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Regioselective N–F and α C(sp^3)–H Arylation of Aliphatic *N*-Fluorosulfonamides with Imidazopyridines

Yuting Xue,[†] Linlin Shi,[†] Xu Wang, Xiaoni Yu, Xinju Zhu,* Xin-Qi Hao,* and Mao-Ping Song

Cite This: https://doi.org/10.1021/acs.orglett.1c02381 Read Online

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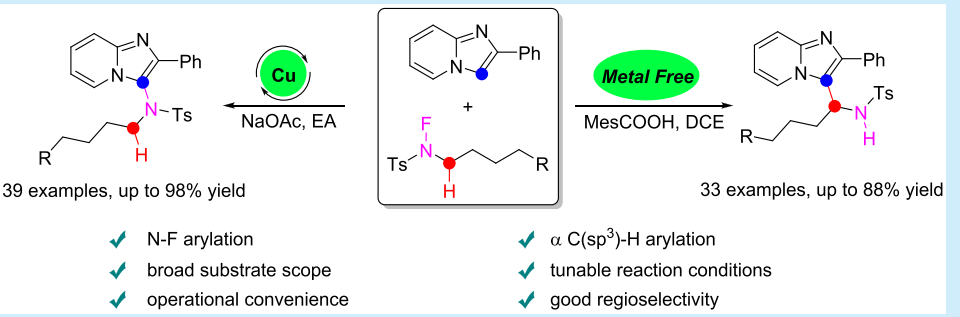


ABSTRACT: A regioselective arylation of aliphatic *N*-fluorosulfonamides with imidazopyridines enabled by breaking of N–F and α C(sp^3)–H bond to form C–N and C–C bonds was described. With CuCl as the catalyst, a radical mechanism was proposed to produce N-arylated aliphatic sulfonamides via a N radical intermediate. Importantly, under acidic conditions, an in situ generated imine was the possible intermediate, which was trapped by imidazopyridines to form α C(sp^3)–H arylated aliphatic sulfonamides. The current protocol featured a broad substrate scope, tunable reaction conditions, operational convenience, and good regioselectivity.

Aliphatic amines are important structural scaffolds that are prevalent in pharmaceutically active molecules and natural products.[1] In this context, considerable attention has been paid to elaborate and diversify aliphatic amines with increased complexity. Nevertheless, the site-selective functionalization of C(sp^3)–H bonds is challenging due to their inert and ubiquitous nature.[2] To solve this problem, transition-metal catalysts have demonstrated versatile reactivity in functionalization of aliphatic amines via a chelation-assisted strategy, which enabled selective β, γ, and δ C(sp^3)–H functionalization.[3] Alternatively, radical strategies involving hydrogen atom transfer (HAT) have also been utilized for regioselective C(sp^3)–H functionalization inspired by the classic Hofmann–Löffler–Frettag (HLF) reaction.[4] The major breakthroughs in the HLF field were achieved by Knowles et al. and Rovis et al., which significantly enhanced distal C(sp^3)–H functionalization via nitrogen-centered radicals.[5]

