Heterogeneous Palladium-Catalysed Heck Reaction of Aryl Chlorides and Styrene in Water Under Mild Conditions

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Received: October 30, 2001; Accepted: February 14, 2002

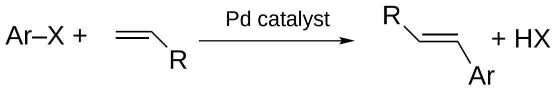
Abstract: The Heck reaction of chlorobenzene and substituted chlorobenzenes with styrene is performed in water using catalytic palladium on carbon. The presence of a reducing agent, a mild base, and a phase-transfer catalyst enhances the reactivity of chloroarenes. Transfer hydrogenation of the stilbene double bond to yield 1,2-diphenylethane is also observed *in situ*. The competing reactions in this system are haloaryl homocoupling and hydrodehalogenation. The effects of various process parameters on substrate conversion and product selectivity are examined for PhCl and PhBr and the unique role of the reducing agent is discussed. A series of filtration experiments indicate that, in this system, the catalysis is heterogeneous and not due to palladium leaching.

Keywords: carbon-carbon; chlorobenzene; formate; hydrogenation; palladium leaching; reductive coupling

Introduction

The Heck reaction[1] is essentially a palladium-catalysed cross-coupling of an aryl halide with an olefin (Scheme 1). In the past three decades, it has become one of the most useful protocols for the formation of carbon-carbon bonds, owing to its broad functional group tolerance.[2] The robustness of this reaction is reflected in its application in several low-tonnage industrial syntheses, e.g., in the production of the non-steroidal anti-inflammatory drug Naproxen™ (500 ton/y).[3] This is not trivial, for although the advantages of catalytic reactions may appear obvious to research chemists in the field of catalysis, few catalytic syntheses are deemed economically viable for the fine chemical and pharmaceutical industries.

The reaction is usually performed using an aryl (or alkenyl) iodide or bromide with a slight excess of the desired alkene and a base in the presence of a homogeneous palladium catalyst, generating an "arylpalladium" reagent *in situ*.[4,5] Economic and environmental incentives, however, are driving forth the search for an active catalytic system for Heck reactions using *chloroarenes* (chlorides are cheaper and more readily available than bromides and iodides, and incur lower E factors,[6] but these advantages are unfortunately offset by their lower chemical reactivity which reflects the higher C-Cl bond energy values[7]). In a recent example, Littke and Fu have shown that P(*t*-Bu)$_3$ is a remarkably effective ligand in some homogeneous Heck-type reactions of aryl chlorides.[8]



Scheme 1.

Heck reactions are most frequently performed in dipolar aprotic organic solvents such as DMF, DMSO, MeCN, and *N*-methylpyrrolidone (NMP). The use of water in these systems is rare, in part owing to the hydrophobic structure of the homogeneous catalysts. To overcome this, the application of water-soluble ligands, high temperature and pressure conditions[9a] (*ca.* 200 °C at 100 bar pressure) as well as ionic liquids as solvent media[9b] have been reported. With the growing interest in the application of heterogeneous catalysts in fine-chemical synthesis,[10] much effort has been invested in the immobilisation of active palladium complexes on various supports and in the application of ligandless supported palladium as a catalyst for Heck processes.[11,12] Although these heterogeneous Pd catalysts have also been studied in organic solvents, it seems reasonable that an appropriate reaction system could be constructed for heterogeneous Heck reactions in water. Ideally, this system would combine the advantages of facile catalyst recycling and ligand-free Heck catalysis with the obvious environmental benefits of using water instead of dipolar aprotic organic solvents.

