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Letter

Cu-Catalyzed Dual C−O Bonds Cleavage of Cyclic Ethers with Carboxylic Acids, NaI, and $TMSCF_3$ to Give Iodoalkyl Ester

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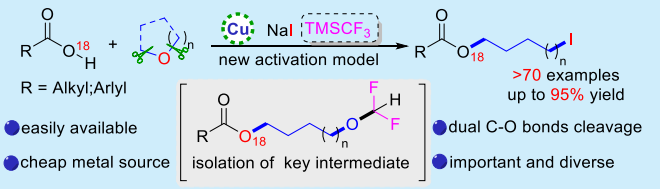
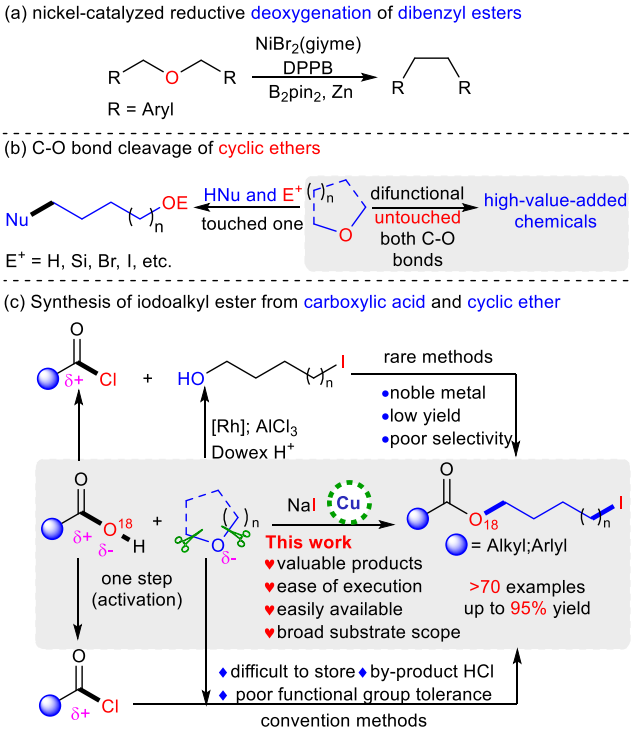
ABSTRACT: Herein, by dual C−O bond cleavage of cyclic ethers with Cu catalysis, we eventually led to the development of a selective three-component coupling of commercially available chemicals, carboxylic acids, ethers, and halogens to synthesize more than 70 iodoalkyl esters in the presence of $TMSCF_3$. This allows for the concise synthesis of highly functionalized iodoalkyl esters directly. And the synthetic insect pheromones were also disclosed.



The C−O bonds are commonly found in small organic molecules and biological macromolecules derived from biomass.[1] In many fundamental organic transformations and biochemical processes, the cleavage of C−O bonds plays an irreplaceable role. Recently, the C(sp^2)−O bond cleavage had enjoyed great success under the transition metal catalysis.[2] In contrast, the alkyl variants with the C(sp^3)−O bonds, particularly the ether, lagged relatively far behind and were restricted to classic nucleophilic substitution reactions. Ethers used as partners in cross-couplings exhibited a myriad of advantages due to their easy availability, stability, and nontoxicity. Although many efforts have been made, though mainly focused on the cleavage one C(sp^3)−O bond from ethers,[3] the dual cleavage of two C(sp^3)−O bonds of ether has rarely been disclosed, recently only one pioneering work was disclosed by Shi et al. with Ni as the catalyst and dibenzyl ethers as substrates (Scheme 1a).[4] Cyclic ethers, such as tetrahydrofuran (THF)/-pyran, are easily obtained from biomass-derived intermediates such as levulinic acid and furfural.[5] Although great progress has been made in ring-opening difunctional reactions,[6] the original oxygen atom in the cyclic ether molecule remains in the synthesized molecules. Selectively eliminating the oxygen from cyclic ethers to get difunctional high-value-added chemicals has never been demonstrated in a one-pot manner, which is an important synthetic challenge (Scheme 1b).