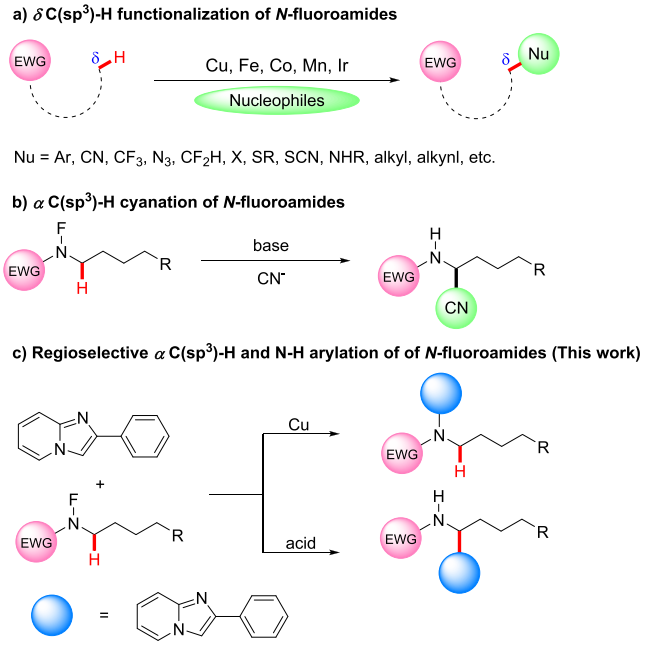
As air-, moisture-, and thermal-stable species,[6a] *N*-fluoroamides were also successfully utilized to realize iron-catalyzed C(sp^3)–H fluorination by Cook et al. in 2016.[6b] The N–F reduction followed by HLF-type HAT regioselectively generates carbon radicals, which allows for further C(sp^3)–H functionalization, including cyclization,[7] halogenation,[8] cyanation,[9] difluomethylation,[10] trifluomethylation,[11] trifluoromethylchalcogenation,[12] thiolation,[13] thiocyanation,[14] azidation,[14b] amination,[15] alkylation,[15a] arylation,[16] alkynlation,[17] and other transformations (Scheme 1a).[18] Nevertheless, these advances mainly confined to δ C(sp^3)–H functionalization of aliphatic *N*-fluoroamides since 1,5-HAT is kinetically more favorable. Meanwhile, most of the above transformations required the addition of transition metals. To the best of our knowledge, C(sp^3)–H functionalization of *N*-fluoroamides at the α position to nitrogen atom is still limited,[19,20] which in some reports utilized substrates without the δ C(sp^3)–H bond.[19a,b] Until now, only C(sp^3)–H cyanation of *N*-fluoroamides was achieved at the α-carbon position under basic conditions (Scheme 1b).[20] Moreover, the exploration of *N*-fluoroamides in other transformations remains to be developed.

Imidazopyridines are unique *N*-heterocycles with wide applications in pharmaceuticals, natural products, catalysis, and optoelectronics.[21] Consequently, considerable efforts have been made to construct and functionalize imidazopyridines.[22] Specially, C–H alkylation and amination have been studied recently.[23] However, regioselective formation C–C and C–N bonds using the same coupling partners has not been reported.

Received: July 16, 2021

https://doi.org/10.1021/acs.orglett.1c02381
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 1. C(sp^3)−H Functionalization of *N*-Fluoroamides

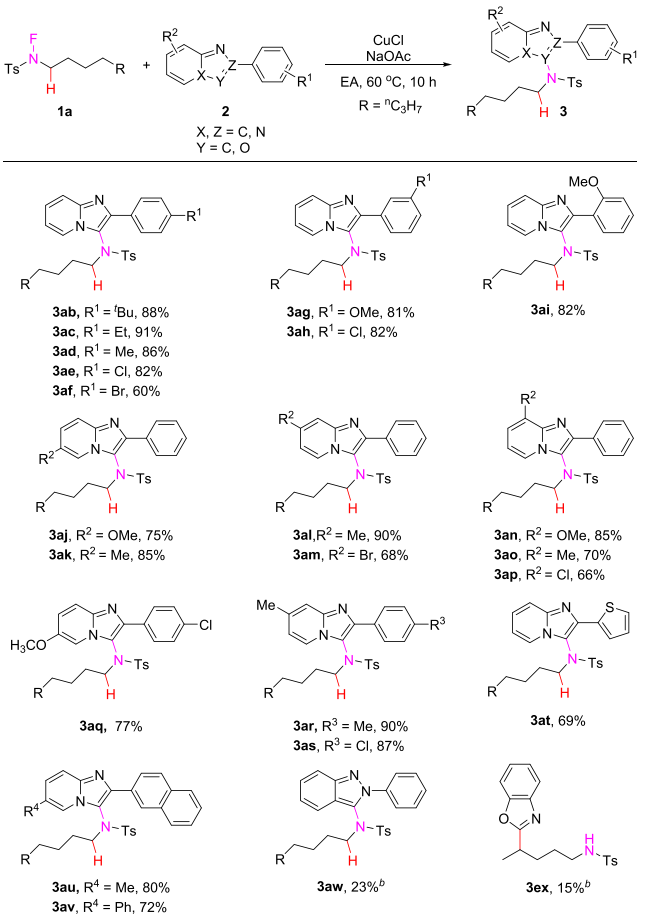


As a continuation of our previous work,[24] we herein develop α C(sp^3)−H and N−F arylation of aliphatic *N*-fluorosulfonamides with imidazopyridines (Scheme 1c). Notably, the regioselectivity was successfully achieved according to tunable reaction conditions. In the presence of Cu salt and base, *N*-fluorosulfonamides were utilized as aminating reagents. On the other hand, *N*-fluorosulfonamides served as alkylating reagents under acidic conditions to give α-arylated aliphatic amines.

