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# Clickable Transformation of Nitriles (RCN) to Oxazolyl Sulfonyl Fluoride Warheads

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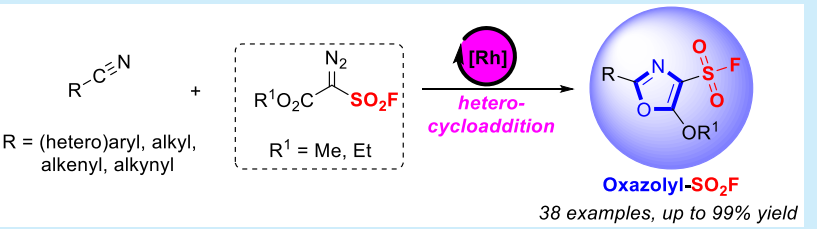


**ABSTRACT:** The protocol for simple, efficient, and mild synthesis of oxazolyl sulfonyl fluorides was developed through $Rh_2(OAc)_4$-catalyzed annulation of methyl-2-diazo-2-(fluorosulfonyl)acetate (MDF) or its ethyl ester derivative with nitriles. This practical method provides a general and direct route to a unique class of highly functionalized oxazolyl-decorated sulfonyl fluoride warheads with great potential in medicinal chemistry, chemical biology, and drug discovery.

Oxazole is an electron-deficient, five-membered N,O-heterocyclic unit that is widely present in fluorescent materials,[1] polymers,[2] organic synthesis intermediates,[3] naturally occurring compounds,[4] and bioactive small molecules.[5] Many oxazolyl-containing molecules such as Oxaprozin (COX-2 inhibitor), Dalfopristin (streptogramin antibiotic), and Suvorexant (insomnia drug) have been witnessed as blockbuster drugs in recent decades (Figure 1a).[6] Given the great

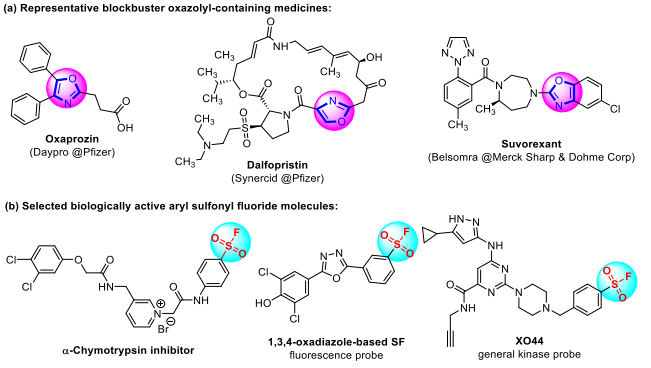


**Figure 1.** Representative blockbuster oxazolyl-containing medicines and biologically active aryl sulfonyl fluoride molecules.

importance and ubiquitous application of oxazole derivatives in aforementioned fields, assembly of functionalized oxazole compound libraries via mild, robust, and facile protocols continues to be a key focus; therefore, corresponding extensive advances have been achieved.[3,7]

On the other hand, sulfur fluoride exchange (SuFEx) chemistry, a new generation of click chemistry that was launched in 2014 has triggered burgeoning interest in the research community, along with numerous successful applications in various fields.[8] Aryl sulfonyl fluorides, which are privileged members of the SuFEx chemistry family, have been successfully exploited as deoxyfluorination reagents,[9] $^{18}$F-radiolabeling agents,[10] polysulfonate precursors,[11] and also participated in many other chemical transformations.[8d] Their unique features of strong electron-withdrawing nature, stability against hydrolysis, and resistance to reduction at the S center also enable them to be renowned as ideal irreversible enzyme inhibitors and reactive chemical probes (Figure 1b).[12] In addition, the SuFEx reactions based on aryl sulfonyl fluorides under defined conditions provide feasible access to a wide variety of sulfonyl functionalized structures of pharmaceutical significance and over 150 FDA approved sulfur ($S^{VI}$)-containing drugs can be obtained in the market to the year of 2019.[13]

Considering the prominent medicinal activity of oxazolyl[5] and ever-growing research importance of sulfonyl fluorides in medicinal chemistry and chemical biology,[12] we envision that constructing diverse oxazolyl sulfonyl fluoride compounds is worthy of great exploration, since it would contribute to enhance the chances of lead compound discovery and new drug candidate identification.[14] However, a cursory index of

