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Iron-Catalyzed Reductive Vinylation of Tertiary Alkyl Oxalates with Activated Vinyl Halides

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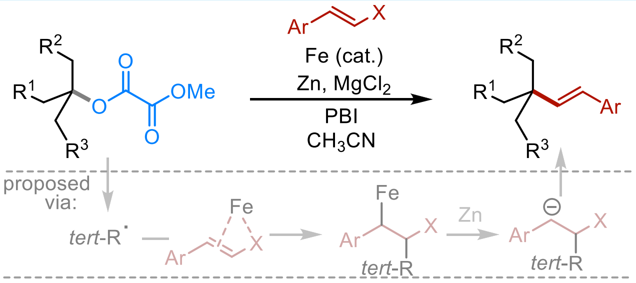
ABSTRACT: We present herein a rare and efficient method for the creation of vinylated all carbon quaternary centers via Fe-catalyzed cross-electrophile coupling of vinyl halides with tertiary alkyl methyl oxalates. The reaction displays excellent functional group tolerance and broad substrate scope, which allows cascade radical cyclization and vinylation to afford complex bicyclic and spiral structural motifs. The reaction proceeds via tertiary alkyl radicals, and the putative vinyl−Br/Fe complexation appears to be crucial for activating the alkene and enabling a possibly concerted radical addition/C−Fe forming process.



The challenges of conversion of unactivated alkyl C(sp^3)−O bonds into C−C bonds and the abundance of alcohols and their derivatives in nature have provided sustained impetuses for the development of C(sp^3)−O bond coupling chemistry.[1,2] However, prominent methods for homolytic cleavage of unactivated alkyl C−O bonds remain limited.[3] Among them, perhaps the Barton radical C−O bond fragmentation strategy represents the most widely used one,[4] which often requires forcing conditions such as UV irradiation and/or toxic radical inducing reagents, e.g., Bu$_3$SnH. The radical intermediates are usually trapped with alkenes conjugated with electron-withdrawing groups, thus limiting the scope of the reaction types.[4] Recently, Overman has demonstrated a visible light mediated Barton C−O bond scission strategy that allows oxalate salts and phthalimidyl-modified oxalyl esters to generate alkyl radicals under Ir-catalyzed oxidative and Ru-catalyzed reductive conditions, respectively.[5] We, on the other hand, disclosed that readily accessible unsymmetrical alkyl methyl oxalyl esters are amenable for the creation of unactivated tertiary alkyl radicals under Zn/MgCl$_2$ conditions that are promoted by Ni.[6] Such a protocol has enabled the development of Ni-catalyzed reductive coupling of tertiary alkyl oxalates with aryl halides to afford arylated all-carbon quaternary stereogenic centers (Figure 1).[6−8] However, the same conditions were not applicable to the equivalent vinylation with vinyl halides (Scheme 1), due to rapid dimerization of vinyl groups upon exposure of vinyl halides to Ni(0).[7] In fact, unlike the relatively well-characterized aryl−Ni complexes in cross-electrophile couplings, the putative vinyl−Ni intermediates have not been isolated.[9] Thus, only special tertiary benzylic halides such as cyclotryptamine substrates are competent for vinylation with vinyl halides, possibly due to matched reactivities.[8b]

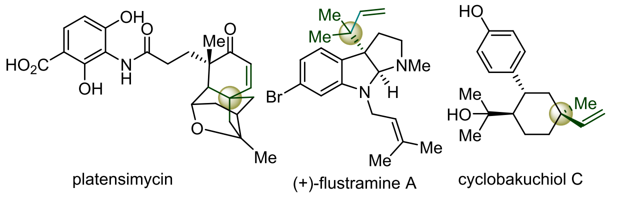
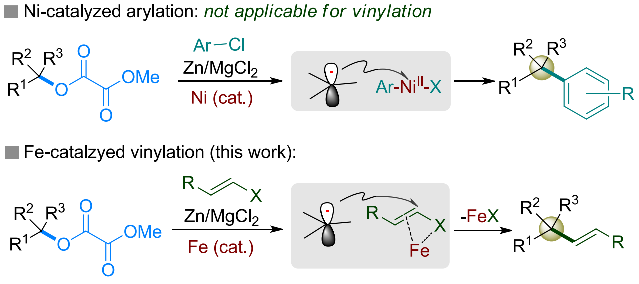


Figure 1. Structures of platensimycin, (+)-flustramine, and cyclobakuchiol C.

