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3-Amino-1-methyl-1*H*-pyridin-2-one-Directed Pd^{II} Catalysis: C(sp^3)−H Activated Diverse Arylation Reaction

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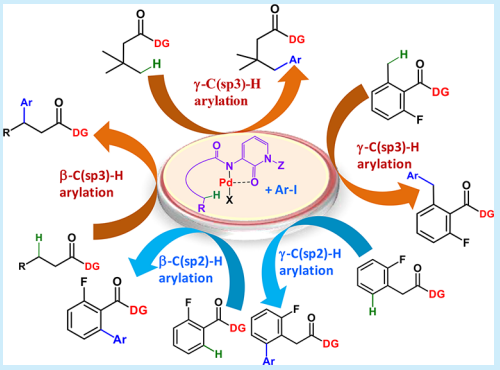
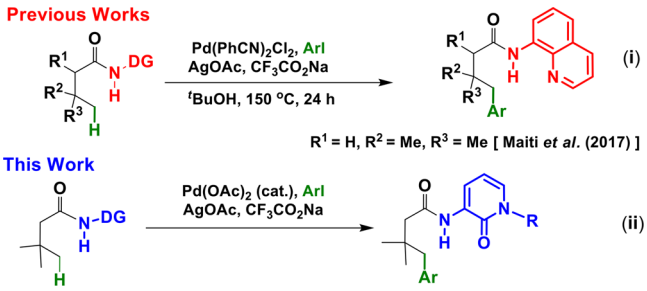
Supporting Information

ABSTRACT: A new bidentate directing group, 3-amino-1-methyl-1*H*-pyridin-2-one, is introduced to achieve a powerful Pd^{II} metallacycle for selective γ-C(sp^3)−H activation and arylation of aromatic and aliphatic carboxylic acid derivatives. The versatility of the directing group is validated for remote arylation of β-C(sp^3)−H, β-C(sp^2)−H, and γ-C(sp^2)−H to achieve therapeutically important 2-pyridone analogues and arylated acid synthons. The traceless removal of the directing group to retrieve the directing element and carboxylic acids makes this method more interesting.



The immense potential of C−H bond activation for organic transformations using organometallic catalysts has been realized in robust and efficient methods for carbon−carbon (C−C) and carbon−heteroatom (C−X) bond formation over the decades.[1] Several monodentate directing groups are reported for palladium-catalyzed direct C−C and C−X coupling.[1c,2] However, catalysis by bidentate directing groups in combination with metal catalysts[1c,2c] is now emerging as a more powerful tool to achieve valuable transformations, which might not be possible with conventional monodentate systems.[3] Arylation reactions are carried out under palladium-, rhodium-, iridium-, copper-, and nickel-mediated catalysis on electron-rich heterocycles.[4,5] In this context, selective C(sp^2)−H- and C(sp^3)−H-activated functionalization using 8-aminoquinoline as a bidentate ligand by Daugulis et al. is very interesting and significant because it is effective for site-selective arylation of aliphatic, alicyclic, and aromatic carboxamide derivatives.[6] The C(sp^2)−H activation is favored by precoordination of the arene-π-cloud to the transition metal as well as subsequent formation of an aryl−metal bond that is typically more stable than the corresponding alkyl−metal bond. However, from both kinetic and thermodynamic viewpoints, metal-catalyzed functionalization of nonactivated C(sp^3)−H bonds is relatively trickier than that of slightly more acidic C(sp^2)−H bonds. Moreover, γ-C(sp^3)−H activation suffers difficulties because of formation of a less favored six-membered cyclopalladation transition state involving alkyl C−H bonds. Corey et al. established that the presence of a phthalimido group at the α-position was beneficial for the arylation of γ-C(sp^3)−H bonds in valine using a bidentate directing group.[7] Progress on γ-C(sp^3)−H functionalization was desired,[8] and it is noteworthy that Carratero et al. performed a remote C(sp^3)−H arylation on dipeptides employing a metal-chelated *N*-(2-pyridyl) sulfonamide.[9] Recently, Maiti et al. reported the pioneering work for distal γ-C(sp^3)−H arylation of aliphatic carboxylic acid derivatives[10] using 8-aminoquinoline[10f] as the directing group (i, Scheme 1).