Our investigation commenced with reaction of *N*-fluorosulfonamide **1a** (0.15 mmol) and 2-phenylimidazo[1,2-α]pyridine **2a** (0.1 mmol) in the presence 5 mol % of $Cu(OAc)_2$ in 1,2-dichloroethane (DCE). Unexpectedly, N−F arylated product **3aa** was isolated in 43% yield as run at 100 °C for 12 h under air (Table S1, entry 1). Next, other Cu salts were investigated, indicating that CuCl was the best choice to afford **3aa** in 52% yield (Table S1, entry 2). When DCE was replaced by EA, the reaction efficient was significantly improved to provide **3aa** in 77% yield (Table S1, entry 3). Moreover, additive NaOAc (0.05 mmol) was found to be beneficial to give the desired product **3aa** in 83% yield (Table S1, entry 4). To further increased the reaction conversion, the temperature and reaction time were screened to generate **3aa** in 87% yield (Table S1, entry 5). The structure of N−F arylated product **3aa** was also determined by X-ray diffraction (see the Supporting Information). During the above exploration, an interesting phenomenon was discovered that, without Cu salt and additive, **3aa** was isolated in 18% yield accompanied by formation of α C(sp^3)−H arylated product **4aa** in 18% yield confirmed by NMR and HRMS analysis (Table S1, entry 6). Considering the "two birds with one stone" strategy, it would be highly desirable if **3aa** and **4aa** could be selectively produced via tunable reaction conditions. When the reaction was carried out in DCE, **4aa** was obtained in 47% yield (Table S1, entry 7). In the presence of NaOAc, the reaction transformation was further increased to give **4aa** in 61% yield (Table S1, entry 8). Finally, α C(sp^3)−H arylated product **4aa** could be isolated in 75% yield using MesCOOH as the additive (Table S1, entry 9).

With the optimized reaction conditions in hand, the substrate scope of imidazopyridines was investigated for the C−N coupling reaction (Scheme 2). In general, different

Scheme 2. Substrate Scope of Imidazopyridines for C−N Coupling[a]



[a]Reaction conditions: **1a** (0.15 mmol), **2** (0.1 mmol), CuCl (5 mol %), NaOAc (0.05 mmol), EA (1 mL), 60 °C, 10 h, under air. [b]$Cu(OTf)_2$ (5 mol %), phen (5 mol %), AcOH (0.1 mmol), DCE (1 mL), 100 °C, 12 h. Isolated yield. EA = ethyl acetate.

substituents at various positions of imidazopyridine ring were well tolerated with electron-donating groups (OMe, ^{t}Bu, Et, and Me) exhibiting increased reactivity. Initially, *para*-, *meta*-, and *ortho*-substituted imidazo[1,2-α]pyridines were employed to provide products **3ab**−**ai** in 60−91% yields. Subsequently, imidazopyridines bearing substituents on the pyridine rings were also explored to afford products **3aj**−**ap** in 66−90% yields. Next, disubstituted imidazopyridines also proceeded smoothly to give products **3aq**−**as** in 77−90% yields. Moreover, when thiophene and naphthalene moieties locate at the C2 position, the corresponding products **3at**−**av** were obtained in 69−80% yield. Finally, indazole was also tested to give N-arylated product **3aw** in 23% yield under modified conditions. However, when benzoxazole was employed, only δ C(sp^3)−H arylated product **3ex** (R = Me) was isolated in 15% yield.

