The importance of phosphine-to-rhodium ratios in enantioselective hydroborations

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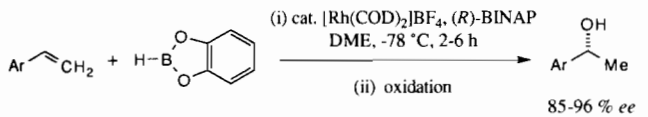
Abstract

Catalyzed hydroborations of several 1,1-disubstituted aryl alkenes were studied. Formation of tertiary alcohols (after oxidation) was favored when high phosphine-to-rhodium ratios were used. Enantioselective variants of this process can give chiral primary and tertiary alcohols with different enantioselectivities indicative of mechanistic differences. Measurements of product optical yields as a function of optical purities of the catalyst gave a linear correlation. The mechanistic implications of these data are discussed.

Key words: Catalysis; Hydroboration; Enantioselectivity; Rhodium complexes; Phosphine complexes

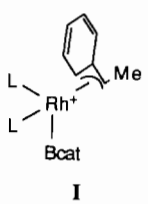
Introduction

Enantioselective hydroborations [1–6] have potential to become an attractive alternative to diastereoselective methods involving optically active boranes. Aryl-substituted alkenes, however, remain the only substrates for which high enantioselectivities have been obtained in catalytic asymmetric hydroboration reactions of alkenes [4, 5]. These substrates are also unique insofar as they react extremely quickly (reaction temperature of −78 °C can be used) and with high regioselectivity in favor of the secondary alcohol (reaction (1)). Hayashi *et al.* proposed that the anomalous reactivity of aryl alkenes could be due to formation of a π-allyl (i.e. η^3-benzyl) complexes of type **I** [4, 5]. Some variation of the commonly accepted mechanism wherein insertion of the alkene into an Rh–B bond precedes insertion into Rh–H could also be involved [7–9], but this issue is open to speculation.



85-96 % *ee*

(1)



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Contributions from several groups have indicated that the ratio of primary to secondary alcohol in this reaction was very sensitive to the catalyst used [4, 5, 8, 10–12]. The phosphine-to-rhodium ratio is critical since partially oxidized catalyst (wherein some ligand is oxidized to triphenylphosphine oxide and the phosphine-to-rhodium becomes <3:1) gives some primary alcohol, whereas complete selectivity for the secondary alcohol is restored when phosphine is added to this oxidized catalyst. Similar trends are observed for catalysts formed *in situ* from $[Rh(COD)Cl]_2$ and phosphines, although the situation can be complicated further by incomplete displacement of COD by the phosphine, at least when PPh_3 is used [8, 13].

This paper describes investigations of 2-phenylpropene and other 1-alkyl-1-aryl alkenes in the catalyzed hydroboration process. The goals of this work were to ascertain whether or not enantioselective hydroborations of these substrates are viable, the effects of phosphine-to-rhodium ratios on regioselectivities and enantioselectivities, and to use enantioselectivities as a mechanistic probe.

Results and discussion

Data for catecholborane hydroborations of 2-phenylpropene are shown in Table 1. Throughout, the catalysts were formed *in situ* from $[Rh(COD)Cl]_2$ and various optically pure bidentate phosphines (Fig. 1).

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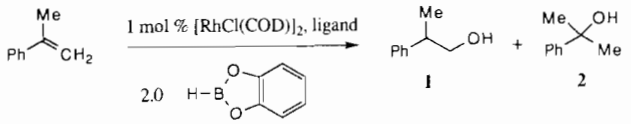
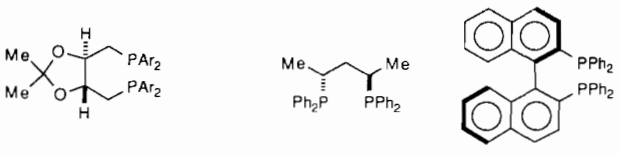
TABLE 1. Hydroborations of 2-phenylpropene



Entry	Ligand	Rh:ligand	1:2	% *ee* of 1 (config.)[a]
1	(*S,S*)-BDPP	1:1	1:1	27 (*R*)
2	(*R*)-BINAP	1:1	6:1	25 (*S*)
3	(*R,R*)-3-MeO-DIOP	1:1	1:4	15 (*R*)
4	(*R,R*)-DIOP	1:1	9:1	27 (*R*)
5	(*R,R*)-DIOP	1:2	1:8	not determined

[a]Determined by HPLC of the corresponding acetates using a CHIRALCEL OB column.

