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Article

Discovery of a Distinctive Reagent for Divergent Arene Trifluoromethylsulfinylation

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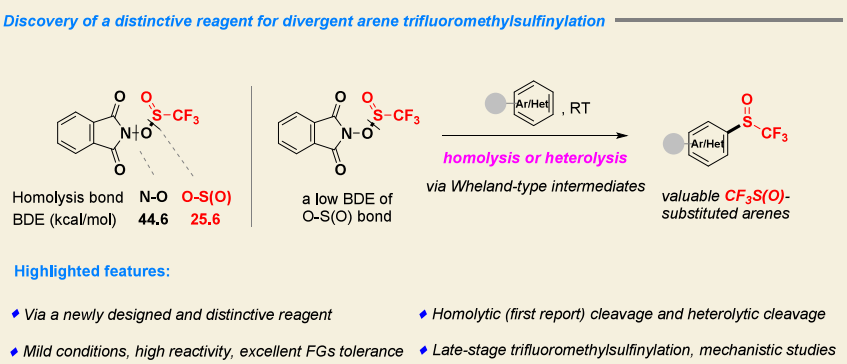

ABSTRACT: Simple and direct arene trifluoromethylsulfinylation is highly desirable in drug design but remains a major challenge. Herein, we report a modular, mild, innate C−H trifluoromethylsulfinylation of a wide variety of arenes via a distinctive trifluoromethylsulfinylating reagent *N*-hydroxyphthalimide-*O*-trifluoromethanesulfinate following divergent efficient pathways. This trifluoromethylsulfinylation can be conducted in a redox-neutral manner at room temperature with light-, metal-, and photocatalyst-free mild conditions. Mechanistic studies and density functional theory (DFT) calculations revealed that the success of this approach hinges upon the design of an activated trifluoromethanesulfite ester that proceeds via homolytic cleavage with a very low bond dissociation energy to generate a dummy aminoxyl radical (PINO) and active $CF_3S(O)$ radical, which could accidentally be transformed into a trifluoromethanesulfonic anhydride, $CF_3S(O)OS(O)CF_3$, for the transfer of the $S(O)CF_3$ group into an exemplary set of strong EDG-substituted arenes. DFT computation corroborates that this novel reagent can be activated by TfOH via heterolytic cleavage to produce highly active $CF_3S(O)OTf$, which is responsible for electrophilic trifluoromethylsulfinylation of the challenging weak EDG-substituted arene substrates through an electrophilic addition−elimination mechanism. Such C−H functionalization using *N*-hydroxyphthalimide-*O*-trifluoromethanesulfinate affords an innovative strategy and marked improvement over functionalization with previously developed reagents. Notably, simple and mild conditions, broad reactivities, good functional group compatibility, divergent reaction modes (homolysis and heterolysis), as well as late-stage trifluoromethylsulfinylation (LST) of complex biologically active molecules in these reactions underline the great potential of *N*-hydroxyphthalimide-*O*-trifluoromethanesulfinate for the preparation of functionalized drug-like molecules.

KEYWORDS: *trifluoromethylsulfinylation, homolytic cleavage and heterolytic cleavage, electrophilic substitution, fluorine chemistry, mechanistic study*

1. INTRODUCTION

The installation of emergent fluoroalkyl groups has shown widespread applications in pharmaceuticals,[1] agrochemicals,[2] and functional materials[3] because they endow their parent molecules with unique physicochemical and biological properties.[4] Thus, tactical "fluorine modification" on bioactive molecules has become a popular strategy in modern pharmaceutical research and development (R&D). Particularly, the $CF_3S(O)$ entity[5] plays a valuable and pivotal role in drug industries because of its distinctive electron-withdrawing and negative lipophilicity properties,[6] membrane permeability, and binding affinity to the target compounds as compared with nonfluorinated analogs. This important pharmacophore ($CF_3S(O)$) could be considered a useful tool for the fine adjustment of ADMET (absorption, distribution, metabolism,

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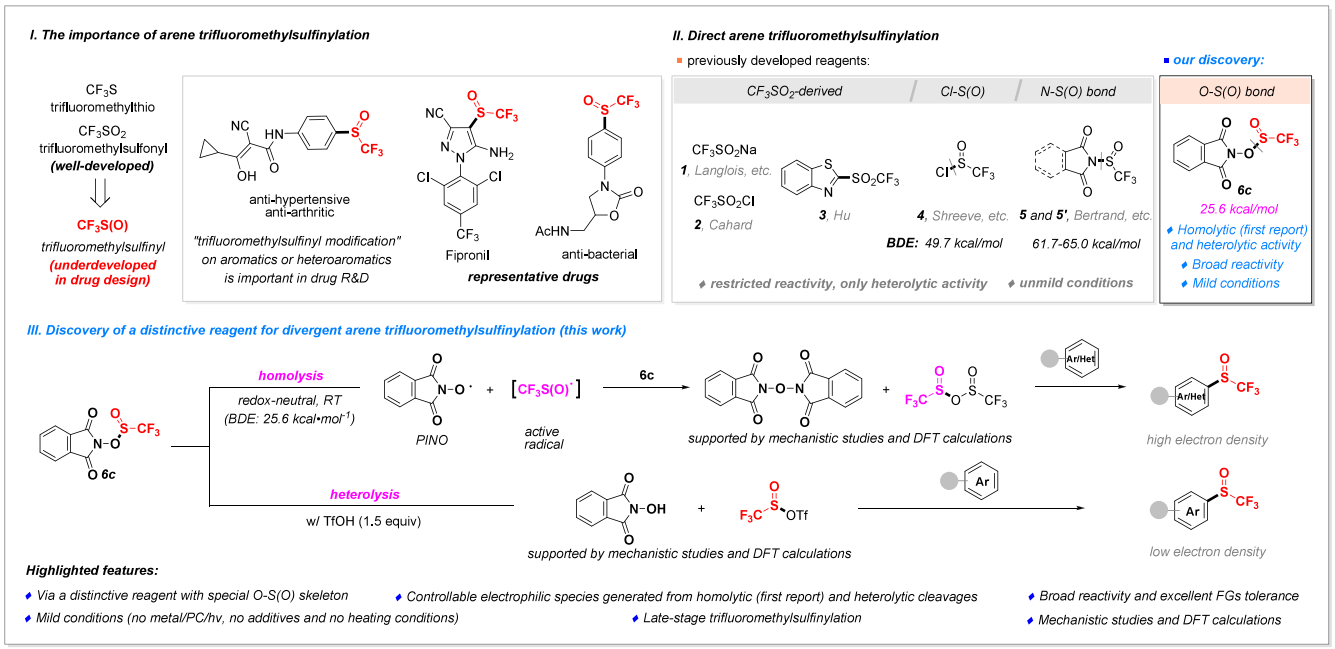
Scheme 1. Discovery of a Distinctive Reagent for Divergent Arene Trifluoromethylsulfinylation



excretion, and toxicity) properties of drug candidates, which can be found on (hetero)aromatics of diverse agrochemicals and pharmaceuticals (Scheme 1I), such as world-famous and broadly used insecticide Fipronil and other $CF_3S(O)$-containing analogues—Flufiprole, antibacterial, antihypertensive, and antiarthritic.[7] These phenomena and their potential values demonstrate the importance and urgency of developing arene trifluoromethylsulfinylation.

