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Visible-light-induced and diastereoselective synthesis of fluorinated tetrahydrofuran derivatives

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The stereocontrolled construction of molecules bearing three contiguous stereocenters is a formidable challenge in synthetic organic chemistry. We report a visible-light-driven, three-component radical cascade that enables the efficient and regioselective formation of fluorinated frameworks containing three consecutive stereocenters. Using trifluoromethyl thianthrenium triflate as a dual-function reagent, the reaction proceeds *via in situ* generation of $CF_3^{\bullet}$ and thianthrene radical cation species under photochemical control. The $CF_3^{\bullet}$ selectively engages in addition to 1,6-dienes to initiate a cascade cyclization/trapping/nucleophilic substitution sequence, forming highly functionalized tetrahydrofuran derivatives in yields up to 85%. This mild and operationally simple protocol exhibits broad nucleophile and substrate scope, including primary, secondary, and tertiary alcohols, as well as water, azide and acetamide sources. Single crystal X-ray diffraction and NMR analyses confirmed the structures and relative configurations of the products. The observed diastereomeric ratios are attributed to the occurrence of hydrogen bonding interactions as suggested by Density Functional Theory (DFT) calculations.

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Introduction

The construction of molecules with three or more contiguous stereocenters is a fundamental challenge in modern synthetic chemistry.[1] Such stereochemically complex frameworks are frequently found in biologically active natural products, pharmaceuticals, and advanced materials (Fig. 1A).[2] The selective formation of multiple stereocenters in a single synthetic sequence requires precise control over stereoselectivity, often relying on transition-metal catalysis,[3] organocatalysis,[4] or radical-mediated transformations.[5] Among different strategies available, radical cascade represents a powerful synthetic tool to construct complex molecular structures with multiple stereocenters in a single operation. Thus, these approaches have attracted significant attention due to their mild reaction conditions, broad functional-group tolerance, and unique reactivity in forging intricate carbon frameworks.

Fluorinated molecules, particularly those containing trifluoromethyl ($-CF_3$) groups, are highly valuable in medicinal chemistry, agrochemicals, and materials science due to their

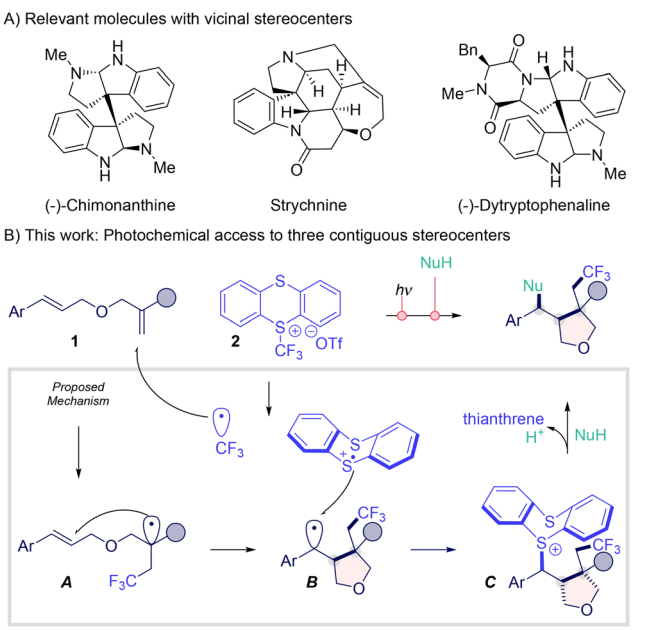

Fig. 1 (A) Representative molecules with vicinal stereocenters. (B) Three-component trifluoromethylation approach for the synthesis of three contiguous stereocenters developed in this work.

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enhanced metabolic stability, lipophilicity, and bioavailability.[6] The introduction of a CF_3 moiety *via* radical pathways has emerged as a powerful tool for the stereoselective construction of complex molecular architectures. Radical trifluoromethylation followed by cascade cyclization and nucleophilic trapping enables the efficient generation of contiguous stereocenters while incorporating fluorine's unique physicochemical properties.[6] These strategies provide access to fluorinated scaffolds with high structural diversity, offering new opportunities in drug discovery and functional material design. A particularly appealing and powerful $CF_3^{\bullet}$ source is trifluoromethyl thianthrenium triflate,[7] which has demonstrated great potential in synthetic radical chemistry since its discovery in 2021.[8] This reagent can undergo homolytic cleavage under 390 nm Kessil® light irradiation, generating a key radical pair: $CF_3^{\bullet}$ and the thianthrene radical cation species ($TT^{\bullet+}$). While $CF_3^{\bullet}$ undergoes the desired transformations, $TT^{\bullet+}$ has also been shown to participate as a valuable reaction intermediate.[7a,b,h]

