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L-*t*-Leucine-Catalyzed Direct Asymmetric Aldol Reaction of Cyclic Ketones

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L-*t*-Leucine-catalyzed direct asymmetric aldol reactions are described. In the aldol reaction of *p*-nitrobenzaldehyde with a cyclic ketone at room temperature, L-*t*-leucine exhibits catalytic activity resulting in moderate to high diastereo- and enantioselectivity. Use of cycloheptanone or cyclooctanone as a substrate resulted in production of the *syn* selective product.

Introduction

Metal-free organocatalysts have been recently developed for various enantioselective reactions. Organocatalysts have several advantages over conventional metal catalysts, such as nontoxicity, stability, and easy manipulation. These important merits have led to the development of organocatalytic asymmetric reactions as a major field in organic chemistry.[1] We are interested in the application of organocatalysts to the synthesis of nitrogen-containing molecules and have described several asymmetric reactions of isoquinoline and carboline derivatives.[2] Since the publication of a pioneering work by List, Lerner, and Barbas,[3] the asymmetric aldol reaction catalyzed by L-proline has been a representative reaction in the field of organocatalysis, and many groups have investigated its application and reaction mechanism.[4] However, there is a drawback to using proline as a catalyst in this reaction, namely, a high loading of the catalyst is required for reasonable yields in the direct aldol reaction of aromatic aldehydes because proline itself reacts with aromatic aldehydes to form iminium salts, followed by decarboxylation.[5] Therefore, various new catalysts have been developed to overcome this problem. Córdova reported primary amine catalyzed direct asymmetric aldol reactions with *anti* selective diastereoselectivities.[6] Subsequently, Lu,[7] Barbas,[8] Gong,[9] Wu et al.,[10] and Luo et al.[11] reported *syn* selective aldol reactions catalyzed by chiral primary amines. According to Luo's report,[11f] a primary amine and an aliphatic ketone form a (*Z*)-enamine to furnish a *syn* selective product. In the case of a cyclic ketone, however, a (*Z*)-enamine cannot be formed. The study of the organocatalyzed direct asymmetric reaction of cyclic ketones to afford *syn* selective products is very rare.[7a,7c,12] Thus, we focused on finding an efficient organocatalyst for *syn* selective asymmetric aldol reactions of cyclic ketones and found that L-*t*-leucine has excellent catalytic activity toward cyclic ketones. To the best of our knowledge, this is the first report that L-*t*-leucine can be used as a catalyst for an asymmetric reaction. In this paper, we report that L-*t*-leucine has unique properties distinct from those of other amino acids, and that L-*t*-leucine efficiently catalyzes direct aldol reactions to yield *syn* selective adducts using cycloalkanones (C7–C8) as electron donors.

Results and Discussion

Our initial experiment was to test the utility of a series of amino acids as catalysts (2.5 mol-%) in the reaction of *p*-nitrobenzaldehyde with cyclohexanone at room temperature. We used L-alanine, L-valine, L-leucine, and L-*t*-leucine as primary amine catalysts, and L-proline as a secondary amine catalyst. As shown in Table 1, L-*t*-leucine exhibited much higher efficiency than the other catalysts (Table 1, Entry 4). A small amount (2.5 mol-%) of L-*t*-leucine catalyzed the aldol reaction and gave high yield and enantioselectivity; however, a large amount (10 mol-%) of the catalyst was required to get satisfactory diastereoselectivity. Experiments aimed at optimizing the conditions for using L-*t*-leucine as a catalyst indicated that 50 equiv. of water in DMSO increased both the diastereo- and enantioselectivity without causing a loss of reactivity. Thus, the aldol reaction of cyclohexanone and *p*-nitrobenzaldehyde in the presence of L-*t*-leucine in DMSO with a small amount of water gave the corresponding β-ketoalcohol in 95% yield, 97%*ee*, and 1:12 (*syn*/*anti*) *dr* (Table 1, Entry 5).

