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Electrophilic Derivatization of Trifluoromethyl-Substituted Semisquarate Using Unsaturated Organosilanes and Subsequent Ring Transformations

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Abstract. To extend the synthetic potential of trifluoromethyl-substituted semisquarate (CF_3-semisquarate) previously synthesized by us as a pluripotent building block, its electrophilic derivatization was investigated. The electrophilic addition of allylic silanes and silyl enolates to CF_3-semisquarate afforded the corresponding 4-hydroxycyclobutenones. Subsequent ring expansion of these products *via* thermolysis or oxidation using lead tetraacetate afforded trifluoromethylated bicyclo[3.2.0]heptenones or (*Z*)-γ-alkylidenetetronates.

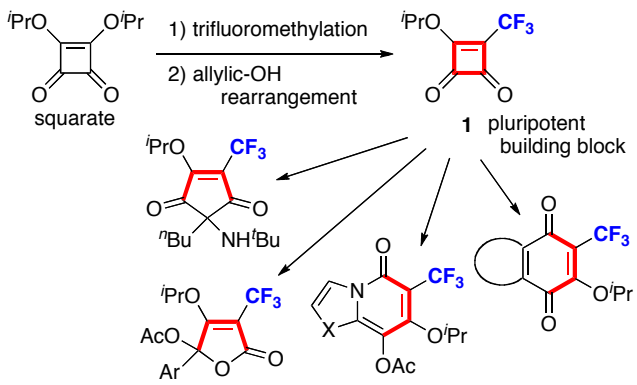
Keywords: fluorine; cyclobutenedione; ring expansion; bicycloalkenone; tetronate

Introduction

Introduction of a fluorine atom into organic compounds improves their original bioavailability and bioactivity.[1] Approximately 20% of commercial pharmaceuticals contain fluorinated groups.[2] A limited number of CF_3-substituted pharmaceuticals is available, and most of them have a CF_3 group on a relatively simple structural unit such as (hetero)aromatics and alkenes.[2] The introduction of a CF_3 group into more complex structures has been extensively studied to expand the diversity of CF_3-substituted molecules.[3]

CF_3-substituted functional molecules are synthesized by two major strategies. One is the traditional building-block method,[4] and the other is the late-stage trifluoromethylation method.[3] Because both the strategies have some advantages and disadvantages, they have been used complement one another. For example, the building-block method can utilize various CF_3-substituted small molecules as inexpensive starting materials; however, relatively tedious synthetic transformations are required to access the final target compounds. On the other hand, late-stage trifluoromethylation reactions enable the streamlined synthesis of the target compounds; however, expensive trifluoromethylation reagents and/or harsh reaction conditions are required. Controlling the selectivity of trifluoromethylation is also a critical issue. In either way, the availability of CF_3-substituted molecules is still largely limited.

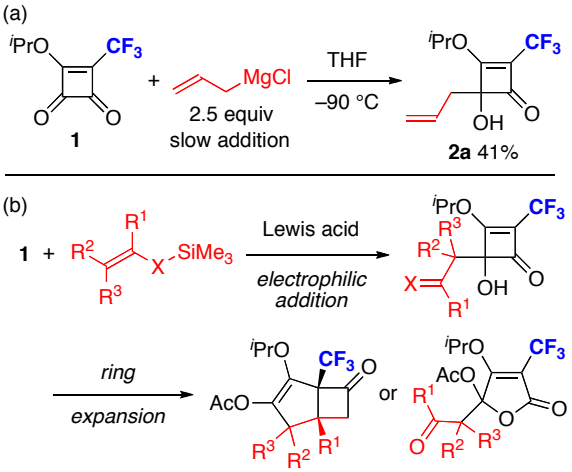
To enable short-step constructions of hitherto inaccessible CF_3-substituted functional molecules, we previously developed a pluripotent building-block strategy (Scheme 1).[5] CF_3-semisquarate **1** was concisely synthesized from commercially available diisopropyl squarate *via* trifluoromethylation using inexpensive Ruppert–Prakash reagent (Me_3SiCF_3) and subsequent rhenium-catalyzed allylic-OH rearrangement. Furthermore, CF_3-semisquarate **1** was transformed into trifluoromethylated quinones, tetronates, fused pyridones, and cyclopentenediones by various ring-expansion reactions.



Scheme 1. Synthesis of CF_3-semisquarate **1** and its ring expansion products.

