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Reductive Allylic Defluorinative Cross-Coupling Enabled by Ni/Ti Cooperative Catalysis

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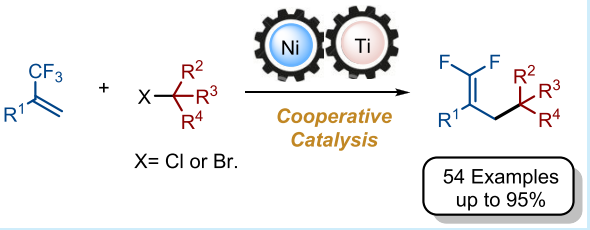
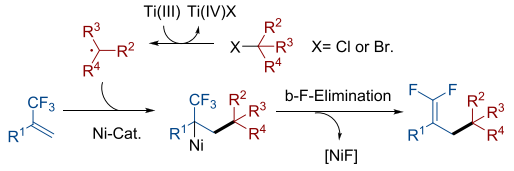
Supporting Information

ABSTRACT: Unactivated alkyl chlorides are abundant building blocks in organic synthesis, but they have been rarely engaged in cross-electrophile coupling. Herein, we report a Ni/Ti-cocatalyzed reductive allylic defluorinative cross-coupling between trifluoromethyl alkenes and unactivated alkyl chlorides and bromides, enabling the efficient preparation of diverse functional-group-rich *gem*-difluoroalkenes. Notably, synthesis of the *gem*-difluoroalkene analogues of azaperone, haloperidol, and benperidol was also accomplished using our method as a key step.



Because the *gem*-difluoroalkene moiety is a bioisostere of the carbonyl group and possesses higher stability in in vivo metabolism,[1] replacing a carbonyl group by *gem*-difluoroalkene in a biologically active compound is expected to result in a superior analogue. However, examples of biologically active *gem*-difluoroalkenes are limited,[1b,2] which is possibly attributed to the lack of methods to prepare these compounds with high structural complexity and functional-group diversity.[3] Organic chemists have striven to achieve this structural motif in the last decades and established two main strategies: (1) *gem*-difluoroolefination of carbonyl or diazo-compounds[4] and (2) organometallics- or strong base-mediated nucleophilic addition to trifluoromethyl alkenes followed by β-F elimination.[5,6] However, synthesis of sterically demanding *gem*-difluoroalkenes with high functionality tolerance has been achieved only very recently through photo-[7] or Ni-catalysis.[8] Last year, we established a Ni-catalyzed reductive allylic defluorinative cross-coupling reaction, affording various *gem*-difluoroalkenes under mild reaction conditions,[8b] but the main disadvantage of this method lies in the use of unstable alkyl iodides and tertiary alkyl bromides as precursors. In contrast, alkyl chlorides are more desirable coupling partners in terms of both stability and availability. Unfortunately, employing alkyl chlorides or primary and secondary alkyl bromides as substrates in our Ni-catalyzed reaction was not successful because the Ni-catalyst turned out to be unable to cleave the corresponding carbon-halide bonds efficiently.[8b] Indeed, the use of unactivated alkyl chlorides in reductive cross-coupling is rare.[9−11] On the other hand, reductive Ti-catalysis finds wide applications in organic synthesis[12] and has been recently discovered to be capable of promoting unactivated C−Cl bond cleavage in the hydroalkylation of electron-deficient alkenes.[9d] Herein, we envisaged a Ni/Ti-cocatalyzed[13,14] reductive allylic defluorinative cross-coupling reaction. In this cooperative catalysis,[15] Ti(III) is responsible for the carbon−halide bond activation, and the generated carbon-centered radicals undergo sequentially Ni-mediated addition to trifluoromethyl alkenes and β-F elimination, enabling the efficient synthesis of diverse *gem*-difluoroalkenes starting from unactivated alkyl chlorides or bromides (Scheme 1).

