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Stereospecific Electrophilic Fluorocyclization of α,β-Unsaturated Amides with Selectfluor

Haiyang Fei,[⊥] Zheyuan Xu,[⊥] Hongmiao Wu, Lin Zhu, Hitesh B. Jalani, Guigen Li, Yao Fu,* and Hongjian Lu*

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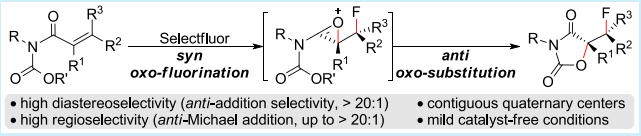
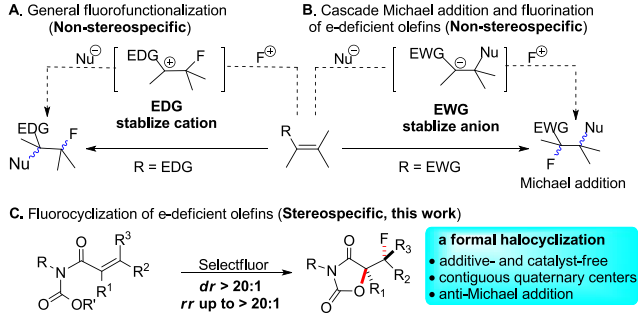
ABSTRACT: An efficient fluorocyclization of α,β-unsaturated amides through a formal halocyclization process is developed. The reaction proceeds under transition-metal-free conditions and leads to the formation of fluorinated oxazolidine-2,4-diones with excellent regio- and diastereoselectivity. The evaluation of the reaction mechanism based on preliminary experiments and density functional theory calculations suggests that a synergetic *syn*-oxo-fluorination occurs and is followed by an *anti*-oxo substitution reaction. The reaction opens a new window in the field of stereospecific fluorofunctionalization.



The electrophilic halofunctionalization of olefins involves cyclic halonium ions, in which a positively charged chlorine, bromine, or iodine is attached to two carbon atoms.[1] These well-documented halonium ions are a key factor in the origin of stereoselectivity in halofunctionalization reactions.[2] One of most important facets of this classical chemistry is the stereochemical outcome, which is dictated by the anti-addition of the starting alkenes. This leads to numerous applications involving the stereoselective construction of halogenated compounds, including natural products.[2,3] However, the formation of a cyclic fluoronium ion from electrophilic fluorine reagents is an exception.[4] The electrophilic fluorofunctionalization of alkenes is mechanistically different from the functionalization with Cl, Br, or I because it involves an acyclic cationic key intermediate instead of a cyclic fluoronium ion, with the consequence that the fluorofunctionalization is not stereospecific and the substrate scope is largely limited to electron-rich olefins (Scheme 1A).[5] For electron-deficient olefins, such as α,β-unsaturated ketones, esters, and amides, a cascade Michael addition and an electrophilic fluorination process forming α-fluorocarbonyl compounds have been shown to take place (Scheme 1B).[6] In these fluorofunctionalization reactions, the stereo information implicit in double bonds cannot be fully transferred to the final products. Electrophilic fluorofunctionalization with anti-addition selectivity, which is common in electrophilic halofunctionalization reactions, is a challenging task and has not been achieved to date.[7,8]

Stereoselective fluorocyclization reactions have attracted much attention[9] because the incorporation of a fluorine atom within the molecular structure significantly modifies the physicochemical properties of the molecule, and fluorinated cyclic and heterocyclic compounds are widely used in pharmaceuticals and agrochemicals.[10] With our interest in the development of fluorocyclization reactions to produce biologically important fluorine-containing molecules,[11] we herein report the first example of the stereospecific electrophilic fluorocyclization of α,β-unsaturated amides (Scheme 1C). 5-*exo* regioselectivity controls this reaction to form a β-fluorocarbonyl compound that is different from the α-fluorocarbonyl compound formed in the cascade Michael addition and the electrophilic fluorination process.[6] The stereochemical outcome is dictated by the geometry of the starting alkenes with overall anti-addition selectivity. The stereoselective construction of two adjacent quaternary carbon centers achieved by this method is also significant because it is a challenging objective, and the number of strategies to

