Palladium-catalysed synthesis of triaryl(heteroaryl)methanes

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Tetraarylmethane derivatives are desirable for a variety of applications, but difficult to access with modern C–C bond-forming reactions. Here we report a straightforward method for palladium-catalysed arylation of aryl(heteroaryl)methanes and diaryl(heteroaryl)methanes with aryl chlorides. This reaction enables introduction of various aryl groups to construct triaryl(heteroaryl)methanes via a C–H functionalization in good to excellent yield, and represents the first step towards a general transition metal catalysed synthesis of tetraarylmethanes.
Tetraarylmethanes and related derivatives are important building blocks, with uses ranging from molecular devices to porous organic frameworks and applications from protein translocation detection to drug delivery. Furthermore, a recent study of 9,000 bioactive compounds by AstraZeneca to evaluate molecular space concluded that most biologically active compounds are linear or disk shaped, and very few are sphere-like molecules. They concluded that chemists should ‘... expand the current arsenal of tools to access less populated space ...’ and ‘... this may prove advantageous as the pharmaceutical industry ventures into new disease areas and new target classes which require different molecular shapes to bind and achieve the desired effect’. Tetraarylmethanes are members of sphere-like molecules that have not been widely explored due to synthetic difficulties.

The classic methods to synthesize tetraarylmethanes are based on Friedel-Crafts arylation (Fig. 1a) and nucleophilic addition of alkyllithium or Grignard reagents to benzophenone derivatives (Fig. 1b). Each of these approaches has well-known limitations. Friedel-Crafts reactions require arenes with electron-donating groups, often afford mixtures of regioisomers, and are not suitable when meta-substituted products are required. Aryl organometallic reagents are typically highly reactive, sensitive to traces of air and moisture, and exhibit limited functional group tolerance.

Transition metal-catalysed cross-coupling reactions have emerged as an excellent method to construct C–C bonds. For example, they have been used with great success in the coupling of aryl halides to diarylmethanes to afford triarylmethanes (Fig. 1c) (Fig. 1c). The application of transition metal catalysts to the synthesis of tetraarylmethanes, however, has proven quite challenging. This may be due to difficulties associated with the transmetallation of the bulky triarylmethyl organometallic species. Thus, there is tremendous unrealized potential in the transition metal catalysed construction of tetraarylmethane derivatives.

We are only aware of a handful of metal catalysed syntheses of tetraarylmethane derivatives. In their synthesis of triarylmethanes, Yorimitsu, Oshima and co-workers noted formation of 8% yield of a tetraarylmethane (Fig. 1c). Despite the intriguing nature of this byproduct, subsequent reports have not been forthcoming. Ghosh and co-workers reported the nickel-catalysed reaction of carbon tetrachloride and PhMgCl to form a 3:2 ratio of triphenylmethyl chloride to tetraphenylmethane (Fig. 1d). These products were not isolated. Recently, the palladium-catalysed arylation of fluorenes by the teams of Wu and Song, Xie, and Huang was reported to give diarylfluorenes (Fig. 1e). Fluorene is more acidic and less sterically demanding than other diarylmethane derivatives. In significant work, the team of Nambo and Crudden outlined the generation of triarylanitritiles, Ar3C–CN, then assemble a 4th heteroaryl group by building on the nitrile (Fig. 1f)30.

Figure 1 | Synthesis of tetraarylmethanes. (a,b) Classic approaches to tetraarylmethanes include the Friedel-Crafts electrophilic aromatic substitution and organometallic additions to triarylmethyl cation precursors. (c) Formation of 8% tetraarylmethane byproduct in the synthesis of triarylmethanes. (d) Arylation of carbon tetrachloride resulted in up to 39% conversion to tetraphenylmethane. (e) Arylation of fluorenes. (f) Sequential arylation/cycloaddition. (g) This work: arylation of 4-benzyl pyridine and (heteroaryl)diphenylmethanes to yield tetraarylmethane derivatives.

Figure 2 | Ligands screening. Preliminary reaction screen of 48 ligands.
Herein, we present a novel palladium-catalysed method for the synthesis of heteroaryl-substituted tetraarylmethane derivatives (Fig. 1g). This effort represents the first high-yielding transition metal catalysed preparation of tetraarylmethane derivatives. It enables the synthesis of a broad range of triaryl(heteroaryl)-methanes, including those with four different aryl groups attached to the central carbon atom.

