General, Straightforward, and Atom-Economical Synthesis of Vinyl Triflimides

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Dedicated to Prof. Barry M. Trost in celebration of his 80th birthday.

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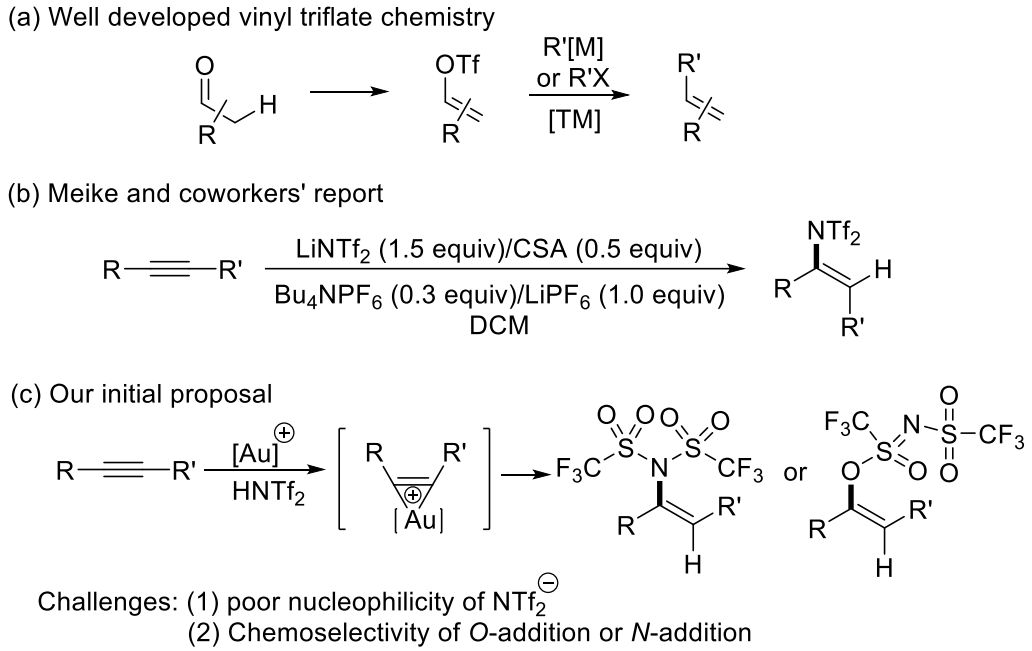
Abstract:

Vinyl triflimides were only accessible recently and their chemistry is yet to be discovered. Herein, we describe a general, straightforward and atom-economical synthesis of these materials from alkynes and triflimide. A vast array of terminal and internal alkynes with broad spectrum of functionalities could be employed to generate various di- and trisubstituted vinyl triflimides regiospecifically with high to specific stereoselectivity. Moreover, the protocol could be conducted on gram scale using terminal and internal alkynes. Preliminarily attempts to probe the unknown reactivity of vinyl triflimides revealed part of its chemical properties.

Vinyl triflates are readily accessible materials[1] and have been widely utilized in organic synthesis,[1a, 2] notably the cross-coupling reactions (Scheme 1a).[3] To the contrary, the chemistry and applications of vinyl triflimides remained unrevealed, presumably due to the limited access to such materials.[4] Recently, Meike and coworkers demonstrated that these materials could be prepared from alkynes using $LiNTf_2$ as the triflimide anion (NTf_2^-) source and Bu_4NPF_6, CSA, and $LiPF_6$ as additives, which enabled access to various vinyl triflimides (Scheme 1b).[4a, 4c] Along the same line, we envisioned that vinyl triflimides might be synthesized using alkynes and triflimide ($HNTf_2$) under gold catalysis conditions in a straightforward and atom-economical fashion[5] (Scheme 1c). Consequently, two major challenges are posed for this proposal. Firstly, the low electron

density nature of the nitrogen atom in $HNTf_2$ and steric bulk around the nitrogen atom renders it a rather weak nucleophile for addition reactions. Indeed, by virtue of such properties, NTf_2^- has been intensively applied as the innocent counterions for cationic gold catalysts.[6] Secondly, the proposed $HNTf_2$ addition reactions might suffer from chemoselectivity issues of *O*-addition or *N*-addition since both reaction patterns are viable in literature with *O*-addition even more favored in some cases.[7]