Scheme 1. Ni/Ti-Cocatalyzed Reductive Allylic Defluorinative Cross-Coupling



For optimization of the reaction conditions, we used the trifluoromethyl alkene **1a** and the tertiary chloride **2a** as standard substrates (Table 1). Screening of all the reaction parameters allowed us to define the optimal conditions: $NiBr_2$ as catalyst, Ti(indenyl)Cl_3 as cocatalyst, **L1** as ligand, DMA as solvent, and Zn as reducing agent at 60 °C (entry 1). The absence of either Ni- or Ti-catalyst in the reaction led to the dramatic decrease of the reaction yield, indicating the synergystic effect of the two catalysts (entries 2 and 3). The use of other pyridine-based ligands **L2**−**L5** delivered no better result (entries 4−7). The other Ni-sources including $NiBr_2$·glyme, NiI_2, and $Ni(acac)_2$ turned out to be substantially less reactive (entries 8−10). The desired reaction proceeded also in other polar solvents, such as DMF, NMP, and DMPU, but the yields were relatively low (entries 11−13). In contrast, only a trace amount of defluorinative product was produced in toluene. When Mn was used as the reductant instead of Zn, the product was obtained in a diminished efficiency (entry 15).

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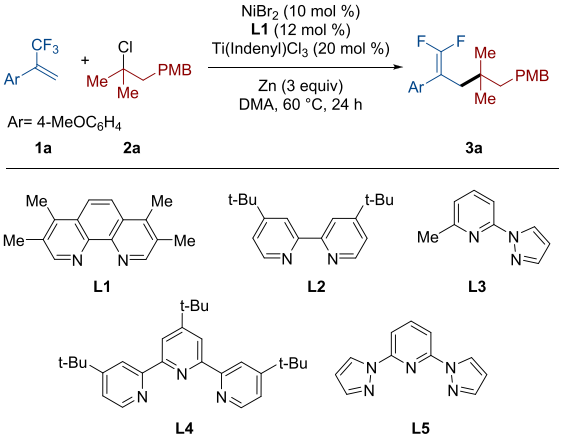
Table 1. Variation of the Reaction Parameters for the Ni/Ti-Cocatalyzed Reductive Allylic Defluorinative Cross-Coupling[a]



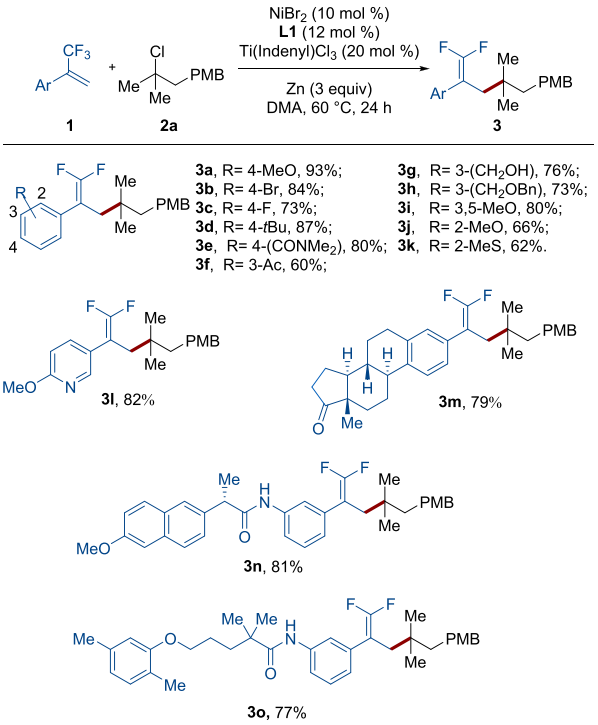
entry	variation from the optimal conditions	yield (%)[b]
1	**none**	**97 (93**[c]**)**
2	without $Ti(indenyl)Cl_3$	25
3	without $NiBr_2$	15
4	**L2** instead of **L1**	93
5	**L3** instead of **L1**	80
6	**L4** instead of **L1**	77
7	**L5** instead of **L1**	70
8	$NiBr_2$·glyme instead of $NiBr_2$	63
9	NiI_2 instead of $NiBr_2$	65
10	$Ni(acac)_2$ instead of $NiBr_2$	21
11	DMF instead of DMA	61
12	NMP instead of DMA	49
13	DMPU instead of DMA	56
14	toluene instead of DMA	trace
15	Mn instead of Zn	55
16	$TiCp_2Cl_2$ instead of $Ti(indenyl)Cl_3$	85
17	25 °C instead of 60 °C	77

[a]Unless otherwise specified, reactions were performed on a 0.2 mmol scale of the trifluoromethyl alkene **1a** using 2.0 equiv of the tertiary chloride **2a**, 10 mol % $NiBr_2$, 12 mol % ligand **L1**, 20 mol % $Ti(indenyl)Cl_3$, and 3 equiv of Zn in 1.0 mL DMA at 60 °C for 24 h. [b]Yields determined by ^{19}F-NMR-spectroscopy using 4-fluoroanisole as an internal standard. [c]Yield of the isolated product after column chromatography.

