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Graphical Abstract

Fishing with Copper Acetylides: Selective Alkynylation of Heteronucleophiles

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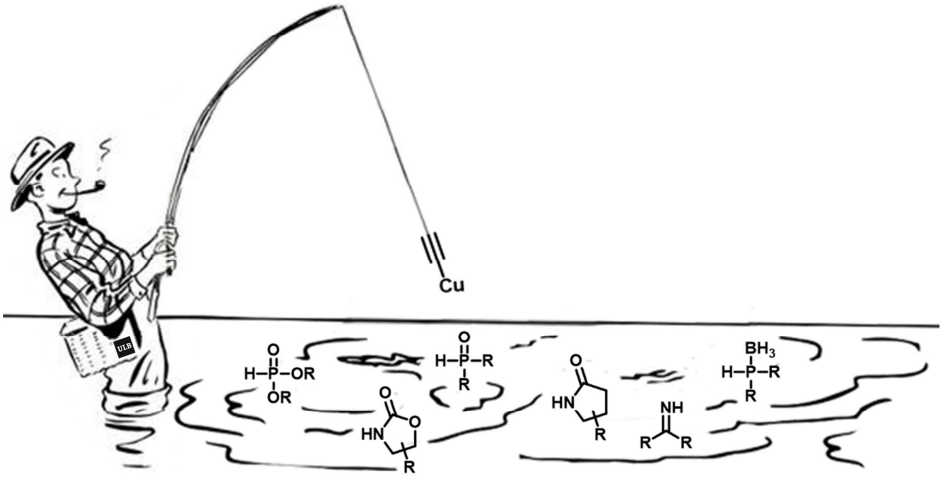

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Dedicated to Prof. Léon Ghosez on the occasion of his retirement from Editorship of Tetrahedron and for his remarkable contributions to organic synthesis

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ABSTRACT

Copper acetylides are readily available and especially convenient reagents for the alkynylation of a broad range of heteronucleophiles. Upon simple activation with molecular oxygen in the presence of suitable ligands and solvents, they readily transfer their alkyne moiety at room temperature, notably yielding a variety of nitrogen- and phosphorus-substituted alkynes. We report in this manuscript an extensive study of the chemoselectivity of this alkynylation based on quantitative ^{13}C NMR analyses. With suitable ligand/solvent combinations, various phosphorus-based nucleophiles can be alkynylated with excellent levels of selectivity, even in the presence of a large excess of nitrogen-nucleophiles. This chemoselective alkynylation could be further extended to an even more challenging selective alkynylation of a nitrogen-nucleophile over another one, further highlighting the synthetic potential of copper acetylides as alkynylating agents that can selectively "fish" a nucleophile without affecting others.

1. Introduction

Among all criteria that have to be taken into account for the development of new transformations, chemoselectivity is certainly one of the most crucial. Processes featuring exquisite levels of chemoselectivity are indeed of utmost importance, for various reasons. Firstly, they avoid tedious, lengthy and wasteful protection/deprotection steps required to mask the reactivity of functional groups that would not be tolerated by non-chemoselective transformations, therefore resulting in step-economical syntheses.[1] Secondly, they enable easy site-selective functionalizations of polyfunctional molecules, therefore facilitating late-stage functionalization and diversity-oriented syntheses.[2] Moreover, such reactions can be used for the selective labelling, chemical modification, functionalization or bioconjugation of complex biomolecules, which has notably had a deep impact in chemical biology and biomedical research.[3] Last but not least, they can be utilized as "chemical warheads" for the functionalization of a given molecule in the presence of others.

While there are many biological systems that are tailored towards specific substrates and that operate with ultimate levels of chemoselectivity, synthetic ones are much more challenging since they rely on much more basic approaches and parameters to ensure decent levels of selectivity. It does therefore represent a highly demanding challenge to develop reagents, catalysts and conditions that can reliably target, with surgical precision, a single reactive functional group out of many. Due to its attractiveness, this approach has however been widely investigated and has resulted in the design of highly efficient, robust and selective reactions, the copper-catalyzed alkyne-azide cycloaddition[4] and related "click" processes[5] certainly being the most representative examples to date.

Among these chemoselective reactions, the ones enabling orthogonal and switchable selectivities are even more attractive both in terms of efficiency and versatility. Not surprisingly, such processes are still rare[6] and the most significant examples include Buchwald's remarkable selective copper-catalyzed N- and O-arylation of aminoalcohols,[7] Alper's chemodivergent palladium-catalyzed carbonylation of aminophenols,[8] Mashima's chemoselective acylation of aminoalcohols[9] or Miller's selective acylations of erythromycin A.[10]

In this context, and based on our long-standing interest in the alkynylation of heteronucleophiles,[11-14] we became interested in assessing the chemoselectivity of such processes with the objective to develop either chemodivergent procedures or to be able to selectively functionalize a given heteronucleophile in the presence of a large excess of others. Among all the alkynylation procedures and alkynylating agents we studied over the years, copper acetylides **1**,[14] readily available and bench-stable reagents, have proven to be the most versatile ones. While these polymeric solids are totally inert under most conditions, we have shown that they can be readily activated by molecular oxygen in the presence of suitable ligands, enabling remarkably efficient

alkynylation of a range of nitrogen-based (lactams $\mathbf{2_N}$,[14a] oxazolidinones $\mathbf{2_{N'}}$,[14a] imines $\mathbf{2_{N''}}$[14b]), phosphorus-based (phosphine oxides $\mathbf{2_P}$,[14d] phosphine-boranes $\mathbf{2_{P'}}$,[14c] phosphites $\mathbf{2_{P''}}$[14a]) and carbon-based (arenes $\mathbf{2_{C\text{-}C''}}$,[14e] trifluoromethyl anion $\mathbf{2_{C'''}}$[14f]) nucleophiles **2** (Figure 1).

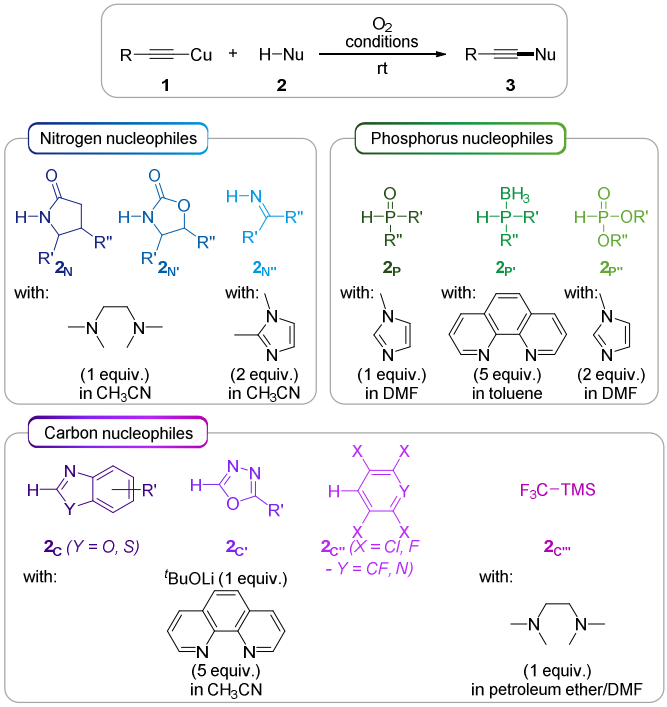
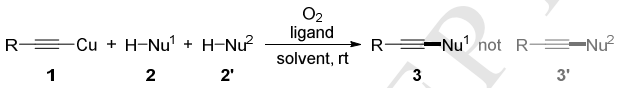


Figure 1. Oxidative alkynylation of N-, P-, and C- nucleophiles with copper acetylides.

Based on the strong solvent and ligand effects on these procedures, we envisioned that the chemoselective alkynylation of a given nucleophile in the presence of another one might be possible with the proper choice of both the ligand and solvent (Scheme 1): we report in this manuscript our efforts towards this chemoselective oxidative alkynylation.



Scheme 1. Goal of this study: chemoselective alkynylation with copper acetylides.

2. Results and discussion

With this goal in mind, we first needed to select the most convenient analytical method that would allow for a fast and reliable quantification of the selectivity of the oxidative alkynylation of a mixture of two heteronucleophiles with a copper acetylide. For this method to be of any usefulness, it should meet the following criteria: (i) it should be non-destructive in order to be able to recover, if required, the alkynylated product(s) after quantitative analysis, (ii) it should allow for a reliable and reproducible quantitative analysis with a small margin of error, (iii) it should be applicable to the analysis of the alkynylation of a broad range of heteronucleophiles with no or minimum re-optimization of the analysis parameters and settings and, (iv) it should be easily amenable to a fast screening of ligands and solvents for the alkynylation.

