Pergamon

Tetrahedron 57 (2001) 861–866

TETRAHEDRON

A novel chiral zirconium catalyst for enantioselective aldol and Mannich-type reactions. Catalytic activation of both aldehydes and imines using a similar chiral Lewis acid

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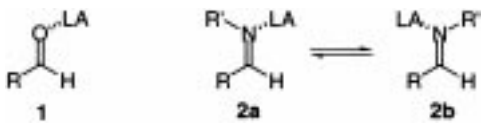
Received 4 July 2000; accepted 14 August 2000

Abstract—A novel zirconium catalyst has been developed for asymmetric aldol reaction of aldehydes with silyl enolates and asymmetric Mannich reactions of imines with silyl enolates. Similar types of catalysts have been successfully used in both reactions, and the desired products were obtained in high yields and high selectivities. For the sense of the chiral induction, reverse enantiofacial selectivities were observed between aldol reactions and Mannich reactions.

1. Introduction

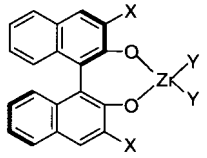
Nucleophilic addition to carbonyl and related compounds, which is one of major fields in organic chemistry, is often used in many organic transformations. Generally, strong nucleophiles attack carbonyls without the aids of activators. On the other hand, in the reactions using rather weak nucleophiles such as silanes and stannanes, Lewis acids are often employed to activate aldehydes and imines.[1–3] Recently, due to the increasing demands on asymmetric synthesis, chiral Lewis acids have been focused for the activation of aldehydes and imines, and catalytic enantioselective reactions using chiral Lewis acids for the synthesis of versatile chiral building blocks have been intensively studied.[4] While several excellent chiral Lewis acids for the activation of aldehydes have been reported, few examples are known for the catalytic activation of imines by chiral Lewis acids.[5] This is partially because coordination forms are different between aldehydes–Lewis acids complexes and imines–Lewis acids complexes. While Lewis acids coordinate to aldehydes in *syn* direction to the hydrogen atoms of the aldehydes (**1**),[6] Lewis acids coordinate to imines in *syn* (**2a**) or *anti* (**2b**) direction to the hydrogen atoms of the imines (Scheme 1).[7]



1 2a 2b

Scheme 1. Activation of aldehydes and imines by Lewis acids.

In this paper, we report examples of effective activations of both aldehydes and imines using a similar chiral zirconium catalyst (**3**).



3a: X = H
3b: X = Cl
3c: X = Br
3d: X = I

1.1. Aldehyde activation (aldol reactions)

The Lewis acid-mediated aldol reactions of silyl enol ethers with aldehydes (Mukaiyama aldol reaction) provide one of the most convenient carbon–carbon bond-forming methods.[8] The first catalytic asymmetric version of this reaction using chiral tin (II) Lewis acids appeared in 1990,[9] and after that, several efficient Lewis acid catalysts based on boron, titanium, copper, etc., have been reported.[10] While these highly selective reactions have been regarded as one of the most efficient reactions for the preparation of chiral β-hydroxy ketone and ester derivatives, temperatures of −78°C and strict anhydrous conditions are required in most cases.[10–12]

We have found that a chiral zirconium catalyst activated aldehydes to create excellent asymmetric environments.[13] In the presence of 10 mol% of a chiral zirconium catalyst prepared from $Zr(O^tBu)_4$, ((*R*)-3,3′-dibromo-1,1′-bi-2-naphthol (*R*)-3,3′-BrBINOL), and propanol, benzaldehyde reacted with 1-trimethylsiloxy-1-methoxy-2-methylpropene

Keywords: zirconium; aldehydes; imines; asymmetric catalysis.
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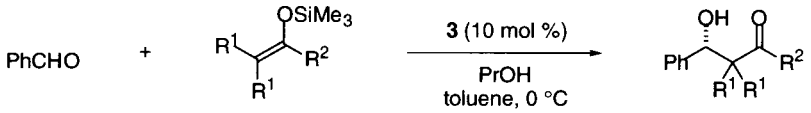
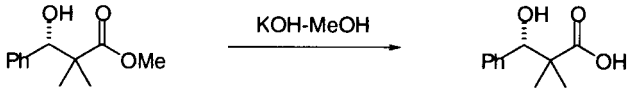
PII: S0040-4020(00)01038-3

