RESEARCH ARTICLE doi.org/10.1002/adsc.70169 ADVANCED SYNTHESIS & CATALYSIS

Facile Synthesis of Chiral *gem*-Difluorocyclopropanes via Rhodium-Catalyzed Hydrogenation

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Abstract: A rhodium-catalyzed asymmetric hydrogenation of *gem*-difluorocyclopropenyl esters or ketones has been achieved, affording the disubstituted *cis*-*gem*-difluorocyclopropanes with high enantio- and diastereoselectivities (up to 99% ee and >20:1 dr). Furthermore, the hydrogenation proceeds smoothly at gram scale without erosion of activity and enantioselectivity. The chiral *gem*-difluorocyclopropane products could be transformed into chiral building blocks and bioactive molecule.

Keywords: asymmetric hydrogenation, *gem*-difluorocyclopropanes, *gem*-difluorocyclopropenes, rhodium catalyst

1. Introduction

Chiral *gem*-difluorocyclopropyls are ubiquitous structural units found in many important natural products and bioactive molecules due to their inherent ring strain of cyclopropane[1] and unique fluorine effect.[2,3]The strategic introduction of a *gem*-difluorocyclopropane unit into a bioactive molecule often enhances the drug's metabolic kinetics, improves the ability to form hydrogen bonds, optimizes acid–base stability, and enhances lipophilicity as well as cell permeability.[4–6] For example, in the research of the bioactive molecules MS-073 and GNE-9822, the introduction of the chiral *gem*-difluorocyclopropyl group resulted in Zosuquidar (an antineoplastic drug in clinical trials for the treatment of acute myeloid leukemia) and GNE-4997 (as an Interleukin-2 Inducible T-Cell Kinase (ITK) inhibitor for the treatment of allergic asthma and inflammatory disorders) which maintained similar drug activity and enhanced the bioavailability[7,8] (**Figure 1**). The development of effective methods for facile synthesis of chiral *gem*-difluorocyclopropyl moieties embedded in biologically active molecules from the readily available starting materials is an important and active area of research among synthetic and medicinal chemists.

The classical methods for synthesis of the enantio-enriched *gem*-difluorocyclopropane compounds include the traditional resolution or separation of stereoisomers by the preparative chiral chromatography,[9–11] kinetic resolution of stereoisomers by biocatalysis,[12,13] diastereoselective Michael addition/cyclization of the enolates with the auxiliary-based approach,[14,15] rhodium-catalyzed kinetic resolution via carbon–carbon bond activation of *gem*-difluorocyclopropanes,[16] and biocatalytic asymmetric cyclopropanation of readily available *gem*-difluoroolefins with diazo compounds[17] (**Figure 2**).

An alternative and more direct route to the preparation of these compounds is through catalytic asymmetric reactions of readily available *gem*-difluorocyclopenes. Since 2020, copper-catalyzed asymmetric reduction[18] and hydrosilylation[19] of *gem*-difluorocyclopenes giving chiral *gem*-difluorocyclopropanes have been reported by Mikami and Ito groups, respectively. Meanwhile, ruthenium-catalyzed asymmetric transfer hydrogenation of *gem*-difluorocyclopropenyl esters or ketones using isopropanol or sodium formate as hydrogen donors provided the chiral *cis*-disubstituted *gem*-difluorocyclopropyl esters or ketones with moderate to excellent yields and ee values.[20,21] Furthermore, cobalt-catalyzed

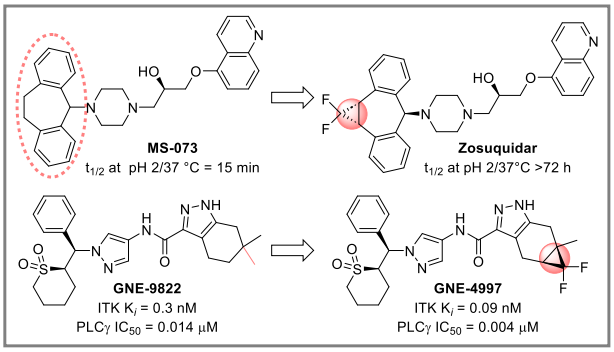


Figure 1. Bioactive compounds modified with a chiral *gem*-difluorocyclopropane unit.