Remarkably, trifluoromethylsulfinylation methods are apparently much less developed due to difficulties in taming the intermediate oxidation state in $CF_3S(O)$ molecules, when compared with extensive research on trifluoromethylthiolation and trifluoromethylsulfonation. Although the indirect strategy by nucleophilic trifluoromethylation of unavailable $ArS(O)X$[8] or special oxidation of aryl trifluoromethyl sulfides[9] has been well developed, multistep synthetic sequences and complex operations may inhibit these synthetic applications. By contrast, simple and direct arene C−H trifluoromethylsulfinylation is highly desirable especially at the late stage of leading compounds of pharmaceutical molecules. Compared to inconvenient nucleophilic methods,[10] electrophilic trifluoromethylsulfinylation represents the most straightforward and promising method due to the native chemical reactivity of aromatics. Up to now, substantial efforts have been engaged in the development of electrophilic trifluoromethanesulfinylating reagents with heterolytic activity and limited substrate scope, including CF_3SO_2-derived sources (CF_3SO_2Na (**1**), CF_3SO_2Cl (**2**), BT-SO_2CF_3 (**3**), Scheme 1II, in the presence of phosphine additives),[11] trifluoromethanesulfinyl chloride ($CF_3S(O)Cl$, **4**),[12] and *N*-trifluoromethylsulfinyl succinimide/phthalimide (**5**/**5′**).[13,14] These reagents were proved efficient for heteroaromatic trifluoromethylsulfinylation, but they were hindered in the conversion of challenging common aromatics, probably due to their limited electrophilic abilities. In 2001, few examples were reported for direct electrophilic trifluoromethylsulfinylation of simple aromatics by triflinate salts in a special triflic acid medium to access aryl trifluoromethyl sulfoxides.[15] However, this strong acidic medium has a limited substrate scope and poor functional group compatibility that is incompatible with acid-sensitive groups (such as OH, CF_3, Bpin, carbonyl, cyclopropane, alkenyl, heterocycle, ester, etc.), inhibiting its synthetic applications for the green chemical industry. Very recently, Liu and co-workers unveiled the trifluoromethylsulfinylation reaction of electron-rich aromatics by $CF_3S(O)Cl$ with the aid of $SnCl_4$ or $FeCl_3$ under the heating conditions.[16] Nevertheless, this protocol may be hindered by the shortcomings of direct use of $CF_3S(O)Cl$ (potential physiological toxicity, high volatility (31 °C), and poor stability) and substantial metal additives.

Despite the aforementioned progress, arene trifluoromethylsulfinylation remains a major challenge and needs to be addressed due to the challenges of the lower electron density of aromatics and the lack of powerful electrophilic $CF_3S(O)$ reagents. Herein, we design a distinctive reagent *N*-hydroxyphthalimide-*O*-trifluoromethanesulfinate with a low BDE (25.6 kcal/mol), which was meaningfully developed to efficiently transfer the $CF_3S(O)$ group for mild, switchable, and divergent arene trifluoromethylsulfinylation via homolytic (first report) and heterolytic cleavage (Scheme 1III). It allows for the mild (room temperature), direct, and operationally simple formation of potentially valuable $Ar-S(O)CF_3$ compounds with broad reactivities and excellent FG tolerance while reacting in a superior fashion to previously developed methods. We prepared a toolkit of this reagent and studied its reactivity across a wide variety of arene substrates, such as aromatics, phenols, heteoaromatics, and building blocks, as well as late-stage trifluoromethylsulfinylation of natural products and drugs under redox-neutral and light/metal/PC-free mild conditions.

2. RESULTS AND DISCUSSION

2.1. Two-Step Scalable Preparation of *N*-Hydroxyphthalimide-*O*-trifluoromethanesulfinate 6c

N-Hydroxyphthalimide-*O*-trifluoromethanesulfinate **6c** can be efficiently synthesized from commercially available *N*-hydroxyphthalimide and cheap trifluoromethylsulfinyl chloride via

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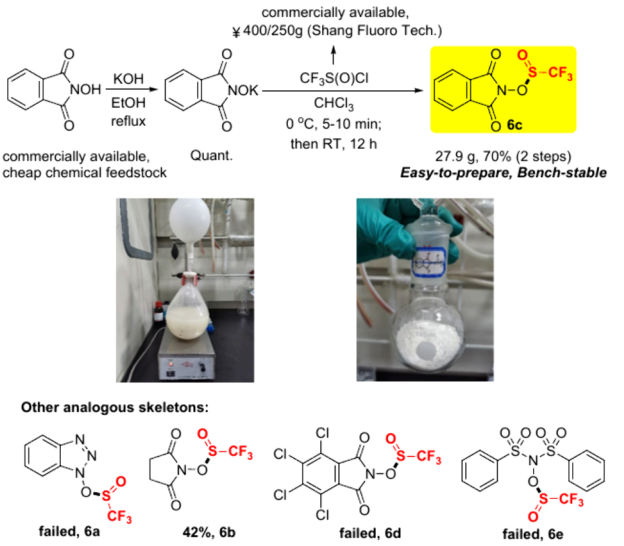
two-step scalable preparation (27.3 g, 70% yield, please see Supporting Information for more details), as shown in Scheme 2. Reagent **6c** is a shelf-stable, isolated as a white solid

Scheme 2. Two-Step Scalable Preparation of *N*-Hydroxyphthalimide-*O*-trifluoromethanesulfinate 6c and Its Analogues



compound. It was slightly moisture-sensitive but not sensitive to light, which can be stored in the refrigerator for several months without decomposition. This reagent has good solubility and relative stability in chlorinated solvents and THF, but noticeable decomposition will occur in acetonitrile and DMF. Detectable decomposition was detected in acidic mediums such as Lewis acids ($MgCl_2$, $AlCl_3$ and $ZnCl_2$, etc.) and Brønsted acids (PTSA and HCl). Moreover, nucleophilic attack of bases (K_2CO_3 and KOH, etc.) may also result in the decomposition of reagent **6c**. Notably, other analogous skeletons with succinimide can also be prepared in 42% yield via this same strategy. However, this reaction mode could not extend to the preparation of trifluoromethylsulfinylating reagents with the skeleton of 1-hydroxybenzotriazole (**6a**), 4,5,6,7-tetrachloro-2-hydroxy-isoindole-1,3-dione (**6d**), or *N*-(phenylsulfonyl)benzenesulfonamide (**6e**).

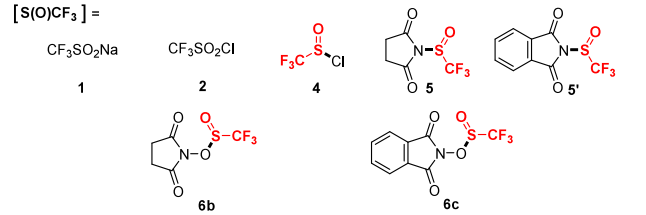
2.2. Reaction Exploration

To address the big challenge of direct arene C−H trifluoromethylsulfinylation, numerous attempts of 1,3-dimethoxybenzene with a range of traditionally electrophilic trifluoromethylsulfinylating precursors (reagents **1**, **2**, **4**, **5**, and **5′**, with or without phosphine or silicon additives) did not give any anticipated products (Table 1, entries 1, 4−8). Inspired by the pioneering work,[15] no desired products were observed when we attempted to employ TfOH as the stoichiometric activator or the reaction solvent (entries 2−3). These outcomes prove that the previously developed electrophilic reagents with X−S(O) bonds (Scheme 1II, X = Cl, N, etc.) have restricted abilities in promoting the envisioned aromatic transformation. As a comparison, 42% and 65% ^{1}H NMR yields of 2,4-dimethoxy-1-((trifluoromethyl)sulfinyl)benzene **8aa** occurred when our developed activated trifluoromethanesulfite esters **6b** and **6c** were studied for this trifluoromethylsulfinylation under room temperature and activator-free conditions (entries 9−10).

