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An Energetic Guide for Estimating Trifluoromethyl Cation Donor Abilities of Electrophilic Trifluoromethylating Reagents: Computations of X−CF_3 Bond Heterolytic Dissociation Enthalpies

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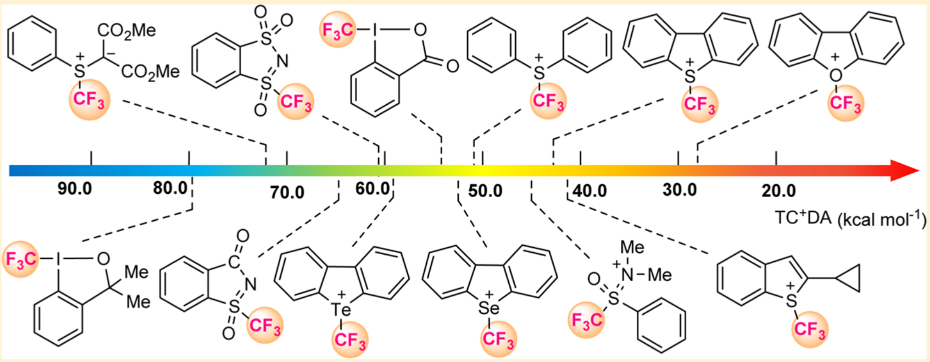
Supporting Information



ABSTRACT: This work established an energetic guide for estimating the trifluoromethyl cation-donating abilities (TC^+DA) of electrophilic trifluoromethylating reagents through computing X−CF_3 bond (X = O, S, Se, Te, and I) heterolytic dissociation enthalpies. TC^+DA values for a wide range of popular reagents were derived on the basis of density functional calculations (M06-2X). A good correspondence has been identified between the computed TC^+DA values and the experimentally observed relative trifluoromethylating capabilities of the reagents. Substituent effects hold good linear free energy relationships on the TC^+DAs of the most widely used reagents including Umemoto reagent, Yagupolskii−Umemoto reagent, and Togni reagents, which allow their trifluoromethylating capabilities to be rationally tuned by substituents and thus extend their synthetic utility. All the information disclosed in this work would contribute to future rational exploration of the electrophilic trifluoromethylation chemistry.

1. INTRODUCTION

The trifluoromethyl (CF_3) group has demonstrated a privileged role in the realm of medicinal chemistry because its incorporation into drug candidates can often profoundly alter their physical, chemical, and biological properties such as lipophilicity, bioavailability, metabolic stability, and protein-binding affinity.[1] As well-known, many pharmaceuticals and agrochemicals contain the trifluoromethyl motif.[1] Besides, the trifluoromethylated molecules are also widely applied in functional materials such as dyes[2] and liquid crystals.[3] Unfortunately, no CF_3-containing compounds exist in Nature. Hence, development of feasible and efficient methods to synthesize CF_3-containing compounds has been a subject of intensive research for years.[4]

Among various methods developed, electrophilic trifluoromethylation is one of the most promising and efficient strategies in the synthesis of CF_3-containing molecules.[5,6] The rapid development of novel electrophilic trifluoromethylation reactions would not have been possible without the availability of a wide variety of power-variable electrophilic trifluoromethylating reagents (Figure 1) developed by several groups, such as Yagupolskii,[7] Umemoto,[8] Shreeve,[9] Magnier,[10] Togni,[5e,11] Shibata,[12] Adachi and Ishihara,[13] and Lu and Shen.[14] Indeed, the invention of these reagents has provided a strong driving force for the discovery of new trifluoromethylation reactions,[5,15,16] which contributes enormously to efficient synthesis of compounds possessing fabulous chemical and biological properties.

Surprisingly, despite significant advances having been achieved in the development of versatile electrophilic trifluoromethylating reagents, the detailed structure−reactivity relationship study of these reagents lagged far behind,[8b,11d,17] that seriously hampered the rational design of novel reagents. Moreover, because the available reagents showed a very broad range of chemical reactivity as sources of trifluoromethyl cation,[5] an ordering of the propensity of all these reagents to release an electrophilic trifluoromethyl group would be of great

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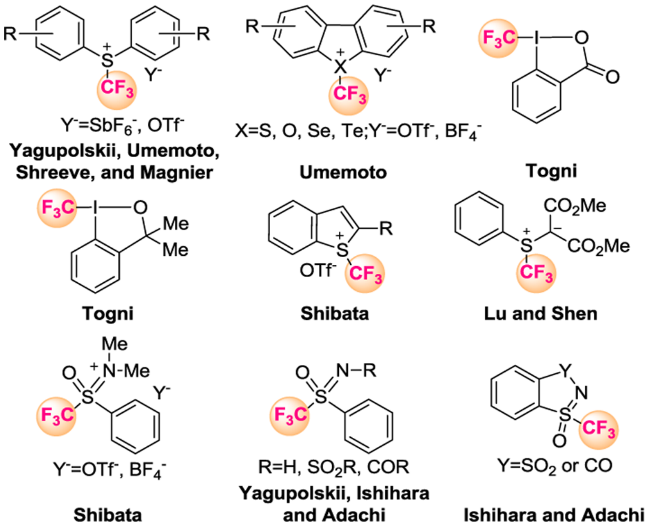


Figure 1. Typical electrophilic trifluoromethylating reagents.

value. Herein, we, for the first time, established an energetic guide for estimating the trifluoromethyl cation-donating abilities (TC^+DA) of electrophilic trifluoromethylating reagents by computing $X-CF_3$ (where X is the atom attaching the CF_3 group) bond heterolytic dissociation enthalpies. The TC^+DA is assessed by the $X-CF_3$ bond heterolytic dissociation enthalpy and is equal to the enthalpy change at 298.15 K for the reaction shown in eq 1 for a neutral reagent and eq 2 for a positively charged reagent. Encouragingly, the initial computation demonstrates a good correspondence between the computed TC^+DA values and the experimentally observed relative trifluoromethylating abilities of the reagents. On the basis of the calculated results, the effects of structure variation on the trifluoromethyl cation releasing ability of the reagents are discussed. The quantitative information disclosed in this work would be of good value for rational design of novel reagents and judicious selection of appropriate reagents for exploring new trifluoromethylation reactions.

