ChemComm

FEATURE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2014, **50**, 10008

Turning unreactive copper acetylides into remarkably powerful and mild alkyne transfer reagents by oxidative umpolung

G. Evano,*[a] K. Jouvin,[b] C. Theunissen,[a] C. Guissart,[a] A. Laouiti,[bc] C. Tresse,[d] J. Heimburger,[b] Y. Bouhoute,[a] R. Veillard,[e] M. Lecomte,[a] A. Nitelet,[a] S. Schweizer,[d] N. Blanchard,[f] C. Alayrac[e] and A.-C. Gaumont[e]

Received 29th April 2014,
Accepted 28th May 2014

DOI: 10.1039/c4cc03198a

www.rsc.org/chemcomm

This is not breaking news: copper acetylides, readily available polymeric rock-stable solids, have been known for more than a century to be unreactive species and piteous nucleophiles. This lack of reactivity actually makes them ideal alkyne transfer reagents that can be easily activated under mild oxidizing conditions. When treated with molecular oxygen in the presence of simple chelating nitrogen ligands such as TMEDA, phenanthroline or imidazole derivatives, they are smoothly oxidized to highly electrophilic species that formally behave like acetylenic carbocations and can therefore be used for the mild and practical alkynylation of a wide range of nitrogen, phosphorus and carbon nucleophiles.

1. Introduction

Organic synthesis is clearly a central science with deep implications in various domains such as biology, medicine, energy or materials science, just to cite a few. Fuelled by the high and growing demand for efficient procedures to assemble complex molecules from simple building blocks, chemical synthesis has reached an impressive level of complexity, even if – contrary to what has been said too many times and despite what one could wish – not all reactions are possible and not all molecules can be easily made. An ever growing number of chemical reactions that were impossible to perform decades ago can now be done with the utmost efficiency and, in some cases, with an almost surgical efficiency. The renaissance of the Huisgen's cycloaddition is certainly one of the most striking examples of a reaction that recently had an important impact on other areas of chemistry and research. In addition, the need for environmentally benign and more sustainable chemical practices requires new ways of carrying out synthesis, which is also an important motivation for the design and development of new processes and the emergence of new synthetic paradigms. However, a downside inherent to today's level of sophistication of chemical synthesis is that many reactions and processes actually rely on too complex reagents and procedures. This clearly limits their widespread application, especially when one just wishes to test a reaction and does not want to spend too much time on the preparation of a reagent, or even on the reaction itself, which brings us back to da Vinci's adage "simplicity is the ultimate sophistication".

This is actually a problem we faced couple of years ago when we started our research program on the chemistry of ynamides.[1,2] We indeed developed a first generation synthesis of ynamides **3** based on a copper-catalysed cross-coupling between a series of vinyl dibromides **1** and nitrogen nucleophiles **2** (Scheme 1, eqn (1)).[3,4] While this procedure was found to be quite efficient and enabled the preparation of more than hundred different ynamides to date, one of the problems we met later on was due to the use of a base, although not a strong one, and heat, which were not compatible with all the ynamides we wanted to prepare. If these problems were only seldom met and were actually more minor limitations of our procedure, its main drawbacks were found to be both the preparation of the vinyl dibromides **1** – conveniently prepared on a gram scale using the Ramirez olefination[5] or the Lautens modification,[6] but a bit more painful to prepare on a 20–50 g scale, – and the volatility of dibromoalkenes substituted with small alkyl chains as

---

[a] *Laboratoire de Chimie Organique, Service de Chimie et PhysicoChimie Organiques, Université Libre de Bruxelles, Avenue F. D. Roosevelt 50, CP160/06, 1050 Brussels, Belgium. E-mail: gevano@ulb.ac.be; Fax: +32 2 650 27 98; Tel: +32 2 650 30 57*

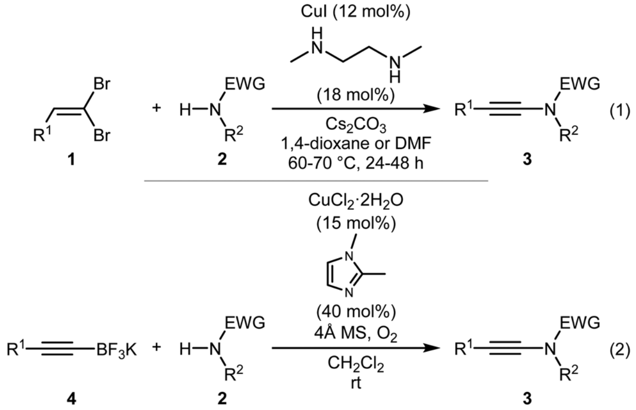
[b] *Institut Lavoisier de Versailles, UMR CNRS 8180, Université de Versailles Saint-Quentin-en-Yvelines, 45, avenue des Etats-Unis, 78035 Versailles Cedex, France*

[c] *Laboratoire de Chimie Hétérocyclique, Produits Naturels et Réactivité, Département de Chimie, Faculté des Sciences de Monastir, Université de Monastir, avenue de l'environnement, 5019 Monastir, Tunisia*

[d] *Laboratoire de Chimie Organique et Bioorganique, Université de Haute-Alsace-ENSCMu, 3 rue A. Werner, 68093 Mulhouse cedex, France*

[e] *Laboratoire de Chimie Moléculaire et Thioorganique, UMR CNRS 6507, INC3M, FR3038, ENSICAEN & Université de Caen Basse-Normandie, 6 bvd Maréchal Juin, 14050 Caen, France*

[f] *Laboratoire de Chimie Moléculaire, ECPM-CNRS UMR7509, Université de Strasbourg, 25 rue Becquerel, 67087 Strasbourg, France*



Scheme 1 First and second generation synthesis of ynamides developed in the group: a need for alternative and more practical solutions.

well as the need for strictly controlled conditions (anhydrous solvents and an inert atmosphere).

In an attempt to address these shortcomings, we next decided to switch to oxidative copper-catalysed cross-couplings which, since they involve a transmetalation–oxidation pathway instead of the more demanding oxidative addition, can usually be performed under milder conditions. Screening various reagents led us to the identification of potassium alkynyltrifluoroborates **4** which were shown to be remarkably efficient alkynylation agents, providing the desired ynamides **3** under the mildest conditions reported at this time (room-temperature, base free, Scheme 1, eqn (2)).[7] While this solved the main limitations we had with our first generation procedure, we quickly realized that the synthesis of the starting materials was now the problematic step. Indeed, they need to be prepared from the corresponding terminal alkynes by a one pot sequence involving the deprotonation–borylation–treatment with toxic and corrosive KHF_2 which renders their synthesis less practical than one could wish and had a disastrous effect on quite a lot of our glassware.[8]

The limitations met during the development of these first and second generation syntheses of ynamides led us to re-evaluate these procedures and to try to identify reagents that would enable a long sought-after practical and user-friendly synthesis. With this goal in mind, we decided that the reagent we would use should meet the following specifications: it should be readily available and easy to make, even on a multigram scale, bench-stable, non-hazardous, non-volatile, non-lachrymatory (which was suggested by some students who had a bad experience handling volatile bromoalkynes and some colleagues who had to suffer from their rather unpleasant smell and side-effects), unreactive but still easily activated under mild conditions. Quite a wish list.

After spending some time imagining all kinds of more or less fancy reagents, we eventually realized that the simplest solution was in fact quite obvious, and even used to be taught on basic organic chemistry classes: the only reagents that could potentially meet all these specifications would be copper acetylides. These compounds, the lazy members of the organocopper family, were first mentioned in 1870 by Carl Glaser, who obtained a bright yellow solid upon mixing phenylacetylene and a solution of copper chloride in ammonia,[9] a reaction that would next become the basis for the analytical detection of terminal alkynes which typically form unreactive bright yellow precipitates upon reaction with an ammoniacal solution of copper sulfate. Apart from the Cadiot–Chodkiewicz[10] or the Castro–Stephens[11] reactions, which require harsh conditions, these polymeric compounds have been only scarcely used later on because of their impressive lack of reactivity. Indeed, they only react with strong electrophiles and they "are hydrolysed only by hydrochloric acid at elevated temperature or by an aqueous solution of alkali metal cyanide".[12] Provided that we could find a way to activate them under mild conditions and reverse their polarity to force them to react with nucleophiles, they could potentially be ideal reagents that could be used for the development of a practical synthesis of ynamides from readily available reagents.