Table 1. Exploration of the Aromatic Trifluoromethylsulfinylation with High Electron Density[a]

Entry	[S(O)CF$_3$]	Additive (1.5 equiv)	Yield (**8aa**, %)[b]
1	**1**	$Ph_2P(O)Cl$ or PCl_3	ND
2	**1**	TfOH	ND
3[c]	**1**	TfOH as the solvent	ND
4[d]	**2**	PCy_3	ND
5	**4**	–	ND
6	**5**	–	ND
7	**5′**	–	ND
8	**5′**	TMSCl or $Ph_2P(O)Cl$	ND
9	**6b**	–	42
10	**6c**	–	65
11[e]	**6c**	–	63

[S(O)CF$_3$] =



[a]Reaction conditions: 1,3-dimethoxybenzene (0.20 mmol), reagent (S(O)CF_3, 2.0 equiv, 0.4 mmol), w/wo additive (1.5 equiv) in DCE (2.0 mL) under nitrogen atmosphere at RT for 12 h. [b]Yields were determined by ^{1}H NMR spectroscopy using 1,2-dibromoethane as an internal standard. [c]TfOH as the reaction solvent. [d]−78 °C to RT. [e]In the dark. TfOH = triflic acid, Tf_2O = trifluoromethanesulfonic anhydride.

Notably, the conversion in the dark still occurred smoothly with a 63% yield, indicating that this reaction will not proceed via a photoinduced EDA complex.

2.3. Reaction Scope

N-Hydroxyphthalimide-*O*-trifluoromethanesulfinate **6c** has been demonstrated with a broad generality of arene substrates. A range of aromatics with electron-donating groups (EDG) or weakly electron-withdrawing groups (EWG) were investigated in moderate to good yields at room temperature, as shown in Table 2. EDGs, including methoxy, benzyloxy, cyclopropane, alkyl, or alkyl ether, and even EWGs (fluoride, chloride, bromide, iodine, trifluoromethyl, ester), were all well-tolerated in this reaction system, delivering the targeted trifluoromethylsulfinyl aromatics in moderate to excellent yields (**8aa**−**8bb**). For 1,3-disubstituted aromatics, the *meta*-position bearing distinct substituted ethers (methoxy, cyclopropane methoxy, benzyloxy, and its derivative) was efficiently trifluoromethylsulfinylated by reagent **6c** to afford trifluoromethylsulfinyl products (**8aa**−**8ae**) under activator-free mild conditions. 1,2-Disubstituted aromatics derived from benzene, pyrocatechol, or 2-methoxyphenylacetic acid also proceeded successfully in 52−59% yields (**8af**−**8ai**). This strategy was also applied to electron-rich trisubstituted aromatics including 1,3,5-trimethoxybenzene, 3,4-dimethoxytoluene, and 2-methoxynaphthalene, to predictably deliver the corresponding coupling products in satisfactory yields (**8aj**−**8al**). Similarly, it was profitable to achieve the envisioned transformation on the *para*-position of monosubstituted electron-donating aromatics

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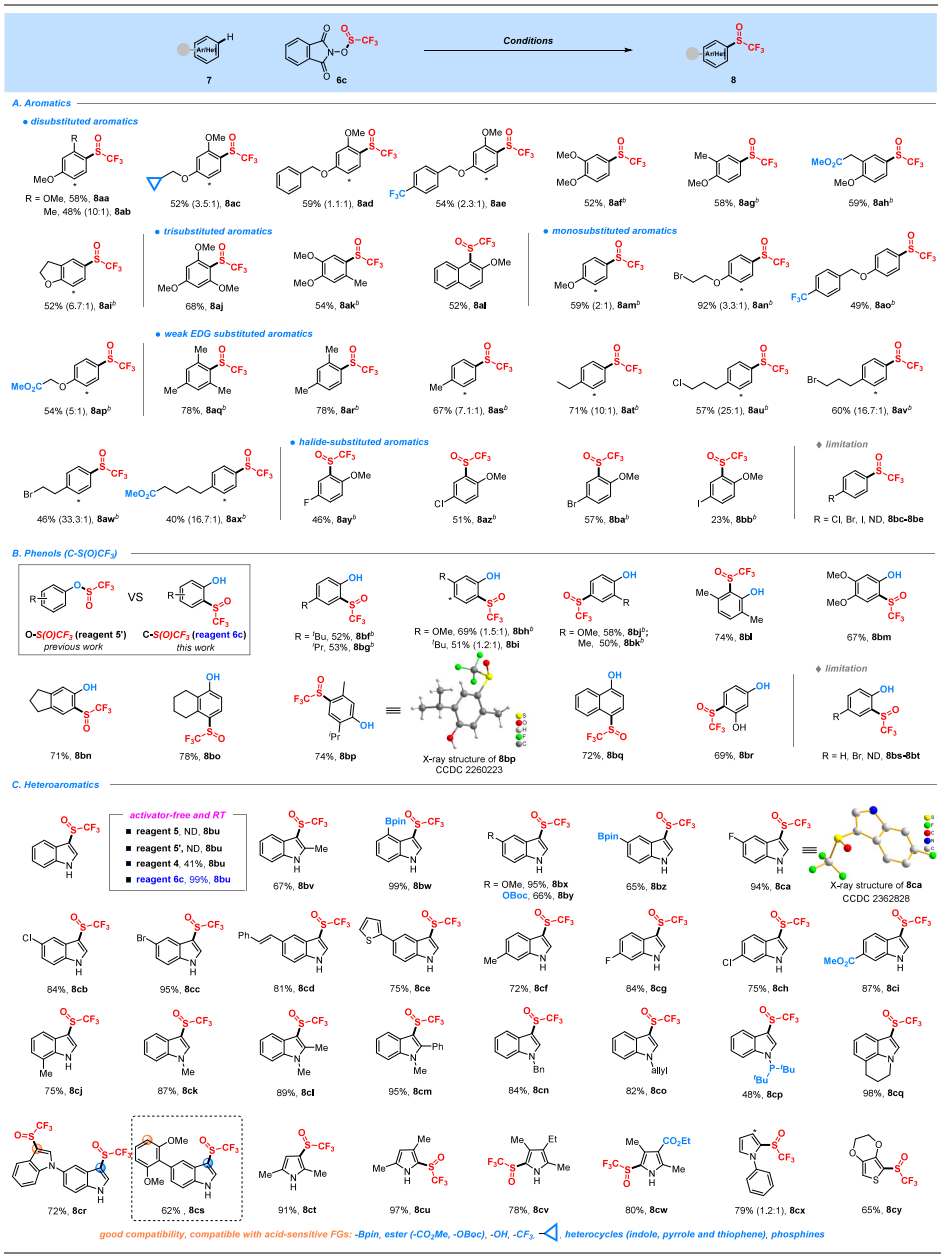
Table 2. Trifluoromethylsulfinylation of Aromatics, Phenols, and Heteroaromatics[a,c]



