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Lewis-Acid-Mediated Intramolecular Trifluoromethylthiolation of Alkenes with Phenols: Access to SCF_3-Containing Chromane and Dihydrobenzofuran Compounds

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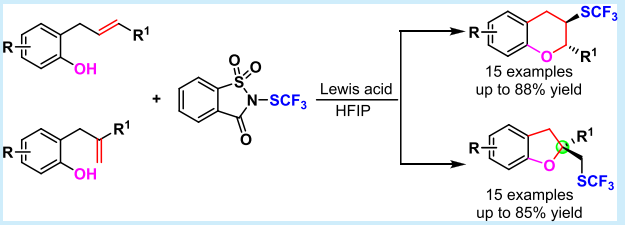
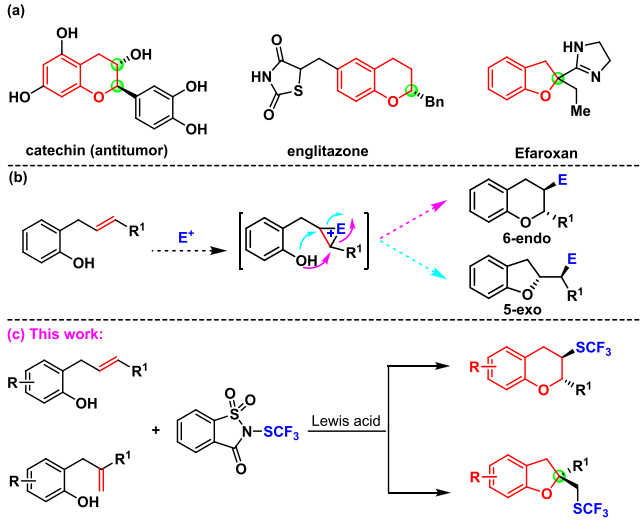
ABSTRACT: A Lewis-acid-mediated intramolecular trifluoromethylthiolation of alkenes with phenols that can offer direct access to SCF_3-containing chromane and dihydrobenzofuran compounds was disclosed for the first time. Numerous SCF_3-containing chromanes were obtained in moderate to good yields using γ-substituted 2-allyphenols as substrates. Meanwhile, various SCF_3-containing dihydrobenzofurans with oxa-quaternary centers were also delivered in moderate to good yields using β-substituted 2-allyphenols as substrates.



The chroman skeleton is widely present in bioactive molecules, such as catechin and englitazone (Scheme 1a).[1] Accordingly, various synthetic strategies have been developed.[2] Among them, the electrophilic addition/cyclization of γ-substituted 2-allyphenols to form 2,3-disubstituted chromans is a direct and efficient method. The method could introduce a transformable and useful group at the three-position of chroman and simultaneously construct two continuous stereocenters (Scheme 1b). However, to our surprise, the successful development of this type of method remains rare.[3] One of the difficulties may be that the reaction requires excellent control of the regioselectivity and diastereoselectivity to solely afford the chroman product, which is shown in Scheme 1b. The mixture of chroman and dihydrobenzofuran would be obtained if the regioselectivity was not well controlled. In addition, the relatively weak nucleophilic capability of the phenolic hydroxyl group may be a limiting factor, and the direct Friedel−Crafts reaction of the phenol moiety is a nonignorable competing reaction. So, the development of the electrophilic addition/cyclization of γ-substituted 2-allyphenols to form 2,3-disubstituted chromans is still challenging. The dihydrobenzofuran moiety is also an important and usual scaffold for natural products and pharmaceutical molecules (Scheme 1a).[4] Consequently, numerous synthetic methods for the preparation of dihydrobenzofuran compounds have been reported.[5] Similarly, only a few examples of the electrophilic addition/cyclization of 2-allyphenols have been documented.[6] Therefore, the development of methods for the straightforward and efficient synthesis of chromans and dihydrobenzofurans is in high demand.

