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Stereogenic Phosphorus-Induced Diastereoselective Formation of Chiral Carbon during Nucleophilic Addition of Chiral H–P Species to Aldehydes or Ketones

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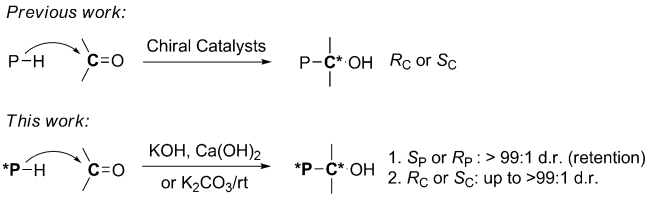
Abstract: P,C-Stereogenic α-hydroxyl phosphinates or phosphine oxides were prepared from the additions of (R_P)-phosphinate to ketones or (R_P)-phosphine oxide to aldehydes, respectively, catalyzed by bases at room temperature in up to >99:1 diasteromeric ratio (d.r.$_P$/d.r.$_C$) and 99% yields. The diastereoselectivity was induced by reversible equilibrium and different stabilities between two diastereomers of adduct, which was caused by the spatial interaction between menthoxyl or menthyl to alkyl groups of aldehydes or ketones.

Keywords: aldehydes · asymmetric synthesis · diastereoselectivity · phosphorus · ketones

Introduction

Optically active phosphorus compounds have attracted extensive attention in recent years because of their potential application as biologically active substances[1] and precursors of ligands for asymmetric catalysis.[2] Among them, α-hydroxyl phosphoric derivatives have particular value because of their utility as the inhibitors of HIV protease[3] or rennin,[4] and as γ-aminobutyric acid (GABA) antagonists[5] or herbicides.[6] The addition of P–H species to carbon–oxygen double bonds, known as the Pudovik reaction,[7] was traditionally used for the preparation of α-hydroxyl phosphoric compounds. The relevant stereoselective approaches were extensively developed by several research groups, and were usually committed to the formation of C-stereogenic phosphoric derivatives by means of addition of nonchiral P–H species to prochiral aldehydes or ketones by employing asymmetric catalysts that concerned heavy metals or ligands that are accessible with difficulty (Scheme 1).[8] The synthesis of α-hydroxyl phosphoric compounds that contain both carbon and phosphorus chiral centers is quite limited.

P-Stereogenic P–H species have attracted growing attention because of their novel applications in the construction of asymmetric P–C bonds.[9] When these compounds were applied to the Pudovik reaction, both carbon and phosphorus chiral centers could be generated, thereby deriving up to four possible stereomers by means of cleavage of the P–H bond and formation of the P–C bond.[10] Owing to the poor induction of the P-stereogenic center to the generation of chiral carbon,[9b,11] to the best of our knowledge, the simultaneous formation of carbon and phosphorus chiral centers with excellent stereoselectivity has scarcely been studied. Recently, Montchamp's group reported P,C-stereogenic α-hydroxyl phosphinates in 94% diastereomeric excess (*de*) by means of Wittig rearrangement.[12] On the basis of the reversible equilibrium for the addition of P–H species to aldehydes or ketones under alkali conditions,[13] it was hoped that the diastereomers of the adduct would show different thermodynamic stabilities that lead to a more stable one being formed predominantly. Herein we disclose the results of additions to aldehydes or ketones with (R_P)-*O*-(−)-menthyl *H*-phenylphosphinate (**1a**)[9c,e] or (R_P)-(−)-menthyl phenylphosphine oxide (**1b**).[14] In these reactions, the P,C-stereogenic α-hydroxyl phosphinates or phosphine oxides were readily obtained in up to >99:1 diasteromeric ratio (d.r.) under mild conditions.



Scheme 1. Comparison of reported results to our current work.

