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To Study the Effect of Fluoroalkylation of Alkenes

Shashank Shekhar Kapoor[1], Dr. Sukeerti Singh[2]

[1]Research Scholar, Sunrise University, Rajasthan
[2]Associate Professor, Sunrise University, Rajasthan

ABSTRACT

Difluoroalkylated chemicals are useful in materials science, pharmacology, and agrochemistry. Nevertheless, there are very few effective ways to create the alkylCF2-alkyl bond, and it is still difficult to introduce a difluoromethylene (CF_2) group into an aliphatic chain at the appropriate location. Here, we describe a novel instance of alkylzirconocene-promoted difluoroalkylation of alkyl- and silyl-alkenes using a range of unactivated difluoroalkyl iodides and bromides when exposed to visible light without the need of a catalyst. In organic synthesis, the resultant difluoroalkylated molecules can be used as flexible synthons. The reaction offers a general way to controllably access fluorinated compounds and can also be used with activated difluoroalkyl, trifluoromethyl, perfluoroalkyl, monofluoroalkyl, and nonfluorinated alkyl halides. According to preliminary mechanistic studies, the process involves a single electron transfer (SET) route initiated by a Zr(III) species, which is produced when alkylzirconocene is photolyzed with blue light.

Keyword: Difluoroalkylated, Perfluoroalkyl, Monofluoroalkyl, Electron, Photolyzed

INTRODUCTION

Applications in materials science, chemical biology, and medicinal chemistry for the site-selective insertion of a fluorine atom or atoms into organic molecules are significant.

One Because CF2 can alter the molecules' metabolic stability, conformation, acidity, and polarity, biochemically active molecules having a difluoromethylene (CF2) moiety at a certain location, for example, have better bioactivities than their nonfluorinated counterparts.

Gemcitabine, vinflunine, lubiprostone, and other significant pharmaceuticals with the CF2 moiety have been found to be effective in treating cancers and other diseases. To this purpose, over the past ten years, efforts have been made to find effective ways to access molecules that contain CF2.

The creation of difluoroalkylated arenes (ArCF2R) with CF2 at the benzylic position is the primary goal of the majority of these sophisticated synthesis techniques. There are currently few effective ways to site-selectively add CF2 to an aliphatic chain.

The conventional technique for creating difluoroalkylated molecules involves using dia-lkylaminosulfur trifluorides, like diethylaminosulfur trifluoride (DAST), to deoxyfluorinate the carbonyl group.