Scheme 1. Formation of C(sp^2)−C(sp^3) Quaternary Carbon Centers via Cross-Electrophile Coupling of Tertiary Oxalates



The vinylated quaternary carbon centers are ubiquitous in bioactive and naturally occurring compounds, e.g., platensimycin, (+)-flustramine, and cyclobakuchiol C (Figure 1).[10] A

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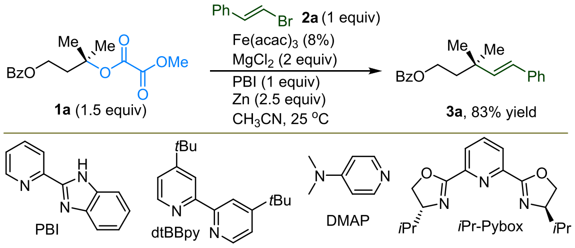
notable strategy for these structural motifs includes addition of unactivated tertiary radicals to alkynes that affords *cis*-alkenes under Fe-catalyzed or photoredox conditions.[11] In addition, Photo/Pd-catalyzed radical/Heck reactions,[12a] photoredox Ru/Ni-catalyzed tertiary alkyl halides with styrenes, and vinyl halides have been unlocked, respectively.[12b,c,14] None of these transformations relies on the coupling of C−O bond substrates with vinyl electrophiles.

Herein, we report a Fe-catalyzed reductive coupling of unactivated tertiary alkyl oxalates with vinyl halides that efficiently creates vinylated all-carbon quaternary centers (Scheme 1). In addition to the use of readily accessible alcohol derivatives, this work highlights the utility of earth-abundant Fe as the catalyst. To our knowledge, Fe catalysts have not been exploited in the field of cross-electrophile couplings except in the cases of in situ Kumada couplings.[15] In a recent work on allylation of tertiary alkyl oxalates with allyl carbonates, Fe was used as a promoter.[16] This work differs from the densely used Ni-catalyzed methods featuring the engagement of C(sp^2)−Ni intermediates. Coordination of vinyl halides with Fe appears to be crucial for alkene activation. More importantly, we propose a mechanism concerning concerted addition of alkyl radical to vinyl halides and formation of benzyl−Fe intermediate, followed by reductive generation of a benzyl carbanion followed by halide elimination and resuming unsaturation to give an *E*-alkene product.

We first examined the coupling of a tertiary alkyl methyl oxalate **1a** with (*E*)-(2-bromovinyl)benzene **2a**. The previous Ni-catalyzed conditions for arylation of tertiary alkyl oxalates in *N*,*N*-dimethylacetamide (DMA) gave **3a** in <15% yield.[6,17] An extensive survey of the reaction conditions led us to identify that a combination of Fe(acac)$_3$ (8 mol %) and 2-(pyridin-2-yl)-1*H*-benzo[d]imidazole (PBI, 1 equiv) with Zn and MgCl$_2$ in acetonitrile at ambient temperature provided the coupling product **3a** in an optimal 83% yield (Table 1, entry 1). The control experiments indicated the necessity of Fe, Zn, and MgCl$_2$ (entries 2−4). However, without PBI, a reasonably good yield was detected (entry 5), but with more alcohol product due to decomposition of **1a**. The use of Mn to replace Zn also generated **3a** in 47% yield (entry 6), wherein the participation of vinyl−Mn is not possible.[9c] While Fe(acac)$_2$ gave **3a** in a good yield, Fe powder was not suitable (entries 7−8). With CH$_3$CN as the solvent, Ni salts enabled the coupling but in low efficiency (entry 9).[17] By contrast, copper salts were incompetent (entry 10).[14] Replacement of PBI with other pyridine-containing additives did not improve the results (entries 11−13). The bromo analog of **1a** proved to be unsuitable (entry 14), indicating a unique feature of C−O bond vinylation of this work. Finally, the reaction on a gram scale gave **3a** in 88% yield (entry 15).