Next, we turned our attention to exploring the generality of *N*-fluorosulfonamides for C−N coupling reactions (Scheme 3). Various aliphatic amides were compatible with the reaction conditions to afford the corresponding products in good yields.

https://doi.org/10.1021/acs.orglett.1c02381
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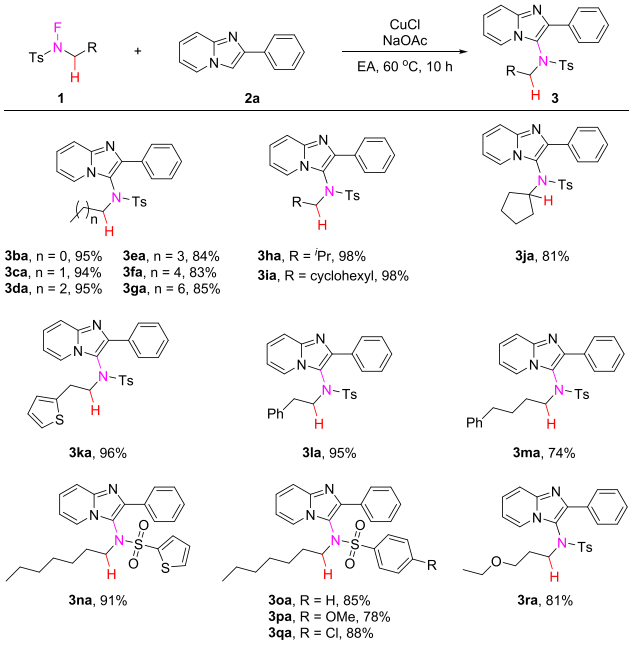
Scheme 3. Substrate Scope of *N*-Fluorosulfonamides for C−N Coupling[a]



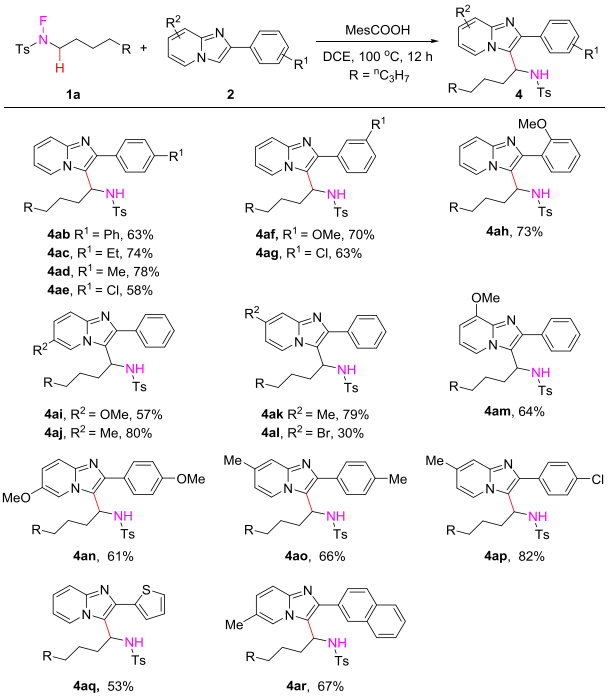
[a]Reaction conditions: **1** (0.15 mmol), **2a** (0.1 mmol), CuCl (5 mol %), NaOAc (0.05 mmol), EA (1 mL), 60 °C, 10 h, under air. Isolated yield. EA = ethyl acetate.

Initially, *N*-fluorosulfonamides bearing different alkyl chain lengths were investigated, which gave products **3ba−ga** in 83−95% yields. Apparently, substrates bearing shorter alkyl chain exhibited higher reactivity. Next, *β*-substituted amide was employed to generate **3ha** and **3ia** in 98% yield. The reaction also worked well with cyclic systems to produce **3ja** in 81% yields, respectively. When (hetero)aryl moieties were introduced onto the aliphatic amides chain, the desired products **3ka−ma** was obtained in 74−96% yields. Additionally, the scope of sulfonamides groups was studied. Thienyl-substituted sulfonamides reacted with imidazopyridine smoothly to provide products **3na** in 91% yield. Meanwhile, sulfonamides bearing electron-donating (OMe) and electron-withdrawing (Cl) groups on the phenyl ring were examined to deliver products **3oa−qa** in 78−88% yields. Finally, ester functionality could survive under the reaction conditions to furnish product **3ra** in 81% yield.