Scheme 1. γ-C(sp^3)−H Activated Functionalization Strategy



2-Pyridone is a core structure of a wide range of compounds, which displayed important biological activities such as jasmonate signaling inhibitor (Jarin-1),[11a] ICE inhibitor (interleukin-1B),[11b] CB2 antagonist,[11c] human leukocyte elastase inhibitor[11d] (Figure 1). It has also been used as a ligand for olefination of arenes.[11e] Recently, we were engaged in the synthesis of 2-pyridone derivatives for their potential application in medicinal chemistry, as synthons for industrial manufacturing, and as organocatalysts for enantioselective synthesis of nitrostyrenes (ee ≥95%).[12] Further, we envisaged

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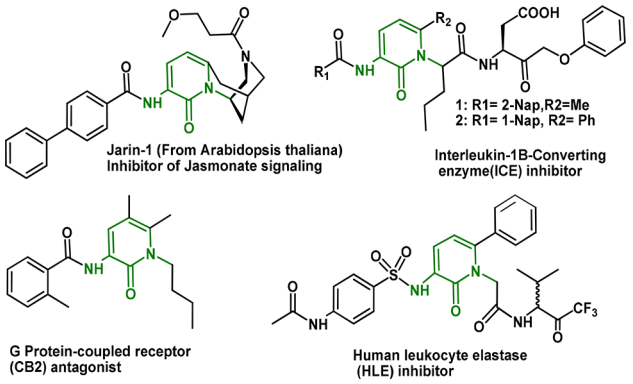
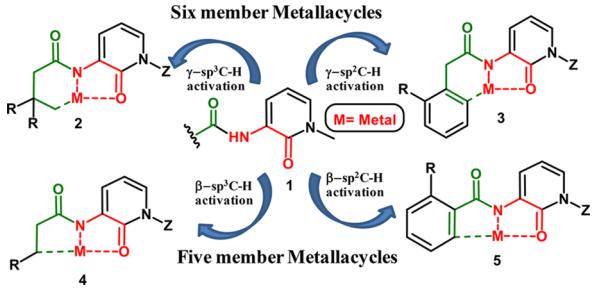


Figure 1. Bioactive 3-amino-2-pyridone derivatives.

that 3-amino-1-methyl-1*H*-pyridin-2-one (AMP, **1**) might be employed as a powerful directing group for activation of several types of C−H bonds through significant improvement of reactivity and selectivity of a suitable chelated metal, which will be able to furnish an array of therapeutically important 2-pyridone-bearing new compounds through late-stage C−H activation. According to our hypothesis, *N*,*O*-bidentate amides will be transformed into the required 5- and 6-membered metallacycles (**2**−**5**, Scheme 2) through activation of close

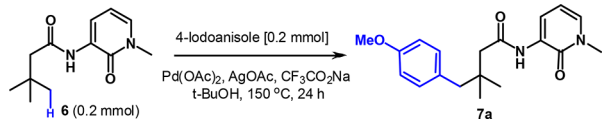
Scheme 2. Formation of Designed AMP Metallacycles



vicinity γ-C(sp^3)−H (**2**) and γ-C(sp^2)−H (**3**) as well as β-C(sp^3)−H (**4**) and β-C(sp^2)−H (**5**), which will eventually perform C−C coupled arylation. Herein, we report an unprecedented selective arylation strategy of a remote γ-C(sp^3)−H bond for both aliphatic and aromatic carboxylic acid derivatives using a new 2-pyridinone-based *N*,*O*-bidentate directing group (ii, iv, Scheme 1). To validate the γ-C(sp^3)−H arylation catalysis as a general strategy, we also established AMP as a versatile directing group for β-C(sp^3)−H, β-C(sp^2)−H, and γ-C(sp^2)−H arylation.

