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FULL PAPER

Selective synthesis of tetrasubstituted olefins by Cu-mediated acetoxythiolation of internal alkynes: scope and mechanistic studies

Pedro Villuendas,[a] Sara Ruiz,[a] Pietro Vidossich,[b],[c] Agustí Lledós,*[b] and Esteban P. Urriolabeitia*[a]

Dedication ((optional))

Abstract: The Cu-mediated synthesis of tetrasubstituted olefins by addition of an acetate group and a thiolate to an unactivated internal alkyne is described. The reaction is fully stereoselective, because only the *E*-alkene is obtained. When the alkyne is asymmetric, the reaction shows also a very high degree of regioselectivity. The mechanism of the reaction was elucidated by DFT methods and shows that it takes place through a mechanism involving Cu-stabilized radical species. Calculations highlight the crucial role of the dimeric copper(II) diacetate in the process, generating the active species in which the sulfur center has an incipient thiyl radical character and accepting, through a series of changes in the oxidation states of the two copper centers, the two electrons released in the addition of two nucleophiles to the alkyne.

Introduction

The synthesis of tetrasubstituted olefins with complete control of the regio- and stereoselectivities is still a challenge for synthetic chemists, as it has been highlighted in recent revisions.[1-7] New synthetic methods are continuously screened and an intensive research, devoted to achieve more performant pathways while keeping simple methodologies, is being developed.[8-18] The interest in these particular substrates resides on their versatility as starting materials, as well as in their pharmacological, photochemical and electrochemical properties.[19-24] Just to mention some well-known examples, (*Z*)-Tamoxifen (Figure 1) is used in the treatment and prevention of breast cancer,[21] iso-Combretastatine A-4 shows antitubulin activity,[22] Rofecoxib (a selective inhibitor of cyclooxygenase-2) displays activity in the prevention of colorectal adenoma,[23] while Nileprost was considered as a promising antiulcer agent.[24]

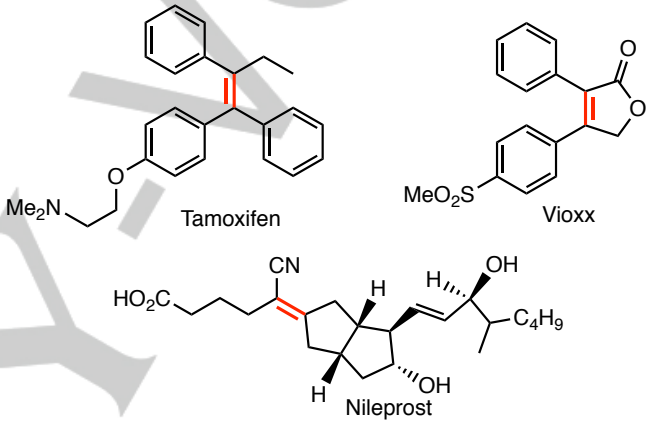

Figure 1. Some examples of tetrasubstituted olefins with recognized pharmacological activity

Some of the most general methods for the synthesis of tetrasubstituted olefins involve addition reactions to internal alkynes, usually carbometallations, which are followed by oxidative couplings, cross couplings or addition of electrophiles.[8-14] Very recently, photoredox-based methods have also been described.[17,18] These methods, however, suffer from some disadvantages: (i) the main one is the highly reactive nature of the organometallic reagents, difficult to handle and unable to be transferred to an industrial scale due to the high costs; (ii) the poor tolerance to the presence of reactive functional groups, due to their nucleophilic character; (iii) the fact that olefins are usually obtained as mixtures of *Z*/*E*-isomers, a problem which increases as the number of different substituents increases. Therefore, as stated above, the availability of tetrasubstituted alkenes with well-defined geometry and good leaving groups, in order to be used as building blocks, is still very limited.

In this contribution, we present a simple method for the fully stereo- and regioselective synthesis of tetrasubstituted *E*-olefins containing two good leaving groups, a thiolate[25,26] and an acetate.[27] The importance and the strategic interest of the thus resulting vinyl sulfides[28] and vinyl acetates[29] as building blocks in organic synthesis is considerable. The process is based on the consecutive addition of two anionic functional groups, one sulfide and one acetate, to an inactivated internal alkyne, promoted by a commercially available salt of Cu(II), as is $[Cu(OAc)_2]_2$* (OAc =

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acetate, see Note at the end of the manuscript), under microwave irradiation in short reaction times (Figure 2c). The detailed mechanism of the reaction has been fully determined using DFT methods and shows that the introduction of the sulfide is made, in fact, in the form of a metal-stabilized radical and that the dimeric nature of the copper reagent has a critical role in the promotion of the reaction.

Previous work dealing with the simultaneous introduction of a sulfide and another heteroatom-based functional group have been reported to occur through one of the following two reactions. The first method (a in Figure 2) is the metal-mediated addition of a preformed S-X bond (X = heteroatom) to an internal alkyne,[4,30-42] through either a mechanism involving radical species[34,37] or a concerted molecular pathway.[35,36,38] That is, the reaction only uses two components, the S-X source and the alkyne. For instance, chlorothiolation or thioallylation processes have been recently described.[4] The strong disadvantage of the method resides in the fact that the S-X bond needs to be pre-formed and usually it is rather unstable, as in the case of sulfenyl chlorides. In this respect, there are no previous reports in the literature for the addition of a S-O bond to an internal alkyne, probably due to the intrinsic unstability of the starting material.

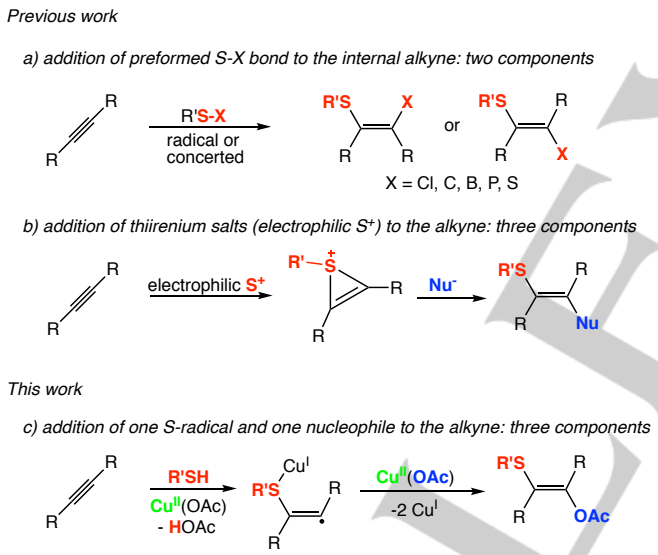

Figure 2. Previous work and relationship with this one

The second method (b in Figure 2) is by far the most developed and starts with the generation of a highly electrophilic sulfur-containing species, which further reacts with the alkyne to give a thiirenium intermediate.[43-51] The olefin is eventually formed by inter- or intramolecular reaction of the thiirenium with a nucleophile. In this case two different species provide one fragment each, this fact resulting in a more versatile method. However, the prefunctionalization of the sulfur reagent, aiming to achieve a highly electrophilic species, is still mandatory. This means additional reaction steps, expensive reagents and more chemical waste. In addition, the formation of S- and O-substituted alkenes using this method is scarcely represented.[44,48,49,51]

Due to this lack of efficient methods, we provide in this contribution a methodologically simple procedure for the synthesis of tetrasubstituted olefins containing sulfides and acetates as functional groups, avoiding prefunctionalization steps, saving reaction time and chemicals, and minimizing waste, while keeping the maximal selectivity (regio- and stereo), the widest versatility and reaction scope, a process which takes place through a different and novel radical-based mechanism.

