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# *Anti*-Diastereoselective Synthesis of $CF_3$-Containing Spirooxazolines and Spirooxazines via Regiospecific Trifluoromethylative Spirocyclization by Photoredox Catalysis

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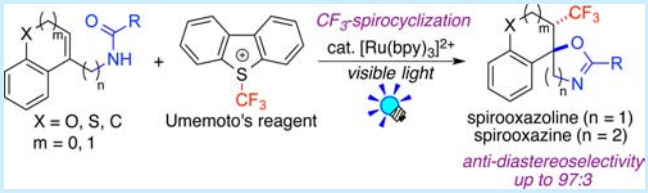
Supporting Information

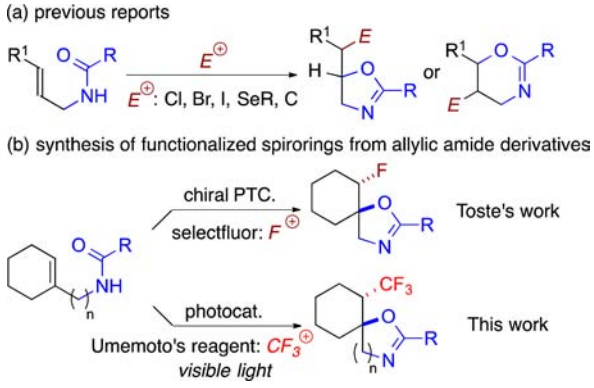
**ABSTRACT:** A novel synthesis of $CF_3$-containing spirooxazolines and spirooxazines has been developed. Regiospecific trifluoromethylative spirocyclization ($CF_3$-spirocyclization) of cyclic alkenes bearing an amide pendant mediated by photoredox catalysis is a useful strategy for construction of a $C(sp^3)-CF_3$ bond and an spirooxazoline or spirooxazine ring onto C=C bonds via a single step. The key intermediate is $\alpha$-$CF_3$-substituted carbocationic species smoothly generated from single-electron-transfer (SET) photoredox processes, which results in diastereoselective spirocyclization. This is the first example of synthesis of $CF_3$-containing spirooxazolines and spirooxazines in *anti*-fashion with respect to the $CF_3$ group and the oxygen atom of the spirocycles.




Spirooxazoline and spirooxazine scaffolds are useful structural motifs in many biologically active molecules.[1] Thus, development of synthetic methodologies for their derivatives has attracted great interest from synthetic chemists for years.

One of the most useful strategies for synthesis of functionalized spirooxazoline and spirooxazine is regioselective cyclization of cyclic alkenes with an amide pendant induced by electrophilic activation of the olefinic moiety. Another good aspect for the reaction of internal alkenes is an opportunity for the construction of two stereogenic centers via a single step. While synthesis of oxazolines and oxazines through cyclization of allylic amides triggered by strongly electrophilic reagents such as halogen and selenium electrophiles has been well-documentated so far (Scheme 1a),[2−4] application of this strategy to the synthesis of *spirooxazolines* and *spirooxazines* has been limited.[5] In 2011, the group of Toste reported that anion-based chiral phase transfer catalyst (PTC) induced asymmetric fluorospirocyclization of allylic amides, leading to fluorinated spirooxazolines (the upper process in Scheme 1b).[5d] But useful synthetic protocols for spiro-fused rings through cyclization accompanied by functionalization, especially carbo-spirocyclization, are still rare.[4]

**Scheme 1. Synthesis of Heterocycles through Functionalization−Cyclization Sequence of Alkenes Bearing an Amide Pendant**




