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Axially Chiral Phosphine-Oxazoline Ligands in Silver(I)-Catalyzed Asymmetric Mannich Reaction of Aldimines with Trimethylsiloxyfuran

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Abstract: A new asymmetric catalytic system for the Mannich reaction of aldimines with trimethylsiloxyfuran is described. The combination of an axially chiral phosphine-oxazoline ligand (*S*)-2-[(*R*)-2′-(diphenylphosphino)-1,1′-binaphthyl-2-yl]-4-phenyl-4,5-dihydrooxazole with silver acetate and 2,2,2-trifluoroacetic acid is a very effective catalytic system in the asymmetric Mannich reaction of various aldimines with trimethylsiloxyfuran in dichloromethane at −78 °C, affording the corresponding adducts in up to 99% yield, 99:1 (*dr*) and 99% *ee* (major diastereoisomer) under mild conditions.

Keywords: aldimines; asymmetric Mannich reaction; axially chiral phosphine-oxazoline ligands; silver acetate; trimethylsiloxyfuran

Introduction

The efficient synthesis of highly functionalized γ-butenolides remains an important challenge in organic chemistry.[1] It has been known that the Lewis acid-catalyzed vinylogous Mannich-type reaction of trimethylsiloxyfuran with aldimines is a powerful synthetic protocol to prepare γ-butenolide derivatives bearing an amine functionality.[2,3] However, the catalytic, asymmetric version of the vinylogous Mannich-type reaction has been little explored. Thus far, Martin and Lopez reported the first catalytic asymmetric addition of trialkylsilyloxyfurans to aldimines in 1999,[2f] affording the adducts in moderate enantioselectivities and chemical yields. More recently, Hoveyda and Snapper have developed a silver(I)-based catalyst using the 2-methyloxyphenyl group as aldimine substituent, leading to the product of a asymmetric vinylogous Mannich-type reaction in excellent diastereo- and enantioselectivity.[4,5] Organocatalyzed asymmetric vinylogous Mannich-type reactions have also been reported lately.[6] Aside from these pioneering investigations, the exploration of new catalytic systems in the asymmetric vinylogous Mannich-type reaction for a wide range of aldimines is still a main challenge at the present time. In this paper, we wish to report axially chiral phosphine-oxazoline ligands (**L1**–**L4**)[7] in the silver(I)-catalyzed asymmetric Mannich reaction of aldimines with trimethylsiloxyfuran under mild conditions,[8] in which a wider range of aldimines can be applied to afford the corresponding adducts in good yields and high enantiomeric excesses for *anti*-γ-butenolides.

Results and Discussion

We initially utilized the Lewis acid AgOAc (10 mol%) combined with chiral phosphine-oxazoline ligands **L1**–**L4** (10 mol%) (Figure 1) as the catalysts and the asymmetric vinylogous Mannich-type reaction of readily available aldimine **1a** with the siloxyfuran as a model reaction in dichloromethane (DCM) or tetrahydrofuran (THF) containing the additive CF_3CH_2OH to develop the optimal reaction conditions (Scheme 1) and the results of these experiments are summarized in Table 1. It was found that (*R,S*)-P-Oxa-Ph (**L1**) is the best chiral ligand in this reaction to afford the corresponding product **2a** in 95% yield with the *anti*-configuration as the major diastereomer (*dr* = 99/1) with 95% *ee* in DCM at −78 °C for 6 h and then naturally warming up to room temperature (20 °C) for 10 h (Table 1, entries 1–3). Furthermore, using THF as the solvent also produced **2a** in 87%

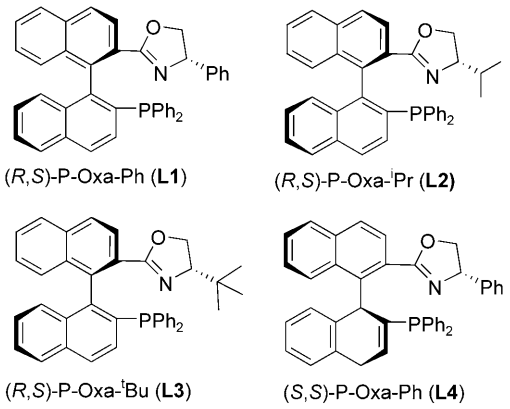


Figure 1. Axially chiral phosphine-oxazoline ligands **L1**–**L4**.