With the goal of accessing three contiguous stereocenters within trifluoromethyl chemistry settings, we focused on 1,6-dienes (**1**) as model substrates (Fig. 1B). Trifluoromethyl thianthrenium triflate (**2**) can serve as an effective $CF_3^{\bullet}$ precursor, selectively reacting with the less hindered olefin in **1** to yield a C-centered radical (**A**) that triggers a cascade cyclization reaction, generating a new benzylic C-centered radical (**B**). This Csp^2-hybridized intermediate is expected to subsequently react with $TT^{\bullet+}$ species to form a sulfonium intermediate (**C**), which can undergo further substitution reactions with a palette of nucleophiles (NuH).

Results and discussion

The feasibility of this three-component reaction for constructing three consecutive stereocenters was evaluated using 1,6-diene **1a**, MeOH as NuH (5 equiv.), and reagent **2** as initial substrates (Table 1). From the outset, we were pleased to observe product **3a** formation in 86% yield after 5 hours of irradiation in dichloromethane (Table 1, entry 1) with a 2.5 : 1 diastereomeric ratio. Screening of alternative non-halogenated solvents proved unproductive (entry 2), giving low conversions when acetone or MeCN was used (entry 3). Reducing the amount of nucleophile to 2.5 equivalents also led to diminished efficiency (entry 4). Interestingly, both the reaction time and the amount of trifluoromethylating reagent could be reduced to 2 hours and 1.2 equivalents, respectively, without compromising the yield (entries 5 and 6). The photochemical nature of this transformation was confirmed, as no reaction occurred in the absence of light irradiation (entry 7). Lastly, an argon atmosphere and 390 nm irradiation are mandatory parameters for the success of the reaction (entry 8).

Having established the optimized reaction conditions for this synthesis of three contiguous stereocenters, we next explored the substrate scope (Table 2). Initially, various

Table 1 Optimization of the reaction conditions[a]

