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Mild and Ligand-Free Pd(II)-Catalyzed Conjugate Additions to Hindered γ-Substituted Cyclohexenones

James A. Jordan-Hore, James N. Sanderson, and Ai-Lan Lee*

*School of Engineering and Physical Sciences, Heriot-Watt University,
Edinburgh EH14 4AS, Scotland, United Kingdom*

a.lee@hw.ac.uk

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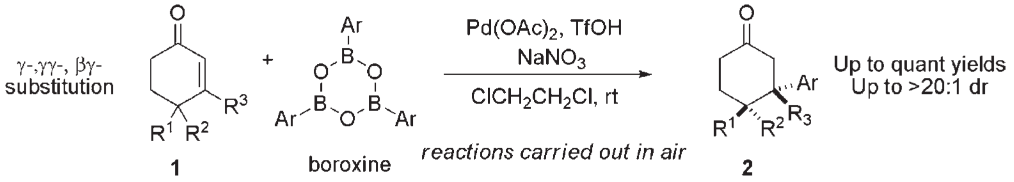
ABSTRACT



Ligand-free cationic Pd(II) catalyst with $NaNO_3$ as an additive is a highly active catalytic system for conjugate additions to sterically hindered γ-substituted cyclohexenones. More challenging $\gamma\gamma$- and $\beta\gamma$-substrates also react well to produce products with quaternary centers in good dr. The conjugate additions occur in a diastereoselective fashion under mild, practical and air-stable conditions, using readily available commercial reagents.

Metal-catalyzed conjugate addition to α,β-unsaturated carbonyl acceptors is a powerful tool for the construction of C−C bonds.[1] For example, copper-catalyzed[1c,d] and rhodium-catalyzed[1a−c] conjugate additions are well-known and widely used methods of constructing C−C bonds. Despite their indisputable utility in the synthetic chemists' toolkit, there are still some drawbacks to the currently available methods. For example, the Cu-catalyzed conjugate additions often involve subzero temperatures as well as air- and moisture-sensitive organometallic reagents that require rigorously anhydrous reaction conditions. Due to the use of such organometallic reagents, some functional groups cannot be tolerated. The alternative Rh-catalyzed additions overcame this issue by utilizing air- and water-stable organoboron reagents. However, this advance comes with other drawbacks, including the high cost of Rh catalysts, as well as the lower tolerance of steric hindrance: *because effective coordination of the acceptor to rhodium is crucial for the reaction, acceptors that bear steric bulk in proximity to the unsaturation will be less reactive.*[1a] Thus, γ-substituted cyclohexenones such as **1** (R_1/R_2 = alkyl or aryl) are unsuitable substrates for the popular Rh-catalyzed reaction.[4] Nevertheless, the products of conjugate additions to γ-substituted cyclohexenones **2** are useful building blocks in organic synthesis;[4b−d] thus a mild, air-stable, diastereoselective and practical procedure for the transformation of **1** to **2** would be an invaluable advancement.

Palladium(II)-catalyzed conjugate additions have recently emerged as a cheaper alternative to the Rh-catalyzed reactions and can be tolerant of air and moisture, unlike the more established Cu-catalyzed versions.[2,3] Herein, we disclose results to demonstrate that in addition to the advantages mentioned above, a new ligandless cationic Pd(II) system now allows for Pd(II)-catalyzed conjugate additions which are *also highly tolerant of steric hindrance*. The conditions are mild, efficient, and practical for the diastereoselective conjugate additions to sterically