$$X-CF_3 \xrightarrow[TC^+DA]{\Delta H_{298}} X^- + {}^+CF_3 \qquad \text{eq 1}$$

$$X^+-CF_3 \xrightarrow[TC^+DA]{\Delta H_{298}} X + {}^+CF_3 \qquad \text{eq 2}$$

2. COMPUTATIONAL METHODS

Truhlar et al.'s M06-2X density functional has been shown to provide accurate predictions for main group thermochemistry.[18] Indeed, the M06-2X functional was found to provide an accuracy higher than other density functionals tested such as B3LYP,[19] O3LYP,[20] X3LYP,[21] BMK,[22] and ωB97X-D[23] for the calculation of known experimental CF_3-related bond dissociation enthalpies. Particularly, the M06-2X/[6-311++G(2df,2p)+Def2-QZVPPD(Se,Te,I)]//M06-2X/[6-31+G-(d)+LANL2DZ(Se,Te,I)] method gives the best results with a mean unsigned error of 0.9 kcal mol^{-1} (see Supporting Information, Table S1). Accordingly, this method was employed for the calculation of the TC^+DA values of electrophilic trifluoromethylating reagents in the present study. The SMD solvation model[24] was used to account for the effects of acetonitrile (AN) solution, one of the most commonly used solvents for trifluoromethylation reactions (see Supporting Information for computational details). All the geometry optimizations were carried out in solution. All calculations were conducted with the Gaussian 09 packages.[25]

3. RESULTS AND DISCUSSION

The TC^+DA values for 99 electrophilic trifluoromethylating reagents in acetonitrile solution are presented in Table 1. For clarity, these reagents are categorized into three families: (a) chalcogenium salt reagents, (b) *S*-CF_3 sulfoximine reagents, and (c) hypervalent iodine reagents.

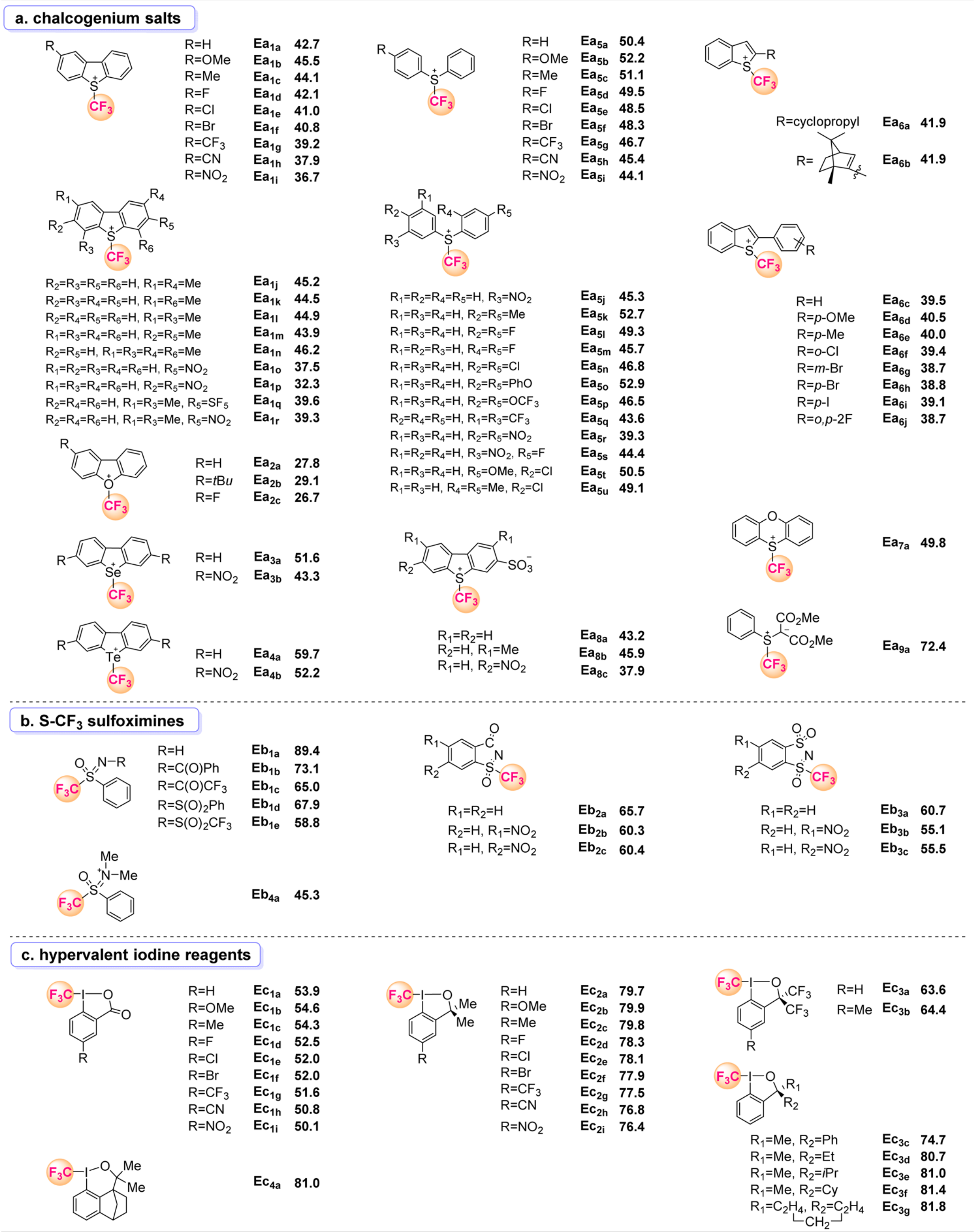
3.1. TC^+DAs of Chalcogenium Salt Reagents (Ea_{1a}–Ea_{9a}).