In addition to their lack of reactivity that was of great interest to us, the preparation of these reagents is especially convenient, unlike other organocopper reagents whose synthesis typically requires the utmost care. Upon simply adding a terminal alkyne **5** to a solution of cuprous iodide in a mixture of ammonia, water and ethanol, a yellow precipitate immediately appears, which is then just collected by filtration, washed and dried to give the desired copper acetylide **6**. Since there has been unfortunately no such thing as an ideal reaction, it ought to be mentioned that in some rare cases (starting from trimethylsilylacetylene or TBS-protected 1-phenylprop-2-yn-1-ol for example), we noted that a couple of copper acetylides lacked the typical polymeric structure and the inherent stability. The synthesis is however in most cases remarkably easy to perform on a multigram scale and examples collected in Fig. 1 are representative of this procedure.[13] These bright yellow polymeric compounds are perfectly stable, can be stored for years at room temperature without signs of degradation and, contrary to certain preconceived

G. Evano

Gwilherm Evano studied chemistry at the Ecole Normale Supérieure in Paris and received his PhD from the Université Pierre et Marie Curie in 2002 under the supervision of Profs. François Couty and Claude Agami. After postdoctoral studies with Prof. James S. Panek at Boston University, he joined the CNRS at the University of Versailles in 2004 and moved to the Université Libre de Bruxelles as an associate professor in 2012. He has coauthored 80 publications, 11 book chapters and recently co-edited "Copper-Mediated Cross-Coupling Reactions", a book dedicated to copper catalysis. His main research interests are the development of new copper-mediated transformations, the chemistry of ynamides and other heteroatom-substituted alkynes and the total synthesis of natural and/or biologically relevant products.

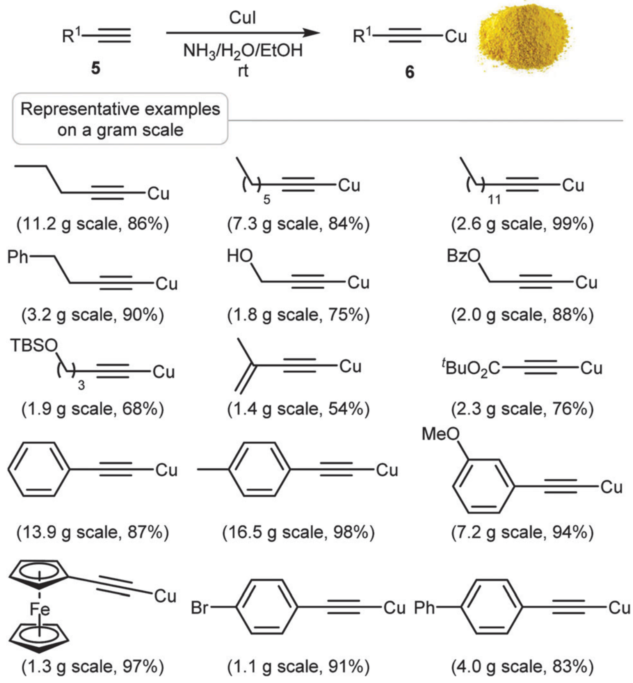


Fig. 1 Synthesis of copper acetylides and representative examples prepared on a gram scale.

ideas, they are neither explosive nor shock sensitive.[14] It should in addition be mentioned that some of them are commercially available.[15]

For more complex alkynes which might not appreciate being soaked in a mixture of ammonia, water and ethanol, the corresponding copper acetylides can be prepared by an alternative procedure which consists in the reaction of these alkynes with finely powdered cuprous iodide in DMF in the presence of potassium carbonate.[13,16] Examples collected in Fig. 2 are representative of this procedure which was shown to be tolerant to a wide range of functional groups and enabled the preparation of copper acetylides from more complex and/or sensitive alkynes.

2. Strategy: oxidative umpolung of copper acetylides

While these alkynylcopper reagents **6** are, although unreactive, nucleophilic species (Scheme 2, eqn (1)), their reactivity had to be reversed in order to act as electrophilic alkynylating agents and transfer their alkyne moiety to nitrogen nucleophiles **2**, giving the corresponding ynamides **3**. The strategy we relied on to reverse the polarity of these copper acetylides was based on their oxidation to copper(III) acetylides **8**,[17] highly electrophilic species that formally behave like acetylenic carbocations – compounds that can hardly be generated otherwise – and that could be trapped by nitrogen nucleophiles **2** and provide, after a reductive elimination step, the desired ynamides **3** (Scheme 2, eqn (2)).

If this strategy might seem to be naive or even counter-intuitive, notably due to the well-known easy dimerization of organocopper reagents in the presence of even traces of oxygen, remarkable reactions have been developed based on the oxidative chemistry of organocopper reagents, an area of organometallic chemistry that clearly deserves to be further explored.[18] This oxidative chemistry of organocopper reagents was first explored systematically by Whitesides who examined the dimerization of a number of organocuprates (Scheme 3, eqn (1)) and the cross-coupling from mixed organocuprates (Scheme 3, eqn (2)).[19] Its synthetic potential was demonstrated only more recently, notably by the Lipshutz,[20] Knochel[21] and Spring[22] groups for the synthesis of unsymmetrical biaryls, dienes and aromatic alkynes. A significant conceptual breakthrough was reported later on by Yamamoto,[23] Snieckus,[24] Ricci,[25] and Knochel,[26] who described the oxidative coupling of amidocuprates (Scheme 3, eqn (3)) – demonstrating that this strategy can also be successfully applied to the formation of carbon–nitrogen bonds – and developed incredibly mild amination procedures based on such oxidative cross-couplings.

Although the oxidative chemistry of aryl, vinyl,[27] alkyl and even fluorinated organocopper/cuprates had been extensively studied when we started this project, copper acetylides had

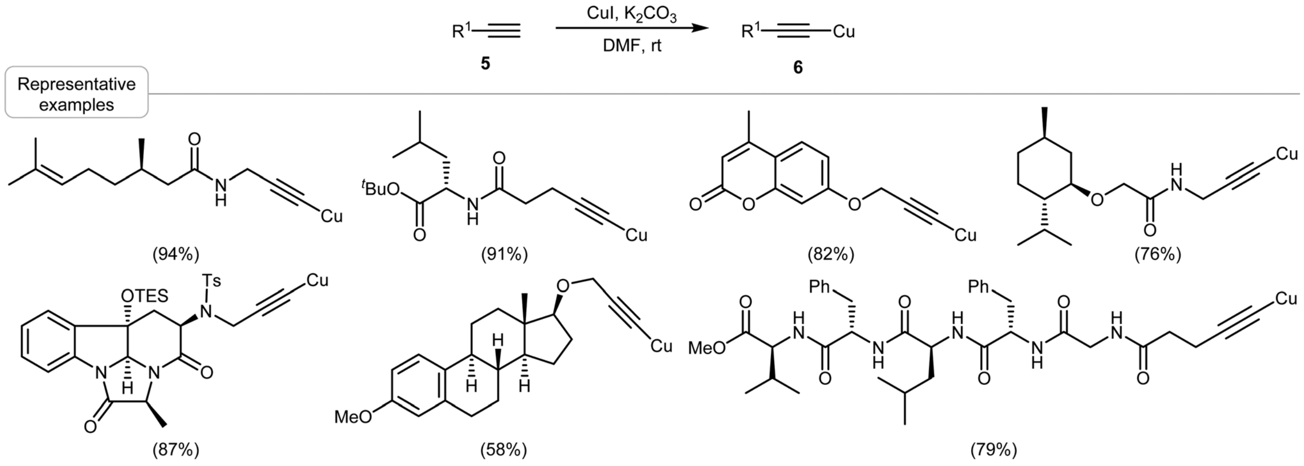
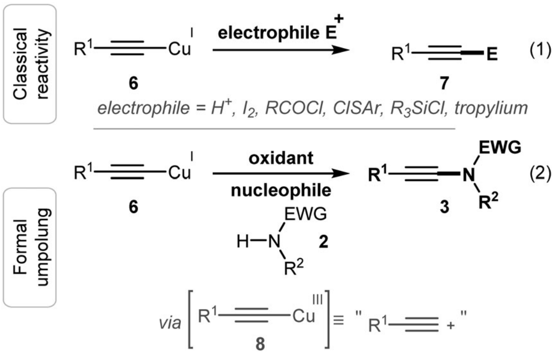
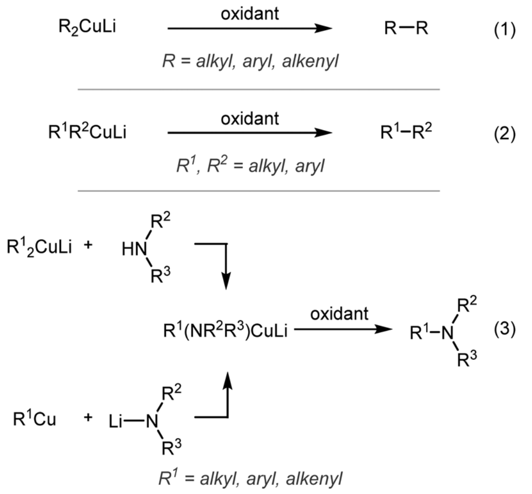


Fig. 2 Synthesis of more complex copper acetylides.



