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Vinyl Triflimides – a Case of Assisted Vinyl Cation Formation

S. Schroeder[a], C. Strauch[a], N. Gaelings[a], and Meike Niggemann*[a]

Abstract: A new concept for selectivity control in carbocation driven reactions has been identified, which allows for the chemo-, regio- and stereoselective addition of nucleophiles to alkynes: Assisted Vinyl Cation Formation, enabled by a Li^+-based supramolecular framework. Mechanistic analysis of a model complex ($Li_2NTf_2^+ \cdot 3\ H_2O$) confirms, that solely the formation of a complex of the transition state of the alkyne protonation with the incoming nucleophile is responsible for the resulting selective N-addition to the vinyl cation. Into the bargain, a general synthetic procedure to previously inaccessible vinyl triflimides is provided, via an operationally simple protocol.

Carbocations are reactive intermediates that drive many transformations in synthetic chemistry. Most prominently they are engaged by enzymes, such as terpene synthases, to selectively build multicyclic skeletons from acyclic precursors.[1] Nevertheless, selectivity guiding principles for carbocation intermediates remain rather elusive in chemical laboratory settings, even after a century of cation research has passed. This may be accounted for by the following reasons: Implementation of conformational preorganization, as resorted to by the enzymes for inducing selectivity, is in its infancy in synthetic chemistry.[2] Catalysts used for cation generation dissociate from the cation, and are no longer present for the selectivity determining bond formation.[3] Combining a cation with a counteranion was successful for a handful of special cases,[4] but never developed into a general principle.

A special member of the carbocation family, the vinyl cation was long regarded as a misbehaved younger sibling of the more prototypical trivalent carbocations. Despite its interesting carbene-like reactivity,[5] little attention has been paid to the development of synthetic methodology.[6] This is certainly due to the widespread misconception, that vinyl cations were highly reactive, uncontrollable reactive intermediates. This myth, that originated in the slow reaction rate = high reactivity/low stability paradigm, established for cations according to Hammond's postulate, was finally debunked by a fundamental study in 2017.[7] It was found, that their stability is similar to trivalent cations and the slow reaction rate of their solvolysis reactions merely a result of a high intrinsic barrier for the energetic penalty of C-rehybridization ($sp^2 \leftrightarrow sp$). This also explains, why they are so difficult to generate.[8] Fortunately, this curse does not come without a blessing. We hypothesize, that it is indeed the vinyl cation's reluctance to form, that may be used to induce selectivity towards a single nucleophile among others.[9] This nucleophile must form a stabilizing complex with the transition state (TS) of the vinyl cation formation by transferring electron density into the nascent p-orbital. It thus becomes obviously the first in line as a reaction partner in what we term an "Assisted Vinyl Cation Formation". A cation that is easier to form does not require the additional stabilization, forms randomly and reacts with the first nucleophile encountered.

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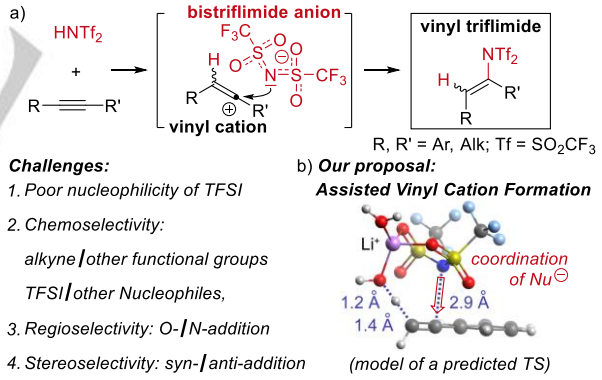
To test this hypothesis and validate the Assisted Vinyl Cation Formation's capacities for inducing selectivity, we chose a seriously challenged borderline case, which, if effective may demonstrate its generality. We turned to the direct hydroaminosulfonation of alkynes with trifluoromethanesulfonimide ($HNTf_2$) in Scheme 1. Although promising in its simplicity, such a reaction suffers from several problems, and has therefore never been realized. Stoichiometric amounts of the superacid $HNTf_2$ undeniably cause poor functional group tolerance, with the protonation of most functionalities being favoured over the alkyne's. The bistriflimide anion (TFSI) is a very poor nucleophile, on account of the heavily delocalized nature of its electron pairs.[10] It is well known for its innocent, non-nucleophilic character as a counteranion. Nevertheless, a few scattered reports indicate for the possibility of its addition to electrophiles[11] such as phenyl cations,[12] vinyl cations[13] and ketenium ions.[14] These reports evidence that regioselectivity is a third challenge. O-addition, of a sulfonyl O-atom, is clearly preferred[13] and mechanistic rationales, let alone studies, of what governs the selectivity are lacking. Finally, a vinyl triflimide with a defined olefin geometry is desirable. Even though the situation is further complicated by equilibration reactions[15] and deviation from the S_N1-type mechanism,[13,16] additions of nucleophiles to vinyl cations are controlled largely by steric effects.[17] Hence, even if any selectivity occurs, it is heavily substrate-dependent and thus unpredictable.



