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Direct Trifluoromethylation of Alcohols Using a Hypervalent Iodosulfoximine Reagent

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Abstract: The direct trifluoromethylation of a variety of aliphatic alcohols using a hypervalent iodosulfoximine reagent afforded the corresponding ethers in moderate to good yields (14–72%). Primary, secondary, and even tertiary alcohols, including examples derived from natural products, underwent this transformation in the presence of catalytic amounts of zinc bis(triflimide). Typical reaction conditions involved a neat mixture of 6.0 equivalents of the alcohol with 1.0 equivalent of the reagent, with the majority of reactions complete within 2 h with 2.5 mol% of the Lewis acid catalyst. Furthermore, experimental evidence was provided that the C–O bond-forming process occurred via the coordination of the alcohol to the iodine atom and subsequent reductive elimination.

In the field of organofluorine chemistry, research efforts towards accessing trifluoromethyl ethers (OCF_3) have never moved faster or more relentlessly than in the last decade. This is evidenced by the emergence of five new trifluoromethoxylating reagents in the past three years alone,[1–5] with several review articles appearing alongside to keep up with the ever-growing body of synthetic methodologies.[6–10] The pronounced interest in this group is due to its high lipophilicity (Hansch parameter: $\pi = +1.04$)[11] relative to CF_3 and F, high electronegativity (Pauling's electronegativity scale: $\chi = 3.7$),[12] good metabolic stability and unique conformational properties.[13] The interest in new methodologies is therefore rapidly increasing from an industrial perspective, as marketed OCF_3-containing pharmaceuticals and agrochemicals remain sparse. However, facile access to such compounds is often impeded by the lack of reagents capable of delivering this functional group under mild conditions at a late stage of a synthetic sequence.

Traditionally, trifluoromethyl ethers were accessed via de novo synthesis under harsh reaction conditions using toxic, difficult-to-handle chemicals, and pre-functionalized compounds, rendering these methods limited in practicality and scope (Scheme 1 a).[7] Trifluoromethoxylated compounds are therefore often obtained via multistep synthesis from expensive building blocks. Recently, several mild reagents have emerged, which employ either a nucleophilic or radical pathway for the formation of the C–OCF_3 bond (Scheme 1 a). Reagents that utilize trifluoromethoxide, such as $TASOCF_3$ [tris(dimethylamino)sulfonium trifluoromethoxide],[14] TFMS (trifluoromethyl arylsulfonate),[4] and TFBz (trifluoromethyl benzoate),[5] have been employed for the synthesis of both aryl and alkyl trifluoromethyl ethers. $TMSCF_3$ has also been employed for the silver-mediated oxidative trifluoromethylation of alcohols.[15] Unfortunately, these compounds have intrinsic limitations, including: 1) degradation of the OCF_3 fragment to fluorophosgene, 2) reagent synthesis from toxic, gaseous, or expensive chemicals, 3) often low yields, 4) the requirement of several additives (including transition-metal catalysts), and 5) need for pre-functionalized materials. In 2018 three radical trifluoromethoxylating reagents were reported; Ngai and co-workers reported the use of benzimidazole[2] and benzotriazole[3] based compounds, while one of our groups reported a pyridine *N*-oxide reagent.[1] The major advantage of these radical-based reagents is the ability to functionalize unactivated arenes under photoredox conditions. Thus far, this method has not been extended beyond arenes and is encumbered by the poor selectivity of the reagents (resulting in mixtures of regioisomeric products) and the requirement for large excess of starting material (5–10 equiv.). A much simpler and highly functional-group-tolerant method for OCF_3 formation is via the electrophilic trifluoromethylation of alcohols; this direct approach is the most practically straightforward. However, it is the least explored, with only two reagents known in the literature that are capable of this transformation. The first reagent, reported in 2007, is an *O*-(trifluoromethyl)dibenzofuranium salt or "Umemoto's reagent" (Scheme 1 b), which was successfully employed for the formation of both aryl and alkyl trifluoromethyl ethers.[16] However, the use of this compound is hampered by the synthetic challenge of preparing the reagent precursors, after which the oxonium salt is