We synthesized 3-amino-2-pyridone **1**[13] according to our hypothesis and transformed it into the corresponding amide **6** (Supporting Information). Compound **6** was subjected to arylation with 4-iodoanisole as an arylating agent in the presence of $Cu(OAc)_2$ (10 mol %) catalyst, AgOAc, and CF_3CO_2Na under heating at 150 °C (oil bath temperature) in *tert*-butyl alcohol, and a trace of **7a** was obtained (entry 1, Table 1). Gratifyingly, upon use of $Pd(OAc)_2$ (1 mol %), the γ-sp^{3}C−H bond arylation reaction successfully afforded the desired monoarylated product **7a** with 24% yield (entry 2). The yield was improved to 40% and 57% upon an increase of catalyst loading (5 and10 mol %, entries 3 and 4). Our studies showed that the yield was drastically reduced (entries 5 and 6) when relatively low boiling protic polar solvents isopropyl alcohol (IPA) and *tert*-amyl alcohol were used. Interestingly, upon use

Table 1. Development and Optimization of γ-C(sp^3)−H Arylation



entry	catalyst (mol %)	base	solvent	time (h)	yield[a] (%)
1	$Cu(OAc)_2$ (10)	CF_3CO_2Na	*t*-BuOH	24	<5[b]
2	$Pd(OAc)_2$ (1)	CF_3CO_2Na	*t*-BuOH	24	24
3	$Pd(OAc)_2$ (5)	CF_3CO_2Na	*t*-BuOH	24	40
4	$Pd(OAc)_2$ (10)	CF_3CO_2Na	*t*-BuOH	24	57
5	$Pd(OAc)_2$ (10)	CF_3CO_2Na	IPA	24	<5[b]
6	$Pd(OAc)_2$ (10)	CF_3CO_2Na	*t*-AmylOH	24	10[b]
7	$Pd(OAc)_2$ (10)	CF_3CO_2Na	DCE	24	64
8	**$Pd(OAc)_2$ (10)**	**CF_3CO_2Na**	**dioxane**	**24**	**71**
9	$Pd(OAc)_2$ (10)	CF_3CO_2Na	toluene	24	47
10	$Pd(OAc)_2$ (10)	CF_3CO_2Na	dioxane	16	35
11	$Pd(OAc)_2$ (10)	CF_3CO_2Na	dioxane	32	69
12	$Pd(OAc)_2$ (10)	CF_3CO_2Na	dioxane	24	<5[b,c]
13	$Pd(OAc)_2$ (10)	CF_3CO_2Na	dioxane	24	20[d]
14	$Pd(PhCN)_2Cl_2$(10)	CF_3CO_2Na	dioxane	24	67
15	$PdCl_2(dppf)_2$(10)	CF_3CO_2Na	dioxane	24	57
16	$Pd(PPh_3)_4$ (10)	CF_3CO_2Na	dioxane	24	30
17	$Pd_2(dba)_3$ (10)	CF_3CO_2Na	dioxane	24	15
18	$Pd(OAc)_2$ (10)	CH_3CO_2Na	dioxane	24	60
19	$Pd(OAc)_2$ (10)	Ag_2CO_3	dioxane	24	45
20	$Pd(OAc)_2$ (10)	K_2CO_3	dioxane	24	<5[b]
21	$Pd(OAc)_2$ (10)	Cs_2CO_3	dioxane	24	<5[b]

[a]Monoarylated product isolated exclusively by column chromatography with traces of diarylated product (<5%, LCMS chromatogram). [b]As per LCMS chromatogram (products not isolated). [c]Reaction performed at 25 °C. [d]100 °C.

of aprotic 1,2-dichloroethane (DCE) and 1,4-dioxane, yields were greatly enhanced (64% and 71%, respectively, entries 7, 8). The yield was insignificant on use of nonpolar toluene (entry 9). The yield dropped to 35% with decreased reaction time (16 h), and remained comparable (69%) upon heating for 32 h (entries 10 and 11). The reaction was attempted at 25 and 100 °C, and formation of the desired product was significantly reduced (entries 12 and 13). Ligand-modified Pd(II) and Pd(0) catalysts were not effective (entries 14−17). Changing the base (CH_3CO_2Na and Ag_2CO_3) also decreased the yield to 60% and 45%, respectively (entries 18 and 19). Inferior reaction performance was observed with the use of other bases, such as K_2CO_3 and Cs_2CO_3 (entries 20 and 21).