The aldol reaction of a range of aromatic aldehydes with cyclohexanone in the presence of L-*t*-leucine was then investigated by using these optimized conditions. Except for the reaction of *p*-nitrobenzaldehyde, all reactions of aryl aldehydes with cyclohexanone required a catalyst loading of

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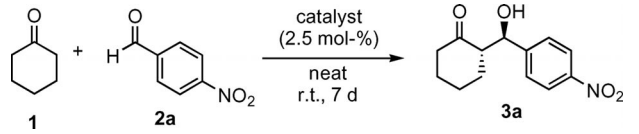
Table 1. L-Amino acid catalyzed asymmetric aldol reaction.



1 2a 3a

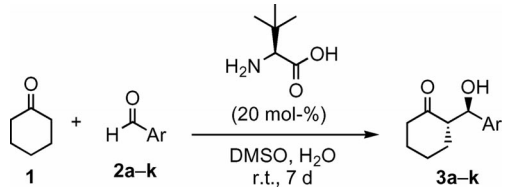
Entry[a]	Catalyst	Yield [%][b]	*dr* (*syn*/*anti*)[c]	*ee* of *anti* [%][d]
1	L-alanine	25	1:3.6	80
2	L-valine	7	1:2.7	87
3	L-leucine	16	1:3.4	82
4	L-*t*-leucine	95	1:2.2	94
5[e]	L-*t*-leucine	95	1:12	97
6	L-proline	11	1:1.2	69

[a] Unless otherwise stated, the reaction was performed with *p*-nitrobenzaldehyde (1 equiv.) and cyclohexanone (10 equiv.) for 7 d. [b] Combined yield of the diastereomers determined by ^{1}H NMR spectroscopy. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC. [e] The reaction was performed with *p*-nitrobenzaldehyde (1 equiv.), cyclohexanone (1.5 equiv.), and L-*t*-leucine (0.1 equiv.) in DMSO in the presence of H_2O (50 equiv.) for 7 d.

20 mol-% to afford the desired aldol product in satisfactory yields. In all cases, L-*t*-leucine efficiently controlled *anti* selectivity and afforded excellent enantioselectivity. The yield was slightly dependent on the electronic and steric features of the substituent on the aldehyde. For example, high yields were obtained with benzaldehydes containing an electron-withdrawing substituent (Table 2, Entries 1–7). Benzaldehyde and 2-naphthaldehyde were less reactive toward cyclohexanone (Table 2, Entries 8 and 9), whereas 4-pyridinecarboxaldehyde and 3-quinolinecarboxaldehyde showed high reactivity (Table 2, Entries 10 and 11).

Next, we studied the utility of several amino acids in the aldol reaction of *p*-nitrobenzaldehyde with cycloheptanone and cyclooctanone; the results are summarized in Table 3.

Table 2. L-*t*-Leucine-catalyzed asymmetric aldol reaction of cyclohexanone.



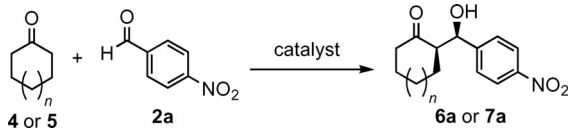
1 2a–k 3a–k

Entry[a]	Ar	Product	Yield [%][b]	*dr* (*syn*/*anti*)[c]	*ee* of *anti* [%][d]
1[e]	4-$NO_2C_6H_4$	**3a**	94	1:12	97
2	3-$NO_2C_6H_4$	**3b**	93	1:8.1	98
3	2-$NO_2C_6H_4$	**3c**	90	1:13	98
4	4-CNC_6H_4	**3d**	89	1:7.3	97
5	3,5-$(CF_3)_2C_6H_3$	**3e**	94	1:5.3	96
6	4-ClC_6H_4	**3f**	70	1:6.7	98
7	4-$CF_3C_6H_4$	**3g**	79	1:5.7	97
8	C_6H_5	**3h**	51	1:9.0	92
9	2-naphthyl	**3i**	58	1:9.0	97
10	4-pyridinyl	**3j**	91	1:6.1	97
11	3-quinolinyl	**3k**	84	1:8.1	96

[a] Unless otherwise stated, the reaction was performed with aldehyde (1 equiv.), cyclohexanone (1.5 equiv.), and L-*t*-leucine (0.2 equiv.) in DMSO in the presence of H_2O (50 equiv.) for 7 d. [b] Combined isolated yield of the diastereomers. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC. [e] The reaction was performed in the presence of 0.1 equiv. of L-*t*-leucine.