[a]Condition A: aromatics, phenols, or heteroaromatics (0.50 mmol), reagent **6c** (1.0 mmol, 2.0 equiv) in DCE (4.0 mL) under nitrogen atmosphere at RT for 12 h. [b]Condition B: aromatics or phenols (0.50 mmol), reagent **6c** (1.0 mmol, 2.0 equiv), and TfOH (0.75 mmol, 1.5 equiv) in DCE (4.0 mL) under nitrogen atmosphere at RT for 12 h. [c]Isolated yields.

with diversely functional ether structures, which demonstrates excellent functional group compatibility with bromine, trifluoromethyl, and ester groups (**8am**−**8ap**). To our delight, this system is also demonstrated by the successful trifluoromethylsulfinylation of weak EDGs-substituted aromatic substrates, such as mesitylene (**7aq**), 1,3-xylene (**7ar**), toluene (**7as**), alkylbenzenes linked with chlorine (**7au**), bromide (**7av**−**7aw**), or ester (**7ax**) functional groups, thus confirming the superiority of our developed procedure. It is noteworthy that good selectivity and acceptable yields were observed for the monosubstituted aromatic substrates. The direct conversions of halogen (Cl/Br/I)-substituted aromatic substrates failed (**7bc**−**7be**); however, in these cases, an electron-donating methoxy group on the *para*-position is beneficial for promoting the arene functionalization, and satisfactory yields could be generated for **8az**−**8bb**. Notably, 4-methoxyfluorobenzene could be trifluoromethylsulfinylated to deliver the desired $CF_3S(O)$-substituted product in 46% yield (**8ay**).

Interestingly, in contrast to traditional *O*-trifluoromethylsulfinylation of phenols,[14b,c] it was found that electron-rich phenols can smoothly produce the previously inaccessible direct *C*-trifluoromethylsulfinylated products by employing this distinctive reagent *N*-hydroxyphthalimide-*O*-trifluoromethanesulfinate under mild reaction conditions (please see single-crystal X-ray analysis of **8bq** in the Supporting Information). In particular, electron-rich phenols with functional groups such as *tert*-butyl, methoxyl, *iso*-propyl, and cycloalkyl were tolerated to

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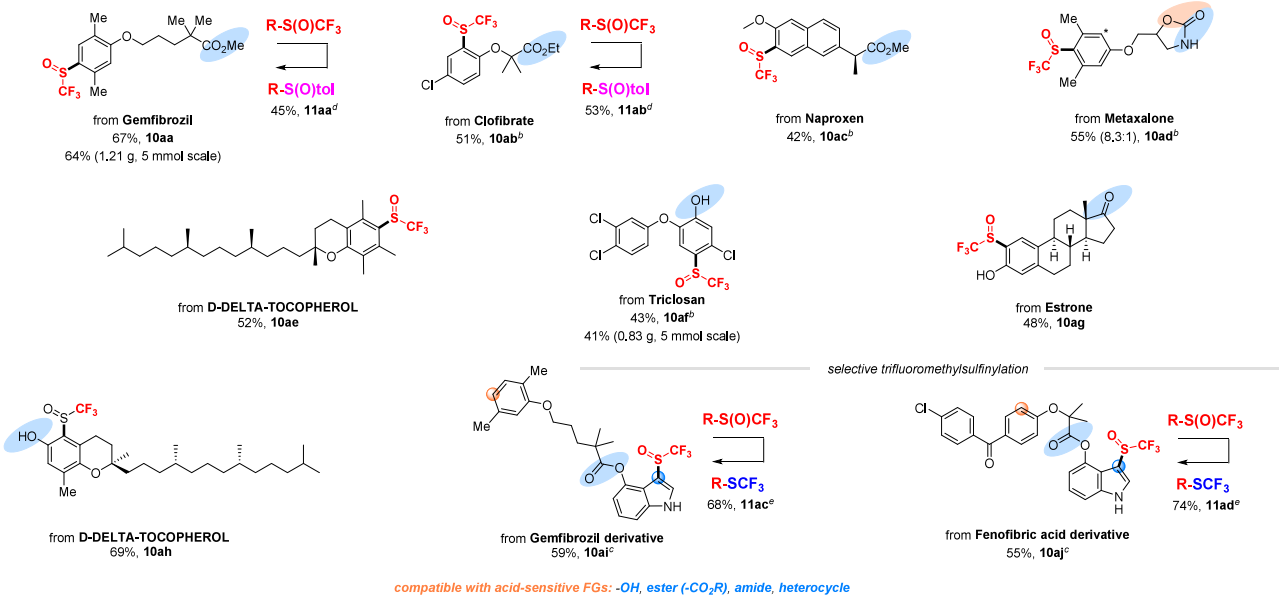
Table 3. Late-Stage Trifluoromethylsulfinylation[a,f]



[a]Reaction conditions: bioactive molecules or natural products (0.50 mmol), reagent **6c** (1.0 mmol, 2.0 equiv) in DCE (4.0 mL) under nitrogen atmosphere at RT for 12 h. [b]TfOH (0.75 mmol, 1.5 equiv) was added. [c]1.2 equiv of reagent **6c** was used. [d]Trifluoromethylsulfinylated compounds (0.50 mmol) and aryl magnesium bromide (2.5 mmol, 5.0 equiv) in THF (4.0 mL) under nitrogen atmosphere at RT for 10 h. [e]Trifluoromethylsulfinylated compounds (0.5 mmol) and PCl_3 (0.3 mmol, 0.6 equiv) in MeCN (4.0 mL) under nitrogen atmosphere at RT for 4 h. [f]Isolated yields.

give moderate to high yields of target trifluoromethylsulfinyl products (**8bf**−**8br**), as summarized in the middle of Table 2. Similarly, 2-naphthol and resorcinol could also be expediently trifluoromethylsulfinylated to give 69−72% yields of *C*-trifluoromethylsulfinylated products (**8bq**−**8br**). However, undecorated phenol and 4-bromophenol with low electron density cannot trigger this envisioned trifluoromethylsulfinylation (**8bs**−**8bt**).