Table 1. Catalytic asymmetric aldol reactions using **3**



R^1	R^2	**3**	PrOH/mol (%)	Yield (%)	ee (%)
Me	OMe	**3c**	20	94	78
Me	OMe	**3d**	20	97	89
Me	OMe	**3b**	20	62	44
Me	OMe	**3a**	20	49	38
Me	OMe	**3d**	50	89	97
H	SEt	**3d**	50	81	92



Scheme 2. Hydrolysis of the aldol adduct.

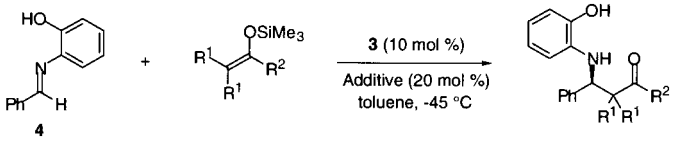
at 0°C in toluene to afford the corresponding aldol adduct in 94% yield with 78% ee. In the absence of propanol, much lower yield and enantiomeric excess were obtained. Other BINOL derivatives were tested in the same system, and the results are summarized in Table 1. When (*R*)-3,3′-diiodo-1,1′-bi-2-naphthol ((*R*)-3,3′-IBINOL) was used, the product was obtained in 89% ee. It was also found that the amount of propanol influenced the selectivity. When 50 mol% of propanol was used, the desired aldol adduct was obtained in 89% yield with 97% ee. The absolute configuration of the aldol adduct was determined to be *S* by comparison of the optical rotation of the corresponding carboxylic acid with that in the literature (Scheme 2).[14] When 1-ethylthio-1-trimethylsiloxyethene was used instead of 1-trimethylsiloxy-1-methoxy-2-methylpropene under the similar reaction conditions, the same high level of yield and selectivity was obtained.

1.2. Imine activation (Mannich reactions)

Asymmetric Mannich reactions of imines with enolate components provide useful routes for the synthesis of chiral β-amino ketones or esters (Mannich bases),[3] which are versatile chiral building blocks for the synthesis of many nitrogen-containing biologically important compounds including β-amino acids, β-lactams, etc.[3a] While several asymmetric Mannich reactions using stoichiometric amounts of chiral sources have already been reported,[15,16] very little is known concerning catalytic asymmetric versions.[5] This is in contrast to the recent progress achieved in catalytic enantioselective aldol reactions of aldehydes with enolate components, especially silyl enolates (Mukaiyama aldol reaction) as mentioned in the previous section. While chiral Lewis acids have played leading roles in these reactions, coordination forms are different (see Introduction). In addition, it is assumed that most Lewis acids would be trapped by basic nitrogen atoms of the starting materials and/or products in Mannich reactions, and that truly catalytic reactions would be difficult to perform. In 1997, we reported the first example of truly catalytic enantioselective Mannich reactions of imines with silyl enolates using a novel zirconium catalyst prepared from $Zr(O^tBu)_4$, (*R*)-6,6′-dibromo-1,1′-bi-2-naphthol ((*R*)-6,6′-BrBINOL), and *N*-methylimidazole (NMI).[17]

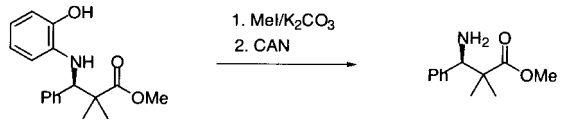
We used 10 mol% of chiral zirconium catalyst **3** in the Mannich reaction of imine **4** with 1-trimethylsiloxy-1-methoxy-2-methylpropene in toluene at −45°C. The catalyst **3** was prepared from $Zr(O^tBu)_4$, (*R*)-3,3′-BrBINOL, and propanol, and was already shown to be effective in the aldol reactions of silyl enol ethers with aldehydes. The Mannich reaction proceeded smoothly to afford the corresponding adduct in 99% yield with 69% ee. It is noted that (*R*)-3,3′-IBINOL gave lower selectivity in this reaction, while (*R*)-3,3′-ClBINOL gave the same level of the yield and selectivity (Table 2). The absolute configuration of the adduct was determined to be *R* by comparison of the optical rotation of the corresponding amino ester with that in the literature (Scheme 3).[18,19] It was interesting to find that the

