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Palladium-Catalyzed Ring-Forming Alkene Aminoaroylation of Unsaturated Hydrazones and Sulfonamides

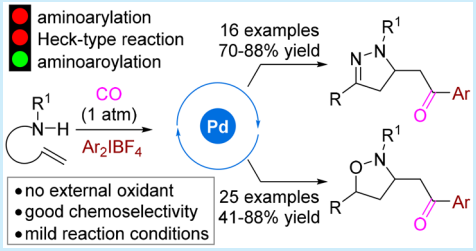
Jun Chen,[†,§] Meng-Nan Yang,[†,§] Jia-Rong Chen,[*,†] and Wen-Jing Xiao[†,‡]

[†]CCNU-uOttawa Joint Research Centre, Hubei International Scientific and Technological Cooperation Base of Pesticide and Green Synthesis, Key Laboratory of Pesticides & Chemical Biology Ministry of Education, College of Chemistry, Central China Normal University, 152 Luoyu Road, Wuhan, Hubei 430079, China

[‡]State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, 345 Lingling Road, Shanghai 200032, China

Supporting Information

ABSTRACT: The first example of a $Pd(OAc)_2$-catalyzed ring-forming alkene aminoaroylation of unsaturated hydrazones and sulfonamides is described. This protocol features the use of diaryliodonium salts as both oxidants and aryl sources, thus enabling mild reaction conditions, good chemoselectivity, a broad substrate scope, and high functional group tolerance. A wide range of synthetically and biologically important functionalized dihydropyrazoles and isoxazolidines have been obtained in good yields.



Over the past decade, palladium-catalyzed ring-forming alkene aminofunctionalizations have been established as a reliable and powerful synthetic tool for construction of a variety of nitrogen heterocycles.[1,2] Most of these reactions involve the coupling between nucleophilic nitrogen-containg alkenes, and aryl or alkenyl halides based on Pd^0/Pd^{II} catalysis. Extensive mechanistic studies have also revealed that nearly all of these processes proceed through Pd^{II}-promoted C−N bond forming aminopalladation as the key step. A series of amides, carbamates, and sulfonamides have proven to be suitable nucleophilic nitrogen sources. Despite tremendous advances and their advantages, however, a strong stoichiometric base or high temperature is typically required to achieve satisfactory reaction efficiency. Thus, development of more general, efficient, and mild ring-forming alkene aminofunctionalization with readily available starting materials to access diversely substituted nitrogen heterocycles is still highly desirable.

In contrast to Pd^0/Pd^{II} catalysis, the Pd^{II}/Pd^{IV} catalysis has recently emerged as a new potentially powerful activation mode to develop novel transformations; the unique reactivity of the Pd^{IV} intermediates enables a wide substrate scope, high functional group tolerance, and mild reaction conditions.[3] For example, the groups of Muniz[4] and Sorensen[5] independently disclosed the first Pd-catalyzed oxidative diamination of sulfonamides and aminoacetoxylation of *N*-tosyl carbamates, respectively; in these processes, $PhI(OAc)_2$ serves as an oxidant or as both an oxidant and a source of acetate (Scheme 1a). Inspired by these pioneering works and the inherent properties of diaryliodonium salts,[6] we have also recently developed a general and mild $Pd(TFA)_2$-catalyzed aminoarylation reaction of *β*,*γ*-unsaturated hydrazones using diaryliodonium salts, leading to a practical access to diversely substituted dihydropyrazoles (Scheme 1b).[7] Mechanistically, we postulate that the overall sequence to be aminopalladation and metal oxidation, followed by aryl-nitrogen bond formation from the Pd^{IV} intermediate; diaryliodonium salts work as external oxidants and aryl sources. Notably, the competing *β*-H elimination from the initially formed alkyl Pd^{II} complex was overriden by its oxidation to Pd^{IV} species. On the basis of this mechanistic scenario, we are proposing to alter the outcome of the subsequent reaction profile of the initially formed alkyl Pd^{II} complex by incorporation of CO-based carbonylation using unsaturated hydrazones and sulfonamides as substrates.[8] The achievement of this reaction mode would enable ring-forming alkene aminoaroylation of unsaturated hydrazones and sulfonamides,[9] thus providing a useful approach to benzoyl-substituted dihydropyrazoles and isoxazolidines (Scheme 1c).[10] To the best of our knowledge, such a transformation is still unknown. However, several challenges might be encountered, such as the direct aminoarylation reaction previously developed by us and an aza-Heck-type reaction. Herein, we wish to report a successful introduction of a strategy of Pd^{II}/Pd^{IV} catalysis for a ring-forming alkene aminoaroylation reaction.

