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Ynamides as Three-Atom Components in Cycloadditions: An Unexplored Chemical Reaction Space

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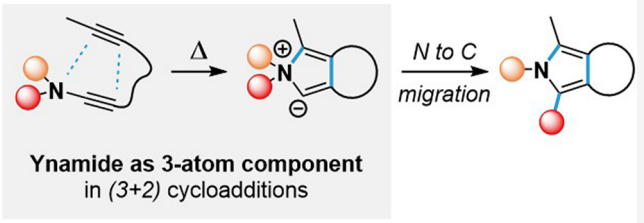
ABSTRACT: While 1,3-dipolar cycloadditions have appeared to be a fertile area for research, as attested by the numerous synthetic transformations and resulting applications that have been developed during the past 60 years, the use of neutral three-atom components (TACs) in (3+2) cycloadditions remains comparatively sparse. Neutral TACs, however, have great synthetic potential given that their reaction with a π system can produce zwitterionic cycloadducts that may be manipulated for further chemistry. We report herein that ynamides, a class of carbon π systems that has seen wide interest over the last two decades, can be used as neutral TACs in thermally induced intramolecular (3+2) cycloaddition reactions with alkynes to yield a variety of functionalized pyrroles. The transformation is proposed to occur in a stepwise manner via the intermediacy of a pyrrolium ylide, from which the electron-withdrawing group on the nitrogen atom undergoes an intramolecular 1,2-shift to produce the neutral pyrrole. This work demonstrates a yet unexplored facet of ynamide reactivity with great potential in heterocyclic chemistry.



INTRODUCTION

1,3-Dipolar cycloaddition reactions, pioneered by the group of Huisgen, have attracted increasing attention over the last 60 years.[1,2] The field has undoubtedly reached an advanced degree of maturity, which reflects nowadays its various synthetic applications[3−7] and the ongoing refinement of its reactivity models.[8−12] From a synthetic point of view, Huisgen reactions are arguably among the most useful transformations to access five-membered heterocycles in an easy, rapid, efficient, and selective manner. 1,3-Dipoles of propargyl-allenyl type ($\mathbf{1}_{prop} \leftrightarrow \mathbf{1}_{all}$), which represent one of the two classes of 1,3-dipoles,[13] are largely employed reaction partners (Figure 1, part A). Their popularity mostly relies on their reactions with alkyne dipolarophiles **2**, which not only allow for the formation of heteroaromatic motifs **3** that are relevant to natural product synthesis and drug discovery[3] but are also particularly useful in bio-orthogonal chemistry[7] and material science.[6]

It is interesting to note that all these heteroaromatics contain at least one N atom as the result of an underlying limitation in the structure of the 1,3-dipole **1**. As noted by Breugst and Reissig in their 2020 review on the Huisgen reaction, for C,N,O-based "allenyl-propargyl type 1,3-dipoles, only nitrogen is possible" as the central atom.[2] This appears to be a logical requirement from a valency and electronegativity standpoint, considering that the central atom of the 1,3-dipole must accommodate a lone pair of electrons in the newly formed neutral cycle. However, discounting their Lewis structure-based charges, the general feature shared by all 1,3-dipoles is the delocalization of four electrons over a three-atom π system. The entirety of three-atom components (TACs)—a general term used to describe a core three-atom framework that participates in (3+2) cycloadditions[14]—that share this criterion is limited not only to 1,3-dipoles but also to some neutral counterparts.[15] Neutral TACs are however exotic species in the field of cycloadditions.[16−18] The very few of them that have been studied to date are usually difficult to manipulate[17] and/or have been partnered with highly reactive species.[16a−e] A cycloaddition between a C-centered TAC **4** analogous to 1,3-dipole **1** and an alkyne **2** could, in principle, be envisaged (Figure 1, part A). In contrast to 1,3-dipolar cycloadditions that directly lead to neutral heteroaromatic products **3**, the resulting zwitterionic cycloadduct **5** would in this case be an unstable species, a feature that could however be exploited in a subsequent step to provide an additional degree of complexity in the transformation. Despite the apparent maturity of the field, such a reactivity profile remains underexplored, leaving plenty to discover in the chemical reaction space of neutral TACs.

In this context, and with the idea to further develop the synthetic potential of cycloaddition reactions, we considered that *N*-alkynyl derivatives **6** could qualify as TACs capable of (3+2) cycloadditions (Figure 1, part B). These species, which

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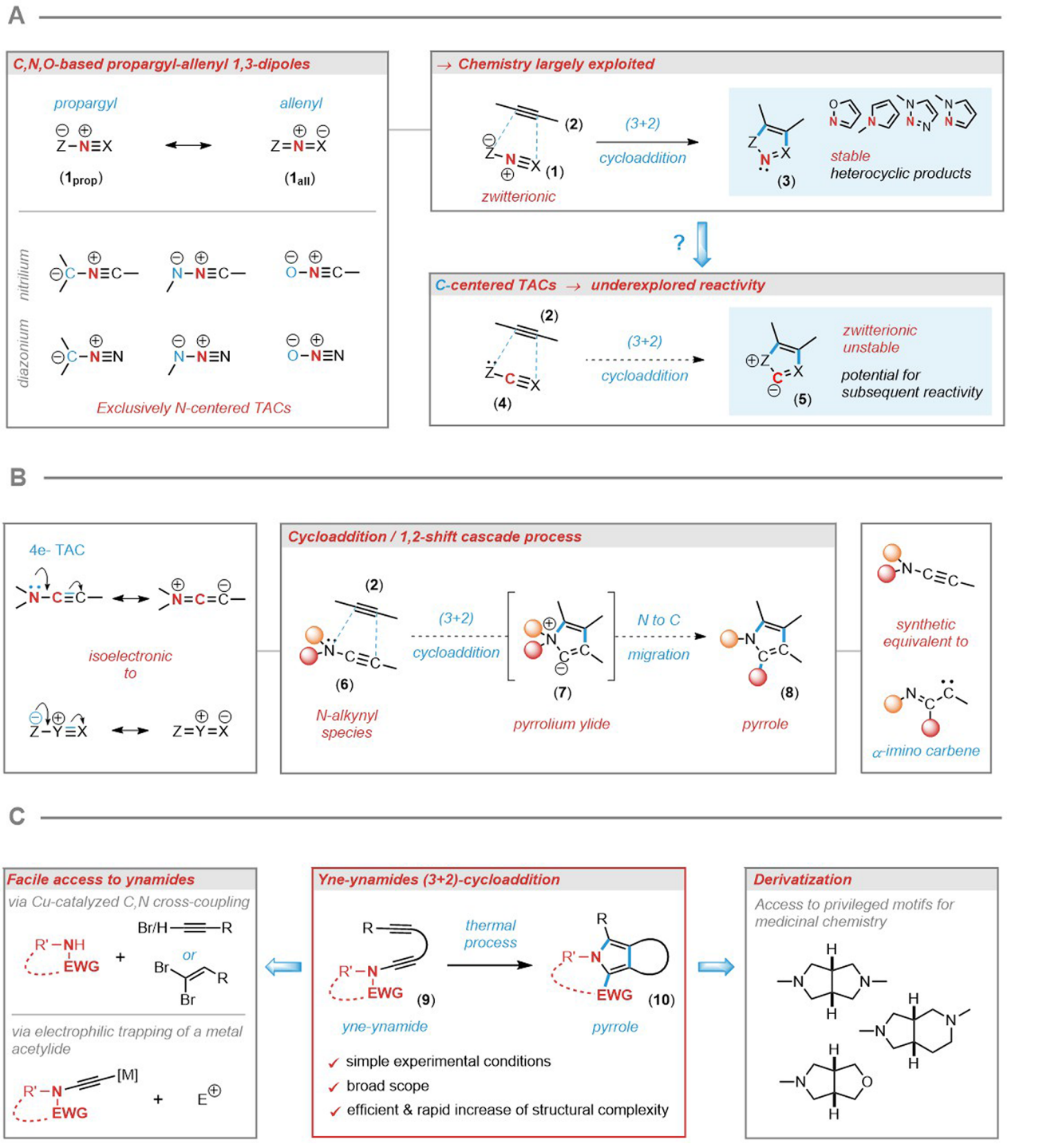