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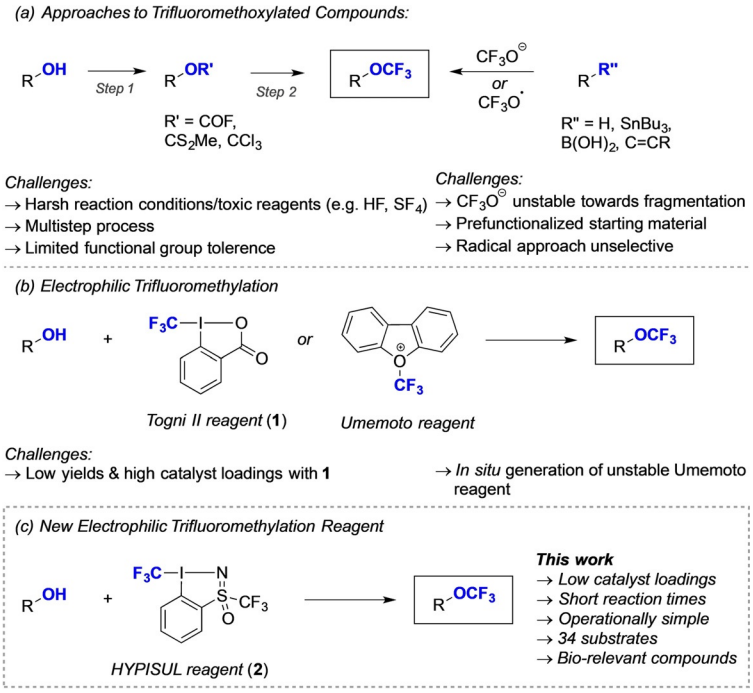


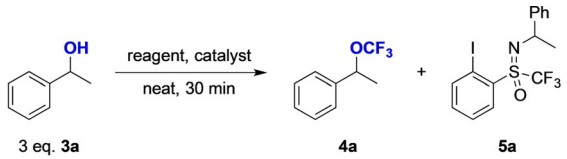
Scheme 1. Synthetic approaches to accessing trifluoromethyl ethers.

generated in situ under photochemical conditions between −70 and −90 °C. In 2009, one of our groups reported the use of hypervalent iodine compound **1** (Scheme 1 b) for the trifluoromethylation of primary and secondary alcohols using zinc triflimide in either catalytic (usually requiring more than 30 mol %) or stoichiometric amounts.[17,18] Trifluoromethylation of triflimide occurred as a competing reaction, requiring large excesses of alcohol to be used (5–75 equiv.) in order to achieve reasonable yields (12–99 %). Despite these advances, the generation of trifluoromethyl ethers from alcohols as a fundamental synthetic transformation remains hindered by impractical reaction conditions. Newer methods that circumvent these issues are highly desirable, thus highlighting the need for improved conditions and reagents which the present study addresses.

Recently, we reported the synthesis and characterization of a new electrophilic trifluoromethylating reagent that combines the hypervalent iodine motif with a sulfoximine ligand ("HYPISUL" reagent **2** in Scheme 1 c).[19] HYPISUL is similarly reactive to the parent Togni-type reagents in the trifluoromethylation of C-, S-, and P-nucleophiles. We anticipated that **2** could prove more efficient in the trifluoromethylation of alcohols compared to **1** due to the presence of a Lewis basic nitrogen atom, which is likely to coordinate to Lewis acidic species more readily. Herein, we report the good reactivity of aliphatic alcohols with the HYPISUL reagent catalyzed by zinc triflimide (2.5–20 mol %); this is an operationally simple setup that gives trifluoromethyl ethers in relatively high yields, with comparatively minimal catalyst and substrate loadings, within short reaction times. In particular, we are able to demonstrate a broader substrate scope for the trifluoromethylation of a variety of secondary and bio-relevant alcohols featuring various functional groups, a significant improvement to the former strategy using **1**, as well as those reported using other reagents. Previously, extensive computational work has been dedicated to deciphering whether reactions involving O- and N-centered nucleophiles with reagents of type **1** occur via a radical, S_N2, or reductive elimination-type pathway with contradictory findings.[20–22] Through a series of control experiments, we provide strong evidence that the mechanism for this reaction involves the coordination of the alcohol substrate to the hypervalent iodine species, affording the trifluoromethyl ether through a reductive elimination process.

