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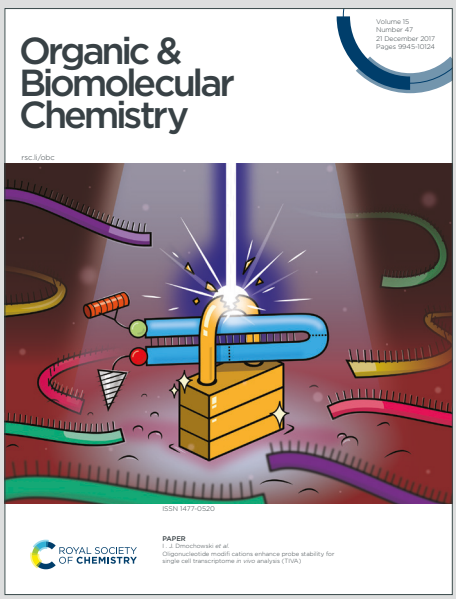

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DOI: 10.1039/D0OB00535E

COMMUNICATION

Synthesis of gem-difluoroalkenes via Nickel-catalyzed allylic defluorinative reductive cross-coupling of trifluoromethyl alkenes with epoxides

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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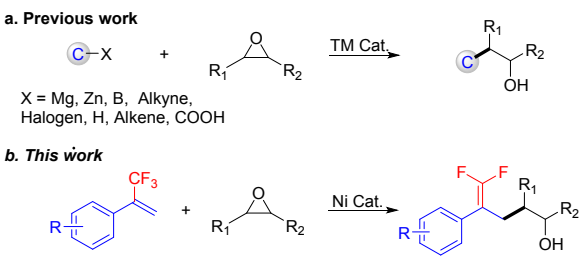
A nickel-catalyzed defluorinative reductive cross-coupling of trifluoromethyl alkenes with epoxides has been developed. Various substituted trifluoromethyl alkenes and epoxides were found to be suitable reaction substrates. This reaction enabled C(sp^3)–C(sp^3) bond construction through allylic defluorinative cross-coupling of trifluoromethyl alkenes under mild reaction conditions. This methodology wash highly compatible with various sensitive functional groups, providing access to a diverse array of functionalized gem-difluoroalkene-containing alcohol compounds.

Introduction

The introduction of fluorine into organic compounds can markedly increase the metabolic stability, lipophilicity, and bioavailability of the parent molecules.[1] Accordingly, fluorine-containing compounds have been widely used in the medicinal, agrochemical, materials, and life sciences.[2] Among these fluorine-containing compounds, *gem*-difluoroalkenes are interesting structural motifs with important applications in agrochemical and medicinal chemistry.[3] For instance, the *gem*-difluoroethylene moiety can serve as a carbonyl bioisostere in drug design, leading to improved pharmaceutical performance. Furthermore, *gem*-difluoroalkenes can be readily transformed into other fluorine-containing structures, such as monofluoroalkenyl, difluoromethylene, and *gem*-difluorocyclopropane groups.[4] Consequently, the efficient synthesis of *gem*-difluoroalkenes has attracted much attention. The direct difluoroolefination of carbonyl or diazo compounds using difluorocarbene precursors or difluoromethyl sulfones provides a universal approach to the preparation of *gem*-difluoroalkenes.[5] Recently, the defluorinative coupling of trifluoromethyl alkenes has provided a more convenient method for the synthesis of *gem*-difluoroalkenes.[6]

Epoxides are readily available and crucial electrophiles in organic synthesis, and have a high tendency toward ring-opening reactions.[7] The ring-opening products of epoxides are important chemical feedstocks that play vital roles in organic chemistry. In the last few decades, various ring-opening reactions of epoxides have been reported using carbon-based reagents,[8] including strongly nucleophilic Grignard reagents.[9] Organoboron and organozinc reagents are usually readily available and have broad functional-group tolerance. In this context, transition-metal-catalyzed Suzuki-type and Negishi-type ring-opening/cross-coupling reactions of epoxides have been realized.[10] Furthermore, reductive ring-opening/coupling reactions of epoxides have been reported, such as reductive couplings of alkynes[11] and aryl halides[12] with epoxides. Heck-type[13] reactions, C–H activation reactions,[14] and decarboxylative cross-coupling reactions[15] of epoxides have also been reported. Based on the importance of fluorine-containing compounds, we envisaged that fluorine-containing compounds could be applied to epoxides ring-opening reactions to synthesize fluorine-containing alcohols. To our knowledge, cross-coupling reactions of fluorine-containing compounds with epoxides have rarely been reported. Herein, we report the first example of the nickel-catalyzed defluorinative reductive cross-coupling of trifluoromethyl alkenes with epoxides. This reaction enabled C(sp^3)–C(sp^3) bond construction through the allylic defluorinative cross-coupling of trifluoromethyl alkenes under mild reaction conditions. The reaction showed a high degree of tolerance toward many sensitive functional groups, providing access to a diverse array of functionalized gem-difluoroalkene-containing alcohol compounds (**Scheme 1**).



