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## Computational and experimental studies of reactive intermediates in glycosylation reactions

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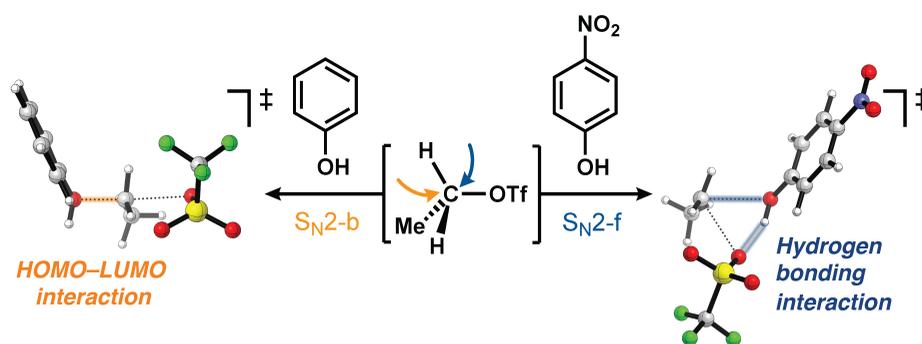
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# Chapter 9 |

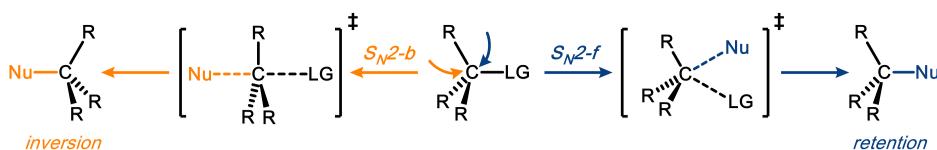
## Backside versus Frontside $S_N2$ Reactions of Alkyl Triflates and Alcohols



**Abstract** | Nucleophilic substitution reactions are elementary reactions in organic chemistry that are used in many synthetic routes. By quantum chemical methods, the intrinsic competition between the backside  $S_N2$  ( $S_N2$ -b) and frontside  $S_N2$  ( $S_N2$ -f) pathways was investigated using a set of simple alkyl triflates as the electrophiles in combination with a systematic series of phenols and partially fluorinated ethanol nucleophiles. It is revealed how and why the well-established mechanistic preference for the  $S_N2$ -b pathway slowly erodes and can even be overruled by the unusual  $S_N2$ -f substitution mechanism going from strong to weak alcohol nucleophiles. Activation strain analyses disclose that the  $S_N2$ -b pathway is favored for strong alcohol nucleophiles because of the well-known intrinsically more efficient approach to the electrophile resulting in a more stabilizing nucleophile–electrophile interaction. In contrast, the preference of weaker alcohol nucleophiles shifts to the  $S_N2$ -f pathway, benefiting from a stabilizing hydrogen bond interaction between the incoming alcohol and the leaving group. This hydrogen bond interaction is strengthened by the increased acidity of the weaker alcohol nucleophiles, thereby steering the mechanistic preference toward the frontside  $S_N2$  pathway.

## Introduction

A fundamental challenge in chemical research is the rational design of chemical reactions. Uncovering the operative mechanisms that steer chemical reactivity paves the way for tuning the reactivity of systems toward the desired pathway to avoid unwanted side reactions. The backside bimolecular nucleophilic substitution ( $S_N2$ -b) is an elementary reaction in synthetic chemistry.<sup>1-4</sup> Besides being in competition with  $S_N1$ -type substitutions, the less common frontside  $S_N2$  ( $S_N2$ -f) substitution can also play a role.<sup>5-9</sup> In general, the regular  $S_N2$ -b substitution proceeds with the inversion of configuration at the carbon atom under substitution (Walden inversion), and is substantially more efficient than the alternative  $S_N2$ -f reaction, which proceeds with retention of configuration (Scheme 1). Both experimental<sup>10-13</sup> and computational<sup>14-24</sup> studies have provided valuable insights into the processes that dictate the  $S_N2$ -b versus  $S_N2$ -f competition.

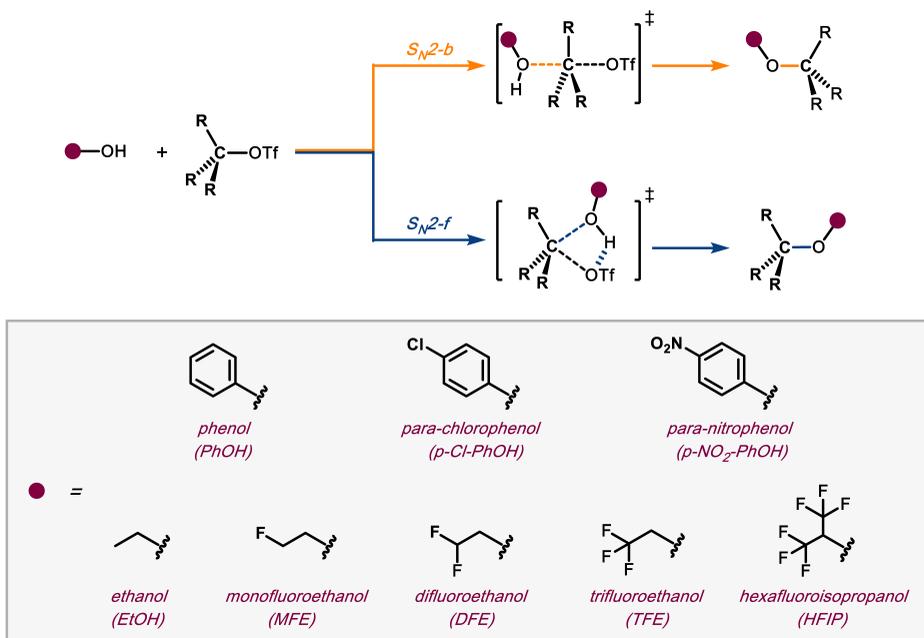


**Scheme 1.**  $S_N2$ -b (orange) and  $S_N2$ -f (blue) pathways. Nu = nucleophile, LG = leaving group.

The dominance of the  $S_N2$ -b reaction stems from the less sterically demanding approach of the nucleophile at the electrophile (*i.e.*, substrate). The  $S_N2$ -f reaction, on the other hand, requires the nucleophile to attack at the same side of the carbon atom, where the leaving group departs, causing closed-shell repulsion. Another factor contributing to the higher reaction barriers found for  $S_N2$ -f reactions is the loss of the primary stabilizing  $\text{HOMO}_{\text{nucleophile}}\text{-LUMO}_{\text{electrophile}}$  interaction because most of the orbital amplitude of the electrophile's LUMO is located at the backside. Both the  $S_N2$ -b and  $S_N2$ -f are accelerated as the basicity of the incoming nucleophile increases (*i.e.*, better electron-donating capacity) or the carbon-leaving group bond becomes weaker.<sup>17</sup>

However, in specific cases, the  $S_N2$ -f pathway has been noted to be a significant or even dominant competing reacting pathway. These substitution reactions show unexpectedly high degrees of retention of stereochemistry.<sup>25-34</sup> For example, the solvolysis of 1-phenylethyl chloride using phenol nucleophiles has been shown to result in phenol ethers with up to 97% retention of configuration at the benzylic carbon.<sup>25</sup> These relatively acidic nucleophiles have been implicated in forming hydrogen bonds during the solvolysis reactions, stabilizing the corresponding frontside transition states over the backside counterparts. *Ab initio* molecular dynamic simulations of chemical glycosylation reactions involving a trichloroacetimidate leaving group have revealed that these reactions may proceed with  $S_N2$ -f character.<sup>35</sup> Here, the analogy to retaining glycosyl transferase enzymes becomes apparent.<sup>36-42</sup> These enzymes have been shown to transfer carbohydrate monosaccharides from a nucleotide diphosphate sugar donor to alcohol acceptors (often other carbohydrates) with retention of configuration at the anomeric center of the donor glycoside through an  $S_N2$ -f-type mechanism. In this process, the diphosphate leaving group of the donor glycoside forms a hydrogen bridge with the incoming nucleophilic alcohol of the acceptor glycoside.

To understand the molecular features that govern the competition between the  $S_N2$ -b and  $S_N2$ -f reaction pathways, here it is analyzed how the reaction profiles of the  $S_N2$ -b and  $S_N2$ -f reaction pathways develop for a series of substitution reactions involving phenolic alcohol nucleophiles and alkyl triflate ( $\text{CH}_3\text{OTf}$ ,  $\text{CH}_3\text{CH}_2\text{OTf}$ ,  $(\text{CH}_3)_2\text{CHOTf}$ ) electrophiles,<sup>43</sup> using density functional theory (DFT; Scheme 2). Phenolic alcohol nucleophiles were selected due to their prominent involvement in  $S_N2$ -f pathways, and their tunable hydrogen bond donating properties, as demonstrated in the earlier described solvolysis experiments.<sup>25–34</sup> To analyze the generality of the reactivity trends for these systems, the reaction pathways of a series of partially fluorinated ethanol derivatives were also explored.<sup>44,45</sup> The triflate leaving group was chosen as it represents one of the most powerful leaving groups in  $S_N2$  reactions. This study provides a systematic overview of reactivity trends over a wide range of reactivities and pathways. The activation strain model (ASM)<sup>46–48</sup> of reactivity in conjunction with Kohn–Sham molecular orbital (KS-MO) theory<sup>49–51</sup> were employed to pinpoint the physical phenomena that control the competition between the backside and frontside  $S_N2$  pathway of the aforementioned reactions.

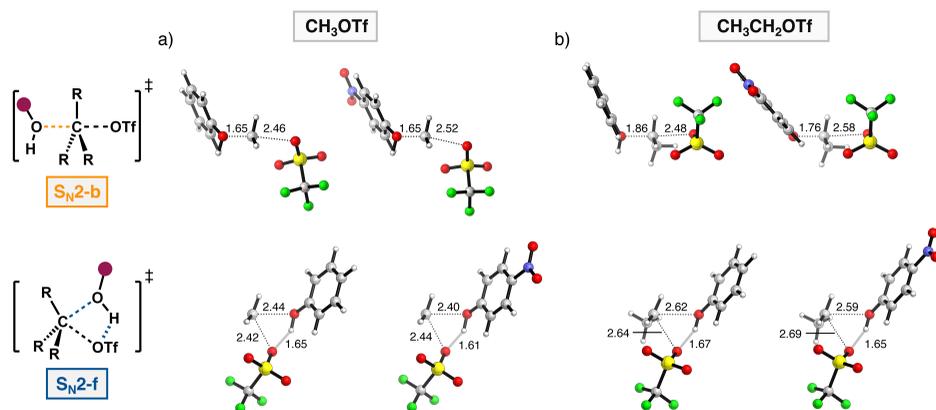


**Scheme 2.** Schematic overview of the computationally analyzed  $S_N2$ -b (orange) and  $S_N2$ -f (blue) reactions (R = H or Me).

## Results and Discussion

### General Trends in Reactivity

The results of the computed reaction profiles of the studied  $S_N2$ -b and  $S_N2$ -f reactions are collected in Table 1-2 and Figure 1 (see Table S14-S15 for all coordinates).<sup>52</sup> Generally, the reaction proceeds from a reactant complex (RC) through a transition state (TS) towards an intermediate (INT), which eventually dissociates into the products (P). Note, that the overall activation energy ( $\Delta E^\ddagger$ ) of the reaction in the gas phase is the energy difference between the TS and the infinitely separated reactants (see, for example, reference 53 and 54 for a more detailed discussion).<sup>55</sup> Representative structures of all stationary points of the reaction profile can be found in Figure S2. Analyzing the structural data of the computed transition states (see Figure 1), it becomes evident that these are relatively 'product-like', which is the direct result of the weak neutral alcohol nucleophiles. The resulting fundamental implications will be discussed later in more detail. Importantly, the computed trends in reactivity at ZORA-OLYP/QZ4P agree well with those calculated at the more accurate (TightPNO)DLPNO-CCSD(T)/CBS(3,4/def2)//ZORA-OLYP/QZ4P<sup>56-64</sup> level (see Table S2-S4).



**Figure 1.** Transition state structures<sup>65</sup> with key bond lengths (in Å) for the  $S_N2$ -b and  $S_N2$ -f reactions of (a) PhOH (left) and *p*-NO<sub>2</sub>-PhOH (right) +  $CH_3OTf$  and (b) PhOH (left) and *p*-NO<sub>2</sub>-PhOH (right) +  $CH_3CH_2OTf$ . Computed at ZORA-OLYP/QZ4P. Atom colors: carbon (gray), hydrogen (white), fluorine (green), nitrogen (blue), oxygen (red), and sulfur (yellow).

Several apparent trends emerge by analyzing the reaction profiles (reactivity trends are consistent for  $\Delta E$  and  $\Delta G$ ; see SI Table S5-S8). In line with previous findings,<sup>66-71</sup> the activation energy for the  $S_N2$ -b increases as the nucleophile becomes less basic (*i.e.*, worse electron-donating capacity), going from PhOH to *p*-Cl-PhOH to *p*-NO<sub>2</sub>-PhOH (see Table 1). Typically, the activation energy for the  $S_N2$ -f pathway also increases along this series. The increasing activation energy along the phenol series correlates well with the decreasing thermodynamic basicity of the nucleophile going from PhOH to *p*-Cl-PhOH to *p*-NO<sub>2</sub>-PhOH. This property is illustrated by the computed proton affinity of these nucleophiles ( $\Delta H_{PA} = \Delta H_{ROH} - \Delta H_{RO^-} + \Delta H_{H^+}$ ; Table S9), which decreases going from  $\Delta H_{PA} = 348.4$  (PhOH) to 341.9 (*p*-Cl-PhOH) to 324.7 (*p*-NO<sub>2</sub>-PhOH) kcal mol<sup>-1</sup>, and is in excellent agreement with experimental measurements as well as other computational studies.<sup>72-79</sup>

**Table 1.** Energies relative to the separated reactants (in kcal mol<sup>-1</sup>) of the stationary points (RC = reactant complex, TS = transition state, INT = intermediate, and P = product) of the  $S_N2$ -b (orange) and  $S_N2$ -f (blue) pathways.<sup>[a]</sup>

Nucleophile	Electrophile						
		CH <sub>3</sub> OTf		CH <sub>3</sub> CH <sub>2</sub> OTf		(CH <sub>3</sub> ) <sub>2</sub> CHOTf	
	RC <sup>[b]</sup>	-2.3	<sup>[d]</sup>	-2.5	<sup>[d]</sup>	-2.6	(-0.2)
	$S_N2$ -b-TS	42.4	(25.5)	40.3	(27.5)	37.5	(23.1)
	$S_N2$ -f-TS	50.8	(48.8)	41.8	(36.6)	32.2	(23.5)
	INT <sup>[c]</sup>	-4.3	(-1.1)	-3.2	0.4	-1.1	2.2
	P	0.8	(1.1)	1.4	(3.3)	3.4	(8.8)
	RC <sup>[b]</sup>	-2.7	(-0.4)	-2.8	(-0.3)	-3.0	(-0.3)
	$S_N2$ -b-TS	44.1	(26.8)	41.7	(28.6)	38.7	(23.6)
	$S_N2$ -f-TS	50.7	(48.6)	41.6	(36.4)	31.8	(23.3)
	INT <sup>[c]</sup>	-3.9	(-0.9)	-2.9	0.6	-0.9	2.0
	P	0.5	(0.9)	1.1	(1.8)	3.1	(3.5)
	RC <sup>[b]</sup>	-3.3	(-0.5)	-3.1	(-0.4)	-3.7	(-0.6)
	$S_N2$ -b-TS	49.7	(32.4)	47.0	(31.0)	<sup>[e]</sup>	<sup>[e]</sup>
	$S_N2$ -f-TS	54.2	(52.0)	44.2	(38.3)	33.3	(23.6)
	INT <sup>[c]</sup>	-2.7	0.1	-1.8	<sup>[d]</sup>	<sup>[d]</sup>	<sup>[d]</sup>
	P	0.4	(0.7)	0.8	(1.6)	2.5	(3.0)

<sup>[a]</sup> Electronic energies computed at the ZORA-OLYP/QZ4P and COSMO(CH<sub>2</sub>Cl<sub>2</sub>)-ZORA-OLYP/QZ4P in parentheses, relative to infinitely separated reactants. <sup>[b]</sup> Only the  $S_N2$ -f pathway involves a very weakly bound reactant complex RC, the energy of which is provided, while the  $S_N2$ -b pathway does not have a stable RC. <sup>[c]</sup> The product complex of the  $S_N2$ -b pathway results in charge separation, inducing a barrierless proton transfer, forming the more stable  $S_N2$ -f intermediate (INT). <sup>[d]</sup> Stationary point is not stable in solution. <sup>[e]</sup> Transition state cannot be located due to the instability of the associated product.