Table 2. Catalytic asymmetric Mannich reactions using **3**



R^1	R^2	**3**	Additive	Yield (%)	ee (%)
Me	OMe	**3c**	PrOH	99	69
Me	OMe	**3d**	PrOH	99	44
Me	OMe	**3b**	PrOH	95	70
Me	OMe	**3a**	PrOH	63	23
Me	OMe	**3c**	H_2O[a]	94	95
H	SEt	**3c**	H_2O[a]	60	79

[a] As a solvent, THF was used instead of toluene, and molecular sieves 3A was added after the preparation of the catalyst (see Experimental).



Scheme 3. Conversion to free amine.

use of water as an additive instead of propanol greatly improved the enantiomeric excess. Namely, when the zirconium catalyst was prepared from $Zr(O^tBu)_4$, (*R*)-3,3′-BrBINOL, and water, imine **4** (R^1=Ph) reacted with 1-trimethylsiloxy-1-methoxy-2-methylpropene to afford the corresponding adduct in 94% yield with 95% ee. Ethylthio-1-trimethylsiloxyethene also reacted with imine **4** under the same reaction conditions to give the desired adduct in 79% ee.

1.3. Catalytic cycle

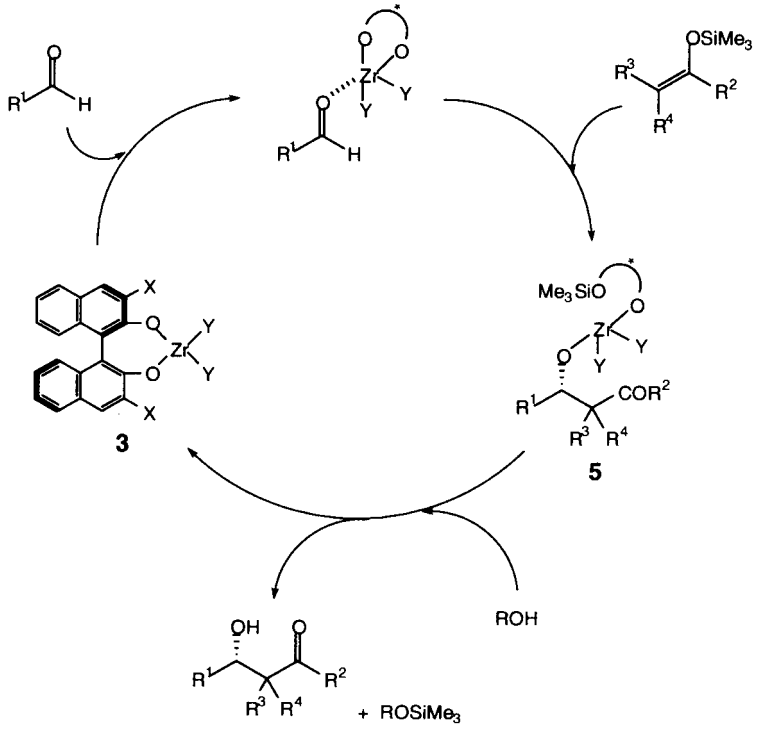
The assumed catalytic cycle of the asymmetric aldol reaction is shown in Scheme 4. Catalyst **3** activates an aldehyde, and a silyl enolate attacks the aldehyde to form key intermediate **5**. When no alcohol is present, it is thought that the catalyst regeneration step (from **5** to **3**) would be slow, and when the reaction is quenched with water, **5** forms a monotrimethylsilylated BINOL derivative detected by GC-MS analysis. On the other hand, **5** immediately reacts with an alcohol to regenerate the catalyst (**3**) along with formation of the aldol adduct and an alcohol trimethylsilyl ether.