The reaction using the titanocene complex $TiCp_2Cl_2$ as cocatalyst afforded a slightly inferior result (entry 16). In addition, lowering the reaction temperature to room temperature had a detrimental effect on the outcome of the studied reaction (entry 17).

With the optimal reaction conditions in hand, we commenced to evaluate the substrate spectrum of this Ni/Ti-cocatalyzed reductive allylic defluorinative cross-coupling reaction (Scheme 2). First, an array of (hetero)aryl trifluoromethyl alkenes bearing electron-withdrawing or -donating substituents were reacted with the tertiary alkyl chloride **2a**, furnishing various *gem*-difluoroalkenes **3a**−**3l** in moderate to high yields. Notably, good tolerance of various functional moieties including aryl bromide (**3b**), amide (**3e**), ketone (**3f**), alcohol (**3g**) and thioether (**3k**) was observed in the studied reactions. Furthermore, we utilized the trifluoromethyl alkenes containing the scaffold of estrone, naproxen, or gemfibrozil as substrates, and the corresponding reactions

Scheme 2. Evaluation of the Substrate Scope the Ni/Ti-Cocatalyzed Reaction by Variation of the Trifluoromethyl Alkenes[a,b]



[a]Unless otherwise specified, reactions were performed on a 0.4 mmol scale of the trifluoromethyl alkenes **1** (0.2 mmol sacle for **3m**−**o**) using 2.0 equiv of the tertiary chloride **2a**, 10 mol % $NiBr_2$, 12 mol % ligand **L1**, 20 mol % $Ti(Indenyl)Cl_3$, and 3 equiv of Zn in 2.0 mL DMA at 60 °C for 24 h. [b]Yields of the isolated product after column chromatography.

afforded the coupling products **3m**−**3o** in good efficiency. Unfortunately, in the case of aliphatic trifluoromethyl alkenes as substrates, an inseparable mixture of the defluorination and the hydroalkylation product was obtained.

Subsequently, we continued to survey the substrate scope of this Ni/Ti-cocatalyzed reaction by varying the structure of tertiary alkyl chlorides (Scheme 3). Gratifyingly, all the reactions posed no problem, providing the products **3p**-**ad** in good to excellent yields. Again, a series of functional groups including ester (**3v**-**ad**), ketone (**3x**), olefin (**3y**) and ferrocene (**3ad**) were well tolerated in these reactions.

Next, we started to study the possibility to utilize secondary alkyl chlorides in this defluorinative cross-coupling reaction (Scheme 4). In the case of linear substrates, the reactions still occurred and the products **4a**−**4d** were obtained in good to high yields with extended reaction time (48 h). However, the reaction using cyclohexyl chloride failed to deliver the desired product **4e** on a synthetically useful level. Gratifyingly, all the reactions with secondary alkyl bromides as precursors furnished the defluorinative products **4a**−**4i** in high to excellent yields. Remarkably, in the absence of the Ti-cocatalyst, only a very low yield could be achieved in the case of the compound **4e**, confirming the essential role of the Ti-complex in this reaction. Moreover, in the case of enantiomerically pure secondary bromides as starting materials, the reactions yielded the products **4h** and **4i** in low diastereomeric ratios, suggesting the participation of secondary carbon-centered radicals in the reaction pathway.