Initially, the optimized conditions used with cyclohexanone were tested with these substrates, but reactions catalyzed by L-*t*-leucine in the presence of water in DMSO yielded undesirable results (Table 3, Entries 5 and 11). In the case of cycloheptanone and cyclooctanone, solvent-free conditions without added water were found to be effective. L-Alanine, L-leucine, and L-proline showed low reactivity towards cycloheptanone (Table 3, Entries 1, 3, and 6), and L-valine ex-

Table 3. L-Amino acid catalyzed asymmetric aldol reaction of cycloheptanone and cyclooctanone.



4 or 5 2a 6a or 7a

Entry[a]	*n*	Catalyst (mol-%)	Time [d]	Product	Yield [%][b]	*dr* (*syn*/*anti*)[c]	*ee* of *syn* [%][d]
1	2	L-alanine (10)	10	**6a**	11	2.7:1	22
2	2	L-valine (10)	8	**6a**	trace	nd[e]	nd[e]
3	2	L-leucine (10)	10	**6a**	7	2.8:1	15
4	2	L-*t*-leucine (10)	6.5	**6a**	87	6.1:1	65
5[f]	2	L-*t*-leucine (30)	8	**6a**	22	1:1	nd[e]
6	2	L-proline (10)	7	**6a**	8	1.3:1	5
7	3	L-alanine (30)	10	**7a**	trace	nd[e]	nd[e]
8	3	L-valine (30)	10	**7a**	trace	nd[e]	nd[e]
9	3	L-leucine (30)	8	**7a**	trace	nd[e]	nd[e]
10	3	L-*t*-leucine (30)	10	**7a**	70	10:1	60
11[f]	3	L-*t*-leucine (30)	10	**7a**	10	2.6:1	nd[e]
12	3	L-proline (30)	10	**7a**	trace	nd[e]	nd[e]

[a] The reaction was performed with *p*-nitrobenzaldehyde (1 equiv.) and cyclic ketone (10 equiv.). [b] Combined yield of the diastereomers determined by ^{1}H NMR spectroscopy. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC. [e] Not determined. [f] The reaction was performed in the presence of H_2O in DMSO.

hibited no catalytic activity in this reaction (Table 3, Entry 2). In contrast, L-*t*-leucine afforded high *syn* selectivity, high enantioselectivity, and good yield (Table 3, Entry 4). For cyclooctanone, no amino acid other than L-*t*-leucine showed significant reactivity in the aldol reaction (Table 3, Entries 10 and 11). These results suggest that L-*t*-leucine has unique features compared to other amino acids.

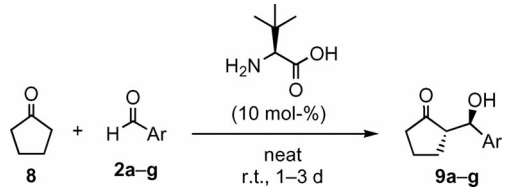
The same reaction conditions, employing L-*t*-leucine as a catalyst, were used with other aldehydes, and the results are summarized in Table 4. First, cycloheptanone was treated with various aromatic aldehydes in the presence of L-*t*-leucine to give the desired product in high yield and *syn* selectivity (Table 4, Entries 1–5). This is the first report of the *syn* selective aldol reaction of cycloheptanone. In the case of cyclooctanone, reaction with aromatic aldehydes gave moderate to high yields (Table 4, Entries 6–10). Although one example of *syn* selective aldol reaction of cyclooctanone with *p*-nitrobenzaldehyde has been reported by Da et al., their reported diastereo- and enantioselectivity was low (*syn*/*anti* = 2.5:1, 19% *ee*).[13]

We also examined aldol reactions of cyclopentanone with substituted benzaldehydes. The reactions were carried out by using L-*t*-leucine under solvent-free conditions without added water, as well as the case of cycloheptanone and cyclooctanone (Table 5). Although L-*t*-leucine gave aldol products with low diastereoselectivities, high enantioselectivities were obtained. These results presumably indicate that the aldol reaction of smaller (less than C7) cyclic ketones using L-*t*-leucine as the catalyst gave *anti* selectivity.

