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Regio- and Stereoselective *N*-addition to an Open Bromo Vinyl Cation

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ABSTRACT

A protocol for the synthesis of thus far inaccessible bromo vinyl triflimides is presented. Our previously reported concept of assisted vinyl cation formation was engaged to achieve both a protonation of relatively electron poor bromo alkynes and a reaction with high regio- and stereoselectivity. To the best of our knowledge, this is the first stereoselective addition of an *N*-nucleophile to an open β-halovinyl cation.

Introduction

Vinyl triflates are versatile building blocks, most prominently used as starting materials in transition- metal catalyzed cross-coupling reactions [1–6]. Vinyl triflimides may provide a similarly versatile reactivity, even though not much is known about the reactivity of these nitrogen-containing analogues [7]. Owing to our recently developed concept of assisted vinyl cation formation (AVCF), vinyl triflimides have become synthetically accessible for the first time [8].

The AVCF provides excellent chemo-, regio- and stereoselectivity *via* the formation of a supramolecular framework of at least two molecules of water and $LiNTf_2$ as a readily available bistriflimide (TFSI) source [8]. For an efficient AVCF, the transition state of the alkyne protonation must be stabilized by the hyperconjugation of both of the TFSI's nitrogen lone pairs into the nascent p-orbital of the vinyl cation. In turn, the second transition state, i.e. that of the C–N bond formation, must be stabilized by a hydrogen bridge between the β-proton and the Li-bound hydroxyl group, which remains from the acidified water molecule that serves as the proton source in the first step. It is this mutual stabilization of both transition states, that perfectly positions the N atom for addition to the vinyl cation (see Scheme 1C) and thus allows for a highly chemo- and regioselective reaction at an open vinyl cation.

Another versatile synthon in organic synthesis is the halogenated olefin. Nevertheless, the stereo- and regioselective synthesis of these building blocks is an ongoing challenge. Although there has been substantial investigation of the electrophilic activation of alkynes by dihalogens or their equivalents [9–14], the stereoselectivity of such reactions still suffers from the lack of control over the nature of the transient intermediate, which heavily depends on the electronics of its substituents. After initial electrophilic addition of the halogen, the formation of either a bridged (cyclic) onium ion such as structure **III** in Scheme 1A or an open vinyl cation such as structure **I** is established [15–19]. Bridged onium ions mostly allow for a reliable stereoselective *anti*-addition of the nucleophileas in examples B I (a) [20] and B I (b) [21]. Alternatively, the coordination of a π-electrophilic Lewis acidic transition metal such as the gold catalyst in example (c) [22] reliably triggers an *anti*-addition of the nucleophile. For open vinyl cations stereochemical outcomes are much less defined and a selective reaction is more difficult to achieve [15–19,23,24]. As shown in Scheme 1B, (d) the addition of the nucleophile may occur from either side of the open vinyl cation, solely governed by steric repulsion. Iodine addition may yield bridged onium ions, while bromine or chlorine additions tend to yield open β-halovinyl cations, in line with the bridging ability of the halogen [15–19,25,26]. The inclination towards a cyclic vs. open intermediate is further influenced by the substitution pattern of the vinyl cation, in that the more stabilizing the α-substituent directly at the positively charged carbon atom, the less likely a cyclic intermediate becomes [27–31]. Furthermore, both the α-and the

