enantioselectivity (Table 4, entries 1 and 2). Bräse and co-workers reported the proline-mediated α amination of α,α-disubstituted aldehydes with high enantioselectivity, but the reaction time was long.[10] For instance, the reaction of 2-phenylpropanal took 3 days with 81% *ee*.[10] When we applied siloxyproline **2** to this reaction, the reaction was completed within 14 h. The α-aminated product was reduced with $NaBH_4$ with isolation of the oxazolidinone derivative in 64% yield with high enantioselectivity (Table 4, entry 3). Thus, siloxyproline **2** is effective not only for cyclic ketones but also for acyclic ketones and substituted aldehydes.

Table 4. α-Amination reaction of acyclic carbonyl compounds and DBAD catalyzed by siloxyproline **2**.[a]

Entry	Starting material	Product	*t* [h]	Yield[b] [%]	*ee*[c] [%]
1[d]			56	64	96
2			4	73	93
3[e]			14	64	78

[a] Unless otherwise shown, reactions were conducted with catalyst **2** (10 mol%), DBAD (1.0 equiv), and carbonyl compound (1.5 equiv) in CH_3CN at room temperature. [b] Yield of isolated product. [c] Determined with the crude mixture before purification. [d] The reaction was performed without solvent with 5 equivalents of ketone. [e] 30 mol% catalyst was employed. After the reaction, the α-aminated product was reduced with $NaBH_4$, and the resultant product was isolated as the oxazolidinone derivative.

The Reaction Mechanism

In the similar proline-mediated α-aminoxylation reaction of carbonyl compounds with nitrosobenzene, Blackmond and co-workers reported a nonlinear correlation between the enantiomeric excess of product and proline with propanal as a nucleophile,[22a] whereas Cordova et al. observed a linear correlation in the reaction of cyclohexanone.[19d]

In the proline-mediated α amination of propanal with DEAD, Blackmond and co-workers observed a nonlinear correlation between the enantiomeric excess of product and proline.[22b] They also observed a product-acceleration phenomenon, and suggested the participation of a reaction pathway that involves a product–proline adduct.[22] They reported that the nonlinear effect could be explained by the eutectic behavior of proline.[22d] Our group observed the nonlinearity of the enantioselectivity of proline in solution and solid, and suggested that the nonlinearity of the α-aminoxylation reaction could be explained by this phenomenon.[25] Although Blackmond and co-workers proposed two parallel catalytic cycles for the α-amination reaction, a single transition state involving one molecule of proline and one molecule of enamine is assured.[22e]

First, we investigated the relationship between the enantiomeric excess of the α-aminated product of cyclohexanone and that of the catalyst. In this study, we employed proline as a catalyst, because the reaction mechanism would be the same for both proline and siloxyproline.

The plot of the enantiomeric excess of proline versus that of the α-aminated product shows a linear correlation (Figure 1). This result, together with that of Blackmond and co-workers, indicates that linearity occurs in the reaction of ketones, whereas nonlinearity occurs in the reaction of aldehydes. In the reaction of ketones, at least, only one proline molecule would be involved in the transition state.

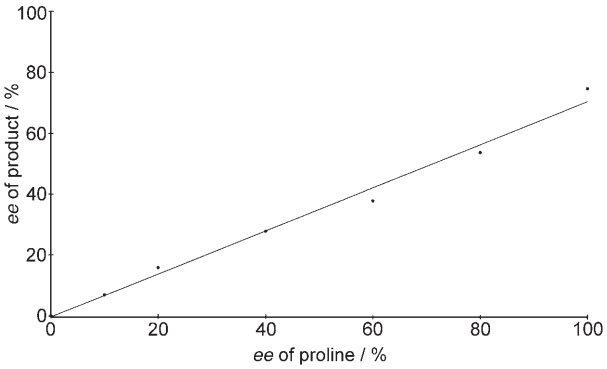


Figure 1. Relation between the enantiomeric excess of proline and that of the α-aminated product in the reaction of cyclohexanone with dibenzyl azodicarboxylate. Reaction conditions: cyclohexanone (0.75 mmol), DBAD (0.5 mmol), proline (0.05 mmol), CH_2ClCH_2Cl (1 mL), room temperature, 2 h.