L-*t*-Leucine provides superior results compared to other amino acids due to its stability under the reaction conditions. According to Orsini's report,[5a] proline and *N*-substituted primary amino acids react with *p*-nitrobenzaldehyde to form an immonium salt which undergoes decarboxylation. The resulting 1-oxapyrrolizidine and 1,3-oxazolidines have been obtained as stable compounds. In our experiments, L-alanine, L-valine, and L-leucine reacted slowly with *p*-nitrobenzaldehyde, and complex ^{1}H NMR spectra consistent with decomposition of these compounds were obtained (see Supporting Information). A proposed decomposition process is shown in Scheme 1. In the case of L-*t*-leucine with *p*-nitrobenzaldehyde, however, the corresponding imine, which is reconverted into L-*t*-leucine and *p*-nitrobenzaldehyde, is formed without decarboxylation. These results suggest that L-*t*-leucine is sufficiently stable to retain its catalytic activity under aldol reaction conditions.

In addition, *anti* selective products were obtained in the aldol reaction of cyclohexanone, whereas the use of cycloheptanone or cyclooctanone gave *syn* products. These results suggest that the cyclohexanone transition state is fundamentally different from that of cycloheptanone or cyclo-

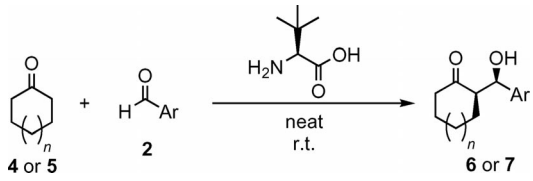
Table 5. L-*t*-Leucine-catalyzed asymmetric aldol reaction of cyclopentanone.



Entry[a]	Ar	Product	Yield [%][b]	*dr* (*syn*/*anti*)[c]	*ee* of *anti* [%][d]
1	4-$O_2NC_6H_4$	**3a**	69	1:2.3	89
2	3-$O_2NC_6H_4$	**3b**	82	1:1.7	90
3	4-NCC_6H_4	**3d**	71	1:1.9	86
4	3,5-$(F_3C)_2C_6H_3$	**3e**	83	1:1.0	91
5	4-$F_3CC_6H_4$	**3g**	68	1:1.0	83

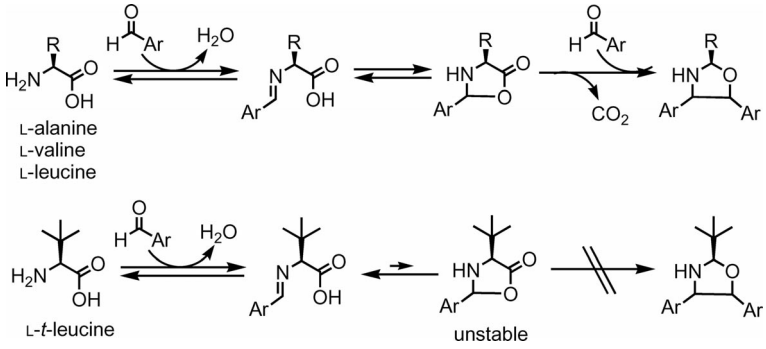
[a] The reaction was performed with aldehyde (1 equiv.), cyclopentanone (10 equiv.), and L-*t*-leucine (0.1 equiv.). [b] Combined isolated yield of the diastereomers. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC.

Table 4. L-Amino acid catalyzed asymmetric aldol reaction of cycloheptanone and cyclooctanone.