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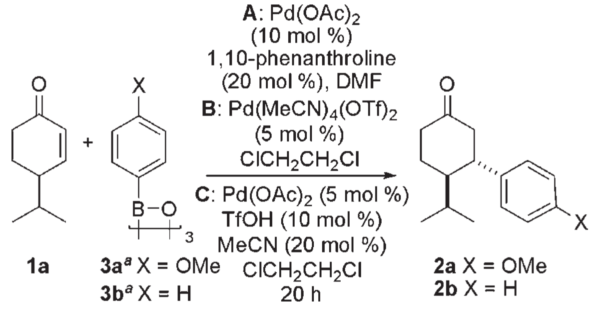
(1) For selected recent reviews, see:(a) Berthon, G.; Hayashi, T. Rhodium- and Palladium-Catalyzed Asymmetric Conjugate Additions. In *Catalytic Asymmetric Conjugate Reactions*; Córdova, A., Ed.; Wiley-VCH: Weinheim, 2010; pp 1−70. (b) Edwards, H. J.; Hargrave, J. D.; Penrose, S. D.; Frost, C. G. *Chem. Soc. Rev.* **2010**, *39*, 2093. (c) Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, 1279. (d) Alexakis, A.; Backvall, J. E.; Krause, N.; Pamies, O.; Dieguez, M. *Chem. Rev.* **2008**, *108*, 2796.

(2) For reviews, see ref 1a and: (a) Gutnov, A. *Eur. J. Org. Chem.* **2008**, 4547. (b) Yamamoto, Y.; Nishikata, T.; Miyaura, N. *Pure Appl. Chem.* **2008**, *80*, 807.

(3) For selected Pd-catalyzed conjugate additions, see: (a) Kikushima, K.; Holder, J. C.; Gatti, M.; Stolz, B. M. *J. Am. Chem. Soc.* **2011**, *133*, 6902. (b) Brozek, L. A.; Sieber, J. D.; Morken, J. P. *Org. Lett.* **2011**, *13*, 995. (c) Lin, S.; Lu, X. *Org. Lett.* **2010**, *12*, 2536. (d) Xu, Q.; Zhang, R.; Zhang, T.; Shi, M. *J. Org. Chem.* **2010**, *75*, 3935. (e) Lin, S.; Lu, X. *Tetrahedron Lett.* **2006**, *47*, 7167. (f) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Chem. Lett.* **2007**, *36*, 1442. (g) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Adv. Synth. Catal.* **2007**, *349*, 1759. (h) Lu, X.; Lin., S. *J. Org. Chem.* **2005**, *70*, 9651. (i) Gini, F; Hessen, B.; Minaard, A. J. *Org. Lett.* **2005**, *7*, 5309. (j) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Organometallics* **2004**, *23*, 4317. (k) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 2768.

10.1021/ol300794a

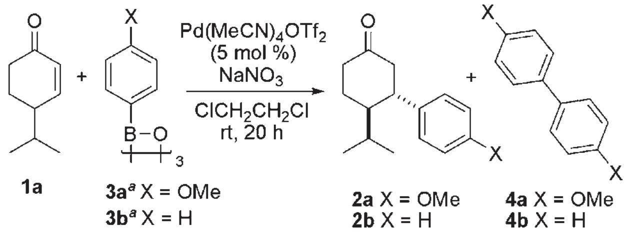
Table 1. Initial Studies: Conditions for Pd(II)-Catalyzed Conjugate Additions



entry	conditions	X	temp (°C)	additive, (1 equiv)	yield of **2**[b] (%)
1	A	OMe	65		83
2	B	OMe	rt		25 conv
3	B	H	rt		<5 conv
4	**B**	**OMe**	**rt**	**$NaNO_3$**	**98**
5	**B**	**H**	**rt**	**$NaNO_3$**	**95**
6	**C**	**OMe**	**rt**	**$NaNO_3$**	**quant**
7[c]	A	OMe	rt		20 conv
8[c]	A	OMe	rt	$NaNO_3$	51 conv
9	No Pd cat.	OMe	rt	$NaNO_3$	0
10	TfOH	OMe	rt	$NaNO_3$	0

[a] Commercial aryl boronic acid was heated under vacuum to generate boroxine, 0.67 equiv used. [b] Isolated yields unless otherwise stated. [c] $ClCH_2CH_2Cl$ was used as solvent.