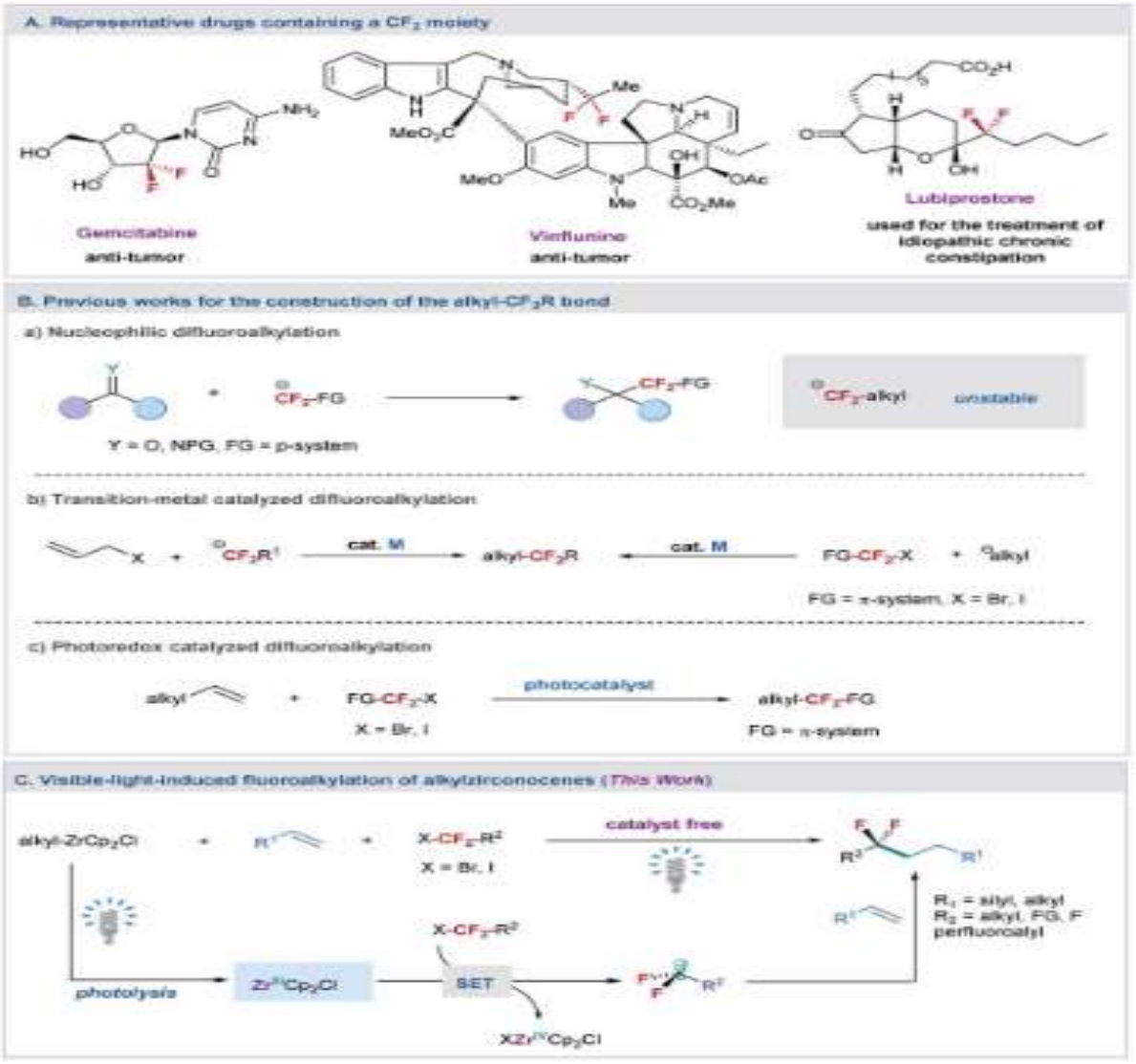

Fig. 1 Strategies For The Difluoroalkylation And Selected Examples Of Pharmaceutical Bearing Cf_2 Moieties

However, this method's synthetic applications are limited by its poor functional group tolerance. The nucleophilic addition of difluor-oalkylating reagents to aldehydes, ketones, and imines is another popular technique for creating such a useful fluorinated structure (Fig. 1B(a)).6c, However, the approach is challenging to form the alkylCF2-alkyl link because of the instability of nucleophilic difluoroalkylating reagents, which often require a p-system next to the CF2 moiety to stabilize the difluoroalkyl anion. While it is well known that aliphatic electrophiles can be nucleophilically substituted with carbon nucleophiles, it is still difficult and has not yet been documented to use a similar approach to react difluoroalkyl halides with aliphatic nucleophiles. To create the alkylCF2-alkyl link in this situation, difluoroalkylation processes catalyzed by transition-metal or photo-redox have been developed.

New techniques that can increase the diversity of the difluoroalkylated structure with site-selective introduction of CF2 into the aliphatic chain at the desired place are much desired in order to get around these restrictions and satisfy the growing demands of the life and materials sciences. In this instance, we present a novel instance of catalyst-free difluoroalkylation of silyl- and alkyl-alkenes using unactivated difluoroalkyl halides facilitated by alkylzirconocenes photolysis. The reaction offers a generic way to access fluoroalkylated alkanes and can also be applied to p-functionalized difluoroalkyl, trifluoromethyl, perfluoroalkyl, monofluoroalkyl, and non-fluoroalkyl halides. According to preliminary mechanistic research, the reaction involves a single electron transfer (SET) route initiated by a Zr(III) species, which is produced when

alkylzirconocenes are photolyzed with visible light. This technique creates a new method for creating the alkyl–fluoroalkyl link using aliphatic alkenes and easily accessible fluoroalkyl halides.

RESULTS AND DISCUSSION

We selected unactivated difluoroalkyl iodide 1a15 and alkylzirconocene 2a as the model substrates, which are inspired by our nickel-catalyzed difluoroalkylation cross-cou- pling,. Alkylzirconocene can be easily prepared from the corresponding alkene 5 and Schwartz reagent (HZrCp2Cl, 6). 16 The intended difluoroalkylated alkane 3a was not produced by directly utilizing the nickel-catalyzed cross coupling. On the other hand, product 3a was produced in 51% yield when the nickel-catalyzed reaction was exposed to a blue LED (12 W), while the hydrodeiodinated by-product 4a was produced in 27% yield. Blue light is crucial for accelerating the reaction, as evidenced by the fact that no reaction happened without the blue LED and that a similar yield could be obtained without the nickel catalyst. The difficulty of creating a difluoroalkyl carbocation (S N1) or the repulsion of the lone pairs of fluorine atoms to the carbon nucleophile (S N2) makes these moderate conditions very different from the problem of S N1 or S N2 substitution of difluoroalkyl halides. 18 This distinction suggests a new mechanism, which is covered in more detail below. These findings encouraged us to explore a number of reaction settings (see the ESI† for specifics). We discovered that using 3.0 equiv. of 2a with NMP as the solvent could produce 3a in 81% yield (62% isolated yield).