Results and Discussion

1.- Synthesis and Characterization of Tetradentate Olefins. We have first optimized the reaction conditions as shown in Equation 1 and Table 1. Benzylmercaptan **1a** was reacted with 3-hexyne **2a** (1:2 molar ratio), and with $[Cu(OAc)_2]_2$ (1 equiv.), using a microwave reactor, to yield selectively the (*E*)-benzylthiohexenylacetate **3aa**. Using hexafluoroisopropanol (HFIP) as solvent we obtained a promising 38% yield of **3aa** (entry 1) after chromatographic purification. In the spectroscopic analysis of the crude only unreacted **1a** was characterized together with **3aa**, and no traces of other isomers (*cis*-, *gem*-), neither hydroarylation or bis-thiolation products, were observed.

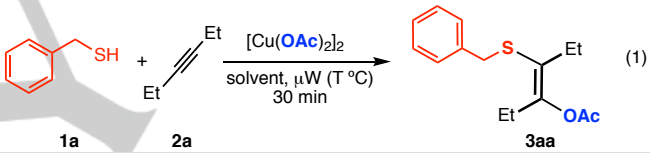

Table 1. Optimization for the synthesis of **3aa**[a]

Entry	Reagent	Solvent	T (°C)	Yield (%)
1	$[Cu(OAc)_2]_2$	HFIP	100	38
2	$[Cu(OAc)_2]_2$	toluene	100	0
3	$[Cu(OAc)_2]_2$	MeOH	100	0
4	-	HFIP	100	0
5	$[Cu(OAc)_2]_2$	HFIP	120	**66**
6	$[Cu(OAc)_2]_2$	HFIP	140	34
7[b]	$[Cu(OAc)_2]_2$ + NaOAc + oxone	HFIP	120	0
8[b]	$[Cu(OAc)_2]_2$ + $PhI(OAc)_2$	HFIP	120	47

[a] 1 mmol of **1a**, 2 mmol of **2a**, 1 mmol of $[Cu(OAc)_2]_2$. [b] 5 mol% of $[Cu(OAc)_2]_2$ and 1 equiv of oxidant and acetate source were used.

No conversion was observed when toluene or methanol were used as solvents (entries 2, 3), as well as in other solvents (regardless their protic/aprotic character and their polarity) such as CH_2Cl_2 or THF. In the same way, the reaction does not progress in the absence of the copper salt (entry 4). The

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temperature and time were also tested and the optimized results were 30 min at 120 °C (entries 5, 6). Longer reaction times or higher temperatures are detrimental. Next, we examined the influence of the acetate source and the possibility to perform the reaction catalytically. The reaction was attempted using 5 mol% $[Cu(OAc)_2]_2$ as catalyst and either oxone/NaOAc or $PhI(OAc)_2$ as oxidants/source of acetates in stoichiometric amounts (entries 7, 8). In the first case the result was negative, and **3aa** was not formed (entry 7). However, $[Cu(OAc)_2]_2$/$PhI(OAc)_2$ was found as a suitable catalytic system for this reaction (entry 8), showing the same selectivity than pure $[Cu(OAc)_2]_2$, although affords **3aa** with a lower yield (47%). This lower yield, together with the substantially higher price of $PhI(OAc)_2$ compared with $[Cu(OAc)_2]_2$, suggest that the best compromise is the use of 1 equivalent of the copper salt. Once the optimized reaction conditions have been determined, a series of internal alkynes **2a-2e** were tested using the optimized conditions (see Chart 1), and moderate to good yields of the (*E*)-acetoxythiolated derivatives **3aa-3ae** were obtained.

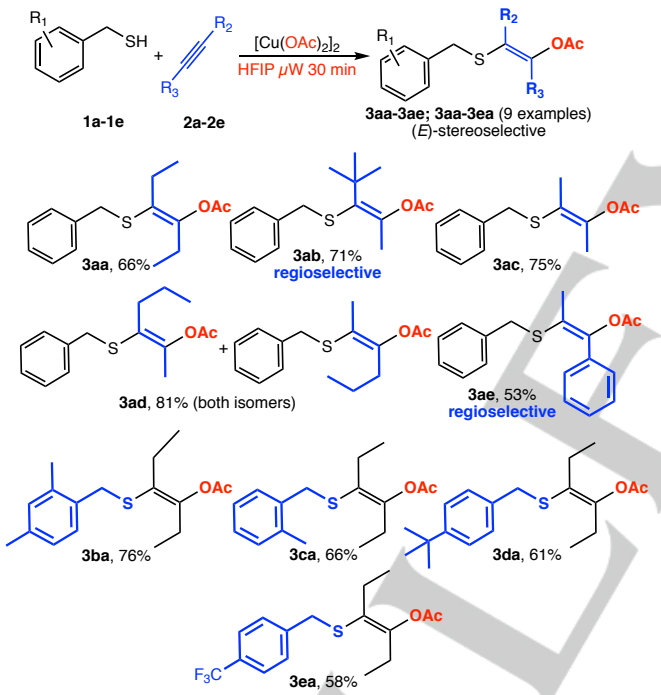

Chart 1. Scope of the reaction of benzylmercaptanes **1** with internal alkynes **2**.

When asymmetrical alkynes are used the reaction takes place with full regioselectivity in the cases of 4,4-dimethyl-2-pentyne (**2b**) or prop-1-ynyl-1-benzene (**2e**), affording the corresponding *E*-alkenes **3ab** and **3ae** as single regioisomers. Instead, a mixture of isomers was obtained with 2-hexyne (**2d**). The characterization of the obtained olefins as (*E*)-isomers is based on the multiplicity of the signals of the functional groups (methyl, ethyl) at the vinylic carbons, and on the values of the homoallylic couplings $^5J_{HH}$ determined for these signals. This is clearly seen in the case of alkene **3ac**, for which both methyl groups show a hyperfine structure of a quartet, due to the mutual coupling, being the coupling constant $^5J_{HH}$ of 1.6 Hz. The high value measured for this coupling constant is really diagnostic because, as it is reported in the literature for (*Z*)- and (*E*)-isomers of 2-butene and also for isomeric tiglic and angelic acids, the *cis*-arrangement (*Z*-olefin) gives consistently values of the $^5J_{HH}$ constant around 1.2 Hz (or even lower), while the trans (*E*)-isomers show values identical to those here observed (1.6 Hz).[52-57] In addition, the regiochemistry for **3ab** and **3ae** has been determined on the basis of the correlations observed in the ^1H-^{13}C HMBC spectra. In the case of **3ab**, the vinylic methyl (2.22 ppm) correlates with both olefinic carbons (151.4 ppm, assigned to the C supporting the OAc group; and 130.7 ppm, assigned to the C bonded to the S-moiety), while the protons of the ^{t}Bu group (1.22 ppm) only correlate with the C at 130.7 ppm, showing that the BnS and tBu groups are on the same olefinic carbon. In the case of **3ae** a similar analysis has been carried out using the =CMe and the ortho protons of the Bn group (see SI). The reaction also tolerates the presence of substituents in the phenyl ring (**1a-1e**), and good yields of **3ba-3ea** were obtained when alkyl groups (Me **1b**, **1c**; ^{t}Bu **1d**) or strong electronwithdrawing groups (-CF_3, **1e**) were tested. However, the use of strong electrondonating groups, such as OMe, gave only small conversions (<5%) due to extensive decomposition.

