Chemical Science

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2022, **13**, 11594

Palladium-catalyzed intramolecular Heck dearomative *gem*-difluorovinylation of indoles†

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Received 6th June 2022
Accepted 13th September 2022

DOI: 10.1039/d2sc03169h

rsc.li/chemical-science

A palladium-catalyzed dearomative reaction of indoles has been developed through a domino Heck/*gem*-difluorovinylation sequence. By taking advantage of a difluorocarbene precursor ($ClCF_2COONa$), the palladium difluorocarbene ([Pd]=CF_2) species was formed smoothly. Then, a migratory insertion/β-H elimination process enabled access to polycyclic indolines containing 1,1-difluoroethylene units in acceptable yields with a broad substrate scope, which also showed dearomative *gem*-difluorovinylation for the first time. Remarkably, the superb diversified transformations allowed the product to install various functional groups.

Introduction

gem-Difluoroalkenes are widely used in the fields of pharmaceuticals, agrochemicals, materials and fine chemicals (Fig. 1A).[1–4] Moreover, a number of valuable compounds can be converted by the transformations of *gem*-difluoroalkenes with radicals, carbon-metal species, and nucleophiles.[5–7] So far, a range of methods have been developed to prepare *gem*-difluoroalkene derivatives.[7–11] Traditionally, the well-known Julia-Kocienski[12–14] and Wittig[15–19] reactions are confined to aldehyde and ketone substrates. In recent years, the defluorinative functionalization of trifluoromethyl olefins has been explored in detail,[20–22] but the synthesis of trifluoromethyl olefins is cumbersome.[23] Besides, *gem*-difluoroalkenes can also be acquired from diazo compounds,[24–27] which have potential safety hazards. Consequently, it is necessary to develop a new strategy to get *gem*-difluoroalkenes.

Transition-metal-catalyzed cross-coupling reactions with carbenes have been extensively studied.[28] C=C double bonds can be constructed smoothly through general procedures of carbene migratory insertion and β-H elimination.[29] Studies mainly focus on nonfluorinated carbenes, and β-H elimination involving difluorocarbene has not been reported. Even the conversion of metal difluorocarbene ([M]=CF_2) is a massive challenge due to limited reaction types.[30] In 2015, Zhang and coworkers reported the first metal difluorocarbene coupling (MeDiC) reaction for synthesizing organofluorine compounds *via* palladium catalysis.[31] Thereafter, several successful transformations of [Pd]=CF_2 were reported,[31–37] but most of the coupling reagents are limited to nucleophilic arylboronic acids and esters (Scheme 1a).[31–35] Furthermore, in the only research involving the coupling of electrophilic aryl halides, the hydrolysis of [Pd]=CF_2 is inevitable (Scheme 1b).[38] On this foundation, we expect to inhibit the hydrolysis by the β-H elimination process to prepare *gem*-difluoroalkenes and expand the coupling of aryl halides with difluorocarbene ulteriorly. Meanwhile, considering the operability as a crystalline solid and low cost, $ClCF_2COONa$ is chosen as the difluorocarbene precursor.[39]

The assembly of polycyclic indoline derivatives remains one of the most interesting subjects in organic synthesis[40–45] due to the fact that many natural products contain constitutional units (Fig. 1B).[46–49] At present, the production of polycyclic indoline scaffolds has been established by palladium-catalyzed intramolecular Heck dearomatization of indoles (Scheme 1c).[50–68] On the one hand, 1,2-difunctionalization of indoles is achieved when the resulting benzyl-Pd species are captured with diverse

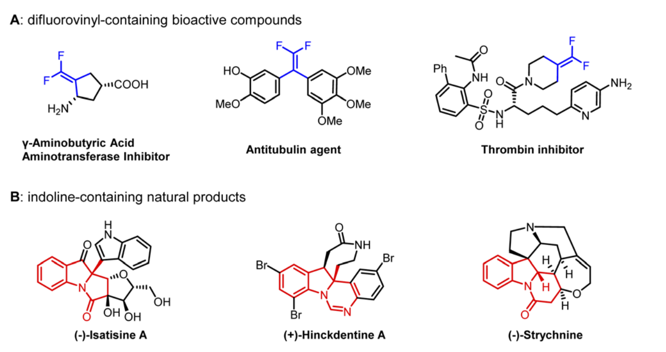

Fig. 1 Molecules containing difluorovinyl and indoline units.