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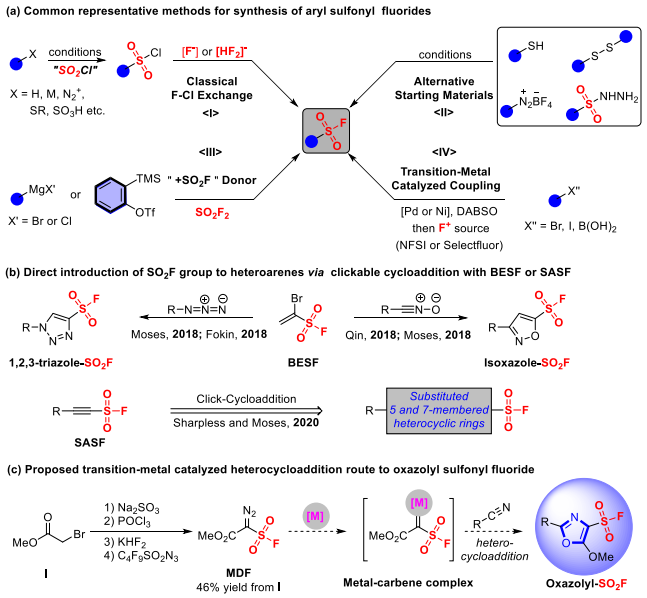
the literature revealed that the aryl sulfonyl fluorides were traditionally prepared via Hal-Ex reactions of corresponding sulfonyl chloride precursors.[8a] Although sulfonyl chlorides have been widely used for synthesizing sulfonyl fluorides, their property of susceptible to nucleophiles (e.g., moisture and amines) has significantly restricted their utilization and storage (Scheme 1a, ⟨I⟩). Consequently, several alternative methods

**Scheme 1. Approaches to (Hetero)Aryl Sulfonyl Fluorides**



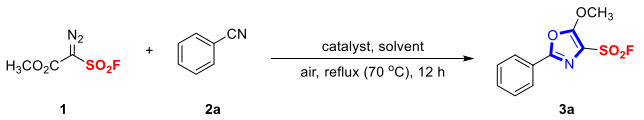

have been explored, including the electrochemical coupling of thiols with KF,[15] oxidation of disulfides with electrophilic selectfluor,[16] fluorosulfonylation of aryldiazonium salts,[17] and fluorination of sulfonyl hydrazides,[18] albeit the requisite feed stocks were not operationally friendly for most of the present protocols (Scheme 1a, ⟨II⟩). Sulfuryl fluoride ($SO_2F_2$) was used for preparing aryl sulfonyl fluorides from reacting with Grignard reagents[19] or arynes[20] (Scheme 1a, ⟨III⟩). In addition, transition-metal-catalyzed fluorosulfonylation of aryl bromides, iodides, or boronic acids represents alternative methods to make aryl sulfonyl fluorides through using DABSO as "$SO_2$" source and NFSI or selectfluor as an electrophilic fluorination reagent (Scheme 1a, ⟨IV⟩).[21] Despite the breadth of accessible methods for making aryl sulfonyl fluorides, oxazolyl sulfonyl fluorides preparation still remains unexplored. Therefore, the high value and unavailability of this class of molecules necessitate robust and effective methods for their synthesis.

Although click chemistry as a synthesis philosophy has evolved rapidly with advent of the thiol-addition chemistry,[22] SuFEx chemistry,[8a] and diazotransfer reaction,[23] the original cycloaddition type of click chemistry is still predominating. In order to achieve clickable cycloaddition, in combination with SuFEx chemistry, new enabling cyclization $SO_2F$-containing synthons including BESF[24] and SASF[25] have been designed to construct a series of heterocyclic molecules decorated with sulfonyl fluorides via effective click-cycloadditions (Scheme 1b). Inspired by these seminal works in Scheme 1b, we assumed the clickable heterocycloaddition methodology would also be feasible for achieving the goal of oxazolyl sulfonyl fluorides preparation.

