Metal-Catalyzed and Metal-Free Alkyne Hydrothiolation: Synthetic Aspects and Application Trends

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Alkyne hydrothiolation – that is, the addition of the SH bond of a thiol across the carbon-carbon triple bond of an unactivated alkyne – belongs to the ample class of hydrofunctionalization reactions whose main feature is their occurrence with total atom economy. Hence this reaction is emerging as a valuable tool for the preparation of sulfur-containing compounds such as vinyl thioethers, which are of interest for their own biological properties and for their use as intermediates in total synthesis. Thus, the first part of this review deals with the various efforts directed towards the preparation of vinyl thioethers in a regio- and diastereoselective manner by metal-catalyzed approaches in recent years. The number of methods employed, with use of a variety of catalysts and reaction conditions, allow the synthesis of vinyl thioethers to be carried out with high efficiency and selectivity. The second part of the article is based on the use of the photoinduced free-radical approach to hydrothiolation, which allows the introduction of two thiol fragments across the carbon-carbon triple bond, thereby leading to the formation of dithioethers. This approach turned out to be especially useful as a ligation tool for the installation of densely functionalized arrays on various scaffolds and complex biomolecular systems. Concluding remarks emphasize the role of the photoinduced free-radical strategy as a complementary tool to copper-catalyzed azide-alkyne cycloaddition.

Introduction

A large number of bioactive organic compounds,[1] as well as important polymeric materials[2] and synthetic reagents[3] contain sulfur atoms. Accordingly, a rich repertoire of a variety of C–S bond-forming reactions[4] is available to synthetic organic chemists. One such reaction is the addition of the S–H bond of a thiol across the π-system of a terminal unactivated alkyne. This direct and atom-economical method, referred to as alkyne hydrothiolation, is promoted by transition-metal complexes or radical initiators and in principle can lead to one of the regio- and stereoisomeric vinyl sulfides A (branched), B (E linear), and C (Z linear) or to mixtures of them [Equation (1)]. Evidently the product A is the result of a Markovnikov course of the addition reaction whereas the stereoisomers B and C both arise from anti-Markovnikov pathways but with opposite stereoselectivity. Vinyl thioethers, in addition to their interesting biological properties[5] are valuable synthetic intermediates in total synthesis[6] and precursors to a wide range of functionalized or bioactive molecules.[7]

Consequently the preparation of these compounds as single stereoisomers is in great demand. To this end, many efforts have been made over the years to control the regio- and stereoselectivity of alkyne hydrothiolation reactions by optimization of the metal catalysts or radical initiators, as well as of the reaction parameters (i.e., solvent and temperature) and the electronic and steric characteristics of the reagents.

Recently, a significant amount of work has been carried out on the applications of alkyne hydrothiolation under free-radical conditions. Several papers reported that under these metal-free conditions the addition of two thiol fragments across the alkyne triple bond takes place to give dithioethers as final products.

This review highlights the remarkably rapid progress in the field by outlining some of the key findings made in recent times. Several reviews on alkyne hydrothiolation have been reported,[8,9] but in this article we focus mainly on the utility and practicability of the various metal-catalyzed systems used en route to vinyl sulfides and then describe the free-radical approach to alkyne double hydrothiolation and its recent applications as a means for bioconjugation and surface modification.
Metal-Catalyzed Hydrothiolation – Regioselectivity and Stereoselectivity Tuning by Choice of Metal

Unlike other hydrofunctionalization reactions – such as hydroamination, for instance – transition-metal-catalyzed additions of thiols to alkynes have been systematically investigated only over the past two decades. This gap was partly due to the widespread belief that sulfur-containing substrates would bind strongly to transition metals, thereby precluding catalysis.\[10\] The first breakthrough in the field was made in 1992 by Ogawa and co-workers, who reported the selective Pd(OAc)\(_2\)-catalyzed addition of thiophenol to oct-1-yn-1-ene (I) to give the branched Markovnikov adduct 2 in excellent yield\[11\] (Scheme 1). This was an important finding because it provided a complementary approach to the free-radical addition, which was known to give mixtures of \(E\) and \(Z\) linear anti-Markovnikov adducts (see section “Metal-Free Hydrothiolation – the Free-Radical Approach”). While the observed regioselectivity under Pd(OAc)\(_2\) catalysis conditions was confirmed by the reactions of other terminal alkynes with two different arenethiols, the major product when PdCl\(_2\)(PhCN)\(_2\) and, especially, Pt(PPh\(_3\))\(_4\) were used as the catalysts was the alkene 3, derived from the isomerization of 2. A more dramatic change in regioselectivity was observed with use of the Rh-based catalyst RhCl(PPh\(_3\))\(_3\), which in fact afforded a mixture of isomers 2, 3, and the \(E\) linear adduct 4 as major product.