The question of whether 5a, rather than 2a, is involved in the creation of 3a was raised because 2a was obtained from the reaction of 6 with sufficient silylalkene 5a. We created 2a by reacting alkylmagnesium bromide 7 with ZrCp 2 Cl 2 in order to determine its function (Scheme 1a). 19. However, when 2a reacted with 1a, no 3a was seen. On the other hand, adding 5a to the reaction might provide the intended result in 48% of cases. These results imply that the substrate that produces 3a with 1a in the reaction is an excess of silylalkene 5a. The addition of another silylalkene, 5b, to the reaction mixture of 1a, 2a, and 5a under blue light irradiation further confirmed this deduction, resulting in the formation of both difluoroalkylated products, 3a and 3a0.

These findings unequivocally show that the alkene is the substrate for the reaction with difluoroalkyl halide since [Zr]-migration from alkylzirconocene to alkene is impossible (Scheme 1d). Furthermore, under the influence of a blue LED, the reaction of alkene 5a with 1a without 2a did not result in 3a, indicating that the alkylzirconocene is crucial for accelerating the process.

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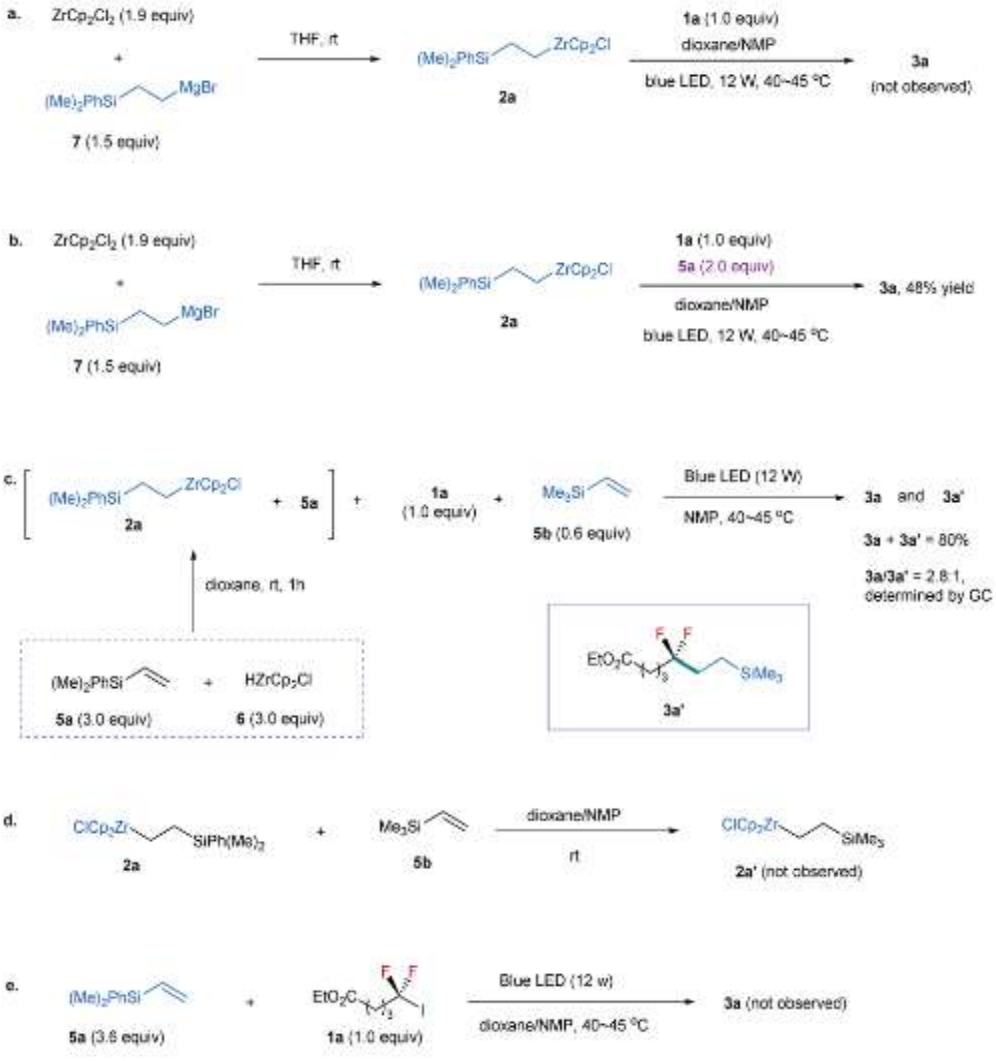
breadth of this technique after determining the viable reaction conditions. In general, silylalkene 5a reacts effectively with a sequence of unactivated difluoroalkyl iodides (ICF 2-alkyl) 1 to produce the equivalent products. The reaction efficiency was unaffected by a chain length of 1. The coupling process went successfully for substrates 1 with a linear aliphatic chain from one to five carbons (3a–3k). Good functional group tolerance was demonstrated by the reaction. Ester, silyl ether, aryl chloride, and nitrile were among the significant functional groups that were compatible with the reaction conditions . Even substrates that contained sulphonate and alkyl chloride (3h and 3k) were good coupling partners and offered good chances for downstream derivatives. With 3.5 equivalents of alkene and 1.8 equivalents of 6, the reaction was not limited to difluoroalkyl iodides because unactivated difluoroalkyl bromides were also appropriate substrates. equivalent yields were obtained when silylalkene 5a was substituted with silylalkene 5b, indicating that the reactivity of 5a and 5b is equivalent. Interestingly, the reaction (3m) also applied to the steric difluoroalkyl iodide that had been substituted with a cyclohexyl group. Together with XCF2-alkyl (X ¼ I, Br), 5a's reaction with functionalized difluoroalkyl bromides went without a hitch (3n–3r). While gem-difluoroproparyl bromides and heteroaryl-substituted difluoromethyl bromide produced yields that were comparable to those of XCF2-alkyl, bromodifluoroacetate and bromodifluoroacetamide shown more reactivity. The synthesis of 3d and 3g on a gram scale without compromising reaction efficiency shows that the process is easily scalable. Chlorodifluoroacetate was also investigated, however the reaction with 5a and 2a produced a poor yield (19%).



