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## COMMUNICATION

### Designing New Togni Reagents by Computation

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**New trifluoromethylating reagents are designed via computational studies inspired by the Togni's experimental research. *Trans* influence and steric effects are important for this rational design. We have found that the Togni derivative with X = SO₂ is the best choice based on its high reactivity and its potential synthesis.**

Fluorinated organic compounds play a conspicuous and increasingly important role in pharmaceuticals, agrochemicals and materials science.[1-6] However, few fluorinated organic compounds have been identified in nature.[6,7] Therefore, it is very important to develop new methods for introducing fluorine into various organic molecules.

Trifluoromethylation is one of the most important reactions among such methods.[8-11] In recent years, the two reagents, Togni I and Togni II,[12] developed by Togni's group (see **Fig. 1**), have been used widely as trifluoromethylating reagents. Their effectiveness is in part due to their highly polarized hypervalent I-C (or I-O) bonds, and they are commercially available.[10,13]

Electrophilic trifluoromethylation by Togni's reagents often needs activation by Lewis acids (see **Fig. 2**), Brønsted acids, or metals to weaken the I-O bond and promote the release of the CF₃⁺

unit.[10,13,14] Lewis acids, Brønsted acids, and metals may disrupt the reaction system, and hence we desire to modify the structures of Togni's reagents to perhaps improve upon their intrinsic reactivity.

*Trans* influence plays an important role in the reactivity of hypervalent iodine reagents. The *trans* ligand has an influence on the stability of the ground state of the molecule, and the *trans* influence can be analyzed in terms of the bond lengths between the central atom and the ligand *trans* to a *trans*-influencing ligand.[15-17] From Togni's research, shortening of the I–CF₃ bond, which is synonymous with lengthening of the I-O bond at the *trans* position, leads to increased electrophilic reactivity.[18,19] A weaker *trans* influence of the I-O bond will cause a shorter I–CF₃ bond. Previous theoretical research[20-22] indicated changing the linker of the hypervalent iodine-based five-membered ring could change the *trans* influence (see **Fig. 3**). Accordingly, the reactivity of the Togni reagents will be changed. Therefore, we designed new Togni derivatives with different linkers to increase reactivity. Moreover, following previous work, the *steric* effect of the methyl group at the *ortho*-position of the aromatic ring may also enhance the reactivity (see **Fig. 3**).[23,24] Thus, here we have designed additional new Togni derivatives using the *ortho*-methyl group.
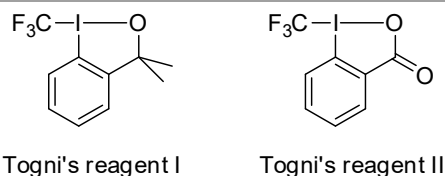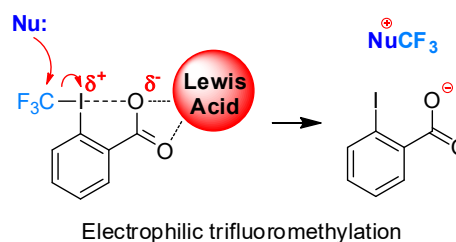


Fig. 1 Qualitative structures of Togni's reagents.



Electrophilic trifluoromethylation

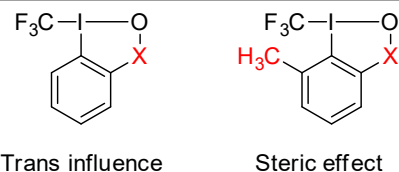**Fig. 2** Togni's reagent II activated by Lewis acids.