A more comprehensive presentation of these results, together with a discussion of the possible mechanistic pathways of the above Pd, Pt, and Rh processes, was reported in a subsequent paper.\[12\] The main conclusion was that by starting from the same materials (an alkyne and a thiol), isomeric vinyl sulfides could be synthesized with excellent selectivity by changing the catalysts [i.e., Pd(OAc)\(_2\), RhCl(PPh\(_3\))\(_3\), and PdCl\(_2\)(PhCN)\(_2\)] and the reaction conditions. However, the scope of the reactions reported by Ogawa was limited to the use of thiophenol and a few other arenethiols, whereas reactions with alkanethiols to give the equally interesting branched and linear alkyl vinyl sulfides remained elusive. This issue was addressed in 2005 by Love and co-workers, who set out to overcome this limitation by studying alkyne hydrothiolation with aromatic and aliphatic thiols catalyzed by a rhodium triazolylborate complex.\[13\]

In fact, although metal catalysts were known to be ineffective for alkyne hydrothiolation with alkanethiols, it was expected that highly electron-rich metal complexes, such as rhodium pyrazolylborates, would be able to activate the S–H bonds of alkanethiols and therefore catalyze their reaction with alkynes. Indeed this hypothesis turned out to be correct, with the hydrothiolation of phenylacetylene with phenylmethanethiol in the presence of catalytic Tp\(^*\)Rh(PPh\(_3\))\(_2\) \[TP*/ = hydrotris(3,5-dimethylpyrazolyl)borate\] being found to proceed rapidly and selectively to give the branched vinyl sulfide 5 in excellent yield (Scheme 2).

The generality and validity of this approach were confirmed by examination of the reactions between aliphatic and aromatic terminal alkynes and alkanethiols (Table 1). Branched vinyl sulfides were formed in good yields, with small amounts of the linear regioisomers also being obtained in some cases.

On the other hand, the selectivity was much lower with aromatic thiols such as thiophenol and \(p\)-substituted derivatives, with mixtures of the branched and linear regioisomers

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**Scheme 1.** Catalyst effect on addition of arenethiol to alkyne 1.

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Metal-Catalyzed and Metal-Free Alkyne Hydrothiolation

Scheme 2. Regioselective addition of benzylthiol to phenylacetylene in the presence of the Rh complex I.

Table 1. Alkyne hydrothiolation with alkanethiols in the presence of the Rh complex I.

Table 2. Hydrothiolation of aryl-alkynes with arenethiols in the presence of the Rh complex I.

[Scheme 3. Solvent effect on the reaction between phenylacetylene and an alkanethiol catalyzed by Wilkinson’s catalyst.]

Table 3. Selected examples of alkyne hydrothiolation catalyzed by Wilkinson’s catalyst.

Another approach to E linear vinyl thioethers was reported in 2010 by Iglesias and Sánchez and their co-workers...
who used rather expensive catalysts such as Au I and Au III complexes. These catalysts proved to mediate the hydrothiolation of terminal aliphatic and aromatic alkynes, with thiophenol providing the E linear isomers in all cases and in nearly quantitative isolated yields (90–97%). Quite remarkably, most reactions were carried out under heterogeneous conditions and therefore the catalyst could be recovered and recycled in several successive runs without any loss of activity and selectivity.

Whereas Ogawa’s and Love’s groups had secured a wide range of routes to branched vinyl sulfides and E linear regioisomers, other groups targeted the regio- and stereoselective synthesis of Z linear anti-Markovnikov isomers. Thus, the group led by Messerle demonstrated that iridium and rhodium complexes containing bidentate N,N-donor ligands (N,N-donor = bis-pyrazolyl) and hybrid P,N-donor ligands (P,N-donor = phosphate-pyrazolyl) were effective catalysts of the hydrothiolation of a series of alkynes with thiophenol at different temperatures and with different reaction times. In particular, with phenylacetylene the reaction afforded mixtures of E and Z linear anti-Markovnikov products, with the latter predominant. On the other hand variable E/Z ratios were registered with propargyl alcohol and pent-1-yne, due to the isomerization of the kinetic Z adduct into the more stable E isomer. Thus, this lack of stereoselectivity and the laborious preparation of rather expensive catalysts made this approach more interesting as a fundamental study on the activity of metal transition complexes rather than as a procedure for the synthesis of vinyl sulfides.

