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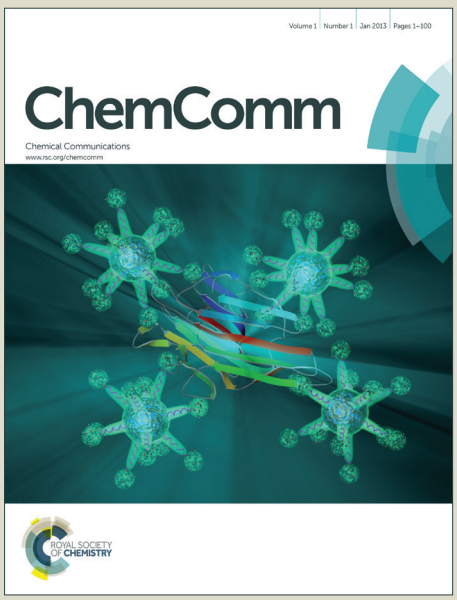

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CF_3-Substituted semisquarate: A pluripotent building block for the divergent synthesis of trifluoromethylated functional molecules†

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The first synthesis of a CF_3-substituted semisquarate was accomplished via nucleophilic trifluoromethylation using CF_3SiMe_3 and subsequent rhenium-catalyzed allylic alcohol rearrangement. The short-step skeletal-divergent synthesis of trifluoromethylated functional molecules was successfully achieved using the CF_3-substituted semisquarate as the platform.

Strategic introduction of a CF_3 group into biologically active molecules has gained increasing importance in drug development.[1] This is because the CF_3 group can dramatically modulate the biological activities of drug molecules:[2] the high lipophilicity of the CF_3 group improves membrane permeability, and the electrostatic/hydrophobic interactions of the CF_3 group also increase the binding ability of drugs with target receptors. Therefore, new methods have been sought for the efficient synthesis of highly valuable trifluoromethylated functional molecules.[3]

The synthesis of trifluoromethylated functional molecules has been conducted according to two major strategies.[3] One is the building-block approach, which utilizes a small trifluoromethylated starting material to assemble the target molecule.[4] Although this approach has long played a central role in synthesizing trifluoromethylated functional molecules from readily available and inexpensive precursors containing a CF_3 group, lengthy multistep synthetic operations are required and hence, it is less atom- and step-economically efficient. The alternative strategy is late-stage trifluoromethylation, which utilizes recently developed mild and selective trifluoromethylation techniques.[5] Although this method enables streamlining of the overall synthetic scheme, expensive reagents and/or promoters are often required and the scope of each trifluoromethylation reaction is confined to a specific class of substrates, lacking skeletal diversity.

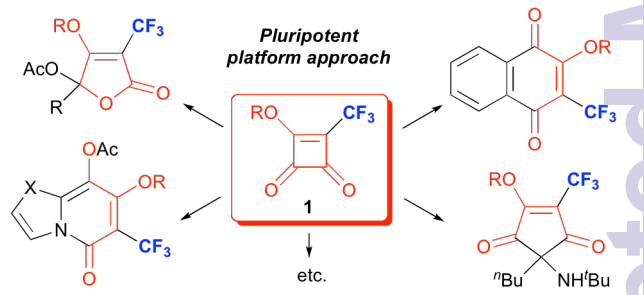

Fig. 1 Novel skeletal-divergent synthetic strategy using CF_3-substituted semiaquarate **1** as a pluripotent platform.

Thus, we envisioned that a strained small-ring compound equipped with a CF_3 group would serve as a novel pluripotent platform for a short-step, skeletal-divergent synthesis of trifluoromethylated functional molecules (Fig. 1). Modern drug-discovery campaigns rely on high-throughput screening of diverse molecular libraries. In this vein, the synthetic chemistry community has focused on diversity-oriented synthetic methodologies to expand the chemical space for the exploration of novel drug leads.[6] However, diversity-oriented synthesis of trifluoromethylated compounds is currently underdeveloped. Herein, we present our endeavors to develop CF_3-substituted semisquarate **1** as a novel trifluoromethylated small-ring platform for the verasatile skeletal-divergent synthesis of CF_3-containing functional molecules.