Diazo compounds have been widely applied in various chemical transformations,[26] and nitriles as abundant and inexpensive feed stocks have also been extensively used for organic synthesis.[27] Accordingly, we designed and synthesized a new reagent methyl 2-diazo-2-(fluorosulfonyl)acetate (MDF) bearing both diazo and $SO_2F$ functionalities via a four-step transformation from methyl 2-bromoacetate (**I**) in total 46% yield. Moreover, we envision that, in the presence of transition-metal catalysts, the diazo group of MDF will be activated to undergo cycloaddition with nitriles, to generate a family of unprecedented 4-sulfonylfluoride substituted oxazole derivatives (Scheme 1c).

Our investigation commenced with testing feasibility of the annulation of 2-diazo-2-(fluorosulfonyl)acetate (MDF) (**1**, diazo-$SO_2F$) and benzonitrile (**2a**) under the catalysis of $Cu(OTf)_2$ (5 mol %) in anhydrous $CHCl_3$, and a negligible yield of 5-methoxy-2-phenyloxazole-4-sulfonyl fluoride (**3a**) was obtained (Table 1, entry 1). Accordingly, other common

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




| entry | catalyst | solvent | yield of **3a**[b] (%) |
|---|---|---|---|
| 1 | $Cu(OTf)_2$ (5 mol %) | $CHCl_3$ | <2 |
| 2 | $Cu(acac)_2$ (5 mol %) | $CHCl_3$ | 5 |
| 3 | $Cu(acac)_2$ (50 mol %) | $CHCl_3$ | 36 |
| 4 | $Rh_2(OAc)_4$ (5 mol %) | $CHCl_3$ | 99 |
| 5 | $Rh_2(OAc)_4$ (2 mol %) | $CHCl_3$ | **96** |
| 6 | $Rh_2(OAc)_4$ (1 mol %) | $CHCl_3$ | 88 |
| 7 | $Rh_2(OAc)_4$ (2 mol %) | DCE | 93[c] |
| 8 | $Rh_2(OAc)_4$ (2 mol %) | MeOH | ND[d] |
| 9 | $Rh_2(OAc)_4$ (2 mol %) | $CHCl_3$ | 81[e] |
| 10 | $Rh_2(OAc)_4$ (2 mol %) | $CHCl_3$ | 70[f] |
| 11 | $Rh_2(OAc)_4$ (2 mol %) | $CHCl_3$ | 87[g] |

[a]Reaction conditions: MDF (**1**, 55 mg, 0.3 mmol, 1.5 equiv) dissolved in anhydrous solvent (1.0 mL) was added with a syringe dropwise to a solution of benzonitrile (**2a**, 21 mg, 0.2 mmol, 1.0 equiv) and catalyst in anhydrous solvent (1.0 mL) heated under reflux. After the addition was over, the resulting mixture was stirred at 70 °C for 12 h. [b]HPLC yield ($t_{R,3a}$ = 5.904 min, $\lambda_{max,3a}$ = 272.5 nm; MeOH/$H_2O$ = 70:30 (v/v)). [c]Reacted at 90 °C. [d]N.D. = not detectable. [e]Regular undried $CHCl_3$ was used. [f]MDF (**1**, 0.24 mmol, 1.2 equiv). [g]Reacted at 60 °C.