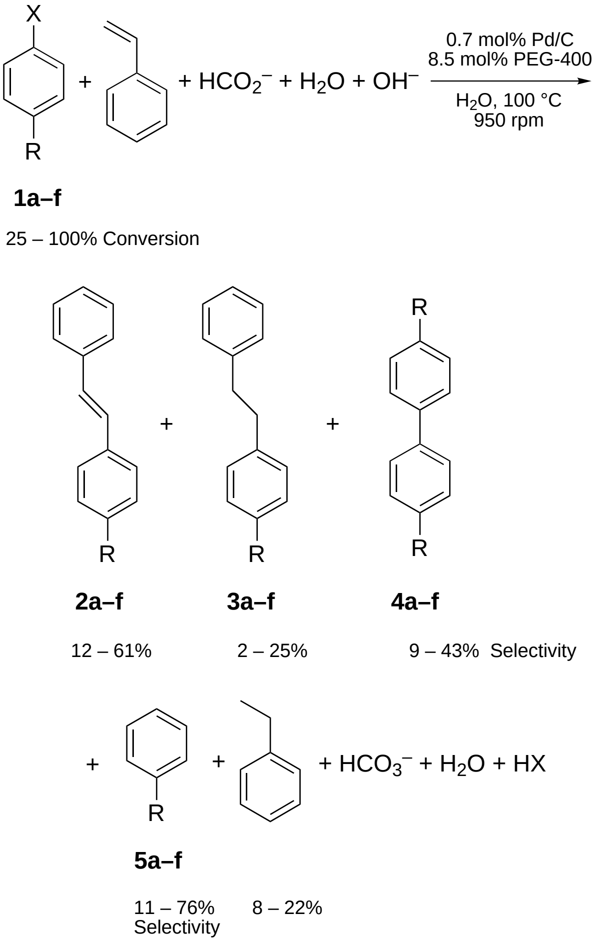
As part of our investigations into heterogeneous palladium-catalysed coupling reactions of haloarenes (and especially aryl chlorides) in water,[13] we examined the possibility of performing Heck reactions under the conditions for reductive aryl-aryl coupling. In this paper, we report the results of the reactions of aryl chlorides, bromides and iodides catalysed by Pd/C in the presence of a reducing agent, and discuss the feasibility of heterogeneous Heck reactions under reductive conditions in water.[14]

Results and Discussion

In a typical reaction (Scheme 2), equimolar amounts of haloarene **1** and styrene, 1.4 equivalents of base, 1.6 equivalents of sodium formate, and catalytic amounts of poly(ethylene glycol) 400 (PEG-400) and Pd/C catalyst were charged to an autoclave with water (the total reaction volume was 50 mL). The autoclave was heated to 100 °C and the reaction was monitored by GC for 5.5 h. In addition to the expected Heck product **2** we observed hydrogenation of the double bond **2** → **3** and also some hydrogenation of styrene to ethylbenzene,[15] plus the respective homocoupling and hydrodehalogenation products **4** and **5**. With the exception of 1 – 2% of 1,1-diphenylethylene, no other products were observed. Conversions and product selectivities for various substrates are shown in Table 1. Substituting methyl methacrylate for styrene we observed a high conversion of PhCl (> 95%), but **4** and **5**, and a tarry polymeric material (presumably PMMA) were the only products. Similarly, only traces of the Heck product **2** were observed when the Pd/C catalyst was substituted with commercial Pd/zeolite and Pd/Al_2O_3.

The presence of the reducing agent, sodium formate, was apparently the key to the unusual activity of PhCl and the substituted chloroarenes in this system. To study this reaction further we examined two model substrates: PhBr **1d**, which is a common substrate in heterogeneous Heck reactions (Table 2), and PhCl **1a**, which is usually unreactive (Table 3). For comparison, we tested in the absence of formate, but otherwise under identical conditions (using NaOH as the base), the reactions of PhCl, PhBr, and PhI. Here, PhBr and PhI yielded similar results (27% and 40% conversion after 25 h, respectively, with quantitative selectivity to the Heck product) while no reaction at all was observed for PhCl.

Table 2 shows the conversion and selectivity for PhBr in the presence of formate under various conditions. In general, although high conversions were observed after a short reaction time (4 h), only moderate selectivities to the Heck products **2** and **3** were obtained, because of the strong competition from the homocoupling and reduction processes under these conditions. When compared to the regular Heck reaction, this protocol is therefore of little synthetic utility. However, these reactions may assist in the interpretation the unusual activity observed for the chloroarenes (*vide infra*).



1–5a: X = Cl, R = H.
1–5b: X = Cl, R = CH_3.
1–5c: X = Cl, R = OCH_3.
1–5d: X = Br, R = H.
1–5e: X = Br, R = OCH_3.
1–5f: X = I, R = H.

Scheme 2.