We started our investigation using 1-phenylethanol (**3 a**, Table 1) as a model substrate in order to examine the possibility of improving the yield of the electrophilic trifluoromethylation of secondary alcohols. This substrate was chosen due to the fact that in our previous work using **1**, we found that benzylic alcohols were particularly difficult to functionalize. Taking 3.0 equivalents of **3 a** and 1.0 equivalent of **2**, we investigated the use of various Lewis acid catalysts (see Supporting Information for details) and found $Zn(NTf_2)_2$ to be the optimal catalyst, giving **4 a** in moderate yields after 30 min under neat reaction conditions. The choice of $Zn(NTf_2)_2$ is advantageous due to the fact that it is a minimally hygroscopic Lewis acid and thus ideal from a practical point of view. The yield of **4 a** could be increased by lowering the catalyst loading from 25 mol % to 2.5 mol % (Table 1, entries 1–3), which suppressed the formation of an *N*-alkylated side product **5 a**. We speculated that **5 a** is produced via the formation of an intermediate carbocation

Table 1. Optimization of reaction conditions for the trifluoromethylation of **3 a** with **2**.



3 eq. **3a** **4a** **5a**

Entry	Reagent	Catalyst (equiv.)	*T* [°C]	Yield **4 a**[a] [%]	Yield **5 a**[a] [%]
1	**2**	$Zn(Ntf_2)_2$ (0.25)	40	4	56
2	**2**	$Zn(Ntf_2)_2$ (0.10)	40	25	28
3	**2**	$Zn(Ntf_2)_2$ (0.025)	40	35	13
4	**2**	–	40	4	10
5	**2**	$Zn(Ntf_2)_2$ (0.025)	23	33	8
6[b]	**2**	$Zn(Ntf_2)_2$ (0.025)	23	46	11
7[b]	**2**	$Zn(Ntf_2)_2$ (0.10)	23	49	10
8	**1**	$Zn(Ntf_2)_2$ (0.025)	23	0	n.d.

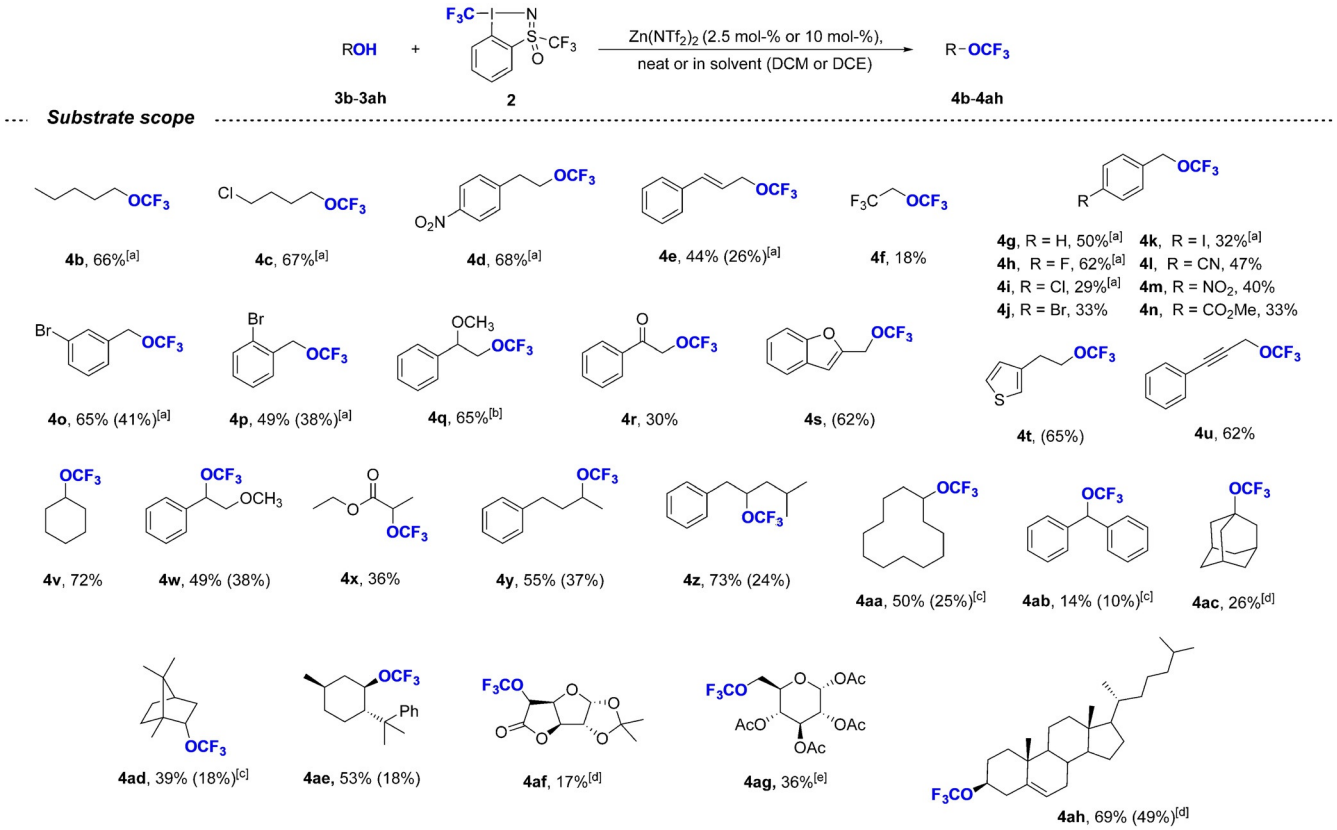
[a] Yields are based on reagent **2** and determined by ^{19}F NMR spectroscopy using trifluoromethoxybenzene as an internal standard. [b] With 6.0 equiv. of **3 a**.