The substrate scope of the γ-C(sp^3)−H arylation was investigated using various aryl iodides (Scheme 3) under the optimized reaction conditions (entry 8, Table 1). A wide range of aryl iodides worked well as a coupling partner with amide substrate (**6**). Both electron-donating and electron-deficient aryl iodides were tolerated for the regioselective insertion to unactivated γ-C(sp^3)−H bond. For instance, an electron-rich aryl iodide, *p*-methyliodobenzene, resulted a yield of 77% after isolation of **7c** by CombiFlash chromatography, whereas *m*-methyliodobenzene provided 64% yield (**7d**). A negligible quantity of the desired product (<5%, not shown) was detected from *o*-methyliodobenzene, which might be due to severe steric crowding in the transition state. Interestingly, the yield was relatively improved (**7e**, 45%) upon use of -nitroiodobenzene. These results indicate that γ-C(sp^3)−H arylation of the

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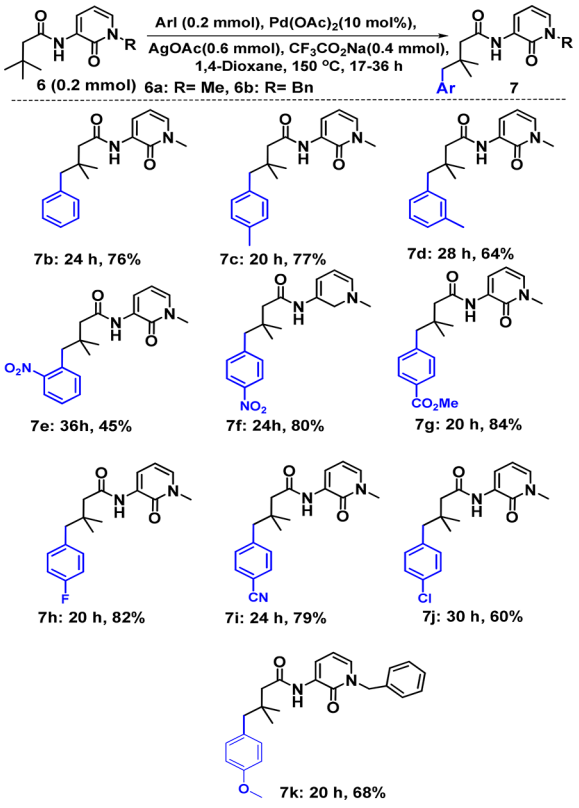
Scheme 3. Synthesized γ-C(sp^3)−H Arylated Products

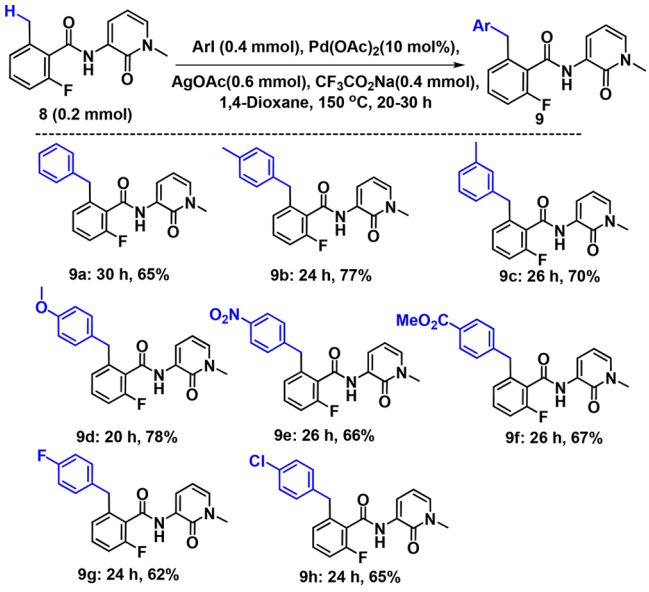


aliphatic amide is favored by electron deficient aryl iodides. Screening with aryl iodides possessing *p*-nitro, *p*-ester, *p*-fluoro, *p*-cyano, and *p*-chloro displayed formation of the corresponding arylated products (**7f−j**) in higher yield (60−84%). Corresponding *N*-benzyl-DG (**6b**) was also employed to obtain the desired product **7k** with moderate yield (68%).

