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Ligand-Free Nickel-Catalyzed Reductive Allylic Defluorinative Cross-Coupling of α-Trifluoromethyl Alkenes with Epoxides

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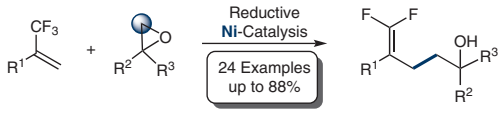

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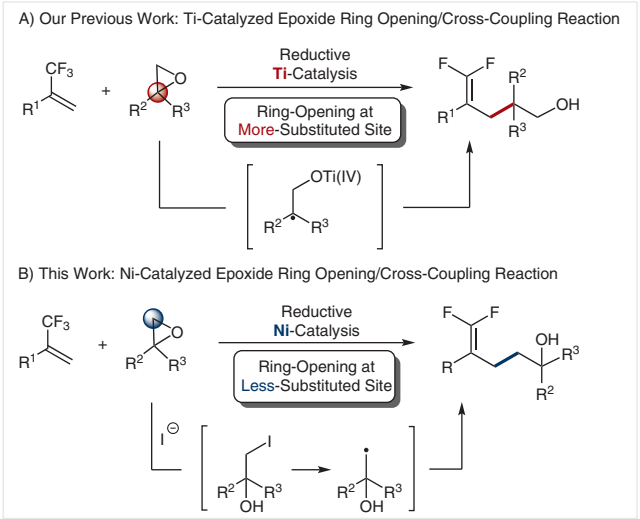
Abstract We report a reductive allylic defluorinative reaction of α-trifluoromethyl alkenes with terminal epoxides, which consists of an iodide-mediated regioselective ring opening and a nickel-catalyzed radical-type cross-coupling, providing diverse tertiary *gem*-difluorobishomoallylic alcohols in moderate to high yields. Notably, this reaction is conducted under mild conditions and requires no external ligand or proton donor.

Key words nickel catalysis, epoxides, difluoroalkenes, defluorination, ring opening

The *gem*-difluoroalkene group is a carbonyl bioisostere that is less susceptible to metabolism.[1] Numerous biologically active compounds bearing a *gem*-difluoroalkene subunit have been reported.[2] Moreover, *gem*-difluoroalkenes can also serve as precursors for the preparation of versatile organofluorines.[3] Conventional syntheses of *gem*-difluoroalkenes rely on one of two main concepts: difluoroolefination of carbonyl, diazo, or hydrazone compounds[4] or nucleophilic addition to α-trifluoromethyl alkenes, involving allylic C–F bond cleavage.[5–7] Recently, a reductive strategy[8] has been also successfully applied, involving the coupling of α-trifluoromethyl alkenes with various electrophiles, permitting the synthesis of sterically demanding *gem*-difluoroalkenes with high compatibility toward various sensitive functional groups.[9] We recently extended the scope of the electrophilic coupling partners to epoxides by using reductive Ti catalysis, in which a Ti(III)-mediated homolytic C–O bond cleavage favors the generation of a more stable carbon-centered radical, permitting selective ring opening at the more-substituted site (Scheme 1A).[9h] Here, we report a complementary reaction involving an-iodide-mediated selective epoxide ring opening by an S_N2 pathway with preferential attack on the less-substituted position, and subsequent allylic defluorinative cross-coupling of α-trifluoromethyl alkenes with the alkyl iodides generated in situ, providing a new route to tertiary *gem*-difluorohomoallylic alcohols (Scheme 1B).[10]



Scheme 1 (A) Our previous work: Ti-catalyzed ring-opening/cross-coupling reaction; (B) This-work: Ni-catalyzed ring-opening/cross-coupling reaction

The α-trifluoromethyl styrene **1a** and the geminally disubstituted epoxide **2a** were selected as model substrates for optimization of the reaction conditions (Table 1). Systematic screening of various reaction parameters allowed us to identify the optimal reactions as follows: NiI_2 (10 mol%) as the catalyst, Zn (3 equiv) as a reducing agent, and NaI (0.5 equiv) as an additive in DMA as a solvent at room temperature for 24 hours. In this case, the desired cross-coupling proceeded predominantly on the less-substituted