**Table 2.** Energies relative to the separated reactants (in kcal mol<sup>-1</sup>) of the stationary points (RC = reactant complex, TS = transition state, INT = intermediate, and P = product) of the S<sub>N</sub>2-b (orange) and S<sub>N</sub>2-f (blue) pathways.<sup>[a]</sup>

Nucleophile	Electrophile						
		CH <sub>3</sub> OTf		CH <sub>3</sub> CH <sub>2</sub> OTf		(CH <sub>3</sub> ) <sub>2</sub> CHOTf	
	RC <sup>[b]</sup>	-2.2	<sup>[c]</sup>	-2.3	<sup>[c]</sup>	-2.3	<sup>[c]</sup>
	S <sub>N</sub> 2-b-TS	35.1	(19.2)	33.9	(22.7)	32.3	(21.5)
	S <sub>N</sub> 2-f-TS	51.5	(49.2)	43.2	(37.5)	34.8	(24.9)
	INT <sup>[c]</sup>	-8.4	(-5.6)	-7.1	(-4.0)	-4.7	(-2.0)
	P	-1.9	(-1.3)	-1.1	(-0.5)	2.5	(2.4)
	RC <sup>[b]</sup>	-1.9	<sup>[d]</sup>	-1.0	<sup>[d]</sup>	-2.0	<sup>[d]</sup>
	S <sub>N</sub> 2-b-TS	37.2	(22.8)	35.5	(25.3)	33.3	(23.4)
	S <sub>N</sub> 2-f-TS	52.4	(50.0)	43.3	(37.7)	34.6	(24.7)
	INT <sup>[c]</sup>	-6.6	(-3.9)	-5.2	(-2.3)	-3.2	(-1.4)
	P	0.9	(1.0)	1.5	(1.6)	3.9	(2.7)
	RC <sup>[b]</sup>	-2.2	<sup>[d]</sup>	-2.4	<sup>[d]</sup>	-2.2	<sup>[d]</sup>
	S <sub>N</sub> 2-b-TS	40.9	(26.0)	38.4	(27.5)	35.6	(25.0)
	S <sub>N</sub> 2-f-TS	54.1	(51.5)	44.8	(38.7)	35.4	(24.9)
	INT <sup>[c]</sup>	-5.4	(-2.8)	-4.3	(-1.3)	-2.7	(-0.6)
	P	0.8	(1.0)	1.4	(1.5)	4.1	(2.9)
	RC <sup>[b]</sup>	-2.3	<sup>[d]</sup>	-1.1	<sup>[d]</sup>	-1.2	<sup>[d]</sup>
	S <sub>N</sub> 2-b-TS	43.8	(24.9)	42.0	(29.2)	38.6	(25.6)
	S <sub>N</sub> 2-f-TS	54.8	(52.4)	45.0	(39.0)	35.4	(24.9)
	INT <sup>[c]</sup>	-5.2	(-2.5)	-4.2	(-1.0)	-3.3	(-0.5)
	P	0.5	(0.7)	1.0	(1.1)	2.4	(2.0)
	RC <sup>[b]</sup>	-2.0	<sup>[d]</sup>	-2.5	(-0.4)	-2.4	(-0.5)
	S <sub>N</sub> 2-b-TS	50.7	(35.8)	45.7	(34.0)	41.4	(28.8)
	S <sub>N</sub> 2-f-TS	57.6	(54.7)	46.6	(39.3)	35.6	(25.6)
	INT <sup>[c]</sup>	-2.9	(-0.7)	-1.8	<sup>[d]</sup>	-0.4	<sup>[d]</sup>
	P	0.9	(0.4)	1.0	(0.5)	2.5	(1.7)

<sup>[a]</sup> Electronic energies computed at the ZORA-OLYP/QZ4P and COSMO(CH<sub>2</sub>Cl<sub>2</sub>)-ZORA-OLYP/QZ4P in parentheses, relative to infinitely separated reactants. <sup>[b]</sup> Only the S<sub>N</sub>2-f pathway involves a very weakly bound RC, the energy of which is provided, while the S<sub>N</sub>2-b pathway does not have a stable RC. <sup>[c]</sup> Product complex of the S<sub>N</sub>2-b pathway results in charge separation, inducing a barrierless proton transfer, forming the more stable S<sub>N</sub>2-f intermediate (INT). <sup>[d]</sup> Stationary point is not stable in solution.

Importantly, in all cases, the activation energy rises significantly more rapidly along this series for the S<sub>N</sub>2-b pathway than for S<sub>N</sub>2-f. For example, in going from PhOH to *p*-Cl-PhOH to *p*-NO<sub>2</sub>-PhOH for CH<sub>3</sub>CH<sub>2</sub>OTf, the S<sub>N</sub>2-b activation energy (S<sub>N</sub>2-b-TS in Table 1) increases from  $\Delta E^\ddagger = +40.3$  to  $+41.7$  to  $+47.0$  kcal mol<sup>-1</sup> ( $\Delta\Delta E^\ddagger = +6.7$  kcal mol<sup>-1</sup>), respectively. While the S<sub>N</sub>2-f activation energy (S<sub>N</sub>2-f-TS in Table 1) rises more moderately from  $\Delta E^\ddagger = +41.8$  to  $+41.6$  to  $+44.2$  kcal mol<sup>-1</sup> ( $\Delta\Delta E^\ddagger = +2.4$  kcal mol<sup>-1</sup>), respectively. Consequently, the preferred reaction pathway switches from S<sub>N</sub>2-b for the stronger alcohol nucleophiles to S<sub>N</sub>2-f for weaker alcohol nucleophiles. Hence, the S<sub>N</sub>2-b prevails for PhOH over the S<sub>N</sub>2-f pathway with CH<sub>3</sub>CH<sub>2</sub>OTf ( $\Delta\Delta E^\ddagger = -1.5$  kcal mol<sup>-1</sup> for the S<sub>N</sub>2-b relative to S<sub>N</sub>2-f). The S<sub>N</sub>2-b and S<sub>N</sub>2-f pathways have roughly equal activation energy for *p*-Cl-PhOH ( $\Delta\Delta E^\ddagger = +0.1$  kcal mol<sup>-1</sup> for the S<sub>N</sub>2-b relative to S<sub>N</sub>2-f), and the S<sub>N</sub>2-f pathway dictates the reaction for the least basic *p*-NO<sub>2</sub>-PhOH ( $\Delta\Delta E^\ddagger = +2.8$  kcal mol<sup>-1</sup> for the S<sub>N</sub>2-b relative to S<sub>N</sub>2-f). These reactivity trends are found regardless of the electrophile (CH<sub>3</sub>OTf, CH<sub>3</sub>CH<sub>2</sub>OTf, (CH<sub>3</sub>)<sub>2</sub>CHOTf). Notably, the set of fluorinated ethanol derivatives (Table 2; CH<sub>3</sub>CH<sub>2</sub>OH, CH<sub>2</sub>FCH<sub>2</sub>OH, CHF<sub>2</sub>CH<sub>2</sub>OH, CF<sub>3</sub>CH<sub>2</sub>OH, and (CF<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>OH), spanning a large range of reactivities, exhibit exactly the same trend.

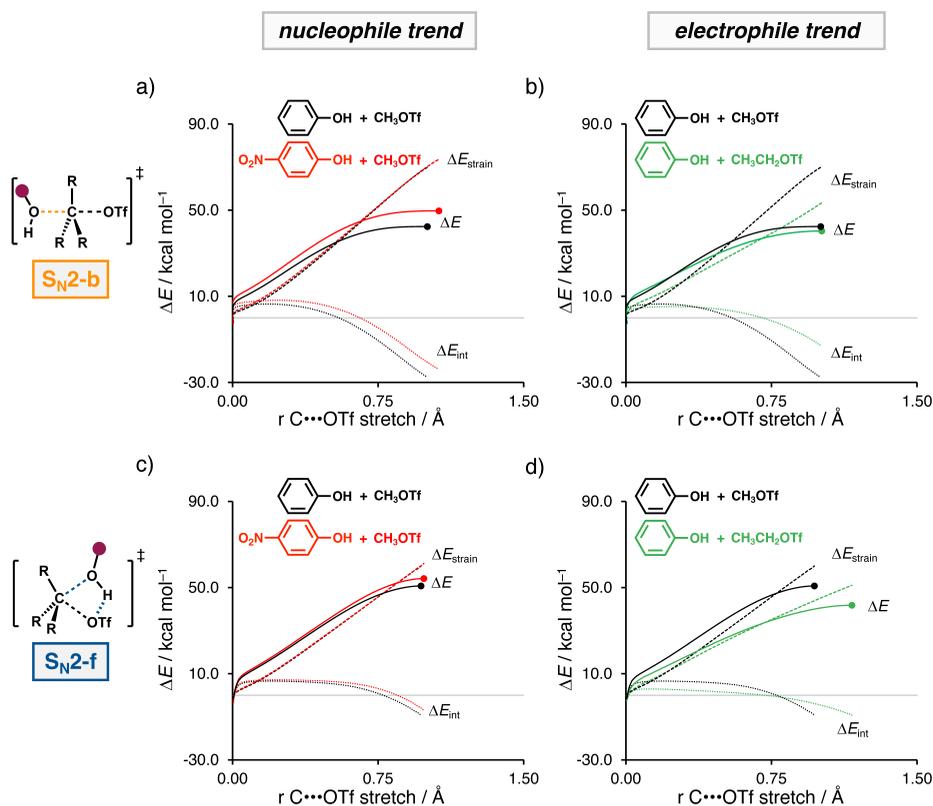
The introduction of alkyl-substituents on the electrophile decreases the activation energies for both S<sub>N</sub>2 pathways for all the neutral alcohol nucleophiles, which is in line with the experimental<sup>80</sup> and computational<sup>81-83</sup> work of the group of Uggerud. Notably, the decrease in activation energy occurs at a considerably faster rate for the S<sub>N</sub>2-f pathway compared to the S<sub>N</sub>2-b reactions within the two series. For example, for PhOH as the nucleophile, in going from CH<sub>3</sub>OTf to CH<sub>3</sub>CH<sub>2</sub>OTf to (CH<sub>3</sub>)<sub>2</sub>CHOTf, the S<sub>N</sub>2-b activation energy decreases from  $\Delta E^\ddagger = +42.4$  to  $+40.3$  to  $+37.5$  kcal mol<sup>-1</sup> ( $\Delta\Delta E^\ddagger = -4.9$  kcal mol<sup>-1</sup>), respectively. While the S<sub>N</sub>2-f activation energy drops steeply from  $\Delta E^\ddagger = +50.8$  to  $+41.8$  to  $+32.2$  kcal mol<sup>-1</sup> ( $\Delta\Delta E^\ddagger = -18.6$  kcal mol<sup>-1</sup>) along the same series. Thus, by the increase of alkyl-substituents on the electrophile, the most prevalent reaction pathway switches from S<sub>N</sub>2-b to S<sub>N</sub>2-f. This reactivity trend is found irrespective of the nucleophile.

To understand the role of solvation on the studied computed reactivity trends, all reaction profiles were calculated in bulk solution with the use of the conductor-like screening model (COSMO) (Table 1 and 2, data in brackets).<sup>84</sup> It is found that bulk solvation<sup>85</sup> in the studied systems using neutral alcohol nucleophiles, lowers the activation energies of both S<sub>N</sub>2 pathways. The solvent stabilizes the developing charges in the transition states, and hence, lowers the overall activation energy. It is noted that this effect is more apparent for the S<sub>N</sub>2-b than S<sub>N</sub>2-f,<sup>86</sup> resulting from the stabilization of the developing charge in the S<sub>N</sub>2-b, in which the leaving group departs as an anion (*e.g.*, TfO<sup>-</sup> in the studied systems) and the addition of the nucleophilic alcohol leads to the build-up of positive charge. In contrast, in the S<sub>N</sub>2-f pathway, the leaving group is protonated by the incoming nucleophilic alcohol, accommodating the developing charge more within the substitution system.<sup>87</sup>

### Activation Strain Analyses

To gain quantitative insight into the factors controlling the reactivity of the  $S_N2$ -b and  $S_N2$ -f reaction pathways, the activation strain model (ASM) was employed.<sup>46–48</sup> As detailed in the Computational Methods section, the ASM is a fragment-based approach in which the reaction profile can be described with respect to the characteristics of the reactants (alcohol and alkyl triflate). The ASM decomposes the total electronic energy ( $\Delta E$ ) of the system, as found in Table 1 and 2, into two chemically intuitive and useful terms: the destabilizing strain (*i.e.*, distortion energy;  $\Delta E_{\text{strain}}$ ) and stabilizing interaction energy ( $\Delta E_{\text{int}}$ ) along the reaction, that is:  $\Delta E = \Delta E_{\text{strain}} + \Delta E_{\text{int}}$ . This method has proven to be a valuable tool for understanding activation energies, and therefore chemical reactivity.<sup>88–93</sup>

Figure 2 shows how the alcohol nucleophile (panels a and c) and degree of substitution on the electrophile (panels b and d) affect the activation energy of both  $S_N2$ -b (top, panel a and b) and  $S_N2$ -f (bottom, panel c and d) reaction pathway. Of note, all other combinations of nucleophiles and electrophiles provide similar trends and can be found in Figures S3–S6.



**Figure 2.** Activation strain analysis of the  $S_N2$ -b and  $S_N2$ -f reactions along the IRC projected on the  $C\cdots OTf$  bond stretch. The left column (a to c) shows the impact of the nucleophile on the activation energy, whereas the right column (b to d) shows the influence of the degree of electrophile substitution. Transition states are indicated with a thick dot and the zero line with a grey line in the ASD. Computed at ZORA-OLYP/QZ4P.

Decreasing the basicity of the alcohol, by changing from PhOH (black) to *p*-NO<sub>2</sub>-PhOH (red) leads to an increase in the activation barrier for both the  $S_N2$ -b (Figure 2a) and  $S_N2$ -f (Figure 2c). In line with earlier work of Bickelhaupt and co-workers,<sup>66-71</sup> this increase is due to a diminished interaction energy between the nucleophile and the electrophile, as can be gauged from the red interaction energy curve of *p*-NO<sub>2</sub>-PhOH, that lies above the black curve of PhOH over the entire course of the reaction. The strain energy is minimally affected by changing the nucleophile.

