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Tandem Radical Fluoroalkylation–Cyclization: Synthesis of Tetrafluoro Imidazopyridines

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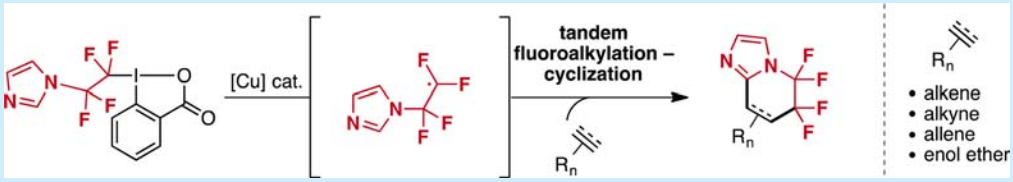
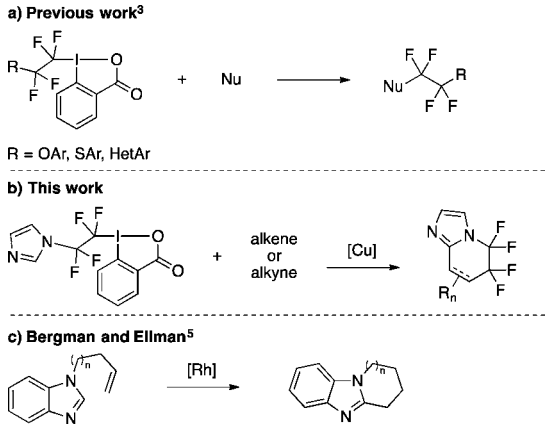
Supporting Information



ABSTRACT: A copper-catalyzed fluoroalkylation–cyclization sequence of alkenes and alkynes enables the synthesis of fluorinated tetra- and dihydroimidazopyridines in moderate to excellent yields within 1 h at 70 °C. This reaction, which is carried out using copper(I) acetate as the catalyst, makes use of a new class of functionalized tetrafluoroethyl reagents based on a hypervalent iodine scaffold.

We recently developed a series of functionalized tetrafluoroethylating reagents[1] based on the known benzo[*d*][1,2]iodoxole and benzo[*d*][1,2]iodoxol-3(1*H*)-one scaffolds.[2] These reagents were designed to transfer phenols, thiophenols, and *N*-hetereocyclic functionalities attached to the tetrafluoroethyl motif to organic nucleophiles (Scheme 1a).

Scheme 1. (a) Electrophilic Fluoroalkylations; (b) Tandem Fluoroalkylation–Cyclization; (c) Annulation of Alkenyl-Substituted Heterocycles



While exploring the potential of these new reagents for fluoroalkylation, we discovered that the reaction of tetrafluoroethylimidazole reagent **1** with 4-phenylbutene (**2a**) in the presence of a catalytic amount of a copper salt yielded tetrahydroimidazo[1,2-*a*]pyridine derivative **3a** containing a 1,1,2,2-tetrafluoroethylene unit (Scheme 1b) and not the expected allylic fluoroalkylation product.[3] This reaction is reminiscent of the work by Bergman and Ellman who described the formation of tetrahydrobenzimidazopyridines and -pyrrolidines from the corresponding benzimidazoalkenes via C–H bond activation using Wilkinson's catalyst (Scheme 1c).[4] Fused imidazoles, such as imidazo[1,2-*a*]pyridine constitute for example a well-known class of allosteric $GABA_A$-receptor agonists as well as proton-channel inhibitors,[5] while their saturated congeners are potent inhibitors of *β*-D-glucosidases.[6] Current synthetic pathways allow easy access to a high degree of functionalization of the imidazole moiety, whereas functionalization of the pyridine ring is remarkably underdeveloped.[7] Concomitantly, partially fluorinated derivatives of tetrahydroimidazo[1,2-*a*]pyridines are difficult to access; thus, the unique structural features of this tetrafluoroethylene fragment within a cyclic moiety remain so far unknown to the best of our knowledge.