On the basis of our recently reported Pd-catalyzed aminoarylation,[7] we examined the feasibility of the target alkene aminoaroylation of *β*,*γ*-unsaturated hydrazone **1a** with diphenyliodonium tetrafluoroborate **2a** under 1 atm of CO at room temperature. Gratifyingly, using the combination of $Pd(TFA)_2$ (10 mol %) and PPh_3 (20 mol %) as the catalyst in the presence of ^{i}PrNEt as a base, the desired reaction indeed worked to give the aminoaroylation product **3aa** in 48% yield (Table 1, entry 1). The product **3aa** was also confirmed by

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Scheme 1. Pd^{II}/Pd^{IV}-Catalyzed Oxidative Cyclization and New Reaction Design

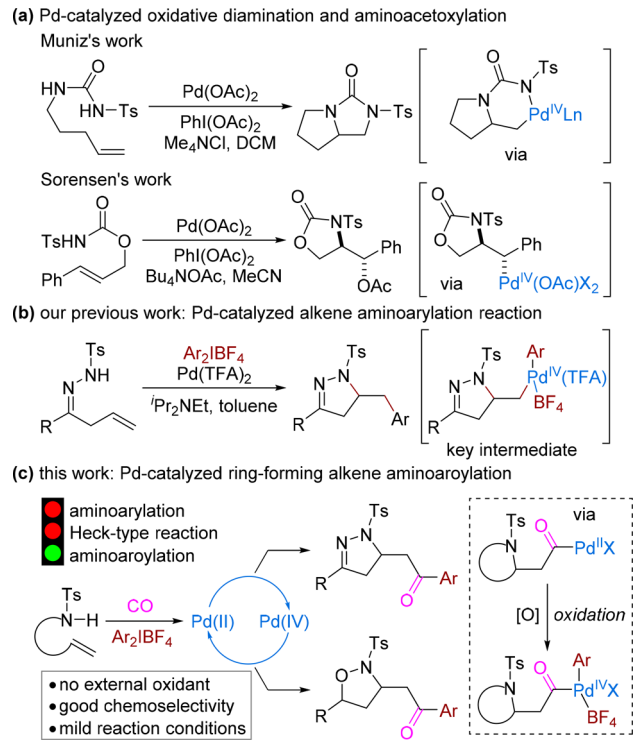
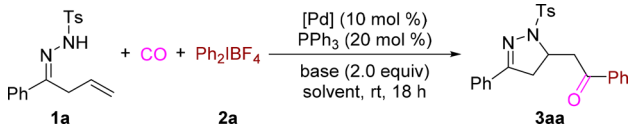


Table 1. Condition Optimization[a]



