Enantioselective Palladium-Catalyzed Arylborylation/Cyclization of Alkenes to Access Boryl-Functionalized Heterocyclic Compounds Containing Quaternary Stereogenic Centers

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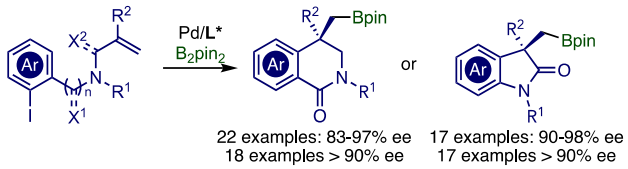
Supporting Information Placeholder



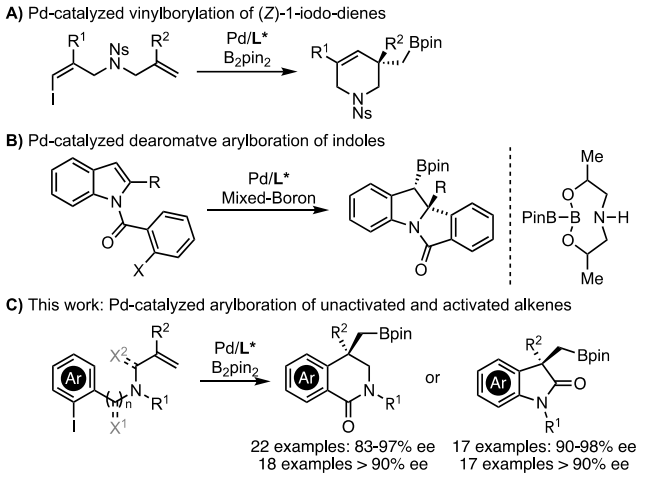
ABSTRACT: Asymmetric palladium-catalyzed arylboration/cyclization of both non-activated and activated alkenes with B_2pin_2 was developed. A wide range of N-allyl-*o*-iodobenzamides and *o*-iodoacryanilides reacted with B_2pin_2 to afford borylated 3,4-dihydroisoquinolinones and oxindoles, respectively, in high yields with high enantioselectivities. The synthetic utility of this enantioselective protocol was highlighted by synthesizing various chiral 3,4-dihydroisoquinolinone and oxindole derivatives containing quaternary stereogenic carbon centers, including enantioenriched Roche anti-cancer agent (*S*)-RO4999200.

Enantioenriched organoboron compounds are versatile building blocks for asymmetric synthesis because they can undergo various stereospecific transformations with minimal loss of their enantiopurity by converting C–B bonds to other C–X (X = carbon or heteroatoms) bonds.[1] Meanwhile, organoboron compounds have become increasingly important for medicinal chemistry and drug discovery because boronic acids can act as a bio-isostere of carboxylic acids to alter the physicochemical properties of lead compounds. For example, Ninlaro and Velcade, two enantiopure alkyl boronic acids, have been approved by the FDA for various therapeutic applications.[2] Therefore, it is highly significant and desirable to introduce boron moieties into core structures of biologically active compounds.

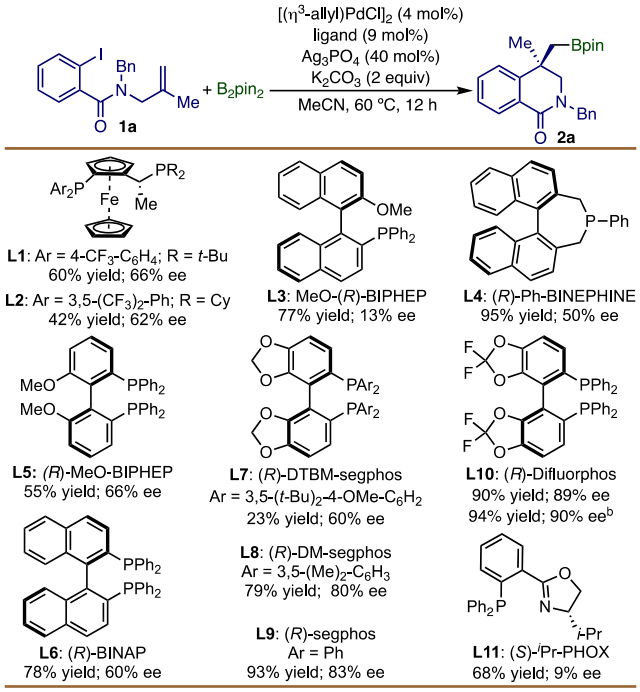
Chiral 3,4-dihydroisoquinolinone and oxindole skeletons are present in numerous bioactive natural products and drug molecules.[3] The enantioselective construction of such structural motifs with the concomitant incorporation of boryl groups is of general interest in medicinal chemistry and drug discovery. Asymmetric carboborylation of alkenes forms both C–C and C–B bonds in one reaction and provides a useful protocol to prepare chiral organoboron compounds.[4] The majority of these asymmetric carboborylation reactions are limited to activated alkenes and generate borylated chiral molecules containing tertiary stereogenic carbons,[5] and the reactions that can form quaternary carbons are rather limited.[6]