Among these reagents, Umemoto's *S*-, *O*-, *Se*-, and *Te*-trifluoromethylated dibenzoheterocyclic onium salts (**Ea_{1a}**–**Ea_{4b}**) have long been known as the so-called power-variable electrophilic trifluoromethylating reagents, which allow effective trifluoromethylation for a wide range of nucleophiles that differ in reactivity.[8] As shown in the Table 1, the TC^+DA value of the widely used *S*-CF_3 onium salt **Ea_{1a}** (Umemoto reagent)[8b] is 42.7 kcal mol^{-1}, which is 14.9 kcal mol^{-1} larger than that of *O*-CF_3 onium salt **Ea_{2a}**,[8d] and is 8.9 and 17.0 kcal mol^{-1} smaller than those of *Se*- and *Te*-CF_3 onium salts (**Ea_{3a}** and **Ea_{4a}**),[8b] respectively. This is in line with the experimental relative electrophilic trifluoromethylating power order observed by Umemoto et al. for *O*-, *S*-, *Se*-, and *Te*-CF_3 onium salts: O > S > Se > Te.[8a]

As expected, the ability to release a trifluoromethyl cation from chalcogenium salts could be depressed by electron-donating substituents and enhanced by electron-withdrawing substituents. For example, incorporation of two nitro groups at the 3,7-positions of *S*-, *Se*-, and *Te*-trifluoromethylated dibenzoheterocyclic onium salts leads to a decrease in TC^+DA value by 10.4, 8.3, and 7.5 kcal mol^{-1}, respectively. Notably, the TC^+DA of dinitro-substituted *Se*-CF_3 reagent **Ea_{3b}** is very close to that of *S*-CF_3 reagent **Ea_{1a}**, indicating that the effect of ring substituents is comparable to the effect of chalcogen variations on the trifluoromethyl cation transfer capability. To quantitatively elucidate the influence and the position of substituents, the effects of remote substituents (at para- and meta-positions) on TC^+DA of **Ea_{1a}** were examined. Figure 2 shows that the TC^+DAs for *S*-(trifluoromethyl)-dibenzothiophenium salts are linearly dependent on the sum of Hammett substituent parameters σ_p and σ_m with a very good correlation coefficient (r = 0.997, eq 3). This indicates that the effects of multiple substituents at the para- and meta-positions are concerted and have good linear additivity. Thus, for mono- or multisubstituted at para- and/or meta-position of Umemoto reagent **Ea_{1a}**, their TC^+DAs can be reliably estimated from eq 3 in Figure 2, provided the corresponding Hammett substituent parameters are available.

The change from heterocyclic to nonheterocyclic system leads to an increase in TC^+DA value as seen for Yagupolskii–Umemoto reagent **Ea_{5a}** (50.4 kcal mol^{-1}),[7,9,10] while reduction of the π-system of Umemoto reagent **Ea_{1a}** leads to a slight decrease in TC^+DA value as seen for Shibata reagent **Ea_{6a}** (41.9 kcal mol^{-1}).[12b] Accordingly, the order of trifluoromethyl cation transfer ability for the three main types of *S*-CF_3 onium salts should increase in the order of Yagupolskii–Umemoto reagent **Ea_{5a}** < Umemoto reagent **Ea_{1a}** < Shibata reagent **Ea_{6a}**. This is consistent with previous experimental observation that Umemoto reagent **Ea_{1a}** could effectively trifluoromethylate aniline, whereas only a trace of trifluoromethylated products were obtained with reagent **Ea_{5a}**.[8b] It should be noted that Umemoto's kinetic studies indicated that the higher reactivity of reagent **Ea_{1a}** compared with reagent **Ea_{5a}** in trifluoromethylation of aniline is due to a steric factor in the transition state.[26] However, the present calculation suggests that reagent **Ea_{1a}**

Table 1. Calculated TC$^+$DA Values for Electrophilic Trifluoromethylating Reagents in Acetonitrile at the SMD-M06-2X/6-311+G(2df, 2p)-Def2-QZVPPD//SMD-M06-2X/6-31+G(d)-LANL2DZ Level of Theory



