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Diastereoselective synthesis of CF₃-dihydrobenzofurans by [4+1] annulation of *in situ*-generated CF₃-*o*-quinone methides and sulfur ylides†

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An efficient and highly diastereoselective synthesis of CF₃-dihydrobenzofurans by the reaction of *in situ*-generated CF₃-*o*QMs in the presence of a base with sulphur ylides is put forward. The generality of the present developed method was well studied with diverse substrates to access the corresponding products in excellent yields. The highly reactive CF₃-*o*QM has been utilized first time for the annulation reaction.

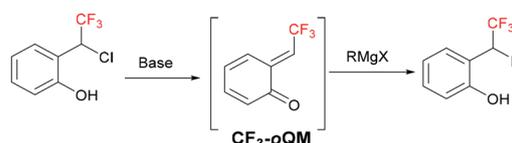
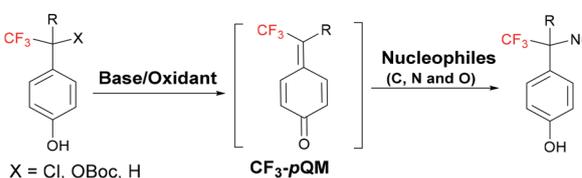
Fluorine or fluoroalkyl group-containing organic molecules occupy a vital position in drug discovery due to the unique impact of fluorine atom in terms of lipophilicity, permeability, and protein-binding.¹ In the last two years, 45% of FDA-approved small molecule pharmaceuticals are fluorinated, which denotes the importance of synthesizing fluorinated molecules, with special emphasis on medicinal chemistry, for the identification of new scaffolds. Among the fluorinated functional groups, the trifluoromethyl group has emerged as one of the imperative fluoroalkyl groups to enhance the bio-efficacy and metabolic stability of the corresponding motifs, which is needed for the identification of lead compounds.² Thus, finding new methods for the inclusion of the CF₃ group into novel biological entities is always desirable and challenging.

In this context, *ortho*-quinone methides (*o*QMs) are powerful reactive intermediates in synthetic organic chemistry to construct complex medium sized rings.^{3,4} Since *o*QM was first observed in 1907, it created a large impact in the synthesis of oxygen-containing benzannulated rings, which are of interest as photochromic materials and biologically active compounds.³ However, the reactions of *o*QMs were restricted to electron-rich substrates due to their high electrophilic nature. However, annulation reactions of diversely substituted *o*QMs (substitution on the exocyclic double bond) were explored extensively for the construction of oxygen-containing complex heterocyclic

structures;³ however, it is quite surprising that annulation reactions involving trifluoromethyl-substituted *o*QM (CF₃-*o*QM) have not been reported yet, especially because CF₃-*o*QM is like a gold mine and could open the realm to construct versatile fluorinated oxygen architectures.

Kato *et al.* were the first to report the nucleophilic addition of Grignard reagents and amines to the *in situ*-generated trifluoromethyl-substituted *ortho*- and *para*-quinone methides

Previous work:

 a) Nucleophilic additions of *in-situ* generated CF₃-*o*QM

 b) Nucleophilic additions of *in-situ* generated CF₃-*p*QM (Ref. 6)


Present work:

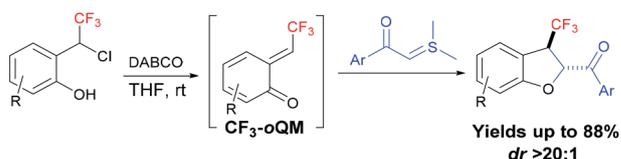
 c) First annulation reaction of *in-situ* generated CF₃-*o*QM


Fig. 1 Previous work vs. the present work.

