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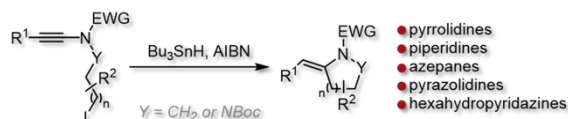
Radical Cyclization of Ynamides to Nitrogen Heterocycles

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Supporting Information Placeholder

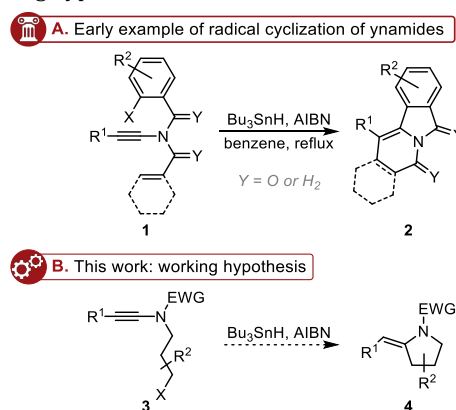


ABSTRACT: An efficient radical cyclization of suitably functionalized ynamides to nitrogen-containing heterocycles is reported. Upon reaction with tributyltin hydride in the presence of catalytic amounts of AIBN in toluene at 80 °C, a range of ynamides bearing a *N*-iodopropyl chain could be smoothly cyclized, in a highly regio- and stereo- selective manner, to the corresponding 2-arylidene-pyrrolidines in good to excellent yields. The exocyclic double bond was in addition shown to be an excellent anchor for further chemical diversification and the generality of this radical cyclization could be highlighted by its extension to the synthesis of other nitrogen heterocycles including piperidines, azepanes, pyrazolidines and hexahydropyridazines.

Over the last two decades, ynamides have emerged as remarkably efficient and versatile building blocks.¹ Their peculiar reactivity combined to their stability, especially when compared to the more labile ynamines,² have indeed caught the attention of an ever-growing number of research groups worldwide. Combined with the development of robust and broadly applicable methods for their preparation,^{3,4} this has resulted in the design of an impressive number of reactions whose successful development can be attributed to the unique reactivity of these nitrogen-substituted alkynes that usually leads to exceptionally high levels of regioselectivity.⁵ They have indeed been shown over the years to be excellent substrates in a range of processes including, among others, cycloadditions, carbometallations, metal-mediated coupling reactions or rearrangements, cycloisomerizations, RCM or sigmatropic rearrangements.¹ With regards to all reactions developed from ynamides, while their use in pericyclic,⁶ metal-mediated, anionic⁷ and cationic⁸ processes has been extensively investigated, radical transformations still remains understudied, despite their strong potential.⁹ The inherent polarization of the triple bond indeed allows for levels of regioselectivity that cannot be attained with other alkynes and, combined with rules for radical ring closures,¹⁰ intramolecular radical addition to ynamides provides excellent opportunities in heterocyclic synthesis. Based on these simple considerations, on our long-standing interest in the chemistry of ynamides,¹¹ on pioneering reports by the Malacria and Courillon group on radical cyclization of ynamides **1** to **2** (Scheme 1A)^{9b} and on our recently reported radical cyclization of *N*-iodoethyl-ynamides to

azetidines,¹² we envisioned that properly substituted ynamides such as **3** bearing a halopropyl chain might be excellent substrates for radical cyclization, which would afford a straightforward entry to pyrrolidines **4** bearing an exocyclic double bond that could be useful for further chemical diversification (Scheme 1B).

Scheme 1. Early examples of radical cyclization of ynamides and working hypothesis.



With this working hypothesis in mind, we first evaluated the reactivity of a set of representative ynamides **3** bearing different electron-withdrawing and radical precursor groups towards the radical cyclization. These ynamides **3** were therefore first reacted under standard conditions for the generation of radical species based on the use of tribu-

tyltin hydride and AIBN (Figure 1). The nature of the electron-withdrawing group was found to have a dramatic impact on the efficiency of the radical cyclization, the use of tosyl-protected ynamines bearing iodo-, bromo- or phenylthiocarbonate- propyl chains resulting in extensive degradation and no trace of the desired pyrrolidine **4** could be detected in the crude reaction mixtures.

