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Letter

Selective Phosphoranation of Unactivated Alkynes with Phosphonium Cation To Achieve Isoquinoline Synthesis

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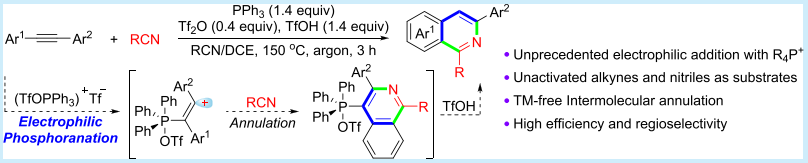
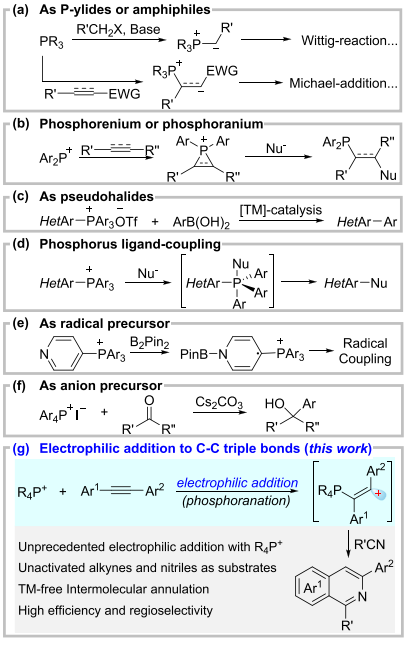


ABSTRACT: We herein develop a selective phosphoranation of alkynes with phosphonium cation, which directs a concise approach to isoquinolines from unactivated alkyne and nitrile feedstocks in a single step. Mechanistic studies suggest that the annulation reaction is initiated by the unprecedented phosphoranation of alkynes, thus representing a unique reaction pattern of phosphonium salts and distinguishing it from existing protocols that largely rely on the utilization of highly functionalized imines/oximes and/or highly polarized alkynes.

As phosphorus chemistry has always been extensively used in biochemistry, materials science, and catalytic chemistry,[1] considerable attention has long been paid to explore novel reactivities of organophosphorus compounds or intermediates (e.g., phosphonium salts). Typically, quaternization of trivalent phosphorus (e.g., phosphine) with an electrophile (e.g., alkyl halides) can produce the corresponding phosphonium salts, which in the presence of a base readily form P-ylides to engage the Wittig reaction, etc.[2] Besides, nucleophilic addition of phosphine to electron-deficient alkenes or alkynes may generate the phosphonium-based amphiphiles to finally accomplish the phosphine-catalyzed Michael addition, Rauhut−Currier reaction, and Stetter reaction, among others (Scheme 1a).[3] In recent years, more diverse reactivities for phosphonium salts have been developed. For example, the Miura/Hirano group disclosed an electrophilic ring-opening process of a transient phosphirenium intermediate,[4] while the Dalla/Taillier group achieved a similar process for the phosphiranium cation (Scheme 1b).[5] The McNally group demonstrated that tetraarylphosphonium salts can serve as pseudohalide handles to couple with aromatic boronic acids (Scheme 1c).[6] They also achieved a number of phosphorus ligand-coupling reactions when treating phosphonium salts with various nucleophiles (Scheme 1d).[7−10] In addition, phosphonium salts were found to be viable radical (Scheme 1e)[11] or anion (Scheme 1f) precursors.[12] Notwithstanding these great advances, the reported reactivities of phosphonium salts largely rely on the transformable potential of the substituents attached to the phosphonium center. Reactivities associated with the inherently strong electrophilicity of phosphonium cation, such as electrophilic addition to C≡C bonds, however, still remain unexploited. Here, we

Scheme 1. (a−f) Reported Reactivities of Phosphonium Species and (g) Electrophilic Addition of Phosphonium Cation to C≡C Bonds (This Work)



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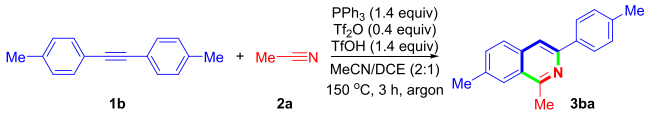
report some novel findings on this reactivity (upper part of Scheme 1g).