Enantioselective Pd-catalyzed Heck/cyclization has recently been emerging as a powerful tool to prepare five-membered chiral heterocyclic compounds,[7] but the analogous reactions that can form six-membered chiral cyclic compounds are rather limited.[8] Various nucleophiles, such as iodide, hydride, cyanide, terminal alkynes and other organometallic reagents, have been used to react with the alkylpalladium intermediates formed in the intramolecular Heck/cyclization step.[9] However, there are only a limited number of asymmetric Heck/cyclization reactions with boron nucleophiles to form enantioenriched borylated heterocyclic compounds.[8a,10] In 2017, The Tong group reported a Pd-catalzyed asymmetric vinylborylation of (*Z*)-1-iodo-dienes with B_2pin_2 to access tetrahydropyridines (Scheme 1A).[8a] Very recently, Jia and Lautens jointly reported a Pd-catalyzed dearomative arylborylation of indoles to prepare tetracyclic indolines, but a special sp^2-sp^3 boron reagent was required to avoid the use of inorganic bases which can cause the proto-deborylation of borylated indoline products (Scheme 1B).[10] Therefore, it still remains significant to develop asymmetric arylborylation reactions to access chiral heterocyclic compounds with readily available starting materials and chiral catalysts. Considering the synthetic versatility of organoboron compounds and the importance of 3,4-dihydroisoquinolinone and oxindole skeletons, we became interested in developing Pd-catalyzed asymmetric arylborylation/cyclization of alkenes with B_2pin_2 to prepare borylated 3,4-dihydroisoquinolinones and oxindoles[11] containing quaternary stereogenic carbon centers (Scheme 1C).[12] Heck/cyclization without further reactions with boron nucleophiles[13] or Miyaura borylation of aryl halides without Heck/cyclization may pose extra challenges to the development of Pd-catalyzed arylborylation/cyclization reactions of alkenes.[14]

Scheme 1. Palladium-catalyzed Heck/cyclization Borylation Reactions.



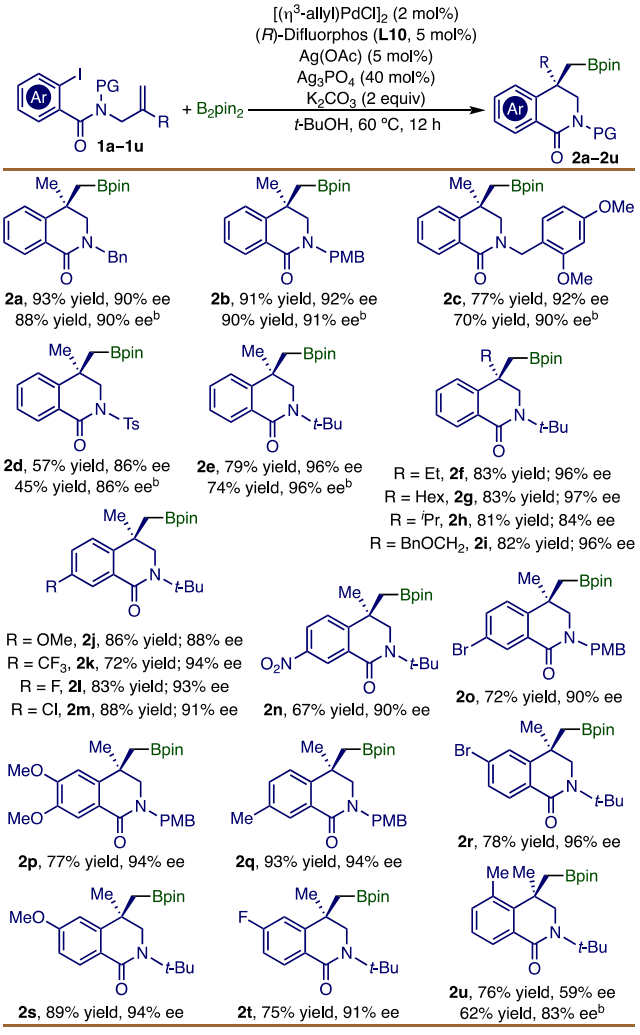
Scheme 2. Evaluation of Chiral Ligands for Pd-Catalyzed Arylborylation of Alkene 1a.[a]