Scheme 1: a) Hydroaminosulfonation of alkynes; b) Model of a predicted complex of the incoming nucleophile with the TS of alkyne ionization: $LiNTf_2 \cdot 2\ H_2O$ with a nascent vinyl cation.

Considering all of the above, we developed an enzyme mimicking synthetic approach, in which the vinyl cation is generated within a supramolecular framework, which shall guide the Assisted Vinyl Cation Formation.[2a,18] Thereby, selectivity will be achieved, not only for alkyne protonation and TFSI among other, more electron rich nucleophiles (H_2O, arene, product), but also for the less favored N-atom within TFSI. Lithium was chosen as a templating metal, for $LiNTf_2$ is among the most readily available TFSI sources. In addition, a recent report highlights the importance of stoichiometric Li^+ for a selective TFSI addition.[12c] In a complex with Li^+, in solution, the TFSI anion adopts a *cis*-conformation and

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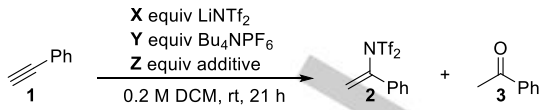
is bound to Li^+ in a η^2-O,O'-mode.[19] As Li^+-Ions strive for a coordination number of 4-6 in non-aqueous solution,[20] it is typically further coordinated to additional TFSI, solvent molecules, or water. Finally, (trace) water molecules are known to significantly impact the outcome of self assembly processes[21] and to enhance the formation and stability of alkaline earth metal complexes.[22] To our delight, in a model complex as shown in Scheme 1 - $LiNTf_2 \cdot 2\ H_2O$ with a nascent vinyl cation - atomic distances are: 1.) Favourable for the transfer of a proton from one of the Li^+-coordinated water molecules. 2.) The N-Atom in TFSI is perfectly positioned for the Assisted Vinyl Cation Formation, and thus selective N-addition. Given the geometry of the predicted TS complex, a stereoselective *syn*-addition, independent of the substituents' sterics, is expected as a bonus.

Our search for conditions that allow for the self-assembly of a complex like the one in Scheme 1, started with the addition of phenylacetylene **1** to a solution of 1 equiv $LiNTf_2$ in dichloromethane (Table 1, entry 1). But it was not before we added Bu_4NPF_6, to improve the solubility of $LiNTf_2$[12c] that we first observed the vinyl triflimide **2** in 47% yield (Table 1, entry 2). The regioselectivity of the addition is governed by the cation stabilizing effect of the α-aryl substituent.[23] Exclusion of water with molecular sieves, or the absence of Li^+ results in inhibition (Table 1, entry 3/4). In line with the model in Scheme 1, this highlights the important role of water and Li^+. Among many proton donors tested, camphorsulfonic acid (CSA, entry 5, others not shown) slightly improves the results.[24] The variation of additives (e.g. Bu_4NSbF_6, Bu_4NBF_4, etc.) identified only $PhMe_2HN^+B(C_6F_5)_4^-$ to allow for a satisfactory conversion, albeit with poor selectivity for N-addition. Significant amounts of acetophenone **3**, as a product of an O-addition-hydrolysis sequence were observed (entry 6, others not shown). Further improvement was achieved by an extensive screening of stoichiometries, solvents and concentrations (exemplary results: entries 7-10). At this stage, the influence of water was investigated once more. In its absence (molecular sieves), the reaction ceases (not shown). Saturating the solvent (DCM) with water, results in a drop of conversion, indicating for inefficient formation of the supramolecular framework (Table 1, entry 11). Increasing the amount of Li^+ via the addition of 1 equiv $LiPF_6$ further enhances the conversion, but again decreases the selectivity (Table 1, entry 13). The N-selectivity was restored by prolonged stirring of the solution before the addition of **1**. This presumably allows for an equilibration of the self-assembled supramolecular framework. The best results were obtained after 24h of stirring time for complex equilibration (entry 15). For comparison, a reaction of $HNTf_2$ with phenylacetylene **1,** resulting in rapid decomposition of the starting material, is also included (Table 1, entry 16).