Figure 1. Ynamides as a novel class of neutral three-atom components in (3+2) cycloadditions. (A) Background: Propargyl-allenyl 1,3-dipoles based on second-row elements react with alkynes to produce stable and neutral N-containing heteroaromatic cycloadducts. Analogous reactivity with C-centered TACs has been underexplored. (B) Proposal: *N*-Alkynyl derivatives react as TACs with alkynes in a cycloaddition/rearrangement sequence involving an unstable pyrrolium ylide cycloadduct intermediate. (C) This work: Readily prepared yne-ynamide derivatives can be cycloisomerized into polycyclic pyrroles via a thermal intramolecular (3+2) cycloaddition process. The transformation is a valuable springboard for the synthesis of various hetero(poly)cyclic motifs.

are isoelectronic carbon-centered analogues of propargyl-allenyl type 1,3-dipoles, could react with an alkyne to produce a pyrrolium ylide cycloadduct **7**. Depending on the nature of the groups attached to the positively charged nitrogen atom in **7**, a formal N to C migration event may occur, leading ultimately to the formation of the neutral and aromatic pyrrole **8**. In the envisaged cycloaddition/rearrangement sequence, the *N*-alkynyl TAC would advantageously appear as the synthetic equivalent of an α-imino carbene, a type of species that has been previously reported to react with alkynes to produce pyrroles.[19]

We report herein the successful implementation of this reactivity principle to the synthesis of polycyclic pyrroles **10** via a thermally induced intramolecular (3+2) cycloaddition of

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yne-ynamide derivatives **9** (Figure 1, part C). Ynamides (*N*-alkynyl amides) were targeted as TACs in this work, as they can be readily accessed with a variety of substitutions on the nitrogen atom,[20] are easy to handle and manipulate, and exhibit enhanced stability as compared to their parent ynamines.[21] It is interesting to note that despite the popular use of ynamides in organic synthesis, their reactivity has been limited, almost exclusively, to the functionalization of their C−C alkynyl portion[22] without any direct participation of the nitrogen atom in the formation of new nitrogen−carbon bonds.[23] The synthetic interest of this new (3+2) cycloaddition was further highlighted by the possibility to derivatize the pyrrole products in various heterobicyclic compounds relevant to medicinal chemistry. A combined experimental and density functional theory (DFT) mechanistic study was also performed to gain insight into the nature of the cycloaddition reaction.

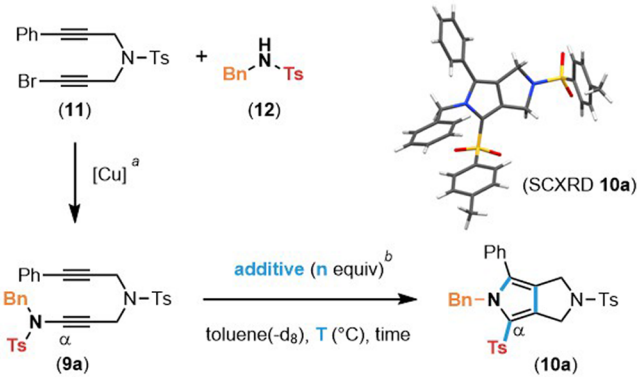
RESULTS AND DISCUSSION

Validation of the Approach, Reaction Optimization, and Scope. We started our investigation with diyne **9a**, which was chosen as a model substrate to validate our reactivity proposal. This diyne was conveniently accessed by Cu-catalyzed coupling between bromoalkyne **11** and sulfonamide **12** (Table 1). The initial choice of the tosyl group on the ynamide moiety was based on the well-documented coupling of sulfonamides under Cu catalysis[20a−c] and the known ability of sulfonyl groups to migrate from sulfonylammonium intermediates.[24]

Heating a solution of **9a** in toluene at 80 °C for 15h led to its slow conversion (42%) mostly into degradation products[25] (entry 1). We could, however, detect in the crude reaction mixture the formation of a new compound in very low amounts (13% NMR yield). This compound was isolated as a solid and its structure pleasingly assigned after ^{1}H NMR analyses as the targeted bicyclic pyrrole **10a**. Single-crystal X-ray diffraction analysis of **10a** confirmed the connection around the pyrrole core and the migration of the tosyl group from the N atom of the ynamide moiety in the substrate to its α carbon in the product (see Table 1). While the yield was low, the formation of **10a** validated our approach and the possibility to use ynamides as TACs in cycloaddition processes. By raising the temperature to 130 °C (oil bath)[26] **9a** was fully consumed after 2 h of reaction and an improved yield of 72% was obtained (entry 2). Running the reaction under argon had almost no influence on the course of the reaction (entry 3). Hypothesizing that the loss of material may be due to deleterious uncontrolled radical processes consuming the diyne substrate,[27] additives known to stop radical chain degradation processes were examined.[28] As seen in entries 4−7, the addition of 2,6-di-*tert*-butyl-4-methylphenol (BHT), a phenolic radical scavenger, proved to be quite beneficial, and an almost quantitative yield of pyrrole **10a** (96%) could be obtained when 1 equiv of the additive was used. Another radical scavenger, γ-terpinene, was slightly beneficial, but not as effective (entry 8). The conditions described in entry 6, employing 0.5 equiv of BHT, were deemed sufficient and were therefore used to evaluate the scope of the transformation. It is interesting to note that the reaction was very selective toward the migration of the tosyl group and that no alternative (4+2) dehydro Diels−Alder cycloadduct[29] derived from **9a** could be observed.

