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Chemo- and Regioselective Ring Construction Driven by Visible-Light Photoredox Catalysis: an Access to Fluoroalkylated Oxazolidines Featuring an All-Substituted Carbon Stereocenter

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Abstract. The unique advantages conferred by incorporation of all-substituted carbon stereocenters in organic molecules have gained widespread recognition. In this work, we describe a three-component cyclization to access *C*-2 fluoroalkylated oxazolidines by fragments assembly of readily available silyl enol ether, fluoroalkyl halide, and chiral amino alcohol in a single reaction vessel, which provides an efficient strategy for expanding the pool of pharmaceutically important heterocycles featuring an all-substituted carbon stereocenter. This process proceeds efficiently in a chemo-, regio-, and stereoselective fashion under mild reaction conditions at room temperature and exhibits broad functional group tolerance. The successful realization of this controlled heteroannulation sequence relies on distinctive perfluoroalkylation, regio- and stereoselective radical cyclization through relay visible-light photoredox catalysis. Moreover, a one-pot procedure directly employing ketone as substrate has also been achieved.

Keywords: Photoredox catalysis; Multicomponent reaction; Oxazolidines; All-substituted carbon stereocenter; Fluoroalkylation

Introduction

Saturated *N*-heterocycles, especially the highly functionalized oxazolidines, have attracted consideration attentions both in academia and industry, in view that they frequently revolutionize privileged pharmaceuticals and important biologically active molecules[1,2] and are also widely used in asymmetric synthesis as an invaluable template in the pool of chiral catalysts and auxiliaries (Scheme 1, 1).[3] Considering the increasing demands in drug discovery for flexible modulations of oxazolidines with structural complexity,[4] the development of new synthetic strategies to access a wider class of these important frameworks from ubiquitous starting materials that could be assembled in an easily accessible fashion are highly sought after.

Conventionally, the synthesis of densely substituted oxazolidine derivatives could be achieved via the direct alkylation of vicinal amino alcohols, but the laborious routes suffered from well-recognized limitations, such as low overall yields as a consequence of lengthy procedure, limited commercial availability of precursors (e.g., specific organic halides and carbonyl compounds), and undesirable side reactions (Scheme 1, 2A).[5] While the functionalization of saturated cyclic amines relying on the activation of α-C–H bond adjacent to nitrogen atom by using transition metal catalysis[6] or via radical-type reactions[7] promised to provide new entries (Scheme 1, 2B),[8] unlike the functionalization of their aromatic counterparts, attempts to derivatize *N*-unprotected cyclic amines by using the same cross-couplings are often faced with the lack of directing groups.[9] To address the paucity of existing methods towards these valuable chemicals containing an additional heteroatom, research efforts have been continuously made for the construction of oxazolidines and oxazoles via cyclization,[10-11] aminohydroxylation,[12] and tin amine protocol (SnAP).[13] Typically, the precise placement of *C*-

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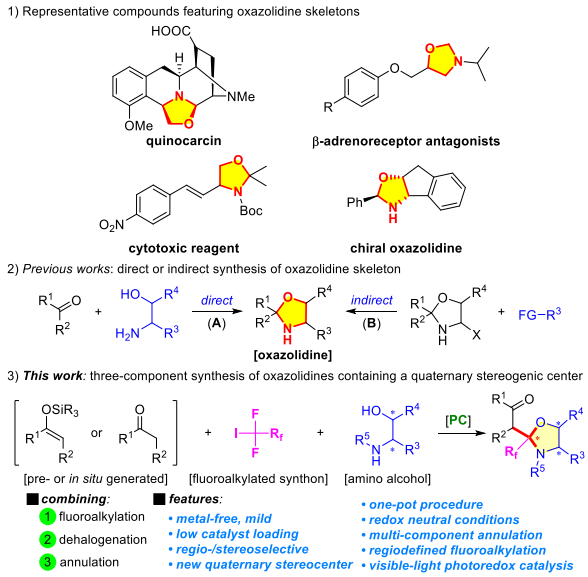


