Transition-Metal-Free Allylic Defluorination Cross-Electrophile Coupling Employing Rongalite

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Abstract

The conversion of CF3-alkenes to gem-difluoroalkenes using reductive cross-coupling strategy has received much attention in recent years, however, the use of green and readily available reducing salt to mediate these reactions remains to be explored. In this work a concise construction of gem-difluoroalkenes, which requires neither a catalyst nor a metal reducing agent, was established. Rongalite, a safe and inexpensive industrial product, was employed as both a radical initiator and reductant. This procedure was compatible with both linear and cyclic diaryliodonium salts, enabling a wide variety of substrates (>70 examples). The utility of this approach was demonstrated through gram-scale synthesis and efficient late-stage functionalizations of anti-inflammatory drugs.

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Keywords

Reductive cross-coupling | Transition metal free | *Gem*-difluoroalkenes | Rongalite | Single electron transfer

Comprehensive Summary

The conversion of CF_3-alkenes to *gem*-difluoroalkenes using reductive cross-coupling strategy has received much attention in

Background and Originality Content

Fluorine-containing moieties can give novel biological functions while also enhancing lipophilicity and metabolic stability in organic compounds.[1] Among the numerous possible fluorine-containing compounds,*gem* -difluoroalkenes have been identified as a unique class of polyfluorinated substances having electronic and spatial distributions that are strikingly similar to those of carbonyl groups.[2] As a result, the addition of fluorine-based functional groups to various molecules could have potential applications in the field of biomedicine.[3]

A variety of protocols for the synthesis of *gem* -difluoroalkenes based on the allylic defluorination of CF_3-alkenes have been developed throughout the last decade.[4-7]Among them, reductive cross-coupling strategy, as an important method for cross-linking of different electrophilic reagents, plays a pivotal role in the construction of *gem* -difluoroalkenes (Scheme 2A). One of the most classic types is the reaction system using transition metal catalysts and metal reductants, which has been well developed through the use of different electrophilic reagents (eg. Alkyl halides, Katritzky salts, NHPI esters, etc) and catalysts (eg. Ni, Ti, Cr, Fe, Co, etc).[8] Afterward, new methods under photoredox-catalyzed conditions along**Scheme 1** Representative pharmaceuticals containing the *gem* -difluoroalkene moiety.

with organic reducing agent (eg. Silanol, Amine, Hantzsch ester, etc) have been developed, a series of *gem* -difluoroalkenes can be synthesized.[9] More recently, electrochemical reactions come into their own. In this type of reaction, it is no longer necessary to add additional reductants, instead, the electrochemical environment itself can provide sufficient electrons for the reductive cross-coupling reaction.[10] Although these three reductive cross-coupling strategies described above have been established in many works. Some reactions still unavoidably used transition metal catalysts or stoichiometric metal reductants, which would result in negative impacts to the environment. Furthermore, some complex reaction conditions with expensive equipment undoubtedly result in much higher costs. Therefore, developing novel, concise and cost-effective reductive cross-coupling synthesis methods for*gem* -difluoroalkenes would be of great interest in synthetic methodology.

Scheme 2 Background and synopsis of the current work.

A recent work by Jiang et al. using formate as an inexpensive single-electron donor to mediate reductive cross-couplings for the construction of alkyl-alkyl sulfones has come to our attention owing to its green and simple conditions (Scheme 2B).[11] Inspired by this work, we were interested in exploring a potentially suitable reducing salt to mediate the allylic defluorination reductive cross-coupling, as it could offer significant synthetic utility despite being rarely reported. On this basis, the present work demonstrates a transition-metal-free allylic defluorination reductive cross-coupling between CF_3-alkenes and diaryliodonium salts mediated by rongalite (Scheme 2C). Notably, this reaction is easy to operate, and the cheap and easily available industrial product rongalite acts as both free radical initiator and reducing agent, avoiding the use of catalysts, metal reducing agents and complex apparatus. As it also provides a new illustration of the allylic defluorination reductive cross-coupling paradigm.

Results and Discussion

To optimize this process, the CF_3-alkene **1a** and diphenyliodonium trifluoromethanesulfonate **2a** were utilized as model substrates (Table 1). Product **3a** was generated in a 13% yield from a reaction involving **1a** , **2a** (2 equiv) and 2 equiv of rongalite performed in N , N -dimethylformamide at 80 °C for 3 hours under argon (entry 1). Subsequent studies with several solvents found that dimethyl sulfoxide offered the best yield (entries 2–5). The impact of rongalite concentration was also investigated, and 4.0 equiv was discovered to be the ideal quantity (entries 6–8). The reaction was suppressed when the temperature was brought down to 70 °C, whereas it was promoted when the temperature was brought up to 90 °C. However, further increases in temperature had a limited effect (entries 9–11). A number of phase transfer reagents were assessed and were all found to promote the reaction, with tetrabutylammonium bromide producing the best result (entries 12–14). The use of diphenyliodonium tetrafluoroborate **2a'** instead of **2a** in conjunction with **1a** did not change the yield significantly (entry 15). Finally, this process was conducted without rongalite and none of the target product was obtained (entry 16).

