Catalyzing the (3+2) Cycloaddition of Neutral TACs: Towards a Generalization of the CuAAC Reactivity Principles

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Abstract: The introduction of the copper-catalyzed azide-alkyne coupling (CuAAC) to 1,3-dipolar cycloadditions was pivotal to their popularization in synthetic chemistry and to their application to multiple other domains of science. The reaction rate enhancement observed when coinage metal acetylide intermediates are involved in the cyclization process greatly expanded the structural and conditional range in which (3+2) cycloadditions may take place with terminal alkynes. Herein we report that comparable rate enhancements, in nature and level, can be observed in the intramolecular (3+2) cycloaddition of terminal alkynes with “neutral” three-atom components (TACs), specifically alkynyl sulfides. Through careful observations amidst reaction optimization, experimental and DFT mechanistic studies, a pathway involving a proton-coupled cyclometallation key step is proposed. The sets of catalytic conditions that have been developed allow to overcome several scope limitations previously presented by the thermally promoted (3+2) cycloaddition of “neutral” TACs, thus expanding their synthetic and applicative potential.

Introduction

The (3+2) cycloaddition reaction of 1,3-dipoles (1), or Huisgen reaction (Figure 1-A), is a common strategy for accessing 5-membered heterocycles (2). Numerous studies have been devoted to this area of synthetic chemistry that has seen diverse applications in various other fields of research.1-4 By definition, 1,3-dipoles are however structurally limited to linear three-atom components that possess a “dipolar” Lewis structure.5 It is therefore of general interest to explore the use of other neutral three-atom components (neutral TACs) in (3+2) cycloadditions, providing an orthogonal set of three-atom synths that may be used to produce 5-membered heterocycles inaccessible with classical 1,3-dipoles. Recently, X-alkynyl functional groups (3), where X is a N- or S-based molecular fragment, have been repurposed as neutral TACs that can participate in (3+2) cycloaddition reactions with alkynes (Figure 1-B).6-16 From an electronic point of view, X-alkynyl motifs (3) share a similar arrangement to propargyl-allenyl type dipoles (1). However, due to their “neutral” Lewis structure, their cycloaddition products (4) are zwitterionic. These reactive zwitterions provide an additional avenue for chemical manipulation, diversifying both the possible cyclization endpoints and the substitution of the neutral products (5) that are ultimately obtained. De facto, X-alkynyl functional groups have a unique synthetic potential that is not directly accessed in classical 1,3-dipoles. (3+2) Cycloadditions involving X-alkynyl groups are, however, more demanding in energy than those involving 1,3-dipoles. For this reason, methodologies developed for these cycloaddition cascades have either used tethering groups7-9,12 or highly reactive arene species.12-14 Our recent studies on the intramolecular (3+2) cycloaddition of alkynyl sulfides with alkynes7 have shown several limitations that are directly associated with this high energy demand, notably, the size of the tether between the cycloaddition partners and the substitution on the “X” heteroatom. These limitations cannot be addressed via the thermal mechanism without making scope-limiting changes on the substrate structure. For this reason, we have considered using catalysis as a means to investigate whether other lower-energy pathways could promote the same type of reaction. Interestingly, a line can be drawn between the methodology limitations we observed and those that have been previously tackled in classical (3+2) reactions between 1,3-dipoles and terminal alkynes (Figure 1-C). The copper-catalyzed azide-alkyne coupling (CuAAC), which makes advantageous use of metal acetylide intermediates, was an important gateway to the use of 1,3-dipolar cycloadditions in click chemistry.15,16 By coupling the rate enhancement offered by metal acetylide catalysis with the (3+2) cycloaddition cascades of neutral TACs, previously underperforming reactions would be greatly enabled, and a multitude of unexplored chemical avenues could be envisaged.