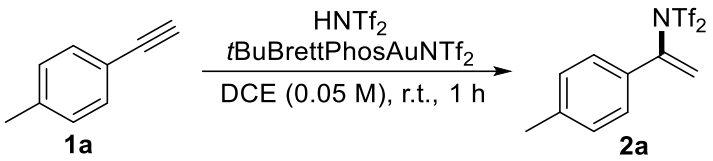


Scheme 1. Research background and our initial proposal

With the aforementioned questions in mind, we directly probed the prospect of our proposal using *p*-tolylacetylene **1a** as the model substrate and *t*BuBrettPhosAuNTf$_2$ as the catalyst (Table 1). Delightfully, the addition reaction proceeded smoothly at room temperature, furnishing the desired product **2a** in 85% yield (entry 1). Increasing the amount of $HNTf_2$ was detrimental (entry 2,3) and significantly decomposed the product while decreasing the amount of gold catalyst engendered comparable results (entry 4,5). Much to our astonishment, the reaction worked identically efficiently even without the gold catalyst (entry 6), indicating that the reaction proceeded via direct protonation of the alkyne to generate vinyl cation[8] followed by NTf_2^- addition. This unexpected discovery is far beyond our initial reaction proposal and the direct coupling of alkyne and $HNTf_2$ was

only known for highly electron rich and reactive aryl ynol ethers, a rather specialized system with only moderate to low yields.[4b]

Table 1. Reaction discovery for terminal alkynes.

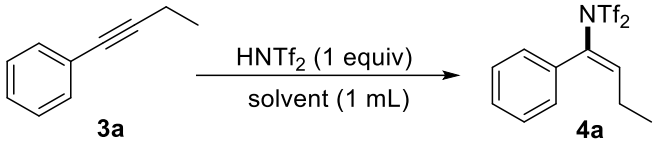


Entry	$HNTf_2$ (equiv)	[Au] (equiv)	Yield[a]
1	1	0.05	85%
2	2	0.05	45%
3	10	0.05	40%
4	1	0.01	88%
5	1	0.025	87%
6	1	0	86%

[a] 0.05 mmol scale. Yield was determined by crude ^{1}H-NMR analysis using dibutyl phthalate as internal standard.

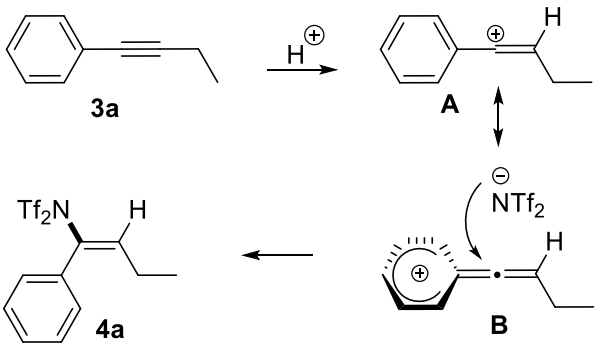
Efforts were turned towards realizing the metal free reactions of internal alkynes and $HNTf_2$ (Table 2). Indeed, the coupling between 1-phenyl-1-butyne **3a** and $HNTf_2$ occurred smoothly at room temperature, giving vinyl triflimide **4a** in 80% yield (E/Z 7.8/1) (entry 1). Interestingly, the regio- and stereoselectivity outcome was consistent with Meike and coworkers' report.[4a] Such selectivities presumably originated from the stabilization effect of the aryl group on the neighbouring vinyl cation of **A** via an allene like resonance structure **B**, where the bulky NTf_2^- attacked from the sterically less hindered side to yield the *syn* adduct **4a** as the major product. [8e-g, 9] Diluting the reaction was beneficial to both yield and stereoselectivity (entry 2,3), presumably by slowing down the acid induced decomposition and olefin isomerization. Another interesting fact of this transformation is that solvent played a critical role. Solvents with Lewis basic sites such as acetonitrile and tetrahydrofuran completely terminated the reaction (entry 4), while less polar and less coordinating solvents such as benzene, chlorobenzene, fluorobenzene and benzotrifluoride promoted the reaction to certain extents (entry 5-8).

Table 2. Reaction discovery and optimization for internal alkynes.