Scheme 1. Electrophilic Fluorofunctionalization



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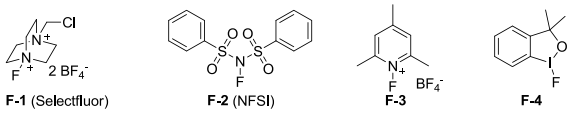
construct these sterically congested structures is limited by thermodynamic problems.[12]

A disubstituted *E*-acrylamide (**1a**) was selected as the model substrate with which to explore the reactivity, regioselectivity, and stereoselectivity of the fluorocyclization reaction (Table 1). Using commercially available Selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo [2.2.2]octane bis-(tetrafluoroborate), **F-1**), the 5-*exo*, anti-addition product (**2a**) was obtained in 97% yield with excellent diastereo- (*dr* > 20/1) and regioselectivity (*rr* > 20/1) (entry 1). **2a** is a known compound, and its relative configuration was confirmed by X-ray crystallographic analysis.[11a] Other F^+ reagents failed to produce **2a** (entry 2), revealing the unique character of Selectfluor.[13] Lower yields were produced when the reaction temperature was decreased or increased (entries 3 and 4). When $MeNO_2$ was used as the solvent, **2a** was provided in good yield (entries 5 and 6), and the yield decreased slightly under basic conditions (entry 7). In an effort to broaden the substrate scope, different ester groups were examined. Compounds containing an ethoxy group gave a good yield (entry 8), but those with a *tert*-butoxy group gave a significantly decreased yield (entry 9), possibly due to the instability of *tert*-butyl esters under the acidic reaction conditions. The addition to the reaction of $NaHCO_3$ improved the yield of **2a** to 81% (entry 10).

The scope of the variously substituted acrylamides was then investigated under optimal conditions (Scheme 2). Substrates with different substituents on the acrylamide nitrogen were examined. Both electron-donating and electron-withdrawing aryl and alkyl substituents are tolerated, leading to moderate to good yields of *N*-aryl(alkyl)-oxazolidine-2,4-diones (**2b**–**e**) with exclusive regio- and diastereoselectivity. *E*-*α*,*β*-dialkyl and *Z*-*α*-phenyl-*β*-alkyl acrylamides were compatible with these reaction conditions, giving **2f** and **2g**, respectively. The spiro compound **2h** was formed with exclusive anti-addition selectivity when a cyclic acrylamide was used. From a medicinal chemistry point of view, both CH_2F group and heterocycles are very important groups that are often involved in the pharmacophores of bioactive compounds.[14] With terminal acrylamides, heterocycles carrying a CH_2F group, products **2i**–**k** were formed in moderate to high yield, illustrating the utility of the method. Because of steric hindrance, it is generally difficult to achieve good reactivity and regioselectivity in the fluorofunctionalization of tetrasubstituted olefins, and only a few symmetrical tetrasubstituted olefins have been used in fluorofunctionalizations.[15] This noncatalytic system has the ability to functionalize fully substituted acrylamides, leading to the stereoselective construction of two contiguous quaternary carbon centers (**2l**–**w**), which otherwise is a challenge.[12] The structure of **2v** was confirmed by X-ray crystallographic analysis (CCDC 1794728). With trialkyl-substituted acrylamides, excellent