Results

Preliminary catalyst screening. Given that the only example of arylation of a triarylmethane derivative we are aware of is Yorimitsu, Oshima and co-workers’ 8% yield of triphenyl(4-pyridyl)methane (Fig. 1c), we chose this starting point for our reaction design. Instead of CsOH, we employed KO-t-Bu, because of the greater solubility of this base. We reasoned that this would also allow us to lower the reaction temperature, and thus use toluene as the solvent. We initiated a search for a suitable catalyst for bis-arylation of 4-benzylpyridine (1a) with bromobenzene (2a) by examining phosphine ligands on microscale using 10 mol% of 1a (see Supplementary Table 1). Thus, 48 electro-nically diverse mono- (20 mol%) and bidentate phosphine ligands (10 mol%) were tested using Pd(OAc)2 (10 mol%) and 4 equiv KO-t-Bu. Reactions were conducted at 110°C for 12 h, cooled, and

| Table 1 | Optimization of diarylation of 1a with 2b or 2d.* |

| entry | L | Pd/L (mol%) | Assay yield (%)\(^1\) |
|-------|---|-------------|-----------------------|
| 1     | L1 | 10/20       | 68\(^1\)              |
| 2     | L2 | 10/20       | 77\(^1\)              |
| 3     | L2 | 10/20       | 76\(^1\)              |
| 4     | L1 | 10/20       | 66                    |
| 5     | L2 | 10/20       | 74                    |
| 6     | L1 | 5/10        | 67                    |
| 7     | L1 | 2.5/5       | 35                    |

*Reactions performed using 1 equiv. of 1a, 4 equiv. of 4-chlorotoluene 2d and 4 equiv. of KO-t-Bu on a 0.25 mmol scale.
\(^1\)Yields determined by 1H NMR analysis of crude mixtures with CH2Br2 as internal standard.
\(^2\)Reaction performed using 4-bromotoluene 2b.
\(^3\)Isolated yield.

| Table 2 | Optimization of diarylation of 4-benzylpyridine 1a with 4-chlorotoluene 2d.* |

| entry | Conc (M) | solvent | base       | 1a:2d:3 | Assay yield (%)\(^1\) |
|-------|----------|---------|------------|---------|-----------------------|
| 1     | 0.1      | toluene | LiO-t-Bu   | 1:4:4   | 10                    |
| 2     | 0.1      | toluene | NaO-t-Bu   | 1:4:4   | 83                    |
| 3     | 0.1      | toluene | LiNC(SiMe\(_3\))\(_2\) | 1:4:4 | 17                    |
| 4     | 0.1      | toluene | NaNC(SiMe\(_3\))\(_2\) | 1:4:4 | 58                    |
| 5     | 0.1      | toluene | KN(SiMe\(_3\))\(_2\) | 1:4:4 | 19                    |
| 6     | 0.05     | toluene | NaO-t-Bu   | 1:4:4   | 12                    |
| 7     | 0.2      | toluene | NaO-t-Bu   | 1:4:4   | 86                    |
| 8     | 0.4      | toluene | NaO-t-Bu   | 1:4:4   | 84                    |
| 9     | 0.2      | THF     | NaO-t-Bu   | 1:4:4   | 90                    |
| 10    | 0.2      | DME     | NaO-t-Bu   | 1:4:4   | 88                    |
| 11    | 0.2      | CPME    | NaO-t-Bu   | 1:4:4   | 81                    |
| 12    | 0.2      | 1,4-dioxane | NaO-t-Bu | 1:4:4 | 82                    |
| 13    | 0.2      | THF     | NaO-t-Bu   | 1:4:4   | 37\(^1\)              |
| 14    | 0.2      | THF     | NaO-t-Bu   | 1:2:2   | 86                    |
| 15    | 0.2      | THF     | NaO-t-Bu   | 1:3:3   | 96(92\(^2\))          |
| 16    | 0.2      | THF     | NaO-t-Bu   | 1:3:4   | 92                    |
| 17    | 0.2      | THF     | NaO-t-Bu   | 1:4:2   | 85                    |
| 18    | 0.2      | THF     | NaO-t-Bu   | 1:4:3   | 93                    |

