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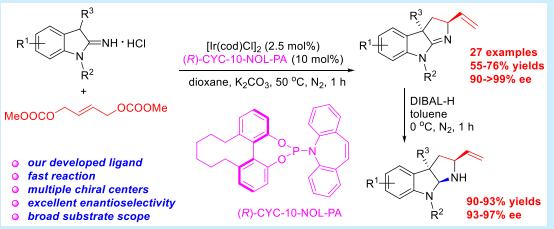
# Highly Enantioselective Iridium-Catalyzed Cascade Double Allylation Strategy: Synthesis of Pyrrolidinoindolines with an All-Carbon Quaternary Stereocenter

Hua Tian, Fei Peng, Pengxiang Zhang, Haijun Yang, and Hua Fu*

Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, China

Supporting Information

**ABSTRACT:** Highly enantioselective cascade double allylations of 1-alkyl-3-alkylindolin-2-imine hydrochlorides with (*E*)-but-2-ene-1,4-diyl dimethyl dicarbonate leading to tetrahydropyrrolo[2,3-*b*]indoles with an all-carbon quaternary stereocenter have been developed. This transformation was catalyzed by an iridium catalyst together with our developed chiral cyclic phosphoramidite ligand. The method shows some advantages including an operationally simple protocol, fast reaction, and excellent diastereoselectivity and enantioselectivity. Furthermore, reduction of the obtained products with diisobutyl aluminum hydride provided the pyrrolidinoindolines with three chiral centers in high yields with excellent diastereoselectivity and enantioselectivity.




The hexahydropyrrolo[2,3-*b*]indole (commonly referred to as the pyrrolidinoindoline) skeleton widely occurs in many alkaloids isolated from various natural sources,[1] and the alkaloids containing the pyrrolidinoindoline framework show diverse biological activities such as antibacterial[2] and anticancer activities[3] and the inhibition of cholinesterase.[4] In particular, the pyrrolidinoindoline compounds with C3a all-carbon quaternary stereocenters (Figure 1) have been assigned

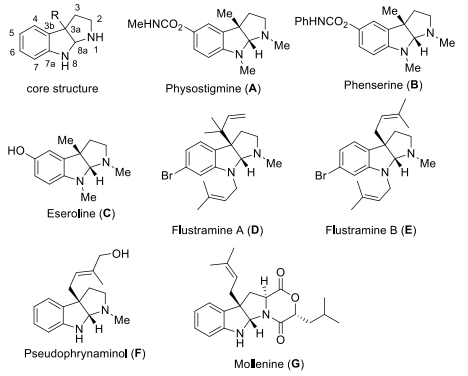



**Figure 1.** Examples of biologically active molecules containing the chiral pyrrolidinoindoline core.

as privileged structures in drug development. For example, physostigmine (**A**), isolated from the African Calabar bean seeds,[5] is an inhibitor of acetyl- and butyryl-cholinesterase and has been applied for treatment of myasthenia gravis, glaucoma, and Alzheimer's disease.[6,7] Phenserine (**B**) as an effective and selective acetylcholinesterase inhibitor[8] has been confirmed to inhibit $\beta$-amyloid plaque deposition and is also used for treatment of Alzheimer's disease.[7c,9] Eseroline (**C**) exhibits potent morphine-like analgesic properties,[10] and (−)-flustramine B (**E**) shows potent anticancer activity.[11] The excellent biological activities have inspired the development of various inventive methods for the enantioselective synthesis of pyrrolidinoindolines.[12]

In previous strategies for the enantioselective synthesis of the core pyrrolidinoindolines, besides use of chiral auxiliaries[13] and the functionalization of L-tryptophan,[14] there still are two asymmetric, catalytic synthetic approaches (Scheme 1):[15] (a) the enantioselective synthesis of 3,3-disubstituted oxindoles is first performed, and then the 3,3-disubstituted oxindoles are transformed into the corresponding pyrrolidinoindolines (Scheme 1a);[16] (b) the cascade C3-functionalization/cyclization of 3-substituted indoles and tryptamines provides the desired pyrrolidinoindolines (Scheme 1b).[11,17] Recently, iridium-catalyzed enantioselective allylations have achieved great progress during the past decade.[18,19] Herein, we report a novel and efficient asymmetric synthetic strategy: highly enantioselective iridium-catalyzed cascade double allylations of 1-alkyl-3-alkylindolin-2-imine hydrochlorides with (*E*)-but-2-ene-1,4-diyl dimethyl dicarbonate, leading to chiral tetrahydropyrrolo[2,3-*b*]indoles, whose reduction with diisobutyl aluminum hydride (DIBAL-H) provides pyrrolidinoindolines with three chiral centers (Scheme 1c).