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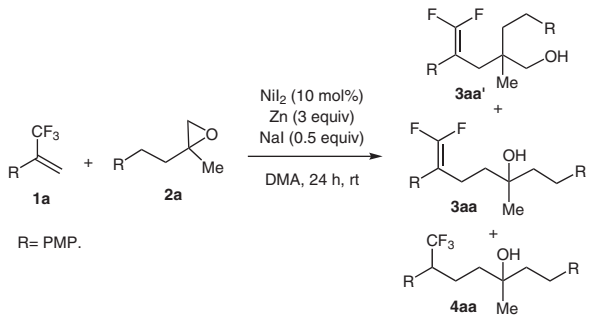
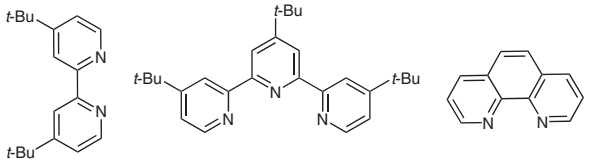
site of the epoxide, affording the inseparable products **3aa** and **3aa′** in 84% combined yield and a regioisomeric ratio of 13:1 (Table 1, entry 1). Surprisingly, the reactions using the pyridine-based ligands **L1–3**, which had proved to be essential in our previous studies,[9b–e] gave inferior results (entries 2–4). The absence of NaI led to a significant decrease in the efficiency of the reaction (entry 5). Performing the reaction under iodide-free conditions by replacing NiI_2 with nickel(II) chloride–ethylene glycol dimethyl ether complex [$Ni(dme)Cl_2$] caused a complete shutdown of this coupling reaction (entry 6). These results confirmed the crucial role of iodide in the reaction. Furthermore, addition of $Et_3N{\cdot}HCl$ as a proton donor resulted in the formation of the hydroalkylation product **4aa** as a byproduct (entry 7). Conducting the reactions in other polar solvents (NMP or THF) gave the product in lower yields and with less regiocontrol (entries 8 and 9), whereas the desired reaction failed to occur in toluene (entry 10). Moreover, the use of Mn as reductant instead of Zn did not improve the outcome of this reaction (entry 11).

With the optimal reaction conditions in hand, we started to evaluate the substrate scope of this Ni-catalyzed reaction (Table 2). Gratifyingly, various aryl trifluoromethyl alkenes containing an electron-donating or electron-withdrawing group were found to be suitable precursors for the cross-coupling reactions with epoxide **2a**, giving a variety of *gem*-difluorobishomoallylic alcohols **3aa–ia** in moderate to high yields and generally as single regioisomers. Notably, sensitive functionalities, including cyano, ester, and ketone groups, were well tolerated. Furthermore, the reaction employing a pyridinyl trifluoromethyl alkene afforded product **3ka** with high efficiency and good regiocontrol. Our reaction was also applied to a substrate derived from gemfibrozil, providing the product **3la** with moderate efficiency and a good regioisomeric ratio. Unfortunately, the desired products were not obtained from α-alkyl-substituted trifluoromethyl alkenes.

Next, we investigated the scope of this reaction by varying the structure of the epoxides (Table 3). To our delight, all the ring reactions using 1,1-disubstituted epoxides as pre-

Table 1 Variations from the Optimal Conditions[a]

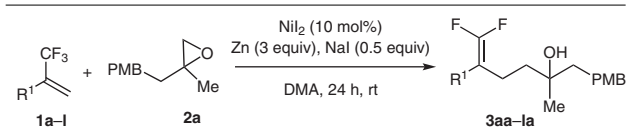


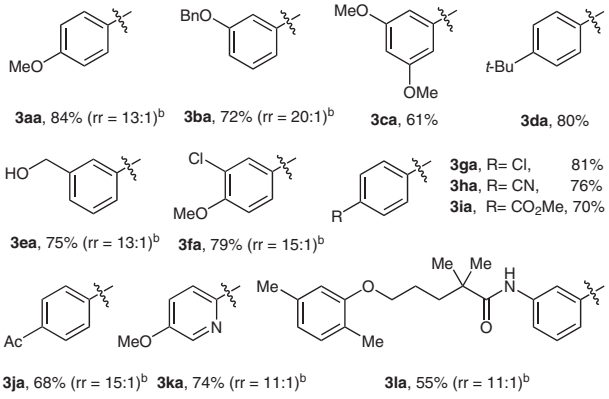


Entry	Variation from optimal conditions	Yield[b] of **3aa** (%)	rr[c]
1	**none**	**86 (84)[d]**	**13:1**
2	**L1** as ligand	18	13:1
3	**L2** as ligand	24	13:1
4	**L3** as ligand	16	13:1
5	no NaI	45	13:1
6	$Ni(dme)Cl_2$ instead of NiI_2; no NaI	0	–
7	$Et_3N{\cdot}HCl$ (1 equiv)	91 (9)[e]	13:1
8	NMP instead of DMA	25	7:1
9	THF instead of DMA	44	2:1
10	toluene instead of DMA	0	–
11	Mn instead of Zn	51	13:1