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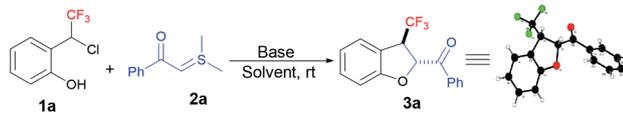
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(Fig. 1a).⁵ After that, there were no reports of this *in situ*-generated CF₃-oQM for any nucleophilic additions and annulations. In 2020, several papers were published on *in situ*-generated CF₃-*para*-quinone methides (CF₃-pQM) by quickly trapping them with different carbon and hetero atom-centered nucleophiles (Fig. 1b).⁶ Notably, Waser *et al.* demonstrated that CF₃-pQM has higher electrophilicity parameter (*E*) when compared to other substituted *para*-quinone methides.^{6d} Similarly, we hypothesized that CF₃-oQMs may also have higher “*E*” in comparison with the corresponding oQMs. Thus, the utilization of this highly reactive CF₃-oQM for annulation reactions is extremely challenging and equally desirable towards the synthesis of novel organofluorine molecules. In continuation of our research interest on oQM-based annulations and the development of new fluorinating methodologies,⁷ herein, we report for the first [4 + 1] annulation of *in situ*-generated CF₃-oQM with sulphur ylide to access trifluoromethyl-substituted dihydrobenzofurans with high diastereoselectivity.

The study was initiated by exposing 2-(1-chloro-2,2,2-trifluoroethyl) phenol **1a** and sulphur ylide **2a** to 1.2 equiv. of Cs₂CO₃ at room temperature in THF. Delightedly, the *in situ*-generated CF₃-oQM was successfully trapped with sulphur ylide to afford the corresponding trifluoromethyl-substituted dihydrobenzofuran **3a** in 80% yield (Table 1, entry 1) with high diastereoselectivity. The investigation of a variety of solvents revealed that THF was the optimal solvent for the [4 + 1] annulation reaction (Table 1, entries 2–5). A quick survey was then conducted with different bases, and organic base DABCO was found to be the best to deliver **3a** in 93% yield (Table 1, entries 6–9). The control experiment showed that the reaction in the absence of a base failed to produce the [4 + 1] annulation product (Table 1, entry 10). The reaction conditions in entry 6 (Table 1) were optimal and gave the product in 93% yield with >20 : 1 dr. The configuration of the obtained product was confirmed as *trans* from the X-ray crystallographic structure of compound **3a** (CCDC 2023269).

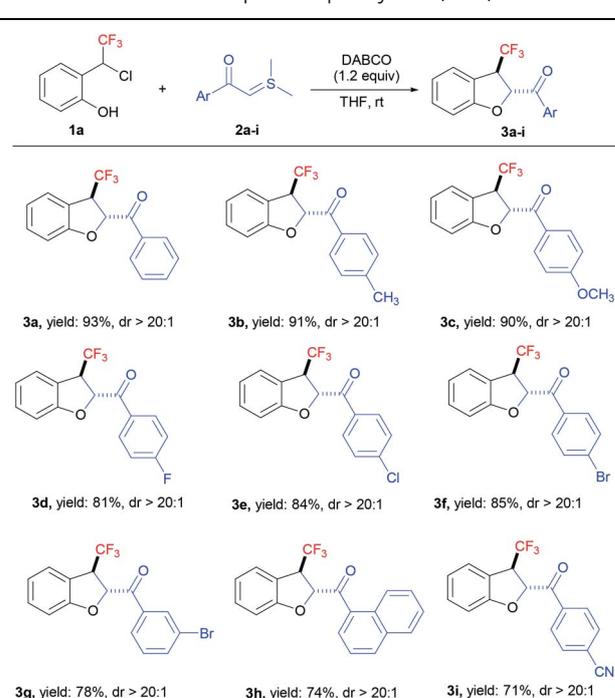
Table 1 Optimization of reaction conditions^a