CF$_3^+$ Source		TC$^+$DA in AN (kcal mol^{-1})
a. chalcogenium salts		
R=H	**Ea$_{1a}$**	**42.7**
R=OMe	**Ea$_{1b}$**	**45.5**
R=Me	**Ea$_{1c}$**	**44.1**
R=F	**Ea$_{1d}$**	**42.1**
R=Cl	**Ea$_{1e}$**	**41.0**
R=Br	**Ea$_{1f}$**	**40.8**
R=CF$_3$	**Ea$_{1g}$**	**39.2**
R=CN	**Ea$_{1h}$**	**37.9**
R=NO$_2$	**Ea$_{1i}$**	**36.7**
R$_2$=R$_3$=R$_5$=R$_6$=H, R$_1$=R$_4$=Me	**Ea$_{1j}$**	**45.2**
R$_2$=R$_3$=R$_4$=R$_5$=H, R$_1$=R$_6$=Me	**Ea$_{1k}$**	**44.5**
R$_2$=R$_4$=R$_5$=R$_6$=H, R$_1$=R$_3$=Me	**Ea$_{1l}$**	**44.9**
R$_1$=R$_3$=R$_4$=R$_6$=H, R$_2$=R$_5$=Me	**Ea$_{1m}$**	**43.9**
R$_2$=R$_5$=H, R$_1$=R$_3$=R$_4$=R$_6$=Me	**Ea$_{1n}$**	**46.2**
R$_1$=R$_2$=R$_3$=R$_4$=R$_6$=H, R$_5$=NO$_2$	**Ea$_{1o}$**	**37.5**
R$_1$=R$_3$=R$_4$=R$_6$=H, R$_2$=R$_5$=NO$_2$	**Ea$_{1p}$**	**32.3**
R$_2$=R$_4$=R$_6$=H, R$_1$=R$_3$=Me, R$_5$=SF$_5$	**Ea$_{1q}$**	**39.6**
R$_2$=R$_4$=R$_6$=H, R$_1$=R$_3$=Me, R$_5$=NO$_2$	**Ea$_{1r}$**	**39.3**
R=H	**Ea$_{2a}$**	**27.8**
R=*t*Bu	**Ea$_{2b}$**	**29.1**
R=F	**Ea$_{2c}$**	**26.7**
R=H	**Ea$_{3a}$**	**51.6**
R=NO$_2$	**Ea$_{3b}$**	**43.3**
R=H	**Ea$_{4a}$**	**59.7**
R=NO$_2$	**Ea$_{4b}$**	**52.2**
R=H	**Ea$_{5a}$**	**50.4**
R=OMe	**Ea$_{5b}$**	**52.2**
R=Me	**Ea$_{5c}$**	**51.1**
R=F	**Ea$_{5d}$**	**49.5**
R=Cl	**Ea$_{5e}$**	**48.5**
R=Br	**Ea$_{5f}$**	**48.3**
R=CF$_3$	**Ea$_{5g}$**	**46.7**
R=CN	**Ea$_{5h}$**	**45.4**
R=NO$_2$	**Ea$_{5i}$**	**44.1**
R$_1$=R$_2$=R$_4$=R$_5$=H, R$_3$=NO$_2$	**Ea$_{5j}$**	**45.3**
R$_1$=R$_3$=R$_4$=H, R$_2$=R$_5$=Me	**Ea$_{5k}$**	**52.7**
R$_1$=R$_3$=R$_4$=H, R$_2$=R$_5$=F	**Ea$_{5l}$**	**49.3**
R$_1$=R$_2$=R$_3$=H, R$_4$=R$_5$=F	**Ea$_{5m}$**	**45.7**
R$_1$=R$_3$=R$_4$=H, R$_2$=R$_5$=Cl	**Ea$_{5n}$**	**46.8**
R$_1$=R$_3$=R$_4$=H, R$_2$=R$_5$=PhO	**Ea$_{5o}$**	**52.9**
R$_1$=R$_3$=R$_4$=H, R$_2$=R$_5$=OCF$_3$	**Ea$_{5p}$**	**46.5**
R$_2$=R$_4$=R$_5$=H, R$_1$=R$_3$=CF$_3$	**Ea$_{5q}$**	**43.6**
R$_1$=R$_3$=R$_4$=H, R$_2$=R$_5$=NO$_2$	**Ea$_{5r}$**	**39.3**
R$_1$=R$_2$=R$_4$=H, R$_3$=NO$_2$, R$_5$=F	**Ea$_{5s}$**	**44.4**
R$_1$=R$_3$=R$_4$=H, R$_5$=OMe, R$_2$=Cl	**Ea$_{5t}$**	**50.5**
R$_1$=R$_3$=H, R$_4$=R$_5$=Me, R$_2$=Cl	**Ea$_{5u}$**	**49.1**
R$_1$=R$_2$=H	**Ea$_{8a}$**	**43.2**
R$_2$=H, R$_1$=Me	**Ea$_{8b}$**	**45.9**
R$_1$=H, R$_2$=NO$_2$	**Ea$_{8c}$**	**37.9**
R=cyclopropyl	**Ea$_{6a}$**	**41.9**
R=	**Ea$_{6b}$**	**41.9**
R=H	**Ea$_{6c}$**	**39.5**
R=*p*-OMe	**Ea$_{6d}$**	**40.5**
R=*p*-Me	**Ea$_{6e}$**	**40.0**
R=*o*-Cl	**Ea$_{6f}$**	**39.4**
R=*m*-Br	**Ea$_{6g}$**	**38.7**
R=*p*-Br	**Ea$_{6h}$**	**38.8**
R=*p*-I	**Ea$_{6i}$**	**39.1**
R=*o*,*p*-2F	**Ea$_{6j}$**	**38.7**
	Ea$_{7a}$	**49.8**
	Ea$_{9a}$	**72.4**
b. S-CF$_3$ sulfoximines		
R=H	**Eb$_{1a}$**	**89.4**
R=C(O)Ph	**Eb$_{1b}$**	**73.1**
R=C(O)CF$_3$	**Eb$_{1c}$**	**65.0**
R=S(O)$_2$Ph	**Eb$_{1d}$**	**67.9**
R=S(O)$_2$CF$_3$	**Eb$_{1e}$**	**58.8**
	Eb$_{4a}$	**45.3**
R$_1$=R$_2$=H	**Eb$_{2a}$**	**65.7**
R$_2$=H, R$_1$=NO$_2$	**Eb$_{2b}$**	**60.3**
R$_1$=H, R$_2$=NO$_2$	**Eb$_{2c}$**	**60.4**
R$_1$=R$_2$=H	**Eb$_{3a}$**	**60.7**
R$_2$=H, R$_1$=NO$_2$	**Eb$_{3b}$**	**55.1**
R$_1$=H, R$_2$=NO$_2$	**Eb$_{3c}$**	**55.5**
c. hypervalent iodine reagents		
R=H	**Ec$_{1a}$**	**53.9**
R=OMe	**Ec$_{1b}$**	**54.6**
R=Me	**Ec$_{1c}$**	**54.3**
R=F	**Ec$_{1d}$**	**52.5**
R=Cl	**Ec$_{1e}$**	**52.0**
R=Br	**Ec$_{1f}$**	**52.0**
R=CF$_3$	**Ec$_{1g}$**	**51.6**
R=CN	**Ec$_{1h}$**	**50.8**
R=NO$_2$	**Ec$_{1i}$**	**50.1**
	Ec$_{4a}$	**81.0**
R=H	**Ec$_{2a}$**	**79.7**
R=OMe	**Ec$_{2b}$**	**79.9**
R=Me	**Ec$_{2c}$**	**79.8**
R=F	**Ec$_{2d}$**	**78.3**
R=Cl	**Ec$_{2e}$**	**78.1**
R=Br	**Ec$_{2f}$**	**77.9**
R=CF$_3$	**Ec$_{2g}$**	**77.5**
R=CN	**Ec$_{2h}$**	**76.8**
R=NO$_2$	**Ec$_{2i}$**	**76.4**
R=H	**Ec$_{3a}$**	**63.6**
R=Me	**Ec$_{3b}$**	**64.4**
R$_1$=Me, R$_2$=Ph	**Ec$_{3c}$**	**74.7**
R$_1$=Me, R$_2$=Et	**Ec$_{3d}$**	**80.7**
R$_1$=Me, R$_2$=*i*Pr	**Ec$_{3e}$**	**81.0**
R$_1$=Me, R$_2$=Cy	**Ec$_{3f}$**	**81.4**
R$_1$=C$_2$H$_4$, R$_2$=C$_2$H$_4$ └CH$_2$┘	**Ec$_{3g}$**	**81.8**