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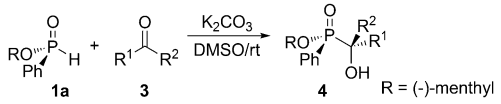
Results and Discussion

Among the base-promoted additions of **1a** or **1b** to aldehydes **2** or ketones **3**—in addition to the combinations of **1a** to **2** that afforded the adduct in poor selectivity[10,15] and **1b** to **3** that cannot occur at room temperature—the reactions of **1a** to **3** and **1b** to **2** exhibited some diastereoselectivity. We found that K_2CO_3 effectively catalyzed the addition of **1a** to ketones in DMSO to afford α-hydroxyl phosphinates **4** stereospecifically with retention of the configuration on the phosphorus atoms.[9,12]

As seen in Table 1, the reactions of most *p*-substituted acetophenones with **1a** gave **4** in excellent yields and more than 90:10 d.r.$_C$. The *meta*-substituted acetophenones afforded **4** in poor to moderate yields and poor d.r.$_C$. Among them, *m*-nitroacetophenones even showed reversed selectivity (Table 1, entry 7). The reactions for some ketones such as *ortho*-substituted acetophenones, *p*-hydroxyacetophenone, α-tetralone, and acetylferrocene cannot take place, and for some ketones such as *p*-aminoacetophenone, 2-acetyl furan, and 1-acetylnaphthene gave poor yields. Acyclic aliphatic ketones gave moderate yields of **4** but in poor d.r.$_C$. As shown in entry 22 of Table 1, the reaction afforded four stereomers in the ratio 5:50:7:38, which were generated from racemic 2-methyl cyclohexanone. For prochiral trifluoroacetophenone, the *O*-phosphorylated product was detected in four stereomers when catalyzed by K_2CO_3; these were generated from different configurations on both the phosphorus and carbon atoms. In the absence of base, C-phosphorylated **4l** was formed predominately in two stereomers, which were derived from the configuration on the α-carbon atom (Table 1, entry 12).

Table 1. Addition to ketones **3** with **1a**.

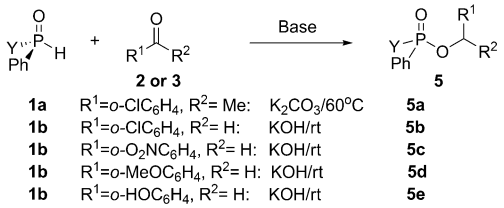


1a **3** **4**

Entry	R^1-CO-R^2, **3**	*t* [h]	Yield[a] [%]	d.r.$_C$[a]
1	Ph, Me	40	**4a**, 75 (37)	90:10
2	*p*-BrC_6H_4, Me	24	**4b**, 97 (74)	98:2
3	*p*-ClC_6H_4, Me	68	**4c**, 90 (71)	99:1
4	*p*-FC_6H_4, Me	54	**4d**, 87 (82)	84:16
5	*m*-BrC_6H_4, Me	60	**4e**, 70 (50)	67:33
6	*p*-$NO_2C_6H_4$, Me	40	**4f**, 48 (20)	84:16
7	*m*-$NO_2C_6H_4$, Me	72	**4g′**, 71 (40)	12:88
8	*p*-$CH_3C_6H_4$, Me	90	**4h**, 93 (80)	99:1
9	*p*-$CH_3OC_6H_4$, Me	96	**4i**, 94 (81)	99:1
10	*p*-PhC_6H_4, Me	88	**4j**, 87 (69)	97:3
11	*m*-$NH_2C_6H_4$, Me	24	**4k**, 35	63:37
12	Ph, CF_3	76	**4l**, 97 (65)	36:64[b,c]
13	2-furyl, Me	107	**4m**, 47 (34)	53:47[c]
14	1-naphyl, Me	48	**4n**, 19	46:54[c]
15	$(CH_2)_5$	24	**4o**, 99 (92)	–
16	$(CH_2)_4$	44	**4p**, 98 (90)	–
17	Me, Me	24	**4q**, 99 (88)	–
18	Et, Et	96	**4r**, 54 (42)	–
19	Et, Me	65	**4s**, 98 (43)	27:73[c]
20	*i*Bu, Me	24	**4t**, 83 (22)	68:32
21	*i*Pr, Me	100	**4u**, 54 (41)	51:49[c]
22	2-Me-cyclohexanone	16	**4v**, 90 (76)	5:50:7:38[c]

[a] Typical procedure: **1a** (0.36 mmol) and **3** (0.36 mmol) were stirred in DMSO (1 mL) in the presence of K_2CO_3 (25% molar) at RT. Yield and d.r.$_C$ were estimated by ^{31}P NMR spectroscopy, and isolated yield is presented in parentheses. Values of d.r.$_C$ were assigned as **4**/**4′** ($S_PR_{\alpha\text{-}C}/S_PS_{\alpha\text{-}C}$) except for unconfirmed diastereomers. [b] The reaction was carried out in diethyl ether without base. [c] The structures of diastereomers were not confirmed.