The weakening of the nucleophile–electrophile interaction can be directly traced back to the electron-withdrawing character of the groups on the nucleophilic alcohol, resulting in a lower-lying (*i.e.*, more stabilized) HOMO going from PhOH to *p*-Cl-PhOH, to *p*-NO<sub>2</sub>-PhOH (see Table S10). Thus, weakening the HOMO<sub>nucleophile</sub>–LUMO<sub>electrophile</sub> orbital interaction (Figure 4a). At the same time, the electron-withdrawing groups also reduce the charge density on the nucleophilic center of the alcohols, weakening the stabilizing electrostatic interactions with the electrophile. This effect is demonstrated in Figure 4c, where the Voronoi deformation density (VDD) atomic charges of the nucleophilic oxygen of the alcohol diminish from –0.181 to –0.163 (see Table S12 for VDD data of all nucleophiles).

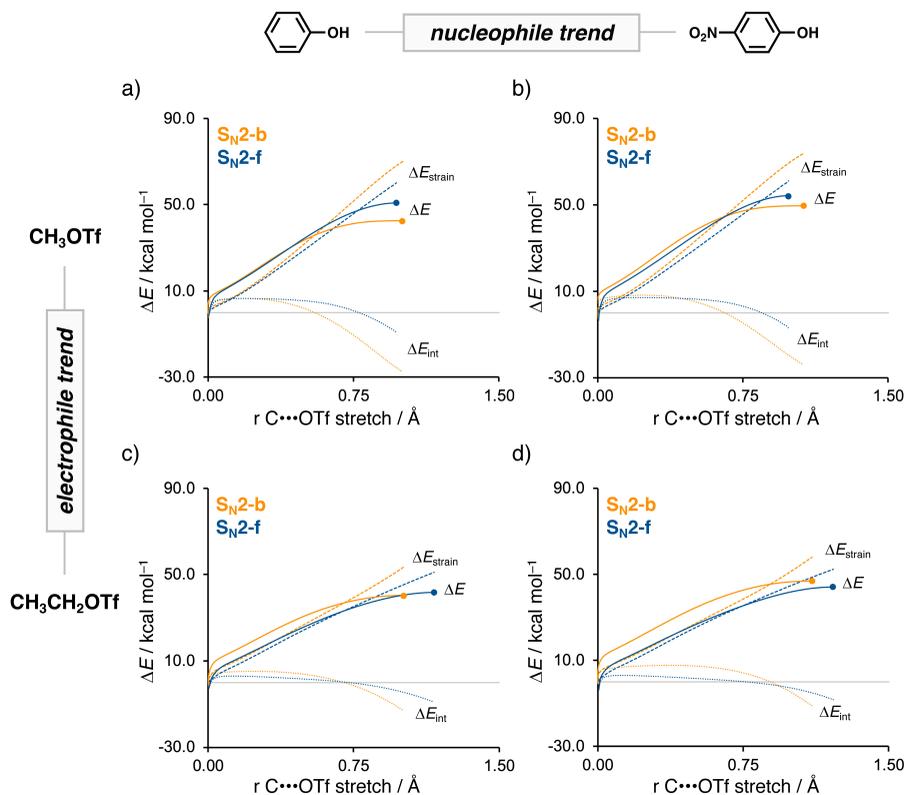
Interestingly, the diminished nucleophile–electrophile interaction for weaker alcohol nucleophiles is significantly more pronounced for the  $S_N2$ -b than the  $S_N2$ -f pathway. Thus, the loss in interaction for weaker alcohol nucleophiles between the nucleophile and electrophile is more evident for the  $S_N2$ -b reactions than for the corresponding  $S_N2$ -f system. This loss in interaction originates directly from the hydrogen bond between the nucleophile and the leaving group of the electrophile in the  $S_N2$ -f pathway, which is not possible in the  $S_N2$ -b reaction (Scheme 2). Potentially, this hydrogen bond between the incoming alcohol and the leaving group can enhance the nucleophilicity of the alcohol and assist the leaving group by stabilizing the developing charges along the reaction. This hydrogen bond strengthens when the alcohol nucleophiles become less basic, partly compensating for the loss of the primary HOMO<sub>nucleophile</sub>–LUMO<sub>electrophile</sub> interaction going from strong to weak nucleophilic alcohols (Figure S7).

Changing the electrophile from CH<sub>3</sub>OTf (black) to CH<sub>3</sub>CH<sub>2</sub>OTf (green) leads to a lowering of both the  $S_N2$ -b (Figure 2b) and  $S_N2$ -f (Figure 2d) activation energy, originating from a less destabilizing strain energy. This stems from the better leaving group ability of the electrophile as the degree of substitution increases. As reported by Vermeeren *et al.*, this effect stems from the increased steric repulsion between the substituents and the leaving group, effectively weakening and elongating the C–OTf bond (see Table S13 for all data).<sup>94</sup> In contrast, the interaction energy between the nucleophile and the electrophile is less stabilizing for the more substituted electrophiles, which is the direct result of the increasing steric repulsion between the incoming nucleophile and the substituents of the electrophile (Figure S7). However, in the studied systems, this factor is not dominant as a result of the weak neutral alcohol nucleophiles, which engage in a relatively weak nucleophile–electrophile interaction.<sup>95,96</sup> Thus, the activation energy decreases for the more substituted electrophiles because of the weaker carbon–leaving group bond, requiring less destabilizing strain energy to break this bond.

To visualize the competition between  $S_N2$ -b and  $S_N2$ -f for these systems, Figure 3 presents four panels to describe the  $S_N2$ -b/ $S_N2$ -f pathways of the reactions: CH<sub>3</sub>OTf + PhOH (panel a), CH<sub>3</sub>OTf + *p*-NO<sub>2</sub>-PhOH (panel b), CH<sub>3</sub>CH<sub>2</sub>OTf + PhOH (panel c), CH<sub>3</sub>CH<sub>2</sub>OTf + *p*-NO<sub>2</sub>-PhOH (panel d). Thus, in the horizontal direction (a to b and c to d) the effect of the alcohol nucleophile on the reaction energy profile can be inspected, while in the vertical direction (a to c and b to d) the effect of the electrophile becomes apparent. Several characteristic trends for the  $S_N2$ -b and  $S_N2$ -f pathways can be derived from the computed activation strain diagrams (ASDs).

In line with previous work on the  $S_N2$ -b/ $S_N2$ -f competition involving anionic X<sup>–</sup> + CH<sub>3</sub>Y → CH<sub>3</sub>X + Y<sup>–</sup> systems with X and Y = F, Cl, Br, and I,<sup>14-24</sup> it was generally found that the  $S_N2$ -b engages in a stronger nucleophile–electrophile interaction. As discussed earlier, this

stronger interaction can be attributed to a more efficient approach of the nucleophile HOMO towards the electrophile LUMO in the  $S_N2$ -b pathway because most of the LUMO orbital amplitude is located at the backside of the electrophile. The build-up of stabilizing interaction energy for the  $S_N2$ -f occurs later along the reaction coordinate than for the  $S_N2$ -b reaction, leading to a weaker nucleophile–electrophile interaction. This delay in interaction energy build-up is the direct result of the more congested nature of the  $S_N2$ -f pathway, which requires the carbon–leaving group bond to elongate, to avoid destabilizing steric repulsion before the nucleophile can come closer and engage in a stabilizing bonding overlap with the  $\sigma^*$  of the electrophile.



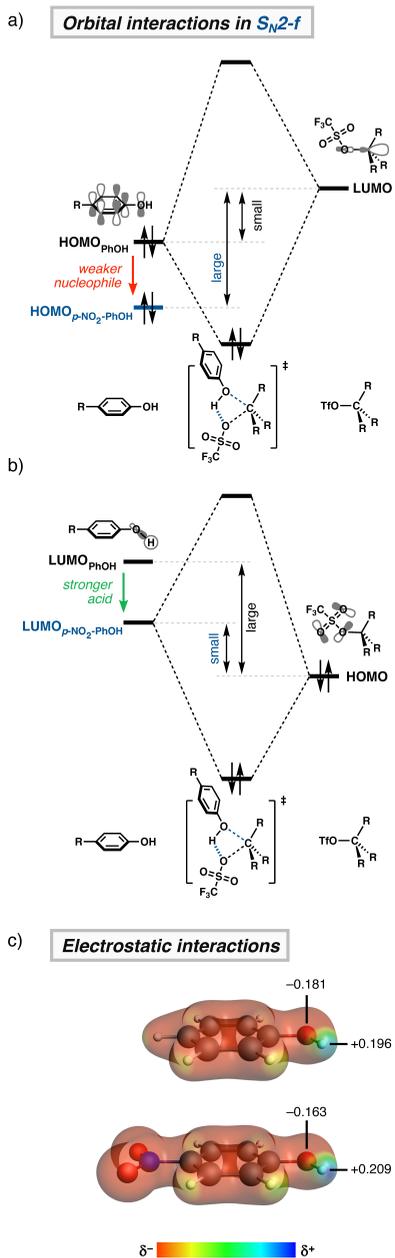
**Figure 3.** Activation strain analysis of the competition between  $S_N2$ -b (orange) and  $S_N2$ -f (blue) reactions along the IRC projected on the  $C\cdots OTf$  bond stretch. Trends in the vertical direction (a to c and b to d) show the impact of the degree of substitution of the electrophile, while the trends in the horizontal direction (a to b and c to d) show the influence of the nucleophile. Transition states are indicated with a thick dot and the zero line with a grey line in the ASM diagram. Computed at ZORA-OLYP/QZ4P.

Notably, the trend for the primary HOMO<sub>nucleophile</sub>–LUMO<sub>electrophile</sub> orbital interaction (Figure 4a) is less pronounced in the overall S<sub>N</sub>2-b/S<sub>N</sub>2-f competition for these alcohol nucleophiles compared to the previously studied anionic X<sup>-</sup> nucleophiles. This trend is less pronounced because the loss of HOMO<sub>nucleophile</sub>–LUMO<sub>electrophile</sub> interaction energy for weaker alcohols in the S<sub>N</sub>2-f pathway is (partly) compensated by a stabilizing hydrogen bond between the nucleophile and the leaving group of the electrophile. As the hydrogen bond becomes stronger for the weaker, and more acidic, alcohol nucleophiles, the S<sub>N</sub>2-b/S<sub>N</sub>2-f competition shifts from S<sub>N</sub>2-b to S<sub>N</sub>2-f. The hydrogen bond leads to stabilizing orbital and electrostatic interactions<sup>97,98</sup> between the incoming nucleophile and the leaving group of the electrophile (see Figure 4 and Figure S8). This hydrogen bond interaction has parallels with the findings of Poater *et al.* using counterions in S<sub>N</sub>2 reactions (MX + CH<sub>3</sub>Y → CH<sub>3</sub>X + MY with M<sup>+</sup> = Li<sup>+</sup>, Na<sup>+</sup>, K<sup>+</sup>, MgCl<sup>+</sup>).<sup>17</sup> Here, the authors found that the metal counterion M<sup>+</sup> interacts with the leaving group Y to stabilize the S<sub>N</sub>2-f pathway.

The orbital interactions for the hydrogen bond stem from the interaction between the lone pair orbitals of the oxygen atoms of the leaving group (*i.e.*, high-lying orbitals, FMOs, including the HOMO) and the σ\* orbital of the H–O bond of the alcohol (Figure 4b). This interaction becomes stronger for the weaker alcohols, which have a lower-lying accepting σ\* orbital, and thus, a smaller LUMO<sub>nucleophile</sub>–HOMO<sub>electrophile</sub> orbital energy gap (see Table S11). The stabilizing electrostatic interactions can be traced back to the δ<sup>-</sup> of the O-atoms of the leaving group interacting with δ<sup>+</sup> of the H-atom of the alcohol (Figure 4c). This electrostatic interaction is strengthened for the more acidic alcohols, giving rise to more δ<sup>+</sup> character at the H-atom of the alcohol. This trend is illustrated in Figure 4c, where the VDD atomic charges of the H-atom of the alcohol increase from +0.196 to +0.209 (see Table S12 for VDD data of all nucleophiles). In other words, the electron-withdrawing group of the weaker alcohol nucleophiles reduces the electron density on the nucleophilic center, weakening the nucleophile–electrophile interaction for both the S<sub>N</sub>2-b and S<sub>N</sub>2-f pathway. At the same time, they make the alcohol nucleophiles more acidic, resulting in stronger electrophile–nucleophile interaction for the S<sub>N</sub>2-f pathway, which is not available for the S<sub>N</sub>2-b reaction.

For the studied systems, the S<sub>N</sub>2-f pathway always proceeds with less destabilizing strain energy than its S<sub>N</sub>2-b counterpart (Figure 3), which can be explained by the lack of the Walden inversion along the S<sub>N</sub>2-f pathway. This result is in contrast with the findings of Bickelhaupt and co-workers.<sup>14,15</sup> They investigated the S<sub>N</sub>2-b and S<sub>N</sub>2-f reactions of X<sup>-</sup> + CH<sub>3</sub>Y, finding that the destabilizing strain energy of the S<sub>N</sub>2-f pathway in all cases is more destabilizing than that of the S<sub>N</sub>2-b pathway. This result was attributed to the repulsion between the anionic X<sup>-</sup> and Y-groups in the frontside pathway, causing more deformation of the electrophile.<sup>99,100</sup> In the systems studied here, the repulsion between the incoming nucleophile and electrophile is less pronounced because of the non-charged nucleophile and the development of a stabilizing hydrogen bond between the incoming alcohol nucleophile and the leaving group.

The introduction of alkyl-substituents on the electrophile leads to a shift from an interaction-controlled to a strain-controlled regime. For CH<sub>3</sub>OTf, the nucleophile can engage in a strong interaction with the electrophile and favors the S<sub>N</sub>2-b due to the intrinsically more efficient approach of the nucleophile HOMO towards the electrophile LUMO. Going to more substituted systems, the primary nucleophile–electrophile interaction diminishes due to the steric repulsion between the reactants, and therefore the system becomes strain-controlled. As mentioned above, for the herein studied systems, the S<sub>N</sub>2-f goes with less destabilizing strain energy, and thus, shifts the preference for S<sub>N</sub>2-b to S<sub>N</sub>2-f. Note that, for the more substituted systems, the S<sub>N</sub>2-f pathway even goes with more stabilizing interaction energy in the initial phase of the reaction owing to the presence of the hydrogen bonding interaction.



**Figure 4.** Schematic molecular orbital diagram for the  $S_N2-f$  pathway of the most important (a)  $\text{HOMO}_{\text{nucleophile}}-\text{LUMO}_{\text{electrophile}}$  and (b)  $\text{LUMO}_{\text{nucleophile}}-\text{HOMO}_{\text{electrophile}}$  hydrogen bonding interaction. (c) Electrostatic interactions derived from molecular electrostatic potential maps (at  $0.03 \text{ Bohr}^{-3/2}$ ) from +0.2 (red) to +0.5 (blue) Hartree  $e^{-1}$  and the Voronoi deformation density<sup>101</sup> of the nucleophilic center at their equilibrium geometries. Computed at ZORA-OLYP/QZ4P.