Next, we focused on the synthesis of CF_3-substituted bicyclo[3.2.0]heptenones *via* the allylation of **1** and subsequent thermal ring expansion. Compound **1** was allylated using allylmagnesium chloride following the previous report (Scheme 2a).[6] However, the desired adduct **2a** was obtained in an unsatisfactory yield. Because this result can be ascribed to the higher

electrophilicity of **1**, we assumed that the Hosomi–Sakurai-type electrophilic allylation using an allylsilane works well for **1**.[7] Herein, we report the electrophilic derivatization of **1** using allylic silanes and silyl enolates and subsequent ring expansions of the obtained products into CF_3-substituted bicyclo[3.2.0]heptenones and tetronates (Scheme 2b).

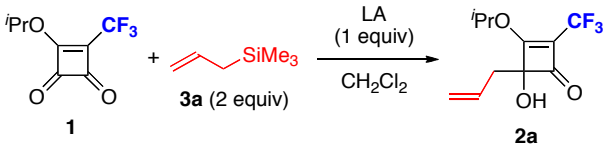


Scheme 2. (a) Addition of allylmagnesium chloride to CF_3-semisquarate **1**, and (b) ring transformations of **1** by the electrophilic addition of unsaturated organosilanes.

Results and discussion

Hosomi–Sakurai-type allylation of CF_3-semisquarate 1 and subsequent transformations of products. At the outset, Lewis acid (LA)-promoted electrophilic allylation was investigated under various reaction conditions (Table 1). In the presence of $ZnCl_2$ (1.0 equiv), a mixture of **1** and allyltrimethylsilane **3a** (2.0 equiv) in CH_2Cl_2 was stirred at 40 °C, but the allylation failed (entry 1). Then, several LAs such as $TiCl_4$, BF_3•OEt_2, and $SnCl_4$ were tested at appropriate temperatures to obtain the desired allylation adduct **2a**. When a strong LA, $TiCl_4$, was used, **1** was consumed in 20 min at –90 °C (entry 2). After the purification by silica gel chromatography, **2a** was obtained in 72% yield. A comparable yield of **2a** was obtained using a milder LA, BF_3•OEt_2, at 25 °C, even though a much longer reaction time of 15 h was required. The best result was obtained when $SnCl_4$ was used as the LA. The reaction was performed at –78 °C for 10 min, and then at 0 °C for 1 h. Because the trimethylsilyl ether of **2a** was observed, the crude mixture was desilylated using silica gel, affording **2a** in 94% yield (entry 4). Reducing the amount of **3a** to 1.5 equiv afforded **2a** in a comparable yield (entry 5). However, a further decrease in the loading of **3a** was found detrimental (entry 6). Moreover, the yield of **2a** decreased significantly when the loading of $SnCl_4$ was reduced to 30 mol % (entry 7). Thus, the conditions shown in entry 5 were used for further investigation.

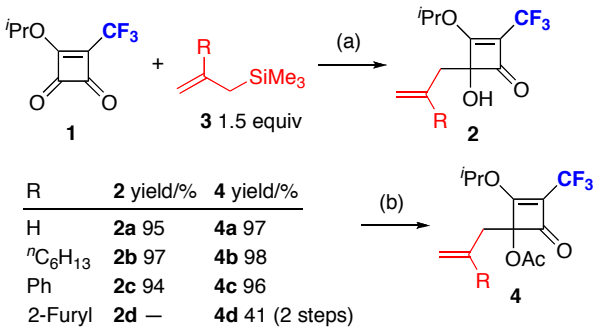
Table 1. Optimization of reaction conditions for the electrophilic allylation of **1**.



Entry	LA	Conditions	Yield (%)
1	$ZnCl_2$	40 °C, 20 h	—
2	$TiCl_4$	–90 °C, 20 min	72
3	BF_3•OEt_2	25 °C, 15 h	71
4	$SnCl_4$	–78 °C, 10 min; 0 °C, 1 h	94
5 [a]	$SnCl_4$	–78 °C, 10 min; 0 °C, 1 h	95
6 [a]	$SnCl_4$	–78 °C, 10 min; 0 °C, 1 h	80
7 [b]	$SnCl_4$	–78 °C, 10 min; 0 °C, 3 h	71

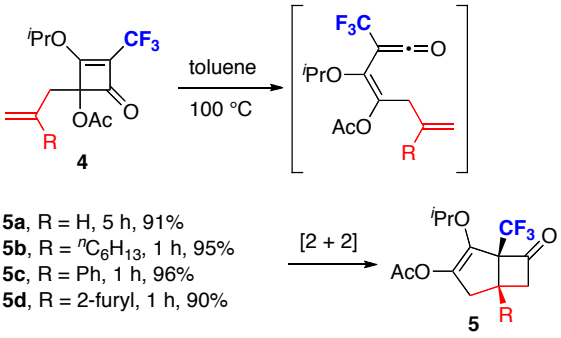
[a] **3a** (1.5 equiv for entry 5 and 1.1 equiv for entry 6). [b] $SnCl_4$ (0.3 equiv).