Table 2. Screen of Additive Equivalents



entry	boroxine	$NaNO_3$ (equiv)	yield of **2**[c] (%)	yield **4**[b] (%)
1	**3a**	0	25	20
2	**3a**	0.05	45	20
3	**3a**	0.1	58	15
4	**3a**	0.2	75	11
5	**3a**	0.5	96	6
6	**3a**	1	98	3
7	**3b**	0	<5	31
8	**3b**	0.05	<5	29
9	**3b**	0.1	<5	21
10	**3b**	0.2	83	18
11	**3b**	0.5	86	10
12	**3b**	1	95	7

[a] Commercial boronic acid was heated under vacuum to generate boroxine, 0.67 equiv used. [b] Entries 1–6: determined by ^1H NMR analysis of the crude mixture. Entries 7–12: isolated yields. [c] Isolated yield.

hindered γ-, γγ-, and βγ-substituted cyclic enones **1**[4] by utilizing a new ligandless $Pd^{2+}/NaNO_3$ system.

Our investigations commenced with optimization of the reaction conditions for the conjugate addition to γ-substituted cyclohexenone **1a** (Table 1). Initially, neutral Pd(II) catalysts were evaluated [$Pd(OAc)_2$, 1,10-phenanthroline, 65 °C, conditions A, entry 1] and were found to provide the highest conversion and yield (83%).

Despite this initial result, we argued that it would be preferable to develop a milder method without the need for elevated temperatures. To this end, cationic Pd(II) complexes were evaluated as possible catalysts, and we were pleased to find $Pd(MeCN)_4(OTf)_2$[5] as a promising catalyst for transforming **1a** to **2a** at room temperature (25% conversion, entry 2). Unfortunately, the same catalyst provided no product **2b** upon replacing boroxine **3a** with phenylboroxine **3b** (entry 3). In order to improve the conversion, a screen of different additives was carried out (see the Supporting Information). To our surprise and pleasure, addition of 1 equiv of inexpensive sodium nitrate greatly enhanced the reaction to result in full conversion and excellent yields of **2** (98% **2a**, 95% **2b**, entries 4 and 5). To simplify the practical procedure even further, we investigated the reaction with in situ formation of the cationic catalyst using only commercially available reagents, and to our delight, the desired product **2a** was formed in quantitative yield (entry 6). Addition of $NaNO_3$ also enhances the neutral Pd(II) reaction (conditions A), but not as efficiently (entries 7 and 8). A control with $NaNO_3$ in the absence of any Pd catalyst, or with only TfOH, provides no product **2** (entries 9 and 10), showing that the reaction is indeed Pd-catalyzed. It should be noted that strictly anhydrous or O_2 free conditions are *not necessary* for conditions A–C; the reactions were all carried out in air with commercial solvents and are thus experimentally practical.

Next, we evaluated the effect of varying amounts of $NaNO_3$ additive in the reaction of **1a** to **2a** and **2b** (Table 2). Using the more reactive p-$MeOC_6H_4$-boroxine **3a**, a clear increase in the yield of product **2a** is observed as the equiv of $NaNO_3$ is gradually increased from 0 to 1 (entries 1–6). The slightly less reactive phenylboroxine **3b** produces no conjugate product **2b** at all with 0, 0.05, and 0.1 equiv of $NaNO_3$ (entries 7–9) but the yield improves significantly with 0.2, 0.5, and 1 equiv of $NaNO_3$ (entries 10–12).[6]

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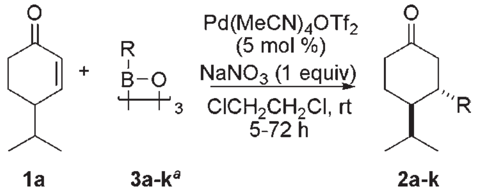
(4) As far as we are aware, there are no examples of Rh-catalyzed 1,4-additions to γ-alkyl/aryl-substituted cyclohexenones, and our attempts to carry out Rh-catalyzed conjugate additions to **1a**, **1g**, and **1h** led to no reaction (see the Supporting Information). There is one isolated example with Pd catalysis (**1g**, 60 °C, moderate 66% yield, ref 3e), but no examples that would lead to diastereoselectivity were tested. As a comparison, using these conditions (ref 3e) with more hindered **1h** led to no reaction (see the Supporting Information). All other methods for these 1,4-additions to γ-substituted cyclohexenones involve air- and moisture-sensitive cuprate addition conditions at subzero temperatures. For example, see: (a) Nevill, C. R., Jr.; Fuchs, P. L. *Synth. Commun.* **1990**, *20*, 761. (b) William, A. D.; Kobayashi, Y. *J. Org. Chem.* **2002**, *67*, 8771. (c) Huffman, J. W.; Thompson, A. L. S.; Wiley, J. L.; Martin, B. R. *Bioorg. Med. Chem.* **2008**, *16*, 322. (d) Piers, E.; Gavai, A. V. *J. Org. Chem.* **1990**, *55*, 2380. (e) Lipshutz, B. H.; Wood, M. R. *J. Am. Chem. Soc.* **1993**, *115*, 12625.