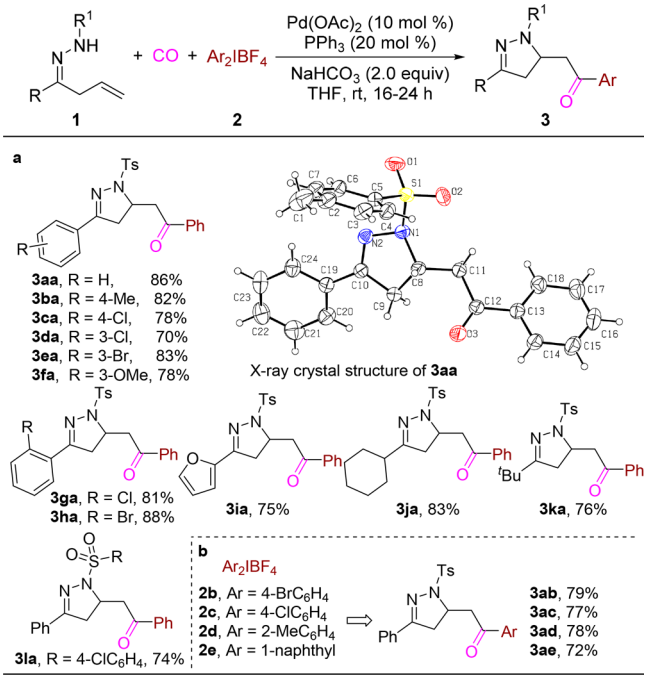
entry	[Pd]	solvent	base	yield (%)[b]
1	$Pd(TFA)_2$	toluene	$^iPr_2NEt$	48
2	$Pd(OAc)_2$	toluene	$^iPr_2NEt$	64
3	$Pd(acac)_2$	toluene	$^iPr_2NEt$	46
4	$Pd(BF_4)_2(MeCN)_4$	toluene	$^iPr_2NEt$	33
5	$PdCl_2(PhCN)_2$	toluene	$^iPr_2NEt$	35
6	$PdCl_2$	toluene	$^iPr_2NEt$	38
7	$Pd(PPh_3)_4$	toluene	$^iPr_2NEt$	47
8	$Pd(OAc)_2$	THF	$^iPr_2NEt$	75
9	**$Pd(OAc)_2$**	**THF**	**$NaHCO_3$**	**86**
10	$Pd(OAc)_2$	THF	Na_2CO_3	76[c]
11	$Pd(OAc)_2$	THF	Cs_2CO_3	60[c]
12	$Pd(OAc)_2$	THF	Et_3N	63[c]
13[d]	$Pd(OAc)_2$	THF	$NaHCO_3$	90[c]

[a]Reaction conditions: **1a** (0.10 mmol), **2a** (0.15 mmol), CO (1 atm), palladium catalyst (10 mol %), PPh_3 (20 mol %), and base (0.20 mmol) in 2.0 mL of solvent at rt for 18 h. [b]Isolated yields. [c]NMR yields, determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [d]With 2 mol % catalyst loading.

single crystal X-ray crystallographic analysis (shown in Scheme 2; CCDC 1837102). Then, we continued to examine a series of commonly used Pd(II) and Pd(0) salts to further improve the yield. It was found that all of these palladium salts proved to be suitable for the reaction, though with variable yields (entries 2–7), and $Pd(OAc)_2$ was indentified to be optimal, giving a 64% yield of **3aa** (entry 2).[11] A brief screening of solvents revealed that use of THF resulted in the reaction being more efficient, producing **3aa** in 75% yield (entry 8). In agreement with our previous study,[7] the bases also have an obvious effect on the current reaction, when using $Pd(OAc)_2/PPh_3$ as the catalyst. Compared to the bases such as $^iPr_2NEt$, Na_2CO_3, Cs_2CO_3, and Et_3N, $NaHCO_3$ proved to be the best, increasing the yield of **3aa** from 75% to 86% (entry 9 vs entries 8 and 10–12). Notably, with 2 mol % of catalyst loading, the reaction also proceeded smoothly with a good NMR yield (entry 13).

With the optimal reaction conditions in hand, we first explored the substrate scope by reacting a range of *β,γ*-unsaturated hydrazones **1** with **2a** under 1 atm of CO on a 0.2 mmol scale (Scheme 2a). As for the aryl-substituted

Scheme 2. Substrate Scope of Pd-Catalyzed Ring-Forming Aminoaroylation of Unsaturated Hydrazones[a,b]



[a]Reaction conditions: **1** (0.20 mmol), **2** (0.30 mmol), CO (1 atm), $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), and $NaHCO_3$ (0.40 mmol) in 4.0 mL of THF at rt for 16–24 h. [b]Isolated yields.

