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# Tunable Gold(I)-Catalyzed [4 + 3] Cycloaddition for Divergent Synthesis of Furan-Fused N,O-Heterocycles

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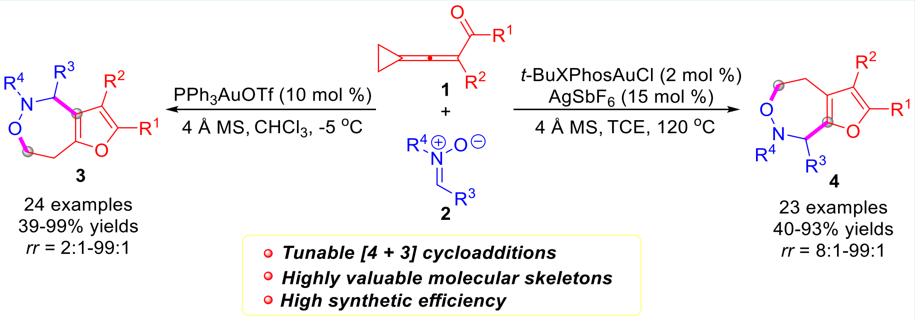
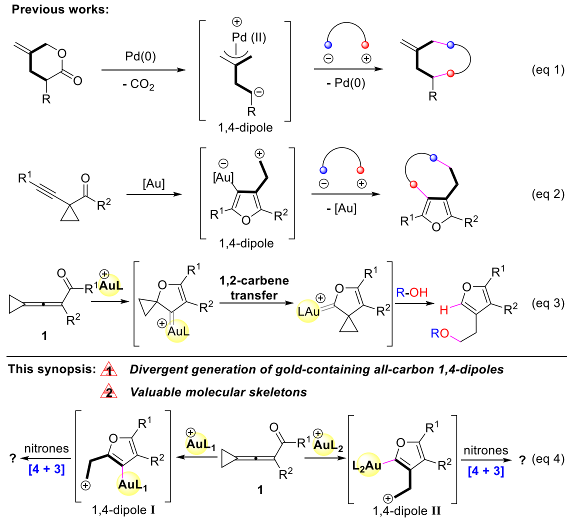


**ABSTRACT:** By choosing suitable ligand-directed gold catalysts, two types of gold-containing all-carbon 1,4-dipoles could be generated selectively from the gold(I)-catalyzed cycloisomerizations of allenyl ketones bearing a cyclopropyl moiety, which undergo [4 + 3] cycloadditions with nitrones to produce two regiomers of furan-condensed N,O-seven-membered rings in moderate to excellent yields highly selectively.

Intermolecular cycloaddition represents a powerful tool to create a myriad of functionalized carbocyclic and heterocyclic frameworks in a highly regio- and stereocontrolled fashion.[1] While traditional protocols by applying stable conjugated 1,3-dipoles to react with unsaturated bonds to produce cyclic motifs are well documented,[2] studies on utilizing nonclassical all-carbon 1,4-dipoles, a class of highly reactive variants without a fully conjugated system,[3] for cycloaddition reactions remain a critical challenge and are of high value in organic chemistry.

Benefiting from the development of the transition-metal catalysis in organic synthesis,[4] a few approaches have been established to enter the polarized four-carbon units, binding a relatively strong carbon−metal bond via elaborate design of substrates.[5] For example, in 2007, an elegant work involving the generation of 1,4-zwitterionic dipoles with a π-allylpalladium moiety from a palladium(0)-catalyzed oxidative addition into the γ-methylidene-δ-valerolactones and decarboxylation process was first disclosed by Hayashi[6] and co-workers (Scheme 1, eq 1). Later, vinyl benzoxazinanone derivatives have also been successfully used as valuable precursors of an aromatic ring containing 1,4-dipoles undergoing a similar decarboxylation process.[7] The homogeneous gold catalysis has emerged as a continuously growing field of investigation.[8] Owing to the exceptional π-acidity of cationic gold(I) complexes to activate unsaturated carbon−carbon bonds, Zhang's group[9] developed the first gold(I)-catalyzed cycloisomerization of 1-(1-alkynyl)cyclopropyl ketones toward