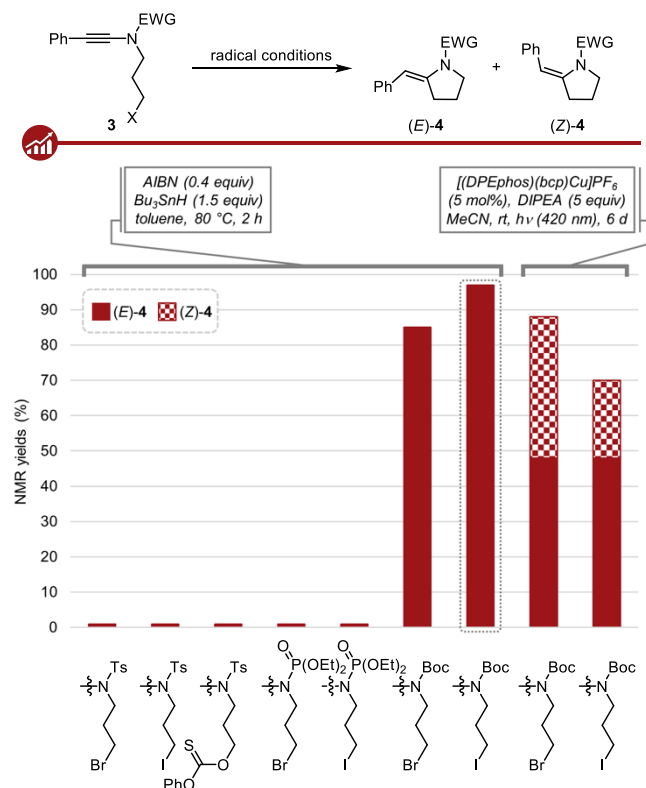


Figure 1. Optimization of the radical cyclization of ynamides to pyrrolidines.

While switching to phosphoramidates¹³ did not bring any improvement, a clean cyclization was achieved starting from Boc-protected ynamines. A better yield could actually be obtained from the iodinated derivative compared to its brominated analogue (97 vs 85% yields) and, importantly, the cyclization was moreover found to be fully diastereoselective, the *E* isomer (*E*)-**4** being obtained exclusively.¹⁴ As a note, the use of a copper-based photoredox catalyst, which we previously demonstrated to be efficient for intramolecular radical additions to ynamides,^{9i,12} resulted in efficient cyclizations, but with low levels of diastereoselectivity and moreover required prolonged reaction times for the cyclization to go to completion.

With the optimal substrates and conditions in hand, we next moved to the study of the scope and limitations of this radical cyclization of ynamides providing an original entry to pyrrolidines. A set of ynamides **3**, readily prepared by alkylation of protected aminopropanol derivatives with bromoalkynes^{4a} followed by deprotection/iodination, were therefore treated with tributyltin hydride in the presence of catalytic amounts of AIBN in toluene at 80 °C for 2 hours. Results summarized in Figure 2 highlight the broad scope of the cyclization, the desired pyrrolidines being obtained in good yields and stereoselectivities, in favor of the *E* isomer, in most cases. The reaction was found to be efficient with

aryl-substituted ynamides, regardless of the electronic properties of the aromatic ring. Electron- rich (**4b-e**) and poor (**4f,g**) aromatic rings were indeed well tolerated and the presence of a chloride in **4f** moreover offers further opportunities for post-functionalization. A thiophene (**4k**) was also found to be compatible with the radical cyclization, a mixture of isomers being however obtained in this case, as with biphenyl derivative **4j**. Diaryl-pyrrolidines such as **4l** can also be obtained, provided that the reaction time was extended to reach full conversion, but the absence of a radical stabilizing group on the starting ynamide totally inhibited the reaction, as shown with the unsuccessful cyclization to **4m**. Moreover, due to the variety of aminopropanol derivatives available, our radical cyclization of ynamides offers an efficient entry to polysubstituted pyrrolidines such as **4n** and **4o**, the presence of the methyl substituent close to the reacting center in the latter resulting however in a loss of stereoselectivity, a mixture of *E* and *Z* isomers being obtained in this case. Finally, it ought to be mentioned that the radical cyclization is not limited to Boc-protected ynamines, as highlighted by the cyclization to mesyl-substituted pyrrolidine **4p** obtained, here again, as a single isomer. Importantly, scaling up the reaction did not affect its efficiency since the cyclized products **4a** and **4p** could be obtained on a gram scale with similar yields (94% and 74%).