Encouraged by the above results, *α* C(sp^3)−H arylation of *N*-fluorosulfonamide **1a** was investigated via structural modification of the imidazopyridine scaffold (Scheme 4). Notably, imidazopyridines bearing Me, OMe, Et, or Ph groups at different positions of C2 phenyl or pyridine rings afforded the excepted products **4ab−ad**, **4af**, **4ah−ak**, and **4am** in 57−80% yields. For Cl and Br substituents, decreased reaction activity was observed to afford products **4ae**, **4ag**, and **4al** in 30−63% yields. Likewise, disubstituted and C2-thienyl substituted imidazopyridines proceeded smoothly to give products **4an−ar** in 53−82% yields.

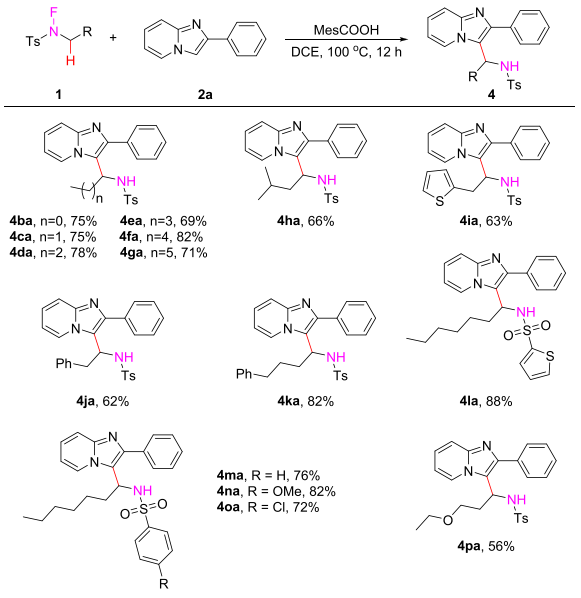
Additionally, a diverse array of *N*-fluorosulfonamides were examined for the C−C coupling reaction (Scheme 5). Varying the length of the aliphatic chains had little effect on the reaction performance to afford products **4ba−ga** in 69−82% yields. For amide bearing branched alkyl chain, the corresponding product **4ha** was isolated in 66% yield. Also,

Scheme 4. Substrate Scope of Imidazopyridines for C−C Coupling[a]



[a]Reaction conditions: **1a** (0.15 mmol), **2** (0.1 mmol), MesCOOH (0.05 mmol), DCE (1 mL), 100 °C, 12 h, under air. Isolated yield.

Scheme 5. Substrate Scope of *N*-Fluorosulfonamides for C−C Coupling[a]



[a]Reaction conditions: **1** (0.15 mmol), **2a** (0.1 mmol), MesCOOH (0.05 mmol), DCE (1 mL), 100 °C, 12 h, under air. Isolated yield.

aliphatic *N*-fluorosulfonamides bearing thienyl and phenyl groups were also employed to provide products **4ia−ka** in 62−82% yields. When sulfonamides were installed with 2-thienyl and *para*-substituted phenyl groups, the desired products **4la−oa** were obtained in 72−88% yields. Furthermore, *N*-fluorosulfonamides with ester functionality was also examined to deliver product **4pa** in 56% yields. Nevertheless, for *α*-

https://doi.org/10.1021/acs.orglett.1c02381
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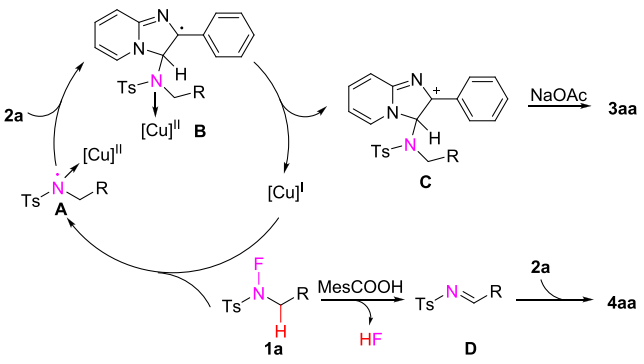
substituted steric hindered amides, no desired products could be obtained (scheme S1).