To realize this unprecedented strategy, we focused on the synthesis of CF_3-substituted semisquarates **1** from semisquarates **3**. This is because various ring transformations of semisquarates have been developed to provide viable routes to valuable functional molecules and complex natural products.[7,8] Thus, the efficient synthesis of **1** would open up extremely feasible routes to diverse trifluoromethylated functional molecules that are unavailable with other methods. According to the reports,[7] the desired **1** can be obtained from 4-hydroxycyclobutenones **2** (E = H) by allylic alcohol rearrangement followed by extrusion of alcohols (Scheme 1). In turn, precursors **2** can be prepared by nucleophilic trifluoromethylation of readily available squarates **3**. Although

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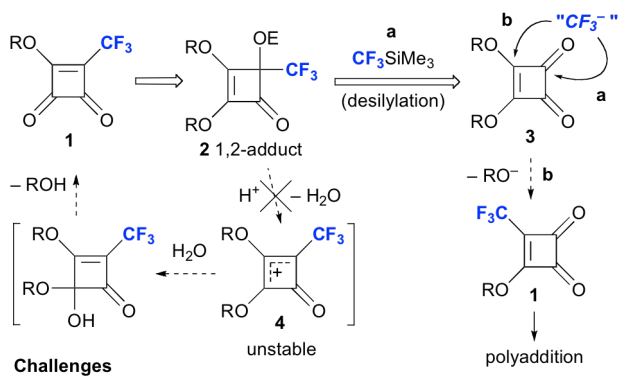
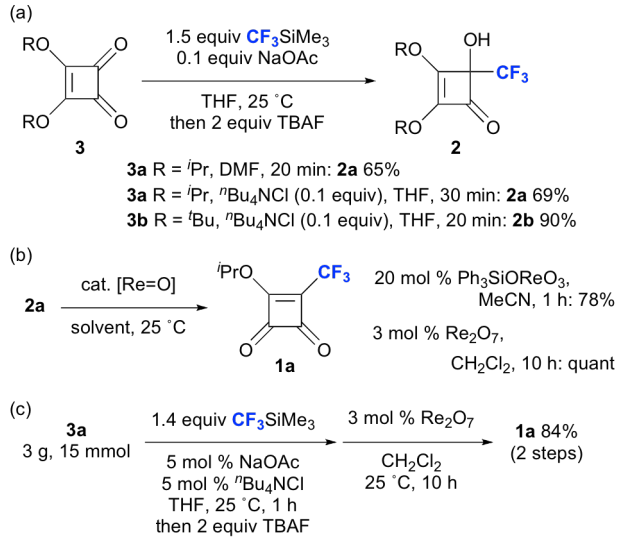


Scheme 1 Challenges in the synthesis of CF_3-semisqauarate **1a**.

organolithium or Grignard reagents have been conventionally used for the derivatization of squarates, the corresponding trifluoromethylation has not been reported. Thus, we selected commercially available CF_3SiMe_3 (Ruppert–Prakash reagent) as the trifluoromethylation agent because it is reported to enable selective nucleophilic trifluoromethylation of various carbonyl compounds under mild reaction conditions.[9] However, the 1,2- vs 1,4-addition selectivity (path **a** vs. **b**, Scheme 1) is highly important for trifluoromethylation of **3** with a crossed vinylogous ester system: 1,4-addition directly produces **1**, which has a higher reactivity than **3**, resulting in undesirable polyaddition. Moreover, the transposition of the hydroxyl group of **2** is anticipated to be infeasible under acidic conditions due to the strong electron-withdrawing effect of the CF_3 group hampering formation of a cationic intermediate, although acid-catalyzed transformation of 4-hydroxy-2-cyclobutenones is a general method to provide semisquarates.[7] With these concerns in mind, we investigated the synthesis of CF_3-semisquarate **1**.

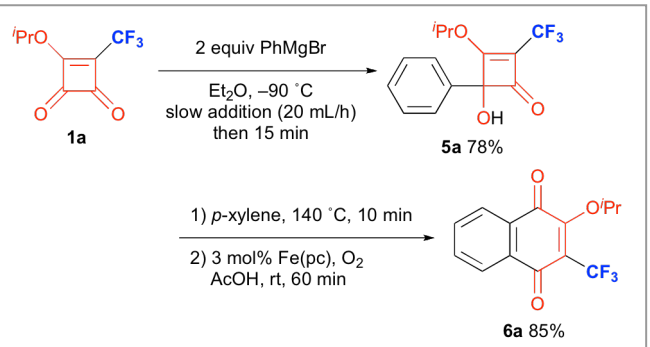


Scheme 2 Trifluoromethylation of suquarates **3** with CF_3SiMe_3 and rhenium-catalyzed transformation of **2a** into **1a**.