The reaction we are reporting was first carried out in methanol at 70 °C, due to the low solubility of the reagent both in apolar solvents and at lower temperatures. The formation of the product was monitored by ^{19}F NMR spectroscopy, showing individual signals for each of the four fluorine atoms. We observed complete consumption of reagent **1** within 1 h at 70 °C. By investigating a series of copper(I) and copper(II) salts (Table 1, entries 1–5), we found that copper(I) acetate gave the best results. The choice of the solvent is crucial for this reaction (Table 1, entries 6–9), with DMF and acetonitrile being superior to other common organic solvents. Interestingly, we found that heating the reaction mixture from ambient temperature to 70 °C over a period of 10 min led to less decomposition of reagent **1** as evidenced by the decreasing amounts of 1-(1,1,2,2-tetrafluoroethyl)-1*H*-imidazole (imCF_2CF_2H, **4**) formed as a byproduct (Table 1, entry 10),

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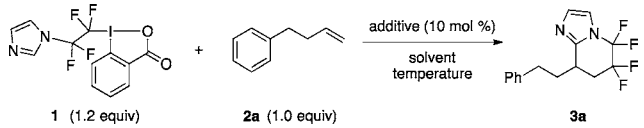
Table 1. Optimization of Reaction Conditions[a]



1 (1.2 equiv) 2a (1.0 equiv) 3a

entry	additive	solvent	temp (°C)	yield (%)[b]
1	CuCl	MeOH	70	29
2	CuOAc	MeOH	70	39
3	$Cu(OTf)_2$	MeOH	70	26
4	$[Cu(OTf)]_2PhH$	MeOH	70	7
5	CuI	MeOH	70	31
6	CuOAc	DMSO	70	36
7	CuOAc	DMF	70	83
8	CuOAc	DCE	70	51
9	CuOAc	CH_3CN	25−70	94
10	CuOAc	DMF	25−70	95
11[c]	CuOAc	DMF	45	78
12[d]	CuOAc	DMF	25	52
13[e]	CuOAc	DMF	25−70	81
14[f]	CuOAc	DMF	25−70	36
15	none	DMF	25−70	–

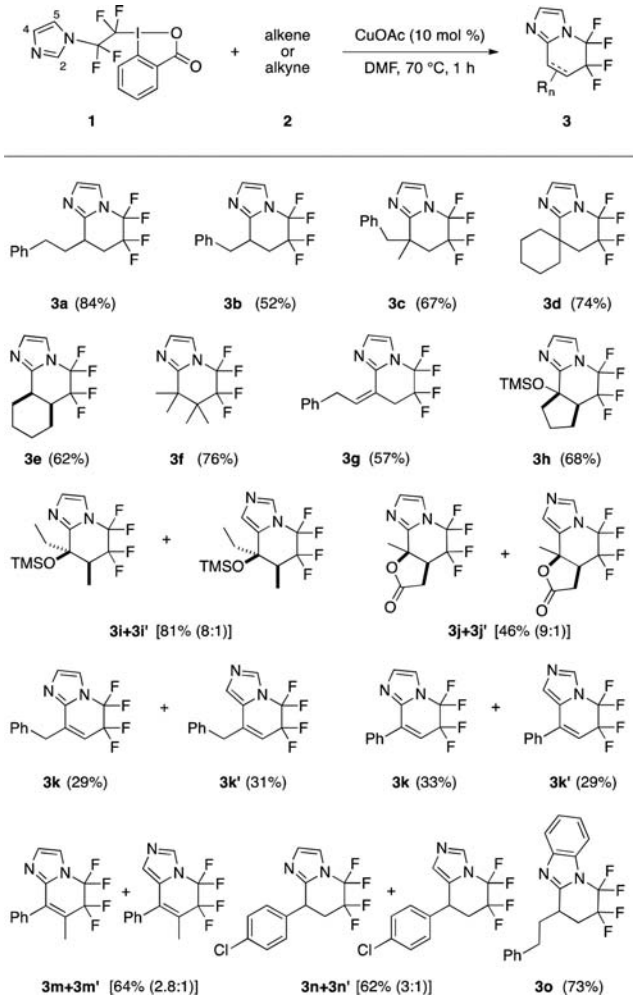
[a]Reaction conditions: Unless otherwise stated **1** (0.8 mmol, 1.2 equiv) and the appropriate copper salt (0.08 mmol, 10 mol %) were reacted with 4-phenylbutene (**2a**) (0.7 mmol, 1.0 equiv) under argon in 1 mL of dry solvent for 1 h at the indicated temperature. [b]The yields are indicated with respect to phenyltrifluoromethoxy ether (0.33 equiv) averaged over the four fluorine resonances. [c]Reaction run for 2 h. [d]Reaction run for 24 h. [e]1.2 equiv of **2a** and 1.0 equiv of **1** were used. [f]Reaction run under air using nondried solvent.

while further increasing the yield. Reaction temperatures lower than 70 °C required much longer reaction times, with partial decomposition of reagent **1**, leading to significantly lower yields (Table 1, entries 11 and 12). Using an excess of substrate **3a** (Table 1, entry 13) gave slightly decreased conversion, whereas carrying out the reaction under air in wet DMF resulted in even lower conversion (36% yield), with the majority of reagent remaining intact (Table 1, entry 14). When no copper additive was used, no product formation was observed, and over 24 h reagent **1** completely degraded leading to several nonidentified byproducts (Table 1, entry 15).