should be more prone to release a trifluoromethyl cation than reagent **Ea$_{5a}$** even in absence of steric effects. In other words, reagent **Ea$_{1a}$** should be intrinsically more reactive than **Ea$_{5a}$** behaving as the source of trifluoromethyl cation. This could be attributed to an additional driving force resulting from restoration of the lost aromaticity for **Ea$_{1a}$**, as a result of transformation of the central 4π antiaromatic five-membered heterocyclic ring to the 6π aromatic heterocycle.[8b,27] Indeed, the increased ability to transfer a trifluoromethyl cation from **Ea$_{6a}$** as compared to that from **Ea$_{1a}$** is consistent with the fact that benzothiophene is more aromatic than dibenzothiophene.[28] This may explain why Shibata reagent **Ea$_{6a}$** presented the advantage of a higher yield over Umemoto reagent **Ea$_{1a}$** in trifluoromethylation of β-keto esters (Scheme 1).[12b] Moreover, a comparison of the TC$^+$DA value of phenoxathiinium salt **Ea$_{7a}$**[8b] with those of **Ea$_{1a}$** and **Ea$_{5a}$** further corroborates that the recovery of aromaticity is an important driving force for releasing the trifluoromethyl cation: the TC$^+$DA value of **Ea$_{7a}$** (49.8 kcal mol^{-1}) is close to that of **Ea$_{5a}$**, but ca. 7 kcal mol^{-1} is greater than that of **Ea$_{1a}$**. Therefore, the recovery of aromaticity[29] could be an important driving force that could be utilized for the design of new electrophilic trifluoromethylating reagents.

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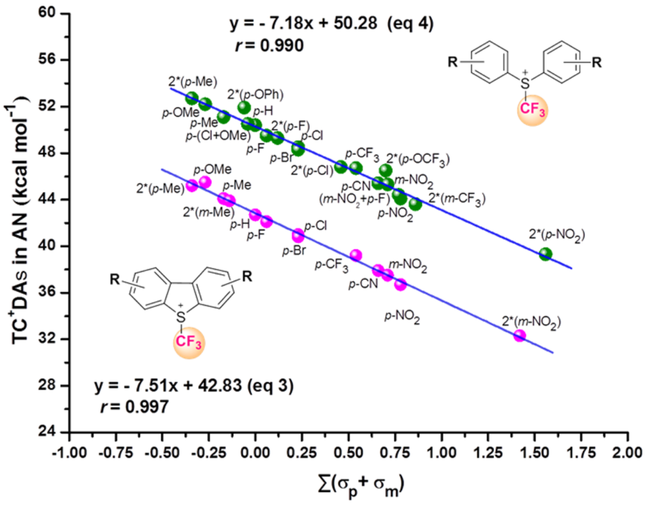
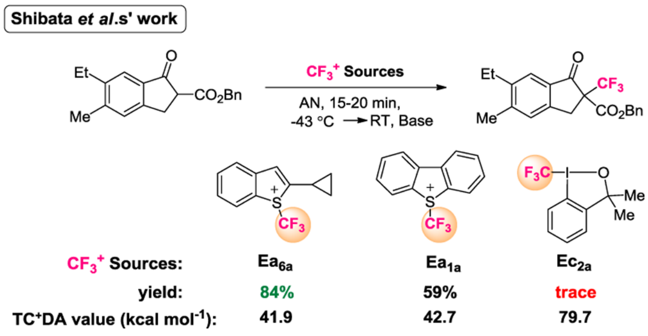


Figure 2. Plots of TC$^+$DA values of para- and meta-substituted Umemoto reagent **Ea$_{1a}$** (the lower left one) and Yagupolskii–Umemoto reagent **Ea$_{5a}$** (the upper right one) against the Hammett substituent parameters.