Next, the scope of β-substituted allylic silanes was investigated (Scheme 3). The electrophilic allylation using allylic silanes **3b** and **3c** bearing an alkyl or phenyl substituent on the β position, respectively, smoothly proceeded with comparable efficiency as **3a**. In contrast, the use of β-(2-furyl)allylic silane **3d** in the presence of $SnCl_4$ formed a complex product mixture. This result is ascribed to the instability of the 2-furyl group under acidic conditions. Therefore, a milder LA, BF_3•OEt_2 (2 equiv), was used at room temperature. Although the desired product **2d** was detected in the crude reaction mixture, its isolation was hampered by its instability. Therefore, the allylation product was isolated after the acetylation (see below).



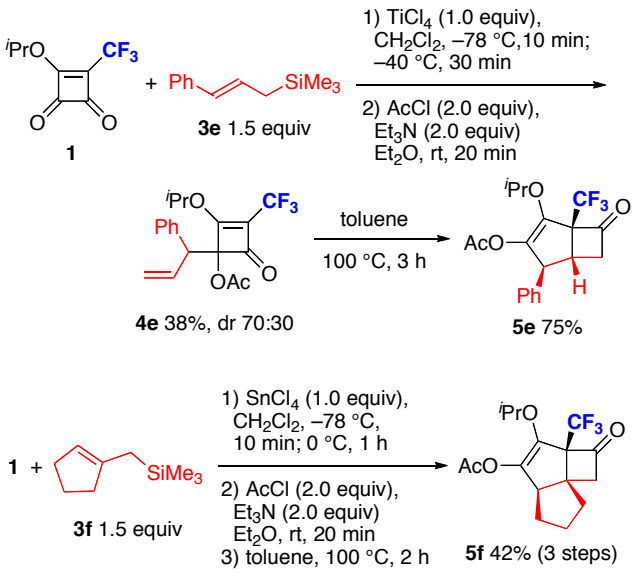
Scheme 3. Electrophilic allylation of **1** and acetylation of the resulting products **2a–d**. Conditions: (a) **3** (1.5 equiv), $SnCl_4$ (1.0 equiv), CH_2Cl_2, –78 °C for 10 min, then 0 °C for 1 h [for **3d**, BF_3•OEt_2 (2.0 equiv), rt, 10 min]; SiO_2, (b) AcCl (2.0 equiv), Et_3N (2.0 equiv), Et_2O, rt, 20 min [for **4d**, 4.0 equiv of AcCl and Et_3N was used].

Next, the ring expansion of allylation products was investigated. Moore and co-workers reported the synthesis of bicyclo[3.2.0]heptenones by the thermal ring opening of 4-allyl-4-hydroxycyclobutenones *via* intramolecular [2 + 2] cycloaddition.[6] However, unprotected **2a** was subjected to thermolysis in toluene at 100 °C, resulting in a complex product mixture. Thus, allylation products **2** were acetylated by treating with acetyl chloride (2.0 equiv) and triethylamine (2.0 equiv) in Et_2O at room temperature (Scheme 3). The acetylation products **4a–c** were obtained in excellent yields. Moreover, crude **2d** was acetylated, affording **4d** in 41% yield over two steps. The obtained product, 4-allyl-4-acetoxycyclobutenones **4a**, was subjected to thermolysis in toluene at 100 °C for 5 h, affording the desired bicyclo[3.2.0]heptenone **5a** in 91% yield (Scheme 4). Notably, the ring expansion of **4b–d** bearing β-substituted allyl groups proceeded in a shorter reaction time (1 h), diastereoselectively affording the corresponding products **5b–d** in high yields.