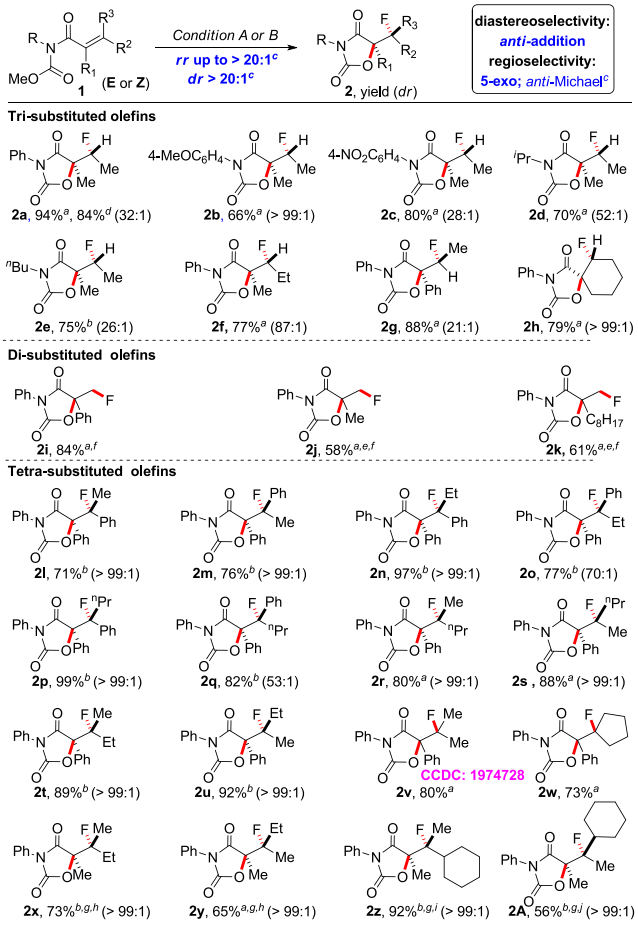
Table 1. Optimization of the Reaction Conditions[a,b,c]

entry	1	R	variation from "condition A"	yield (2a) (%)[b]	*dr*[c]	*rr*[c]
1	**1a**	**Me**	**none**	**97**	>20:1	>20:1
2	**1a**	Me	other F^+ reagent[d]	ND		
3	**1a**	Me	30 °C	64	>20:1	>20:1
4	**1a**	Me	70 °C	90	>20:1	>20:1
5	**1a**	Me	other solvents[e]	ND		
6	**1a**	Me	$MeNO_2$	94	>20:1	>20:1
7	**1a**	**Me**	**additional $NaHCO_3$**[f]	**74**	>20:1	>20:1
8	$\mathbf{1a_1}$	Et	none	86	>20:1	>20:1
9	$\mathbf{1a_2}$	^{t}Bu	none	46	>20:1	>20:1
10	$\mathbf{1a_2}$	^{t}Bu	additional $NaHCO_3$[f]	81	>20:1	>20:1



[a]Condition A: **1** (0.1 mmol), Selectfluor (0.2 mmol), CH_3CN (1 mL), 60 °C, 8 h. [b]^{1}H NMR yield using CH_2Br_2 as an internal standard. [c]*rr* and *dr* were determined by ^{19}F NMR of crude products. [d]**F-2**, **F-3**, or **F-4** was screened. [e]$PhCH_3$, ^{t}BuCN, 1,4-dioxane, MeOH, DMF, or DMSO was screened. [f]2.0 equiv $NaHCO_3$.

Scheme 2. Scope of Acrylamides[a,b,c]



[a]Condition A, see footnote a in Table 1. [b]Condition B: condition A with additional $NaHCO_3$ (2.0 equiv). [c]Isolated yield and *rr* (5-*exo*/6-*endo* products) and *dr* (anti-/syn-addition product) were determined by ^{19}F NMR, 6-*endo* products were not observed in most cases, and relative stereochemistry was tentatively assigned by analogy to **2a** and **4c** based on ^{19}F NMR. (See Table S6.) [d]5 mmol of **1a**. [e]Ethyl ester as substrate. [f]Contaminated with <10% side product. [g]Isolated yield of 5-*exo* product and 6-*endo* product was observed as a minor product. [h]3.3:1 (*rr*). [i]13:1 (*rr*). [j]1.5:1 (*rr*).