1 **2**

species, which then reacts with the nitrogen of the sulfoximine moiety. This was tentatively verified by using (*R*)-1-phenylethanol with **2**, which gave **5a** as a mixture of diastereomers (see Supporting Information for details). Useful yields with **2** could be obtained by decreasing the temperature to 23 °C (entry 5) and increasing the amount of substrate **3a** to 6.0 equivalents to give **4a** in 46% (entry 6). When we examined compound **1** under the same reaction conditions, no product was formed (entry 8); however, by stirring the reaction at 40 °C for 3.5 h, 27% of **4a** was obtained (see Supporting Information).

With the optimized conditions in hand, we sought to examine and broaden the substrate scope. Starting with aliphatic alcohols, which are the least prone to side-product formation (Scheme 2, **3b**–**3e**), we found that using just 6.0 equivalents of the starting material, an increased catalyst load of 10 mol%, under neat conditions gave yields between 44–68% in under 2 h. Benzylic alcohols (**3g**–**3n**) gave slightly lower yields due to the increased likelihood of forming the *N*-alkylated side product, which was minimized by lowering the catalyst loading in most cases to 2.5 mol%. This methodology is most amenable to benzylic alcohols bearing electron-withdrawing groups; halides in *o*-, *m*-, and *p*-positions were all well tolerated (**4h**–**4k**, **4o**, **4p**) as well as nitrile (**4l**), nitro (**4m**), and ester (**4n**) groups. Trifluoromethylation of an alcohol bearing an α-methoxy group gave the product (**4q**) in good yields (65%), but an α-carbonyl function (**4r**) was less well tolerated (30% yield). We then turned our attention to compounds containing synthetically useful motifs, such as heteroarenes (**3s** and **3t**), an alkyne (**3u**) and alkene (**3e**), which proceeded to give the trifluoromethoxy-containing products in good yields (44–65%). To our delight, secondary alcohols (**3v**–**3aa**) gave moderate to good yields (36–73%) when using 2.5 mol% catalyst in all cases, something that could not easily be achieved using **1**. Surprisingly, we found adamantanol (**3ac**) to be a viable tertiary substrate, giving a 26% yield when employing 10 mol% catalyst with CH_2Cl_2 as solvent. Furthermore, we were pleased to find these reaction conditions amenable to biologically relevant compounds such as borneol (**3ad**), (−)-8-phenylmenthol (**3ae**), carbohydrate derivatives (**3af** and **3ag**), and cholesterol (**3ah**). Given that these substrates are often valuable, we could reduce the amount of starting material used from 6.0 to 3.0 equivalents by increasing the reaction time, for example **4ah** was obtained in 69% yield with 6.0 equivalents after 3 d, upon reducing the amount of **3ah** to 3.0 equivalents and extending the reaction period to 13 d, 72% of **4ah** was formed.

