OL Organic Letters

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Hydrosilafluorenes as Recyclable Coupling Reagents for Direct Amidation of Carboxylic Acids with Amines

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Cite This: https://doi.org/10.1021/acs.orglett.5c04034 Read Online

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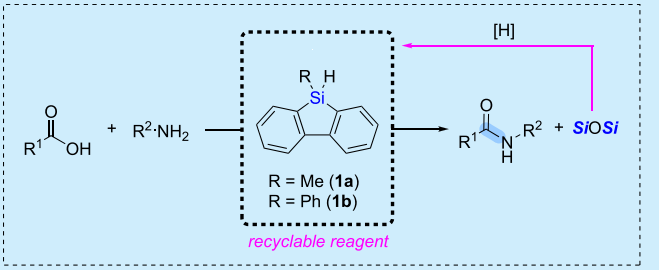
ABSTRACT: We have discovered both 9-methyl- and 9-phenyl-9*H*-9-silafluorene as effective reagents for direct amidation. The protocol is performed under open-air conditions without rigorous exclusion of moisture, producing amides in high yields with only H_2 and disiloxane as byproducts. The disiloxane byproduct can be reduced in a separate step to recycle the silafluorenes. This breakthrough represents the first example of a recyclable organosilane coupling reagent and is a significant step toward developing greener amidating agents.



The amide bond is one of the most significant functional groups in nature (e.g., proteins), pharmaceuticals (present in approximately 50% of the top 200 small molecule drugs in 2024),[1] and commodity chemicals.[2,3] It is no surprise then that the preparation of amides is among the most frequently performed chemical reactions. Common coupling reagents are effective but are also wasteful and raise safety concerns;[2,4] HATU for example has been reported as an immune sensitizer,[5] and HOBt possesses explosive properties.[6] The American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable identified sustainable and catalytic amide bond formation as a key research area in 2007,[7] and this goal was re-emphasized in 2018,[8] highlighting it as an unmet critical target for synthetic method development.

Organosilanes are emerging as alternative amide coupling reagents because of molecular silicon's natural abundance,[9,10] ease-of-handling, and low inherent toxicity.[11] There has been notable progress in the field of organosilane coupling reagents, with recent examples including dichlorosilafluorene,[12] $Si(OMe)_4$,[13] $MeSi(OMe)_3$,[14] Ph_2SiH_2,[15,16] and $PhSiH_3$.[17,18] Substituted triphenylsilanols have also been explored as silicon-centered molecular catalysts; practical adoption of this method is limited by catalyst degradation and narrow substrate scope.[19]

In this work, we sought to innovate in the area of silane amide coupling reagents using strain-release Lewis acidity.[20,21] We identified 9-methyl-9*H*-9-silafluorene (**1a**) and 9-phenyl-9*H*-9-silafluorene (**1b**) as readily synthetically accessible potential coupling reagents (Figure 1), inspired by Charette and co-workers' previous application of the silafluorene scaffold to activate carboxylic acids as electrophiles.[12] However, using a monohydrosilane instead of a dichlorosilane[12] is crucially advantageous because: 1) hydrosilanes are typically easier to handle (e.g., stable in open air) than chlorosilanes, and 2) the byproduct of a tertiary silane is

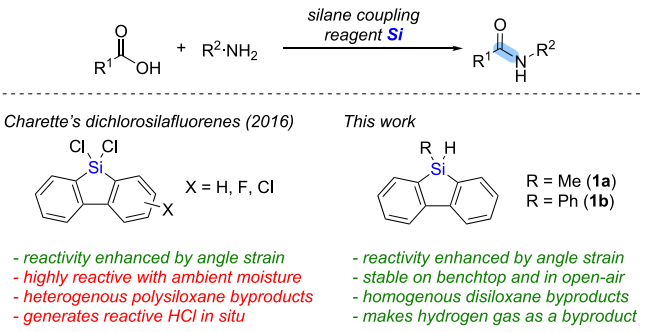


Figure 1. Silafluorene-mediated amide coupling reactions.

presumptively a small molecule disiloxane, which is easier to further manipulate (e.g., reduced to regenerate the hydrosilane) than a polysiloxane byproduct of a reaction using a primary or secondary silane.