First, $[Ir(cod)Cl]_2$-catalyzed cascade double allylations of 1-methyl-3-phenethylindolin-2-imine hydrochloride (**1h**) with (*E*)-but-2-ene-1,4-diyl dimethyl dicarbonate (**2**) were used as the model to optimize conditions including ligands, solvents,

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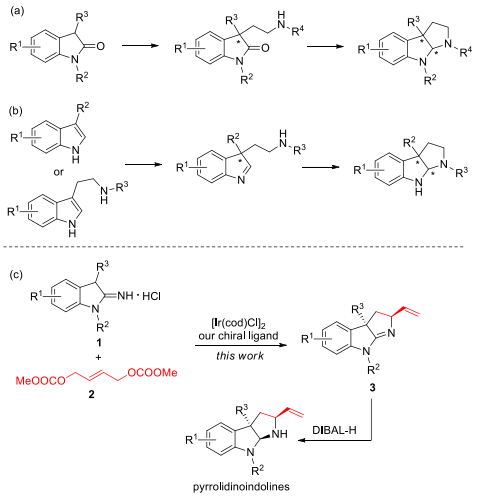
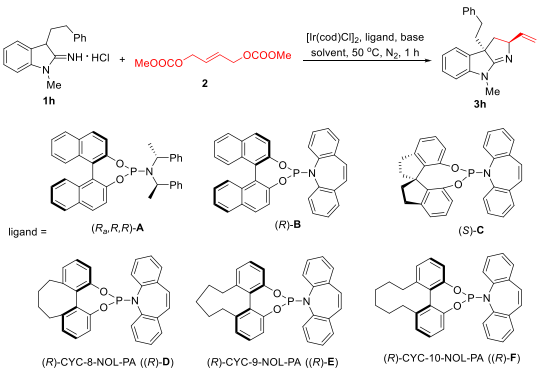
**Scheme 1. Two Common Catalytic Asymmetric Synthetic Approaches (a and b) and Our Route (c) to Chiral Pyrrolidinoindolines**




and bases. As shown in Table 1, six chiral phosphoramidite ligands including three common ligands, ($R_a$,$R$,$R$)-**A**, (*R*)-**B**, and (*S*)-**C**, and our developed three cyclic ligands, (*R*)-CYC-8-NOL-PA ((*R*)-**D**), (*R*)-CYC-9-NOL-PA ((*R*)-**E**), and (*R*)-CYC-10-NOL-PA ((*R*)-**F**) with different dihedral angles,[20] were tested using $K_2CO_3$ as the base in tetrahydrofuran (THF) under a nitrogen atmosphere at 50 °C (entries 1−6), and the results showed that (*R*)-**F** provided the highest yield with 94% ee (entry 6). The reaction did not work in the absence of ligand (entry 7). We attempted variation of temperature (entries 8 and 9) and found that 50 °C was suitable for the reaction (compare entries 6, 8, and 9). The effect of solvents was investigated (entries 10−12), and dioxane afforded better results, 69% yield and 96% ee (entry 10). Other bases, $K_2CO_3$, $K_3PO_4$, NaOAc, and diisopropylethyamine (DIPEA), were attempted (entries 13−16), and $K_2CO_3$ provided a 70% yield with 98% ee (entry 13). Addition of 3 Å molecular sieves did not afford higher yield and ee value (compare entries 13 and 17). We changed the amounts of **2** (compare entries 13, 18, and 19) and found that 1.3 equiv of **2** was suitable (entry 13). Elongation of time did not lead to better results (entry 20). When amounts of $[Ir(cod)Cl]_2$ and (*R*)-**F** were changed (entry 21), the experiment showed that the condition was inferior to that in entry 13. According to the results above, we think that (*R*)-**F** as the ligand, dioxane as the solvent, and $K_2CO_3$ as the base at 50 °C are suitable in the present iridium-catalyzed cascade double allylations.