We report herein our successful efforts to unlock part of the TAC synthetic potential, demonstrating that metal acetylide catalysis can be advantageously employed to promote the (3+2) cycloaddition of neutral TACs, specifically alkynyl sulfides, in their reaction with intramolecularly tethered terminal alkynes (Figure 1-D).
Figure 1. Coinage metal catalysis in the (3+2) cycloaddition of X-alkynes with terminal alkynes. A) 1,3-dipolar cycloadditions have a high inherent thermal barrier, and metal catalysis provides an alternative low-energy pathway; B) X-alkynes participate as neutral three-atom components in (3+2) cycloadditions, followed by a thermodynamically favored quenching step. Catalysis could also theoretically favor the process; C) Rate enhancements by metal catalysis has enabled the use of 1,3-dipolar cycloadditions in synthetic and bioorthogonal chemistry; D) Terminal alkyne-alkynyl sulfides as a platform to study the effect of coinage metal catalysis for neutral three-atom components.

Through reaction optimization, mechanistic studies and scope investigations, it was established that a proton-coupled cyclometallation step would most likely be responsible for the efficiency of the catalytic process in the case of neutral three-atom components. Using this new platform, previous limitations imposed by substitution on the alkynyl sulfide and linker structures are now greatly reduced, and previously inaccessible reaction intermediates and products can be obtained and investigated for their synthetic potential.

Results and Discussion

Initial Investigations and Evaluation of Reaction Parameters In the course of our studies on the thermally promoted (3+2) cycloaddition cascade of yne-alkynyl sulfides, it was observed that terminal alkyne derivatives of type (6), would produce significant amounts of 3,4-fused thiophene (7) when subjected to conditions promoting a Sonogashira coupling. Further investigations unveiled that this cyclization process was catalyzed at room temperature in the presence of a copper salt and a base (Figure 2) yielding two types of thiophene products having either “lost” or “retained” the R alkyl group initially attached to the S atom ((7) or (8)).

Figure 2. Initial investigations on yne-alkynyl sulfide substrates.

respectively). The same thiophene derivatives could be observed for a few S-(alkyl) substituted substrates (Entries 1-3). Notably, while phenyl substitution on the...
alkyne terminus was previously beneficial to the thermally promoted (3+2) cycloaddition,²⁷ the reverse was observed under catalytic conditions (Entry 4), with substrate (9) remaining unaltered. These observations also countered analogous tests previously made on the terminal alkyne-yramid scaffold (10), where no catalysis whatsoever had been observed using copper salts and various bases. Two important considerations were drawn from these observations: 1) the need for base in conjunction with a terminal alkyne suggested that the observed catalytic effect likely involved the formation of a copper acetylide; and 2) since sulfides are known to chelate coinage metals favorably, while amides do not (from the nitrogen atom), chelation from the heteroatom to the metal may play an important role in favouring this reaction pathway. These observations are reminiscent of the factors previously established as promoting the azide-alkyne cycloaddition in the CuAAC process, which may provide clues on the mechanism of the present transformation. Since a drastic reduction in required temperature (from 130 °C to room temperature) was observed, further investigations in this transformation were done, considering that this new set of conditions could be leveraged to tackle previous limitations observed with the thermal (3+2) cycloaddition process.

The “migration” event leading to products of type (8), whose formation was not observed under thermal conditions, was found to be strongly dependent on the nature of the alkyl group. The optimization of this process, despite its interest, was not considered in the present study. Our attention was focused on the formation of thiophene products of type (7) in order to strictly compare the results obtained under thermal and catalytic conditions. The drastic rate enhancement of this (3+2) process by a copper catalyst was quite reminiscent of the CuAAC process, which has also been shown to proceed via the intermediacy of copper acetylanes.¹⁷ On the basis that azide-alkyne couplings have also been successfully catalyzed by other coinage metals,¹⁸ it was considered that the nature of the metal catalyst was a critical factor to be evaluated (Figure 3-A, entries 1-4). Along with significant rate enhancements, a great improvement in selectivity towards the desired thiophene (7a) was observed when opting for a silver catalyst (entry 2), providing an already excellent set of conditions for this transformation. The reaction could also be promoted by a gold catalyst (entry 3) but was inhibited when the gold species was stabilized by a bulky ligand (entry 4). It is noteworthy that non strongly ligated gold(I) species tend to suffer reduction by trialkylamines, which likely explains the poor reaction conversion when Me2S•AuCl was used as the catalyst.