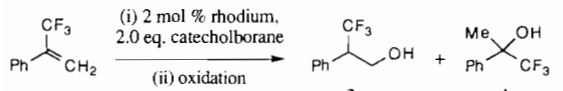


Ar = Ph; (*R,R*)-DIOP (*R,R*)-BDPP (*R*)-BINAP

Ar = 3-MeOC$_6$H$_4$; (*R,R*)-3-MeO-DIOP

Fig. 1. Ligands used in this study.

TABLE 2. Hydroborations of 2-phenyl-3.3.3-trifluoropropene



Entry	Catalyst	Rh:ligand	3:4[a]
1	[Rh(COD)Cl]$_2$/(*S,S*)-BDPP	1:2	14:86
2	Rh(COD)$_2$BF$_4$/(*S,S*)-BDPP	1:2	11:89
3	Rh(COD)$_2$BF$_4$/(*S,S*)-BDPP	1:1	14:86
4	Rh(COD)$_2$BF$_4$/(*S,S*)-BDPP	1:2	37:63[b]
5	[Rh(COD)Cl]$_2$/(*R*)-BINAP	1:2	33:67
6	Rh(COD)$_2$BF$_4$/(*R*)-BINAP	1:2	80:20[c]
7	Rh(COD)$_2$BF$_4$/(*R,R*)-DIOP	1:1	>90:10
8	Rh(COD)$_2$BF$_4$/(*R,R*)-DIOP	1:2	72:28
9	Rh(COD)$_2$BF$_4$/(*R,R*)-3MeO-DIOP	1:2	74:26

[a]Determined by ^{19}F NMR and capillary GC of the silylated products. [b]30% conversion. [c]45% conversion.

Two of the four phosphines used gave more primary alcohol when the phosphine-to-rhodium ratio was 1:1 (entries 2 and 4), but more tertiary alcohol was formed when 3-MeO-DIOP was used. Increasing the phosphine-to-rhodium ratios from 1:1 to 2:1 for DIOP (entries 4 and 5) caused a reversal of the regioselectivity in favor of the tertiary alcohol.

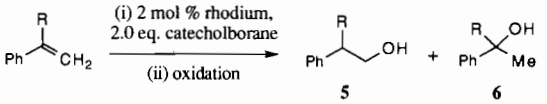
Table 2 shows data for catalyzed hydroborations of Ph(CF$_3$)C=CH$_2$ [14]. Collectively these results show that the regioselectivities are ligand dependent. Tertiary alcohols were always favored for BDPP (entries 1–4), whereas more primary alcohol was obtained when BINAP or DIOP was used (entries 5–9). Increasing the phosphine-to-rhodium ratio for the latter ligands gave more tertiary alcohol, but in the case of BINAP the reaction rate was severely retarded so that a diminished conversion was obtained (entry 6).

Catalyzed hydroborations of Ph(CF$_3$)C=CH$_2$ and of Ph(Et)C=CH$_2$ can give chiral primary and chiral secondary alcohols. It was of interest to see if the optical yields would be the same for both products. In the event, Table 3 shows different optical yields were obtained in the enantioselective hydroborations of these 1,1-disubstituted alkenes.

For Ph(CF$_3$)C=CH$_2$ the levels of induction in both products **5** and **6** were too low to allow formulation of meaningful conclusions concerning the mechanism from the face selectivities. However, for Ph(Et)C=CH$_2$ the optical yields were higher and one important observation was made: the absolute configurations of the primary and tertiary alcohols are derived from addition to the same enantiotopic face of the alkene substrate, but the extent of asymmetric induction is greater for tertiary alcohols than primary alcohols.