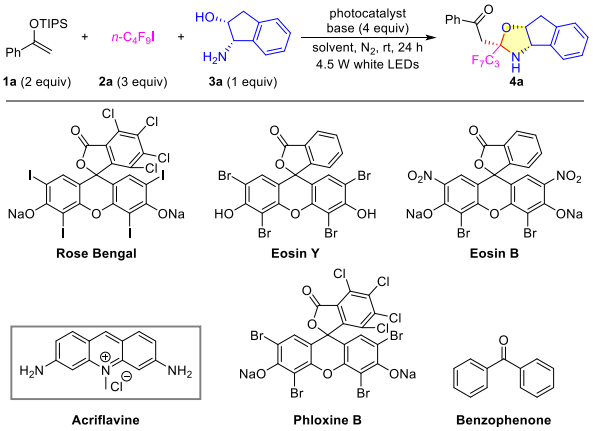
Scheme 1. Representative compounds featuring oxazolidines skeletons and strategies for the synthesis of oxazolidine derivatives.

substituents on *N*-heterocycles has been readily achieved by Bode[13] by means of combining carbonyl compounds with bespoke SnAP reagents. However, the requirement of stoichiometric copper, the toxicity of organotin compound, and the necessity of prefunctionalization of SnAP reagents have somewhat limited the implementation of this strategy. More importantly, one of the apparent difficulties of these approaches is the generation of all-substituted stereogenic centres in oxazolidine skeleton, which is still a particularly daunting task even in the field of asymmetric synthesis.[14]

On the other hand, it is well-known that installing fluorine atoms or higher homologue fluoroalkyl groups (R_f) on organic molecules might exert profound changes on chemical and physical properties of organic molecules with minor spatial alteration.[15] However, to the best of our knowledge, few of the above reported methods deal with the synthesis of fluorinated oxazolidines which might exhibit improved biological and pharmaceutical activity as a result of the incorporation of fluorine atom in the molecules. Therefore, the strategic exploitation of fluorine-containing building blocks[16] for rapid assembly of oxazolidines pharmacophores bearing R_f group and an all-substituted carbon center will be of great value and highly desirable.[17] In continuation of our task to develop efficient strategies for the construction of fluoro-containing heterocycles from readily available starting materials,[18] herein we describe an unprecedented three-component heteroannulation for directly constructing modular *C*-2 fluoroalkylated oxazolidines by taking advantage of visible-light photoredox catalysis under mild reaction conditions (Scheme 1, 3). This protocol distinguishes itself by broad functional group tolerance with spatially defined substituents and heteroatoms in a chemo-, regio-, and diastereoselective manner, which provides an attractive complement to the existing methods for the synthesis of organofluorine compounds where preformed or commercially available saturated *N*-heterocycles were directly employed for fluoro-functionalization.

Results and Discussion

Table 1. Optimization of reaction conditions[a]



Entry	Photocatalyst [x mol%]	Base	Solvent	Yield [%][b]
1	Rose Bengal (3)	DABCO	MeCN	5
2	$Ru(bpy)_3Cl_2·6H_2O$ (3)	DABCO	MeCN	34
3	Eosin Y (3)	DABCO	MeCN	52
4	Eosin B (3)	DABCO	MeCN	28
5	Acriflavine (3)	DABCO	MeCN	64