This C−O bond vinylation method displayed excellent compatibility for a broad range of tertiary alkyl oxalates when coupling with (*E*)-(2-bromovinyl)benzene (Figure 2). The all-carbon quaternary centers containing geminal dimethyl groups were effectively created (e.g., **4**−**36**). Moderate to good yields were obtained for cholesterol and cholic acid derived **37**−**38**. The more sterically demanding tertiary alkyl oxalates containing ethyl and propyl groups proved to be compatible, as evident in the products of **39**−**42**, although a low yield was observed for **42** that contains the dipropyl- and phenylethyl-connected carbon center. Such sterically congested steric centers have not been reported in the previous methods pertaining to tertiary alkyl radicals.[11−14] The reaction also exhibited moderate coupling efficiency for tertiary alkyl substrates within closed rings, as evident in **43**−**46** including 3-, 4-, 6-, and 12-membered ones. The bicyclic cyclotryptamine product **47** was obtained in 41% yield. Finally, the simultaneous vinylation of the dioxalates was successful as exemplified by **48**. A wide range of functional groups were tolerated. The notable ones include ester, silyl ether, alkyl bromide, aryl chloride and iodide, and an acidic amide proton.

Table 1. Optimization of the Reaction of 1a with 2a



entry	variation from the standard conditions	yield (%)[a]
1	none	83[b]
2	w/o MgCl$_2$	no reaction
3	w/o Zn	trace
4	w/o Fe(acac)$_3$	trace
5	w/o PBI	59
6	Mn instead of Zn	47
7	Fe(acac)$_2$ instead of Fe(acac)$_3$	78
8	Fe powder instead of Fe(acac)$_3$	8
9	Ni(acac)$_2$	31
10	CuCl$_2$	trace
11	DMAP instead of PBI	21
12	dtbbp instead of PBI	45
13	*i*Pr-Pybox instead of PBI	24
14	3-bromo-3-methylbutyl benzoate instead of **1a**	5
15	3.0 mmol of **2a**	88[b]

[a]NMR yield using 2,5-dimethyl furan as the internal standard from a mixture containing other impurities after quick flash column chromatography. [b]Isolated yield (average of 2 independent runs).

Next, we explored the suitability of various vinyl halides for the coupling with **1a**. The reactions were compatible with 1-aryl-conjugated vinyl halides. The aryl moieties bearing electron-withdrawing groups in general resulted in higher coupling yields (e.g., **3b**−**3e**) than those with electron-donating ones (e.g., **3j**). Among the methoxy-substituted products **3l**−**3n**, the *ortho*-one was the most effective. The (*Z*)-(2-bromovinyl)benzene gave the trans-product **3n** in 67% yield. *cis*-Alkenyl bromide was fully recovered in the absence of oxalate **1a**. Interestingly, vinyl iodide and chloride generated **3n** and **3a** in 63% and 77% yields, respectively. Good coupling results were also observed for thiophenyl, furyl, ferrocenyl, and vinyl conjugated vinyl bromides as manifested by the examples of **3r**−**3t** and **3v**. (2,2-Difluorovinyl)benzene afforded *cis*-1-fluoro-2-phenyl **3u** in 58% yield. 1,1-Diphenyl and 1-phenyl-1-methyl substituted vinyl bromides were competent to generate **3w** and **3x** in 58% and 32% yields, whereas conversion of (*E*)-((2-bromovinyl)oxy)benzene to **3y** was inefficient. Finally, a screening of different alkenes including styrene revealed that only allyl carbonate gave an allylated product in 10% yield (Figure 3).