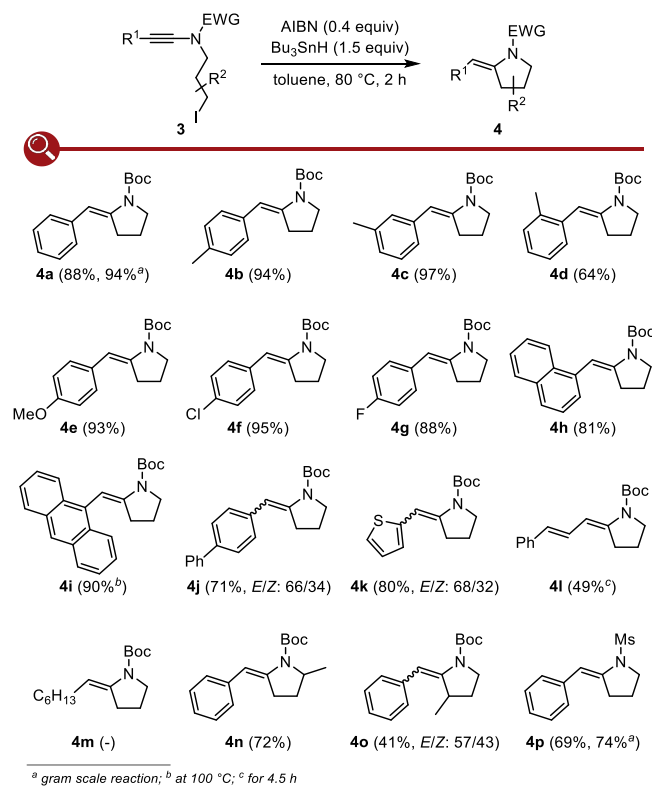


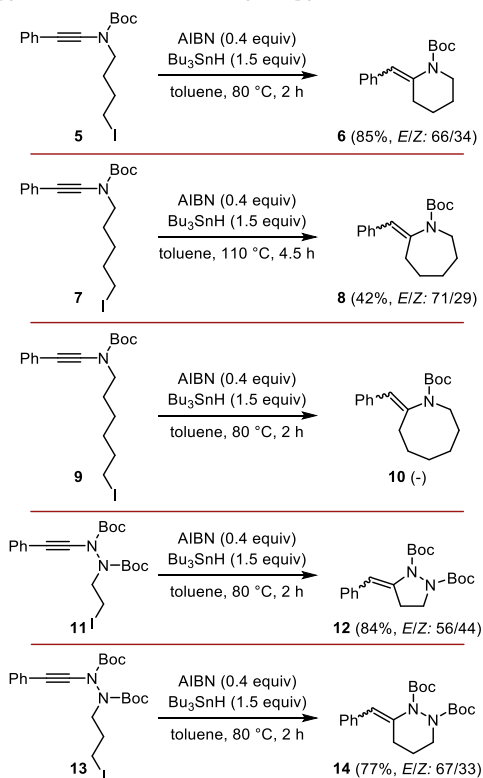
Figure 2. Scope of the radical cyclization of ynamides to pyrrolidines.