Encouraged by the superior performance of *N*-hydroxyphthalimide-*O*-trifluoromethanesulfinate **6c** with aromatics and phenols, we then shifted our efforts to common trifluoromethylsulfinylation of a wide range of electron-rich heteroaromatics (Table 2, bottom). Our attempts with the mixing of Bertrand's reagents (**5** or **5′**)[13] and indole in DCE did not give any desired products under room temperature and activator-free conditions, while 41% yield of $CF_3S(O)$-substituted indole **8bu** was generated when commercial reagent $CF_3S(O)Cl$ (**4**) was employed. However, compared to previously reported electrophilic strategies for indole substrates,[11c−f,14c] this highly active reagent *N*-hydroxyphthalimide-*O*-trifluoromethanesulfinate **6c** could afford the desired 3-trifluoromethylsulfinyl indole in a quantitative yield (99%) at room temperature without the help of any activators. The substitution position of the trifluoromethylsulfinyl fragment on heterocycles was confirmed at the 3-position by single crystal diffraction (**8ca**), which implies that this trifluoromethylsulfinylation may proceed via an electrophilic substitution process. Reactions of a variety of indoles with electron-donating or -withdrawing substituted groups at the 2-, 4-, 5-, 6- or 7-position and reagent **6c** all underwent trifluoromethylsulfinylation smoothly to generate a set of fascinating trifluoromethylsulfinyl indoles (**8bu**−**8cs**) in good to quantitative yields (48−99%) under mild conditions. This reaction showed excellent functional group compatibility, as many functional groups including methoxyl, *tert*-butoxycarbonyl, pinacol borate, vinyl, fluoride, chlorine, bromide, and ester were all tolerated to give the corresponding products in satisfactory conversions. In particular, pinacol borate and bromide substituents (**8bw**, **8bz**, **8cc**) were reserved in this system, thus allowing subsequent functional-group orthogonal transformations. Besides, a heterocyclic substituent thiophen on the indole ring could successfully deliver the desired trifluoromethylsulfinylated product in 75% yield after simple column-based purification (**8ce**). Moreover, *N*-protected indoles (such as methyl, benzyl, and allyl groups and di-*tert* butyl phosphine) were efficiently trifluoromethylsulfinylated to afford the corresponding products (**8ck**−**8cp**). Furthermore, sterically hindered 2-methyl or phenyl indoles and lilolidine with a strained ring were also effective to give the 3-trifluoromethylsulfinylindoles in 89−98% yields (**8cl**−**8cm**, **8cq**). Notably, the reaction of reagent **6c** with 1′*H*-1,5′-biindole generated the ditrifluoromethylsulfinyl product, while 5-(2,6-dimethoxyphenyl)-1*H*-indole showed a good yield and excellent selectivity for indole over the phenyl ring under the standard conditions (**8cr**−**8cs**). In addition to structurally diverse indoles, direct trifluoromethylsulfinylation of electron-rich pyrroles also occurred smoothly in the current reaction (**8ct**−**8cx**). 2,5-Dimethyl-1*H*-pyrrole or 2,4-dimethylpyrrole was efficiently trifluoromethylsulfinylated to afford monotrifluoromethylsulfinylated products in excellent yields (**8ct**−**8cu**). Strikingly, the reaction of the electron-poor pyrrole activated by an electron-donating methyl substituent with our developed reagent **6c** could successfully generate an 80% yield of the corresponding trifluoromethylsulfinylated compounds under the optimal

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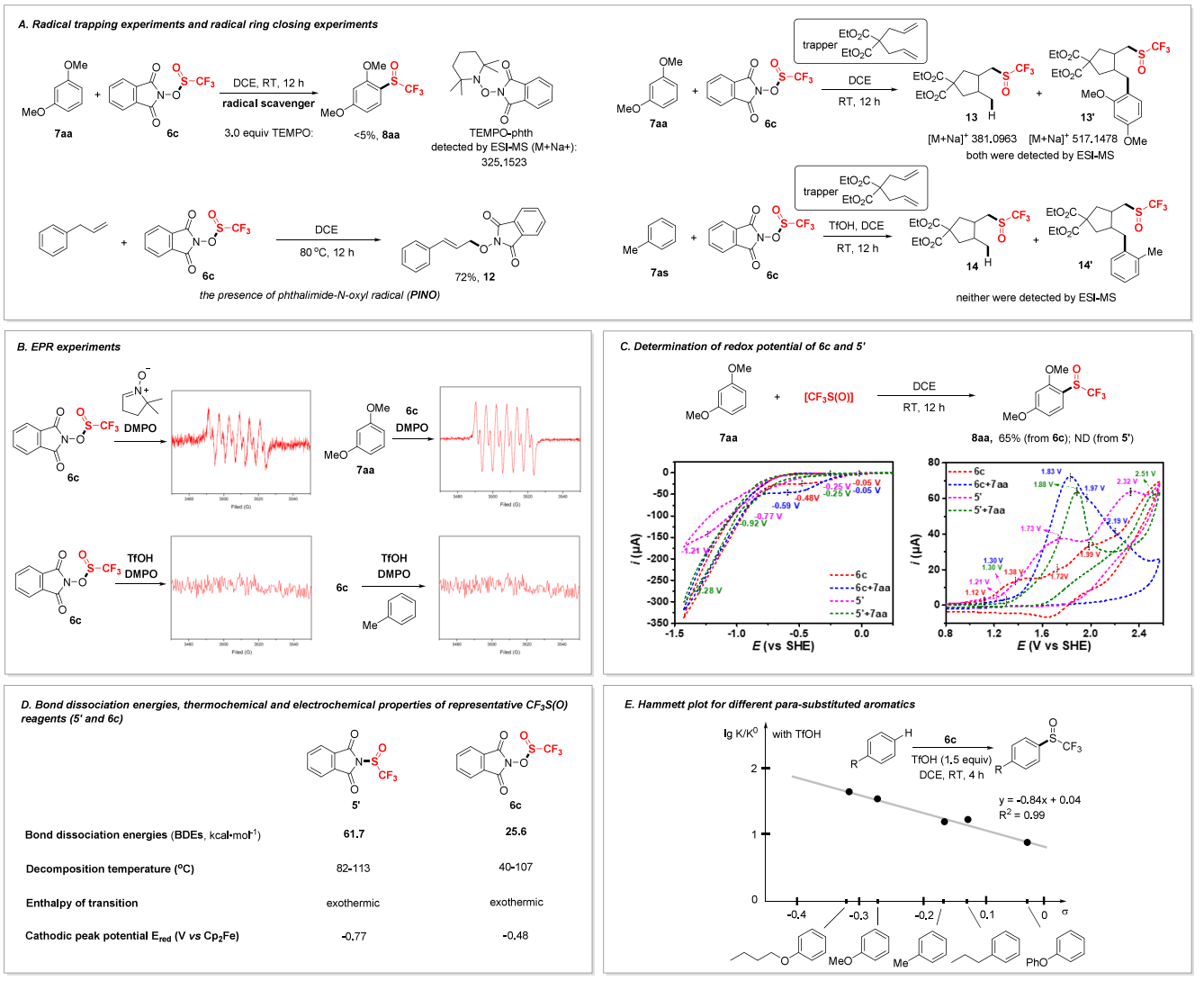
Scheme 3. Mechanistic Studies



conditions (**8cw**). Moreover, *N*-phenylpyrrole and thiophene were tested with **6c** at room temperature to deliver the envisioned trifluoromethylsulfinylated heteroaromatics in 65−79% yields (**8cx**−**8cy**).

As a significant advance to Wakselman's method,[15] the employment of mild reaction conditions made this protocol display superb functional-group tolerance for trifluoromethylsulfinylation of aromatics, phenols, and heteroaromatics, especially tolerating acid-sensitive groups including hydroxyl, trifluoromethyl, ester, cyclopropane, pinacol borate, and heterocycles. Notably, this simple and mild method also features sustainable utilization of the original starting material *N*-hydroxyphthalimide (NHPI), which was isolated in 99% recovery yield by filtration and could efficiently synthesize **6c** in two steps from the recycled NHPI in 68% yield on a 20 mmol scale (please see Supporting Information for more details).