To gain insight into the reaction details, the assembly of alkene-tethered tertiary alkyl oxalates **49a**−**c** with (*E*)-(2-

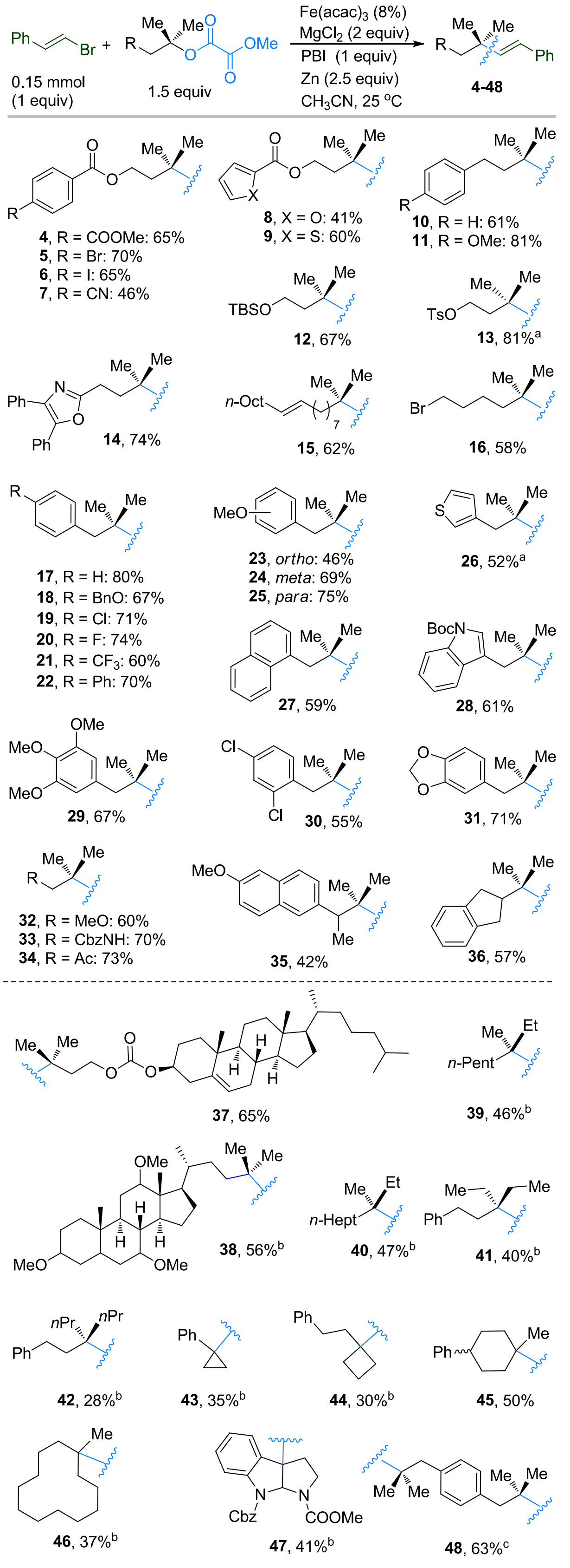


Figure 2. Scope of tertiary alkyl methyl oxalates. (a) (*E*)-1-(4-(2-Bromovinyl)phenyl)ethanone (1 equiv) as the vinyl bromide. (b) Oxalate (1 equiv), (*E*)-(2-bromovinyl)benzene (3 equiv), Fe(acac)$_3$ (35% mmol), Zn (5 equiv), PBI (2.5 equiv). (c) Oxalate (1 equiv), (*E*)-(2-bromovinyl)benzene (3 equiv).