On the other hand, a similar catalytic cycle is postulated in the Mannich reactions (Scheme 5). The bidentate coordination of imines to the zirconium was proved to be essential, since almost no chiral induction was observed when the imines derived from aniline or 2-methoxyaniline were used. The zirconium catalyst **3** coordinates to an imine to form zirconium complex **6**. A silyl enol ether attacks the imine to produce **7**, whose trimethylsilylated oxygen atom attacks the zirconium center to afford the product along with regeneration of the catalyst **3**. The product was obtained as a trimethylsilylated form without the acidic work-up.

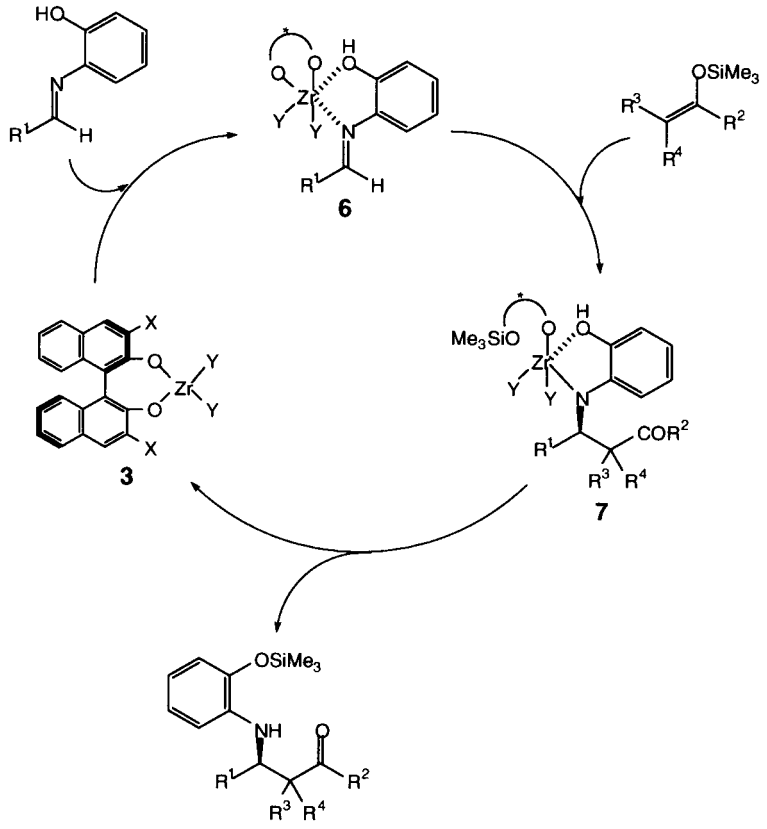
As for the sense of the chiral induction, reverse enantiofacial selectivities were observed between aldol reactions and Mannich reactions. While silyl enolates attack aldehydes from the *re*-face of the aldehydes in aldol reactions, the *re*-face of imines are shielded and silyl enolates are expected to attack to the *si*-face of imines in Mannich reactions. The reverse selectivities observed here would be ascribed to the difference of the coordination form between aldehydes–Lewis acids complexes and imines–Lewis acids complexes, and it should be noted that such coordination forms were well-controlled by using the similar zirconium catalyst in these reactions.

2. Conclusion

We have developed a novel chiral zirconium catalyst which can activate both aldehydes and imines successfully. While catalytic asymmetric aldol reactions of aldehydes with silyl enolates proceeded smoothly in high selectivities, catalytic Mannich reactions of imines with silyl enolates are also performed in high yields and high enantioselectivities by using the similar types of the catalysts. Although both catalysts are based on zirconium and BINOL derivatives, slight modifications of ligands and reaction conditions were needed to obtain the highest yields and selectivities. Lewis acids activate both aldehydes and imines, but activation



Scheme 4. Assumed catalytic cycle of the aldol reactions.



Scheme 5. Assumed catalytic cycle of the Mannich reactions.

forms are different between them. It should be noted that the similar catalysts were successfully used for the activation of both aldehydes and imines, and that reverse enantiofacial selectivities were observed between aldehyde additions and imine additions. These results will be helpful to design novel chiral catalysts for many other addition reactions of carbonyl and related compounds.