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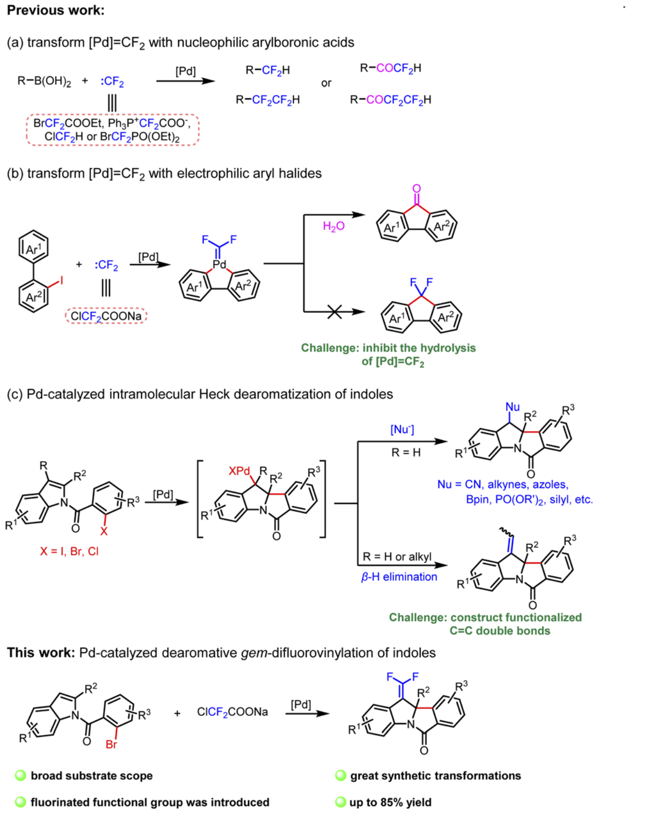
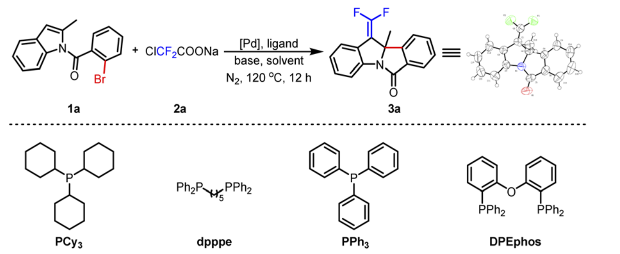
† Electronic supplementary information (ESI) available: CCDC 2101086, 2101084 and 2103217. For ESI and crystallographic data in CIF or other electronic format see https://doi.org/10.1039/d2sc03169h



Scheme 1 Pd-catalyzed transformations of :CF_2 and dearomatization of indoles.

Table 1 Condition optimization[a]



Entry	[Pd]	Ligand	Base	Solvent	Yield[b] (%)
1	$Pd(OAc)_2$	PCy_3	K_2CO_3	DCE	45
2	$Pd(OAc)_2$	PCy_3	K_3PO_4	DCE	20
3	$Pd(OAc)_2$	PCy_3	NEt_3	DCE	Trace
4	$Pd(OAc)_2$	dpppe	K_2CO_3	DCE	39
5	$Pd(OAc)_2$	PPh_3	K_2CO_3	DCE	26
6	$Pd(OAc)_2$	DPEphos	K_2CO_3	DCE	60
7	$Pd(TFA)_2$	DPEphos	K_2CO_3	DCE	42
8	$PdCl_2$	DPEphos	K_2CO_3	DCE	NR
9	$Pd(OAc)_2$	DPEphos	K_2CO_3	1,4-Dioxane	Trace
10	$Pd(OAc)_2$	DPEphos	K_2CO_3	Toluene	Trace
11[c]	$Pd(OAc)_2$	DPEphos	K_2CO_3	DCE	63
12[c,d]	$Pd(OAc)_2$	DPEphos	K_2CO_3	DCE	73
13[c,d,e]	**$Pd(OAc)_2$**	**DPEphos**	**K_2CO_3**	**DCE**	**79**
14[c,d,e,f]	$Pd(OAc)_2$	DPEphos	K_2CO_3	DCE	NR
15[c,d,e,g]	$Pd(OAc)_2$	DPEphos	K_2CO_3	DCE	20
16[c,d,e,h]	$Pd(OAc)_2$	DPEphos	K_2CO_3	DCE	Trace