**Scheme 1. Transition-Metal-Based Approaches to All-Carbon 1,4-Dipoles and Our Envisaged Strategy toward 1,4-Dipoles I and II under Gold Catalysis**



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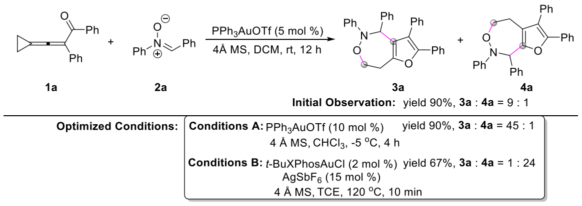
conceptually novel gold-containing all-carbon 1,4-dipoles (Scheme 1, eq 2). These strategies have offered new opportunities to trigger the formation of all-carbon 1,4-dipoles and modulate their reactivity to participate in some cycloaddition reactions.[10] To the best of our knowledge, the generation of diverse all-carbon 1,4-dipoles using allenes[11] as well designed precursors by means of $\pi$-metal catalysis and ligand effect is still unknown.

Allenyl ketones (**1**) with a highly strained cyclopropylidene group adjacent at the end of the cumulated double bond are a subunit of thermally stable, yet activated allenic derivatives.[12] The versatile reactivity makes these compounds highly attractive synthetic building blocks in organic synthesis. Recently, we[13] have developed a regioselective synthesis of polysubstituted furans from the cycloisomerization/ring opening of allenyl ketones bearing a cyclopropyl moiety with alcohols, displaying an unprecedented 1,2-gold carbene transfer reactivity (Scheme 1, eq 3). Our group's continued interest in transition-metal-catalyzed transformation of allenyl ketones prompted us to investigate the potential of these derivatives as the precursors of two kinds of furan-containing 1,4-dipoles **I** and **II** for cycloaddition reactions (Scheme 1, eq 4). As a result, herein we report the gold(I)-catalyzed divergent synthesis of furan-fused seven-membered N,O-heterocyclic compounds via the tandem cycloisomerization and formal [4 + 3] cycloaddition of allenyl ketones (**1**) with various nitrones.

Nitrones have found wide application in 1,3-diploar cycloadditions for the preparation of a plethora of N,O-heterocyclic derivatives.[14] Thus, they were selected as a coupling partner for processing cycloadditions with the envisaged gold-containing all-carbon 1,4-dipoles **I** or **II** for optimization studies. Upon addition of cyclopropyl-tethered allenyl ketone **1a** to a solution of *N*,$\alpha$-diphenyl nitrone **2a**, 100 mg of 4 Å MS, and 5 mol % of $PPh_3AuOTf$ in DCM at room temperature, a mixture of the anticipated cycloadducts **3a** and **4a** was obtained in 90% total yield with 9:1 ratio (Scheme 2).

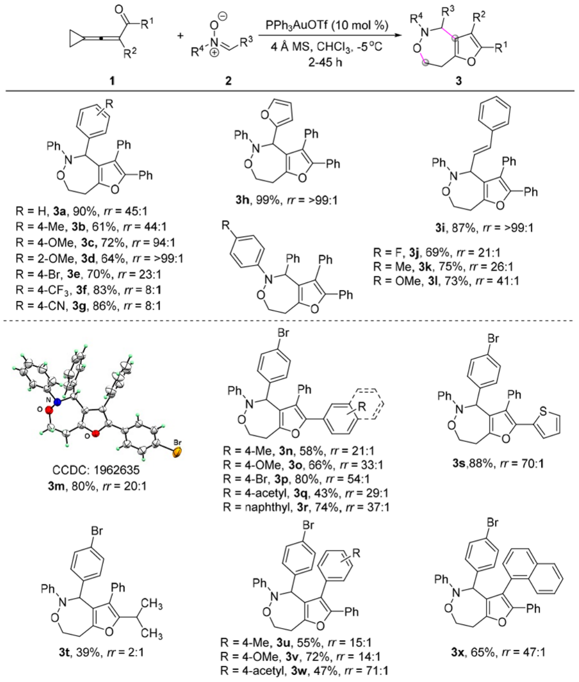
## Scheme 2. Initial Observation and Optimized Reaction Conditions for Selectively Producing 3a and 4a



We subsequently carried out a systematic optimization (for details, see Table S1 and Table S2 in the Supporting Information). Two catalytic protocols for the selectively producing **3a** (90% yield, rr = 45:1) and **4a** (67% yield, rr = 1:24) were established by employing different gold(I) catalysts (Scheme 2).