(5) Drent, E.; Van Broekhoven, J. A. M.; Doyle, M. J. *J. Organomet. Chem.* **1991**, *417*, 235.

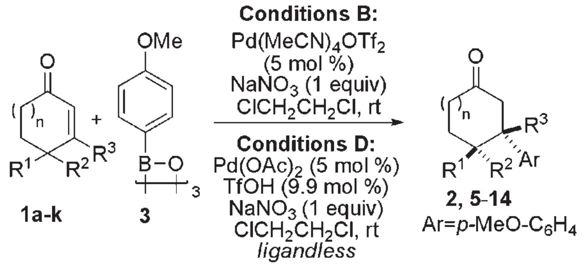
Table 3. Boroxine Scope

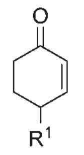
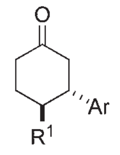
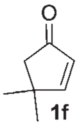
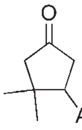
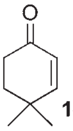
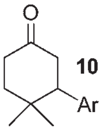
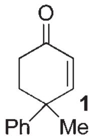
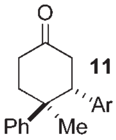
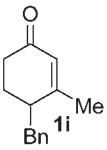
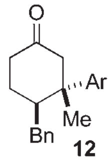
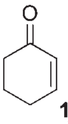
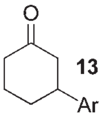
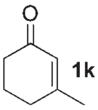
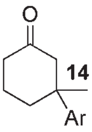


entry	R (entries 1−11) reagent (entry 12)	time (h)	dr[c]	yield[b] (%)
1	Ph	18	15:1	95, **2b**
2	*p*-$MeOC_6H_4$	5	12:1	98, **2a**
3	*p*-$EtO_2CC_6H_4$	48	>20:1	83, **2c**
4	*p*-FC_6H_4	48	12:1	88, **2d**
5	*p*-BrC_6H_4	48	>20:1	91, **2e**
6	*p*-$OHCC_6H_4$	36	>20:1	85, **2f**
7	*p*-HOC_6H_4	18	10:1	98, **2g**
8	*m*-$O_2NC_6H_4$	72	>20:1	89, **2h**
9	*m*-MeC_6H_4	18	>20:1	89, **2i**
10	*m*-ClC_6H_4	18	>20:1	84, **2j**
11	*o*-$MeOC_6H_4$	18	>20:1	73, **2k**
12	$PhB(OH)_2$	48	N/A	0[c]

[a] Commercial boronic acids were either heated under vacuum or refluxed under Dean−Stark conditions to generate boroxine, 0.67 equiv used. [b] Isolated yield. [c] Determined by ^1H NMR analysis of the crude mixture.