Another group, led by Yorimitsu and Oshima, developed an approach to Z linear anti-Markovnikov vinyl sulfides. In this case, no transition-metal catalyst was employed. Instead, the reaction was base-catalyzed by cesium carbonate, although potassium carbonate proved to be an effective catalyst as well. The role of the metal consisted of the formation of a cesium thiolate from Cs2CO3 followed by substitution of chloride ion in NiCl2 by PhS– to generate the nucleophilic anion PhS– from PhSH, followed by generation of the nucleophilic anion PhS– from PhSH, followed by substitution of chloride ion in NiCl2 by PhS– to give the catalytic active species Ni(SPh)2 or the insoluble oligomer [Ni(SPh)2]n. Optimized conditions, however, required the use of TEMPO (2,2,6,6-tetramethylpiperidin-N-oxyl) as a radical inhibitor to suppress the base-free radical reaction leading to substantial amounts of the E linear isomer. The scope of the reaction was also investigated, with a range of aryl alkynes and aliphatic thiols and potassium carbonate as a base catalyst. Although the yields were satisfactory, low stereoselectivity was observed with aryl alkynes bearing electron-withdrawing substituents, and in some cases the E linear isomers were the major products. A serious limitation was encountered in the observation that attempted hydrothiolation of phenylacetylene with aromatic thiols as adducts of TEMPO (2,2,6,6-tetramethylpiperidin-N-oxyl) as a radi-
suppressed and the formation of the Markovnikov products 8 and 9 was increased substantially. High yields and Markovnikov selectivity were obtained in a range of solvents including chloroform, dioxane, hexane, and toluene, with the last of these being the solvent of choice owing to its high boiling point. Notably, the reaction was insensitive to the presence of a certain amount of water in the selected organic solvent or to the use of NiCl₂ hexahydrate. A final investigation was carried out into the scope of the reaction. Unfortunately, this topic was studied only with variation of the alkylene while the effect of using different thiols instead of thiophenol remained unexplored. Thus, aliphatic alkynes bearing groups with heteroatoms (NMe₂, OMe, SPh, OH, CN, CO₂Me) that could bind to the metal and therefore retard alkylene coordination required longer reaction times and higher temperature. Nevertheless, high selectivities and yields were observed for the different alkynes employed, with the exception of methyl propiolate because of very fast non-catalytic side reactions.

Continuation of the work on Ni-catalyzed hydrothiolation was reported by the same research group in 2006.[20] The new study was aimed at overcoming some limitations of the NiCl₂-catalyzed process and consequently improving the regioselectivity toward the formation of the branched Markovnikov vinyl sulfides A while avoiding the double bond isomerization leading to the internal trans/cis alkenes B and above all suppressing the side reaction affording the bis(arythio)alkenes D (Scheme 5). In this study the designed Ni-based catalysts were CpNi(NHC)Cl complexes (NHC=N-heterocyclic carbene) that, unlike the NiCl₂ employed in the previous work,[18] enabled the reaction to take place under homogeneous conditions. Four different complexes were considered; the one incorporating N,N'-bis(2,4,6-trimethylphenyl)imidazol-2-ylidine (IMes) as a ligand turned out to be the most effective catalyst of the reaction between thiophenol and hept-1-yne (Scheme 6). In this study the designed Ni-based catalysts were CpNi(NHC)Cl complexes (NHC=N-heterocyclic carbene) that, unlike the NiCl₂ employed in the previous work,[18] enabled the reaction to take place under homogeneous conditions. Four different complexes were considered; the one incorporating N,N'-bis(2,4,6-trimethylphenyl)imidazol-2-ylidine (IMes) as a ligand turned out to be the most effective catalyst of the reaction between thiophenol and hept-1-yne (Scheme 6). Indeed, this reaction afforded the Markovnikov-type adduct 8 in good yield, whereas the internal alkene 9 was not observed and the only side products were the E and Z linear anti-Markovnikov adducts. Attempts to optimize the reaction conditions in order to improve yield and selectivity were made by changing solvent, alkylene/PhSH ratio, and the amount of Et₃N. However, this appeared to be a difficult task because, for example, the variation of one parameter might give a better yield but low selectivity and/or be accompanied by the formation of a new side-product, namely a diene arising from the insertion of two molecules of alkylene into the Ni complex. Remarkable results were obtained with certain substituted alkynes and arenethiols. For example, the reactions between 4-methoxybenzenethiol and various alkynes produced very good yields of the Markovnikov-type products (67–87%) and excellent Markovnikov/anti-Markovnikov selectivities, in the range from 26:1 to 31:1. A mechanistic study of the system and X-ray structural determination of a key intermediate showed that the reaction involved three steps: (1) a nickel-based substitution of chloride for the ArS group, (2) alkylene insertion into the Ni-S bond, and (3) protonolysis of the Ni–C bond.