Next, we looked into alkenes 5's substrate range. Compounds 5 with a varied chain length produced the appropriate products (8a–8k) in a smooth reaction with XCF 2-alkyl (X ¼ I, Br). Styrene, however, was irrelevant to the reaction. Because of the strong electron-withdrawing effect of the CF2 group, which allows the difluoroalkyl iodides and bromides to accept an electron relatively more easily than their nonfluorinated counterparts via a SET pathway, the alkyl bromides

are less reactive than the difluoroalkyl iodides and bromides, as evidenced by the successful production of 8i and 8j with alkyl bromide intact. Most significantly, a substrate containing boronate could also be used in the reaction (8k and 8m).

The generated boronate-containing products should function as a flexible building block for organic synthesis since boronate is a helpful synthetic tool in organic synthesis. Notably, norbor-nene produced compound 8l in 76% yield, and the cyclic alkene had no effect on the reaction efficiency. Difluoroacetate bromide also reacted smoothly with alkenes, including linear and cyclic alkenes, producing the corresponding products 8m–8q with great efficiency. With moderate to good yields, the reaction can also be extended to trifluoromethyl, perfluoroalkyl, and monofluoroacetyl iodides and bromides (9a–9c). Interestingly, the reaction also applied to nonfluorinated alkyl halides. The coupling was effective for tertiary alkyl bromide with an ester group (9d) and 2-bromomalonate (9e); even Boc-protected 4-iodo-piperidine produced 9f in good yield, indicating the versatility and benefit of this visible light-induced, catalyst-free approach.

We hypothesized that alkylzirconocene might functionalize an initiator in the reaction as it is crucial for accelerating the process but is not the substrate for producing the intended product. This allows us to create alkylCF 2-alkyl linkages by combining a basic alkylzirconocene with various alkenes and fluoroalkyl halides.