[a]Reaction conditions: **1a** (0.050 mmol), B_2pin_2 (0.100 mmol), [(η^3-allyl)PdCl]$_2$ (2.0 μmol), ligand (4.5 μmol), K_2CO_3 (0.100 mmol), Ag_3PO_4 (0.020 mmol), and MeCN (1 mL) at 60 °C for 12 h; Yields were determined by NMR analysis of crude reaction mixtures using 4-dimethylaminopyridin (DMAP) as an internal standard; The ee values were determined by chiral HPLC analysis. [b]*t*-BuOH as solvent and Ag(OAc) (2.5 μmol) as additive.

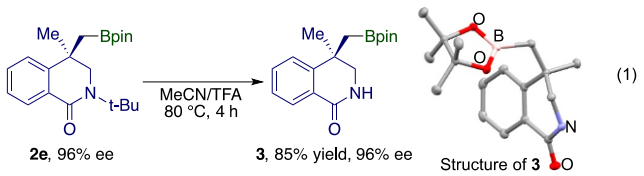
We initiated to study the palladium-catalyzed enantioselctive arylborylation by evaluating the reaction between *N*-allyl-*o*-iodobenzamide **1a** with B_2pin_2. We first tested several palladium catalysts generated in situ from [(η^3-allyl)PdCl]$_2$ and various chiral phosphine ligands for this reaction (Scheme 2). In general, the reactions were conducted with Ag_3PO_4 and K_2CO_3 as base in acetonitrile at 60 °C, and borylated isoquinolin-2-one **2a** was identified as the major product. The reactions conducted with the combination of [(η^3-allyl)PdCl]$_2$ and Josiphos-type ligands **L1** or **L2** afforded **2a** only in modest yields with 66% and 62% ee, respectively. The reactions carried out with palladium catalysts containing chiral monophosphine ligands **L3** or **L4** proceeded in high yields but with low enantioselectivity. Similar results were obtained when (*R*)-MeO-biphep (**L5**) and (*R*)-binap (**L6**) were employed for this reaction. We then tested segphos-type ligands with different steric properties (**L7**, **L8**, and **L9**) for this Pd-catalyzed arylborylation reaction and found that the reaction catalyzed by the combination of [(η^3-allyl)PdCl]$_2$ and sterically least hindered (*R*)-segphos (**L9**) afforded **2a** in 93% yield with 83% ee. The reaction performed with a palladium catalyst containing (*R*)-difluorphos (**L10**) generated **2a** in 90% yield with 89% ee. In addition, we also tested the arylborylation of **1a** with the palladium catalyst ligated by (*S*)-iPr-Phox (**L11**), which was selective for Pd-catalyzed asymmetric vinylborylation of alkenes.[8a] However, this reaction formed **2a** with very low enantioselectivity (9% ee). We then evaluated other reaction parameters, such as temperatures, solvents, and additives, for the arylborylation of **1a** (see the Supporting Information for the details), and found that the reaction catalyzed by [(η^3-allyl)PdCl]$_2$ and (*R*)-difluorphos with 5 mol% Ag(OAc) as additive in *t*-BuOH afforded **2a** in 94% yield with 90% ee.