A variety of strategies were employed in the synthesis of the yne-ynamide substrates in order to vary the substitution pattern on the ynamide, the alkyne moiety, and the nature of the chain tethering them (see Supporting Information for details).[30] As seen from the results compiled in Tables 2 and 3, the reaction exhibits good functional group compatibility, and a variety of bicyclic cycloadducts could be obtained from yne-ynamides **9a−ak**. As for the nature of the alkyne terminus (Table 2, part A), the reaction proceeded rapidly and cleanly for all screened aryl derivatives **9a−h**. An array of electron-donating (EDG) and electron-withdrawing groups (EWG) were well tolerated on the aromatic moiety, leading to the desired pyrroles in yields ranging from 79% to 97% after only 1 h of reaction at 130 °C. Heteroaromatic substituents were also shown to be compatible, as attested by the conversion of thiophene and pyridine derivatives **9i−j** into pyrroles **10i−j** with respective 82% and 90% yields. Pleasingly, a C-sp^2-hybridized alkenyl substituent was also tolerated and cyclohexenyl derivative **10k** could be formed in 83% yield after 2 h of reaction. The use of a conjugated 1,3-diyne unit was, however, detrimental to the yield of the reaction. In the case of substrate **9l**, the major product obtained was **10l**, with a modest yield of 33%, and byproducts derived from a potential (4+2) hexadehydro Diels−Alder reaction, if present, were only minor.[31] While the reaction of alkyl-substituted derivative **9m** and terminal alkyne **9n** proceeded very slowly and with low yields (15−20%), that of trimethylsilyl (TMS)-substituted alkyne **9o** was comparatively very efficient (80%), yet slow.

Table 1. Optimization of the Reaction Conditions



entry	T (°C)	additive	n (equiv)	time (h)	conversion (%)[c]	yield (%)[c]
1[d]	80			15	42	13
2	130			2	100	72
3[e]	130			2	100	69
4	130	BHT	0.1	2	100	79
5	130	BHT	0.25	2	100	86
6	130	BHT	0.5	2	100	90
7	130	BHT	1	2	100	96 (90)[f]
8	130	γ-terpinene	1	2	100	77

[a]Reaction conditions: $CuSO_4 \cdot 5H_2O$ (10 mol %), 1,10-phenanthroline (20 mol %), K_3PO_4 (2 equiv), toluene, 80 °C, 48%; see SI for more details. [b]Unless otherwise noted, reactions were performed with 0.05 mmol of **9a** in screw-cap NMR tubes in toluene-d_8 (0.1 M) under air and monitored by ^{1}H NMR spectroscopy. [c]Conversions and yields were determined by ^{1}H NMR spectroscopy using mesitylene as internal standard. [d]In a sealed vial in toluene (0.1 M). Conversion and yield were determined by analysis of the crude reaction mixture using mesitylene as a standard. [e]NMR tube was purged with argon. [f]Isolated yield.

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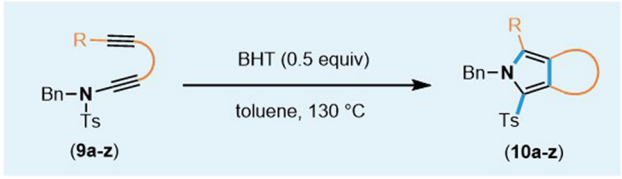
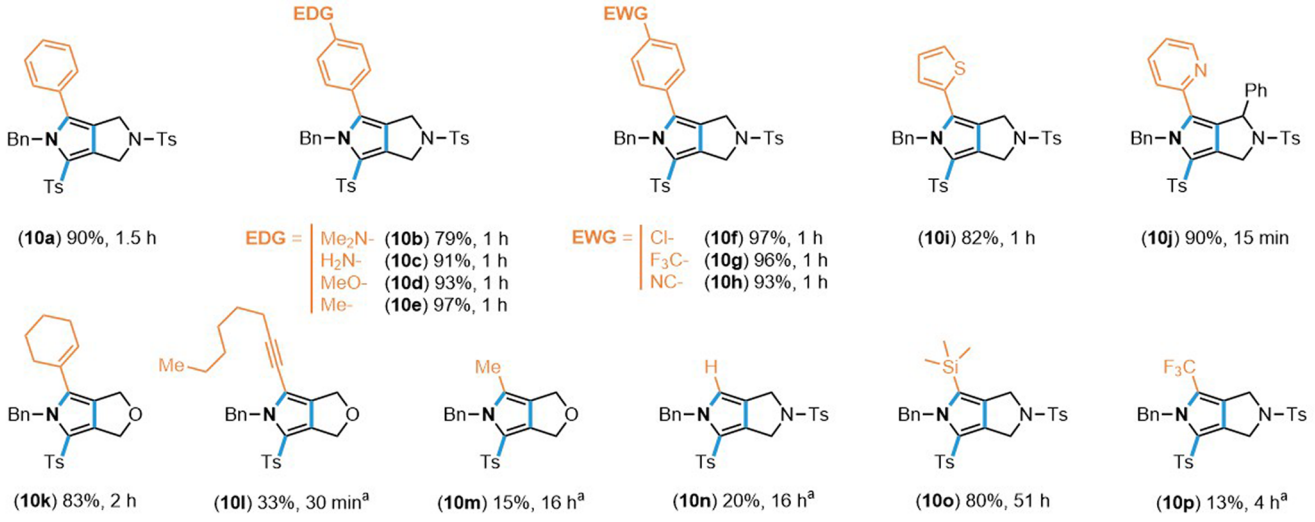
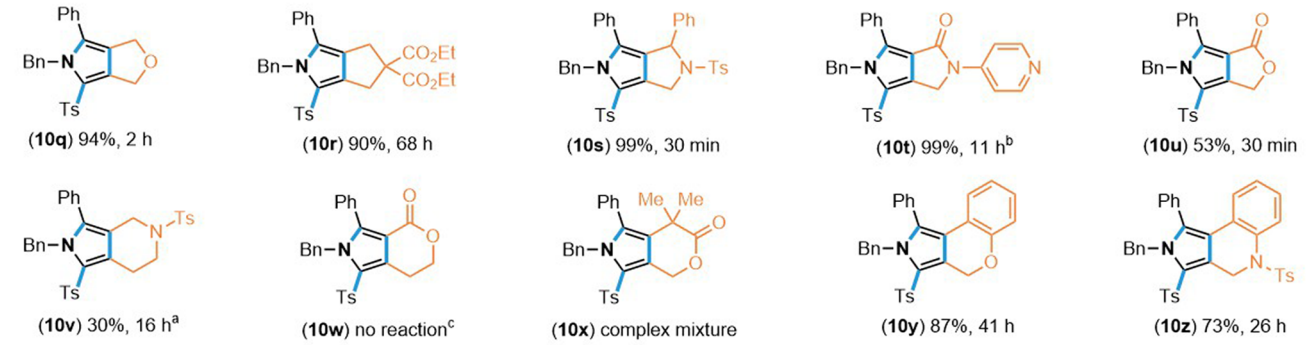
Table 2. Yne-ynamide (3+2) Rearrangement: Reaction Scope of Alkynes and Linkers[d]