Scheme 1. Electrophilic Trifluoromethylation of *β*-Keto Esters



A good linear correlation between the calculated TC$^+$DAs of para- and meta-substituted Yagupolskii–Umemoto reagent **Ea$_{5a}$** and the Hammett substituent constants σ_p and σ_m was obtained as well (see eq 4, Figure 2). Interestingly, the two slopes are very close to each other for the linear regression equation of heterocyclic (**Ea$_{1a}$**) and nonheterocyclic (**Ea$_{5a}$**) system (−7.5 vs −7.2), indicating that substituent effects on the trifluoromethyl cation donating ability of the two systems are very similar in magnitude. Previously, Shreeve and co-workers demonstrated an excellent example of altering electrophilic trifluoromethylating potential of reagent **Ea$_{5a}$** by placing electron-withdrawing substituents on the benzene rings during trifluoromethylation of pyrrole (Scheme 2).[9] Indeed, the computed TC$^+$DA values of the respective reagents are in parallel with the experimentally observed electrophilic trifluoromethylating abilities. This further demonstrates the importance of the TC$^+$DA parameters of electrophilic trifluoromethylating reagents for reaction planning and optimizing. With eqs 3 and 4 in hand, the TC$^+$DA values of the two popular types of *S*-CF$_3$ reagents now could be rationally tuned by substituents. Finally, consistent with Umemoto and co-workers' experimental observation that the reactivity of the zwitterionic type of *S*-CF$_3$ reagent **Ea$_{8a}$** is almost the same as that of Umemoto reagent **Ea$_{1a}$**,[8c] the calculated TC$^+$DA values for **Ea$_{8a}$** and **Ea$_{1a}$** are quite close to each other (43.2 vs 42.7 kcal mol^{-1}). Also, the TC$^+$DA value of Lu and Shen's *S*-CF$_3$ ylide reagent **Ea$_{9a}$** (72.4 kcal mol^{-1}) was predicted to be higher than that of the Yagupolskii–Umemoto reagent **Ea$_{5a}$** by 22.0 kcal mol^{-1}. This might account for the experimental observation that a high reaction temperature was required for electrophilic trifluoromethylation of *β*-keto esters with the reagent **Ea$_{9a}$**.[14]

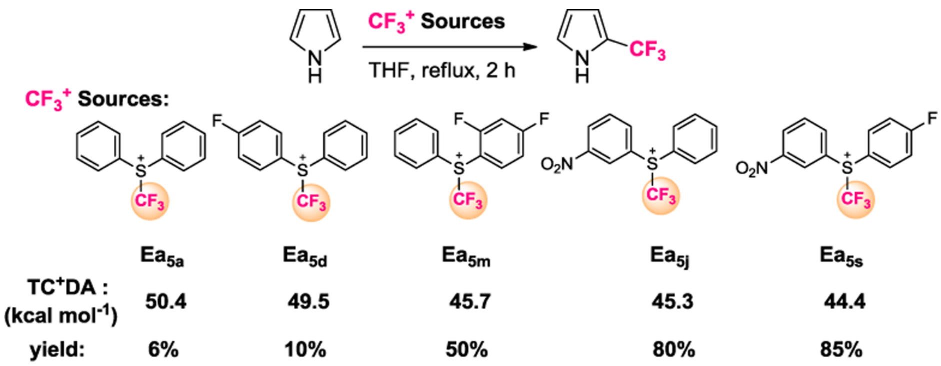
3.2. TC$^+$DAs of *S*-CF$_3$ Sulfoximine Reagents (Eb$_{1a}$–Eb$_{4a}$).

The largest TC$^+$DA value calculated in this study is that of *S*-CF$_3$ sulfoximine **Eb$_{1a}$** (89.4 kcal mol^{-1}),[30] indicating the least propensity of this reagent to transfer a trifluoromethyl cation. The ability to release a trifluoromethyl cation can be enhanced considerably through functionalization at nitrogen with a strong electron-withdrawing group as for Adachi and Ishihara's reagents **Eb$_{1b}$** (73.1 kcal mol^{-1}) and **Eb$_{1d}$** (67.9 kcal mol^{-1}).[13] Compared to the acyclic *S*-CF$_3$ sulfoximine **Eb$_{1d}$**, the transfer of a trifluoromethyl cation becomes more favorable from Adachi and Ishihara's cyclic reagents **Eb$_{2a}$** and **Eb$_{3a}$** by 2.2 and 7.2 kcal mol^{-1}, respectively. Noticeably, according to the calculated TC$^+$DA values, the *S*-CF$_3$ sulfoximine salt reagent **Eb$_{4a}$** developed by Shibata and co-workers[12a] should have the strongest trifluoromethylating ability among those sulfoximine-based reagents. This could provide an explanation for Magnier and co-workers' intriguing finding that **Eb$_{4a}$** could readily transfer its electrophilic trifluoromethyl group to the terminal acetylenic carbon, while no reaction occurred for neutral *S*-CF$_3$ sulfoximine **Eb$_{1e}$** (Scheme 3).[31]

3.3. TC$^+$DAs of Hypervalent Iodine Reagents (Ec$_{1a}$–Ec$_{4a}$).

The TC$^+$DA value of Togni's hypervalent iodine reagent[11a] **Ec$_{1a}$** (53.9 kcal mol^{-1}) was predicted to be ca. 26 kcal mol^{-1} smaller than that of reagent **Ec$_{2a}$** (79.7 kcal mol^{-1}), which is in accord with the previous experimental finding that reagent **Ec$_{1a}$** is much more reactive than **Ec$_{2a}$** in trifluor-

Scheme 2. Trifluoromethylation of Pyrrole with Yagupolskii–Umemoto Reagents



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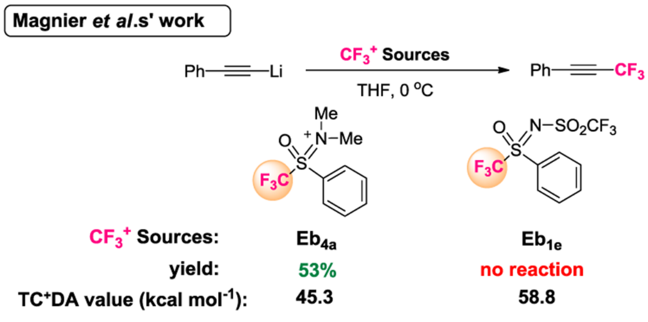
Scheme 3. Electrophilic Trifluoromethylations with S-CF$_3$ Sulfoximine Reagents