Thiophenols with different substituents **4a, 4d, 4f, 4g** were also reacted with alkynes **2a-2e**, under the same reaction conditions, to give the corresponding (*E*)-phenylthiohexenylacetates **5aa-5ae** and **5da-5ga** in good to excellent yields (Chart 2).

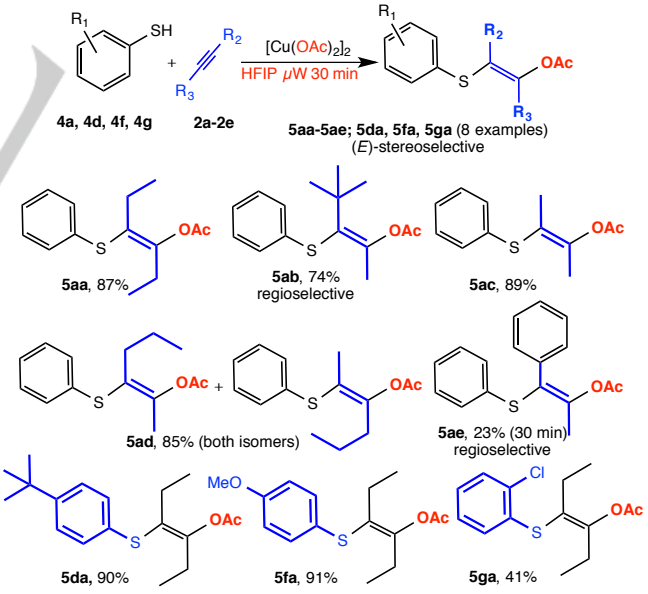

Chart 2. Scope of the reaction of thiophenols **4** with internal alkynes **2**.

As expected, the reaction of 4,4'-dimethyl-2-pentyne (**5ab**) and 1-phenyl-1-propyne (**5ae**) were fully regioselective, although in the latter the yield decreased notably. On the other hand, some substituted thiophenols (**4d**, **4f**, **4g**) were tested in this reaction.

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Unlike mercaptans, thiophenols with electrondonating groups such as *p*-OMe (**4f**) reacted efficiently and excellent yields were observed. The yields dropped when *o*-Cl substituent was used (**4g**), and no reaction was observed when other electron-poor thiophenols as *p*-$CF_3C_6H_4SH$ (**4e**) or F_5C_6SH were used. Therefore, the substituents in the aryl ring tune the reactivity of the reaction, and this effect is more pronounced for thiophenols **4** than for benzylmercaptanes **1**.

2.- Mechanistic Considerations. Aiming to get more insight in the reaction and to explain the observed selectivities, we undertook the study of its mechanism. When the reaction of thiophenol **4a** with alkyne **2a** is carried out in presence of stoichiometric amounts of a radical scavenger (TEMPO) the reaction is completely quenched, and no conversion at all was detected. Therefore, the reaction seems to take place through a mechanism involving radicals in the case of thiophenol. When benzylmercaptane **1a** was reacted with alkyne **2a** in the presence of TEMPO a partial quench of the reaction was observed, because a 34% yield of **3aa** was obtained instead of the 66% obtained under standard conditions. This suggests that the radicals are not the only intermediates for benzylmercaptane, and that the classical anionic pathway[58] can coexist with the former. Due to these facts, we have focused our attention in the coupling of thiophenol **4a** and alkyne **2a**, because it seems that in this case a single mechanism is taking place. A series of control experiments, resumed in Chart 3, were conducted using **4a** as substrate.

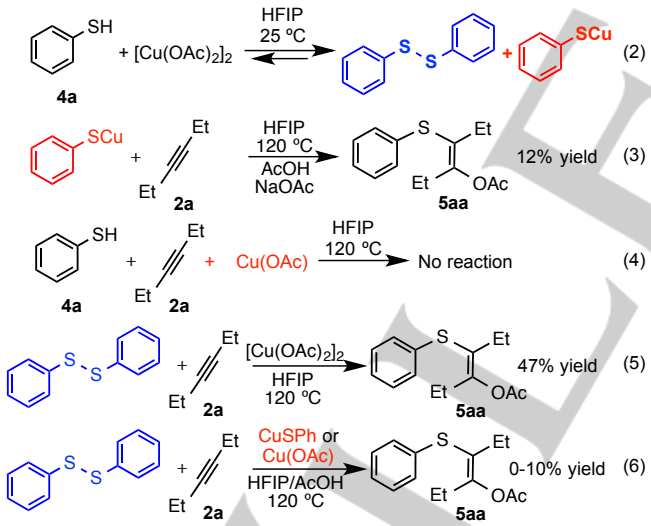


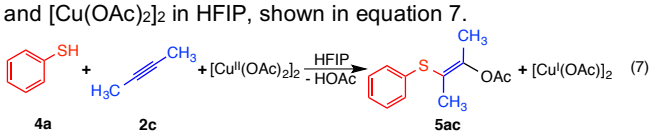
Chart 3. Experiments for mechanism determination.

When thiophenol **4a**, $[Cu(OAc)_2]_2$ and 3-hexyne **2a** were mixed at room temperature a clear reaction takes place, from which a pale yellow solid precipitated. The solid was filtered and identified as $[CuSPh]_n$, while the disulfide PhSSPh was isolated from the solution.[59-61] The same result (formation of CuSPh and PhSSPh) was obtained from the treatment of **4a** with $[Cu(OAc)_2]_2$ (equation 2, Chart 3), showing that the alkyne does not participate in the early stages of the reaction. Interestingly, it is remarkable that both in presence and in absence of the alkyne, the blue color does not disappear completely, indicating that the redox reaction is not complete and that the dimer $[Cu(OAc)_2]_2$ is still present in the mixture. Therefore, both Cu(II) and Cu(I) species are present in the starting mixture and, in principle, we must consider both of them as plausible promoters of the coupling. The isolated Cu(I) complex $[CuSPh]_n$ was then subjected to further treatment with 3-hexyne **2a** and either acetic acid (AcOH) or sodium acetate (NaOAc) under experimental coupling conditions (1:2 molar ratio, HFIP, 120 °C, 30 min microwave irradiation; equation 3, Chart 3). This reaction affords **5aa** but only in a marginal 12% yield (compare with 87% yield of **5aa** in Chart 2). This result suggests that Cu(I) species does not promote the formation of **5aa**. In the same way, the reaction of **4a** with 3-hexyne **2a** and $Cu^{I}(OAc)$ under coupling conditions does not take place at all (equation 4, Chart 3). These results are good evidences of the role of the oxidation state of the Cu, pointing to Cu(II) as being the promoter of the coupling reaction.

We have also examined the source of the PhS moiety. The reaction of the disulfide PhSSPh with alkyne **2a** in the presence of $[Cu(OAc)_2]_2$ under coupling conditions (equation 5, Chart 3) takes place with formation of **5aa** in a moderate 47% yield. Because it seems that several sources of the PhS unit are available (PhSH and/or Ph_2S_2), we have examined the reactivity of Ph_2S_2 as source of PhS with two Cu(I) complexes, CuSPh and CuOAc (equation 6, Chart 3). In both cases, the yields of **5aa** are in the range 0-10%. Clearly this result indicates that, while the oxidation state of the Cu complex and the ligands around it are critical, the source of the thiophenolate could be more flexible, being PhSH the optimal one.

We have also analyzed the different phases of the reaction after completion, the solid residue and the solution, in order to determine which is the oxidation state of the Cu at the end of the reaction. Therefore, once the reaction was finished, the solid residue was separated by filtration and the solution was evaporated to dryness, and no further workup was performed. The two fractions were analysed by XPS, and the results gathered show that in both cases the Cu present is in oxidation state (+1). This is based on the position of the Cu2P4/2 and CuLMM bands and, mainly, on the Auger CuLMM peak (see Supporting Information for full details). This result allows to discard the presence of Cu(II) or Cu(0) in the final mixture.

