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Highly Regio- and Diastereoselective Synthesis of CF_3-Substituted Lactones *via* Photoredox-Catalyzed Carbolactonization of Alkenoic Acids

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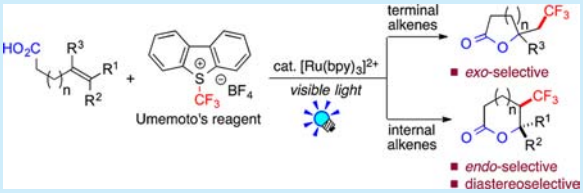
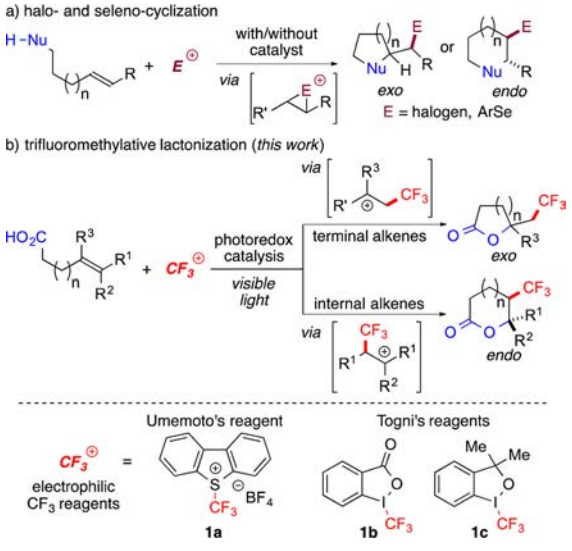
Supporting Information

ABSTRACT: Trifluoromethylative lactonization of both terminal and internal alkenoic acids by photoredox catalysis has been developed. The use of a Ru photocatalyst and Umemoto's reagent as a CF_3 source is key in the present carbolactonization. This is the first example of a highly *endo*- and diastereoselective synthesis of CF_3-substituted five-, six-, and seven-membered ring lactones from internal alkenoic acids.



Electrophile-involved cyclization of alkenes bearing a nucleophilic pendant is one of the most important reactions in organic chemistry and has been used for the synthesis of biologically relevant molecules.[1,2] In particular, the reaction of internal alkenes is fascinating from the viewpoint of construction of two stereogenic centers *via* a single step. Strongly electrophilic reagents such as halogen and selenium reagents induce efficient halo- and seleno-cyclization of internal alkenes, and their *exo*/*endo*- and stereoselectivity is variable depending on the steric and electronic factors of both alkene and nucleophilic pendants as well as the catalyst used (Scheme 1a). In contrast, related efficient and selective carbocyclization is still under development; especially, carbolactonization of internal alkenoic acids is extremely limited.[3] Thus, the development of a novel strategy for carbolactonization is highly valuable for modern synthetic organic chemistry.

Scheme 1. Electrophile-Involved Cyclization of Alkenes with a Nucleophilic Pendant



Since 2008, photoredox catalysis with well-defined ruthenium(II) polypyridine complexes (e.g., $[Ru(bpy)_3]^{2+}$) and the relevant cyclometalated iridium(III) derivatives has become a versatile synthetic tool because these compounds can readily catalyze single-electron transfer (SET) processes under visible light irradiation.[4] We are interested in photoredox-catalyzed radical trifluoromethylation[5,6] using shelf-stable electrophilic trifluoromethylating reagents ($^+\boldsymbol{CF_3}$) such as Umemoto's reagent **1a** and Togni's reagents **1b** and **1c**[7] because the trifluoromethyl (CF_3) group is a prevailing structural motif in many biologically active molecules as well as functional materials.[8,9] Despite significant progress in the synthesis of organofluorine compounds,[10] new methods for incorporation of a CF_3 group into diverse organic skeletons are very desirable. Recently, our group reported the highly regioselective trifluoromethylative difunctionalization of alkenes[3b,c,11] through a putative β-CF_3-substituted carbocation intermediate generated by photoredox catalysis.[6] Based on these results, we envisaged photoredox-catalyzed trifluoromethylative lactonization of alkenoic acids with "$^+\boldsymbol{CF_3}$" reagents (Scheme 1b).

