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The Difluoromethyl Group as a Masked Nucleophile: A Lewis Acid/Base Approach

Jacob B. Geri, Michael M. Wade Wolfe, and Nathaniel K. Szymczak*

Department of Chemistry, University of Michigan, 930 N. University, Ann Arbor, Michigan 48109, United States

Supporting Information

ABSTRACT: The difluoromethyl group (R−CF_2H) imparts desirable pharmacokinetic properties to drug molecules and is commonly targeted as a terminal functional group that is not amenable to further modification. Deprotonation of widely available Ar−CF_2H starting materials to expose nucleophilic Ar−CF_2^- synthons represents an unexplored, yet promising route to construct benzylic Ar−CF_2−R linkages. Here we show that the combination of a Brønsted superbase with a weak Lewis acid enables deprotonation of Ar−CF_2H groups and capture of reactive Ar−CF_2^- fragments. This route provides access to isolable and reactive Ar−CF_2^- synthons that react with a broad array of electrophiles at room temperature. The methodology is highly general in both electrophile and difluoromethyl (hetero)arene and can be applied directly to the synthesis of benzylic difluoromethylene (Ar−CF_2−R) linkages, which are useful lipophilic and metabolically resistant replacements for benzylic linkages in medicinal chemistry.

Benzylic methylene linkages (Ar−CH_2−R) are ubiquitous structural motifs in synthetic chemistry due to their facile synthesis, which is enabled by easy access to $ArCH_2^+$, $ArCH_2^·$, and $ArCH_2^-$ equivalents. The efficiency with which molecules can be decorated with $ArCH_2^-$ groups has led to their use in many (>100)[1] approved drugs, but their weak C−H bonds (90 kcal/mol)[2] can be susceptible to metabolic oxidation and reduce a drug's biological half-life. Doubly benzylic Ar−CH_2−Ar groups (C−H bond: 82 kcal/mol)[2] are less stable, and are only present in 17 approved drugs.[1] Replacement of the −CH_2− group with the more metabolically stable and lipophilic difluoromethylene (Ar−CF_2−R) linkage is an attractive strategy for structure−activity relationship (SAR) optimization, but remains underutilized (Figure 1a).[3] Synthetic pathways to these units are limited, and only three singly benzylic Ar−CF_2−R units and one doubly benzylic Ar−CF_2−Ar unit have been included in commercial pharmaceuticals.[4]

Existing methodologies for the construction of Ar−CF_2−R linkages require reagents that are toxic, explosive, and of limited scope (Figure 1b).[5] The most common retrosynthetic disconnection is at the C−F bonds of the CF_2 unit through ketone deoxyfluorination using trifluorosulfuranes (e.g., DAST; Et_2NSF_3)[6] and radical fluorination of C−H bonds.[7] However, each of these strategies present significant challenges. Deoxyfluorination of ketones is unreliable and generates explosive byproducts. Radical C−H fluorination is more attractive, but the indiscriminate reactivity of F· leads to low functional group tolerance. In a recent industrial synthesis of a