At the outset of this study, the trifluoromethylation of **3** with CF_3SiMe_3 was investigated (Scheme 2a). Mukaiyama and co-workers previously reported that trifluoromethylation of aldehydes efficiently proceeded in DMF at 0 ˚C with an acetate salt promoter (5 mol %).[10] They also showed that the same reaction could be performed in THF with comparable efficiency when $^nBu_4NOAc$ was used as the promoter. This method was expected to be applicable to squarates. Thus, the desired product **2a** was obtained in 65% yield after desilylation with tetrabutylammonium fluoride (TBAF) when commercially available diisopropyl squarate **3a** was treated with CF_3SiMe_3 (1.5 equiv) and NaOAc (0.1 equiv) in DMF at 25 ˚C for 20 min. Because a readily removable solvent was desired for further studies (see below), we conducted the trifluoromethylation reaction in THF. In the presence of NaOAc (0.1 equiv) and $^nBu_4NCl$ (0.1 equiv), **3a** reacted with CF_3SiMe_3 in THF for 30 min to afford **2a** in a comparable yield (69%). Moreover, di(*tert*-butyl) ester **3b** also underwent trifluoromethylation under the same conditions to afford **2b** in a higher yield (90%). The successful trifluoromethylation of **3** is quite surprising because trifluoromethylation of vinylogous esters using CF_3SiMe_3 was reported to be unsuccessful.[11]

The problematic allylic rearrangement of 4-hydroxycyclobutenones **2** was investigated next. As anticipated, acidic conditions using aqueous HCl, triflic acid, trifluoroacetic anhydride/pyridine, $TiCl_4$, or $Ti(O^iPr)_4$ failed to convert **2a** into **1a**. Therefore, we turned to transition-metal oxo-complex catalysts because they promote transposition of allylic alcohols without the intermediacy of an unfavorable allylic cation intermediate. Although the use of vanadium and molybdenum catalysts ($VO(OSiPh_3)_3$ (10 mol %)[12a] or MoO_2Cl_2/NaO^tBu (10 mol %)[12b] in CH_2Cl_2 at 25 ˚C) resulted in no reaction, rhenium-based catalysts exhibited remarkable catalytic activity.[13] Upon treatment with $Ph_3SiOReO_3$ (2 mol %) in MeCN at 25 ˚C, **2a** was completely consumed within 1 h and the desired semisquarate **1a** was isolated in 78% yield by distillation (Scheme 2b). Moreover, **1a** was quantitatively obtained when Re_2O_7 (3 mol %), the precursor of $Ph_3SiOReO_3$, was used as the catalyst in CH_2Cl_2, albeit with a longer reaction time (10 h).‡ In striking contrast, di(*tert*-butyl) ester **2b** decomposed under the same reaction conditions. To streamline the preparation of **1a**, we performed the trifluoromethylation of **3a** and subsequent allylic rearrangement in one pot, without purification of **2a**, and **1a** was obtained in 84% yield over two-steps on a 3 g scale (Scheme 2c).

With the preparative method of **1a** established, we demonstrated the potential of **1a** for the synthesis of trifluoromethylated functional molecules. First, we focused on the synthesis of trifluoromethylated quinones because their typical synthesis requires a multistep process and/or an expensive trifluoromethylation agent.[14] Moreover, despite their biological importance, the scope of the previous synthesis is confined to relatively simple benzo- and naphthoquinones and there is no example of the synthesis of heterocyclic derivatives to the best of our knowledge. The transformation starts with the addition of an organometallic



Scheme 3 Synthesis of trifluoromethylated naphthoquinone **6a** from **1a**.