Isoquinolines are prevalent in many natural products, bioactive molecules, and synthetic pharmaceuticals.[13] Also, they are in increasing demand as crucial ligands for the preparation of organic light emitting diode (OLED) materials[14] and asymmetric catalysts.[15] Therefore, numerous named reactions based on condensation chemistry[16−19] have been developed, and annulation of (2-halo)aromatic imines[20] or oximes[21] with C−C multiple bonds or cyclization of 2-alkynylbenzyl azides[22] or 2-alkylnyl aromatic imines[23] or oximes[24] are also promising under transition metal catalysis. These approaches have shown great potential in synthesizing isoquinolines but often require lengthy steps to obtain highly functionalized substrates and usage of toxic and precious catalysts. Therefore, developing a step- and cost-economical approach is still of high interest. In 2016, the Maulide group reported an elegant protocol toward isoquinoline synthesis, wherein a metal-free annulation of ynamides with nitriles was realized at 120 °C under microwave conditions. In this reaction, the use of trifluoromethanesulfonic acid (TfOH) is essential for the activation of ynamides to a reactive vinyl cation.[25] Despite its effectiveness, this method favors highly polarized alkynes and did not tame less-polarized alkynes. On the basis of this consideration, we hypothesized that a much stronger alkyne activator might be crucial to open up an avenue for the annulation of unactivated alkynes with nitriles. Herein, by adopting the strong electrophilicity of the phosphonium center, we present an unprecedented electrophilic addition of phosphonium cation to unactivated alkynes, which triggers a subsequent intermolecular annulation with nitriles to afford diverse 3-arylated isoquinolines in a single step (Scheme 1g).

To verify the feasibility of our assumption, we initiated our investigations on this annulation reaction using bis(*p*-tolyl)-acetylene (**1b**) and acetonitrile as model substrates. The desired isoquinoline product **3ba** was obtained in 96% yield when using 1.4 equiv of PPh_3 as the phosphorus source, 0.4 equiv of Tf_2O, and 1.4 equiv of TfOH as the additives in a mixed solvent of acetonitrile (MeCN)/1,2-dichloroethane (DCE) (2:1, v/v) at 150 °C for 3 h under an argon atmosphere (entry 1 in Table 1, at standard conditions). Control experiments showed that only 15% yield or none of compound **3ba** was observed without PPh_3 or Tf_2O/TfOH (entries 2 and 3), which imply that a phosphornium species[26,27] induced annulation rather than a common phosphine-catalyzed transformation being involved in this reaction.[3] Triarylphosphines bearing either electron-donating or electron-withdrawing groups exhibited suboptimal activities (entries 4−9), while biarylalkylphosphine and trialkylphosphine gave inferior results (entries 10 and 11). Use of $(C_4F_9SO_2)_2O$ led to a significantly reduced yield of compound **3ba** (entry 12). The choices of solvents were also important for this reaction (entry 13). Changes in the loading of PPh_3 (entry 14), Tf_2O (entry 15), or TfOH (entry 16) caused decreased yields of compound **3ba** by 10−30%. Other endeavors, such as shortening the reaction time or lowering the reaction temperature, were also attempted, but none of them afforded superior results (entries 17 and 18).

With the optimal reaction conditions in hand, we sought to demonstrate the generality of this annulation reaction. As summarized in Scheme 2, the scope with respect to symmetric diarylalkynes was first examined. Generally, the aryl ring with