*Reactions performed using Pd(OAc)2 (5 mol%), PCy\(_3\) (10 mol%), 1.0 equiv. of 1a and 4 equiv. of 2d on a 0.25 mmol scale.
\(^1\)Yields determined by 1H NMR analysis of crude mixtures with CH2Br2 as internal standard.
\(^2\)The reaction temperature was 80°C.
\(^3\)Isolated yield.
Table 3 | Scope of aryl chlorides 2 in benzylic C–H bis-arylation of aryl(4-pyridyl)methanes 1.

|        | Pd(OAc)₂ (5 mol%) | L (10 mol%) | NaO\(_2\)Bu solvent | 100 °C, 12 h |
|--------|-------------------|-------------|----------------------|-------------|
| 1      |                   |             |                      |             |
| 2a     | <4,4\'-di-tert-butylbiphenyl> | <4,4\'-di-tert-butylbiphenyl> | <4,4\'-di-tert-butylbiphenyl> |

| 4a     | 74%†               |             |                      |             |
| 4b     | 92%‡               |             |                      |             |
| 4c     | 91%†               |             |                      |             |
| 4d     | 99%                |             |                      |             |
| 4e     | 94%†               |             |                      |             |
| 4f     | 93%♭               |             |                      |             |
| 4g     | 84%♭               |             |                      |             |
| 4h     | 96%                |             |                      |             |
| 4i     | 91%♭               |             |                      |             |
| 4j     | 85%♭               |             |                      |             |
| 4k     | 83%                |             |                      |             |
| 4l     | 82%                |             |                      |             |
| 4m     | 94%¶               |             |                      |             |
| 4n     | 61%¶               |             |                      |             |
| 4o     | 57%¶               |             |                      |             |
| 4p     | 84%¶               |             |                      |             |
| 4q     | 91%♭               |             |                      |             |
| 4r     | 86%♭               |             |                      |             |
| 4s     | 94%                |             |                      |             |
| 4t     | 87%                |             |                      |             |

*Isolated yields; reactions conducted on a 0.1 mmol scale using Pd(OAc)₂ (5 mol%), PCy₃ (10 mol%), 1 (1 equiv), 2 (3 equiv) and NaO₂Bu (3 equiv) in THF (0.2 M) at 100 °C.
†Reactions conducted on a 0.1 mmol scale using 1 (equiv), 2 (4 equiv) and NaO₂Bu (4 equiv) in THF (0.2 M) at 100 °C.
‡Reactions conducted on a 0.25 mmol scale.
¶Reactions conducted on a 0.1 mmol scale using Pd(OAc)₂ (5 mol%), cataCXium A (10 mol%), 1 (1 equiv), 2 (4 equiv) and NaO₂Bu (4 equiv) in 1,4-dioxane (0.2 M) at 100 °C.
§Reactions conducted on a 0.1 mmol scale using Pd(OAc)₂ (5 mol%), cataCXium A (10 mol%), 1 (1 equiv), 2 (4 equiv) and NaO₂Bu (4 equiv) in 1,4-dioxane (0.1 M) at 100 °C.

Repeating the bis-arylation reaction in Fig. 2 using 4-benzylpyridine 1a and 4-bromotoluene 2b with PCy₃ (L1) and cataCXium A (L2) on laboratory scale (0.25 mmol) led to the desired product in 68% isolated yield (entry 3). Considering that aryl chlorides are more abundant and less expensive than aryl bromides, we examined aryl chlorides. In the event, the reaction of 4-benzylpyridine 1a with PCy₃, we chose to first optimize the reaction with the more economical and readily available PCy₃. As outlined below, more challenging substrates gave better results with cataCXium A. To begin with, the catalyst loading was examined. Changing the loading from 10 to 5 mol% resulted in no change in AY (entry 6). Further reducing the amount of catalyst to 2.5 mol%, however, resulted in a drop to 35% (entry 7).