Scheme 3. Scope of *N*-allyl-*o*-iodobenzamides.[a]



[a]Reaction conditions: alkene **1** (0.100 mmol), B_2Pin_2 (0.200 mmol), [(η^3-allyl)PdCl]$_2$ (2.0 μmol), (*R*)-difluorphos (**L10**, 5.0 μmol), K_2CO_3 (0.200 mmol), Ag_3PO_4 (0.040 mmol), Ag(OAc) (5.0 μmol), *t*-BuOH (1.0 mL), 60 °C, 24 h, and yields of isolated products; The ee values were determined by chiral HPLC analysis. [b](*R*)-segphos (**L9**, 5.0 μmol) was used.

The scope of N-allyl-*o*-iodobenzamides for this Pd-catalyzed asymmetric arylborylation reaction is summarized in Scheme 3. First, we performed the reactions of N-allyl-*o*-iodobenzamides containing various substituents on the nitrogen atom (**1a**–**1e**) in the presence of palladium catalysts ligated by (*R*)-segphos (**L9**) and (*R*)-difluorphos (**L10**), and these reactions afforded 3,4-dihydroisoquinolinone products (**2a**–**2e**) in good yields (42–90%) with high enantioselectivity (86–96% ee). Among **1a**–**1e**, substrate **1e**, which contains a *tert*-butyl group on the nitrogen atom, reacted with the highest enantioselectivity (96% ee). We then explored the asymmetric arylborylation of N-allyl-*o*-iodobenzamides containing varied substituents on the alkene unit (**1e**–**1i**) and at various positions of *o*-iodoaryl units (**1j**–**1u**). In general, these N-allyl-*o*-iodobenzamides reacted smoothly in the presence of 2 mol% [(η^3-allyl)PdCl]$_2$ and 4 mol% (*R*)-difluorphos (**L10**) to give the desired products (**2e**–**2t**) in high yields (67–93%) with high enantioselectivity (84–97% ee). N-allyl-*o*-iodobenzamide **1u**, which contains an *ortho*-disubstituted iodoaryl group, reacted to form product **2u** with only modest enantioselectivity (59% ee) when (*R*)-difluorphos (**L10**) was used as chiral ligand. However, the enantioselectivity of this reaction could be improved to 83% ee when it was catalyzed by the palladium compound ligated by (*R*)-segphos (**L9**). This palladium-catalyzed transformation could tolerate several functionalities, such as tosyl (**2d**), trifluoromethyl (**2k**), chloro (**2m**), nitro (**2n**) and bromo (**2o** and **2r**) moieties. The absolute configuration of **2e** was assigned as (*R*) by single-crystal X-ray diffraction analysis on compound **3**,[15] which was derived from **2e** by removing the *tert*-butyl group on the nitrogen under acidic conditions (eq 1).

