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Diastereoselective synthesis of 5,5-disubstituted 3,3-difluorotetrahydrofurans

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ABSTRACT

The diastereoselective synthesis of 5,5-disubstituted 3,3-difluorotetrahydrofurans **2** was achieved using β,β-difluorohomoallylic alcohols **1** as the key starting material in the presence of ICl (3.0 equiv) and *tert*-BuOK (1.5 equiv) in THF. The corresponding iodocyclization products **2** were obtained in good to moderate yields with excellent diastereo- and regioselectivities (d.r. = >20/1, 5-*endo*-trig only).

The introduction of fluorine atoms into biologically active compounds represents an important strategy in medicinal chemistry to improve biological activity.[1] As a notable example, tetrahydrofurans bearing fluorine atoms at the 3-position are known for their useful biological properties such as anticancer and antiviral activities (Fig. 1).[2]

In general, synthetic strategies to prepare for fluorinated compounds can be categorized into two distinct methods: direct fluorination or the building block method. Both methodologies can be applied in a stereoselective manner for the synthesis of 3-monofluorotetrahedrofurans (Eqs. (1) and (2), Fig. 2). The direct fluorocyclization of unsaturated alcohols using electrophilic fluorinating reagents such as Selectfluor, *N*-fluorobenzenesulfonimide (NFSI), and F-TEDA-BF_4 has received considerable attention owing to the accessibility of the starting materials and interesting challenge of controlling regio- and stereoselectivities (Eq. (1), Fig. 2).[3] On the other hand, these direct cyclizations cannot be applied for the construction of 3,3-difluorotetrahedrofuran moieties because double fluorocyclization is fundamentally impossible; therefore, as a typical direct method for such compounds, deoxyfluorination from ketones is often applied using diethylaminosulfur trifluoride (DAST) or its analogues (Eq. (3), Fig. 2).[4] This direct method is also used for synthesizing medicinal compounds such as Gemcitabine [5]; however, reactions with DAST often exhibit limited substrate scopes.

Iodocyclization with homoallylic alcohols is a useful reaction to construct tetrahydrofurans,[6] and this strategy has been applied for the synthesis of 3-monofluorotetrahydrofurans using allylic monofluorides featuring alcohol groups (Eq. (2), Fig. 2).[3c] Interestingly, the transition state can be controlled by the location of the fluorine atom; the lone pair of fluorine can stabilize the partial positive charge of the I_2-π complex and minimize the interaction between the C—I bond and electron-withdrawing $\sigma^*_{C\text{-}F}$ orbital. These orbital interactions regulate the direction of cyclization and result in the high diastereoselectivity of the iodocyclization.[3c] Allylic difluorides have attracted similar interest; however, due to the lack of robust and reliable synthetic routes towards allylic difluorides, related chemistries have remained unexplored to date. Recently, our group reported the stereoselective synthesis of α,α-difluoro-γ,γ-disubstituted butenals using organocatalysis, which facilitated the preparation of various 3,3-disubstituted homoallylic difluorides with a single stereoisomer, the *E*-isomer, including difluorohomoallylic alcohols **1**.[7] Herein, we report the diastereoselective synthesis of 5,5-disubstituted 3,3-difluorotetrahedrofurans as a synthetic application of fluorinated alcohols **1**. Notably, the iodocyclization of homoallylic alcohols can give a mixture of regioisomers due to the cyclization pathway – 5-*endo*-trig and 4-*exo*-trig-based on Baldwin's rule (Eq. (4), Fig. 2).[8]

First, the iodocyclization was screened in the reaction of difluorohomoallylic alcohol **1a** in the presence of various bases and iodine in THF (Table 1). Triethylamine (TEA) as an organic base did not induce any reaction, and the starting material was

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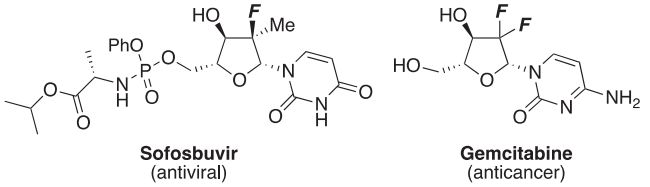

Fig. 1. Bioactive fluorinated tetrahydrofurans.

recovered quantitatively (entry 1, Table 1). On the other hand, inorganic bases gave a trace amount of the target iodocyclization product **2a**, even though a majority of the starting material remained (entries 2–5, Table 1).

Next, solvents with varying polarities were screened, and unfortunately no significant solvent effects were observed (entries 5–8, Table 1). Other sources of iodine such as *N*-iodosuccinimide (NIS) or iodine monochloride (ICl) were also screened using higher reaction temperatures to ensure the completion of the reaction (entries 9–11, Table 1).[9] Fortunately, the reaction with ICl resulted in the total consumption of starting material **1a** and give iodocyclized product **2a** in 71% yield after 0.5 h, in addition to trace byproducts (entry 11, Table 1). At a higher concentration, the reaction exhibited a cleaner outcome, but small amounts of byproducts were still observed (entry 12, Table 1). Finally, at room temperature, the reaction resulted in a quantitative conversion of **2a** in 95% yield (entry 13, Table 1). Notably, all reaction conditions resulted in excellent diastereo- and regioselectivities (d.r. = >20/1, 5-*endo*-trig product only).