A



B



[a]A complex mixture of products was observed; yield assessed by ^{1}H NMR of reaction crude. [b]Reaction run at 60 °C in $CDCl_3$ without BHT. [c]No reaction was observed up to 160 °C (using microwave irradiation); degradation of substrate at 200 °C. [d]Unless otherwise noted, reactions were performed at 0.02−0.07 mmol scale in sealed tubes with 0.5 equiv of BHT in toluene (0.1 M) under air.

This result demonstrated that increasing the steric demand around the alkyne does not affect the efficiency of the cycloaddition process but considerably decreases its rate. Finally, the electron-poor trifluoromethylated alkyne **9p** did not prove to be an appropriate reaction partner, and only a low 13% of the desired pyrrole **10p** was observed.

A variety of alkyne-ynamide linkers proved compatible with the (3+2) cycloaddition process (Table 2, part B). In general, substrates with a three-membered linker led to the formation of cycloadducts similarly to model substrate **9a**, as exemplified by the formation of **10q** in 94% yield from a substrate possessing an ether linkage. Amide and ester tethers were both compatible (see **10t** and **10u**). Notably, the reaction of **9t** could even be performed at a lower temperature of 60 °C. The all-carbon malonate derivative **9r** also reacted well (90%), although surprisingly slowly.[32] The introduction of a phenyl substituent in the tether had a pronounced effect on the rate of the reaction, as attested by the rapid and efficient formation of pyrroles **10s** and **10j** (>90% yield, <0.5 h). Four-membered linkers were also investigated, but the cycloaddition process proved to be less efficient in this case. Derivative **9v**, which differs from model substrate **9a** only by the presence of an extra CH_2 unit in its linker, led to a poor yield (30%) and very unselective reaction. No reaction or only degradation was observed for carboxylic ester derivatives **9w** and **9x**. In contrast, excellent yields were obtained for geometrically restricted phenol and aniline derivatives **9y** and **9z** (87% and 73%). These variations in tether length, nature, and substitution (Table 2, part B) clearly demonstrate that higher yields and

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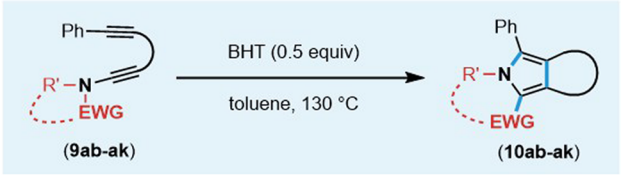
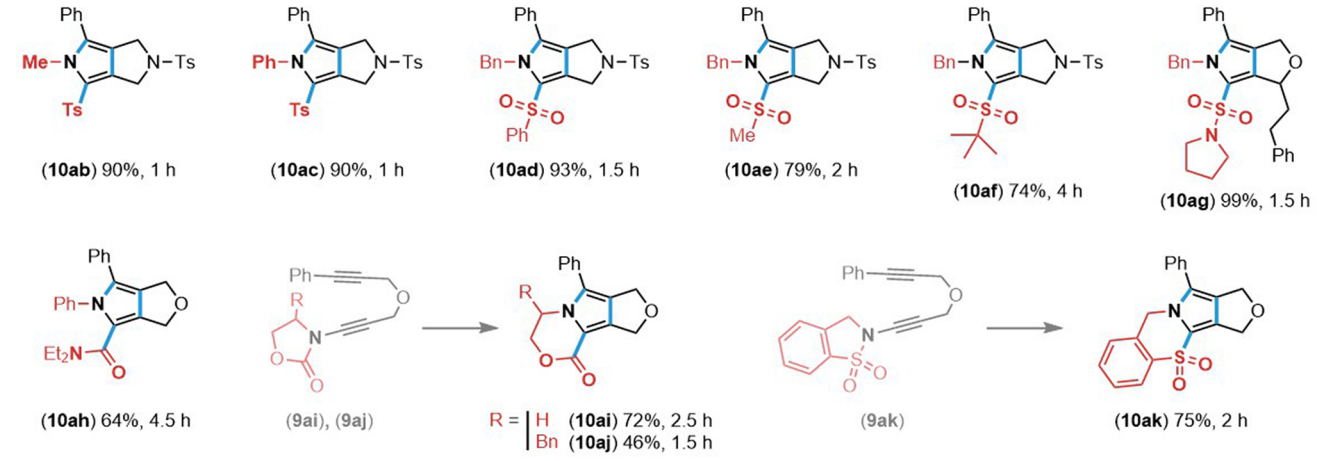
Table 3. Yne-ynamide (3+2) Rearrangement: Reaction Scope of Amides[a]





[a]Reactions were performed at 0.02−0.07 mmol scale in sealed tubes with 0.5 equiv of BHT in toluene (0.1 M) under air.

shorter reaction times can be attained when the cyclization conformation can be easily accessed.

Three-membered linkers leading to the formation of 5,5-fused bicyclic products and geometric restrictions imposed by linker substitution are favorable kinetic factors. As an example, merging the favorable three-atom tosylamide linker and a dimethyl-induced Thorpe−Ingold effect in **9aa** led to an extremely efficient transformation that proceeded at room temperature (Figure 2).

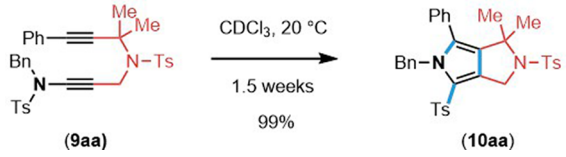


Figure 2. Room-temperature (3+2) rearrangement. Reaction was performed at 0.013 mmol scale in a screw-cap NMR tube in $CDCl_3$ (0.025 M) under air.