## Conclusions

The competition between backside and frontside  $S_N2$  nucleophilic substitution reactions ( $S_N2$ -b and  $S_N2$ -f) of neutral alcohol nucleophiles with alkyl triflates was studied. Both substitution reactions are slowed when the basicity of the alcohol decreases (*i.e.*, worse electron-donating capacity). However, the  $S_N2$ -b pathway slows down more rapidly than the corresponding  $S_N2$ -f reactions for the studied series of phenol and fluorinated ethanol nucleophiles. As a result, in going from strong to weak alcohol nucleophiles, the preference for the  $S_N2$ -b pathway slowly erodes and the unusual  $S_N2$ -f can become most favorable.

Using the activation strain model, the physical factors that govern these reactivity trends were investigated. The higher activation energies for the  $S_N2$ -b and  $S_N2$ -f substitution reactions of the weaker alcohols can be traced to the weakening of the primary nucleophile–electrophile interaction between the alcohol nucleophile and the electrophile. Importantly, the overall loss in interaction for the weaker alcohol nucleophiles with the electrophiles in the  $S_N2$ -f reactions is less apparent than for the corresponding  $S_N2$ -b system. This difference is caused by the hydrogen bond between the nucleophile and the leaving group of the electrophile. This hydrogen bond develops along the reaction coordinate in the  $S_N2$ -f pathway, an interaction that is not possible in the  $S_N2$ -b reaction.

The hydrogen bond strengthens when the alcohol becomes more acidic, compensating for the loss of the primary nucleophile–electrophile interaction going from strong to weaker alcohols. This favorable interaction makes the frontside substitution reactions more favorable for the most acidic nucleophiles, especially in combination with electrophiles that allow for the accumulation of significant positive charge by lengthening the carbon–leaving group bond. It is envisioned that these findings extend well beyond the systems studied here, aiding in understanding the  $S_N2$ -b/ $S_N2$ -f competition better and designing more effective substitution reactions.

## Supporting information

### Computational Methods

#### General Computational Methods

All calculations have been carried out using the Amsterdam Density Functional (ADF; ADF2018.105) software package.<sup>102,102–104</sup> Geometries were optimized at ZORA-OLYP/QZ4P.<sup>105–108</sup> In previous benchmark studies, Bickelhaupt and co-worker have shown that OLYP reproduces  $S_N2$  barriers from highly correlated *ab initio* within only a few kcal mol<sup>-1</sup>.<sup>109–112</sup> Relativistic effects were accounted for by using the zeroth-order regular approximation (ZORA).<sup>108</sup> The basis set used, denoted QZ4P, can be described as core triple- $\zeta$ , valence quadruple- $\zeta$ , with four sets of polarization functions.<sup>107</sup> The accuracies of the fit scheme (Zlm fit) and the integration grid (Becke grid) were, for all calculations, set to VERYGOOD.<sup>113,114</sup> All stationary points were confirmed by vibrational analysis: for equilibrium structures, all normal modes have real frequencies, whereas transition states have one normal mode with an imaginary frequency. The optimized structures were illustrated using CYLview.<sup>65</sup> The reaction pathway, towards both the reactant complex and the product complex/intermediate, of the studied substitution reactions were obtained by performing intrinsic reaction coordinate (IRC) calculations,<sup>115–117</sup> which, in turn, were analyzed using the PyFrag program.<sup>118</sup> To account for bulk solvation the conductor-like screening model (COSMO) was used.<sup>119–122</sup> The electronic energies of all stationary points were, for reference purposes, re-computed at COSMO(CH<sub>2</sub>Cl<sub>2</sub>)-ZORA-OLYP//ZORA-OLYP/QZ4P, (TightPNO)DLPNO-CCSD(T)/CBS(3,4/def2)//ZORA-OLYP/QZ4P//ZORA-OLYP/QZ4P and SMD(CH<sub>2</sub>Cl<sub>2</sub>)-(TightPNO)DLPNO-CCSD(T)/CBS(3,4/def2)//ZORA-OLYP/QZ4P. The DLPNO-CCSD(T)<sup>56–62</sup> computations were carried out using ORCA5.04.<sup>63,64</sup>

### Thermochemistry

For the thermochemistry calculations, a standard approach was used whereby the geometries were optimized, and the vibrational frequencies were obtained through numerical differentiation of the analytical gradient. Enthalpies at 298.15 K and 1 atm ( $\Delta H$ ) were calculated from the electronic bond energies and vibrational frequencies by using a standard thermochemistry relation for an ideal gas [Eq. S1].

$$\Delta H = \Delta E_{\text{trans}} + \Delta E_{\text{rot}} + \Delta E_{\text{vib},0} + \Delta(\Delta E_{\text{vib},298}) + \Delta(pV) \quad (\text{S1})$$

$\Delta E_{\text{trans},298}$ ,  $\Delta E_{\text{rot},298}$ , and  $\Delta E_{\text{vib},0}$  are the differences between the reactants in the translational, rotational, and zero-point vibrational energy, respectively, whereas  $\Delta E_{\text{vib},298}$  takes the vibrational energy change upon going from 0 to 298.15 K into account. When COSMO was used, entropies were corrected according to the approach of Martin-Hay-Pratt.<sup>123–125</sup> This correction is important because the ideal gas approximation ignores the solvent suppression effect on the rotational and translational degrees of freedom of the solute, which can lead to a large overestimation of the entropy contributions to the Gibbs free energy in solution. In the specific case of bimolecular reactions occurring in dichloromethane at 298.15 K, as in this study, this correction amounts to  $-3.52 \text{ kcal mol}^{-1}$  for all TSs, RCs, and INTs. Finally, the change of the Gibbs free energy ( $\Delta G$ ) in solution was then calculated according to Eq. S2.

$$\Delta G = \Delta H - T\Delta S \quad (\text{S2})$$

### Activation Strain Model

The activation strain model of chemical reactivity, also known as the distortion/interaction model, is a fragment-based approach in which the reaction profiles can be described with respect to, and understood in terms of the characteristics of, the reactants. It considers the rigidity of the reactants and to which extent they need to deform during the reaction, plus their capability to interact with each other as the reaction proceeds. With the help of this model, the total energy, *i.e.*,  $\Delta E(\zeta)$ , is decomposed into the strain and interaction energy,  $\Delta E_{\text{strain}}(\zeta)$  and  $\Delta E_{\text{int}}(\zeta)$ , respectively, and project these values onto the reaction coordinate  $\zeta$  [Eq. (S3)].

$$\Delta E(\zeta) = \Delta E_{\text{strain}}(\zeta) + \Delta E_{\text{int}}(\zeta) \quad (\text{S3})$$

In this equation, the strain energy,  $\Delta E_{\text{strain}}(\zeta)$ , is the penalty that needs to be paid to deform the reactants from their equilibrium to the geometry they adopt during the reaction at the point  $\zeta$  of the reaction coordinate. On the other hand, the interaction energy,  $\Delta E_{\text{int}}(\zeta)$ , accounts for all the chemical interactions that occur between these two deformed reactants along the reaction coordinate. The total strain energy can, in turn, be further decomposed into the strain energies corresponding to the deformation of the nucleophile,  $\Delta E_{\text{strain,nucleophile}}(\zeta)$ , as well as from the electrophile,  $\Delta E_{\text{strain,electrophile}}(\zeta)$  [Eq. S4].

$$\Delta E_{\text{strain}}(\zeta) = \Delta E_{\text{strain,nucleophile}}(\zeta) + \Delta E_{\text{strain,electrophile}}(\zeta) \quad (\text{S4})$$

In the herein presented activation strain and accompanied energy decomposition diagrams, the intrinsic reaction coordinate (IRC) is projected onto the carbon–leaving group (C•••OTf) stretch. This critical reaction coordinate undergoes a well-defined change during the reaction from the reactant complex via the transition state to the product and is shown to be a valid reaction coordinate for studying bimolecular reactions. The ASM has been used to analyze the factors affecting the reaction paths of cycloaddition reactions, nucleophilic substitution reactions, eliminations reactions as well as epoxide opening reactions.<sup>66,68,93,126,127</sup>

### Energy Decomposition Analysis

The interaction energy, *i.e.*,  $\Delta E_{\text{int}}(\zeta)$ , between the deformed reactants can be further analyzed in terms of quantitative Kohn-Sham molecular orbital (KS-MO) theory together with a canonical energy decomposition analysis (EDA).<sup>50,51</sup> The EDA decomposes the  $\Delta E_{\text{int}}(\zeta)$  into the following three energy terms [Eq. S5].

$$\Delta E_{\text{int}}(\zeta) = \Delta V_{\text{elstat}}(\zeta) + \Delta E_{\text{Pauli}}(\zeta) + \Delta E_{\text{oi}}(\zeta) \quad (\text{S5})$$

Herein,  $\Delta V_{\text{elstat}}(\zeta)$  is the classical electrostatic interaction between the unperturbed charge distributions of the (deformed) reactants and is usually attractive. The Pauli repulsion,  $\Delta E_{\text{Pauli}}(\zeta)$ , includes the destabilizing interaction between the fully occupied orbitals of both fragments due to the Pauli principle. The orbital interaction energy,  $\Delta E_{\text{oi}}(\zeta)$ , accounts for, amongst others, charge transfer between the fragments, such as HOMO–LUMO interactions.

### Proton Affinity

Proton affinities (PA), are calculated at 298.15 K and 1 atm ( $\Delta H_{\text{PA}}$ ) from electronic bond energies ( $\Delta E$ ) and vibrational frequencies using standard thermochemistry relations for an ideal gas [Eq. S6].<sup>128,129</sup>

$$\Delta H_{\text{PA}} = \Delta E + \Delta E_{\text{trans},298} + \Delta E_{\text{rot},298} + \Delta E_{\text{vib},0} + \Delta(\Delta E_{\text{vib},0})_{298} + \Delta(pV) \quad (\text{S6})$$

Here,  $\Delta E_{\text{trans},298}$ ,  $\Delta E_{\text{rot},298}$ , and  $\Delta E_{\text{vib},0}$  are the differences between the alcohol (*i.e.*, ROH) and the separated alkoxide and proton species (*i.e.*, H<sup>+</sup> + RO<sup>-</sup>; the proton and the alkoxide) in translational, rotational, and zero-point vibrational energy, respectively. The last term,  $\Delta(\Delta E_{\text{vib},0})_{298}$ , is the change in the vibrational energy difference when going from 0 to 298.15 K. The molar work term  $\Delta(pV)$  is  $(\Delta n)RT$ , where  $\Delta n = +1$ , for one alcohol dissociating into two separate species, namely the H<sup>+</sup> and the alkoxide.

### Voronoi Deformation Density

The atomic charge distribution was analyzed by using the Voronoi Deformation Density (VDD) method.<sup>101</sup> The VDD method partitions the space into so-called Voronoi cells, which are non-overlapping regions of space that are closer to nucleus A than to any other nucleus. The charge distribution is determined by taking a fictitious promolecule as reference point, in which the electron density is simply the superposition of the atomic densities of all atoms A [Eq. (S7)]:

$$\rho_{\text{promolecule}}(\mathbf{r}) = \sum_A \rho_A(\mathbf{r}) \quad (\text{S7})$$

The change in density in the Voronoi cell when going from this promolecule to the final molecular density  $\rho(\mathbf{r})$  of the interacting system is associated with the VDD atomic charge Q. The VDD atomic charge Q<sub>A</sub> of atom A is calculated according to [Eq. (S8)].

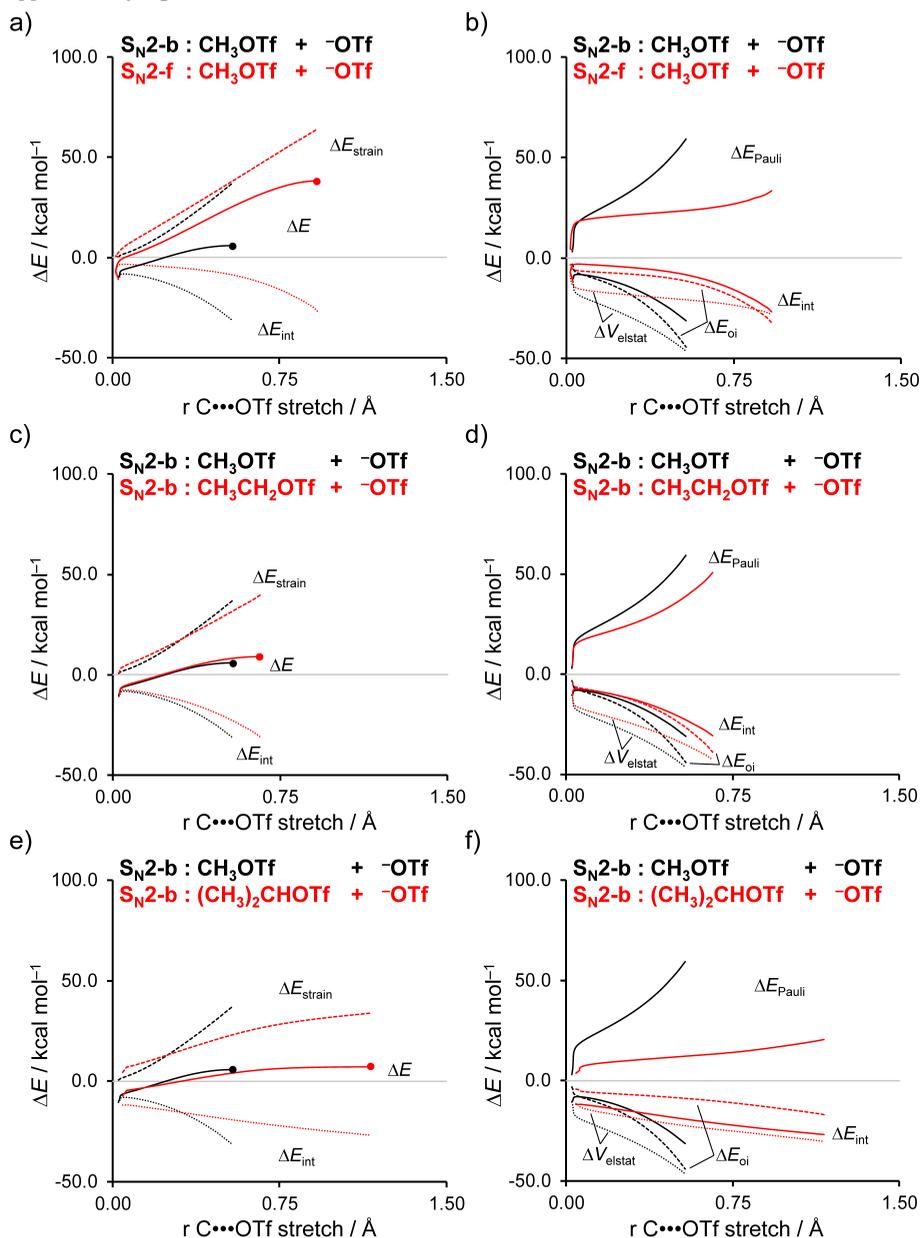
$$Q_A^{\text{VDD}} = - \int_{\text{Voronoi cell of A}} [\rho(\mathbf{r}) - \rho_{\text{promolecule}}(\mathbf{r})] d\mathbf{r} \quad (\text{S8})$$

So, instead of computing the amount of charge contained in an atomic volume, the flow of charge from one atom to the other upon formation of the molecule is computed. The physical interpretation is therefore straightforward. A positive atomic charge Q<sub>A</sub> corresponds to the loss of electrons, whereas a negative atomic charge Q<sub>A</sub> is associated with the gain of electrons in the Voronoi cell of atom A.