3. Experimental

3.1. General

^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-LA300, JNM-LA400, or JNM-LA500 spectrometer in $CDCl_3$ unless otherwise noted. Tetramethylsilane (TMS) served as internal standard (δ=0) for ^{1}H NMR, and $CDCl_3$ was used as internal standard (δ=77.0) for ^{13}C NMR. High-performance liquid chromatography was carried out using following apparatuses; SHIMADZU LC-10AT (liquid chromatograph), SHIMADZU SPD-10A (UV detector), and SHIMADZU C-R6A Chromatopac. Column chromatography was conducted on Silica gel 60 (Merck) and preparative thin-layer chromatography was carried out using Wakogel B-5F. Toluene was distilled and dried over MS 4A. THF was distilled from Na–benzophenone. Propanol was distilled in the presence of Mg, dried over MS 4A, and stored under argon. All silyl enol ethers were prepared according to the modified House's procedure.[20] BINOL derivatives were prepared according to Snieckus' methods.[21]

3.2. A typical experimental procedure for asymmetric aldol reactins

To a suspension of 3,3′-IBINOL (24 mg, 0.044 mmol) in toluene (0.5 ml) was added $Zr(O^tBu)_4$ (15.3 mg, 0.04 mmol) in toluene (1.0 ml) at room temperature. The mixture was stirred for 30 min, and then propanol (20–50 mol%) in toluene (1.0 ml) was added. After stirred for 30 min at this temperature, toluene solutions of an aldehyde (0.4 mmol) and a silyl enol ether (0.48 mmol) were successively added at 0°C. The mixture was stirred for 18 h, and saturated $NaHCO_3$ aq. was added to quench the reaction. The aqueous layer was extracted with dichloromethane, and the crude product was treated with THF-1N HCl (20:1) at 0°C to hydrolyze a small amount of a silylated adduct. After a usual work up, the crude adduct was chromatographed on silica gel to give the desired adduct. The optical purity was determined by chiral HPLC analysis.

3.2.1. (*S*)-Methyl 3-hydroxy-2,2-dimethyl-3-phenylpropanoate. ^{1}H NMR ($CDCl_3$) δ 1.12 (s, 3H), 1.15 (s, 3H), 3.73 (s, 3H), 4.90 (s, 1H), 7.25–7.36 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 19.0, 23.1, 47.6, 52.1, 78.7, 127.6, 127.8, 139.9, 178.2. HPLC: Daicel Chiralcel OJ, hexane/^{i}PrOH=9/1, flow rate=0.5 ml/min: t_R=18.3 min (*S*), t_R=22.0 min (*R*). Absolute configuration was determined after basic hydrolysis of the sample with 97% ee: $[\alpha]_D^{25}$=+5.70° (*c* 2.49, MeOH) (lit.[13a] (*R*)-isomer; $[\alpha]_D^{24}$=−7.1° (*c* 1.0, MeOH), lit.[13b] (*R*)-isomer; $[\alpha]_D^{24}$=−5.2° (*c* 0.98, MeOH)).

3.2.2. (*R*)-*S*-Ethyl 3-hydroxy-3-phenyl-propanethioate.

^{1}H NMR ($CDCl_3$) δ 1.26 (t. 3H, J=7.4 Hz), 2.87–3.08 (m, 5H), 5.17 (dd, 1H, J=3.7, 8.8 Hz), 7.10–7.36 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 14.5, 23.4, 52.6, 70.8, 125.6, 127.8, 128.5, 142.3, 199.0. HPLC: Daicel Chiralcel OD, hexane/^{i}PrOH=19/1, flow rate=0.8 ml/min: t_R=12.1 min (*S*), t_R=13.4 min (*R*). 92% ee: $[\alpha]_D^{27}$=+51.6° (*c* 0.67, benzene) (lit.[22] (*S*)-isomer; $[\alpha]_D^{28}$=−56.3°(c 1.40, benzene, 92% ee)).