2.4. Synthetic Applications

The superb functional group tolerance and high efficiency of this strategy enabled its application to the late-stage trifluoromethylsulfinylation modification of complex medicinally relevant fragments (Table 3), thereby accelerating the discovery of innovative drugs. For example, direct arene trifluoromethylsulfinylation modifications via *N*-hydroxyphthalimide-*O*-trifluoromethanesulfinate were successfully achieved for Plasma Lipids regulators, Clofibrate and Gemfibrozil (51−67%, **10aa**−**10ab**). The polysubstituted aromatic compound from carboxylic acid anti-inflammatory drug Naproxen was coupled with reagent **6c** to yield the corresponding trifluoromethylsulfinylated product **10ac** in 42% yield. Another clinically commonly used pharmaceutical Metaxalone bearing an oxazolidin-2-one skeleton was also tested as a superior candidate, delivering the target molecule **10ad** in 55% yield under the optimized conditions. Notably, a complex aromatic ring from dehydroxylated *D*-Delta-Tocopherol was also compatible to convert effectively into a 52% yield of trifluoromethylsulfinyl-substituted arene (**10ae**). Moreover, the expected *C*-trifluoromethylsulfinylated product **10af** was observed if we employed this novel reagent **6c** to decorate polysubstituted phenol compound Triclosan, which represents a famous broad-spectrum antibacterial disinfectant. In particular, under the standard conditions, bioactive phenol substrates Estrone and *D*-Delta-Tocopherol furnished *C*-trifluoromethylsulfinylated products in 48% and 69% yields,

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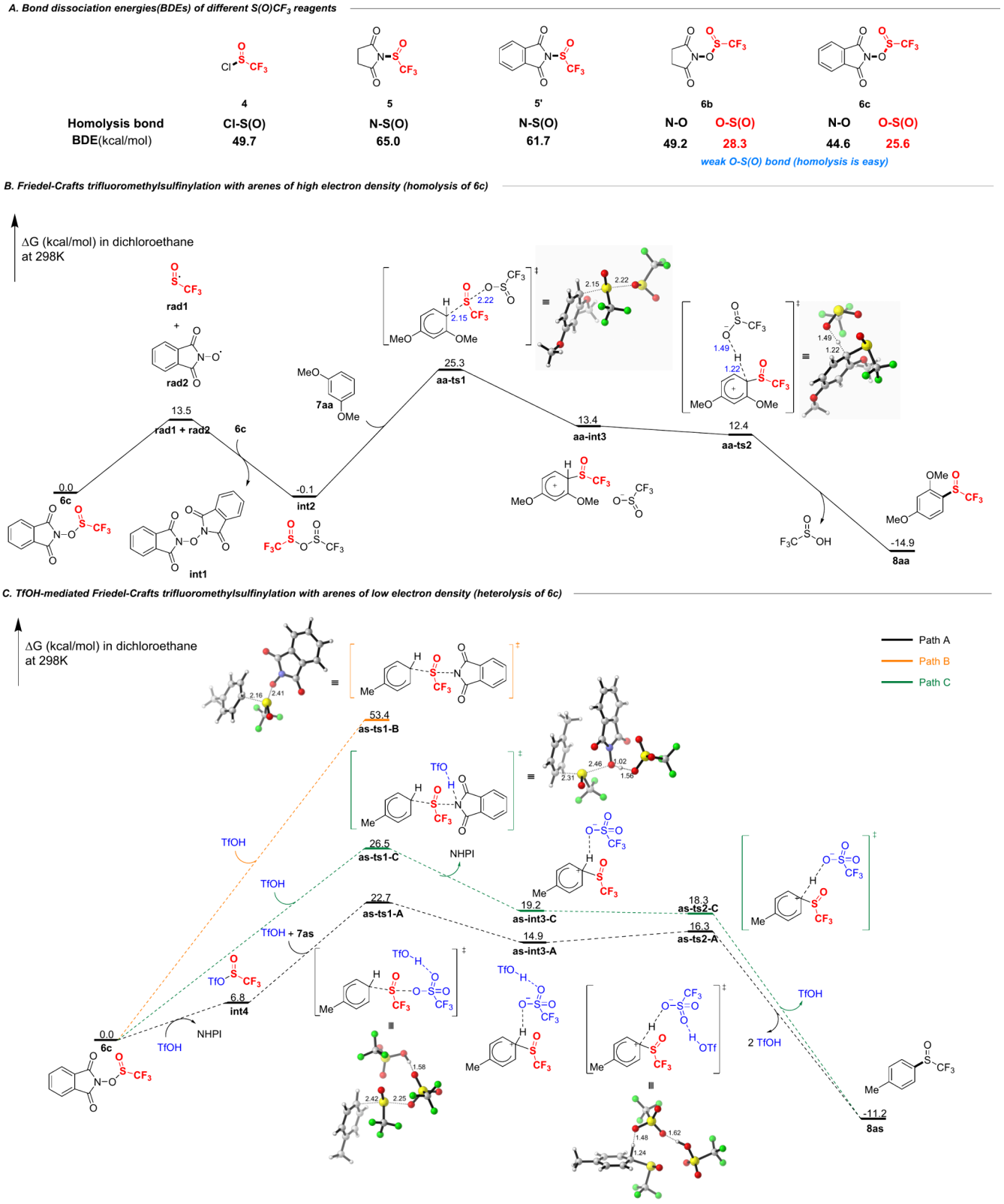
Scheme 4. Bond Dissociation Energies (BDEs) of Different $S(O)CF_3$ Reagents and DFT Calculations on Trifluoromethylsulfinylation of Arenes with High/Low Electron Density[a]



[a]Free energies (kcal/mol) are computed at the M06-2X/6-311++g(2df,2p)-SMD(dichloroethane)//M06-2X/6-31+g(d)-SMD(dichloroethane) level of theory.

respectively (**10ag−10ah**). Similarly, introducing a trifluoromethylsulfinyl group into indole derived from the hypolipidemic drug (Gemfibrozil and Fenofibric acid) could occur selectively via this direct arene trifluoromethylsulfinylation

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strategy (**10ai**−**10aj**). These elegant examples highlight the good tolerance (ester, amide, hydroxyl, heterocycle), wide applicability, and compatibility of the method and its enrichment of the toolbox for the late-stage trifluoromethylsulfinyl modification of biologically active molecules, natural products, and drugs.

Subsequently, gram-scale syntheses were conducted with good yields to highlight the practical utility of this protocol (**10aa**, **10af**). Further conversions of the $CF_3S(O)$ group to other important residues were then demonstrated to show the potential application values of trifluoromethylsulfinylated molecules. Gemfibrozil and Clofibrate derivatives assembled with a $CF_3S(O)$ moiety were treated with aryl Grignard reagent and could furnish the valuable diaryl sulfoxides with a reserved sulfur oxidation state (45−53%, **11aa**−**11ab**). Since the trifluoromethylthio group (CF_3S)[17] has been proven as a valuable and popular structural motif in pharmaceuticals and pesticides, we then investigated the conversion of *C*-trifluoromethylsulfinyl compounds to this important fluorinated residue. Pleasingly, under the condition of trivalent phosphine PCl_3 as the reductant, trifluoromethylsulfinyl-based substrates from Gemfibrozil and Fenofibric acid can be readily converted to CF_3S-substituted molecules in excellent yields (68−74%, **11ac**−**11ad**).