Based on these specifications, "classical" techniques such as HPLC, UPLC, SFC or GC were eliminated due to the need for a lengthy optimization of the parameters for each nucleophile that would be utilized for the study of the selectivity of the alkynylation. Moreover, ^{1}H NMR analysis turned out to be of little use in this case due to overlapping signals. We therefore decided to focus our efforts on quantitative ^{13}C NMR analysis, an analytical method that is clearly under-utilized by synthetic chemists despite its strong potential and reliability.

2.1. Assessing the feasibility and reliability of quantitative ^{13}C NMR analyses for the study of the alkynylation of heteronucleophiles with copper acetylides.

Quantitative analysis of product ratios is indeed more conveniently performed with ^{13}C NMR spectroscopy[15,16] due to the greater range of chemical shift compared to ^{1}H NMR spectroscopy. In addition, natural-abundance ^{13}C NMR can be employed with rather limited amounts of material (in the tens of mg range) and yields spectra that exhibit simple first-order patterns, typically singlet signals in ^{1}H-decoupled spectra. However, this technique generally requires long measurement times for the analyses to be quantitative and to achieve sufficient signal-to-noise ratio. More precisely, a long relaxation delay (D1) is required for the longitudinal magnetizations, *i.e.* the nuclear spin-state populations, to return to equilibrium before the next pulse. Typically, this recovery process exhibits an exponential time-dependence and is characterized by a single relaxation time T_1. For spectra recorded using a flip angle of 90°, the repetition time, which is defined as the sum of the acquisition time (AQ) and D1, must be at least five times the longest T_1 value (Figure 2). Furthermore, quantitative ^{13}C NMR spectra must be recorded with inverse-gated broadband ^{1}H decoupling, *i.e.* with ^{1}H irradiation turned on only during acquisition (Figure 2), to prevent the buildup of nuclear Overhauser effects. This results in a significant drop in signal-to-noise ratio compared to routine spectra and this has to be compensated by further signal averaging. Considering that T_1 values can reach several tens of seconds for ^{13}C, it is clear that longitudinal relaxation is a central issue in quantitative analysis.

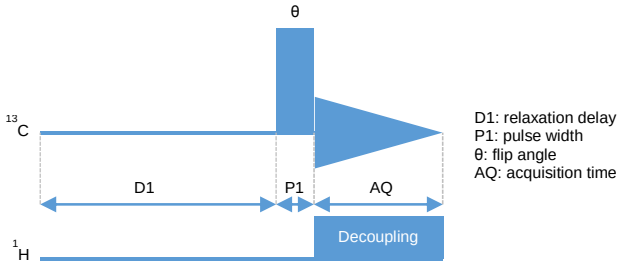


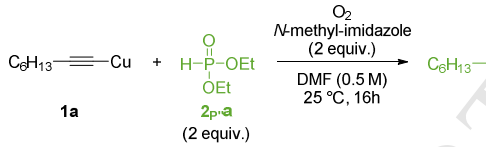
Figure 2. Pulse sequence for the acquisition of ^{13}C NMR spectra with inverse-gated ^{1}H decoupling.

One possibility to shorten the T_1 relaxation times, and therefore be able to perform a quantitative ^{13}C NMR analysis in a reasonable measurement time, is to use a paramagnetic relaxation agent. Dipolar interactions with unpaired electrons, whose magnetic moment is about 658 times larger than that of ^{1}H, will then dominate and substantially speed up the ^{13}C relaxation processes.

If we now consider the system we want to study (Scheme 1), the first step is therefore to choose a relaxation agent that would allow for a sufficient decrease of T_1 relaxation times but would not cause significant line broadening. Importantly, the relaxation agent should not interfere, complex or react with any species

present in the reaction mixture. Considering the fact that paramagnetic copper(II) salts are generated in a quantitative manner after the oxidative alkynylation, we first envisioned using these byproducts as inherent relaxation agents. After considerable experimentation, we could not however obtain reliable enough quantitative ^{13}C NMR analyses and therefore switched to the commonly used relaxation agent chromium(III) acetylacetonate, $Cr(acac)_3$.

The optimum concentration of this agent was first determined using the model alkynylation of diethylphosphite **2$_{P'}$a** with oct-1-ynylcopper **1a**, a reaction we had previously shown to smoothly provide alkynylphosphonate **3$_{P'}$a** (Scheme 2). After reaction with 2 equivalents of *N*-methyl-imidazole in DMF under an atmosphere of oxygen for 16 hours at 25 °C (to make sure the analyses would not be biased by variations of the room temperature), the crude reaction mixture was quenched with an aqueous mixture of saturated ammonium chloride and 28% ammonium hydroxide (1:1 solution) to remove all copper salts, and extracted with ethyl acetate. Combined organic layers were next washed with water and brine, dried over $MgSO_4$, filtered and concentrated to dryness. The crude mixture was finally dissolved in $CDCl_3$ (1 mL) before adding the relaxation agent, $Cr(acac)_3$. By measuring the ^{13}C T_1 relaxation times by means of the inversion-recovery method, we determined that the use of 0.075 M of $Cr(acac)_3$ is ideal and allows for relaxation times below 0.6 s for all carbons of alkynylphosphonate **3$_{P'}$a**, without significant signal broadening. We also checked its stability in the presence of the relaxation agent and no degradation could be observed, even after 10 days. We then adjusted the acquisition parameters and recorded a ^{13}C spectrum (Figure 3) from which we extracted integral data for all the signals of **3$_{P'}$a**. These data confirmed the quantitative analysis and, which is an important point for our studies, demonstrated that we could compare the intensities measured for carbon bearing a different number of hydrogen atoms, including quaternary carbons. As a note, deconvolution was not strictly required to obtain reliable results.

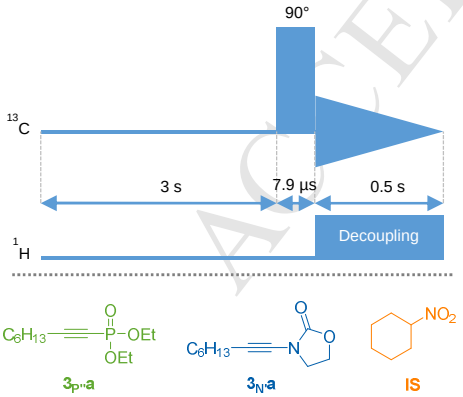


Scheme 2. Model reaction selected for the validation of the quantitative ^{13}C NMR analysis.

Having demonstrated the efficiency of $Cr(acac)_3$ as relaxation agent and optimized the acquisition parameters, we next decided to ascertain the viability of our procedure for the quantitative analysis of a mixture of two representative hetero-substituted alkynes, a crucial point before its use with real systems. With this goal in mind, we therefore prepared a series of mixtures containing known quantities of alkynylphosphonate **3$_{P'}$a** and ynamide **3$_{N'}$a** together with nitrocyclohexane **IS**, a compound which is totally inert towards the different species involved in our whole study and which was therefore selected as an internal standard. The signal of the carbon bearing the nitro substituent has in addition a chemical shift that is in the center of the spectral window and will not overlap with those of the compounds we want to study. Precisely measured quantities of the three compounds were therefore dissolved in $CDCl_3$ together with $Cr(acac)_3$ (to reach the 0.075 M optimal concentration): gratifyingly, the analysis of these samples with the optimized conditions summarized in Figure 3 demonstrated that the ratio determined by ^{13}C NMR are in excellent agreement with the calculated ones (≤5%). A representative ^{13}C NMR spectrum of such a model mixture is shown in Figure 3.

2.2. Chemoselective alkynylation of phosphites vs oxazolidinones.

Having demonstrated the feasibility and the reliability of quantitative ^{13}C NMR analyses that enable an excellent discrimination between an ynamide and an alkynylphosphonate and the quantification of the ratio of these two heterosubtituted alkynes, we next moved to a systematic screening of the influence of the nature of both the ligand and solvent on the chemoselectivity. Oct-1-ynylcopper **1a** was selected as a model copper acetylide for this study and was reacted with 2 equivalents of diethylphosphite **2$_{P'}$a** and oxazolidinone **2$_{N'}$a** – both nucleophiles being excellent reaction partners for oxidative alkynylations with copper acetylides, reactions that in addition proceed at similar rates[14a] – in the presence of representative ligands (1 equivalent in the case of bidentate ligands, 2 in the case of monodentate ones) and solvents that we previously found to be efficient for the oxidative alkynylation of various heteronucleophiles under an atmosphere of oxygen (balloon) at



Sample	3$_{P'}$a/IS			3$_{N'}$a/IS			3$_{P'}$a/3$_{N'}$a		
	Calc.	NMR	Diff.	Calc.	NMR	Diff.	Calc.	NMR	Diff.
1	0.865	0.887	3%	0.843	0.834	1%	1.026	1.063	4%
3	0.930	0.979	5%	0.220	0.223	1%	4.216	4.390	4%
4	0.151	0.157	4%	0.140	0.142	1%	1.076	1.100	2%