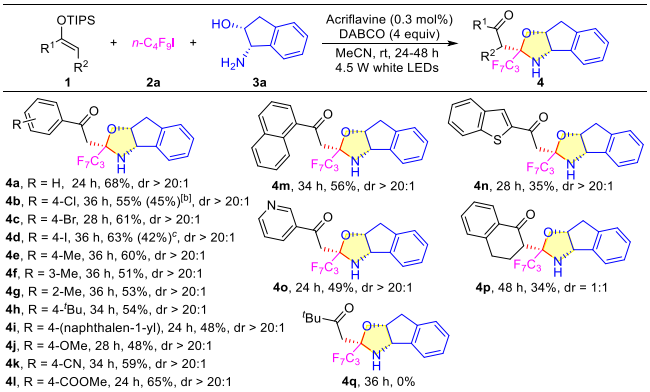
6	--	DABCO	MeCN	trace
7	Phloxine B (3)	DABCO	MeCN	trace
8	Benzophenone (3)	DABCO	MeCN	trace
9	Acriflavine (1.5)	DABCO	MeCN	72
10	**Acriflavine (0.3)**	**DABCO**	**MeCN**	**75 (68)[c]**
11	Acriflavine (0.3)	-	MeCN	0
12	Acriflavine (0.3)	DBU	MeCN	trace
13	Acriflavine (0.3)	Et_3N	MeCN	22
14	Acriflavine (0.3)	$^iPr_2NH$	MeCN	48
15	Acriflavine (0.3)	Cs_2CO_3	MeCN	0
16	Acriflavine (0.3)	DABCO	THF	54
17	Acriflavine (0.3)	DABCO	DCE	18
18	Acriflavine (0.3)	DABCO	DMF	58
19	Acriflavine (0.3)	DABCO	acetone	34
20	Acriflavine (0.3)	DABCO	MeCN	<5[d]
21	Acriflavine (0.3)	DABCO	MeCN	56[e]
22	Acriflavine (0.3)	DABCO	MeCN	58[f]

[a] Reaction conditions: **1a** (0.6 mmol), **2a** (0.9 mmol), **3a** (0.3 mmol), photocatalyst (0.0009-0.009 mmol) and base (1.2 mmol) in solvent (2.0 mL) at room temperature by irradiation with blue LEDs (4.5 W) under N_2 for 24 h. [b] Yields and diastereoselectivities (>20:1 dr) were determined by NMR analysis of crude reaction mixture (1,4-dimethoxybenzene as an internal standard). [c] Isolated yield. [d] TMS enol ether was used in place of TIPS enol ether **1a**. [e] TES enol ether was used in place of TIPS enol ether **1a**. [f] TBS enol ether was used in place of TIPS enol ether **1a**.

Initially, we investigated the model reaction of triisopropylsilyl (TIPS) enol ether **1a**, perfluorobutyl iodide (**2a**), and (1*S*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (**3a**) in the presence of 3 mol% of rose bengal as a catalyst and 4.0 equiv of triethylenediamine (DABCO) as a base in acetonitrile at room temperature under the irradiation of white LEDs for 24 h, which fortunately delivered 5% NMR yield of fluoroalkylated oxazolidine **4a** with good *C*-2 selectivity (Table 1, entry 1). Evaluation of various visible-light photoredox catalysts (entries 2-8) led to the discovery of acriflavine as a more efficient catalyst for the desired annulation, whose loading could be decreased as low as 0.3 mol%, affording the *N*-unprotected heterocycle **4a** in 75% NMR yield and 68% isolated yield (entry 10). Notably, all the reactions proceeded with excellent diastereoselectivities (>20:1 dr), which probably could be attributed to the *cis*-addition mode of chiral amino alcohol **3a**.[5b] Additionally, attempts to use other bases (entries 12-15) and solvents (entries 16-19) did not lead to any improvement of product yield, and noticeable decomposition of enolsilanes were observed under these conditions (entries 12-19).[19] Moreover, based on previous works,[18] we envisaged hat the relative stability and the appropriate steric hindrance of Si-protective groups should be beneficial to the reaction. As expected, employment of trimethylsilyl (TMS, entry 20), triethylsilyl (TES, entry 21), or *tert*-butyldimethylsilyl (TBS, entry 22) groups remarkably impaired the reaction efficiency, as compared to the use of TIPS as protecting group (entry 10).