2.5. Mechanistic Studies and Proposed Mechanism

To gain deeper insights into the divergent arene trifluoromethylsulfinylation via this distinctive reagent, a series of mechanistic studies were conducted (Scheme 3, please refer to the Supporting Information for more details). Only a trace amount of trifluoromethylsulfinylated dimethoxybenzene (**8aa**) was obtained when TEMPO served as the radical scavenger under standard conditions. Through the ESI-MS analysis, we observed the generation of TEMPO-phth but not the well-defined TEMPO-$S(O)CF_3$ species. Additionally, when diallylmalonate was employed as the radical clock trapper, corresponding cyclization adducts (**13** and **13′**) were detected by ESI-MS, suggesting that a trifluoromethylsulfinyl radical is definitely generated in our developed arene trifluoromethylsulfinylation of electron-rich aromatics (Scheme 3A, top). Our attempts with **6c** and allyl benzene to give a high yield of 2-(cinnamyloxy)isoindoline-1,3-dione (**12**) suggest that phthalimide-*N*-oxyl (PINO) may be present in this process (Scheme 3A bottom). The above experimental results and EPR experiment (Scheme 3B) imply that **6c** and aromatics with high electron density may have undergone the homolytic cleavage, producing two free radicals: the dummy PINO radical and the desired $CF_3S(O)$ radical. Moreover, when arene with low electron density **7as** was used in the radical clock reaction and EPR experiment (Scheme 3A and 3B), none of the radical addition products (**14** and **14′**) and EPR signals were observed, indicating that the conversion of arene with low electron density is probably a nonfree radical process.

According to the cyclic voltammetry tests (Scheme 3C), reagent **5′** exhibits relatively poor redox potential compared to **6c**, where onset, second, and third reduction potentials of **5′** are located at −0.25, −0.77, and −1.21 V vs SHE (**6c**, onset, second reduction potentials at −0.05 and −0.48 V vs SHE). This phenomenon may disclose that reagent **6c** is more prone to generate a trifluoromethylsulfinyl radical, when compared to reagent **5′**. According to differential scanning calorimetry/thermogravimetric analysis (DSC-TGA), *N*-hydroxyphthalimide-*O*-trifluoromethanesulfinate starts to decompose at 40−107 °C under melting, which is lower than N−S framework trifluoromethyl sulfoxide reagent **5′** (Scheme 3D). For a detailed analysis of the various transitions upon heating, please see the DSC-TGA analysis in the Supporting Information. This phenomenon is also consistent with the bond dissociation energy of reagents **5′** and **6c** (61.7 and 25.6 kcal·mol^{-1}, respectively). In addition, we further characterized the electrochemical properties of **5′** and **6c**. The cyclic voltammetry test of **6c** shows an irreversible reduction wave with a cathodic peak potential of −0.48 V (vs SHE) and −0.77 V of **5′**. This result discloses that reagent **6c** is more prone to generate the trifluoromethylsulfinyl radical, when compared to trifluoromethylsulfinylating reagent with N−S framework (**5′**).

Moreover, the Hammett plot for different *para*-substituents (phenoxy, *n*-propyl, methyl, methoxy, *n*-butyloxy) of aromatic rings exhibits a good negative correlation (Scheme 3E), suggesting that the reaction of *N*-hydroxyphthalimide-*O*-trifluoromethanesulfinate and arene substrates with low electron density proceeds likely via an electrophilic aromatic substitution mechanism.

Furthermore, density functional theory (DFT) calculations were conducted to gain a better understanding of the detailed mechanism at the M06-2X/6-311++G(2df,2p)-SMD-(dichloroethane)//M06-2X/6-31+G(d)-SMD-(dichloroethane) level of theory. Based on the above mechanistic experiments, we then discovered that reagents **6b** and **6c** possess considerably lower bond dissociation energies of $O-S(O)CF_3$ (BDE: 28.3, 25.6 kcal·mol^{-1}) than previous developed analogues (**4**, **5**, and **5′**, Scheme 4A). Additionally, the BDE of the N−O bond between **6b** and **6c** was 49.2 and 44.6 kcal·mol^{-1}, with a higher energy barrier than breaking the $O-S(O)CF_3$ bond. These results disclose that the generation of trifluoromethylsulfinyl radicals via the homolytic scission of the O−S(O) bond of **6b** and **6c** is achievable in the absence of TfOH. For substrates with high electron density, the reaction begins with the homolysis of **6c**, generating the trifluoromethylsulfinyl radical (**rad1**) and the phthalimide-*N*-oxyl radical (PINO, **rad2**) (Scheme 4B). Since the SET or HAT process by PINO is disadvantageous, the pathway involving radical electrophilic aromatic addition between the trifluoromethylsulfinyl radical and the electron-rich substrate **7aa** is ruled out (see Supporting Information for more computational details). As a comparison, through the $CF_3S(O)$ radical transferring to another **6c** molecule, 2,2′-oxybis-(isoindoline-1,3-dione) (phthOphth, **int1**) and an activated intermediate (trifluoromethanesulfonic anhydride, **int2**) might be reasonably formed. Subsequently, a stepwise electrophilic aromatic substitution process occurs. The activated **int2** attacked the strong electron-donating substituted substrate **7aa** through **aa-ts1**, leading to the Wheland-type[18] intermediate **aa-int3**. Finally, deprotonation of **aa-int3** by the trifluoromethanesulfinate anion ($CF_3SO_2^-$) results in the formation of desired product **8aa**. For substrates with a low electron density, the vital role of TfOH was studied (Scheme 4C). DFT calculations unveil another electrophilic aromatic substitution mechanism, where TfOH can increase the electrophilicity of $CF_3S(O)$ for arene substrates with a low electron density, which require TfO^- as the leaving group (path A). Activation of reagent **6c** by TfOH occurs through the *in situ* formation of trifluoromethanesulfinic trifluoromethanesulfonic anhydride **int1**. Subsequently, with the assistance of another TfOH molecule, **int1** undergoes electrophile transfer of the $S(O)CF_3$ group to substrate **7as**, surmounting