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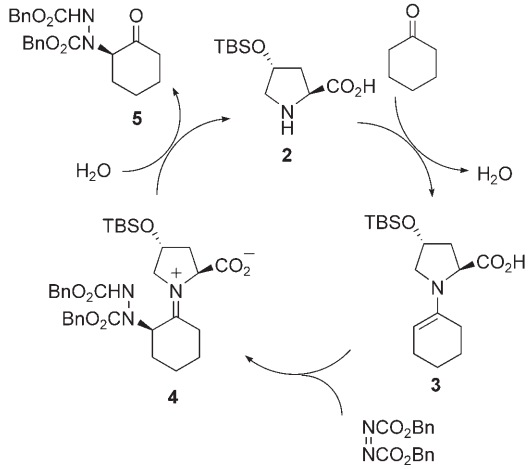
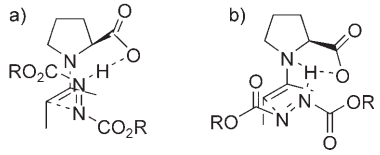
The reaction mechanism is thought to be as follows (Scheme 2). Siloxyproline **2** reacts with the ketone to generate enamine **3** and water. Enamine **3** reacts with azodicarboxylate to afford iminium ion **4**, which is hydrolyzed with water to afford α-aminated product **5** and regenerate **2**.



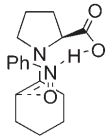
Scheme 2. The reaction mechanism of α amination.

As for the transition state, which determines the absolute configuration, two models have been proposed. List proposed the transition-state model shown in Scheme 3a,[5] whereas a different transition-state model, such as that in Scheme 3b, was proposed by Jørgensen and co-workers in the α amination of ketones and aldehydes.[6,8]



Scheme 3. Transition-state models proposed by a) List and b) Jørgensen and co-workers.

On the other hand, for the α aminoxylation of ketones catalyzed by proline with nitrosobenzene as an electrophile, we proposed the transition-state model shown in Scheme 4.[18b,c] Cheong and Houk performed an ab initio calculation on the α aminoxylation of propanal and nitrosobenzene catalyzed by proline and found a transition state similar to our model.[26] This calculation was not for α amination but for α aminoxylation. Moreover, the calculation was not for a ketone but for an aldehyde. To determine the transition state for the α amination of a ketone, we performed a quantum mechanical computational study of the α amination of acetone and dimethyl azodicarboxylate catalyzed by proline by using restricted B3LYP (RB3LYP) calculations with the 6-31G(d) basis set.[27]



Scheme 4. Transition-state model in the reaction of nitrosobenzene proposed by Hayashi et al.

There are *trans* and *cis* conformers of dimethyl azodicarboxylate, whose symmetries are C_i and C_2, respectively (Figure 2). The *trans* isomer is 2.14 kcal mol^{-1} lower in

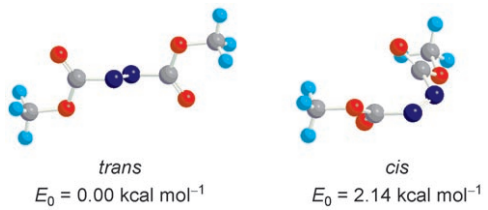
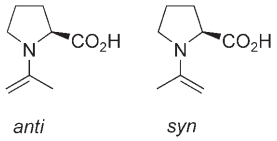


Figure 2. The conformers of dimethyl azodicarboxylate. C = gray, H = turquoise, O = red, N = dark blue.

energy than the *cis* isomer. As for the enamine generated from acetone and proline, there are two possible conformers, *anti* and *syn*, in which the olefin is situated on the opposite or the same side of the carboxylic acid, respectively (Scheme 5). In the α aminoxylation of the enamine generated from propanal and proline, the transition-state energy for the *syn* conformer is much higher than that for the *anti* conformer because of the energetic cost in distorting the molecular geometry to accommodate proton transfer to the more proximal nitrogen atom. In the present α-amination reaction, the transition-state energy for the *syn* conformer is expected to be much higher than that for the *anti* conformer; hence, calculations were performed only for the *anti* conformer, that is, a quantum mechanical computational study of the reaction of the *anti* enamine with two (*trans* and *cis*) conformers of dimethyl azodicarboxylate was performed. Four transition states, two each for the *trans* and *cis* conformers of dimethyl azodicarboxylate, were located along the reaction coordinates for α amination (Figure 3). The most stable transition structure is TS1, in which dimethyl azodicarboxylate adopts the *trans* conformation. This is similar to that proposed for the α aminoxylation of nitrosobenzene. We did not detect a transition state similar to that in Scheme 3b.