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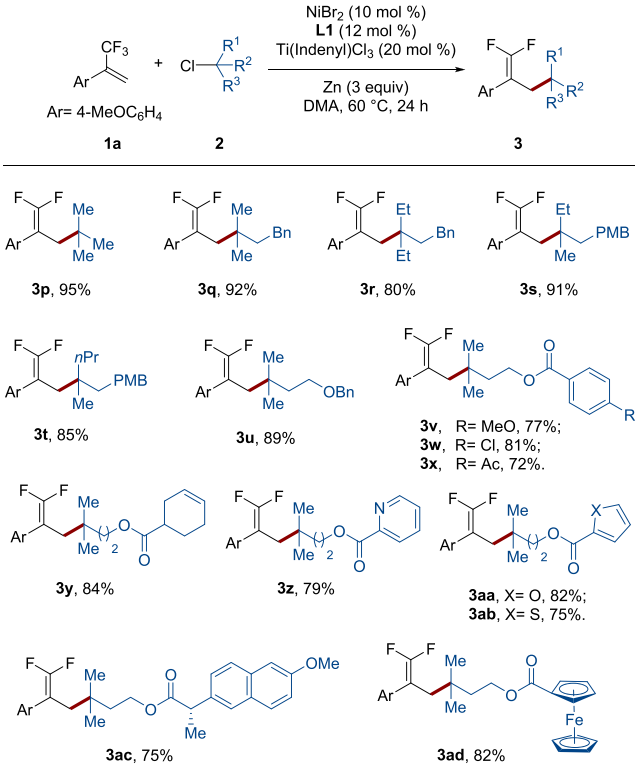
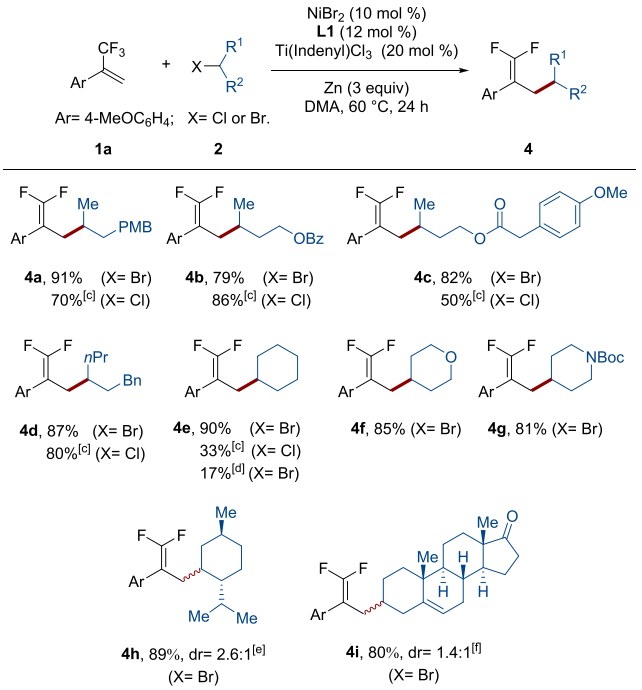
Scheme 3. Evaluation of the Substrate Scope the Ni/Ti-Cocatalyzed Reaction by Variation of *tert*-Alkyl Chlorides[a,b]



[a]Unless otherwise specified, reactions were performed on a 0.4 mmol scale of the trifluoromethyl alkene **1a** (0.2 mmol scale for **3ac**) using 2.0 equiv of the tertiary chlorides **2**, 10 mol % $NiBr_2$, 12 mol % ligand **L1**, 20 mol % Ti(indenyl)Cl_3, and 3 equiv of Zn in 2.0 mL of DMA at 60 °C for 24 h. [b]Yields of the isolated products.

Scheme 4. Evaluation of the Substrate Scope the Ni/Ti-Cocatalyzed Reaction by Variation of *sec*-Alkyl Chlorides/Bromides[a,b]



[a]Unless otherwise specified, reactions were performed on a 0.4 mmol scale of the trifluoromethyl alkene **1a** (0.2 mmol scale for **4h** and **4i**) using 2.0 equiv of the secondary bromides **2**, 10 mol % $NiBr_2$, 12 mol % ligand **L1**, 20 mol % Ti(indenyl)Cl_3, and 3 equiv of Zn in 2.0 mL of DMA at 60 °C for 24 h. [b]Yields of the isolated products. [c]Reaction time: 48 h. [d]Reaction performed without Ti(indenyl)Cl_3. [e]Determined by ^{19}F-NMR-spectroscopy. [f]Determined by ^{13}C NMR-spectroscopy.