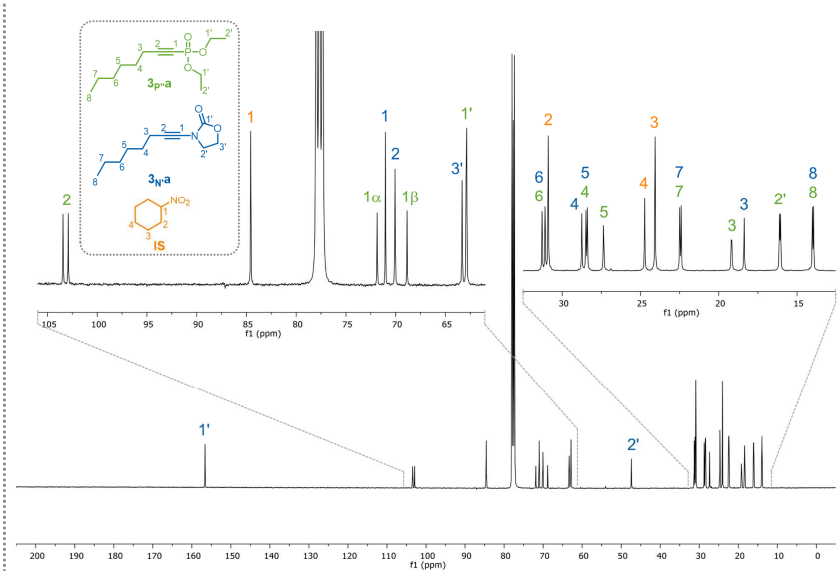


Figure 3. Optimized ^{13}C NMR pulse sequence, analysis of product ratios in model mixtures and representative ^{13}C NMR spectrum (100 MHz, $CDCl_3$, 25 °C). *The α and β notation refers to the two resonances observed for the C1 carbon coupling with a phosphorous nucleus.*

25 °C for 16 h and with a stirring rate of 375 rpm. The crude mixtures were then treated as previously described and dissolved in $CDCl_3$ (1 mL) before adding 1 equivalent of the internal standard, nitrocyclohexane, and $Cr(acac)_3$ (0.075 M). Quantitative ^{13}C NMR analyses of the crude mixtures according to our optimized procedure described above enabled the determination of the yields of alkynylphosphonate **3$_{P''}$a** and ynamide **3$_{N'}$a**: results from these studies are collected in Figure 4.

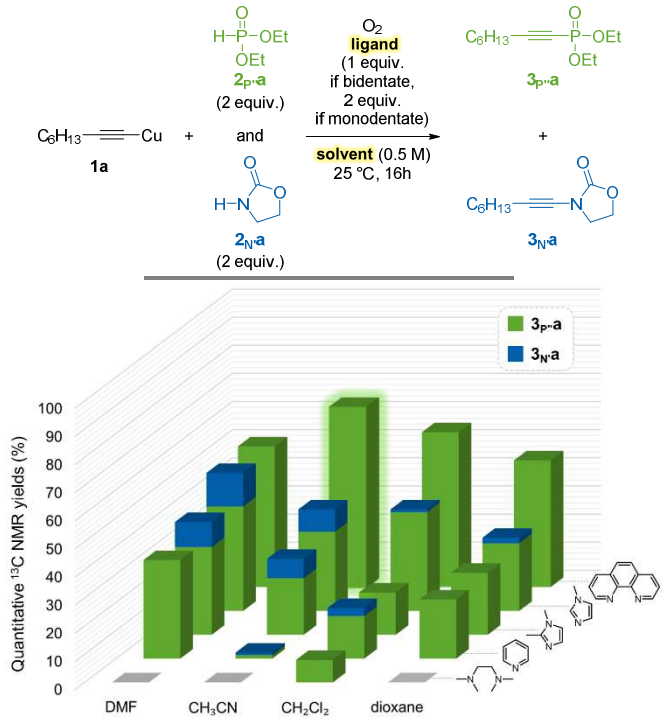


Figure 4. Ligand and solvent effects on the chemoselectivity of the oxidative alkynylation of a phosphite *vs* an oxazolidinone with a copper acetylide. *Quantitative ^{13}C NMR yields determined with nitrocyclohexane as internal standard and $Cr(acac)_3$ as relaxation agent.*

As evidenced by these results, there is a net selectivity in favor of the alkynylation of the starting phosphite **2$_{P''}$a**, the corresponding alkynylphosphonate **3$_{P''}$a** being formed predominantly or exclusively. Importantly, the reactions went to completion in all cases, the difference to 100% of the added products yields corresponding to competing dimerization and protonation of the starting copper acetylide.

Among the five ligands evaluated, phenanthroline turned out to be by far the most efficient one, promoting the formation of **3$_{P''}$a** with a complete chemoselectivity regardless of the nature of the solvent. The best solvent used in combination with this ligand was found to be acetonitrile, favoring the alkynylation to **3$_{P''}$a** in 64% yield. Compared to our originally reported procedure for the oxidative alkynylation of phosphites,[14a] which relied on the use of *N*-methyl-imidazole as the ligand in DMF, the presence of the additional oxazolidinone clearly has a deep impact on the alkynylation since, in the absence of this extra nucleophile, *N*-methyl-imidazole was found to be a better ligand for the alkynylation of phosphites compared to phenanthroline, therefore revealing a subtle effect of the competing coordination of the ligand and the nucleophiles to the oxidized copper acetylide. The use of bidentate ligand certainly inhibits the coordination of the oxazolidinone, a weaker ligand for copper than the phosphite, which might account for both the ligand effect observed and the chemoselectivity of the alkynylation. The absence of even traces of ynamide **3$_{N'}$a** with TMEDA as the ligand, which we previously showed to promote a fast and high-yielding alkynylation of **2$_{N'}$a** regardless the nature of the solvent,[14a] also highlights the dramatic influence of the phosphite on its alkynylation.

Having determined the optimal system for the selective alkynylation of a phosphite in the presence of an oxazolidinone, we next decided to further push its limits by increasing the amount of oxazolidinone. Another set of experiments was therefore performed using 2, 4, 6, 10 and 20 equivalents of oxazolidinone **2$_{N'}$a** compared to the starting phosphite **2$_{P''}$a**. The exact same procedure was utilized to obtain the quantitative ^{13}C NMR yields and product ratios. As evidence by the results summarized in Figure 5, the chemoselectivity was in favor of the alkynylation of the phosphite in all cases, even in the presence of 20 equivalents of oxazolidinone, a quite remarkable feature. Quite logically, the amount of ynamide **3$_{N'}$a** increased together with the proportion of oxazolidinone, reaching however only 7% with 20 equivalents.

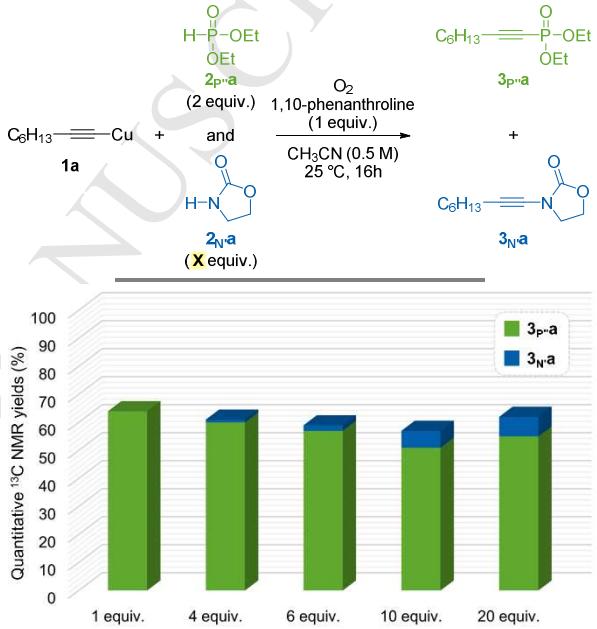


Figure 5. Influence of the amount of oxazolidinone on the chemoselectivity of the oxidative alkynylation of a phosphite. *Quantitative ^{13}C NMR yields determined with nitrocyclohexane as internal standard and $Cr(acac)_3$ as relaxation agent.*

To further assess the efficiency of our conditions, we next evaluated the generality of this chemoselective alkynylation by reacting various copper acetylides **1** with 2 equivalents of diethylphosphite **2$_{P''}$a** and 20 of oxazolidinone **2$_{N'}$a** under our optimized conditions. The chemoselectivity was assessed by quantitative ^{13}C NMR analyses of crude reaction mixtures and by comparison with ^{13}C NMR data of all possible pure alkynylated products prepared according to our previously reported procedures.[14] As highlighted by results collected in Figure 6, a total chemoselectivity was observed, for some unclear reason, with all aromatic copper acetylides. The resulting alkynylphosphonates **3$_{P''}$b-f** are in addition formed in higher yields compared to **3$_{P''}$a**, regardless of the electronic nature of the aryl group. All together, these results further highlight the robustness of our procedure that enables selectively "fishing" a phosphite in the presence of a large excess of an oxazolidinone. To conclude this study, the influence of the starting phosphite **2$_{P''}$** was finally evaluated in combination with oct-1-ynylcopper **1a**: its nature was shown to have a limited impact on the chemoselectivity, the corresponding alkynylphosphonates

3$_{P''}$a,**g**,**h** being predominantly formed together with minor amounts of the corresponding ynamide **3$_{N'}$a** (5-7%). In the case of diisopropylphosphite, the reduced efficiency of its oxidative alkynylation can be attributed to increased steric hindrance close to the reacting center and its reduced ability to coordinate copper.