[a] Unless otherwise specified, reactions were performed on a 0.2 mmol scale of the α-trifluoromethyl alkene **1a** with epoxide **2a** (2.0 equiv), NiI_2 (10 mol%), NaI (0.5 equiv), and Zn (3.0 equiv) in *N*,*N*-dimethylacetamide (DMA; 1.0 mL) at rt for 24 h.
[b] Combined yield of **3aa** and **3aa′** determined by ^{19}F-NMR spectroscopy with 4-fluoroanisole as an internal standard.
[c] Regioisomeric ratio **3aa**/**3aa′**.
[d] Combined yield of **3aa** and **3aa′** isolated by column chromatography.
[e] Yield of **4aa** determined by ^{19}F-NMR spectroscopy with 4-fluoroanisole as an internal standard.

Table 2 Substrate Evaluation by Varying the Structure of the α-Trifluoromethyl Alkene[a]

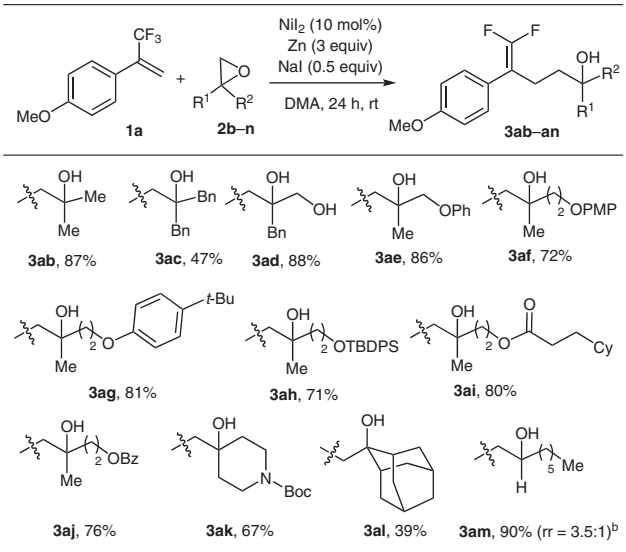




[a] Unless otherwise specified, reactions were performed on a 0.4 mmol scale of the α-trifluoromethyl alkene **1a–k** (0.2 mmol scale for **1l**) with epoxide **2a** (2.0 equiv), NiI_2 (10 mol%), NaI (0.5 equiv), and Zn (3.0 equiv) in DMA (1.0 mL) at rt for 24 h. Yields of the isolated products are reported. The products were obtained as single regioisomers unless stated otherwise.
[b] Determined by ^{19}F-NMR spectroscopy.

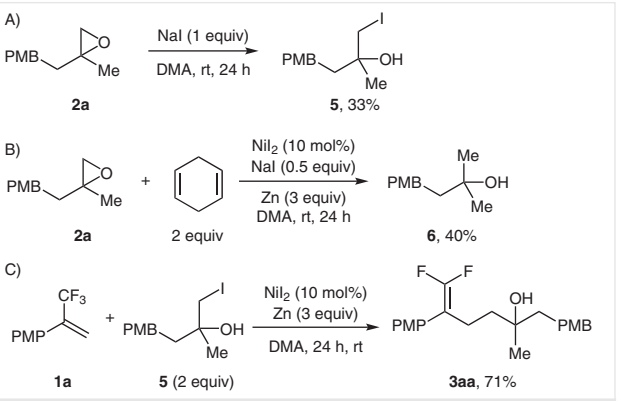
cursors proceeded exclusively on the less-substituted site, delivering an array of tertiary *gem*-difluorobishomoallylic alcohols **3ab–al** in moderate to high yields. In the case of monosubstituted epoxide **2m**, two separable regioisomers were obtained in a high combined yield. However, reactions using tetrasubstituted epoxides as substrates were unsuccessful.

Table 3 Substrate Evaluation by Varying the Structure of the Epoxide[a]



[a]Unless otherwise specified, reactions were performed on a 0.4 mmol scale of the α-trifluoromethyl alkene **1a** with epoxide **2b–n** (2.0 equiv), NiI_2 (10 mol%), NaI (0.5 equiv), and Zn (3.0 equiv) in DMA (1.0 mL) at rt for 24 h. Yields of the isolated products are reported. Unless otherwise noted, the products were obtained in pure form.
[b]Determined by ^{19}F-NMR spectroscopy.