omethylation of *p*-toluenesulfonic acid.[11b] Examination of the para-substituent effect on TC$^+$DAs of Togni reagents $\mathbf{Ec_{1a}}$ and $\mathbf{Ec_{2a}}$ obtained a good linear correlation between the TC$^+$DA values and the Hammett σ_p constants (Figure 3). Modification of $\mathbf{Ec_{2a}}$[11b,d] on its side-chain by replacing the two methyl groups with electron-withdrawing CF$_3$ leads to a decrease in TC$^+$DA value by 16.1 kcal mol^{-1} ($\mathbf{Ec_{2a}}$: 79.7 kcal mol^{-1} vs $\mathbf{Ec_{3a}}$: 63.6 kcal mol^{-1}), while substitution with electron neutral alkyl groups (Et, *i*Pr, etc.) causes only a slight increase in TC$^+$DA values for $\mathbf{Ec_{3d}}$–$\mathbf{Ec_{3g}}$ (80.7–81.8 kcal mol^{-1}). The calculated TC$^+$DA value of $\mathbf{Ec_{4a}}$[11b] is close to that of $\mathbf{Ec_{2a}}$ (81.0 vs 79.7 kcal mol^{-1}), suggesting that the change from five- to six-membered ring does not much affect the trifluoromethyl cation releasing ability. Finally, comparison of the TC$^+$DA values of Togni reagents $\mathbf{Ec_{1a}}$ and $\mathbf{Ec_{2a}}$ with those of Umemoto reagent $\mathbf{Ea_{1a}}$ and Shibata reagent $\mathbf{Ea_{6a}}$ reveals that the ability to transfer a trifluoromethyl cation from Togni's hypervalent iodine reagents should be intrinsically weaker than from the two S-CF$_3$ reagents. This might account for Shibata and co-workers' observation that trifluoromethylation of *β*-keto esters with Shibata reagent $\mathbf{Ea_{6a}}$ and Umemoto reagent $\mathbf{Ea_{1a}}$ gave 84% and 59% yields, respectively, but only trace products were obtained using Togni reagent $\mathbf{Ec_{2a}}$ (Scheme 1).[12b]

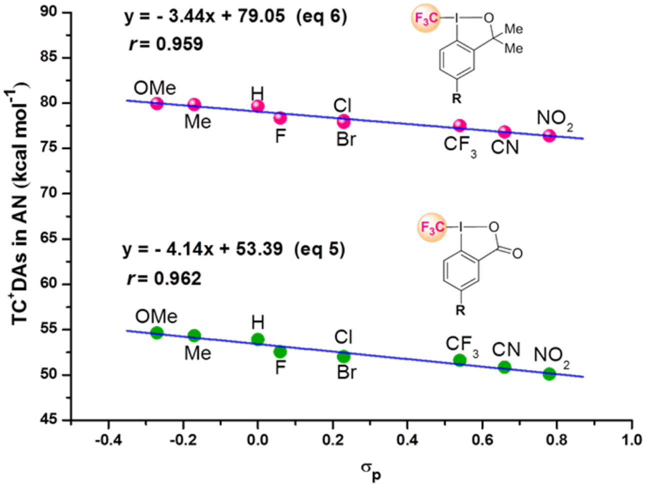


Figure 3. Plots of TC$^+$DA values of para-substituted Togni reagents against the Hammett substituent parameters.

As mentioned above, Togni's hypervalent iodine reagent $\mathbf{Ec_{2a}}$ is in fact a weak trifluoromethyl cation donor; however, this reagent was utilized quite successfully in trifluoromethylation of a wide range of nucleophiles.[5e] A careful examination of literature reveals that strong Brönsted/Lewis acids were often required for activating $\mathbf{Ec_{2a}}$ so as to facilitate transferring a trifluoromethyl cation.[2d,6e,32] For instance, it was reported that trifluoromethylation of benzotriazole with reagent $\mathbf{Ec_{2a}}$ in the presence of a catalytic amount of strong acid HNTf$_2$ gave 41% yield, whereas no CF$_3$ transfer was observed in the absence of HNTf$_2$ (Figure 4a).[6e] Indeed, activation of $\mathbf{Ec_{2a}}$ by protonation could lead to a significant enhancement in the electrophilic trifluoromethylating capability, as verified by the TC$^+$DA value of the protonated $\mathbf{Ec_{2a}}$ (39.3 kcal mol^{-1}, Figure 4b), which is 40.4 kcal mol^{-1} lower than that of the unactivated reagent. This may also be the reason that a catalytic amount of strong acid was necessary for trifluoromethylation of benzotriazole with reagent $\mathbf{Ec_{2a}}$.[6e] It is worth emphasizing that Togni's hypervalent iodine reagents offer a unique opportunity in synthesis, as their trifluoromethyl cation-donating capabilities could be tuned by adding Brönsted/Lewis acids as activators. Compared with chemical modification, the approach through adding Brönsted/Lewis acids of different acidities to activate these reagents is a very attractive strategy due to its simplicity, economy, and effectiveness. In fact, such a strategy has already been shown to be useful in a variety of asymmetric catalytic reaction systems.[33]

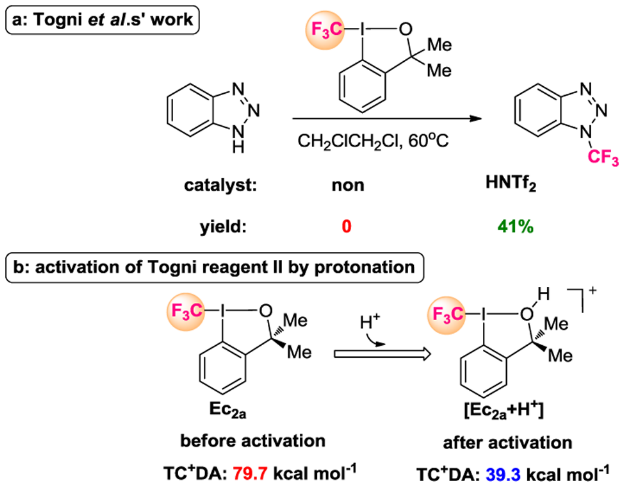


Figure 4. (a) Trifluoromethylation of benzotriazole with Togni reagent $\mathbf{Ec_{2a}}$ in the presence/absence of HNTf$_2$, and (b) the calculated TC$^+$DA value of protonated $\mathbf{Ec_{2a}}$.