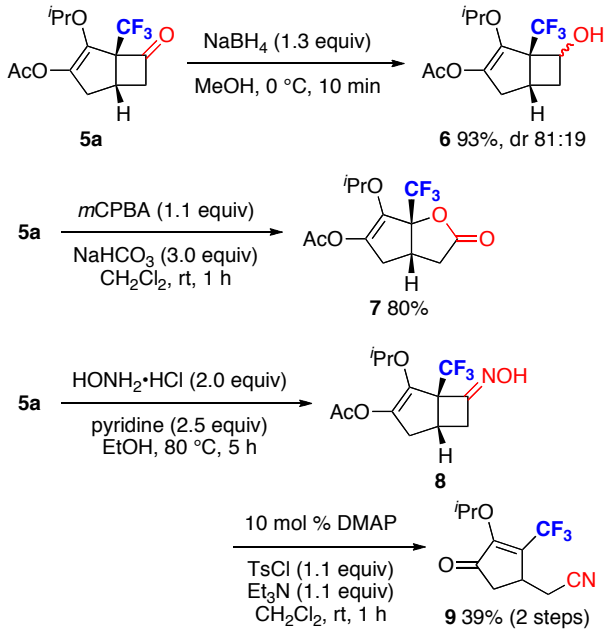
Scheme 4. Synthesis of bicyclo[3.2.0]heptenones **5a–d** by the thermal ring expansion of cyclobutenones **4a–d**.

The abovementioned optimized allylation procedure was found to be inefficient for γ-phenyl-substituted allylsilane **3e**. Nevertheless, the use of a strong LA, $TiCl_4$, enabled the electrophilic addition of **3e** (Scheme 5). Thus, in the presence of $TiCl_4$ (1.0 equiv), the reaction of **1** with **3e** (1.5 equiv) in CH_2Cl_2 at –78 °C for 10 min and then at –40 °C for 30 min produced **2e**. Although it was difficult to separate **2e** from the byproducts, the corresponding 4-acetoxycyclobutenone **4e** was isolated as a diastereomeric mixture (dr 70:30) in 38% yield after the acetylation. Subsequently, the thermolysis of **4e** in toluene at 100 °C for 3 h afforded bicyclo[3.2.0]heptenone **5e** as the exclusive diastereomer in 75% yield.[8] On the other hand, the reaction with cyclopentenylmethylsilane **3f** proceeded using $SnCl_4$. However, the expected product **2f** and its acetylation product **4f** were inseparable from the byproducts. Therefore, crude **4f** was directly applied to thermal ring expansion, affording the desired tricyclic product **5f** in 42% yield over three steps.

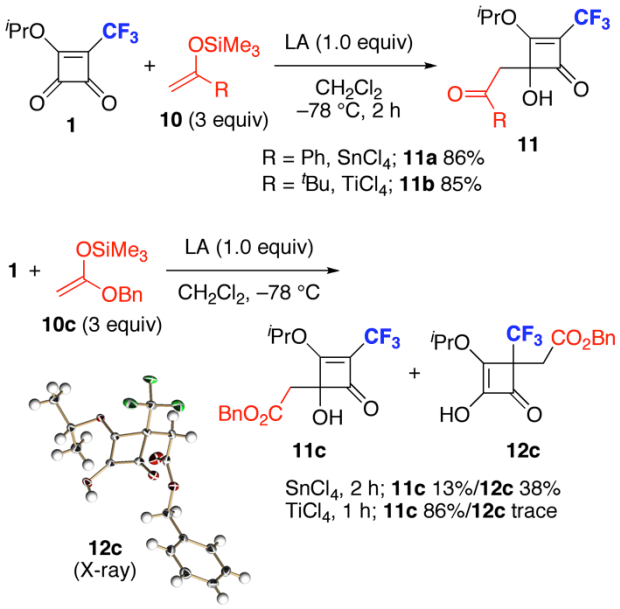


Scheme 5. Reactions using γ-substituted allylic silanes **3e** and **3f** and subsequent ring expansion.

The obtained bicyclo[3.2.0]heptenones **5** have a synthetically useful cyclobutanone ring, which can be further transformed by taking advantage of the ring strain. To achieve this goal, selective reactions are required to avoid unfavorable side reactions involving the reactive 2-alkoxy enol acetate moiety. Thus, the reactivity of **5a** with various anionic nucleophiles such as lithium phenylacetylide, vinylmagnesium bromide, trimethylsilyldiazomethane, allylboronic acid pinacol ester, and sulfonium ylide ($Me_3SO^+I^-$/NaH) was investigated. However, these nucleophiles showed negligible reactivity, resulting in the recovery of **5a**, even though the reduction of **5a** using $NaBH_4$ smoothly afforded **6** in 93% yield with a diastereomeric ratio of 81:19 (Scheme 6). These results indicate that the adjacent electron-rich CF_3 group effectively blocks the access of anionic nucleophiles to the carbonyl group of **5a** from the convex face, and only the smallest anionic nucleophile, hydride, can attack the carbonyl group from both the convex and concave faces. On the other hand, the treatment of **5a** with *m*-chloroperbenzoic acid at ambient temperature afforded the expected Baeyer–Villiger oxidation product **7** as a single regioisomer in 80% yield.[9] Furthermore, the reaction of **5a** with hydroxylamine at 80 °C produced oxime **8**. Because the purification of oxime **8** was difficult, crude **8** was directly treated with *p*-toluenesulfonyl chloride (TsCl) and triethylamine in the presence of 10 mol % 4-(*N*,*N*-dimethylamino)pyridine (DMAP) at ambient temperature, affording the Beckmann fragmentation product **9** in 39% overall yield with concomitant deacetylation.[10]