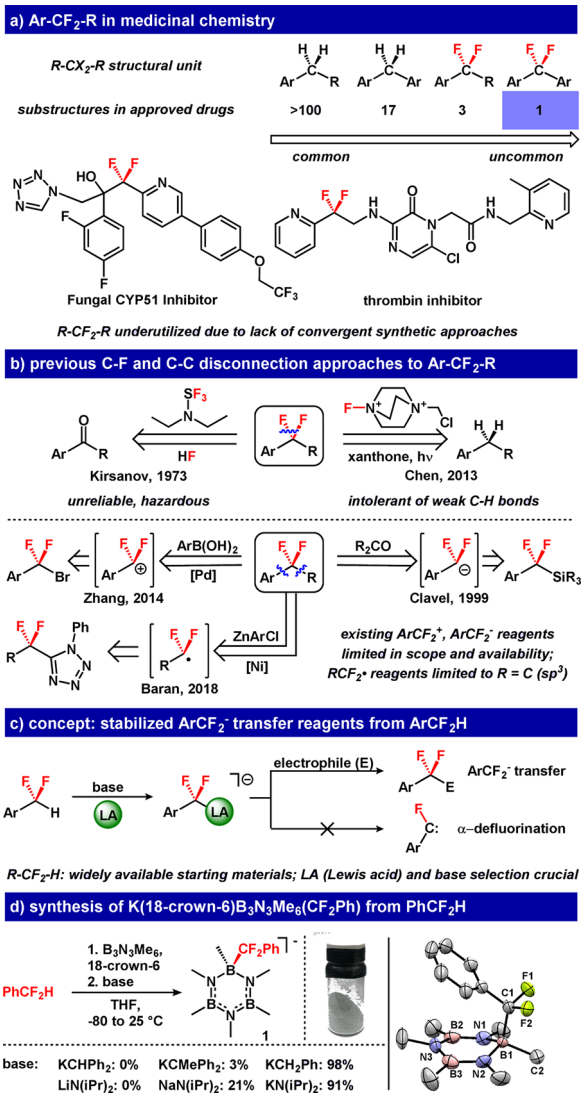

Figure 1. (a) Underrepresentation of Ar−CF_2−R groups in medicinal chemistry. (b) Retrosynthetic strategies for Ar−CF_2−R linkages. (c) $ArCF_2H$ groups as $ArCF_2^-$ precursors. (d) Synthesis of **1**. 18-Crown-6 omitted for clarity.

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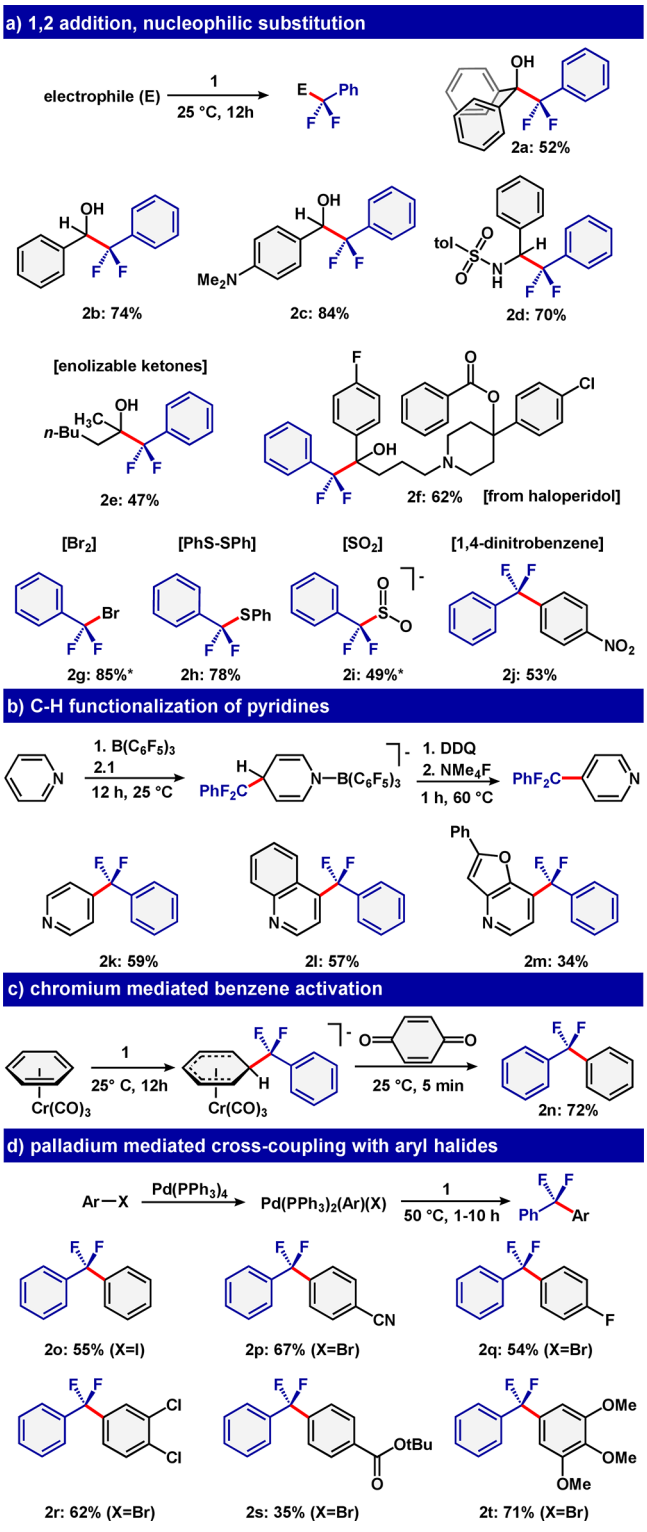