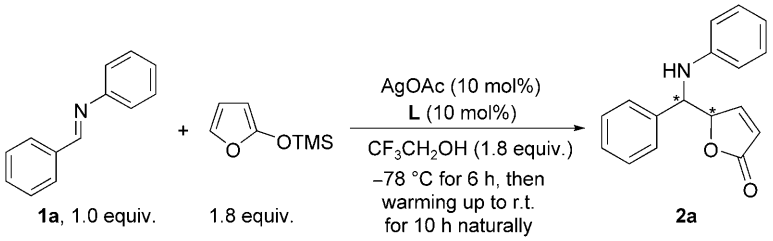
yield as the *anti*-configuration as the major diastereomer ($dr = 99/1$) with 85% *ee* (Table 1, entry 1). The (*S,S*)-P-Oxa-Ph **L4**, a diastereomeric isomer of **L1**, afforded low yield and poor stereoselectivity under identical conditions (Table 1, entry 4).

Next, we further optimized the reaction conditions using **L1** as the ligand to examine the temperature, solvent and additive effects in this reaction and the results of these experiments are summarized in Table 2, Table 3 and Table 4, respectively. It was found that the reaction temperature should be kept at −78 °C for 6 h and then warming up to room temperature (20 °C) naturally for 10 h to give the adduct in higher yield as well as higher diastereoselectivity and enantioselectivity (Table 2, entries 1–5). Reducing the reaction time at −78 °C to 2 h afforded **2a** in lower yield and diastereoselectivity (Table 2, entry 6). The examination of solvents effect revealed that DCM is the best solvent to afford **2a** in higher yield as well as diastereoselectivity and enantioselectivity (Table 3, entries 1–5). The additives are also crucial to this reaction and we found that **2a** could be obtained in higher enantioselectivity in the presence of CH_3CH_2OH, CF_3CH_2OH or BnOH under the standard conditions (Table 4, entries 1–6).[9] Using

Table 2. Temperature effect in the combination of **L1**/AgOAc/CF_3CH_2OH in DCM.

Entry	*T* [°C]	Yield [%][c] **2a**	anti:syn[d] **2a**	*anti*, *ee* [%][e] **2a**
1	r.t.	58	11:1	55
2	0 to r.t.[a]	45	9:1	84
3	−20 to r.t.[a]	43	6:1	93
4	−40 to r.t.[a]	75	18:1	97
5	−78 to r.t.[a]	95	99:1	96
6	−78 to r.t.[b]	68	14:1	96

[a] Reaction was kept at this temperature for 6 h, then the reaction mixture was warmed up to room temperature naturally for 10 h under the standard conditions.
[b] Reaction was kept at this temperature for 2 h and then the reaction was warmed up to room temperature naturally for 14 h under the standard conditions.
[c] Yields of the purified *syn* and *anti* products.
[d] Determined from ^{1}H NMR spectroscopic data.
[e] Determined by chiral HPLC.



Scheme 1. Reaction of aldimines with trimethylsiloxyfuran.

Table 1. Examination of ligands **L1–L4** in DCM or THF.

Entry	Ligand	Yield [%][a] **2a**	*anti:syn*[b] **2a**	*anti*, *ee* [%][c] **2a**
1	(*R,S*)-P-Oxa-Ph (**L1**)	95,[d] 87[e]	99:1,[d] 99:1[e]	96,[d] 85[e]
2	(*R,S*)-P-Oxa-^{i}Pr (**L2**)	64[d]	99:1	92
3	(*R,S*)-P-Oxa-^{t}Bu (**L3**)	49[d]	99:1	86
4	(*S,S*)-P-Oxa-Ph (**L4**)	25[d]	1:1.5	24

[a] Yields of the purified *syn* and *anti* products.
[b] Determined from ^{1}H NMR spectroscopic data.
[c] Determined by chiral HPLC.
[d] Reaction was performed in DCM.
[e] Reaction was performed in THF.

Table 3. Solvent effect in the combination of **L1**/AgOAc/CF_3CH_2OH.