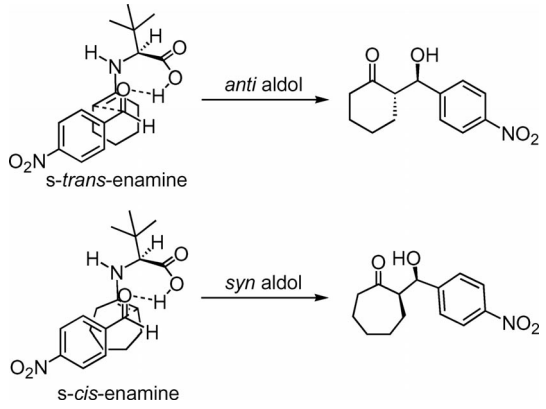
Entry[a]	*n*	Ar	Catalyst (mol-%)	Time [d]	Product	Yield [%][b]	*dr* (*syn*/*anti*)[c]	*ee* of *syn* [%][d]
1	2	4-$O_2NC_6H_4$	10	7	**6a**	84	6.1:1	63
2	2	3-$O_2NC_6H_4$	20	7	**6b**	84	6.7:1	71
3	2	4-NCC_6H_4	20	7	**6d**	89	5.7:1	62
4	2	3,5-$(F_3C)_2C_6H_3$	20	7	**6e**	94	5.9:1	64
5	2	4-pyrydinyl	20	7	**6j**	89	6.7:1	50
6	3	2,4-$(O_2N)_2C_6H_3$	30	10	**7i**	82	4.0:1	58
7	3	4-$O_2NC_6H_4$	30	10	**7a**	68	10:1	60
8	3	4-NCC_6H_4	30	10	**7d**	51	10:1	51
9	3	3,5-$(F_3C)_2C_6H_3$	30	10	**7e**	79	13:1	31
10	3	4-pyrydinyl	30	10	**7j**	71	10:1	53

[a] The reaction was performed with aldehyde (1 equiv.) and cyclic ketone (10 equiv.). [b] Combined isolated yield of the diastereomers. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC.



Scheme 1. Reactions between amino acids and aryl aldehyde.

octanone. According to previous reports,[6c,14] the *anti* product is formed through the s-*trans*-enamine, but the *syn* product is formed via the s-*cis*-enamine in aldol reactions of cyclic ketones. Plausible transition states are shown in Scheme 2. Molecular mechanics calculations suggest that L-*t*-leucine has a tendency to afford the s-*cis*-enamine in the case of cycloheptanone and cyclooctanone, but the s-*trans*-enamine for cyclohexanone.[15] That is, the *tert*-butyl group of L-*t*-leucine influences the stability of the enamines to make one isomeric enamine dominant. The approach of an aldehyde, and the hydrogen bond formed between the hydrogen of the carboxyl group of L-*t*-leucine and the oxygen in the aldehyde, apparently results in a rigid transition state. At this point, the aryl group of the aldehyde is located on the opposite side of the carboxyl group of L-*t*-leucine due to steric effects. Therefore, the s-*cis* enamine attacks the *Re* face of the aldehyde to generate the *syn* product in the case of seven- and eight-membered rings.



Scheme 2. Proposed transition states of *anti*- and *syn*-aldol reactions.

Conclusions

In summary, we have developed an L-*t*-leucine-catalyzed asymmetric direct aldol reaction, which gives access to optically active compounds in moderate to high yield. Compared to reactions with other amino acid catalysts, L-*t*-leucine gave far better results. In the case of cycloheptanone or cyclooctanone, the L-*t*-leucine-catalyzed reaction afforded the product with high *syn* selectivity. We are currently investigating the possibility of improving the enantioselectivity and understanding the mechanisms controlling the generation of optically active products.