We finally investigated the scope of ynamides and the corresponding EWGs that could participate in the N to C migration step of the rearrangement (Table 3). Pleasingly, the benzyl group in model substrate **9a** could be replaced by a methyl or phenyl group without noticeable change in efficiency. *N*-Me and *N*-Ph pyrroles **10ab** and **10ac** were both isolated in 90% yield after 1 h of reaction. Alkylsulfones **9ae** and **9af**, as well as sulfonamide **9ag**, reacted similarly to arylsulfones (**9a** and **9ad**). Carbonyl-based EWGs were also very well tolerated in this transformation. For instance, urea derivative **9ah** efficiently rearranged into pyrrole **10ah** (64%) via a migration of the carboxamide moiety. In the case of cyclic carbamate derivatives, such as oxazolidinones **9ai** and **9aj**, the shifting of the EWG resulted in a ring expansion, providing novel tricyclic structures. This strategy could also be applied to saccharin-derived ynamide **9ak**, which could be readily converted into polycyclic pyrrole **10ak**.

Overall, examples collected in Tables 2 and 3 testify to the broad applicability of this cycloisomerization process, which allows for a rapid increase of structural complexity under simple experimental conditions and from relatively easily accessible substrates.

Applications and Derivatizations. To further highlight the synthetic potential of the method, the reaction of model substrate **9a** was conducted at a gram scale starting from bromoalkyne **11** and tosylamide **12** (Figure 3, part A). A two-step procedure involving copper catalysis and thermal rearrangement with minimum intermediate workup successfully yielded 1.97 g of pyrrole **10a** (50% yield). Conveniently, the white product precipitates out of solution once cooled to room temperature. This single preliminary result is highly encouraging when considering developing a cascade transformation from haloalkynes and diverse amides.

Structural diversification in pyrrole products could also be further expedited in the development of a one-pot coupling/cyclization sequence (Figure 3, part B). The coupling strategy devised here relies on the *in situ* formation of an imine as the bridging functionality between the cycloaddition partners. By simply mixing and matching propargyl amines **13a,b** with amidopropynals **14a−c** in the presence of molecular sieves, followed by mild heating, a small library of bicyclic pyrroles **15aa−bc** could be rapidly obtained in moderate yields.[33]

In addition to the structural diversity that can be achieved by varying the nature of the migrating EWG (*vide supra*) the presence of this group at position 2 of the pyrrole ring can also be advantageously employed to operate functional group

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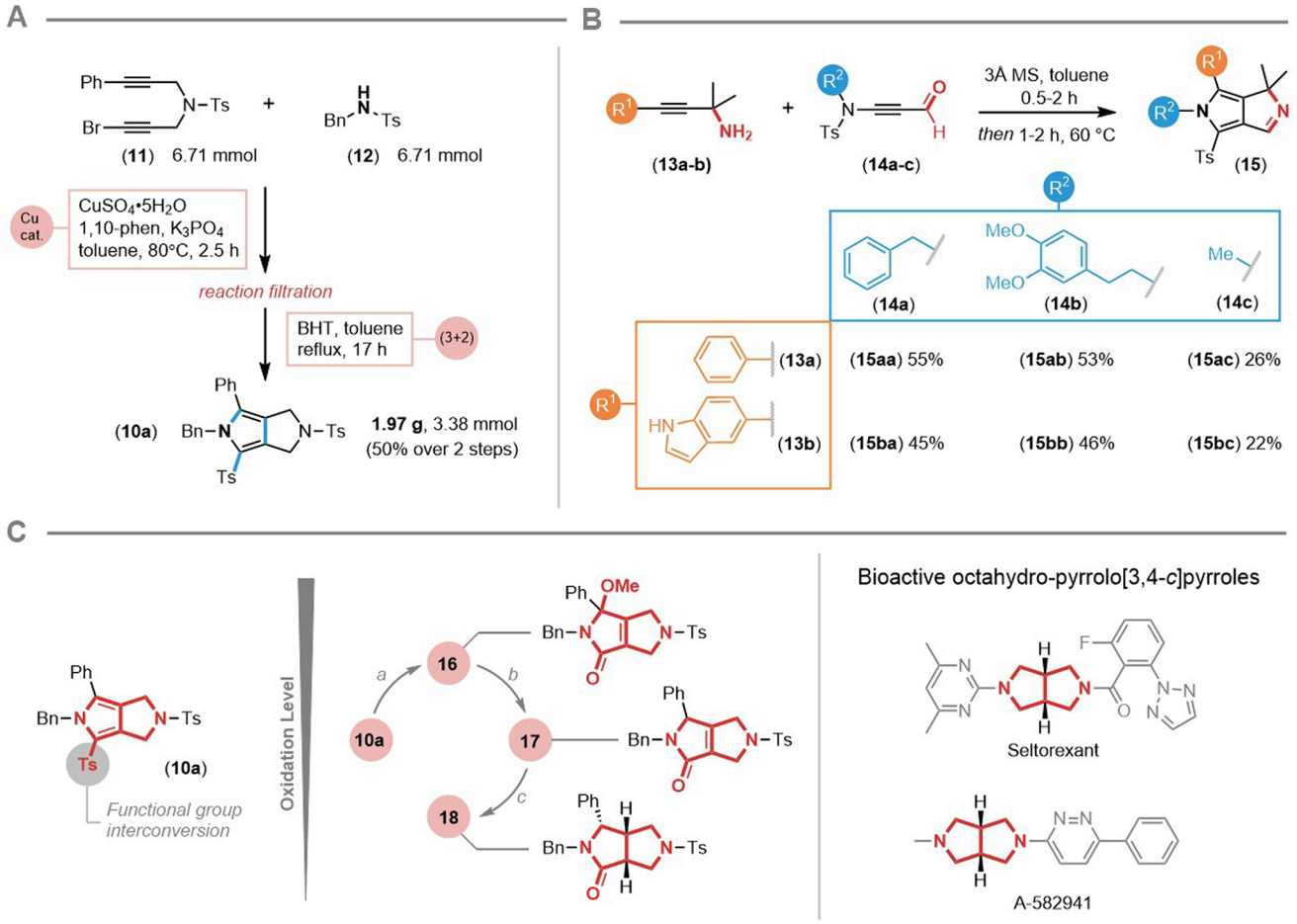

Figure 3. Applications and derivatizations of pyrrole products. (A) Two-step, no purification, gram-scale synthesis of pyrrole **10a**. (B) Combinatorial approach to the rapid synthesis of a small library of bicyclic fused pyrroles via a one-pot condensation/(3+2) sequence. (C) Accessing various oxidation levels of the pyrrolo[3,4-*c*]pyrrole core via key pyrrolone derivatives: (a) Oxone, KBr, MeOH, 45 °C, 2 h, 58%; (b) Et_3SiH, $BF_3{\cdot}OEt_2$, DCM, reflux, 3 h, 73%; (c) H_2, 10% Pd/C, EtOH, rt, 1 h, 91% (see Supporting Information for more details).

interconversions. The tosyl group, in particular, was found to be easily cleaved in an oxidative dearomatization process on the pyrrole (Figure 3, part C). As an example, treatment of pyrrole **10a** with a mixture of Oxone and KBr in methanol led to the formation of 5-methoxypyrrol-2-one derivative **16** in 58% yield. Alone, this demonstrates a rapid pathway to highly functionalized polycyclic γ-lactams, a structural motif found in a large array of bioactive compounds.[34] Sequential reduction of **16** allows for the synthesis of pyrrolone **17** and then lactam **18** in a stereoselective manner. This rapid redox sequence highlights the synthetic usefulness of the migrating sulfonyl group that can be easily manipulated to access various oxidation levels of the pyrrolo[3,4-*c*]pyrrole core, whose fully reduced version is a privileged motif in medicinal chemistry (see Seltorexant,[35] A-582941,[36] Figure 3, part C).