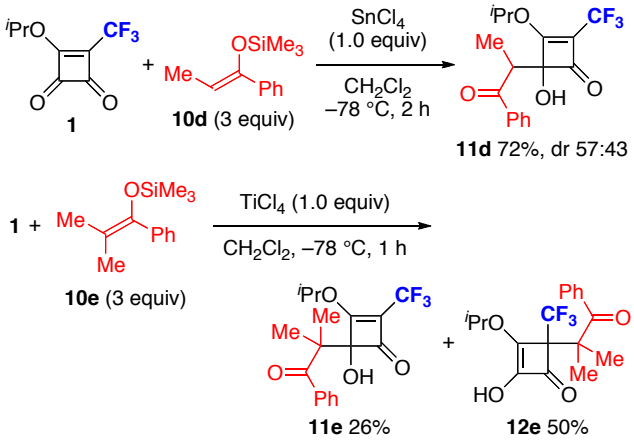
Scheme 6. Ring transformation of **5a**.



Scheme 7. Mukaiyama-type aldol reactions of **1** using silyl enolates **10a–c**.

Mukaiyama-type aldol reactions of CF_3-semisquarate 1 and subsequent transformations of products. In the previous section, we achieved the Hosomi–Sakurai-type electrophilic allylation of CF_3-semisquarate **1** and subsequent transformations of the allylation products. Then, the Mukaiyama-type aldol reaction of **1** using silyl enolates was briefly investigated.[11] In a similar manner as the abovementioned allylation, the reaction of **1** with acetophenone-derived silyl enolate **10a** (3.0 equiv) in the presence of $SnCl_4$ (1.0 equiv) at –78 °C for 2 h afforded the desired aldol adduct **11a** in 86% yield (Scheme 7). In striking contrast, the reaction with bulky silyl enolate **10b** bearing a *tert*-butyl group did not proceed in the presence of $SnCl_4$. Thus, a stronger LA, $TiCl_4$, was used to promote the reaction of **1** with **10b** otherwise under the same conditions. As a result, **11b** was successfully obtained in 85% yield. Next, a more electron-rich silyl ketene acetal **10c** was used as the silyl enolate. Although the reaction with **10c** proceeded in the presence of $SnCl_4$ at –78 °C for 2 h, an unexpected 1,4-addition product **12c** was obtained as the major product in 38% yield along with **11c** (13% yield). The structure of **12c** was unambiguously confirmed by single-crystal X-ray analysis. Notably, the use of $TiCl_4$ instead of $SnCl_4$ resulted in the predominant formation of 1,2-adduct **11c** in 86% yield.

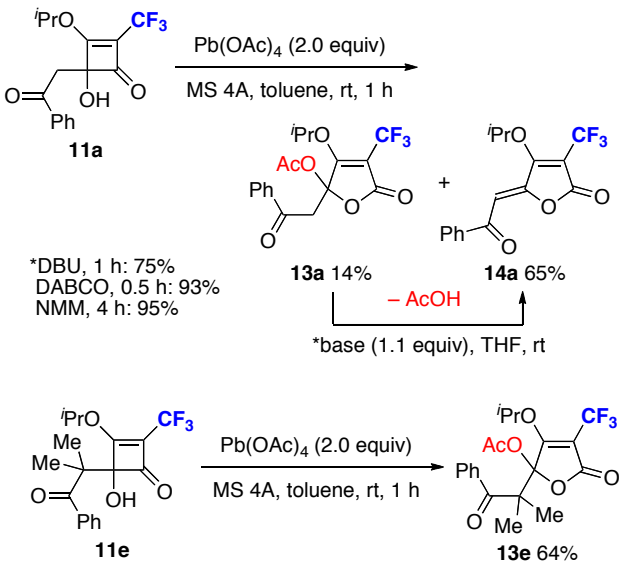
Next, the influence of γ-substituents on the Mukaiyama-type aldol reaction was investigated (Scheme 8). The reaction of **1** with silyl enolate **10d** bearing a methyl substituent at the γ-position to the silyl group in the presence of $SnCl_4$ at –78 °C for 2 h afforded **11d** in 72% yield with a diastereomeric ratio of 57:43. On the other hand, silyl enolate **10e** bearing two methyl substituents at the γ-position to the silyl group was found to be unreactive when $SnCl_4$ was used. Thus, the reaction of **1** with **10e** was performed using $TiCl_4$, affording 1,2-adduct **11e** and 1,4-adduct **12e** in 26% and 50% yields, respectively. Thus, the γ-substituents not only reduce the reaction efficiency, but also alter the regioselectivity.