**Fig. 3** Designed Togni derivatives showing *trans* influence and *steric* effect.

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In the present research, computational studies were conducted to verify our hypotheses. The M06-2X[25] method was chosen as the functional, and cc-pVQZ(-PP)[26-28] [the (-PP) suffix here represents the pseudopotential for iodine] used as the basis set. Structures were optimized in acetonitrile solvent with Truhlar's SMD method (Solvation Model based on the Quantum Mechanical Charge Density).[29] Our previous work showed that M06-2X/cc-pVQZ(-PP) describes the structures and energies of hypervalent iodine reagents reliably.[20,21]

The highly electronegative linkers are expected to weaken the *trans* influence (lengthening the I-O bond and shortening the I-CF$_3$ bond), leading to the more active electrophilic trifluoromethylation reactions (**Fig. 2**).[18-19] In the present study, eight Togni reagents (**1 - 8**) with high electronegativity linkers are investigated (**Fig**. **4** and **Table 1**). Among these, the newly designed Togni reagents, as well as the known Togni reagent I (**8**) and Togni reagent II (**4**) are included.

The *trans* influence of the linkers may be assessed in terms of the length of either the I-CF$_3$ bond or the I-O bond, and these bond distances for the eight Togni derivatives are reported in Table 1. From compound 1 to compound 8, the I-CF$_3$ bond distance (bond 5-6 in Table 1) sequentially increases from 2.194 Å to 2.257 Å, and the I-O bond (bond 5-4 in Table 1) decreases from 2.478 Å to 2.105 Å. This indicates that *trans* influence for the linkers of compound 1 is the weakest, while the compound 8 is the strongest. Table 1 also reports the dihedral angles (2-1-5-4) for the structures (1-8), which are measures of the torsion for the five-membered ring. In two of these (X = CO and BOH), the carbon atom in C=O and the boron atom in BOH display sp$^2$ hybridization to form a $\Pi_5^6$ conjugation system, leading to the planar five-membered rings. For other structures, since the linker central atoms take the sp$^3$ hybridization without forming $\Pi_5^6$ cyclic conjugation systems, the five-membered rings are not necessarily planar. In fact, most of these structures have nonplanar five-membered rings with the dihedral angles (2-1-5-4) in the range from 7° to 21°. Table 1 shows that there is no correlation between the dihedral angle and the reactivity.

We studied the reactivity of a model trifluoromethylation reaction (shown at the top of **Fig. 4**), which includes the I-O bond breaking and the I-CF$_3$ bond hetero-cleavage. Since we have found that no energy barrier for such reactions exist, the reaction free energies were computed to assess the reactivity, which was supported by Xue, Cheng, and co-workers.[30-32] **Table 1** shows that the reaction free energies steadily increase from **1** to **8**, corresponding to the I-CF$_3$ and I-O distance changes, indicating the correlation between the electrophilic reactivity and the *trans* influence.

This strong correlation between the electrophilic reactivity and the *trans* influence may be seen more clearly in **Fig. 4** (red line). That is, the weaker the *trans* influence, the more reactive the Togni derivative should be. This conclusion is supported by results for the known Togni reagent II (**4**) and Togni reagent I (**8**). Our predicted reaction free energy for Togni reagent II (**4**, 39.3 kcal mol$^{-1}$) is lower than that for Togni reagent II (**8**, 63.7 kcal mol$^{-1}$) by 24 kcal mol$^{-1}$, and this is consistent with the experimental result that Togni II is more reactive than Togni I.[18] To examine the eight Togni derivatives, we found that the newly designed derivative with the -SO$_2$- linker (**1**) has the lowest reaction free energy (only 25.1 kcal mol$^{-1}$), even lower than that of Togni's reagent II (**4**) by 14 kcal mol$^{-1}$. This suggests that our predicted structure **1** has the potential to be the most reactive reagent among **1** - **8**.
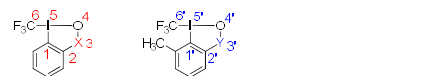