3.4. TC$^+$DA Scale of Representative Reagents. For easy comparison, Figure 5 compiles a TC$^+$DA scale for representative electrophilic trifluoromethylating reagents. It should be pointed out that (a) the scale refers to the commonly used high polar acetonitrile solution, and changes in the relative positions of the charged and neutral reagents could be expected in low or nonpolar solvents. The charged reagents are expected to be less stable in low or nonpolar solvents[34] and thus should be more apt to transfer a trifluoromethyl cation to substrates. (b) Like the cases for trifluoromethylthio cation-donating ability (Tt$^+$DA),[35] methyl cation affinity (MCA),[36] and halenium affinity (HalA)[37] scales that recently appeared, the TC$^+$DA parameter describes a thermodynamic property of a reagent and may be well applied under thermodynamically controlled conditions. For the cases that are heavily perturbed by steric effects or other kinetic elements, a more detailed energetic analysis of transition states should have to be pursued.[38] (c) If an electrophilic trifluoromethylation reaction is initiated by a single electron transfer (SET) mechanism, the TC$^+$DA

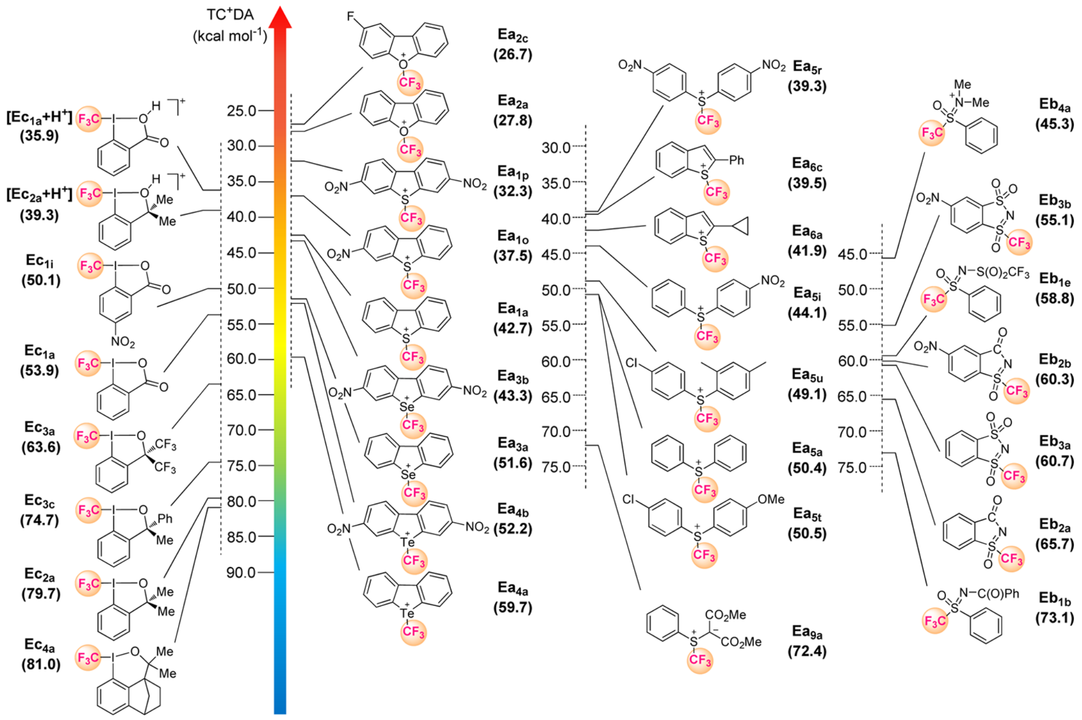


Figure 5. Calculated TC$^+$DAs for electrophilic trifluoromethylating reagents in acetonitrile at the SMD-M06-2X/6-311++G(2df, 2p)-Def2-QZVPPD//SMD-M06-2X/6-31+G(d)-LANL2DZ level of theory.

parameter will have its limitation in predicting reactivity. Overall, the TC$^+$DA parameter can be proposed to be a basic means for predicting electrophilic trifluoromethylating capability of a given reagent when the reaction proceeds not via an SET mechanism and the steric factor is not significant. Despite possible limitations, this scale would be valuable for experimental chemists in the rational design of novel reagents and judicious selection of appropriate reagents for new reactions, considering that a reasonable correspondence has been identified between the computed TC$^+$DA values and the experimentally observed relative trifluoromethylating abilities of the reagents.

4. CONCLUSION

To summarize, in this work we have addressed a fundamental question in the field of electrophilic trifluoromethylation. We have established the trifluoromethyl cation-donating abilities of electrophilic trifluoromethylating reagents though computing X−CF$_3$ bond heterolytic dissociation enthalpies. A good correspondence has been found between the computed TC$^+$DA values and the experimentally observed relative trifluoromethylating abilities of the popular reagents. The substituent effects hold very good Hammett linear free energy relationships on the TC$^+$DAs of the most commonly used Umemoto reagent, Yagupolskii−Umemoto reagent, and Togni reagents. It is believed that the information disclosed in this work would greatly facilitate future rational exploration of trifluoromethylation chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02821.

Computational details, Table S1, and optimized geometries of all computed species (PDF)

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Notes

The authors declare no competing financial interest.

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