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (2.0 equiv.), [Pd] (10 mol%), ligand (20 mol%), base (3.0 equiv.) and solvent (2.0 mL) at 120 °C for 12 h under a N_2 atmosphere. [b] Isolated yield. [c] DPEphos (12 mol%). [d] 4 Å MS (100 mg) was added. [e] DCE (3.0 mL). [f] **2a** changed by $BrCF_2TMS$. [g] **2a** changed by $ClCF_2COOEt$. [h] $Pd(OAc)_2$ (5 mol%). NR = no reaction.

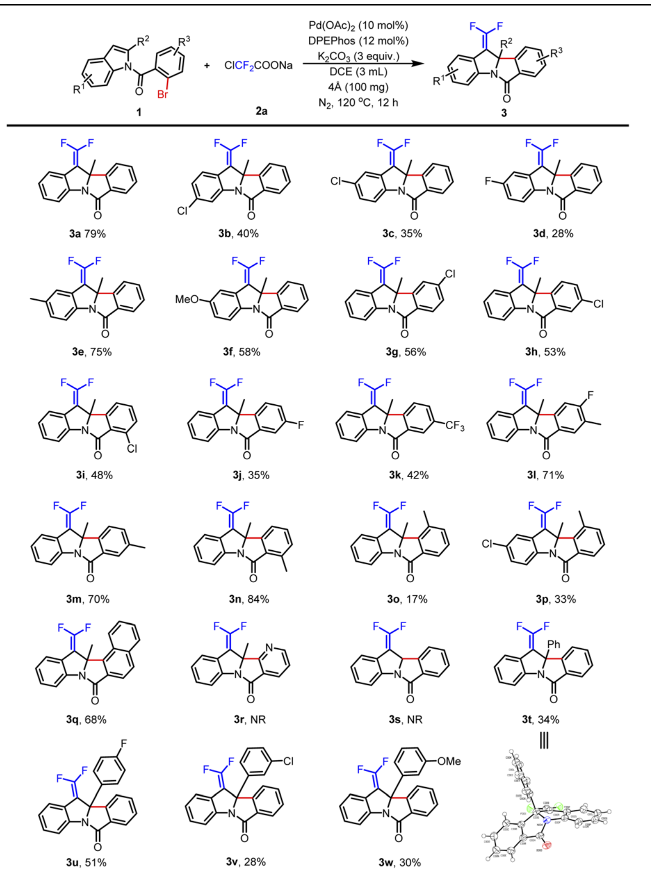
nucleophiles that can effectively form various C–X (H, C, N, O, P, B, and Si) bonds. On the other hand, the reactions can be terminated by β-H elimination to construct C=C double bonds.[48,60,64–66] However, limited precursors restrict the installation of functionalized C=C double bonds. Inspired by our first attempt at dearomatization of indoles,[67] we present herein an innovative idea for synthesizing *gem*-difluoroalkenes from *N*-(2-bromobenzoyl)indoles and $ClCF_2COONa$. Remarkably, it is the first report of dearomative *gem*-difluorovinylation.

