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Highly selective *syn* glycolate aldol reactions with boron enolates of Masamune norephedrine esters

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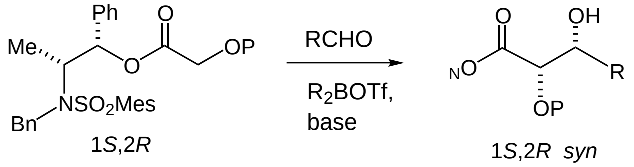
Abstract—Boron enolates of norephedrine-based glycolate esters reacted with various aldehydes to produce *syn* aldol products in high yield and selectivity. The outcome is consistent with a *Z* enolate reacting through a closed transition state with reversal of the enolate facial selectivity relative to the propionate enolates. © 2001 Elsevier Science Ltd. All rights reserved.

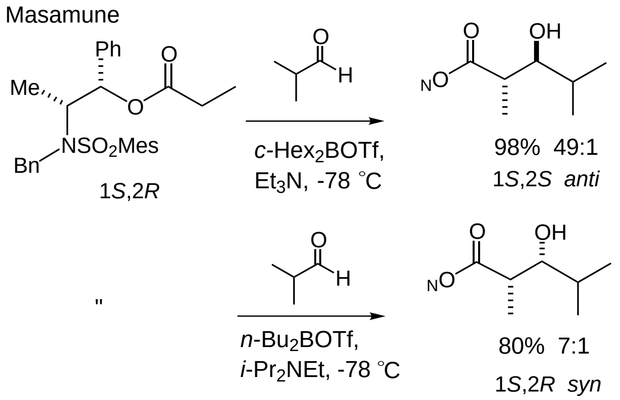
Aldol reactions with glycolate esters and aldehydes have been used extensively to produce differentially protected 1,2-diol products. Various auxiliary and ligand-based approaches have been successful with preformed enolates being the most common.[1] While some success has been found for *anti* stereoselection, the majority of cases involve *syn* outcomes using a boron enolate of Evans' oxazolidinone glycolate.[2] A systematic study examining a range of aldehydes has not been reported in this case. We recently reported the use of a 4-oxapyrone auxiliary, constrained to an *E* enolate to produce *anti* products.[3] Catalytic glycolate aldols have been very limited with only a few cases reported. Kobayashi's tin glycolates with good selectivity for either the *syn* or *anti* diols remain the prime examples.[4] Recently proline catalysis has been extended to hydroxy-ketone aldol reactions.[5] We now report the use of norephedrine glycolate esters to produce *syn* products with a range of aldehydes (Scheme 1). The stereoinduction is consistent with a reversal of the enolate facial selectivity.[6]

An ester auxiliary allows for both *E* and *Z* enolates leading to either *anti* or *syn* aldol products (Scheme 2).[6a] Masamune reported that with dicyclohexylboron triflate and triethylamine the *E* enolate produces *anti* product. In this case, the (1*S*,2*R*) propionyl substrate, derived from (1*S*,2*R*)-(+)-norephedrine, gives the *S*,*S*-product. Di-*n*-butylboron triflate and Hünig's base, forms the *Z* enolate and produces *syn* products with moderate selectivity. It is important to note that the facial selectivity of the *Z* enolate is reversed relative to the *E* enolate giving product with (2*S*,3*R*) stereochemistry.

The methyl and benzyl glycolate esters were made using carbodiimide (EDCI, ethyldimethylaminocarbodiimide hydrochloride) coupling with the Masamune norephedrine amide **1** (Mes, mesityl)[6a] and **2** (Scheme 3).[7] Conditions for the aldol reaction included various combinations of boron triflates and amine bases (Table



Scheme 1.



Scheme 2.

Keywords: aldol reaction; glycolate; enolate; diols; diastereoselection.