Figure 3. Yne-alkynyl sulfides bearing three-atom linkers. A) Optimization of the catalyzed (3+2) cyclization for model substrate (9a); B) Terminal alkynes are a structural limitation in analogous thermal-promoted (3+2) cycloadditions; C) Scope of the catalyzed (3+2) cyclization for 3-atom linkers.
A control experiment showed that only trace amounts of the desired thiophene product were formed in the absence of base (entry 5). However, the use of base as an additive could be avoided by employing a mildly basic acetate counteranion on the metal catalyst (AgOAc, entry 6). The choice of solvent proved to be a crucial element also affecting the rate of the reaction. While exchanging DCM for the protic EtOH increased the selectivity of the reaction towards (7a) (entry 7), the use of acetic acid had the largest effect on reaction rate. In this case, a full and selective conversion of the substrate was observed at the first analysis after 5 minutes (entry 8).19-24 Wondering if the same effect could be effective under copper catalysis, an analogous set of conditions was developed using copper(I) acetate in acetic acid. An impressive enhancement in reaction rate was similarly observed in this case (entry 9).

The improvement brought by these new sets of conditions is quite striking. What previously yielded poor yields after multiples hours of heating at 130°C (Figure 3-B) can now be achieved quantitatively in minutes at room temperature. These initial results made this catalytic approach promising in terms of functional groups tolerance, and the possibility to limit degradation pathways, all of which could result in a cleaner reaction profile towards the desired 3,4-fused thiophene (7). The optimized AgOAc/AcOH system was consequently employed for a series of terminal alkynes and alkynyl sulfides tethered by various 3-atom linkers (Figure 3-C). Substrates with tosylamide (6a-d), carbamate (6e), ether (6f,g), and ester (6h) linkers gave quasi-quantitative yields (>92%) of the desired thiophenes in minutes. Only in the case of the amide linker in (6i) was the yield in thiophene slightly lower (81%), a result that may be attributed to the electron-poor nature of this specific alkynyl sulfide (See Supporting Information, section 6.1). In line with our previous experience on the use of a malonate-derived linker,7 (6j) resulted in a much slower reaction time, but in an excellent yield.

Towards an Understanding of the Reaction Mechanism

The remarkable rate increase observed when acetic acid was use as the solvent was quite informative. It suggested a mechanism more complex in nature than the simple formation of a copper acetylide, which is naturally favoured under more basic conditions. In the case of the CuAAC reaction, the rate increase by carboxylic acids has been ascribed to two factors: 1) the displacement of the equilibrium of copper acetylide species towards a catalytically active dinuclear acetylide complex (Figure 4-A-i),20-23 and 2) the expedited protodemetalation of the resulting organocopper heterocycle (Figure 4-A-ii).20-24 Similar effects could be envisaged in the present transformation.

A third effect by mild acids can be hypothesized when considering the mechanism generally proposed for CuAAC, which features a metallacycle of type (11) as a key intermediate in the cycloaddition process (Figure 4-B). Notably, the rate-limiting step of the cyclization portion in this mechanism is the formation of the first C-N bond,25-27 which results in a lone pair of electrons being stabilized on the central nitrogen atom of the azide moiety. Transposition of this mechanism onto the yne-alkynyl sulfide system shows a similar event could occur to form an analogous metallacycle (12). However, such a mechanistic scenario would result in an unstable lone pair of electrons being localized onto the central carbon atom, making the initial C-C bond formation endergonic. This lone pair development could be confirmed by NBO analysis of metallacycle III-B, and the corresponding negative charge could be visualized by ESP analysis of the optimized cupracyclic intermediate (Figure 4-C). It can be considered, however, that such an anion would be quite short-lived or nonexistent in a process involving the use of acetic acid as the solvent. It was therefore conjectured that protic sources could participate in stabilizing this charge development both at the transition state and in the cupracyclic intermediate (Figure 4-A-iii). This stabilization could partly explain the rate-increasing effect observed when weak acids are employed.