In the case of PhCl **1a**, the choice of base and phase-transfer catalyst (PTC) had a significant effect on product selectivity (Table 3). The best results were obtained using sodium carbonate, Na_2CO_3, which is a much milder base than NaOH. Indeed, the substituted chloroarenes (Table 1 above) yielded Heck products only in the presence of mild bases such as Na_2CO_3 or KF.[16]

Note the selective hydrogenation of the double bond, **2** → **3**. While the formate/water/palladium is a known hydrogenation system,[17] this, to our knowledge, is the first time that the reaction is achieved in a one-pot

Table 1. Reactions of haloarenes with styrene.[a]

Entry	Substrate **1**	Conversion [%][b]	Selectivity [%][b]			
			2	**3**	**4**	**5**
1	**1a**	60	19	5	44	31
2	**1a**[c]	80	60	< 5	25	11
3	**1a**[d]	63	44	–	30	25
4	**1b**	70	0	0	20	80
5	**1b**[c]	60	30	< 5	35	30
6	**1b**[e]	40	25	< 5	30	40
7	**1c**	48	0	0	9	91
8	**1d**[c]	50	32	< 5	40	18
9	**1d**[f]	100	32	6	40	18
10	**1e**	64	13	0	67	20
11	**1f**[c]	50	31	< 5	35	23
12	**1f**[g]	100	34	8	37	16

[a] Standard reaction conditions (unless noted otherwise): substrate, 44.0 mmol; styrene 44.0 mmol; HCOONa, 70.0 mmol; catalyst, 0.7 mol % of substrate (based on Pd content, e.g., if the catalyst contains 1 mol Pd then 140 mol substrate were used); PEG-400, 1.5 g (8.5 mol % of substrate); NaOH, 125 mmol; water (total reaction volume 50 mL); 950 rpm mechanical stirring for 5.5 h at 100 °C.

[b] Conversion and selectivity of the respective product ***n*a – f**, based on GC area, corrected by the presence of an internal standard for ArX, not including the separate hydrogenation of styrene to ethyl benzene (8 – 22%).

[c] 62.5 mmol Na_2CO_3 was used in place of NaOH.

[d] 70.0 mmol $Zn_{(s)}$ (powder, < 10 μm particle size) was used in place of HCOONa.

[e] 62.5 mmol KF was used in place of NaOH.

[f] 100% conversion after 4 h.

[g] 100% conversion after 2.5 h.

Table 2. Reactions of PhBr **1f** under reductive conditions.[a]

Entry	Parameter	Conversion [%][b]	Selectivity [%][b]			
			2d	**3d**	**4d**	**5d**
	NaOH [mmol]					
1	50	63	12	7	19	52
2	125	100	32	10	40	18
3	250	100	31	12	40	17
	t [°C]					
4	90	81	26	8	38	28
5	100	100	32	10	40	18
6	110	100	34	12	38	16
	Pd/C [mol %]					
7	0.5	77	28	7	30	35
8	0.7	100	32	10	40	18
9	1.0	100	34	8	42	16
	PEG-400 [mol %]					
10	2.5	93	27	16	35	22
11	5.0	100	28	14	38	20
12	8.5	100	32	10	40	18
13	10.0	100	26	9	33	32

[a] Standard reaction conditions: PhBr, 44.0 mmol; styrene 44.0 mmol; HCOONa, 70.0 mmol; catalyst, 0.7 mol % of substrate (based on Pd content, e.g., if the catalyst contains 1 mol Pd then 140 mol substrate were used); PEG-400, 1.5 g (8.5 mol % of substrate); NaOH, 125 mmol; water (total reaction volume 50 mL); 950 rpm mechanical stirring at 100 °C for 4 h.

[b] Based on GC area, corrected by the presence of an internal standard for PhBr, not including the separate hydrogenation of styrene to ethyl benzene (*ca.* 15%).