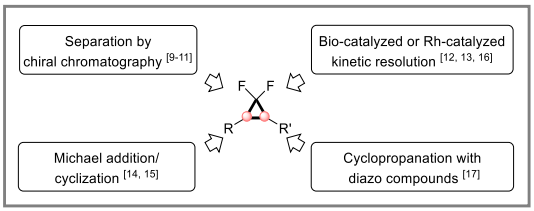
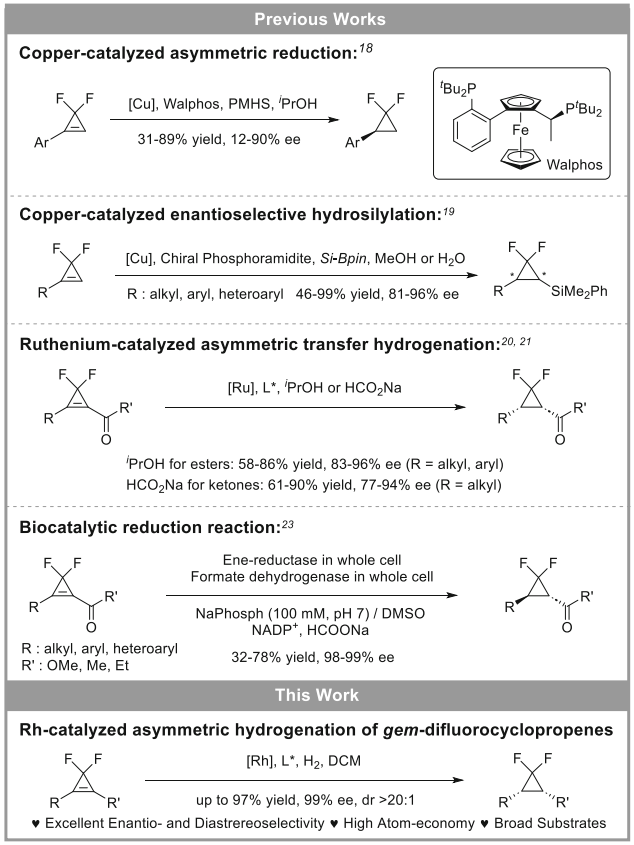


Figure 2. The classical methods for synthesis of chiral *gem*-difluorocyclopropanes.

hydroalkylation of *gem*-difluorocyclopropenes has also been achieved, thereby facilitating the access to chiral *gem*-difluorocyclopropanes.[22] Recently, Cossy and coworkers disclosed a biocatalytic enantioselective reduction of *gem*-difluorocyclopropenyl esters and ketones using ene-reductases (EREDs), affording *trans*-*gem*-difluorocyclopropyl esters and ketones with excellent enantioselectivities and moderate yields.[23] Despite significant advancements in asymmetric synthesis of *gem*-difluorocyclopropanes, the development of new catalytic systems remains crucial owing to the diversity of substrates. Herein, we report a rhodium-catalyzed asymmetric hydrogenation of *gem*-difluorocyclopropenyl esters or ketones, affording the disubstituted *cis*-*gem*-difluorocyclopropanes with excellent enantio- and diastereoselectivities (**Scheme 1**).

2. Results and Discussion

In light of the significant advancements achieved over the past four decades in rhodium-catalyzed asymmetric hydrogenation of olefins,[24–26] we opted for an effective rhodium-based catalytic system for asymmetric hydrogenation of readily available *gem*-difluorocyclopropenes. However, there may be the following challenges in the hydrogenation process that need to be addressed: first, the presence of both carbonyl and olefin in the substrates might cause problems with chemo- and enantioselectivity during hydrogenation process; second, the C─F bond is



Scheme 1. Syntheses of *gem*-difluorocyclopropanes from *gem*-difluorocyclopropenes.