Interestingly, some other clues from the literature also point towards the possible intermediacy of such metalacycles. In previous studies on yne-alkynyl sulfide substrates, the Yoshimatsu group has observed the copper-catalyzed incorporation of exogeneous terminal alkynes onto the substrates to yield cyclized diene-ylene products with a surprisingly specific stereochemistry.28 During our studies, the same type of diene-ylene species were observed as by-products alongside the desired thiophenes. We propose that they occur from a common 6-membered metalacyclic intermediate. Further discussion on the topic can be found in the supporting information (Section 6.1).

In order to evaluate the involvement of mono- and/or bis-metallic species in the mechanism and the explicit role of acetic acid in this transformation, five potential cyclization pathways were characterized via DFT studies (Figure 5). Calculations were carried out using the Gaussian16 software.29 Stationary point optimization and frequency calculations were performed using the PBE0/def2SVP level of theory, with empirical dispersion correction (GD3-BJ).30 This methodology has previously shown reasonable accuracy for comparatively low computation cost in benchmarking studies concerning transition metal-mediated transformations,31 and has been used in recent mechanistic work involving metal-catalyzed (3+2) cycloadditions.32 A solvation model using SMD33 (acetic acid) was also applied.
Figure 4. Identifying the role of protic sources in the metal catalyzed yne-alkynyl sulfide (3+2) cycloaddition. A) Previous studies have hypothesized that protic sources help in: (i) increasing the formation of the more catalytically active bis-copper acetylide and (ii) in protodemetalation for catalyst turnover. (iii) In the case of alkynyl sulfides, protic sources are likely also involved in favouring the formation of metalacyclic intermediates; B) Transposition of the CuAAC mechanism onto the yne-alkynyl sulfide system reveals the presence of a non-stabilized lone pair of electrons on metallacycle (12); C) The electrostatic potential map (isovalue = ± 0.08) of the intermediate metallacycle shows negative charge development on the central carbon atom.

Figure 5. DFT studies on the stepwise (3+2) cyclization event. Free energies in parentheses reported in kcal/mol.
Single point energy calculations were finally performed using the same methodology, but with the use of def2TZVP augmented basis set. To get some insight into the C-C bond formation event and compare the energy demand as a function of metallic nuclearity and acid co-catalysis, the energy of the five pre-cyclization complexes I-A to I-E was normalized to 0. The conformational equilibria of substrates and the distribution between various copper complexes (and their possible aggregates) were not examined. The stabilization imparted by the geminal acetylide complex in the di-copper mechanism was however estimated by comparing the energy of complexes I-B and I-C, showing a large gap of 18.7 kcal/mol in favor of the geminal di-Cu complex I-B.

For the C-C bond formation step, calculated transition state barriers range between 11.4 and 16.1 kcal/mol. Notably, the two lowest barriers (TS II-B and II-D) are those involving a geminal di-copper acetylide complex. It is worth noting that formation of metallacycles I-A and I-B, which do not involve any additional stabilization of the charge development on the central carbon atom, were both calculated to be endergonic processes. As hypothesized, transition states which involve concerted protonation of the central carbon atom during the C-C bond formation event (II-C,D,E) could be located on the PES. The resulting metallacycles III-C, III-D and III-E, which involve stabilization of the charge, are all favorable exergonic processes. The C-S bond formation step was found to be facile and unlikely to be turnover-limiting. The transition state IV-D leading from metallacyle III-D to thionium V-D could also be located, showing a low energy barrier of 6.6 kcal/mol. From this thionium intermediate, a sequence of de-alkylation from sulfur and decomplexation /protodemetalation of the copper units would lead to the observed thiophene products.

**Figure 6.** A) Thiophenium intermediates and a 1,2-aryl migration product could be observed by NMR for S-(aryl) substrates. An intermediate thiophenium triflate salt (14a-OTf) was isolated and its structure was confirmed by single crystal x-ray diffraction studies; B) Kinetic studies with a stoichiometric quantity of catalyst allowed identification of intermediates (13c-Ag) and (14c-Ag-OTf). Mechanistic modelling favors catalysis via bis-metallated intermediates.
Supplementary calculations were performed on pathways A, B and D using AgOAc as the catalyst. They were found to be in qualitative agreement with the outcome of the calculations performed using CuOAc (See Supporting Information, Section 6.7). These results may also suggest that a similar proton-coupled cycloaddition could be in play for CuAAC reactions when these are run in the presence of an acid.