Results and discussion

With this thinking in mind, *N*-acyl indole **1a** and $ClCF_2COONa$ were selected as model substrates in the palladium/ligand catalytic system to explore the optimal conditions (Table 1). As expected, when $Pd(OAc)_2/PCy_3$ was used as a catalyst with K_2CO_3 in 1,2-dichloroethane (DCE) at 120 °C for 12 h, the process of dearomative *gem*-difluorovinylation was carried out smoothly to afford the expectant product **3a** in 45% yield (Table 1, entry 1). The structure of **3a** was confirmed by X-ray crystallographic analysis (see the ESI†). Then, K_3PO_4 and NEt_3 as bases were tested, but they were unfavorable for the reaction compared to K_2CO_3 (Table 1, entries 2 and 3). And several ligands such as dpppe, PPh_3, and DPEphos were studied, and the results showed that DPEphos was a suitable ligand to get **3a** in 60% yield (Table 1, entries 4–6). Substituting $Pd(TFA)_2$ for $Pd(OAc)_2$, the yield of the target product decreased to 42% (Table 1, entry 7). When $PdCl_2$ was used as the catalyst, **3a** was not generated (Table 1, entry 8). Only a trace amount of **3a** was obtained by changing the solvent to 1,4-dioxane or toluene (Table 1, entries 9 and 10). We reduced the amount of ligand to 12 mol%, and the yield of the final product was 63% (Table 1, entry 11). To our delight, when 4 Å molecular sieves (4 Å MS) were added to the reaction, the yield of the desired product improved to 73% (Table 1, entry 12). On this foundation, the amount of DCE was raised to 3 mL, and the yield of product **3a** further increased to 79% (Table 1, entry 13). Afterwards, difluorocarbene precursors such as $BrCF_2TMS$ and $ClCF_2COOEt$ were investigated with unsatisfactory results (Table 1, entries 14 and 15). The result was poor when the amount of $Pd(OAc)_2$ was lowered to 5 mol% (Table 1, entry 16). Finally, we determined that the best reaction conditions were to use $Pd(OAc)_2$ (10 mol%), DPEphos (12 mol%), K_2CO_3 (3.0 equiv.), and 4 Å MS (100 mg) in DCE (3 mL) under N_2 at 120 °C for 12 h.

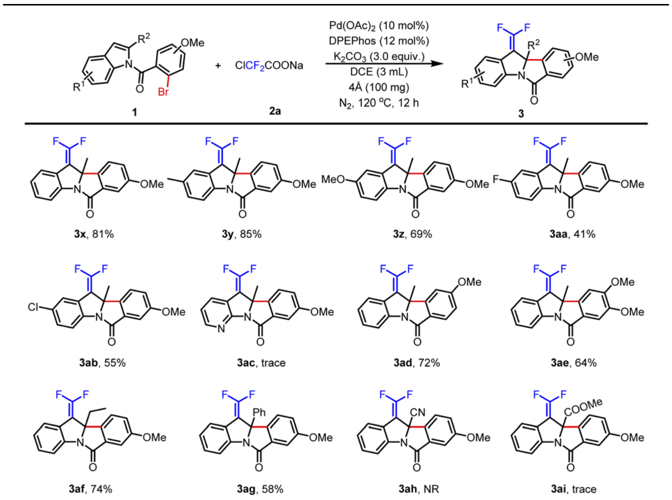
The optimal reaction conditions for the synthesis of **3a** were evaluated by using indole derivatives containing different substituents and $ClCF_2COONa$. As shown in Table 2, electron-donating and electron-withdrawing groups on indoles' C5 and C6 positions could afford the desired products in 28–79% yields (**3a–3f**), and electron-donating groups helped to get better

Table 2 Substrate scope[a]



[a] Reaction conditions: **1** (0.2 mmol), **2a** (2.0 equiv.), $Pd(OAc)_2$ (10 mol%), DPEPhos (12 mol%), K_2CO_3 (3.0 equiv.), 4 Å MS (100 mg) and DCE (3.0 mL) at 120 °C for 12 h under a N_2 atmosphere. Isolated yield. NR = no reaction.

Table 3 Substrate scope[a]

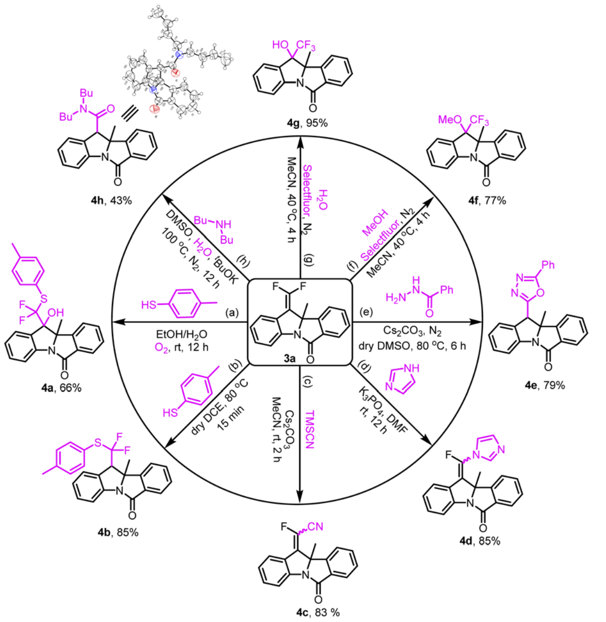


[a] Reaction conditions: **1** (0.2 mmol), **2a** (2.0 equiv.), $Pd(OAc)_2$ (10 mol%), DPEPhos (12 mol%), K_2CO_3 (3.0 equiv.), 4 Å MS (100 mg) and DCE (3.0 mL) at 120 °C for 12 h under a N_2 atmosphere. Isolated yield. NR = no reaction.