Meanwhile, the ester moieties are extremely common in natural products[7] and medicines, as well as in dyes, fragrances,[8] and insect pheromones.[9] And the alkyl iodides are also the versatile reaction center in organic synthesis as substrates in many frequently used reactions.[10] Therefore, the combination of these two moieties as iodoalkyl esters would be interesting, which are the important synthetic intermediates in organic synthesis. However, the synthesis of iodoalkyl esters is less straightforward (Scheme 1c).

Scheme 1. Reductive Deoxygenation of Ethers



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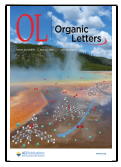

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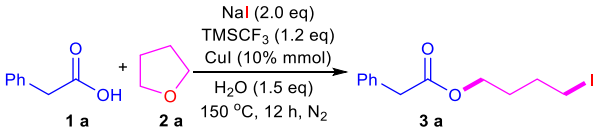
Previous approaches for the iodoalkyl esters require the preparation of necessary intermediates, such as acyl chloride[11] or corresponding alcohols,[12] in as many as three steps from carboxylic acids, which can often lead to poor functional group compatibility or a lengthy functional group protection/deprotection process. Herein, we demonstrated efficient copper-catalyzed cyclic ethers and carboxylic acids to give iodoalkyl ester via dual C−O bonds of cyclic ethers cleavage (Scheme 1c).[13] We choose THF as the deoxygenation target and use abundant, stable, and nontoxic carboxylic acid as the nucleophile[6c] and difluorocarbene generated in situ from $TMSCF_3$ as the O receptor.[14] With this oxygen acceptor, we promoted the formation of an oxonium ion intermediate and facilitated the removal of oxygen atoms by the ring opening of ethers. This protocol is the direct synthesis of iodoalkyl esters from carboxylic acids and cyclic ethers and dramatically simplifies access to such privileged structures.

At first, we started to study the reaction of phenylacetic acid **1a** and THF **2a** and screened a series of conditions (Table 1; also see Table S1 in the Supporting Information, SI). After optimization of reaction conditions, the formulation took place to give **3a** in 88% yield when the reaction was conducted at 150 °C using CuI as the catalyst in the presence of 2 equiv of NaI (Table 1, entry 1). If no copper catalyst was used, the desired product was formed in less than 5% yield (entry 2). Meanwhile, when CuBr was used as a catalyst under the standard condition instead of CuI, the desired product **3a** was generated in a 28% yield. Without NaI and H_2O, the reaction can proceed but in a lower yield (entries 4, and 8). The lower amount of NaI and $TMSCF_3$ resulted in a lower yield of **3a** (entries 5, 6, and 7). At 120 °C, the desired product was generated in 25% yield in a prolonged time (entry 10).

Table 1. Optimization of the Reaction Conditions[a]