9-Methyl- (**1a**) and 9-phenyl-9*H*-9-silafluorene (**1b**) were synthesized from commercially available 2,2′-dibromobiphenyl according to a modified literature procedure.[22−24] The 9-hydrosilafluorenes were handled in open air and stored on the benchtop for several months with no observable decomposition.

We began by investigating the amidation capability of the silafluorenes in comparison to their acyclic analogues to test the effects of ring strain (Figure 2). Under conditions adapted from our previous work,[16] the acyclic analogues of **1a**

Received: September 26, 2025
Revised: November 11, 2025
Accepted: November 13, 2025

https://doi.org/10.1021/acs.orglett.5c04034
Org. Lett. XXXX, XXX, XXX−XXX

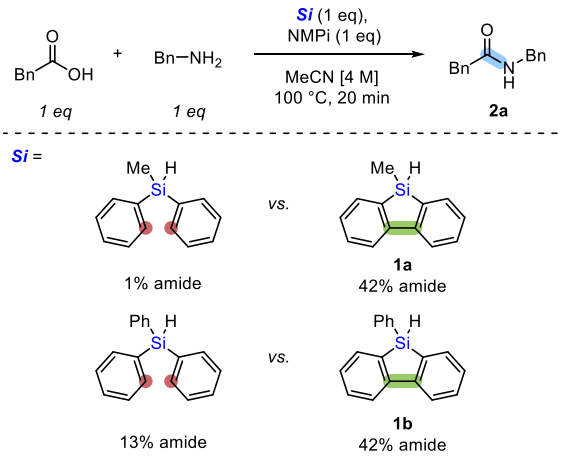
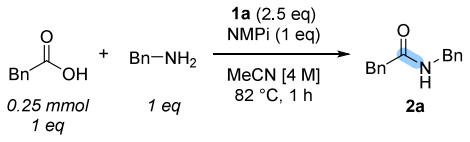


Figure 2. Acyclic vs cyclic tertiary hydrosilanes as coupling reagents. NMR yields reported using ethyl acetate as an internal standard.

(Ph_2MeSiH) and **1b** ($HSiPh_3$) produced minimal amide (**2a**) (1% and 13% NMR yield, respectively). In contrast, the use of silacycles **1a** and **1b** as coupling reagents proved moderately effective under these conditions. These results indicate that ring strain plays a key role in enhancing the silane's amidation activity. **1a** was chosen as the coupling reagent for continued study (over **1b**) due to the relative cost of starting materials.

Under the optimized reaction conditions (Table 1, entry 1), amide (**2a**) was formed in 88% isolated yield. Amidation was

Table 1. Optimization Results



Entry	Deviation from standard conditions	NMR Yield of **2a** (%)[a]
1	-	89 (88)
2	1 eq **1a**, No NMPi	0[b]
3	No silane	0[b]
4	1 eq silane	42[b]
5	30 min	85
6	N_2 atmosphere, 30 min	87
7	60 °C, 2 h	91 (88)
8	Ethyl acetate, 30 min	78 (73)[c]

[a]Isolated yield in parentheses. NMR yield obtained using ethyl acetate as an internal standard. [b]Heated at 100 °C for 20 min. [c]NMR yield obtained using nitrobenzene as an internal standard.

only observed in the presence of both *N*-methyl pyrrolidine (NMPi) and silane (Table 1, entries 2 and 3). Other bases such as Hünig's base and *N*-methyl morpholine provided amides in lower yields (Table S8). When one equivalent of silane (**1a**) was used, the yield of **2a** dropped to 42% NMR yield (Table 1, entry 4). The reaction can be carried out within 30 min to afford **2a** without a significant change in the yield (Table 1, entry 5). Performing the reaction under nitrogen atmosphere minimally impacted the yield of **2a** (Table 1, entry 6). Reducing the temperature to 60 °C and running the reaction over 2 h afforded **2a** in 88% isolated yield (Table 1, entry 7); this "low and slow" method would be useful for applying this method to more sensitive molecules. Interestingly, ethyl acetate could also be used as a solvent, forming **2a** in 73% isolated yield (Table 1, entry 8). While MeCN remains the solvent of choice for the substrate scope, this result shows that ethyl acetate can be used as a greener alternative without significantly compromising efficiency. Preliminary characterization of the silane byproduct of the amidation suggested that the byproduct of the reaction was the disiloxane **3a;** we confirmed this by obtaining an X-ray crystal structure (Figure S2).