3.3. A typical experimental procedure for asymmetric Mannich reactions

To 3,3′-BrBINOL (20 mg, 0.044 mmol) in THF (0.5 ml) was added $Zr(O^tBu)_4$ (15.3 mg, 0.04 mmol) in THF (1.0 ml) solution at room temperature. The mixture was stirred for 30 min. and then water (20 mol%) in THF (1.0 ml) was added. After stirred for 30 min at this temperature, MS 3A (125 mg) and THF solutions of an imine (0.4 mmol) and a silyl enol ether (0.48 mmol) were successively added at 0°C. The mixture was stirred for 18 h, and saturated $NaHCO_3$ aq. was added to quench the reaction. The aqueous layer was extracted with dichloromethane, and the crude product was treated with THF-1N HCl (20:1) at 0°C to remove the silyl group. After a usual work up, the crude adduct was chromatographed on silica gel to give the desired adduct. The optical purity was determined by chiral HPLC analysis.

3.3.1. (*R*)-Methyl 2,2′-dimethyl-(2-hydroxyphenyl)-amino-3-phenylpropionate. ^{1}H NMR ($CDCl_3$): δ 1.21 (s, 3H), 1.24 (s, 3H), 3.68 (s, 3H), 4.57 (s, 1H), 6.36–6.76 (m, 4H), 7.21–7.28 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 19.9, 24.2, 47.3, 52.3, 64.3, 113.2, 114.1, 117.6, 120.8, 127.3, 127.9, 128.3, 135.6, 138.9, 144.0, 178.0. HPLC Daicel Chiralpak AD, hexane/^{i}PrOH=9/1, flow rate=1.0 ml/min: t_R=9.3 min (3*R*), t_R=16.0 min (3*S*). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. found: C, 72.28; H, 7.20; N, 4.62. HRMS: Calcd for $C_{18}H_{21}NO_3$ (M^+) 299.1522, found 299.1497.

3.3.2. (*S*)-*S*-Ethyl 3-(2-hydroxyphenyl)amino-3-phenylpropanethioate. ^{1}H NMR ($CDCl_3$): δ 1.67 (t, 3H, J=7.3 Hz), 2.83 (q, 2H, J=7.3 Hz), 2.97 (dd, 1H, J=5.4, 14.9 Hz), 3.07 (dd, 1H, J=8.1, 14.9 Hz), 4.81 (dd, 1H, J=5.4, 8.1 Hz), 6.44–6.71 (m, 4H), 7.20–7.33 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.4, 23.6, 51.4, 56.1, 114.4, 114.6, 118.8, 121.1, 126.3, 127.4, 128.6, 134.9, 141.7, 144.7, 198.4. HPLC: Daicel Chiralpak AS, hexane/^{i}PrOH=19/1, flow rate=1.0 ml/min: t_R=26.6 min (3*R*), t_R=38.2 min (3*S*). Anal. Calcd for $C_{17}H_{19}NO_2S$: C, 67.74; H, 6.35; N, 4.65. found: C, 68.00; H, 6.54; N, 4.54. HRMS: Calcd for $C_{17}H_{19}NO_2S$ (M^+) 301.1138, found 301.1102.

3.4. Removal of *N*-protecting group

The Mannich adduct (0.4 mmol), a CH_3I/acetone (1:5) solution (5 ml), and K_2CO_3 (299 mg) were combined at room temperature. After the mixture was stirred for 8 h, NH_4Cl aq. was added to quench the reaction. After a usual work up, methyl 3-[(2′-methoxy-phenyl)amino]-2,2-dimethyl-3-phenyl-propionate was obtained quantitatively. Oxidative cleavage using cerium ammonium nitrate (CAN) was performed according to the literature method.[18] The absolute configuration assignment was made by comparison of the optical rotation of *N*-free amino ester with that in the literature.[19]

3.4.1. (*R*)-Methyl 3-amino-2,2-dimethyl-3-phenylpropionate. ^{1}H NMR ($CDCl_3$): δ 1.20 (s, 3H), 1.25 (s, 3H), 3.65 (s, 3H), 3.87 (brs, 1H), 7.23–7.35 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 20.6, 24.1, 52.0, 55.6, 127.3, 127.7, 127.9, 128.3, 176.9. Hydrochloride: $[\alpha]_D^{26}$=+34.6 (*c* 0.17, 1N HCl) (lit.[19] $[\alpha]_D^{23}$=−32.8 (*c* 1.1, 1N HCl)).

Acknowledgements

This work was partially supported by CREST, Japan Science and Technology Corporation (JST), and a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan.

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