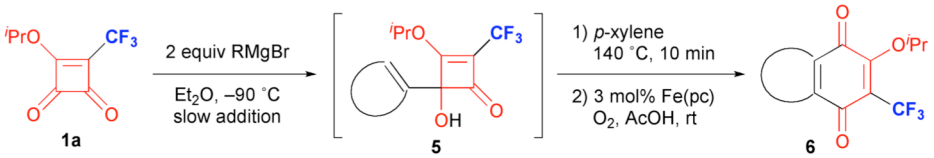
reagent to afford 4-hydroxy-2-cyclobutenones (Scheme 3). Although aryllithium reagents have been generally used for this purpose,[8] the use of milder Grignard reagents under carefully controlled conditions was required to suppress overaddition due to the string electrophilicity of the CF_3-substituted cyclobutenedione system. Thus, PhMgBr (2.0 equiv) was added to a solution of **1a** in Et_2O via a syringe pump (20 mL/h) for 30 min at –90 ˚C and selectively afforded **5a** in 78% yield. Thermolysis of **5a** in *p*-xylene at 140 ˚C for 10 min, followed by aerobic oxidation in the presence of an iron phthalocyanine (pc) complex (3 mol%)[15] afforded the desired naphthoquinone **6a** in 85% yield.‡

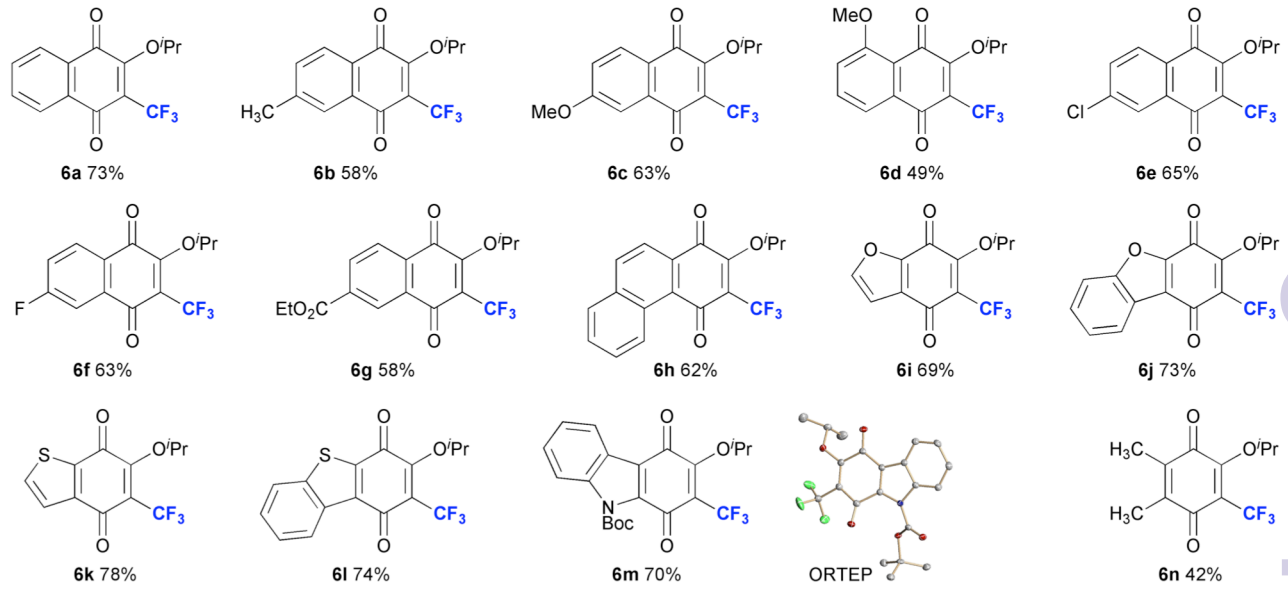
The scope of the quinone synthesis is summarized in Table 1. To streamline the synthetic procedure for quinones **6**, addition of the Grignard reagent to **1a** and subsequent ring expansion and aerobic oxidation were performed in one pot without purification of hydroxycyclobutenone **5**. As a result, naphthoquinones **6a–6g** were obtained in 49–73% yields ov… three steps. Both electron-donating and electron-withdrawin… groups were compatible with the reaction conditions. … particular, a reactive ester functional group was tolerate… this three-step procedure. Phenanthrenequinone **6h** could als… be synthesized by using 2-naphthyl Grignard reagent. A… significance of this method is the applicability to heterocycl… systems. Thus, heterocyclic quinones **6i–6m**, containing furan, benzofuran, thiophene, benzothiophene, and protected indo… rings, were obtained in good yields. Among these heterocyclic quinones, **6m** is particularly interesting as a possible intermediate for the synthesis of a trifluoromethylated analog of carbazomycin G.[16] A good quality single crystal of **6m** wa… obtained, and X-ray diffraction analysis was performed … confirm that the initial Grignard reagent added to the mor… electrophilic carbonyl group conjugated with the CF_3 grou… (see Supplementary Information). Benzoquinone **6n** was … obtained using an alkenyl Grignard reagent, albeit in a moderate yield.