copper catalysts were screened, most of which did not significantly improve the yield of corresponding desired oxazole **3a** (see the Supporting Information for details). Elevating the loading of $Cu(acac)_2$ from 5 mol % to 50 mol % still resulted in unsatisfying yield (Table 1, entries 2 and 3). Notably, switching the catalyst to $Rh_2(OAc)_4$ provided the desired annulated product **3a** in almost-quantitative yield, indicating that the rhodium catalyst was much more effective and suitable for this cyclization reaction (Table 1, entry 4). Subsequent optimization revealed that 2 mol % $Rh_2(OAc)_4$ was essential for this transformation since further reducing the catalyst to 1 mol % led to an obviously decreasing yield of product **3a** (Table 1, entries 5 and 6). Because solvents can act in a static sense to change the energies of the reactants and products,[28] the evaluation on the influence of solvent was also conducted, and the halogenated solvents ($CHCl_3$ and DCE) were found to be suitable for this transformation, while the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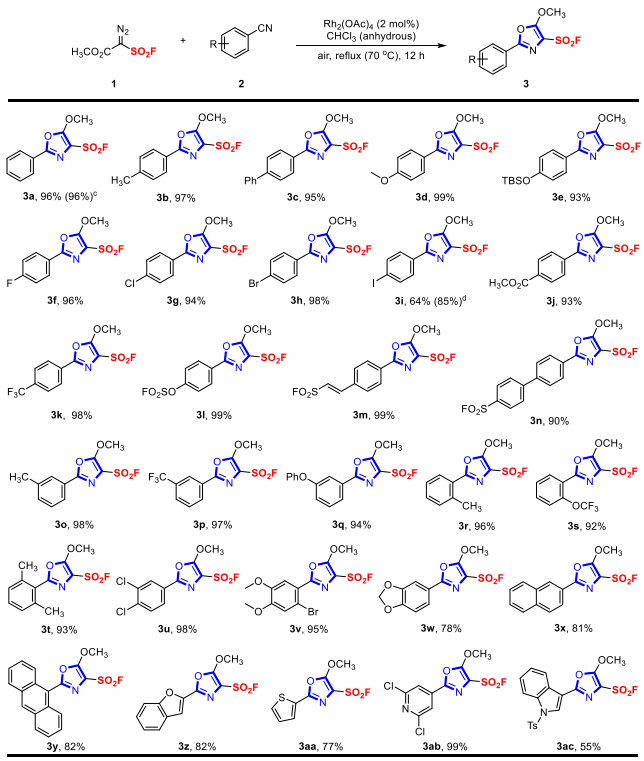
protonic solvent MeOH was not effective for this annulation (Table 1, entries 5 and 7 vs entry 8). It was noteworthy that the moisture in the solvent can significantly deteriorate the cyclization efficiency (Table 1, entry 5 vs entry 9). In addition, other factors such as the stoichiometry of reagents and reaction temperature were also investigated (Table 1, entries 10 and 11), revealing that 1.5 equiv of MDF and 70 °C were the best conditions for the desired transformation. Therefore, the condition of entry 5 in Table 1 was eventually chosen for the preparative runs described hereafter.

In order to evaluate the functional group tolerance and substrate scope of this methodology, a large variety of structurally and electronically diverse aryl nitriles were examined under the optimized reaction conditions as collected in Scheme 2. In addition, the research results revealed that

**Scheme 2. Substrate Scope Using Aryl Nitriles**[a,b]

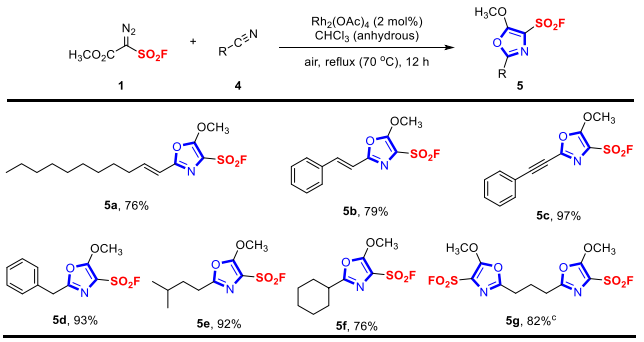



[a]Reaction conditions: aryl nitrile (**2**, 0.5 mmol, 1.0 equiv), MDF (**1**, 137 mg, 0.75 mmol, 1.5 equiv), $Rh_2(OAc)_4$ (2 mol %, 4.5 mg) and anhydrous $CHCl_3$ (4.0 mL), reflux (70 °C), 12 h. [b]Isolated yields. [c]The reaction was conducted on a 5 mmol scale (**2a**, 516 mg). [d]MDF (**1**, 182 mg, 1.0 mmol, 2.0 equiv) was used.