Scheme 1 Cross-Coupling Reactions of Epoxides

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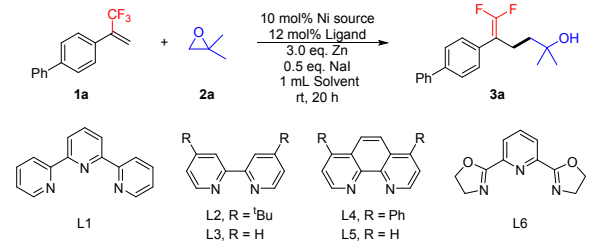
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Results and discussion

To optimize the reaction conditions, we selected trifluoromethyl-substituted alkene **1a** and isobutylene oxide (**2a**) as model substrates (**Table 1**). Systematic screening of all reaction parameters was conducted to obtain optimal reaction conditions, under which the desired product **3a** was obtained in

Table 1 Optimization of the reaction conditions

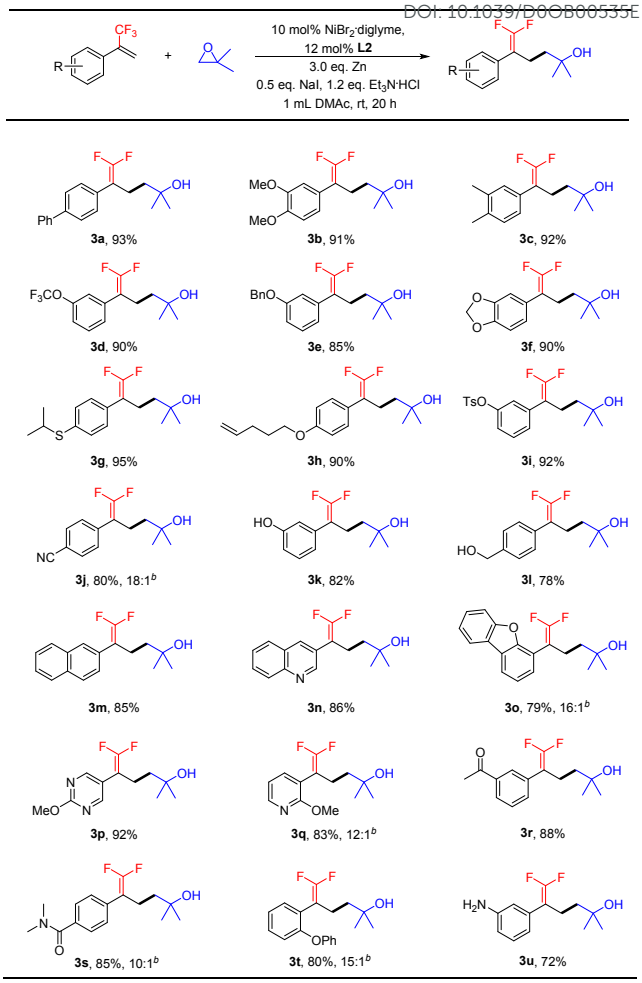


Entry[a]	Ni source	Ligand	Addtive	Solvent	Yield%
1	$NiBr_2$·diglyme	L1	-	DMAc	trace
2	$NiBr_2$·diglyme	L2	-	DMAc	trace
3	$NiBr_2$·diglyme	L1	Et_3N·HCl	DMAc	52
4	**$NiBr_2$·diglyme**	**L2**	**Et_3N·HCl**	**DMAc**	**96**
5	$NiBr_2$·diglyme	L3	Et_3N·HCl	DMAc	43
6	$NiBr_2$·diglyme	L4	Et_3N·HCl	DMAc	61
7	$NiBr_2$·diglyme	L5	Et_3N·HCl	DMAc	66
8	**$NiBr_2$·diglyme**	**L6**	**Et_3N·HCl**	DMAc	**95**
9	$NiCl_2(PPh_3)_2$	L2	Et_3N·HCl	DMAc	57
10	$Ni(acac)_2$	L2	Et_3N·HCl	DMAc	26
11	$NiBr_2$·diglyme	L2	Et_3N·HCl	MeCN	51
12	$NiBr_2$·diglyme	L2	Et_3N·HCl	NMP	73
13[b]	$NiBr_2$·diglyme	L2	Et_3N·HCl	DMAc	2
14	$NiBr_2$·diglyme	L2	H_2O	DMAc	5
15[c]	$NiBr_2$·diglyme	L2	MeOH	DMAc	80
16[c]	$NiBr_2$·diglyme	L2	EtOH	DMAc	66
17	$NiBr_2$·diglyme	L2	NH_4Cl	DMAc	31
18[d]	-	L2	Et_3N·HCl	DMAc	0
19[e]	$NiBr_2$·diglyme	L2	Et_3N·HCl	DMAc	0

[a] 1a (0.2 mmol), 2a (3 equiv.), Et_3N·HCl (1.2 equiv.) in 1 mL solvent at rt for 20 h. [b] Mn instead of Zn. [c] 5 equiv. alcohol instead of Et_3N·HCl. [d] no Ni source. [e] no NaI. The yield was determined by GC using triphenylmethane as internal standard. NMP = 1-methyl-2-pyrrolidinone.

