

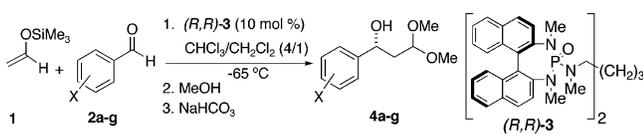
Lewis Base Catalyzed Enantioselective Aldol Addition of Acetaldehyde-Derived Silyl Enol Ether to Aldehydes

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Chiral phosphoramidate catalyzed-enantioselective aldol addition of an acetaldehyde-derived trialkylsilyl enol ether to aromatic aldehydes provides protected aldol products in good yields with good to excellent enantioselectivities. Preliminary studies show that the aldolization intermediate (a chlorohydrin adduct) can be trapped with *tert*-butyl isocyanide to form an α -hydroxy lactone with good selectivity in a single-pot operation.

Despite recent advances in the catalytic, enantioselective aldol additions of ketone and ester derived silyl enol ethers to aldehydes,¹ the analogous transformation employing silyl enol ethers derived from aldehydes is rather limited. Several competing reaction pathways are associated with the latter reaction, namely: (1) self-condensation of the starting aldehyde to provide homo aldol products,² (2) dehydration of the desired aldol product,³ (3) multiple addition of the aldehyde-derived enolate to the desired aldol product leading to the formation of oligomers,^{2,4} and (4) Tischenko-type processes.⁵

Two existing strategies that have found some success for the catalytic, enantioselective crossed aldol reaction

of aldehydes employ either enzymes⁶ or chiral amines⁷ as catalysts. In 1994, Wong et al. reported an enzyme-catalyzed aldol reaction of acetaldehyde with itself in rather low yield, limiting the synthetic utility of this method.^{6c} Barbas et al. reported the proline-catalyzed aldol addition of acetaldehyde to aldehydes in good enantioselectivity albeit low yield.⁸ Notable successes have been achieved by MacMillan and co-workers,^{7a,9} who have disclosed proline-catalyzed aldehyde–aldehyde aldol reactions to provide aldol products in synthetically useful yield and selectivity, although controlling the rate of the addition of aldehydes is required for these reactions.

In recent years, Lewis base catalysis has emerged as a viable strategy for catalytic, enantioselective aldol additions including directed, crossed aldol reactions of aldehydes.¹⁰ Previous studies from these laboratories have shown that chiral phosphoramidate-catalyzed aldol additions of preformed trichlorosilyl enolates derived from aldehydes to a variety of aliphatic and aromatic aldehydes provide aldol products in high yield with moderate to good enantioselectivity and high diastereoselectivity.^{10b,c} Contemporaneous studies led to the development of a new concept, the Lewis base activation of Lewis acids,¹¹ which has afforded great success in the enantio- and diastereoselective aldol addition of silyl ketene acetals derived from esters¹¹ and ketones¹² to aldehydes as well as enantioselective Passerini-type reactions.¹³ The generality of these reactions as well as the creation of desired products in high yield and selectivity significantly enhance the synthetic potential of this approach. The extension of these methods to the aldol addition of the trimethylsilyl enol ether of acetaldehyde to other aldehydes is investigated, and the results are reported herein. In addition, preliminary studies of the in situ trapping of the aldolate intermediate with an

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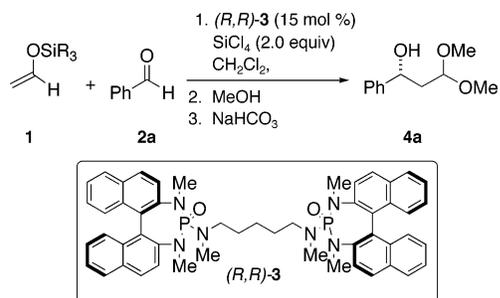
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TABLE 1. Survey of Trialkylsilyl Group in Aldol Addition

entry	R ₃ Si-	T, °C	yield, ^a %	er ^b
1	Me ₃ Si- (1a)	-78	77 ^c	92.7/7.3
2	Et ₃ Si- (1b)	-78	15 ^c	nd ^e
3	PhMe ₂ Si- (1c)	-78	5 ^c	nd
4	<i>t</i> -BuMe ₂ Si- (1d)	-78	5 ^c	nd
5	Me ₃ Si- (1a)	-67	72 ^d	88.3/11.7

^a Yield of aldol products after column chromatography. ^b er determined by CSP-SFC, OD column. ^c After 35 h. ^d After 24 h. ^e Not determined.

isocyanide to afford the desired lactone and/or hydroxy amide are also reported.