With the optimized conditions in hand, the substrate scope for the iridium-catalyzed cascade double allylations of 1-alkyl-3-alkylindolin-2-imine hydrochlorides (**1**) with (*E*)-but-2-ene-1,4-diyl dimethyl dicarbonate (**2**) was surveyed (Table 2). Variation of substituents $R^3$ in **1** was attempted, and we found that various alkyl groups including substituted benzyls (**3a**−**3g**), phenethyl (**3h**−**3j**), and alkyls (**3k**−**3m**) were feasible. The reaction afforded good reactivity (55−78% yields) and excellent enantioselectivity (90−98% ee). Subsequently, we explored variation of substituents $R^1$ in **1** (**3n**−**3u**), and the results showed that the influence of electronic effect including electron-donating (**3n** and **3o**), slight electron-withdrawing (**3p**−**3r**), and strong electron-withdrawing groups (**3s**−**3u**) on the phenyl rings was not obvious in reactivity and

**Table 1. Optimization of Conditions**[a]




| entry | ligand | solvent | base | yield of 3 h (%)[b] | ee of 3 h (%)[c] |
|---|---|---|---|---|---|
| 1 | ($R_a$,$R$,$R$)-**A** | THF | $Cs_2CO_3$ | 0 | |
| 2 | (*R*)-**B** | THF | $Cs_2CO_3$ | 57 | 93 |
| 3 | (*S*)-**C** | THF | $Cs_2CO_3$ | 10 | |
| 4 | (*R*)-**D** | THF | $Cs_2CO_3$ | 68 | 92 |
| 5 | (*R*)-**E** | THF | $Cs_2CO_3$ | 60 | 82 |
| 6 | (*R*)-**F** | THF | $Cs_2CO_3$ | 72 | 94 |
| 7 | | THF | $Cs_2CO_3$ | 0 | |
| 8[d] | (*R*)-**F** | THF | $Cs_2CO_3$ | 15 | |
| 9[e] | (*R*)-**F** | THF | $Cs_2CO_3$ | 62 | 91 |
| 10 | (*R*)-**F** | dioxane | $Cs_2CO_3$ | 69 | 96 |
| 11 | (*R*)-**F** | DMF | $Cs_2CO_3$ | 46 | 67 |
| 12 | (*R*)-**F** | MeCN | $Cs_2CO_3$ | 20 | 58 |
| 13 | (*R*)-**F** | dioxane | $K_2CO_3$ | 70 | 98 |
| 14 | (*R*)-**F** | dioxane | $K_3PO_4$ | 58 | 92 |
| 15 | (*R*)-**F** | dioxane | NaOAc | 27 | 64 |
| 16 | (*R*)-**F** | dioxane | DIPEA | 35 | 82 |
| 17[f] | (*R*)-**F** | dioxane | $K_2CO_3$ | 70 | 98 |
| 18[g] | (*R*)-**F** | dioxane | $K_2CO_3$ | 61 | 92 |
| 19[h] | (*R*)-**F** | dioxane | $K_2CO_3$ | 70 | 98 |
| 20[i] | (*R*)-**F** | dioxane | $K_2CO_3$ | 66 | 98 |
| 21[j] | (*R*)-**F** | dioxane | $K_2CO_3$ | 55 | 89 |

[a]Reaction conditions: under nitrogen atmosphere, 1-methyl-3-phenethylindolin-2-imine hydrochloride (**1h**) (0.1 mmol, 1.0 equiv), (*E*)-but-2-ene-1,4-diyl dimethyl dicarbonate (**2**) (0.13 mmol, 1.3 equiv), $[Ir(cod)Cl]_2$ (2.5 μmol, 2.5 mol %), ligand (0.01 mmol, 10 mol %), base (0.36 mmol, 3.6 equiv), solvent (1.0 mL), temperature (50 °C), time (1 h) in a sealed Schlenk tube. The dr values were determined by $^1$H NMR analysis of the crude reaction mixtures after the removal of solvent, and the results showed dr > 50:1. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]At room temperature (~25 °C). [e]At 80 °C. [f]In the presence of 3 Å molecular sieves (30 mg). [g]Using 0.1 mmol of **2**. [h]Using 0.2 mmol of **2**. [i]Reaction time (12 h). [j]$[Ir(cod)Cl]_2$ (1.0 μmol, 1 mol %), (*R*)-**F** (4.0 μmol, 4 mol %). Absolute configuration of **3h** was determined by comparing the structure of **11** (absolute configuration of **11** was assigned by X-ray diffraction analysis).