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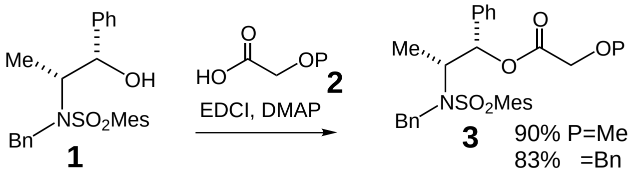
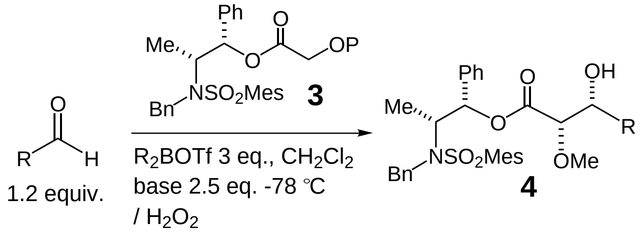


Scheme 3.

1). The optimal combination was freshly prepared dicyclohexyl boron triflate[8] and either triethylamine or Hünig's base (diisopropylethylamine). An enolization time of 2 h was critical where the glycolate, boron triflate, and base were allowed to react before addition of the aldehyde. Yields were dramatically reduced if shorter times were used. Entry 1 shows an isolated yield of 98% with a ratio of 19:1. Only two isomers were observed. Lower amounts of base or triflate gave lower yields with comparable selectivities (entry 2). Hünig's base also produced the *syn* diastereomer (entry 3). Di-*n*-butylboron triflate (3 equiv.) gave product in much lower yield (entry 4, 30%) and selectivity. Di-*n*-butylboron triflate and triethylamine gave only a trace of product. The methyl glycolate (P = Me) also gave high yields and selectivity similar to the benzyl ether (entry 6). TBS ethers were also explored and only a trace amount of product was obtained even over extended times and at warmer temperatures. Titanium tetrachloride, tin triflate, and boron chlorides with base, known conditions for *E* enolate formation, were also ineffective.[9]

The optimal conditions were applied to a range of aldehydes using the methyl glycolate auxiliary derived from (+)-norephedrine (Table 2).[10] Alkyl aldehydes including branched substrates gave (1*S*,2*R*) *syn* products in high yield and selectivity. With isovaleraldehyde (entry 3) the selectivity fell off to 14:1. Benzaldehyde (entry 4) reacts with very high selectivity. Cinnamaldehyde drops off to 9:1. Phenylacetylene carboxaldehyde goes down to 2:1 selectivity (entry 6). Other unsaturated aldehydes investigated show trends that are in accord with these results. Methacrolein also gave high selectivity at 24:1. Tiglic aldehyde shows reduced 9:1 selectivity, as with isovaleraldehyde, and β-methylbutenal is much reduced to 2:1. α-Methyl cinnamaldehyde (entry 9) gives good selectivity at 9:1 with 83% yield. In contrast, the methoxy glycolate oxazolidinone with this substrate gave a 3:2:2:1 mixture in this case. Branched unsaturated aldehydes with this auxiliary have also been problematic.[2f]

Table 1.

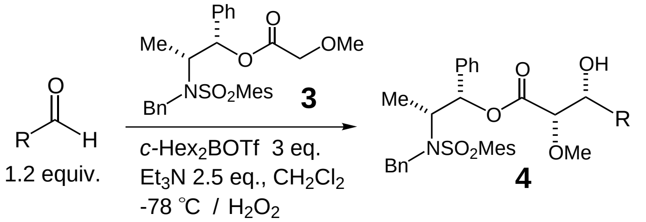


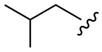
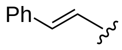
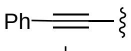
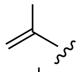
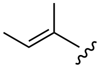
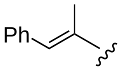
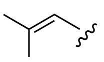
Entry	Ald. R	Enolate P	Borane R	base	yield%[a]	dr[b]
1	*i*-Pr	Bn	*c*-Hex	Et_3N	98%	19:1
2	*i*-Pr	Bn	*c*-Hex	Et_3N	66%	20:1[c]
3	*i*-Pr	Bn	*c*-Hex	*i*-Pr_2NEt	88%	19:1
4	*i*-Pr	Bn	*n*-Bu	*i*-Pr_2NEt	30%	3:1
5	*i*-Pr	Bn	*n*-Bu	Et_3N	>3%	ND
6	*i*-Pr	Me	*c*-Hex	*i*-Pr_2NEt	88%	25:1
7	Ph	TBS	*c*-Hex	Et_3N	>3%	ND

[a]Isolated, chromatographed material. [b]Determined by ^1H NMR.
[c]2.0 equiv. base used.