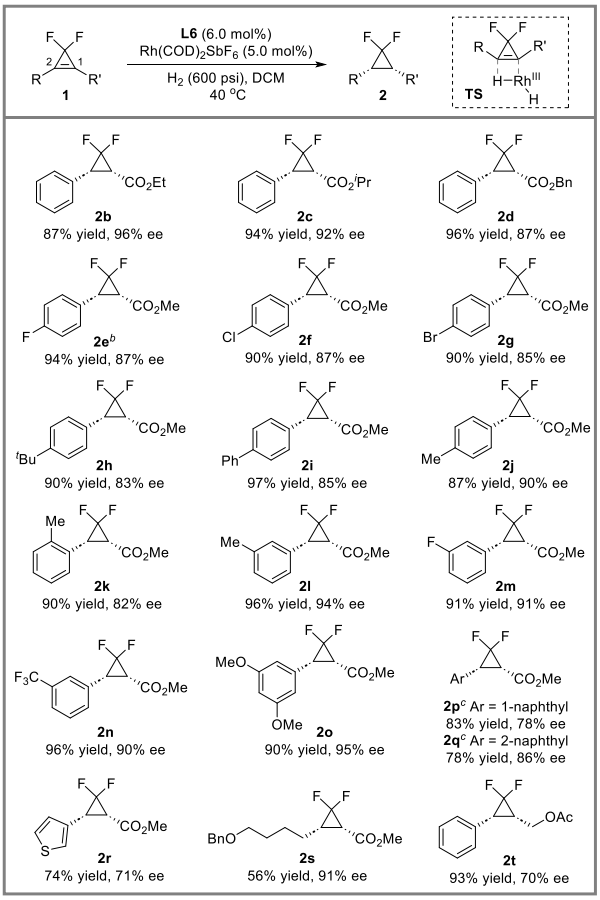
prone to easy cleavage in the presence of transition-metal-catalyzed systems.

To probe the feasibility of rhodium-catalyzed asymmetric hydrogenation for synthesis of chiral *gem*-difluorocyclopanes, *gem*-difluorocyclopropenyl ester **1a** was chosen as the model substrate in the presence of $Rh(COD)_2SbF_6$/**L1** and THF (tetrahydrofuran).

To our delight, the desired hydrogenation product **2a** was obtained in 79% yield with 30% ee. Considering that the effect of solvents played a significant role in asymmetric hydrogenation, a range of different solvents were screened (entries 1–5). The hydrogenation in DCM (dichloromethane) exhibited excellent activity albeit moderate 48% of enantioselectivity (entry 4). Next, the use of other rhodium precursors resulted in lower yields or ee values (entries 6–8). To further improve the activity and enantioselectivity, some commercially available chiral ligands were evaluated (entries 9–15). It is noteworthy that the planar-chiral biphosphine ligand (*R*)-Phanephos **L6** afforded the desired hydrogenation product **2a** in 80% yield with 94% ee (entry 13). And a better yield was obtained when the loading of chiral ligand **L6** increased from 5.5 mol% to 6.0 mol% (entry 16). To ensure that other substrates proceeded smoothly, the loading of ligand **L6** was maintained at

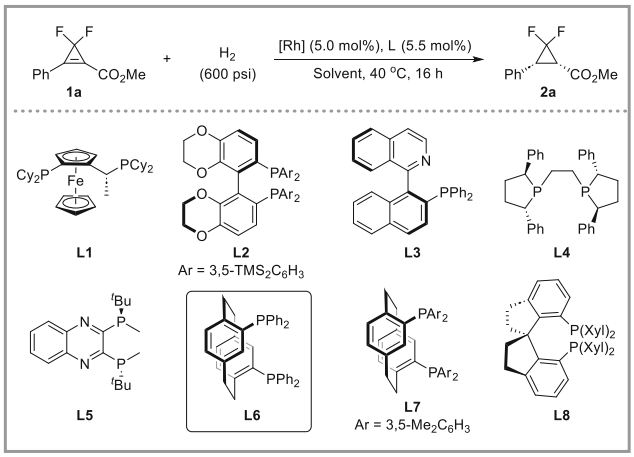
6.0 mol%. Thus, the optimal condition was identified at 0.4 mmol scale (entry 17): $Rh(COD)_2SbF_6$ (5.0 mol%), (*R*)-PhanePhos (6.0 mol%), H_2 (600 psi), DCM (6.0 mL), and at 40 °C for 16 h.