In order to further extend the scope of the intramolecular radical addition to ynamides, we next envisioned using this strategy to the preparation of other nitrogen heterocycles (Scheme 2). The length of the chain between the ynamide and the iodine atom was therefore first extended in order to obtain higher ring systems. This turned out to be actually

rather fruitful, benzylidene- piperidine **6** and azepane **8** being obtained from the corresponding ynamides **5** and **7** in good and moderate yields, respectively, and as single regioisomers resulting from 6- and 7- exo-dig cyclizations. Compared to the pyrrolidine series, the lower ring strain in these higher nitrogen heterocycles however results in reduced levels of stereoselectivity. While the radical cyclization of ynamides was found to be efficient for the synthesis of 5-, 6- and 7- membered ring nitrogen heterocycles, higher ring systems could however not be obtained, the radical activation of *N*-iodohexyl-ynamide **9** resulting in competing reduction, azocane **10** being thus undetectable in the crude reaction mixture.

The cyclization was found to be equally efficient starting from *N*-alkynyl-hydrazides, readily prepared according to the Batey's procedure,¹⁵ and in which the length of the carbon chain between the hydrazide and the iodine atom can be easily modulated. As highlighted in Scheme 2, pyrazolidine **12** and hexahydropyridazine **14** can be obtained in good yields, although with moderate levels of stereoselectivity, by radical cyclization of the corresponding yne-hydrazides **11** and **13**, the electron-rich exocyclic double bond in these compounds being a useful and versatile handle for further functionalization.

Scheme 2. Radical cyclization of ynamides to piperidines, azepanes, pyrazolidines and hexahydropyridazines.



After studying in detail the scope of our intramolecular radical addition to ynamides for the formation of a variety of nitrogen heterocycles, and in a final effort to demonstrate its synthetic usefulness, we finally evaluated the reactivity of the electron-rich exocyclic double bond installed in the course of the cyclization. With this goal in mind, a set of representative substrates **4a**, **6**, **8** and **14** was first subjected to

catalytic hydrogenation, a reaction that was best performed using palladium on carbon in methanol under a slight pressure of hydrogen. As demonstrated with representative results summarized in Figure 3 (top), the reduction of the exocyclic double bond proceeded smoothly to afford the corresponding saturated pyrrolidine **15**, piperidine **16**, azepane **17** and hexahydropyridazine **18**. In addition to the reduction of the alkene, its electron-rich and polarized nature enables its activation with electrophiles yielding a transient activated iminium ion that can be then trapped *in situ* with various nucleophiles. In this perspective, Boc- and Ms-protected pyrrolidines **4a** and **4p** were reacted with two representative electrophilic halogenating agents, namely NBS and NFSI (Figure 3, bottom). The reaction of **4p** with NBS was found to strongly depend on the nature of the solvent since an allylic bromination to **19** was observed in chloroform while the use of dichloromethane enabled the addition of the N-Br bond across the double bond, affording **20** as a mixture of diastereoisomers. In a similar vein, and following a procedure from the Hsung group,¹⁶ treatment of **4a** with NFSI in the presence of water in acetonitrile at 40 °C initiated an activation of the enamide in **4a** by the electrophilic fluorination agent followed by trapping of the resulting highly reactive iminium ion by water to afford **21** with a reasonable level of diastereoselectivity. Finally, the double bond in **4a** could also be smoothly dichlorocyclopropanated to spirocyclic pyrrolidine **22** with chloroform and sodium hydroxide under phase-transfer conditions.

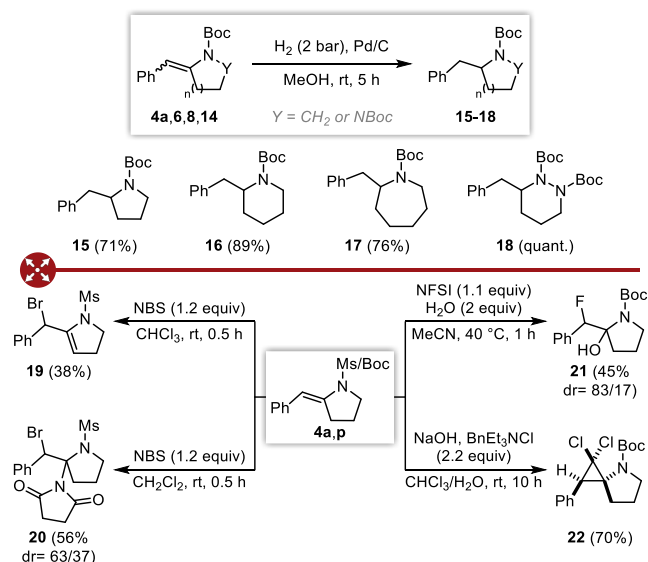
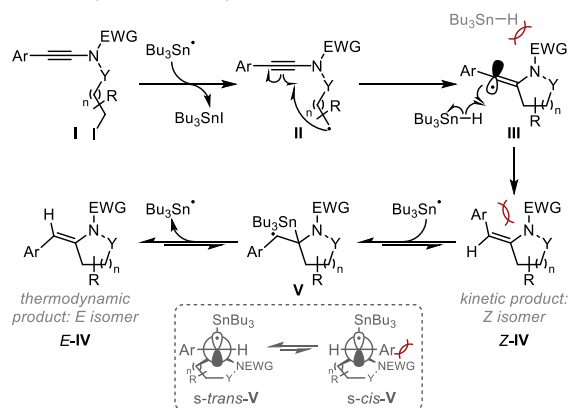