The substrate scope of the current protocol is expanded by this alternative process, which eliminates the need to prepare distinct alkylzirconocenes and permits fluoroalkylation of a range of alkenes with various functional groups that are sensitive to HZrCp 2 Cl. Thus, by reacting allylbenzene with HZrCp 2 Cl, we produced alkylzirconocene 2c. Scheme 2B illustrates how the application of bromodifluoroacetate and the cyclobutene derivative to 2c under blue light irradiation produced product 10a in 50% yield. Given that difluoroacetyl and a four-membered ring are significant structural motifs in medicinal chemistry, compound 10a would be useful in the production of compounds with biological activity. Additionally useful to the reaction was the terminal alkene with an amide proton, which produced 10b in a good yield. Unactivated difluoroalkyl bromides and iodides were also effective coupling partners to react with a range of complex molecule-derived alkenes (10c–10h), in addition to bromodifluoroacetate. Alkenes containing estone and sulbactam exhibited a smooth difluoroalkylation process (10d and 10e). Decuxostat containing a heteroarene was similarly susceptible to the reaction (10h), as were peptide and carbohydrate derivatives (10f and 10g). Therefore, the suggested protocol offers a simple path for medicinal chemistry applications.

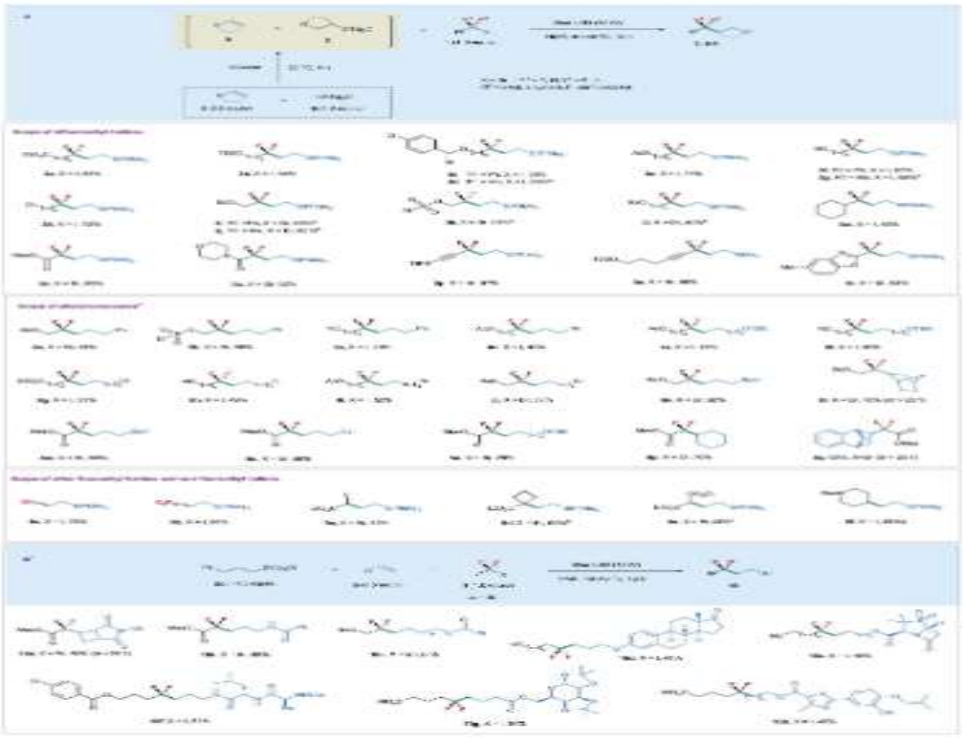


Fig. 2 (A) Lkylzirconocene Promoted Fluoroalkylation Of Alkenes With (Fluoro)Alkyl Halides Under The Irradiation Of Blue Light

CONCLUSIONS

To sum up, we have created a broad, catalyst-free technique for fluoroalkylation of alkenes that is aided by alkylzirconocenes' photolysis. The reaction has a wide range of substrates and a high tolerance to functional groups. Fluoroalkyl halides, such as difluoroalkyl, trifluoromethyl, perfluoroalkyl, and monofluoroalkyl bromides and iodides, as well as a broad variety of silyl- and alkyl-alkenes, were appropriate substrates. Specifically, the reaction opens up a new pathway for the formation of alkylCF2-alkyl bonds due to the widely available unactivated difluoroalkyl halides and aliphatic alkenes' flexibility. The reaction's applicability to nonfluorinated alkyl halides further illustrates the protocol's universality. Additionally, the substrate scope is greatly expanded by using simple alkylzirconocene rather than producing distinct alkylzirconocenes between HZrCp2Cl and a number of alkenes. This includes a range of complex compounds that are sensitive to HZrCp2Cl. The transformations of difluoroalkylated molecules have also shown the synthetic utility of this approach, offering promising prospects in medicinal chemistry. According to preliminary mechanistic research, the reaction involves a SET pathway triggered by a Zr(III) species, which is produced when alkylzirconocenes are photolyzed with blue light. This fascinating route might spark a lot of interest in employing organozirconium photolysis for organic synthesis.

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