With the optimized reaction conditions in hand, we set out to investigate the substrate scope of the reaction by using a broad range of silyl enol ethers **1**. As summarized in Table 2, triisopropyl((1-phenylvinyl)oxy)silanes **1** containing diverse substituents of varying electronic character and steric hindrance on aromatic rings were smoothly converted into the corresponding products **4a-l** in satisfactory yields with excellent diastereoselectivities (>20:1 dr). Notably, functional groups, such as halogens (Cl, Br, I, **1b-d**), cyano (**1k**), and methoxycarbonyl (**1l**) were well

Table 2. Substrate scope of various silyl enol ethers[a]



[a] Standard conditions; yields of isolated products; diastereoselectivity was determined by ^1H NMR analysis of crude reaction mixture. [b] For 24 h. [c] 1 mmol scale for 24 h.

tolerated under the mild reaction conditions, which could be retained for late-stage manipulation. In a

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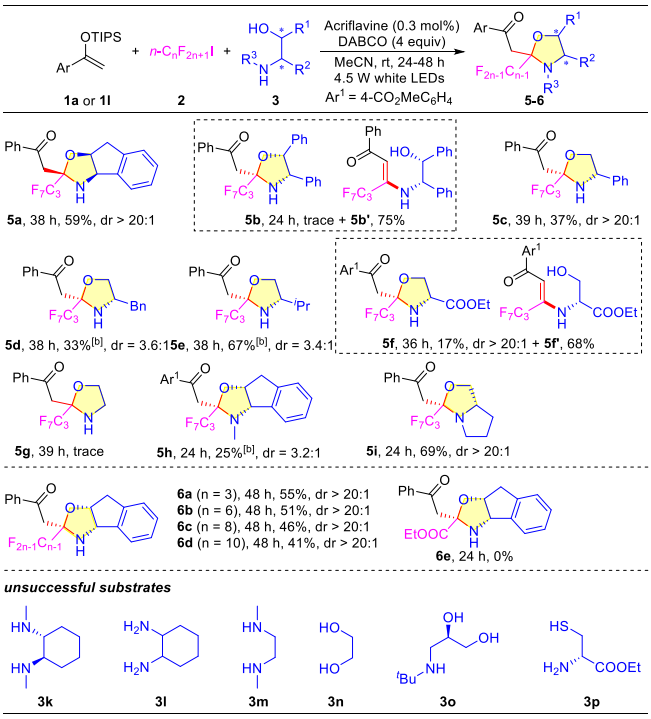
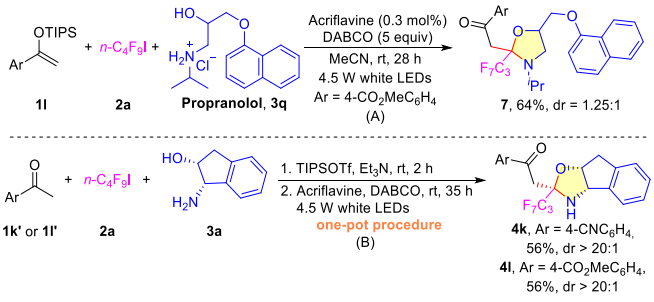
same streamlined manner, substrates featuring polycyclic and heteroaromatic motifs, such as naphthalene (**1m**), benzo[*b*]thiophene (**1n**), and pyridine (**1o**) also worked without difficulty to afford the densely functionalized oxazolidines **4m-o** in 35-56% yields. In addition, structural variation with the presence of an α-substituent in cyclic enolsilane **1p** did not interfere with the intermolecular formal [4+1] annulation, which provided access to a spirocyclic oxazolidine nuclei **4p** bearing an all-substituted carbon center at *C*-3 position in 34% yield. However, alkyl variant **1q** was proven to be an inappropriate candidate for our reaction system (**4q**). It should be mentioned that the relative configuration of heterocycle **4i** was tentatively assigned from the COSY and NOESY analysis (see Supporting Information for details). The ability to facilely assemble special *N*-heterocycles from simple and readily available acyclic building blocks, as demonstrated by the present protocol, will provide efficient means for the construction and derivatization of valuable products.

Table 3. Substrate scope of various β-amino alcohols and perfluoroalkyl halides[a]



[a] Standard conditions; yields of isolated products; diastereoselectivity was determined by ^{1}H NMR analysis of crude reaction mixture. [b] Only major diastereomers are shown.