To explore the reaction mechanism, a set of control experiments were conducted. Performing the reaction in the presence of sulfonamide led to no formation of C−N coupling product **3aa** and C−C coupling product **4aa** (Scheme S2a), indicating sulfonamide is not an intermediate for both transformations. Meanwhile, it suggests that N−F bond is an important driving force to achieve α C(sp^3)−H and N−F arylation of aliphatic amides. When the reaction was carried out in the presence of 1.0 equiv of TEMPO, no product of **3aa** (trace, if any) was detected. Nevertheless, the addition of radical scavenger (1.0 and 2.0 equiv) did not hinder generation of the C−C coupling product, which gave **4aa** in 53% and 46% yields, respectively (Scheme S2b). The above experiments demonstrate that a N radical is generated during N−F arylation while α C(sp^3)−H does not undergo a radical mechanism. Moreover, during the formation of **4pa**, an imine intermediate **5** was detected by HRMS analysis (Scheme S2c). The imine intermediate mechanism was further verified through nucleophilic addition between imine **6** and **2a** in the presence of MesCOOH, HF, or a combination of MesCOOH and HF, which afforded product **7** in the range of 17−27% yield. Without the addition of acid, product **7** could not be obtained. (Scheme S2d). Finally, two 1 mmol scale production experiments were conducted to give **3aa** and **4aa** in 72% and 67% yields, respectively (Scheme S2e).

On the basis of the above mechanistic studies and a previous report,[20] plausible mechanisms were proposed for N−F and α C(sp^3)−H arylation of *N*-fluorosulfonamides (Scheme 6).

Scheme 6. Proposed Reaction Mechanism



Initially, a single electron transfer (SET) between Cu(I) species and *N*-fluorosulfonamide **1a** afforded a copper(II)-coordinated amidyl radical **A**, which underwent a radical addition process to provide intermediate **B**. Next, reductive elimination of intermediate **B** would provide cation intermediate **C**, accompanied by the regeneration of Cu(I) species for the next catalytic cycle. Finally, the desired product **3aa** was obtained with the assistance of NaOAc. On the other hand, MesCOOH-assisted HF elimination of *N*-fluorosulfonamide **1a** via a hydrogen bonding effect could generate imine intermediate **D**, which was intercepted by the nucleophile **2a** to form the desired product **4aa**.

In conclusion, we have developed Cu-catalyzed N−F arylation and metal-free α C(sp^3)−H arylation of *N*-fluorosulfonamides with imidazopyridines under air. The reactions involved the formation of a N radical or imine intermediate to afford the corresponding functionalized aliphatic amines via tunable reaction conditions. Notably, this provided an effective strategy to achieve α C(sp^3)−H arylation of *N*-fluorosulfonamides, which overrides the classic HLF-type 1,5-HAT process. Under the optimized conditions, a broad range of substrate was well tolerated to give the corresponding products in up to 98% yield with good regioselectivity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02381.

Experimental procedures, crystallographic data, and NMR spectra for new compounds (PDF)

Accession Codes

CCDC 2096697 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 Authors

Xinju Zhu − *College of Chemistry, Zhengzhou University, Zhengzhou 450001, P. R. China;* orcid.org/0000-0003-1966-3480; Email: zhuxinju@zzu.edu.cn

Xin-Qi Hao − *College of Chemistry, Zhengzhou University, Zhengzhou 450001, P. R. China;* orcid.org/0000-0003-1942-8309; Email: xqhao@zzu.edu.cn

Authors

Yuting Xue − *College of Chemistry, Zhengzhou University, Zhengzhou 450001, P. R. China*

Linlin Shi − *College of Chemistry, Zhengzhou University, Zhengzhou 450001, P. R. China;* orcid.org/0000-0001-9089-2388

Xu Wang − *College of Chemistry, Zhengzhou University, Zhengzhou 450001, P. R. China*

Xiaoni Yu − *College of Chemistry, Zhengzhou University, Zhengzhou 450001, P. R. China*

Mao-Ping Song − *College of Chemistry, Zhengzhou University, Zhengzhou 450001, P. R. China;* orcid.org/0000-0003-3883-2622

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c02381

Author Contributions

†Y.X. and L.S. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the National Natural Science Foundation of China (Nos. 21803059, U1904212, and U2004191) and the Natural Science Foundation of Henan Province (202300410477) is gratefully appreciated.

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