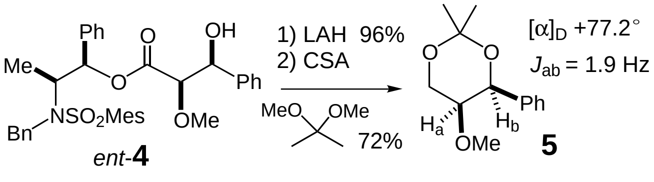
The relative and the absolute stereochemistry were established by acetonide formation and ^1H NMR *J*-coupling constant measurement (Scheme 4).[11] A *cis* equatorial–axial relationship was observed showing a

Table 2.



entry	R	yield%[a]	dr[b]
1	*i*-Pr-	88	25:1
2	Et-	84	16:1
3		92	14:1
4	Ph-	87	37:1
5		81	9:1
6		75	2:1
7		76	24:1
8		92	9:1
9		83	9:1
10		85	2:1

[a]Isolated, chromatographed material. [b]Determined by ^1H NMR.



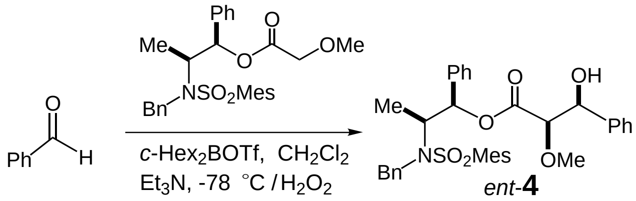
Scheme 4.

low 1.9 Hz value revealing the *syn* stereochemistry of the precursor.[12] Using the enantiomeric (1*R*,2*S*)-(−)-norephedrine glycolate, the aldol adduct *ent*-**4** with benzaldehyde was produced. The known acetonide **5** then was made and its optical rotation (+77.2°) was compared with the literature value (+77.7°)[13] to establish the absolute stereochemistry as (1*R*,2*S*).

A more detailed study was made on the stoichiometry dependence of the reagents (Table 3). With 1 equiv. of boron triflate and amine a low 59% yield was obtained with 17:1 selectivity with the (1*R*,2*S*) isomer as product. When 1 equiv. of base together with 3 equiv. of boron triflate were used the reaction did not occur. When run with 2.5 equiv. of base and one of triflate a yield of 65% was obtained with high 24:1 selectivity. Only when using 2.5 equiv. of base with excess borane was product obtained in high yield and selectivity.

The propionate diastereoselectivity follows the classic Zimmerman–Traxler model (Fig. 1). The *E* enolate from dicyclohexylboron triflate gives *anti* product through a closed arrangement with boron acting as Lewis acid (line A). The less hindered di-*n*-butylboron triflate gives the *Z* enolate and forms *syn* product through a six-ring process. However, the expected product where the stereocenter at C-2 is inverted giving 1*R*,2*S* is not obtained (line B). Instead, the 1*S*,2*R* isomer is formed with 7:1 selectivity. Two transition state arrangements can account for the face reversal. Path C is the opposite chair arrangement that uses the opposite enolate face. An open path D involves two boron groups in an antiperiplanar alignment. The *Z* enolate in path B, with the methyl group now in a pseudoaxial position, incurs an unfavorable steric interaction with the axial *n*-butyl group on boron and the phenyl group of the auxiliary. The opposite enolate face adopts a more favorable conformation now with the butyl and phenyl groups in remote positions (line C).[14] The *n*-butylboron–base combination was not further studied for stoichiometry dependence to distinguish between C and D.[6a] With dicyclohexylboron triflate, the same *anti* isomer is formed when one or more equivalents are used.

Table 3.



ent-**4**

equiv. Et_3N	equiv. c-Hex_2BOTf	yield%[a]	dr[b]
1.0	1.0	59%	17:1
1.0	3.0	0	-
2.5	1.0	65%	24:1
3.0	3.0	92%	37:1

[a]Isolated, chromatographed material. [b]Determined by ^{1}H NMR.