Figure 2. (a) Reactions with ketones, aldehydes, imines, disulfides, Br_2, SO_2, and 1,4-dinitrobenzene. (b) Two-phase C−H difluorobenzylation of pyridines. (c) Chromium(0)$(CO)_3$ mediated benzene C−H difluorobenzylation. (d) Palladium-mediated difluorobenzylation.

thrombin inhibitor containing an Ar−CF_2−R linkage, significant effort was expended to avoid either of these routes and ultimately the molecule was built outward from bromodifluoroacetate.[8]

In contrast to the late-stage fluorination strategies described above, fragment coupling with [$ArCF_2$] units enables a more modular synthetic approach. However, electrophilic $ArCF_2^+$ and radical $ArCF_2\cdot$ based disconnections present significant limitations: electrophilic $ArCF_2Br$ starting materials are not widely available, radical cross-coupling between sulfone (R−CF_2−SO_2R)[9] electrophiles and aryl zinc nucleophiles is limited to aliphatic RCF_2 transfer, and generation of Ar−$CF_2\cdot$ from Ar−CF_3[10] requires strong reductants and the reported scope in radicalphile is limited. Compared to electrophilic and radical methodologies,[11] reactions with $ArCF_2^-$ nucleophiles are underdeveloped despite the wide availability of *C*- electrophilic (Ar−X, carbonyl, imine) functional groups. $ArCF_2SiMe_3$ reagents are the only access point to this reactivity manifold, but synthetic routes to these reagents are highly limited in scope.[5c,12]

In contrast to the poor availability of $ArCF_2SiMe_3$ pronucleophiles, difluoromethyl arenes ($ArCF_2H$) could be ideal masked $ArCF_2^-$ nucleophiles upon deprotonation. Recent progress in transition metal catalyzed difluoromethylation has made these compounds accessible and structurally diverse starting materials.[13] However, $ArCF_2H$ groups have low acidity (no reaction with $KN(SiMe_3)_2$)[14] and, if deprotonated, the revealed $ArCF_2^-$ fragment is unstable to α-fluoride elimination.[15] The use of compatible pairs of strong bases, which deprotonate $ArCF_2H$ groups, and Lewis acids, which stabilize fluoroalkyl anions, may address these issues.[16] Appropriate selection of a Lewis acid that can capture $ArCF_2^-$ after $ArCF_2H$ deprotonation, and later release $ArCF_2^-$ in reactions with electrophiles could enable the broad-scope synthesis of a new class of nucleophilic difluorobenzylation reagents.

Three key requirements must be met to transform $ArCF_2H$ groups into useful $ArCF_2^-$ synthons using Brønsted base/Lewis acid pairs: (1) the base used for C−H deprotonation must be sufficiently strong, (2) the Lewis acid must not irreversibly bind the Brønsted base (Figure 1c), and (3) the Lewis acid must be capable of both $ArCF_2^-$ capture/stabilization and $ArCF_2^-$ release to facilitate subsequent reactions with electrophiles. We hypothesized that $PhCH_2^-$, a strong base, and hexamethylborazine ($B_3N_3Me_6$), a privileged Lewis acid for the stabilization of fluoroalkyl anions, could satisfy these criteria. Though pK_a measurements for $ArCF_2$−H bonds are unavailable, we anticipated that KCH_2Ph would be capable of deprotonating HCF_2Ph,[15] satisfying criterion (1). This base (KCH_2Ph) forms a reversible adduct with $B_3N_3Me_6$, satisfying criterion (2). In silico studies revealed that $B_3N_3Me_6$ has a $PhCF_2^-$ affinity of −23.3 kcal/mol, which is similar to CF_3^- (−22.6 kcal/mol). $B_3N_3Me_6$-CF_3^- adducts readily release CF_3^-, suggesting that $B_3N_3Me_6$ could serve an appropriate Lewis acid for both stabilization and transfer of $PhCF_2^-$, satisfying criterion (3).[16a,b]