Scheme 2 Strategy: oxidative umpolung of copper acetylides.



Scheme 3 Brief overview of the oxidative chemistry of organocopper reagents.

been for some reasons left aside, despite the important potential of their oxidative umpolung. Motivated by what had been reported on the oxidative chemistry of organocopper reagents and excited by what we envisioned from the extension of this chemistry to alkynylcopper reagents, we therefore decided to embark on the study of their oxidative umpolung, which will be fully described in the following sections.

3. Oxidative alkynylation of nitrogen nucleophiles with copper acetylides: finally reaching a practical synthesis of ynamides

Our experience in copper catalysis[28] turned out to be quite useful for the development and optimization of the oxidative alkynylation of nitrogen nucleophiles with copper acetylides. Indeed, while no reaction was observed when such a reagent was reacted with pyrrolidin-2-one, which was chosen as the model nucleophile for our preliminary studies, in the presence of oxygen, the role of nitrogen ligands classically used in copper-catalysed reactions turned out to be critical and TMEDA proved to be by far the best ligand for this transformation. Upon simply mixing a copper acetylide **6** and an excess of the nitrogen nucleophile **2** in acetonitrile, in the presence of TMEDA and under an atmosphere of oxygen (balloon) at room temperature, an especially smooth and clean reaction occurs within 24 to 48 hours and the corresponding ynamides **3** can be isolated in good to excellent yields. Representative examples shown in Fig. 3 are illustrative of this procedure which, as we hoped, simply relies on a mix-and-stir process.[13]

Besides the operational ease, two notable features of this reaction are its little sensitivity to solvent effects, the alkynylation being performed in acetonitrile, dichloromethane, toluene, THF, dioxane, DMF, ethanol, mixtures of THF and water or even without solvent with similar efficiency, and its self-indicating nature. Indeed, the endpoint of the reaction is remarkably easy to detect since it turns from a yellow heterogeneous mixture to a deep blue homogeneous solution upon completion (Fig. 4): the time has come for a quick filtration to get the ynamide.

The optimized conditions for the alkynylation rely on the use of an excess (4 equivalents) of the nitrogen nucleophile – to minimize, and even suppress in most cases, the Glaser–Hay dimerization of the copper acetylides – which might constitute a limitation of this process. It should be noted however that a 1 : 1 ratio can also be used: if the yield is reduced (*ca.* 60–70% of the ynamide isolated) in this case and the dimerization is more important (*ca.* 10–20% of the dimer is observed), this might

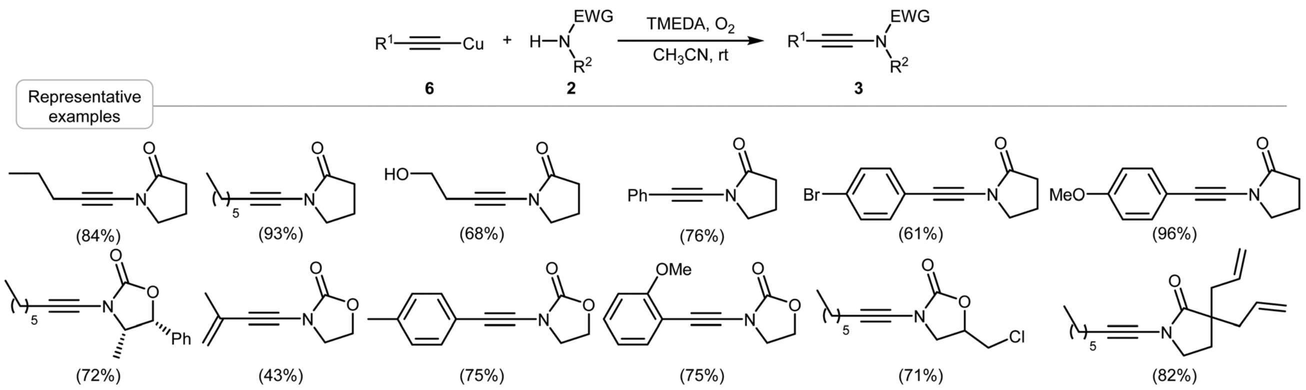


Fig. 3 Facile synthesis of ynamides by oxidative alkynylation of nitrogen nucleophiles with copper acetylides: a mix-and-stir reaction. Standard conditions: 2 mmol **6**, 8 mmol **2**, 2 mmol TMEDA, 1 atm. O_2, 4 mL of CH_3CN, rt, 24–48 h.

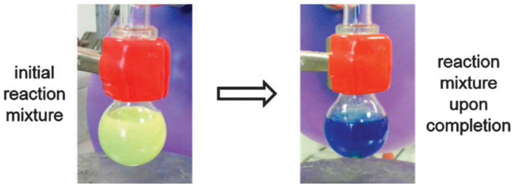
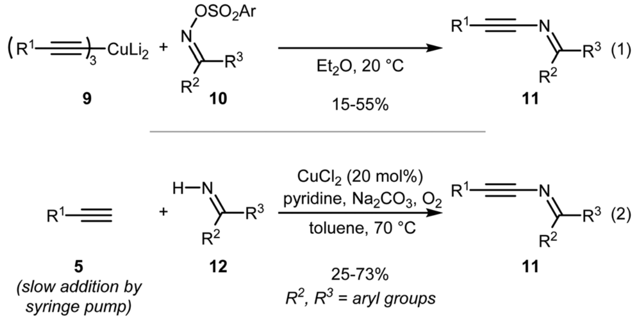


Fig. 4 Self-indicating nature of the oxidative alkynylation.



Scheme 4 Classical synthesis of ynimines and first generation synthesis developed in the group.

however be useful for the alkynylation of complex and/or precious nitrogen nucleophiles that cannot be used in excess. The main limitation lies in fact in the nature of the nitrogen nucleophile itself since the presence of bulky substituents α to the reacting centre was found to slow down the reaction and acyclic amides such as *N*-methyl-acetamide showed no reactivity under the reaction conditions, which might be attributed to increased steric hindrance, lower chelating ability or lower acidity.

Motivated by the development of this practical procedure which can be performed, even on a big scale, with an attractive operational ease, we decided to investigate the reactivity of other nitrogen nucleophiles, which could also provide a user-friendly access to other classes of nitrogen-substituted alkynes that can hardly be obtained using more classical approaches.

Being involved for quite some years in the chemistry of ynamides at this time, the choice of the other nitrogen nucleophiles we could study was quite obvious. The behaviour of imines in this transformation would be next investigated since it might offer an easy access to ynimines, provided that the alkynylation of imines would be faster than their easy dimerization to azines. Indeed, if the development of practical methods for the synthesis of ynamides had a quite important impact on this field which has dramatically blossomed over the past decade, we felt that the development of other classes of nitrogen-substituted alkynes would allow us to further expand their chemistry and enable the design of chemical transformations impossible to develop with more standard ynamides. Ynimines **11**, which combine both the reactivity of ynamines and imines and share with ynamides an increased stability due to their geometry that involves a decreased conjugation of the nitrogen lone pair with the alkyne, possess a remarkable and rare combination of six consecutive electrophilic, nucleophilic, acidic and basic sites which makes them unique reagents and building blocks. Despite their potential, their reactivity had however only been scarcely studied when we became interested in these compounds, which is with no possible doubt due to the lack of general methods available for their synthesis. Their classical preparation indeed relies on the low-yielding reaction of higher order alkynylcuprates **9** with oxime tosylates **10** (Scheme 4, eqn (1)).[29] In an attempt to address these limitations, we first developed an alternative procedure based on a direct copper-catalysed oxidative alkynylation of imines **12** with terminal alkynes **5** under Stahl's conditions (Scheme 4, eqn (2)):[4e] if this procedure indeed provided an improved access to ynimines **11**, the need for a slow addition of the alkyne with a syringe pump rendered this reaction less practical than we expected on a big scale. In addition, only diarylimines could be cleanly alkynylated and arylalkylimines were found to be reluctant reaction partners, which was a main issue to further develop the chemistry of these building blocks.