excellent yield. Based on recent studies on the nickel-catalyzed defluorinative reductive cross-coupling of trifluoromethyl alkenes, we first examined analogous catalytic conditions, but almost no product was detected (entries 1 and 2). Surprisingly, when an equivalent amount of Et_3N·HCl was added, a moderate reaction yield was obtained (entry 3). Under these conditions, a series of ligands was screened, and optimal reaction conditions obtained (entry 4). Reactions employing alternative ligands, such as the related bis(pyridine) and phenanthroline, furnished the product in moderate yields (entries 5 to 7). Switching ligand **L2** to PyBOX also resulted in excellent reactivity (entry 8). When alternative nickel sources, such as $NiCl_2(PPh_3)_2$ and $Ni(acac)_2$, were used as catalysts, the product was obtained, but with reduced efficiency (entries 9 and 10). Solvents other than DMAc, such as MeCN and NMP, gave decreased reaction yields (entries 11 and 12). Replacing Zn with Mn as reductant resulted in a significant decrease in reaction yield (entry 13). When using proton sources other than Et_3N·HCl, only EtOH resulted in a slightly better yield (entries 14 to 17). Reactions performed without a nickel source did show product formation (entry 18). Without NaI, almost no product was observed under standard conditions (entry 19). Using other additives, such as NaCl or NaBr, the yield is very low (see SI).

Table 2 Scope of the of trifluoromethyl alkenes[a]



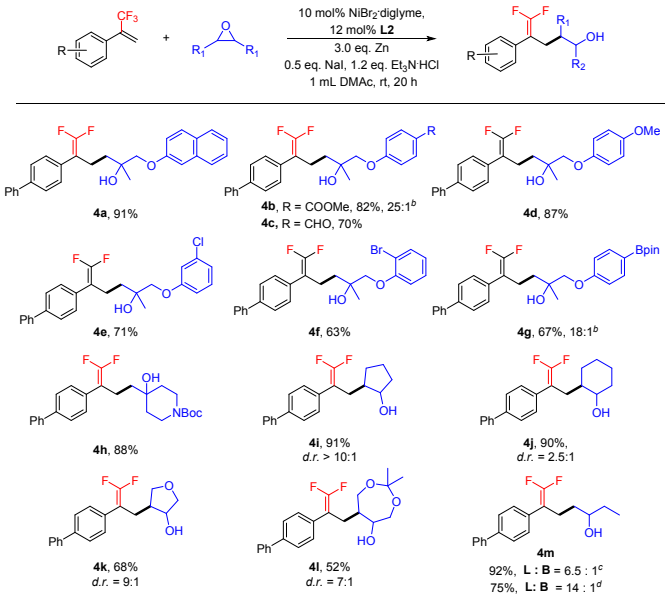
[a] Isolated yield for 0.2 mmol scale reaction. 10 mol % $NiBr_2$·diglyme, 12 mol % **L2**, 3 equiv. Zn, 0.5 equiv. NaI and 1.2 equiv. Et_3N·HCl in 1 mL DMAc. [b] **Product ratio** = desired product/addition by-product. The product ratio > 35:1 unless otherwise noted.