According to Mayr's nucleophilicity scale,¹⁴ aldehyde-derived enolates are considerably less reactive toward electrophiles than ketone or ester-derived counterparts and therefore create an additional challenge for the intended crossed aldol addition. With this in mind, we initially aimed to establish the viability of this aldol process through studies of various factors that can influence the rate of the aldol addition, including reaction temperature and the steric bulk of the trialkylsilyl groups of the enol ethers.¹⁵ Gratifyingly, in the presence of 15 mol % of chiral phosphoramidate (*R,R*)-**3**, the aldol addition of trimethylsilyl enol ether **1a** to benzaldehyde **2a** went to completion within 35 h to afford aldol product **4a** in 77% yield with good enantioselectivity (entry 1, Table 1). The stable and isolable aldol product **4a** was obtained by quenching the reaction with methanol.^{10b} Control experiments revealed that no aldol product was formed in the absence of the dimeric phosphoramidate catalyst at -50 °C after 5 h, highlighting the crucial role of the Lewis base in effecting this aldol addition.

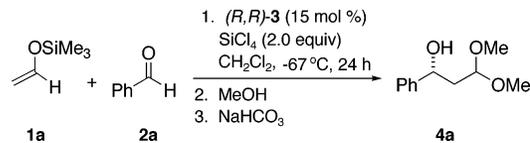
Interestingly, the steric bulk of the trialkylsilyl groups of the enol ethers **1b–d** had a dramatic effect on the yield and rate of the aldol addition (entries 2–4). The remaining mass balance in these cases was benzaldehyde recovered in the form of its dimethyl acetal after workup. These results suggest that either the increased steric hindrance of the nucleophile slows down a rate-determining C–C bond-forming step or the turnover-limiting step is the capture of the trialkylsilyl group by chloride after the aldolization.¹⁶ Finally, it was found that carrying out the reaction of **1a** with benzaldehyde in the presence of

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(15) Other factors include the reaction concentration and catalyst loadings. It was found that the aldol addition can be run at 0.25–0.5 M with 15% mol catalyst to afford aldol products in good yield and selectivity.

(16) The second mechanistic scenario implies reversible aldolization, which is very unlikely on the basis of the high enantioselectivity observed in the reaction.

15 mol % of the dimeric catalyst at -67 °C for 24 h afforded the desired aldol product in 72% yield (entry 5). Although a slight decrease in enantioselectivity was observed at this temperature, the reaction time was reduced significantly as compared to those run at -78 °C (entry 5 vs entry 1).

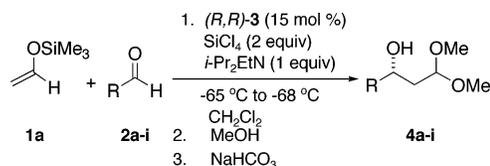
TABLE 2. Effect of Hünig Base on Yield and Enantioselectivity

entry	<i>i</i> -Pr ₂ EtN, equiv	yield, ^a %	er ^b
1	none	72	88.3/11.7
2	0.2	85	92.6/7.4
3	1.0	84	97.1/2.9

^a Isolated yield from column chromatography. ^b er determined by CSP-SFC, OD column.

Previous studies from these laboratories have demonstrated that Hünig base (*i*-Pr₂EtN) can be used to prevent the cleavage of trialkylsilyl enol ethers and thus improve the yield of the aldol addition products.¹² In the present case, adventitious acid could destroy the TMS enol ether **1a** and also catalyze the aldol addition, thus providing a nonselective pathway that could lead to erosion in selectivity. To test this hypothesis, the aldol reaction between **1a** and benzaldehyde was run in the presence of various amounts of Hünig base (Table 2). Gratifyingly, the enantiomeric ratio of the aldol product **4a** substantially increased (entry 3, Table 2). Both the yield and the selectivity improved in these crossed aldol reactions as compared to those run in the absence of Hünig base.