With the optimal condition in hand, the substrate scope was investigated (**Scheme 2**). First, various esters were evaluated. The ethyl ester (**1b**), isopropyl ester (**1c**), and benzyl ester (**1d**) performed very well, delivering the products **2b–2d** in 87–96% yields with 87–96% ee. Subsequently, both electron-deficient and electron-rich *gem*-difluorocyclopropenyl methyl ester derivatives (**1e–1i**) exhibited good compatibility (90–97 yields, 83–87% ee). And this catalyst system was also well suitable for the corresponding *gem*-difluorocyclopropanes (**2j–2l**) with methyl at different positions of the phenyl at C2 position (87–96 yields, 82–94% ee). Since the best result was obtained with methyl at the *meta*-position, substrates with various electron-withdrawing or electron-donating substituents at the *meta*-position of phenyl ring were evaluated, giving the products **2m–2o** in 90–96% yields with 90–95% ee. For 1-naphthyl-substituted substrate **1p** and 2-naphthyl-substituted substrate **1q** at C2 position, although no desired products **2p** and **2q** were obtained under the standard conditions, desired products **2p** and **2q** with only hydrogenation of *gem*-difluorocyclopropenyl could be obtained when the temperature was reduced to 8 °C and the reaction time was shortened to 1 h (**Table 1**). This methodology



Scheme 2. Substrate scope: *gem*-difluorocyclopropenyl esters. Reaction condition: **1** (0.4 mmol), $Rh(COD)_2SbF_6$ (5.0 mol%), **L6** (6.0 mol%), DCM (6.0 mL), H_2 (600 psi) at 40 °C for 16 h, and ee values were determined by HPLC with chiral columns. [b]ee value was determined by GC with chiral column. [c]8 °C for 1 h.

Table 1. Evaluation of reactionparameters.



Entry[a]	Sol.	[Rh]	L	Conv. [%][b]	Yield [%][b]	Ee [%][c]
1	THF	$Rh(COD)_2SbF_6$	**L1**	>95	79	30
2	Tol.	$Rh(COD)_2SbF_6$	**L1**	28	17	9
3	EA	$Rh(COD)_2SbF_6$	**L1**	>95	95	27
4	DCM	$Rh(COD)_2SbF_6$	**L1**	>95	92	48
5	DCE	$Rh(COD)_2SbF_6$	**L1**	>95	87	44
6	DCM	$[Rh(COD)Cl]_2$	**L1**	>95	66	1
7	DCM	$Rh(COD)_2BF_4$	**L1**	>95	94	45
8	DCM	$Rh(NBD)_2BF_4$	**L1**	19	15	1
9	DCM	$Rh(COD)_2SbF_6$	**L2**	59	37	94
10	DCM	$Rh(COD)_2SbF_6$	**L3**	65	14	34
11	DCM	$Rh(COD)_2SbF_6$	**L4**	28	9	21
12	DCM	$Rh(COD)_2SbF_6$	**L5**	84	55	33
13	DCM	$Rh(COD)_2SbF_6$	**L6**	>95	80	94
14	DCM	$Rh(COD)_2SbF_6$	**L7**	>95	70	73
15[d]	DCM	$Rh(COD)_2SbF_6$	**L8**	85	37	83
16[e]	DCM	$Rh(COD)_2SbF_6$	**L6**	>95	86	92
17[e,f]	DCM	$Rh(COD)_2SbF_6$	**L6**	>95	94/92[g]	92

[a] Reaction conditions: **1a** (0.2 mmol), [Rh] (5.0 mol%), chiral ligand (5.5 mol%), solvent (3.0 mL), H_2 (600 psi), 40 °C, 16 h. (Tol. = toluene, EA = ethyl acetate, DCE = $C_2H_4Cl_2$, COD = 1,5-cyclooctadiene);

[b] Determined by NMR, and in all cases dr > 20:1. The absolute configuration of **2a** was assigned as (1*S*,3*R*)-**2a** by optical rotation analogy;[20]

[c] Determined by HPLC with chiral columns;

[d] In this case, dr = 1.4:1;

[e] PhanePhos (6.0 mol%);

[f] The reaction was conducted at 0.4 mmol scale and DCM was 6.0 mL;

[g] Isolated yield.