We next focused on the bases (LiO₂Bu, NaO₂Bu, LiN(SiMe₃)₂, NaN(SiMe₃)₂ and KN(SiMe₃)₂) and reaction concentration (Table 2, entries 1–8). LiO₂Bu and LiN(SiMe₃)₂ gave low yields (10–17%), probably because their stable aggregates result in less reactive bases (entries 1 and 3)⁵¹. NaN(SiMe₃)₂ and KN(SiMe₃)₂ are stronger bases, but resulted in some decomposition and lower yields (entries 4 and 5). The best combination from this screen was 5 mol% Pd(OAc)₂, 10 mol% PCy₃ and NaO₂Bu in toluene (0.2 M) for 12 h at 100 °C (entry 2). Solvents play an important role in deprotonative cross-coupling reactions. Therefore, four additional solvents (THF, DME, CPME and 1,4-dioxane) were examined at 100 °C.
Among these, THF led to 90% AY of the diarylation products (entries 9–12). Reducing the reaction temperature to 80 °C resulted in a decrease in the AY to 37% (entry 13). The 4-benzylpyridine: 4-chlorotoluene: base ratio was next explored (entries 14–18). The use of a 1:3:3 ratio rendered 96% AY and 92% isolated yield (entry 15).

**Diarylation of aryl(4-pyridyl)methanes.** Under the optimized reaction conditions (Table 2, entry 15), the deprotonative cross-coupling process (DCCP) with various aryl(4-pyridyl)methanes and aryl chlorides generally gave products in good to excellent yields (Table 3). Coupling of 4-benzylpyridine and alkyl substituted derivatives with chlorobenzene or analogues possessing alkyl substituents in the meta or para positions resulted in products 4a–4e in 74–99% yield. Coupling with sensitive substrates, such as 4-chlorobenzonitrile and 4-chlorobenzophenone, required cataCXium A, furnishing 93 and 84% yield of 4f and 4g, respectively. In the absence of the palladium catalyst, 4-chlorobenzophenone gave 33% AY of the triarylmethane and no tetraarylmethane product.

Using cataCXium A, reaction with 3-chloroanisole and 1-chloro-3,5-dimethoxybenzene provided the bis-arylated products 4h and 4i in 96 and 91% yield, respectively. Good yields were obtained using electron rich 4-chloro anisole (82–83%, 4k–l). Using 4-chloro-N,N-dimethylaniline under the standard conditions provided 4j in 85% yield (cataCXium A as the ligand). Heterocyclic compounds are present in many pharmaceuticals. The heterocyclic catechol derivative 4m formed in 94% yield (cataCXium A). With cataCXium A, 3-pyridylchloride and 5-chloro-1-methyl-1H-indole underwent reaction to give products 4n–4p in 57–84% yield. Benzylpyridines possessing benzyl groups with 4-OMe, 4-F and 3-CF₃ furnished products in 86–94% yield (4q–4t) (4q and 4r employed cataCXium A). It is noteworthy that many of these yields are high, despite undergoing two coupling events.

**Monoarylation of diaryl(heteroaryl)methanes.** The ability to synthesize tetraarylmethanes with four different aryl groups would provide greater synthetic flexibility. Based on the successful bis-arylation of 4-benzyl pyridines above, we explored the

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**Table 4 | Scope of aryl chlorides 2 in benzylic C–H arylation of diaryl(4-pyridyl)methanes 5.**

| 2  | 5  | Pd(OAc)₂ (5 mol%) | L (10 mol%) | NaOt-Bu | solvent | 100 °C, 12 h |
|----|----|-------------------|------------|---------|---------|-----------|
| 6a | 4a | 97%               |            |         |         |           |
| 6b | 4b | 96%               |            |         |         |           |
| 6c | 4c | 92%               |            |         |         |           |
| 6d | 4d | 97%               |            |         |         |           |
| 6e | 4e | 96%               |            |         |         |           |
| 6f | 4f | 91%               |            |         |         |           |
| 6g | 4g | 89%               |            |         |         |           |
| 6h | 4h | 97%               |            |         |         |           |
| 6i | 4i | 97%               |            |         |         |           |
| 6j | 4j | 78%               |            |         |         |           |
| 6k | 4k | 92%               |            |         |         |           |
| 6l | 4l | 88%               |            |         |         |           |
| 6m | 4m | 94%               |            |         |         |           |
| 6n | 4n | 96%               |            |         |         |           |
| 6o | 4o | 77%               |            |         |         |           |
| 6p | 4p | 73%               |            |         |         |           |
| 6q | 4q | 78%               |            |         |         |           |
| 6r | 4r | 76%               |            |         |         |           |
| 6s | 4s | 77%               |            |         |         |           |
| 6t | 4t | 91%               |            |         |         |           |