Because it shows high lipophilicity and strong electron-withdrawing ability, introducing a SCF_3 group into compounds can make the compounds have unique chemical, biological, and physical properties.[7] Thus SCF_3-containing compounds broadly exist in pesticides, medicine, and functional materials.[8] The development of methods for the efficient and rapid synthesis of SCF_3-containing compounds has attracted much

Scheme 1. Design for the Synthesis of SCF_3-Containing Chromane and Dihydrobenzofuran Compounds



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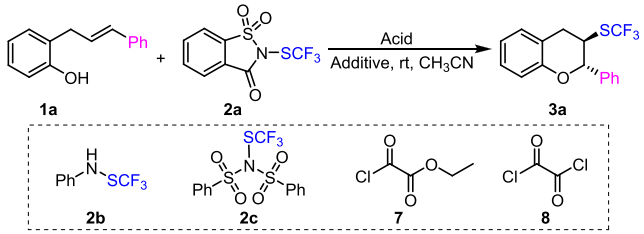
attention, and various outstanding research works have been disclosed.[9] For example, the Billard and Shen groups have independently explored some different useful SCF_3 reagents and achieved a number of fairly synthetic methods.[10,11] The Zhao group developed a variety of novel enantioselective trifluoromethylthiolations of alkene-catalyzed chiral sulfide compounds.[12] However, trifluoromethylthiolations of alkenes with phenols to afford SCF_3-containing chromans and dihydrobenzofurans have not been reported. Considering the importance of chroman and dihydrobenzofuran units and SCF_3-containing compounds and combined with our interest in fluorine and organosulfur chemistry,[13] we hope to study the trifluoromethylthiolations of γ-substituted 2-allyphenols to afford 2,3-disubstituted chromans and β-substituted 2-allyphenols to produce dihydrobenzofurans with oxa-quaternary centers (Scheme 1c). In this Letter, we report our preliminary results.

Initially, (*E*)-cinnamylphenol (**1a**) was chosen as a model substrate with *N*-trifluoromethylthiosaccharin **2a** (Shen's reagent) as the SCF_3 source to study the transformation for the synthesis of chromanes (Table 1). The desired product **3a**

Table 1. Screening of Reaction Conditions for the Synthesis of SCF_3-Containing Chromanes[a]



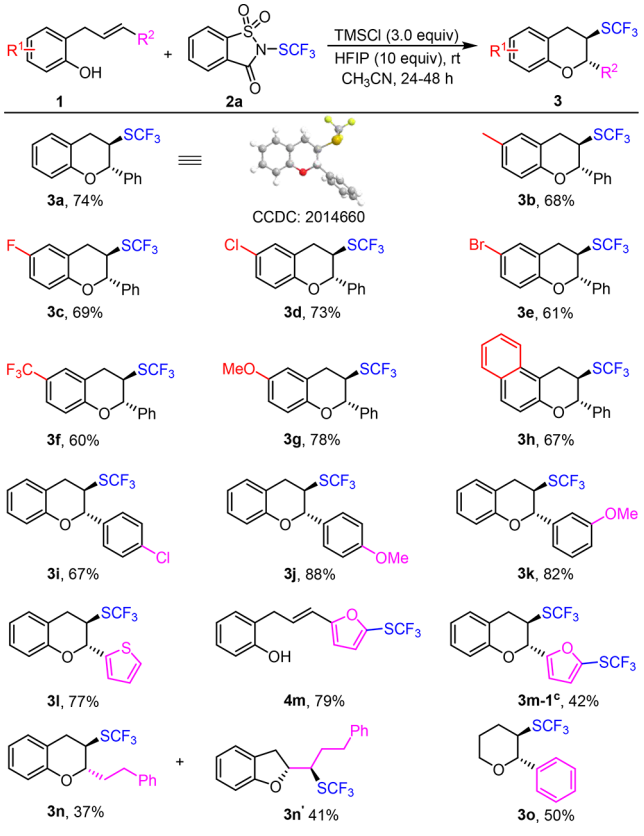
entry	acid (equiv)	SCF_3 source	additive	yield (%)[b]
1	AcCl (3.0)	**2a**		46
2	**7** (3.0)	**2a**		58
3	**8** (3.0)	**2a**		53
4	TMSCl (3.0)	**2a**		60
5	$BF_3{\cdot}Et_2O$ (1.0)	**2a**		
6	HCl (3.0)	**2a**		34
7	CF_3CO_2H (1.0)	**2a**		
8	CH_3SO_3H (1.0)	**2a**		
9	CF_3SO_3H (1.0)	**2a**		
10	TMSCl (3.0)	**2b**		26
11	TMSCl (3.0)	**2c**		
12[c]	TMSCl (3.0)	**2a**	PhSePh[c]	55
13[c]	TMSCl (3.0)	**2a**	$(PhSe)_2$[c]	41
14[d]	TMSCl (3.0)	**2a**	HFIP[d]	68
15[e]	**TMSCl (3.0)**	**2a**	**HFIP**[e]	**74**
16[e]		**2a**	HFIP[e]	