Entry	Base	Solvent	Yield ^b	dr ^c
1	Cs ₂ CO ₃ (1.2 equiv.)	THF	80%	>20 : 1
2	Cs ₂ CO ₃ (1.2 equiv.)	DCM	62%	>20 : 1
3	Cs ₂ CO ₃ (1.2 equiv.)	CH ₃ CN	51%	>20 : 1
4	Cs ₂ CO ₃ (1.2 equiv.)	Toluene	Trace	—
5	Cs ₂ CO ₃ (1.2 equiv.)	MeOH	Trace	—
6	DABCO (1.2 equiv.)	THF	93%	>20 : 1
7	DBU (1.2 equiv.)	THF	65%	>20 : 1
8	Et ₃ N (1.2 equiv.)	THF	Trace	—
9	K ₂ CO ₃ (1.2 equiv.)	THF	45%	>20 : 1
10	—	THF	NR	—

^a Reaction conditions: **1a** (0.6 mmol), **2a** (0.5 mmol), base (0.6 mmol) in solvent (2 mL) at rt. ^b Isolated yields. ^c dr was determined by ¹⁹F NMR.

With the determination of optimized conditions, the substrate scope for the [4 + 1] annulation reaction was scrutinized by the reaction of compound **1a** with a broad array of sulphur ylides (Table 2). First, the reaction of electron-rich substrates **2b** (CH₃) and **2c** (OCH₃) afforded CF₃-dihydrobenzofurans **3b** (91%) and **3c** (90%) in very good yields, respectively. The halogen-containing sulphur ylides **2d**, **2e**, and **2f** (F, Cl, and Br) also proceeded smoothly to furnish the required products **3d–f** in excellent yield (up to 85%) and we observed a slight improvement in the yield from fluoro to bromo substrates. Further, the reaction of naphthalene-derived sulphur ylide **2h** also participated well in the reaction to deliver the required CF₃-dihydrobenzofuran **3h** in 74% yield. The electron-deficient substrate **2i** (CN) also underwent the [4 + 1] annulation reaction very well to give CF₃-dihydrobenzofuran **3i** in 71% yield. CF₃-oQM generated *in situ* from compound **1a**, was trapped with a wide range of sulphur ylides without any effect on the substituents to yield the required trifluoromethyl-substituted dihydrobenzofurans in good yields with high diastereoselectivity (dr > 20 : 1).

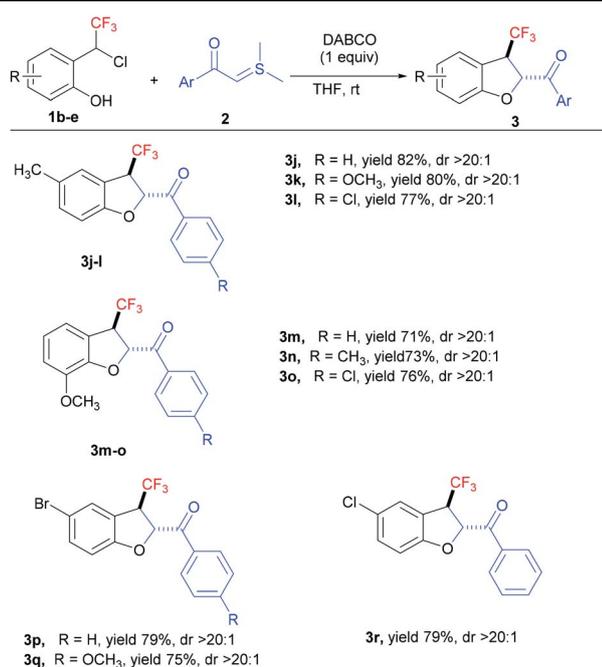
Next, we investigated the substrate scope with respect to *ortho*-hydroxy-CF₃-benzyl chlorides **1b–d** to delineate the generality of the present [4 + 1] annulation under the standard reaction conditions (Table 3). The reactions with CF₃-benzyl chlorides having electronically dissimilar groups as substituents, proceeded well to furnish the desired products in good yields. The reaction of methyl (**1b**)- and methoxy (**1c**)-substituted CF₃-benzyl chlorides with a variety of sulphur ylides delivered the corresponding CF₃-dihydrobenzofurans **3j–o** in

Table 2 The substrate scope of sulphur ylides (**2a–i**)^a

^a Reaction conditions: **1** (0.6 mmol), **2** (0.5 mmol), DABCO (0.6 mmol), THF (2 mL). Isolated yield. dr was determined by ¹⁹F NMR.