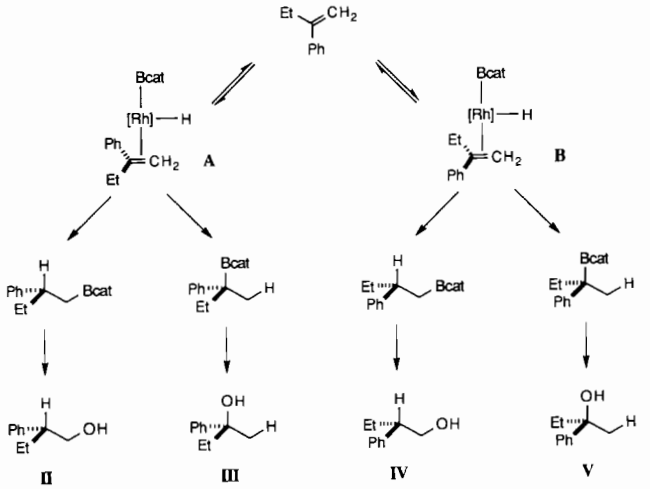
It is not proven that η^2-intermediates are involved in this process, the reaction could, for instance, proceed directly via η^3-benzyl complexes (see **I**). It is certain, however, that the reaction does allow orientation of the metal on the two enantiotopic faces of the alkene to give both enantiomers of the two products. For the purpose of this discussion, we shall assume that the reaction proceeds via the rhodium-to-alkene π-complexes **A** and **B** and that these are intermediates in the formation of both primary and tertiary alcohols after oxidation (Scheme 1). Higher enantioselection was obtained for formation of tertiary alcohols so formation of intermediates **A** and **B** cannot be stereodeterminant (i.e. irreversible). It follows that alkene insertion to give primary alcohols (via complexes **II** and **IV**) has little preference for intermediate **A** or intermediate **B**, but insertion to give the tertiary alkyl rhodium complexes is more favorable from **A** than from **B**. These arguments are invalid if the reaction does not involve common intermediates for formation of primary and secondary alcohols, but the conclusion is the same:

TABLE 3. Simultaneous enantioselective syntheses of primary and tertiary alcohols



Entry	R	Catalyst	5 (*ee*, config.):6 (*ee*, config.)
1	CF_3	$Rh(COD)_2BF_4$/(*S*,*S*)-BDPP	9 (13, *R*): 75 (0)
2	CF_3	$[Rh(COD)Cl]_2$/(*S*,*S*)-BDPP	15 (15, *R*):85 (20)[a]
3	Et	$[Rh(COD)Cl]_2$/(*S*,*S*)-BDPP	53 (30, *R*):47 (84, *S*)
4	Et	$Rh(COD)_2BF_4$/(*R*,*R*)-DIOP	73 (13, *R*):27 (43, *S*)

[a]The absolute configuration of tertiary alcohol **6** with $R = CF_3$ was not determined.



Scheme 1. A possible reaction pathway for formation of primary and tertiary alcohols in the hydroboration process.

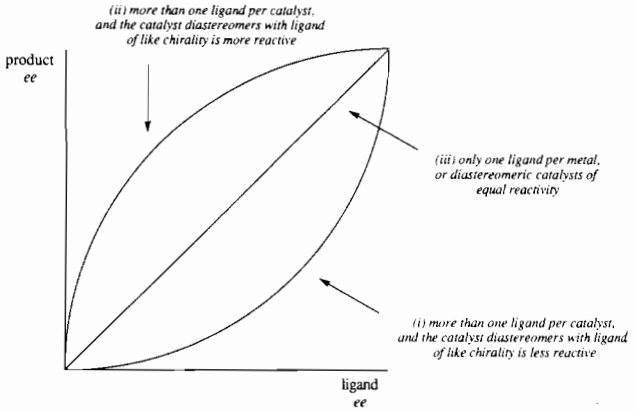


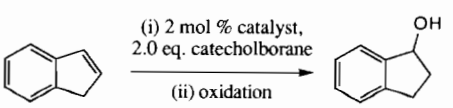
Fig. 2. Principles of asymmetric amplification.

there are significant mechanistic differences for the formation of primary and tertiary alcohols in this process.