Potassium carbonate did not show catalytic activity toward the addition of **1b** to aldehydes at room temperature. When catalyzed by KOH in DMSO or $Ca(OH)_2$ in DMF, the reactions occurred in excellent yields and selectivities to afford α-hydroxyl phosphine oxides **6**. On the basis of ^{31}P NMR spectroscopy, the peaks for major diastereomers of **6**, which were confirmed to have $R_PS_{\alpha\text{-}C}$ structure by X-ray crystallography, were located at upper field relative to minor ones. As seen in Table 2, the addition of **1b** to various aromatic and aliphatic aldehydes was examined. In most cases, the formation of **6** reached yields of 99% and up to >99:1 d.r.$_C$ ($R_PS_{\alpha\text{-}C}$-/$R_PR_{\alpha\text{-}C}$-**6/6′**). The reaction of some aromatic aldehydes, respectively, catalyzed by two bases, gave similar yields and d.r.$_C$. Some *ortho*-substituted benzaldehydes gave poor yields of **6** when catalyzed by KOH; they suffered from the side reaction that generated **5** (Table 1, entry 10–13 and Scheme 2). The side reaction could be clearly avoided when $Ca(OH)_2$ was employed as catalyst, except for the case of salicylaldehyde. As seen in entry 13 of Table 1, $Ca(OH)_2$ slightly improved the formation of **6** to 31% yield, which was decomposed upon purification with preparative TLC. The yields for the reactions of aliphatic aldehydes were lower than that of aromatic aldehydes, and in some cases they did not reach 99%. For paraldehyde, the d.r.$_C$ was poor when catalyzed by KOH, and it was improved to >99:1 when catalyzed by $Ca(OH)_2$.

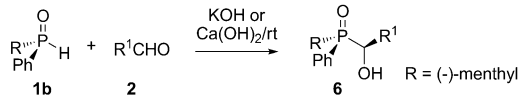


Scheme 2. Formation of **5** by means of Phospha–Brook rearrangement.

The major side reaction for both additions of **1a** to **3** and **1b** to **2** was the formation of **5** by means of Phospha–Brook rearrangement.[16] As seen in Scheme 2, *ortho*-substituted or electron-withdrawing group (EWG)-containing aromatic aldehydes or ketones, especially when catalyzed by a stronger base or when the reaction was carried out under heating conditions, tended to form **5**. For example, *o*-chloroacetophenone and **1a** afforded trace **4** under typical conditions in Table 1. At elevated temperature, **5a** was obtained as the major product.

The 59:41 d.r.$_C$ of **4b**/**4b′**, which was isolated from the reaction of **1a** to **3b** for 30 minutes, was improved to 94:6 and

Table 2. Addition to aldehydes **2** with **1b**.