When primary alkyl chlorides were employed as substrates, no cross-coupling reaction occurred at all. In contrast, primary alkyl bromides turned out to be pertinent precursors for this Ni/Ti-cocatalyzed reaction, and the corresponding *gem*-difluoroalkenes **5a**–**5n** were furnished in good to excellent yields (Scheme 5). Again, the significant influence of Ti-cocatalysis was observed in the case of compound **5a**, since only a trace amount of the defluorinative product could be generated when conducting the reaction without the Ti-cocatalyst.

γ-Amino butyrophenones are reported to be dopamine 2 antagonists, and many of them are commercialized medications or under the clinical investigation for treatment of mental diseases.[16] In order to demonstrate the utility of our method, the *gem*-difluoroalkene analogues of azaperone, haloperidol, and benperidol were readily synthesized using our Ni,Ti-cocatalyzed reductive allylic defluorinative cross-coupling reaction as a key step followed by some simple functionality conversions including saponification, iodination, and base-mediated *N*-alkylation (Scheme 6).

Although it has been reported that Ti(III) is capable of cleaving the carbon–halide bond in the radical pathway in nonpolar solvent,[9d] the poor result of our defluorinative reaction in toluene raised doubt whether the same process occurs in this case. To verify it, we conducted the radical trapping reactions employing the tertiary alkyl chloride **2a** and the primary alkyl bromide **2ao** with 1,4-cyclohexadiene as a hydrogen-radical source under our standard conditions in the absence of Ni-salt (Scheme 7). In both cases, the dehalogenated products **11** and **12** were obtained in good yields, confirming that Ti(III) is also able to promote the homolytic cleavage of carbon–halide bonds in DMA under reductive conditions.

Furthermore, it is known that Ti(III) is able to catalyze radical hydroalkylation of electron-deficient alkenes using secondary or tertiary alkyl chlorides in the presence of NEt_3·HCl as a proton donor in nonpolar solvents.[9d] When the Ni-catalyst was replaced by NEt_3·HCl in our reaction, hydroalkylation of the trifluoromethyl alkene **1a** did not occur, and a small amount of the defluorinative product was afforded, instead. This result reveals the indispensable role of Ni-catalyst in the C–C bond-forming step for the defluorinative reaction in DMA. In contrast, when the reaction was conducted in toluene using $TiCp_2Cl_2$ as a catalyst, the hydroalkylation product **13** could be formed as the single product in a high yield (Scheme 8).

In summary, we developed a Ni,Ti-cocatalyzed reductive allylic defluorinative cross-coupling reaction between trifluoromethyl alkenes and unactivated alkyl chlorides and bromides. In this cooperative catalysis, the challenging unactivated carbon–chloride or carbon–bromide bonds are cleaved by the Ti(III)-catalyst in a radical pathway, while the following C–C bond formation and *β*-F elimination are facilitated by the Ni-catalyst. This new method offers an efficient entry to a broad range of *gem*-difluoroalkenes with a good tolerance of

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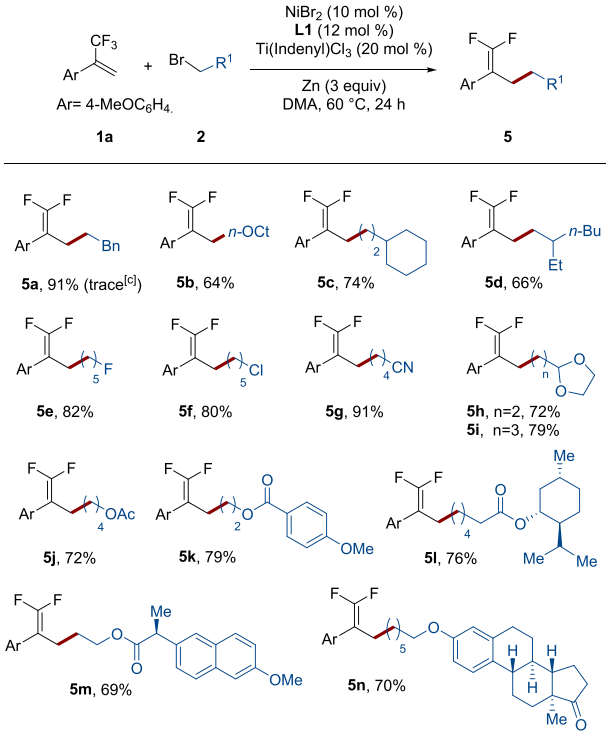
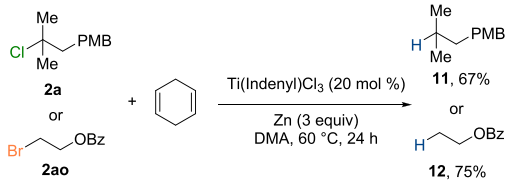
Scheme 5. Evaluation of the Substrate Scope the Ni/Ti-Cocatalyzed Reaction by Variation of *pri*-Alkyl Bromides[a,b]