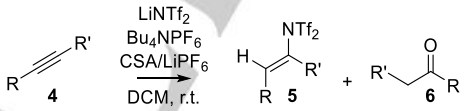
Table 1. Optimization.

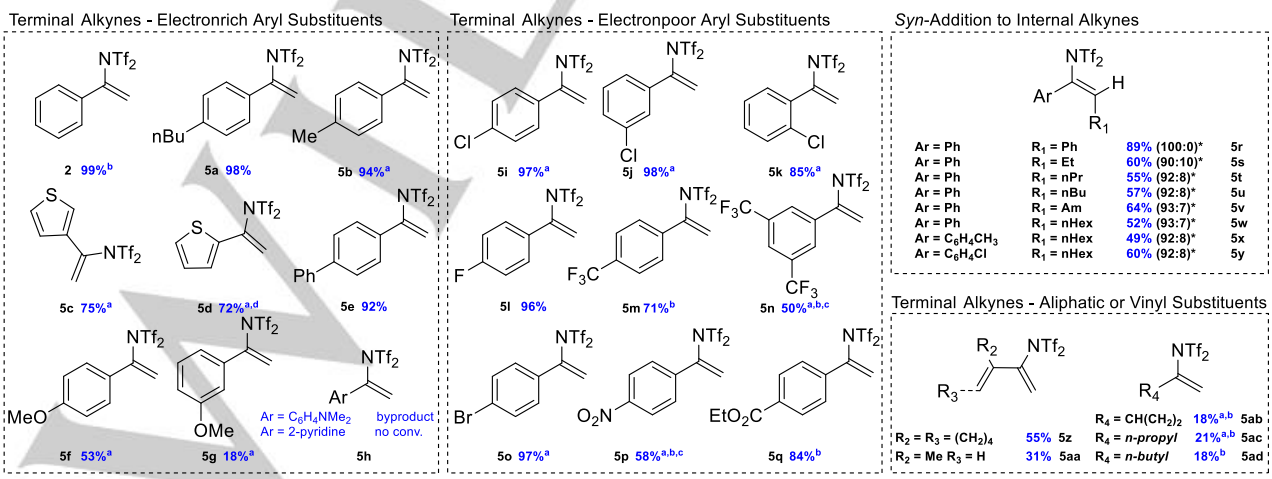


Entry	X	Y	Z	additive	**2** [%]	**3** [%]
1	1.5	-	-	-	0	0
2	1.5	0.3	-	-	47	4
3	1.5	0.3	-	MS 4Å	4	0
4	-	-	1.5	Bu_4NNTf_2	0	0
5	1.5	0.3	0.1	CSA	57	2
6	1.5	-	0.5/0.1	CSA/$PhMe_2HN^+B(C_6F_5)_4^-$	52	48
7	1	0.1	1.5	CSA	44	1
8	1.5	1	0.5	CSA	70	9
9	3	0.1	3	CSA	31	2
10[a]	5	0.3	0.5	CSA	67	13
11[a,b]	1.5	0.3	0.5	CSA	35	12
12[a]	1.5	0.3	0.5/2	CSA/KPF_6	60	7
13[a]	1.5	0.3	0.5/1.0	CSA/$LiPF_6$	76	24
14[a,c]	1.5	0.3	0.5/1.0	CSA/$LiPF_6$	80	20
15[a,d]	**1.5**	**0.3**	**0.5/1.0**	**CSA/$LiPF_6$**	**99**	**1**
16	-	-	1.25	$HNTf_2$	traces	-

[a] c = 0.33 M, [b] solvent saturated with water, [c] a solution of all other reagents stirred 1h before addition of **1**, [d] 24h stirring before addition of **1**.