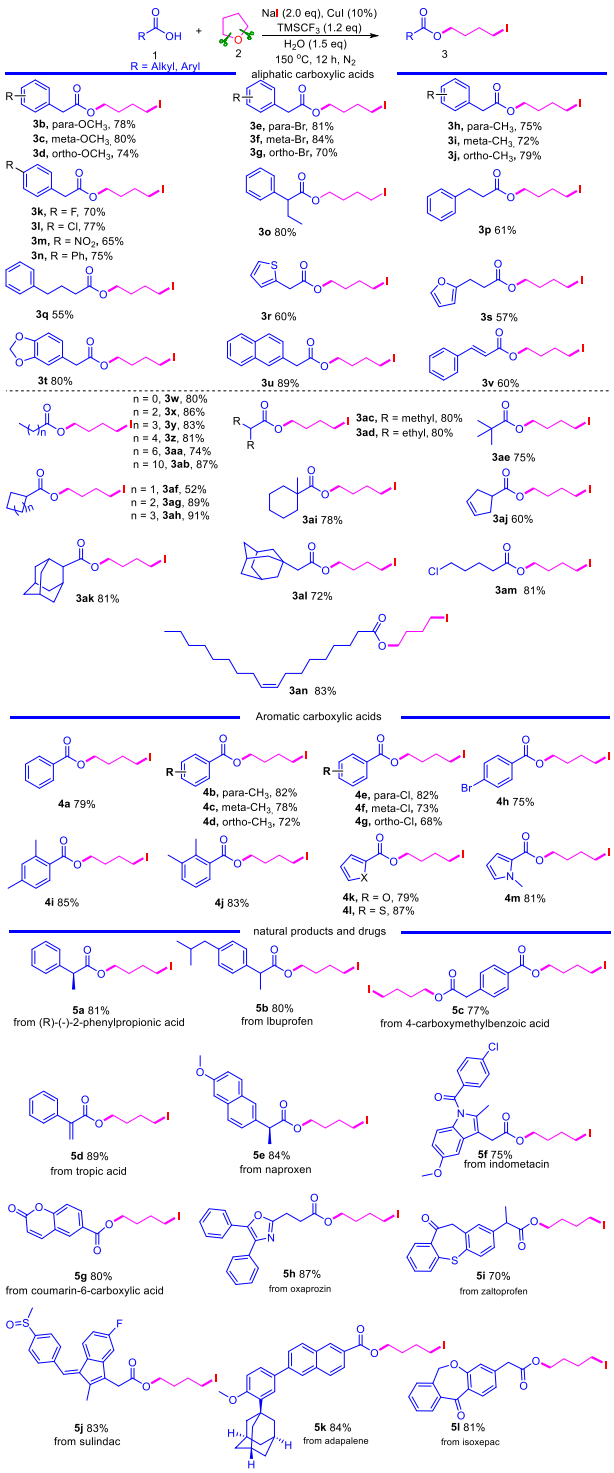


entry	variation from standard conditions	yield of **3a**[b]
1	none	88% (84%)
2	no CuI	<5%
3	CuBr instead of CuI	28%
4	no NaI	8%
5	NaI (1.2 equiv)	35%
6	$TMSCF_3$ (0.8 equiv)	74%
7	$TMSCF_3$ (0.5 equiv)	46%
8	no H_2O	15%
9	110 °C	trace
10	120 °C, 16 h	25%

[a]Reaction conditions: **1a** (0.3 mmol, 1.0 equiv), **2a** (1 mL, 41 equiv, c = 0.3 M), NaI (0.3 mmol, 2.0 equiv), $TMSCF_3$ (0.36 mmol, 1.2 equiv), and H_2O (0.45 mmol, 1.5 equiv), 150 °C, 12 h under N_2. [b]GC yield using *n*-dodecane as the internal standard; the number in parentheses is isolated yield.

With the optimized conditions in hand (Table 1, entry 1), we investigated the substrate scope of this transformation. As summarized in Scheme 2, this protocol is highly efficient and has a broad substrate scope. First, a myriad of phenylacetic acid derivatives containing electron-donating (**3b**−**3d**, **3h**−**3j**, **3n**) substituents was to give the corresponding alkyl iodides in moderate to excellent yields (72−80%). And, bromo, fluoro, and chloro substituents were compatible in this reaction and produced the corresponding products without breaking the C−X bonds (**3e**−**3g**, 70−84%; **3k**−**3m**, 65−77%). Second, the steric properties of the α-substituted acids insignificantly affected the yields of the reaction. For example, tertiary acetic acid derivatives were all suitable substrates, affording the corresponding alkyl iodides in good yields (**3o**, 80%). Third,

Scheme 2. Scope of Aliphatic Carboxylic Acids[a]



[a]**1a** (0.3 mmol, 1.0 equiv), **2a** (1 mL, 41 equiv, *c* = 0.3 M), NaI (0.3 mmol, 2.0 equiv), $TMSCF_3$ (0.36 mmol, 1.2 equiv), and H_2O (0.45 mmol, 1.5 equiv), 150 °C, 12 h under N_2. isolated yield.