Mechanistic Studies. Aside from investigating the synthetic potential of the transformation, a combined experimental and theoretical study was performed to gain knowledge on its mechanism and the parameters that may influence its course. Kinetic studies using NMR monitoring and analysis were performed showing a first-order dependence on the yne-ynamide substrates and no kinetic dependence on the BHT additive (see Supporting Information, Figures SI-1 and SI-2), suggesting a unimolecular rate-limiting step. With this knowledge, the transformation can be simplified into two main events: a (3+2) cyclization event and a 1,2 migration of the EWG with the involvement of a common pyrrolium ylide intermediate. Considering that products derived from a spontaneous 1,2-shift of the EWG on ynamides have never been observed to date, the cyclization event is much more likely to occur first. Several mechanistic considerations can be made for both events when elaborating the reaction pathway (Figure 4, part A).

The mechanism of classical (3+2) dipolar cycloadditions has been a hot topic of debate during the past century,[11,12] and both closed-shell (Figure 4, part A, path a) and open-shell (Figure 4, part A, path b) processes have been defended. While ynamides are typically used in two-electron processes, radical addition to ynamides to obtain enamine radical intermediates has seen growing interest.[37] In order to gain more information on this transformation, a series of *para*-substituted phenyl-derived substrates **9ah** were investigated to probe electronic effects on the alkyne moiety (see Supporting Information, Table SI-1). Plotting the experimentally determined rate constants in a Hammett plot (Figure 4, part B) resulted in an interesting U-shaped curve. Such a shape suggests three possibilities: the cyclization event may proceed (a) via a type II cycloaddition process,[38] (b) via a diradical species,[12] or (c) via divergent mechanisms.[39] The result obtained with the CF_3-subtituted phenyl derivative is noteworthy. It fits well on the

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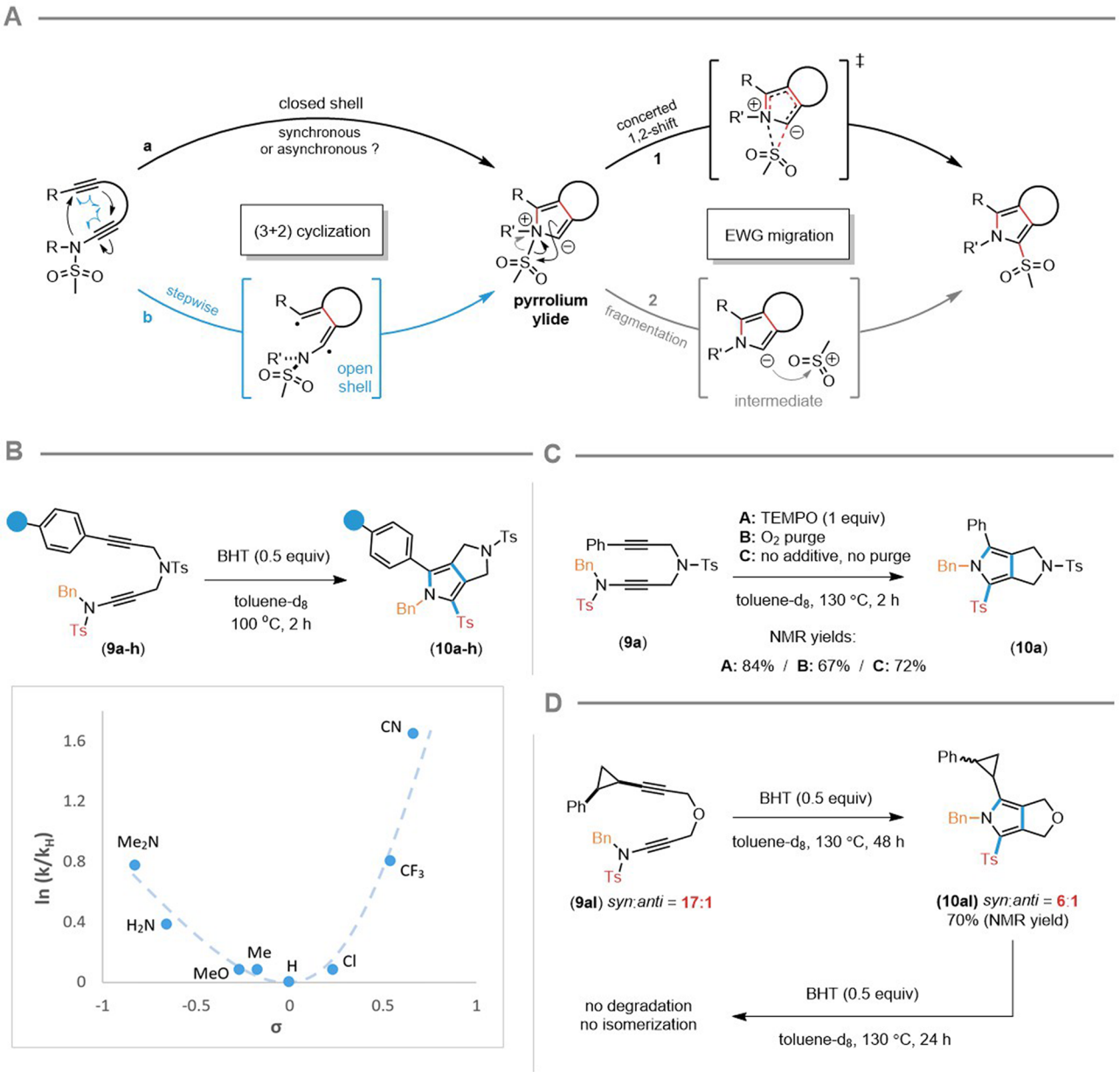

Figure 4. Mechanistic considerations for the yne-ynamide (3+2) rearrangement. (A) Both closed- and open-shell pathways were considered for the (3+2) cycloaddition step of the reaction. Both intramolecular and intermolecular pathways were considered for the 1,2-migration of the EWG. (B) Hammett plot. An uncommon U-shape was observed in the plot produced from substrate series **9a–h**. (C) Effect of persistent radicals. No byproduct and no significant lowering of yield were observed in the presence of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) or at a high concentration of O_2. (D) Radical clock experiment. The use of an intramolecular *syn*-disubstituted phenylcyclopropyl probe allowed the observation of cyclopropyl isomerization via ring opening, suggesting the involvement of a radical species. A control experiment shows the isomerization does not occur in the pyrrole product (see Supporting Information for more details).

obtained curve, and since the CF_3 substituent is known to significantly destabilize the formation of radicals at benzylic positions,[40] this result may be an indication that a closed-shell process is in play. However, the nature of the hypothesized radical (benzylic yet also vinylic) may differ from those previously studied, and an open-shell process cannot be ruled out.

