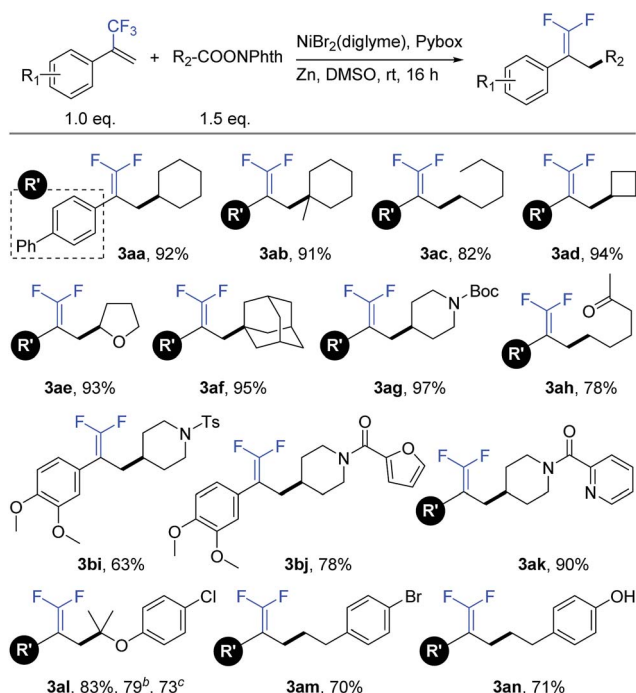
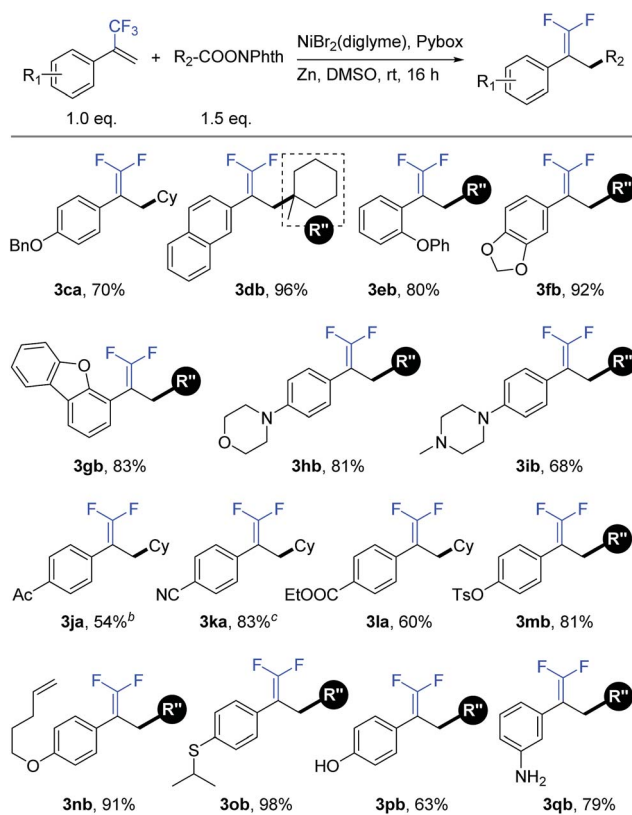


Table 2 Substrate scope of redox-active esters^a

^a Isolated yield for 0.2 mmol scale reaction. Reaction conditions are the same as those for Table 1, entry 17. ^b Isolated yield for 0.2 mmol scale one-pot reaction. ^c Isolated yield for 5.0 mmol scale one-pot reaction. Ratio of desired product/addition by-product >50 : 1 unless otherwise noted. Boc = *tert*-butoxycarbonyl. Ts = tosyl.

(3ka), and ethoxycarbonyl (3la) also survived during the defluorinative reductive cross-coupling process. The tolerance of aryl tosylate (3mb) and intramolecular terminal alkene (3nb) afforded further functionalization possibilities. Finally, more active groups that have been difficult substrates in transition-metal-catalyzed cross-coupling reactions, such as sulfoether (3ob), unprotected phenolic hydroxyl (3pb), and primary amine (3qb), were compatible with this defluorinative reductive cross-coupling.¹⁷