Table 2. Scope of the Hydroaminosulfonation.





Conditions: 1.5 equiv $LiNTf_2$, 0.3 equiv Bu_4NPF_6, and 0.5 equiv $LiPF_6$ were stirred for 24 hours at rt in 0.6 ml (0.33M) dichloromethane. Alkyne **4** (0.2 mmol) was added and stirring was continued for an additional 21 hours. [a] 1 hour stirring before addition of alkyne **4**; [b] 0.5 equiv CSA added; [c] 85°C, 1,2-dichloroethane; [d] TMS-protected acetylene used as precursor; * E:Z ratio determined by NMR-spectroscopic analysis.

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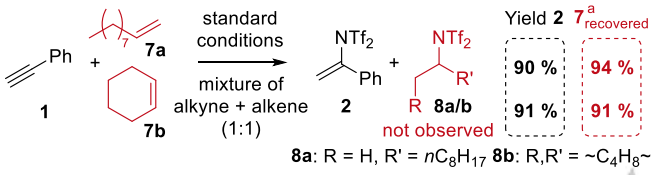
We turned to evaluating the scope. As their vinyl cation intermediates are well stabilized[23] α-aryl substituted terminal alkynes **4** gave vinyl triflimides **5** with excellent selectivity and yields (Table 2, entry **5a**-**q**). The best results were obtained for alkynes **4** with moderately electron poor aryl groups, as unassisted background vinyl cation formation, leading to O-addition of TFSI, begins to interfere when the alkyne bears electron rich aryl substituents (entry **5c**-**h**). Consistent with our expectations and the mechanism discussed below, vinyl triflimide formation proceeds via a *syn*-addition for internal alkynes, again with excellent chemo- and regioselectivity (entry **5r**-**y**). Owing to the poor stabilization provided by α-vinyl or even α-alkyl substituents, such vinyl cations are notoriously difficult to generate. Intermolecular reactions require either elaborate starting materials[13] or catalysts.[5a] Therefore, it is remarkable that the Assisted Vinyl Cation Formation enables such reactions, albeit with moderate yields (entry **5z**-**ad**). Intrigued by the finding that olefin moieties remained intact (entry **5z/aa**), a competition experiment was run to confirm the reactions selectivity for the alkyne (Scheme 2).



Scheme 2: Competition experiments in the presence of olefins. [a] Determined by gas-chromatographic analysis.

TFSI addition to olefins was not observed. Apart from minor amounts of decomposition, again ascribed to background reactions, the olefins in **7a** / **7b** remained unaffected.

For a better understanding of the mechanism we turned to DFT based computational analysis. We are certain that Assisted Vinyl Cation Formation is a general phenomenon, which may contribute to (unexpected) selectivity in all reactions that proceed via a positively charged vinyl cation-like TS. In the following, an easily applicable strategy for its confirmation is provided. In addition, the following key questions shall be answered:

1.) *Is really a complex with the TS of the vinyl cation formation responsible for the observed reactivity and selectivity?*
2.) *Why is Li⁺ required for an efficient formation of that complex?*