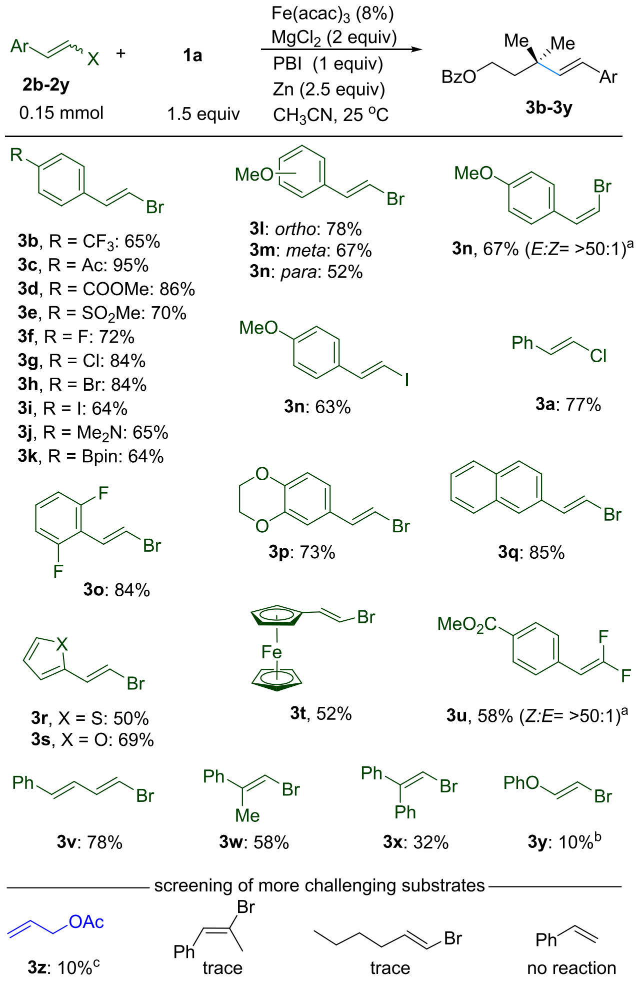
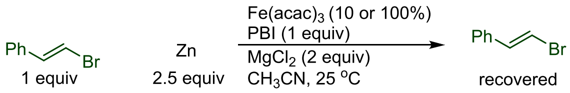


Figure 3. Scope of vinyl bromides. (a) The *E*/*Z* ratio was determined by ^{1}H NMR. (b) NMR yield using 2,4-dimethyl furan as the internal reference. (c) DMA as solvent and allylated product was formed.

bromovinyl)benzene was performed using the standard method. The formation of cyclization/coupling products **50a−c** supported that the oxalates proceed through a C−O bond radical scission process (Figure 4). Based on our previous studies, the generation of a tertiary radical arose from reduction of the oxalate with Zn/MgCl$_2$,[6] perhaps promoted by low-valent Fe. Thus, we further extended the radical cyclization/vinylation cascade strategy to afford the more complex bicyclic and spiral products **50d−g** as single diastereomers. All these examples showcased the utility of this work in the preparation of sophisticated structures. Of note is the facile construction of two consecutive all-carbon quaternary centers in **50g**. The radical cyclization/vinylation process also features the transformation of more stable tertiary alkyl radicals to primary and secondary ones, suggesting that the latter two are kinetically more favored for subsequent vinylation.

The reaction did not seem to involve in situ conversion of vinyl bromide to vinyl−Zn. In the absence of oxalate **1a**, (*E*)-(bromovinyl)benzene was primarily recovered under the standard conditions or with stoichiometric Fe(acac)$_3$ (eq 1),



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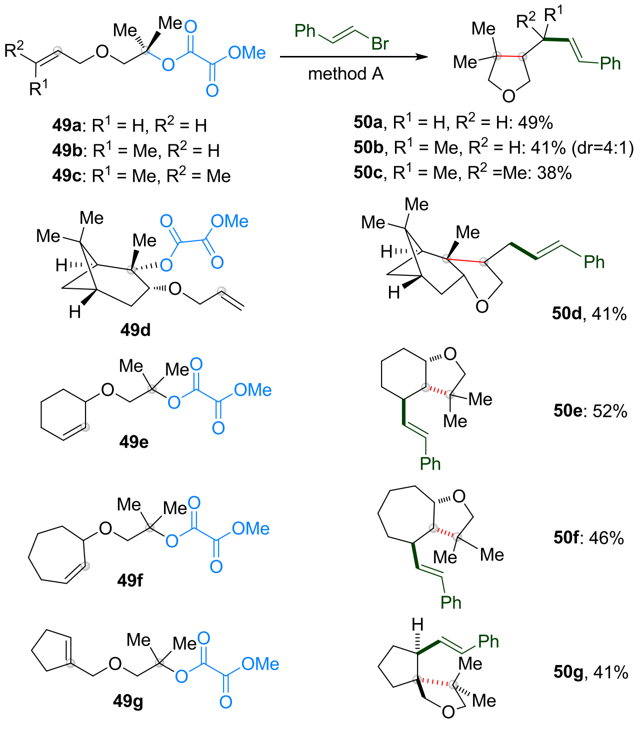
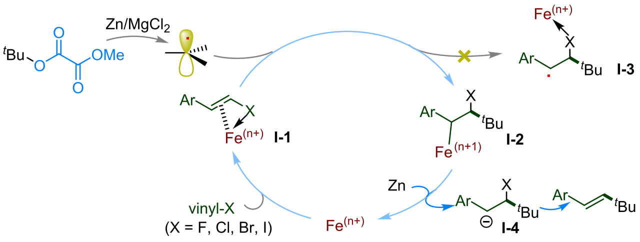


Figure 4. Cascade radical cyclization/vinylation of **49a−g**.