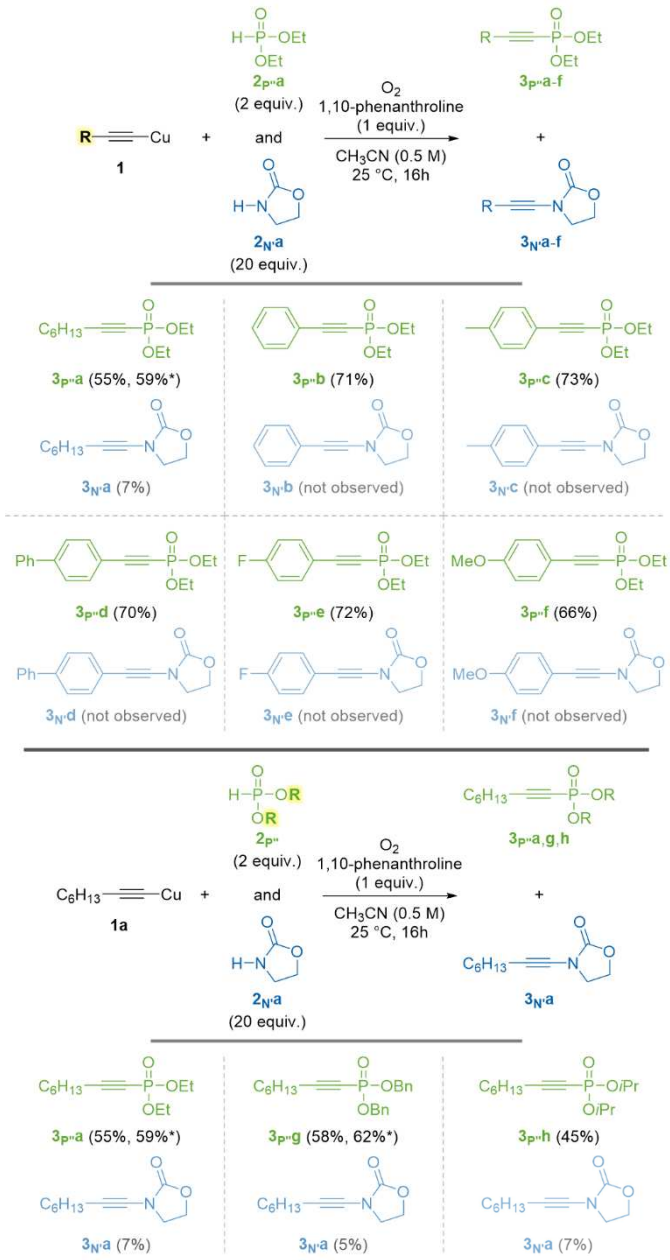


Figure 6. Assessing the generality of the chemoselective oxidative alkynylation of phosphites in the presence of an oxazolidinone. *Quantitative ^{13}C NMR yields determined with nitrocyclohexane as internal standard and Cr(acac)$_3$ as relaxation agent.* * *denotes isolated yields.*

At this point of our studies, we have demonstrated the feasibility of a chemoselective oxidative alkynylation of phosphites, even in the presence of a 10-fold excess of an oxazolidinone. The nature of the starting copper acetylide was shown to have a pronounced effect on the chemoselectivity, aryl-substituted ones providing full control of the chemoselectivity while the use of an alkyl-substituted one still provides minor amounts of an ynamide in the presence of a large excess of the oxazolidinone compared to the starting phosphite.

To further assess and expand the scope of this chemoselective alkynylation, we then moved to other N- and P-nucleophiles: this study is described in the following section.

2.3. Chemoselective alkynylation of P- and N- nucleophiles.

To further investigate the influence of the nature of both the P- and N- nucleophiles on their alkynylation, we indeed briefly investigated the behavior of other nucleophiles for which we had previously shown that they could be successfully transformed to the corresponding phosphorus- or nitrogen- substituted alkynes.[14] With this goal in mind, diphenylphosphine oxide **2$_{P}$a** and dicyclohexylphosphine-borane **2$_{P'}$a** were first reacted with oct-1-ynylcopper **1a** in the presence of 10 equivalents of oxazolidinone **2$_{N'}$a** under the conditions optimized for the selective alkynylation of phosphites (Figure 7). To our greatest pleasure, the same trend was observed with these two P-nucleophiles since the corresponding phosphorus-substituted alkynes, namely alkynylphosphine oxide **3$_{P}$a** and alkynylphosphine-borane **3$_{P'}$a** were formed as the exclusive or major products, respectively, the lower yield obtained for **3$_{P'}$a** being attributed to its lower stability under the reaction conditions.

We could moreover also successfully demonstrate that the chemoselective alkynylation of phosphites in the presence of N-nucleophiles is not limited to oxazolidinones since alkynylphosphonate **3$_{P''}$a** was still found to be the major product in the presence of an excess of γ-lactam **2$_{N}$a**, its alkynylation to **3$_{N}$a** being limited, especially when considering the 10/1 ratio between **2$_{P''}$a** and **2$_{N}$a** utilized.

Having previously demonstrated that imines readily react with copper acetylides under oxidative conditions,[14b] we finally moved to the study of the selectivity of the alkynylation of diethylphosphite **2$_{P''}$a** in the presence of benzophenone imine **2$_{N''}$a**. In this case, the use of an excess of this nucleophile was prohibited since it could not be eliminated during the workup, which considerably complicated further quantitative ^{13}C NMR analyses. A 1:1 ratio of **2$_{P''}$a** and **2$_{N''}$a** was therefore utilized and a high selectivity in favor of the phosphite was observed again in this case. This selectivity was in addition shown to be independent of the nature of the starting copper acetylide **1** as demonstrated with the exclusive formation of alkynylphosphonates **3$_{P''}$a-f**, not a trace of the ynimines **3$_{N''}$a-f** being detected in crude reaction mixtures.

Remarkably, a screening of ligands (not shown) revealed that the chemoselectivity could be reversed, replacing 1,10-phenanthroline by pyridine under the exact same conditions favoring the formation of ynimine **3$_{N''}$a**, although formed in a modest 33% yield due to competing dimerization and protonation of the starting copper acetylide **1a**, over the alkynylation of diethylphosphite **2$_{P''}$a** to **3$_{P''}$a** (6%).

As evidenced by all results described in this section, copper acetylides can be utilized as highly selective alkynylation agents provided that the right ligand/solvent combination is utilized. In a final attempt to bring this chemoselective alkynylation one step further, we finally addressed a more complicated case in which two nitrogen-nucleophile could compete with the activated copper acetylides, which is at the core of the next and final section of this article.