To probe the mechanism and understand the requirement for two-plus equivalents of silane to achieve full consumption of starting material, the hydroxy- (**4a**, presumptive direct byproduct of amidation) and disiloxane (**3a**, observed byproduct) derivatives of **1a** were independently synthesized and then tested as potential coupling reagents under the standard conditions (Figure 3). Under the amidation

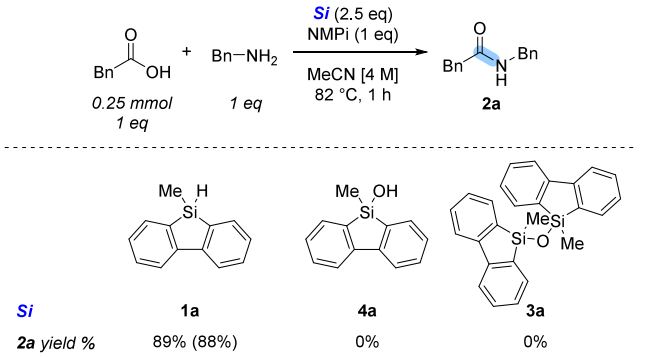


Figure 3. Amidation activity of methylsilafluorene derivatives. NMR yields reported using ethyl acetate as an internal standard. Isolated yield in parentheses.

conditions, the silanol (**4a**) was spontaneously converted to the disiloxane (**3a**) and no amidation was observed. When disiloxane (**3a**) was attempted as the coupling reagent, no reaction was observed. A test reaction between **1a** and **4a** in the presence of NMPi led to complete conversion to **3a** (Figure S6). The results suggest that silanol (**4a**) is a transient byproduct, while disiloxane (**3a**) represents the unreactive resting state in hydrosilafluorene-mediated amidation. This observation aligns with the findings by Braddock and Lickiss, who reported that triarylsilanols degrade to form the inactive disiloxanes over the course of an amidation reaction.[19] Therefore, although silanols generally may possess amidating activity, **4a** simply condenses into inactive disiloxane (**3a**) under the investigated conditions.

A substrate scope was carried out using the standard conditions developed (Figure 4). We began by coupling aliphatic carboxylic acids with primary amines to make secondary amides. Changing the substituents on the aliphatic carboxylic acid did not seem to impact the yield of amide significantly since **2a**−**2c** were formed in high yields alike. Amide **2a** was synthesized in 84% yield at the 1 mmol scale. A branched, bioactive aliphatic carboxylic acid (ibuprofen) was also successfully amidated using benzylamine to form **2d** in 95% yield. We then surveyed different primary amines as substrates. Amide **2e** was made in 90% yield. Electron donating group (−OMe) or electron withdrawing group ($-CF_3$) at the *para*- position on the benzylamine was tolerated as **2f** and **2g** were formed in 76% and 87% yield, respectively. Other primary amines, such as butylamine, reacted to form **2h** in 84% yield. Substituents at the α-position of the amine substrate