[a]Reaction conditions: Unless otherwise noted, the reaction was conducted with **1a** (0.1 mmol), **2a** (0.13 mmol), and acid (0.3 mmol) in CH_3CN (1 mL) at room temperature under Ar for 24 h. [b]Isolated yield. [c]0.1 equiv of additive was used. [d]HFIP (1.0 equiv) was added. [e]HFIP (10 equiv) was added.

was obtained in 46% yield when acetyl chloride (AcCl) was used as the Lewis acid in CH_3CN (1 mL) at room temperature (entry 1). It is worth mentioning that the reaction was achieved with excellent regioselectivity and diastereoselectivity. To improve the yield, a series of acids including the Lewis acid and Brønsted acid were examined (entries 2–9). The use of trimethylchlorosilane (TMSCl) gave the best result, affording the product in 60% yield (entry 4). Interestingly, only using the acids containing chloride ions could produce the desired product **3a**. It could be explained that the more active compound CF_3SCl was formed in situ, which is the real SCF_3 source in this system. (For details, see the SI.) After determining TMSCl to be the acid, some other widely used SCF_3 reagents were tested, such as $PhNHSCF_3$ developed by Billard[10] and $(PhSO_2)_2NSCF_3$ developed by Shen.[11d] It was found that no better result was observed in this system (entries 10 and 11). Next, we turned our attention to the screen additive. Inspired by Zhao's work,[14] diphenyl selenide (PhSePh) and diphenyl diselenide ($(PhSe)_2$) were first considered. However, both of the two additives resulted in decreasing the yield (entries 12 and 13). To our delight, the use of hexafluoroisopropanol (HFIP) as an additive can obviously improve the conversion and then increase the yield.[15] After carefully screening the amount of HFIP, the best result was obtained, producing the product **3a** in 74% yield when 10 equiv of hexafluoroisopropanol was used (entry 15). It was found that the reaction hardly happened when using only HFIP in the absence of TMSCl (entry 16). Thus we surmised that the role of HFIP is as a cooperative activator.

With the optimized conditions in hand, the generality of this tandem trifluoromethylthiolation/cyclization reaction was evaluated with a wide range of 2-allyphenol derivatives (Scheme 2). First, a number of substrates with different

Scheme 2. Substrate Scope of γ-Substituted 2-Allyphenols for the Synthesis of SCF_3-Containing Chromanes[a,b]



[a]Reaction conditions: Unless otherwise noted, the reaction was conducted with **1** (0.1 mmol), **2a** (0.13 mmol), TMSCl (0.3 mmol), and HFIP (1.0 mmol) in CH_3CN (1 mL) at room temperature under Ar. [b]Isolated yield. [c]2.5 equiv of **2a** was used.

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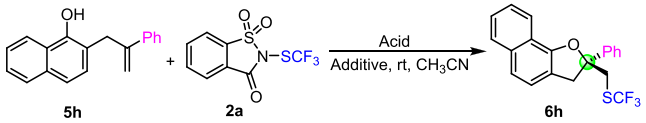
substituents at the four-position of phenol were investigated. In general, the desired products were obtained in moderate yields (**3b**–**g**). It was found that the electron-rich substituent can improve the yield, whereas the electron-deficient substituent decreases the yield (**3g** vs **3f**). 2-Naphthol substrate **1h** is also suitable for the transformation, delivering the corresponding product **3h** in 67% yield. Next, a series of substrates with different 1,2-disubstituted alkenes were subjected to the reaction (**3i**–**n**). Similarly, the substrate with an electron-rich alkene gave a higher yield than the electron-deficient alkene (**3j** vs **3i**). The position of the substituent at the phenyl group did not obviously affect the yield (**3j** vs **3k**). To our delight, the substrate with thiophene **1l** was well-tolerated, affording the product **3l** in 77% yield, but when the compound with furan **1m** was used as the substrate, the desired cyclization product was hardly observed, and the product **4m** was mainly obtained in 79% yield under standard reaction conditions. We speculated that ditrifluoromethylthiolation/cyclization product **3m-1** could be obtained when the amount of **2a** was further increased. As expected, the product **3m-1** was produced in 42% yield using 2.5 equiv of **2a** and **1m** as the substrate. The substrate with nonactivated alkyl alkene **1n** was examined, and the reaction still happened smoothly. It was found that SCF_3-containing chroman and dihydrobenzofuran were simultaneously obtained in 78% combined yield with an approximate ratio of 1:1. Finally, normal alkyl alcohol **1o** was tested, giving single 6-*endo* product **3o** in 50% yield. It should be noted that the relative configuration of **3a** was determined by X-ray crystallography.