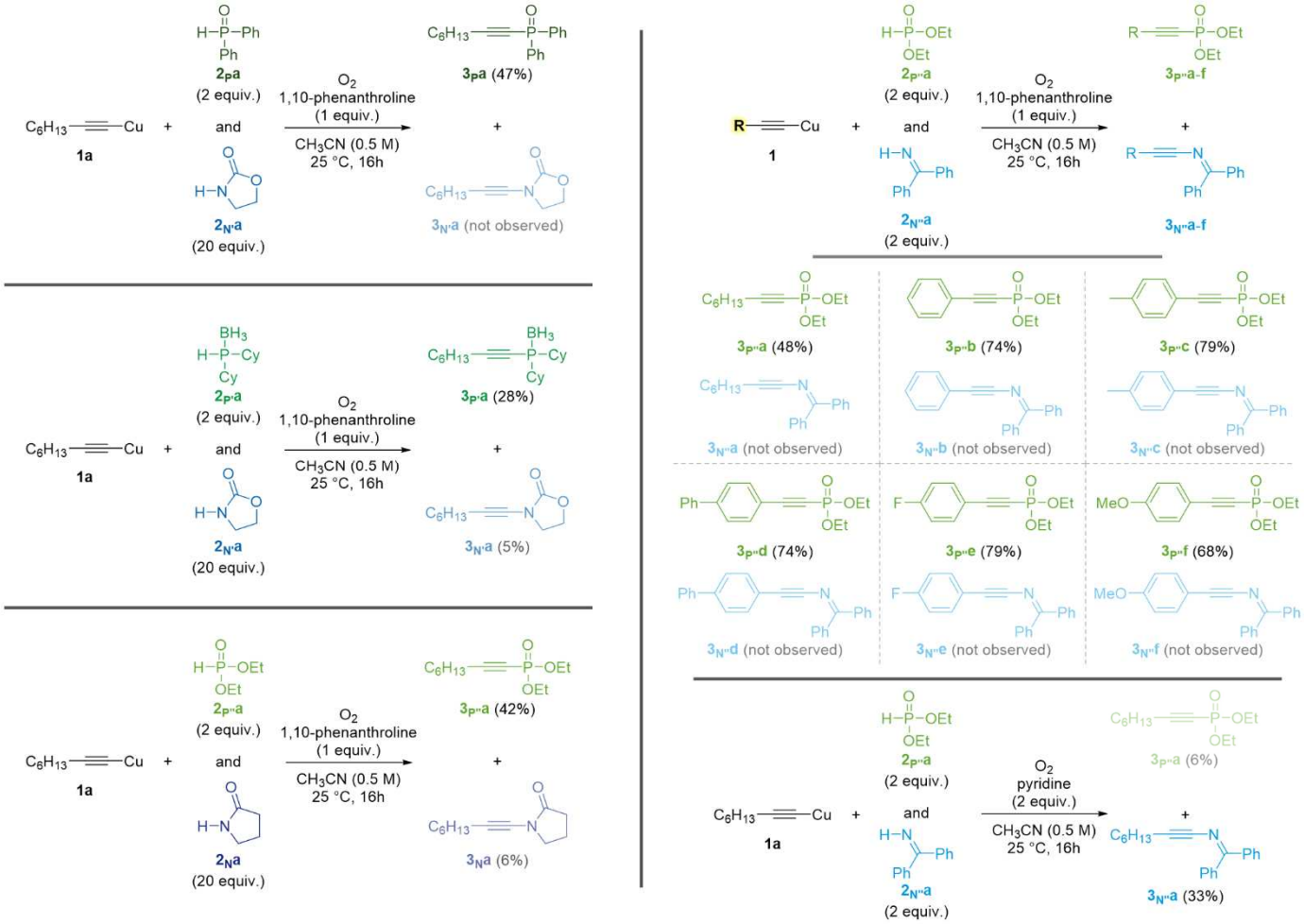


Figure 7. Chemoselective alkynylation of P- and N- nucleophiles. *Quantitative ^{13}C NMR yields determined with nitrocyclohexane as internal standard and Cr(acac)$_3$ as relaxation agent.*

2.4. Chemoselectivity of the oxidative alkynylation of two N-nucleophiles.

For this study, we selected two nucleophiles with different coordination properties towards copper in order to maximize the chances of success of this challenging reaction: oxazolidinone **2$_{N'}$a** and benzophenone imine **2$_{N"}$a**. The exact same systematic study of the influence of both the ligand and solvent performed for the competition experiments between an oxazolidinone and a phosphite was then undertaken in order to assess the chemoselectivity of the alkynylation: results from this study are illustrated in Figure 8. Due to the close reactivity between the two heteronucleophiles evaluated, ynamide **3$_{N'}$a** and ynimine **3$_{N"}$a** are readily formed with a number of ligand/solvent combinations, ynamide **3$_{N'}$a** being the major product in most cases. Although benzophenone imine **2$_{N"}$a** could not be alkynylated in a fully selective manner, various systems promoted a clean and totally chemoselective alkynylation of oxazolidinone **2$_{N'}$a** to the corresponding ynamide **3$_{N'}$a**, the best compromise between efficiency and selectivity being obtained using TMEDA in dichloromethane which afforded **3$_{N'}$a** in 75% yield together with only 5% of **3$_{N"}$a**.

The chemoselectivity of this oxidative alkynylation was finally tested starting from another oxazolidinone, **2$_{N'}$b**: upon reaction with oct-1-ynylcopper **1a** and TMEDA in dichloromethane in the presence of 2 equivalents of benzophenone imine **2$_{N"}$a** , ynamide **3$_{N'}$g** could be selectively formed in 74% yield without a trace of ynimine **3$_{N"}$a** (Scheme 3), therefore confirming the generality of this chemoselective alkynylation.

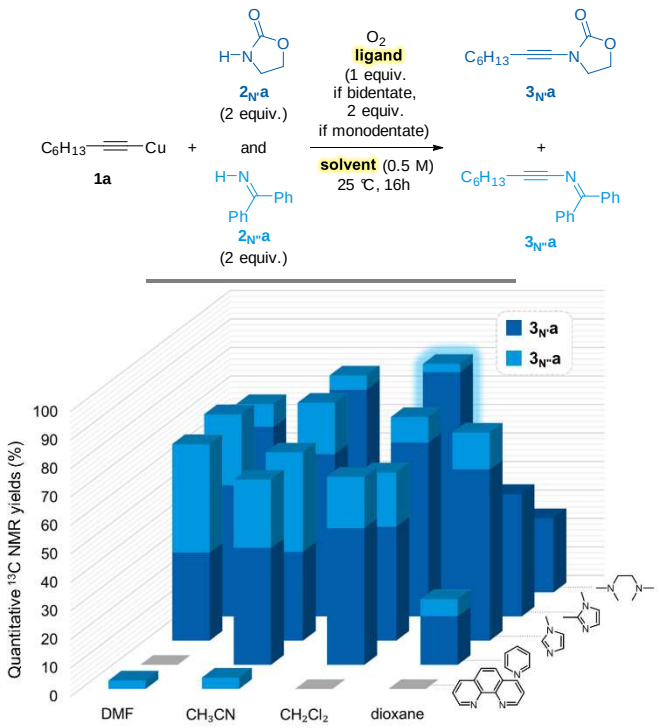
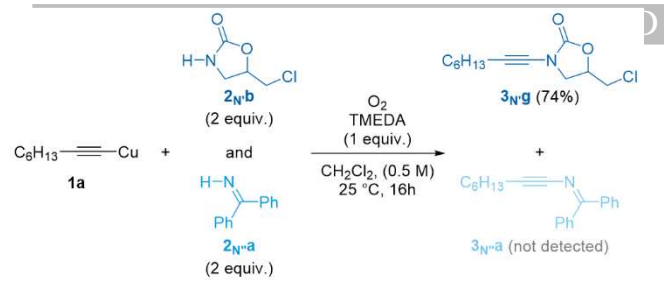


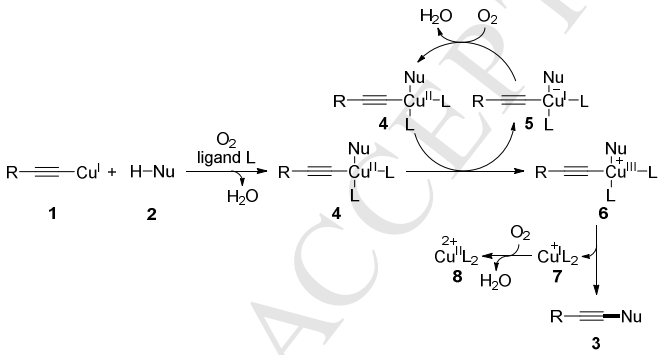
Figure 8. Ligand and solvent effects on the chemoselectivity of the oxidative alkynylation of an oxazolidinone *vs* an imine with a copper acetylide. *Quantitative ^{13}C NMR yields determined with nitrocyclohexane as internal standard and Cr(acac)$_3$ as relaxation agent.*



Scheme 3. Chemoselective oxidative alkynylation of 5-(chloromethyl)oxazolidin-2-one in the presence of benzophenone imine. *Quantitative ^{13}C NMR yield determined with nitrocyclohexane as internal standard and Cr(acac)$_3$ as relaxation agent.*

2.5. Discussion of the chemoselectivity of the oxidative alkynylation of two N-nucleophiles.

In order to be able to discuss the trends observed for the chemoselective alkynylation with copper acetylides, we first need to discuss its mechanism. The first step of the reaction involves simultaneous oxidation of the starting copper(I) acetylide **1** by molecular oxygen and the coordination of both the ligand **L** (2 ligands in the case of a monodentate one, 1 in the case of bidentate ligands) and the heteronucleophile **2** yielding to a putative copper(II) acetylide species **4** (Scheme 4). Indeed, we have demonstrated that **1** is totally inert towards all ligands and heteronucleophiles discussed in this study and that it does not either readily react when treated with molecular oxygen in the presence of a ligand or a heteronucleophile only: molecular oxygen, a nucleophile and a ligand are therefore required to trigger the reaction. Dismutation of this copper(II) acetylide **4** to the corresponding copper(I) **5** and copper(III) **6** acetylides, as in the Cham-Lam-Evans reaction,[17] would then occur, the former being re-oxidized by molecular oxygen to **4** while the later would undergo a final reductive elimination yielding heterosubstituted alkyne **3** and a copper(I) complex **7** that would eventually be oxidized to the corresponding copper(II) complex **8**.