Entry	Solvent	T [°C]	Yield [%][c] **2a**	*anti:syn*[d] **2a**	*anti*, *ee* [%][e] **2a**
1	DCM	−78 to r.t.[a]	95	99:1	96
2	THF	−78 to r.t.[a]	87	99:1	85
3	Toluene	−78 to r.t.[a]	43	49:1	80
4	CH_3CN	−20[b]	95	33:1	81
5	DMF	−10[b]	40	33:1	61

[a] Reaction was kept at this temperature for 6 h, then the reaction mixture was warmed up to room temperature naturally for 10 h under the standard conditions.
[b] Reaction was kept at this temperature for 16 h under the standard conditions.
[c] Yields of the purified *syn* and *anti* products.
[d] Determined from ^{1}H NMR spectroscopic data.
[e] Determined by chiral HPLC.

Table 4. Additive effect in the combination of **L1**/AgOAc in DCM.

Entry	Additive (1.8 equiv.)	Yield [%][a] **2a**	*anti:syn*[b] **2a**	*anti*, *ee* [%][c] **2a**
1	CH_3CH_2OH	87	99:1	95
2	CF_3CH_2OH	95	99:1	96
3	BnOH	64	99:1	97
4	*i*-PrOH	83	11:1	87
5	*t*-BuOH	95	14:1	76
6	None	90	99:1	82

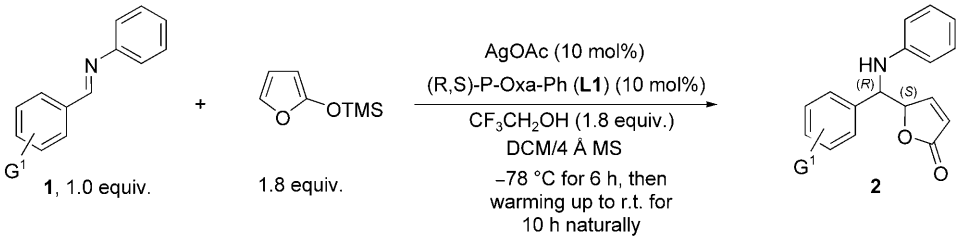
[a] Yields of the purified *syn* and *anti* products.
[b] Determined from ^{1}H NMR spectroscopic data.
[c] Determined by chiral HPLC.

CF_3CH_2OH as the additive, **2a** was produced in higer yield and enantioselctivity. Thus, the best reaction conditions are those using 10 mol% of AgOAc and 10 mol% of chiral ligand **L1** as the catalyst and carrying out the reaction in DCM at −78 °C for 6 h and then warming up to room temperature naturally for 10 h in the presence of CF_3CH_2OH.

Under these optimum conditions, we next examined the generality of this reaction with various aldimines **1**, without 2-methyloxyphenylaldimine which has been an essential effect in Hoveyda's asymmetric vinylogous Mannich-type reaction system,[4a] with the siloxyfuran and the results are summarized in Table 5 and Table 6, respectively. Aldimines **1b**–**1f** having a G^1 substituent at the *ortho*-, *meta*- or *para*-position of the phenyl ring gave the corresponding asymmetric vinylogous Mannich-type products **3b**–**3f** in 80–86% yields, *dr*s of 2:1–20:1 and 93–99% enantiomeric excesses for the *anti*-diastereoisomers (Table 5, entries 1–5). On the other hand, as for aldimines **1g**–**1k** having the G^2 substituent at the *meta*- or *para*-position of the phenyl ring, the corresponding adducts **2g**–**2k** were formed in 64–95% yields, *dr*s of 5:1-99:1 as well as 87–99% enantiomeric excesses for the *anti*-diastereoisomers under the standard conditions (Table 6, entries 1–5). The absolute configuration of products **2** was unequivocally assigned as (*R*,*S*) by an X-ray diffraction study of **2g** bearing a bromine atom at the benzene ring (Figure 2, see the Supporting Information).[10] In the case of aldimine **1l** having substituents on the both of the phenyl ring (G^1=*p*-Br and G^2=*p*-Br), the corresponding adduct **2l** was obtained in 76% yield as well as 2:1 *dr* and 90% *ee* for the major diastereoisomer under identical conditions, indicating the broad substrate generality of this novel asymmetric catalytic system (Table 6, entry 6).