The trifluoromethyl group ($CF_3$) is widespread in pharmaceutical and agrochemical fields because it influences chemical and metabolic stability, lipophilicity, and binding selectivity, resulting in unique bioactive properties.[6,7] Recently, photoredox catalysis[8] with ruthenium(II) polypyridine complexes (e.g., $[Ru(bpy)_3]^{2+}$: bpy = 2,2′-bipyridine) and the relevant cyclometalated iridium(III) derivatives has been recognized as a powerful tool for radical trifluoromethylation.[9,10] For the past few years, our group has been extensively developing photoredox-catalyzed trifluoromethylative difunctionalization of olefins.[11] Our protocol is featured by (i) the use of shelf-stable electrophilic trifluoromethylating reagents such as Umemoto's reagent **1**[12] as a trifluoromethyl radical source and (ii) regioselective generation of $\alpha$-$CF_3$-substituted carbocationic intermediate from olefins through single-electron-transfer (SET) photoredox processes, which is rather difficult to generate by other methods. We expected that application of photoredox-catalyzed trifluoromethylation to cyclic alkenes bearing a nucleophilic amide moiety leads to $CF_3$-containing spirooxazolines and spirooxazines through intramolecular nucleophilic attack of the oxygen atom in the amide functionality to an $\alpha$-$CF_3$-substituted carbocationic intermediate.

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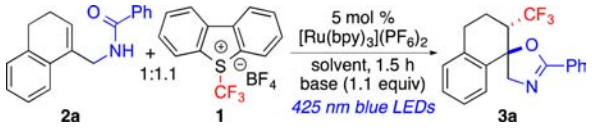
Herein we describe the regiospecific trifluoromethylative spirocyclization ($CF_3$-spirocyclization) of cyclic alkenes bearing an amide pendant mediated by photoredox catalysis, i.e., photoredox-catalyzed oxytrifluoromethylation,[4c,10e,l,11a,g] to be a versatile protocol for access to $CF_3$-containing spirooxazolines and spirooxazines. In addition, this is the first report on predominant formation of *anti*-diastereomers of $CF_3$-containing spirocyclic compounds.[13]

We initially examined the photocatalytic reaction of *N*-((3,4-dihydronaphthalen-1-yl)methyl)benzamide (**2a**) with Umemoto's reagent **1** in the presence of 5 mol % $[Ru(bpy)_3](PF_6)_2$ in acetone-$d_6$ at room temperature under visible light irradiation with blue LED lamps ($\lambda_{max}$ = 425 ± 15 nm). After 1.5 h, **2a** was completely converted but the corresponding spirooxazoline **3a** was not formed at all (Table 1, entry 1). Instead, a *N*-protonated compound type of **3a** was likely to be formed (see the Supporting Information). Therefore, addition of a base, $K_2CO_3$ and 2,6-lutidine, was tested. $K_2CO_3$ showed a result similar to entry 1 possibly due to its low solubility (entry 2). In contrast, to our delight, 2,6-lutidine yielded the product **3a** in a good yield (91%) with good diastereoselectivity (77:23 dr) (entry 3). Next, to improve the diastereoselectivity, the reaction was conducted at −78 °C (in a dry ice−methanol bath), resulting in better diastereoselectivity (84:16 dr) (entry 4). Use of $CD_2Cl_2$ as a solvent also afforded the product smoothly (90% yield) but with a slightly lower diastereoselectivity (74:26 dr) (entry 5). Finally, the reaction did not proceed at all either in the dark or in the absence of a photocatalyst (entries 6 and 7). To our surprise, 2,6-lutidine also promoted the reaction to some extent even in the absence of the photocatalyst (entries 7 and 8).[14] But, even after a longer reaction time, the yield was much lower than that obtained by photoredox catalysis, suggesting that the reaction promoted by 2,6-lutidine is not the main reaction pathway of the present photocatalysis.

With the optimal reaction conditions in hand, the preparative scale experiments were performed. Then, we found that the catalyst loading can be reduced to 0.5 mol %. The obtained $CF_3$-containing spirooxazolines **3** were summarized in Scheme 2.