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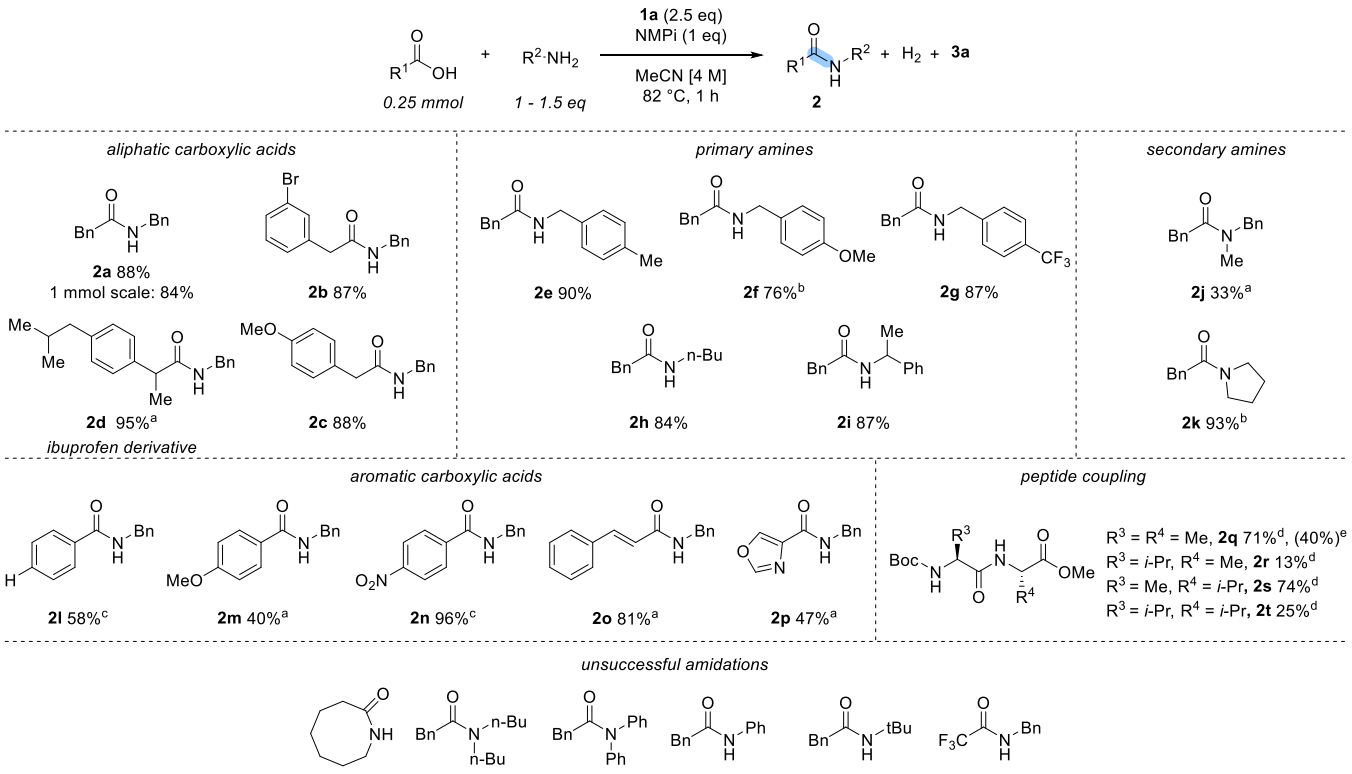

Figure 4. Substrate scope. Isolated yields reported. Deviation from the standard conditions: [a]21 h; [b]30 min; [c]60 °C. 21 h; [d]0.5 eq 4-dimethylaminopyridine, 21 h; [e]2 eq of NMPi, 60 °C, 21 h. NMR yield reported using ethyl acetate.

were also tolerated as **2i** was synthesized in 87% yield. Secondary amines reacted much slower to form amides, even with prolonged heating (**2j**). However, cyclic amines such as pyrrolidine formed the amide in high yield (**2k**). Aromatic carboxylic acids were then reacted with benzylamines to form aryl amides. Amides **2l**−**2n** were successfully prepared under prolonged heating. Since both 1) silanes are reducing reagents[25,26] and 2) H_2, which should be noted is a flammable gas, is formed as a byproduct, we wanted to verify that a reducible functional group would not be hydrogenated under the amidation conditions. Amide **2o** was made in 81% yield, with the alkene functionality intact. A heterocyclic amide (**2p**) was formed in moderate yield of 47% from oxazole-4-carboxylic acid. Dipeptides **2q**−**2t** were prepared in yields ranging from 13% to 74% yield under modified reaction conditions including DMAP, a common additive to improve yields in peptide synthesis.[12,15,27,28] The methyl ester group remained intact under the conditions. The coupling of two valines (**2t**) was less productive than the coupling of two alanines (**2q**) presumably due to steric interference; bulky substitution on the carboxylic acid coupling partner alone (**2r**) had a greater (negative) impact on reaction efficiency than bulky substitution on only the amine partner (**2s**).

We also discovered some limitations of the explored conditions: sterically hindered primary amines, secondary amines, and aniline were not successfully amidated, and the preparation of a macrocyclic amide and trifluoroacetamide were also unsuccessful.