With optimized reaction conditions in hand, we next evaluated the substrate scope of trifluoromethyl alkenes in the Ni-catalyzed allylic defluorinative cross-coupling reaction (**Table 2**). First, many aryl and heteroaryl-substituted trifluoromethyl alkenes were coupled with isobutylene oxide (**2a**), affording the corresponding products in excellent isolated yields. Notably, this reaction showed good tolerance of a wide range of synthetically useful functional groups, including ether (**3b**, **3e**), trifluoromethoxy (**3d**), ketal (**3f**), hydroxyl (**3l**), cyano (**3j**), naphthalene (**3m**), ketone (**3r**), and amide (**3s**) groups. The tolerance of aryl tosylate (**3i**) and terminal alkene (**3h**) groups provides opportunities for further product functionalization. Both electron-rich and electron-poor trifluoromethyl alkenes afforded the desired products in good yield. In addition to the styrene system, heterocycles, such as quinoline (**3n**), dibenzofuran (**3o**), pyrimidine (**3p**), and pyridine (**3q**), were also compatible with the reaction under the reductive conditions,

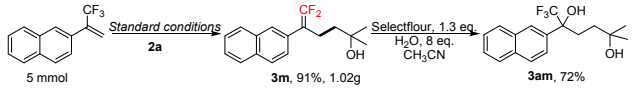
affording the corresponding products in good to high yields. Some active groups that are incompatible with transition-metal-catalyzed cross-coupling reactions, such as sulfoether (**3g**), unprotected phenolic hydroxyl (**3k**), and amine (**3u**) groups, were compatible with this defluorinative reductive cross-coupling reaction. The products were obtained as a mixture with addition by-products.

We next evaluated the substrate scope of epoxides in this defluorinative reductive cross-coupling reaction (**Table 3**). Importantly, many functional groups were tolerated, including naphthalene (**4a**), ester (**4b**), aldehyde (**4c**), and ether (**4d**) groups. Aryl-X (X = Cl, Br) bonds (**4e**, **4f**) did not hinder the reaction, providing the possibility for further cross-coupling reactions at the halogenated positions. Aryl borate (**4g**) was also tolerated in this reaction. Cyclic epoxides also participated in the coupling reactions. Additional functional groups, such as carbamate (**4h**), ether (**4k**), and ketal (**4l**), were also tolerated. Acyclic monosubstituted epoxides (**4m**) also afforded the corresponding products in good yields. Branched β-iodohydrin can be generated when using monosubstituted epoxides as substrate. So a mixture of linear and branched products was obtained. When ethanol was used as a proton source, the product selectivity was improved. Unfortunately, styrene oxides were not suitable reaction substrates. We observed isomerization to ketone and self-coupling. Maybe the iodohydrin intermediate of styrene oxide was instable.

Table 3 Scope of epoxides[a]



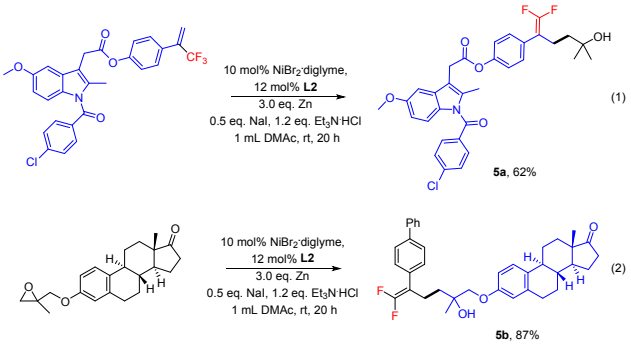
[a] Isolated yield for 0.2 mmol scale reaction. [b] **Product ratio** = desired product/addition by-product. The product ratio > 30:1 unless otherwise noted. [c] $Et_3N·HCl$ as proton source. [d] EtOH as proton source.