hydrazones, it was found that variation of the electronic or steric properties of the subsituents on the phenyl ring has no obvious effect on the reaction. Along with **1a**, hydrazone substrates **1b–1h** with an electron-donating (e.g., Me, MeO) or electron-withdrawing (e.g., Cl, Br) group at the *para*-, *meta*-, or *ortho*-positions of the phenyl ring participated in the reaction smoothly. The corresponding products **3ba–3ha** were isolated in 70–88% yields. Furthermore, the reaction with 2-furyl-substituted hydrazone **1i** also worked well to give the expected product **3ia** in 75% yield. Once again, cyclic and linear aliphatic hydrazones, such as **1j** and **1k**, reacted well to furnish **3ja** and **3ka** in 83% and 76% yields, respectively. As demonstrated in the synthesis of **3la**, variation of the withdrawing Ts group is also viable with a good yield.

Then, we attempted to extend the current catalytic system to a representative set of readily avaible symmetric diaryliodonium salts **2b–2e** by reacting with **1a** (Scheme 2b). Again, diaryliodonium salts **2b–2d** bearing functional groups such as Br, Cl, and Me at the *para*- or *ortho*-positions of the phenyl ring

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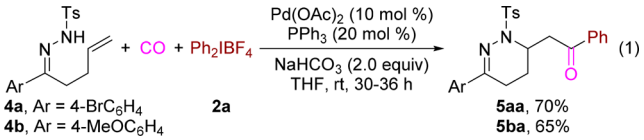
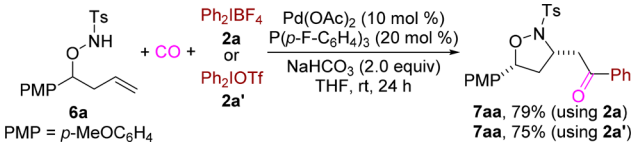
were all well tolerated, affording products **3ab**–**3ad** in good yields (77–79%). The current catalytic system also proved to be suitable for 1-naphthyl-substituted substrate **2e**, leading to formation of product **3ae** in 72% yield.

Interestingly, when reacting γ,δ-unsaturated hydrazones such as **4a** and **4b** with diphenyliodonium tetrafluoroborate **2a**, synthetically and biologically important tetrahydropyridazines **5aa** and **5ba**, formed in a 6-*endo* cyclization/aroylation fashion, were obtained in 70% and 65% yields, respectively (eq 1). This result also highlights the synthetic potential of the current protocol.



As a continuation of our ongoing research for the synthesis of structurally diverse isoxazolidines,[9] we then attempt to expand the Pd-catalyzed alkene aminoaroylation strategy to include unsaturated sulfonamides. The reaction would provide a complementary method for incorporation of a benzoyl group into the isoxazolidine scaffold. After an extensive condition optimization,[11] we finally established that a combination of $Pd(OAc)_2$ and tris(4-fluorophenyl)phosphane allowed the model reaction between *N*-sulfonyl-*O*-butenyl hydroxylamine **6a** to proceed smoothly under the same conditions (Scheme 3). The desired product 3,5-*cis* **7aa** was obtained exclusively in

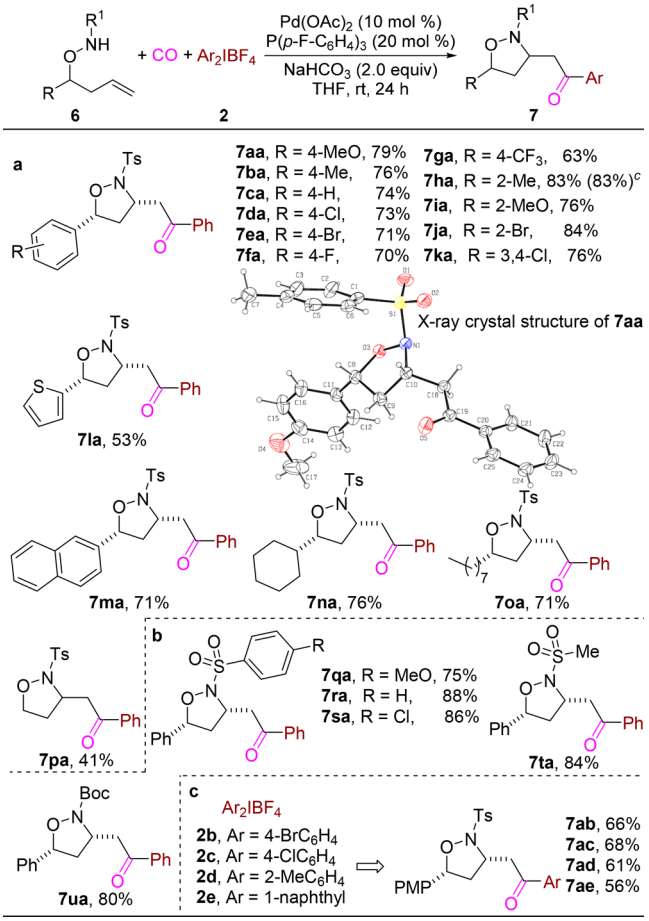
Scheme 3. Pd-Catalyzed Ring-Forming Aminoaroylation of Unsaturated Sulfonamide 6a