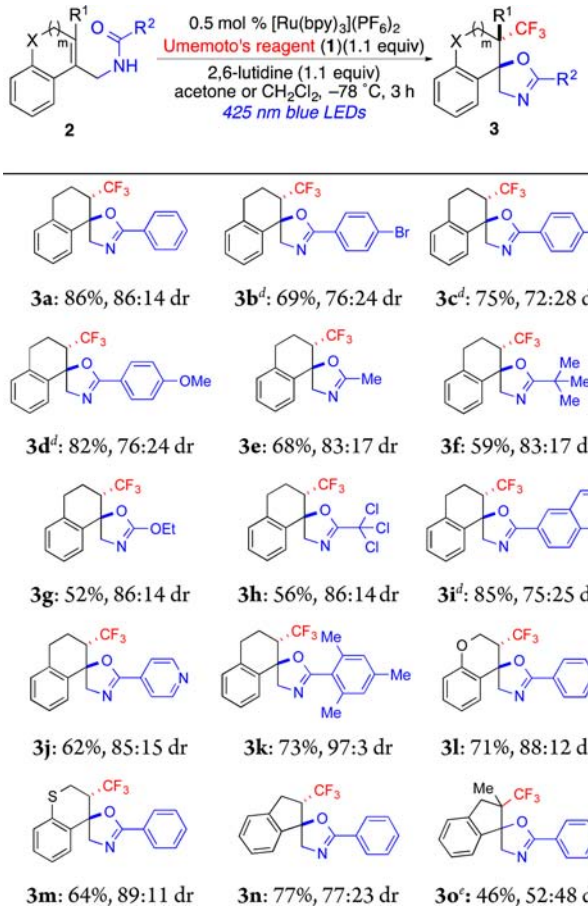
**Table 1. Optimization of the Photocatalytic $CF_3$-Spirocyclization of Allylic Amide (2a)[a]**




| entry | base | solvent | temp | % yield of **3a**[b] | dr[b] |
|---|---|---|---|---|---|
| 1 | none | acetone-$d_6$ | rt | –[c] | – |
| 2 | $K_2CO_3$ | acetone-$d_6$ | rt | –[c] | – |
| 3 | 2,6-lutidine | acetone-$d_6$ | rt | 91 | 77:23 |
| 4 | 2,6-lutidine | acetone-$d_6$ | −78 °C | 91 | 84:16 |
| 5 | 2,6-lutidine | $CD_2Cl_2$ | −78 °C | 90 | 74:26 |
| 6[d] | 2,6-lutidine | acetone-$d_6$ | −78 °C | 0 | – |
| 7[e] | none | acetone-$d_6$ | −78 °C | 0 | – |
| 8[e] | 2,6-lutidine | acetone-$d_6$ | −78 °C | 28, 37[f] | 74:26[f] |

[a]Reaction conditions: A mixture of $[Ru(bpy)_3](PF_6)_2$ (1.25 $\mu$mol, 5 mol %), **1** (28 $\mu$mol, 1.1 equiv), **2a** (25 $\mu$mol, 1.0 equiv), and solvent (0.4 mL) was irradiated by 3 W blue LEDs ($\lambda$ = 425 ± 15 nm). [b]Yields and diastereomer ratios (dr) were determined by $^1$H NMR spectroscopy using $SiEt_4$ as an internal standard. [c]Protonated **3a** was formed. [d]In the dark. [e]No photocatalyst. [f]Reaction time = 8 h.

**Scheme 2. Scope of the Present Photocatalytic $CF_3$-Spirocyclization of Allylic Amides (2)[a,b,c]**




[a]Reaction conditions: see the Supporting Information. [b]Yields were obtained after purification. [c]Diastereomer ratios (dr) were determined by $^1$H and $^{19}$F NMR spectra of crude reaction mixtures. [d]$CH_2Cl_2$ was used as a solvent due to solubility of substrate. [e]Reaction was carried out in the presence of 1.7 equiv of **1** at 0 °C for 4 h.