The synthetic utility of the product can be displayed by removal of the N-aryl group with ceri-

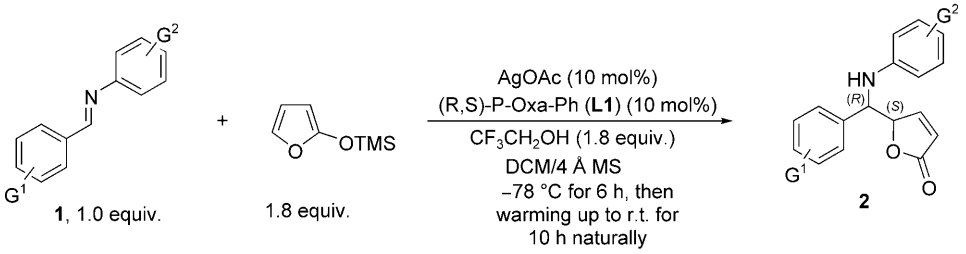
Table 5. Examination of imines having different substituents (G^1) on the aromatic ring.



Entry	G^1	Yield [%][a] **2**	*anti:syn*[b] **2**	*anti*, *ee* [%][c] **2**
1	**1b**, *p*-NO_2	**2b**, 80	2:1	95
2	**1c**, *p*-OMe	**2c**, 81	7:1	99
3	**1d**, *p*-Br	**2d**, 86	4:1	99
4	**1e**, *m*-Br	**2e**, 81	7:1	93
5	**1f**, *o*-Br	**2f**, 84	20:1	94

[a] Yields of the purified *syn* and *anti* products.
[b] Determined from ^{1}H NMR spectroscopic data.
[c] Determined by chiral HPLC.

Table 6. Examination of imines having different substituents (G^2 and G^1) on the aromatic ring.



Entry	G^1	G^2		Yield [%][a] **2**	*anti:syn*[b] **2**	*anti*, *ee* [%][c] **2**
1	H	*p*-Br	**1g**	**2g**, 77	10:1	87
2	H	*p*-Cl	**1h**	**2h**, 83	5:1	94
3	H	*p*-OMe	**1i**	**2i**, 91	99:1	99
4	H	*p*-Me	**1j**	**2j**, 64	12:1	94
5	H	*m*-F	**1k**	**2k**, 95	10:1	97
6	*p*-Br	*p*-Br	**1l**	**2l**, 76	2:1	90

[a] Yields of the purified *syn* and *anti* products.
[b] Determined from ^{1}H NMR spectroscopic data.
[c] Determined by chiral HPLC.

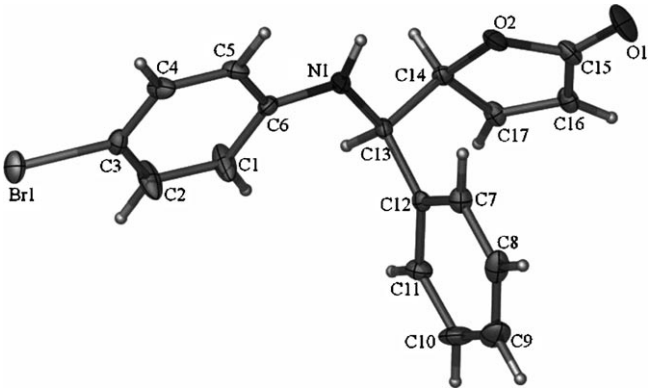
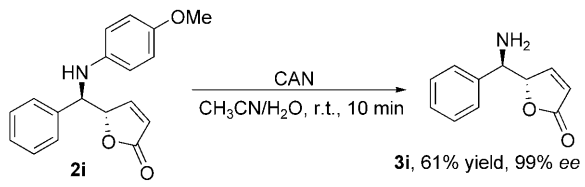


Figure 2. ORTEP drawing drawing of the X-ray crystal structure of **2g**.

um(IV) ammonium nitrate (CAN) in $MeCN/H_2O$ under mild conditions,[4a,11] affording the corresponding amino compound **3i** in 61% yield and high *ee* value (Scheme 2).