The glycolate *syn* aldol pathway begins with *Z* enolate formation (Fig. 2). Under all conditions investigated with the glycolate–auxiliary substrate, including various boron compounds and bases, only *syn* products have been obtained. The Lewis basic ether forms a five-membered ring coordinated enolate overriding any steric effect imposed by the ligands on boron.[15] Two options for product formation can be considered, either a closed transition state or an antiperiplanar open arrangement. The same *S*,*R* product is again obtained when either 1 or 3 equiv. of boron and base are used and the yield and selectivity increases as the number of equivalents are increased. The lack of reactivity when 1 equiv. of base and three of boron were used is most likely the result of a favorable boron–amine complex equilibrium that prevents enolate formation.[16] On the other hand, excess base with boron triflate favors complete enolization and the reaction proceeds through a

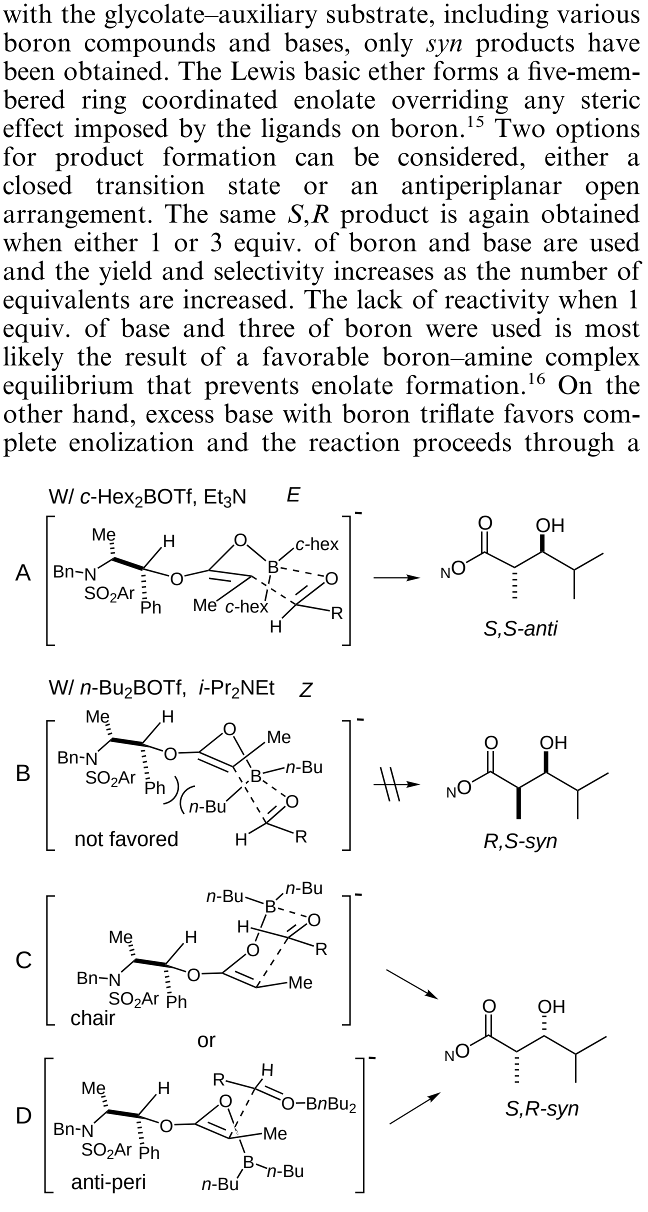


Figure 1. Propionate Masamune aldol T.S.