Herein we disclose a novel protocol for regiocontrolled carbolactonization of both terminal and internal alkenoic acids by photoredox catalysis. It is remarkable that photoredox-catalyzed trifluoromethylative lactonization of internal alkenoic acids bearing a variety of functional groups proceeds with high *endo*- and diastereoselectivity under mild reaction conditions.

We initially tested the photocatalytic trifluoromethylative cyclization of 4-phenyl-4-pentenoic acid (**2a**) with Umemoto's reagent **1a** using 5 mol % of $[Ru(bpy)_3](PF_6)_2$ in CD_3CN under visible light irradiation (blue LEDs: λ_{max} = 425 nm) for 2.5 h. As a result, trifluoromethyllactonization proceeded in an

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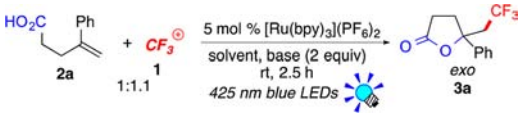
exo-selective manner to give the dihydrofuranone derivative with 2,2,2-trifluoroethyl substituent **3a** in 86% NMR yield (Table 1, entry 1). The choice of $^{+}CF_3$ reagents turned out to be crucial for the yield of **3a**. Togni's reagents **1b** and **1c** gave **3a** in low yields (entries 2 and 3). We found that the addition of a base such as K_2HPO_4 and K_2CO_3 resulted in a clean reaction, affording better yields of 96% and 95%, respectively (entries 4 and 5). Acetone and acetonitrile solvents are suitable for the present photocatalytic reaction (entries 6 and 7). Notably, product **3a** was obtained neither in the dark nor in the absence of a photocatalyst (entries 8 and 9).

Table 1. Trifluoromethylative Lactonization of 4-Phenyl-4-pentenoic Acid 2a[a]

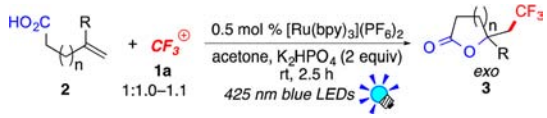


entry	CF_3 source	base	solvent	% yield of **3a**[b]
1	**1a**	none	CD_3CN	86
2	**1b**	none	CD_3CN	37
3	**1c**	none	CD_3CN	69
4	**1a**	K_2HPO_4	CD_3CN	96
5	**1a**	K_2CO_3	CD_3CN	95
6	**1a**	K_2HPO_4	acetone-d_6	99
7	**1a**	K_2HPO_4	dmso-d_6	69
8[c]	**1a**	K_2HPO_4	acetone-d_6	0
9[d]	**1a**	K_2HPO_4	acetone-d_6	0

[a]Reaction conditions: A mixture of $[Ru(bpy)_3](PF_6)_2$ (1.25 μmol, 5 mol %), **1** (28 μmol, 1.1 equiv), and **2** (25 μmol, 1.0 equiv) in solvent (0.5 mL) was irradiated by 3 W blue LEDs (λ = 425 ± 15 nm) at room temperature. [b]Yields were determined by ^{1}H NMR spectroscopy. [c]In the dark. [d]No photocatalyst.

The results of *exo*-selective trifluoromethylative cyclization for various terminal alkenoic acids **2** are summarized in Table 2.

Table 2. Scope of the Present *exo*-Trifluoromethylative Lactonization of Terminal Alkenoic Acids[a,b]