enantioselectivity. Higher yields (69−74%) and excellent ee values (94−98% ee) were observed. When substituents $R^2$ were ethyl (**3v**), propyl (**3w**), butyl (**3x** and **3y**), benzyl (**3z**), and phenylpropyl (**3aa**), the reaction also afforded satisfactory results. The present reaction exhibited tolerance of various functional groups including C−F, C−Cl, and C−Br bonds and ether, nitro, $CF_3$, and cyano groups.

A large-scale experiment was attempted using reaction of **1h** (2 mmol, 574 mg) with **2** (2.6 mmol, 530 mg) as the example under the standard conditions, and product **3h** was obtained in 68% yield with 96% ee (Scheme 2). Therefore, the present


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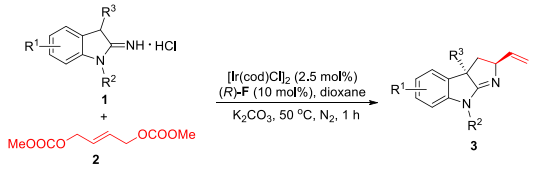
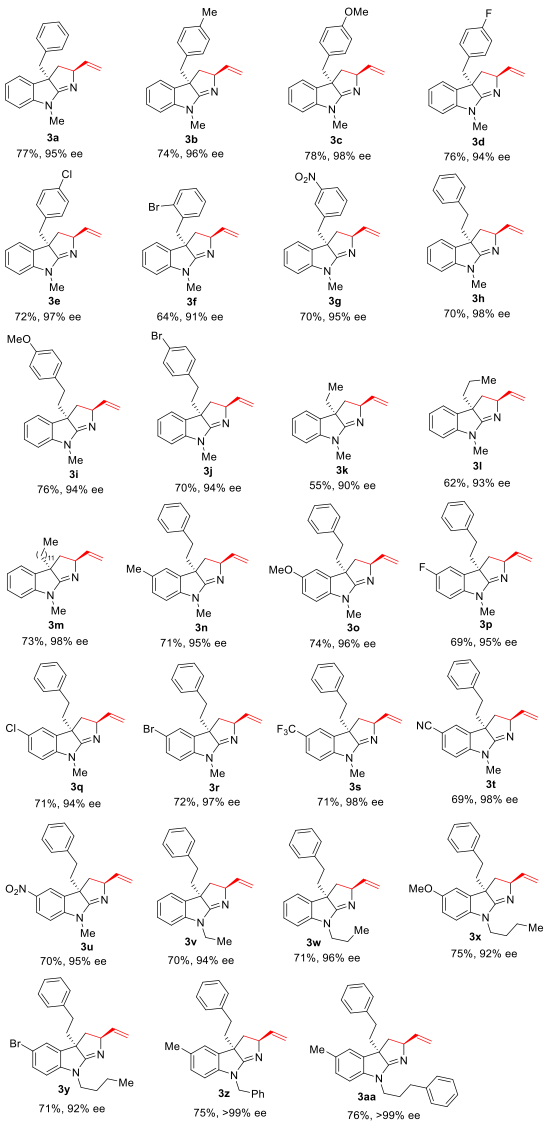
**Table 2. Substrate Scope for Iridium-Catalyzed Asymmetric Synthesis of Various Tetrahydropyrrolo[2,3-*b*]indoles**[a]