Entry	Solvent	Temp./Time	Yield (E/Z)[a]
1	DCM	r.t./1 h	80% (7.8/1)
2	DCM[b]	r.t./1 h	51% (6.3/1)
3	DCM[c]	r.t./1 h	89% (8.7/1)
4	MeCN/DME/THF/ 1,4-dioxane/MTBE/ Pyridine/DMSO/DMF	80 °C/12 h	N. R.
5	benzene	40 °C/4 h	63% (6.9/1)
6	Chlorobenzene	r.t./4 h	72% (6.9/1)
7	Fluorobenzene	r.t./3 h	73% (6.3/1)
8	Benzotrifluoride	r.t./3 h	85% (5.5/1)

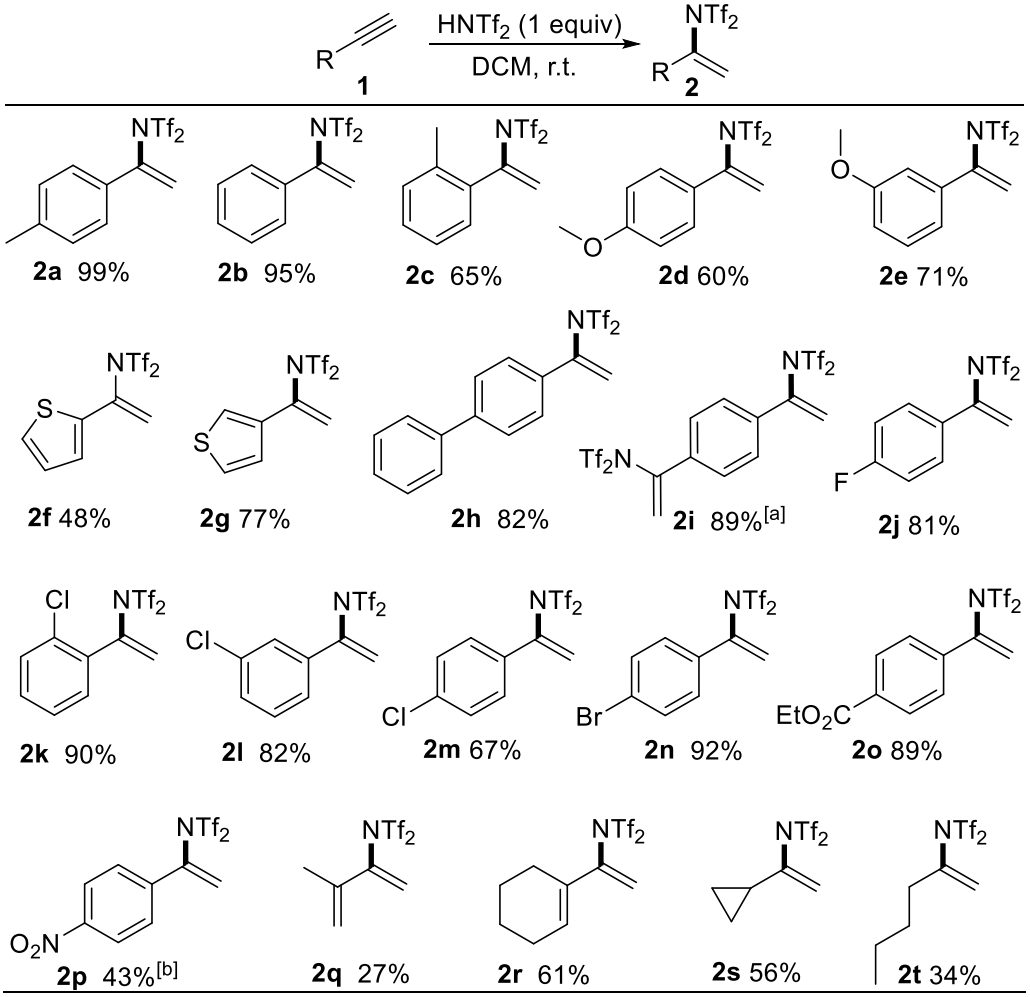
[a] 0.05 mmol scale. Yield and the E/Z ratio were determined by crude ^{1}H-NMR analysis using dibutyl phthalate as internal standard. [b] 0.5 mL. [c] 2.0 mL.



Scheme 2. Rationale for the regio- of stereoselective outcome for the reaction of **3a**.