With the improved reaction conditions in hand, the scope of the chiral phosphoramidate-catalyzed aldol addition was examined. Aromatic aldehydes of varying electronic nature afforded aldol products in moderate to good yields with excellent enantioselectivities (Table 3). Aromatic aldehydes underwent aldol additions to give the desired aldol products in good yields and selectivities (Table 3, entries 1–3). The aldol product of 1-naphthal-

TABLE 3. Enantioselective Aldol Additions of 1a

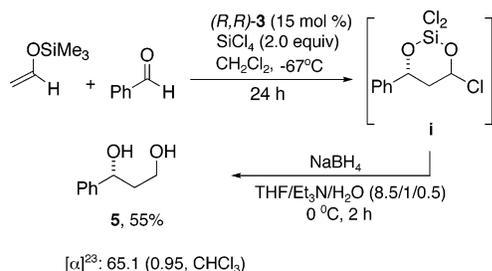
entry	R	product	yield, ^a %	er ^b
1	C ₆ H ₄	4a	80	97.1/2.9
2	2-naphthyl	4b	85	97.1/2.9
3	1-naphthyl	4c	78	92.2/7.8
4	4-CF ₃ C ₆ H ₄	4d	84	98.1/1.9
5	4-ClC ₆ H ₄	4e	81	97.9/2.1
6	cinnamyl	4f	60	98.2/1.8
7	4-MeOC ₆ H ₄	4g	30	91.2/8.8
8	<i>a</i> -methylcinnamyl	4h	<10	nd ^c
9	<i>n</i> -butyl	4i	nr ^d	

^a Yield of analytically pure materials. ^b er determined by CSP-SFC, Daicel Chiralpak, OD, AS, and AD columns. ^c Not determined. ^d No reaction.

dehyde was formed in slightly lower yield and selectivity than that of 2-naphthaldehyde (entries 2 vs 3) although the overall selectivity is good. Electron-deficient aldehydes gave rise to aldol products with good yield and enantioselectivities as well (entries 4 and 5). Although the yield of aldol product from cinnamaldehyde was modest, excellent enantioselectivity was preserved (entry 6). Electron-rich aromatic aldehydes such as anisaldehyde afforded the desired aldol product in rather low yield with modest enantioselectivity (entry 7).¹⁷ Finally, α -methylcinnamaldehyde and pentanal were unreactive (entries 8 and 9). Increasing the reaction temperature and concentration did not improve the results significantly.

The absolute configuration of aldol products was determined through correlation with the known diol **5**,¹⁸ which was obtained by direct in situ reduction of the aldolate intermediate **i** with sodium borohydride (Scheme 1). The dextrorotatory diol has been unambiguously assigned the *R* configuration, thus allowing for the assignment of configuration of **4a** as *R* as well.¹⁹

SCHEME 1



One of the unique features of this type of aldol reaction is the formation of the chlorohydrin intermediate **i**,²⁰ a masked aldol adduct which plays a crucial role in preventing side reactions such as multiple enolate additions. However, the intermediacy of **i** also presents an intriguing opportunity for a second C–C bond-forming process if it were reactive toward strong nucleophiles such as isocyanides¹³ or silyl ketene acetals.¹¹ Low-temperature ¹H NMR experiments revealed that *tert*-butyl isocyanide can add to the chlorohydrin intermediate **i** at about -46 °C to provide lactone **6** and hydroxy amide **7**²¹ in a single-pot operation after workup (Scheme 2). The diastereoselectivity of formation of lactone **6** was determined through ¹H NMR analysis of the crude material, and the relative syn configuration of the two stereogenic centers of the lactone was established through

(17) There are two problems associated with this class of aldehyde. First is the inherent low reactivity because of the poorer electrophilicity of the aldehyde carbonyl group. Second, the electron-rich nature of the aromatic ring facilitates the ionization of the hydroxyl group of the aldol product under acidic quenching conditions to generate a methanol adduct. Attempts to buffer the methanol during the quench were fruitless.