An attempt was made to gain information about the catalytically active species in the hydroboration process, i.e. does it contain more than one chiral phosphine. Analogy with 'asymmetric amplification' in other systems [15–17] indicates that when catalysts of less than 100% optical purity are used in catalyzed hydroborations, one of three outcomes are possible: (i) the enantiomeric excess of the product decreases proportionately more than that of the catalyst; (ii) the enantiomeric excess of the product decreases proportionately less than that of the catalyst; (iii) the two factors are linearly related. In the first case the active catalyst has two (or more) ligands and the diastereomer with ligands of like chirality is less reactive. In the second case the active catalyst has two (or more) ligands but the diastereomer with ligands of like chirality is more reactive. The third case implies the catalytically active species has only one ligand, or that it has more than one and all possible diastereomers are equally reactive (to within experimental error, Fig. 2). Strictly, the term 'asymmetric amplification' can only be applied to case (ii).

To test this phenomenon in catalyzed hydroborations, an aryl substituted alkene was required for which the optical purity of the product alcohol could be determined accurately. Consequently, indene was selected (reaction (2)) because the optical purity of the product can be determined via HPLC on a CHIRALCEL OB column. Two catalyst formulations were used: $[Rh(COD)Cl]_2$/2 equiv. DIOP and $[Rh(COD)Cl]_2$/4 equiv. DIOP.

Intuitively, we suspect that only one ligand per catalyst is involved in catalyzed hydroboration processes because the coordination sphere of rhodium would not simultaneously support two bidentate ligands, a coordinated alkene, and σ hydride and borocatecholate ligands. However, another possibility is that the catalyst is a rhodium dimer with more than one ligand. The results for the asymmetric amplification experiments are shown in Fig. 3(a) and (b). Both catalyst formulations gave linear relationships between the optical activities of the product and the ligand. These experiments provide no evidence to suggest that more than one ligand per catalyst is involved.



(2)

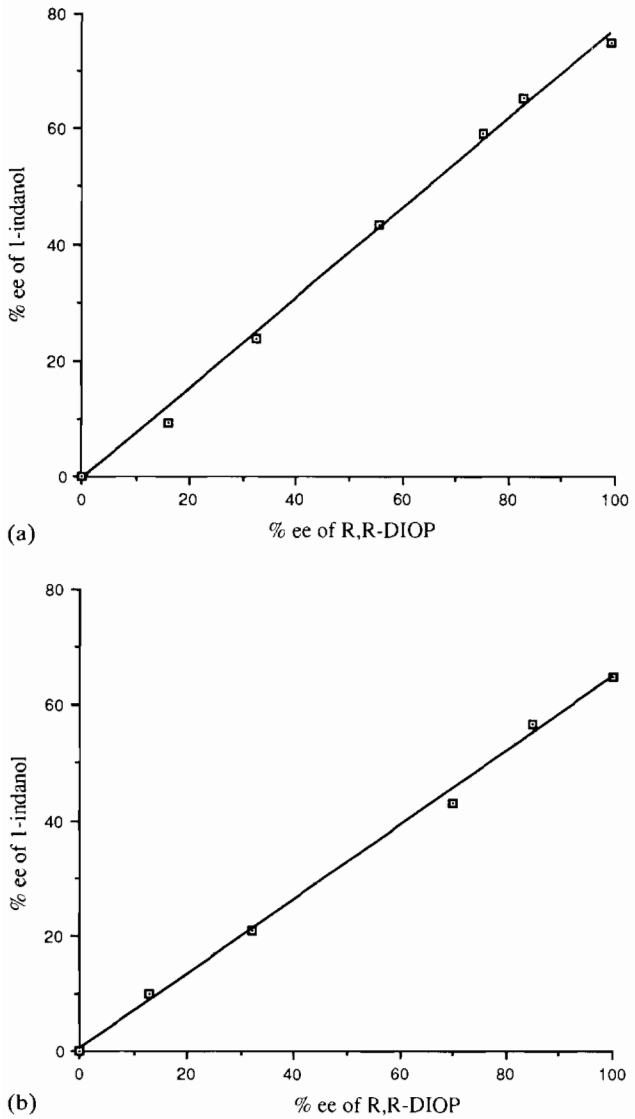


Fig. 3. Optical yields of 1-indanol as a function of the optical purity of the DIOP used in reaction (2): (a) $[Rh(COD)Cl]_2$:(*R*,*R*)-DIOP = 1:2; (b) $[Rh(COD)Cl]_2$:(*R*,*R*)-DIOP = 1:4.