In order to probe the formation of thiophenium intermediates, the facile de-alkylation mechanism observed with S-(alkyl) thiopheniums was made non-operant by using S-(aryl) substrates and attempting the formation of the corresponding S-(aryl) thiophenium salts. Satisfyingly, quantitative formation of the thiophenium acetate salt (14a-OAc-d$_5$) was observed by NMR analysis when S-(phenyl) alkynyl sulfide derivative (13a) was subjected at room temperature to the optimized AgOAc/ACOH catalytic conditions (Figure 6-A). This result seemed to indicate that thiophenium salts are common intermediates in the metal-catalyzed (3+2) of alkynyl sulfides. Heating at 70 °C, the in situ formed thiophenium salt 14a-OAc-d$_5$ quantitatively generated the 2-phenyl thiophene (15a-d$_5$), a result in agreement with the previously reported thermal rearrangement of S-(aryl) benzothiophenium salts.$^{34}$ Based on previous studies$^{34}$ and a cross-over experiment (See Supporting Information, Section 6.6), the transformation of S-(aryl) thiophenium salts (14) to thiophenes (15) likely proceeds via a 1,5-sigmatropic rearrangement of the aryl group, resulting in its migration from sulfur to the adjacent carbon atom, with consecutive loss of acetic acid. While isolating the acetate salt of this thiophenium derivative proved challenging, an alternative procedure to access the triflate salt (14a-OTf) was developed (Figure 6-B, see Supporting Information, Sections 6.4 and 6.5 for optimization and scale-up details). Under these new operative conditions, the salt could be easily obtained with good purity by simple trituration. Crystals of (14a-OTf) were then grown and analyzed by SCXRD, confirming the identity of the thiophenium salt. To our knowledge, simple S-(aryl) thiophenium salts such as (14) have not been previously reported. The central S atom of (14a-OTf) adopts a pyramidal geometry with the phenyl group lying in a perpendicular position to the thiophenium core. The interatomic S-C$_{Ph}$ bond length and bond angle formed between the C$_{Ph}$-S bond and the thiophene core plan were found to be 1.783 Å and 117.9° respectively. The x-ray structure of (14a-OTf) is in line with that of analogous S-(aryl) dibenzothiophenium salts,$^{35,36}$ a class of S-(aryl) sulfonium salts commonly employed in cross-coupling reactions and photoredox catalysis,$^{37,38}$ as well as acceptors in EDA complexes,$^{39}$ S-(Aryl) organo-sulfur(IV) compounds are routinely accessed by aromatic C-H functionalization using activated sulfoxides precursors, a strategy that generally limits the scope to electron-rich (hetero)aromatics.$^{36,40}$ Since the S-C$_{Ar}$ bond is pre-installed in the case of (14a-OTf), this limitation could a priori be lifted. The use of S-(aryl) thiophenium salts in redox processes is the subject of current investigations.

Given the efficiency and selectivity of this transformation, an analogous substrate (13c) was synthesized and used in a stoichiometric experiment to test our mechanistic hypotheses (Figure 6-C). When this substrate was dissolved in the presence of excess triethylamine and a stoichiometric quantity of silver triflate, a few important observations could be made: 1) the formation of silver acetylide (13c-Ag) was immediate and quantitative; 2) no bis-silver thiophenium intermediate of type (14c-Ag$_2$-OTf) was observed; and 3) the mono-silver thiophenium (14c-Ag-OTf) was produced in a quantitative manner along with a small amount of fully protonated thiophenium (14c-OTf). The results of this experiment support that protonation is a key component in the (3+2) cyclization to thiophenium intermediates. Kinetic modelling was subsequently performed using the COPASI software$^{41}$ to further evaluate the viability of mono-metallic versus bis-metallic pathways as presented in Figure 6-B (See Supporting Information for procedures, Section 6.3). The reaction of silver acetylide (13c-Ag) with the ammonium salt does not seem to follow simple uni- or bimolecular kinetics, which renders the mono-metallic pathway unlikely. On the other hand, a model that proceeds through catalytic formation of bis-silver intermediates (the dual metal catalysis mode) was found to appropriately fit with the experimental data.