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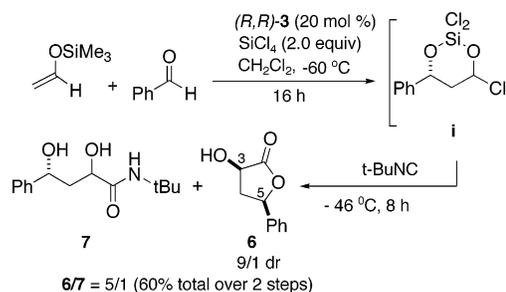
(19) The configuration of other aldol products was assigned by analogy.

(20) Although this intermediate has been detected previously in reactions of trichlorosilyl enolates (ref 10), we have independently identified it in these additions as well. Interestingly, **i** exists as a mixture of diastereomers; see the Supporting Information.

(21) The configuration of the α -carbon bearing a hydroxyl group in **7** has not been established. Selective formation of either **6** or **7** under different quenching conditions is being investigated.

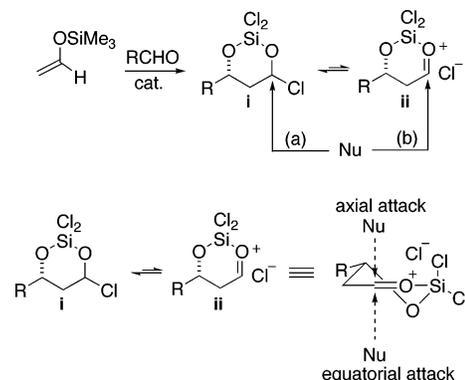
difference NOE experiments.²² Because the absolute configuration at C(5) has been established previously, the syn configuration allows for the full description of the stereostructure of the product.

SCHEME 2



The origin of the observed diastereoselectivity can be interpreted through either of two limiting mechanistic hypotheses for the addition of *tert*-butyl isocyanide to the chlorohydrin intermediate **i**. In these hypotheses, the isocyanide either displaces chloride in an S_N2-type fashion from intermediate **i** or through an oxocarbenium intermediate such as species **ii** in an S_N1-type process (Scheme 3). Low-temperature ¹H NMR analysis indicated that the diastereomeric chlorohydrins **i** are formed in a ca. 1:1 ratio.²⁰ Therefore, in the limiting S_N2-type mechanism, they must interconvert and react preferentially via the *cis* isomer to account for the diastereoselectivity observed for **6**. In the limiting S_N1-type process, the selectivity depends on the relative rate of axial and equatorial attack of the nucleophile on intermediate **ii** (Scheme 3). Axial attack leads directly to chairlike conformer of the product, thus favoring the formation of the *R,R* (*l*) diastereomer.

SCHEME 3



In summary, chiral phosphoramidate-catalyzed aldol reactions of the TMS enol ether derived from acetaldehyde with aromatic aldehydes provides aldol products in high yield and enantioselectivity. Aldol products obtained in these cases are of *R* configuration. The chemistry described herein provides the first example of stereoselective multiple carbon–carbon bond formation by trapping an aldolate intermediate in situ with an iso-

(22) See the Supporting Information for details. The identity of the lactone was further confirmed by comparison of its spectroscopic data with those previously reported: Casey, G. *Tetrahedron Lett.* **1992**, *33*, 8159–8162.

cyanide to provide direct access to lactones and hydroxy amides from aldehydes in a one pot operation. These results highlight the synthetic utility of this method. The expansion of scope of aldehyde structure is currently being investigated.

Experimental Section

General Experimental Procedures. See the Supporting Information.