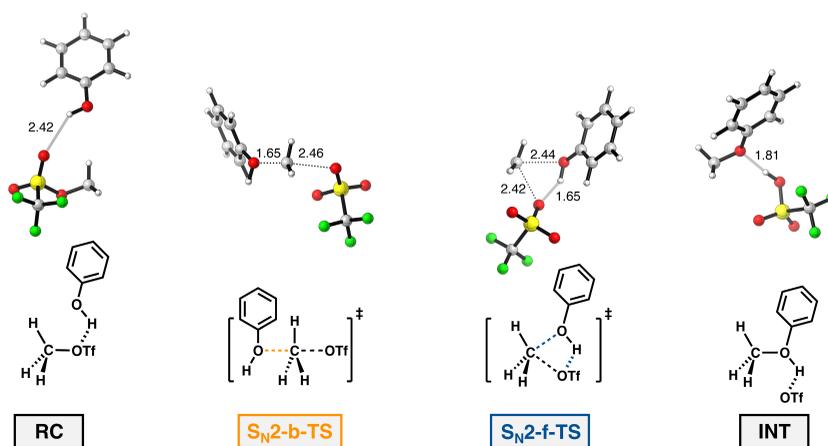
### Projecting ill-defined reaction paths onto well-defined reaction paths.

For two of the computed systems (2,2,2-trifluoroethanol–(CH<sub>3</sub>)<sub>2</sub>CHOTf and 1,1,1,3,3,3-hexafluoro-2-propanol–(CH<sub>3</sub>)<sub>2</sub>CHOTf), an S<sub>N</sub>2-f transition state could not be established within the specific computational method. To provide some quantitative insight into these reactions, these nucleophiles were projected onto the reaction path (as obtained from the IRC and used in the ASM) of the S<sub>N</sub>2-f reaction of 2,2-difluoroethanol with (CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>OTf. To this end, all 200 geometries of this reaction path were altered to represent either 2,2,2-trifluoroethanol or 1,1,1,3,3,3-hexafluoro-2-propanol. Subsequently, these geometries were partially optimized with freeze constraints on the leaving group, the electrophile, and the nucleophilic OH-group. In other words, for 2,2,2-trifluoroethanol, only the CH<sub>2</sub>CF<sub>3</sub> part was optimized, and for 1,1,1,3,3,3-hexafluoro-2-propanol, only the (CF<sub>3</sub>)CH part was optimized. The maxima of these *pseudo*-reaction paths were considered to be the transition states. The entire *pseudo*-reaction paths were used for further ASM analysis.

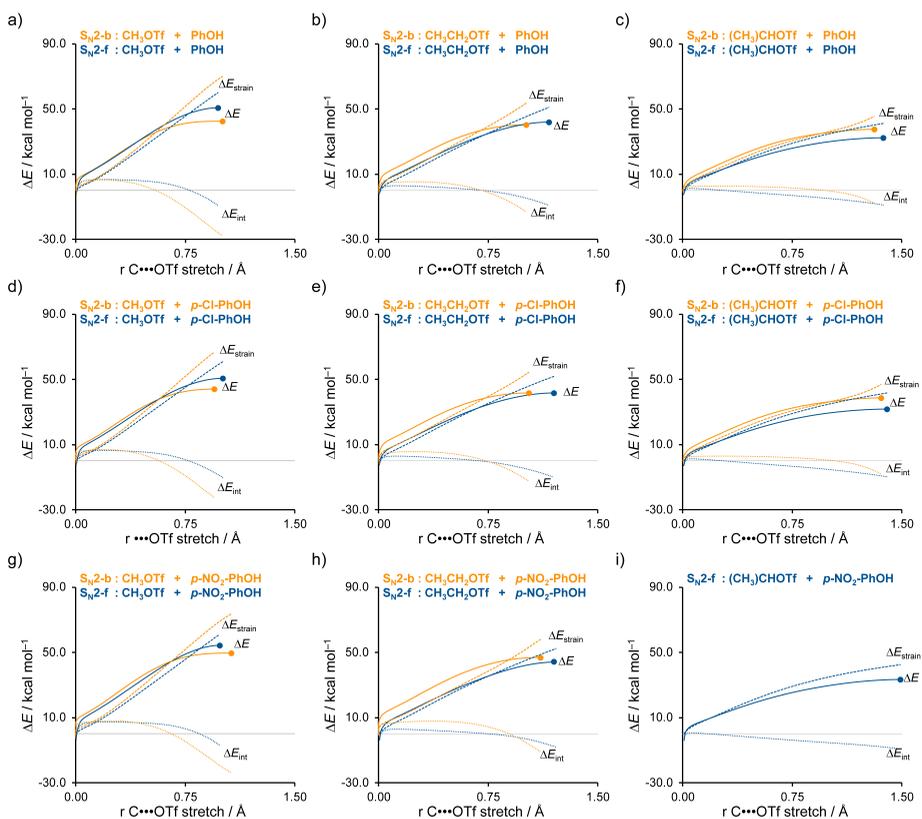
## Supplementary Figures and Tables



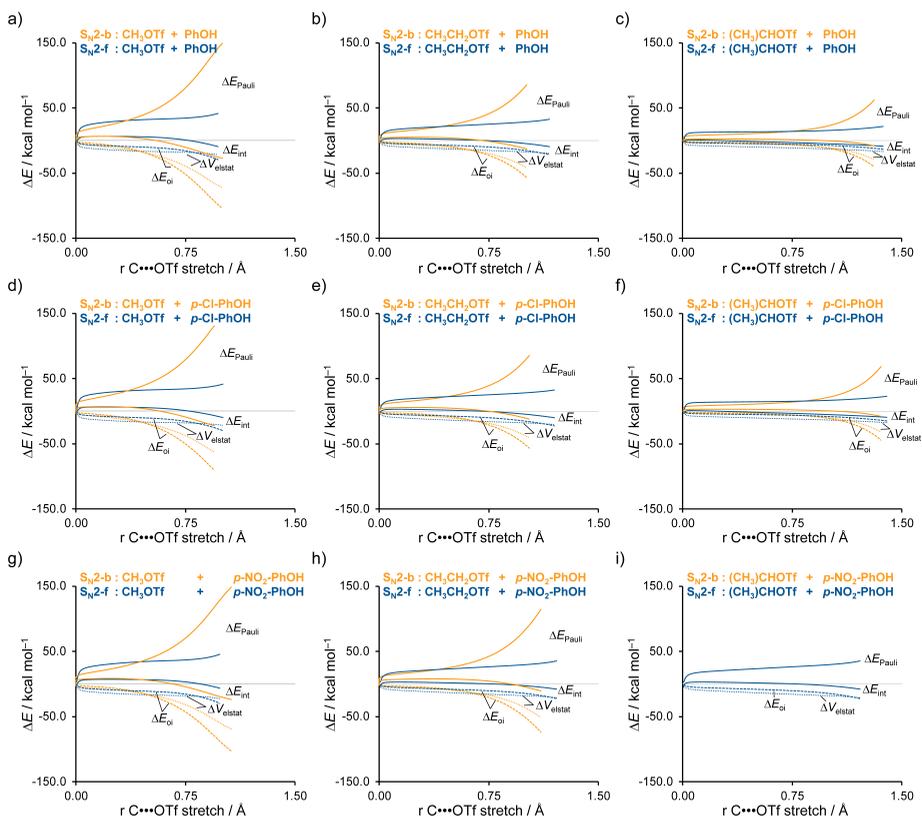
**Supplementary Figure S1.** Activation strain analysis and energy decomposition analysis of the  $S_N2$ -b triflate inversions of  $CH_3OTf$  (a-f),  $CH_3CH_2OTf$  and  $(CH_3)_2CHOTf$  (c, d), and the  $S_N2$ -f triflate inversions of  $CH_3OTf$  (a, b), along the IRC projected on the C...OTf bond stretch. All plots show one of the above-mentioned transition states compared with the  $S_N2$ -b triflate inversions of  $CH_3OTf$ . Transition states are indicated with a thick dot and the zero line with a grey line in the ASM diagram. Computed at ZORA-OLYP/QZ4P.



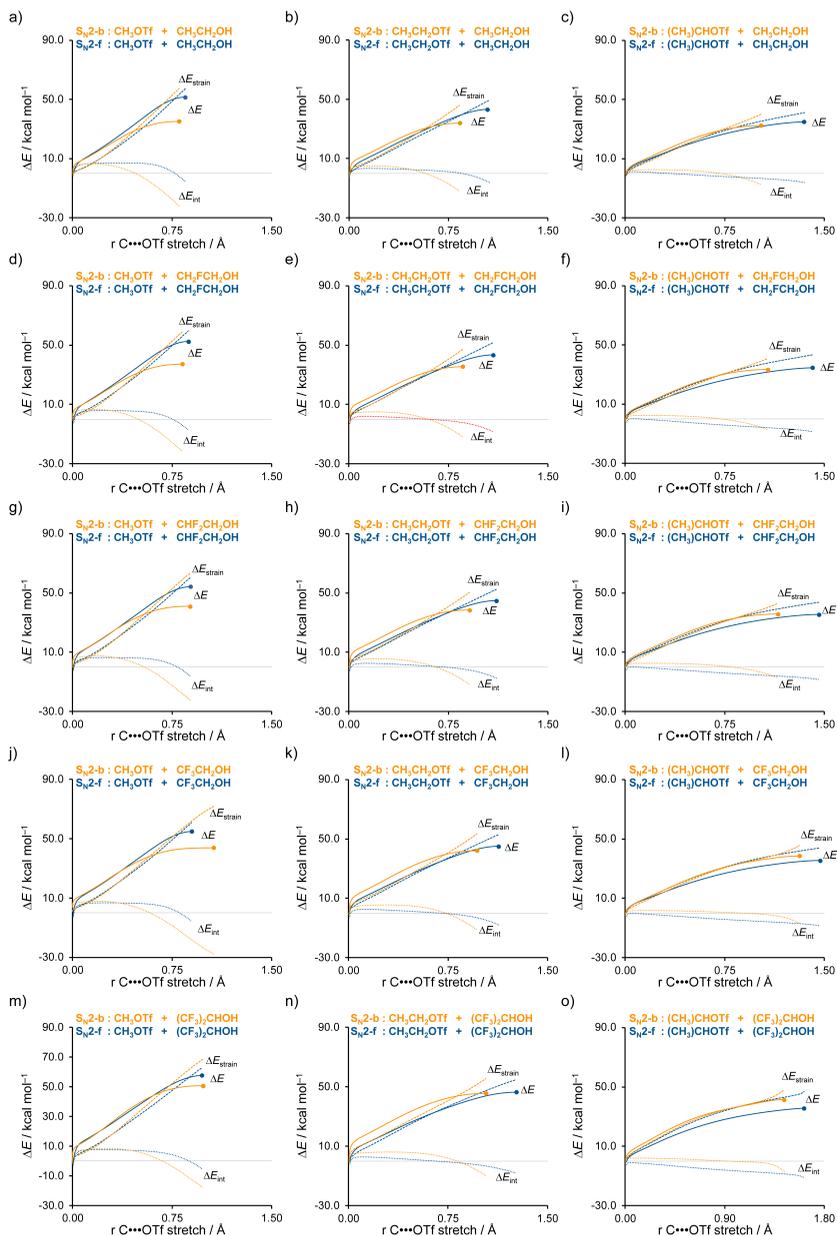
**Supplementary Figure S2. Stationary points** for the  $S_N2$ -b and  $S_N2$ -f reactions of PhOH +  $CH_3OTf$ . RC = reactant complex,  $S_N2$ -b-TS = backside transition state,  $S_N2$ -f-TS = frontside transition state, INT = intermediate, and P = product) of the  $S_N2$ -b (orange) and  $S_N2$ -f (blue) pathways.<sup>[Fout! Bladwijzer niet gedefinieerd.]</sup> Only the  $S_N2$ -f pathway involves a very weakly bound reactant complex RC, while the  $S_N2$ -b pathway does not have a stable RC. The product complex of the  $S_N2$ -b pathway results in charge separation, inducing a barrierless proton transfer, forming the more stable  $S_N2$ -f intermediate.



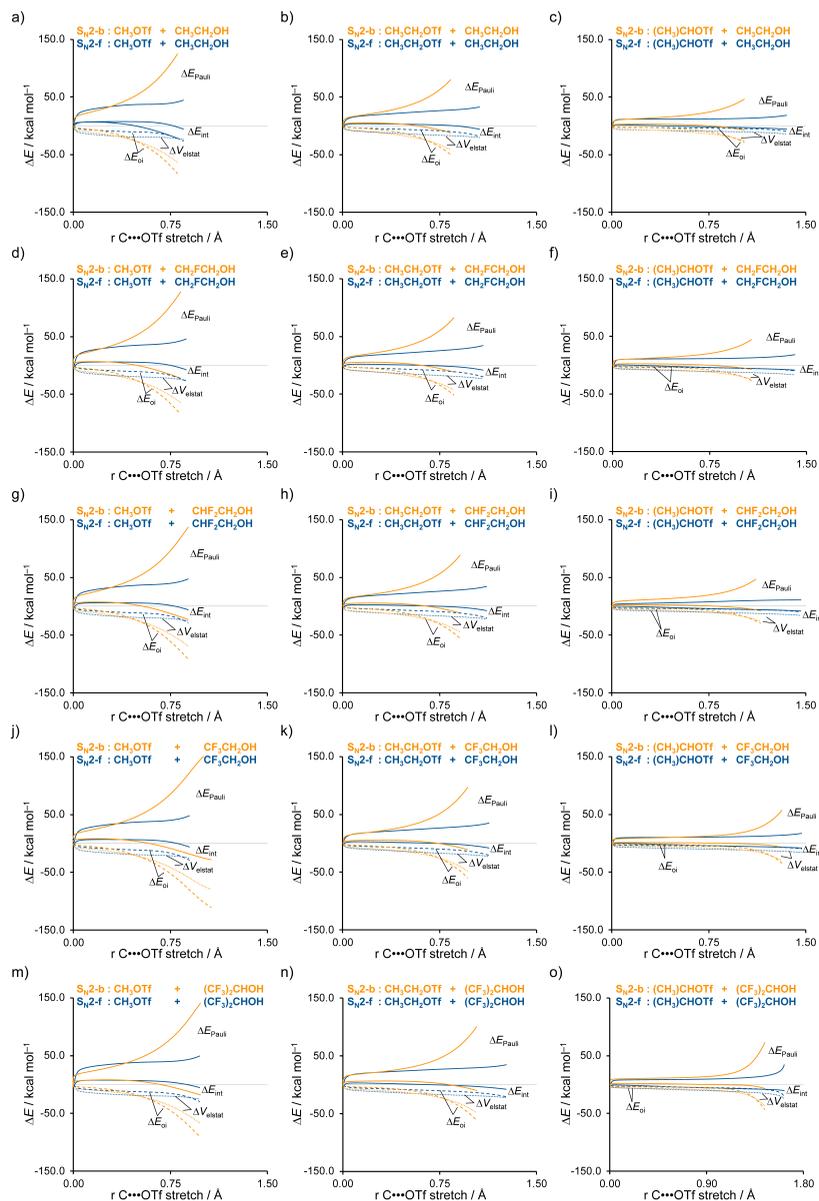
**Supplementary Figure S3.** Activation strain analysis of the competition between  $S_N2$ -b (orange) and  $S_N2$ -f (blue) reactions of phenol(-derivates) with  $\text{CH}_3\text{OTf}$ ,  $\text{CH}_3\text{CH}_2\text{OTf}$  and  $(\text{CH}_3)\text{CHOTf}$  along the IRC projected on the  $\text{C}\cdots\text{OTf}$  bond stretch. Trends in the vertical direction (a to d to g, b to e to f, and c to f to i) show the influence of the nucleophile on this competition, whereas trends in the horizontal direction (a to b to c, d to e to f, and g to h to i) the impact of the degree of substitution on the electrophile. Transition states are indicated with a thick dot and the zero line with a grey line in the ASM diagram. Computed at ZORA-OLYP/QZ4P.