most of the substrates afforded their corresponding cyclization products in high to excellent yields, regardless of the nitriles functionalized with electron-donating (methyl, phenyl, and ether group) or electron-withdrawing (halogen, ester group, trifluoromethyl, and trifluoromethoxy) substituents on the aromatic rings. Note that the transformation proceeded smoothly without any obvious influence caused by electronic factors (e.g., **3d** vs **3k** and **3r** vs **3s**). In addition, this reaction system provided an effective synthesis of silicon ether and sulfonyl fluoride simultaneously containing oxazole molecule (**3e**), which can be an interesting unit for polymer chemistry. The halogen substituents were well-accompanied and delivered expected products with excellent yields (**3f**–**3h**, yields of 94%–98%). Notably, the 4-iodobenzonitrile (**2i**) also exhibited satisfying efficiency when increasing the loading of MDF (**1**) to 2.0 equiv. Three versatile synthons of the SuFEx chemistry resident in the aryl nitriles remained intact during this annulation reaction, including aryl fluorosulfate ($OSO_2F$, **3l**), ethenesulfonyl fluoride (ESF, **3m**), and aryl sulfonyl fluoride ($ArSO_2F$, **3n**). Besides, the position of substituents on the aromatic rings exhibited little influence on the efficiency. The steric hindered nitrile (**2r**) accomplished its transformation with comparable yield to its *para*- or *meta*-substituted analogues (**3r** vs **3b** and **3o**). To our delight, the multisubstituted nitriles were also smoothly converted to their oxazole products under the identical conditions (**3t**–**3w**). Considering the optical ability of polycyclic molecules and applications of oxazole skeleton in fluorescent materials,[1] 2-naphthalene nitrile and 9-anthracene nitrile were also tested and furnished their final products **3x** and **3y** with isolated yields of 81% and 82%, respectively. The heteroaromatic substrates containing O, S, and N atoms also turned out to be suitable starting materials, resulting in good to excellent yields (**3z**–**3ab**, 77%–99% yields). The Ts-protected indole moiety was compatible with this reaction system as well, albeit a moderate yield of **3ac** was obtained. Remarkably, a scale-up reaction of MDF (**1**) and benzonitrile (**2a**) was also conducted providing 96% isolated yield of target product **3a**, which demonstrated the excellent practicability of our developed method for construction of 4-sulfonylfluoride-substituted oxazoles.

The subsequent exploration demonstrated that this catalytic system was also suitable for cyclizing allylic, propargylic, and aliphatic nitriles with MDF (**1**), generating the corresponding poly-substituted $SO_2F$-functionalized oxazoles (Scheme 3, **5a**–

**Scheme 3. Scope of Converting Allylic, Propargylic, and Aliphatic Nitriles to Oxazoles**[a,b]




[a]Reaction conditions: nitrile (**4**, 0.5 mmol, 1.0 equiv), MDF (**1**, 137 mg, 0.75 mmol, 1.5 equiv), $Rh_2(OAc)_4$ (2 mol %, 4.5 mg) and anhydrous $CHCl_3$ (4.0 mL), reflux (70 °C), 12 h. [b]Isolated yields. [c]MDF (**1**, 274 mg, 3.0 equiv) and $Rh_2(OAc)_4$ (5 mol %, 11 mg) were used.

**5g**) in pleasing yields (76%–97%). The reactions of allylic nitriles adjacent to long aliphatic chain (**4a**) or phenyl (**4b**) both worked well with 100% retention of *E*-configuration. In addition, the 5-methoxy-2-(phenylethynyl)oxazole-4-sulfonyl fluoride (**5c**) was readily accessible in quantitative yield by using propargylic nitrile (**4c**) as the cyclization partner. As for alicyclic nitrile **4f**, the steric hindrance of cyclohexane structure frustrated the anticipated transformation obviously, leading to only a 76% yield of oxazole **5f**. Besides, the nitrile **4g** containing two reaction sites was also successfully bifunction-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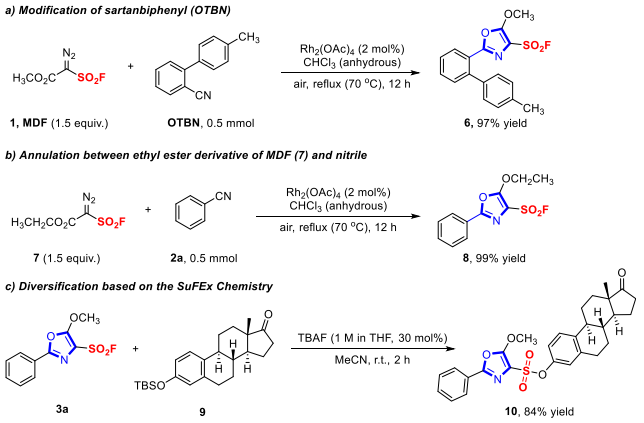
alized when we enhanced the loading of Rh catalyst and MDF during the operation.