A prerequisite for further analyses of reaction determining TSs is a viable reaction pathway. Even though quasi-classical molecular dynamic calculations are more accurate for the analysis of the relatively flat regions of the energy surface in cation chemistry,[25] conventional transition state theory should be sufficient to gain a qualitative picture of reactivity,[26] and thus to answer the question whether or not coordination of the nucleophile to the TS occurs. Extensive initial trials with complexes of different compositions revealed the model complex of TFSI with 2 Li^+ ions and 3 H_2O in Figure 1 to represent the lowest level of complexity that allows for the computation of a reaction coordinate all the way from the reactants to product **2**. Although the reaction path is unusual with a prelocated shoulder, it is free of intermediates and all barriers are realistic (see SI).[27] This complex is obviously just a truncated model of what the certainly oligomeric structure[19a,19e] may look like, but given the important roles of H_2O and additional Li^+ on the reaction outcome, it may be a good compromise, providing realistic results at acceptable computational costs. In this model, the proton for the alkyne ionization originates from a water molecule that is acidified by the coordination to both of the Li^+ ions. To confirm the complex of the incoming nucleophile with the TS for the alkyne protonation, we turned to NBO analysis of various structures along the computed reaction path.[28] The TS is indeed stabilized by a hyperconjugation of both of the TFSI's nitrogen lone pairs into the nascent p-orbital of the vinyl cation (Figure 3, $\mathbf{B^1}$ and $\mathbf{B^2}$). After the ionization this hyperconjugation intensifies ($\mathbf{C^1}$, $\mathbf{C^2}$) until coalescing into the TS of C-N bond closure ($\mathbf{D^1}$, $\mathbf{D^2}$). It occurs with a barrier of only 3.2 kcal/mol, due to a strong stabilization provided by a hydrogen bridge ($\mathbf{D^3}$),[29] that is the reminder of the acidic O-H bond, the protagonist of the first TS. Thus, both TSs mutually stabilize each other, resulting in a reduced activation energy for the whole process. This also explains the observed selectivities, for reaction only occurs if both

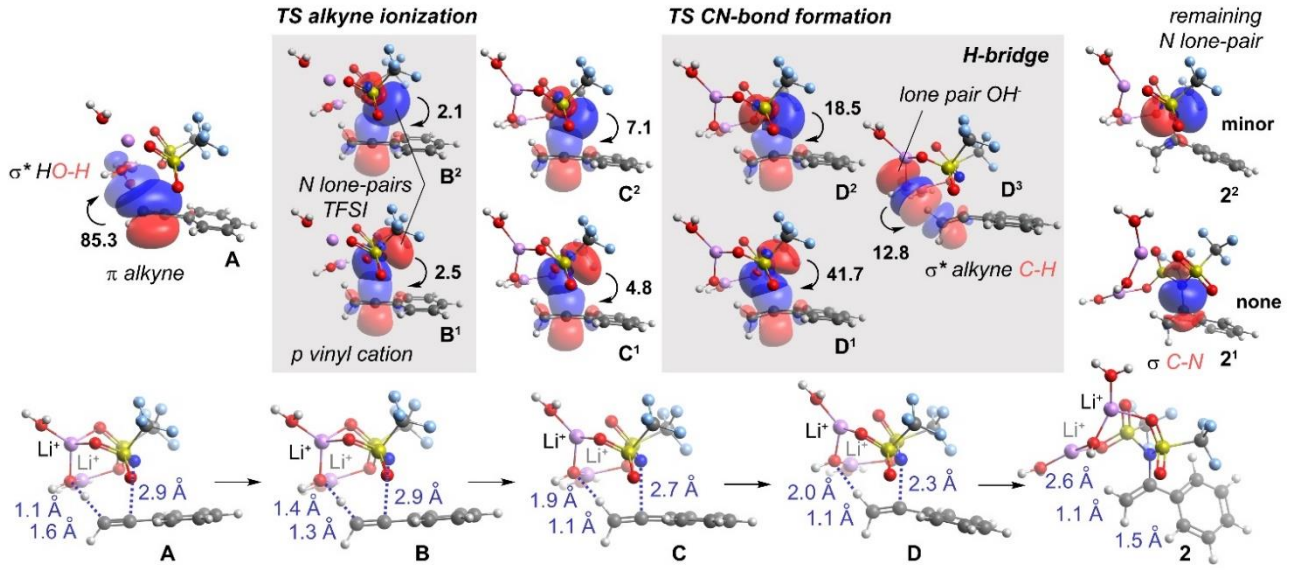


Figure 1. Hyperconjugative energies of NBO's were analyzed for various structures (model complex $Li_2NTf_2^+ \cdot 3\ H_2O$ with alkyne **1**; M06-2X/6-31+G(d,p)) along the reaction coordinate (see SI). The NBO 3.1 program was used to analyse selected structures and stationary points[28] Molecules and orbitals were rendered with Avogadro 1.2.0. Selected hyperconjugative energies are displayed in kcal/mol.