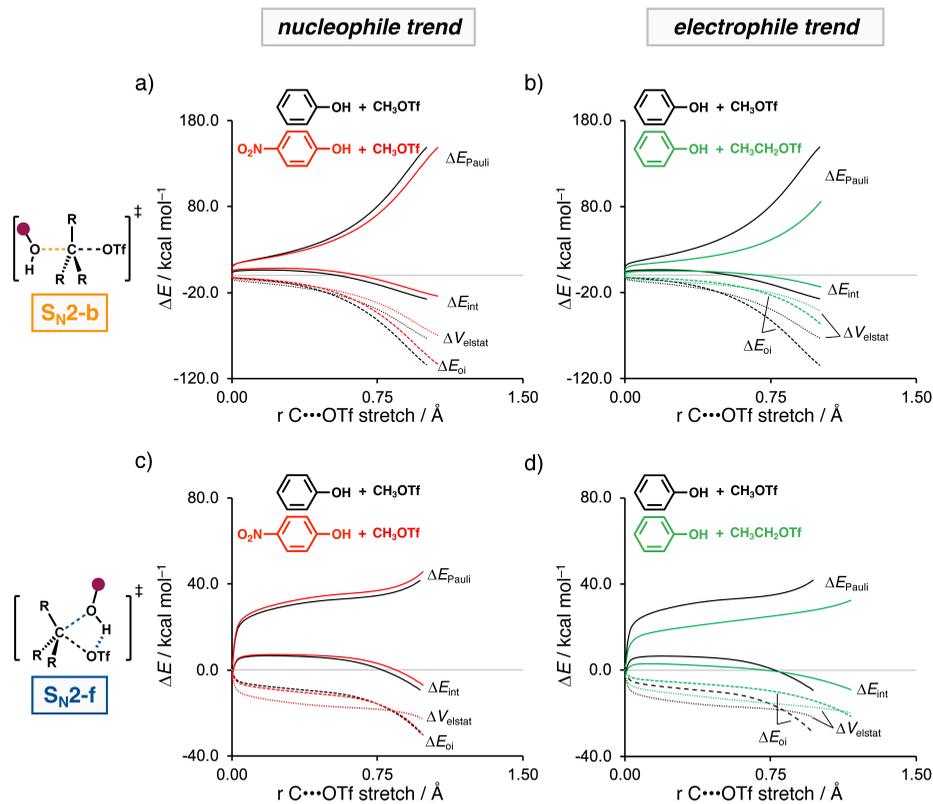
**Supplementary Figure S4.** Energy decomposition analysis of the competition between S<sub>N</sub>2-b (orange) and S<sub>N</sub>2-f (blue) reactions of phenol(-derivates) with CH<sub>3</sub>OTf, CH<sub>3</sub>CH<sub>2</sub>OTf and (CH<sub>3</sub>)CHOTf along the IRC projected on the C•••OTf bond stretch. Trends in the vertical direction (a to d to g, b to e to f, and c to f to i) show the influence of the nucleophile on this competition, whereas trends in the horizontal direction (a to b to c, d to e to f, and g to h to i) the impact of the degree of substitution on the electrophile. The zero line is indicated with a grey line in the EDA diagram. Computed at ZORA-OLYP/QZ4P.



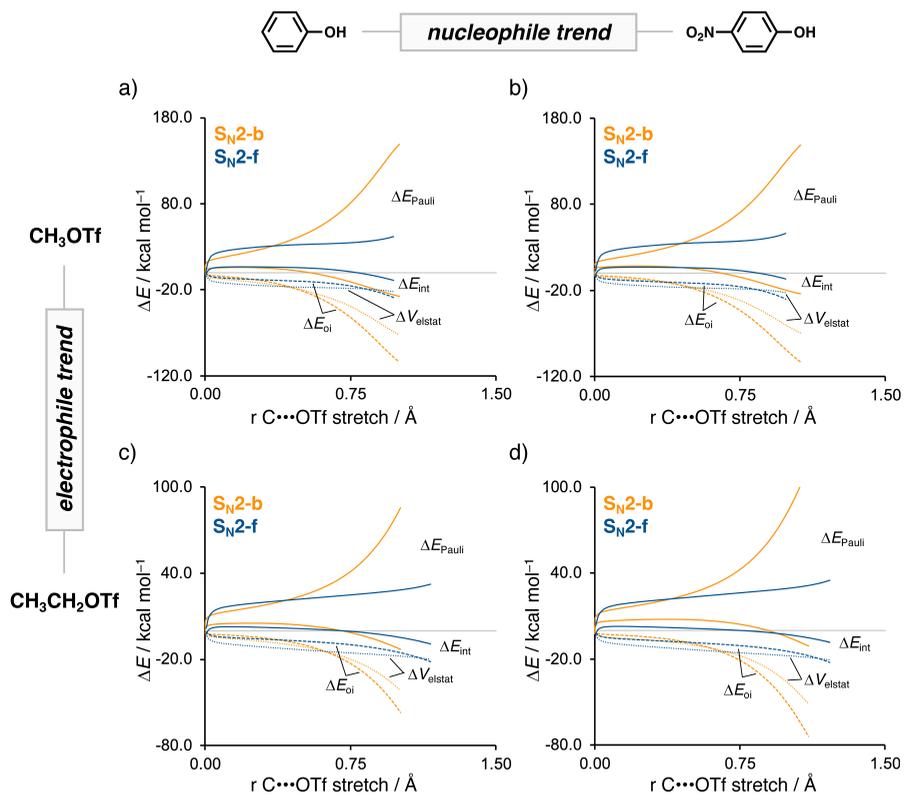
**Supplementary Figure S5.** Activation strain analysis of the competition between  $S_N2$ -b (orange) and  $S_N2$ -f (blue) reactions of ethanol(-derivates) with  $\text{CH}_3\text{OTf}$ ,  $\text{CH}_3\text{CH}_2\text{OTf}$  and  $(\text{CH}_3)\text{CHOTf}$  along the IRC projected on the  $\text{C}\cdots\text{OTf}$  bond stretch. Trends in the vertical direction (a to d to g to j to m, b to e to h to k to n and c to f to i to l to o) show the influence of the nucleophile, whereas trends in the horizontal direction (a to b to c, d to e to f, and g to h to i, j to k to l and m to n to o) show the impact of the degree of substitution on this competition. Transition states are indicated with a thick dot and the zero line with a grey line in the ASM diagram. Computed at ZORA-OLYP/QZ4P.



**Supplementary Figure S6.** Energy decomposition analysis of the competition between S<sub>N</sub>2-b (orange) and S<sub>N</sub>2-f (blue) reactions of ethanol[derivates] with CH<sub>3</sub>OTf, CH<sub>3</sub>CH<sub>2</sub>OTf and (CH<sub>3</sub>)CHOTf along the IRC projected on the C...OTf bond stretch. Trends in the vertical direction (a to d to g to j to m, b to e to h to k to n and c to f to i to l to o) show the influence of the nucleophile, whereas trends in the horizontal direction (a to b to c, d to e to f, and g to h to i, j to k to l and m to n to o) show the impact of the degree of substitution on the electrophile on this competition. The zero line is indicated with a grey line in the EDA diagram. Computed at ZORA-OLYP/QZ4P.



**Supplementary Figure S7.** Energy decomposition analysis of the  $\text{S}_{\text{N}}2\text{-b}$  and  $\text{S}_{\text{N}}2\text{-f}$  reactions along the IRC projected on the  $\text{C}\cdots\text{OTf}$  bond stretch. The left column (a to c) shows the impact of the nucleophile on the activation energy, whereas the right column (b to d) shows the influence of the degree of substitution on the electrophile. The zero line is indicated with a grey line in the EDA diagram. Computed at ZORA-OLYP/QZ4P.



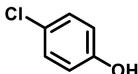
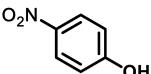
**Supplementary Figure S8.** Energy decomposition analysis of the competition between  $S_N2$ -b (orange) and  $S_N2$ -f (blue) reactions along the IRC projected on the  $\text{C}\cdots\text{OTf}$  bond stretch. Trends in the vertical direction (a to c and b to d) show the impact of the degree of substitution on the electrophile on this competition, whereas trends in the horizontal direction (a to b and c to d) show the influence of the nucleophile. The zero line is indicated with a grey line in the EDA diagram. Computed at ZORA-OLYP/QZ4P.

**Supplementary Table S1.** Energies relative to the separate reactants (in kcal mol<sup>-1</sup>) of the transition states (TS) of the S<sub>N</sub>2-b and S<sub>N</sub>2-f pathways.<sup>[a-d]</sup>

Nucleophile	Electrophile			
	CH <sub>3</sub> OTf	CH <sub>3</sub> CH <sub>2</sub> OTf	CH <sub>3</sub> ) <sub>2</sub> CHOTf	
	S <sub>N</sub> 2-b-TS <sup>[a]</sup> (OLYP)	5.9	9.0	7.2
	S <sub>N</sub> 2-f-TS <sup>[a]</sup> (OLYP)	38.2	[e]	[e]
	S <sub>N</sub> 2-b-TS <sup>[b]</sup> (COSMO-OLYP)	22.1	23.8	19.1
	S <sub>N</sub> 2-f-TS <sup>[b]</sup> (COSMO-OLYP)	50.5	[e]	[e]
	S <sub>N</sub> 2-b-TS <sup>[c]</sup> (DLPNO-CCSD(T))	1.4	4.1	8.0
	S <sub>N</sub> 2-f-TS <sup>[c]</sup> (DLPNO-CCSD(T))	41.9	[e]	[e]
	S <sub>N</sub> 2-b-TS <sup>[d]</sup> (SMD-DLPNO-CCSD(T))	15.1	16.8	17.2
	S <sub>N</sub> 2-f-TS <sup>[d]</sup> (SMD-DLPNO-CCSD(T))	48.7	[e]	[e]

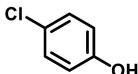
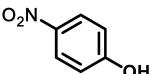
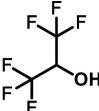
<sup>[a]</sup> Electronic energies computed at ZORA-OLYP/QZ4P. <sup>[b]</sup> Electronic energies computed at COSMO(CH<sub>2</sub>Cl<sub>2</sub>)-ZORA-OLYP//ZORA-OLYP/QZ4P. <sup>[c]</sup> Electronic energies computed at (TightPNO)DLPNO-CCSD(T)/CBS(3,4/def2)//ZORA-OLYP/QZ4P. <sup>[d]</sup> Electronic energies computed at SMD(CH<sub>2</sub>Cl<sub>2</sub>)-(TightPNO)DLPNO-CCSD(T)/CBS(3,4/def2)//ZORA-OLYP/QZ4P. <sup>[e]</sup> Transition state could not be located.

**Supplementary Table S2.** Energies relative to the separate reactants (in kcal mol<sup>-1</sup>) of the stationary points (RC = reactant complex, TS = transition state, INT = intermediate, and P = product) of the S<sub>N</sub>2-b and S<sub>N</sub>2-f pathways.<sup>[a]</sup>

Nucleophile	Electrophile			
	CH <sub>3</sub> OTf	CH <sub>3</sub> CH <sub>2</sub> OTf	(CH <sub>3</sub> ) <sub>2</sub> CHOTf	
	RC <sup>[b]</sup>	-4.4	-4.8	-5.0
	S <sub>N</sub> 2-b-TS	32.9	33.1	31.4
	S <sub>N</sub> 2-f-TS	56.0	45.9	35.8
	INT <sup>[c]</sup>	-10.9	-10.4	-8.5
	P	1.0	2.8	8.4
	RC <sup>[b]</sup>	-4.6	-4.7	-5.2
	S <sub>N</sub> 2-b-TS	34.7	34.5	32.3
	S <sub>N</sub> 2-f-TS	57.5	46.6	36.1
	INT <sup>[c]</sup>	-10.3	-9.8	-8.3
	P	0.8	1.9	3.9
	RC <sup>[b]</sup>	-5.4	-5.9	-6.2
	S <sub>N</sub> 2-b-TS	39.4	36.6	<sup>[d]</sup>
	S <sub>N</sub> 2-f-TS	57.9	46.3	35.9
	INT <sup>[c]</sup>	-8.4	-7.5	-5.5
	P	0.8	1.9	3.6
	RC <sup>[b]</sup>	-4.2	-4.3	-4.3
	S <sub>N</sub> 2-b-TS	27.4	27.2	28.0
	S <sub>N</sub> 2-f-TS	54.4	45.4	38.1
	INT <sup>[c]</sup>	-14.4	-13.7	-13.9
	P	-0.4	0.3	3.6
	RC <sup>[b]</sup>	-1.6	-3.1	-4.3
	S <sub>N</sub> 2-b-TS	28.4	27.9	28.5
	S <sub>N</sub> 2-f-TS	53.9	44.0	37.0
	INT <sup>[c]</sup>	-12.2	-11.5	-9.1
	P	2.2	2.9	5.4
	RC <sup>[b]</sup>	-4.2	-4.5	-4.5
	S <sub>N</sub> 2-b-TS	31.7	30.6	30.6
	S <sub>N</sub> 2-f-TS	56.0	45.7	38.0
	INT <sup>[c]</sup>	-10.7	-10.2	-8.1
	P	2.0	2.6	5.7
	RC <sup>[b]</sup>	-4.0	-3.5	-3.3
	S <sub>N</sub> 2-b-TS	34.9	34.3	33.7
	S <sub>N</sub> 2-f-TS	56.8	45.9	38.0
	INT <sup>[c]</sup>	-10.3	-9.9	-8.8
	P	1.8	2.3	3.6
	RC <sup>[b]</sup>	-4.2	-4.8	-4.7
	S <sub>N</sub> 2-b-TS	41.4	37.4	35.5
	S <sub>N</sub> 2-f-TS	58.6	46.1	34.2
	INT <sup>[c]</sup>	-7.2	-5.0	-4.3
	P	1.9	2.0	3.0

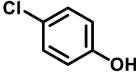
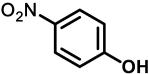
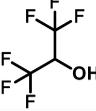
<sup>[a]</sup> Electronic energies computed at (TightPNO)DLPNO-CCSD(T)/CBS(3,4/def2)//ZORA-OLYP/QZ4P. <sup>[b]</sup> Only the S<sub>N</sub>2-f pathway involves a very weakly bound reactant complex RC, the energy of which is provided, while the S<sub>N</sub>2-b pathway does not have a stable RC. <sup>[c]</sup> The product complex of the S<sub>N</sub>2-b pathway results in charge separation, inducing a barrierless proton transfer, forming the more stable S<sub>N</sub>2-f intermediate (INT). <sup>[d]</sup> Transition state cannot be located due to the instability of the associated product.