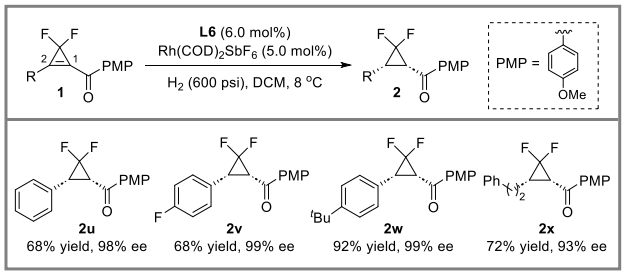
was also compatible with thienyl or alkyl-substituted substrates, affording the chiral products (**2r** and **2s**) with 71–91% ee. In addition, the asymmetric hydrogenation of the *gem*-difluorocyclopropene **1t** with an acetoxymethyl group could proceed smoothly in 93% yield with moderate 70% ee.

To further extend this methodology, the rhodium-catalyzed asymmetric hydrogenation of readily available *gem*-difluorocyclopropenyl ketones was investigated (**Scheme 3**). No desired product **2u** was observed under the standard condition, whereas **2u** was successfully obtained in 68% yield with 98% ee by reducing the temperature and shortening the reaction time (8 °C, 1 h). For the methoxybenzoyl *gem*-difluorocyclopropenyl ketones, this catalytic system could demonstrate good compatibility. The substrates with fluorine and *tert*-butyl at the *para*-position of the phenyl (**1v** and **1w**) were also tolerated. Notably, for alkyl-substituted *gem*-difluorocyclopro-penyl ketone **1x**, corresponding product **2x** could be obtained in moderate 72% yield and excellent 93% ee.

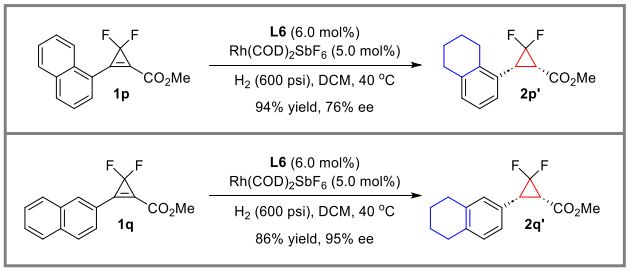
Notably, asymmetric hydrogenation of 1-naphthyl- and 2-naphthyl-substituted *gem*-difluorocyclopropenyl esters (**1p**, **1p**) at 40 °C for 16 h afforded the products **2p'** and **2q'** with asymmetric hydrogenation of C=C double bond and partial hydrogenation of naphthalene ring (**Scheme 4**). It is likely that as the number of fused carbon rings increased, the average delocalization energy gradually decreased, providing a basis for the rhodium-catalyzed partial hydrogenation of naphthalene ring.[27,28] In this case, the intermediates **2p** and **2q** continued to be further hydrogenated to give the tetrahydronaphthalenes **2p'** and **2q'**.

To demonstrate the practicability of this methodology, a gram-scale experiment on asymmetric hydrogenation of **1a** was conducted under the above standard conditions (**Scheme 5**), giving the chiral product **2a** in 91% yield with 93% ee without erosion of activity and enantioselectivity.

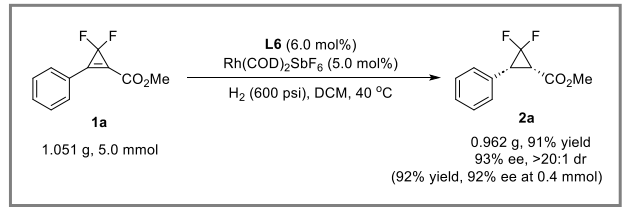
Next, synthetic applications of hydrogenation products were performed (**Scheme 6**). The chiral product *cis*-(1*S*,3*R*)-**2** could be epimerized to the more thermodynamically stable *trans*-(1*R*,3*R*)-**3** in the presence of