Table 1 . Optimization of the Reaction Conditions[a,b]

Entry	Solvent	Equiv of rongalite	Temp (°C)	Yield (%)[b]
1	DMF	2	80	13
2	DMSO	2	80	20
3	NMP	2	80	Trace
4	CH_3CN	2	80	Trace
5	THF	2	80	11
6	DMSO	3	80	57
7	DMSO	4	80	68
8	DMSO	5	80	65
9	DMSO	4	70	60
10	DMSO	4	90	75
11	DMSO	4	100	74
12[c]	DMSO	4	90	82
13[d]	DMSO	4	90	79
14[e]	DMSO	4	90	84
15[e,f]	DMSO	4	90	81
16[e]	DMSO	0	90	N.D.

[a] Reaction conditions: **1a** (0.20 mmol),**2a** (0.40 mmol), rongalite (equiv as stated), solvent (2.0 mL), T (as stated), 3 h, under Ar. [b] Isolated yields based on **1a** . [c] Bu_4NF (1.0 equiv) was added. [d] Bu_4NCl (1.0 equiv) was added. [e] Bu_4NBr (1.0 equiv) was added.[f] Diphenyliodonium tetrafluoroborate**2a'** was used in place of **2a** .

Following that, the scope of substrates appropriate for this cross-coupling reaction using ideal conditions was explored and the suitability of several diaryliodonium salts was demonstrated (Scheme 3). Substrates bearing alkyl (products **3b** and **3c**), alkoxy (**3d**), halogen (**3e** –**3g**) and electron-withdrawing (**3h** and **3i**) substituents at the*para* -site of the benzene ring were basically compatible with this process and gave the corresponding products in considerable results (70–82%). Additionally, *meta* -substituted diaryliodonium salts containing electron-neutral, electron-donating, and electron-withdrawing groups gave products **3j** –**3p** in good yields (69–85%). Notably, C(sp^2)-F, C(sp^2)-Cl and C(sp^2)-Br groups were discovered to be unreactive using the current reaction circumstances, implying that halogen-based substituents could be exploited for further elaborations. Although*ortho* -substituted substrates appeared to be rigid, moderate to good yields of the corresponding products could still be achieved (**3q** –**3v** , 65–74%). Furthermore, more sterically-hindered, multi-substituted substrates were also successfully employed in this process, affording **3y** –**3aj** in significant yields (59–82%). Polyfluorinated diaryliodonium salts also performed smoothly with CF_3-alkenes, yielding products**3ak** and **3al** in 63% and 55% yields, respectively. Bulkier substrates based on naphthalene and biphenyl skeletons participated in this reaction to give **3am** and **3an** in 60–68% yields. Notably, a series of cyclic diaryliodonium salts was assessed and products**3ao** –**3aq** were obtained in 60–68% yields.

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Scheme 3 Trials to determine the allowable range of diaryliodonium salts.

[a] Reaction conditions:**1a** (0.20 mmol),**2** (0.40 mmol), rongalite (0.80 mmol), Bu_4NBr (1.0 equiv), DMSO (2.0 mL), 90 °C, 3 h, under Ar.[b] Isolated yields based on **1a** .[c] X = OTf. [d] X = BF_4.

Subsequently, the effects of substituents on the CF_3-alkene were examined (Scheme 4). Using CF_3-alkenes with alkyl (**4a** –**4c**), alkoxy (**4d** –**4f**), and halogen (**4g** –**4i**) substituents on the aromatic ring, the

reaction was observed to proceed well, and the target products were isolated in yields ranging from 60% to 85%. The reaction involved both*ortho* - and *meta* -substituted CF_3-alkenes, resulting in the excellent-yield products **4j** and **4k** , respectively. It was discovered that this reaction was also compatible with electron-withdrawing moieties such -CF_3, -Ac, and -COOEt, which gave the corresponding products **4l** –**4n**in yields of 59–64%. Furthermore, heteroatom groups, such as trimethylsilyl (**4o**), amine (**4p**), -SMe (**4q**) and -OH (**4r**) moieties, were discovered to be suitable for this reaction. Experiments using polycyclic aromatic hydrocarbons as substituents established that products **4s** –**4w** could be obtained in good yields (65–82%). Also, this reaction worked well in the presence of heterocycle-substituted substrates (**4x** -**4ab**), with yields of 52-76%. In order to illustrate the usefulness of this reaction, the late-stage functionalizations of the anti-inflammatory drugs *ibuprofen* and*naproxen* were assessed. These reactions gave the target products**4ac** and **4ad** in yields of 73% and 66%, respectively.

