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Nickel-catalyzed allylic defluorinative alkylation of trifluoromethyl alkenes with reductive decarboxylation of redox-active esters†

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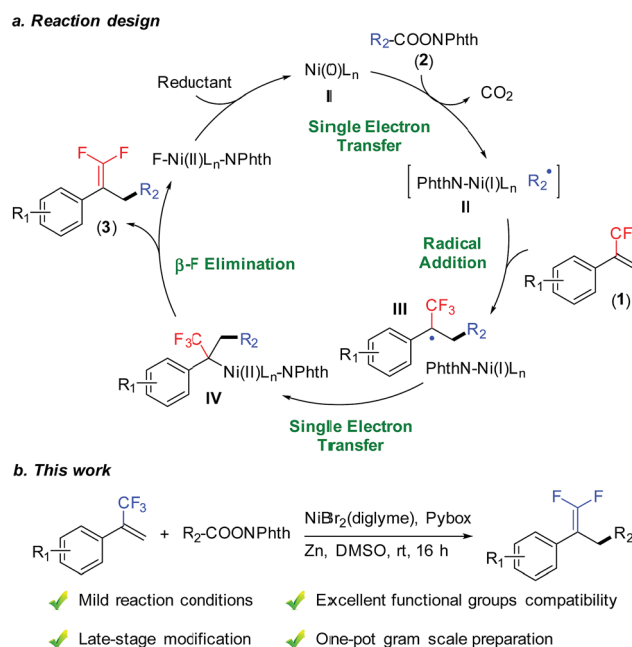
Herein, we report a nickel-catalyzed allylic defluorinative alkylation of trifluoromethyl alkenes through reductive decarboxylation of redox-active esters. The present reaction enables the preparation of functionalized *gem*-difluoroalkenes with the formation of sterically hindered C(sp³)-C(sp³) bonds under very mild reaction conditions, while tolerating many sensitive functional groups and requiring minimal substrate protection. Therefore, this method provides an efficient and convenient approach for late-stage modification of biologically interesting molecules.

Introduction

Efficient strategies for introducing fluorine-containing fragments into organic compounds exert positive influences on biochemical sciences, because these fluorochemicals have superior bioactivity and physicochemical characteristics compared to their non-fluorinated counterparts.¹ Among them, *gem*-difluoroalkenes are a class of structurally superior fluorine-containing compounds, and they have attracted substantial interest in agrochemistry and medicinal chemistry. For instance, the *gem*-difluoroethylene moiety is widely used as an ideal carbonyl group bioisostere in drug design.² In addition, the *gem*-difluoroethylene moiety can be easily transformed into other fluorine-containing structures such as monofluoroalkenyl, difluoromethylenyl, and trifluoromethyl groups.³ To date, various strategies have been developed for the preparation of *gem*-difluoroalkenes, including the conventional ones, such as direct difluoroolefination of carbonyl or diazo groups.⁴ More recently, defluorinative functionalization of trifluoromethyl alkenes has been applied to the synthesis of *gem*-difluoroalkenes.⁵ For example, Hayashi reported a rhodium-catalyzed cross coupling of 1-(trifluoromethyl)alkenes with arylboroxines to access 1,1-difluoroalkenes with C(sp²)-C(sp³) bond construction.⁶ Molander realized an example of defluorinative alkylation of trifluoromethyl alkenes using radical precursors (potassium organotrifluoroborates, alkylbis(catecholato)silicates and trimethylsilylamines) under photocatalysis conditions.⁷

Despite the great successes achieved, general methods to obtain *gem*-difluoroalkenes with readily available reagents under mild conditions are still required.

Reductive cross-coupling reactions represent a versatile tool for accurate construction of C-C bonds from cheap, abundant, and stable electrophiles as compared with methods using the corresponding organometallic reagents.⁸ Recently, reductive decarboxylative coupling has been exploited for generating alkyl radicals from alkanolic acids, complementing the use of alkyl halides beneficially.⁹ As part of our ongoing interest in alkene functionalization reactions^{9b,10} and fluorinated olefin

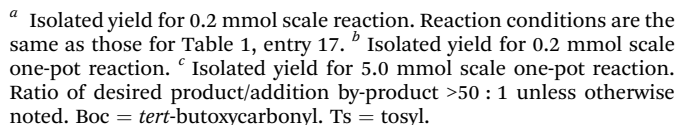


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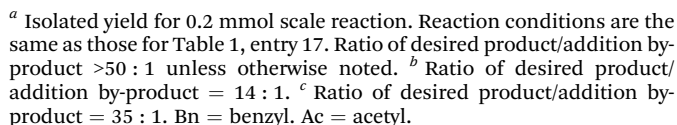
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Fig. 1 Nickel-catalyzed allylic defluorinative alkylation. NPhth = phthalimide.