We felt that these limitations could be addressed by using copper acetylides **6** as alkynylating agents: the optimization of this reaction revealed that it was now best performed with 1,2-dimethylimidazole (DMI) as the ligand which enabled the direct alkynylation of imines **12** in acetonitrile at room temperature over 12 hours.[13b,30] The desired ynimines **11** could be obtained in fair to good yields and the alkynylation of arylalkylimines that we could not perform using our first generation synthesis could be, to our delight, readily achieved using the oxidative alkynylation with copper acetylides. Representative ynimines that can be easily prepared using this procedure are shown in Fig. 5.

After spending quite some time studying the oxidative alkynylation of nitrogen nucleophiles, moving down the periodic table was quite tempting and, since many phosphorus-containing molecules are quite good ligands for copper, we felt that their alkynylation should be feasible and might provide interesting routes to phosphorus-substituted alkynes. The account of our

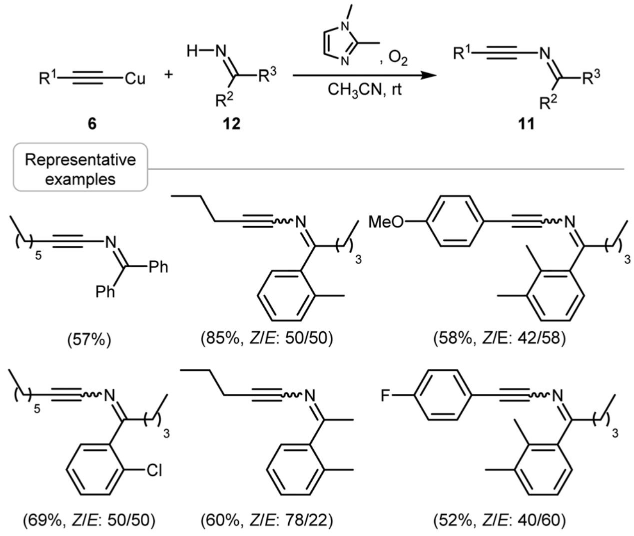


Fig. 5 Click alkynylation of imines with copper acetylides for the synthesis of ynimines. Standard conditions: 2 mmol **6**, 8 mmol **12**, 4 mmol DMI, 1 atm. O_2, 8 mL of CH_3CN, rt, 12 h.

journey with copper acetylides will therefore continue with these nucleophiles and the development of practical procedures for their alkynylation.

4. Oxidative alkynylation of phosphorus nucleophiles with copper acetylides: practical entries to phosphorus-substituted alkynes

Besides the motivation of expanding the scope of our alkynylation to other classes of nucleophiles, the development of a general process for the synthesis of phosphorus-substituted alkynes[31] – building blocks that are of great interest in organic synthesis, catalysis and medicinal chemistry as well – was also strongly encouraging and alkynylphosphonates **14** were chosen as our first targets in this series. They are indeed classically prepared by phosphorylation of lithium or magnesium acetylides with highly toxic chlorophosphates, a reaction that might seem to be simple but that is typically low yielding. To address the limitations associated with this procedure, several metal catalysed reactions have been developed.[32] If they indeed provide improved routes to alkynylphosphonates, they are however in most cases far to be as practical as one could wish and we felt that this gap could be filled by developing a hopefully facile alkynylation of dialkylphosphites **13** with copper acetylides **6**.

A brief optimization of this reaction did not prove us wrong and quickly revealed that this oxidative alkynylation was indeed remarkably facile, actually even more than what we initially anticipated. Upon simply mixing a dialkylphosphite **13** with a copper acetylide **6** and *N*-methyl-imidazole (NMI) in DMF at room temperature, there is actually even not enough time to go and get a balloon of oxygen in most cases since leaving the reaction mixture open to the air with a strong stirring is enough for the reaction to proceed. Letting the reaction stir at room temperature a little longer facilitates the purification since the generated cupric salts chelate most of the excess of the starting dialkylphosphite, forming complexes that are water soluble and therefore easily removed during the extraction. Here again, the reaction is easily performed on a multigram scale by simply mixing all the reagents and waiting for the reaction to change colour and turn to a deep blue homogeneous solution. This reaction is now performed in the organic chemistry teaching lab at the ULB, which is quite a good test for the robustness of a process: the students usually like it (easy to perform, no anhydrous solvents or an inert atmosphere, no need for TLCs, no painful column, no smelly chemicals…) and even the less talented students or the ones who abhor organic chemistry can do it, unless the flask ends up in the rotavapor water bath or on the floor. Selected examples shown in Fig. 6 are representative of the alkynylphosphonates **14** that can be easily prepared by this oxidative alkynylation of dialkylphosphites.[13]

Motivated by these results, we next started thinking at other phosphorus nucleophiles that could be used. While phosphines were immediately discarded from these studies due to their easy oxidation, we felt that phosphine–boranes, protected forms of phosphines that can be easily deprotected upon reaction with DABCO, could be interesting surrogates, although their use in oxidative processes without oxidation was unprecedented. Provided that secondary phosphine–boranes **15** would be alkynylated before being oxidized and that an appropriate ligand which would not induce their decomplexation could be found, their oxidative alkynylation might provide the mildest synthesis of alkynylphosphine–boranes **16** – stable precursors of alkynylphosphines which hold great potential for the development of metal-catalysed reactions[33] – reported to date.[33a,34]

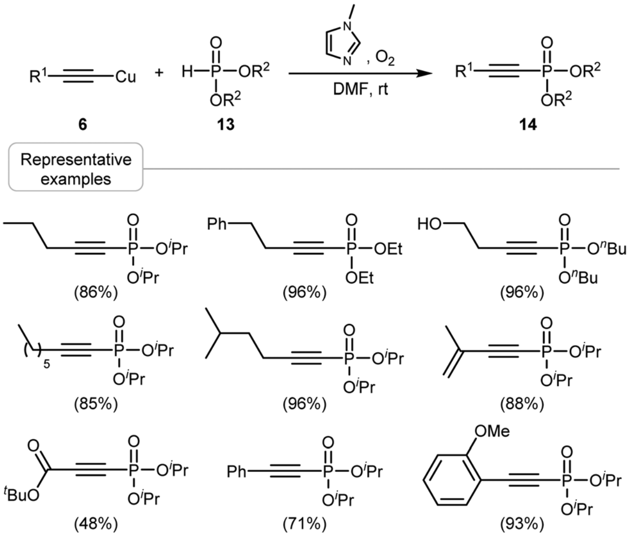


Fig. 6 Oxidative alkynylation of dialkylphosphites: a practical entry to alkynylphosphonates. Standard conditions: 2 mmol **6**, 8 mmol **13**, 4 mmol NMI, 1 atm. O$_2$, 4 mL of DMF, rt, 1–12 h.

The choice of both ligands and solvents that would be compatible with the sensitivity of phosphine–boranes left little room for the optimization but gratifyingly, a combination of 1,10-phenanthroline and toluene allowed for a clean alkynylation and a wide number of alkynylphosphine–boranes **16** (selected examples shown in Fig. 7) could be easily obtained under mild and practical conditions.[35]

These alkynylphosphine–boranes could next be transformed into the corresponding alkynylphosphines and alkynylphosphine oxides upon treatment with DABCO followed by oxidation in the latter case. Interestingly, an almost complete retention of configuration was observed when starting from an enantiomerically enriched phosphine–borane such as **18** (Scheme 5), which might turn out to be especially useful for the synthesis of optically enriched alkynylphosphines and might additionally provide interesting insights into the reaction mechanism of these oxidative alkynylation which is, we have to admit it, still quite mysterious to us.

As overviewed in this section, copper acetylides turned out to be remarkably useful for the alkynylation of phosphorus nucleophiles under unmatched mild conditions, therefore enabling the easy preparation of various P-substituted alkynes with an attractive operational ease. After spending quite some

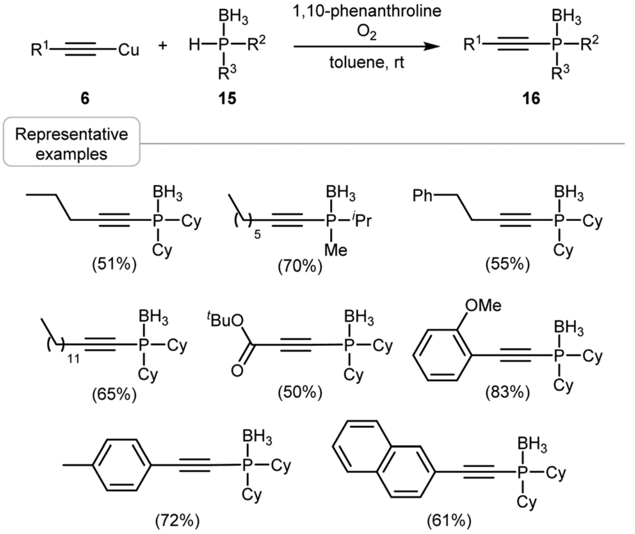
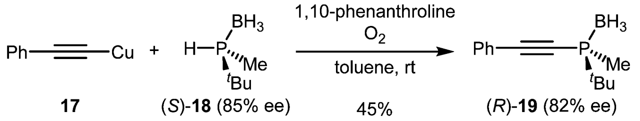


Fig. 7 More challenging P-nucleophiles: oxidative alkynylation of phosphine–boranes. Standard conditions: 0.24 mmol **6**, 0.66 mmol **15**, 1.2 mmol 1,10-phenanthroline, 1 atm. O_2, 0.6 mL of toluene, rt, 6–8 h.