To solely synthesize SCF_3-containing dihydrobenzofurans, we considered that the use of β-substituted 2-allyphenol as a substrate would be a better choice. Therefore, we turned our attention to exploring the trifluoromethylthiolation/cyclization of β-substituted 2-allyphenols (Table 2). It is a pity that the desired product **6h** was obtained in only 51% yield under the previously described standard conditions using **5h** as the substrate (entry 1). The yield was not satisfactory, and thus screening a more suitable reaction condition for this type of alkene substrate is necessary. As shown in Table 2, three Lewis acids were first conducted based on the previously described results, and the product was afforded in 58% yield when ethyloxalyl chloride **7** was used as an acid (entry 3). Adding HFIP can also promote the reaction, and the yield was increased to 64%. Other conditions have also been investigated, but the yield was not further improved. Therefore, the conditions of entry 5 were chosen as the optimal conditions.

Table 2. Screening of Reaction Conditions for the Synthesis of SCF_3-Containing Dihydrobenzofurans[a]

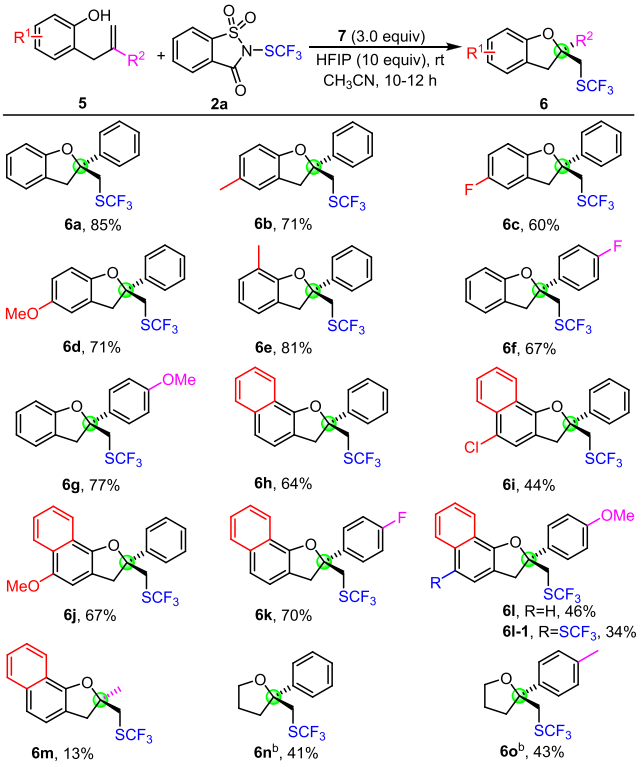


entry	acid (equiv)	SCF_3 source	additive	yield (%)[b]
1	TMSCl (3.0)	**2a**	HFIP	51
2	AcCl (3.0)	**2a**		53
3	**7** (3.0)	**2a**		58
4	**8** (3.0)	**2a**		56
5[c]	**7** (**3.0**)	**2a**	**HFIP**	**64**

[a]Reaction conditions: Unless otherwise noted, the reaction was conducted with **5h** (0.1 mmol), **2a** (0.13 mmol), and acid (3.0 equiv) in CH_3CN (1 mL) at room temperature under Ar for 6 h. [b]Isolated yield. [c]HFIP (10 equiv) was added.

Subsequently, the scope of the reaction was investigated with a variety of β-substituted 2-allyphenols and 2-(2-substituted ally)-1-naphthols. In general, the desired products were obtained in moderate to good yields (Scheme 3). Compared with **5h**, β-substituted 2-allyphenols always gave higher yields, except for **5c** (**5a**–**g**).

Scheme 3. Substrate Scope of β-Substituted 2-Allyphenols for the Synthesis of SCF_3-Containing Dihydrobenzofurans[a]



[a]Reaction conditions: Unless otherwise noted, the reaction was conducted with **5** (0.1 mmol), **2a** (0.13 mmol), **7** (0.3 mmol), and HFIP (1.0 mmol) in CH_3CN (1 mL) at room temperature under Ar. Isolated yield. [b]TMSCl was used instead of **7**.