Scheme 5. Ni-catalyst-induced alkyne hydrothiolation.


Another metal employed by Beletskaya and co-workers as a catalyst of the model hydrothiolation of phenylacetylene with thiophenol was copper.[21] Among various salts that were tested as sources of the metal [CuI, CuBr, CuCl, Cu₂O, Cu(OAc)₂, CuSO₄], the one that turned out to be the most effective was CuI [Equation (4)]. Indeed, use of this salt led to the formation of a reaction mixture composed of the two linear anti-Markovnikov adducts 11 (Z isomer) and 12 (E isomer) with a great prevalence of the former. Use of the other copper salts either failed to give any product or produced mixtures of 11, 12, and the branched Markovnikov adduct 13 in comparable amounts. These results were obtained with aprotic solvents (THF and DMF), whereas in a mixture of protic solvents such as i-AmOH/ethylene glycol, the 11/12 ratio was completely reversed in favor of the latter. The preferential or exclusive formation of the E isomer was also observed on heating the reaction mixture or on increasing the reaction time, this suggesting that under those conditions Z-to-E isomerization took place.

A remarkable advancement towards the development of a broad-scope approach to Z linear anti-Markovnikov vinyl thiioethers of type C (see Equation (1)) with high regio- and stereoselectivity was made in 2012 by Gerber and Frech,
through the use of the aminophosphine-based palladium complex ([P(NC5H10)(C6H11)2]2Pd(Cl)2) III.[22] Notably, this catalyst was quantitatively prepared in one step from a readily available palladium complex and 1-(dicyclohexylphosphanyl)piperidine. Thus, a range of sulfur-containing alkenes of type C were obtained in excellent yields within a few minutes at 120 °C with N,N-dimethylpyrrolidone (NMP) and NaOH as the solvent and base, respectively, in the presence of only 0.05 mol-% of the catalyst. A typical reaction is shown in Equation (5), but similar results were obtained from reactions between terminal aromatic alkenes and a wide range of aliphatic and aromatic thiols. On the other hand, reactions with aliphatic alkynes took place with different regioselectivity to give branched Markovnikov-type products A in good yields. This variation in product selectivity obtained with aliphatic alkynes was ascribed to their low ligating tendency favoring, in contrast with aromatic alkynes, insertion into the Pd–S bond over nucleophilic attack.

Whereas most of the early studies of alkyne hydrothiolation employed some late transition-metal catalysts as reported above, in 2009 Marks and co-workers focused their attention on the use of f-element catalysts.[23] Thus, they reported the first use of a thorium-based complex to affect reactions of a broad range of terminal alkenes with aromatic, benzylic, and aliphatic thiols, affording Markovnikov-type branched vinyl thioethers with high degrees of selectivity. Steric and electronic effects of alkenes and thiols on the rates of various reactions were discussed. Unfortunately, most of the reactions were not carried out on a preparative scale and so yields of isolated products were not reported. However, the formation of small amounts of anti-Markovnikov products arising from competitive metal-free radical reactions was occasionally observed; to suppress these side-reactions the addition of the radical inhibitor γ-terpinene was employed.