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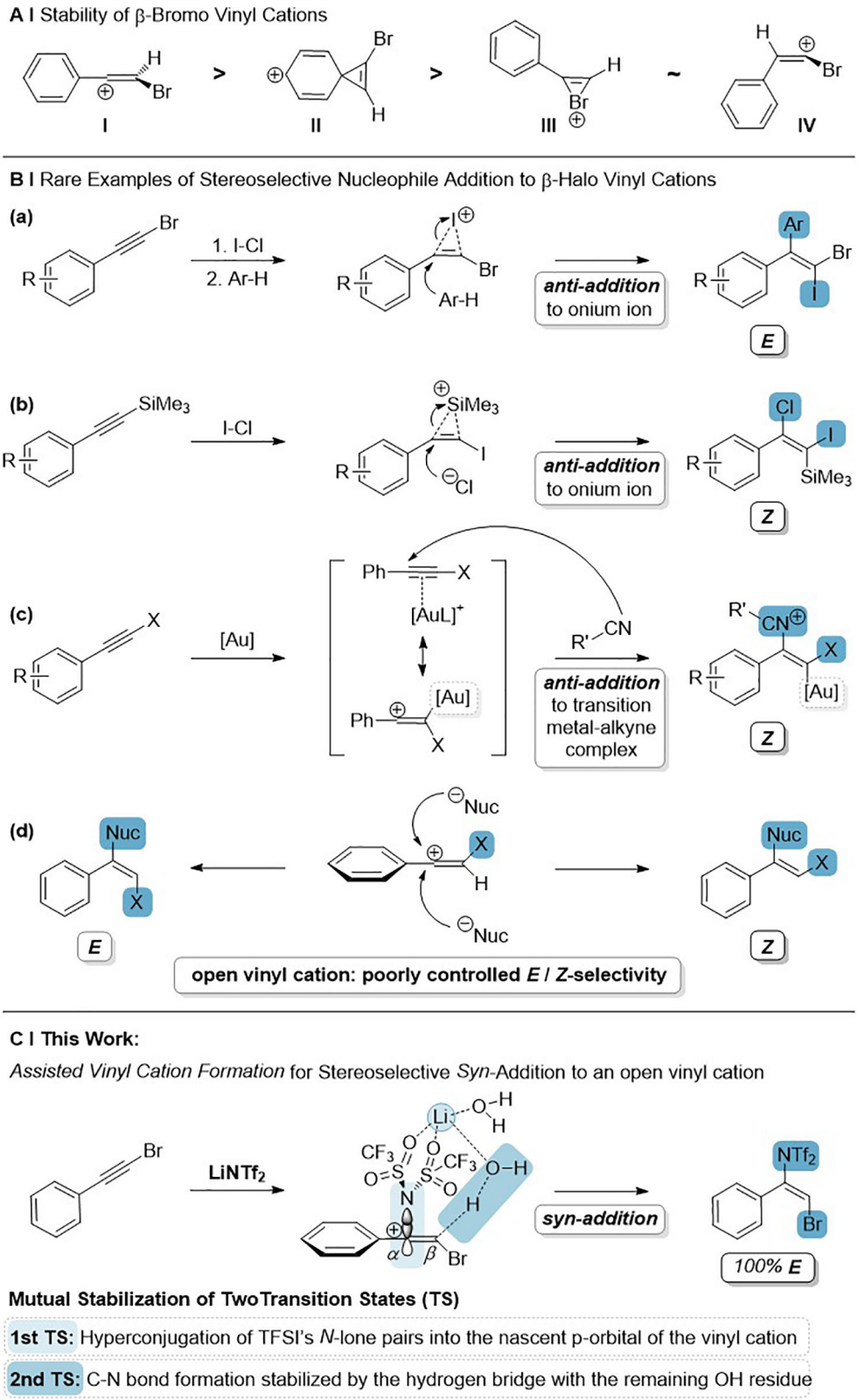


Scheme 1. Representative examples of reactions at β-halovinyl cations and reaction design.

β-substituent may also engage in neighbouring group participation itself and even evolve into a full-blown bridged species such as structure **II** in Scheme 1A or the transient silyl-onium species in example B I (a) [32,33].

Finally, the situation is further complicated by potential low barrier rearrangements (*e.g.* to structure **IV** in Scheme 1A) [15–19,34], which allow the vinyl cation to quickly equilibrate to its most stabilized substitution pattern.

A second route towards the same β-halovinyl cation intermediates may be the protonation of a haloalkyne. Even though the lower electron density in such alkynes makes this process more difficult, it has been realized in a few cases [35–37]. Although its origins remain to be elucidated in detail, excellent stereoselectivity was achieved in some of these reactions [36,37]. Nevertheless, to the best of our knowledge, a selective *syn*-addition of an N–H bond, that is extremely rare even for transition-metal catalyzed reactions, has never been achieved across a haloalkyne [38,22,39].

Hence, to showcase the first selective addition of a nitrogen nucleophile to an open β-halovinyl cation and at the same time provide synthetic access to highly interesting bromo vinyl triflimides we designed our reaction according to the following principles: 1) Aryl substituted bromo alkynes were chosen as substrates. Computational analysis suggests that α-phenyl-β-bromo vinyl cations generally favor open bromo vinyl cations and rearrangements are disfavored because the α-phenyl-β-bromo vinyl cation is already in its most stable form (see Scheme 1A) [40,41]. 2) AVCF has been used for efficient stereocontrol at the open vinyl cation [8].