Scheme 5. The *anti* and *syn* conformers of the enamine formed from acetone and proline.

The enamine prepared from acetone and proline has conformational freedom with regard to rotation of the carboxy group. We investigated the energy profile for rotation of the carboxy group in this enamine (Figure 4). The calculated rotational-energy profile indicates a rotational barrier of

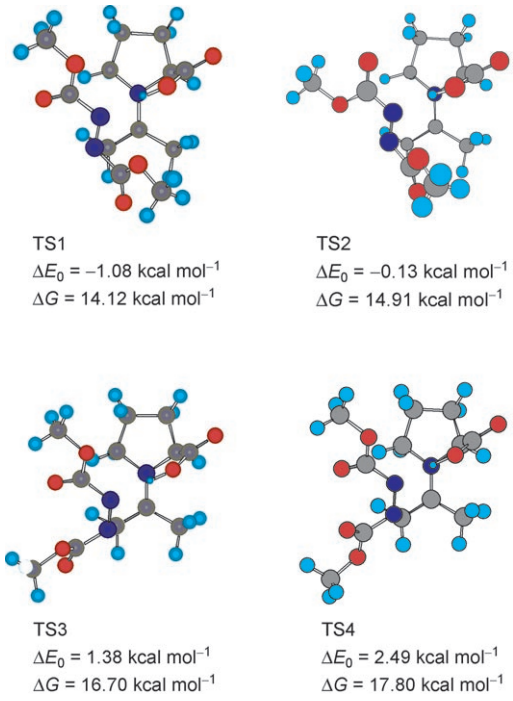


Figure 3. Transition states of the α-amination reaction of acetone and dimethyl azodicarboxylate catalyzed by proline. ΔE_0 and ΔG are the enthalpies (including zero-point energy) and free energies (at 298 K) of the transition states. Energy values are relative to the reactants and are given in kcal mol^{-1}.

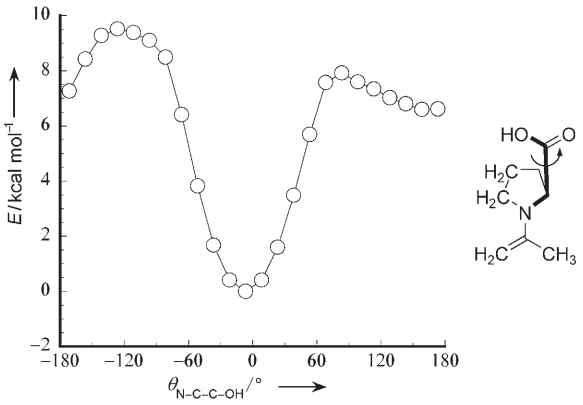


Figure 4. Energy profile according to the dihedral angle $\theta_{N-C-C-OH}$.

about 10 kcal mol^{-1} and only one rotational minimum with the N−C−C−OH dihedral angle of about 0°, at which the proton of the carboxylic acid and the nitrogen atom of proline are located close to each other. This dihedral angle is also about 0° in the transition states, in which the carboxy proton, the carboxy oxygen atom, and the nitrogen atom of azodicarboxylate are almost collinearly arranged. This indicates that the N−C−C−OH dihedral angle remains almost unchanged on going from the global minimum of the starting enamine to the transition states. In other words, the intrinsic conformation of the enamine with respect to the carboxy group appears to be suitable for promoting the reaction. The quantum mechanical calculation, which was performed with acetone, a simple ketone, and proline as a catalyst, would be applicable to the reaction of cyclic ketones catalyzed by siloxyproline.

Conclusions

In summary, we have found that siloxyproline **2** is an effective organocatalyst in the α amination of carbonyl compounds with dibenzyl azodicarboxylate. Although limitations still exist, siloxyproline **2** can enlarge the synthetic utility of the α amination of carbonyl compounds to afford products with excellent enantioselectivity, whereas the parent proline does not provide good results. A small amount of water is essential for attaining the excellent enantioselectivity. The transition-state structure was found for the reaction of acetone and dimethyl azodicarboxylate catalyzed by proline.