### Applying Catalysis to Tackle Previous Limitations

The one-pot metal-catalyzed (3+2) cycloaddition to S-(aryl) thiophenium salts and their rearrangement to the corresponding 2-aryl thiophenes constituted a more efficient and selective pathway to (3+2) cycloaddition products than previously observed under thermal conditions. In fact, the analogous substrate (16), which was previously studied by our group,$^7$ had only produced a complex mixture upon heating (Figure 7-A). A scope with substrates possessing differently substituted aryl groups was then performed using this new catalytic cascade (Figure 7-B). A range of electron-rich to electron-poor phenyl derivatives were evaluated (13a-i), all providing excellent yields of 2-aryl substituted fused thiophenes. Even derivative (13j) showed good reactivity in generating bis-thiophene (15j), although requiring a long reaction time for completion. In most cases, the catalyzed (3+2) component of the reaction was completed immediately at 70°C, while the 1,2-migration of the aryl group required several hours of heating. The reactivity of an S-(alkynyl)
alkynyl sulfide (17) was also evaluated but did not fare well under the AgOAc/AcOH catalytic conditions. The alternative method developed making use of AgOTf/PyrHOTf in TFE/DCM proved to be useful (Figure 8). In this case, the alkynyl migration seemed to be quite facile (no thiophenium intermediate was observed during the reaction) and the 2-alkynyl thiophene (18) was directly obtained in a modest but non optimized 33% yield. From a general synthetic point of view, these results demonstrated the interest of using TACs in cycloadditions process and the higher degree of functionalization that can be reached as compared to classical 1,3-dipolar cycloadditions. The single result obtained with bis-alkynyl thioether (17) demonstrated that the cyclization-cascade process could be extended to substrates possessing Csp hydrated substituents on the S atom.

Figure 8. (3+2) cyclization with 1,2-migration of an alkynyl group.

The singular slow kinetics observed for the formation of product (7j) (Figure 3-C) foreshadows an issue that was rapidly discovered for structures with linkers comprising more than 3 atoms. In the representative case of substrate (6k), no conversion could be observed after 22 hours with the AgOAc/AcOH catalytic system at room temperature (Figure 9-A, entry 1). This issue could not be solved solely by raising the temperature (entry 2). Under these modified conditions, the formation of a silver mirror was observed during the course of the reaction as an indication of catalyst degradation. The starting material was also fully consumed to produce the enol acetate (19k) whose structure results from the addition of acetic acid to the alkyne moiety of the alkynyl sulfide. This process was found independent of the metal catalyst (see Supporting Information, Section 2.2). The catalyst degradation could be alleviated by the alternate use of copper(I) acetate in combination with sodium ascorbate as a co-catalyst (entry 3). This modification provided a small quantity of the desired thiophene, but starting material degradation by acetic acid remained highly competitive. Swapping acetic acid to the mildly acidic trifluoroethanol successfully repressed the formation (19k) (entry 4) while still promoting the production of the desired thiophene. A final parameter was left to optimize, which was minimizing the formation of alkyl migration products (8) and (8'). Although the mechanism of the migration event was not well understood, it was anticipated that changing the tert-butyl group to a primary alkyl chain could suppress this pathway (be it pericyclic, cationic or radical in nature). This hypothesis proved to be true when using the n-propyl group (entry 5), for which none of (8) or (8') were observed. Finally, the more expensive copper(I) acetate was replaced by copper(II) acetate to no detriment of the obtained yield (entry 6), compromising instead for a slightly longer induction period to active catalysis.