Scheme 8. Reactions using γ-substituted silyl enolates **10d** and **10e**.

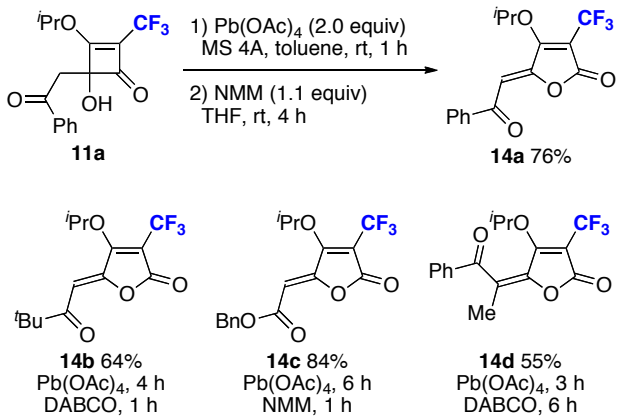
The concise synthesis of γ-alkylidenetetronate is an important research topic because diverse bioactive γ-alkylidenetetronate derivatives are known.[12]

Previously, we reported the synthesis of γ-alkylidenetetronates *via* the oxidative ring expansion of 4-hydroxycyclobutenones prepared by the addition of lithium enolates to squarates.[13] Similarly, we envisioned that α-CF_3-substituted γ-alkylidenetetronates can be obtained *via* the oxidative ring expansion of the aldol adducts obtained above. Thus, the oxidative ring expansion of representative 4-hydroxycyclobutenone **11a** was investigated (Scheme 9). We recently found that oxidative ring expansion using $Pb(OAc)_4$ was promoted by adding MS 4A.[14] Thus, the treatment of **11a** with $Pb(OAc)_4$ (2.0 equiv) in the presence of MS 4A in toluene at room temperature for 1 h afforded (*Z*)-γ-alkylidenetetronate **14a** as the major product in 65% yield along with the γ-acetoxy product **13a** in 14% yield. Subsequently, upon treatment with a base in THF at ambient temperature, the minor product **13a** underwent the elimination of acetic acid, affording **14a**. As the base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO), and *N*-methylmorpholine (NMM) were effective. In particular, DABCO and NMM converted **13a** to **14a** in high yields. The oxidative ring expansion of **11e** without any proton for abstraction afforded **13e** as the exclusive product in 64% yield.



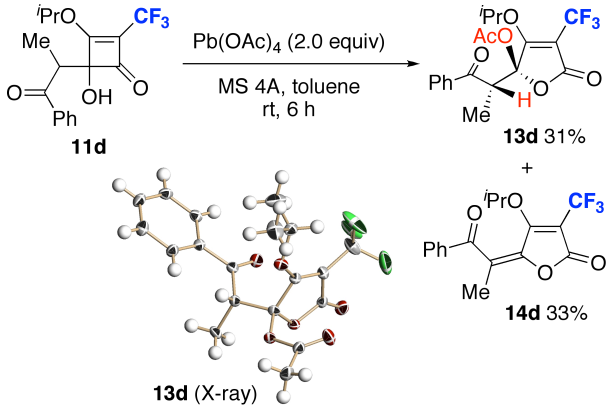
Scheme 9. Oxidative ring expansion of **11a** and **11e** using $Pb(OAc)_4$.