Next, we examined the scope of substrates able to undergo this fluoroalkylation−cyclization cascade reaction. Compounds containing isolated double bonds are well-suited substrates for this reaction, with both mono- and disubstituted olefins being well tolerated (**3a−e**) (Scheme 2). Methylenecyclohexane affords the expected spirocyclic product **3d** in good yields, while cyclohexene gives fused tricyclic product **3e**.

Furthermore, it is noteworthy that even tetrasubstituted alkenes such as tetramethylethylene are suitable substrates, giving the corresponding fully substituted tetrahydropyridine product **3f** in 76% yield. Allene **2g** is also a competent reaction partner for this transformation, giving product **3g** in 57% yield, bearing an exocyclic double bond. Silyl enol ethers are also excellent substrates in this reaction (**3h** and **3i**), affording the desired products in 68% and 81% yield, respectively. Reaction of either (*E*)- or (*Z*)-configured silyl enol ether **2i** afforded the same single diastereoisomeric form of product **3i** (with the TMSO and methyl substituents in mutual *cis*-configuration) as confirmed by X-ray crystallography of the corresponding alcohol **5** (see Figure 1 and Supporting Information (SI)).[8] This finding further corroborates our mechanistic proposal

Scheme 2. Substrate Scope for Tandem Electrophilic Fluoralkylation/Cyclization[a]



[a]Reaction conditions: **1** (0.6 mmol, 1.2 equiv), copper(I) acetate (0.05 mmol, 0.1 equiv), and **2a** (0.5 mmol, 1.0 equiv) were reacted in dry DMF (7.5 mL) under an argon atmosphere for 1 h with heating from ambient temperature to 70 °C within 10 min. The yields are reported as isolated yields after flash column chromatography.

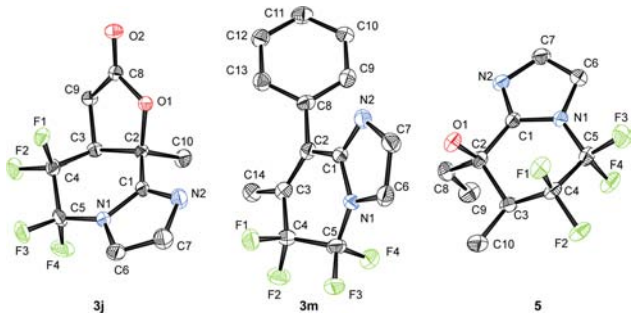


Figure 1. ORTEP representation of compounds **3j** (CCDC 1441837), **3m** (CCDC 1441838), and **5** (CCDC 1441840).

(*vide infra*). Also notable is that the unsaturated α-angelica lactone successfully engaged as the substrate to yield a mixture of compounds **3j** and **3j′** in moderate yield (46%). Furthermore, we were pleased to find that alkynes are also compatible starting materials under identical reaction conditions, furnishing the corresponding dihydroimidazopyridines

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3k–m. To our surprise, however, the products were formed as a mixture of two constitutional isomers. The first one corresponding to the expected structure, while the second isomer results from the attack of imidazole C5 instead of C2 for ring closure. (Formation of trace amounts of a second isomer was already observed for some of the aforementioned substrates.) Unfortunately, substrates bearing conjugated double bonds such as styrene failed to react under these conditions. Only the π-donating *para*-chlorostyrene yielded the desired product **3n** in 62% yield, as a 3:1 mixture of both constitutional isomers. When using a benzimidazole derived reagent, this methodology could be further expanded to the generation of a tricyclic ring system **3o**, under the same reaction conditions. The corresponding product could be isolated in 73% yield.