*Isolated yields; reactions conducted on a 0.1 mmol scale using Pd(OAc)₂ (5 mol%), PCy₃ (10 mol%) (1 equiv), 2 (2 equiv) and NaOt-Bu (2 equiv) in THF (0.2 M) at 100 °C.
†Reactions conducted on a 0.1 mmol scale using Pd(OAc)₂ (5 mol%), cataCXium A (10 mol%), 5 (1 equiv), 2 (2 equiv) and NaOt-Bu (2 equiv) in 1,4-dioxane (0.2 M) at 100 °C.
‡Reactions conducted on a 0.1 mmol scale using Pd(OAc)₂ (5 mol%), cataCXium A (10 mol%), 5 (1 equiv), 2 (2 equiv) and NaOt-Bu (2 equiv) in 1,4-dioxane (0.1 M) at 100 °C.
monoarylation of diaryl(4-pyridyl)methanes 5 (Table 4). Triarylmethanes are readily prepared by arylation of diphenylmethane derivatives using our prior approach (see Supplementary Methods)\(^3\).

Employing diaryl(4-pyridyl)methanes with two phenyl groups or one phenyl and one alkyl substituted aryl, aryl chlorides with alkyl or neutral groups furnished 6\(a\) and 6\(b\) in 97 and 96% yield, respectively. Aryl chlorides with 3-CN, 3-CF\(_3\), 4-COPh, 4-CN, 4-CF\(_3\), 4-F and 3-OMe reacted with 89–97% yield (6\(c\)–6\(i\)). Aryl chlorides bearing electron-donating groups 4-OMe and 4-NMe\(_2\), as well as catechol, underwent coupling in 78–92% yield (6\(j\)–6\(l\)). Heterocyclic aryl chlorides, including 3-pyridyl, 5-(N-methyl indole), and 6-quinolyl participated in the coupling with cataCXium A in 73–96% yield (6\(m\)–6\(r\)). Diaryl(4-pyridyl)methanes with a phenyl and 3,5-bis-CF\(_3\) aryl groups substituted aryl also participated in DCCP to produce the desired products 6\(s\) and 6\(t\) in 77 and 91% yield, respectively. In addition to the high yields generally observed in the synthesis of tetraaryl methane derivatives, it is noteworthy that many of the products contain chiral quaternary centres.

Due to the significance of heterocycles in drug discovery and in material science, we chose diphenyl(2-benzothiazolyl)methane (8\(a\)), diphenyl(2-benzoxazolyl)methane (8\(b\)) prepared from 2-methylthiazole (7\(a\)), 2-methylbenzoxazole (7\(b\)) using the literature approach\(^2\) (see General Methods A and Supplementary Methods) and diphenyl(2-pyridyl)methane (8\(c\)) to expand the scope of our tetraaryl methane synthesis (Table 5). Heteroaryl chlorides such as 3-chloropyridine and 6-chloroquinoline underwent coupling with diphenyl(heteroaryl)methanes (8), to furnish tetraaryl methane derivatives (9), in high isolated yields (86–94%). In addition, 5-chlorobenzothiophene and 1-(4-chlorophenyl)-1\(H\)-pyrrole proved to be suitable aryl chlorides, furnishing products 9\(c\) and 9\(d\) in 61 and 63% yield, respectively. Diphenyl(2-pyrindyl)methane coupled with 4-chlorotoluene to give 9\(g\) in 93% yield. With this catalyst system, less acidic diphenyl(3-pyridyl)methane did not afford the desired product under the optimized reaction conditions.

To demonstrate the potential utility of our method, we performed a gram scale reaction of 4-benzylpyridine 1\(a\) with 4-chlorobenzophenone 2\(j\). The desired product 4\(g\) was obtained in 79% yield (1.88 g, Fig. 3), demonstrating the reaction is scalable (see Supplementary Methods).

Kato and co-workers reported a liquid-crystalline bowl-shaped molecule that form columnar and micellar cubic structures, using triary(4-pyridyl)methane moieties as building blocks\(^1\). In order to apply our method, we synthesized the same compound (Fig. 4) from the reaction product 4\(q\) (Table 3). It is noteworthy that Kato synthesized triary(4-pyridyl)methane was based...
Figure 4 | Transformation of reaction product. Synthesis of liquid crystal former 11.