Table 3. Effects of base and PTC on the reactions of PhCl **1a**.[a]

Entry	Parameter	Time [h]	Conversion [%][b]	Selectivity [%][b]			
				2a	**3a**	**4a**	**5a**
	Base						
1	NaOH	5.5	60	19	5	43	32
2	Na_2CO_3	5.5	80	60	2	26	11
3	Cs_2CO_3	5.5	58	28	5	36	30
4	$NaHCO_3$	5.5	71	41	10	25	24
5	KF	5.5	92	38	tr	56	5
6	Triethanolamine	5.5	25	9	0	14	76
	PTC						
7	PEG-400	5.5	60	19	5	43	32
8	PEG-400[c]	5.5	80	60	2	26	11
9	PEG-400[c]	24.0	100	27	33	20	19
10	β-cyclodextrin	4.0	95	3	25	36	35
11	β-cyclodextrin[c]	5.5	56	20	20	26	33
12	β-cyclodextrin[c]	22.0	100	0	47	23	25
13	1:1 mixture[c, d]	24.0	93	33	20	24	20

[a] Standard reaction conditions (unless noted otherwise): substrate, 44.0 mmol; styrene, 44.0 mmol; HCOONa, 70.0 mmol; catalyst, 0.7 mol % of substrate (based on Pd content, e.g., if the catalyst contains 1 mol Pd then 140 mol substrate was used); PEG-400, 1.5 g (8.5 mol % of substrate); NaOH, 125 mmol; water (total reaction volume 50 mL); 950 rpm mechanical stirring at 100 °C.

[b] Based on GC area, corrected by the presence of an internal standard for PhCl, not including the separate hydrogenation of styrene to ethyl benzene (*ca.* 15%).

[c] 62.5 mmol Na_2CO_3 was used in place of NaOH.

[d] A 1:1 mol/mol mixture of PEG-400 and β-cyclodextrin was used.

process together with a Heck reaction. The fact that more hydrogenation was observed with β-cyclodextrin, regardless of the base used (*cf.* Table 3, entries 10 and 12) may be attributed to the ability of these phase-transfer reagents to effect inverse PTC in formate/palladium systems.[18]

The catalyst, the reducing agent, and the substrate are all mutually immiscible when water is used as a reaction medium (water is not really a "solvent" here). This means that mass-transfer may slow down the reaction, but it also means that once the Pd(0) catalyst has been regenerated (through reaction with formate and water) the chances of reaction, even for the inactive substituted chloroarenes, are high.

Because of the high TOF and TON values that are often observed with certain *homogeneous* palladium-catalysed Heck systems[19] there is a continuous debate about whether the heterogeneous Heck catalysts are truly heterogeneous or not (i.e., does palladium remain on the catalyst surface or does it leach into solution during the reaction when solid/liquid catalysis is employed?). Recent research attributed the catalytic activity of some "heterogeneous" palladium catalysts to Pd(II) ions leached from the surface of alumina and ion-exchange resins into DMA,[20] and the leaching and redeposition of supported palladium from carbon and silica supports into NMP has also been investigated.[21] In this respect it was essential to study the possible effects of leaching in our formate/water/Pd/C system prior to any claim of heterogeneous catalysis. Filtration of the solid catalyst is an effective method for this, provided that other reaction parameters are unchanged and that the filtration is performed after a significant amount of time has passed (immediate filtration can sometimes give misleading results as the leaching process can be slow).[22] A series of filtration experiments was performed in which the solid catalyst was filtered off at various conversions and at different temperatures. All of these experiments indicated that the Pd/C alone is responsible for the catalysis. One such reaction profile is shown for example in Figure 1, wherein after 4 h of reaction the solid catalyst was hot-filtered and the reaction was monitored for a further 2 h. When it was clear that no reaction takes place in the absence of the solid catalyst, the very same catalyst batch was added back to the reaction, and the reaction resumed, showing that a significant amount of substrate and formate (the reducing agent) remained. Note that some formate [and probably some dihydrogen generated from the reaction $HCO_2^- + H_2O \rightarrow HCO_3^- + H_2$ in the presence of Pd/C[23]] was lost during the filtration process, but the catalyst retained its activity as shown when a fresh batch of formate was added at t = 10 h.