Experimental Section

General Information

All reactions were carried out under argon atmosphere and monitored by thin-layer chromatography with Merck 60 F_{254} precoated silica-gel plates (0.25 mm thickness). Specific optical rotations were measured on a JASCO P-1020 polarimeter. FTIR spectra were recorded on a JASCO FT/IR-410 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 instrument. High-resolution mass spectrometry (HRMS) was performed on a Bruker-Daltonics micrOTOF focus instrument. Preparative thin-layer chromatography was performed with Merck silica gel 60 F_{254} and Wakogel B-5F purchased from Wako Pure Chemical Industries, Japan. Flash chromatography was performed with Merck silica gel Art 7734 and silica gel 60N from Kanto Chemical Co. Int., Tokyo, Japan.

Syntheses

Typical procedure for asymmetric α amination of cyclic ketones (Table 3, entry 3): 4-*tert*-Butyldimethylsiloxyproline (**2**; 12.3 mg, 0.05 mmol) was added to a stirred solution of cyclohexanone (78 μL, 0.75 mmol), DBAD (149 mg, 0.5 mmol), and water (81 μL) in 1,2-dichloroethane (1 mL), and the reaction mixture was stirred for 20 h at 0 °C. The mixture was directly purified by flash chromatography (ethyl acetate/hexane = 1:10) to give *N*,*N*′-bis(benzyloxycarbonyl)-2-hydrazinohexanone (176.3 mg, 89 %, 98 % *ee*) as a colorless oil. The enantioselectivity was determined by HPLC of the crude sample with a Chiralpak IA column (hexane/2-propanol = 10:1), 1.0 mL min^{-1}; t_R(major) = 41.15 min, t_R(minor) = 38.13 min

(2*R*,5*R*)-2,5-Bis[*N*,*N*′-bis(benzyloxycarbonyl)hydrazino]cyclopentanone: Siloxyproline **2** (24.6 mg, 0.1 mmol) was added to a solution of cyclopentanone (221 μL, 2.5 mmol) and DBAD (149 mg, 0.5 mmol) in 1,2-dichloroethane (1 mL), and the reaction mixture was stirred for 48 h at room temperature. The mixture was directly purified by flash chromatography (ethyl acetate/hexane = 1:5) to afford (2*R*,5*R*)-2,5-bis[*N*,*N*′-bis(benzyloxycarbonyl)hydrazino]cyclopentanone (77.8 mg, 46 %, 99 % *ee*) as a white solid. The enantioselectivity was determined by HPLC of the crude sample with a Chiralpak OD-H column (hexane/2-propanol = 10:1), 1.0 mL min^{-1}; t_R(major) = 50.55 min, t_R(minor) = 28.97 min.

(*R*)-3-Benzyloxycarbonylamino-4-methyl-4-phenyloxazolidin-2-one (Table 4, entry 3): DBAD (89.5 mg, 0.3 mmol) was added to a suspension of **2** (22.1 mg, 0.09 mmol) and 2-phenylpropanal (60 mL, 0.45 mmol) in CH_3CN (2.25 mL) at room temperature, and the reaction mixture was stirred for 14 h. After addition of MeOH (1.2 mL) and $NaBH_4$ (45 mg, 1.2 mmol) at 0 °C, the reaction mixture was stirred for 30 min at the same temperature. The reaction mixture was further stirred for 12 h at room temperature after the addition of methanolic NaOH (1 M, 10 mL). Vola-

tile materials were removed under reduced pressure, and the organic materials were extracted with ethyl acetate (3×30 mL). The organic phase was washed with brine and dried over $MgSO_4$, and the volatile materials were removed under reduced pressure. Purification by silica-gel column chromatography (ethyl acetate/hexane = 1:5–1:2) gave (*R*)-3-benzyloxycarbonylamino-4-methyl-4-phenyloxazolidin-2-one (62.7 mg, 64%, 78% *ee*) as a colorless oil. The enantioselectivity was determined by HPLC of the crude sample with a Chiralpak IA column (hexane/2-propanol = 10:1), 1.0 mL min^{-1}; t_R(major) = 17.01 min, t_R(minor) = 19.80 min.

(*R*)-2-[*N*,*N*′-Bis(benzyloxycarbonyl)hydrazino]cyclohexanone:[12b] The enantiomeric excess was determined by HPLC of the crude sample with a Chiralpak IA column (hexane/2-propanol = 10:1), 1.0 mL min^{-1}; t_R(major) = 41.15 min, t_R(minor) = 38.13 min.