results (**3e–3f**). Compared with the electron-withdrawing groups that provided related products in 35–56% yields (**3g–3k**), the electron-donating group on *N*-benzoyl was more conducive to the reaction in 70–84% yields (**3l–3n**). However, due to the influence of steric hindrance, the substrate with a methyl group at the C3 position of *N*-benzoyl provided the corresponding product **3o** in only 17% yield. When both indole and *N*-benzoyl were substituted, the desired product **3p** was obtained in 33% yield. A substrate containing a naphthalene ring was tried and led to **3q** in 68% yield, but heteroaromatic bromine (pyridine-containing) and non-substituted indole (R^2 = H) failed (**3r–3s**). In the cases of phenyl and substituted phenyl (4-fluorophenyl, 3-chlorophenyl, and 3-methoxyphenyl) attached at the C2 position of indoles, the protocol went smoothly with 28–51% yields (**3t–3w**). The structure of **3t** was confirmed by X-ray crystallographic analysis (see the ESI†).

Furthermore, the substrate scope was extended with a methoxyl group substituent at the *N*-benzoyl position (Table 3). Indole without a substituent on the benzene ring produced **3x** in 81% yield. With electron-donating groups (Me- and MeO-) at the C5 position of indoles, the desired products **3y–3z** were obtained in 69–85% yields. In contrast, the corresponding products were obtained in lower yields when halogen groups (F- and Cl-) were assembled at the same position (**3aa–3ab**). And then, 7-azaindole was tested but failed to obtain product **3ac**. Next, the desired product **3ad** was smoothly produced in 72% yield by changing the methoxy group at the C4 position of *N*-benzoyl. In addition, a dimethoxy group substituted substrate was also tolerated with this procedure and provided the product **3ae** in 64% yield. Finally, C2-substituted indoles were studied. Although 2-ethyl indole and 2-phenyl indole could afford the anticipated products **3af–3ag** in 58–74% yields, cyano and ester groups were the failed choices (**3ah–3ai**). In short, installing MeO- on the *N*-benzoyl was an excellent choice to improve the yields.

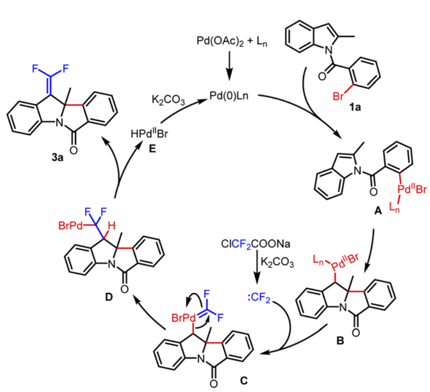
The synthetic transformations of product **3a** indicated the practicability of the method (Scheme 2). *gem*-Difluorovinyl was successfully transformed into eight useful functional groups. Firstly, α-difluoro(thio)methylated alcohol **4a** was obtained in 66% yield by a three-component reaction between compound **3a**, *p*-toluenethiol and oxygen under mild conditions. And the coupling of **3a** with *p*-toluenethiol resulted in α,α-difluoroalkylthioether **4b** in 85% yield in dry DCE at 80 °C for 15 min. When **3a** was treated with trimethylsilyl cyanide and imidazole, the nucleophilic vinylic substitution reaction (S_NV) worked well and afforded the corresponding products **4c** and **4d** in good yields. Moreover, the cyclization of **3a** with benzoyl hydrazine was explored, thus accessing unsymmetrical 2,5-disubstituted 1,3,4-oxadiazole in 79% yield with the assistance of Cs_2CO_3 (**4e**). Besides, the fluoro-functionalization reactions of **3a** with selectfluor and *O*-nucleophiles were conducted smoothly in acetonitrile. Therefore, α-CF_3 derivatives **4f** and **4g** could be synthesized in ideal yields. Remarkably, in the presence of potassium *tert*-butoxide and water, **3a** has successfully worked