Results and discussion

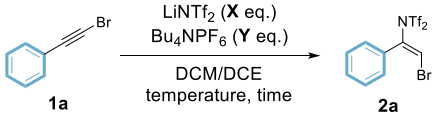
Given the importance of the self-assembly of a Li-TFSI-H_2O supramolecular framework from $LiNTf_2$ and adventitious water for an efficient assisted vinyl cation formation, we started our investigation by applying our previous, extensively optimized reaction conditions [8]. In a first attempt we were able to obtain only 21% of **2a** (determined *via* ^{1}H NMR analysis) (Table 1, Entry 1). This is likely due to the electron-withdrawing effect of the bromo substituent in **1a**, making the protonation of the acetylene significantly more challenging. Increasing the amount of the Bu_4NPF_6 additive, which aids $LiNTf_2$ solubilization and complex formation had no significant influence on the results (Entries 2–3). Surprisingly, prolonged stirring of the solution before the addition of acetylene **1a**, for establishing an equilibration of the Li-complex, had no effect on the reaction outcome (not shown).

A first improvement was achieved in the presence of additional TFSI. In fact, with a combination of an increased amount of $LiNTf_2$ (2.0 eq.) and a moderate amount of Bu_4NPF_6 (0.6 eq.) we were able to improve the product formationto 49% (Entry 4). Finally, a solvent and temperature screening revealed that a switch to dichloroethane and prolonged heating of the reaction mixture up to 60 °C leads to a significantly higher yield of 74% (Entry 5). Additional heating (up to 80 °C) with different amounts of $LiNTf_2$ did not prove beneficial (Entries 6–8).

With the optimized conditions in hand (Table 1, Entry 5) we turned our attention to evaluating the reaction scope. Various bromo alkynes bearing different electronic moieties on the aryl substituent were subjected to AVCF (Table 2). Gratifyingly, aromatic acetylenes with both, electron-withdrawing or electron-donating aryl groups gave bromo vinyl triflimides **2a–o** in moderate to good yields and excellent selectivity. We indeed obtained all products regioselectively as a single (*E*)-isomer only.

The electronic bias on both C atoms of the alkyne is important for nucleophilic addition of the triflimide anion to the vinyl cation intermediate. Firstly, the difference in cation stabilizing ability between the substituents on the two C atoms ensures regioselective addition at the position adjacent to the aryl substituent [15–19]. Alkynes with moderately electron-withdrawing aryl substituents in the *para*-position gave triflimides **2f**,**g**,**l** in good yields (54–69%) since their vinyl cation intermediates are still stabilized enough. However, alkynes bearing stronger electron-withdrawing groups, such as the trifluoromethyl group in **1h**, show only moderate triflimide yields (18%). The strong electron-withdrawing effect of the trifluoromethyl substituent destabilizes the α-aryl-β-halovinyl cation [27–31], thus impeding the protonation step. Notably,

Table 1
Optimization of the reaction conditions.



1a **2a**

Entry[a]	X	Y	T [°C]	t (h)	Yield (%)[b]
1	1.5	0.3	rt	19	21
2	1.5	0.6	rt	19	28
3	1.5	0.9	rt	19	30
4[c]	2.0	0.6	rt	19	49
5[c]	2.0	0.6	60°C	24	74
6[c]	1.5	0.6	60°C	24	52
7[c]	2.0	0.6	80°C	24	58
8[c]	1.5	0.6	80°C	24	64

Entry[a]	X	Y	T [°C]	t [h]	Yield **2a** [%][b]
1	1.5	0.3	rt	19	21
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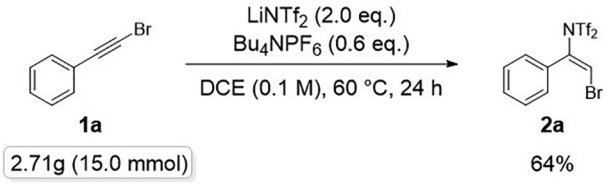
3	1.5	0.9	rt	19	30
4[c]	2.0	0.6	rt	19	49
5[c]	2.0	0.6	60 °C	24	74
6[c]	1.5	0.6	60 °C	24	52
7[c]	2.0	0.6	80 °C	24	58
8[c]	1.5	0.6	80 °C	24	64

[a] Reagents and conditions: **1a** (0.2 mmol, 1.0 eq), $LiNTf_2$ (**X** eq.), Bu_4NPF_6 (**Y** eq.), CH_2Cl_2 (2 mL).
[b] Yield determined *via* ^{1}H NMR spectroscopy with Bu_4NPF_6 as an internal standard.
[c] Reaction was performed in 1,2-dichloroethane (DCE) (2 mL).