(*R*)-2-[*N*,*N*′-Bis(benzyloxycarbonyl)hydrazino]-4,4-dimethylcyclohexanone: IR (KBr): $\tilde{\nu}$ = 1745, 1726, 1691, 1498, 1417, 1301, 1218, 1105, 738, 698 cm^{-1}; ^{1}H NMR (CD_3SOCD_3): δ = 0.92 (s, 3H), 1.14 (s, 3H), 1.42–1.84 (m, 3H), 2.10–2.22 (m, 1H), 2.40–2.56 (m, 2H), 4.66 (dd, J = 6.4, 13.0 Hz, 1H), 4.88–5.15 (m, 4H), 7.20–7.44 (m, 10H), 8.72 ppm (br s, 1H); ^{13}C NMR (CD_3SOCD_3): δ = 25.1, 31.7, 32.1, 37.5, 38.8, 40.2, 40.5, 40.7, 40.9, 41.1, 41.3, 41.5, 42.8, 67.1, 68.0, 128.1, 128.3, 128.6, 128.7, 129.1, 137.2, 137.4, 156.4, 157.2, 205.9 ppm; HRMS (ESI): *m*/*z* calcd for $C_{24}H_{29}N_2O_5$: 425.2071 $[M+H]^+$; found: 425.2092; enantiomeric excess was determined by HPLC of the crude sample with a Chiralcel OD-H column (hexane/2-propanol = 30:1), 1.0 mL min^{-1}; t_R(major) = 25.24 min, t_R(minor) = 34.10 min.

(*R*)-7-[*N*,*N*′-Bis(benzyloxycarbonyl)hydrazino]-1,4-dioxaspiro[4.5]decane-8-one: IR (KBr): $\tilde{\nu}$ = 2925, 2363, 1745, 1699, 1654, 1508, 1412, 1301, 1224, 1095 cm^{-1}; ^{1}H NMR (CD_3SOCD_3): δ = 1.87–1.98 (m, 1H), 1.98–2.07 (m, 1H), 2.11–2.29 (m, 2H), 2.30–2.40 (m, 1H), 2.50–2.65 (m, 1H), 3.82–4.13 (m, 4H), 4.77–4.97 (m, 1H), 5.04–5.25 (m, 4H), 5.11–5.17 (m, 4H), 7.28–7.46 (m, 10H), 8.93 ppm (br s, 1H); ^{13}C NMR (CD_3SOCD_3): δ = 33.3, 36.2, 37.8, 64.7, 64.8, 66.9, 67.7, 107.4, 127.7, 127.9,128.3, 128.7, 136.7, 136.9, 155.8, 156.8, 203.9 ppm; HRMS (ESI): *m*/*z* calcd for $C_{24}H_{26}N_2O_7$: 455.1813 $[M+H]^+$; found: 455.1824; enantiomeric excess was determined by HPLC of the crude sample with a Chiralcel OD-H column (hexane/2-propanol = 30:1), 1.0 mL min^{-1}; t_R(major) = 25.26 min, t_R(minor) = 34.24 min

(*R*)-2-[*N*,*N*′-Bis(benzyloxycarbonyl)hydrazino]-4-thiopyran-1-one: IR (KBr): $\tilde{\nu}$ = 3284, 2929, 2361, 1742, 1721, 1509, 1457, 1328, 1260, 1216 cm^{-1}; ^{1}H NMR (CD_3SOCD_3): δ = 2.76–2.86 (m, 2H), 2.86–2.96 (m, 2H), 2.97–3.04 (m, 1H), 3.10 (dd, J = 5.3, 13.3 Hz, 1H), 3.20 (t, J = 13.3 Hz, 1H), 4.79 (dd, J = 5.1, 11.0 Hz, 1H), 5.09–5.20 (m, 4H), 7.24–7.50 (m, 10H), 9.05 ppm (br s, 1H); ^{13}C NMR (CD_3SOCD_3): δ = 28.5, 31.5, 44.3, 66.9, 67.8, 127.8, 128.0, 128.3, 128.7, 136.6, 136.9, 155.6, 156.9 ppm; HRMS (ESI): *m*/*z* calcd for $C_{21}H_{26}N_2O_5S$: 415.1322 $[M+H]^+$; found: 415.1336; enantiomeric excess was determined by HPLC of the crude sample with a Chiralcel IA column (hexane/2-propanol = 10:1), 1.0 mL min^{-1}; t_R(major) = 63.45 min, t_R(minor) = 48.28 min.