Because actinide catalysts were rather expensive and their non-negligible radioactivity could cause safety problems, Weiss and Marks addressed their efforts towards the Markovnikov vinyl sulfide synthesis to the use of zirconium(IV) complexes.[24] This choice was not casual but it rather arose from the observation that organozirconium complexes mediated alkyne hydroamination (i.e., a process formally analogous to hydrothiolation) with Markovnikov selectivity. Thus, a set of organozirconium complexes was tested as potential precatalysts. The complexes Cp*ZrBn3 (Cp* = C5Me5, Bn = benzyli) and CGCZrMe2 (CGC = Me2SiCp”’NCMe3, Cp”’= C5Me4) were found to be the most effective and selective in activating two model reactions: namely those between hex-1-ynyl and pentane-1-thiol and between hex-1-yne and benzylmercaptop. Hence, the Cp*ZrBn3 complex was employed for mediation of the hydrothiolation of a broad range of aliphatic and aromatic alkenes by aromatic, benzylic, and aliphatic thiols featuring variations in steric and electronic characteristics. Use of sterically encumbered thiols appeared to decrease the reactivity, whereas use of conjugated alkynes exhibited significantly enhanced rates. Nevertheless in all cases examined the Markovnikov selectivity yielding branched vinyl sulfides was achieved (Table 4). Experiments on a preparative scale afforded these products with isolated yields of up to 72% and 99% selectivity. However, this approach was also occasionally not totally selective because, in addition to the branched Markovnikov product, a mixture of anti-Markovnikov isomers was also formed as the result of a non-organometallic, radical mechanism, which fortunately could be suppressed by addition of a radical inhibitor. It may be suspected that occurrence of the radical side-reaction was induced by traces of air entering the system during the refilling steps. Nevertheless, it is worth pointing out that an earlier approach by Mizobe and co-workers using RhIII complexes was also plagued by the presence of substantial amounts of side products derived from the radical process.[25] Therefore the contribution of the Marks group constituted a remarkable improvement. Notably, the synthetic application reported by these authors was accompanied by a detailed kinetic study and a mechanism was outlined in which alkyne insertion into the Zr–SR bond took place, followed by a thiol-induced Zr-C protonolation.

While substantial advancements in the field were established by the aforementioned approaches carried out by various research groups, metal-catalyzed alkyne hydrothiolation as an atom-economical synthetic tool and a stimulus to the development of new organocatalysts continued to attract the interest of a range of able researchers. Hence, Castarlenas and co-workers, starting from some considerations on the plausible reaction pathways leading to regioselective alkyne-thiol adducts (i.e., linear and branched isomers), designed and synthesized Rh-N-heterocyclic carbene compounds and employed them as catalysts in alkyne hydrothiolation experiments.[26] Branched vinyl sulfides were known to be more valuable synthetic intermediates than linear isomers,[7a] so Rh1 complexes were selected, because their general tendency to favor the latter could be reversed by ligand control.[13–15] Indeed, it was found that phenylacetylene hydrothiolation with a thiophenol underwent a regioselectivity switch from the E linear anti-Markovnikov vinyl sulfide to the branched Markovnikov adduct [see Equation (1)] when mononuclear Rhenium[IPr(ppy)(η2-olefin)] [IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-carbene; ppy = pyridine; olefin = cyclooctene or ethylene] catalysts in the presence of pyridine were used. Similar trends were observed in reactions between various alkynes and thiophenol, as well as between phenylacetylene and different thiols. It has to be noted, however, that the formation of the E linear adduct was never totally suppressed and that all runs were carried out on NMR scale so that these results...
Table 4. Alkyne hydrothiolation mediated by the Cp*ZrBn3 complex.

<table>
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<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>Product</th>
<th>Yield[a] (selectivity[b])</th>
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<td>n-C8H18</td>
<td>Et</td>
<td><img src="image1" alt="image" /></td>
<td>95% (96%)</td>
</tr>
<tr>
<td>2</td>
<td>n-C8H18</td>
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<td><img src="image2" alt="image" /></td>
<td>79% (84%)</td>
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<tr>
<td>3</td>
<td>n-C8H18</td>
<td>tBu</td>
<td><img src="image3" alt="image" /></td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>n-C8H18</td>
<td>Ph</td>
<td><img src="image4" alt="image" /></td>
<td>94% (94%)</td>
</tr>
<tr>
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<td>n-C8H15</td>
<td><img src="image5" alt="image" /></td>
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</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>n-C8H15</td>
<td><img src="image6" alt="image" /></td>
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</tr>
<tr>
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<td>tBu</td>
<td>n-C8H15</td>
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<tr>
<td>8</td>
<td><img src="image8" alt="image" /></td>
<td><img src="image9" alt="image" /></td>
<td><img src="image10" alt="image" /></td>
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can hardly be extended to a preparative scale. On the other hand, a fine study on the complex interplay between electronic and steric factors induced by the carbene moiety, pyridine, and hydride ligand was carried out to account for the observed regioselectivity. A proposed mechanism proceeded through addition of the S–H bond to RhI intermediates and successive alkyne migratory insertion and reductive elimination steps.