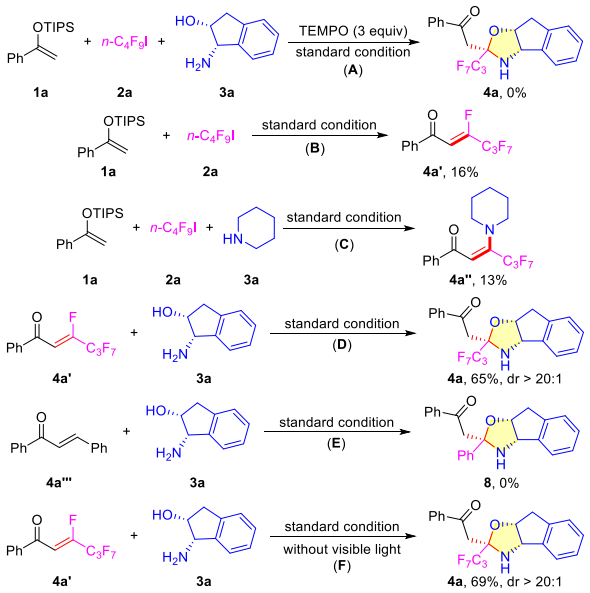
Subsequently, the present catalytic protocol was successfully extended to the use of various β-amino alcohols with different degrees of substitution and stereochemistry (Table 3). It was found that the configuration of amino alcohols **3** only has a slight impact on the reactivity, as elucidated by the observation that the use of (1*R*, 2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (**3b**) with opposite configuration also led to the corresponding product **5a** with reversed stereochemistry in 59% yield with >20:1 dr. It should be noted that the use of (1*R*, 2*S*)-2-amino-1,2-diphenylethan-1-ol as substrate only resulted in the exclusive formation of alkenylated product **5b'** in 75% yield, no anticipated product **5b** was obtained which might be owing to the negative influence of steric effects. In contrast, other enantiopure amino alcohols possessing potentially epimerizable stereogenic centers, such as phenylglycinol, phenylalaninol, valinol, and methyl serinate, could be transformed into synthetically useful oxazolidine derivatives **5c-f** without any detectable racemization under mild reaction conditions, albeit in slightly decreased yields. These results will resonate with drug discovery programs from chiral amino alcohols concerning *N*-heterocycles synthesis.[4] Unfortunately, simple amino alcohol of 2-aminoethan-1-ol almost could not react under the optimal reaction conditions (**5g**). Furthermore, we were able to accomplish the conversion of related *N*-alkyl-protected amino alcohols to heterocyclic products **5h** and **5i** in 25% and 69% yields, respectively. Finally, various perfluoroalkyl halides (except bromodifluoroacetate) with 3-10 carbon chain length were amenable to the mild reaction conditions, producing *C*-2 perfluoroalkylated products **6a-d** in appreciable yields with >20:1 diastereoselectivities. Unfortunately, other types of di-nucleophiles, including (1*R*,2*R*)-N^1,N^2-dimethylcyclohexane-1,2-diamine (**3k**), cyclohexane-1,2-diamine (**3l**), N^1,N^2-dimethylethane-1,2-diamine (**3m**), ethane-1,2-diol (**3n**), (*R*)-3-(*tert*-butylamino)propane-1,2-diol (**3o**), and ethyl *D*-cysteinate (**3p**), failed to produce any products under the optimized reaction conditions.



Scheme 2. Transformation of propranolol to oxazolidine 7 and one-pot heteroannulation.

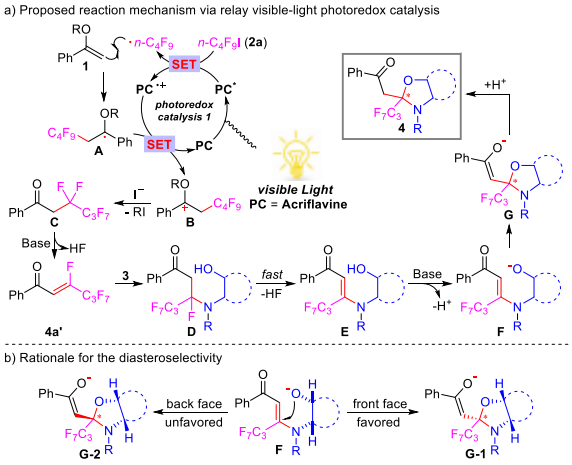
Impressively, propranolol hydrochloride **3q** as an amino alcohol exhibited good reactivity and well participated in this photocatalytic multicomponent heteroannulation to produce the oxazolidine-modified adduct **7** in 64% yield (Scheme 2, A). This result indicates that the present methodology will not only be useful in synthetic chemistry, but also be beneficial to drug discovery for the rational design of drug for