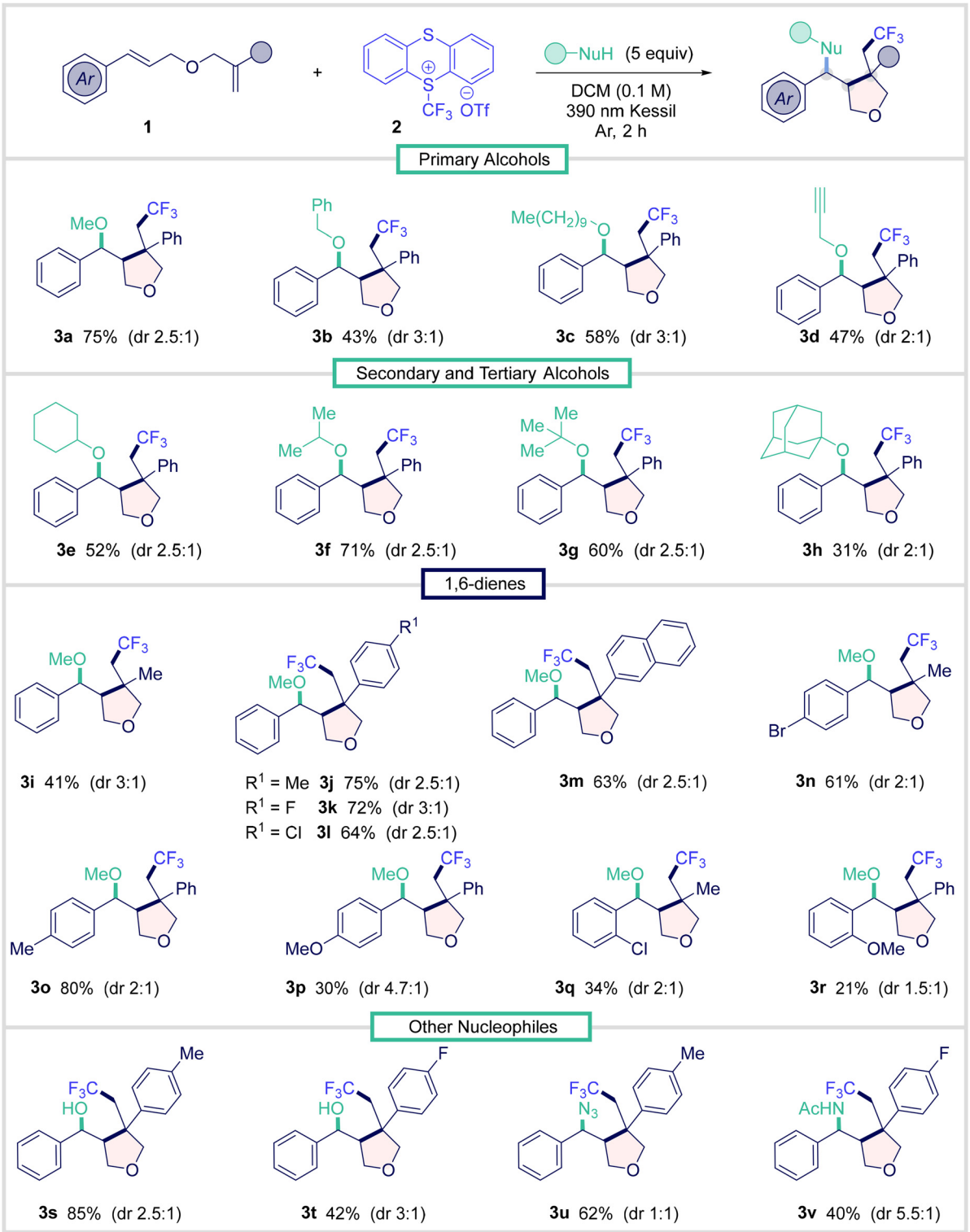
1a (1 equiv) **2** (1.5 equiv) **3a**

Entry	Deviation from the above	Yield[b] (%)
1	None	86
2	DMF, 1,4-dioxane or DMA instead of DCM	Traces
3	Acetone or MeCN instead of DCM	38
4	2.5 equiv. of MeOH	51
5	2 h of irradiation	86
6	1.2 equiv. of **2** and 2 h of irradiation	87
7	No light irradiation	0
8	No Ar, or 525 nm	0

[a] Reaction conditions: **1a** (0.1 mmol, 1 equiv.), **2** (0.15 mmol, 1.5 equiv.) and MeOH (0.50 mmol, 5 equiv.) in 1 mL of DCM (0.1 M) under an argon atmosphere and irradiated using a 390 nm Kessil® lamp for 5 h. [b] Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard.