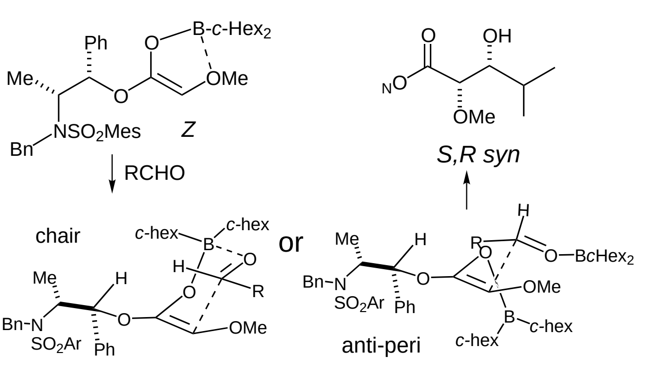


Figure 2. Glycolate aldol T.S.

closed transition state. Partitioning to other isomers would be seen if open arrangements with excess boron triflate Lewis acid activation were operative. In summary a new asymmetric glycolate aldol process with high yields and selectivities is reported. The ease of synthesis, protection, and convenient auxiliary removal through ester cleavage with lithium hydroxide or DIBAL will lead to applications where differentially protected *syn* diols are needed.

Acknowledgements

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7. Preparation of glycolate esters **3**: A solution of alcohol **1** (10.0 g, 23.6 mmol), methoxyacetic acid (2.58 g, 2.2 mL, 28.67 mmol) and DMAP (0.288 g, 2.35 mmol) in CH_2Cl_2 (150 mL) was cooled to 0°C and treated with EDCI (5.43 g, 28.32 mmol). The reaction mixture was stirred at 0°C for 2 h and then at 25°C for 6 h. The solution was concentrated and the residue was dissolved in EtOAc (750 mL) and water (150 mL). Organic layer was separated, washed with satd NH_4Cl (150 mL) and brine (100 mL). The organic layer was dried (Na_2SO_4) and concentrated. Purification of the concentrate by silica gel column chromatography gave **3** (10.53 g, 90%) as a fine white solid; R_f 0.40 (35% EtOAc/Hexanes); mp 87–89°C; $[\alpha]_D$ −3.6 (*c* 6.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.17 (m, 8H), 6.96–6.93 (m, 2H), 6.87 (s, 2H), 5.93 (d, 1H, $J=4.1$ Hz), 4.64 (AB q, 2 H, $J=17.3$ Hz), 4.05 (dq, 1 H, $J=4.1$ and 6.8 Hz), 3.82 and 3.68 (AB q, 2 H, $J=16.3$ Hz), 3.32 (s, 3H), 2.51 (s, 6H), 2.26 (s, 3H), 1.12 (d, 3 H, $J=6.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.90, 142.75, 140.33, 138.79, 138.10, 133.42, 132.33, 128.62, 128.58, 128.16, 127.44, 127.34, 126.11, 78.64, 69.63, 59.49, 56.74, 48.20, 23.16, 21.03, 12.75; HRMS (FAB) calcd for $C_{28}H_{33}NNaO_5S$ (M^++Na) 518.1977, found 518.1990. Anal. calcd for $C_{28}H_{33}NO_5S$: C, 67.85; H, 6.71; N, 2.83. Found: C, 67.78; H, 6.82, N, 2.91%. The benzyl and TBS glycolates were made in a similar fashion.
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10. General procedure: To a stirred solution of **3** (100 mg, 0.20 mmol) in CH_2Cl_2 (15 mL) cooled to −78°C was added NEt_3 (51.08 mg, 0.07 mL, 0.50 mmol) dropwise for 5 min. The reaction mixture was stirred for another 5 min after the addition. A solution of *c*-Hex_2BOTf (1.0 M in hexane, 0.6 mL, 0.60 mmol) was added dropwise over 5–7 min and the reaction mixture was allowed to stir for 2–3 h at −78°C. Aldehyde (0.24–0.26 mmol) in CH_2Cl_2 (2 mL) was precooled to −78°C and added via cannula to the enolate solution over 5 min. The reaction mixture was stirred at −78°C for 2 h and at 0°C for 2 h. The reaction was quenched by addition of pH 7.0 buffer (1 mL), followed by MeOH (1 mL) and 30% H_2O_2 (0.5 mL) and allowed to warm to rt. The reaction mixture was diluted with CH_2Cl_2 (75 mL) and washed with aq. $NaHCO_3$ (5 mL). The organic layer was separated and the aqueous layer was back extracted with ether. The combined organic extracts were treated with aq. HCl (10%, 10 mL)