Table 3 The substrate scope of *ortho*-hydroxy CF₃-benzyl chloride (1b–e)

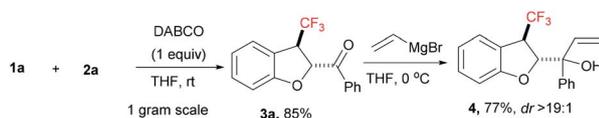


^a Reaction conditions: **1** (0.6 mmol), **2** (0.5 mmol), DABCO (0.6 mmol), THF (2 mL) at rt. Isolated yield. dr was determined by ¹⁹F NMR.

excellent yields with good diastereoselectivity. Further, CF₃-oQMs generated from the bromo (**1d**)- and chloro (**1e**)-substituted CF₃-benzyl chlorides were also successfully trapped to deliver the desired products **3p–r** in good yields (up to 79% with >20 : 1 dr).

To determine the synthetic utility of the present transformation, we executed a gram scale [4 + 1] annulation reaction of compound **1a** with **2a** under applied reaction conditions, which gave CF₃-dihydrobenzofuran **3a** in 85% yield (Scheme 1). Later, we exposed compound **3a** to vinyl magnesium bromide at 0 °C in THF to furnish the corresponding alcohol **4** in good yield with excellent diastereoselectivity (dr > 19 : 1).

The plausible reaction mechanism for the base-catalyzed [4 + 1] annulation of *ortho*-hydroxy-CF₃-benzyl chloride **1a** with compound **2a** is depicted in Fig. 2. Initially, CF₃-oQM was generated in the presence of a stoichiometric amount of base.^{5,8} This highly electrophilic CF₃-oQM undergoes nucleophilic addition with compound **2a** to form a new C–C bond in **TS I**; the diastereoselectivity in **TS I** arises due to the favourable steric repulsions between the trifluoromethyl group and sulphur ylide, resulting in the final compound with *trans* configuration. Finally, the intramolecular nucleophilic substitution in **TS I** by



Scheme 1 The synthetic transformation of compound **3a**.

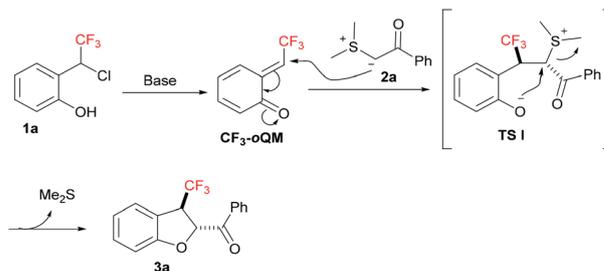


Fig. 2 The plausible reaction mechanism.

oxygen with a sulphonium moiety furnishes the desired CF₃-dihydrobenzofuran **3a** in good yield.

Conclusions

In conclusion, we demonstrated a novel method for the synthesis of CF₃-dihydrobenzofurans **3** via [4 + 1] annulation of *ortho*-hydroxy-CF₃-benzyl chlorides **1** with sulphur ylides **2** under basic conditions in good yields (up to 93%) and diastereoselectivities (>20 : 1). The highly reactive CF₃-oQM, due to the electron-withdrawing nature of the CF₃ group, was trapped successfully in the present [4 + 1] annulation. This annulation is the first example for the trapping of trifluoromethyl-substituted oQM. The core skeleton of dihydrobenzofuran obtained in the present protocol has received huge attention in literature,⁹ and CF₃ present at a strategic position may improve the biological activities of molecules tremendously. Further, the expansion of annulation reactions *via in situ*-generated CF₃-oQMs is in progress in our laboratory to construct versatile trifluoromethyl-substituted oxygen-containing heterocycles.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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