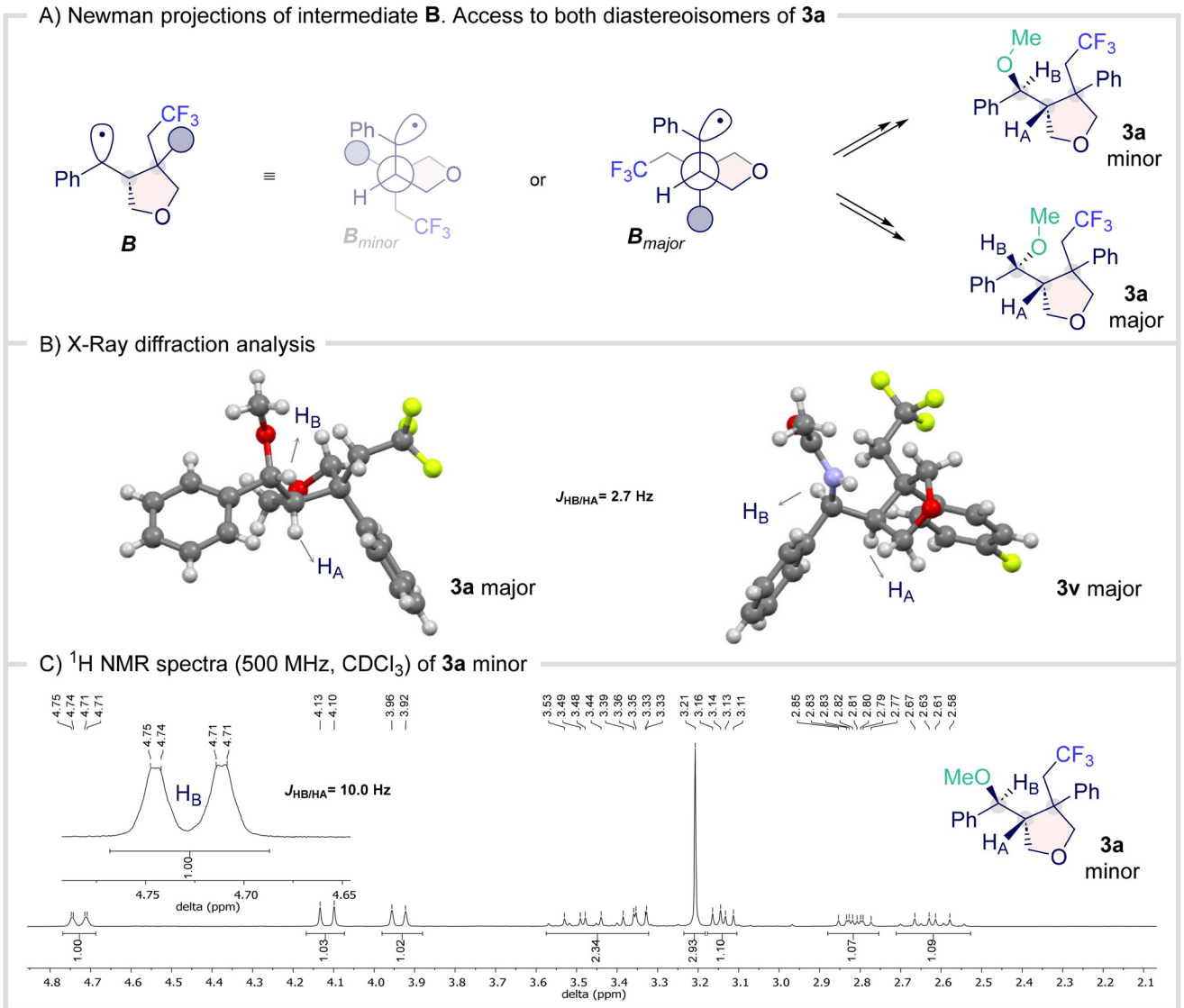
primary alcohols were examined, including benzyl alcohol, *n*-decanol, and propargyl alcohol, affording the desired products (**3a–3d**) in yields ranging from 43% to 75%. Both cyclic (**3e**) and acyclic (**3f**) secondary as well as tertiary (**3g–3h**) alcohols were also suitable nucleophiles, enabling the efficient construction of three consecutive stereocenters. Substrates in which the phenyl ring next to the *exo*-methylene position was replaced by a methyl group (**3i**) also delivered the desired product in moderate yield. Unfortunately, when a hydrogen atom was present at this position, the reaction led to complex mixtures. In addition, attempts to extend the methodology to other heterocyclic frameworks were unsuccessful (see the SI for details). Furthermore, substituted phenyl and naphthyl derivatives (**3j–3m**) were well tolerated, furnishing CF_3-containing tetrahydrofuran products in good yields. Substitution on the second aryl ring (indicated as Ar in the reaction given in Table 2) was also explored; weakly electron-withdrawing (**3n**) and weakly electron-donating groups (**3o**) were well tolerated, whereas strongly electron-donating substituents resulted in reduced efficiency (**3p**) likely due to side reactions involving the electron-rich aromatic system. Furthermore, steric effects influenced the reaction outcome, giving lower yields with *ortho*-substituted phenyl rings (**3q–3r**). In all cases, the three contiguous stereocenters were obtained in dr that ranged from 2 : 1 to 4.7 : 1. Finally, the scope of nucleophiles could be extended beyond alcohols to include water, $TMSN_3$, and MeCN, which provided the corresponding hydroxylated (**3s–3t**), azidated (**3u**), and acetamide (**3v**) derivatives in moderate to good yields and the same levels of dr, except for the azide **3u** (dr 1 : 1). The relative configurations of the major diastereomers **3a** and **3v** were unambiguously established by ^{1}H NMR analysis ($J_{HA/HB}$ = 2.7 Hz, see the SI) and further confirmed by single crystal X-ray diffraction (Scheme 1B). Notably, despite the presence of three contiguous stereocenters, only two diastereomers were detected. For compound **3a**, the minor diastereomer could be isolated during the purification process. Its

Table 2 Substrate scope evaluation[a]