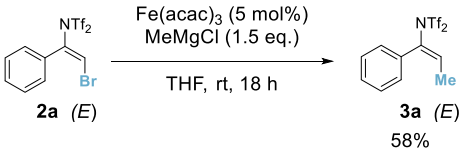
the influence of the position of either electron-donating (**1i**–**k**) or electron- withdrawing groups (**1l**–**n**) on the arene is less important; only *ortho*-substitution with a methoxy group lead to a diminished yield of **2k** (17%). In line with our previous work, alkynes **1i**–**k** with electron-donating groups on the aromatic moiety led to only average product formation despite the enhanced positive charge delocalization. The strong stabilization may result in an increased lifetime of the open vinyl cation, leading to side products and decomposition. Nevertheless, the very electron-rich heteroaromatic alkyne **1o** was a suitable substrate (45%). Finally, non-aryl substituted triflimide **2p** was synthesized in moderate yield (27%), emphasizing the efficiency of the assisted vinyl cation formation. A limitation of the method is reached when the alkyne substituent is a simple alkyl group. Its comparatively poor cation stabilizing ability prohibits bromo alkyne protonation and no conversion of these substrates was observed.

In our previous work, we performed extensive mechanistic analysis showing that the mutual stabilization of the transition states of alkyne protonation and C–N bond formation results in a selective *syn*-addition [8]. Given that poor selectivity is expected for the predicted open α-aryl-β-halovinyl cation and the triflimide adds selectively, yielding the (*E*)-bromo triflimide as the unrivaled *syn*-addition product, strongly indicates that the reaction proceeds effectively *via* the same mechanism of assisted vinyl cation formation.

The efficient self-assembly of a supramolecular framework of $LiNTf_2$ and water is crucial for an efficient reaction. Such a process may be influenced by a multitude of factors and prove difficult in reactions on increased scale. Hence, to verify the applicability of this protocol with larger amounts of substrate, a gram-scale synthesis (Scheme 2) was performed, yielding phenyl triflimide **2a** in an only slightly lower 64% yield.



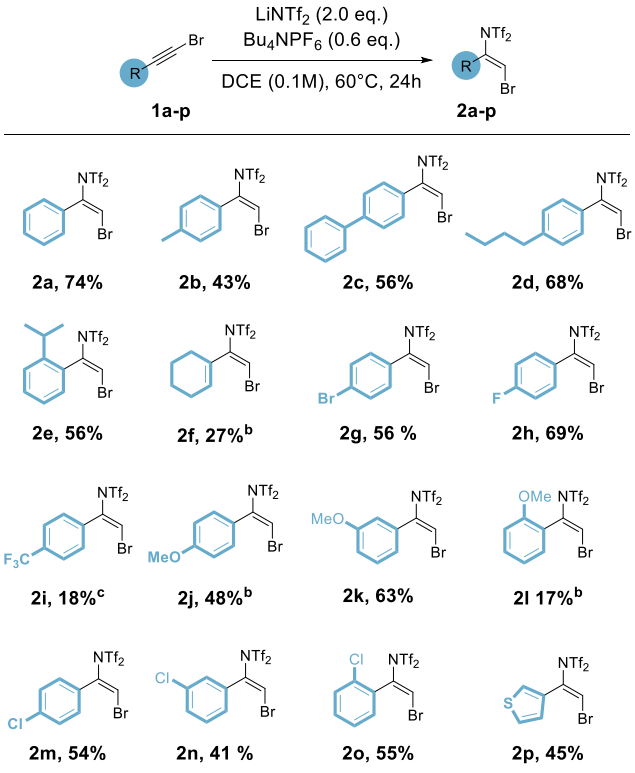
Scheme 2. Gram-scale synthesis of bromo vinyl triflimide **2a**.



Scheme 3. Functionalization of **2a** *via* iron catalyzed cross-coupling reaction.

As already stated above, very little is known about the reactivity of vinyl triflimides. Bromo vinyl triflimides are completely unexplored, naturally, as this is the first protocol providing synthetic access. Because it may demonstrate a first hint of their potential as building blocks, the derivatization reaction that was necessary to unambiguously prove the (*E*)-geometry of the olefin's substitution pattern is shown in Scheme 3. In this reaction the bromine moiety is substituted by a methyl group under preservation of the stereo information in an iron catalyzed cross-coupling reaction [42].

Table 2
Scope of bromo vinyl triflimides.



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[a]Reagents and conditions: **1a-p** (0.5 mmol), $LiNTf_2$ (1.0 mmol), Bu_4NPF_6 (0.6 mmol), DCE (5 mL), 60 °C, 24 h.
[b]Reaction at room temperature.
[c]80 °C, 76 h. The stereochemistry was determined by NOE-experiments (see ESI).

Conclusion

In summary, our previously reported concept of assisted vinyl cation formation proved suitable for an unprecedented stereoselective addition of an *N*-nucleophile to an open β-halovinyl cation. At the same time, a rare case of haloalkyne protonation was realized. Thereby, bromo vinyl triflimides have become synthetically accessible for the first time.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153173.

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