In the case of 4-atom linkers, it is again a staggering improvement from the thermal conditions. 4-Atom linkers and terminal alkynes both previously proved to be scope-limiting elements in the thermal (3+2) cycloaddition. Heating the yne-alkynyl sulfide (6k) at 200 °C for 4 hours was not long enough for full conversion. A large amount (85%) of unselective degradation of the starting material occurred, and only 9% NMR yield of the desired thiophene was observed (Figure 9-B). With the newly optimized
copper-catalyzed conditions, full consumption of the starting material took place in only 30 min at 80 °C, and the desired thiophene could be obtained in 93% isolated yield (Figure 9-C). These conditions were applied to a selection of yne-alkynyl sulfide substrates bearing linkers composed of 4 to 6 atoms. In the case of 4-atom linkers, the substrates tolerated these conditions quite well, showing rapid conversion for o-phenylene derivative (6m), and a comparable yield for (6n) possessing a free alcohol. Lactone (7o) could also be obtained over a longer period of reaction, but in a lesser yield (28%). On the other hand, in the presence of 5-atom linkers, higher temperatures were required and poor conversions were observed when evaluated with a 10 mol% catalyst loading. At higher catalyst loadings, good results were obtained with (6p) bearing a simple 5-atom linker (59%). At this temperature, however, the sensitivity of homopropargyl groups (6q) proved to be more significant, and a lower 29% yield of (7q) was obtained. While propargyl carboxylates were tolerated for substrates with a lower linker size (see Figure 3-C), their 3,3-sigmatropic rearrangement seemed to be competitive in the case of (6r), leading to a negligible yield of the desired thiophene (7r). Silylated alkynes, which are known to undergo desilylative metatation, were also considered as alternative substrates to terminal alkynes. Trimethylsilyl alkyne (6s) was pleasingly observed to convert selectively to its corresponding thiophene (7s). Interestingly, the

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Figure 9. A) Optimization of the (3+2) cyclization for model substrates (6k) and (6l); B) Longer linkers present a scope limitation for thermal (3+2) reactions; C) Scope of the catalyzed (3+2) cyclization for longer linkers. *Substrate seems to degrade via a copper-catalyzed [3,3]-sigmatropic rearrangement; †2 equivalents of acetic acid were used.

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unreacted substrate remained fully silylated, which seems to indicate that the metalation step is rate-limiting for this class of substrates. A limit in reactivity was reached in the case of 6-atom tethers. The catalyzed (3+2) cycloaddition could also be successfully observed but only with the additional help of geometrical constraint, such as in the case of the ortho-phenylene derived linker found in (6t).

It is important to note that at higher temperature, catalyst degradation in the form of metallic copper can be observed in significant amounts. While this scope selection shows the potential of this catalytic method for the formation of fused thiophenes, further optimization and screening of stabilizing ligands may help in lowering catalyst loadings.

Figure 10. A) The catalyzed (3+2) cyclization provides pre-functionalized 3,4-fused thiophenes. The core structure can be subsequently diversified to reach motifs closer to medicinally relevant compounds; B) Scaled-up synthesis of substrate (6n) and catalyzed (3+2) cyclization. Multiple diversifications of the fused thiophene core via linker modifications. See Supporting Information for experimental details.