Because NaI proved to be essential in the studied reaction, we speculated, on the basis of the mechanism that we proposed previously,[9b] that an iodide-mediated ring opening of the epoxides might occur in situ, providing alkyl iodides as partners with the α-trifluoromethyl alkenes. To verify this, we performed several control experiments (Scheme 2). First, we treated the epoxide **2a** with NaI in the absence of NiI_2 and Zn, affording the ring-opening product **5** in a moderate yield (Scheme 2A). Moreover, the reaction of the epoxide **2a** with cyclohexa-1,4-diene as a hydrogen-atom donor under the standard reaction conditions led to the formation of the deiodination product **6**, suggesting that the in situ-generated iodide **5** might be further reduced to the corresponding alkyl radical (Scheme 2B). When the epoxide **2a** was replaced by the iodide **5** in the reductive cross-coupling reaction with the α-trifluoromethyl alkene **1a** under NaI-free conditions, the same cross-coupling product as the reaction using epoxide was obtained in a good yield. These results confirm the feasibility of the iodide-mediated ring-opening reaction and subsequent coupling of the generated alkyl iodides with α-trifluoromethyl alkenes under ligand-free conditions.



Scheme 2 Control experiments

In conclusion, we have developed a domino epoxide ring-opening/defluorinative cross-coupling reaction employing terminal epoxides and α-trifluoromethyl alkenes as substrates.[11] This process is efficiently catalyzed by NiI_2 under ligand-free conditions, offering an efficient entry to a variety of tertiary *gem*-difluorobishomoallylic alcohols with good tolerance of sensitive functional moieties.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707170.

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(10) While this manuscript was under preparation, Lu et al. reported a related reductive cross-coupling of α-trifluoromethyl alkenes with epoxides, see: Lu, X.-Y.; Jiang, R.-C.; Li, J.-M.; Liu, C.-C.; Wang, Q.-Q.; Zhou, H.-P. *Org. Biomol. Chem.* **2020**, *18*, 3674.

(11) **4-Aryl-5,5-difluoropent-4-en-1-ols (3aa–la, 3ab–am); General Procedure**

A Schlenk tube equipped with a stirrer bar was charged with NiI_2 (8.8 mg, 0.04 mmol, 10 mol %), NaI (30 mg, 0.2 mmol, 0.5 equiv), and Zn (78 mg, 1.2 mmol, 3 equiv). The tube was then evacuated and filled with N_2 (three cycles). DMA (1.0 mL) was added under N_2, followed by the appropriate trifluoromethyl alkene **1** (0.4 mmol, 1.0 equiv) and epoxide **2** (0.8 mmol, 2.0 equiv). The mixture was stirred at rt for 24 h, and then the reaction was quenched by addition of H_2O. The aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude material was purified by column chromatography (silica gel, PE–EtOAc).

7,7-Difluoro-1,6-bis(4-methoxyphenyl)-3-methylhept-6-en-3-ol (3aa)

Colorless oil; yield: 126 mg (84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 7.9 Hz, 2 H), 7.08 (d, *J* = 8.6 Hz, 2 H), 6.89 (d, *J* = 8.8 Hz, 2 H), 6.82 (d, *J* = 8.6 Hz, 2 H), 3.80 (s, 3 H), 3.77 (s, 3 H), 2.60–2.53 (m, 2 H), 2.49–2.42 (m, 2 H), 1.77–1.68 (m, 2 H), 1.59–1.53 (m, 2 H), 1.23 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.7, 157.8, 153.2 (dd, *J* = 289.1, 286.2 Hz), 134.3, 129.3 (t, *J* = 3.4 Hz, 2 C), 129.2 (2 C), 125.7 (t, *J* = 2.8 Hz), 114.0 (2 C), 113.9 (2 C), 91.9 (dd, *J* = 20.6, 14.3 Hz), 72.4, 55.3 (2 C), 43.9, 39.9 (t, *J* = 2.3 Hz), 29.4, 26.7, 22.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –92.39 (d, *J* = 46.6 Hz, 1 F), –92.58 (d, *J* = 46.7 Hz, 1 F). HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{22}H_{26}F_2NaO_3$: 399.1742; found: 399.1741.