After determining the optimal conditions, the substrate scope was investigated with regard to either R^1 or R^2 of alcohol **1** (Table 2). Generally, electron-donating groups on the aromatic rings of R^1 did not influence the reaction outcome regardless of the substitution pattern, and the products were obtained in good yields and excellent selectivities (entries 2–5, Table 2). On the other hand, electron-withdrawing groups on R^1 resulted in slightly lower yields, but excellent selectivity was maintained (entries 6–8, Table 2). Benzyl groups as aliphatic substrates resulted in sluggish reactions and required a slightly higher reaction temperature, and gave a mixture of diastereotopic isomers (entry 9, Table 2). Notably, the *E*/*Z* ratios of starting materials **1e** and **1i** were 5/1 and 3/1, respectively (entries 5 and 9, Table 2), and for example, the *Z*-form of **1e** remained intact after the *E*-form was totally transformed into **2e**, and this difference in reactivity enhanced the diastereoselectivity of the iodocylization.[6d,6h] Other substituents on R^2, such as Et and H instead of Me, also resulted in excellent regio- and stereoselectivity with good chemical yields of 71% and 81%, respectively (entries 10 and 11, Table 2).

The structures of **2** were determined by comparison of the chemical shifts and coupling constants with those of **2a**, for which the ring structure and stereochemistry were revealed by 2D NMR. The ring size of **2a** was confirmed by HSQC to be a tetrahydrofuran, not oxetane, because the carbon attached to proton H_a appeared at 35.9 ppm in the ^{13}C NMR, and such carbons are not adjacent to the oxygen atom of oxatane structures.[10] Next, the NOESY spectrum showed a strong cross peak between H_a and a phenyl group (see Supporting Information for more details); therefore, the final structure of **2a** is depicted in Fig. 3. The unambiguous structure of **2** allowed for the investigation of the

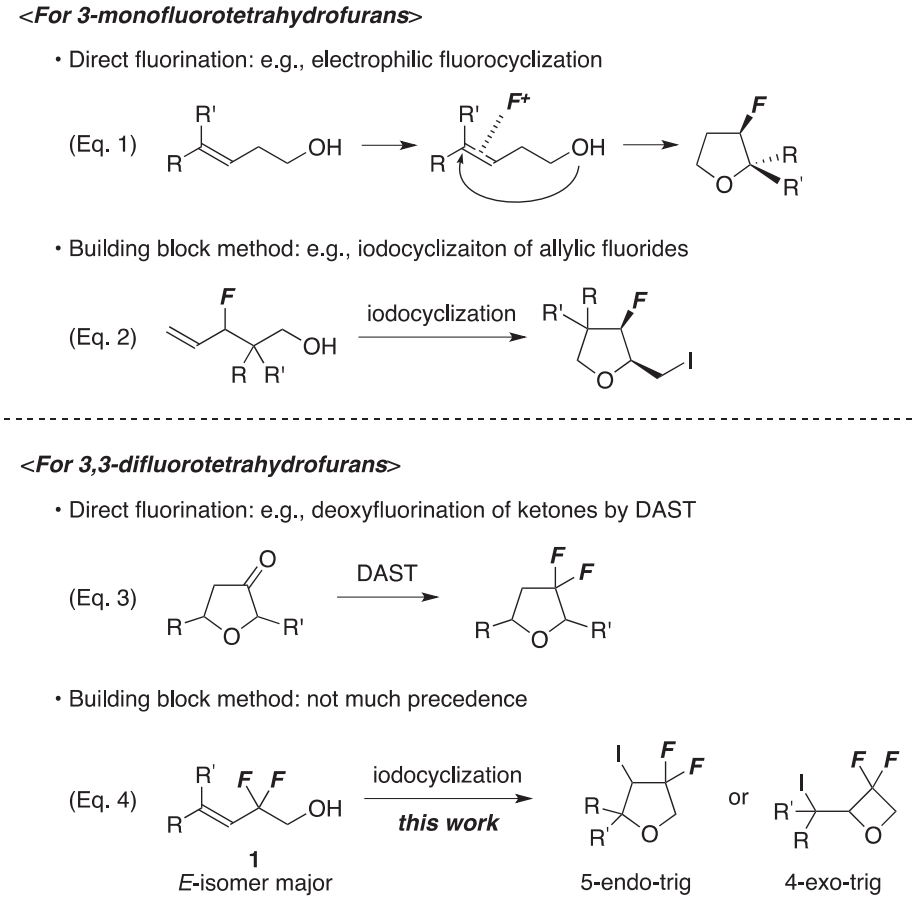

Fig. 2. Synthetic protocols for fluorotetrahydrofurans.