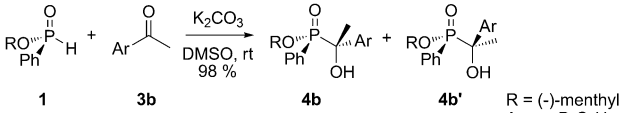


1b **2** **6**

Entry	R^1CHO, **2**	Base	t [h]	Yield[a] [%] **6**	d.r.$_C$[a]	Yield [%] **5**
1	C_6H_5	A	24	**6a**, >99 (80)	>99:1	–
2	*p*-ClC_6H_4	A	23	**6b**, >99 (81)	98:2	–
3	*p*-$O_2NC_6H_4$	B	17	**6c**, 53 (40)	82:18	–
4	*p*-MeC_6H_4	A	24	**6d**, >99	98:2	–
		B	11	**6d**, >99 (75)	>99:1	–
5	*p*-*i*PrC_6H_4	B	11	**6e**, >99 (86)	95:5	–
6	*p*-$MeOC_6H_4$	A	23	**6f**, >99	98:2	–
		B	11	**6f**, >99 (78)	>99:1	–
7	*p*-$Me_2NC_6H_4$	A	5	**6g**, >99 (85)	>99:1	–
		B	11	**6g**, 80	96:4	–
8	*o*-FC_6H_4	A	24	**6h**, 98 (80)	98:2	–
9	*o*-ClC_6H_4	A	24	**6i**, >99 (81)	97:3	–
		B	10	3		**5b**, 97 (80)
10	*o*-BrC_6H_4	A	5[b]	**6j**, >99	98:2	–
		A	24	**6j**, 98 (78)	>99:1	–
11	*o*-$O_2NC_6H_4$	A	23	**6k**, 63 (50)	98:2	**5c**, 27
12	*o*-$MeOC_6H_4$	A	24	**6l**, >99 (78)	>99:1	–
		B	11	**6l**, 42	95:5	**5d**, 58
13	*o*-HOC_6H_4	A	24	31	98:2	**5e**, 42
		B	12	5		**5e**, 95 (83)
14	*m*-BrC_6H_4	B	11	**6m**, >99 (79)	>99:1	–
15	3,4,5-$(MeO)_3C_6H_2$	A	25	**6n**, >99 (78)	>99:1	–
16	*i*Pr	B	11	**6o**, 93 (74)	>99:1	–
17	$(Me_2)CHCH_2$	A	24	**6p**, >99 (85)	98:2	–
18	$nC_{11}H_{23}$	B	5	**6q**, 77	58:42	–
		B	23	**6q**, 80 (65)	>99:1	–
19	H, $(CH_2O)_n$	A	41	**6r**, >99 (83)	–	–
20	Me, $(CHMeO)_3$	B	16	**6s**, 87	60:40	–
		A	36	**6s**, 90 (75)	>99:1	–

[a] Typical procedure: **1b** (0.38 mmol) and **2** (0.38 mmol) were stirred in solvent (0.5 mL) in the presence of 25% molar base. A) $Ca(OH)_2$ was used in DMF. B) KOH was used in DMSO. Yield and d.r.$_C$ were estimated by ^{31}P NMR spectroscopy, and the isolated yield is presented in parentheses. Values of d.r.$_C$ were assigned as **6/6′** ($R_PS_{\alpha\text{-}C}$/$R_PR_{\alpha\text{-}C}$). [b] Three molar equivalents of aldehyde were used.

97:3 when the mixture was stirred with K_2CO_3 for 1.5 and 5 hours, respectively. At the same time, a trace amount of **1a** was detected by ^{31}P NMR spectroscopy. In fact, the reaction of **1a** to **3b** was completed within 1 hour, and prolonged reaction times only improved the ratio of **4b**/**4b′**. As seen in Scheme 3, d.r.$_C$ of **4b**/**4b′** was observed in as 60:40, 90:10, and 97:3 when **1a** and **3b** were stirred for 0.25, 10, and 24 hours, respectively. A similar improvement in d.r.$_C$ over time was also observed for the addition of **1b** to **2** when catalyzed by KOH or $Ca(OH)_2$ (entry 10 and 18 of Table 2), and acquiring the best d.r.$_C$ took a shorter time in the case of the former.



1 **3b** **4b** **4b'**

0.25 h	60	:	40
1 h	62	:	38
5 h	77	:	23
10 h	90	:	10
24 h	97	:	3
72 h	98	:	2

Scheme 3. Improvement of d.r.$_C$ for **4b**/**4b′** over reaction time.

On the basis of these consequences, we believed that both additions of **1a** to **3** and **1b** to **2** were reversible, and the thermodynamic stabilities for the two diastereomers **4**/**4′** or **6**/**6′** were different. In the presence of base, a more unstable **4′** or **6′** would have a stronger tendency to be converted back to **1** and **2**/**3** through a reversible equilibrium, which would then be converted to **4**/**6** after enough time.