79% yield (CCDC 1837103). As demonstrated in the reaction of **6a** and **2a**′, the diaryliodonium salt with other counteranions could also be well tolerated, with **7aa** being formed in comparable yield.

Next, we continued to investigate the generality and limitation of the method by applying the standard conditions to a range of unsaturated sulfonamides. As summarized in Scheme 4, the catalytic system also demonstrated a broad substrate scope and high functional group tolerance regarding the unsaturated sulfonamides. In addition to **6a**, the reactions of substrates **6b**–**6g** bearing an electron-rich, neutral, or electron-poor phenyl ring all worked well; substituents such as MeO, Cl, Br, F, and CF_3 were all well tolerated, giving products **7ba**–**7ga** in 63%–76% yields. Moreover, as shown in the cases of **6h**–**6k**, the substitution pattern of the aryl moiety has no obvious effect on the reaction, and products **7ha**–**7ka** were obtained in 76–84% yields. Notably, the present catalytic system could also maintain its efficiency when applied on a synthetically useful scale (1.0 mmol), resulting in the formation of **7ha** with a comparable yield. Moreover, 2-thienyl- and 2-naphthyl-substituted substrates **6l** and **6m** reacted well to furnish the corresponding products **7la** and **7ma** in good yields. Once again, as shown in the synthesis of isoxazolidines **7na** and **7oa**, the current reaction could be extended to those substrates containing a cyclic or linear aliphatic moiety. Simple substrate

Scheme 4. Substrate Scope of Pd-Catalyzed Ring-Forming Aminoaroylation of Unsaturated Sulfonamides[a,b]



[a]Reaction conditions: **6** (0.20 mmol), **2** (0.30 mmol), CO (1 atm), $Pd(OAc)_2$ (10 mol %), $P(p\text{-}FC_6H_4)_3$ (20 mol %), and $NaHCO_3$ (0.40 mmol) in 4.0 mL of THF at rt for 24 h. [b]Isolated yields. [c]1.0 mmol scale.

6p also proved to be suitable for the reaction, though with only a moderate yield. Remarkably, switching the tosyl group to its analogue such as those in substrates **6q**–**6s**, or a methanesulfonyl group (e.g., **6t**), could also allow formation of the expected products **7qa**–**7ta** in high yields. Interestingly, substrate **6u** with an easily removable Boc group participated in the reaction smoothly as well with product **7ua** isolated in 80% yield. Finally, it was also found that all of the diaryliodonium salts **2b**–**2e** reacted well with unsaturated sulfonamide **6a**, and the corresponding products **7ab**–**7ae** were afforded in 56–68% yields. In accordance with our previously reported radical alkene hydroamination of unsaturated sulfonamides,[9] all of these 3,5-disubstituted isoxazolidines were formed as a single diastereomer, probably due to the steric effect involved in the ring-forming aminopalladation process.[1]

To further demonstrate the synthetic potential of the method, we subjected the enantiopure unsaturated sulfonamide (*R*)-**6a** to the standard conditions (eq 2). The reaction also proceeded smoothly to give chiral product **7aa** in 72% yield with >99% ee. This result confirms that the labile benzylic stereocenter in **6a** was not affected by the current reaction conditions.