Methods

General procedure A. An oven-dried 8.0 ml reaction vial equipped with a stir bar was charged with 2-methylthiazole (7a, 0.50 mmol, 1.0 equiv) or 2-methylbenzoazole (7b, 0.50 mmol, 1.0 equiv) and chlorobenzene (2e, 3.0 equiv) in a glove box under nitrogen atmosphere at room temperature. A stock solution containing Pd(OAc)2 (5.6 mg, 0.025 mmol, 5 mol%) and PCy3 (14.0 mg, 0.05 mmol, 10 mol%) in dry o-xylene (2.5 ml). Then, NaOr-Bu (3.0 equiv) was added to the reaction mixture. The vial was capped, removed from the glove box, and heated to 130 °C for 12 h with stirring. The reaction mixture was quenched with three drops of H2O, diluted with 3 ml of ethyl acetate, and filtered over a pad of MgSO4 and silicon gel. The crude material was loaded onto a deactivated silica gel column and purified by flash chromatography to afford the desired products 8a and 8b in 81 and 49% yield, respectively.

General procedure B. An oven-dried 8 ml reaction vial equipped with a stir bar was charged with aryl(4-pyridyl)methanes (1, 0.10 mmol, 1.0 equiv) or diaryl(heteroaryl)methanes (5, 0.10 mmol, or 8, 0.20 mmol, 1.0 equiv) and aryl chlorides (2, 2.0–4.0 equiv) in a glove box under a nitrogen atmosphere at room temperature. A stock solution containing Pd(OAc)2 (1.1 mg, 0.005 mmol, 5 mol%) and PCy3 (2.8 mg, 0.01 mmol, 10 mol%) in dry THF or cатаCКuM (3.6 mg, 0.01 mmol, 10 mol%) in dry 1,4-dioxane was taken up by syringe and added to the reaction vial under nitrogen. Then, NaOr-Bu (2.0–4.0 equiv) was added to the reaction mixture. The vial was capped, removed from the glove box, and heated to 100 °C for 12 h with stirring. The reaction mixture was quenched with three drops of H2O, diluted with 3 ml of ethyl acetate, and filtered over a pad of MgSO4 and silicon gel. The pad was rinsed with ethyl acetate (3 × 2 ml) and the combined solutions were concentrated in vacuo. The crude material was loaded onto a deactivated silica gel column and purified by flash chromatography to afford the desired products.

Discussion

Our research team has been interested in the catalytic functionalization of weakly acidic sp3-hybridized C–H bonds through a DCCP. These reactions involve a weakly acidic C–H of the substrate (pronucleophile) that is reversibly deprotonated through a DCCP. These reactions involve a weakly acidic C–H of the substrate (pronucleophile) that is reversibly deprotonated under the reaction conditions. Subsequently, the nucleophile undergoes catalyst promoted arylation or vinylation. This method has been particularly successful with the generation of triarylmethanes. Tetraarylmethane derivatives are challenging to efficiently prepare by both classical and state-of-the-art methods. The breadth of their applications has outpaced chemists’ ability to prepare them in a concise fashion. Cross-coupling methods represent an appealing approach to tetraarylmethane derivatives, but to date successful reports of such processes are still lacking. Outlined herein is a palladium-catalysed DCCP for direct arylation of aryl(heteroaryl)methanes and diaryl(heteroaryl)methanes with aryl chlorides to provide triaryl(heteroaryl)methanes. Unlike traditional cross-coupling procedures, which employ prefunctionalized coupling partners, our approach relies on reversible deprotonation of the diarylmethane derivatives under the conditions used for the catalytic C–C bond forming reaction. Under our reaction conditions, a variety of triaryl(heteroaryl)methanes were prepared in good to excellent yields. This communication represents the first steps towards our goal of developing metal catalysed approaches for the construction of a wide range of tetraarylmethanes.

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Author contributions
S.Z. performed the experiments, B.-S.K. and J.M. performed the initial reaction development. C.W. performed screening experiments. P.J.W. devised the project and provided overall supervision. All authors contributed to writing the manuscript.

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