Table 1. Reaction Optimization and Control Studies[a]



entry	variation from the standard conditions	yield (%)[b]
1	none	96
2	no PPh_3	15
3	no Tf_2O and TfOH	0
4	$(4\text{-Me-Ph})_3P$ instead of PPh_3	76
5	$(3\text{-Me-Ph})_3P$ instead of PPh_3	73
6	$(4\text{-MeO-Ph})_3P$ instead of PPh_3	58
7	$(4\text{-F-Ph})_3P$ instead of PPh_3	77
8	$(4\text{-Cl-Ph})_3P$ instead of PPh_3	72
9	$(2\text{-Br-Ph})Ph_2P$ instead of PPh_3	63
10	PPh_2Et instead of PPh_3	57
11	tricyclohexylphosphine (PCy_3) instead of PPh_3	11
12	$(C_4F_9SO_2)_2O$ instead of Tf_2O	77
13	MeCN, MeCN/dichloromethane (DCM) (2:1), or MeCN/DCE (1:2) as the solvent	89, 83, or 89
14	with 1.0, 1.2, or 2.0 equiv of PPh_3	72, 78, or 75
15	with 0.2 or 0.6 equiv of Tf_2O	66 or 81
16	with 1.2 or 2.0 equiv of TfOH	80 or 87
17	reaction time of 2 h	81
18	reaction temperature of 120 °C	75

[a]Reaction conditions: compound **1b** (0.10 mmol), Tf_2O (0.4 equiv), TfOH (1.4 equiv), and MeCN/DCE (1.2 mL, 2:1, v/v), under argon at 150 °C for 3 h. [b]Yields are determined by ^1H nuclear magnetic resonance (NMR) with mesitylene as the internal standard.

electron-donating substituents (e.g., Me, *t*Bu; 88−92% yield) displayed significantly higher efficiency than those with electron-withdrawing groups (e.g., F; 40% yield) (**1b** or **1c** versus **1d**). However, when the electron-donating groups were positioned *ortho* to the alkynyl moiety (**1e** versus **1b**) or the annulated site (**1f** versus **1b**), yields of the corresponding products were reduced by 10−20%, which can be attributed to the effects of steric hindrance. Next, the scope of unsymmetric alkyne substrates was evaluated. In general, monosubstituted alkynes bearing either electron-donating (**1g**−**1k**) or weak electron-withdrawing (**1l**−**1n**) groups achieved good to excellent yields of the desired products (59−85% yield), with the annulation occurring mostly on less electron-rich aromatic rings. Notably, electron-donating substituents showed marked differences in regioselectivity. For instance, phenyl- or phenoxyl-substituted alkyne yielded compound **3ga** or **3ha** as the sole product, while alkyl substituents afforded mixtures of isoquinolines in 10:1 regioselectivity (**3ia**/**3ia′** and **3ja**/**3ja′**). Weak electron-withdrawing substituents, such as halides, exhibited poor selectivity (**1l**−**1n** versus **1i**−**1j**), among which the fluoro substituent displayed the highest regioselectivity (**1l** versus **1m** versus **1n**; ratio of isomers is 4.7:1, 1.7:1, and 1.1:1, respectively). Improving the electronic biases between two aromatic rings by introducing strong electron-withdrawing groups, such as trifluoromethyl (**1o**), ester (**1p**), and cyano groups (**1q**), into alkyne substrates significantly increased the regioselectivities, as the reaction selectively cyclized on the electron-deficient aromatic ring in a synthetically useful yield (**3oa**/**3oa′**, **3pa**, and **3qa**; 23−43% yield). As expected, installing substituents into both *ortho* positions to the alkynyl moiety on either aromatic ring gave pure isoquinoline products in good yields (**3ra**−**3ta**; 53−77%