3.- Mechanism determination by DFT methods. With these data in hand (Cu(II) as starting catalyst, Cu(I) as final species, PhSH as source of thiolate, radical intermediates), we have attempted the full determination by DFT methods of the mechanism of the acetoxythiolation of internal alkynes. We have selected as model the coupling of 2-butyne **2c** with thiophenol **4a** and $[Cu(OAc)_2]_2$ in HFIP, shown in equation 7.



As two nucleophiles are added to the alkyne, two electrons must be removed at the end of the reaction. Therefore, as in the oxidative coupling reactions, there is a need for an oxidant to take these two electrons, keeping the entire process electroneutral.[62]

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Copper(II) acetate has been the most used oxidant in this type of reactions, but full understanding of its role in the catalytic cycles is still under discussion.[62] Related with this point, modeling of the copper(II) acetate reagent deserves some words. In the solid state it occurs as a dinuclear dihydrate $[Cu(OAc)_2]_2{\cdot}(H_2O)_2$ with a paddle-wheel structure.[63] Recent studies by electrospray ionization mass spectrometry (ESI-MS) of its speciation behavior in organic solvents as methanol support an extensive aggregation of $Cu(OAc)_2$ in such media.[64] Accordingly, we have modeled the Cu(II) reagent as a dimeric $[Cu(OAc)_2]_2{\cdot}(H_2O)$. The same description has been employed in a recent theoretical study of oxidative-coupling reactions.[65] In this way, for every equivalent of product **5ac** formed, two Cu(II) centers are reduced to Cu(I) along the reaction (equation 7).

Another issue concerns the ground state of $[Cu(OAc)_2]_2$ that exhibits temperature-dependent magnetic behavior. In the solid state the two unpaired electron spins in the two Cu(II) centers are antiferromagnetically coupled with J = -296 cm^{-1}.[66,67] That value implies an energy difference between the open-shell singlet (OSS) and triplet (T) states of 0.8 kcal mol^{-1} in favor of the open-shell singlet.[68] We have considered both electronic states in the computational study, with no significantly different results regarding the reactivity. We focus the discussion in the triplet potential energy surface. OSS results can be found in the Supporting Information. As the reaction ends up in low spin products, a change in the spin state occurs. Accurate calculation of energy splitting between the low-spin and high-spin states is difficult due to the strong functional dependence it displays.[69-72] Benchmark calculations of copper reactions involving copper in different oxidation states have shown that the hybrid TPSSh functional (10% Hartree-Fock exchange) with the Grimme dispersion correction, performed best.[73] We have chosen this functional for the computational study, though other functionals (B97D, B3LYP-D3, M06 and ωB97XD) have been used for calibration purposes (see Supporting Information).

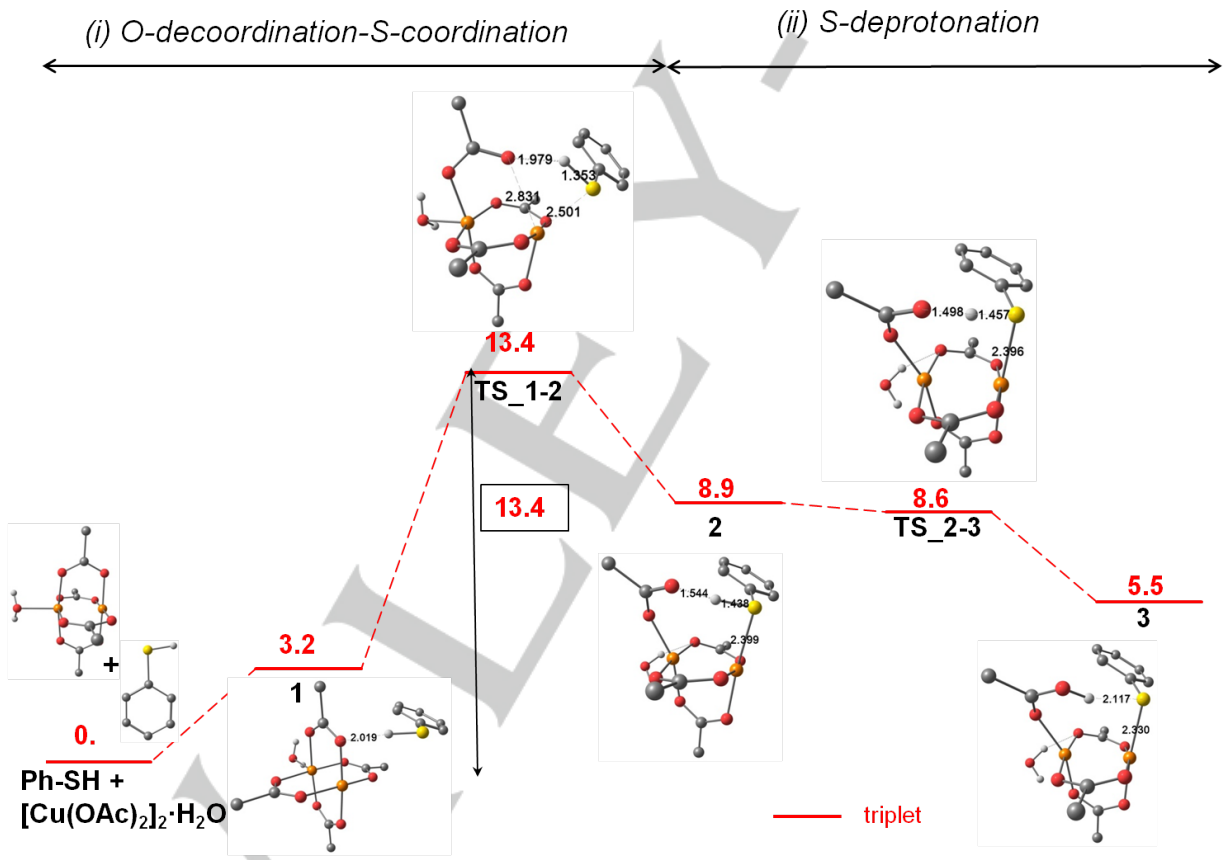

Figure 3. Gibbs energy profile at 393.15 K in HFIP solvent for the reaction of **4a** with $[Cu(OAc)_2]_2$. Energies in kcal mol^{-1}.

3.1.- First Step: S-Coordination-Deprotonation. Control experiments, described above, demonstrated that the alkyne is not reacting at the early stages of the reaction. Therefore, we initially studied the reaction of thiophenol **4a** with $[Cu(OAc)_2]_2$. The Gibbs energy profile for this step is depicted in Figure 3. The reaction begins with the approach of thiophenol to the copper dimer (structure **1**, Figure 3) and the decoordination of one arm of one bridging acetate (**TS_1-2**), with the subsequent bonding of the sulfur atom to one copper center and the orientation of the Ph-SH proton towards the unbounded oxygen atom of the κ^1 acetate

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(**2**). Then, in a practically barrierless process (**TS_2-3**),[74] the SH proton is transferred to this acetate, yielding intermediate **3**. This step shows a close relationship with the concerted metalation-deprotonation process, also called ambiphilic metal−ligand assistance, extensively discussed for carboxylate-assisted CH bond activation processes.[75] The main differences with the reactions involving CH bonds are the involvement of an SH bond, which rupture is much easier than that of a CH bond, and that the reaction takes place in the triplet potential energy surface. We have used a localized orbital approach to analyze the electronic rearrangements taking place along the reaction mechanism. Accordingly, Kohn-Sham orbitals are transformed to maximally localized orbitals and the orbital centroids are used to track the formation and breakage of bonds and the changes in oxidation states.[76-78] A full account of the calculations and their outcome is provided in the Supporting Information. We comment through the text on three key intermediates (**3**, **4** and **5$_{brid}$**, Figure 4).