Addition of $PhCF_2H$ to an equimolar combination of $B_3N_3Me_6$, KCH_2Ph, and 18-crown-6 in THF at 25 °C afforded [K(18-crown-6)][$PhCF_2$−$B_3N_3Me_6$] (**1**) in 98% chemical yield and 72% isolated yield (>9 g scale) as a crystalline solid (Figure 1d). Similar reactions carried out using $KC(Me)Ph_2$ (3%) and $KCHPh_2$ (0%) provided a significantly lower yield of **1**, and allowed the pK_a of $PhCF_2H$ to be bracketed between 41 ($PhCH_3$) and 35 (Ph_2CHMe). We also investigated the use of bulky diisopropylamide bases (Li, Na, and $KN(iPr)_2$) and found that $KN(iPr)_2$ afforded the product in high yield (91%), whereas Na- (21%) and $LiN(iPr)_2$ (0%) afforded lower yields of CF_2Ph^- containing product, consistent

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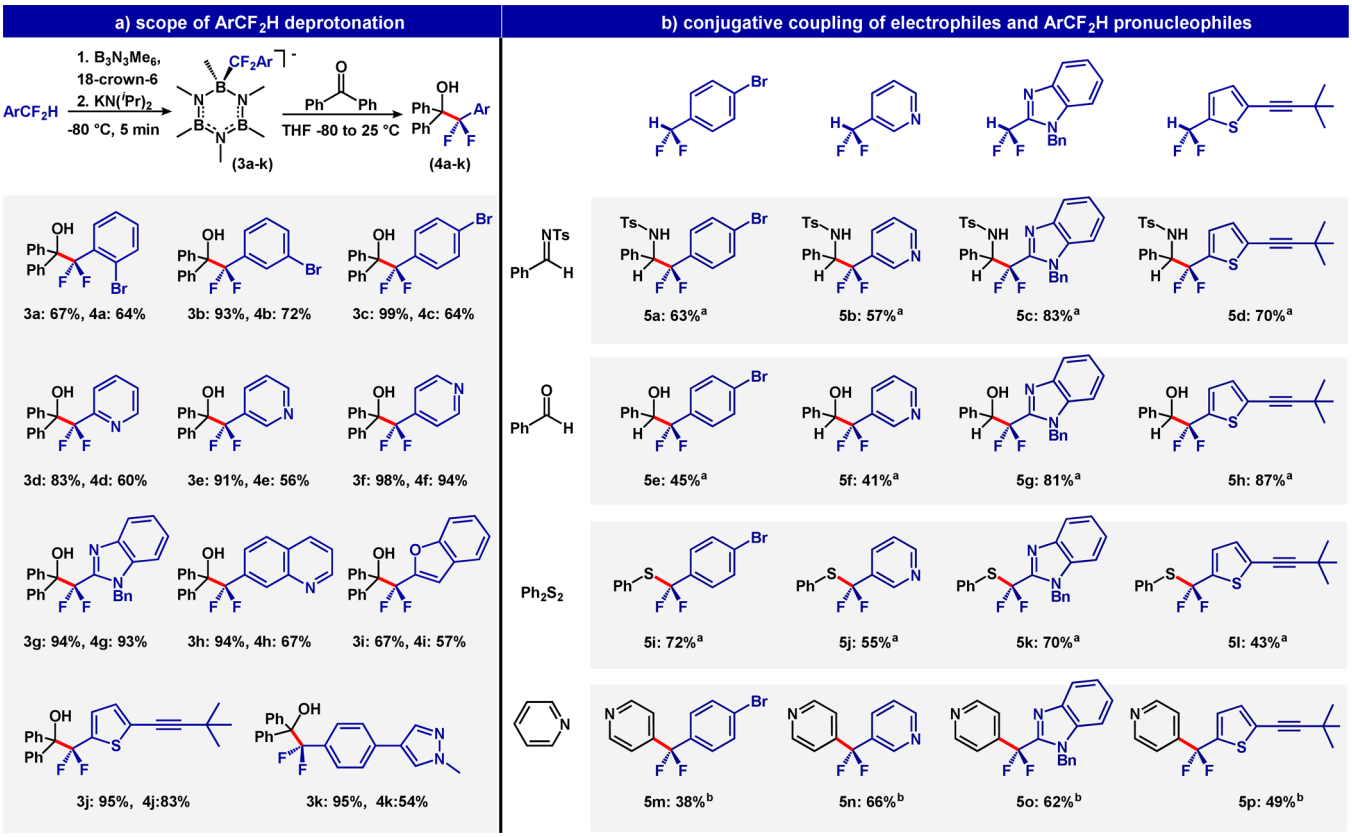