Conclusions

Asymmetric hydroborations of 1,1-disubstituted alkenes are possible, at least where one of the substituents is an aryl group. Higher phosphine-to-rhodium ratios favor the formation of tertiary alcohols, and the preference formation of tertiary alcohols is greater with BDPP than with BINAP or DIOP. Different enantioselectivities arc obtained for primary and tertiary alcohols formed in this process, indicative of fundamental mechanistic differences for the formation of the two products. 'Asymmetric amplification' experiments provide no evidence for there being more than one phosphine ligand per catalyst molecule. The data described here does not eliminate this possibility, however, and the results show that phosphine-to-rhodium ratios have significant effects on the behavior of catalysts formed *in situ* from $[Rh(COD)Cl]_2$.

Experimental

General procedures

High field NMR spectra were recorded on a Bruker AF300 (^1H at 300 MHz, ^{13}C at 75.4 MHz) or a Bruker AC250 (^1H at 250 MHz, ^{13}C at 62.9 MHz, ^{19}F at 235 MHz) instrument in $CDCl_3$. ^1H chemical shifts are reported in δ ppm relative to $CHCl_3$ (7.25 ppm) as an internal standard, ^{13}C chemical shifts are reported in δ ppm relative to $CDCl_3$ (77.10 ppm) as an internal reference and ^{19}F chemical shifts are reported relative to CF_3COOH as external standard. Thin layer chromatography was performed on silica gel 60 F_{254} plates from Whatman. Flash chromatography was performed on SP Silica Gel 60 (230–600 mesh ASTM). HPLC was performed on a Rainin Rabbit HP system using a CHIRALCEL OB column from Daicel Chemical Industries. Gas chromatography was carried out on a Shimadzu GC9A using a 50 m methyl phenyl (5%) silicone fused silica capillary column from Quadrex. Tetrahydrofuran (THF) was distilled immediately before use from sodium benzophenone ketyl. The catalyst precursors $[Rh(COD)Cl]_2$ and $Rh(COD)_2BF_4$ were prepared as described in the literature [18]. Catecholborane was purchased from Aldrich Chemical Co. and was distilled under reduced pressure before use. (*R*)-BINAP and (*S*,*S*)-BDPP were obtained from Strem Chemicals, (*R*,*R*)-DIOP was prepared according to a literature procedure [19] and (*R*,*R*)-3-MeO-DIOP [20] was prepared analogous to a published procedure for (*R*,*R*)-2-MeO-DIOP [20, 21]. 3,3,3-Trifluoro-2-phenyl-1-propene was prepared according to a literature procedure. Organic solutions were dried over anhydrous $MgSO_4$.

Catalyzed hydroborations of 2-phenylpropene, 2-phenylbut-1-ene and 3,3,3-trifluoro-2-phenyl-1-propene

A Schlenk tube charged with 4.9 mg of $[Rh(COD)Cl]_2$ (0.01 mmol, 0.02 equiv.) and 0.02 or 0.04 mmol of chiral phosphine was evacuated/flushed with argon three times. Subsequently, 2 ml of THF and 1 mmol of substrate were added and the stirred reaction mixture was cooled to −78 °C, catecholborane (240 mg, 2 mmol) was added, and after stirring at −78 °C for 20 min, the Schlenk tube was placed in a refrigerator at 5 °C. The reaction was followed by TLC. Slower conversion was observed if 2 equiv. of phosphine were present; typical reaction times at 5 °C are 2 days for 2-phenylpropene and 2-phenylbut-1-ene, and 7 days for 3,3,3-trifluoro-2-phenyl-1-propene. Upon completion of the reaction 1 ml of ethanol was added at 0 °C followed

by 1.7 ml of 3 M NaOH solution and 1 ml of 30% H_2O_2. The mixture was stirred for 6 h at 20 °C and then diluted with 10 ml of 1 M NaOH solution. Extraction with diethyl ether (3×75 ml), washing of the combined organic fractions with 1 M NaOH solution (50 ml), water (50 ml) and saturated NaCl solution (50 ml) and evaporating the solvent after drying provided the crude products. The ratio of primary to tertiary alcohols in the crude reaction product was determined by capillary gas chromatography or ^{19}F NMR for compounds **5** and **6** (R = CF_3). The primary product alcohols **1** and **5** (R = Et) were separated from the tertiary alcohols **2** and **6** (R = Et) by flash chromatography (15% EtOAc in hexane).