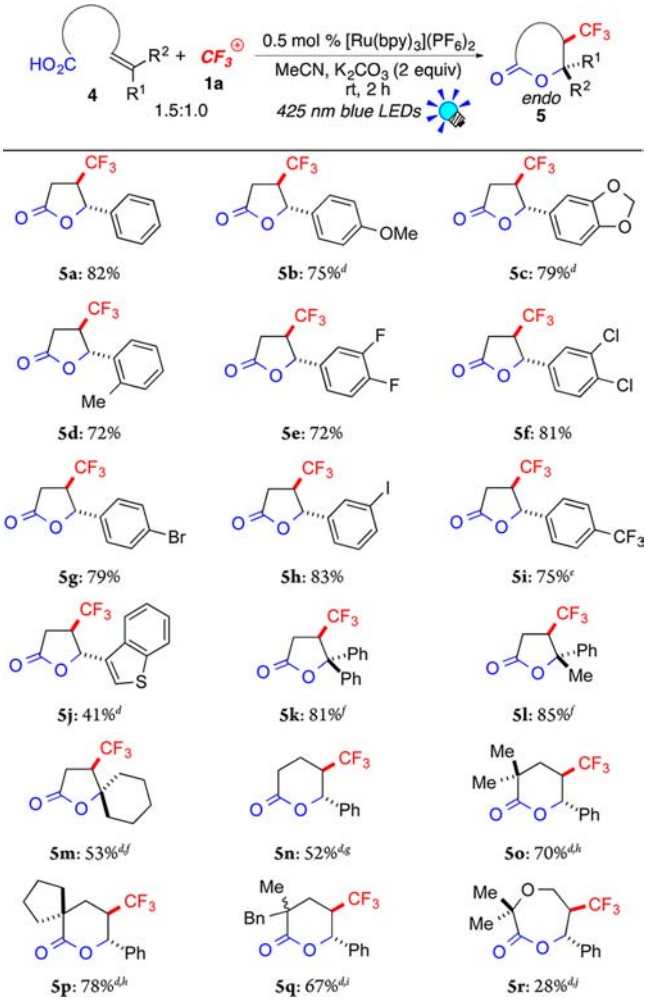
entry	*n*	R	% yield of product
1	1	Ph	**3a**: 90
2	1	*p*-$MeOC_6H_4$	**3b**: 83
3	1	*p*-FC_6H_4	**3c**: 82
4	1	*p*-ClC_6H_4	**3d**: 79
5	1	*p*-BrC_6H_4	**3e**: 76
6	2	Ph	**3f**: 69[c]
7[d]	1	H	**3g**: 60[c]

[a]Reaction conditions: see Supporting Information. [b]Isolated yields. [c]Yields were determined by ^{1}H NMR spectroscopy. [d]**2g**/**1a** = 1.5.

Reactions of 4-aryl-4-pentenoic acid derivatives with electron-donating (OMe: **2b**), electron-withdrawing (F: **2c**), and halogen (Cl and Br: **2d** and **2e**) groups on the benzene ring afforded the corresponding five-membered ring lactones in 83% (**3b**), 82% (**3c**), 79% (**3d**), and 76% (**3e**) yields, respectively. The present photocatalytic system can be extended to the construction of a six-membered ring lactone (**3f**) in good yields. It should be noted that the present *exo*-selective carbolactonization is also applicable to unactivated 4-pentenoic acid (**2g**).

Next, we investigated photoredox-catalyzed trifluoromethylative cyclization of internal alkenoic acids **4** (Scheme 2).

Scheme 2. Scope of the Present *endo*-Trifluoromethylative Lactonization of Internal Alkenoic Acid[a–c]



[a]Reaction conditions: see Supporting Information. [b] Isolated yields. [c] The *trans*/*cis* ratios were determined by ^{1}H and ^{19}F NMR spectroscopies of crude reaction mixtures. [d] Acetone was used as solvent. [e] *trans*/*cis* = >20:1. [f] 2.0 equiv of 2,6-lutidine were used in place of K_2CO_3. [g] *trans*/*cis* = 8.9:1. [h] *trans*/*cis* = >49:1. [i] *trans*/*cis* (C3, C5) = 1:1. [j] *trans*/*cis* = >35:1.

Remarkably, the reaction of (*E*)-4-phenyl-3-butenoic acids (**4a**) proceeded with high *endo*- and diastereoselectivity to give (4*R**,5*R**)-4-trifluoromethyl-5-phenyldihydrofuran-2(3*H*)-one (**5a**) in 82% isolated yield as a single isomer. The reaction of (*E*)-4-aryl-3-butenoic acid derivatives with a methyl substituent, Me (**4d**), a methoxy group, MeO (**4b**), and a methylenedioxy substituent (**4c**) on the benzene ring produced diastereoselectively the corresponding 5-*endo* cyclized products **5b**–**d** in high yields (72–79% yields). In addition, this reaction was amenable to internal alkenes bearing halogen atoms, F (**4e**), Cl (**4f**), Br (**4g**), and I (**4h**), and the CF_3-substituted five-membered ring *endo*-lactones (**5e**–**h**) were obtained in high yields (72–83% yields) as a single diastereomer. A strongly