Given the remarkable success in alkyne hydrothiolation achieved by various groups with the use of rhodium complexes, owing to their high activity and their regio- and stereoselectivity for either Markovnikov or anti-Markovnikov products under mild reaction conditions, Yang and Rioux addressed the problem of large-scale applications of these catalysts.[27] Several drawbacks to the use of homogeneous rhodium complexes for industrial production of vinyl sulfides had been pointed out, such as their high cost and difficulties in their separation from the product mixtures, this being a serious obstacle to their recyclability. The problem was elegantly solved by immobilization of the popular Wilkinson’s catalyst RhCl(PPh3)3 on ordered mesoporous silica nanoparticles (e.g., SBA-15) through the formation of covalent Rh–P and Rh–N bonds (to give Rh-P-SBA-15 and Rh-N-SBA-15, respectively). The effect of these catalysts on regio- and stereoselectivity in the benchmark reaction between phenylacetylene and thiophenol turned out to depend on the functional groups linked to the rhodium complex. In particular, whereas Rh-N-SBA-15 induced the formation of a mixture of anti-Markovnikov E + Z adducts with the Z isomer 11 as the major product, completely reversed stereoselectivity in favor of the E isomer 12 was obtained in the presence of Rh-P-SBA-15 (Scheme 7). In both cases Markovnikov addition was totally suppressed. The reaction was carried out in a set of solvents, but DCE was found to be the best choice for the formation of the E linear anti-Markovnikov vinyl sulfide product 12 without the presence of the Z isomer 11 and the branched Markovnikov adduct 13. Finally, the alkyne range was next studied, with thiophenol as the thiol substrate in the presence of Rh-P-SBA-15 in DCE. Aromatic, aliphatic, and internal alkynes were hydrothiolated to give the E linear anti-Markovnikov products with 100% selectivity and without any traces of the Z isomers. Reaction temperatures were in the 25–60 °C range whereas the reaction times were between 20 and 40 h. Similar conditions were adopted in the study of the scope of the thiols, with phenylacetylene as the alkyne substrate, and also in these cases high conversion values and good to excellent regio- and stereoselectivities in favor of the E linear isomers were obtained. As a final experiment it was verified that the observed catalysis was due to the heterogeneous catalyst Rh-P-SBA-15 and not to leached rhodium species in solution, and it was also demonstrated that the above catalyst could be recovered by filtration and reused at least six times without any significant loss of catalytic activity and regioselectivity. Thus it was correctly concluded that a well-defined supported rhodium catalyst had been developed for the hydrothiolation of alkynes with thiols and that the process represented a green methodology for the synthesis of regio- and stereodefined vinyl sulfides.

Scheme 7. Effects of Rh catalysts on the hydrothiolation of phenylacetylene.
lar, these studies revealed that heteroaromatic thiols Het-SH (Het = benzothiazole, benzoazole, thiazoline, pyridine) added selectively to aryl acetylenes in a Markovnikov fashion to give branched vinyl sulfides [Equation (6)], whereas aromatic and aliphatic thiols added to phenylacetylene in an anti-Markovnikov way under the same conditions to afford mixtures of $E$ and $Z$ linear isomers with net prevalence of the former [Equation (7)]. In both processes the yields of isolated vinyl sulfides were in the 80–90% range. However, in the cases of the reactions between phenylacetylene and $p$-nitrothiophenol or $o$-aminothiophenol, the $Z$ isomers were formed as the major products. No mechanistic study to account for the observed switch in selectivity was carried out, although tentative explanations based on differences in the nucleophilic characters of the reacting thiols were advanced.

$$\text{Ph}=\equiv + \begin{array}{c} \text{S} \\ \text{N} \end{array} \text{SH} \xrightarrow{\text{In(OT)}_3, \text{toluene, reflux}} \text{Ph}=\equiv + \begin{array}{c} \text{S} \\ \text{S} \end{array} \xrightarrow{90\%}$$

(Equation 6)

$$\text{Ph}=\equiv + \begin{array}{c} \text{SH} \\ \end{array} \xrightarrow{\text{In(OT)}_3, \text{toluene, reflux}} \text{Ph}=\equiv \xrightarrow{85\% (E/Z = 10 : 1)}$$

(Equation 7)

A few points appear worth consideration before closing this excursus on alkyne hydrothiolation mediated by organometallic chemistry. From the studies mentioned it appears that the main goal, consisting of control of the regio- and stereo- and stereoselectivity of the addition of aromatic and aliphatic thiols to a wide range of alkynes, has been reached. Thanks to a variety of advances made over the years by various groups, the highly selective synthesis of isomeric vinyl sulfides on a preparative scale is now possible. Some simple organometallic catalysts have been developed that also appear accessible to non-expert researchers in the field. A point that remains to be explored is whether these methods can be employed in the target-oriented synthesis of complex and highly functionalized molecular constructions.