2-Phenyl-1-butanol (**5**, *R = Et*). The enantiomeric excess for 2-phenyl-1-butanol was determined via formation of the MPTA-ester derivatives [22] (2 equiv. of (*R*)-Mosher's acid, DCC, DMAP, CH_2H_2, 24 h) and integration of the ^1H NMR and ^{19}F spectra. R_f 0.25 (15% EtOAc in hexane); ^1H NMR (300 MHz, $CDCl_3$): δ 0.82 (t, $^3J_{HH}$ 7.4 Hz, 3H), 1.32 (s, OH), 1.54–1.77 (m, 2H), 2.65–2.70 (m, 1H), 3.70–3.77 (m, 2H), 7.18–7.35 (m, 5H). ^{19}F NMR MPTA-ester (235 MHz, $CDCl_3$): δ 4.82 (*R,R*-diastereomer), 4.91 (*R,S*-diastereomer).

2-Phenyl-2-butanol (**6**, *R = Et*). R_f 0.4 (15% EtOAc in hexane); ^1H NMR (250 MHz ,$CDCl_3$): δ 1.19 (t, $^3J_{HH}$ 7.2 Hz, 3H), 1.50 (s, 3H), 1.79 (q, $^3J_{HH}$ 7.2 Hz, 2H), 2.68 (br s, OH), 7.14–7.42 (m, 5H). Optical purity was determined by a chiral shift experiment using an Eu(hfc)$_3$ derivative and the absolute configuration was established by optical rotatory measurements [23].

3,3,3-Trifluoro-2-phenyl-1-propanol (**5**, *R = CF_3*. ^{19}F NMR (235 MHz, $CDCl_3$): δ 9.10 (d, $^3J_{HF}$ 9.5 Hz). The optical purity of the compound was determined by ^1H NMR and ^{19}F NMR analysis of the MPTA-ester.

1,1,1-Trifluoro-2-phenyl-2-propanol (**6**, *R = CF_3*). ^1H NMR (300 MHz, $CDCl_3$): δ 1.85 (s, 3H), 3.44 (br s, OH), 7.46 (m, 3H), 7.70 (d, $^3J_{HH}$ 7.7 Hz, 2H); ^{19}F NMR (235 MHz, $CDCl_3$): δ −4.32 ppm. The optical purity was determined by chiral shift experiment of the acetate (3 equiv. Ac_2O, cat. DMAP, CH_2Cl_2, reflux for 6 h) using a Eu(III)(hfc)$_3$ shift reagent.

Catalyzed hydroborations of indene

Stock solutions of DIOP of varying optical purity were prepared by dissolving known amounts of (*R,R*)-DIOP and (*S,S*)-DIOP in THF. These solutions were used in the catalyzed hydroboration of indene via the procedure described for disubstituted 1-phenylalkenes (*vide supra*). Two sets of experiments with different rhodium-to-phosphine ratios were performed simultaneously. The reaction mixtures were stored at −5 °C for 5 days. The 1-indanol:2-indanol ratio in the crude reaction product was determined by ^1H NMR. The two product alcohols were separated by flash chromatography (15% EtOAC in hexane) and the optical purity of 1-indanol was determined by HPLC analysis using a CHIRALCEL OB column.

1-Indanol. R_f 0.22 (15% EtOAc in hexane); ^1H NMR (300 MHz, $CDCl_3$): δ 1.92–1.99 (m, 1H), 2.40–2.48 (m, 1H), 2.80–2.88 (m, 1H), 3.01–311 (m, 1H), 3.90 (br s, OH), 5.20 (t, $^3J_{HH}$ 6.2 Hz, 1H), 7.26–7.37, 7.43–7.48 (m, 4H).

2-Indanol. R_f 0.15 (15% EtOAc in hexane); ^1H NMR (250 MHz, $CDCl_3$): δ 2.34 (s, 1H), 2.88 (dd, $^3J_{HH}$ 3.3, $^2J_{HH}$ 16.3 Hz, 2H), 3.19 (dd, $^3J_{HH}$ 5.9, $^2J_{HH}$ 16.3 Hz, 2H), 4.60–4.67 (m, 1H), 7.15–7.27 (m, 4H).

Acknowledgements

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