[a] Reaction conditions: **1a** (0.4 mmol, 1 equiv.), **2** (0.48 mmol, 1.2 equiv.) and NuH (2.0 mmol, 5 equiv.) in 4 mL of DCM (0.1 M) under an argon atmosphere and irradiated using a 390 nm Kessil® lamp for 2 hours.

relative configuration was assigned based on ^{1}H NMR data, with the coupling constant ($J_{HA/HB}$ = 10.0 Hz) providing key structural information (**3a** minor, Scheme 1C). As discussed for the mechanism given in Fig. 1B, light-induced homolysis of reagent **2** generates $CF_3^{\bullet}$ and $TT^{\bullet+}$. Then, radical addition of $CF_3^{\bullet}$ species to the less hindered alkene of the 1,6-diene fur-



Scheme 1 (A) Newman projections of intermediates $\mathbf{B}_{major}$ and $\mathbf{B}_{minor}$ and access to **3a major** and **3a minor** from $\mathbf{B}_{major}$. (B) Single crystal X-ray diffraction of compounds **3a major** and **3v major**. (C) ^{1}H NMR spectra of **3a minor**.

nishes intermediate **A**, which undergoes diastereoselective 5-*exo-trig* cyclization to give radical intermediate **B**. As previously reported by Zhu and co-workers,[9] this cyclization step is highly selective, with $\mathbf{B}_{major}$ being the thermodynamically favored isomer (Scheme 1A). According to DFT calculations performed at the dispersion corrected PCM-ωB97xD/def2-SVP level, this is followed by a highly exergonic ($\Delta G \approx -21$ kcal mol^{-1}) trapping of $\mathbf{B}_{major}$ by TT$^{\bullet+}$ (Fig. 2). This radical recombination yields two diastereomeric sulfonium intermediates **INT1** and **INT1′**, which are nearly degenerate (ΔG = 0.6 kcal mol^{-1}), therefore indicating that the observed diastereoselectivity should take place in a different step. Indeed, the decisive stereochemical outcome arises in the subsequent bimolecular nucleophilic substitution (S_N2) step. Our calculations suggest that nucleophilic attack by methanol preferentially occurs from the same face as the tetrahydrofuran oxygen due to the occurrence of a stabilizing hydrogen-bond interaction between the incoming alcohol and the heterocyclic oxygen atom (Fig. 2). This interaction not only directs the nucleophilic addition but also stabilizes the corresponding transition-state energy (**TS**) in comparison with the analogous S_N2 reaction involving **TS′**, where this noncovalent interaction is absent. As a consequence, the formation of intermediate **INT2**, which would lead to the observed major diastereomer **3a** (dr $\approx$ 3 : 1), is favored along the entire reaction coordinate from both kinetic ($\Delta\Delta G^{\ddagger}$ = 3.1 kcal mol^{-1}) and thermodynamic ($\Delta\Delta G$ = 10.1 kcal mol^{-1}) points of view. In contrast, when $TMSN_3$ is used as the nucleophile (**3u**), no hydrogen-bonding interaction is possible, and a 1 : 1 diastereomeric ratio is experimentally observed, which further supports the crucial role of this hydrogen-bond interaction in the stereodetermining S_N2 step.