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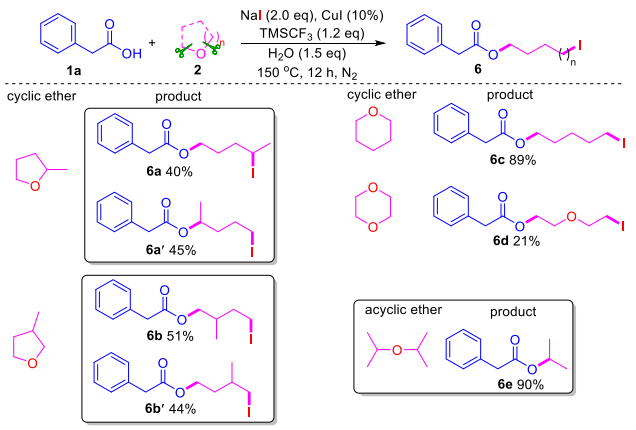
although 3-phenylpropionic acid and 4-phenylbutyric acid gave reduced yields (**3p**, 61% and **3q**, 55%), the reactions proceeded smoothly with various heteroaryl acetic acids, giving the desired products in satisfying yields. Functional groups such as thienyl (**3r**), furyl (**3s**), acetal (**3t**), and naphthalene (**3u**) were all compatible. In addition, the functionalized alkyl iodides were also successful for cinnamic acid (**3v**, 60%) containing sensitive group substituents. Simultaneously, primary acyclic carboxylic acids are some of the most readily available feedstocks, such as acetic acid (**3w**, 80%), valeric acid (**3y**, 83%), and lauric acid (**3ab**, 87%), and participated in smooth deoxygenation coupling. Notably, some sensitive functionalities in conventional coupling reactions, including alkenes (**3an**, 83%) and alkyl chlorides (**3am**, 81%), were well-tolerated, leading to products without isomerization or dehalogenation. Remarkably, secondary alkyl carboxylic acids, cyclic with varying ring sizes (**3af**–**3al**, 52–91%), were all viable coupling partners, including cyclobutene carboxylic acid (**3af**) and cyclopentane carboxylic acid (**3ag**) or cyclohexane carboxylic acid (**3ah**). And, several tertiary alkyl cyclic carboxylic acids (**3ai**, 78%) could be employed to access alkene products with quaternary carbon centers in exclusive configuration. It is worth noting that cyclopentane-3-ene-1-carboxylic acid (**3aj**, 60%) can be used to obtain products with an exclusive configuration of the stable. Then, bridged systems, such as adamantane carboxylic acid (**3ak**) and adamantane acetic acid (**3al**), formed the desired products efficiently. In principle, carboxylic acids are nucleophiles, and thus a variety of aromatic carboxylic acids should be effective substrates A diverse range of weakly electron-donating (Me and DiMe) and electron-withdrawing functional groups (Cl, Br,) at the ortho, meta, and para positions of a phenyl ring attached to the carboxylic acid group were entirely compatible (**4a**–**4l**, 72–85%). Decarboxylative coupling of THF with heteroarenes, such as furoic acids, thiophene carboxylic acids, and *N*-methylpyrrolecarboxylic acids, led to products (**4m**–**4o**, 79–87%) with moderate yields and good selectivity.

Surprisingly, the iodination of complex natural products and drug molecules has a high degree of chemical selectivity, as demonstrated by the reactions of lbuprofen (**5b**, 80%), naproxen, (**5e** 84%), indometacin (**5f**, 75%), oxaprozin (**5h**, 87%), zaltoprofen (**5i**, 70%), sulindac (**5j**, 83%), adapalene (**5k**, 84%), isoxepac (**5l**, 81%), and 4-carboxymethylbenzoic acid (**5c**, 77%). Moreover, naturally occurring acids such as tropic acid (**5d**), (*R*)-(−)-2-phenylpropionic acid (**5a**), and coumarin-6-carboxylic acid (**5g**) underwent smooth transformations as well.

We then turned our attention to testing the versatility of ethers for these ring-opening reactions. As shown in Scheme 3, the reaction system can tolerate a series of cyclic and acyclic ethers. Symmetrical cyclic ethers such as tetrahydropyran and 1,4-dioxane were well tolerated in this reaction and afforded iodoalkanes derivatives **6c** (89%) and **6d** (21%). However, when 2-methyltetrahydrofuran and 3-methyltetrahydrofuran were used in this reaction, an inseparable mixture of **6a**, **6b** and **6a′**, **6b′** was obtained in good yield with low selectivity (1:1). In addition, acyclic ethers were also explored as substrates. The carbonylation and cleavage of the ether proceeded smoothly, and the corresponding ester was produced in 90% yield (**6e**).