As depicted in Scheme 4a, sartanbiphenyl (**OTBN**),[29] which is one of the key pharmaceutical precursors for the formal

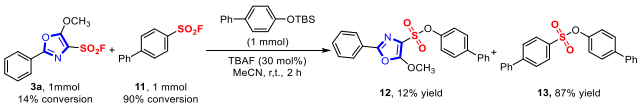
**Scheme 4. Studies on the Reaction Practicability and Diversification of Oxazole−$SO_2F$**




synthesis of the drugs of Losartan, Valsartan, Irbesartan, and Olmesartan, can also be transformed to the corresponding oxazolyl sulfonyl fluoride (**6**) in almost-quantitative yield after annulation with MDF (**1**) under the standard conditions. Besides, the ethyl ester derivative of MDF (**7**) prepared via the similar procedures of MDF (**1**) was found to be another excellent cycloaddition partner to generate the corresponding annulated product (**8**) in 99% yield through this developed methodology. Furthermore, viewing the multitudinous applications of sulfonate in academic research and industrial production,[30] and prominent reactivity of sulfonyl fluoride for synthesis of sulfonate,[8] a TBAF-catalyzed SuFEx reaction of oxazole-$SO_2F$ (**3a**) with TBS-protected Estrone (**9**) was also presented, resulting in a novel estrone sulfonate derivative (**10**) for further utilizations (see Scheme 4c).

To compare the SuFEx reactivity of oxazolyl and regular aryl sulfonyl fluorides with *tert*-butyldimethylsilyl (TBS) ether of phenol, an intermolecular competition experiment was conducted in the presence of 30 mol % TBAF (see Scheme 5). The results indicated that the reactivity of oxazolyl sulfonyl

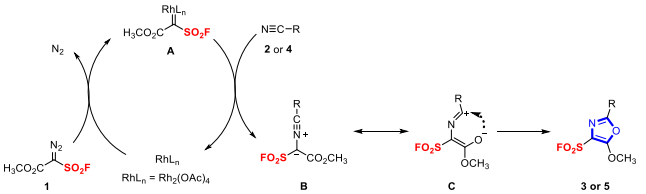
**Scheme 5. SuFEx Reactivity Comparison between Oxazolyl and Aryl Sulfonyl Fluorides**




fluoride (**3a**) was inferior to that of regular aryl counterpart (**11**), as demonstrated by the consumption of starting materials **3a** and **11** (14% and 90%, respectively), while the generation of their corresponding SuFEx products (**12** and **13**) exhibited yields of 12% and 87%, respectively.

On the basis of the experiment results and previous studies,[31] a plausible mechanism for this Rh-catalyzed annulation reaction was postulated in Scheme 6. The transformation started with the insertion of $RhL_n$ to MDF (**1**) to form an electrophilic rhodium carbene complex **A** as the key intermediate with concomitant release of $N_2$. The subsequent nucleophilic attack of nitrile (**2** or **4**) N atom to

**Scheme 6. Proposed Reaction Mechanism**




rhodium carbene complex **A** led to the formation of intermediate **B**, and the regenerated $RhL_n$ was applied for the next catalytic cycle process. Afterward, the intramolecular 1,5-dipolar cyclization of intermediate **C**, a resonance contributor from intermediate **B**, finally provided the desired 4-sulfonylfluoride substituted oxazoles (**3** or **5**).

In conclusion, methyl 2-diazo-2-(fluorosulfonyl)acetate (MDF), as an enabling cycloaddition fluorosulfonylation partner, was designed and synthesized. In addition, a Rh-catalyzed 1,5-dipolar annulation of MDF with nitriles was accomplished in mild, practical, and robust manners for a clickable assembly of a class of unprecedented oxazolyl sulfonyl fluorides. Further studies on the biological activity of these resultant sulfonyl fluoride-containing oxazoles and chemical transformations of MDF or its other ester derivatives are underway in our laboratory.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03298.

General methods, synthetic procedures, and characterization (PDF)

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### Notes

The authors declare no competing financial interest.

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