Characterization of the potential energy surface for the closed-shell (3+2) cycloaddition was possible using DFT calculations at both the B3LYP/6-31G(d) and M06-2X/6-31+G(d) levels of theory[41] (Figure 5, part A). For the phenyl-derived model **I-Ph**, the (3+2) cycloaddition step was found to be rate-limiting with a transition state **TS-I-Ph** calculated to be 30.3 kcal/mol higher than **I-Ph** using the M06-2X method.[42] The methyl-derived model **I-Me** required a higher energy of around 35 kcal/mol for the corresponding transition state **TS-I-Me**. It is worth noting that in both cases, the (3+2) cycloaddition step was quite asynchronous, with significantly more C–C bonds having been formed at the transition state.

The proposed pyrrolium ylide intermediates **II-Ph** and **II-Me** were convincingly located as stable minima in this pathway using both B3LYP (10–12 kcal/mol) and M06 (~3 kcal/mol) methods.

The plausibility of a closed-shell process, as supported by DFT calculations, does not rule out an open-shell pathway for the cycloaddition step.[43] To probe the possibility of an open-

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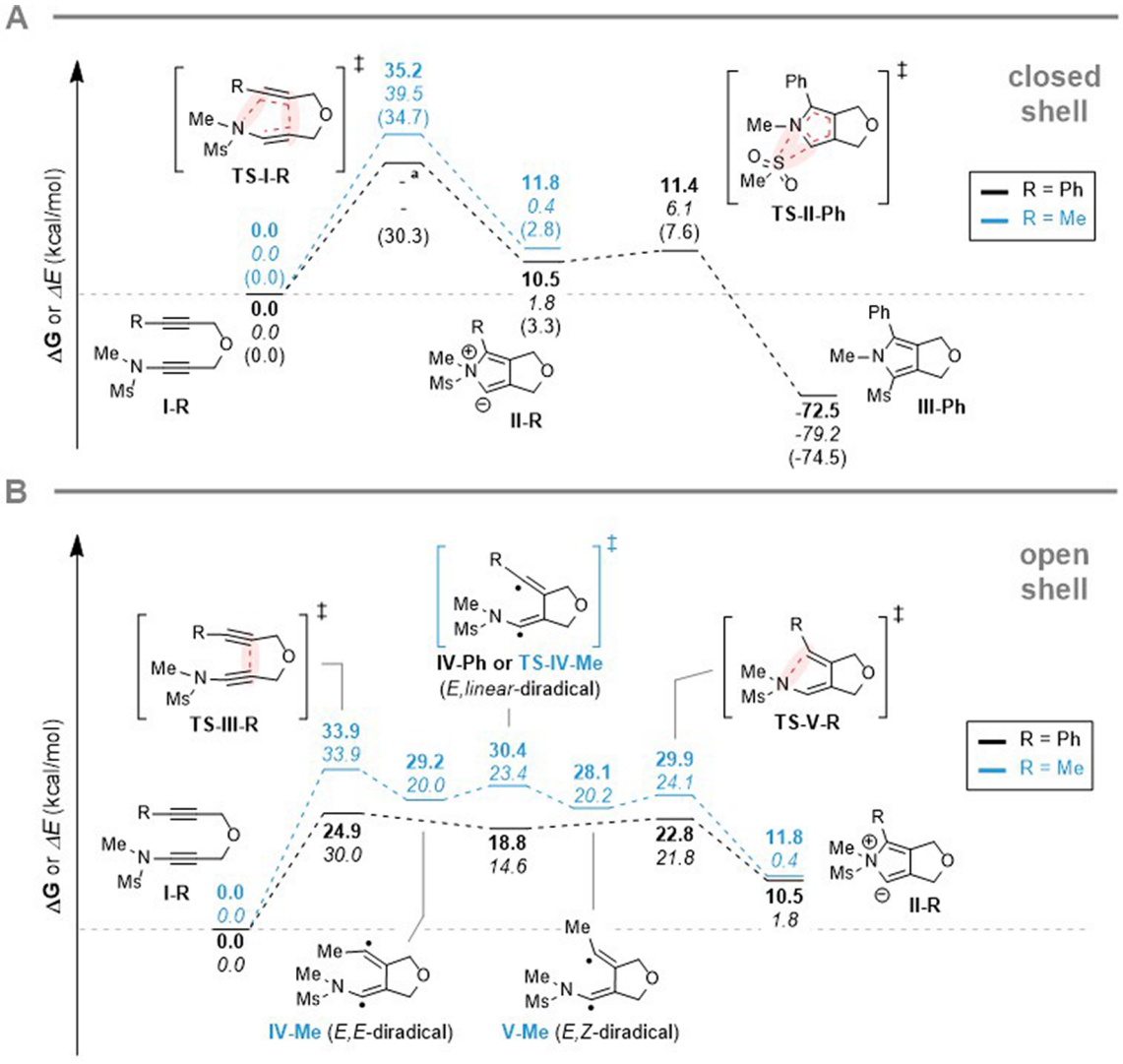

Figure 5. DFT calculations of closed- and open-shell potential energy surfaces for the (3+2) yne-ynamide rearrangement. All calculations were done under the following parameters: gas phase, 1 atm, 298 K. Intrinsic reaction coordinate (IRC) calculations were performed to connect the transition states to their corresponding local minima (dotted lines). **Values in bold**: Relative Gibbs free energy at the B3LYP/6-31G(d) level of theory. *Values in italics*: Relative electronic energy at the B2PLYPD/*aug*-cc-pVDZ//B3LYP/6-31G(d) level of theory. (Values in parentheses): Relative Gibbs free energy at the M06-2X/6-31+G(d) level of theory. (A) Closed-shell potential energy surface. (B) Open-shell (singlet diradical) potential energy surface. The *unrestricted* functionals were employed for the calculation of the open-shell surface. [a]A stable closed-shell **TS-I-Ph** could only be located using the M06-2X functional (see Supporting Information for more details).