γ-Alkylidenetetronates were also obtained in a straightforward manner as the exclusive products when the crude mixture of **13** and **14** was treated with NMM or DABCO (Scheme 10). In this way, **14a** was obtained in 76% yield over two steps from **11a**. Other γ-alkylidenetetronates **14b–d** were also obtained from the corresponding aldol adducts **11b–d** in moderate-to-good overall yields. Notably, the alkylidene moiety of **14d** has (*E*)-configuration in contrast to others, as unambiguously confirmed by the X-ray diffraction study (Figure S1).[15]



Scheme 10. Direct transformation of aldol adducts **11a–d** to γ-alkylidenetetronates **14a–d**.

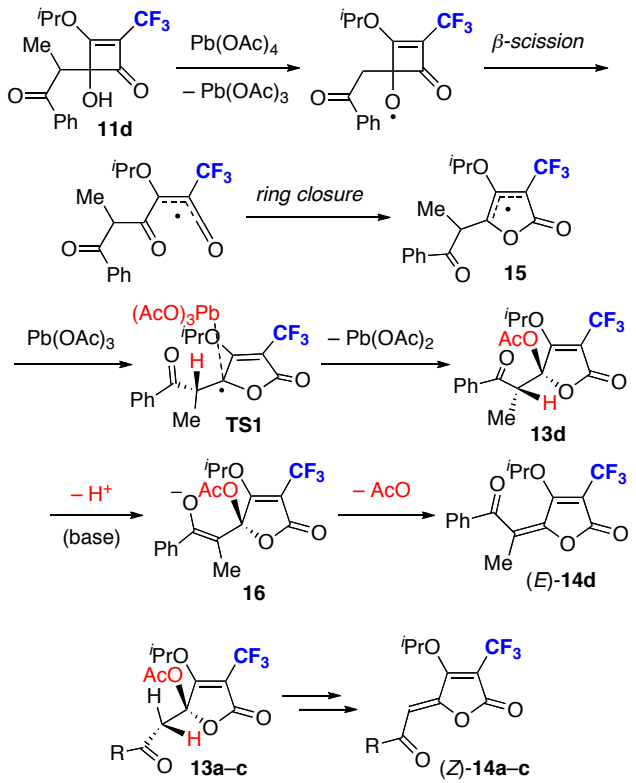
To obtain insights into the stereoselective formation of **14d**, the oxidative ring expansion of **11d** was revisited by omitting the treatment with DABCO (Scheme 11). Although the precursor **11d** was obtained as a mixture of approximately 1:1 diastereomers, γ-acetoxytetronate **13d** was obtained as a single diastereomer in 31% yield along with (*E*)-**14d** in 33% yield. Because a good quality single crystal was obtained, the relative configuration of **13d** was unambiguously confirmed.



Scheme 11. Oxidative ring expansion of **11d** to **13d** and (*E*)-**14d**.

According to the abovementioned observations, the stereoselective formation of **13d** and (*E*)-**14d** can be explained by the following reaction mechanism (Scheme 12). The one-electron oxidation of alcohol **11d** triggered the β-scission of the resulting oxy radical intermediate, which underwent ring closure to produce a cyclic radical intermediate **15**. Subsequent coupling of **15** with $Pb(OAc)_3$ proceeds *via* **TS1**, in which the less bulky carbonyl group is oriented to the isopropoxy group. Consequently, $Pb(OAc)_3$ accesses the radical center from the less hindered face, thus diastereoselectively producing **13d**. Subsequent deprotonation produces enolate intermediate **16**; further elimination of acetate anion from **16** affords

(*E*)-**14d** as a single stereoisomer. In contrast, the elimination of AcOH from **13a–c** proceeds from the conformers with one of the two methylene protons oriented to the isopropoxy group, thus exclusively producing the (*Z*)-isomers.



Scheme 12. Plausible mechanism for the stereoselective formation of (*Z*)-**14a–c** and (*E*)-**14d**.

Conclusion

We successfully achieved the electrophilic derivatization of the CF_3-semisuquarate *via* Lewis-acid-mediated additions of allylsilanes and silyl enolates. The reactions of allylsilanes selectively afford 4-hydroxycyclobutenones as 1,2-addition products, which were converted into bicyclo[3.2.0]heptenones *via* acetylation and subsequent thermal ring expansion. Moreover, the ring transformations of the cyclobutanone moiety of the bicyclo[3.2.0]heptenone was demonstrated to show the synthetic potential of the products.

Silyl enolates also selectively underwent 1,2-addition, although a 1,4-adduct was predominantly formed from a γ,γ-disubstituted silyl enolate. The obtained 4-hydroxycyclobutenones were subjected to oxidative ring expansion using $Pb(OAc)_4$. The produced tetronate derivatives were treated with bases to abstract AcOH, affording γ-alkylidenetetronates. It was disclosed that the stereochemistry of the alkylidene moiety depends on the substitution pattern of the carbon α to the carbonyl group.