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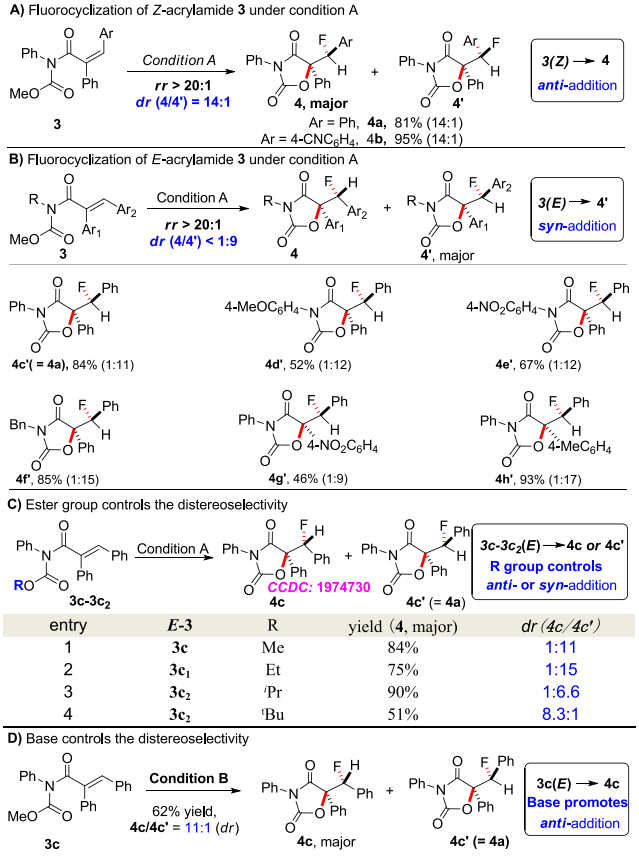
diastereoselectivity was achieved (*dr* > 20/1) but with moderate regioselectivity (*rr* = 1.5/1 to 13/1, **2x**–**A**). When the reaction was performed on the 5 mmol scale, **2a** was obtained in 84% yield. The isomeric *E*- and *Z*-acrylamide (**1**) can produce isomer products (**2**), respectively, with exclusive diastereoselectivity (**2l** vs **2m**, **2n** vs **2o**, **2p** vs **2q**, **2r** vs **2s**, **2t** vs **2u**, **2x** vs **2y**, and **2z** vs **2A**), and the anti-(cascade Michael addition/fluorination) was observed to be regioselective.

When *Z*-*α*,*β*-diaryl acrylamides (**3**) were used as the substrate, the desired anti-addition products were obtained, with, however, a small amount of syn-addition products (**4a** and **4b**, anti-/syn-addition (*dr*) = 14/1, Scheme 3A). Although

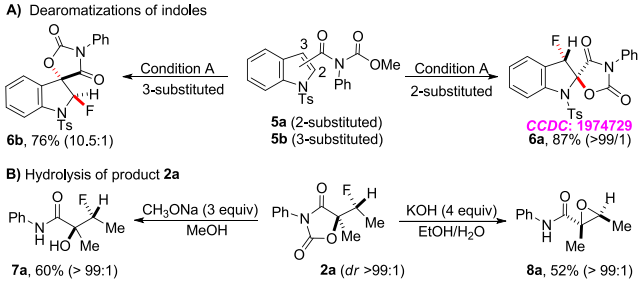
Scheme 3. Scope of *α*,*β*-Diaryl Acrylamides



the level of diastereoselectivity achieved is high, it differs from the results in Scheme 2, revealing the exclusive formation of anti-addition products. Interestingly, the formal syn-addition selectivity was observed when *E*-*α*,*β*-diaryl acrylamides (**3**) were used (Scheme 3B). The syn-addition products were produced in good to high yield and with high diastereoselectivity (**4c**–**f′**, anti-/syn-addition (*dr*) = 1/12 to 1/15) when *N*-alkyl or *N*-phenyl substrates were used. Acrylamides with a 4-$NO_2C_6H_4$ or 4-MeC_6H_4 group in the *α*-position were tolerated (**4g′** and **4h′**). When the ester group was studied, it was found that the diastereoselectivity of the reaction could be controlled by varying the ester functionality (Scheme 3C). When the methoxyl was replaced by *tert*-butoxyl, the *dr* value of products changed from 1/11 to 8.3/1 under condition A, providing **4c** as the major product (entry 4, Scheme 3C). The relative structure of **4c** was confirmed by X-ray crystallographic analysis (CCDC 1794730). In addition, basic conditions could promote the anti-addition selectivity, as observed in Scheme 3D (see similar results for the acrylamides used in Scheme 2, shown in the SI), and the anti-addition product (**4c**) was obtained with high diastereoselectivity. These results offer an opportunity to prepare products with the desired diastereoselectivity by adding base or tuning the ester group in the substrates.