Silyl esters have been well-documented as intermediates in silane-mediated amidation reactions.[29] To investigate whether 9-hydrosilafluorene-mediated amidation proceeds through the presumed silyl ester intermediate, an amidation reaction was performed in two steps (Figure 5). DCM was employed as the

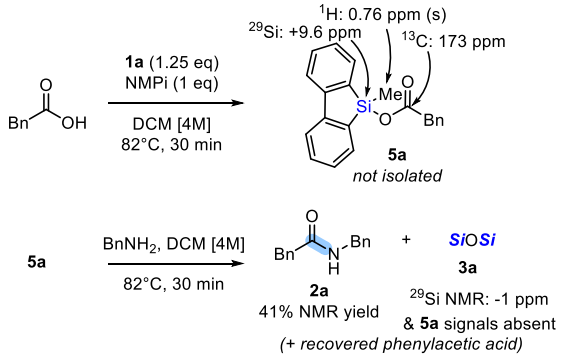

Figure 5. Silyl ester intermediate observed by NMR spectroscopy. SiOSi = methyldisiloxane (**3a**).

solvent to minimize adventitious water content, which might have resulted in the undesired hydrolysis of the silyl ester intermediate during its prolonged presence in this experiment. In the first step, the reaction was set up with the omission of the benzyl amine and the crude mixture was analyzed by ^{1}H, ^{13}C, and ^{29}Si NMR; this showed the formation of the silyl ester intermediate **5a**. When benzylamine was subsequently added to this crude reaction mixture (containing largely the silyl ester), amide **2a** was observed in 44% NMR yield, with the phenylacetic acid mass balance and disiloxane (**3a**) as the sole silane byproduct. When the silanol (**4a**) was independently synthesized and then added to the silyl ester intermediate (**5a**), phenylacetic acid was recovered and disiloxane was observed as the sole silane species (Figure S12). This shows that the transient silanol − the presumed unobserved direct byproduct of amidation − can unproductively react with the silyl ester to form the disiloxane. This further elucidates the mechanism

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underlying the necessity for a 2-fold amount of silane to enact efficient amidation.

We envisioned reducing disiloxane (**3a**) to 9-methyl-9*H*-9-silafluorene (**1a**), with the aim of developing a recyclable coupling reagent (Figure 6). To explore this, amide **2a** was

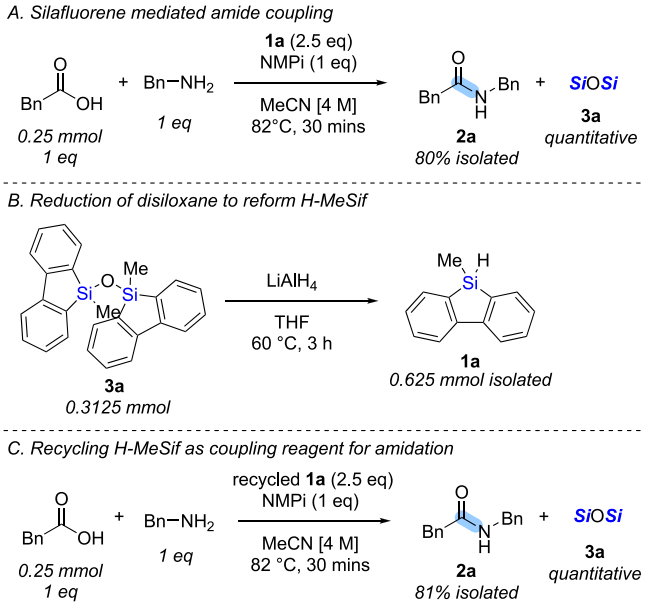

Figure 6. Demonstrating the recyclability of coupling reagent **1a**.

prepared using the optimized reaction conditions. **2a** and the disiloxane (**3a**) were isolated separately by column chromatography in 80% isolated yield and quantitative recovery, respectively. Next, the disiloxane was reduced using $LiAlH_4$ to form **1a** quantitatively, and then this recaptured **1a** was used in another amidation reaction to form **2a** in 81% isolated yield (with disiloxane again quantitatively recovered). Only a limited number of recyclable (carbon-based) amide coupling reagents have been reported in the literature.[30,31] Among recyclable silicon coupling reagents, silica gel[32] and mesoporous silicas[33−35] are the only known examples, both of which 1) are heterogeneous and 2) require high temperatures for reactivation prior to reuse. This method recycles **2a**, in a single step within 3 h.