Table 4. $\gamma,\gamma\gamma,\beta\gamma$-Substituted Cyclic Enone Scope



entry (cond.)	substrate	product	dr[a]	yield (%)[b]
1 (B)	 **1a-1e**	 **2, 5-8**	12:1	98
	1a R^1 = *i*-Pr	**2a** R^1 = *i*-Pr		
2 (B)	**1b** R^1 = Ph	**5** R^1 = Ph	>20:1	91
3 (B)	**1c** R^1 = Bn	**6** R^1 = Bn	8:1	92
4 (B)	**1d** R^1 = *n*-octyl	**7** R^1 = *n*-octyl	8:1	94
5 (B)[c]	**1d** R^1 = *n*-octyl	**7** R^1 = *n*-octyl	11:1	80
6 (B)	**1e** R^1 = *t*-Bu	**8** R^1 = *t*-Bu	>20:1	75
7 (B)	 **1f**	 **9**	N/A	69
8 (B)[d]	 **1g**	 **10**	N/A	81
9 (**D**)			N/A	83
10 (B)[d]	 **1h**	 **11**	-	<5
11 (**D**)[c]			8:1	75
12 (**D**)[f]	 **1i**	 **12**	8:1	76
13 (**D**)	**1a**	**2b**	12:1	quant
14 (**D**)	 **1j**	 **13**	N/A	82
15 (**D**)[g]			N/A	94
16 (B)	 **1k**	 **14**	N/A	83

[a] Determined by ^1H NMR analysis of the crude mixture, *anti/syn* ratio. [b] Isolated yields. [c] Reaction carried out at 0 °C for 48 h. [d] Reaction warmed to 45 °C; no reaction at rt [e] 20 mol % cat.; with 10 mol %, the yield is 64%. [f] 10 + 5 mol % cat., [g] No $NaNO_3$ was added.

As for the role of $NaNO_3$, we observed that the gradual increase in $NaNO_3$ equivalents, and thus, the improvement in the yield of **2** is also accompanied by a reduction in the formation of biaryl side product **4**, which is a common side product in Pd(II)-catalyzed reactions with boronic acids/boroxines.[7] A control subjecting boroxine **3a** to conditions B in Table 1 without any substrate **1a** provides (a) 100% homocoupled **4a** in the absence of $NaNO_3$ and (b) only 30% conversion to **4a** in the presence of $NaNO_3$. Therefore, we propose that one of the roles of $NaNO_3$ as an additive is the suppression of the homocoupling side reaction,[6] which is a significant side reaction especially when hindered enones are employed as substrates.

With these optimized and mild conditions in hand, we set out to investigate the scope of the aryl boroxine substrates (Table 3). Pleasingly, a series of *para*-substituted electron-donating and -withdrawing aryl boroxines react smoothly to provide the products **2a**−**g** in good to excellent diastereoselectivities and yields (entries 2−7). Even bromo- as well as unprotected formyl- and hydroxy-substituted aryls add smoothly (entries 5−7); such functional groups would be incompatible with the Cu-catalyzed conjugate addition method (vide supra). Since the bromo functionality is tolerated under these Pd(II) conditions, these can be introduced as a handle for further reaction through Pd(0)-catalyzed cross-couplings. *Ortho*- and *meta*-substituted

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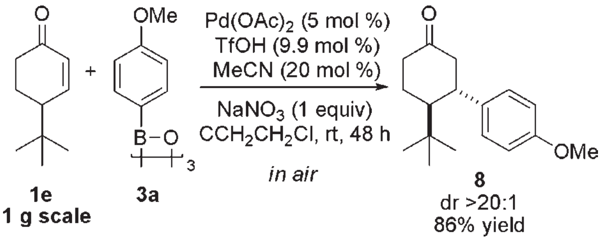
(6) $NaNO_3$ is only sparingly soluble in $ClCH_2CH_2Cl$. It should also be noted that the use of $Pd(MeCN)_2(NO_3)_2$ produces a poor yield (only 37% conv with **1a** and **3a**); thus, the $NaNO_3$ additive in Table 2 is not functioning by a simple anion exchange. See the Supporting Information for further studies regarding solubility and amount of $NaNO_3$ required, as well as further studies on the role of $NaNO_3$.

(7) For example, see:Yoo, K. S.; Yoon, C. H.; Jung, K. W *J. Am. Chem. Soc.* **2006**, *128*, 16384and references cited therein.

aryl boroxines also add in excellent dr and good yields (entries 8−11). During initial investigations, we observed a positive correlation between the proportion of boroxine[8] in the commercial "boronic acid" reagents and the yield. A control reaction using pure boronic acid $PhB(OH)_2$ instead of the boroxine produced no reaction (entry 12), indicating that the active reagent in these reactions is indeed the boroxine.