Upon the identification of a set of reaction conditions, we turned to explore the generality of the cycloaddition between allenyl ketones **1** and a variety of nitrones **2** for the selective formation of cycloadducts **3** (Scheme 3). Neither electron-donating nor electron-withdrawing substituents on the $\alpha$-phenyl rings of nitrones affected the efficiency of the cycloaddition, furnishing the corresponding cycloadducts **3a–g** in good yields, albeit a lower regioselectivity was found in the case of strong electron-withdrawing groups (**3f** and **3g**). Nitrones bearing 2-furyl and styryl groups at the $\alpha$-position, as well as those with different substituents on the *N*-phenyl rings, all worked well in this reaction, furnishing their respective products (**3h–l**) with high yields and excellent regioselectivities. Subsequently, the capacity of different cyclopropyl-tethered allenyl ketones **1** was defined. A benzene ring with 4-Br, 4-Me, 4-OMe, and 4-acetyl groups, as well as 2-naphthyl and 2-thienyl, were well tolerated at the $R^1$ position, delivering the desired product (**3m–s**) in modest to good yields with overwhelming selectivities (rr > 20:1). Nevertheless, low yield and poor regioselectivity (39%, rr = 2:1) were obtained in the case of the isopropyl-substituted substrate (**3t**). Varying the substituents of aromatic rings at the $R^2$ position, the reaction proceeded smoothly to afford **3u–x** in 47–72% yields with high regioselectivities.

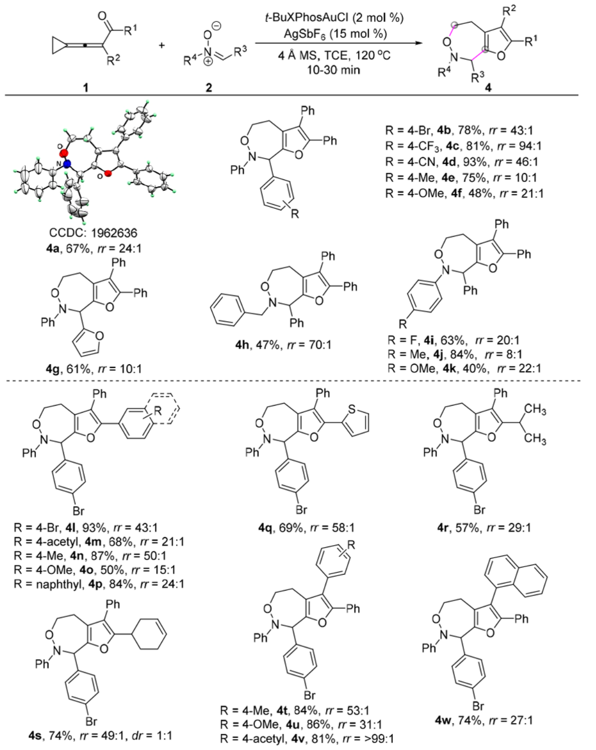
## Scheme 3. Scope of the PPh$_3$AuOTf-Catalyzed Reaction for the Synthesis of 3[a,b]



[a] The reaction was carried out using **1** (0.2 mmol, 1 equiv) and **2** (0.6 mmol, 3 equiv), 100 mg of 4 Å MS, and 10 mol % of $PPh_3AuOTf$ under $N_2$ atmosphere. [b] Isolated yield of **3**; ratio determined by $^1H$ NMR analysis of the crude product.