**Supplementary Table S3.** Energies relative to the separate reactants (in kcal mol<sup>-1</sup>) of the stationary points (RC = reactant complex, TS = transition state, INT = intermediate, and P = product) of the S<sub>N</sub>2-b and S<sub>N</sub>2-f pathways.<sup>[a]</sup>

Nucleophile	Electrophile			
	CH <sub>3</sub> OTf	CH <sub>3</sub> CH <sub>2</sub> OTf	(CH <sub>3</sub> ) <sub>2</sub> CHOTf	
	RC <sup>[b]</sup>	-1.9	-2.3	-2.6
	S <sub>N</sub> 2-b-TS	15.0	19.4	17.3
	S <sub>N</sub> 2-f-TS	49.3	35.1	22.7
	INT <sup>[c]</sup>	-1.1	-6.5	-4.3
	P	1.9	3.9	9.8
	RC <sup>[b]</sup>	-2.1	-2.2	-2.5
	S <sub>N</sub> 2-b-TS	16.5	20.7	17.6
	S <sub>N</sub> 2-f-TS	50.0	35.2	22.7
	INT <sup>[c]</sup>	-7.0	-6.0	-4.4
	P	1.7	3.0	5.0
	RC <sup>[b]</sup>	-2.5	-2.8	-3.0
	S <sub>N</sub> 2-b-TS	20.7	19.9	<sup>[d]</sup>
	S <sub>N</sub> 2-f-TS	50.1	35.0	22.6
	INT <sup>[c]</sup>	-5.1	-3.9	-1.2
	P	1.7	3.1	5.0
	RC <sup>[b]</sup>	-1.7	-1.8	-1.9
	S <sub>N</sub> 2-b-TS	9.0	14.0	15.7
	S <sub>N</sub> 2-f-TS	47.9	35.1	24.2
	INT <sup>[c]</sup>	-12.2	-11.1	-8.9
	P	0.4	1.2	4.5
	RC <sup>[b]</sup>	-2.0	-1.4	-2.2
	S <sub>N</sub> 2-b-TS	11.4	15.5	17.2
	S <sub>N</sub> 2-f-TS	47.9	34.6	24.0
	INT <sup>[c]</sup>	-10.1	-9.0	-7.6
	P	2.7	3.4	4.9
	RC <sup>[b]</sup>	-2.2	-2.3	-2.3
	S <sub>N</sub> 2-b-TS	14.2	17.5	18.6
	S <sub>N</sub> 2-f-TS	49.3	35.3	24.4
	INT <sup>[c]</sup>	-8.6	-7.8	-6.4
	P	2.6	3.3	5.0
	RC <sup>[b]</sup>	-1.8	-1.4	-1.3
	S <sub>N</sub> 2-b-TS	14.2	19.7	20.3
	S <sub>N</sub> 2-f-TS	49.9	35.5	24.3
	INT <sup>[c]</sup>	-8.0	-7.4	-6.1
	P	2.3	2.9	4.1
	RC <sup>[b]</sup>	-2.7	-3.0	-2.8
	S <sub>N</sub> 2-b-TS	25.0	24.0	22.2
	S <sub>N</sub> 2-f-TS	50.0	33.9	21.8
	INT <sup>[c]</sup>	-4.7	-2.6	-1.6
	P	1.4	1.7	2.8

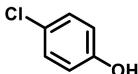
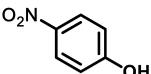
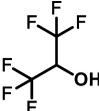
<sup>[a]</sup> Electronic energies computed at SMD(CH<sub>2</sub>Cl<sub>2</sub>)-(TightPNO)DLPNO-CCSD(T)/CBS(3,4/def2)//ZORA-OLYP/QZ4P. <sup>[b]</sup> Only the S<sub>N</sub>2-f pathway involves a very weakly bound reactant complex RC, the energy of which is provided, while the S<sub>N</sub>2-b pathway does not have a stable RC. <sup>[c]</sup> The product complex of the S<sub>N</sub>2-b pathway results in charge separation, inducing a barrierless proton transfer, forming the more stable S<sub>N</sub>2-f intermediate (INT). <sup>[d]</sup> Transition state cannot be located due to the instability of the associated product.

**Supplementary Table S4.** Energies relative to the separate reactants (in kcal mol<sup>-1</sup>) of the stationary points (RC = reactant complex, TS = transition state, INT = intermediate, and P = product) of the S<sub>N</sub>2-b and S<sub>N</sub>2-f pathways.<sup>[a]</sup>

Nucleophile	Electrophile				
	CH <sub>3</sub> OTf		CH <sub>3</sub> CH <sub>2</sub> OTf		
	RC <sup>[b]</sup>	[d]	[d]	[d]	[d]
	S <sub>N</sub> 2-b-TS	28.6	(25.5)	28.8	(27.5)
	S <sub>N</sub> 2-f-TS	48.0	(48.8)	35.2	(36.6)
	INT <sup>[c]</sup>	-0.7	(-1.1)	0.4	[d]
	P	0.9	(1.1)	1.7	(3.3)
	RC <sup>[b]</sup>	[d]	(-0.4)	[d]	(-0.3)
	S <sub>N</sub> 2-b-TS	29.4	(26.8)	29.4	(28.6)
	S <sub>N</sub> 2-f-TS	47.8	(48.6)	35.0	(36.4)
	INT <sup>[c]</sup>	-0.7	(-0.9)	0.6	0.6
	P	0.9	(0.9)	1.5	(1.8)
	RC <sup>[b]</sup>	[d]	(-0.5)	[d]	(-0.5)
	S <sub>N</sub> 2-b-TS	32.8	(32.4)	32.7	(31.0)
	S <sub>N</sub> 2-f-TS	51.3	(52.0)	[e]	(38.3)
	INT <sup>[c]</sup>	[d]	[d]	[d]	[d]
	P	0.7	(0.7)	1.1	(1.6)
	RC <sup>[b]</sup>	[d]	[d]	[d]	[d]
	S <sub>N</sub> 2-b-TS	22.5	(19.2)	24.0	(22.7)
	S <sub>N</sub> 2-f-TS	48.5	(49.2)	35.9	(37.5)
	INT <sup>[c]</sup>	-5.9	(-5.6)	-4.9	(-4.0)
	P	-1.3	(-1.3)	1.2	(-0.5)
	RC <sup>[b]</sup>	[d]	[d]	[d]	[d]
	S <sub>N</sub> 2-b-TS	24.3	(22.8)	25.5	(25.3)
	S <sub>N</sub> 2-f-TS	49.3	(50.0)	36.2	(37.7)
	INT <sup>[c]</sup>	-4.1	(-3.9)	-2.5	(-2.3)
	P	0.8	(1.0)	1.4	(1.6)
	RC <sup>[b]</sup>	[d]	[d]	[d]	[d]
	S <sub>N</sub> 2-b-TS	26.6	(26.0)	27.3	(27.5)
	S <sub>N</sub> 2-f-TS	51.0	(51.5)	37.0	(38.7)
	INT <sup>[c]</sup>	-3.0	(-2.8)	-1.2	(-1.3)
	P	0.9	(1.0)	1.5	(1.5)
	RC <sup>[b]</sup>	[d]	[d]	[d]	[d]
	S <sub>N</sub> 2-b-TS	28.2	(24.9)	28.5	(29.2)
	S <sub>N</sub> 2-f-TS	51.7	(52.4)	[e]	(39.0)
	INT <sup>[c]</sup>	[c]	(-2.5)	-1.0	(-1.0)
	P	0.8	(0.7)	1.3	(1.1)
	RC <sup>[b]</sup>	[d]	[d]	[d]	(-0.4)
	S <sub>N</sub> 2-b-TS	33.7	(35.8)	32.8	(34.0)
	S <sub>N</sub> 2-f-TS	53.8	(54.7)	[d]	(39.3)
	INT <sup>[c]</sup>	-0.9	(-0.7)	-1.0	[d]
	P	0.3	(0.4)	1.3	(0.5)

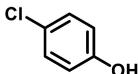
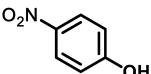
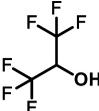
<sup>[a]</sup> Electronic energies computed at COSMO(CH<sub>2</sub>Cl<sub>2</sub>)-ZORA-OLYP/QZ4P with in brackets energies computed at COSMO(CH<sub>2</sub>Cl<sub>2</sub>)-ZORA-OLYP//ZORA-OLYP/QZ4P. <sup>[b]</sup> Only the S<sub>N</sub>2-f pathway involves a very weakly bound reactant complex RC, the energy of which is provided, while the S<sub>N</sub>2-b pathway does not have a stable RC. <sup>[c]</sup> The product complex of the S<sub>N</sub>2-b pathway results in charge separation, inducing a barrierless proton transfer, forming the more stable S<sub>N</sub>2-f intermediate (INT). <sup>[d]</sup> Stationary point is not stable. <sup>[e]</sup> Transition state cannot be located due to instability of the associated product.

**Supplementary Table S5.** Energies relative to the separate reactants (in kcal mol<sup>-1</sup>) of the stationary points (RC = reactant complex, TS = transition state, INT = intermediate, and P = product) of the S<sub>N</sub>2-b and S<sub>N</sub>2-f pathways.<sup>[a]</sup>

Nucleophile	Electrophile			
	CH <sub>3</sub> OTf	CH <sub>3</sub> CH <sub>2</sub> OTf	(CH <sub>3</sub> ) <sub>2</sub> CHOTf	
	RC <sup>[b]</sup>	-3.0	-3.5	-3.0
	S <sub>N</sub> 2-b-TS	41.5	39.7	36.5
	S <sub>N</sub> 2-f-TS	48.3	39.4	29.3
	INT <sup>[c]</sup>	-4.4	-2.5	-1.2
	P	0.4	1.3	3.3
	RC <sup>[b]</sup>	-3.3	-3.9	-3.5
	S <sub>N</sub> 2-b-TS	43.1	41.0	37.7
	S <sub>N</sub> 2-f-TS	48.1	39.1	29.5
	INT <sup>[c]</sup>	-4.1	-2.8	-1.0
	P	0.2	1.0	3.0
	RC <sup>[b]</sup>	-3.9	-3.9	-4.0
	S <sub>N</sub> 2-b-TS	48.5	46.2	<sup>[d]</sup>
	S <sub>N</sub> 2-f-TS	51.0	41.0	30.2
	INT <sup>[c]</sup>	-2.9	-1.7	1.0
	P	0.0	0.6	2.4
	RC <sup>[b]</sup>	-2.2	-2.6	-2.7
	S <sub>N</sub> 2-b-TS	34.9	33.5	31.4
	S <sub>N</sub> 2-f-TS	49.6	41.1	32.0
	INT <sup>[c]</sup>	-8.1	-6.6	-4.1
	P	-2.4	-1.5	2.2
	RC <sup>[b]</sup>	-2.0	-1.0	-1.8
	S <sub>N</sub> 2-b-TS	37.0	35.1	32.3
	S <sub>N</sub> 2-f-TS	50.3	41.7	31.6
	INT <sup>[c]</sup>	-6.3	-4.8	-2.7
	P	0.3	1.1	3.5
	RC <sup>[b]</sup>	-2.3	-2.9	-2.1
	S <sub>N</sub> 2-b-TS	40.6	37.9	34.5
	S <sub>N</sub> 2-f-TS	51.9	42.4	32.2
	INT <sup>[c]</sup>	-5.1	-3.8	-2.2
	P	0.3	1.0	3.7
	RC <sup>[b]</sup>	-2.9	-2.3	-2.3
	S <sub>N</sub> 2-b-TS	43.7	41.4	37.3
	S <sub>N</sub> 2-f-TS	52.5	42.5	31.6
	INT <sup>[c]</sup>	-4.9	-4.3	-2.8
	P	0.0	0.6	2.0
	RC <sup>[b]</sup>	-3.4	-3.1	-3.5
	S <sub>N</sub> 2-b-TS	50.1	45.0	40.1
	S <sub>N</sub> 2-f-TS	54.5	43.3	31.9
	INT <sup>[c]</sup>	-3.2	-1.9	-0.6
	P	0.4	0.7	2.2

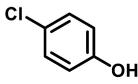
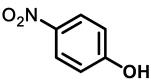
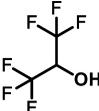
<sup>[a]</sup> Enthalpies computed at the ZORA-OLYP/QZ4P, relative to infinitely separated reactants. <sup>[b]</sup> Only the S<sub>N</sub>2-f pathway involves a very weakly bound reactant complex RC, the energy of which is provided, while the S<sub>N</sub>2-b pathway does not have a stable RC. <sup>[c]</sup> The product complex of the S<sub>N</sub>2-b pathway results in charge separation, inducing a barrierless proton transfer, forming the more stable S<sub>N</sub>2-f intermediate (INT). <sup>[d]</sup> Transition state cannot be located due to instability of the associated product.

**Supplementary Table S6.** Energies relative to the separate reactants (in kcal mol<sup>-1</sup>) of the stationary points (RC = reactant complex, TS = transition state, INT = intermediate, and P = product) of the S<sub>N</sub>2-b and S<sub>N</sub>2-f pathways.<sup>[a]</sup>

Nucleophile	Electrophile			
		CH <sub>3</sub> OTf	CH <sub>3</sub> CH <sub>2</sub> OTf	(CH <sub>3</sub> ) <sub>2</sub> CHOTf
	RC <sup>[b]</sup>	[d]	[d]	[d]
	S <sub>N</sub> 2-b-TS	56.7	50.1	48.3
	S <sub>N</sub> 2-f-TS	60.7	51.2	41.2
	INT <sup>[c]</sup>	[d]	[d]	[d]
	P	1.3	2.0	3.5
	RC <sup>[b]</sup>	[d]	[d]	[d]
	S <sub>N</sub> 2-b-TS	58.6	53.5	49.6
	S <sub>N</sub> 2-f-TS	60.6	50.9	39.5
	INT <sup>[c]</sup>	[d]	[d]	[d]
	P	1.1	1.7	3.1
	RC <sup>[b]</sup>	[d]	[d]	[d]
	S <sub>N</sub> 2-b-TS	63.7	59.0	[e]
	S <sub>N</sub> 2-f-TS	65.4	54.7	41.9
	INT <sup>[c]</sup>	[d]	[d]	[d]
	P	0.9	1.3	2.6
	RC <sup>[b]</sup>	[d]	[d]	[d]
	S <sub>N</sub> 2-b-TS	47.9	46.1	42.7
	S <sub>N</sub> 2-f-TS	61.4	52.5	43.2
	INT <sup>[c]</sup>	[d]	[d]	[d]
	P	-1.5	-0.8	2.2
	RC <sup>[b]</sup>	[d]	[d]	[d]
	S <sub>N</sub> 2-b-TS	50.3	47.8	43.7
	S <sub>N</sub> 2-f-TS	62.8	51.7	42.9
	INT <sup>[c]</sup>	[d]	[d]	[d]
	P	0.9	1.6	3.4
	RC <sup>[b]</sup>	[d]	[d]	[d]
	S <sub>N</sub> 2-b-TS	54.3	51.0	46.2
	S <sub>N</sub> 2-f-TS	64.4	54.2	42.9
	INT <sup>[c]</sup>	[d]	[d]	[d]
	P	0.8	1.3	3.5
	RC <sup>[b]</sup>	[d]	[d]	[d]
	S <sub>N</sub> 2-b-TS	57.5	54.3	49.0
	S <sub>N</sub> 2-f-TS	65.0	54.4	44.3
	INT <sup>[c]</sup>	[d]	[d]	[d]
	P	0.6	1.0	1.8
	RC <sup>[b]</sup>	[d]	[d]	[d]
	S <sub>N</sub> 2-b-TS	63.9	58.4	52.2
	S <sub>N</sub> 2-f-TS	69.5	57.4	47.0
	INT <sup>[c]</sup>	[d]	[d]	[d]
	P	0.7	1.0	2.4

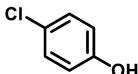
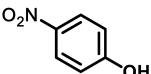
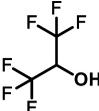
<sup>[a]</sup> Gibbs free energies computed at the ZORA-OLYP/QZ4P, relative to infinitely separated reactants. <sup>[b]</sup> Only the S<sub>N</sub>2-f pathway involves a very weakly bound reactant complex RC, the energy of which is provided, while the S<sub>N</sub>2-b pathway does not have a stable RC. <sup>[c]</sup> The product complex of the S<sub>N</sub>2-b pathway results in charge separation, inducing a barrierless proton transfer, forming the more stable S<sub>N</sub>2-f intermediate (INT). <sup>[d]</sup> Stationary point is not stable. <sup>[e]</sup> Transition state cannot be located due to instability of the associated product.