First, substituents on the amide pendants were explored. Substrates with benzene rings bearing halogens, Br (**2b**) and I (**2c**), and an electron-donating group, MeO (**2d**), and aliphatic groups, Me (**2e**) and $^t$Bu (**2f**), afforded the corresponding spirooxazoline products (**3b−f**) in good to high yields (59−86%) with moderate to good diastereoselectivities (72:28−86:14 dr). Amide functionalities with an alkoxy group, OEt (**2g**), a trichloromethyl group (**2h**), a naphthyl group (**2i**), and a pyridyl group (**2j**) tolerated the present photocatalytic system (**3g−3j**: 52−85%, 75:25−86:14 dr). Remarkably, the alkene with a bulky mesitylamide pendant (**2k**) gave **3k** in a 73% yield with excellent diastereoselectivity (97:3 dr). Next, structures of cyclic alkenes were investigated. Reactions of *N*-((2*H*-benzopyran-4-yl)-methyl)benzamide (**2l**) and *N*-((2*H*-thiocromen-4-yl)methyl-benzamide (**2m**) proceeded without any retardation regardless of the ether and sulfide functionalities to give the corresponding $CF_3$-spirocyclized products in good yields (**3l**: 71%, 88:12 dr and **3m**: 64%, 89:11 dr) in a diastereoselective manner, respectively. The reaction of *N*-((1*H*-inden-3-yl)methyl)benzamide (**2n**) also afforded a good yield of the $CF_3$-containing spirooxazoline (**3n**: 77%) but with slightly lower diastereoselectivity (77:23 dr) compared to the dihydronaphthalenyl skeleton (**3a**). A tetrasubstituted alkene, ((1*H*-2-methyl-inden-3-yl)methyl)-



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benzamide (**2o**), could be also applied to the present reaction, leading to the $CF_3$-spirooxazoline with a quaternary carbon atom **3o** (46%) but virtually with no diastereoselectivity (52:48 dr). These results suggest that the present photocatalytic system is amenable to diastereoselective synthesis of $CF_3$-containing spirooxazolines from cyclic alkenes with various amide pendants. Diastereoselectivity is considerably dependent on the substituent of the amide group and the structure of the cyclic alkenes.

The stereochemistry of the major diastereomer of $CF_3$-spirooxazolines **3c** and **3n** was unequivocally confirmed by single-crystal X-ray analysis.[15] An ORTEP drawing of the major diastereomer (1*R**,2*S**)-**3n** is depicted in Figure 1. These results revealed *anti*-stereochemistry for the nucleophilic cyclization process with respect to the $CF_3$ group.

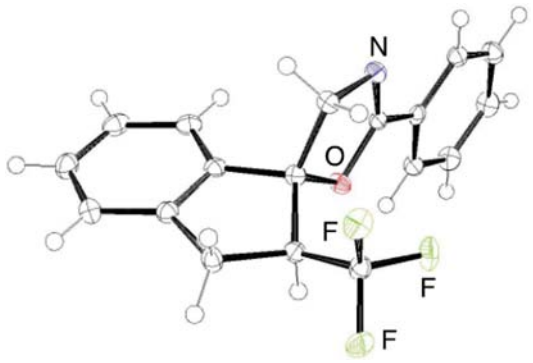
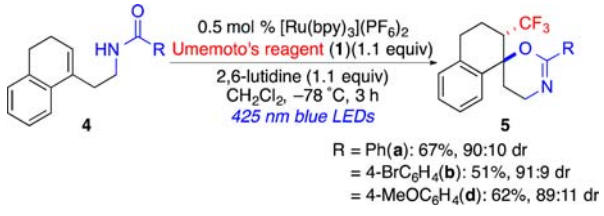



**Figure 1.** An ORTEP drawing of the major diastereomer of $CF_3$-containing spirooxazoline (1*R**,2*S**)-**3n**. The thermal ellipsoids are set at a 50% probability level.