The scope of the selective cycloaddition reaction for the synthesis of **4** is demonstrated in Scheme 4. Likewise, a wide range of nitrones were employed to react with cyclopropyl-tethered allene ketone **1a**, the reaction performed well to afford **4a–k** in modest to high yields with well-controlled regioselectivity. Nitrones with electron-deficient substituents at $\alpha$-phenyl rings provided the corresponding cycloadducts (**4b–d**) in higher yields than electron-rich ones (**4e–g**). *N*-Benzyl and various substituted N-aromatic nitrones were compatible, giving the cycloadducts **4h–k** in acceptable yields. The substrate scope of allenyl ketones **1** was then examined. It was found that both electron-deficient and electron-rich groups on the benzene ring, as well as 2-naphthyl, 2-thienyl, isopropyl, and 4-cyclohexenyl at the $R^1$ position, were compatible, furnishing the targeted molecules (**4l–s**) in high yields (up to 93%) and regioselectivities (rr > 15:1). Various aromatic rings could be properly installed at the $R^2$ position to afford the

### Scheme 4. Scope of the *t*-BuXPhosAuCl/$AgSbF_6$-Catalyzed Reaction for the Synthesis of 4[a,b]

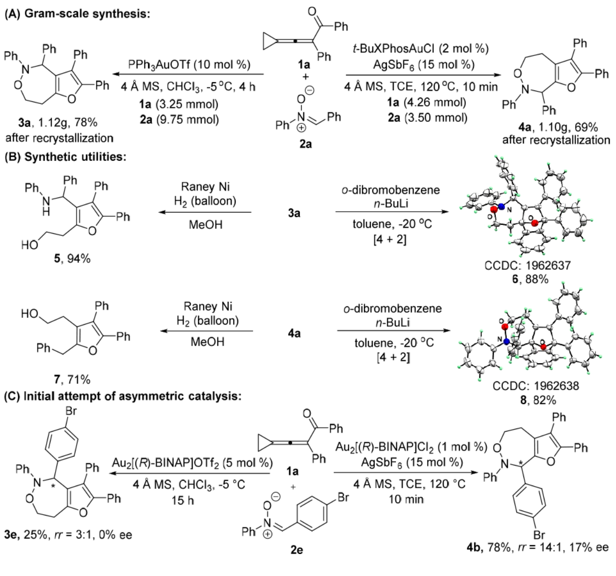


[a]The reaction was carried out using **1** (0.24 mmol, 1.2 equiv), **2** (0.2 mmol, 1 equiv), and 100 mg of 4 Å MS, with a combination of 2 mol % of *t*-BuXPhosAuCl and 15 mol % of $AgSbF_6$ in TCE at 120 °C under $N_2$ atmosphere. [b]Isolated yield of **4**; ratio determined by $^1$H NMR analysis of the crude product.

desired compounds (**4t–w**) in good yields with excellent regioselectivity.

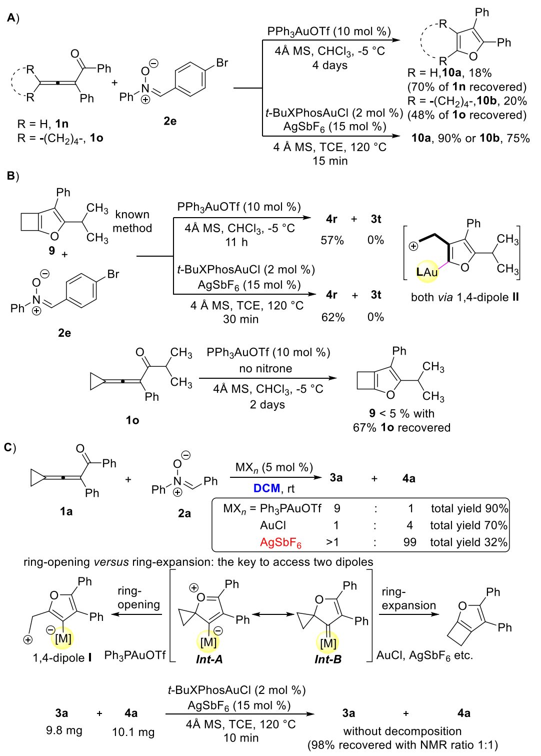
To demonstrate the scalabilities and synthetic utilities of the two reactions, several transformations were performed. As depicted in Scheme 5, the reactions could be easily enlarged to a gram scale, affording 1.12 g of **3a** and 1.10 g of **4a** after recrystallization. Both **3a** and **4a** could undergo chemoselective hydrogenation by treatment with $H_2$/Raney Ni to produce **5** and **7** in high yields. In addition, **3a** and **4a** also underwent [4 + 2] cyclizations with benzyne generated from *o*-dibromobenzene/*n*-BuLi under −20 °C to solely afford **6** and **8** in high yields with excellent stereoselectivities. Furthermore, the attempt of asymmetric reactions by employing (*R*)-BINAP as the ligand was made. The reaction provided the desired **3e** in 25% yield (rr = 3:1) and 0% ee. On contrast, the reaction rendered 17% enantiomeric excesses with a synthetically useful yield in the case of the formation of **4b**, indicating the potential of developing an enantioselective process of synthetic value.