The P-retention additions for both **1a** and **1b**, as well as the $R_{\alpha\text{-}C}$ and $S_{\alpha\text{-}C}$ configuration for **4** and **6**, respectively, were confirmed by crystallography. In the one-dimensional chain structures (as seen in the Supporting Information), the α-hydroxyl and the P=O bond are in an *anti*-periplanar position in the cross conformation of **4** and **6** because of the existence of intermolecular hydrogen bonds. As for **4** generated from acetophenones, the stabilities of the two diastereomers are controlled by the repulsion between menthoxyl to aryl or methyl of the acetophenone moieties. For *para*-substituted acetophenones, it was observed that the isopropyl group of menthyl faced toward the plane of the benzene ring, and two methyl groups of isopropyl were oriented in the direction far toward benzene ring. In this manner, the spatial interaction between isopropyl and aryl might be reduced (Figure 1). For *meta*-substituted acetophenones, the increased volume of the aryl group resulted in strong repulsion toward methoxyl and poor selectivities for the formation of **4**. In some cases, **4′** was formed as major diastereomer (Table 1, entry 7). The *ortho*-substituted aryls have larger volumes, and the reaction of the corresponding acetophenones cannot occur under typical conditions in Table 1. In these cases, only **5** was formed by means of Phospha–Brook rearrangement at elevated temperature (Scheme 2). Density functional calculations of **4b**/**4b′** and **4g**/**4g′** showed that **4b** and **4g′** have lower energy than their associated diastereomers, respectively, which was consistent with the results in Table 1 (as shown in the Supporting Information).

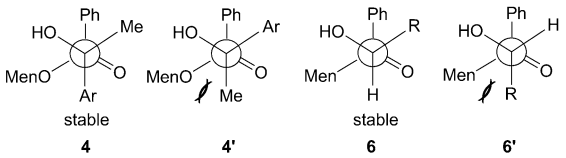


Figure 1. Supposed conformation of **4**/**4′** and **6**/**6′**.

Similarly, the menthyl close to R also resulted in the instability of **6′**. The better diastereoselectivity for the reaction of **1b** to **3** over **1a** to **2** could be ascribed to the fact that the stereogenic phosphorus atom in **1b** is more bulky than that in **1a**, which could also explain the poor selectivity for the

addition of **1a** to **2** and the poor reactivity for the addition of **1b** to **3**.

After our work was completed, we noticed that Couzijn and Minnaard et al. reported the addition of P-stereogenic *tert*-butylphenylphosphine oxide to aldehydes in the presence of base, diastereoselectively affording α-hydroxyphosphine oxides in >20:1 d.r.[17] Their work confirmed the reversible equilibrium of the addition and revealed the conversion of less stable diastereomers to more stable ones by undertaking the reaction at 50 or 80 °C. Our results in Table 2 and Scheme 2 showed that elevated temperatures can lead to side reactions such as Phospha–Brook rearrangement or racemization of P–H species, which might be used to explain the higher yields and diasteromeric ratio in our addition of **1b** to **3** at room temperature.

Conclusion

In summary, base-catalyzed addition of **1** to aldehydes or ketones was a stability-controlled diastereoselective reaction. The less stable diastereomers of the adduct can be converted to more stable ones by means of reversible equilibrium and prolonged reaction time. Although thermodynamically controlled diastereoselective reactions are widely applied in asymmetric synthesis, the similar P-involving reaction that utilizes a reversible equilibrium is, to the best of our knowledge, quite rare. Our research supplied a convenient and useful method for the simultaneous formation of both phosphorus and carbon chiral centers.

Experimental Section

*Typical Procedure for Preparation of α-Hydroxyphosphinates **4** by Means of Addition of **1a** to Ketones **3***

Ketone **3** (0.368 mmol) and potassium carbonate (0.013 g, 0.092 mmol) were added in turn to a solution of R_P-(−)menthyl phenylphosphinate **1a** (0.103 g, 0.368 mmol) in DMSO (1 mL). The mixture was stirred at room temperature for 24 to 100 h, and the reaction was monitored with ^{31}P NMR spectroscopy (≈0.1 mL suspension of reaction mixture dissolved in 0.5 mL chloroform). After the reaction finished, water (2 mL) was added to the mixture, and the solid was filtered and dried in air. The crude product was recrystallized with CH_2Cl_2/petroleum ether (PE) to afford pure **4**.

