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Letter

Titanocene-Catalyzed Reductive Domino Epoxide Ring Opening/Defluorinative Cross-Coupling Reaction

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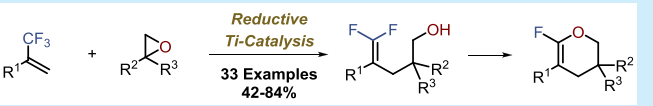
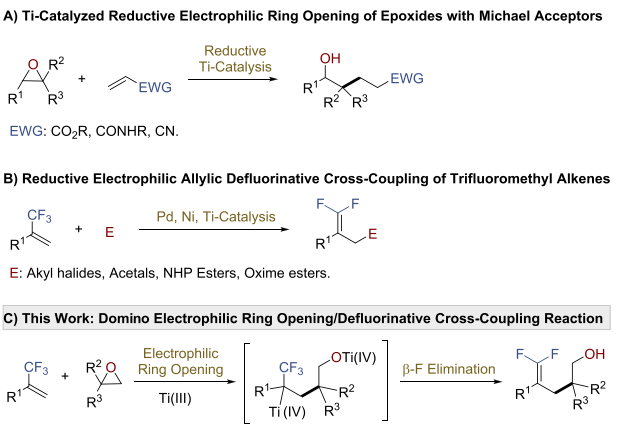
ABSTRACT: Herein, we report a method for efficient synthesis of *gem*-difluorobishomoallylic alcohols starting from trifluoromethyl-substituted alkenes and epoxides via a titanocene-catalyzed reductive domino reaction, which consists of a Ti(III)-mediated radical-type ring opening and the following allylic defluorinative cross-coupling reaction via sequential radical addition and β-F elimination. Notably, complete regioselectivity and high tolerance of functionalities can be achieved in this reaction. Furthermore, diverse 6-fluoro-3,4-dihydro-2*H*-pyrans have been prepared through derivatization of the cross-coupling products in one single step.



Ring opening of epoxides provides a powerful method to approach vicinal difunctionalized molecules. In comparison to the well-established nucleophilic ring opening reaction,[1] the complementary electrophilic variant is distinguished by a unique reaction pathway and more desirable for C−C bond formation due to the avoidance of using highly reactive organometallics.[2] Early contributions in this field mainly focused on the use of stoichiometric transition metals to realize the umpolung of the epoxides.[3] In the last decades, significant progress has been achieved in the titanocene-catalyzed electrophilic radical-type ring opening of epoxides, in which various Michael acceptors have been successfully utilized as the coupling partners (Scheme 1A).[4−6] Furthermore, the cooperative catalysis of Ni and Ti allows the use of aryl halides as the electrophiles in the ring opening reaction of epoxides,[7] while hydrogenation[8] and isomerization[9] of epoxides involving Ti as a catalyst provide efficient access to diverse alcohols.

gem-Difluoroalkenes are contained as a subunit in numerous biologically active compounds and agrochemicals.[10] Furthermore, as a metabolically more-stable bioisostere of carbonyl groups, *gem*-difluoroalkenes promise superior phamaceutical performance to their carbonyl analogues.[11] In addition, *gem*-difluoroalkenes can also serve as versatile building blocks for synthesis of other fluorine-containing compounds.[12] Therefore, various strategies including functional-group conversion,[13] nucleophilic addition to trifluoromethyl alkenes,[14] and a photocatalytic approach[15] have been developed for synthesis of *gem*-difluoroalkenes over the last decades. Recently, transition-metal-catalyzed reductive allylic defluorinative cross-coupling reactions of easily accessible trifluoromethyl alkenes[16] with various electrophiles including organohalides,[17] acetals,[18] *N*-hydroxyphthalimide (NHP) esters,[19] and oxime esters[20] have emerged as a reliable method to prepare sterically demanding and functional-group-rich *gem*-difluoroalkenes (Scheme 1B). Herein, we envisage that the scope of this reductive strategy could be extended to epoxides via engaging titanocene catalysis, to enable the synthesis of *gem*-difluorobishomoallylic alcohols. The designed reaction consists of two key elementary steps, which are the Ti(III)-mediated