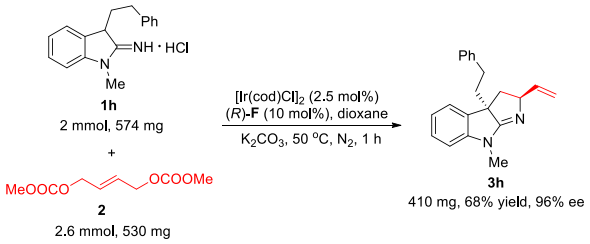

**3**, yield, ee value




[a]Reaction conditions: under a nitrogen atmosphere, **1** (0.1 mmol, 1.0 equiv), **2** (0.13 mmol, 1.3 equiv), $[Ir(cod)Cl]_2$ (2.5 $\mu$mol, 2.5 mol %), (*R*)-**F** (0.01 mmol, 10 mol %), $K_2CO_3$ (0.36 mmol, 3.6 equiv), dioxane (1.0 mL), temperature (50 °C), time (1 h) in a sealed Schlenk tube. The dr values were determined by $^1H$ NMR analysis of the crude reaction mixtures after the removal of dioxane, and the results showed dr > 50:1. Isolated yield and the ee values were determined by HPLC analysis. Absolute configurations of the products (**3a**−**3aa**) were determined by comparing the structure of **11** (absolute configuration of **11** was assigned by X-ray diffraction analysis).

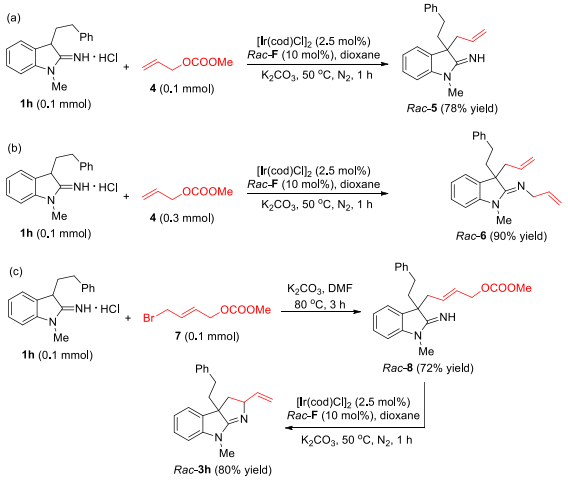
method for the iridium-catalyzed cascade double allylations is an effective strategy for construction of chiral pyrrolidinoindolines.

**Scheme 2. Large-Scale Synthesis of 3h**




In order to explore the mechanism of the iridium-catalyzed cascade double allylations, three control experiments were performed. As shown in Scheme 3, reaction of **1h** with

**Scheme 3. Investigation of the Reaction Mechanism**




equivalent allyl methyl carbonate (**4**) using *Rac*-**F** as the ligand afforded *Rac*-**5** containing a C3a all-carbon quaternary center in 78% yield (Scheme 3a), which showed that reaction of **1** with **2** in Table 2 started at the C3a position of **1**. Reaction of **1h** with 3 equiv of allyl methyl carbonate (**4**) led to diallylating product *Rac*-**6** in 90% yield (Scheme 3b), which indicated the secondary allylation in Table 2 occurred on the NH of **1** after the first allylation of the C3a position in **1**. Coupling of **1h** with equivalent (*E*)-4-bromobut-2-en-1-yl methyl carbonate (**7**) in the presence of $K_2CO_3$ first formed *Rac*-**8** in 72% yield, and then intramolecular cyclization of *Rac*-**8** under the standard conditions provided *Rac*-**3h** in 80% yield (Scheme 3c), which showed that the intramolecular secondary *N*-allylation of **V** in Scheme 4 was feasible.

According to the experiments above and previous references,[21] a reaction pathway of the iridium-catalyzed cascade double allylations is suggested in Scheme 4. First, treatment of **1** with $K_2CO_3$ yields **I**, and reversible isomerization of **I** forms **II**. Coordination of **2** with in situ formed IrXL* from $[Ir(cod)Cl]_2$ and phosphoramide ligand (*R*)-**F** affords complex **III**,[21b] and leaving of carbon dioxide ($CO_2$) in **III** gives the allyl−iridium cation intermediate **IV** and methoxy anion. Reaction of **II** with **IV** leads to chiral allylating product **V**, freeing IrXL* and MeOH. Finally, intramolecular *N*-allylation of **V** affords the target product (**3**) under catalysis of IrXL*.