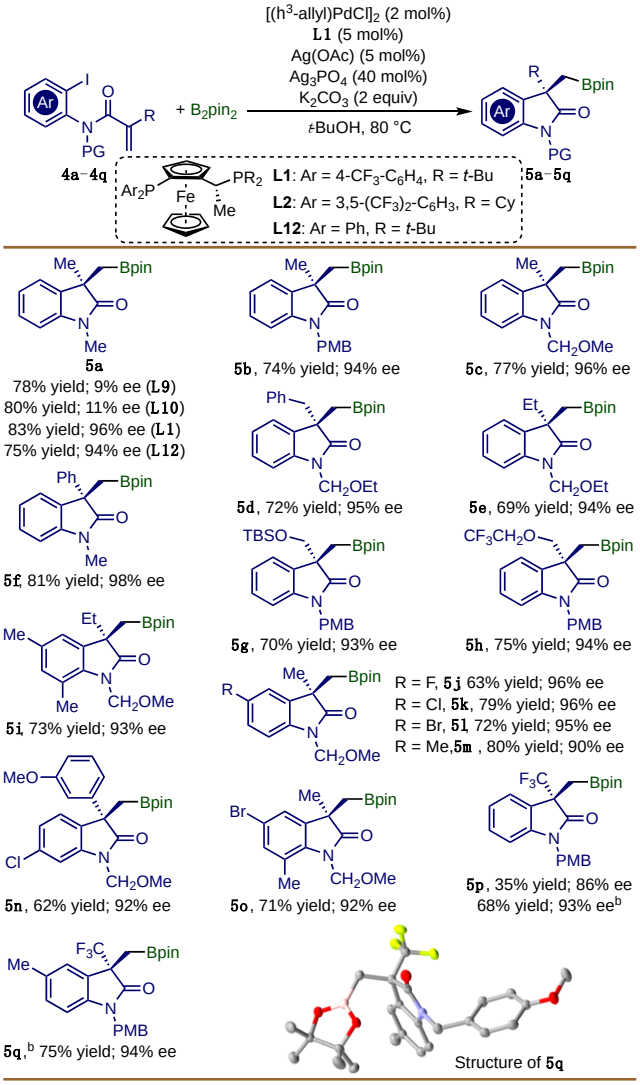


2e, 96% ee **3**, 85% yield, 96% ee Structure of **3**

After establishing the scope for enantioselective syntheses of 3,4-dihydroisoquinolin-1-ones, we subsequently tested this Pd-catalyzed asymmetric arylborylation with *o*-iodoacrylanilides, a family of activated alkenes, to prepare boryl-functionalized chiral oxindoles (Scheme 4). When catalyzed by [(η^3-allyl)PdCl]$_2$ and **L9** or **L10**, *o*-iodoacrylanilide **4a** reacted with B_2pin_2 to afford oxindole **5a** with very low enantioselectivity (9% ee and 5% ee when **L9** and **L10** were employed, respectively). However, after evaluating various chiral ligands for the arylborylation reaction of **4a** (see the Supporting Information for the details), we found that the palladium compounds containing Josiphos-type ligands **L1** or **L12** catalyzed this reaction effectively with excellent enantioselectivity (96% and 94% ee).

The scope of *o*-iodoacrylanilides that undergo this asymmetric arylborylation reaction was evaluated with 2 mol% [(η^3-allyl)PdCl]$_2$ and 5 mol% **L1** and the results are summarized in Scheme 3. *o*-Iodoacrylanilides containing various protecting groups on nitrogen atom (**4a**–**4d**) and various substituents on the alkene units (**4d**–**4h**) reacted with B_2pin_2 to afford the desired oxindoles (**5a**–**5h**) in high isolated yields (69–81%) with excellent enantioselectivity (94–98% ee). In addition, a series of *o*-iodoacrylanilides derived from various substituted anilines (**4i**–**4o**) also underwent this asymmetric arylborylation to afford the corresponding oxindoles (**5i**–**5o**) with high enantioselectivity (94–96% ee). Furthermore, this reaction could be employed to prepare chiral boryl-containing oxindoles with trifluoromethylated quaternary stereogenic centers (**5p** and **5q**), albeit with a different palladium catalyst ligated by Josiphos-type ligand **L2**. The absolute configuration of **5q** was assigned as (*S*) by single-crystal X-ray diffraction analysis.[15]

Scheme 4. Scope of *o*-Iodoacrylanilides.[a]