| Reagents | 1(X=SO$_2$) | 2(X=PO$_2$H) | 3(X=CF$_2$) | 4(X=CO) | 5(X=BOH) | 6(X=NCH$_3$) | 7(X=CH$_2$) | 8(X=C(CH$_3$)$_2$) |
|---|---|---|---|---|---|---|---|---|
| bond (Å) 5-4 | 2.478 | 2.315 | 2.265 | 2.263 | 2.184 | 2.158 | 2.118 | 2.105 |
| bond (Å) 5-6 | 2.194 | 2.207 | 2.207 | 2.212 | 2.232 | 2.239 | 2.254 | 2.257 |
| angle (°) 2-1-5-4 | 16.8 | 6.9 | 0.0 | 0.0 | 0.0 | 20.8 | 15.1 | 14.3 |
| reaction energy | 25.1 | 32.7 | 37.0 | 39.3 | 48.1 | 55.7 | 57.4 | 63.7 |
| Reagents | 1'(Y=SO$_2$) | 2'(Y=PO$_2$H) | 3'(Y=CF$_2$) | 4'(Y=CO) | 5'(Y=BOH) | 6'(Y=NCH$_3$) | 7'(Y=CH$_2$) | 8'(Y=C(CH$_3$)$_2$) |
| bond (Å) 5-4' | 2.658 | 2.401 | 2.297 | 2.284 | 2.212 | 2.156 | 2.125 | 2.108 |
| bond (Å) 5-6 | 2.198 | 2.206 | 2.217 | 2.224 | 2.239 | 2.254 | 2.266 | 2.272 |
| angle (°) 2-1-5-4' | 25.3 | 26.6 | 19.7 | 14.5 | 17.8 | 27.1 | 24.8 | 22.6 |
| reaction energy | 22.4 | 28.2 | 30.0 | 32.8 | 40.7 | 52.6 | 53.2 | 59.5 |

**Table 1.** The geometries and the trifluoromethylation reaction energies (see **Fig. 4**) of eight Togni reagents.

Steric effects were further considered, and thus the ortho-methyl group was introduced into **1 - 8** to form **1' - 8'**. The strong correlation between the electrophilic reactivity and the *trans* influence is maintained (blue line in **Fig. 4**). Furthermore, the steric effect of the ortho-methyl group in **1' - 8'** makes the reaction free energies lower than those of structures **1 - 8** by 2.7 - 7.4 kcal mol$^{-1}$ (**Table 1** and **Fig. 4**). This change is thought from the steric effect of the ortho-methyl group, and it makes the electrophilic trifluoromethylation reaction easier. From our computational results, we suggest the Togni derivative **1'** to be the most reactive reagent among **1' - 8'**.
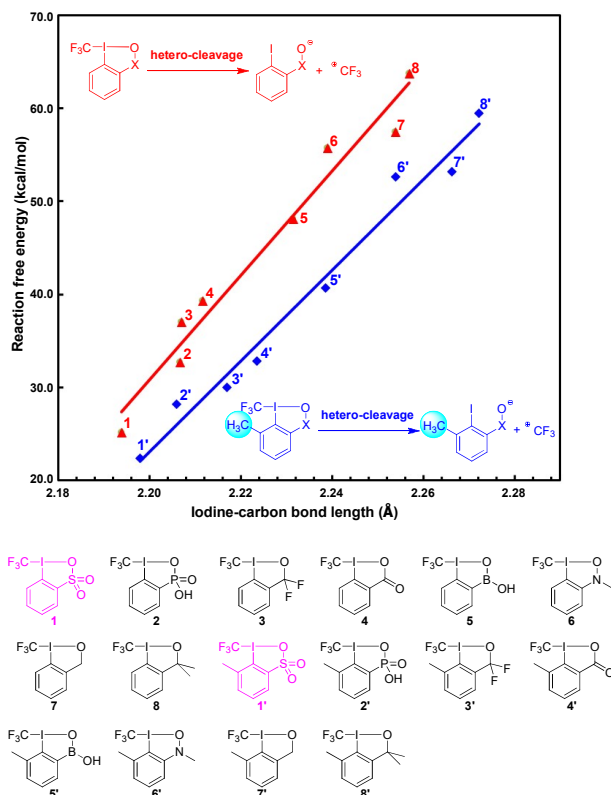