We attempted reduction of **3** with several reducing agents, and the results showed that diisobutyl aluminum hydride (DIBAL-H) was optimal (see Supporting Information for details). As shown in Scheme 5, reductions of four obtained



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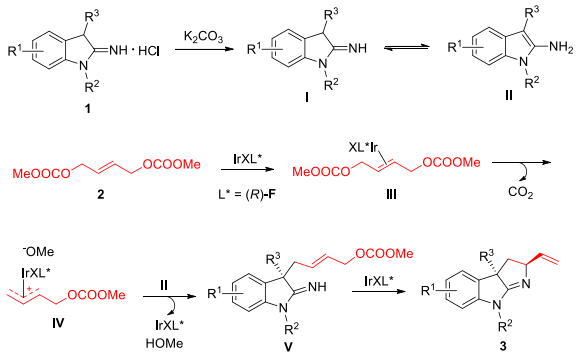
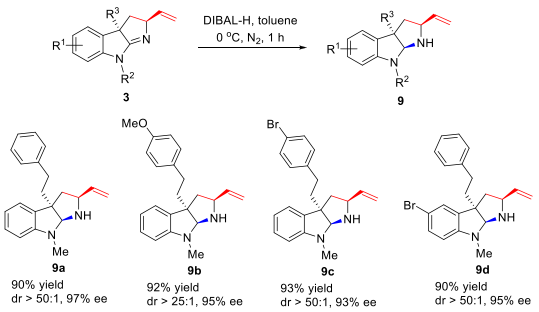
**Scheme 4. Possible Reaction Mechanism**

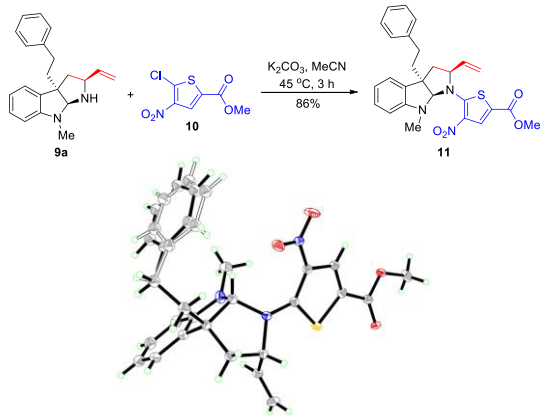


**Scheme 5. Reduction of the Obtained 3 with DIBAL-H Leading to Pyrrolidinoindolines**



products **3h**, **3i**, **3j**, and **3r** with DIBAL-H were used as the examples, and the corresponding pyrrolidinoindolines (**9a**–**9d**) with three chiral centers were prepared in high yields (90–93%) with excellent diastereoselectivity (dr > 25:1 or 50:1) and enantioselectivity (93–97% ee). To ascertain absolute configurations of products **3a**–**3aa** and **9a**–**9d**, compound **11** was synthesized via coupling of **9a** with methyl 5-chloro-4-nitrothiophene-2-carboxylate (**10**) in the presence of base ($K_2CO_3$) in MeCN at 45 °C (Scheme 6). A single crystal of **11**

**Scheme 6. Synthesis and Crystal Structure of 11**



was prepared in ether at 4 °C, and its absolute configuration was unambiguously confirmed by X-ray diffraction analysis (see the Supporting Information for details).

In summary, we have developed an efficient and highly enantioselective method for the iridium-catalyzed cascade double allylations of 1-alkyl-3-alkylindolin-2-imine hydrochlorides with (*E*)-but-2-ene-1,4-diyl dimethyl dicarbonate enabled by our developed chiral cyclic phosphoramidite ligand, and various chiral tetrahydropyrrolo[2,3-*b*]indoles with an all-carbon quaternary stereocenter were obtained in good yields. The method shows some advantages including an operationally simple protocol, fast reaction, and excellent diastereoselectivity and enantioselectivity. Further reduction of the obtained tetrahydropyrrolo[2,3-*b*]indoles provided the corresponding pyrrolidinoindolines with three chiral centers in high yields with excellent dr and ee values. We believe that the highly enantioselective cascade double allylation strategy will find wide applications.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03382.

Experimental details, NMR data, and HPLC spectra (PDF)

### Accession Codes

CCDC 1905629 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: fuhua@mail.tsinghua.edu.cn.

### ORCID

Hua Fu: 0000-0001-7250-0053


### Notes

The authors declare no competing financial interest.

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