With the optimal reaction conditions established, the substrate scope was systematically investigated. Aryl substituted terminal alkynes proved to be generally suitable coupling partners, furnishing vinyl triflimides in moderate to excellent yields (Scheme 3). Notably, the phenylacetylene **1b** and *p*-tolylacetylene **1a** cases enabled near

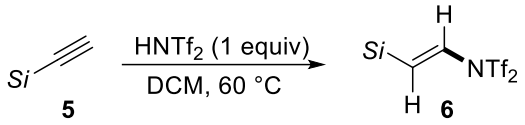
quantitative yield while steric bulkier *o*-tolylacetylene **1c** diminished the yield to 65%. Electronically, the substituents on the phenyl rings were widely ranged from the representative electron donating methoxy group **2d** to the electron withdrawing nitro group **2p**. Halogens were well tolerated at the *ortho*, *meta*, and *para* positions on the phenyl rings, providing handles for late stage functionalizations (**2j-2n**).[10] In addition, medicinally relevant heterocycles such as thiophenes were compatible in this protocol (**2f, 2g**). Gratifyingly, the terminal alkynes were not restricted to aryl ones. Vinyl (**1q, 1r**) and alkyl (**1s, 1t**) substituted terminal alkynes reacted with $HNTf_2$ as well, albeit with moderate to low yields owing to their poor stabilization effect on the vinyl cations compared to the aryl ones.



[a] 2 equiv of $HNTf_2$ used. [b] DCE as solvent, 80 °C.

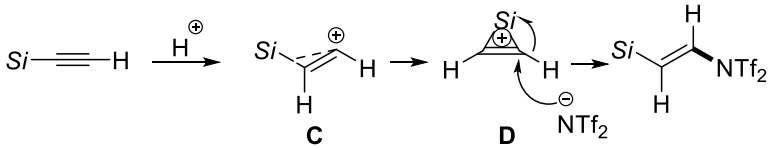
Scheme 3. Scope of aryl, vinyl and alkyl substituted terminal alkynes.

Interestingly, when silyl substituted terminal alkynes **5** were utilized, anti-Markovnikov type products **6** were formed in moderate to excellent yields with exclusive *E* configuration. One could readily anticipate the utility of vinyl triflimide **6** as an elegant two carbon building block with both a protected amine group and a silyl group, which, especially the TMS group, could be easily transformed through electrophilic substitution, oxidation and cross coupling reactions into other functionalities.[11] The specific regio- and stereoselectivity outcome could be attributed to the *β*-silicon effect as depicted in Scheme 5,[12] where the vinyl cation of **C** was stabilized by the neighbouring carbon-silicon bond to form species **D** and then NTf_2^- attacked from the opposite side to the silyl group. Owing to the *β*-silicon effect, varying the silyl groups only influenced the yield but not the regio- and stereoselectivity.



Entry	*Si*	Time	Yield	Entry	*Si*	Time	Yield
1	TMS	4h	30%	3	TBS	6h	55%
2	TES	6h	62%	4	TIPS	8h	92%