**Supplementary Table S7.** Energies relative to the separate reactants (in kcal mol<sup>-1</sup>) of the stationary points (RC = reactant complex, TS = transition state, INT = intermediate, and P = product) of the S<sub>N</sub>2-b and S<sub>N</sub>2-f pathways.<sup>[a]</sup>

Nucleophile	Electrophile			
		CH <sub>3</sub> OTf	CH <sub>3</sub> CH <sub>2</sub> OTf	(CH <sub>3</sub> ) <sub>2</sub> CHOTf
	RC <sup>[b]</sup>	-0.5	-0.7	-0.6
	S <sub>N</sub> 2-b-TS	24.6	26.9	22.1
	S <sub>N</sub> 2-f-TS	46.4	34.2	20.6
	INT <sup>[c]</sup>	-1.2	[d]	[d]
	P	0.7	3.1	8.7
	RC <sup>[b]</sup>	-1.0	-1.3	-0.8
	S <sub>N</sub> 2-b-TS	25.8	27.9	22.6
	S <sub>N</sub> 2-f-TS	46.0	33.9	20.9
	INT <sup>[c]</sup>	-1.0	[d]	[d]
	P	0.6	1.6	3.3
	RC <sup>[b]</sup>	-1.1	-0.9	-1.0
	S <sub>N</sub> 2-b-TS	31.3	30.2	[e]
	S <sub>N</sub> 2-f-TS	48.8	35.1	20.4
	INT <sup>[c]</sup>	0.1	[d]	[d]
	P	0.3	1.4	2.9
	RC <sup>[b]</sup>	[d]	[d]	[d]
	S <sub>N</sub> 2-b-TS	19.1	22.3	20.6
	S <sub>N</sub> 2-f-TS	47.2	35.4	22.1
	INT <sup>[c]</sup>	-5.2	-3.5	-1.4
	P	-1.8	-0.9	2.2
	RC <sup>[b]</sup>	[d]	[d]	[d]
	S <sub>N</sub> 2-b-TS	22.6	24.9	22.4
	S <sub>N</sub> 2-f-TS	47.9	36.1	21.7
	INT <sup>[c]</sup>	-3.7	-1.9	-1.0
	P	0.4	1.2	3.3
	RC <sup>[b]</sup>	[d]	[d]	[d]
	S <sub>N</sub> 2-b-TS	25.8	27.0	23.9
	S <sub>N</sub> 2-f-TS	49.3	36.3	21.7
	INT <sup>[c]</sup>	-2.5	-0.8	-0.1
	P	0.4	1.1	2.5
	RC <sup>[b]</sup>	-0.6	[d]	[d]
	S <sub>N</sub> 2-b-TS	24.7	28.6	24.3
	S <sub>N</sub> 2-f-TS	50.1	36.5	21.1
	INT <sup>[c]</sup>	-2.1	-1.1	0.1
	P	0.2	0.8	1.7
	RC <sup>[b]</sup>	-1.4	-1.0	-1.7
	S <sub>N</sub> 2-b-TS	35.1	33.2	27.5
	S <sub>N</sub> 2-f-TS	51.6	35.9	21.9
	INT <sup>[c]</sup>	-0.9	[d]	[d]
	P	-0.2	0.2	1.4

<sup>[a]</sup> Enthalpies computed at the COSMO(CH<sub>2</sub>Cl<sub>2</sub>)-ZORA-OLYP/QZ4P, relative to infinitely separated reactants. <sup>[b]</sup> Only the S<sub>N</sub>2-f pathway involves a very weakly bound reactant complex RC, the energy of which is provided, while the S<sub>N</sub>2-b pathway does not have a stable RC. <sup>[c]</sup> The product complex of the S<sub>N</sub>2-b pathway results in charge separation, inducing a barrierless proton transfer, forming the more stable S<sub>N</sub>2-f intermediate (INT). <sup>[d]</sup> Stationary point is not stable. <sup>[e]</sup> Transition state cannot be located due to instability of the associated product.

**Supplementary Table S8.** Energies relative to the separate reactants (in kcal mol<sup>-1</sup>) of the stationary points (RC = reactant complex, TS = transition state, INT = intermediate, and P = product) of the S<sub>N</sub>2-b and S<sub>N</sub>2-f pathways.<sup>[a]</sup>

Nucleophile	Electrophile			
		CH <sub>3</sub> OTf	CH <sub>3</sub> CH <sub>2</sub> OTf	(CH <sub>3</sub> ) <sub>2</sub> CHOTf
	RC <sup>[b]</sup>	[d]	[d]	[d]
	S <sub>N</sub> 2-b-TS	36.3	33.7	30.4
	S <sub>N</sub> 2-f-TS	55.2	42.4	29.0
	INT <sup>[c]</sup>	[d]	[d]	[d]
	P	1.6	3.8	8.8
	RC <sup>[b]</sup>	[d]	[d]	[d]
	S <sub>N</sub> 2-b-TS	37.8	36.9	31.0
	S <sub>N</sub> 2-f-TS	54.9	42.1	27.4
	INT <sup>[c]</sup>	[d]	[d]	[d]
	P	1.5	2.4	3.5
	RC <sup>[b]</sup>	[d]	[d]	[d]
	S <sub>N</sub> 2-b-TS	42.9	39.5	[e]
	S <sub>N</sub> 2-f-TS	59.7	45.3	28.6
	INT <sup>[c]</sup>	[d]	[d]	[d]
	P	1.2	2.2	3.1
	RC <sup>[b]</sup>	[d]	[d]	[d]
	S <sub>N</sub> 2-b-TS	28.5	31.3	28.3
	S <sub>N</sub> 2-f-TS	55.6	43.3	29.7
	INT <sup>[c]</sup>	[d]	[d]	[d]
	P	-1.0	-0.2	2.1
	RC <sup>[b]</sup>	[d]	[d]	[d]
	S <sub>N</sub> 2-b-TS	32.3	34.1	30.3
	S <sub>N</sub> 2-f-TS	56.8	42.6	29.5
	INT <sup>[c]</sup>	[d]	[d]	[d]
	P	1.0	1.6	3.1
	RC <sup>[b]</sup>	[d]	[d]	[d]
	S <sub>N</sub> 2-b-TS	35.9	36.5	32.1
	S <sub>N</sub> 2-f-TS	58.3	44.6	28.9
	INT <sup>[c]</sup>	[d]	[d]	[d]
	P	1.0	1.4	2.3
	RC <sup>[b]</sup>	[d]	[d]	[d]
	S <sub>N</sub> 2-b-TS	35.0	38.0	32.5
	S <sub>N</sub> 2-f-TS	59.1	44.8	30.3
	INT <sup>[c]</sup>	[d]	[d]	[d]
	P	0.8	1.1	1.6
	RC <sup>[b]</sup>	[d]	[d]	[d]
	S <sub>N</sub> 2-b-TS	45.4	43.1	36.0
	S <sub>N</sub> 2-f-TS	63.0	46.5	33.5
	INT <sup>[c]</sup>	[d]	[d]	[d]
	P	0.1	0.5	1.6

<sup>[a]</sup> Gibbs free energies (TS were corrected by the Martin-Hay-Pratt approach) computed at the COSMO(CH<sub>2</sub>Cl<sub>2</sub>)-ZORA-OLYP/QZ4P, relative to infinitely separated reactants. <sup>[b]</sup> Only the S<sub>N</sub>2-f pathway involves a very weakly bound reactant complex RC, the energy of which is provided, while the S<sub>N</sub>2-b pathway does not have a stable RC. <sup>[c]</sup> The product complex of the S<sub>N</sub>2-b pathway results in charge separation, inducing a barrierless proton transfer, forming the more stable S<sub>N</sub>2-f intermediate (INT). <sup>[d]</sup> Stationary point is not stable. <sup>[e]</sup> Transition state cannot be located due to instability of the associated product.

**Supplementary Table S9.** Heterolytic proton affinity ( $\Delta H_{PA}$ ) energies in kcal mol<sup>-1</sup>.<sup>[a-d]</sup>

Alcohol	OLYP <sup>[a]</sup>	(CH <sub>2</sub> Cl <sub>2</sub> )- OLYP <sup>[b]</sup>	DLPNO- CCSD(T) <sup>[c]</sup>	(CH <sub>2</sub> Cl <sub>2</sub> )- DLPNO- CCSD(T) <sup>[d]</sup>
Phenol	348.4	297.9	349.0	304.0
<i>p</i> -Chlorophenol	341.9	296.1	342.4	301.8
<i>p</i> -Nitrophenol	324.7	285.8	327.6	293.8
Ethanol	375.0	315.1	379.0	325.5
2-Fluoroethanol	369.8	311.7	373.7	322.4
2,2-Difluoroethanol	364.2	308.0	366.3	318.0
2,2,2-Trifluoroethanol	359.7	305.3	361.4	314.6
1,1,1,3,3,3-Hexafluoro-2- propanol	343.6	295.9	345.1	303.3

<sup>[a]</sup> Computed at ZORA-OLYP/QZ4P. <sup>[b]</sup> Computed at COSMO(CH<sub>2</sub>Cl<sub>2</sub>)-ZORA-OLYP/QZ4P//ZORA-OLYP/QZ4P. <sup>[c]</sup> Computed at (TightPNO)DLPNO-CCSD(T)/CBS(3,4/def2)//ZORA-OLYP/QZ4P. <sup>[d]</sup> Computed at SMD(CH<sub>2</sub>Cl<sub>2</sub>)-(TightPNO)DLPNO-CCSD(T)/CBS(3,4/def2)//ZORA-OLYP/QZ4P.

**Supplementary Table S10.** HOMO energies of nucleophiles.<sup>[a,b]</sup>

Alcohol	HOMO energy (eV)	
	OLYP <sup>[a]</sup>	(CH <sub>2</sub> Cl <sub>2</sub> )-OLYP <sup>[b]</sup>
Phenol	-5.374	-5.459
<i>p</i> -Chlorophenol	-5.395	-5.376
<i>p</i> -Nitrophenol	-6.269	-6.049
Ethanol	-6.112	-6.249
2-Fluoroethanol	-6.473	-6.520
2,2-Difluoroethanol	-6.829	-6.757
2,2,2-Trifluoroethanol	-7.132	-7.016
1,1,1,3,3,3-Hexafluoro-2-propanol	-7.727	-7.547

<sup>[a]</sup> Computed at ZORA-OLYP/QZ4P. <sup>[b]</sup> Computed at COSMO(CH<sub>2</sub>Cl<sub>2</sub>)-ZORA-OLYP/QZ4P// ZORA-OLYP/QZ4P.

**Supplementary Table S11.** LUMO energies of nucleophiles.<sup>[a,b]</sup>

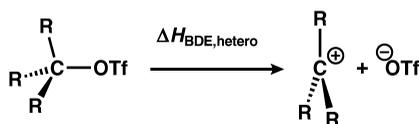
Alcohol	LUMO energy (eV)	
	OLYP <sup>[a]</sup>	(CH <sub>2</sub> Cl <sub>2</sub> )-OLYP <sup>[b]</sup>
Phenol	-1.052	-1.100
<i>p</i> -Chlorophenol	-1.409	-1.324
<i>p</i> -Nitrophenol	-3.108	-3.216
Ethanol	-0.845	-0.650
2-Fluoroethanol	-0.776	-0.640
2,2-Difluoroethanol	-0.902	-0.644
2,2,2-Trifluoroethanol	-1.088	-0.753
1,1,1,3,3,3-Hexafluoro-2-propanol	-1.106	-0.788

<sup>[a]</sup> Computed at ZORA-OLYP/QZ4P. <sup>[b]</sup> Computed at COSMO(CH<sub>2</sub>Cl<sub>2</sub>)-ZORA-OLYP/QZ4P// ZORA-OLYP/QZ4P.

**Supplementary Table S12.** Voronoi deformation density on the oxygen and hydrogen atom of the alcohol group of nucleophiles.

	Voronoi deformation density (VDD)			
	OLYP <sup>[a]</sup>		(CH <sub>2</sub> Cl <sub>2</sub> )-OLYP <sup>[b]</sup>	
Alcohol	O-atom	H-atom	O-atom	H-atom
Phenol	-0.181	0.196	-0.205	0.222
<i>p</i> -Chlorophenol	-0.177	0.200	-0.200	0.225
<i>p</i> -Nitrophenol	-0.163	0.209	-0.178	0.237
Ethanol	-0.225	0.156	-0.262	0.177
2-Fluoroethanol	-0.229	0.168	-0.262	0.181
2,2-Difluoroethanol	-0.220	0.170	-0.247	0.187
2,2,2-Trifluoroethanol	-0.213	0.173	-0.242	0.192
1,1,1,3,3,3-Hexafluoro-2-propanol	-0.201	0.183	-0.220	0.200

<sup>[a]</sup> Computed at ZORA-OLYP/QZ4P. <sup>[b]</sup> Computed at COSMO(CH<sub>2</sub>Cl<sub>2</sub>)-ZORA-OLYP/QZ4P//ZORA-OLYP/QZ4P.

**Supplementary Table S13.** R<sub>3</sub>C-OTf (R = H or Me) bond lengths (in Å) and heterolytic bond dissociation energies  $\Delta H_{\text{BDE, hetero}}$  energies.

Electrophile	<i>r</i> (C-X) <sup>[a]</sup>	OLYP <sup>[a]</sup>	(CH <sub>2</sub> Cl <sub>2</sub> )-OLYP <sup>[b]</sup>	DLPNO-CCSD(T) <sup>[c]</sup>	CH <sub>2</sub> Cl <sub>2</sub> -DLPNO-CCSD(T) <sup>[d]</sup>
CH <sub>3</sub> OTf	1.457	190.4	68.3	189.3	73.5
CH <sub>3</sub> CH <sub>2</sub> OTf	1.475	146.8	37.5	152.6	44.8
(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub> OTf	1.496	125.9	23.6	139.8	38.3

<sup>[a]</sup> Computed at ZORA-OLYP/QZ4P. <sup>[b]</sup> Computed at COSMO(CH<sub>2</sub>Cl<sub>2</sub>)-ZORA-OLYP/QZ4P//ZORA-OLYP/QZ4P. <sup>[c]</sup> Computed at (TightPNO)DLPNO-CCSD(T)/CBS(3,4/def2)//ZORA-OLYP/QZ4P. <sup>[d]</sup> Computed at SMD(CH<sub>2</sub>Cl<sub>2</sub>)-(TightPNO)DLPNO-CCSD(T)/CBS(3,4/def2)//ZORA-OLYP/QZ4P.

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