Both electron-rich groups at the four-positions of phenol and alkene part gave higher yields than the electron-deficient groups (**6d** vs **6c** and **6g** vs **6f**). We found that 4-methoxynaphthalen-1-ol **5j** gave a 67% yield, whereas when using 4-chloronaphthalen-1-ol **5i** as the substrate, the yield was decreased to 44%. To our delight, the product **6k** was produced in 70% yield with the use of electron-deficient substrate **5k**. It is interesting that the further Friedel–Crafts product **6l-1** (34% yield), except for the desired product **6l** (46% yield), was also observed using electron-rich substrate **5l**. Unfortunately, product **6m** was obtained in only 13% yield when nonactivated 1,1-disubstituted alkene **5m** was examined. Likewise, alkene alcohol substrates **5n** and **5o** were also conducted, affording the corresponding products in moderate yields.

To evaluate the practicability of these two trifluoromethylthiolation/cyclization reactions, 1 mmol scale transformations of **1j** and **5f** were carried out, respectively. To our delight, product **3j** was obtained in 83% yield, and **6f** was produced in

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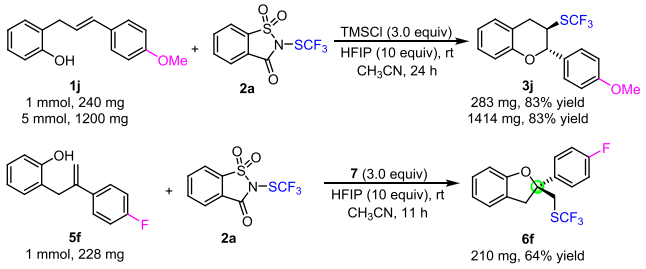
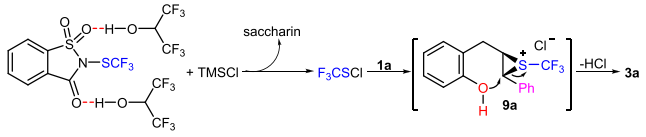
64% yield (Scheme 4). The yields of the two reactions were basically maintained. Furthermore, a 1 g scale reaction of **1j** was also performed, delivering product **3j** in 83% yield.

Scheme 4. 1 mmol Scale Reactions



To gain further insight into this transformation, some ^{1}H NMR and ^{19}F NMR spectroscopy studies were performed. (For details, see the SI.) On the basis of previous works and our results, a possible mechanism for the intramolecular trifluoromethylthiolation of 2-allyphenol is proposed in Scheme 5. The active compound CF_3SCl is first formed in

Scheme 5. Proposed Mechanism



the presence of Shen's reagent **2a**, HFIP, and TMSCl. (See the ^{19}F NMR data in the SI.) HFIP may act as an activator via the hydrogen-bonding interaction and provide a proton for the formation of saccharin. (See the ^{1}H NMR data in the SI.) Additionally, TMSCl also can directly activate Shen's reagent **2a** to form CF_3SCl. Next, compound CF_3SCl undergoes electrophilic addition to (*E*)-cinnamylphenol **1a**, generating CF_3-substituted thiiranium ion intermediate **9a**, which is attacked by a phenolic hydroxyl group, and the desired 6-*endo* product **3a** will form after further deprotonation. The collaborative process determines the excellent diastereoselectivity of this reaction. When the R^2 group is an aromatic ring, the substrates have a strong electronic bias for thiiranium ion opening, which could account for the excellent regioselectivity. By contrast, the substrate with an alkyl group is unbiased, so the regioselectivity of **1n** is poor. For 1,1-disubstituted (whatever substituent) alkenes, the regioselectivity also results from the distinct electronic bias for the thiiranium ion opening.

In summary, we successfully developed a tandem trifluoromethylthiolation/cyclization of alkenes with phenols, which could provide a direct and modular approach to SCF_3-containing chromane and dihydrobenzofuran compounds for the first time. These two transformations feature simple and mild conditions and broad substrate toleration and are transition-metal-free. A variety of chromanes and dihydrobenzofurans were synthesized in moderate to good yields. We are investigating the catalytic enantioselective manner of this type of reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02744.

Experimental procedures, characterizations and analytical data of products, and NMR spectra (PDF)

Accession Codes

CCDC 2014660 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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