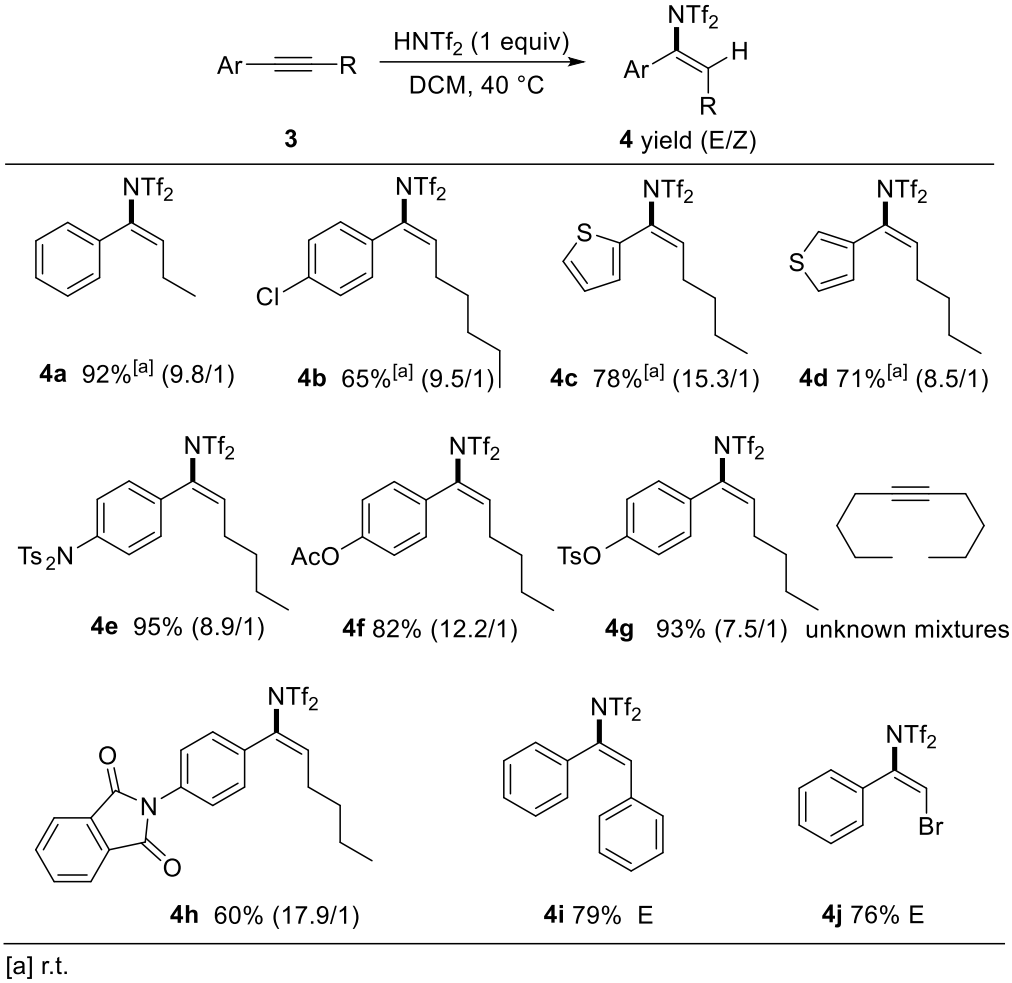
Scheme 4. Scope of silyl substituted terminal alkynes.



Scheme 5. Rationale for the regio- of stereoselective outcome for the reaction of **5**.

Besides terminal alkynes, internal alkynes such as aryl/aryl substituted alkynes reacted facilely with $HNTf_2$, generating trisubstituted vinyl triflimides with specific regioselectivity and high stereoselectivity (Scheme 6, **4a-4h**). The substrate scope could be further expanded to diphenylacetylene and bromophenylacetylene, efficiently furnishing more

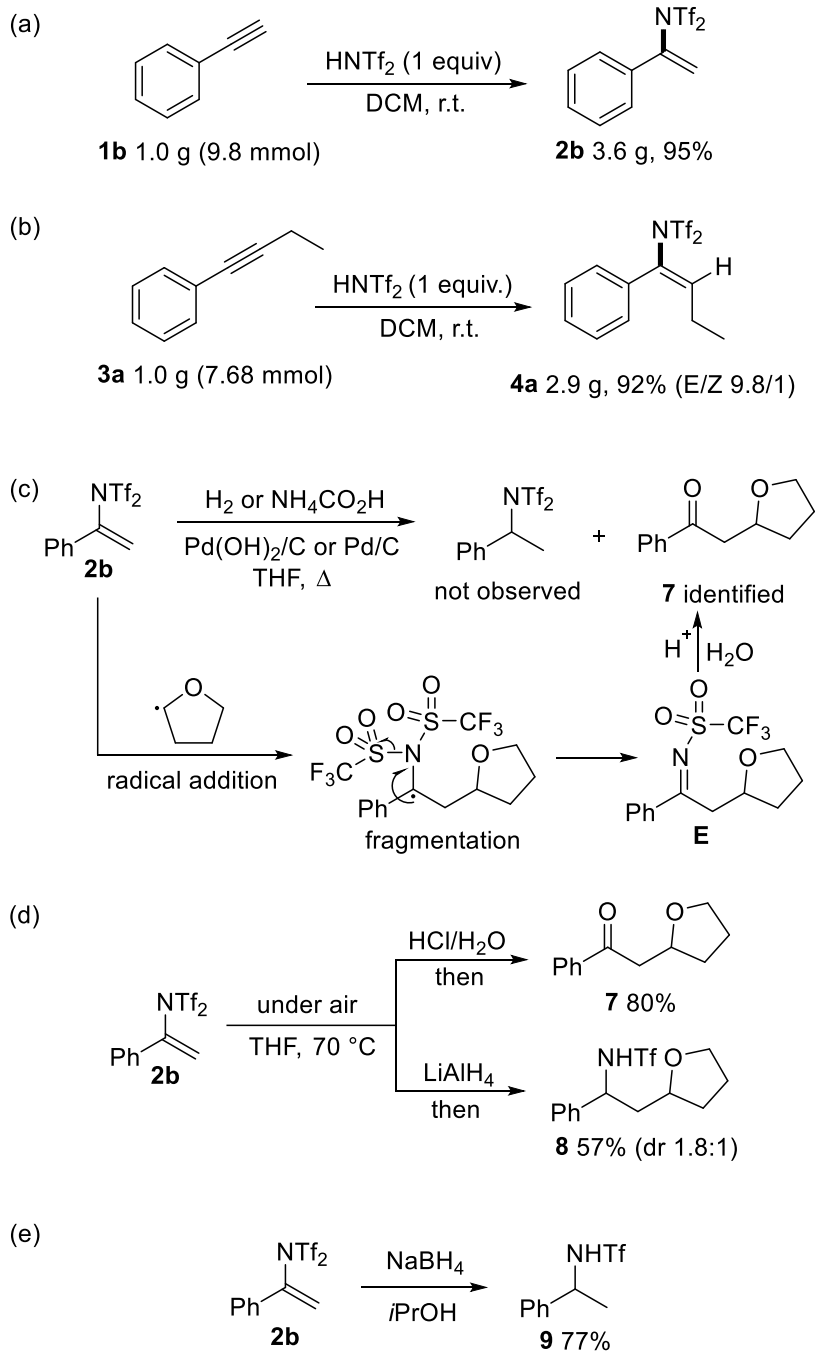
functionalized vinyl triflimides (**4i, 4j**) with exclusive *E* configuration. Unfortunately, the reaction between alkyl/alkyl substituted internal alkynes such as 5-decyne with $HNTf_2$ gave no desired product but mixtures of unknown compounds.