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electron-withdrawing group such as a trifluoromethyl group, CF_3 (**4i**), did not hinder the reaction. Moreover, alkenoic acid with benzothiophene (**4j**), a heteroarene, was also tolerated and the 5-*endo* cyclization proceeded with exclusively *trans*-selectivity to give the CF_3-substituted lactone (**5j**) in 41% yield. The structure of **5j** was unequivocally confirmed by single-crystal X-ray analysis (Figure 1).[12]

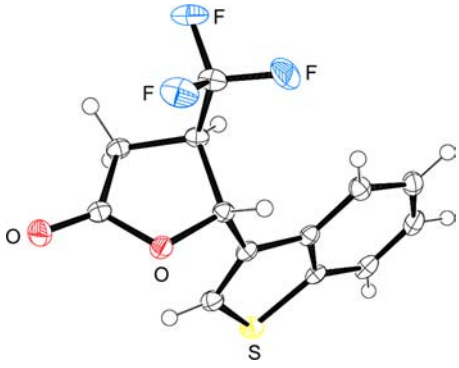
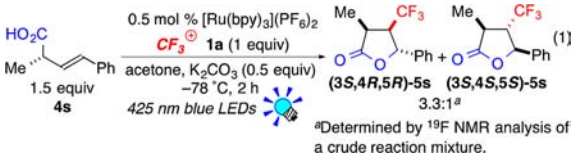


Figure 1. Single-crystal X-ray analysis of **5j**. The thermal ellipsoids are set at a 50% probability level.

The present 5-*endo* cyclization was extended to the reaction of 1,1,2-trisubstituted internal alkenoic acids. The trifluoromethyllactonization of 4,4-diphenyl-3-butenoic acid (**4k**) gave the *endo*-lactone (**5k**) with a quaternary carbon center in 81% yield.[13] In the reaction of (*E*)-4-phenyl-3-pentenoic acid (**4l**), only the *trans*-isomer with the diastereoselective formation of a quaternary carbon center (**5l**) was obtained in 85% yield. It is noteworthy that the reaction of *β*-cyclohexylidenepropionic acid (**4m**) afforded the spirocyclic *endo*-lactone product (**5m**) in 53% yield, indicating that this trifluoromethylative lactonization can be applied to an alkyl-substituted alkenoic acid as well as an aryl-substituted one.

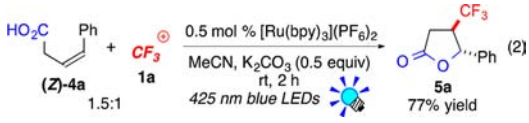
Furthermore, the present protocol enables *endo*- and diastereoselective synthesis of CF_3-substituted six- and seven-membered ring lactones. The reaction of (*E*)-5-phenyl-4-pentenoic acid (**4n**) proceeded with 6-*endo* cyclization to produce the CF_3-substituted six-membered ring lactone (**5n**) in 52% yield with a high level of diastereocontrol (8.9:1 dr). Notable improvements in yield and diastereoselectivity were observed when the alkenoic acids bearing dialkyl substituents at the *α*-position of the carboxyl group (**4o**−**q**) were used. Indeed, the 6-*endo* cyclized products (**5o**−**q**) were obtained in good yields (67−78%) with excellent diastereoselectivities (*trans*/*cis* (C5, C6) = >49:1 dr). The structure of **5o** was determined by X-ray analysis (see Supporting Information).[12] In addition, the present method was also applicable to the synthesis of the CF_3-substituted seven-membered ring *endo*-lactone (**5r**). These results show that photoredox-catalyzed trifluoromethyllactonization of both terminal and internal alkenoic acids allows us to easily access a variety of lactones containing a CF_3 group in a regioselective manner. In particular, it is worth noting that highly *endo*- and diastereoselective carbolactonization of internal alkenoic acids is an unprecedented transformation to the best of our knowledge.