**Metal-Free Hydrothiolation – the Free-Radical Approach**

Alkyne hydrothiolation induced by radical initiators or by UV/Vis light irradiation has been the subject of intense research in the past few decades, mainly from the viewpoint of physical organic chemistry studies. Its synthetic value was undervalued, however, very likely because of the widespread observation that the reaction afforded mixtures of hardly separable anti-Markovnikov $E$- and $Z$-vinyl sulfides. Two excellent reviews were published, one in 2010 outlining mainly the applications in polymer and material synthesis and another (which in fact appeared in the middle of 2012, while this manuscript was in preparation) dealing with applications for bioconjugations. Moreover, a special article highlighting the role of this reaction, hereafter referred to as thiol-yne coupling (TYC), for creating highly functional materials was reported in 2010. The main property of TYC is its capacity to introduce across the triple bond not only one but two thiol fragments to yield bis-addition products, namely dithioethers. The free-radical mechanism (Scheme 8) that is generally accepted involves as a first step the addition of a thyl radical across the carbon-carbon triple bond to afford a carbon-centered $\beta$-sulfanyl-substituted vinyl radical, which subsequently abstracts a hydrogen from another thiol, generating a vinyl sulfide intermediate and regenerating a thyl radical. Then, the vinyl sulfide is capable of undergoing a second thyl radical addition, actually a thiol-ene coupling (TEC) process, to give a dithioether as the final product. Thus, after complete reaction, each alkyne functional group has combined with two thiols, thus establishing the alkyne as a functional component in the TYC reaction. However, depending on the nature of the alkyne employed, the thiol/alkyne ratio, the temperature, and the reaction time, TYC can be interrupted at the stage of the monoaddition step, thus allowing the isolation of the vinyl sulfide intermediate (see below). Because this is a mixture of $E$ and $Z$ isomers and the final dithioether is also a mixture of stereoisomers, due to the formation of a stereocenter with $R$ or $S$ configuration, it can be concluded that TYC lacks stereoselectivity. This might prevent the introduction of TYC among the click processes for which the formation of a single stereoisomer is a prerequisite. Nevertheless, TYC reactions have several positive attributes: they proceed at room temperature with high efficiency and rapid kinetics, in the presence of oxygen and water and without expensive and potentially toxic metal catalysts, and are highly tolerant of a numerous functional groups. Moreover, TYC is orthogonal to a wide range of chemistries including the phosphine-catalyzed nucleophilic thiol-ene reaction. Finally, TYC can be promoted by the greenest of all catalysts, such as irradiation with UV/Vis light in the 254–470 nm range, conditions that are well tolerated by delicate biomolecules such as carbohydrates, peptides, proteins, and nucleotides. Another factor that broadens the scope of TYC is the vast number of available thiols and terminal alkynes, the synthesis of the latter having been motivated in recent years for use in copper-catalyzed azide-alkyne cycloaddition (CuAAC). Given these premises, here we discuss only work using TYC that was reported after the publication of the aforementioned reviews: that is, from 2012 onwards.