Next, we sought to examine the inter- and intramolecular selectivity of the reagent (Figure 1). The intermolecular selectivity was tested using 2-methoxy-2-phenylethanol and 2-methoxy-1-phenylethanol; 75:25 selectivity was observed for primary vs. secondary alcohol functionalization. Taking heptane-



Scheme 2. Substrate scope of trifluoromethylation of aliphatic alcohols with **2**. For all substrates which are oils no heating was required, in cases where the starting material was a solid the reaction was conducted at the melting point of the compound if applicable or in solvent. Yields were based on reagent **2** and determined by ^{19}F NMR analysis. Yields of isolated products are given in parenthesis. [a] 10 mol% catalyst was used. [b] 20 mol% catalyst was used. [c] Reaction in 1,2-dichloroethane (0.25 M in **2**). [d] 10 mol% catalyst was used, reaction in CH_2Cl_2 (0.13 M in **2**). [e] 20 mol% catalyst was used, reaction in CH_2Cl_2 (0.13 M in **2**).

1,6-diol, we found the reagent to have 56:40 chemoselectivity for primary alcohols vs. secondary, further highlighting the good reactivity of **2** with secondary alcohols. The chemoselectivity for primary alcohols over tertiary gave 73:27 selectivity when using 3-(hydroxymethyl)-1-adamantol.

Finally, given the improved reactivity of reagent **2**, we speculated whether improved yields would also be observed for phenols compared to that reported with **1**.[17] However, taking phenol and 4-chlorophenol, poor selectivity for *O*-trifluoromethylation was observed in both cases (11 and 16%, respectively) with *C*-trifluoromethylated side-products observed by NMR spectroscopy.

In order to gain insight into why compound **2** outperforms **1** for this transformation, DFT calculations were performed. Investigating the natural charges on the carboxylate and sulfoximine ligands, we found the lowest natural charge to be on the nitrogen atom in **2**, suggesting a stronger and thus more favorable coordination of **2** with zinc triflimide. Based on our previous findings,[17] we expected the reagents to form a 2:1 reagent·Zn adduct, DFT calculations on the optimized adducts indicated that $[ZnNTf_2(\mathbf{2})_2]NTf_2$ is thermodynamically favored compared to $[ZnNTf_2(\mathbf{1})_2]NTf_2$ by 6 kcal mol^{-1} in solution (see Supporting Information for details). To further validate the predicted stoichiometry, ^{19}F NMR experiments were conducted, which showed a downfield shift of the I-CF_3 signal upon addition of increasing amounts of $Zn(NTf_2)_2$ as a result of the increasing iodonium character of **2**.[23] Broadened signals were observed upon addition of up to 0.50 equiv. of the zinc catalyst, with sharpened signals observed thereafter suggesting the likelihood of a 2:1 adduct.

To probe the mechanism of this reaction we carried out selected experiments, which led us to conclude that a reductive elimination pathway is operative. Firstly, we examined whether the reaction involves radical intermediates: the reaction between **2** and **3h** was conducted in the presence of known radical acceptors (see Supporting Information for further details).

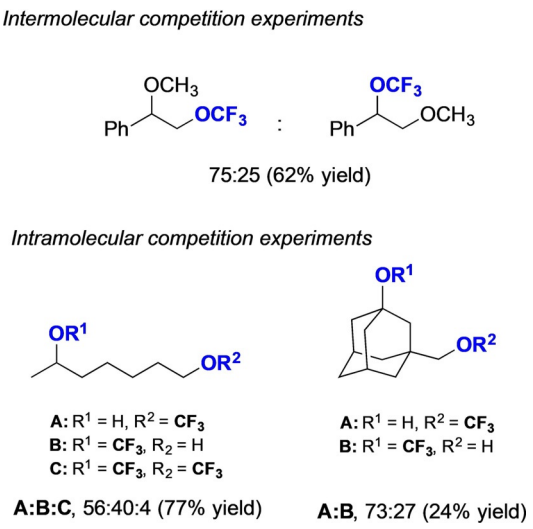


Figure 1. Selectivity of reagent **2** for primary, secondary, and tertiary alcohols.. Yields were based on reagent **2** and determined by ^{19}F NMR spectroscopy.