Scheme 5 Oxidative alkynylation of an optically enriched phosphine–borane with retention of configuration.

time evaluating the reactivity of heteronucleophiles in this reaction, we recently decided to embark on a more difficult task, the alkynylation of carbon nucleophiles.

5. First studies of the oxidative alkynylation of carbon nucleophiles with copper acetylides: a user-friendly synthesis of trifluoromethylated alkynes

Indeed, while there is a plethora of strategies and methods to form C(sp)–C(sp), C(sp)–C(sp^2), and C(sp)–C(sp^3) bonds, efforts are clearly still required to develop efficient reagents and procedures to perform transformations that can still be considered as challenging to date such as, for example, the direct alkynylation of C–H bonds in arenes or the synthesis of trifluoromethylated alkynes. We felt that the formal generation of acetylenic carbocations by oxidation of copper acetylides might be potentially useful in this area and would also constitute an interesting opportunity to gain additional insights into the reactivity of these species.

We therefore first decided to evaluate the possibility of preparing trifluoromethylated alkynes **21**,[36,37] useful fluorinated building blocks in organic synthesis and medicinal chemistry,[38] by oxidative coupling between copper acetylides **6** and a source of CF_3^-. The Ruppert–Prakash reagent $TMSCF_3$ **20** was chosen for this reaction and its optimization, where the high volatility of the trifluoromethylated alkynes **21** formed had to be taken into consideration, revealed that this transformation was best performed using TMEDA as the ligand in a mixture of petroleum ether and DMF.[39] Representative trifluoromethylated alkynes **21** that could be prepared using this transformation which, in comparison with previously reported procedures, does not require heating, nor a source of fluoride to activate the Ruppert–Prakash reagent **20** or slow addition of one reagent, are shown in Fig. 8.

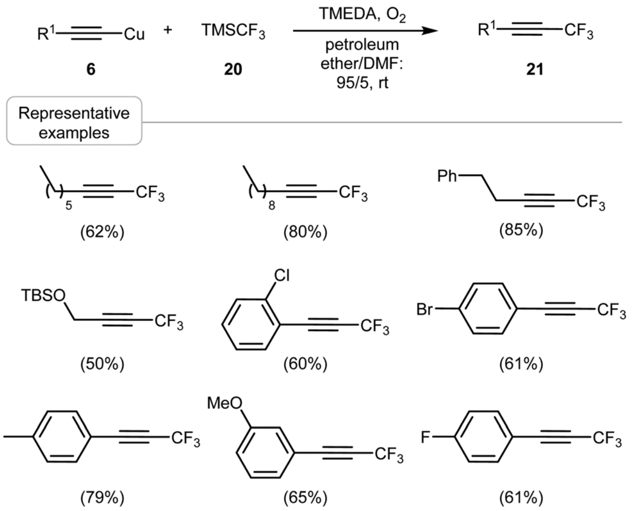


Fig. 8 Oxidative alkynylation of the Ruppert–Prakash reagent: direct entry to trifluoromethylated alkynes. Standard conditions: 0.5 mmol **6**, 2 mmol **20**, 0.5 mmol TMEDA, 1 atm. O_2, 0.1 mL DMF, 1.9 mL pet. ether, rt, 24 h.

Besides providing a practical entry to trifluoromethylated alkynes, this oxidative alkynylation of the Ruppert–Prakash reagent demonstrated the possibility of using copper acetylides

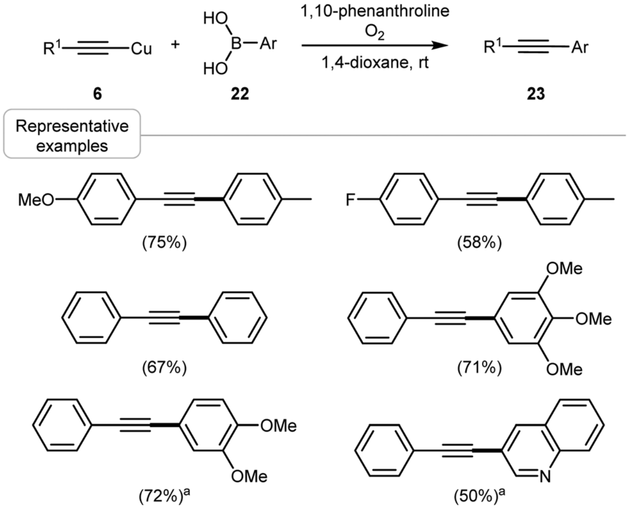


Fig. 9 Expanding the scope of the oxidative alkynylation with copper acetylides: facile alkynylation of arylboronic acids (bonds formed shown in bold). [a] Using a 1 : 1 mixture of MeOH and 2,6-lutidine instead of 1,4-dioxane. Standard conditions: 0.5 mmol **6**, 1 mmol **22**, 0.5 mmol 1,10-phenanthroline, 1 atm. O_2, 2 mL of 1,4-dioxane, rt, 48–72 h.

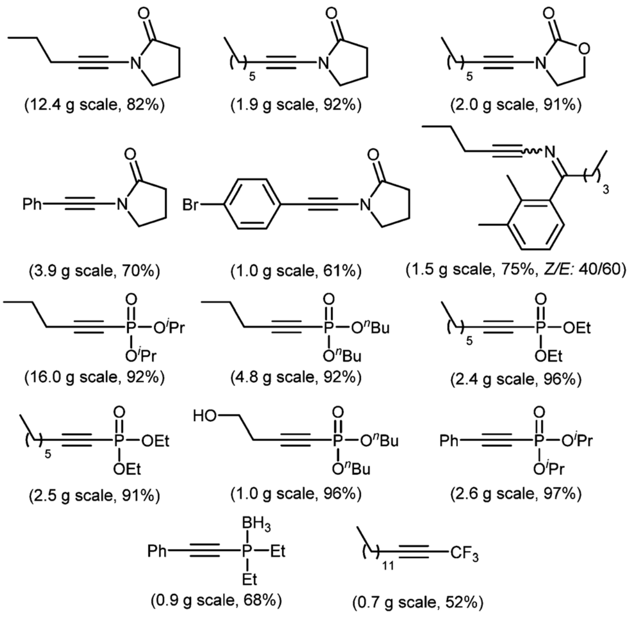


Fig. 10 Gram scale alkynylation.

for the alkynylation of carbon nucleophiles, even poor ones. This opens up the way for the alkynylation of other families of carbon nucleophiles such as arenes that could potentially be directly alkynylated without the need for pre-functionalization, a challenging reaction that holds great potential and is currently under study in the group.

In addition, this alkynylation is not restricted to the use of nucleophilic species since we have demonstrated that organometallic reagents can be used with similar efficiency, although the homodimerization of the starting copper acetylides was a bit more problematic in this case. Indeed, the oxidative alkynylation could be extended to the use of arylboronic acids **22** which could be coupled with various copper acetylides **6**. Upon reaction with molecular oxygen in 1,4-dioxane and in the presence of 1,10-phenanthroline at room temperature, a smooth oxidation–transmetalation–reductive elimination occurred yielding the corresponding aromatic alkynes **23** in fair to good yields (Fig. 9).[40]

Besides the practical benefits which have already been mentioned, some of the main advantages associated with these procedures are the remarkably mild reaction conditions. All alkynylations are indeed readily performed at room temperature without the need for a base or other additives typically required in such processes. A ligand and molecular oxygen are all that are required for the alkynylation to proceed, which we felt would be especially interesting for the alkynylation relying on more complex substrates or acetylides that will be overviewed in the closing section of this article.