Scheme 2 Synthetic transformations of **3a**: (a) **3a** (0.2 mmol), 4-methylbenzenethiol (0.4 mmol), and EtOH/H_2O (2.0 mL, v/v = 2 : 1) at rt for 12 h under an O_2 atmosphere; (b) **3a** (0.2 mmol), 4-methylbenzenethiol (0.24 mmol), and dry DCE (40 μL) at 80 °C for 15 min; (c) **3a** (0.3 mmol), Cs_2CO_3 (0.03 mmol), TMSCN (0.9 mmol), and dry MeCN (1.0 mL) at rt for 2 h; (d) **3a** (0.6 mmol), K_3PO_4 (1 mmol), imidazole (0.5 mmol), and DMF (1 mL) at rt for 12 h; (e) **3a** (0.2 mmol), benzoyl hydrazide (0.24 mmol), Cs_2CO_3 (0.4 mmol), and dry DMSO (1 mL) at 80 °C for 6 h under a N_2 atmosphere; (f) **3a** (0.2 mmol), selectfluor (0.3 mmol), dry MeOH (1 mmol), and dry CH_3CN (0.8 mL) at 40 °C for 4 h under N_2 atmosphere; (g) **3a** (0.2 mmol), selectfluor (0.3 mmol), H_2O (1.6 mmol), and dry CH_3CN (0.8 mL) at 40 °C for 4 h under a N_2 atmosphere; (h) **3a** (0.2 mmol), ${}^tBuOK$ (0.6 mmol) and dibutylamine (0.4 mmol), H_2O (0.02 mL),and DMSO (1.2 mL) at 100 °C for 12 h under a N_2 atmosphere. Isolated yield.

with dibutylamine to provide arylacetamide **4h** in 43% yield. And we confirmed the structure of **4h** by X-ray crystallographic analysis (see the ESI†).

Based on previous research and our understanding on palladium-catalyzed Heck dearomatization of indoles, a possible reaction process is shown in Scheme 3. The Pd(0) species was formed under the action of the ligand, and the reaction was initiated by the oxidative addition of Pd(0) to aryl bromide to afford the Pd(II) species **A**. The benzyl-Pd(II) intermediate **B** was generated by the intramolecular coordination and migratory insertion of the Pd(II) species into indole. Difluorocarbene, which formed from $ClCF_2COONa$ *in situ* in the presence of bases, was captured by intermediate **B** to provide the Pd(II)$=CF_2$ species **C**. Following carbene migratory insertion,[34] the σ-alkyl-Pd(II) species **D** was obtained. Then, the β-hydride elimination of the species **D** resulted in the final product **3a** and Pd(II) species **E**. Finally, with the assistance of a base, Pd(0) was regenerated for the next catalytic cycle.



Scheme 3 Plausible reaction mechanism.

Conclusions

In summary, polycyclic indoline derivatives containing 1,1-difluoroethylene units are prepared by palladium-catalyzed intramolecular Heck dearomatization of indoles with $ClCF_2COONa$. β-H elimination involving [Pd]$=CF_2$ provides a new synthetic course for *gem*-difluoroalkenes. In addition, it is the first report of dearomative *gem*-difluorovinylation, which has a broad substrates scope and acceptable yields. Further diversified transformations of the product show the practicability of this methodology.

Data availability

All data associated with this study are available in the article and ESI.†

Author contributions

G. Wang, W. Q. Li, T. X. Liu, B. Wang, and C. Y. Ma carried out the methodology, synthesis, characterization, and analysis. Y. Xia and G. Wang prepared the manuscript. W. W. Jin, Y. H. Zhang, and F. Xue revised the manuscript. C. J. Liu and Y. Xia directed the project and supervised the whole experiment. All authors read and approved the final manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful to the Natural Science Foundation of Xinjiang Uygur Autonomous Region (2020D01C077), the National Natural Science Foundation of China (Grant No. 21961037, 21861036, 21702175, and 21572195), the Program for Tianshan Innovative Research Team of Xinjiang Uygur Autonomous Region (2021D14011), the Key Program of Natural Science Foundation of Xinjiang Uygur Autonomous Region (2022D01D06) and the Program of Tianchi Doctor (tcbs201909) for the support of this research.

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