To further demonstrate the high compatibility of this reaction with diverse functional groups, we exploited its application as an easy-to-use tool for the modification of natural products and drug molecules (Table 4). As an illustration, lithocholic acid derivative **2o** smoothly reacted with **1a** to afford the desired product **3ao** with 74% isolated yield. Another example is of dehydrocholic acid ester **2p** containing three base-sensitive ketone groups, which performed well during this modification process. In the modification of more complex gibberellic acid ester **2q**, the desired product **3aq** was obtained in 22% yield despite the presence of an ester group, internal and terminal alkenes, and unprotected secondary and tertiary alcohol groups in the reactant. Modification of a niflumic acid derivative **1r** produced the corresponding product **3ra** while tolerating the ester group, pyridine ring, and secondary amine. Indometacin derivative **1s** could react with **2a** to provide product **3sa** in 68% yield, without affecting either the indole ring or aryl chloride.

Table 3 Substrate scope of trifluoromethyl alkenes^a

In competition experiments, tertiary alkyl electrophiles exhibited better reactivity than both primary and secondary ones. For instance, we obtained **5be** and **5bf** as the sole products (Scheme 1, eqn (1)), in which carbon–carbon bonds were formed at the tertiary alkyl bromide sites, while the primary and secondary alkyl sulfonates survived. Interesting results were obtained for the substrates (**5ag** and **5ah**) containing tertiary and primary or secondary alkyl bromides (Scheme 1, eqn (2)). Cyclization products (as the sole product for **5ag** and the main product for **5ah**) were generated firstly through allylic

Table 4 Modification of natural products and drug molecules^a

^a Isolated yield for 0.2 mmol scale reaction. Reaction conditions are the same as those for Table 1, entry 17. Ratio of desired product/addition by-product >50 : 1 unless otherwise noted. ^b Ratio of desired product/addition by-product = 7 : 1.

defluorinative alkylation of the tertiary alkyl bromide and then intramolecular cyclization at the primary or secondary sites.¹⁸ Finally, using a trifluoromethyl alkene containing an acrylamide (**1u**) provided a mixture of mono-alkylation (**3uba**, defluorinative alkylation) and di-alkylation (**3ubb**, defluorinative alkylation and Giese addition) products (Scheme 1, eqn (3)).¹⁹

To examine the reaction mechanism, the nonmetallic reducing agent TDAE was used to replace Zn(0), which provided

Table 5 Expansion to alkyl halides^a

^a Isolated yield for 0.2 mmol scale reaction. Reaction conditions: trifluoromethyl alkenes (1.0 eq.), alkyl halides (1.5 eq.), NiBr₂(diglyme) (10%), Pybox (15%), Zn (3.0 eq.), DMAc (0.2 M), rt, 16 h. Ratio of desired product/addition by-product >50 : 1 unless otherwise noted.



Scheme 1 Competition experiments. Isolated yield for 0.2 mmol scale reaction. Reaction conditions for eqn (1) and eqn (2) are the same as those for Table 5. Reaction conditions for eqn (3) are the same as those for Table 1, entry 17. Ratio of desired product/addition by-product >50 : 1 unless otherwise noted.



Scheme 2 Mechanistic probes. Isolated yield for 0.2 mmol scale reaction. Reaction conditions are the same as those for Table 1, entry 17. Ratio of desired product/addition by-product >50 : 1 unless otherwise noted. TDAE = 1,1,2,2-tetrakis(dimethylamino)ethylene.

an appreciable amount of product and revealed that the activation of redox-active esters might proceed through a single-electron-transfer (SET) process rather than *in situ* formation of organozinc reagents (Scheme 2, eqn (4)).²⁰ An optically pure redox-active ester (**1r**) was used to study the stereochemistry, which led to a racemic product (**3ar**) in 85% isolated yield (Scheme 2, eqn (5)). Collectively, the above results supported a radical-type reaction mechanism for this defluorinative reductive cross-coupling.²¹

Conclusions

We developed a nickel-catalyzed defluorinative reductive cross-coupling of trifluoromethyl alkenes with redox-active esters.

This reaction enables convenient and efficient preparation of *gem*-difluoroalkenes through C(sp³)-F bond cleavage and C(sp³)-C(sp³) bond formation. Under mild reaction conditions, many sensitive functional groups were tolerated, therefore providing a robust approach for late-stage protecting-group-free modification of natural products or drug molecules. A one-pot synthesis at the gram scale further demonstrated the usability and applicability of this new method. Preliminary mechanistic studies suggested a nickel-catalyzed radical-type process. Our next challenge is the extension of the reaction to an asymmetric version.

Conflicts of interest

The authors declare no competing interests.

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