6. Pushing the limits of the oxidative alkynylation: insights into real life situations

How many times have we all faced the situation in which trying to apply a procedure that had been reported on tens or

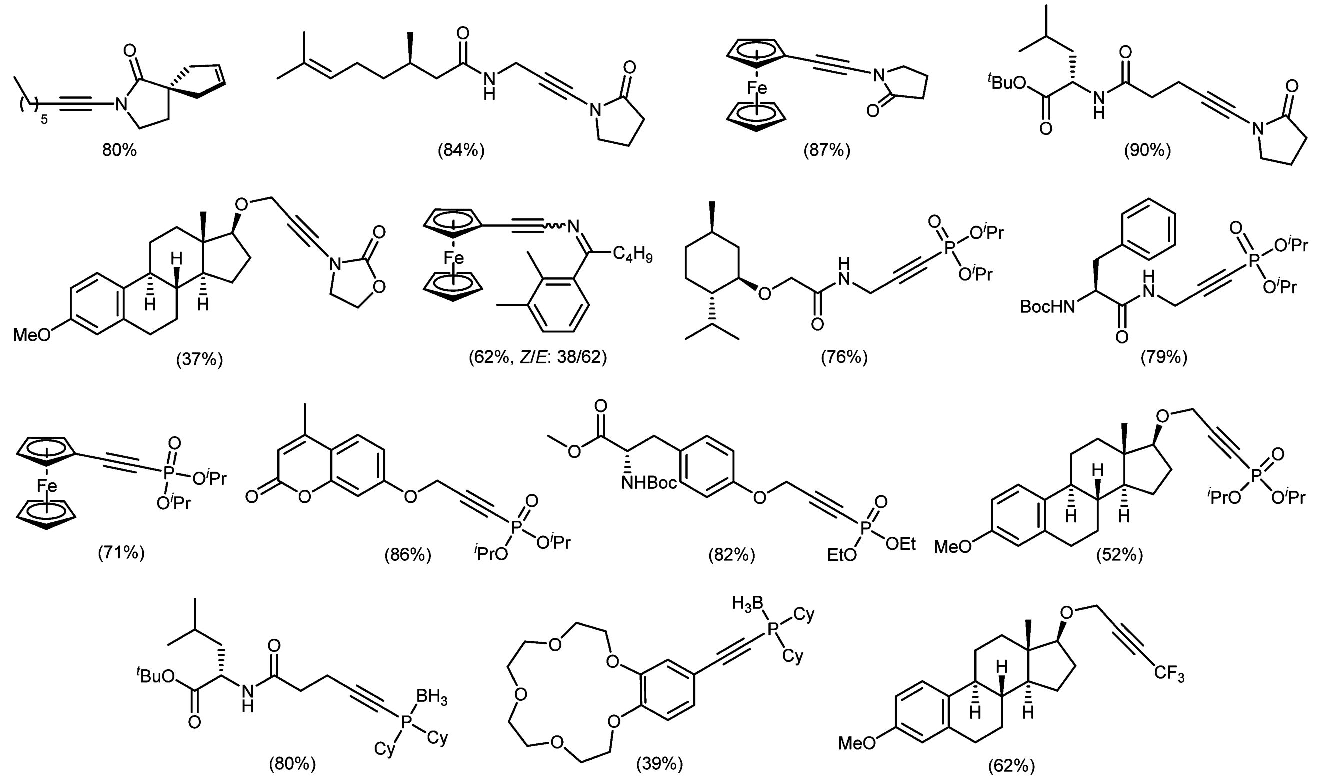


Fig. 11 Oxidative alkynylation with more complex substrates: towards "real life" situations.

hundreds of examples turned out to be a complete failure? This usually happens when scaling up the reaction or when switching to more complex and/or sensitive substrates which are poor reaction partners. In the worst case, they cannot even stand the reaction conditions which typically results in this kind of TLCs which makes you wonder how on earth it is possible that a reaction could give so many different products. Call it "molecular diversity"... or just a reaction which was not as robust or whose scope was not as broad as you had wished.

With a set of procedures enabling the alkynylation of various nucleophiles under mild and practical conditions, we wanted to address the scope of these reactions in "real life" situations and try to push them to their limits.

The first point we did carefully and extensively address was the scale up of the reaction, a key parameter if we wanted to make sure our oxidative alkynylation could be easily applied on a gram scale, one of the main goals we had in mind when we started looking at the development of a practical synthesis of ynamides. Fig. 10 summarizes our efforts in this direction and demonstrates that various N-, P-, and CF_3-substituted alkynes can be readily and easily prepared on a gram scale by oxidative alkynylation of the corresponding nucleophiles with copper acetylides.

The mild reaction conditions also enable the preparation of more complex heterosubstituted/trifluoromethylated alkynes that can hardly be prepared with other methods due to their sensitivity, such as the ones collected in Fig. 11. The reaction tolerates a wide number of functional groups, as long as they are not too sensitive to oxidation (benzylic alcohols and unprotected indoles are therefore to be avoided, which are the only two cases of functional groups that we found to be incompatible with the oxidative alkynylation). Base- or heat-sensitive heterosubstituted alkynes can be readily prepared and epimerization was demonstrated not to be an issue due to the mild conditions that are fully compatible with the presence of epimerisable stereocentres. Due to the stoichiometry of the alkynylation which is better performed with an excess of the nucleophile in order to minimize the dimerization of the starting copper acetylides, it ought to be mentioned that all alkynylations developed are however better performed with complex copper acetylides rather than with complex nucleophiles that cannot be used in excess and therefore give lower – although still acceptable – yields of the corresponding alkynylated products.

Conclusions

In conclusion, we have developed a set of procedures enabling both the activation and the umpolung of otherwise unreactive copper acetylides. These bright yellow, rock-solid polymeric reagents that are easily prepared on a multigram scale from the corresponding terminal alkynes were shown to be ideal reagents for the alkynylation of a wide range of nucleophiles under especially mild conditions. Upon activation with molecular oxygen in the presence of readily available, simple and cheap ligands, these copper acetylides readily transfer their alkyne moieties to give the corresponding alkynylated products at room temperature and without the need for special precautions. These self-indicating, mix-and-stir reactions can in addition be easily performed on a big scale and with complex substrates, demonstrating the remarkable behaviour and efficiency of copper acetylides under mild oxidizing conditions. Ynamides, ynimines, alkynylphosphonates, alkynylphosphine–boranes and trifluoromethylated alkynes were shown to be easily obtained using this strategy. Future directions will involve expanding this reaction to the use of other nucleophiles: O-nucleophiles were quite tempting since their oxidative alkynylation would provide an interesting entry to ynol ethers, compounds that are still challenging to prepare.[41] If alcohols and phenols were found to be poor nucleophiles for this transformation, most certainly due to their poor ability to chelate copper, the use of the corresponding alkoxides was found to be a lot more efficient but, unfortunately, the highly sensitive ynol ethers formed were readily hydrolysed to the corresponding aliphatic esters which were isolated at the end of the reaction. With the little success met for the use of O-nucleophiles, current studies focus on the use of other C-nucleophiles such as cyanide, whose alkynylation would provide an interesting synthesis of cyanoalkynes, and, probably more importantly, arenes. Preliminary studies have demonstrated the possibility of using copper acetylides under oxidative conditions for the direct alkynylation of C–H bonds in arenes at room temperature and a lot of efforts are currently underway in the group to develop this synthetically useful transformation.

Due to the numerous possibilities for post-synthetic functionalization one can envision using the alkyne introduced with these reactions, the use of these oxidative alkynylations for the challenging – but highly motivating – chemoselective and/or iterative functionalization of multifunctional substrates is also being investigated. This will also involve a better apprehension of the reaction mechanism(s) associated with these alkynylations: definitely not the easiest part of this project.

Of course, one could definitely argue that these reactions are stoichiometric in copper and that they are totally at the opposite direction of the "environmentally benign" or "green" reactions one should focus on instead of wasting such amounts of copper. It would indeed be hard to argue that quite some copper is lost in the process and that the "atom economy" is not ideal, even if the copper salts can be recycled afterwards. Does that make them "environmentally messy" reactions that should be discarded that easily? This is a fair criticism that we have had to face many times and that prompted us to briefly have a look at the "greenness" of these oxidative alkynylations. The outcome was quite surprising since it was found to strongly depend on the green reaction metrics considered. Indeed, the comparison of our three generation syntheses of ynamides based on the use of 1,1-dibromoalkenes (catalytic in copper), potassium alkynyltrifluoroborates (also catalytic in copper), and copper acetylides (obviously not) is quite illustrative: the ones that have "reasonable" reaction mass efficiencies and/or E factors have horrible scores on the EcoScale and *vice versa*. But after all, is not it the efficiency and practicability that matter as long as no especially nasty or polluting reagents are involved?