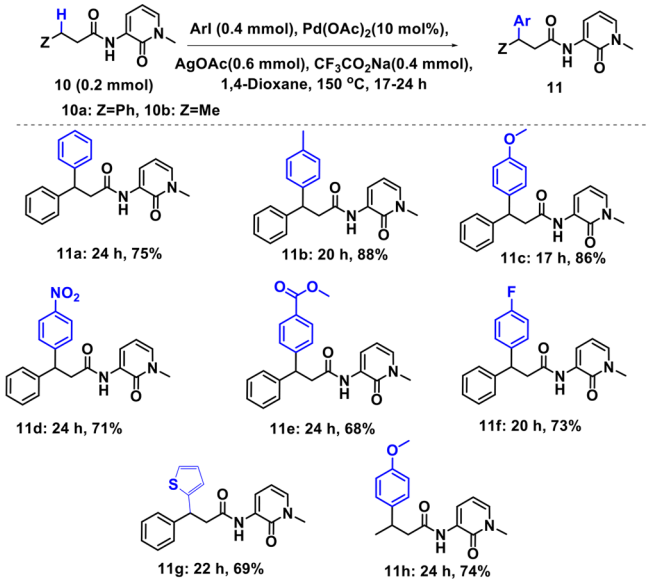
It is well established that fluorine-containing aryl moieties are highly important in pharmaceuticals and agrochemicals. In going forward and considering our main objective in this work as C(sp^3)−H bond activation, we chose fluorine-containing substrate **8** (Scheme 4) as our next starting material for arylation. We are delighted to report that exclusive mono-arylated products were obtained under the optimized reaction conditions. Activated aryl iodides such as 4-Me, 3-Me, and 4-OMe resulted higher yield (**9b−d**, 70−78%) with respect to unsubstituted PhI (**9a**, 65%). The yield was significantly reduced in the case of deactivated aryl iodides (**9e−h**, 53−66%). In contrast to the purely aliphatic γ-C(sp^3)−H bond arylation (Scheme 3), herein electron-donating group bearing aryl iodides appeared to be more effective for benzylic γ-C(sp^3)−H bond arylation of amide **8**.

After successful γ-C(sp^3)−H arylation, we explored our protocol for β-C(sp^3)−H arylation, and amide **10** was chosen to be the next substrate (Scheme 5). To our delight, β-C(sp^3)−H-arylated compounds (**11a−h**) were obtained using both electron-deficient and electron-rich aryl as well as heterocyclic thiophene iodides in good yield (68−88%). In contrary to the previous two reactions (Schemes 3 and 4), herein both the γ-C(sp^3)−H and β-C(sp^3)−H bonds activated arylation reactions (Scheme 5) were favored at the benzylic position with activated aryl iodides. Reproducibility and scalability of this method were successfully tested by performing a gram-scale reaction (**11a**).

Scheme 4. γ-C(sp^3)−H Bond Activated Arylation of Fluorine Substrates



Scheme 5. β-C(sp^3)−H Activated Arylation



General applicability of the catalytic C−C coupling strategy was visualized for even C(sp^2)−H-activated arylation. The precursor **12** and **13** were tested successfully to achieve arylated desired products **14a** and **14b** through β-C(sp^2)−H activation, as well as **15a** and **15b** involving γ-C(sp^2)−H functionalization. Both of the C(sp^2)−H bonds were efficiently arylated in 10−14 h at 100 °C (Scheme 6) to obtain the desired products in 70−82% yield.

Finally, diversity of the Pd^{II}-DG-AMP-catalyzed C−H activation was employed for arylation of a chiral amino acid derivative (**16**, Scheme 7). Herein, phthalimide-protected L-valine amide (**16**) was selectively transformed into the desired γ-arylated product (**17**, dr 4:1) despite an available β-hydrogen and labile chiral center.