Figure 3. (a) Scope of $ArCF_2H$ deprotonation, $ArCF_2^-$ stabilization by $B_3N_3Me_6$, and transfer of $ArCF_2^-$ equivalents. (b) Coupling a pool of four distinct $ArCF_2^-$ nucleophiles and a pool of four distinct electrophiles. [a]12 h, 25 °C. [b]1. Pyridine and $B(C_6F_5)_3$, 5 min, −80 °C; $ArCF_2H$, $B_3N_3Me_6$, 18-crown-6, and KN(iPr), 10 min, −80 °C; 2. Pyridine−$B(C_6F_5)_3$ and $ArCF_2$−$B_3N_3Me_6^-$, 12 h, 25 °C; 3. DDQ, 15 min, 25 °C; 4. NMe_4F, 1 h, 60 °C (combined yield through five steps).

with α-defluorination by these more Lewis acidic countercations. Defluorination is not promoted by less Lewis acidic $B_3N_3Me_6$ or K(18-crown-6)$^+$.

We experimentally evaluated the ability of **1** to transfer CF_2Ph^- equivalents to electrophiles. **1** readily difluorobenzylates a variety of simple carbonyl and imine containing electrophiles (**2a**−**2d**, 52−84%) (Figure 2). These reactions proceeded to completion at room temperature in 12 h. Unlike the analogous CF_3^- transfer reagent ([K(18-crown-6)][CF_3−$B_3N_3Me_6$]), **1** can transfer $PhCF_2^-$ to enolizable carbonyl compounds (**2e**−**2f**, 47% to 62%). The nucleophilic addition of $ArCF_2^-$ tolerates tertiary amines, tosyl groups, esters, and aromatic halides, and the functional group tolerance is highlighted by the selective difluorobenzylation of haloperidol benzoyl ester (**2f**), a derivatized antipsychotic. Sulfur dioxide also undergoes 1,2-addition to afford potassium difluorobenzylsulfinate (**2i**, 49%), which is an oxidatively activated $PhCF_2$· proradical capable of facilitating addition to α/β-unsaturated tosyl amides.[17] In addition to 1,2-addition reactions, **1** can also difluorobenzylate diphenyldisulfide (Ph_2S_2) and bromine (Br_2) (**2h**, 78%; **2g**, 85%).

Doubly benzylic difluoromethylene linkages are especially difficult to synthesize using current methodologies. The only available approaches use $ArCF_2Br$ starting materials, which must be synthesized through radical bromination or deoxyfluorination strategies. Using **1**, dinitrobenzene can be directly difluorobenzylated in a net nucleophilic aromatic substitution (S_NAr) reaction (**2j**, 53%). When activated with a bulky and strong Lewis acid, $B(C_6F_5)_3$, pyridines also react with **1** to generate a LA-stabilized anionic σ-adduct, which can be oxidized with DDQ and deprotected with NMe_4F to generate the aromatic 4-difluorobenzylated pyridine. These reactions can be conducted in one pot with a single solvent, affording the final product in good combined yield through four telescoped steps (**2k**−**2m**, 34−59%). An alternative activation strategy for nonheterocyclic arenes, such as benzene, is to use chromium(0) tricarbonyl. Treatment with **1** affords a stable σ-adduct that can be oxidized with benzoquinone to afford diphenyl difluoromethane (**2n**, 72%).

In addition to direct difluorobenzylation of activated arenes, we assessed the ability of **1** to access Ar−CF_2−Ar species from widely available aryl bromides and iodides through palladium-mediated cross coupling. $Ar/ArCF_2$ coupling reactions are currently limited to pathways in which $ArCF_2^-$ ligands are constructed through either:CF_2 insertion[18] or $ArCF_2Br$ oxidative addition,[19] which present challenges for broad scope applications; notably, reactions using nucleophilic $ArCF_2^-$ reagents are unknown. We used $Pd(PPh_3)_4$ as a readily available stoichiometric reagent to mediate Ar−Br and Ar−I cross-coupling reactions with **1** as a transmetalation reagent. Treating *in situ* generated $Pd(PPh_3)_2(Ar)X$ species with **1** afforded Ph−CF_2−Ar products (**2o**−**2t**, 35−71%), representing the first example of cross coupling using a nucleophilic $ArCF_2^-$ transmetalation reagent. This synthetic route provides a complementary strategy to access less electrophilic aryl halide coupling partners that are not amenable to direct nucleophilic addition reactions.