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

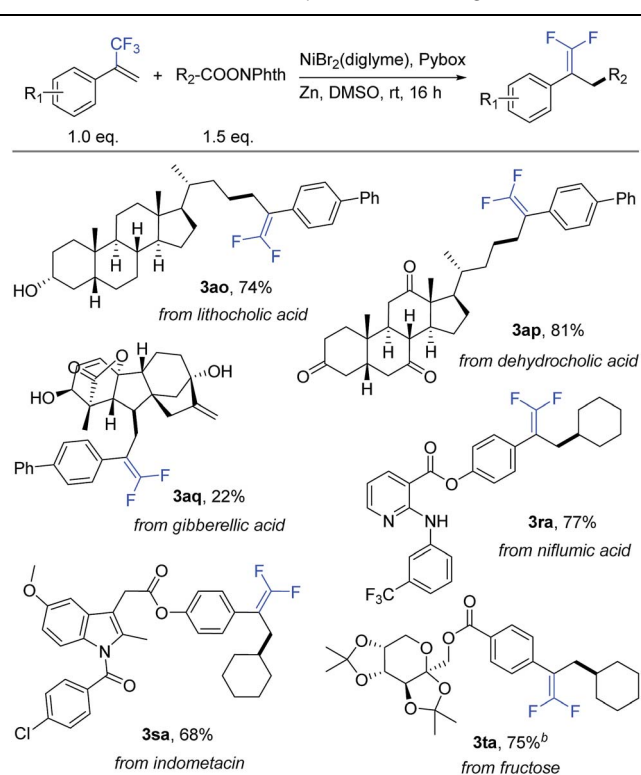
^a Isolated yield for 0.2 mmol scale reaction. Reaction conditions are the same as those for Table 1, entry 17. Ratio of desired product/addition by-product >50 : 1 unless otherwise noted. ^b Ratio of desired product/addition by-product = 14 : 1. ^c Ratio of desired product/addition by-product = 35 : 1. Bn = benzyl. Ac = acetyl.

Finally, fructose derivative 1t was also a good substrate and afforded product 3ta with a satisfactory 75% isolated yield. Therefore, this defluorinative reductive cross-coupling presents an attractive opportunity for late-stage protecting-group-free modification of biologically interesting molecules.

Similar to our previous studies,^{9b,10a,11a} we herein show that this allylic defluorinative alkylation reaction could be applied to alkyl halides (Table 5), which perhaps less surprising is also practical. Several sensitive functional groups were examined, such as thiophene (5ba), cyano (5bb), aldehyde (5bc), and phenolic hydroxyl (5bd), and good to excellent yields were obtained in all cases.

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

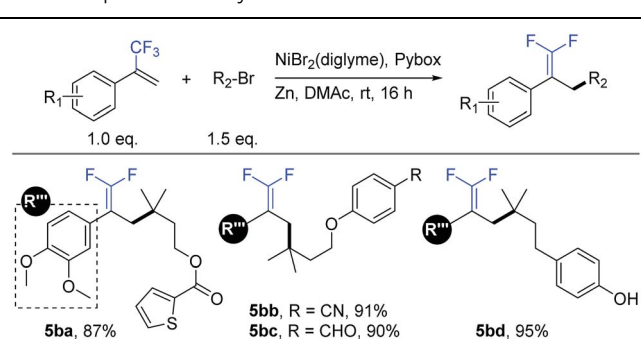


Table 4 Modification of natural products and drug molecules^a

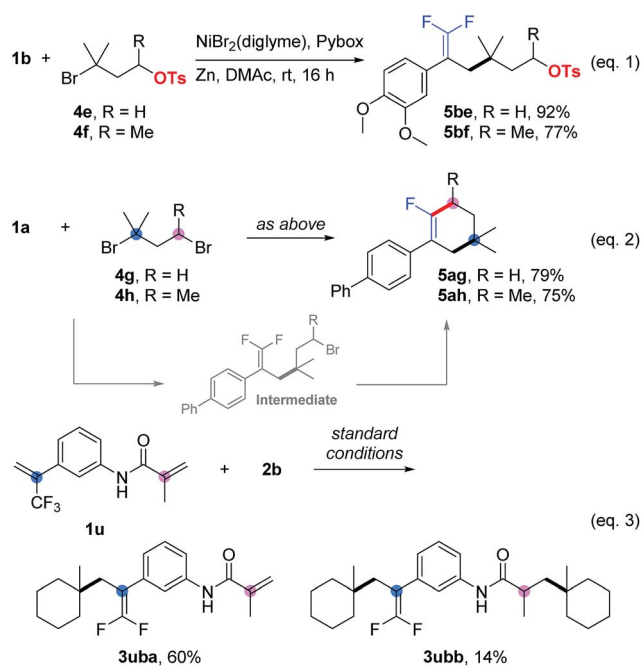
^a Isolated yield for 0.2 mmol scale reaction. Reaction conditions are the same as those for Table 1, entry 17. Ratio of desired product/addition by-product >50 : 1 unless otherwise noted. ^b Ratio of desired product/addition by-product = 7 : 1.

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

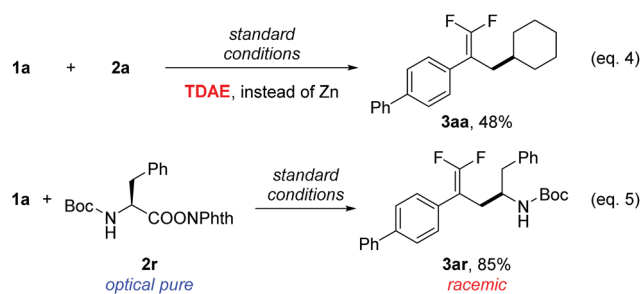
To examine the reaction mechanism, the nonmetallic reducing agent TDAE was used to replace Zn(0), which provided

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.



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