Next, a series of γ-substituted cyclohexenones were investigated (Table 4).[9] An aromatic γ-substituent (**1b**) compares favorably with **1a** to produce **5** in excellent yield and diastereoselectivity (91%, > 20:1, entry 2). Reduction of steric bulk of the γ substituent from *i*-Pr (**1a**) to benzyl (**1b**) and *n*-octyl (**1c**) still produces an excellent yield of **6** and **7**, respectively (92% and 94%), although the dr is slightly lower (8:1, entries 3−4). Cooling the reaction to 0 °C improves the dr to 11:1 (entry 5). Pleasingly, even bulky *t*-Bu is tolerated as a γ-substituent, producing the *anti* diastereomer **8** exclusively in 75% yield (entry 6). In order to demonstrate the practicality of the Pd(II)-catalyzed method, a scaled up reaction (**1** g of substrate **1e**) was carried out with 5 mol % of the in situ formed $Pd(MeCN)_4OTf_2$ catalyst to yield the desired product **8** in a good 86% yield (Scheme 1).

Scheme 1. Practical, Scaled Up In Situ Method



In order to push the reaction further, $\gamma\gamma$-disubstituted cyclic enones were evaluated as possible substrates (entries 7−11). While the reaction proceeded well with **1f** (entry 7), standard conditions B are no longer sufficient to promote the reaction with **1g** and **1h**, reflecting the extra steric bulk introduced by the γ quaternary center in these substrates. However, the reaction proceeded smoothly with **1g** upon warming to 45 °C (entry 8), but even heat is not sufficient to promote the reaction of more hindered **1h** (entry 10).

In an effort to develop an even more active catalyst system for these difficult $\gamma\gamma$-disubstituted cyclic enones, we evaluated the in situ formation of *ligandless* cationic Pd(II) catalyst (conditions D, no MeCN added). Gratifyingly, these ligandless conditions proved excellent for the conjugate additions to bulky $\gamma\gamma$-disubstituted cyclic enones under mild conditions. Addition to **1g** and **1h** now occurs smoothly under rt, and with a good 8:1 dr for **11** (entries 9 and 11). In comparison, the original neutral conditions A (Table 1) require 60 °C for conversion with **1h** and produce **11** with a poor 2.5:1 dr as a result (51% yield), showing the importance of an active yet mild rt procedure. Pleasingly, even the challenging β,γ-disubstituted cyclohexenone **1i** reacts under conditions D to form a β quaternary center in **12** with a good 8:1 dr and 76% yield (entry 12). At this point, we decided to evaluate these new conditions D with our original model substrate **1a** and were delighted to find a quantitative yield of **2b** in less than 1 h (entry 13). Although optimized for hindered γ-cycohexenones, conditions B/D are also suitable for less hindered **1j**[2] (entry 14) and β-substituted **1k**[3a,c] (entry 16), producing the desired products **13** and **14** in good yields. Interestingly, the reaction works better without $NaNO_3$ for **1j** (entry 15), suggesting that $NaNO_3$ is only necessary for challenging substrates where aryl homocoupling would otherwise be competitive, such as hindered substrates **1a**−**i**. Finally, if the use of chlorinated solvents is a concern, preliminary studies show trifluorotoluene[10] to be a plausible alternative solvent with conditions D: reaction of **3a** with **1a** produces **2a** in 76% yield and 5.5:1 dr.

In conclusion, we have developed mild, high-yielding, and diastereoselective (up to > 20:1) Pd(II)-catalyzed conjugate additions to sterically hindered γ-,$\gamma\gamma$- and $\beta\gamma$-substituted cyclohexenones, substrates which are too hindered for Rh-catalyzed procedures. The Pd(II) procedure is not only air-stable and practical but is also tolerant of functional groups which are usually incompatible with the more sensitive Cu-catalyzed procedures. Crucially, we have developed a highly active, ligandless cationic Pd(II) system and discovered that inclusion of sodium nitrate as an additive greatly enhances the reactivity of the cationic Pd(II) catalyst for conjugate additions. Future work will focus on developing further uses for this catalyst system.

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Supporting Information Available. Experimental procedures, spectroscopic data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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