and brine (20 mL). The ether layer was dried over anhydrous Na_2SO_4 and concentrated. Radial chromatographic purification provided the aldol products whose ^{1}H NMR characterization provided the diastereomeric ratio. Benzaldehyde major isomer: white foam; R_f 0.32 (35% EtOAc/Hexanes); $[\alpha]_D$ +43.5 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30–7.18 (m, 11H), 7.13–7.08 (m, 2H), 6.83 (s, 2H), 6.78–6.76 (m, 2H), 5.73 (d, 1 H, $J=5.8$ Hz), 4.86 (apparent dd, 1 H, $J=5.4$ and 4.8 Hz), 4.63 (A of AB q, 1 H, $J=16.3$ Hz), 4.33 (A of AB q, 1 H, $J=16.3$ Hz), 4.14–4.05 (m, 1H), 3.78 (d, 1 H, $J=5.8$ Hz), 3.26 (s, 3H), 3.02 (d, 1 H, D_2O exchangeable, $J=4.6$ Hz), 2.39 (s, 6H), 2.28 (s, 3H), 1.03 (d, 3 H, $J=6.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.13, 142.75, 140.55, 138.78, 138.39, 137.60, 132.99, 132.31, 128.60, 128.57, 128.48, 128.41, 128.32, 128.22, 127.51, 126.87, 85.31, 78.80, 74.08, 59.37, 56.49, 48.09, 23.07, 21.07, 14.38; HRMS (FAB) calcd for $C_{35}H_{39}NNaO_6S$ (M^++Na) 624.2396, found 624.2380. Adducts from other aldehydes were adequately characterized by NMR, MS, and optical rotation.

11. *ent*-**4** (0.133 g, 0.22 mmol) in THF at 0°C was reduced with $LiAlH_4$ (0.025 g, 0.66 mmol) to give, after work-up and purification, a diol (0.039 g, 96%); R_f 0.12 (50% EtOAc/Hexanes); $[\alpha]_D$ +53.3 (*c* 3.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41–7.26 (m, 5H), 4.78 (d, 1 H, $J=6.6$ Hz), 3.71 (dd, 1 H, $J=3.6$ and 11.9 Hz), 3.46 (s, 3H), 3.41 (dd, 1 H, $J=3.9$ and 11.9 Hz), 3.34 (td, 1 H, $J=3.9$ and 6.6 Hz), 2.82 (b, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.51, 128.64, 128.19, 126.97, 85.89, 73.99, 60.31, 58.91; HRMS (FAB) calcd for $C_{10}H_{15}O_3$ (M^++H) 183.1021, found 183.1035. To the solution of diol (0.039 g, 0.21 mmol) in CH_2Cl_2 (6 mL) was added 2,2-dimethoxypropane (0.20 g, 0.25 mL, 1.9 mmol) and camphor sulfonic acid (0.005 g, 0.021 mmol). After 2 h, the reaction was quenched with NEt_3 (0.2 mL) and concentrated. Flash chromatographic purification gave acetonide **5** (0.034 g, 72%) as an oil; R_f 0.58 (50% EtOAc/Hexanes); $[\alpha]_D$ +77.2 (*c* 3.4, $CHCl_3$) (lit. (see Ref. 14) $[\alpha]_D$ +77.7 (*c* 1.2, $CHCl_3$)); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45–7.24 (m, 5H), 5.02 (d, 1 H, $J=1.9$ Hz), 4.13 (dd, $J=1.9$ and 12.7 Hz), 4.08 (dd, 1 H, $J=1.9$ and 12.7 Hz), 3.19 (q, 1 H, $J=1.9$ Hz), 3.06 (s, 3H), 1.56 (s, 3H), 1.55 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.96, 128.25. 127.57, 126.67, 99.25, 75.70, 73.47, 62.37, 58.46, 29.45, 19.08; HRMS (FAB) calcd for $C_{13}H_{19}O_3$ (M^++H) 223.1334, found 223.1336.
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