Further, a traceless removal of the directing group was established (Scheme 8) through treatment of arylated product

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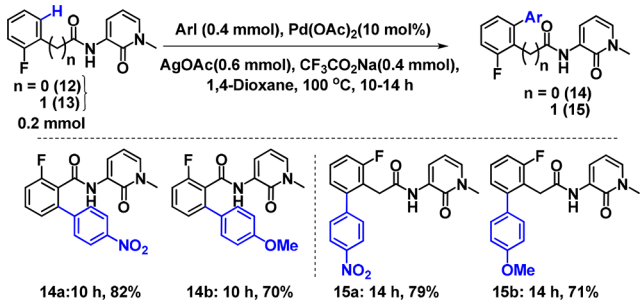
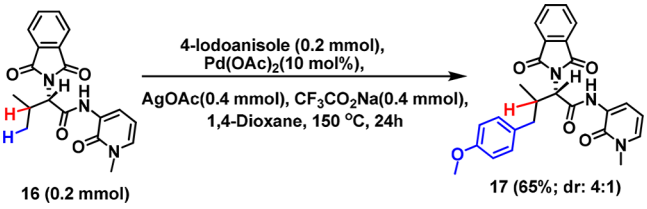
Scheme 6. β-C(sp^2)−H and γ-C(sp^2)−H Activated Arylation

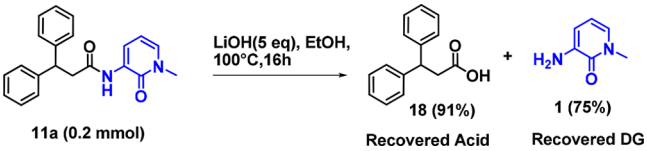


Scheme 7. γ-C(sp^3)−H Arylation of L-Amino Acid Derivative



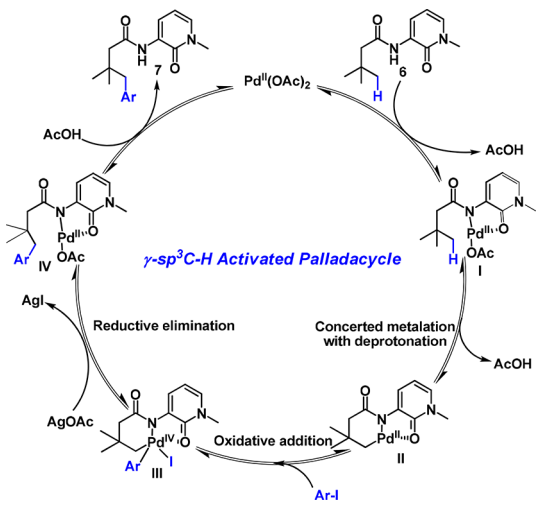
(**11a**) with LiOH at 100 °C to obtain the desired arylated acid (**18**) along with the recovered DG-AMP (**1**).

Scheme 8. Hydrolysis and Recovery of DG-AMP and Acid



In our studies, we observed that the reaction did not occur in the absence of AgOAc, procatalyst Pd^{II}, or DG-AMP. Thus, the combination of these compounds is crucial for sustaining the catalytic cycle. With the control experiments and literature reports,[6b,14] we propose the following mechanism through a Pd^{II}/Pd^{IV} redox cycle with our new DG-AMP (Scheme 9). We presume that $Pd(OAc)_2$ first complexes with the bidentate DG to generate an active catalyst **I** with the expulsion of AcOH. The reactive Pd^{II}-DG activates a C(sp^3)-Hin the close vicinity

Scheme 9. Possible Catalytic Cycle with the DG-AMP



leading to a generation of cyclometalated **II**. Oxidative addition of aryl iodide will form a putative intermediate **III** of Pd^{IV}, which may immediately undergo reductive elimination with C−C coupled arylation (**IV**). Finally, the product **7** will be released through regeneration of Pd^{II} procatalyst for the next palladacycle.

In conclusion, we report a new *N,O*-directing group AMP for Pd^{II}-catalyzed selective distal C(sp^3)−H arylation. The generality of the strategy is validated through arylation of several types of C(sp^3)−H as well as C(sp^2)−H at the β- and γ-positions of the amide analogues.This C−H activation method opens up a new window to synthesize therapeutically important 2-pyridone compounds, acid synthons, and new amino acid derivatives through late-stage C−H activation, which will find considerable application in the chemical science and its allied branches.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01618.

Detailed experimental procedures, spectroscopic data and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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