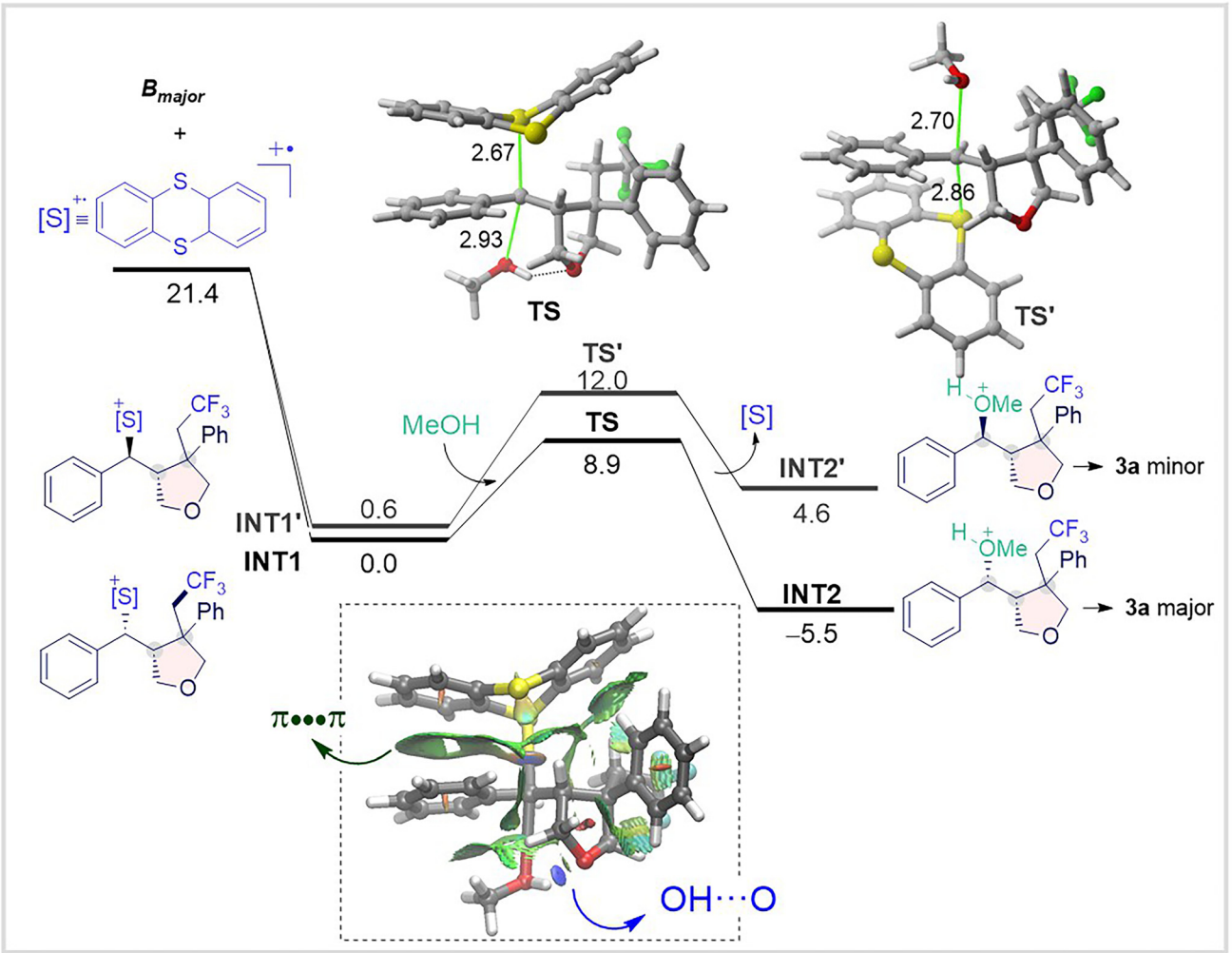


Fig. 2 Computed reaction profile for the formation of CF_3-tetrahydrofuran derivatives. Relative free energies (ΔG, at 298 K) and bond distances are given in kcal mol^{-1} and angstroms, respectively. All data have been computed at the PCM-ωB97xD/def2-SVP level. Inset: contour plot of the reduced density gradient isosurfaces (density cutoff of 0.05 au) for TS. The greenish and blue surfaces indicate attractive noncovalent interactions.

Conclusions

We have developed a visible-light-mediated, three-component radical cascade process that enables the construction of fluorinated tetrahydrofuran derivatives bearing three contiguous stereocenters. The transformation proceeds through selective radical trifluoromethylation, cascade cyclization, and $TT^{\bullet+}$ trapping, followed by nucleophilic substitution under mild, transition-metal-free conditions. The reaction exhibits broad functional group tolerance and substrate scope, delivering products in good to excellent yields. The short reaction time, temperature and the recovery of the thianthrene are key features of this synthesis of three contiguous stereocenters. Mechanistic studies, supported by X-ray crystallography, NMR analysis and DFT calculations, confirm the relative configurations of the products and highlight the key steric factors and noncovalent interactions influencing the diastereoselectivity. This work demonstrates the potential of trifluoromethyl thianthrenium reagents as versatile tools for complex molecular assembly and provides a powerful platform for the stereoselective incorporation of fluorinated motifs.

Author contributions

All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: characterization of compounds, mechanistic investi-

gation, computational details, and spectroscopic data. See DOI: https://doi.org/10.1039/d6qo00585c.

CCDC 2537548 and 2537549 contain the supplementary crystallographic data for this paper.[10a,b]

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