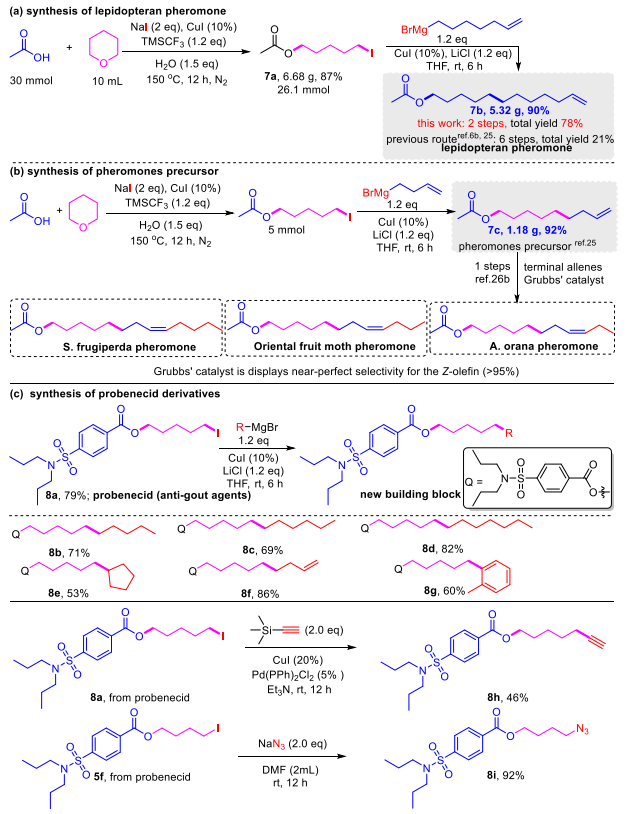
In the case of asymmetric cyclic ethers, the cleavage could be readily scaled up from substrate commercial acetic acid to 30 mmol without loss of efficiency (**7a**, 87%) (Scheme 4a). To further prove the synthetic utility of our strategy, we chose 5-iodophenylacetate (**7a**) as the target molecule, which is a key intermediate one of the insect pheromones (Scheme 4a). It is worth noting that the lepidopteran pheromone (**7b**, 90%) can be easily obtained by using **7a** and a Grignard reagent. The final product could be obtained in the two-step synthesis with a total yield of 78%. And the price of the substrates is very cheap. Compared with the previous method, our route not only significantly reduces the number of steps (2 steps vs 6 steps) but also avoids the use of strong bases (KOH), strong reducing agents (Na and $LiAlH_4$), and toxic thionyl chloride.[9b,16] Additionally, the alkene metathesis of non-8-en-1-yl acetate

Scheme 3. Substrate Scope of Ethers[a]



[a]**1a** (0.3 mmol, 1.0 equiv), **2** (1 mL, 41 equiv, c = 0.3 M), NaI (0.3 mmol, 2.0 equiv), $TMSCF_3$ (0.36 mmol, 1.2 equiv), and H_2O (0.45 mmol, 1.5 equiv), 150 °C, 12 h under N_2. isolated yield.

Scheme 4. Synthetic Applications[a]



[a]Reaction conditions: see the Supporting Information.

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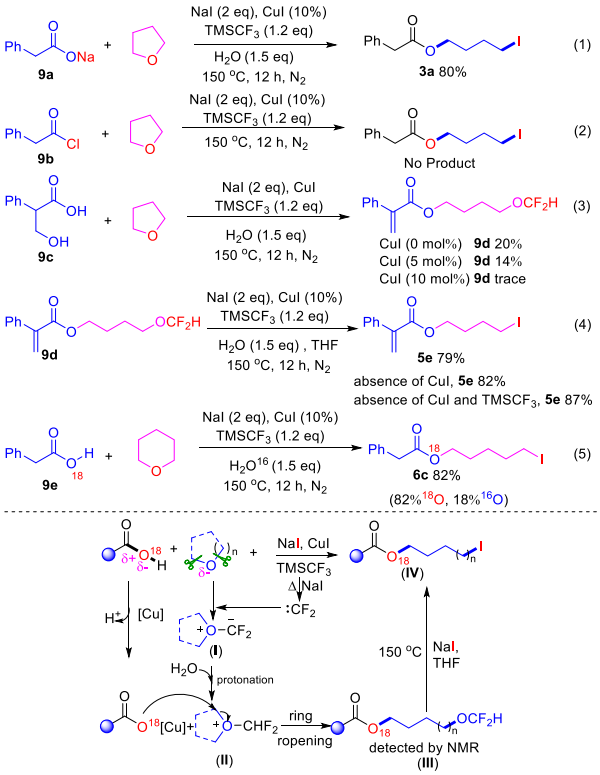
(**7c**, 92% yield) can be used to transform, in a one-pot process, a terminal alkene into the pheromone derivative:[15,16] *A. orana* pheromone, Oriental fruit moth pheromone, and *S. frugiperda* pheromone (Scheme 4b). Meanwhile, our strategy could introduce very valuable functional groups in one step on the iodine position of alkyl iodide derivatives as well (Scheme 4c).[17] For example, alkylation (**8b**−**8g**, 52−86%), terminal ethynylation (**8h**, 46%), and azidation (**8i**, 92%).