### Scheme 5. Gram-Scale Synthesis, Synthetic Application, and Attempt of Asymmetric Catalysis



To gain some mechanistic insights into these transformations, control experiments were conducted (Scheme 6).

### Scheme 6. Mechanistic Investigations



First, allenyl ketones **1n** and **1o** were subjected to react with nitrone **2e** under two established sets of conditions. In the presence of $Ph_3PAuOTf$ (10 mol %) or a combination of *t*-BuXPhosAuCl (2 mol %) and $AgSbF_6$ (15 mol %), both reactions cleanly led to the formation of substituted furans **10a–b** with distinct efficiency, yet the desired cycloadducts were not detected (Scheme 6, eq A). These results clearly suggest that the high strained cyclopropyl moiety plays important roles in these reactions. Then, the furan-fused cyclobutene **9** was employed to react with **2e** under two types of gold catalysts. To our surprise, the cycloadduct **4r** involving the 1,4-dipole **II** was solely obtained in 57% and 62% yields under these conditions, and the regiomer **3t** was not formed. Moreover, the treatment of substrate **1o** with 10 mol % of $Ph_3PAuOTf$ in the absence of nitrone led to quite slow transformation to furan-fused cyclobutene intermediate **9** (Scheme 6, eq B). These results indicate that the furan-fused cyclobutene may be a key intermediate in the formation of the cycloadduct **4**, and the cationic gold(I) catalyst dominates the

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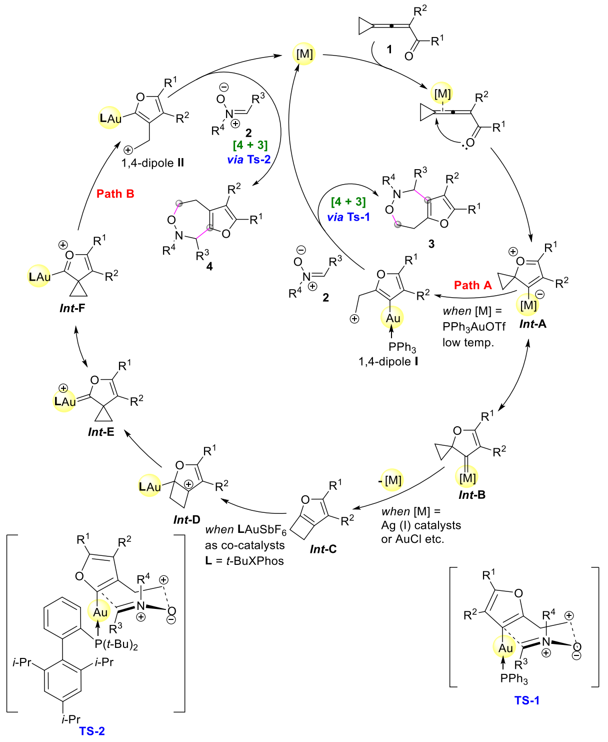
ring opening of furan-fused cyclobutene to generate 1,4-dipole **II**. The rate of formation of furan-fused cyclobutene might be the key point in selectively producing compounds **4** in reactions involving cyclopropyl-tethered allenyl ketones **1** and nitrones **2** catalyzed by *t*-BuXPhosAuCl (2 mol %) and $AgSbF_6$ (15 mol %). Finally, we noticed that the reactions gave the different ratios of **3a** and **4a** in the presence of different $\pi$-metal catalysts in DCM at room temperature. In addition, the mixture of **3a** and **4a** did not decompose in the combination of *t*-BuXPhosAuCl (2 mol %) and $AgSbF_6$ (15 mol %) at 120 °C (Scheme 6, eq C). Marshall,[15] Hashmi,[16] and Gevorgyan[17] have presented fruitful results in transition-metal (Rh, Ag, Pd, Au, Cu, etc.) catalyzed cycloisomerization of allenyl ketones which have been served as cyclic metal carbene precursors.[18] Thus, it is reasonable to assume that the reaction of **1a** catalyzed by $\pi$-metals would afford spirocyclic oxonium/carbene intermediates **Int-A**/**Int-B**. The phosphine ligand-directed gold(I) may promote the ring opening of spirocyclic oxonium **Int-A** to form 1,4-dipole **I**, while $AgSbF_6$ and AuCl etc. promote a fast ring expansion to deliver furan-fused cyclobutene and its further transformations.