Yet another issue that we had to resolve was the "release and capture" of the palladium catalyst into solution under these conditions. Thus, it can be envisaged that Pd(II) that has been leached into the solution undergoes reduction and aggregates as palladium black

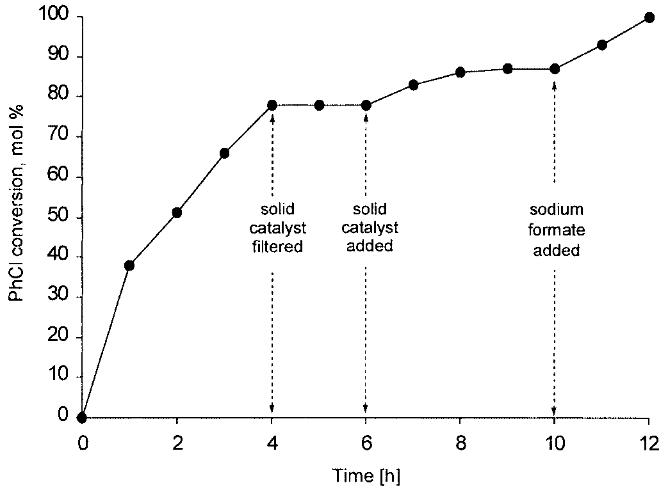


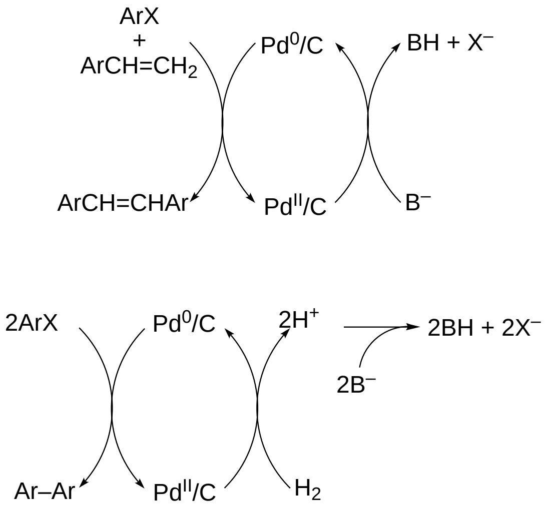
Figure 1. Profile for the Heck reaction of chlorobenzene **1a** with styrene in water. Reaction conditions: 5% Pd/C (0.7 mol % relative to PhCl), $NaHCO_2$ (160 mol %), Na_2CO_3 (140 mol %), PEG-400 (8.5 mol %), water (50 mL total reaction volume), 950 rpm mechanical stirring at 100 °C in an autoclave (the autogeneous pressure was 1 – 1.5 atm).

under our reaction conditions. A control experiment using 0.7 mol % of $Pd(OAc)_2$ showed 9.3% conversion after 1 h and 16% conversion after 8 h, ruling out fast precipitation of Pd(II) under these conditions.

In another control experiment we used zinc powder to regenerate the Pd(0) catalyst (using the dihydrogen generated *in situ* through the reaction $Zn_{(s)} + H_2O_{(l)} \rightarrow ZnO_{(s)} + H_{2(g)}$ that is also catalysed by Pd/C).[24] As shown in Table 1, entry 3, the selectivity and conversion were similar to experiments using formate, indicating that catalyst regeneration is probably *via* the reaction of dihydrogen with supported Pd(II)/C.

The above evidence supports the claim of a heterogeneous Heck reaction in this case. Indeed, the use of water (as opposed to DMA or NMP in the systems where leaching was observed, *cf.* Refs.[20,21]) probably promotes the stability of the heterogeneous catalyst, as the extraction of possible Ar–Pd(II)–X species into water would not be favoured.

The reactions of PhBr and PhI with styrene in the absence of formate (*vide supra*) may provide some insight into the workings of this system. It is not surprising that no coupling or reduction was observed (there is less than 1 mol % Pd^0 present, and it would be all oxidised to Pd^{2+} after 1 cycle of hydrodehalogenation or C-C coupling). Note, however, that significant conversions (27% of PhBr and 40% of PhI) are observed, and selectivity to the Heck product is high. Thus, we can infer that in the presence of styrene there is a competition between the Heck coupling (for which a base is sufficient to regenerate the catalyst which stays as Pd^0 at the end of the cycle, see Scheme 3, top) and the Ullmann-type coupling (which requires regeneration of the palladium catalyst using an electron source, e.g., dihydrogen from formate + water; Scheme 3, bottom). For X = Cl, $k_{\mathrm{Heck}} \ll k_{\mathrm{coupling}}$ so that in the absence of a reducing agent the catalytic cycle terminates as all of the Pd^0 is oxidised to Pd^{2+}. When formate is introduced, the number of Pd^0 sites remains sufficiently high so that Heck coupling can also occur.