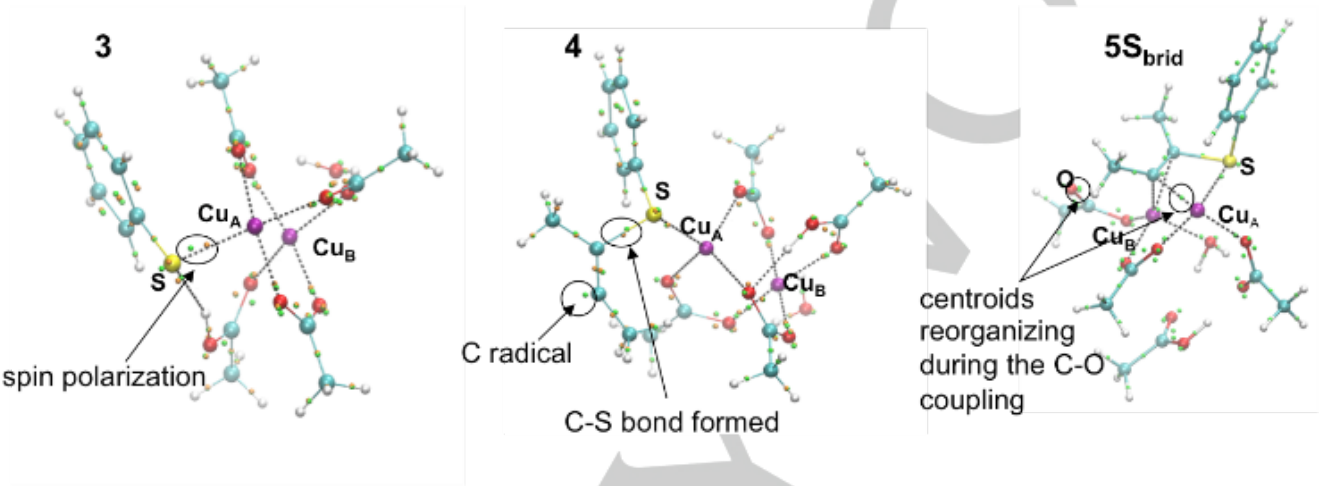

Figure 4. Localized orbital analysis of **3**, **4** and **5S$_{brid}$**. C atoms are shown as cyan spheres, O in red, S in yellow, H in white, Cu in purple and localized orbital centroids as small green (for α electrons) and orange (for β ones) spheres. Selected centroids are highlighted (see main text).

Although the coordination-deprotonation of the thiol does not entail change of the oxidation state in the copper centers and both Cu ions keep an oxidation state II, a fraction of spin density has been transferred to the sulfur atom in **3**, where the bond between S and Cu$_A$ is spin polarized (note the separation of α and β centroids in Figure 4 and the spin density plot in the Supporting Information). This polarization is backed by the Mulliken spin densities, which increase on S (from 0.0 to 0.21) and decrease on Cu$_A$ (from 0.59 to 0.50) with respect to the initial adduct **1** (see Supporting Information). The incipient thiyl radical character of the sulfur center can account for the formation of the disulfide PhSSPh that was isolated from the solution when [Cu(OAc)$_2$]$_2$ and thiophenol **4a** were mixed (equation 2). Recent work on photoinduced, copper-catalyzed C-S cross-couplings with aryl halides highlighted the significant radical character of the sulfur center of thiolate ligands in copper(II)-thiolate complexes.[79,80] Intermediate **3** will be the active species that reacts with the alkyne in the following step. Whatever the functional employed, it is formed with a low barrier (13.4 kcal mol^{-1} at the TPSSh-D3/BS2 level). This step is slightly endergonic, with the formed intermediate **3** lying 5.5 kcal mol^{-1} above the separated reactants (Figure 3).

3.2.- Second Step: C-S Coupling. The second step involves the formation of the S-C bond, by attack of the Cu-stabilized S-centered incipient thiyl radical in **3** to the alkyne **2c**. While the attack of a free S-centered radical to an alkyne is a well-documented feature,[81,82] the reactivity of a metal-stabilized thiyl radical with an unsaturated fragment is much less common.[83-86] **3·alkyne** is the Wan der Waals complex formed between **3** and the alkyne (the shortest Cu-C$_{alkyne}$ and S-C$_{alkyne}$ distances are 3.20 and 4.0 Å, respectively). This intermediate is taken as origin of energy in the S- and O-addition to alkyne reactions (Figures 5, 6). Due to the entropic penalty, probably overestimated,[87] it lies 6.1 kcal mol^{-1} above the separated reactants. Approaching the alkyne to the sulfur center induces significant changes in the electron distribution of the system. After crossing transition state **TS_3-4**, a C-S bond is formed (intermediate **4**). In **4**, the S–C bond is formed by an α electron from S and a β electron from a π orbital of the C–C triple bond (see α and β centroids shared by the two atoms along the S–C axis, Figure 4). Consequently, an α electron is left on the other C of the multiple (now double) bond, in accordance with a vinyl radical character of this intermediate. The S–Cu$_A$ bond is no longer spin polarized, having Cu$_A$ received a β electron and thus been reduced to Cu(I). Cu$_B$ remains in oxidation state II (see spin density plot and localized orbital analysis in the Supporting Information). The process may be formally seen as a single electron-transfer (SET) process, in which Cu$_A$ oxidizes the alkyne to form a carbon radical. However, the process takes place intramolecularly within the organometallic complex, whereas SET processes are often understood to take place intermolecularly. Furthermore, the C radical is generated via a rearrangement of the electron pairing around the S atom, as highlighted by the

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localized orbital analysis, rather than a long-range electron transfer. Because of these reasons, we prefer not to use the SET terminology to describe this pathway. The S-addition entails a rather high Gibbs-energy barrier (27.7 kcal mol^{-1} at the TPSSh-D3/BS2 level), yet readily accessible under the experimental conditions (T = 120 °C).

The process described above can be related with the metal-free radical addition of thiols to alkynes, named, by analogy with the 'ene'-counterpart, 'thiol–yne coupling' (TYC).[81,82] In this organic reaction a sulfanyl radical (RS·) is initially created in the presence of radical sources (peroxides, irradiation with UV light). Then, this sulfanyl radical adds to the carbon–carbon multiple bond to afford a β-sulfanyl-substituted vinyl radical; subsequently, in a radical chain mechanism, hydrogen transfer from the starting thiol affords a vinyl sulfide and a new sulfanyl radical that sustains the chain. The whole process, although regioselective, at least with terminal alkynes, is usually scarcely stereoselective, since the vinyl sulfide products are often formed as mixtures of both *E*- and *Z*-stereoisomers.[88,89]

In **4** the S-C coupling has already taken place. **4** reorganizes with a very low barrier (3.8 kcal mol^{-1} at the TPSSh-D3/BS2 level) to create a Cu-C bond (intermediate **5T)**, losing its character of vinyl radical and placing the Cu-bonded carbon atom in the right position to be attacked by an acetate ligand in the next step. In **5T** the Cu_2 core has returned to a Cu^{II}-Cu^{II} oxidation sate. At this point a crossing from the triplet to the singlet potential energy surfaces takes place easily (from **5T** to **5S**). In **5S**, the system is not spin polarized (singlet state). Interestingly, compared to **4**, the oxidation state of the copper ions has changed, from Cu_A(I), Cu_B(II) in **4** to Cu_A(III), Cu_B(I) in **5S** (see Supporting Information). The geometries at the metal centers (Cu_A: square planar, Cu_B: tetrahedral) are consistent with this assignment. Passing from **5T** to **5S** implies the Cu^{II} disproportionation to Cu^{I} and Cu^{III}.[90,91] In the past few years Cu^{III} species have gained relevance as important intermediates in copper-catalyzed reactions.[91]

3.- Third Step: C-O Coupling. The C-O bond is formed in the last step, which entails the addition of an acetate ligand to the carbon center. It takes place in the singlet potential energy surface, starting from **5S** (Figure 6).[92] The stereoselectivity of the final alkene is decided in this step.