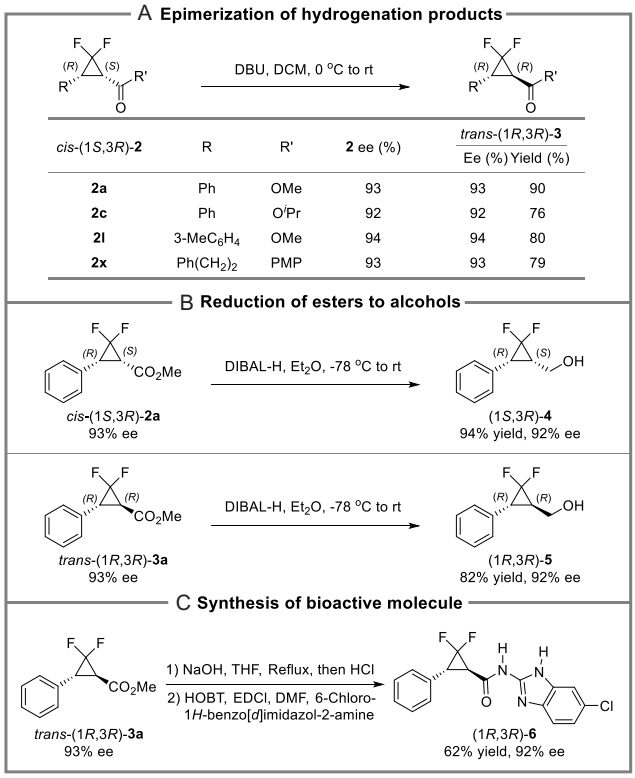
Scheme 3. Substrate scope: *gem*-difluorocyclopropenyl ketones. Reaction condition: **1** (0.4 mmol), $Rh(COD)_2SbF_6$ (5.0 mol%), **L6** (6.0 mol%), DCM (6.0 mL), H_2 (600 psi), 8 °C, 1 h, ee values were determined by HPLC with chiral column.



Scheme 4. Hydrogenation of both C=C double bond and naphthalene ring.



Scheme 5. Gram-scale experiment.



Scheme 6. Diverse transformations. A) Epimerization of hydrogenation products. B) Reduction of esters to alcohols. C) Synthesis of bioactive molecule.

DBU with good yields (Scheme 6A).[29] Meanwhile, the chiral esters could be reduced to the primary alcohols using diisobutylaluminum hydride as the reductant (Scheme 6B).[20] Furthermore, *trans*-(1*R*,3*R*)-**3** could be converted into the bioactive molecule **6**, which could serve as the LPA receptor antagonist for the treatment of proliferative diseases, with overall 62% yield through the hydrolysis and condensation reactions (Scheme 6C).[30] Notably, for all the above processes, no erosion of optical purity was observed.

3. Conclusions

In conclusion, we have successfully developed a rhodium-catalyzed asymmetric hydrogenation of *gem*-difluorocyclopropenes for synthesis of *cis*-*gem*-difluorocyclopropanes with up to 99% ee and >20:1 dr. Moreover, the asymmetric hydrogenation could proceed smoothly at gram scale without any erosion of activity and enantioselectivity. The chiral product *gem*-difluorocyclopropanes could be transformed into several chiral building blocks and biologically active molecule.

4. Experimental Section

Typical Procedure for the Synthesis of 2: Bis(1,5-cycloocatadiene) rhodium(I) hexafluoroantimo-nate (11.1 mg, 0.02 mmol, 5.0 mol%) and chiral ligand (*R*)-PhanePhos (13.8 mg, 0.024 mmol, 6.0 mol%) were placed in a vial. The vial was then transferred to a glove box filled with nitrogen gas and the degassed anhydrous dichloromethane (2.0 mL) was added. The mixture was stirred at room temperature for 10 min. Afterward, the mixture was transferred by a syringe to a stainless steel autoclave, in which *gem*-dfluorocyclopropenyl esters **1** (0.40 mmol) and dichloromethane (4.0 mL) had been placed beforehand. The hydrogenation was performed under 600 psi of hydrogen at 8 °C for 1 h or at 40 °C for 16 h. Then, the autoclave was returned to room temperature. After releasing the hydrogen, the autoclave was opened, and the volatiles were removed under the reduced pressure. Flash chromatography on silica gel using hexanes/ethyl acetate (50/1 to 30/1) or hexanes/diethyl ether (5/1) as the eluent afforded the chiral reductive products **2**. The optical purity of the chiral reductive products **2** was determined by the chiral HPLC or GC analysis.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Mu-Wang Chen *designed the experiments.* ***Sai-Nan Yin****,* ***Zheng Liu*** *and* ***Xinsheng Zhang*** *performed the experiments, analyzed and discussed the project data.* ***Sai-Nan Yin*** *wrote the first draft of manuscript.* ***Mu-Wang Chen*** *and* ***Yong-Gui Zhou*** *supervised the project and contributed to the writing and editing of the manuscript.*

Data Availability Statement

The data that supports the findings of this study are available in the supplementary material of this article.

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