Based on previous mechanistic studies by Hoveyda and co-workers,[4a,12] an activated complex is initially associated through chelation of chiral Ag(I) and aldimine substrate during the reaction. We have optimized the structure of this kind of activated complex using **L1**, substrate **1a** and Ag(I) at HF/3-21G* level (Figure 3, see the Supporting Information). The optimized structure shows that substrate **1a** is indeed associated with Ag(I) and the phenyl group in substrate **1a** is close to the phenyl group on the oxazoline ring in **L1**. The optimized structure of the activated complex throws light on explanation of the enantio-/diastereoselectivity. Herein, we propose several plausible mechanistic models (Scheme 3) to rationalize the



Scheme 2. Removal of the N-aryl group with CAN.

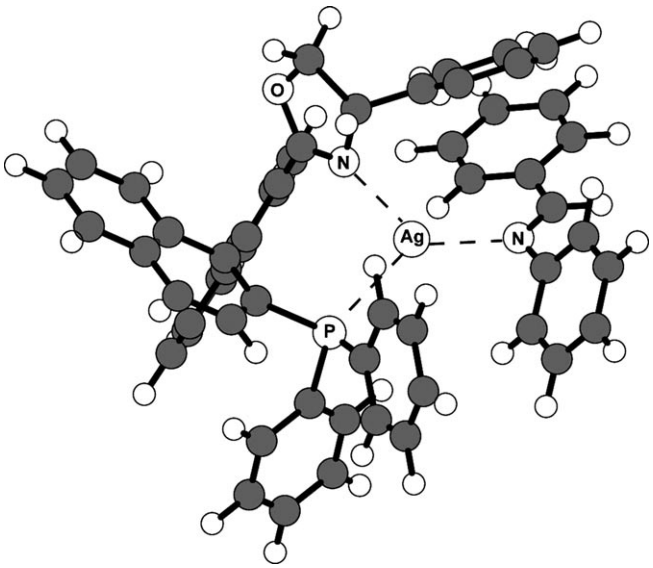
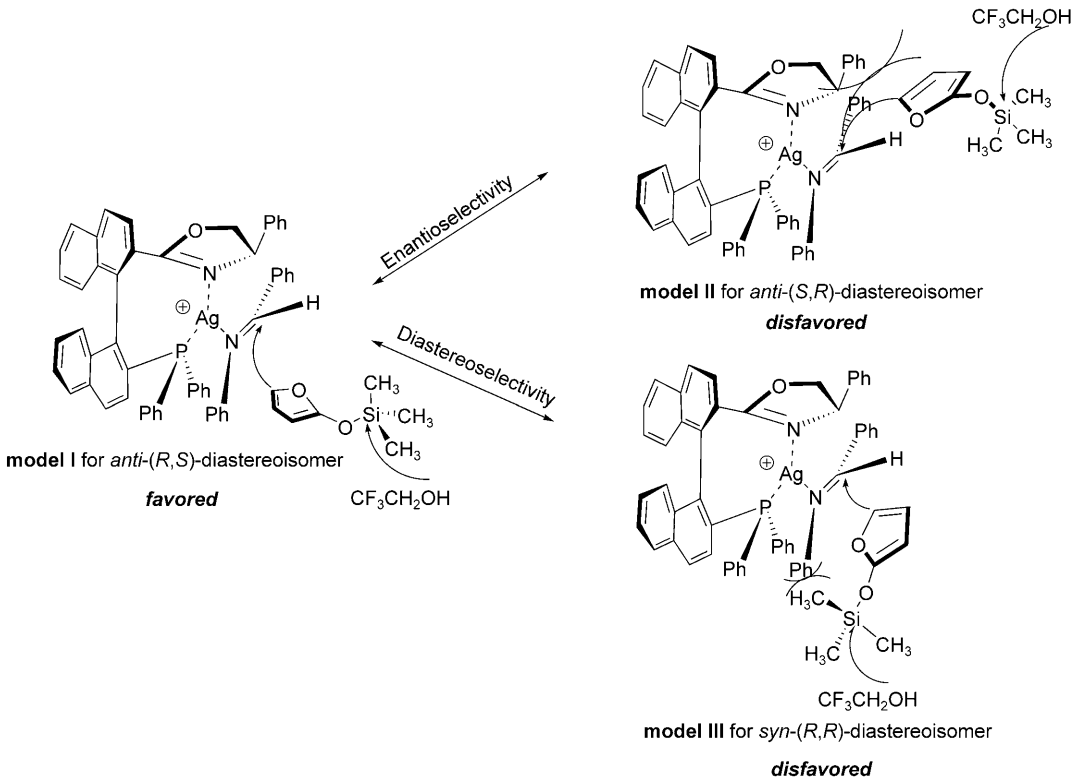


Figure 3. The structure of the activated complex optimized at the HF/3-21G* level.