Control of stereogenic centers is the next stage for this work. We tested the diastereocontrolled reaction utilizing the adjacent substituent. The reaction of (*S*)-4-phenyl-2-methyl-3-butenoic acid (**4s**) afforded the CF_3-substituted *endo*-lactones (**5s**) in 60% yield as a mixture of only two of four possible diastereomers (3.3:1 dr) with a moderate level of stereocontrol (eq 1). Lowering the reaction temperature to −78 °C improved



the diastereoselectivity (cf. 2.4:1 at rt). This result implies that the facial-selective introduction of the CF_3 group is key for the stereoselective reaction.

To gain insight into the mechanism, we conducted the photocatalytic cyclization of (*Z*)-alkenoic acid ((**Z**)-**4a**) (eq 2).

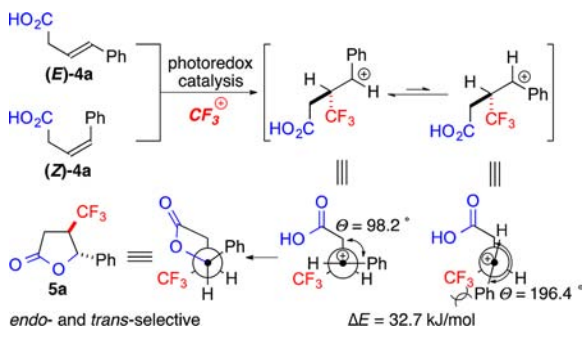


The reaction provided a product identical to the one obtained from the (*E*)-isomer **4a**. This *trans*-selective formation strongly supports the two isomeric substrates producing the same intermediate.

The reaction appears to proceed through a mechanism similar to that of the previously reported oxy- and amino-trifluoromethylation of alkenes by photoredox catalysis.[6a,c] Sequential SET photoredox processses in the course of the reaction of $^{+}CF_3$ with alkenoic acids **2** and **4** by $[Ru(bpy)_3]^{2+}$ under visible light irradiation produces a *β*-CF_3-substituted carbocation intermediate in a highly regioselective manner through radical transformation (for the fully proposed mechanism, see Supporting Information). Nucleophilic attack of the dangling carboxylic acid affords the CF_3-substituted lactone product. To elucidate high diastereoselectivity, we performed DFT calculations for possible conformations of a generable *β*-CF_3 carbocation from **4a**. It was revealed that, in the most favorable conformation, the CF_3 group and the phenyl group are arranged in an *anti*-fashion presumably because of steric repulsion between the CF_3 and the Ph groups (see Supporting Information).[14,15] Subsequent intramolecular nucleophilic addition of the COOH group to the carbocationic center gives the *trans*-product, which is actually obtained by the experiments (Scheme 3).

In conclusion, we have developed trifluoromethylative lactonization of both terminal and internal alkenoic acids by photoredox catalysis under mild conditions. Regioselective trifluoromethylation of C=C bonds and intramolecular

Scheme 3. A Plausible Reaction Mechanism for High Diastereoselectivity Observed for 5a



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nucleophilic attack of a pendant carboxylate to the β-CF_3 carbocation intermediate achieves highly regiocontrolled carbolactonizaton of alkenoic acids. In particular, this operationally easy trifluoromethylative cyclization protocol for internal alkenoic acids enables us to access a variety of CF_3-substituted five- and six-membered ring *endo*-lactones bearing many functional groups in a diastereoselective manner. Furthermore, this photocatalytic cyclization can be applied successfully to the synthesis of a CF_3-substituted seven-membered ring *endo*-lactone. This is the first example of *endo*-carbolactonization of internal alkenoic acids. Further studies on stereoselective trifluoromethylation are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Details of experimental procedures and full spectroscopic data for all new compounds, crystallographic data of **5j** (CCDC 962013) and **5o** (CCDC 962014), and results of computational analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) **5j** and **5o**: Molecular structures are shown in Supporting Information. CCDC 962013 and CCDC 962014 contain the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(13) The reaction of **4k** with K_2CO_3 as a base gave **5k** and the nontrifluoromethylated lactone as a byproduct. The byproduct may be derived from a competitive proton-mediated reaction. In contrast, the use of 2,6-lutidine prevents formation of the byproduct.

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