General Procedure for the Aldol Addition of 1a to Benzaldehyde. (R)-(2,2-Dimethoxyethyl)benzenemethanol (4a). A 10-mL, two-necked, round-bottomed flask fitted with a magnetic stirbar, rubber septum, nitrogen inlet, and Teflon-coated thermocouple was charged with a stirred solution of **3** (126.4 mg, 0.15 mmol, 0.15 equiv), freshly distilled benzaldehyde (102 μ L, 1.0 mmol), and *i*-Pr₂EtN (174 μ L, 1.0 mmol) in 2 mL of dry methylene chloride at -65 °C. Silicon tetrachloride (229 μ L, 2.0 mmol, 2.0 equiv) was added slowly via syringe. The resulting solution was stirred for a few minutes before enol ether **1a** (179 μ L, 1.2 mmol, 1.2 equiv) was added dropwise via syringe. The reaction mixture was stirred at -65 °C under N₂ for 24 h and then was cooled to -78 °C, whereupon dry methanol (10 mL) was added slowly such that the internal temperature was maintained below -50 °C during the addition. The resulting mixture was stirred for 30 min and then allowed to warm to room temperature (23 °C). Next, the methanolic mixture was quickly poured into a vigorously stirred, cold, saturated, aqueous sodium bicarbonate solution (40 mL), and the resulting mixture was stirred at room temperature for about 30 min. A cloudy white solution was observed during this period. The mixture was filtered through Celite, and the aqueous layer was separated and extracted with methylene chloride (3 \times 20 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Silica gel column chromatography (hexanes/ethyl acetate, 3/1) followed by bulb-to-bulb distillation afforded 157.0 mg (80%) of **4a** as a clear, colorless oil. Data for **4a**: bp 140 °C (0.25 mmHg, ABT); ¹H NMR (400 MHz, CDCl₃) 7.22–7.28 (m, 4 H, H-aryl), 7.15–7.20 (m, 1 H, H-aryl), 4.78 (dd, *J* = 9.0, 3.2, 1 H, HC(1)), 4.46 (t, *J* = 5.6, 1 H, HC(3)), 3.29 (s, 3 H, H₃C(3)), 3.25 (s, 3 H, H₃C(3)), 3.22 (s, br, 1H, (OH)), 1.85–2.02 (m, 2 H, H₂C(2)); ¹³C NMR (400 MHz, CDCl₃) 144.1 (C(5)), 128.4 (C(7)), 127.4 (C(6)), 125.6 (C(8)), 103.4 (C(3)), 70.8 (C(1)), 53.6 (C(4)), 52.9 (C(4)), 41.5 (C(2)); IR (neat) 3446 (br), 3088 (w), 3064 (w), 3030 (m), 2934 (s), 2834 (s), 2360 (w), 1957 (w), 1651 (w), 1668 (w), 1604 (w), 1495 (w), 1455 (m), 1386 (w), 1193 (w), 1125 (w), 1047 (w), 941 (w), 914 (w), 846 (w), 760 (m); MS (FI) 196 (M⁺, 18), 184 (8), 164 (100), 121 (17), 75 (56); [α]_D²⁴ +35.21 (*c* = 1.46, EtOH); TLC *R*_f 0.28 (hexane/EtOAc, 3/1) [silica gel, DNP]; SFC (*R*)-**4a**, *t*_R 3.84 min (97.1%); (*S*)-**4a**, *t*_R 4.53 min (2.9%) (column: OD, MeOH 5%, pressure 125 psi, flow 2.5 mL/min). Anal. Calcd for C₁₁H₁₆O₃: C, 67.32; H, 8.22. Found: C, 67.28; H, 8.20.

In Situ Trapping of the Aldolate Intermediate with tert-Butyl Isocyanide. To a stirred solution of **3** (168.5 mg, 0.20 mmol, 0.20 equiv), freshly distilled benzaldehyde (102 μ L, 1 mmol), and *i*-Pr₂EtN (87 μ L, 0.5 mmol) in 2 mL of dry methylene chloride in a 10-mL, two-necked, round-bottomed flask fitted with a magnetic stirbar, rubber septum, nitrogen inlet, and