When using CBr_4 and styrene, the formation of product **4h** was unimpeded, indicating that this transformation occurs without the formation of radical species. Using 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as a radical trap, product formation was completely inhibited due to the oxidation of the alcohol substrate[24] and formation of the corresponding hydroxylamine which is trifluoromethylated by **2**, as previously observed with Togni-type reagents.[25] Two possible mechanistic pathways after formation of the 2:1 adduct (**I**) can then be postulated.[17] The first, an S_N2-type pathway, involves the intermolecular attack of the nucleophile onto the CF_3 moiety. Alternatively, the nucleophile may coordinate to the iodine atom to give the intermediate **III**; the trifluoromethoxy-containing product is then formed after reductive elimination (Scheme 3). To examine the S_N2-type pathway we carried out the reaction using the corresponding alcoholate generated using NaH, the reagent and catalyst were added after 10 mins of stirring; however no product was formed, suggesting that an S_N2 reaction is unlikely (see Supporting Information, Table S1). Additionally, taking a sterically hindered nucleophile, diphenylmethanol (**3ab**), we found that the corresponding trifluoromethyl ether was formed in moderate yield, and the *N*-alkylated side-product, **5ab**, was detected in 78% yield by GC–MS, (**5ab** was characterized by XRD, see Supporting Information for details), further refuting an S_N2 mechanism. The formation of the side-products of type **5** is facilitated by the coordination of the alcohol to the iodine atom in **II** (depicted in Scheme 3), C–OH cleavage subsequently occurs due to the proximity to the zinc(II) center which acts as a hydroxide scavenger, giving the carbocationic R^+ species. To validate this hypothesis, we conducted an additional control experiment taking iodosulfoximine **6** (Scheme 3) and **3a** under the standard reaction conditions. In this case the side-product was not formed, hence coordination of the alcohol to the hypervalent iodine center is essential. These experiments strongly support the mechanistic pathway depicted in Scheme 3.

In conclusion, we describe the reactivity of reagent **2** with aliphatic alcohols, which gives trifluoromethyl ethers in an efficient and atom-economic manner compared to many former strategies. Using only 1.0 equivalent of **2** and minimal catalyst loadings (2.5–20 mol%), a wide variety of trifluoromethyl ethers can be accessed. The reaction shows high chemoselectivity, allowing for the selective trifluoromethylation of alcohols in the presence of many functional groups. We were particularly pleased to find that the substrate scope could be expanded to a variety of secondary alcohols and biologically relevant molecules. Finally, we provide compelling experimental evidence that this reaction occurs through a reductive elimination process. We anticipate this method to be highly useful as a simple and practical method and continue to explore the potential of reagent **2** in our labs.

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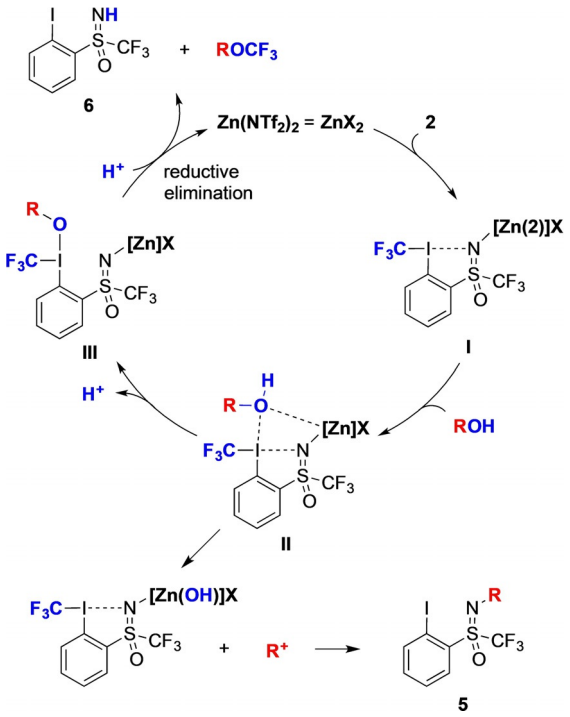

Scheme 3. Mechanistic proposal for the zinc-catalyzed trifluoromethylation of alcohols using reagent **2**.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: hypervalent iodine · organofluorine compounds · sulfoximines · trifluoromethylation · trifluoromethylethers

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