Because indoline is a key fragment of some promising anticancer, anti-inflammatory, and antihypertensive agents,[16] the fluorocyclization of indoles in a pyrrole ring, forming fluorine-containing indolines, has been investigated but was found, however, to have low to moderate diastereocontrol.[17] When indoles with the substituent in the two- or three-position were investigated in this reaction, the biheterocyclic spiro compounds (**6a** and **6b**) were obtained in good yield with excellent regio- and diastereoselectivity (Scheme 4A). The

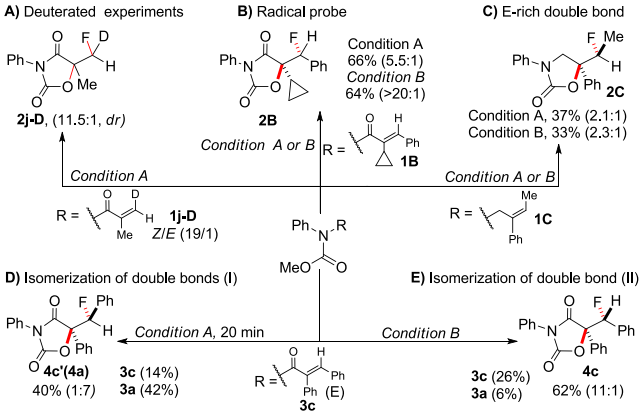
Scheme 4. Applications in Dearomatization and Hydrolysis



relative configuration of **6a** was confirmed by X-ray crystallographic analysis (CCDC 1974729). The hydrolysis of product **2a** under different basic conditions provided an *α*-hydroxy-*β*-fluoroamide (**7a**) and an oxirane-2-carboxamide (**8a**),[18] respectively, with no effect on the relative configuration (Scheme 4B).

To gain an understanding of the mechanism, several experiments were carried out and are described in Scheme 5.

Scheme 5. Mechanistic Studies



When the substrate (**1j-D**) containing one deuterium atom in the terminal position of the double bond was used, the product **2j-D** was achieved with good diastereoselectivity (Scheme 5A). The relative stereochemistry of **2j-D** has not yet been determined. When a cyclopropyl group was used as a radical probe under basic condition B, no ring-opened products were observed, and the 5-*exo* product (**2B**) was achieved with exclusive diastereoselectivity (Scheme 5B), suggesting that no radical intermediate was involved. When an alkyl olefin was

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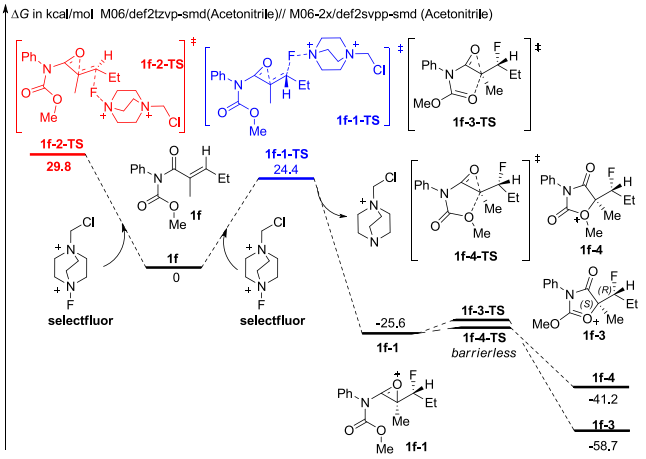
used in place of compounds containing an electron-deficient double bond, the expected 5-*exo* product (**2C**) was formed, but with low diastereoselectivity (Scheme 5C), implying that the carbonyl group of acrylamides is critical.[19] When the reaction of *E*-α,β-diphenyl acrylamide (**3c**) was performed with a reduced reaction time under the reaction condition A, the double-bond isomer of **3c** (**3a**) was observed in 42% yield, and the syn-addition product (**4c′**) was the major product (Scheme 5D). Under condition B, a small amount of the double-bond isomer (**3a**) was found, and the anti-addition product (**4c**) was the major product (Scheme 5E). These results show that the overall syn-addition products were observed in some cases, possibly due to the isomerization of double bond under the acidic reaction conditions and that the use of base could prevent the isomerization of the acrylamides. The possible reason why the antiselectivity was achieved in the reaction of substrate $\mathbf{3c}_2$ (Scheme 3C) is that its electrophilic fluorocyclization might be faster than the isomerization of the double bond.