To shed light on the possible pathway of this ring-opening reaction, we performed several preliminary experiments as depicted in Scheme 5. When phenylacetic acid (**1a**) was

Scheme 5. Control and Mechanistic Proposal



replaced by sodium phenylacetate (**9a**), cyclic ethers corresponding to iodoalkanes were obtained. Meanwhile, when phenyl acetyl chloride (**9b**) instead of **1a** was treated with THF (**2a**) under standard conditions, any corresponding product could not be detected. These results indicate the important role of the carboxyl oxygen (eqs 1 and 2). Subsequently, when the tropic acid, namely, 3-hydroxy-2-phenylpropanoic acid (**9c**), was added into this system in the absence of CuI, 4-(difluoromethoxy)butyl 2-phenylacrylate (**9d**) was obtained in 20% yield alongside a trace amount of **3a**. Meanwhile, with 5−10 mol % CuI, the yield of compound **9d** decreases rapidly,; therefore, we speculate that the amount of cuprous iodide may hinder the formation of **9d** or accelerate the conversion of **9d** (eq 3). To our surprise, when **9d** was employed for the reaction in the absence of CuI or in the absence of CuI and $TMSCF_3$, of note, substrate **9d** could be converted to the desired product **5e** with good results (eq 4). These results further indicate that **9d** is the intermediate of this reaction. Finally, treatment of substrate **9e** under standard conditions afforded the corresponding ^{18}O-containing product **6c**-^{18}O determined by GC−MS and HRMS (SI) analysis (eq 5).[18]

On the basis of the current results and previous reports, a plausible mechanism was depicted in Scheme 5. It was reported that in the presence of a NaI, a CF_3^- anion would lose an F^- to form difluorocarbene,[14d] which further reacted with dialkyl ethers to give unsteadily a difluoromethylene oxonium (**I**). This ylide intermediate (**I**) can be protonated in the presence of water to obtain the difluoromethyl oxonium cation intermediate (**II**).[19] Since the oxonium salt is known to be a strong electrophilic reagent, we hypothesized that the difluoromethyl dialkyloxonium cation (**II**) will be attacked by a nucleophilic site generated from a carboxylic acid with CuI to give (since the copper(I) reagent has Lewis acidic behavior, it can combine with carboxyhydroxyl groups to hinder the side reaction between difluorocarbene and carboxylic acid and at the same time increase the nucleophilicity of carboxylic acid) difluoromethyl ether under suitable conditions to generate intermediate **III** (detected by ^1H NMR).[20] Later, iodoalkyl ester (**IV**) can be obtained by in situ exchange of CF_2HO−iodide in the presence of NaI at elevated temperatures.[20]

In summary, we have developed ring-opening iodization reactions between cyclic ethers and carboxylic acids, enabled by a copper and $TMSCF_3$ synergistic combination, affording a wide array of structurally diverse iodoalkyl esters with excellent functional group compatibility. This strategy for iodoalkyl esters synthesis can improve the step-economy and synthetic efficiency. Tackling this challenge of selectively eliminating the oxygen from cyclic ethers yields high-value-added chemicals.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c00732.

Detailed experimental procedures, characterization data, MS and ^1H, ^{13}C, and ^{19}F NMR spectral data for raw materials and obtained products (PDF)

FAIR data, including the primary NMR FID files, for compounds **3a**−**3z**, **3aa**−**3an**, **4a**−**4m**, **5a**−**5n**, **6a**−**6e**, **7a**−**7c**, **8a**−**8i**, **9d** (ZIP)

HRMS data (ZIP)

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Author Contributions

All authors have approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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