X-ray crystallographic analysis of products **3j**, **3m**, and **5** (Figure 1) unequivocally confirmed the original structural assignment, including the described regioselectivity of this reaction. Noteworthy is that five of the six atoms of the tetrahydropyridine ring of **3j** lie in the same plane shared with the imidazole unit.[6a] Only atom C4 lies out of plane, enforced by two fluorine atoms adopting one gauche and one antiperiplanar orientation and the two other fluorine atoms displaying a double gauche relationship with respect to one another (similar constitution applies to compound **3m**).

Using 1D and 2D NMR spectroscopic experiments it was possible to establish the preferred conformation of compound **3a** in solution. The large coupling constants for fluorine atoms F^1 and F^2 (200 Hz), and F^3 and F^4 (256 Hz), respectively, have been interpreted as geminal coupling constants, meaning that F^1 and F^2 are part of one difluoromethylene unit, as are F^3 and F^4. This is furthermore supported by a very strong interaction between the corresponding atoms as observed by $^{19}F-^{19}F$ NOESY. $^1H-^{19}F$ HOESY experiments showed cross-peaks arising from a strong contact between fluorine atoms F^3 and F^4 as well as protons H^1 and H^2 (Figure 2). This indicates that the

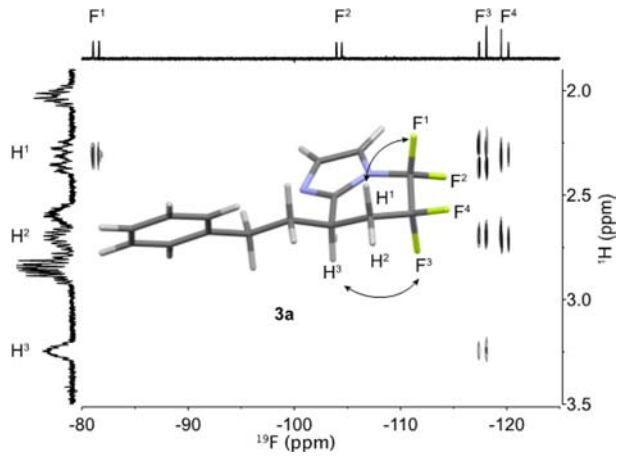


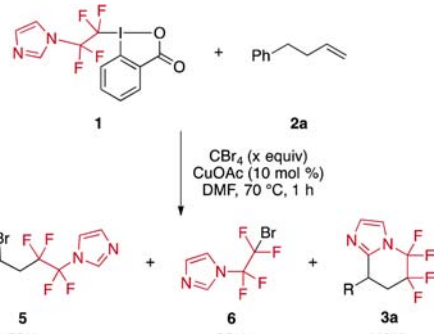
Figure 2. $^1H-^{19}F$ HOESY spectrum indicating the spatial relationship between selected atoms.

difluoromethylene unit CF^3F^4 is linked to CH_2, and not to nitrogen. Weaker interactions were observed between fluorine atom F^1 and proton H^1 as well as fluorine atom F^3 and proton H^3. These contacts are only possible if atoms F^1, F^3, H^1, and H^3 occupy pseudoaxial positions.

In order to obtain insight into the possible mechanistic pathways of this reaction, we conducted kinetic studies as well as trapping experiments. A kinetic profile was established, monitoring the formation of **3a** and the consumption of **1** by ^{19}F NMR at 70 °C and at 40 °C (see SI). Both reaction profiles are indicative of a first-order consumption of reagent and of the absence of any induction period. The fact that only styrenes bearing a π-donor are suitable substrates, while other styrenes fail to react, suggests that the crucial step in this reaction is the attack of the double bond on the formally electrophilic fluoroalkyl group. The works of Bergman and Ellman show that a rhodium–carbene complex will undergo cyclization with an appropriate olefin.[9] On the other hand, based on several reports postulating the generation of CF_3 radicals in copper-catalyzed trifluoromethylations,[10] along with the possibility of a radical cyclization as described by Aldabaggah and co-workers,[11] we addressed the possible formation of radical intermediates by selected experiments.[12] The formation of $imCF_2CF_2H$ **4** (Scheme 4) is most likely due to H-abstraction by the radical species **I1** (Scheme 4) from the solvent, which could be confirmed by the generation of $imCF_2CF_2D$ in DMF-*d*7. Therefore, we speculated that trapping an alkyl radical, formed by the combination of **I1** and the substrate, would be stronger evidence for a radical mechanism, as **I1** could also be formed by a nonproductive pathway.