Scheme 4. Proposed mechanism for the oxidative alkynylation of heteronucleophiles with copper acetylides.

Based on this mechanism, the discrimination between two heteronucleophiles happens during the very first step of the process yielding to copper(II) acetylide **4** coordinated to both the ligand and the deprotonated nucleophile. As a simplification, nucleophiles with better coordinating properties to copper(II) would be therefore preferentially alkynylated, which is in agreement with the fact that phosphites, which are better ligands for copper(II) than oxazolidinones, selectively react with copper acetylides. The strong ligand and solvent effects observed and the reversal of selectivity observed with phosphites and imines however show that the situation is not that simple: multiple coordination of the nucleophile(s) to copper and the effect of the ligand on the ease of the oxidation and disproportionation steps as well as on the stability of copper acetylide intermediates also have a clear influence on both the outcome and the selectivity of the reaction.

3. Conclusions and outlook

In continuation of our studies on the use of copper acetylides as readily available and convenient reagents for the alkynylation of heteronucleophiles, we have now demonstrated, based on quantitative ^{13}C NMR analyses, that they can in addition be used for chemoselective alkynylations. With suitable ligand/solvent combinations, various phosphorus-based nucleophiles (phosphites, phosphine oxides, phosphine boranes) can be alkynylated with excellent levels of selectivity, even in the presence of a 10-fold excess of nitrogen-nucleophiles (oxazolidinones, lactams, imines). This chemoselective alkynylation could be further extended to the quite challenging selective alkynylation of a nitrogen-nucleophile, namely an oxazolidinone, over another one, further highlighting the synthetic potential of copper acetylides. "Fishing" with copper acetylides clearly has a strong potential for the selective modification of a heteronucleophile in a complex mixture, which should be quite handy for the site-selective functionalization of polyfunctional molecules, late-stage functionalizations, selective labelling or bioconjugation of complex biomolecules. Further studies on the reactivity of copper acetylides, on the mechanism associated to their oxidative activation and on their use for the modification of complex and polyfunctional molecules are underway and will be reported in due course.

4. Experimental section

4.1. General methods and materials

All reactions were carried out in oven-dried glassware under an oxygen atmosphere. Dichloromethane and acetonitrile were freshly distilled from calcium hydride under argon. *N*,*N*-dimethylformamide and dioxane were bought over molecular sieves in AcroSeal® bottles from Acros Organics and used as supplied. Copper acetylides were prepared according to our previously reported procedure.[14a,f,h] All other reagents were used as supplied.

4.2. ^{13}C NMR parameters and processing

^{13}C spectra were recorded at 25°C using an internal deuterium lock on a Varian VNMRS 400 spectrometer, operating at 100.56 MHz for ^{13}C, equipped with a 5 mm Automated Triple Broadband (ATB) probe. The solvent was used as internal standard for chemical shift referencing (δ_C 77.16 ppm for $CDCl_3$). The spectra were recorded in 3 h with the following acquisition parameters: a spectral width of 254 ppm (25510 Hz) centered at about 90 ppm, a 90° pulse width of 7.9 µs, an acquisition time of 0.5 s, a relaxation delay D1 of 3 s and 3600 repetitions. ^1H decoupling was applied only during acquisition (inverse-gated decoupling) using a WALTZ-16 scheme with a ^1H pulse width of 85 µs. The processing, which was completed with the software VNMRJ, included exponential apodization of the FID with a line-broadening factor (lb) of 2 Hz, zero-filling up to 256k points, Fourier transform, phase correction, chemical shift referencing and baseline correction. The integration limits were fixed at ± 0.3 ppm with respect to the center of each peak unless another peak was present in this range. In that case, a common boundary was set right in between these two peaks.

4.3. General procedure for the oxidative alkynylations, sample preparation for quantitative ^{13}C NMR analysis and characterization data

A 5 mL round bottom flask was successively charged with the two nucleophiles (1.0 mmol to 10.0 mmol), the alkynylcopper reagent (0.5 mmol) and the solvent (1 mL). The resulting bright yellow slurry was then treated with the ligand (0.5 mmol if bidentate and 1.0 mmol if monodentate) and the reaction mixture was stirred at 25 °C for 16 hours and at 375 rpm and under an atmosphere of oxygen (balloon). The reaction was then diluted with 15 mL of an aqueous mixture of saturated ammonium chloride and 25% ammonium hydroxide (1:1 solution) and extracted with 3x10 mL of ethyl acetate. Combined organic layers were washed with 10 mL of water and 10 mL of brine, dried over $MgSO_4$ and concentrated to dryness. Nitrocyclohexane (65 µL, 0.5 mmol) and chromium(III) acetylacetonate (27 mg, 75 µmol) were added to the crude and it was dissolved in 1 mL of $CDCl_3$.

Some of these reactions were performed in duplicate to compare the ^{13}C NMR yields with the isolated ones.

4.3.1.1. ***Diethyl (oct-1-yn-1-yl)phosphonate 3$_{P}$a.*** This compound has been previously reported.[18] Colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 4.07 (dt, J = 7.1 Hz and J_{H-P} = 15.7 Hz, 4H), 2.27 (dt, J = 7.1 Hz and J_{H-P} = 4.4 Hz, 2H), 1.57-1.45 (m, 2H), 1.39-1.16 (m, 6H), 1.29 (t, J = 7.1 Hz, 6H), 0.82 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 103.3 (d, J_{C-P} = 53.2 Hz), 70.5 (d, J_{C-P} = 303.3 Hz), 63.0 (d, J_{C-P} = 5.5 Hz), 31.2, 28.6, 27.5, 22.6, 19.3 (d, J_{C-P} = 4.6 Hz), 16.2 (d, J_{C-P} = 7.2 Hz), 14.1.

4.3.1.2. ***3-(Oct-1-yn-1-yl)oxazolidin-2-one 3$_{N}$a.*** Pale yellow oil; ^1H NMR (300 MHz, CDCl3): δ 4.39 (dd, J = 9.1 and 7.7 Hz, 2H), 3.86 (dd, J = 9.3 and 7.8 Hz, 2H), 2.28 (t, J = 7.0 Hz, 2H), 1.72-1.17 (m, 8H), 0.87 (t, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3): δ 156.8, 71.3 70.1, 62.9, 47.1, 31.4, 28.8, 28.6, 22.6, 18.5, 14.1; IR (ATR) ν_{max} 2929, 2858, 2269, 1767, 1415, 1301, 1206, 1115, 1035, 976, 751 cm^{-1}; ESIHRMS *m/z* calcd for $C_{11}H_{18}NO_2$ $[M+H]^+$ 196.1338, found 196.1341.

4.3.1.3. ***Diethyl (phenylethynyl)phosphonate 3$_{P}$b.*** This compound has been previously reported.[19] Colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51-7.47 (m, 2H), 7.38 (tt, J = 7.5 and 1.4 Hz, 1H), 7.33-7.27 (m, 2H), 4.21-4.11 (m, 4H), 1.34 (dt, J = 7.1 Hz and J_{H-P} = 0.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.5 (d, J_{C-P} = 2.4 Hz), 130.7, 128.5, 119.4 (d, J_{C-P} = 6.0 Hz), 99.0 (d, J_{C-P} = 52.4 Hz), 78.3 (d, J_{C-P} = 299.2 Hz), 63.2 (d, J_{C-P} = 5.5 Hz), 16.1 (d, J_{C-P} = 7.1 Hz).

4.3.1.4. ***3-(Phenylethynyl)oxazolidin-2-one 3$_{N}$b.*** This compound has been previously reported.[20] Colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 7.48-7.40 (m, 2H), 7.37-7.28 (m, 3H), 4.54-4.45 (m, 2H), 4.07-3.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.0, 131.7, 128.4, 128.3, 122.3, 79.1, 71.3, 63.2, 47.2.

4.3.1.5. ***Diethyl (p-tolylethynyl)phosphonate 3$_{P}$c.*** This compound has been previously reported.[19] Colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 4.22-4.12 (m, 4H), 2.32 (s, 3H), 1.35 (dt, J = 7.1 Hz and J_{H-P} = 0.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.3, 132.5 (d, J_{C-P} = 2.4 Hz), 129.3, 116.4 (d, J_{C-P} = 6.0 Hz), 99.6 (d, J_{C-P} = 53.2 Hz), 77.7 (d, J_{C-P} = 300.5 Hz), 63.1 (d, J_{C-P} = 5.5 Hz), 21.7, 16.1 (d, J_{C-P} = 7.1 Hz).