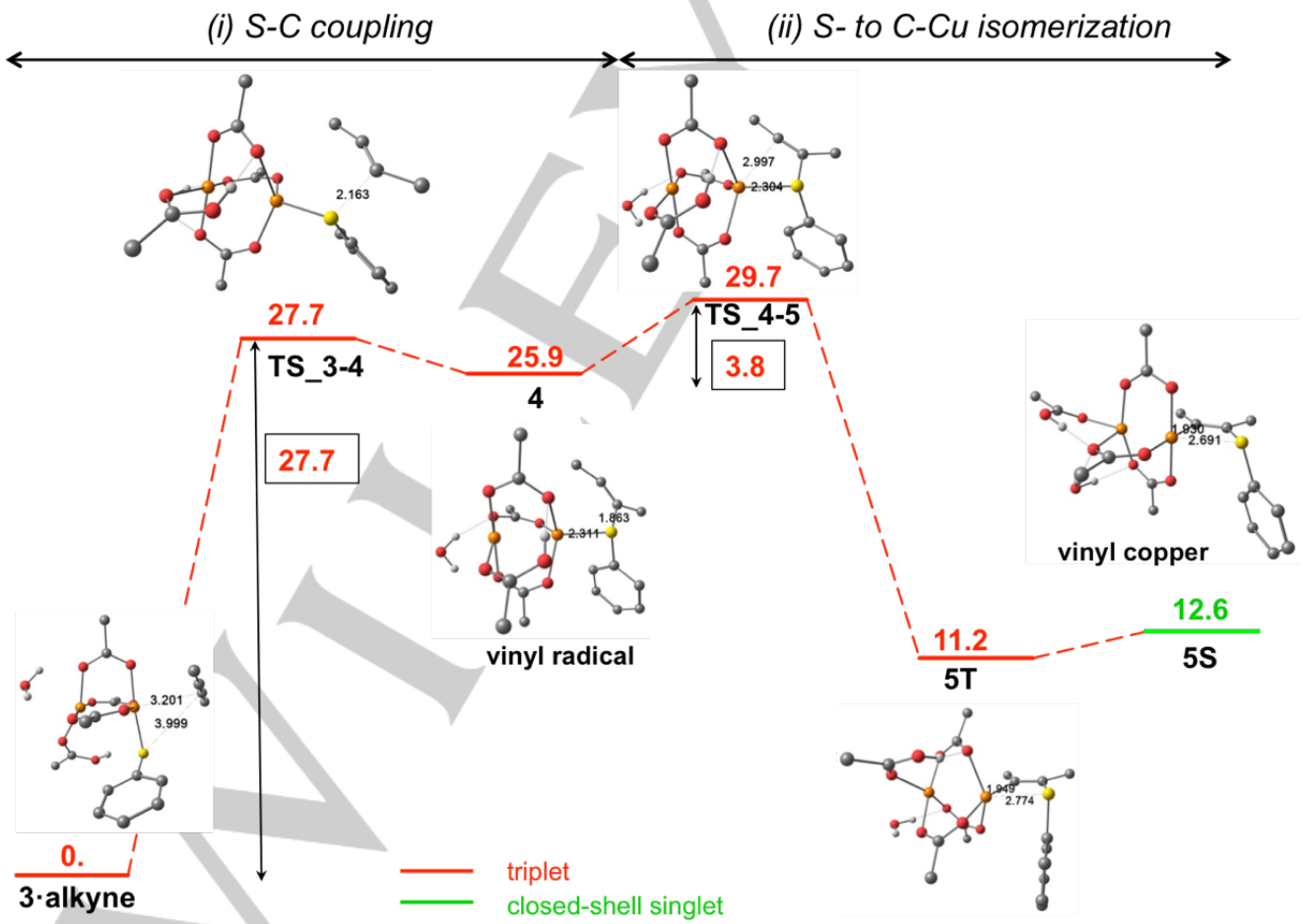

Figure 5. Gibbs energy profile at 393.15 K in HFIP solvent for the S-C coupling step. Energies in kcal mol^{-1}.

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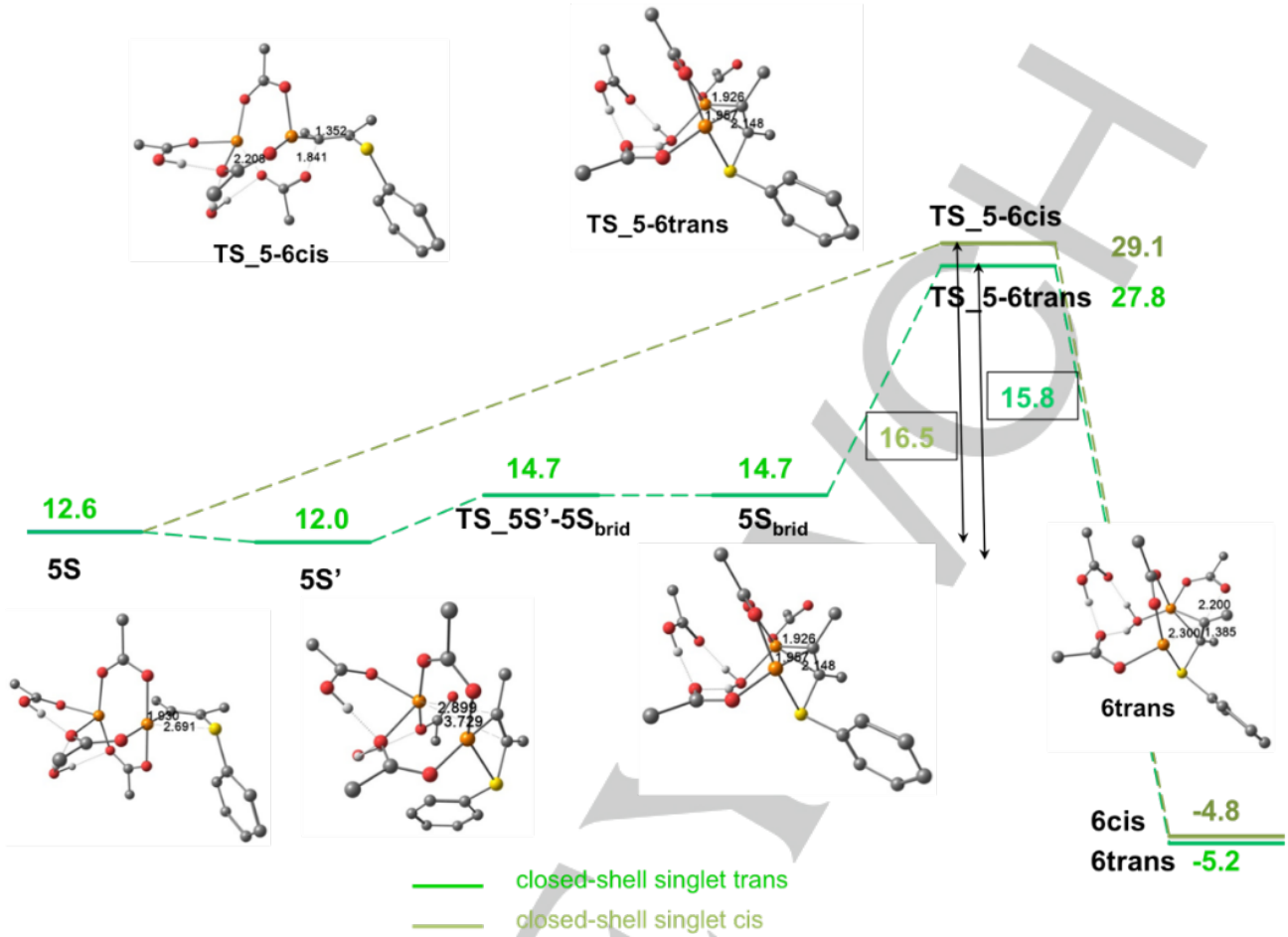