treating high blood pressure.[20] Additionally, considering procedural simplicity and synthetically ready accessibility, a two-step, one-flask procedure was designed by utilizing *in situ* prepared enolsilanes from related ketones (**1k'** and **1l'**) with TIPSOTf in the presence of Et_3N, followed by exposure to the present photocatalytic conditions. Gratifyingly, the one-pot reaction proceeded efficiently as well, giving rise to the corresponding products **4k** and **4l** both in 56% yields in a succinct way (Scheme 2, B).



Scheme 3. Control experiments.

To gain insights into the putative mechanism of the above reaction, several control experiments were performed (Scheme 3). When the model reaction was treated with radical scavengers of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO, 3 equiv) under standard reaction conditions, no anticipated product **4a** was detected (Scheme 3, A), indicative of the involvement of a radical-type mechanism in the reaction. In addition, control experiment B showed that when enolsilane **1a** was reacted with **2a** under well-established reaction conditions, (*Z*)-3,4,4,5,5,6,6,6-octafluoro-1-phenylhex-2-en-1-one (**4a'**), which is considered to be the key intermediate of the reaction, could be isolated in 16% yield. The intermediacy of **4a'** was further demonstrated by the fact that piperidine could trap the possible intermediate **4a'** to produce β-aminated ketone **4a''** in 13% yield (Scheme 3C). Treatment of this intermediate **4a'** with amino alcohol **3a** did lead to the product **4a** in 65% yield (Scheme 3, D), suggesting that the three-component model reaction should proceed via the formation of intermediate **4a'** through an intermolecular α-perfluoroalkylation followed by ensuing defluorination. Notably, the fluoro-substituent was also crucial for the reactivity, in light of the fact that chalcone (**4a'''**) could not be converted into the corresponding cyclized product **8** under the standard conditions (Scheme 3, E). Moreover, when the isolated intermediate **4a'** was subjected to cyclization with amino alcohol under optimized reaction conditions in the absence of visible light, the formation of product **4a** was almost unaffected (Scheme 3, F), thereby indicating that the ring-closure step mostly takes place via a conventional Michael addition route rather than a radical-type reaction pathway.



Scheme 4. Proposed reaction mechanism and rationale for the high diastereoselectivity obtained.

On the basis of above control experiments and literature survey,[21,22] a radical-type fluoroalkylation/defluorination/annulation mechanism driven by relay visible-light photoredox catalysis is depicted in Scheme 4a. First, the postulated photocatalytic cycle begins with single electron transfer (SET) from excited-state acriflavine* (E^{red} = -1.19 V vs SCE in MeCN) to perfluorobutyl iodide (**2a**, E^{red} = -1.10 V vs SCE in MeCN) to produce an electrophilic *n*-C_4F_9 radical and a radical cation $PC^{\bullet+}$ by irradiation with visible light (see Supporting Information for details). Addition of the formed perfluoroalkyl radical to silyl enol ether **1** affords tertiary radical species **A**, which is subsequently oxidized by $PC^{\bullet+}$ to close the first photocatalytic cycle and generate α-perfluoroalkylated ketone **C** after rapid attack by an I^- ion through carbocation **B**. Next, α,β-desaturation of unstable carbonyl compound **C** is enabled to give intermediate **4a'** by means of eliminating a molecule of HF under basic conditions.[18a] Subsequently, amino alcohol **3** undergoes Michael-type reaction with intermediate **4a'** followed by fast *β*-F elimination to generate the enone **E**. The observed regioselectivity results from the comparatively stronger nucleophilicity of nitrogen atom over oxygen one. The key species of alkenylated compound **E** undergoes intramolecular Michael addition to produce the cyclized product **4**. Other alternative rationales for the formation of alkoxy radical via a proton coupled electron transfer (PCET)

process[21,22] or the formation of the radical-cation intermediate via oxidizing the double bond of compound **E** could be excluded.[23] The diastereoselectivity of this transformation is set during the course of cyclization mainly due to the configuration of chiral amino alcohol, enabling the intramolecular addition to occur preferentially from the less hindered front face (Scheme 4b).[24]