### Scheme 7. Proposed Reaction Pathways for the Cyclization of Allenyl Ketones Bearing a Cyclopropyl Moiety 1 Catalyzed by $\pi$-Metals



Although the full mechanistic details of these transformations remain to be elucidated, plausible mechanisms for the reactions are outlined in Scheme 7. Electrophilic [M] activation of the electron-rich double bond in allenone moiety **1** could induce a nucleophilic-type cyclization that would lead to the formation of the spirocyclic oxonium/carbene forms **Int-A**/**Int-B**. When $PPh_3AuOTf$ was employed, the ring opening of the spiro-cyclopropyl ring that attached at **Int-A** might yield a gold-containing all-carbon 1,4-dipole **I**[5,9a] (**Path A**). The following intermolecular [4 + 3] cycloaddition of 1,4-dipole **I** with nitrone **2** via **TS-1** might give the cycloadduct **3**. It is noted that an alternative pathway via direct $S_N2$-type nucleophilic attack of nitrone's oxygen atom on the cyclopropyl ring of **Int-A** followed by ring-closure reaction to afford the [4 + 3] cycloadduct **3**[14d] is also highly possible. When the ligand-free catalysts such as $AgSbF_6$, AuCl, or combined catalytic systems, etc. were applied, the metal-carbene resonance **Int-B** might undergo a fast ring-expansion reaction followed by elimination of [M] to provide the key intermediate furan-fused cyclobutene **Int-C**. In the case of using *t*-BuXPhosAu$SbF_6$ and $AgSbF_6$ as cocatalysts, the cationic gold species might dominantly reactivate to the highly strained C—C double bond of **Int-C** to form **Int-D**, which would transform to the key cyclic gold carbene **Int-E** and its spirocyclic oxonium structure **Int-F** by ring contraction. Subsequently, intermediate **Int-F** underwent ring-opening to generate a regio-switched gold-containing all-carbon 1,4-dipole **II** (**Path B**), which could cyclize with nitrone **2** to produce the alternative **4** via **TS-2**. Similarly, a $S_N2$-type nucleophilic attack of **Int-F** with nitrone **2** followed by ring closure might also occur to furnish the cycloadduct **4**.

In summary, the gold-catalyzed tandemn cycloisomerizations and formal [4 + 3] cycloadditions of allenyl ketones bearing a cyclopropyl moiety with nitrones were developed to provide a diverse range of furan-fused N,O-heterocycles in very high regio- and stereoselectivity. Furan derivatives not only represent versatile building blocks in organic synthesis but also have been frequently found as key skeletons in many bioactive natural products, pharmaceutical substances, and functional materials. Taking advantage of this strategy, studies to address the further applications of these novel dipoles in gold catalysis and the development of asymmetric variants of these annulations, as well as their application in the synthesis of biologically relevant molecules, are currently underway in our laboratory.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04312.

Experimental procedures and copies of $^1H$ and $^{13}C$ NMR spectra for all new compounds (PDF)

### Accession Codes

CCDC 1962635–1962638 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.

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## Notes

The authors declare no competing financial interest.

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