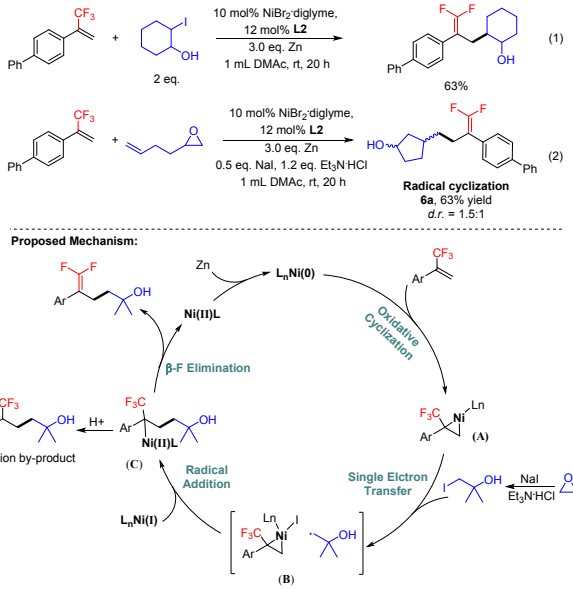
Scheme 2 A gram-scale reaction and derivatization of product

To demonstrate the scalability of the defluorinative reductive cross-coupling, we performed the reaction on a gram scale, which afforded the product in 91% yield (**Scheme 2**). To further demonstrate the synthetic application of the product, a fluoro-hydroxylation of **3m** was performed using Hu's protocol,[16] providing α-CF_3 alcohol **3am** in a yield of 72%.

Next, we demonstrated the defluorinative reductive cross-coupling reactions for the late-stage modification of biologically active molecules containing trifluoromethyl alkenes or epoxides (**Scheme 3**). As an example, an indomethacin derivative smoothly reacted with isobutylene oxide to afford desired product **5a** in 62% isolated yield with retention of the aryl chloride moiety. Furthermore, the modification of an estrone derivative produced corresponding product **5b** in high yield while tolerating the ketone group.



Scheme 3 The modification of complex molecules



Scheme 4 Mechanism experiments and proposed mechanism

The reaction mechanism was investigated using several experiments. First, the product was obtained in moderate yield when iodohydrin was used instead of epoxide in the absence of sodium iodide (**Scheme 4, eq. 1**). These results indicated that the β-iodohydrin was an intermediate in the reaction. Next, an epoxide containing a pendant homoallyl group was tested, with only the ring-closure isomer obtained (**Scheme 4, eq. 2**). Using Ni(0) as the starting metal source, the reaction also has a high yield (see SI). The above observations were consistent with a radical-type reaction mechanism.[17] Based on the above results and previous reports, a possible reaction mechanism is shown in Scheme 4. Initially, a Ni(0) complex is formed under the

reductive reaction conditions, followed by the oxidative cyclization with the trifluoromethyl-substituted alkenes to generate **A**. The β-iodohydrin then reacts with the **A** to give a β-hydroxyalkyl radical and a LNi(III) complex **B** through a single-electron transfer. The addition of hydroxyalkyl radical to the three-membered ring Ni(III) complex **B** to give a LNi(II) complex **C**. Next, this Ni(II) species **C** undergoes β-fluorine elimination to afford the corresponding products. Finally, the initial Ni(0) complex is regenerated by reaction with the reducing agent.

Conclusions

In summary, we have developed a nickel-catalyzed defluorinative reductive cross-coupling of trifluoromethyl alkenes with epoxides. Various substituted trifluoromethyl alkenes and epoxides were found to be suitable reaction substrates. The reaction shows a high degree of tolerance toward various sensitive functional groups. This radical addition reaction has more excellent functional group compatibility and higher yield over the previous Ni-catalyzed reactions. It providied access to diverse array of functionalized gem-difluoroalkene-containing alcohols, which are valuable chemical feedstocks for synthetic chemistry and medicinal chemistry. This study also provides a method for the modification of complex organic molecules containing trifluoromethyl alkenes or epoxides.

This work was supported by the University Natural Science Research Key Project of Anhui Province and Anhui Natural Science Foundation.

Conflicts of interest

There are no conflicts to declare.

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DOI: 10.1039/D0OB00535E

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