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TSs work in concert, which is only possible when the selectivity inducing geometry is assumed in both TSs.

For more insight into the role of the Li^+, the reaction coordinate of a reaction of $HNTf_2$ with phenylacetylene **1** was also computed (see SI, TS of ionization shown in Figure 2). In the absence of Li^+ no orbital of the vinyl cation was found to interact with the TFSI's (see SI), and as a result, we were unable to locate a TS for TFSI addition. Why are these interactions so markedly different in both cases? In the presence of Li^+ the TFSI is locked into a *cis*-conformation, in its absence it adopts the more favorable *trans*-conformation (Figure 2).[30] This leads to a significantly different orientation of the N-lone pairs in the respective TFSI anions after ionization. With *cis*-TFSI both lone pairs are close to, and in favorable orientation for an interaction with the p-orbital of the vinyl cation. With *trans*-TFSI all lone pairs are out of reach by several Å (see SI). As no addition occurs, only decomposition of the starting material is observed (*cf.* Table 1, entry 16). This clearly confirms that solely the favorable orientation of the TFSI's lone pairs, and thus the Assisted Vinyl Cation Formation govern the selectivity in this challenging reaction.

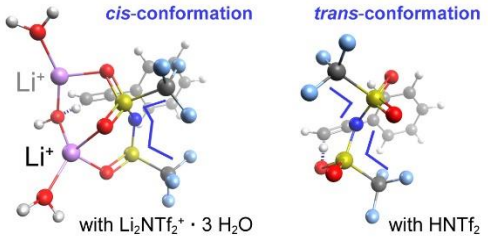

Figure 2: Computed TSs of alkyne **1** ionization in presence of the model complex $Li_2NTf_2^+ \cdot 3\ H_2O$ (left) or $HNTf_2$ (right) (M06-2X/6-31+G(d,p)).

In summary, Assisted Vinyl Cation Formation has been identified as a new concept for the chemo-, regio- and stereoselective addition of nucleophiles to alkynes. A first strategy for its realization was implemented, using a self-assembled Li^+-based supramolecular framework to guide the bistriflimide's nitrogen lone pair into the right position, while at the same time providing a proton for the alkyne ionization. That a selection of the bistriflimide anion among better nucleophiles was achieved, clearly demonstrates the efficiency of the concept. Furthermore, a strategy was developed, which allows for a straightforward confirmation of Assisted Vinyl Cation Formation's being responsible for an observed selectivity, via the analysis of transition state stabilizing hyperconjugative energies of NBO's. Into the bargain, the first protocol for the preparation of formerly inaccessible vinyl triflimides was developed.

Keywords: Vinyl Cation, Triflimides, *Syn*-Addition to Alkynes, Hydroaminosulfonation, Enzyme Mimicking Synthesis

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Layout 2:

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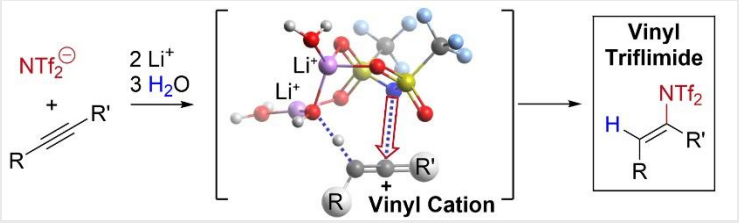
Survival of the weakest. A new concept for selectivity control in carbocation driven reactions has been identified, which allows for the chemo-, regio- and stereoselective addition of nucleophiles to alkynes: Assisted Vinyl Cation Formation. Mechanistic analysis elucidates its role in a seriously challenged borderline case and provides a straightforward strategy for the analysis of Assisted Vinyl Cation Formation.



*Author(s), Corresponding Author(s)**

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