Scheme 3. Simplified representation of the heterogeneous Heck reaction (top) that does not require an additional reducing agent for ArBr/I, and the Ullmann-type coupling (bottom) that yields supported $Pd^{II}(X^-)_2$ at the end of the catalytic cycle and therefore requires a stoichiometric reducing agent (in this case dihydrogen that is obtained in the catalytic reaction of water and formate in the presence of Pd^0/C).

For X = Br and X = I, on the other hand, it appears that $k_{\mathrm{Heck}} \sim k_{\mathrm{coupling}}$, so that the catalyst remains long enough in the Pd^0 state to effect 40 – 70 turnovers (depending on reaction conditions) even in the absence of formate. However, when formate is added to the system there are, in addition to the Pd^{2+} and Pd^0 sites, also $Pd(H^-)_2$ sites,[13b] and these may enhance the transfer of electrons to coordinated ArX molecules, so that more coordinations of ArX to the catalyst result in reaction (i.e., higher conversion, typically 4 – 5.5 h for 80–100% conversion, see Tables 2 and 3) but with lower selectivity.

Conclusion

In conclusion, we have shown here that under the proper reductive conditions and with the use of a mild base it is possible to perform Heck reactions in water with chlorobenzene and substituted chloroarenes in a heterogeneous, ligand-less system at moderate temperatures.

Experimental Section

General Remarks

Atomic absorption (AA) analysis of palladium was performed on an GBC 903 instrument at 247.6 nm with a slit width of 0.7 mm. ICP analysis was performed on a Spectroflame Modula instrument. Calibration was performed with standard palladium solution samples. Other experimental apparatus and analysis methods have been described in detail previously.[25]

General Procedure for Heterogeneous Heck Coupling

As example, *trans*-stilbene from PhCl and styrene: 44 mmol C_6H_5Cl, 44 mmol styrene, 70 mmol $NaHCO_2$, 62.5 mmol Na_2CO_3, 0.3 mmol of 5% Pd/C (0.7 mol % relative to PhCl), and 1.5 g PEG-400 (8.5 mol % relative to PhCl) were mixed (950 rpm) in water (50 mL total reaction volume) at 100 °C in an autoclave. Reaction progress was monitored by GC for 5.5 h. The mixture was cooled and filtered to remove Pd/C. Extraction of the organic mass was performed with CH_2Cl_2.

The experiment with homogeneous palladium acetate was carried out similarly except that 0.7 mol % palladium [as $Pd(OAc)_2$] was used instead of Pd/C. Conversion and selectivity: (1 h) 9% conversion, 52% PhH, 20% Ph–Ph, 27% PhCH=CHPh; (8 h) 16% conversion, 54% PhH, 23% Ph–Ph; 23% PhCH=CHPh.

Procedure for Hot Catalyst Filtration

The stirring was stopped at a predetermined time and the hot reaction mixture (80 – 90 °C) was filtered through a G3 filter (20 – 40 μm) that was preheated and kept hot using a laboratory hot-air blower. The solid material was then washed with water (3 × 15 mL) and CH_2Cl_2 (3 × 15 mL). Analysis of the aqueous phase using AA showed only 4 ppm palladium. This aqueous phase was then re-filtered through a new G3 filter to make sure that the catalyst does not leach and then remain on the filter. A second AA analysis showed 3 ppm palladium. ICP analysis of the organic phase showed the palladium concentration to be below the detection limit (10 ppb).

Acknowledgements

We thank Dr. Gino P. F. van Strijdonck (Universiteit van Amsterdam) for discussions on the Heck reaction mechanism.

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[15] This background reaction which accounts for 8 – 22% of the styrene conversion (depending on reaction conditions, see Tables 1 – 3) is discounted in the following discussion that is based in all cases on ArX conversion and selectivity.

[16] Note that the increase in the amount of the Heck product **2** was concurrent with a decrease in the hydrodehalogenation product **5**. In the presence of a milder base it may be that less HCl is scavenged off the catalyst, shifting the balance between the coupling, hydrodehalogenation, and Heck reactions (cf. Ref.[7a]). For a discussion on the respective role of adsorbed HCl and H_2 on the Pd surface, see: S. Mukhopadhyay, G. Rothenberg, D.

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