We thus carried out the reaction in the presence of CBr_4 in order to observe bromofluoroalkylated product **5** deriving from the intermolecular recombination of **I2** with $Br^\bullet$ (Scheme 3).[13]

Scheme 3. Trapping of Alkylradical Intermediates Using CBr_4[a]



	5	6	3a
CBr_4 (1 equiv)	25%	35%	40%
CBr_4 (5 equiv)	26%	65%	6%
CBr_4 (25 equiv)	23%	80%	0%

[a]Yields are based on averaged ^{19}F NMR yields.

Indeed, we observed the formation of **5** in about 25% yield as determined by ^{19}F NMR spectroscopy and GC-MS in the presence of 1, 5, and 25 equiv of CBr_4, while $imCF_2CF_2Br$ **6** was generated as a major product for this series of reactions (35%, 65%, and 80% respectively). Full characterization of compound **5** confirmed the assigned regioselectivity, indicating that indeed secondary radical **I2** needs to be formed before recombination with the bromine radical occurs. In parallel to the formation of both brominated species, product formation is gradually inhibited in the presence of increasing amounts of radical trapping agent CBr_4 (40%, 6%, and 0% of **3a**, respectively). In the absence of **1**, no bromoalkyl product could be observed, confirming that CBr_4 is not the primary source of radicals. The fact that both (*E*)- and (*Z*)-configured silyl enol ether **2i** afford the same single diastereoisomer **3i** (*vide supra*) is supportive of our proposed stepwise radical mechanism. Product **3i** can only be formed from (*E*)-**2i** by

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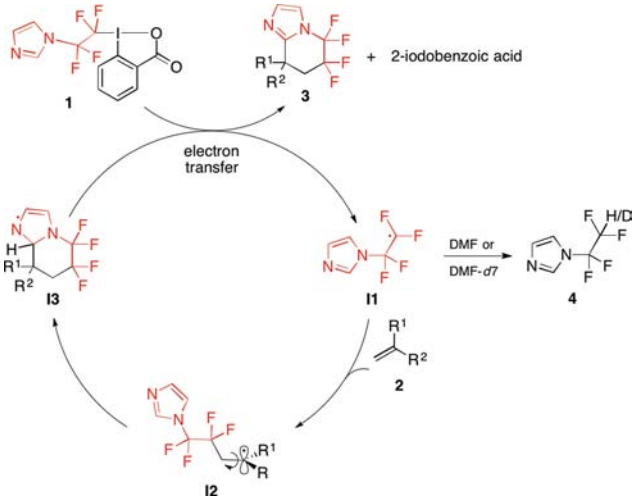
rotation around the former double bond to react via the thermodynamically favored transition state (**I2**) (Scheme 4) to give *cis*-isomer **3i**.

Scheme 4. Mechanistic Proposal



As demonstrated previously, in the absence of catalyst, neither product nor $imCF_2CF_2H$ **4** was formed, reinforcing the hypothesis that the initial step, i.e. the formation of radical **I1**, requires the presence of a copper species, though its exact mechanistic role remains unknown. We can thus formulate a mechanistic proposal where radical **I1** adds to the double bond of the substrate, resulting in the formation of radical intermediate **I2** (Scheme 4). The latter can then recombine with carbon C2 of the imidazole moiety, yielding cyclic intermediate **I3**. This radical species is then able to transfer one proton and one electron to a new molecule of **1**, possibly via a copper shuttle, forming the product, regenerating the fluoroalkyl **I1** radical, and giving 2-iodobenzoic acid as a byproduct.

In summary, we demonstrated the successful synthesis of fluorinated tetra- and dihydropyridines by a tandem fluoroalkylation−cyclization sequence. Our preliminary investigations clearly favor a radical mechanism. The described protocol could furthermore be extended to the formation of tricyclic tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyridine. The reaction, which is performed using readily available copper acetate for activation, is completed within 1 h, furthermore demonstrating the practicality of this process. We are currently exploring similar cyclization processes targeting an expanded scope of partially fluorinated heterocycles, not restricted to imidazopyridines.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00018.

Experimental procedures, spectral data for all new compounds (PDF)
Crystallographic data for **3j** (CCDC 1441837) (CIF)
Crystallographic data for **3m** (CCDC 1441838) (CIF)
Crystallographic data for **3o** (CCDC 1441839) (CIF)
Crystallographic data for **5** (CCDC 1441840) (CIF)

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Author Contributions

J.C. and N.F. contributed equally.

Notes

The authors declare no competing financial interest.

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