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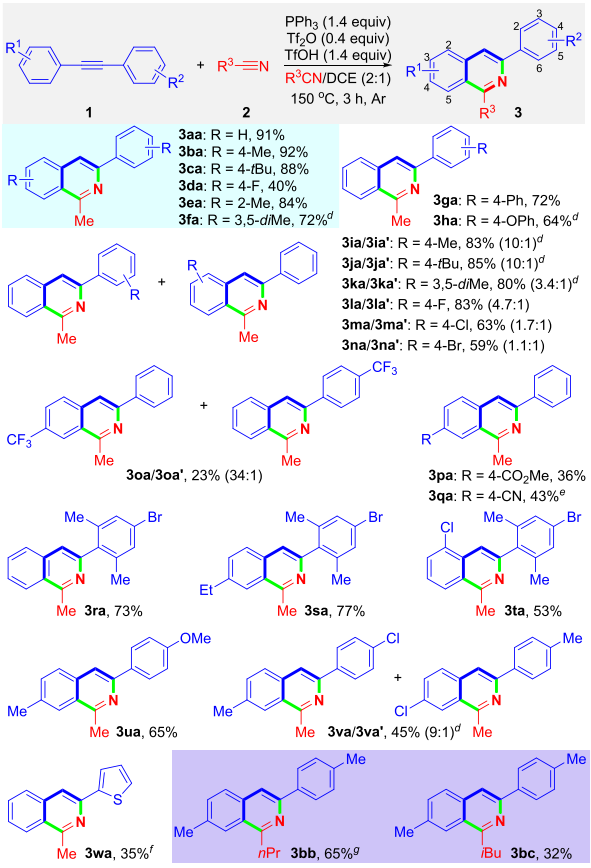
Scheme 2. Scope with Respect to Alkynes and Nitriles[a,b,c]

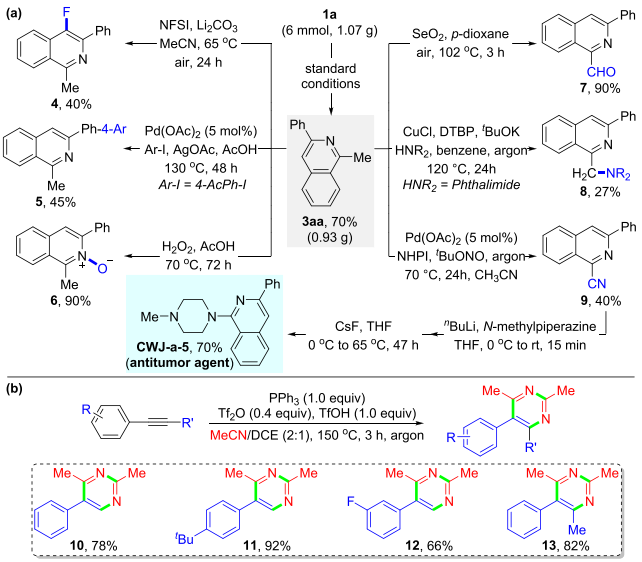


[a]Reaction conditions: compound **1** (0.10 mmol), PPh_3 (1.4 equiv), Tf_2O (0.4 equiv), TfOH (1.4 equiv), and R^3CN/DCE (1.2 mL, 2:1, v/v), under argon at 150 °C for 3 h. [b]Yields of isolated products. For isomers, products are isolated as mixtures. Positions of the substituents are labeled as indicated in the scheme. [c]Numbers in parentheses indicate the ratio of isomers. [d]With CH_3CN/DCE (1.2 mL, 1:2, v/v). [e]With PPh_3 (2.8 equiv), Tf_2O (0.8 equiv), and TfOH (2.8 equiv). [f]With TfOH (1.0 equiv). [g]With *n*PrCN/DCE (0.6 mL, 1:2, v/v).

yield). Moreover, alkynes possessing substituents on both aromatic rings were smoothly converted to the desired products in moderate to good yields (**3ua** and **3va**/**3va′**, 65 and 45% yield). Pleasingly, not only the benzene ring but also thiophene could be employed, affording a 3-thienyl-substituted isoquinoline derivative in 35% yield (**3wa**). Finally, butyronitrile and isovaleronitrile were compatible with this protocol as well, and the corresponding isoquinoline products were obtained in 32−65% yields (**3bb** and **3bc**).

To showcase the practicality of our strategy, gram-scale synthesis and further transformations were thereby conducted (Scheme 3). First, a 6 mmol scale reaction was performed, and product **3aa** was isolated in 70% yield (0.93 g). Because fluorinated compounds are important in pharmaceuticals, agrochemicals, and materials,[28] a fluorine atom was readily incorporated into compound **3aa** to produce compound **4** in 40% yield with NFSI/Li_2CO_3. Direct C−H arylation of compound **3aa** with palladium catalysis afforded product **5** in 45% yield, which showed an unusual *para*-regioselectivity compared to common 2-phenylpyridine substrates (preferring *ortho*-C−H functionalization[29]). Oxidation on the nitrogen atom can smoothly deliver compound **6** in 90% yield. In