Scheme 4 Trials to determine the allowable range of CF_3-alkenes.

[a] Reaction conditions: **1** (0.20 mmol),**2a** (0.40 mmol), rongalite (0.80 mmol), Bu_4NBr (1.0 equiv), DMSO (2.0 mL), 90 degC, 3 h, under Ar.[b] Isolated yields based on **1** .

In addition to the late-stage functionalizations stated above, this method was also carried out on a larger 5 mmol scale, yielding the target product in a 66% isolated yield (Scheme 5).

Scheme 5. Gram-scale synthesis. [a] For details, see the Supporting Information.

A number of control experiments were carried out to elucidate the mechanism underlying this reductive cross-coupling reaction. No significant formation of product **3a** was observed in the case that CF_3-alkene **1a** was reacted with diaryliodonium salt **2a** in the presence of TEMPO, indicating that this transformation likely involves radicals (Scheme 6a). A standard radical trapping experiment with 1,1-diphenylethylene was also carried out and radical adduct **5** was identified by gas chromatography-mass spectrometry while product **3a** was obtained in a 58% yield (Scheme 6b). In other trials, 1.0 equiv of H_2O was added to the reaction to trap any anions that may have been generated and the un-defluorinated product **3a'**was detected by gas chromatography-mass spectrometry, while product**3a** was separated in a 72% yield (Scheme 6c). A plausible reaction mechanism is showed in Scheme 6d based on the present control experiments and previous work.[12] At the beginning, the pyrolysis of rongalite generates $SO_2{}^{2-}$ and also releases HCHO and H^+. Subsequently, the $SO_2{}^{2-}$ that is gradually released and diaryliodonium salt **2** undergo a single electron transfer process to produce aryl radical **A** . The reaction of this radical and CF_3-alkene **1** furnishes the radical intermediate **B** . Finally, **B** is reduced by either a sulfur dioxide anion or a sulfur dioxide radical anion to give anion species **C** . The latter undergoes defluoridation to deliver the desired *gem* -difluoroalkene product **3** . It is worth noting that the chemoselective radical reduction in this reaction is vital to realizing this transformation.

Scheme 6. Mechanistic study.

Conclusions

In summary, a transition-metal-free allylic defluorination reductive cross-coupling between CF_3-alkenes and diaryliodonium salts was established for the construction of*gem* -difluoroalkenes. The industrial product rongalite was employed as both a radical initiator and reductant. A catalyst was not required and the use of the control-release rongalite instead of a metal powder reducing agent promoted a sequential and highly selective single-electron transfer process. Through this method, anti-inflammatory drugs could be subjected to late-stage functionalization and a scaled-up version of this synthesis was also achieved.

Experimental

All the materials and solvents were commercially available and used without further purification. TLC analysis was performed using pre-coated glass plates. Column chromatography was performed using silica gel (200–300 mesh). ^{1}H spectra were recorded in $CDCl_3$ and DMSO-d_6 on 600/400 MHz NMR spectrometers and resonances (δ) are given in parts per million relative to tetramethylsilane. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, h = quintet, p = sextet, m

= multiplet), coupling constants (Hz) and integration. ^{13}C spectra were recorded in $CDCl_3$ and DMSO-d_6 on 150/100 MHz NMR spectrometers and resonances (δ) are given in ppm.^{19}F spectra were recorded in $CDCl_3$ and DMSO-d_6 on 376 MHz NMR using TMS as internal standard. High-resolution mass spectra (HRMS) were obtained by electrospray ionization (ESI) on a TOF mass analyzer. The X-ray crystal-structure determinations of **3ae** were obtained on a Bruker SMART APEX CCD system. Rongalite was commercially available (CAS No: 149-44-0) and purchased from TCI corporation.

General procedure for the rongalite-mediated allylic defluorination reductive cross-coupling

A 25 mL Schlenk-type tube (with a Teflon screw cap and a side arm) equipped with a magnetic stir bar was charged with the mixture of CF_3-alkene 1 (0.20 mmol), diaryliodonium salt 2 (0.40 mmol), rongalite (0.80 mmol), and DMSO (2.0 mL), the mixture was stirred at 90 °C (metal heating block) for 3 hours under argon atomosphere. After cooling to room temperature, the mixture was quenched with water (25 mL), extracted with EtOAc (3 × 50 mL), the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent: PE/EA) to afford the corresponding products.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2023xxxxx.

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Transition-Metal-Free Allylic Defluorination Cross-Electrophile Coupling Employing Rongalite Xiang-Long C
The conversion of CF_3-alkenes to *gem*-difluoroalkenes using reductive cross-coupling strategy has received much attention in