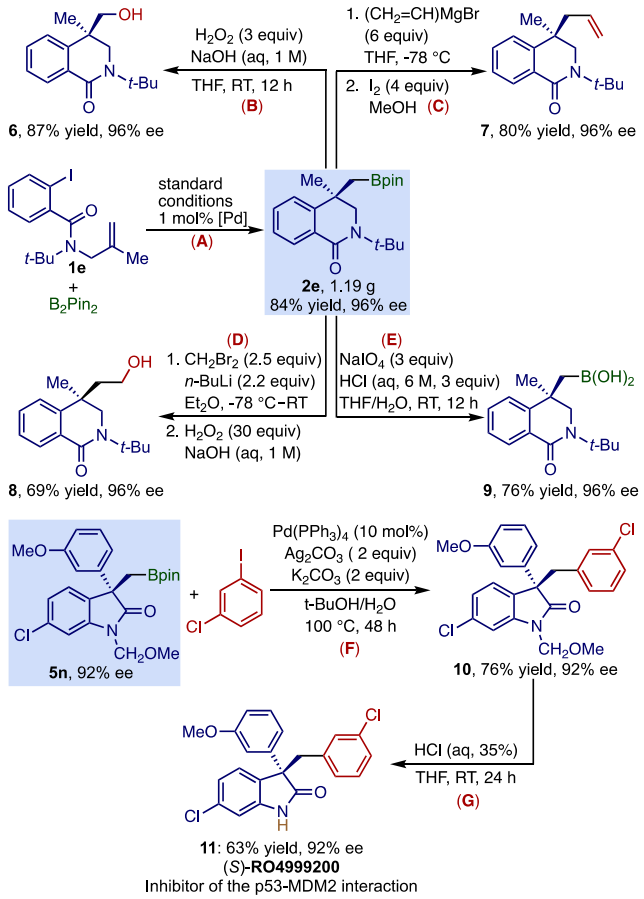


[a]Reaction conditions: alkene **4** (0.100 mmol), B_2Pin_2 (0.200 mmol), [(η^3-allyl)PdCl]$_2$ (2.0 μmol), ligand **L1** (5.0 μmol), K_2CO_3 (0.200 mmol), Ag_3PO_4 (0.040 mmol), Ag(OAc) (5.0 μmol), *t*-BuOH (1.0 mL), 80 °C, 24 h, and yields of isolated products; The ee values were determined by chiral HPLC analysis. [b]Ligand **L2** (5.0 μmol) was used..

To show the utility of this enantioselective protocol, we conducted a gram-scale arylborylation reaction between alkene **1e** and B_2pin_2 with a reduced catalyst loading of 0.5 mol% [(η^3-allyl)PdCl]$_2$ and 1.2 mol% (*R*)-segphos (**A** in Scheme 5),

and this reaction proceeded to full conversion of **1e** at 80 °C in 14 h and afforded **2e** in 84% isolated yield with excellent enantioselectivity (96% ee). The synthetic versatility of boryl-functionalized 3,4-dihydroisoquinolin-1-one and oxindole products was highlighted by a series of stereospecific transformations that occurred without loss of enantiopurity. For example, chiral alkylboronate **2e** could be oxidized by H_2O_2 to form enantioenriched alcohol **6** in 87% yield (**B** in Scheme 5). Vinylation of **2e** with vinylmagnesium bromide afforded allyl substituted 3,4-dihydroisoquinolin-1-one **7** in 80% yield (**C** in Scheme 5). Homologation of **2e** with $LiCH_2Br$ followed by the oxidation with H_2O_2 produced chiral alcohol **8** in 69% yield (**D** in Scheme 5). In addition, acidic hydrolysis of alkylboronate **2e** in the presence of $NaIO_4$ generated boronic acid **9** in 76% isolated yield (**E** in Scheme 5). Furthermore, we have demonstrated that this protocol could be employed to synthesize (*S*)-**RO4999200**, an inhibitor of the p53-MDM2 interaction, in high yield with high enantioselectivity (**F** and **G** in Scheme 5).[16] The cross-coupling reaction between boryl-functionalized oxindole **5n** and 3-chloroiodobenzene in the presence of 10 mol% $Pd(PPh_3)_4$ produced MOM-protected oxindole **10** in 76% yield with 92% ee, and subsequent MOM-deprotection with aqueous HCl in THF afforded **(*S*)-RO4999200** in 82% yield with 92% ee.

Scheme 5. Gram-scale Synthesis of 2e, Derivatization of 2e, and Synthesis of (*S*)-RO4999200 from 5n.



In summary, we have developed an enantioselective protocol to construct boryl-containing quaternary carbon stereocenters via Pd-catalyzed asymmetric arylborylation/cyclization of alkenes with B_2pin_2. In the presence of chiral palladium catalysts ligated by (*R*)-segphos (**L9**) or (*R*)-difluorphos (**L10**), a series of N-allyl-*o*-iodobenzamides, a family of non-activated alkenes, reacted to afford chiral 3,4-dihydroisoquinolinones in high yields with high enantioselectivity. For the arylborylation of *o*-iodoacrylanilides, which contain activated alkene units, to form boryl-functionalized oxindoles, palladium catalysts containing chiral Josiphos-type ligands **L1** or **L2** were needed. The chiral isoquinolinone or oxindole products can be readily derivatized to several other chiral molecules containing quaternary stereogenic carbons by enantiospecific transformations of their carbon-boron bonds. Diversifying substrates for this asymmetric Pd-catalyzed arylborylation/cyclization and their applications in the synthesis of complex molecules with quaternary stereogenic centers will be the subject of future studies.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details, characterization data, and copies of NMR spectra of all compounds (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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