Scheme 3. (a) Gram-Scale Synthesis of 3aa and Its Late-Stage Diversification and (b) Utilization of the Optimal Reaction Conditions



addition, the methyl group in compound **3aa** can readily convert into aldehyde **7** by SeO_2 (90% yield) or phthalimidated compound **8** via a copper-catalyzed dehydrogenative C−H/N−H coupling (27% yield). Notably, exposure of compound **3aa** to the $Pd(OAc)_2$/NHPI/*t*BuONO system[30] gave nitrile compound **9** (40% yield), which, after successive treatments with *n*-BuLi and *N*-methylpiperazine,[31] was formally transformed into the antitumor agent CWJ-a-5 in 70% yield. Moreover, as pyrimidines are fundamental structural motifs in various function molecules,[32] some elegant methods with nitriles and ketone or *N*-vinylacetamides as the regents and Lewis/Brønsted acids as the promoter have been developed.[33] Fortunately, when subjecting aromatic terminal alkynes and 1-aryl aliphatic alkynes to our reaction conditions, polysubstituted pyrimidines **10**−**13** can be obtained in 66−92% yields as well.

To shed light on the reaction mechanism, some ^{31}P NMR experiments were performed to elucidate the transformations between phosphorus-containing species (please refer to Section 15 in the Supporting Information). First, the ^{31}P NMR spectra indicate that mixing PPh_3 with Tf_2O in DCE mainly produces $(TfOPPh_3)^+Tf^-$ with a chemical shift of δ 54.3 ppm,[26] while PPh_3 with TfOH in DCE merely produces $(HPPh_3)^+(OTf)^-$ with a chemical shift of δ 5.1 ppm.[27] Second, after the addition of Tf_2O to the pre-formed DCE solution of PPh_3 and TfOH, the ^{31}P NMR spectra show that $(HPPh_3)^+(OTf)^-$ can be partially converted into $(TfOPPh_3)^+Tf^-$ upon heating the corresponding solution to 150 °C. Further, the pre-formed phosphonium salt $(TfOPPh_3)^+Tf^-$ or $(HPPh_3)^+(OTf)^-$ was subjected to the MeCN/DCE solution of diphenylacetylene at 150 °C for 3 h, respectively, and $(TfOPPh_3)^+Tf^-$ delivered compound **3ba** in 43% yield, while only a 6% yield was obtained with $(HPPh_3)^+(OTf)^-$ (mechanistic studies a and b of Scheme 4). These results unequivocally confirmed that $(TfOPPh_3)^+Tf^-$ is indispensable for our annulation process. Finally, ^1H NMR revealed 41% deuterium incorporation at the 4 position of compound **3ba** when performing the reaction under the standard conditions (using TfOD instead of TfOH) (Scheme

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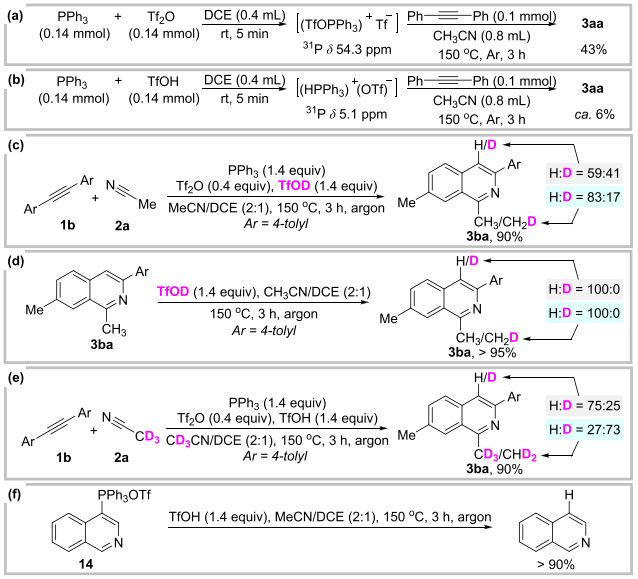
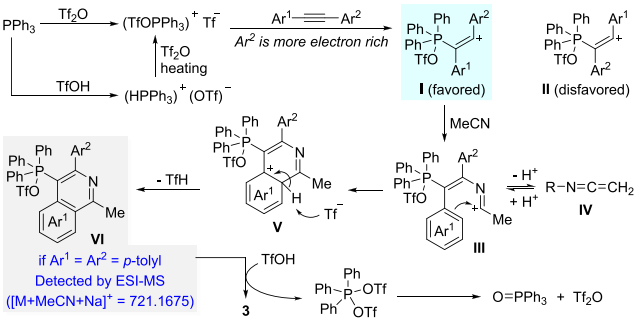
Scheme 4. Mechanistic Studies