Scheme 1. (A) Ti-Catalyzed Reductive Electrophilic Ring Opening of Epoxides with Michael Acceptors; (B) Reductive Electrophilic Allylic Defluorinative Cross-Coupling of Trifluoromethyl Alkenes; (C) Domino Electrophilic Ring Opening/Defluorinative Cross-Coupling Reaction



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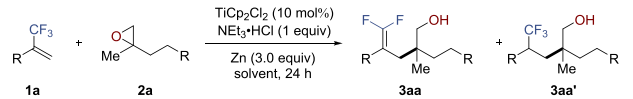
radical-type ring opening of epoxides and the following allylic defluorinative cross-coupling via β-F elimination (Scheme 1C).

For optimization of the reaction conditions, the trifluoromethyl alkene **1a** and the terminal epoxide **2a** were selected as the standard substrates (Table 1). Initially, the reaction was performed in THF at room temperature with $TiCp_2Cl_2$ (10 mol %) as a catalyst, NEt_3·HCl as a proton donor, and Zn as a reductant, affording an inseparable mixture of the desired *gem*-difluoroalkene **3aa** and the hydroalkylation product **3aa′** (entry 1). This ring opening reaction occurs exclusively on the more-substituted site. A similar result was obtained when conducting the reaction in toluene (entry 2). In contrast, the reaction in DMF delivered compound **3aa** as the only product in a moderate yield (entry 3). In order to achieve higher conversion of **1a**, we carried out the reaction at 60 °C (entry 4) and 80 °C (entry 5), respectively. However, it turned out that the formation of the byproduct **3aa′** benefited from a higher reaction temperature. Next, the catalyst loading was increased to 20 mol % (entry 6). In this case, the product **3aa** could be obtained in a good yield (81%). Moreover, performing the reaction with Ti(indenyl)Cl_3 instead of $TiCp_2Cl_2$ resulted in a slightly lower efficiency (entry 7). In addition, replacing Zn with Mn as the reducing agent gave rise to an inferior result (entry 8). In the absence of the proton donor NEt_3·HCl, the reaction could still proceed, albeit in a lower yield (entry 9). The diminished efficiency is likely due to the relatively slow liberation of the titanocene catalyst via Zn/Ti-cation exchange in comparison to the protonation process.

Table 1. Optimization of the Reaction Conditions[a]



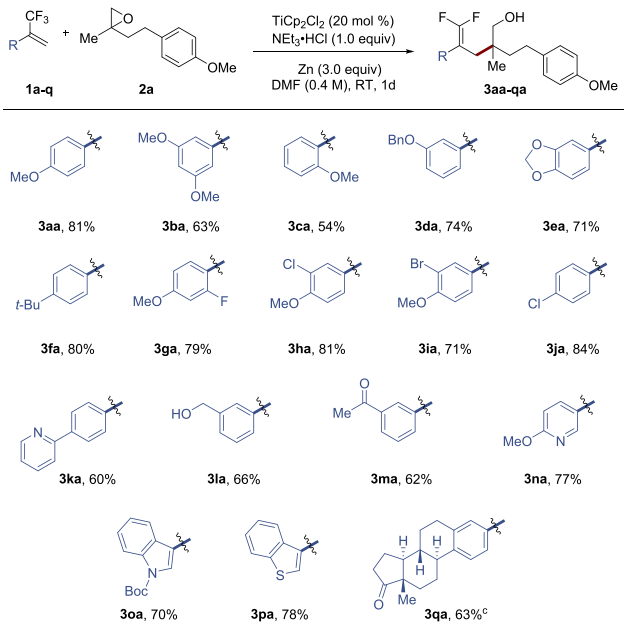
R= 4-MeOC$_6$H$_4$.