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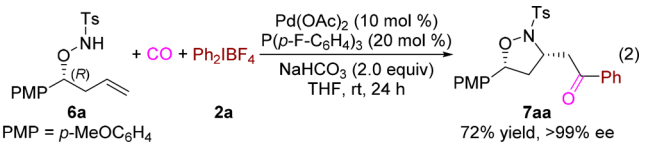
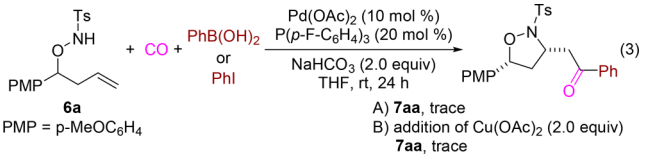
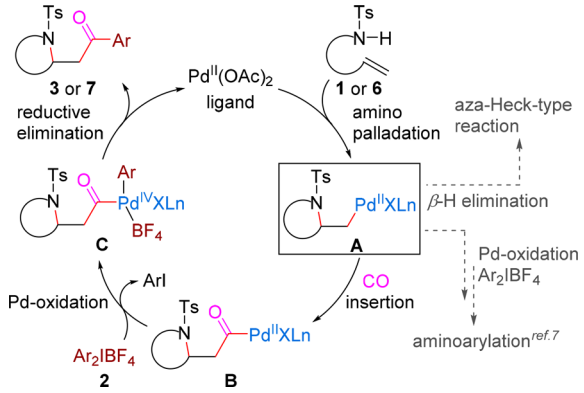


To gain some insight into the mechanism, we examined the use of phenylboronic acid or iodobenzene as an aryl source under the standard conditions; however, no desired product was detected (eq 3). Moreover, even when adding $Cu(OAc)_2$ as a standard oxidant for mediating Pd^0/Pd^{II} catalysis, no expected product **7aa** was obtained either.[5] Control experiments also confirmed that the ligand is critical to the reaction, as significant Pd-black was formed without a phosphorus ligand.[11]



At the current stage, we could not rule out the possibility of a Pd^0/Pd^{II} catalytic cycle.[11] On the basis of our recent mechanistic study on the aminoarylation reaction of β,γ-unsaturated hydrazones[7] and literature reports,[3,6,12] we currently believe that Pd^{II}/Pd^{IV} catalysis should be the predominant pathway for the reaction (Scheme 5). An initial

Scheme 5. Mechanistic Proposal



C–N bond forming nucleophilic amino-palladation results in the formation of the alkyl palladium intermediate **A**, which undergoes a facile CO insertion to give acyl Pd^{II} complex **B**. Then, Pd-oxidation of **B** by the diaryliodonium salt **2** gives rise to Pd^{IV} intermediate **C** that would undergo reductive elimination more readily than intermediate **A** to give the final products. The diaryliodonium salt **2** works as both aryl sources and oxidants. The insertion of CO and change in the oxidation state of palladium should be the main elements that suppress the competing aza-Heck-type reaction and aminoarylation of intermediate **A**.[8]

In conclusion, we have developed a general and efficient $Pd(OAc)_2$-catalyzed ring-forming alkene aminoaroylation of unsaturated hydrazones and sulfonamides with diaryliodonium salts and 1 atm of CO. This protocol characterizes use of diaryliodonium salts as both oxidants and aryl sources, mild reaction conditions, good chemoselectivity, a broad substrate scope, and high functional group tolerance. A range of differently substituted dihydropyrazoles and isoxazolidines were obtained in good yields. Further application of this aminoaroylation strategy to other nucleophilic N–H-containing alkenes is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01208.

Experimental procedures, full analysis data for new compounds, and copies of NMR spectra (PDF)

Accession Codes

CCDC 1837102–1837103 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: chenjiarong@mail.ccnu.edu.cn.

ORCID

Jia-Rong Chen: 0000-0001-6054-2547

Wen-Jing Xiao: 0000-0002-9318-6021

Author Contributions

§J.C. and M.-N.Y. contributed equally.

Notes

The authors declare no competing financial interest.

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