**Fig. 4** Correlation between reaction free energies and *trans* influence for eight Togni derivatives. The red line is for those structures without the *steric* effect, while the blue line is for those with the *steric* effect of the *ortho*-methyl group.
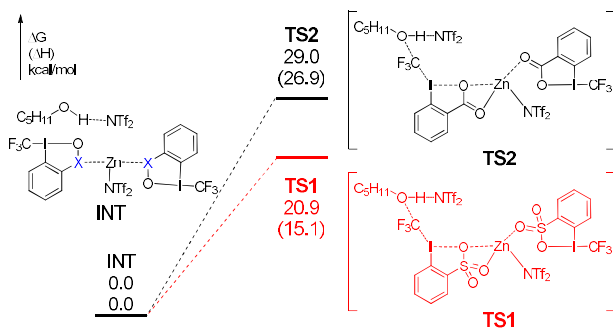
**Fig. 5** Relative free energies (kcal/mol) of **TS1** (X = SO$_2$) and **TS2** (X = CO).[36]

The dihedral angles (2'-1'-5'-4') for structures 1' - 8' are reported in Table 1. These angles (from 15° to 27°) are generally somewhat larger than those of their analogues (1 - 8). This is expected, because the CF$_3$ group is driven out-of-the-plane by the added methyl group to reduce the steric hindrance, and this would cause more torsion of the five-membered ring.

Furthermore, the reactivity of Togni reagents can also be evaluated kinetically. In electrophilic trifluoromethylation, the Togni's reagents are generally activated by Lewis acids, such as Sc(OTf)$_3$,[33] Cu(OTf)$_2$,[34] Zn(NTf$_2$)$_2$,[35] etc. For example, in 2009, Togni's group reported the Zn(NTf$_2$)$_2$ mediated trifluoromethylation of aliphatic alcohols with Togni II (**4**), and their ESI-MS measurements detected a cationic species of [Zn(**4**)$_2$(NTf$_2$)]$^+$.[35] Combining $^{19}$F NMR measurements, they suggested the reactive intermediate in this reaction to be [Zn(**4**)$_2$(NTf$_2$)$_2$]. Soon after, Li and co-authors conducted computational research of the mechanism for this Zn(NTf$_2$)$_2$ mediated trifluoromethylation reaction. With the Togni's reagent activated by the Lewis acid Zn$^{2+}$, it readily undergoes an S$_N$2 type nucleophilic attack at the CF$_3$ group by pentanol with a reasonable energy barrier.[13]

In the present study, we predict such a mechanism of trifluoromethylation for our designed new Togni reagents (derivative 1), and compared with that for the known Togni II (**4**). The energy barriers for the S$_N$2 zinc-mediated trifluoromethylation reactions are shown in Fig. 5. The free energy of the transition state relative to the intermediate [Zn(1)$_2$(NTf$_2$)$_2$] for derivative 1 is predicted to be 20.9 kcal mol$^{-1}$ (TS1, Fig. 5), which is about 8.1 kcal mol$^{-1}$ lower than that (29.0 kcal mol$^{-1}$) of TS2 for the known Togni II (**4**). This kinetic result confirms that our newly suggested Togni reagent (derivative 1) is more reactive for trifluoromethylation than the known Togni reagents.

In summary, based on our understanding of trans influence and steric effect in hypervalent iodine reagents, we have designed new Togni derivatives. Comparing the reaction free energy difference (14.2 kcal mol$^{-1}$) and the transition state energy barrier difference (8.1 kcal mol$^{-1}$) between 1 and **4**, we conclude that the Togni derivative 1 (Fig. 4) is the best choice, based on its highest reactivity and its potential for synthesis.[10,37-40] In addition to 1, Togni derivatives 2, **3**, 1' **2'** and 3' (Fig. 4) are also rational choices for trifluoromethylation with high reactivity.

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