The experience we have had with many different processes and reagents for the synthesis of hetero-substituted alkynes and the search for practical reactions led us to the development of the oxidative chemistry of copper acetylides. Their efficiency immediately struck us and the operational use we insisted on in this manuscript was the greatest motivation for these studies: all one has to do is to mix one of these reagents and a nucleophile in the presence of the appropriate ligand and oxygen at room temperature. The reaction changes colour and that is it. The main issue that one might have is actually when comes the time to wash the fritted funnel that was used during the synthesis of the copper acetylide: this is when you realize how unreactive such compounds are otherwise.

Acknowledgements

This work was mainly supported by the Université Libre de Bruxelles, the Université de Versailles Saint-Quentin-en-Yvelines, the CNRS, the FNRS (Incentive Grant for Scientific Research no. F.4530.13), the ANR (project DYNAMITE ANR-2010-BLAN-704), the CMCU/PHC Utique (grant 10G1025) and the Fondation Raoul Follereau. Additional support from the Région Basse-Normandie, the Université de Strasbourg and the Université de Haute-Alsace is acknowledged. ML, AN and CT gratefully acknowledge the Fonds pour la formation a la Recherche dans l'Industrie et dans l'Agriculture (F.R.I.A.) for graduate fellowships.

Notes and references

1 For reviews, see: (*a*) G. Evano, A. Coste and K. Jouvin, *Angew. Chem., Int. Ed.*, 2010, **49**, 2840; (*b*) K. A. DeKorver, H. Li, A. G. Lohse, R. Hayashi, Z. Lu, Y. Zhang and R. P. Hsung, *Chem. Rev.*, 2010, **110**, 5064; (*c*) G. Evano, K. Jouvin and A. Coste, *Synthesis*, 2013, 17.

2 For selected examples of our work with ynamides, see: (*a*) A. Fadel, A. Legrand, G. Evano and N. Rabasso, *Adv. Synth. Catal.*, 2011, **353**, 263; (*b*) W. Gati, M. M. Rammah, M. B. Rammah, F. Couty and G. Evano, *J. Am. Chem. Soc.*, 2012, **134**, 9078; (*c*) G. Compain, K. Jouvin, A. Martin-Mingot, G. Evano, J. Marrot and S. Thibaudeau, *Chem. Commun.*, 2012, **48**, 5196; (*d*) W. Gati, M. M. Rammah, M. B. Rammah and G. Evano, *Beilstein J. Org. Chem.*, 2012, **8**, 2214; (*e*) A. Laouiti, M. M. Rammah, M. B. Rammah, J. Marrot, F. Couty and G. Evano, *Org. Lett.*, 2012, **14**, 6; (*f*) W. Gati, F. Couty, T. Boubaker, M. M. Rammah, M. B. Rammah and G. Evano, *Org. Lett.*, 2013, **15**, 3122; (*g*) A. Laouiti, F. Couty, J. Marrot, T. Boubaker, M. M. Rammah, M. B. Rammah and G. Evano, *Org. Lett.*, 2014, **16**, 2252; (*h*) H. A. Laub, G. Evano and H. Mayr, *Angew. Chem., Int. Ed.*, 2014, **53**, 4968.

3 (*a*) A. Coste, G. Karthikeyan, F. Couty and G. Evano, *Angew. Chem., Int. Ed.*, 2009, **48**, 4381; (*b*) A. Coste, F. Couty and G. Evano, *Org. Synth.*, 2010, **87**, 231; (*c*) K. Jouvin and G. Evano, *Chim. Oggi*, 2011, **29**, 31; (*d*) K. Jouvin, A. Coste, A. Bayle, F. Legrand, G. Karthikeyan, K. Tadiparthi and G. Evano, *Organometallics*, 2012, **31**, 7933.

4 For selected other general methods for the synthesis of ynamides, see: (*a*) M. O. Frederick, J. A. Mulder, M. R. Tracey, R. P. Hsung, J. Huang, K. C. M. Kurtz, L. Shen and C. J. Douglas, *J. Am. Chem. Soc.*, 2003, **125**, 2368; (*b*) J. R. Dunetz and R. L. Danheiser, *Org. Lett.*, 2003, **5**, 4011; (*c*) Y. Zhang, R. P. Hsung, M. R. Tracey, K. C. M. Kurtz and E. L. Vera, *Org. Lett.*, 2004, **6**, 1151; (*d*) T. Hamada, X. Ye and S. S. Stahl, *J. Am. Chem. Soc.*, 2008, **130**, 833; (*e*) W. Jia and N. Jiao, *Org. Lett.*, 2010, **12**, 2000.

5 F. Ramirez, N. B. Desal and N. McKelvie, *J. Am. Chem. Soc.*, 1962, **84**, 1745.

6 (*a*) Y.-Q. Fang, O. Lifchits and M. Lautens, *Synlett*, 2008, 413; (*b*) C. Bryan, V. Aurregi and M. Lautens, *Org. Synth.*, 2009, **86**, 36.

7 K. Jouvin, F. Couty and G. Evano, *Org. Lett.*, 2010, **12**, 3272.

8 An especially useful improved procedure for the synthesis of organotrifluoroborate salts under non-etching conditions was reported later on. See: A. J. J. Lennox and G. C. Lloyd-Jones, *Angew. Chem., Int. Ed.*, 2012, **51**, 9385.

9 C. Glaser, *Justus Liebigs Ann. Chem.*, 1870, **154**, 137.

10 W. Chodkiewicz and P. Cadiot, *C. R. Acad. Sci.*, 1955, **241**, 1055.

11 R. D. Stephens and C. E. Castro, *J. Org. Chem.*, 1963, **28**, 3313.

12 J. F. Normant, *Synthesis*, 1972, 63.

13 (*a*) K. Jouvin, J. Heimburger and G. Evano, *Chem. Sci.*, 2012, **3**, 756; (*b*) C. Theunissen, M. Lecomte, K. Jouvin, A. Laouiti, C. Guissart, J. Heimburger, E. Loire and G. Evano, *Synthesis*, 2014, 1157.

14 Except for copper carbide and bis copper acetylides such as the copper derivative of *p*-diethynylbenzene, alkynylcopper reagents are stable to shock and heat: E. C. Royer, M. C. Barral, V. Moreno and A. Santos, *J. Inorg. Nucl. Chem.*, 1981, **43**, 705.

15 Phenylethynylcopper is available from Alfa Aesar and other copper acetylides (around 20 of them) from other suppliers.

16 N. A. Bumagin, A. B. Ponomarev, A. N. Ryabtsev and I. P. Beletskaya, *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, 1988, **37**, 507.

17 For the formation of carbon–nitrogen bonds involving organocopper(III) intermediates, see: (*a*) L. M. Huffman and S. S. Stahl, *J. Am. Chem. Soc.*, 2008, **130**, 9196; (*b*) A. Casitas, A. E. King, T. Parella, M. Costas, S. S. Stahl and X. Ribas, *Chem. Sci.*, 2010, **1**, 326.

18 For general references on the oxidation of organocopper reagents, see: (*a*) D. S. Surry and D. R. Spring, *Chem. Soc. Rev.*, 2006, **35**, 218; (*b*) S. J. Aves and D. R. Spring, in *Patai Series: The Chemistry of Functional Groups. The Chemistry of Organocopper Compounds*, ed. Z. Rappoport and I. Marek, John Wiley & Sons Ltd, Chichester, 2009, vol. 24, pp. 585–602.

19 (*a*) G. M. Whitesides, J. San Filippo, C. P. Casey and E. J. Panek, *J. Am. Chem. Soc.*, 1967, **89**, 5302; (*b*) G. M. Whitesides, W. F. Fischer, J. San Filippo, R. W. Bashe and H. O. House, *J. Am. Chem. Soc.*, 1969, **91**, 4871; (*c*) W. H. Mandeville and G. M. Whitesides, *J. Org. Chem.*, 1974, **39**, 400.

20 B. H. Lipshutz, K. Siegmann, E. Garcia and F. Kayser, *J. Am. Chem. Soc.*, 1993, **115**, 9276.

21 S. R. Dubbaka, M. Kienle, H. Mayr and P. Knochel, *Angew. Chem., Int. Ed.*, 2007, **46**, 9093.

22 (*a*) D. S. Surry, X. Su, D. J. Fox, V. Franckevicius, S. J. F. Macdonald and D. R. Spring, *Angew. Chem., Int. Ed.*, 2005, **44**, 1870; (*b*) D. S. Surry, D. J. Fox, S. J. F. Macdonald and D. R. Spring, *Chem. Commun.*, 2005, 2589; (*c*) S. J. Aves, K. G. Pike and D. R. Spring, *Synlett*, 2010, 2839.