(*R*)-3-[*N*,*N*′-Bis(benzyloxycarbonyl)hydrazino]-*N*-(1,1-dimethylethyloxycarbonyl)pyperidin-1-one: IR (KBr): $\tilde{\nu}$ = 3288, 3065, 3033, 2975, 1702, 1498, 1413, 1281, 1219, 1051 cm^{-1}; ^{1}H NMR (CD_3SOCD_3): δ = 1.47 (s, 9H), 2.44 (dt, J = 4.2, 15.6 Hz, 1H), 2.50–2.56 (m, 1H), 2.99–3.07(m, 1H), 3.15–3.24 (m, 1H), 3.36 (dd, J = 10.9, 12.4 Hz, 1H), 4.02–4.13 (m, 1H), 4.39 (ddd, J = 2.2, 6.8, 13.0 Hz, 1H), 5.11–5.17 (m, 4H), 7.28–7.44 (m, 10H), 9.16 ppm (br s, 1H); ^{13}C NMR (CD_3SOCD_3): δ = 28.5, 40.1, 42.6, 45.5, 66.9, 67.9, 80.2, 127.8, 127.9, 128.3, 128.7, 136.5, 136.8, 154.4, 155.6, 156.8, 202.0 ppm; HRMS (ESI): *m*/*z* calcd for $C_{26}H_{31}N_3O_7Na$: 520.2054 $[M+Na]^+$; found: 520.2057; enantiomeric excess was determined by HPLC of the crude sample with a Chiralcel OD-H column (hexane/2-propanol = 10:1), 1.0 mL min^{-1}; t_R(major) = 37.27 min, t_R(minor) = 32.17 min.

(*R*)-2-[*N*,*N*′-Bis(benzyloxycarbonyl)hydrazino]cycloheptanone: IR (KBr): $\tilde{\nu}$ = 3298, 2924, 2362, 1743, 1684, 1543, 1509, 1457, 1427, 1304 cm^{-1}; ^{1}H NMR (CD_3SOCD_3): δ = 1.05–1.29 (m, 1H), 1.33–1.99 (m, 7H), 2.15–2.52 (m, 2H), 4.96–5.09 (m, 1H), 5.10–5.31 (m, 4H), 6.83–7.03 (m, 1H), 5.09–5.20 (m, 4H), 7.21–7.41 ppm (m, 10H); ^{13}C NMR (CD_3SOCD_3): δ = 23.6, 27.9, 28.8, 29.7, 41.7, 67.7, 68.4, 68.5, 127.9, 128.7, 128.1, 128.2, 128.3, 128.4, 128.7, 137.1, 137.7, 156.8, 209.5 ppm; HRMS (ESI): *m*/*z* calcd for $C_{21}H_{26}N_2O_5S$: 411.1914 $[M+H]^+$; found: 411.1929; enantiomeric excess was determined by HPLC of the crude sample with a Chiralpak IA column (hexane/2-propanol = 10:1), 1.0 mL min^{-1}; t_R(major) = 52.29 min, t_R(minor) = 32.76 min.

(*R*)-2-[*N*,*N*′-Bis(benzyloxycarbonyl)hydrazino]cyclopentanone: IR (KBr): $\tilde{\nu}$ = 2920, 2852, 1719, 1496, 1454, 1408, 1219, 1055, 748, 697 cm^{-1}; ^{1}H NMR (CD_3SOCD_3): δ = 0.26 (s, 2H), 1.09 (s, 2H), 1.92–2.53 (m, 2H), 5.29–5.43 (m, 5H), 7.48–7.68 ppm (m, 10H); ^{13}C NMR (CD_3SOCD_3): δ = 18.2, 26.3, 35.7, 66.8, 67.7, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.22, 128.24, 128.4, 128.56, 128.59, 128.6, 128.7, 128.8, 137.1, 156.8, 212.1 ppm; HRMS (ESI): *m*/*z* calcd for $C_{21}H_{22}N_2O_5Na$: 405.1421 $[M+Na]^+$; found: 405.1426; enantiomeric excess was determined by HPLC of the crude sample with a Chiralpak AS-H column (hexane/2-propanol = 10:1), 1.0 mL min^{-1}; t_R(major) = 14.73 min, t_R(minor) = 19.59 min.