Conclusion

In summary, an efficient strategy involving relay visible-light photoredox catalysis has been developed for accessing modular fluoroalkylated oxazolidines with spatially defined substituents commencing from readily available silyl enol ethers, fluoroalkyl halides, and chiral amino alcohols. This process enables annulation in a chemo-, regio-, and diastereoselective manner under metal-free, ambient conditions and exhibits broad functional group tolerance, which represents a valuable entry to the divergent synthesis of saturated *N*-heterocycles. Moreover, the one-pot procedure directly employing ketones as an enolsilane precursor also has been achieved with good synthetic efficiency. Mechanistic studies showed that the reaction presumably proceeded through a radical-type reaction pathway via the formation of *β*-fluoro-substituted enone **4a'** as a key intermediate.

Experimental Section

Synthesis of 2-((2*R*,3a*S*,8a*R*)-2-(perfluoropropyl)-3,3a,8,8a-tetrahydro-2*H*-indeno[1,2-*d*]oxazol-2-yl)-1-phenylethan-1-one (4a).

A solution of triisopropyl((1-phenylvinyl)oxy)silane (**1a**, 165 mg, 0.6 mmol), perfluorobutyl iodide (**2a**, 311 mg, 0.9 mmol), (1*S*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (**3a**, 45 mg, 0.3 mmol), acriflavine (0.2 mg, 0.0009 mmol), and 1,4-diaza[2.2.2]bicyclooctane (134.5 mg, 1.2 mmol) in MeCN (2.0 mL) was stirred under nitrogen atmosphere (by 3 times' vacuum evacuation/N_2 backfill cycles) by irradiation with 4.5 W white LEDs at room temperature for 24-48 h. Upon completion of the reaction (indicated by TLC), solvent was removed under vacuum and the residue was purified by flash silica gel column chromatography (300-400 mesh) using petroleum ether/ethyl acetate (200/1) as eluent to afford the pure 2-((2*R*,3a*S*,8a*R*)-2-(perfluoropropyl)-3,3a,8,8a-tetrahydro-2*H*-indeno[1,2-*d*]oxazol-2-yl)-1-phenylethan-1-one (**4a**, 91 mg, 68%).

Synthesis of methyl 4-(2-(3-isopropyl-5-((naphthalen-1-yloxy)methyl)-2-(perfluoropropyl)oxazolidin-2-yl)acetyl)benzoate (7).

A solution of methyl 4-(1-((triisopropylsilyl)oxy)vinyl)benzoate (**1l**, 201 mg, 0.6 mmol), perfluorobutyl iodide (**2a**, 311 mg, 0.9 mmol), propranolol hydrochloride (**3q**, 89 mg, 0.3 mmol), Acriflavine (0.2 mg, 0.0009 mmol), and 1,4-diaza[2.2.2]bicyclooctane (DABCO, 168 mg, 1.5 mmol) in MeCN (2.0 mL) was stirred under nitrogen atmosphere (by 3 times' vacuum evacuation/N_2 backfill cycles) by irradiation with 4.5 W white LEDs at room temperature for 28 h. Upon completion of the reaction (indicated by TLC), solvent was removed under vacuum and the residue was purified by flash silica gel column chromatography (300-400 mesh) using petroleum ether/ethyl acetate (50:1) as eluent to afford the pure methyl 4-(2-(3-isopropyl-5-((naphthalen-1-yloxy)methyl)-2-(perfluoropropyl)oxazolidin-2-yl)acetyl)benzoate (**7**, 118 mg, 64% yield).

Acknowledgements

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FULL PAPER

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