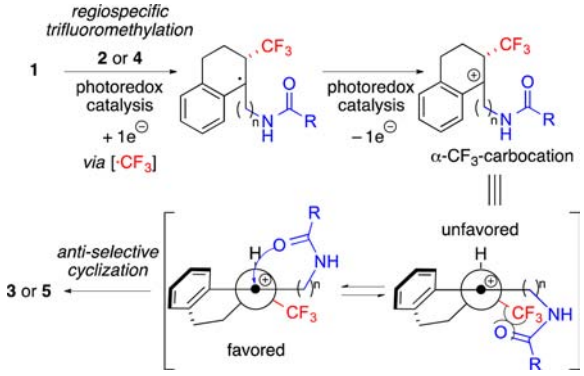
Extension to amides with longer tethers, *N*-(2-(3,4-dihydronaphthalen-1-yl)ethyl)benzamides **4**, was further examined (Scheme 3). It was observed that the corresponding $CF_3$-containing spirooxazines **5** were obtained in good yields (51−67% yield).[15] It should be noted that diastereomer ratios of the products (**5a**, **5b**, **5d**) (89:11−91:9 dr) were substantially enhanced compared to the above-mentioned spirooxazolines with the five-membered rings (**3a**, **3b**, **3d**) with the same substituent on the amide pendant. Single-crystal X-ray analysis for the major diastereomer of **5b** revealed the present spirocyclization also proceeded in an *anti*-fashion (see the Supporting Information). These results show that the present reaction system serves as a facile synthetic method for both *anti*-$CF_3$-spirooxazolines and -spirooxazines from cyclic alkenes with amide tethers.

**Scheme 3. Diastereoselective Synthesis of $CF_3$-Containing Spirooxazines**




The reaction appears to proceed through a mechanism similar to that of the previously reported photocatalytic oxytrifluoromethylation[11a] (for the full proposed mechanism, see the Supporting Information). SET photoredox processes mediated by $[Ru(bpy)_3]^{2+}$ for the reaction of Umemoto's reagent **1** with cyclic alkenes **2** or **4** generates an $\alpha$-$CF_3$-substituted carbocationic intermediate regiospecifically. This key intermediate undergoes intramolecular nucleophilic attack of the dangling amide moiety in an *anti*-fashion presumably due to the steric factor of the $CF_3$ substituent. These regiospecific trifluoromethylation and *anti*-selective cyclization processes lead to the predominant formation of *anti*-diastereomers of $CF_3$-containing spirooxazolines **3** or spirooxazines **5** (Scheme 4).

**Scheme 4. A Plausible Reaction Mechanism for *Anti*-Diastereoselectivity**




In conclusion, we have developed a simple synthesis of both $CF_3$-containing spirooxazolines and spirooxazines from cyclic alkenes bearing an amide pendant through trifluoromethylative spirocyclization ($CF_3$-spirocyclization) mediated by photoredox catalysis under mild conditions. Regiospecific radical trifluoromethylation and *anti*-selective nucleophilic attack of the amide pendant to the $\alpha$-$CF_3$-substituted carbocationic intermediate lead to the formation of $CF_3$-spirocycles in good to excellent diastereoselectivity. This is the first example of an access to *anti*-diastereomers of $CF_3$-containing spirooxazolines and spirooxazines. Further studies on stereoselective trifluoromethylation are underway in our laboratory.

## ■ ASSOCIATED CONTENT

### Supporting Information

Details of experimental procedures, control experiments and full spectroscopic data for all new compounds, crystallographic data for (1*R**,2*S**)-**3c** (CCDC 1049302), (1*R**,2*S**)-**3n** (CCDC 1049303), and (1*R**,2*S**)-**5b** (CCDC 1049304). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01694.

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### Notes

The authors declare no competing financial interest.

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(13) Only one example of $CF_3$-containing spirooxazoline was reported in ref 4b, but it is a *syn*-diastereomer, which is different from the stereochemistry observed for the present reaction.

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(15) (1*R**,2*S**)-**3c**, (1*R**,2*S**)-**3n**, and (1*R**,2*S**)-**5b**: Molecular structures are shown in the Supporting Information. CCDC 1049302, CCDC 1049303, and CCDC 1049304 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.




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