4.3.1.6. ***3-(p-Tolylethynyl)oxazolidin-2-one 3$_{N}$c.*** White solid; MP: 123°C; ^1H NMR (300 MHz, CDCl3): δ 7.33 (d, J = 8.1 Hz, 2H), 7,11 (d, J = 7.8 Hz, 2H), 4.47 (dd, J = 9.3 and 7.7 Hz, 2H), 3.99 (dd, J = 9.3 and 7.7 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.1, 138.5, 131.7, 129.2, 119.0, 78.4, 71.4, 63.1, 47.2, 21.6; IR (ATR) ν_{max} 2263, 1752, 1417, 1217, 1199, 1164, 1031, 818, 746, 707 cm^{-1}; ESIHRMS *m/z* calcd for $C_{12}H_{12}NO_2$ $[M+H]^+$ 202.0868, found 202.0870.

4.3.1.7. ***Diethyl ([1,1'-biphenyl]-4-ylethynyl) phosphonate 3$_{P}$d.*** This compound has been previously reported.[19] White solid; ^1H NMR (400 MHz, $CDCl_3$): δ 7.62-7.52 (m, 6H), 7.45-7.39 (m, 2H), 7.37-7.32 (m, 1H), 4.27-4.17 (m, 4H), 1.39 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4, 139.6, 133.0 (d, J_{C-P} = 2.4 Hz), 128.9, 128.2, 127.1, 127.0, 118.2 (d, J_{C-P} = 5.5 Hz), 99.0 (d, J_{C-P} = 53.1 Hz), 78.9 (d, J_{C-P} = 299.5 Hz), 63.2 (d, J_{C-P} = 5.6 Hz), 16.1 (d, J_{C-P} = 7.1 Hz).

4.3.1.8. ***3-([1,1'-biphenyl]-4-ylethynyl)oxazolidin-2-one 3$_{N}$d.*** This compound has been previously reported.[21] White solid; ^1H NMR (400 MHz, $CDCl_3$): δ 7.61-7.49 (m, 6H), 7.47-7.41 (m, 2H), 7.38-7.32 (m, 1H), 4.53-4.47 (m, 2H), 4.06-4.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.0, 141.1, 140.4, 132.1, 129.0, 127.8, 127.1 (2C), 121.2, 79.7, 71.3, 63.2, 47.2.

4.3.1.9. ***Diethyl (4-fluorophenylethynyl) phosphonate 3$_{P}$e.*** This compound has been previously reported.[19] Colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50-7.44 (m, 2H), 7.02-6.94 (m, 2H), 4.19-4.08 (m, 4H), 1.31 (dt, J = 7.1 Hz and J_{H-P} = 0.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8 (d, J_{C-F} = 253.5 Hz), 134.8 (dd, J_{C-F} = 8.9 and J_{C-P} = 2.4 Hz), 116.0 (d, J_{C-F} = 22.3 Hz), 115.6 (dd, J_{C-P} = 5.7 and J_{C-F} = 3.5 Hz), 97.8 (d, J_{C-P} = 53.1 Hz), 78.6 (d, J_{C-P} = 243.1 Hz), 63.2 (d, J_{C-P} = 5.6 Hz), 16.1 (d, J_{C-P} = 7.1 Hz).

4.3.1.10. ***3-(4-Fluorophenylethynyl)oxazolidin-2-one 3$_{N}$e.*** White solid; MP: 114°C; ^1H NMR (300 MHz, CDCl3): δ 7.45-7.38 (m, 2H), 7,04-6.95 (m, 2H), 4.48 (dd, J = 9.3 and 7.7 Hz, 2H), 4.00 (dd, J = 9.3 and 7.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.6 (d, J_{C-F} = 248 Hz), 156.0, 133.8 (d, J_{C-F} = 8.4 Hz), 118.3 (d, J_{C-F} = 3.5 Hz), 115.7 (d, J_{C-F} = 21.9 Hz), 78.7, 70.3, 63.2, 47.1; IR (ATR) ν_{max} 2268, 1754, 1416, 1208, 1195, 1165, 1091, 835, 744 cm^{-1}; ESIHRMS *m/z* calcd for $C_{11}H_9FNO_2$ $[M+H]^+$ 206.0617, found 206.0618.

4.3.1.11. ***Diethyl (4-methoxyphenylethynyl) phosphonate 3$_{P}$f.*** This compound has been previously reported.[19] Colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, J = 8.9 Hz, 2H), 6.83 (d, J = 8.9 Hz, 2H), 4.22-4.12 (m, 4H), 3.79 (s, 3H), 1.36 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.5, 134.4, 114.3, 111.3 (d, J_{C-P} = 5.7 Hz), 99.9 (d, J_{C-P} = 53.8 Hz), 77.2 (d, J_{C-P} = 302.1 Hz), 63.2 (d, J_{C-P} = 5.5 Hz), 55.4, 16.1 (d, J_{C-P} = 7.1 Hz).

4.3.1.12. ***3-(4-Methoxyphenylethynyl)oxazolidin-2-one 3$_{N}$f.*** This compound has been previously reported.[20] White solid; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39-7.35 (m, 2H), 6.83-6.79 (m, 2H), 4.46-4.41 (m, 4H), 3.98-3.92 (m, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 156.2, 133.5, 114.1, 114.0, 77.7, 70.9, 63.1, 55.3, 47.2.

4.3.1.13. ***Dibenzyl (oct-1-yn-1-yl)phosphonate 3$_{P}$g.*** Colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30-7.20 (m, 10H), 4.99 (d, J_{H-P} = 8.7 Hz, 4H), 2.20 (dt, J = 6.3 Hz and J_{H-P} = 4.5 Hz, 2H), 1.43 (tt, J = 7.5 and 6.6 Hz, 2H), 1.30-1.13 (m, 6H), 0.81 (t, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.7, 128.5, 127.6, 127.0, 104.4 (d, J_{C-P} = 53.3 Hz), 70.3 (d, J_{C-P} = 292.5 Hz), 68.3 (d, J_{C-P} = 5.3 Hz), 31.2, 28.5, 27.3, 22.4, 19.2, 14.0; IR (ATR) ν_{max} 2923, 2205, 1452, 1260, 990 cm^{-1}; ESIHRMS *m/z* calcd for $C_{22}H_{28}O_3P$ $[M+H]^+$ 371.1776, found 371.1774.

4.3.1.14. ***Diisopropyl (oct-1-yn-1-yl) phosphonate 3$_{P}$h.*** Colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 4.51-4.34 (m, 2H), 2.01 (dt, J = 6.6 Hz and J_{H-P} = 4.8 Hz, 2H), 1.25 (tt, J = 7.8 and 7.2 Hz, 2H), 1.11-0.96 (m, 6H), 1.02 (d, J = 6.6 Hz, 12H), 0.56 (t, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 102.5 (d, J_{C-P} = 52.5 Hz), 71.5 (d, J_{C-P} = 300.0 Hz), 71.0 (d, J_{C-P} = 22.5 Hz), 30.7, 28.1, 27.0, 23.4 (d, J_{C-P} = 4.5

Hz), 23.2 (d, J_{C-P} = 4.9 Hz), 22.1, 18.8, 13.5; IR (ATR) ν_{max} 2979, 2213, 1377, 1257, 983 cm^{-1}; ESIHRMS *m/z* calcd for $C_{14}H_{28}O_3P$ $[M+H]^+$ 275.1776, found 275.1778.

4.3.1.15. ***(Oct-1-yn-1-yl)diphenylphospgine oxide 3Pa.*** This compound has been previously reported.[22] Yellow oil; ^{1}H NMR (300 MHz, CDCl3): δ 7.85-7.77 (m, 4H), 7.50-7.41 (m, 6H), 2.43 (td, *J* = 7.1 and J_{H-P} = 3.5 Hz, 2H), 1.61 (app. quint., *J* = 7.5 Hz, 2H), 1.45-1.34 (m, 2H), 1.34-1.22 (m, 4H), 0.86 (t, *J* = 6.8 Hz, 3H) ; ^{13}C NMR (75 MHz, CDCl3): δ 133.5 (d, J_{C-P} = 121.0 Hz), 132.1 (d, J_{C-P} = 2.8 Hz), 130.9 (d, J_{C-P} = 11.1 Hz), 128.6 (d, J_{C-P} = 13.3 Hz), 109.9 (d, J_{C-P} = 30.3 Hz), 75.0 (d, J_{C-P} = 174.0 Hz), 31.2, 28.6, 27.6 (d, J_{C-P} = 1.5 Hz), 22.5, 19.8 (d, J_{C-P} = 3.0 Hz), 14.1.