Figure 6. Gibbs energy profile at 393.15 K in HFIP solvent for the C-O coupling step. Energies in kcal mol^{-1}

Direct attack of a monodentate acetate ligand of **5S** in *cis* with respect the vinyl group produces the C-O coupling with a Gibbs energy barrier of 16.5 kcal mol^{-1} with respect **5S** (**TS_5S-6cis**, Figure 6). In this process, the Cu_A(III) center in **5S** becomes a copper(I) center in the product **6-cis**. However, this mode of attack yields the (*Z*)-isomer of the olefin, which is not experimentally observed. All the attempts we have done to obtain the (*E*)-isomer directly from **5S** has been unsuccessful. We have also considered a *trans* addition to the alkyne by going *via* η^2-vinyl pathway, as originally proposed for *trans* hydrosilylation,[93] but we have not been able to find such a η^2-vinyl intermediate in this system. All the optimizations starting from such structure revert to the initial η^1-vinyl-copper intermediate **5S**. Exploring alternative routes for the *trans* addition, we found that the flexibility of the dicopper-acetate scaffold allows a very easy rearrangement (through **TS_5S'-5S$_{brid}$**, Figure 6) of the vinyl ligand, passing from a terminal to a bridging coordination, in which the vinyl ligand is bonded to both copper centers (**5S$_{brid}$**). The structure of **5S$_{brid}$** has a σ,π-vinyl ligand: the C=C unit is bonded to one copper center (Cu_A) by a σ(Cu-C) bond and by a π(C=C)-Cu to Cu_B. In this sense, it is reminiscent of the proposed η^2-pathway.[93] In **5S$_{brid}$** Cu_A and Cu_B keep their +3 and +1 oxidation states, respectively (Figure 4).

From this intermediate the *trans* addition takes place, with a lower barrier (15.8 kcal mol^{-1} from **5S'**, **TS_5S$_{brid}$-6trans**, Figure 6) and yields a slightly more stable product (**6trans**). Analysis of the electron rearrangements in this step, by following the displacement of the centroids of localized orbitals (in the Supporting Information), reveals that one O-electron pair of the acetate bonded to Cu_B attacks the carbon atom η^2-coordinated to Cu_B and which forms the σ(Cu-C) with Cu_A. At the same time that the C-O bond is being formed, the σ(Cu-C) bond is breaking, and this bonding electron pair is being transferred to the Cu_A. In this way, Cu_A is reduced from +3 to +1 oxidation state and two Cu(I) centers are present in **6trans**. Overall, the two Cu(II) centers of the reagent have accepted the two electrons released in the acetoxythiolation process.

As acetate anions may be present in the reaction medium, we have also considered the possibility that the *trans* attack occurs from an external non-bonded AcO^- (see Supporting Information). This reaction has a slightly higher barrier (16.3 kcal mol^{-1}) than that from the coordinated acetate (15.8 kcal mol^{-1}, **TS_5-6trans**) but still lower than the *cis* attack.

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Conclusions

The work here reported achieves the synthesis of tetrasubstituted olefins from reaction of benzylmercaptanes or thiophenols with internal alkynes promoted by $[Cu(OAc)_2]_2$, in such a way that one sulfide fragment and one acetate group are incorporated to the alkyne skeleton. This method presents some remarkable features, namely: (a) the selectivity displayed by the process, because only the cross-coupling product is formed: the products from bis-thiolation, bis-acetoxylation or the thiol-yne derivatives were not observed at all. In addition, (b) the stereoselectivity of the process is complete, since only the (*E*)-isomer of the olefin is formed; and (c) high levels of regioselectivity are also achieved when asymmetrical alkynes are used. Additional features are (d) its versatility, since a wide array of substituents in the alkyne and the thiolate are tolerated; (e) its simplicity, because the substrates do not need previous transformations nor activations with specific reagents; (f) the type of products resulting from the reaction, since they contain two good leaving groups and an orthogonal reactivity is easily envisaged; and (g) the whole process is mediated by $[Cu(OAc)_2]_2$, a simple complex with an earth-abundant metal, cheap, showing a low toxicity and high sustainability. DFT calculations underline the key role of the dimeric copper(II) diacetate in the process. It confers the thiyl radical character to the Cu-coordinated thiol, generating the active species **3**. Moreover, by means of a sequence of changes of the oxidation states of the two copper centers accepts the two electrons released in the addition of two nucleophiles to the alkyne.

Experimental Section

General Remarks. The reactions were performed without special precautions to exclude air and/or moisture. The solvents were of commercial grade and used as received. All reactions were carried out under microwave heating on a CEM™ S-class Microwave Synthesis System, at 120 °C (150 W). Flash column liquid chromatographies were performed on aluminium oxide 90 neutral (50-200 μm). Infrared spectra (4000-380 cm^{-1}) were recorded on a Perkin-Elmer Spectrum One IR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions at 25 °C on Bruker AV300 spectrometers (δ in ppm, J in Hz) at ^1H operating frequency of 300.13 MHz. ^1H and ^{13}C spectra were referenced using the solvent signal as internal standard. ESI (ESI^+) mass spectra were recorded using an Esquire 3000 ion-trap mass spectrometer (Bruker Daltonic GmbH) equipped with a standard ESI/APCI source. Samples were introduced by direct infusion with a syringe pump. Nitrogen served both as the nebulizer gas and the dry gas. HRMS and ESI (ESI^+) mass spectra were recorded using an MicroToF Q, API-Q-ToF ESI with a mass range from 20 to 3000 *m/z* and mass resolution 15000 (FWHM). X-ray photoelectron spectroscopy (XPS) was carried out on an ESCAPlus Omicron spectrometer using a monochromatized Mg X-ray source (1253.6 eV). Data were analyzed using Casa XPS software package.

General experimental procedure for the synthesis of tetrasubstituted olefins: To a solution of the thiol **1a-1e** or **4a-4g** (1 mmol) and the corresponding alkyne **2a-2e** (2 mmol) in HFIP (4 mL), $[Cu(OAc)_2]_2$ (181 mg, 0.5 mmol) was added. The reaction mixture was heated in a microwave reactor at 120 °C for 30 min. After that, the solvent was removed to dryness and the solid residue was purified by flushed column chromatography in neutral alumina using dichloromethane as eluent. Further purification was performed using column chromatography on SiO_2 and Et_2O/hexane 5:95 to 25:75 as eluents.