To further investigate the reaction mechanism, density functional theory (DFT) calculations were conducted on the reaction of **1f** (Scheme 6). The *syn*-oxo-fluorination of olefin

Scheme 6. DFT Calculations for the Reaction of 1f



for the reaction of **1f** with Selectfluor is achieved through **1f-1-TS** with an active free energy of 24.4 kcal/mol. In comparison, the *anti*-oxo-fluorination of olefin through **1f-2-TS**, is a pathway associated with an active free energy of 29.8 kcal/mol. The electrostatic interaction between the C═O of the amide and the ammonium ion of Selectfluor may induce the *syn*-oxo-fluorination of olefin. The formation of the cyclic oxonium ion intermediate **1f-1** is exothermic by 25.6 kcal/mol. The subsequent *anti*-oxo substitution of **1f-1** is essentially barrierless and leads exothermically to intermediates **1f-3** and **1f-4**, which can generate the same overall anti-addition product **2f**. This mechanism suggests an unusual synergetic *syn*-oxo-fluorination process of electron-deficient olefins, which may find broader applications in the stereospecific synthesis of fluorinated molecules.

In conclusion, we have developed a stereospecific, electrophilic fluorocyclization reaction, whose regio- and diastereoselectivity are similar to those of the classical electrophilic halofunctionalizations. Using acrylamides as substrates, this reaction provides fluorinated oxazolidine-2,4-diones with excellent regio- and diastereoselectivity. Products containing two contiguous quaternary carbon centers including a quaternary C−F bond were also constructed. The carbonyl group of acrylamides is critical in the selectivity problem encountered with other alkenes and serves as a device that can deliver regio- and diasterocontrol in the fluorocyclization process. The use of the easily handled Selectfluor reagent, readily prepared acrylamides, and mild reaction conditions are important features of this reaction. Preliminary experiments and DFT calculations demonstrate that this transformation goes through a cascade synergetic *syn*-oxo-fluorination followed by an *anti*-oxo-substitution process. The results obtained in this study provide a foundation for the further development of the stereocontrolled synthesis of fluorinated compounds through the fluorofunctionalization of olefins with predictable anti-addition selectivity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00620.

Experimental procedures and copies of ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

Accession Codes

CCDC 1974728−1974730 contain 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

Yao Fu − *Hefei National Laboratory for Physical Sciences at the Microscale, CAS Key Laboratory of Urban Pollutant Conversion, Anhui Province Key Laboratory of Biomass Clean Energy, iChEM, University of Science and Technology of China, Hefei, Anhui 230026, China;* orcid.org/0000-0003-2282-4839; Email: fuyao@ustc.edu.cn

Hongjian Lu − *Institute of Chemistry and BioMedical Sciences, Jiangsu Key Laboratory of Advanced Organic Materials, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, China;* orcid.org/0000-0001-7132-3905; Email: hongjianlu@nju.edu.cn

Authors

Haiyang Fei − *Institute of Chemistry and BioMedical Sciences, Jiangsu Key Laboratory of Advanced Organic Materials, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, China*

Zheyuan Xu − *Hefei National Laboratory for Physical Sciences at the Microscale, CAS Key Laboratory of Urban Pollutant Conversion, Anhui Province Key Laboratory of Biomass Clean Energy, iChEM, University of Science and Technology of China, Hefei, Anhui 230026, China*

Hongmiao Wu − *Institute of Chemistry and BioMedical Sciences, Jiangsu Key Laboratory of Advanced Organic Materials, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, China*

Lin Zhu − *Institute of Chemistry and BioMedical Sciences, Jiangsu Key Laboratory of Advanced Organic Materials, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, China*

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Hitesh B. Jalani − *Department of Pharmacy and Yonsei Institute of Pharmaceutical Science, Yonsei University, Incheon 21983, South Korea;* orcid.org/0000-0002-2442-9798

Guigen Li − *Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79409-1061, United States;* orcid.org/0000-0002-9312-412X

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00620

Author Contributions

[⊥]H.F. and Z.X. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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