*(S)-(−)-Menthyl [(R)-1-(4-bromophenyl)-1-hydroxyethyl]phenylphosphinate (**4b**)*

Compound **4b** was obtained as a white solid (0.126 g, yield: 74%). M.p. 176.2–177.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (dd, J = 16.1, 8.1 Hz, 3H), 7.39 (d, J = 8.4 Hz, 2H), 7.31 (t, J = 9.8 Hz, 4H), 4.40–4.16 (m, 1H), 3.78 (br, 1H), 2.05–1.84 (m, 1H), 1.77 (d, J = 14.1 Hz, 3H), 1.76–1.55 (m, Hz, 4H), 1.35 (t, J = 11.5 Hz, 1H), 1.21 (br, 1H), 1.04–0.82 (m, 5H), 0.82–0.57 ppm (m, 6H); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 38.31 ppm (s); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 140.56 (s), 133.70 (d, J = 8.3 Hz), 132.43 (s), 130.96 (s), 129.86 (s), 128.23 (s), 127.88 (d, J = 11.8 Hz), 121.56 (s), 78.04 (d, J = 7.7 Hz), 75.48 (s), 74.35 (s), 49.11 (d, J = 4.5 Hz), 43.27 (s), 34.16 (s), 31.65 (s), 25.48 (s), 24.91 (s), 22.74 (s), 22.02 (s), 21.31 (s), 15.42 ppm (s); elemental analysis calcd (%) for $C_{24}H_{32}O_3PBr$: C 60.13, H 6.73; found: C 60.02, H 6.81.

*Typical Procedure for Preparation of α-Hydroxyphosphine Oxides 6 by Means of Addition of **1b** to Aldehydes **2***

Aldehydes **2** (0.38 mmol) and calcium hydroxide (7.6 mg, 0.10 mmol) were added in turn to a solution of R_P-(−)menthylphenylphosphine oxide **1b** (0.1 g, 0.38 mmol) in DMF (0.5 mL) (method A; for method B, the same molar amount of potassium hydroxide was used in the same volume of DMSO). The mixture was stirred at room temperature for about 24 h, and the reaction was monitored with ^{31}P NMR spectroscopy (≈0.1 mL suspension of reaction mixture dissolved in chloroform (0.4 mL)). After the reaction finished, acetic acid (0.1 mL) was added to the mixture, followed by the addition of methanol (3 mL). The mixture was filtered through silica gel and concentrated under vacuum. The residue was purified by recrystallization with MeOH/Et_2O to afford pure **6**.

*(R_P)-(−)-Menthyl[(S)-hydroxy(phenyl)methyl]phenylphosphine oxide (**6a**)*

Compound **6a** was obtained from method A as white solid (139 mg, yield: 80%). M.p. 133.5–135 °C. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 41.12 ppm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.46 (m, 2H), 7.40 (t, J = 7.5 Hz, 1H), 7.27 (d, J = 9.7 Hz, 3H), 7.10 (dt, J = 14.1, 6.8 Hz, 3H), 6.92 (d, J = 7.4 Hz, 2H), 5.35 (dd, J = 10.4, 3.8 Hz, 1H), 3.08 (td, J = 22.2 Hz, 1H), 2.39 (s, 2H), 1.73 (s, 1H), 1.64–1.37 (m, 2H), 1.37–1.15 (m, 3H), 1.14–0.93 (m, 2H), 0.93–0.81 (m, 3H), 0.72 (d, J = 6.7 Hz, 3H), 0.24 ppm (d, J = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.20, 131.90–131.00 (m), 128.38–127.37 (m), 127.10 (d, J = 3.9 Hz), 71.15 (d, J = 84.1 Hz), 43.20 (d, J = 3.9 Hz), 37.68 (dd, J = 64.1, 8.1 Hz), 34.36 (d, J = 34.9 Hz), 33.42 (d, J = 13.1 Hz), 28.21 (d, J = 3.2 Hz), 24.88 (d, J = 11.9 Hz), 22.91, 21.63, 15.37 ppm; elemental analysis calcd (%) for $C_{23}H_{31}O_2P$: C 74.57, H 8.43; found: C 74.39, H 8.41.

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