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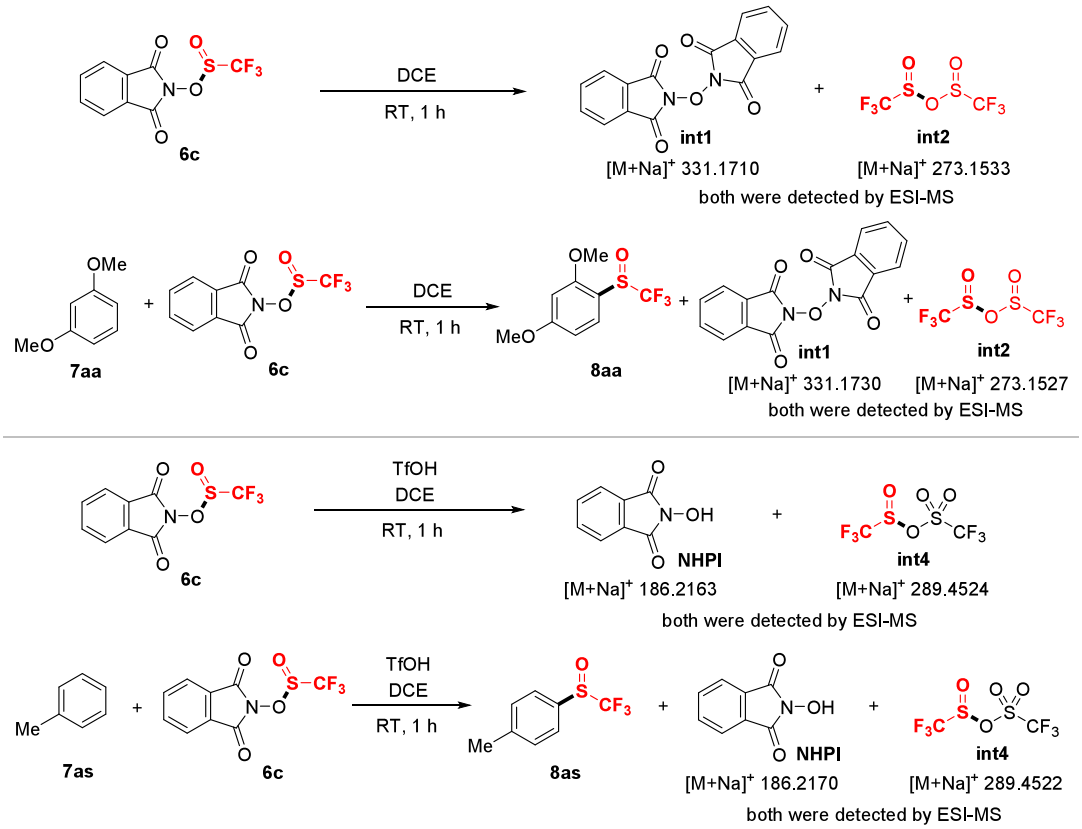
Scheme 5. Capture of Key Intermediates by ESI-MS



a 22.7 kcal/mol barrier via transition state **ts1−2TfOH**. This process yields Wheland-type intermediate **int2−2TfOH**. Finally, deprotonation of the intermediate **int2−2TfOH** occurs with the trifluoromethanesulfonate anion and forms product **8as**. Notably, direct or one-TfOH-assisted electrophilic transfer of the $S(O)CF_3$ group from reagent **6c** to **7as** requires a high barrier (paths B and C).

We then exploited the ESI-MS analysis in order to further support the key intermediates (**int1**, **int2**, **NHPI**, and **int4**, Scheme 4) in DFT calculations for this controllable Friedel−Crafts trifluoromethylsulfinylation (Scheme 5). We found that 2,2′-oxybis(isoindoline-1,3-dione) (**int1**) and $CF_3S(O)OS(O)CF_3$ (**int2**) generated from homolytic cleavage were both detected by ESI-MS when **6c** was stirred at room temperature for 1 h in DCE solvent. Similarly, after mixing **6c** and **7aa** in DCE, we also observed the generation of **int1** and **int2**. Moreover, heterolytic intermediates *N*-hydroxyphthalimide (NHPI) and $CF_3S(O)OTf$ (**int4**) were also detected when **6c** and TfOH reacted in DCE for 1 h; the mixture of **6c**, **7as**, and TfOH could also produce the key species of NHPI and **int4**, which were confirmed by mass spectrometry analysis.

Based on the detailed mechanistic studies, DFT calculations, and relevant literature,[19] plausible mechanisms for simple and direct arene trifluoromethylsulfinylation via *N*-hydroxyphthalimide-*O*-trifluoromethanesulfinate **6c** were proposed. *N*-Hydroxyphthalimide-*O*-trifluoromethanesulfinate proceeds via homolytic cleavage to produce a dummy radical (phthalimide-*N*-oxyl radical, PINO) and activated $CF_3S(O)$ radical due to the weak O−S(O) bond (BDE: 25.6 kcal·mol^{-1}). This active $CF_3S(O)$ radical might induce the generation of $CF_3S(O)OS(O)CF_3$ (**int2**) for the controllable trifluoromethylsulfinylation of an exemplary set of arenes with a high electron density. By contrast, *N*-hydroxyphthalimide-*O*-trifluoromethanesulfinate tends to undergo heterolytic scission with the assistance of TfOH, generating NHPI and highly active trifluoromethylsulfinyl species ($CF_3S(O)OTf$, **int4**), which smoothly undergo electrophilic trifluoromethylsulfinylation of the challenging weak EDG-substituted arene substrates to give trifluoromethylsulfinylated arenes. Furthermore, from DFT calculations, it can be seen that the activation of reagent **6c** by TfOH is crucial for this Friedel−Crafts trifluoromethylsulfinylation, and excessive TfOH (1.5 equiv) could promote this transformation.

3. CONCLUSIONS

In summary, we design a distinctive trifluoromethylsulfinylating reagent *N*-hydroxyphthalimide-*O*-trifluoromethanesulfinate with a low BDE (25.6 kcal/mol), which displays excellent reactivities of a wide variety of arenes following divergent reaction modes (homolysis (first report) and heterolysis). Notably, this arene trifluoromethylsulfinylation can be conducted in a redox-neutral manner under room temperature without light, transition metal, or photocatalyst. We use a novel and powerful *N*-hydroxy-phthalimide-*O*-trifluoromethanesulfinate toolkit, readily synthesized from cheap materials via two-step preparation, for the direct functionalization of a rich portfolio of arenes, including aromatics, phenols, and even challenging common aromatics with low electron density, which would otherwise require programmed, multistep processes. Such C−H functionalization using *N*-hydroxyphthalimide-*O*-trifluoromethanesulfinate with tunable reactivities affords an innovative strategy over functionalization with previously developed reagents. This methodology exhibits remarkable substrate generality and excellent functional group

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compatibility, especially compatibility with acid-sensitive groups (OH, CF_3, Bpin, carbonyl, cyclopropane, alkenyl, heterocycle, ester, and phosphine). Detailed mechanistic studies and DFT calculations suggest that the success of this approach hinges upon the design of an activated trifluoromethanesulfite ester with a very low bond dissociation energy (25.6 kcal·mol^{-1}), which could be homolytically cleaved to generate a dummy aminoxyl radical (PINO) and an active $CF_3S(O)$ radical. This $CF_3S(O)$ radical could activate *N*-hydroxyphthalimide-*O*-trifluoromethanesulfinate to yield a trifluoromethanesulfonic anhydride, $CF_3S(O)OS(O)CF_3$, for the successful trifluoromethylsulfinylation of an exemplary set of arenes with high electron density. Additionally, DFT computation corroborates that this novel reagent can be activated by TfOH via heterolytic cleavage to produce highly active $CF_3S(O)OTf$, which is responsible for the electrophilic trifluoromethylsulfinylation of the challenging weak EDG-substituted arene substrates through an electrophilic addition−elimination mechanism. Notably, late-stage trifluoromethylsulfinylation (LST) of complex biologically active molecules in these reactions underlines the great potential of *N*-hydroxyphthalimide-*O*-trifluoromethanesulfinate for the preparation of functionalized drug-like molecules. We expect this promising reagent will be of great power and popular utility to pharmaceutical chemists in new drug design.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.5c00072.

Experimental procedures, mechanistic studies, DFT calculations, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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