shell process and the involvement of radical species, the reaction of model substrate **9a** was performed in the presence of TEMPO (Figure 4, part C). No TEMPO-derived product could be detected. The transformation proceeded smoothly and produced **10a** in the same reaction time and with an even better yield than without any additive. TEMPO is likely to behave similarly to BHT in intercepting runaway radicals. A similar observation was made when the sealed reaction tube was purged with O_2 gas before heating (Figure 4, part C). No oxidized product derived from **9a** was observed, and the yield in **10a** was almost unchanged. It should be noted, however, that particularly short-lived diradicals would unlikely be affected by other molecules in the reaction medium. Therefore, an intramolecular radical probe **9al** that features a *syn*-disubstituted cyclopropyl alkynyl group was prepared (Figure 4, part D). 2-Phenylcyclopropyl carbinyl radicals are known to undergo very rapid ($k_{20\ °C} = 2.7 \times 10^{11}\ s^{-1}$) ring opening[44] and would therefore probe the involvement of radical species in the process. A significant amount of isomeric product was observed in the rearrangement of **9al** to **10al**, which may indicate that the formation of a radical at the α position of the cyclopropyl group is participating. NMR kinetic analyses during the reaction (Supporting Information, Table SI-2) and a control experiment (Figure 4, part D) suggest minimal *cis*/*trans* isomerization to be occurring at the cyclopropyl motif in either the starting material or the product.

The open-shell potential energy surface was characterized at the unrestricted UB3LYP/6-31G(d) level of theory (Figure 5, part B). Interestingly, the phenyl-derived model led to a transition state **TS-III-Ph** of about 25 kcal/mol for the C−C bond forming and rate-limiting conversion of **I-Ph** into biradical intermediate **IV-Ph**, found at 18.8 kcal/mol. The barrier for the C−N bond formation (**TS-V-Ph**) was only slightly higher at 22.8 kcal/mol. In the case of methyl-derived model **I-Me**, an open-shell transition state **TS-III-Me** could be located slightly higher at 33.9 kcal/mol. The minima associated

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with diradicals **IV-Me** and **V-Me** could also be located with respective free energies of 29.2 and 28.1 kcal/mol. The small barrier **TS-IV-Me** of radical center inversion allows accessing the right conformation for the cyclization to occur. The subsequent C−N bond formation has a barrier **TS-V-Me** at 29.9 kcal/mol to produce the cyclic ylide. Although differing slightly in magnitude, single-point energy calculations done along the open-shell pathway using the more accurate B2PLYPD/*aug*-cc-pVDZ level of theory show a very similar qualitative picture for the diradical process. This method has previously shown good correlation with high-level computations regarding the formation of diradical species from diynes[45] and diradical (3+2) processes.[43]

Considering both experimental observations and DFT calculations, a divergence in open- or closed-shell processes may happen for the (3+2) cycloaddition step depending on the substitution at the alkyne terminus. The clear U-shaped Hammett plot obtained along with the radical probe experiments support such a possibility. While DFT studies show a slight favor for the open-shell pathway, neither pathway can be completely ruled out yet. At the moment, both closed-shell and open-shell processes can still be considered as viable processes. In any case, the cyclization step was found asynchronous, and intermediates, if formed, are extremely short-lived. A common point observed in the computation of both pathways, nevertheless, is a higher activation energy for alkyl-substituted alkynes, which fits with the significantly slower reaction times observed for scope examples **10m** and **10n**.

The second step of the process, the N to C migration of the EWG, may occur via an intramolecular 1,2-shift (Figure 4, part A, path 1) or via a fragmentation/recombination sequence (Figure 4, part A, path 2).

These two possibilities could be distinguished in a crossover experiment as shown in Figure 6. When an equimolar mixture

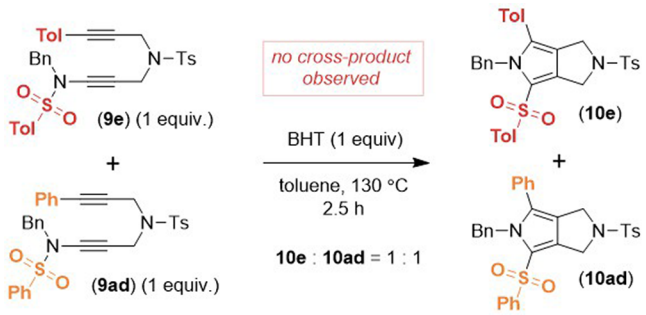

Figure 6. Crossover experiment. Reaction was performed at 0.05 mmol scale in a sealed tube with 1 equiv of BHT in toluene (0.1 M) under air. Reaction crude was analyzed by MS-APCI (atmospheric pressure chemical ionization) (see Supporting Information for more details).

of structurally comparable **9e** and **9ad** substrates was heated, only the respective pyrroles **10e** and **10ad** were obtained. Since no crossover product was observed (Supporting Information, Figure SI-4), an intermolecular process could be ruled out,[46] thus leaving an intramolecular 1,2-shift of the EWG as the most probable pathway. This 1,2-shift was easily located on the closed-shell potential energy surface (Figure 5, part A). A very low barrier located at 6.1 kcal/mol was found for the migration of the sulfonyl group. This migration can rather be described as a [1,5]-sigmatropic rearrangement of the sulfonyl group along the π system of the pyrrolium cycle, immediately followed by relaxation to the final "flat" aromatic structure.

CONCLUSION

In summary, an efficient and easy-to-perform thermal (3+2) rearrangement of yne-ynamide derivatives into polycyclic pyrroles has been developed, expanded, and mechanistically investigated. Aside from the large variety of substituted alkynes and linkers that were shown to efficiently promote the cyclization reaction, a notable observation remains that all the ynamides investigated herein efficiently behaved as TACs in cycloaddition reactions to form pyrroles. The (3+2) cycloaddition step may occur through a concerted or a singlet diradical pathway, depending on the substitution of the reacting alkyne. A subsequent 1,2-migration of the EWG likely proceeds in a concerted intramolecular fashion from a pyrrolium ylide intermediate.

The reactivity described herein brings to light an underestimated character of ynamides: these should be considered not only as electronically enriched polarized alkynes but more accurately as a three-atom system sharing a π electron cloud. Capitalizing onto this character may help in designing and developing novel transformations in the field of heterocyclic chemistry. It is ultimately our hope that this investigation will encourage and help to expand the use of neutral TACs in (3+2) cycloaddition reactions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c04051.

Synthetic procedures, characterization data, and spectroscopic data for all new compounds; experimental data associated with mechanistic studies (PDF)

Accession Codes

CCDC 2062485 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

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(15) The term "neutral" is employed here as a means to distinguish TACs that do not possess formal charges in their Lewis structure, as opposed to classical 1,3-dipoles. Other neutral species yielding (3+2) cycloadducts, such as cyclopropanes, are not discussed here since they do not fit within Domingo's definition of TACs.

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