[a] r.t.

Scheme 6. Scope of internal alkynes.

To highlight the application potential of this atom-economical transformation for organic synthesis, gram-scale reactions were performed on both a terminal alkyne (phenylacetylene **1b**) and an internal alkyne (1-phenyl-1-butyne **3a**), both giving comparable results to the corresponding small scale reactions (Scheme 7a,b). With gram quantities of vinyl triflimides prepared, we probed the reactivities of such materials aiming to reveal their undiscovered chemistry. Standard olefin manipulations such as hydrogenation,[13] hydroboration/oxidation,[14] and epoxidation[15] were performed on vinyl



Scheme 7. Gram-scale synthesis and transformations of vinyl triflimides.

triflimide **2b**. Surprisingly, distinct from the parent styrene, this triflimide substituted styrene **2b** was rather resistant to these operations with starting materials either intact or decomposed. During the attempts to hydrogenate the double bond of **2b**, THF functionalized ketone **7** was identified, which might originate from the THF radical

addition/fragmentation/hydrolysis sequence (Scheme 7c). Indeed, the vinyl triflimide **2b** could be fully consumed by simply stirring in THF under air at 70 °C.[16] When the reaction mixture was hydrolyzed with aqueous hydrochloride, the THF functionalized ketone **7** was isolated in 80% yield. On the other hand, when the reaction was worked up with $LiAlH_4$, THF functionalized amine **8** was isolated as a pair of inseparable diastereomers, shedding light on the intermediacy of imine **E**. Furthermore, the vinyl triflimide **2b** could be cleanly reduced into secondary amine **9** by sodium borohydride, thus realizing a two-step transition metal free reductive hydroamination of phenylacetylene.

In summary, we have established a general, straightforward and fully atom-economical synthesis of vinyl triflimides from alkynes and $HNTf_2$. In contrast to the previous systems, our strategy does not require the use of aryl ynol ethers or the use of multiple additives. A vast array of readily accessible terminal and internal alkynes with broad spectrum of functionalities could be employed and various di- and trisubstituted vinyl triflimides were generated regiospecifically with high to specific stereoselectivity. Gram-scale reactions could be performed on both terminal and internal alkynes, highlighting its synthetic potential for organic synthesis. Moreover, preliminary attempts to probe the unknown reactivity of vinyl triflimides were implemented using vinyl triflimide **2b** as a model substrate, which revealed its distinct chemical properties from styrene. The new synthetic method described here is expected to set the stage for the discovery of new chemical transformations of vinyl triflimides. Application of these materials in the synthesis of biologically active compounds and analogs of natural products are currently underway.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: vinyl triflimide • hydroamination • triflimide • alkyne transformation • atom economy

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