Computational Details. Density functional theory (DFT) calculations were performed with the TPSSh density functional,[94,95] supplemented with the Grimme's dispersion correction D3.[96] This functional accurately reproduces the relative energies of spin sates of first-row transition metal complexes,[97] and predicts reactivity at Cu^{III}.[73] Additional calibration calculations were carried out with the B97D, B3LYP-D3, ωB97XD and M06 functionals (Supporting Information). All intermediates and transition states were fully optimized in hexafluoroisopropanol solution (HFIP, ε = 16.7) using the continuum method SMD.[98] Gibbs energies in HFIP were calculated at 393.15 K. All energy values reported in the main text correspond to Gibbs energies in HFIP in kcal mol^{-1}. See Supporting Information for further details on the calculations

Characterization of tetrasubstituted olefins. Selected examples are shown here. For full details, see Supporting Information.

3ab: Colourless oil (214 mg, 71%). ^1H NMR (CD_2Cl_2, 300.13 MHz, r.t.) δ_H: 1.22 (s, 9H, CMe_3), 2.17 (s, 3H, C(O)Me), 2.22 (s, 3H, =CMe), 3.85 (s, 2H, CH_2S), 7.3-7.5 (m, 5H, Ph). $^{13}C\{^1H\}$ NMR (CD_2Cl_2, 75.47 MHz, r.t.) δ_C: 20.7, 21.3, 30.4, 37.9, 41.1, 127.0, 128.4, 129.1, 130.7, 138.2, 151.4, 168.7. $(ESI)^+$ *m/z*: $[M+K]^+$ (100) 317. HRMS (ESI-TOF) *m/z:* $[M+Na]^+$ calcd for $C_{16}H_{22}NaO_2S$ 301.1238, obtained 301.1223.

3ac: Colourless oil (177 mg, 75%). ^1H NMR ($CDCl_3$, 300.13 MHz, r.t.) δ_H: 1.86 (q, 3H, $^5J_{HH}$ = 1.5 Hz, =CMe), 1.93 (q, 3H, $^5J_{HH}$ = 1.5 Hz, =CMe), 2.15 (s, 3H, C(O)Me), 3.84 (s, 2H, CH_2S), 7.2-7.4 (m, 5H, Ph). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.47 MHz, r.t.) δ_C: 17.6, 20.7, 37.1, 117.5, 127.0, 128.4, 128.8, 138.3, 148.6, 168.3. $(ESI)^+$ *m/z*: $[M+K]^+$ (100) 275. HRMS (ESI-TOF) *m/z:* $[M+Na]^+$ calcd for $C_{13}H_{16}NaO_2S$ 259.0769, obtained 259.0777.

5aa: Colourless oil (217 mg, 87%). ^1H NMR (CD_2Cl_2, 300.13 MHz, r.t.) δ_H: 0.89 (t, 3H, $^3J_{HH}$ = 7.6 Hz, CH_2CH_3), 0.94 (t, 3H, $^3J_{HH}$ = 7.6 Hz, CH_2CH_3), 2.02 (q, 2H, $^3J_{HH}$ = 7.2 Hz, CH_2CH_3), 2.11 (s, 3H, C(O)Me), 2.55 (q, 2H, $^3J_{HH}$ = 7.3 Hz, CH_2CH_3), 7.0-7.1 (m, 1H, SPh), 7.2-7.4 (m, 4H, SPh). $^{13}C\{^1H\}$ NMR (CD_2Cl_2, 75.47 MHz, r.t.) δ_C: 11.8, 12.7, 20.8, 24.6, 25.4, 123.0, 126.0, 128.2, 129.3, 136.2, 155.8, 169.1. $(ESI)^+$ *m/z*: $[M+K]^+$ (100) 289. HRMS (ESI-TOF) *m/z:* $[M+Na]^+$ calcd for $C_{14}H_{18}NaO_2S$ 273.0925, obtained 273.0921.

5ab: Yellow oil (195 mg, 74%). ^1H NMR (CD_2Cl_2, 300.13 MHz, r.t.) δ_H: 1.24 (s, 9H, CMe_3), 2.19 (s, 3H, =CMe), 2.22 (s, 3H, C(O)Me), 7.0-7.1 (m, 1H, SPh), 7.2-7.4 (m, 4H, SPh). $^{13}C\{^1H\}$ NMR (CD_2Cl_2, 75.47 MHz, r.t.) δ_C: 20.8, 21.1, 30.1, 38.1, 124.7, 125.7, 127.8, 128.9, 137.7, 153.3, 168.8. $(ESI)^+$ *m/z*: $[M+K]^+$ (70) 303. HRMS (ESI-TOF) *m/z:* $[M-H+H_2O]^+$ calcd for $C_{15}H_{21}O_3S$ 281.1211, obtained 281.1201.

5ac: Yellow oil (198 mg, 89%). ^1H NMR (CD_2Cl_2, 300.13 MHz, r.t.) δ_H: 1.71 (q, 3H, $^3J_{HH}$ = 1.5 Hz, =C-*Me*), 2.07 (q, 3H, $^3J_{HH}$ = 1.5 Hz, =C-*Me*), 2.09 (s, 3H, C(O)Me), 7.0-7.1 (m, 1H, SPh), 7.2-7.4 (m, 4H, SPh). $^{13}C\{^1H\}$ NMR (CD_2Cl_2, 75.47 MHz, r.t.) δ_C: 17.9, 18.1, 20.9, 117.3, 126.3, 128.7, 129.4, 135.5, 150.9, 168.7. $(ESI)^+$ *m/z*: $[M+K]^+$ (100) 261. HRMS (ESI-TOF) *m/z:* $[M+Na]^+$ calcd for $C_{12}H_{14}NaO_2S$ 245.0612, obtained 245.0619.

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Keywords: C-S coupling • C-O coupling • Copper(II) • tetrasubstituted alkenes • DFT methods

***Note**: The simplification of the nomenclature of $[Cu(OAc)_2]_2$ to $Cu(OAc)_2$ is not trivial, at least in this work. In fact, the dimeric structure of the copper(II) acetate plays one of the most critical points of the work, and is closely related with the reason of the success of the reaction. The cooperative behavior between the two Cu centers during the reaction is the central fact allowing the reaction to take place, and it is difficult to imagine an explanation of the reaction based on a mononuclear $Cu(OAc)_2$ derivative. For those reasons, the dimer formula $[Cu(OAc)_2]_2$ has been used throughout the text instead of the monomer formula $Cu(OAc)_2$.

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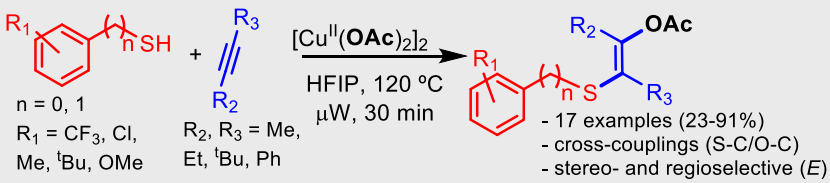

The Cu-mediated synthesis of tetrasubstituted *E*-olefins by stereo- and regioselective addition of an acetate group and a thiolate to an unactivated internal alkyne is described. The mechanism has been determined by DFT methods and shows that it takes place through Cu-stabilized radical intermediates.

Pedro Villuendas, Sara Ruiz, Pietro Vidossich, Agustí Lledós and Esteban P. Urriolabeitia**

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Synthesis of tetrasubstituted olefins by Cu-mediated acetoxythiolation of internal alkynes: scope and mechanistic studies

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