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We next investigated the activation of difluoromethyl arenes beyond $PhCF_2H$. A wide variety of difluoromethyl (hetero)-arenes react with $KN(iPr)_2/B_3N_3Me_6$/18-crown-6 in THF at −80 °C to form stabilized $ArCF_2^-$ synthons **3a**−**3k** in high yield (Figure 3a). When KCH_2Ph was used in place of $KN(iPr)_2$, significantly lower yields were observed. Aryl bromides are not tolerated by electrochemical and photoredox benzylic fluorination methods,[7,10,20] and are susceptible to *o*-metalation/benzyne formation. However, we accessed these nucleophilic $ArCF_2^-$ units through deprotonation/capture reactions. 2- (**3a**, 67%), 3- (**3b**, 93%), and 4- (**3c**, 99%) bromobenzenes were all transformed into $B_3N_3Me_6/ArCF_2^-$ adducts in high yield. Difluoromethyl heteroarenes were also deprotonated to reveal $ArCF_2^-$ synthons. In addition resonance-activated 2- and 4-difluoromethylpyridine (**3d**, 83%, **3f**, 98% chemical yield), 3-difluoromethylpyridine and 7-difluoromethylquinoline were deprotonated in high yield (**3e**, **3h**, 91%, 94%). Difluoromethylated five-membered heterocycles also undergo $ArCF_2H$ deprotonation, with 2-difluoromethyl benzofuran (**3i**, 67%), *N*-benzyl-2-difluoromethyl-benzimidazole (**3g**, 94%), 1-difluoromethyl-4-(1-methyl-4- pyrazolyl)benzene (**3k**, 95%), and 2-difluoromethyl-5-(*tert*-butylacetylenyl)-thiophene (**3j**, 95%) providing access to $B_3N_3Me_6/ArCF_2^-$ adducts. The generated reagents efficiently transfer $ArCF_2^-$ to Ph_2CO, affording the 1,2-addition products from $ArCF_2H$ (**4a**−**4j**). Finally, a control reaction that omitted $B_3N_3Me_6$ from the reaction to form **4b** did not afford the desired product. This result illustrates the synergistic requirement of a compatible Lewis acid/base pair for both $ArCF_2^-$ capture and transfer.

We demonstrated the robustness of this methodology by combining a pool of four structurally distinct difluoromethyl-(hetero)arenes with a pool of four representative organic electrophiles (Figure 3b; imine, aldehyde, disulfide, and LA-activated pyridine) to generate 16 unique products (**5a**−**5p**, 41−87%) over two steps. The reactions provide rapid access to structural diversity from simple precursors. Notably, several of the products contain first-in-class $Ar-CF_2-R$ linkages, such as imidazole-CF_2−SR (**5c**) and thiophene-CF_2-carbamine (**5d**), structural cores that can be mapped onto biologically active nonfluorinated molecules.

In conclusion, we have developed a general approach for the conversion of common difluoromethyl (hetero)arenes into stabilized, structurally diverse, and previously inaccessible $ArCF_2^-$ transfer reagents. The reagents are highly reactive, transferring $ArCF_2^-$ to a wide variety of organic electrophiles to form $ArCF_2-C$ bonds, and enable four new methods for the construction of $Ar-CF_2-Ar$ linkages. We anticipate that the use of difluoromethyl groups as sources of $ArCF_2^-$ will enable the introduction of difluoromethylene linkages as easily accessible functional groups that will find applications in drug discovery.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b06093.

Crystallographic information for **1** (CIF)

Synthetic details, characterization (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*nszym@umich.edu

ORCID

Nathaniel K. Szymczak: 0000-0002-1296-1445

Notes

The authors declare the following competing financial interest(s): A patent application on this material has been submitted.

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