entry	solvent	T (°C)	yield **3aa** (%)[b]	yield **3aa′** (%)[b]
1	THF	RT	58	39
2	toluene	RT	15	30
3	DMF	RT	42	0
4	DMF	60	76	19
5	DMF	80	55	43
6[c]	DMF	RT	85 (81)[d]	0
7[c,e]	DMF	RT	75	3
8[c,f]	DMF	RT	65	0
9[c,g]	DMF	RT	59	0

[a]Unless otherwise specified, reactions were performed on a 0.2 mmol scale of the trifluoromethyl alkene **1a** using 2.0 equiv of the epoxide **2a**, 10 mol % $TiCp_2Cl_2$, 1.0 equiv of NEt_3·HCl, and 3.0 equiv of Zn in 0.5 mL of solvent for 24 h. [b]NMR yields are determined by ^{19}F NMR spectroscopy using 4-fluoroanisole as an internal standard. [c]Reaction was performed with 20 mol % $TiCp_2Cl_2$. [d]Yield of the isolated product after column chromatography. [e]Ti(indenyl)Cl_3 was used instead of $TiCp_2Cl_2$. [f]Mn was used instead of Zn. [g]Reaction was performed without NEt_3·HCl.

After establishing the optimal reaction conditions, we started to evaluate the substrate scope of this titanocene-catalyzed reaction (Scheme 2). First, diverse aryl trifluoromethyl alkenes (**1a–l**) with electron-donating or electron-withdrawing substituents were reacted with the epoxide **2a**. To our delight, all these reactions proceeded smoothly, furnishing the corresponding *gem*-difluorobishomoallylic alcohols **3aa–la** in moderate to good yields and complete regiocontrol. Notably, aryl bromide (**3ia**), alcohol (**3la**), and ketone (**3ma**) were well-tolerated in this reaction. Furthermore, heteroaryl trifluoromethyl alkenes **1n–p** posed no problem, and the coupling products **3na–pa** were obtained in good efficiency. Our method is also applicable for the reaction employing the trifluoromethyl alkene **1q** derived from estrone, providing compound **3qa** in a moderate yield. Unfortunately, the reactions utilizing alkyl- or alkynyl-substituted trifluoromethyl alkenes failed to deliver the desired products in analytically pure form and are contaminated with inseparable hydroalkylation products. In the case of internal alkenes as precursors, no conversion of the alkenes could be achieved.

Scheme 2. Evaluation of the Substrate Scope of the Trifluoromethyl Alkenes[a,b]



[a]Unless otherwise specified, reactions were performed on a 0.4 mmol scale of the trifluoromethyl alkenes **1a–q** using 2.0 equiv of the epoxide **2a**, 20 mol % $TiCp_2Cl_2$, 1.0 equiv of NEt_3·HCl, and 3.0 equiv of Zn in 1.0 mL of DMF at room temperature for 24 h. [b]Yields are of the isolated product after column chromatography. [c]Reaction was performed on a 0.2 mmol scale.

Next, we continued to explore the versatility of this method by varying the structure of the epoxides (Scheme 3). When geminal disubstituted epoxides **2b–p** were employed as substrates, all the reactions afforded the products **3ab–ap** in moderate to good yields and perfect regioselectivities. Functionalities including carbamate (**3ae**), ether (**3af–ak**), silyl ether (**3al**), ester (**3am** and **3an**), and imide (**3ao**) turned out to be compatible under the standard reaction conditions. In the case of the aliphatic monosubstituted epoxide **2p**, the couping reaction still occurred on the substituted carbon exclusively, providing the corresponding primary bishomoallylic alcohol **3ap** as the single product. In addition, the reaction using cyclohexane oxide **2q** yielded two separable stereoisomers **3aq** in a moderate diastereomeric ratio. However, styrenyl oxide was found to be an unsuitable precursor in this Ti-catalyzed reaction. When 1,2-disubstituted epoxides were employed as substrates, the product was formed as a mixture of four inseparable isomers concerning both regio- and stereochemistry in low selectivities.