4c). However, no deuterium product was detected upon reacting compound **3ba** with TfOD in MeCN/DCE at 150 °C for 3 h (Scheme 4d). Besides, a H/D exchange was also observed on the methyl group (mechanistic studies c and e of Scheme 4), which may be attributed to the deprotonation of nitrilium species into keteneimines.[34] Finally, upon treatment of the pre-synthesized compound **14** with TfOH, a nearly quantitative amount of isoquinoline was detected (Scheme 4f). These findings suggest that the phosphorane-type (or phosphonium) compounds most likely serve as a key intermediate to release the final products through an irreversible protonation reaction.

On the basis of the preliminary mechanistic studies, a tentative mechanism is proposed for the phosphonium-mediated annulation reaction in Scheme 5. The electrophile

Scheme 5. Proposed Mechanism



$(TfOPPh_3)^+Tf^-$ [generated from the reaction of PPh_3 and Tf_2O or from the conversion of $(HPPh_3)^+(OTf)^-$] undergoes an electrophilic addition reaction with alkynes to form the phosphorane-containing vinyl cation **II** (disfavored) or **I** (favored as the electron-rich nature of Ar^2 may stabilize cation **I**), which may readily react with acetonitrile to form the corresponding *N*-vinylnitrilium intermediate **III** (may form keteneimine **IV** after deprotonation[32]). Intermediate **III** then undergoes an electrophilic cyclization to give compound **V**, which subsequently forms compound **VI** [detected by electrospray ionization mass spectrometry (ESI−MS)] immediately upon reaction with anion Tf^-. The phosphorane-type compound **VI** may function as an isoquinoline anion equivalent, and a fragmentation-trapping event is driven by forming Ph_3PO (can be isolated) in the presence of TfOH to finally deliver product **3**.[12b]

In summary, we have reported a selective phosphoranation reaction of unactivated alkynes with phosphonium cation, which leads to the successful synthesis of various isoquinoline derivatives efficiently and regioselectively. This strategy marks a significant differentiation from reported reaction patterns and utilizations of phosphonium species. Besides, it provides a complementary yet effective platform to previous protocols for the elaboration of isoquinoline derivatives from simple readily available alkyne and nitrile feedstocks in a single step. The annulation reaction is believed to involve a series of cationic intermediates, thereby ensuring high regioselectivity. In addition, diverse modifications of the products indicate a broad potential for this reaction in the development and synthesis of new medicinal and pharmaceutical agents. Further application of the phosphoranation reaction is under investigation in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01237.

FAIR data, including the primary NMR FID files, for compounds **3aa**−**3ha**, **3ia**/**3ia′**−**3oa**/**3oa′**, **3pa**−**3ua**, **3va**/**3va′**, **3wa**, **3bb**, **3bc**, **4**−**13**, CWJ-a-5, **3ba** with TfOD, and **3ba** with CD_3CN (ZIP)

FAIR data for compounds **3aa**−**3ha**, **3ia**/**3ia′**−**3oa**/**3oa′**, **3pa**−**3ua**, **3va**/**3va′**, **3wa**, **3bb**, **3bc**, **4**−**13**, CWJ-a-5, **3ba** with TfOD, and **3ba** with CD_3CN (ZIP)

Experimental details and characterization of new compounds (PDF)

Accession Codes

CCDC 2080984 contains 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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Author Contributions

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Notes

The authors declare no competing financial interest.

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