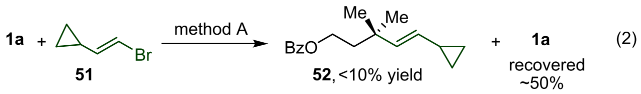
suggesting that oxidative insertion of vinyl bromide to low valent Fe forming vinyl−Fe is less likely,[18] which differs from the Ni-catalyzed method.[19] Since Fe(acac)$_2$ also resulted in **3a** in a good yield (Table 1, entry 7) whereas Fe powder is essentially incompetent (Table 1, entry 8), it is reasonable to conclude that the reaction may involve Fe^{I} or Fe^{II} as the actual catalytic species, consistent with the proposal in Hu's addition of tertiary alkyl radicals to alkynes.[11a]

Although the details of the reaction mechanism require considerably more insightful studies, it appears that coordination of vinyl bromide with low valent Fe to give **I-1** may play an important role for the radical addition process (Scheme 2).[20] By mixing Fe(acac)$_3$ or Fe(acac)$_2$ with **2a**, ^{1}H NMR spectra indicated two new peaks appeared in ranges of 3.5−4.0 and 5.3−5.5 ppm with respect to the individual spectra of **2a** and Fe(acac)$_3$ (Figures S1−S2).[17] These results clearly indicated complexation of Fe with vinyl bromide. In contrast, the lack of reactivity for styrene (Figure 3) prompts us to conclude that leaving groups such as halide in vinyl halides are crucial to push the reaction to move forward, likely due to its induction of formation of **I-1**.

Scheme 2. Formation of C(sp^2)−C(sp^3) Quaternary Carbon Centers via Cross-Electrophile Couplings



Interestingly, the deliberately designed radical clock vinyl bromide **51** only resulted in cyclopropyl ring retention product **52**, albeit in a low yield (eq 2).[17] Thus, addition of a tertiary alkyl radical to β-carbon of styryl bromide−Fe complex **I-1** to give a benzylic radical intermediate **I-3** is less likely.[21] Instead, we propose that formation of C−Fe bonded intermediate **I-2** is plausible via a concerted process. Elimination of Fe and Br affords the vinylated product. A concerted elimination process can be ruled out, since both *E*- and *Z*-alkenyl bromides gave the *E*-product (e.g., **3n**). In a recent study by Walsh, addition of a stable secondary benzyl radical to an analog of **51** did not give a cyclopropyl ring-opening product. An anionic intermediate was proposed in their addition step.[22] Formation of a benzyl anion **I-4** is possible, which explains the formation of styryl fluoride **3u** by elimination of F$^-$, since release of a fluorine radical from the benzyl radical **I-3** is less operative. Taken together, it appears that benzyl-Fe $^{n+1}$ intermediate **I-2** may further be reduced by Zn to afford benzyl carbanion **I-4** and Fe^{n+}; single bond rotation occurs prior to elimination of halides from **I-4** that furnishes an *E*-vinyl product.



In summary, we have demonstrated unactivated tertiary alkyl oxalates and aryl-conjugated vinyl bromides underwent efficient cross-electrophile coupling to furnish sterically demanding vinylated quaternary stereogenic centers. The reactions feature the exceptionally rare Fe-catalyzed reductive coupling and the unusual unactivated tertiary alkyl C−O bond radical fragmentation. The substrates are readily accessible, and the vinyl products are amenable for diverse functional group conversions (e.g., to acids and aldehydes),[23] all rendering this method intriguing for preparation of complex structures as showcased by the examples of the radical cyclization/coupling manifolds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00561.

Detailed experimental procedures, characterization of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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