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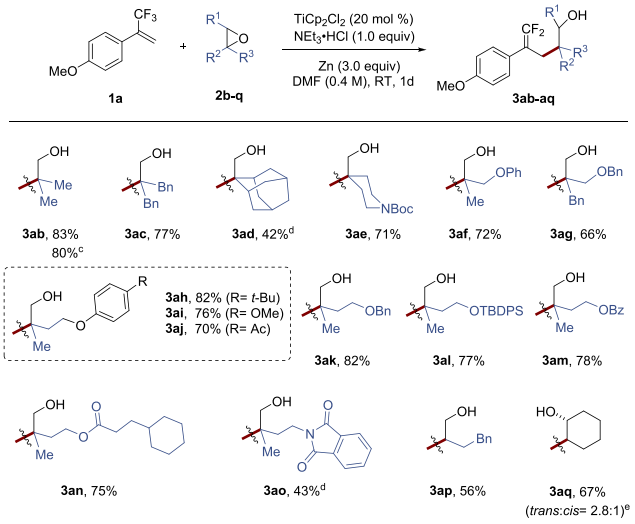
Scheme 3. Evaluation of the Substrate Scope of the Epoxides[a,b]



[a]Unless otherwise specified, reactions were performed on a 0.4 mmol scale of the trifluoromethyl alkene **1a** using 2.0 equiv of the epoxides **2b−q**, 20 mol % $TiCp_2Cl_2$, 1.0 equiv of NEt_3·HCl, and 3.0 equiv of Zn in 1.0 mL of DMF at room temperature for 24 h. [b]Yields are of the isolated products after column chromatography. [c]Reaction was performed on a 1 mmol scale. [d]Reactions were performed with 30 mol % $TiCp_2Cl_2$ at 40 °C. [e]Determined by ^1H NMR spectroscopy of the crude product.

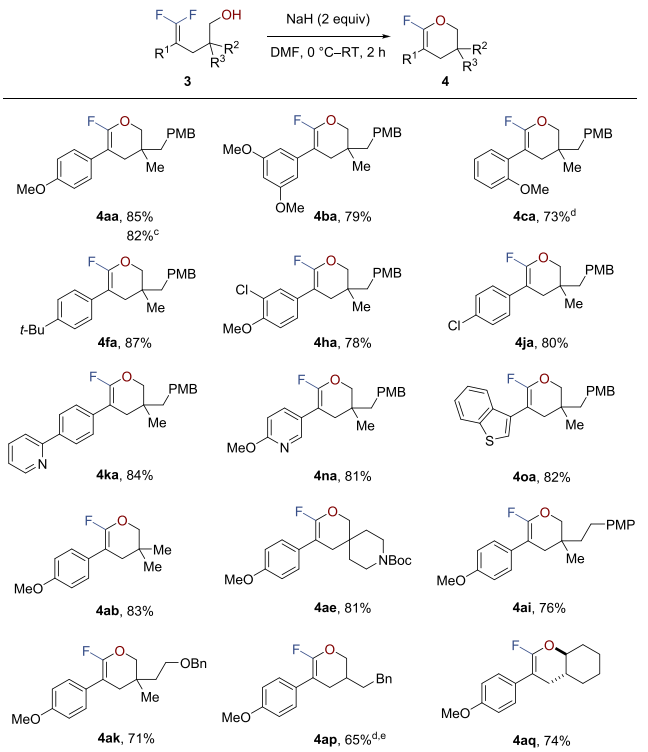
By taking advantage of the nucleophilic primary alcoholic moiety contained in all the coupling products, various 6-fluoro-3,4-dihydro-2*H*-pyrans **4** were readily synthesized in good to excellent yields upon treatment of the *gem*-difluorobishomoallylic alcohols **3** with NaH in THF (Scheme 4). It is noteworthy that monofluorinated alkenes are bioisosteres of peptide bonds in pharmaceutical research.[21]

To verify the radical reaction pathway of the ring opening process, an enantioenriched epoxide **2g** was subjected to the standard reaction conditions. The defluorinative cross-coupling product **3ag** was obtained in racemic form, whereas the enantiomeric excess of the recovered epoxide **2g** remained unchanged throughout the course of the reaction (Scheme 5).