The mild conditions employed in the catalyzed (3+2) cycloaddition allows good functional group tolerance, directly providing functionalized 3,4-fused thiophenes. By joining the (3+2) methodology with post-cyclization functionalization of the linker structure, routes to a variety of medicinally relevant fused thiophene scaffolds were exemplified (Figure 10-A). Alkynyl sulfides, although seeming as “exotic” functional groups, are quite easily accessed. For instance, S-(n-octyl) alkynyl sulfide (20) was conveniently prepared in three steps and an 82% overall yield from commercially available materials using robust and scalable chemistry (see Supporting Information, Section 3.5), without need of any purification by chromatography (Figure 10-B). This sequence made the preparation of yne-alkynyl sulfide (6n) straightforward at larger scale. Increasing the copper-catalyzed (3+2) transformation to gram-scale gave a comparable yield (77%) of (7n) as previously obtained at lower scale (79%) (see Figure 9-C) with a slightly modified procedure (Supporting Information, Section 5.4). The alcohol group itself was employed as a useful handle, via oxidation and condensation chemistry,
towards three new fused thiophene cores (22), (23) and (24), ultimately accessing several medicinally-relevant core structures.\textsuperscript{42-45} While thieno spiro lactone (25) (Figure 10-C) could not be easily obtained via the (3+2) transformation due to substrate synthesis issues, predictable oxidation of the ether linker from scope example (7g) provided an alternate route to the same structure. This specific fused thiophene constitutes an analogous core to thiophene-based $\sigma_1$ receptor ligands.\textsuperscript{46,47} Finally, we were intrigued by the possibility that the reactivity principle developed for alkynyl sulfide derivatives could be expanded to another class of closely related X-alkynyl groups: alkynyl selenides. To this end, substrate (26) was prepared and reacted under the previously optimized AgOAc/AcOH catalytic conditions (Figure 11).

![Figure 11. Methodology applied to alkynyl selenides.](image)

Overall mechanistic proposal

The reaction was found efficient and selective providing selenophene (27) in very good yield (86%), without need of purification. 3 or 3,4-substituted selenophenes are of interest in material science, as their incorporation as building blocks in materials can be often beneficial in terms of optoelectronic properties.\textsuperscript{48-50} Further studies on the application of this methodology to the synthesis of 3,4-fused selenophenes will be disclosed in due course.

Conclusion

By recognizing that heteroatom-substituted alkynes are isoelectronic to classical propargyl-allenyl type 1,3-dipoles, a novel class of (3+2) cycloadditions making use of neutral three-atom components has been developed over the last several years. The thermal variant of this cycloaddition proceeds, however, via unstable zwitterionic intermediates which makes it prohibitively high in energy for certain substrates. By considering the reactivity principles at the heart of the CuAAC reaction, a set of catalytic conditions was successfully developed for the (3+2) cycloaddition between X-alkynes (a neutral three-atom component) and terminal alkynes, permitting a dramatic decrease in required reaction temperature. This rate enhancement was instrumental in expanding the scope of the reaction and permitting the isolation of key thiophenium intermediates.

From optimization and mechanistic studies, pathways as shown in Figure 12 are now proposed as a general mechanistic overview of the reactivity offered by the copper-catalyzed (3+2) cycloaddition of thioalkynes with alkynes. In the first stage of the catalytic transformation, an equilibrium of metal acetylide species ultimately provides a catalytically active geminal bis-metallic acetylide complex. This complex undergoes a cyclization reaction to produce a fleeting metallacyclic intermediate similar in nature to that proposed for the CuAAC reaction. Due to the “neutral” nature of alkynyl sulfides, this cyclization must be proton-coupled to be thermodynamically favourable. Ring contraction ensues to form key metallated thiophenium intermediates. Turnover of the catalyst liberates protonated thiophenium salts, some of which can be observed and isolated. Finally, these thiophenium salts decompose following different predictable pathways, depending on structure and reaction conditions, to produce various 3,4-fused thiophene products.
Fundamentally, this study demonstrates that mechanistic pathways akin to the ones involved in coinage metal-catalyzed 1,3-dipolar cycloadditions are also accessible to neutral three-atom components. Applying this general concept to the (3+2) cycloaddition of neutral three-atom components may unveil yet undiscovered reactivities in cycloaddition chemistry.

Supporting Information

The authors have cited additional references in the Supporting Information. These were supplemented to the following References section 51–54

CCDC deposition number for x-ray data of (14a-OTf) is 2260026.

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Author contributions

Project finances were managed by F.G. Conceptualization and development of the project were done by D.C. and F.G. Experimental work was shared between D.C., A.P. and M.G. The manuscript was written by D.C. and F.G.

References

5. Although often having poor dipole moments, these species are still referred to, this day, as “1,3-dipoles”. This distinction is used to clarify the subsequent use of the term “neutral” three-atom components.

19. Great rate enhancements have also been reported for the CuAAC process in the presence of carboxylic acids, see following references 20-24.