4.3.1.16. ***Dicyclohexyl(oct-1-yn-1-yl)phosphine-borane 3P'a.*** White solid; MP: 41 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.34 (td, *J* = 6.8 and J_{H-P} = 3.3 Hz, 2H), 1.94–1.65 (m, 12H), 1.54–1.18 (m, 18H), 0.89 (t, *J* = 7.0 Hz, 3H), 0.85– -0.28 (br. m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 110.3 (d, J_{C-P} = 10.3 Hz), 68.6 (d, J_{C-P} = 93.0 Hz), 32.3 (d, J_{C-P} = 37.6 Hz), 31.3, 28.5, 28.0 (d, J_{C-P} = 1.4 Hz), 26.9 (d, J_{C-P} = 3.5 Hz), 26.8, 26.6 (d, J_{C-P} = 3.9 Hz), 26.5, 26.0 (d, J_{C-P} = 1.0 Hz), 22.6, 20.0 (d, J_{C-P} = 2.1 Hz), 14.1; IR (ATR) ν_{max} 2928, 2852, 2376, 2345, 2194, 1445, 1055, 1000, 852, 754, 740, 616, 517, 465, 406 cm^{-1}; ESIHRMS *m/z* calcd for $C_{20}H_{38}PBNa$ $[M+Na]^+$ 343.2702, found 343.2695.

4.3.1.17. ***1-(Oct-1-yn-1-yl)pyrrolidin-2-one 3Na.*** Pale yellow oil; ^{1}H NMR (300 MHz, CDCl3): δ 3.57 (t, *J* = 7.4 Hz, 2H), 2.33 (t, *J* = 8.1 Hz, 2H), 2.23 (t, *J* = 7.2 Hz, 2H), 2.02 (app. quint, *J* = 7.6 Hz, 2H), 1.44 (app. quint, *J* = 7.2 Hz, 2H), 1.36-1.12 (m, 6H), 0.80 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.0, 72.5, 71.3, 50.0, 31.3, 29.5, 28.8, 28.5, 22.4, 18.6, 18.5, 14.0; IR (ATR) ν_{max} 2930, 2857, 2260, 1719, 1399, 1367, 1297, 1218, 1169, 1091, 813, 756 cm^{-1}; ESIHRMS *m/z* calcd for $C_{12}H_{20}NO$ $[M+H]^+$ 194.1545, found 194.1542.

4.3.1.18. ***N-(Diphenylmethylene)-oct-1-yn-1-amine 3N'a.*** Pale orange oil; ^{1}H NMR (300 MHz, CDCl3): δ 7.73 (d, *J* = 7.5 Hz, 2H), 7.48-7.44 (m, 6H), 7.40-7.35 (m, 2H), 2.43 (t, *J* = 6.8 Hz, 2H), 1.45-140 (m, 2H), 1.31-1.23 (m, 6H), 0.88 (t, *J* = 9.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.2, 138.2, 136.5, 131.2, 129.6, 129.2, 128.6, 128.3, 128.0, 96.5, 83.7, 31.5, 29.1, 28.4, 22.6, 20.3, 14.2; IR (ATR) ν_{max} 2919, 2848, 2246, 1661, 1444, 1313, 1274, 761, 692, 638 cm^{-1}; ESIHRMS *m/z* calcd for $C_{21}H_{24}N$ $[M+H]^+$ 290.1909, found 290.1902.

4.3.1.19. ***N-(diphenylmethylene)-2-phenylethynamine 3N'b.*** Orange solid; MP: 85 °C; ^{1}H NMR (300 MHz, CDCl3): δ 7.71 (d, *J* = 7.4 Hz, 2H), 7.50-7.49 (m, 2H), 7.44-7.42 (m, 4H), 7.33 (d, *J* = 7.6 Hz, 2H), 7.16-7.18 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.7, 137.9, 136.3, 131.6, 131.5, 130.1, 129.5, 129.0, 128.8, 128.3, 128.1, 127.8, 124.7, 94.2, 91.9; IR (ATR) ν_{max} 2966, 2899, 2181, 1388, 1235, 1065, 550 cm^{-1}; ESIHRMS *m/z* calcd for $C_{21}H_{16}N$ $[M+H]^+$ 282.1283, found 282.1291.

4.3.1.20. ***N-(diphenylmethylene)-2-(4-methylphenyl)ethynamine 3N'c.*** Orange solid; MP: 83 °C; ^{1}H NMR (300 MHz, CDCl3): δ 7.80 (d, J = 6.1 Hz, 2H), 7.60-7.42 (m, 8H), 7.28 (d, J = 3.2 Hz, 1H), 7.21 (d, J = 6.7 Hz, 1H), 6.82 (d, J = 7.0 Hz, 2H), 3.81 (s, 3H); 13C NMR (75 MHz, CDCl3): □ 176.3, 159.5, 133.2, 131.4, 129.9, 129.4, 128.8, 128.3, 128.0, 113.9, 94.7, 91.3, 55.3; IR (ATR) ν_{max} 3057, 1504, 1445, 1322, 808, 766, 693 cm^{-1}.

4.3.1.21. ***N-(diphenylmethylene)-2-([1,1'-biphenyl]-4-yl)ethynamine 3N'd.*** Orange solid; MP: 90 °C; ^{1}H NMR (300 MHz, CDCl3): δ 7.89-7.83 (m, 2H), 7.68-7.51 (m, 9H), 7.50-7.29 (m, 8H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.6, 140.6, 140.5, 138.3, 135.6, 132.1, 130.1, 129.7, 129.6, 129.4, 128.9, 128.8, 128.4 (2C), 128.2, 128.1, 127.9, 127.6, 127.0 (2C), 123.8, 94.4, 92.9; IR (ATR) ν_{max} 3059, 1485, 1445, 1323, 909, 840, 763, 670 cm^{-1}.

4.3.1.22. ***N-(diphenylmethylene)-2-(4-fluorophenyl)ethynamine 3N'e.*** Orange solid; MP: 80 °C; ^{1}H NMR (300 MHz, CDCl3): δ 7.70 (d, *J* = 7.3 Hz, 2H), 7.48-7.42 (m, 6H), 7.33 (d, *J* = 7.6 Hz, 2H), 7.16-7.12 (m, 2H), 6.86 (t, *J* = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, CDCl3): δ 177.2, 162.3 (d, J_{C-F} = 248 Hz), 137.8, 136.4, 133.4, 131.7, 130.2, 129.5, 128.8, 128.4, 128.1, 120.7, 115.4, 93.0, 91.6; IR (ATR) ν_{max} 2987, 2966, 2900, 2172, 1392, 1254, 1066 cm^{-1}; ESIHRMS *m/z* calcd for $C_{21}H_{15}NF$ $[M+H]^+$ 300.1189, found 300.1203.

4.3.1.23. ***N-(diphenylmethylene)-2-(4-methoxyphenyl)ethynamine 3N'f.*** Yellow oil; ^{1}H NMR (300 MHz, CDCl3): δ 7.80 (d, *J* = 6.1 Hz, 2H), 7.60-7.42 (m, 8H), 7.28 (d, *J* = 3.2 Hz, 1H), 7.21 (d, *J* = 6.7 Hz, 1H), 6.82 (d, *J* = 7.0 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.3, 159.5, 133.2, 131.4, 129.9, 129.4, 128.8, 128.3, 128.0, 113.9, 94.7, 91.3, 55.3; IR (ATR) ν_{max} 2958, 2825, 2166, 1603, 1505, 1438, 1324, 1239, 1172, 1023, 821, 688 cm^{-1}; ESIHRMS *m/z* calcd for $C_{22}H_{18}NO$ $[M+H]^+$ 312,1388 found 312.1388.

4.3.1.24. ***5-(Chloromethyl)-3-(oct-1-yn-1-yl)oxazolidin-2-one 3N'g.*** Colorless oil; ^{1}H NMR (300 MHz, CDCl3): δ 4.84-4.76 (m, 1H), 3.93 (A of ABX syst, *J* = 9.0 and 9.0 Hz, 1H), 3.73-3.65 (m, 3H), 2.24 (t, *J* = 7.0 Hz, 2H), 1.47 (app quint., *J* = 7.4 Hz, 2H), 1.37-1.20 (m, 6H), 0.84 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.5, 72.5, 71.4, 69.5, 49.6, 44.4, 31.3, 28.7, 28.5, 22.5, 18.3, 14.0; IR (ATR) ν_{max} 2967, 2927, 2268, 1764, 1420, 1223, 1113, 1050, 742 cm^{-1}; ESIHRMS *m/z* calcd for $C_{12}H_{19}ClNO_2$ $[M+H]^+$ 244.1104, found 244.1109.

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Supplementary Material

Copies of ^{1}H and ^{13}C NMR spectra for all products, copies of ^{13}C NMR spectra and selected data for quantitative ^{13}C NMR analyses.