Figure 3. Chemical diversification of representative 2-benzylidene nitrogen heterocycles.

We finally focused our attention on the mechanism of this intramolecular radical addition to ynamides. While the mechanism itself, depicted in Scheme 3, is definitely not surprising and clearly follows a classical pathway involving the homolytic cleavage of the C-I bond in **I** followed by an exo-dig radical addition of the resulting radical species **II** to the polarized triple bond followed by a final reduction of the transient vinylic radical **III**, the stereochemical outcome of the process however deserves some comments. Indeed, the *E* isomer is formed exclusively, or at least predominantly, in most cases which was not expected at first. As shown in

Scheme 3, this *E* isomer (*E-IV*) cannot reasonably arise from the reduction of the intermediate vinylic radical **III**. α -Aryl-substituted vinyl radicals being linear π -radicals rather than bent σ -radicals,¹⁷ the direct reduction of **III** to *E-IV* is hardly possible due to the sterical clash between the incoming tributyltin hydride and the bulky electron-withdrawing group. The final reduction would therefore kinetically favor the formation of the *Z* isomer *Z-IV* onto which a reversible addition of the tributyltin radical $\text{Bu}_3\text{Sn}\cdot$ – a reaction that has been demonstrated to happen with TTMSS¹⁸ and observed with $\text{Bu}_3\text{Sn}\cdot$ ¹⁹ – would trigger its isomerization to the thermodynamic, more stable *E* isomer *E-IV*. Moreover, the elimination of $\text{Bu}_3\text{Sn}\cdot$ from transient adduct **V** to *E-IV* would also be favored from a kinetic point of view since the *s-cis* conformer of **V** involved in the elimination to *Z-IV* suffers from a severe allylic interaction, which is avoided in the elimination to *E-IV* involving the *s-trans* conformer of **V**. As a note, the presence of higher ring systems and/or an intracyclic substituent α to the double bond reduces both the difference in the energy required for the reduction of **III** to *Z-IV* and *E-IV* and the difference in the relative stability of these two isomers (as well as the energy difference between conformers *s-cis-V* and *s-trans-V*), explaining the lower diastereoselectivity noted with such substrates.

Scheme 3. Rationalization of the stereochemical outcome of the radical cyclization of ynamides.



In conclusion, we have reported an original and efficient radical cyclization of suitably functionalized ynamides to nitrogen-containing heterocycles. A range of ynamides bearing a *N*-iodopropyl chain could be smoothly cyclized, in a highly regio- and stereo- selective manner, to the corresponding 2-arylidene-pyrrolidines in good to excellent yields. The exocyclic double bond was shown to be an excellent anchor for further chemical diversification and the generality of this radical cyclization could be highlighted by its extension to the synthesis of other nitrogen heterocycles including piperidines, azepanes, pyrazolidines and hexahydro-pyridazines. Besides providing a useful and versatile entry to a range of nitrogen heterocycle, this cyclization also brings additional insights into the understudied radical chemistry of ynamides. Further studies in this area are undergoing and will be reported in due time.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization, copies of ¹H and ¹³C NMR spectra for all new compounds (PDF).

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