Scheme 3. Mechanistic models.

enantio-/diastereoselectivity. The siloxylfuran may approach the activated complex from one face of the imine as shown in model **I** or another face of the imine as shown in model **II**. If the siloxyfuran reaches the activated complex as shown in the model **II**, a strong steric repulsion may arise between the phenyl group on the oxazoline ring in **L1**, the phenyl group of **1a** and siloxyfuran. Thus, the siloxyfuran prefers to approach the activated complex as shown in model **I**, resulting in good enantioselectivity. Similarly, we envisaged that the steric repulsion may exist between the substrate and siloxyfuran in model **III**, and the model **I** is still preferable, which leads to the *anti*-diastereoisomer as the major product. However, the diastereoselectivity is not so good with respect to some substrates, probably due to the weak steric effects in these cases.

Conclusions

In summary, we have developed a new catalytic, asymmetric vinylogous Mannich-type reaction system applicable to a wide range of aldimines which do not possess a 2-methyloxyphenyl group and siloxyfuran using an axially chiral phosphine-oxazoline ligand [(*R*,*S*)-P-Oxa-Ph]/AgOAc/CF_3CH_2OH combination. The catalytic system reported here afforded asymmetric vinylogous Mannich-type products **3** in up to 99% yield and 99% *ee* (major diastereoisomer). Current efforts are in progress to extend this chiral phosphine-oxazoline ligand/AgOAc/BnOH combination to other catalytic enantioselective reactions in our laboratory.

Experimental Section

Typical Procedure

AgOAc (0.02 mmol) and chiral phosphine-oxazoline ligand **L1** (0.02 mmol) were added into a Schlenk tube and then DCM (0.5 mL) was added into the reaction vessel. The resulting solution was stirred for 0.5 h at room temperature. Aldimine **1a** (0.20 mmol) and CF_3CH_2OH (0.36 mmol) were added followed by another 0.5 mL of DCM. The mixture was cooled to −78 °C, and stirred for 0.5 h, then siloxyfuran (0.36 mmol) was added. The mixture was allowed to stir at −78 °C for 6 h, then warmed to room temperature naturally for 10 h. The reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (1.0 mL). After the mixture had been stirred for 10 min at room temperature, the resulted mixture was extracted by DCM for three times and the organic layer was dried over anhydrous Na_2SO_4. Then the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (elution with petroleum ether/EtOAc = 6:1) to give previously known **2a**[2] as a plae yellow solid; yield: 95%, 96% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 4.38 (1H, d, J = 6.4 Hz, NH), 4.84 (1H, dd, J = 4.4, 6.4 Hz, CH), 5.41 (1H, ddd, J = 1.2, 2.0, 4.4 Hz, CH), 6.04 (1H, dd, J =

2.0, 6.0 Hz, CH), 6.54 (2H, d, $J=7.6$ Hz, ArH), 6.70 (1H, t, $J=8.0$ Hz, ArH), 7.10 (2H, dd, $J=7.6$, 8.0 Hz, ArH), 7.24–7.31 (5H, m, ArH), 7.34 (1H, dd, $J=1.2$, 6.0 Hz, CH); the enantiomeric excess was determined by HPLC with a Chiralcel OD-H column ($\lambda=254$ nm; eluent: hexane/isopropyl alcohol = 80/20; flow rate: 0.9 mL min^{-1}): $t_{major}=25.73$ min, $t_{minor}=36.64$ min; *ee*% = 96%; $[\alpha]_D^{20}$: −134.8 (*c* 1.20, $CHCl_3$).

Supporting Information

Spectroscopic data and chiral HPLC traces of the compounds shown in Tables 1–6 and the detailed descriptions of experimental proceduresare available as Supporting Information.

Acknowledgements

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