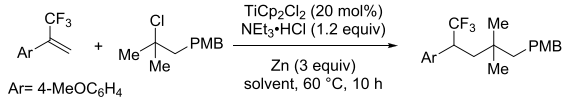
[a]Unless otherwise specified, reactions were performed on a 0.4 mmol scale of the trifluoromethyl alkene **1a** (0.2 mmol scale for **5l**–**n**) using 2.0 equiv of the primary bromides **2**, 10 mol % $NiBr_2$, 12 mol % ligand **L1**, 20 mol % Ti(indenyl)Cl_3, and 3 equiv of Zn in 2.0 mL of DMA at 60 °C for 24 h. [b]Yields of the isolated products. [c]Reaction performed without Ti(indenyl)Cl_3.

diverse functional moieties. Moreover, we have successfully synthesized the *gem*-difluoroalkene analogues of azaperone, haloperidol, and benperidol using this Ni,Ti-cocatalyzed reaction as a key step.

Scheme 7. Radical Trapping Reactions with 1,4-Cyclohexadiene



Scheme 8. Ti-Catalyzed Hydroalkylation of Trifluoromethyl Alkene 1a



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03102.

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

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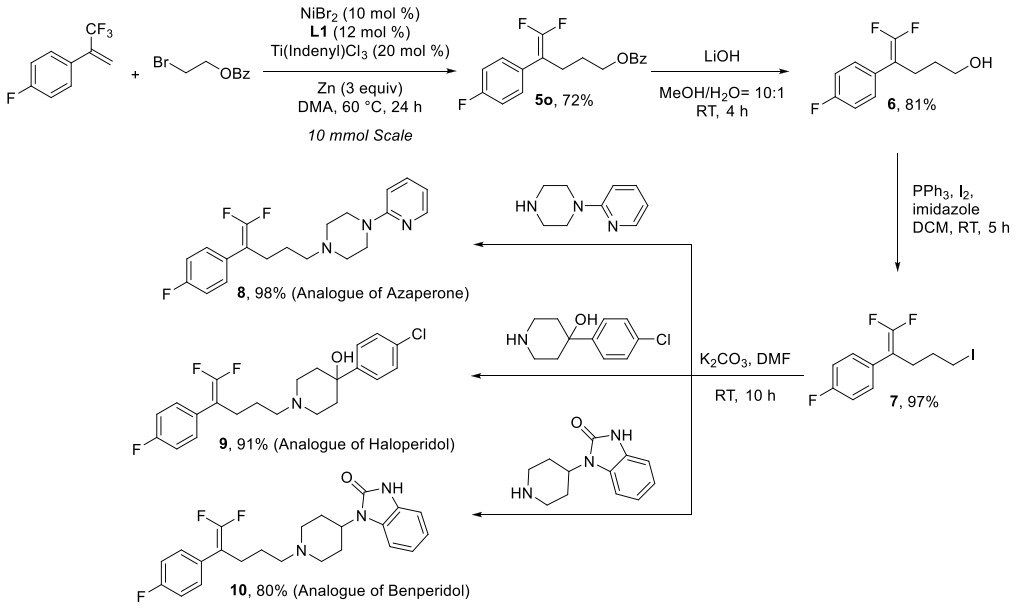
Notes

The authors declare no competing financial interest.

Scheme 6. Synthesis of *gem*-Difluoroalkene Analogues of Biologically Active γ-Amino-Butyrophenones



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