A plausible mechanistic pathway for 9-hydrosilafluorene-mediated amidation is shown in Figure 7. The silafluorenes readily form the silyl ester in the presence of NMPi, as evidenced by spontaneous H_2 evolution, which was not observed when the acyclic silanes (Figure 2) were used. This suggests that the ring strain impacts silyl ester formation. Consistent with our previous Ph_2SiH_2 study,[16] NMPi plays a role in the formation of the silyl ester as a general base by facilitating proton transfer: upon its addition to the carboxylic acid in the presence of the hydrosilafluorene at room temperature, we observed immediate H_2 evolution. Coordination between the NMPi and **1a** was ruled out as no significant shift change was observed in the ^{29}Si NMR (Figure S5).

The silyl ester intermediate is converted to the amide product in the presence of the amine partner. The direct byproduct of this addition/elimination-type substitution is presumably silanol, which subsequently condenses with another equivalent of hydrosilafluorene or an equivalent of the silyl ester to form the disiloxane (as demonstrated by experiment in Figure 3). The disiloxane is unreactive under the

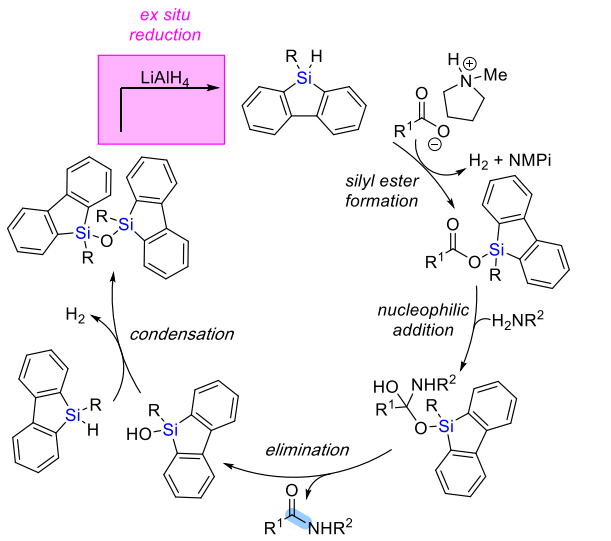

Figure 7. Plausible reaction pathway for 9-hydrosilafluorene-mediated amidation. R = methyl or phenyl.

amidation conditions used, however it can be isolated and then reduced in a separate step to regenerate hydrosilafluorene to be used for another amidation reaction.

This study demonstrates 9-hydrosilafluorenes **1a** and **1b** as effective tertiary silane amide coupling reagents. Ring-strain plays a key role in the reactivity of the 9-hydrosilafluorenes as the acyclic analogues have significantly reduced amidation activity. Both **1a** and **1b** are air-stable, and the amidation can be carried out without the exclusion of air or moisture. The silane byproduct is a small molecule disiloxane which can be isolated by column chromatography and then reduced using $LiAlH_4$ to regenerate the hydrosilane. This process represents the first example of a recyclable molecular silane amide coupling reagent.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.5c04034.

Experimental procedures, full optimization data, spectroscopic data (^1H NMR, ^{13}C NMR, ^{29}Si NMR, and HRMS), and crystallographic data (PDF)

Accession Codes

Deposition Numbers 2477930−2477931 and 2477935 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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https://doi.org/10.1021/acs.orglett.5c04034
Org. Lett. XXXX, XXX, XXX−XXX

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was funded by the Natural Sciences and Engineering Research Council of Canada (NSERC), Toronto Metropolitan University, and an Ontario Graduate Scholarship. The authors wish to thank Prof. Daniel Foucher (TMU), Prof. Christine Le (York University), and Prof. Thomas Baumgartner (York University) for their logistical assistance in obtaining X-ray crystallographic structures.

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https://doi.org/10.1021/acs.orglett.5c04034
Org. Lett. XXXX, XXX, XXX−XXX