23 H. Yamamoto and K. Maruoka, *J. Org. Chem.*, 1980, **45**, 2739.

24 M. Iwao, J. N. Reed and V. Snieckus, *J. Am. Chem. Soc.*, 1982, **104**, 5531.

25 (*a*) A. Alberti, F. Canè, P. Dembech, D. Lazzari, A. Ricci and G. Seconi, *J. Org. Chem.*, 1996, **61**, 1677; (*b*) F. Canè, D. Brancaleoni, P. Dembech, A. Ricci and G. Seconi, *Synthesis*, 1997, 545.

26 (*a*) V. del Amo, S. R. Dubbaka, A. Krasovskiy and P. Knochel, *Angew. Chem., Int. Ed.*, 2006, **45**, 7838; (*b*) N. Boudet, S. R. Dubbaka and P. Knochel, *Org. Lett.*, 2008, **10**, 1715; (*c*) M. Kienle, S. R. Dubbaka, V. del Amo and P. Knochel, *Synthesis*, 2007, 1272.

27 For another area of the oxidative chemistry of organocopper reagents, the oxidation of vinylcopper species by oxenoids yielding enolates, see: (*a*) D. Zhang and J. M. Ready, *Org. Lett.*, 2005, **7**, 5681; (*b*) Y. Minko, M. Pasco, L. Lercher, M. Botoshansky and I. Marek, *Nature*, 2012, **490**, 522; (*c*) Y. Minko, M. Pasco, L. Lercher and I. Marek, *Nat. Protoc.*, 2013, **4**, 749.

28 *Copper-Mediated Cross-Coupling Reactions*, ed. G. Evano and N. Blanchard, Wiley, Hoboken, 2013.

29 E.-U. Würthwein and R. Weigmann, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 923.

30 A. Laouiti, K. Jouvin, F. Bourdreux, M. M. Rammah, M. B. Rammah and G. Evano, *Synthesis*, 2012, 1491.

31 For reviews, see: (*a*) K. M. Pietrusiewicz and M. Stanković, in *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*, ed. A. de Meijere, Thieme, Stuttgart, 2005, vol. 24, pp. 1073–1086; (*b*) A. Kondoh, H. Yorimitsu and K. Oshima, *Chem. – Asian J.*, 2010, **5**, 398; (*c*) E. Bernoud, R. Veillard, C. Alayrac and A.-C. Gaumont,

Molecules, 2012, **17**, 14573; (*d*) G. Evano, A.-C. Gaumont, C. Alayrac, I. E. Wrona, J. R. Giguere, O. Delacroix, A. Bayle, K. Jouvin, C. Theunissen, J. Gatignol and A. C. Silvanus, *Tetrahedron*, 2014, **70**, 1529.

32 For selected examples, see: (*a*) G. Hägele, S. Goudetsidis, E. Wilke, J. Seega, H. Blum and M. Murray, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1990, **48**, 131; (*b*) M. Lera and C. J. Hayes, *Org. Lett.*, 2000, **2**, 3873; (*c*) Y. Gao, G. Wang, L. Chen, P. Xu, Y. Zhao, Y. Zhou and L.-B. Han, *J. Am. Chem. Soc.*, 2009, **131**, 7956.

33 For selected examples, see: (*a*) T. Imamoto, Y. Saitoh, A. Koide, T. Ogura and K. Yoshida, *Angew. Chem., Int. Ed.*, 2007, **46**, 8636; (*b*) A. Ochida, H. Ito and M. Sawamura, *J. Am. Chem. Soc.*, 2006, **106**, 16486; (*c*) H. Ito, H. Ohmiya and M. Sawamura, *Org. Lett.*, 2010, **12**, 4380.

34 For representative examples, see: (*a*) S. Ortial and J.-L. Montchamp, *Org. Lett.*, 2011, **13**, 3134; (*b*) E. Bernoud, C. Alayrac, O. Delacroix and A.-C. Gaumont, *Chem. Commun.*, 2011, **47**, 3239.

35 K. Jouvin, R. Veillard, C. Theunissen, C. Alayrac, A.-C. Gaumont and G. Evano, *Org. Lett.*, 2013, **15**, 4592.

36 For classical methods for the synthesis of trifluoromethylated alkynes, see: (*a*) J. E. Bunch and C. L. Bumgardner, *J. Fluorine Chem.*, 1987, **36**, 313; (*b*) N. Yoneda, S. Matsuoka, N. Miyaura, T. Fukuhara and A. Suzuki, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 2124; (*c*) T. Konno, J. Chae, M. Kanda, G. Nagai, K. Tamura, T. Ishihara and H. Yamanaka, *Tetrahedron*, 2003, **59**, 7571; (*d*) F. G. Drakesmith, O. J. Stewart and P. Tarrant, *J. Org. Chem.*, 1968, **33**, 280; (*e*) A. R. Katritzky, M. Qi and A. P. Wells, *J. Fluorine Chem.*, 1996, **80**, 145; (*f*) T. Hiyama and M. Fujita, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 1352; (*g*) A. J. Laurent, I. M. Le Dréan and A. Selmi, *Tetrahedron Lett.*, 1991, **32**, 3071; (*h*) T. Umemoto and S. Ishihara, *J. Am. Chem. Soc.*, 1993, **115**, 2156; (*i*) C. Urban, F. Cadoret, J.-C. Blazejewski and E. Magnier, *Eur. J. Org. Chem.*, 2011, 4862.

37 For recently reported methods for the direct trifluoromethylation of alkynes and synthetic equivalents, see: (*a*) L. Chu and F.-L. Qing, *J. Am. Chem. Soc.*, 2010, **132**, 7262; (*b*) X. Jiang, L. Chu and F.-L. Qing, *J. Org. Chem.*, 2012, **77**, 1251; (*c*) K. Zhang, X.-L. Qiu, Y. Huang and F.-L. Qing, *Eur. J. Org. Chem.*, 2012, 58; (*d*) H. Zheng, Y. Huang, Z. Wang, H. Li, K.-W. Huang, Y. Yuan and Z. Weng, *Tetrahedron Lett.*, 2012, **53**, 6646; (*e*) Z. Weng, H. Li, W. He, L.-F. Yao, J. Tan, J. Chen, Y. Yuan and K.-W. Huang, *Tetrahedron*, 2012, **68**, 2527; (*f*) D.-F. Luo, J. Xu, Y. Fu and Q.-X. Guo, *Tetrahedron Lett.*, 2012, **53**, 2769; (*g*) X. Wang, J. Lin, C. Zhang, J. Xiao and X. Zheng, *Chin. J. Chem.*, 2013, **31**, 915; (*h*) H. Serizawa, K. Aikawa and K. Mikami, *Chem. – Eur. J.*, 2013, **19**, 17692; (*i*) N. Iqbal, J. Jung, S. Park and E. J. Cho, *Angew. Chem., Int. Ed.*, 2014, **53**, 539.

38 T. Konno, *Synlett*, 2014, 1350–1370.

39 C. Tresse, C. Guissart, S. Schweizer, Y. Bouhoute, A.-C. Chany, M.-L. Goddard, N. Blanchard and G. Evano, *Adv. Synth. Catal.*, 2014, DOI: 10.1002/adsc.201400057.

40 F. Verna, C. Guissart, J. Pous and G. Evano, *Monatsh. Chem.*, 2013, **144**, 525.

41 (*a*) R. H. Smithers, *Synthesis*, 1985, 556; (*b*) M. A. Pericas, F. Serratosa and E. Valenti, *Tetrahedron*, 1987, **43**, 2311; (*c*) A. Moyano, F. Charbonnier and A. E. Greene, *J. Org. Chem.*, 1987, **52**, 2919; (*d*) G. Himbert and A. Loffler, *Synthesis*, 1992, 495; (*e*) D. Bruckner, *Synlett*, 2000, 1402; (*f*) B. Darses, A. Millet, C. Philouze, A. E. Greene and J.-F. Poisson, *Org. Lett.*, 2008, **10**, 4445; (*g*) J. R. Sosa, A. A. Tudjarian and T. G. Minehan, *Org. Lett.*, 2008, **10**, 5091; (*h*) K. Jouvin, A. Bayle, F. Legrand and G. Evano, *Org. Lett.*, 2012, **14**, 1652; (*i*) V. J. Gray, B. Slater and J. D. Wilden, *Chem. – Eur. J.*, 2012, **18**, 15582; (*j*) L. Marzo, A. Parra, M. Frías, J. Alemán and J. L. García Ruano, *Eur. J. Org. Chem.*, 2013, 4405.