Experimental Section

Reaction of CF_3-semisquarate 1 with Allylsilane 3a: To a solution of **1** (52.3 mg, 0.25 mmol) in dry CH_2Cl_2 (1.5 mL) was added $SnCl_4$ (1.0 M in CH_2Cl_2, 250 µL, 0.25 mmol) at –78 °C under an argon atmosphere. After stirring for 10 min, allyltrimethylsilane **3a** (60 µL, 0.375 mmol) was added to the reaction mixture. The reaction mixture was further stirred for 10 min at –78 °C and then 1 h at 0 °C. The reaction was quenched with H_2O (10 mL). After warming to room temperature, the aqueous solution was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo*. To the obtained crude product was added silica gel (500 mg) and CH_2Cl_2 (1 mL). The mixture was stirred for 30 min and then concentrated *in vacuo*. The obtained crude product was purified by silica gel column chromatography (hexane/AcOEt 4:1) to afford **2a** (59.6 mg, 95% yield) as a pale-yellow solid.

Acetylation of 4-Allyl-4-hydroxycyclobut-2-en-1-one 2a: To a solution of **2a** (250.3 mg, 1.0 mmol) in dry Et_2O (10 mL) was added triethylamine (280 µL, 2.0 mmol), and acethyl chloride (142 µL, 2.0 mmol) at room temparature under an argon atmosphere. After stirring for 10 min, the reaction was quenched with H_2O (10 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo*. The obtained crude product was purified by silica gel column chromatography (hexane/AcOEt 6:1) to afford **4a** (284.2 mg, 97% yield) as a colorless oil.

Thermal Ring Expansion of 4-Acetoxy-4-allylcyclobutenone 4a: A solution of **4a** (88.1 mg, 0.3 mmol) in toluene (6 mL) was heated at 100 °C for 5 h under an argon atmosphere. The solvent was removed *in vacuo*. The obtained crude product was purified by silica gel column chromatography (hexane/AcOEt 6:1) to afford **5a** (80.5 mg, 91% yield) as a colorless oil.

Reaction of CF_3-semisquarate 1 with Silyl Enolate 10a: To a solution of **1** (62.4 mg, 0.3 mmol) in dry CH_2Cl_2 (2.0 mL) was added $SnCl_4$ (1.0 M in CH_2Cl_2, 300 µL, 0.3 mmol) at –78 °C under an argon atmosphere. After stirring for 10 min, trimethyl((1-phenylvinyl)oxy)silane **10a** (184 µL, 0.9 mmol) was added to the solution, and the resulting reaction mixture was stirred –78 °C for 2 h. The reaction was quenched with H_2O (10 mL). After warming to room temperature, the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo*. The obtained crude product was purified by silica gel column chromatography (hexane/AcOEt 4:1) to afford **11a** (84.7 mg, 86% yield) as a pale-yellow oil.

One-pot Oxidative Ring Expansion/Acetic Acid Elimination from 4-Hydroxy-4-phenacylcyclobutenone 11a: To a degassed suspension of $Pb(OAc)_4$ (348.6 mg, 0.79 mmol) and activated MS 4A powder (400.2 mg) in dry toluene (1.0 mL) was added a solution of **11a** (129.0 mg, 0.39 mmol) in dry toluene (3.0 mL) at room temperature under an argon atmosphere. The solution was stirred at room temperature for 1 h. To this solution was added H_2O (10 mL), and insoluble materials were filtered off with AcOEt. The filtrate were extracted with AcOEt (3 × 10 mL). The combined organic layer was washed with sat. $NaHCO_3$ (10 mL) and dried over Na_2SO_4. The solvents were removed *in vacuo*, and the obtained crude product was treated with *N*-methylmorpholine (48 µL, 0.43 mmol) in THF (8 mL) at room temperature for 4 h. After concentration *in vacuo*, the obtained crude product was purified by silica gel column chromatography (hexane/AcOEt 6:1) to afford **14a** (97.1 mg, 76%) as a yellow solid.

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[15] The stereochemistry of **14b** was confirmed by its preliminary crystallographic data, albeit with lower resolution owing to the disordered CF_3 group (Figure S1). The supplementary crystallographic data for this paper (CCDC 1518014–1518017) can also be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

Electrophilic Derivatization of Trifluoromethyl-Substituted Semisquarate Using Unsaturated Organosilanes and Subsequent Ring Transformations

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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