(2*R*,5*R*)-2,5-Bis[*N*,*N*′-bis(benzyloxycarbonyl)hydrazino]cyclopentanone: IR (KBr): $\tilde{\nu}$ = 2923, 2850, 1756, 1702, 1678, 1513, 1424, 1347, 1322, 1229 cm^{-1}; ^{1}H NMR (CD_3SOCD_3): δ = 2.00 (br s, 2H), 2.31 (br s, 2H), 4.36 (br s, 2H), 5.19 (s, 8H), 7.42 ppm (br s, 20H); ^{13}C NMR (CD_3SOCD_3): δ = 18.6, 22.9, 36.1, 65.2, 66.9, 67.2, 68.1, 128.2, 128.25, 128.3, 128.4, 128.7, 128.8, 129.2, 136.9, 137.1, 137.2, 137.5, 155.7, 157.2, 206.3 ppm; HRMS (ESI): *m*/*z* calcd for $C_{37}H_{36}N_4O_9Na$: 703.2374 $[M+Na]^+$; found: 703.2356; enantiomeric excess was determined by HPLC of the crude sample with a Chiralpak OD-H column (hexane/2-propanol = 10:1), 1.0 mL min^{-1}; t_R(major) = 50.55 min, t_R(minor) = 28.97 min.

(*R*)-2-[*N*,*N*′-Bis(benzyloxycarbonyl)hydrazino]-3-pentanone: IR (KBr): $\tilde{\nu}$ = 3296, 1718, 1559, 1507, 1419, 1296, 1221, 1074, 742, 697 cm^{-1}; ^{1}H NMR (CD_3SOCD_3): δ = 0.82 (br s, 3H), 1.12 (d, J = 3.6 Hz, 3H), 2.22–2.72 (m, 2H), 4.45–4.60 (m, 1H), 4.95–5.10 (m, 4H), 7.12–7.36 (m, 10H), 9.32–9.60 ppm (br s, 1H); ^{13}C NMR (CD_3SOCD_3): δ = 8.2, 13.4, 32.2, 39.9, 40.1, 40.3, 40.5, 40.7, 40.9, 41.2, 67.2, 68.2, 128.2, 128.5, 128.8, 129.15, 129.17, 137.0, 137.2, 156.2, 157.3, 208.6 ppm; HRMS (ESI): *m*/*z* calcd for $C_{21}H_{24}N_2NaO_5$: 407.1577 $[M+Na]^+$; found: 407.1599; enantiomeric excess was determined by HPLC of the crude sample with a Chiralpak IA column (hexane/2-propanol = 10:1), 1.0 mL min^{-1}; t_R(major) = 19.87 min, t_R(minor) = 15.91 min.

(*R*)-3-[*N*,*N*′-Bis(benzyloxycarbonyl)hydrazino]-2-butanone: IR (KBr): $\tilde{\nu}$ = 3302, 1718, 1507, 1457, 1405, 1300, 1220, 1049, 742, 697 cm^{-1}; ^{1}H NMR (CD_3SOCD_3): δ = 1.36 (d, J = 6.8 Hz, 3H), 2.23 (s, 3H), 4.71 (dd, J = 6.4, 13.2 Hz, 1H), 5.28 (d, J = 12.0 Hz, 4H), 7.38–7.62 (m, 10H), 9.74 ppm (br s, 1H); ^{13}C NMR (CD_3SOCD_3): δ = 13.3, 27.1, 40.1, 40.3, 40.5, 40.7, 40.9, 41.1, 41.3, 64.1, 67.3, 68.2, 128.2, 128.5, 128.8, 129.2, 137.0, 137.2, 156.1, 157.2, 205.9 ppm; HRMS (ESI): *m*/*z* calcd for $C_{20}H_{22}N_2NaO_5$: 393.1421 $[M+Na]^+$; found: 393.1445; enantiomeric excess was determined by HPLC of the crude sample with a Chiralpak IA column (hexane/2-propanol = 10:1), 1.0 mL min^{-1}; t_R(major) = 17.68 min, t_R(minor) = 14.29 min.

(*R*)-3-Benzyloxycarbonylamino-4-methyl-4-phenyloxazolidin-2-one:[10] The enantiomeric excess was determined by HPLC of the crude sample with a Chiralpak IA column (hexane/2-propanol = 10:1), 1.0 mL min^{-1}; t_R(major) = 17.01 min, t_R(minor) = 19.80 min.

Acknowledgements

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