A proposed reaction mechanism was depicted in Scheme 6. Initially, Ti(III) is generated under reductive conditions and subsequently carries out the reductive ring opening of epoxides **2** at the more-substituted site.[4] The resultant carbon-centered radical **I** performs radical addition to the trifluoromethyl alkenes **1** to afford a CF_3-substituted carbon radical **II**. It is known that general alkyl radicals are able to perform oxidative addition to Ti(III), which is known as an elementary step in the Ti-mediated deoxygenation of epoxides.[5b] Therefore, we believe that the more-electron-deficient CF_3-substituted carbon-radical **II** could be involved in a similar reaction with Ti(III). The following Ti(IV)-mediated *β*-F elimination from the generated complex **III** provides the intermediate **IV**, which could stay in equilibrium with the zinc alkoxide **V** through ion exchange between Zn(II) and Ti(IV). The protonation of either the complex **IV** or **V** by NEt_3·HCl leads to the formation of the product **3**. The reduction of Ti(IV) by Zn regenerates Ti(III) for the next catalytic cycle.

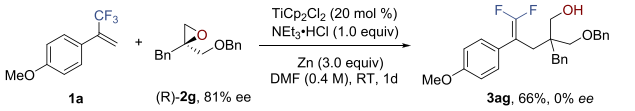
In summary, we successfully applied epoxides as the electrophilic coupling partner in the reductive allylic

Scheme 4. Derivatization of *gem*-Difluorobishomoallylic Alcohols to 6-Fluoro-3,4-dihydro-2*H*-pyrans[a,b]

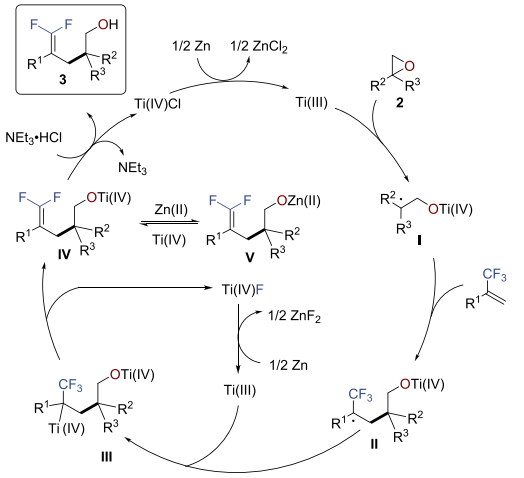


[a]Unless otherwise specified, reactions were performed on a 0.15 mmol scale of the *gem*-difluorobishomoallylic alcohols **3** using 2.0 equiv of the NaH in 1.0 mL of DMF for 2 h. [b]Yields are of the isolated products. [c]Reaction was performed on a 1 mmol scale. [d]Reaction was performed on a 0.1 mmol scale of *gem*-difluoroalkenes. [e]Reaction time: 5 h.

Scheme 5. Reaction Employing the Enantioenriched Epoxide 2g



Scheme 6. Proposed Reaction Mechanism



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defluorinative coupling reaction with trifluoromethyl alkenes under the catalysis of titanocene with the assistance of Zn as the reducing agent. A reaction mechanism involving Ti-mediated regioselective epoxide ring opening and β-F elimination has been proposed. This protocol provides an efficient entry to *gem*-difluorobishomoallylic alcohols, which can be further converted into a series of 6-fluoro-3,4-dihydro-2*H*-pyrans through a simple base-mediated nucleophilic substitution reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00960.

Representative experimental procedures and necessary characterization data for all new compounds are provided (PDF)

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Notes

The authors declare no competing financial interest.

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