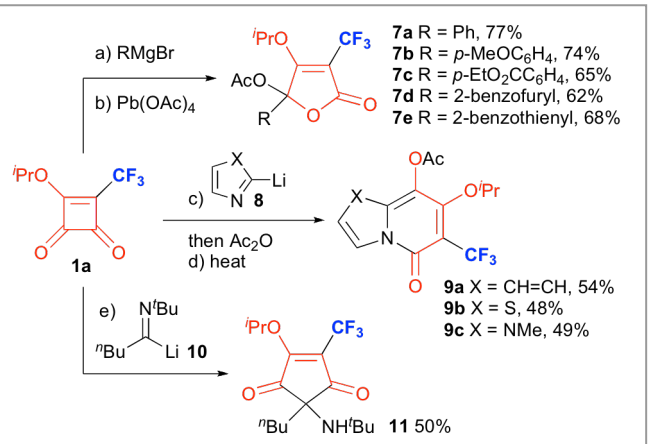
Having elucidated the feasibility of **1a** as a platform for the synthesis of trifluoromethylated quinones, we carried … other ring-expansion reactions to demonstrate the skelet… diversity of the manifolds available from **1a**. Thus, the Grignard addition products were further treated with $Pb(OAc)_4$ (2 equi… in toluene at room temperature.[17] As a result, oxidative radical ring expansion efficiently proceeded to afford tetronate derivatives**7a–e** in 62–77% overall yields (Scheme 4).‡

In addition to Grignard reagents used above, organolithium… reagents **8** derived from heteroaromatic compounds could b… used for the transformation of **1a** (Scheme 4). For example, 2

Table 1 One-pot synthesis of quinones **6a–n** and hydroquinone **8** from **1a**.







Scheme 4 Synthesis of trifluoromethylated naphthoquinone **6a** from **1a**. (a) RMgBr (2 equiv), Et_2O, –90 ˚C, slow addition; (b) $Pb(OAc)_4$ (2 equiv), toluene, rt, 1 h; (c) **8** (1.1 equiv), Et_2O, –90 ˚C, then Ac_2O (2.2 equiv); (d) *p*-xylene, 100 ˚C, 0.5 h; (e) **10** (1.0 equiv), Et_2O, –78 ˚C, 0.5 h, then aq NH_4Cl.

pyridyllithium (1.1 equiv) was added to **1a** at –90 ˚C, then workup with acetic anhydride afforded 4-acetoxycyclobutenone, which was directly subjected to thermolysis in *p*-xylene at 100 ˚C for 30 min without isolation.[18a] As a result, 4*H*-quinolizin-4-one **9a** was successfully obtained in 54% overall yield.‡ Similarly, the use of lithiated thiazole and *N*-methylimidazole delivered 5*H*-thiazolo[3,2-*a*]pyridine-5-one **9b** and 1-methylimidazo[1,2-*a*]pyridine-5(1*H*)-one **9c** in 48% and 49% yields, respectively. On the other hand, addition of an imidoyl lithiate **10** derived from *tert*-butylisonitrile and *n*-butyllithium to **1a** at –78 ˚C for 30 min[18b] and quenching with aqueous NH_4Cl afforded 2-amino-4-cyclopentene-1,3-dione **11** in 50% yield.‡

In conclusion, we have successfully achieved the efficient synthesis of an unprecedented CF_3-substituted semisquarate by (1) nucleophilic silyltrifluoromethylation of commercially available diisopropyl squarate, and (2) oxorhenium-catalyzed transformation of the resultant hydroxycyclobutenone to the targeted CF_3-substituted semisquarate. Moreover, skeletal-diversified ring transformations of the CF_3-substituted semisquarate were successfully implemented by selective addition of Grignard and organolithium reagents at low temperatures and subsequent ring expansion of the intermediate products. Consequently, a variety of CF_3-substituted functional molecules including quinones, butenolides, nitrogen heterocycles, and aminocyclopentenedione were synthesized in a short synthetic sequence.

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‡ Plausible mechanisms are provided in ESI.

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