Experimental Section

General Information: All materials were purchased from commercial suppliers and used without further purification. Progress of the reactions was monitored by thin-layer chromatography (TLC) performed on Merck Art. 5715 Kieselgel 60 F_{254}/0.25 mm thickness plates. Visualization was accomplished with UV light and cerium sulfate–ammonium molybdate solution followed by heating. Column chromatography was performed by using forced flow of the indicated solvent on Sigma H-type silica Gel 60N (100–210 μm). ^{1}H and ^{13}C NMR spectra were recorded with a JEOL JNM AL-400 instrument (400 MHz for ^{1}H and 100 MHz for ^{13}C) or a JEOL JMN ECA-500 instrument (500 MHz for ^{1}H and 125 MHz for ^{13}C) in deuterated solvent, using tetramethylsilane (δ = 0.0 ppm for ^{1}H NMR spectra) and $CDCl_3$ (δ = 77.0 ppm for ^{13}C NMR spectra) as internal standards. Optical rotations were measured with a JASCO P1020 polarimeter operating at the sodium D line at room temperature. HPLC analyses were performed with Shimadzu equipment (254 λ absorbance Detector) using Daicel Chemical Industries, Ltd. Chiralcel OD, Chiralcel OJ-H, Chiralpak AD-H, or Chiralpak IC columns with hexane/isopropyl alcohol or hexane/ethyl acetate. HPLC methods were calibrated with the corresponding racemic mixtures. High-resolution mass spectra (HRMS) were measured with a JEOL JMS-MS700V using *p*-nitrobenzyl alcohol as a matrix. The known compounds have been identified by comparison of spectroscopic data with those reported. The absolute configurations of the optically active compounds were determined on the basis of the measured optical rotation compared with literature values.

Typical Procedure for Organocatalyzed Direct Aldol Reaction of Cyclohexanone: To a mixture of aldehyde (0.5 mmol) and L-*t*-leucine (0.1 mmol) in DMSO (2.0 mL) was added H_2O (25 mmol) and cyclohexanone (1.5 mmol), and the mixture was stirred at room temperature. The reaction was monitored by TLC analysis. After 7 d, brine was added, and the mixture was extracted with CH_2Cl_2 (3×). The combined organic extracts were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, gradient) to give the desired product.

Typical Procedure for Organocatalyzed Direct Aldol Reaction of Cycloheptanone: To a mixture of aldehyde (0.5 mmol) and L-*t*-leucine (0.1 mmol) was added cycloheptanone (5 mmol), and the mixture was stirred at room temperature. The reaction was monitored by

TLC analysis. After 7 d, brine was added, and the mixture was extracted with CH_2Cl_2 (3×). The combined organic extracts were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, gradient) to give the desired product.

Typical Procedure for Organocatalyzed Direct Aldol Reaction of Cyclooctanone: To a mixture of aldehyde (0.25 mmol) and L-*t*-leucine (0.075 mmol) was added cyclooctanone (2.5 mmol), and the mixture was stirred at room temperature. The reaction was monitored by TLC analysis. After 10 d, brine was added, and the mixture was extracted with CH_2Cl_2 (3×). The combined organic extracts were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, gradient) to give the desired product.

Supporting Information (see footnote on the first page of this article): Characterization data including ^1H and ^{13}C NMR spectra for aldol products, and HPLC traces for all results in Tables 2, 4, and 5.

Acknowledgments

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[15] In order to study the selectivity of the reaction, we have calculated the stability of the enamine isomers in four cycloalkanones. In the case of cyclopentanone and cyclohexanone, the heats of formation for the s-*trans* enamines, which were made from the cycloalkanones and L-*t*-leucine, were lower than those of s-*cis* enamines (for cyclopentanone: s-*trans*-enamine, –105.10 kcal/mol; s-*cis*-enamine, –104.97 kcal/mol; for cyclohexanone: s-*trans*-enamine, –115.25 kcal/mol; s-*cis*-enamine, –114.88 kcal/mol). Thus, it was suggested that the s-*trans*-enamines were slightly more stable than the s-*cis*-enamines. In the case of cycloheptanone and cyclooctanone, however, the heats of formation for s-*trans*-enamines were higher than those of s-*cis* enamines (for cycloheptanone: s-*trans*-enamine, –118.12 kcal/mol; s-*cis*-enamine, –118.78 kcal/mol; for cyclooctanone: s-*trans*-enamine, –121.89 kcal/mol; s-*cis*-enamine, –122.77 kcal/mol). These results indicated that the s-*cis*-enamines were dominant intermediates to afford the *syn* selectivity. Although the other amino acids have the same tendency to afford s-*cis*-enamine geometry with cycloheptanone or cyclooctanone, the desired products were obtained in very low yields because the reaction of the amino acid with aldehydes gives rise to decomposition products.

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