Teflon-coated thermocouple was added silicon tetrachloride (229 μ L, 2.0 mmol) slowly via syringe at -60 °C. The resulting solution was stirred for a few minutes before enolate **1a** (179 μ L, 1.2 mmol, 1.2 equiv) was added dropwise. The reaction mixture was stirred at -60 °C under N₂ for 16 h. Next, a solution of *tert*-butyl isocyanide (170 μ L, 1.5 mmol, 1.5 equiv) in 1 mL of dry methylene chloride was added slowly, and the reaction mixture was allowed to warm to -46 °C and was then stirred at this temperature for 8 h. The mixture was first cooled to -75 °C, and dry methanol (3 mL) was then added dropwise. The resulting solution was stirred at this temperature for \sim 40 min. Next, the reaction mixture was transferred slowly to a vigorously stirred, cold, saturated, aqueous sodium bicarbonate solution (25 mL) via a cannula. The mixture was then stirred at room temperature for about 1 h and then was filtered through Celite. The aqueous layer of the filtrate was separated and extracted with methylene chloride (3 \times 25 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Purification of the product by silica gel column chromatography (ether/hexane, 3/2) followed by recrystallization (hexane/ethyl acetate, 4/1) afforded 89.1 mg (50%) of **6** and 25.1 mg (10%) of **7** as a white solid. Data for **6**: mp 100 °C; ¹H NMR (500 MHz, CDCl₃) 7.36–7.44 (m, 5 H, H-aryl), 5.37 (dd, *J* = 10.9, 5.1, 1 H, HC(4)), 4.70 (ddd, *J* = 11.2, 8.1, 2.9, 1 H, HC(2)), 3.01 (ddd, *J* = 12.6, 8.3, 5.7, 1 H, H₂C(3)), 2.77 (d, *J* = 2.9, 1 H, (OH)), 2.21–2.30 (m, 1 H, H₂C(3)); ¹³C NMR (500 MHz, CDCl₃) 176.9 (C(1)), 137.7 (C(5)), 129.1 (C(7)), 128.9 (C(6)), 125.9 (C(8)), 77.7 (C(4)), 69.0 (C(2)), 39.5 (C(3)); IR (Nujol) 3411 (br), 2952 (s), 2924 (s), 2854 (s), 1760 (w), 1459 (m), 1377 (w), 1324 (w), 1310 (w), 1223 (w), 1195 (w), 1124 (w), 992 (w), 937 (w); MS (FI) 178 (100); [α]_D²⁴ +38.02 (*c* = 1.38, EtOH); TLC *R*_f 0.12 (hexane/Et₂O, 2/3) [silica gel, ceric ammonium molybdate]. Anal. Calcd for C₁₀H₁₀O₃: C, 67.41; H, 5.66. Found: C, 67.19; H, 5.34. Data for **7**: mp 126 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.27–7.34 (m, 5 H, H-aryl), 6.63 (br, 1 H, (HN)), 4.99 (dd, *J* = 10.3, 2.2, 1 H, HC(4)), 4.57 (br, 1 H, (OH)), 4.23 (dd, *J* = 9.8, 2.2, 1 H, HC(2)), 3.23 (br, 1 H, (OH)), 2.26 (dt, *J* = 14.6, 2.4, 1 H, H₂C(3)), 1.82–1.91 (m, 1 H, H₂C(3)), 1.34 (s, 9 H, 3 \times (H₃C(10))); ¹³C NMR (400 MHz, CDCl₃) δ 172.2 (C(1)), 143.7 (C(5)), 128.6 (C(7)), 127.9 (C(6)), 125.5 (C(8)), 75.3 (C(4)), 72.9 (C(2)), 50.7 (C(9)), 42.8 (C(3)), 28.6 (C(10)); IR (Nujol) 3359 (br), 3194 (br), 2917 (s), 2855 (s), 2725 (w), 2672 (w), 2362 (w), 1955 (w), 1891 (w), 1651 (m), 1532 (w), 1461 (s), 1376 (s), 1366 (m), 1342 (w), 1293 (w), 1283 (w), 1228 (w), 1213 (w), 1200 (w), 1170 (w), 1151 (w), 1094 (w), 1070 (w), 1024 (w), 1008 (w), 996 (w); MS (FI) 251 (100); [α]_D²⁴ +38.64 (*c* = 2.5, EtOH); TLC *R*_f 0.17 (ether/hexane, 3/2) [silica gel, ceric ammonium molybdate]. Anal. Calcd for C₁₄H₂₄N₃O₃: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.60; H, 8.55; N, 5.66.

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Supporting Information Available: Full experimental procedures and characterization data for all aldol products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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