![Scheme 8. Free-radical mechanism of alkyne hydrothiolation.](image-url)
Although free-radical alkyne hydrothiolation originally revealed its potential as a means of access to dithiethers, there was some interest on the use of this metal-free approach for the preparation of biologically active vinyl sulfides. Thus, Reddy and co-workers finalized TYC between the substituted phenylmethanethiol 15 and (2,4,6-trimethoxyphenyl)acetylene (16) in the presence of Et3B/hexane as a radical initiator for the synthesis of the (Z)- and (E)-styryl benzyl sulfides 17 and 18, respectively\(^3\) (Scheme 9). Quite remarkably, the sulfone 20 derived from the \(E\) isomer 18 was a well-known precursor of \((E)\)-ON 01910-Na (Rigosertib\(^4\)), a phase III clinical stage anticancer agent. Because \((E)\)-ON 01910-Na could be also synthesized by Knoevenagel condensation,\(^3\) the TYC-based approach was mainly directed toward the formation of the \(Z\) isomer 17. Indeed, it was emphasized that this isomer would provide access to \((Z)\)-ON 01910-Na in sufficient quantities for characteriza-
tion and comparison of its pharmacokinetic and biological activities with those of the \(E\) isomer. Hence, a detailed study of the reaction between 15 and 16 was carried out by chang-
ing the solvent, temperature, time, and catalyst, thus estab-
lishing optimized conditions for production of either the \(Z\) adduct 17 or the \(E\) isomer 18 with excellent yields (82 and 95\%) and selectivities \((Z)/E: 86:14\) and \(0:100\). Then, each isolated isomer was oxidized to the corresponding sulfone, without isomerization, by standard methods (oxone at room temperature to give 19 and \(H_2O_2/\text{AcOH}\) at 5 °C to give 20). Finally, each sulfone was transformed into the cor-
responding \((Z)\)-ON 01910-Na and the \(E\) isomer by suitable elaboration of the nitro group (reduction to an amino group and alkylation of this with methyl 2-bromoacetate, followed by saponification of the resulting methyl glycinate).

Notably, in vitro cytotoxicity assays were carried out with the final \(Z\) and \(E\) isomers as well as their precursors. Differences in activity were observed, depending on the ste-
reochemistry of the double bond, the oxidation state of the sulfur atom, and the substituents on the phenyl ring of the benzyl group. It is worth closing this issue by noting that this work demonstrated for the first time the efficiency and fidelity of free-radical alkyne hydrothiolation for obtaining \((E)\)- and \((Z)\)-alkenyl sulfides selectively in the absence of metal catalysts and validated the method as a means for the preparation of products of pharmacological relevance.

A contribution dealing with the use of TYC as a dual hydrothiolation tool came from work carried out by our group.\(^3\) It consisted of the TYC-based construction of glycoclusters on a chemically and thermally stable cubic scaffold constituted of oxygen and silicon atoms and cur-
rently known as polyhedral oligomeric silsesquioxane (POSS).\(^3\) POSS glycoconjugates have received significant attention due to their rigid globular architecture, on which a precise clustering of sugar molecules in space can be displayed. The synthesis of POSS glycoconjugates was carried out in our laboratory by addition of various sugar thiols to each alkynyl group of the octavalent propargylated POSS, hexadecavalent glyco-POSS conjugates were ob-
tained as final products (Figure 1), yields varied from good to excellent (50–82\%). As a demonstration of the biological relevance of the glyoclusters thus obtained, their affinities towards certain lectins were measured by the Enzyme-
Linked Lectin Assay (ELLA). In particular, the affinity of the \(N\)-acetylglucosamine-based cluster towards wheat germ agglutinin (WGA) revealed a remarkable glycoside cluster effect with up to a 9.0 × 10^2-fold increase in binding com-
pared to monovalent GlcNAc.

The preparation of sugar-coated membranes for the selective recognition of lectins was published in 2013 by Xu and co-workers.\(^4\) Microporous polypropylene membranes (MPPMs) were functionalized with alkyne units through plasma treatment of the surface followed by UV-induced graft polymerization with 3-(trimethylsilyl)propargyl methacrylate (Scheme 10). After removal of the trimethylsilyl protecting group under basic conditions, the terminal triple bond was subjected to photoinduced \((\lambda_{\text{max}} 365 \text{ nm})\) radical coupling with the tetra-acetylated glucosyl thiol in the presence of the initiator DPAP. A standard transesterification protocol (MeONa in MeOH) gave the glycosylated membranes with sugar density ranging from 0.5 to 3 mmolcm\(^{-2}\), depending on the grafting density of the methacrylate. The recognition properties of these membranes were investi-
gated with two fluorescence-labeled lectins: concanavalin-

![Scheme 9. Synthesis of anticancer agent \((E)\)-ON 01910-Na (Rigosertib\(^4\)) and isomer \((Z)\)-ON 01910-Na.](image-url)
A (Con A), which selectively binds to glucose, and peanut agglutinin (PNA), which shows high affinity towards galactosamine and galactose. Because the experiments demonstrated that the glucosylated membranes specifically adsorb Con A and are easily regenerated by treatment with 1 M acetic acid, these materials can be used as stationary phases for affinity chromatography.

Scheme 10. Preparation of glycosylated membranes by 3-(trimethylsilyl)propargyl methacrylate grafting onto microporous polypropylene membranes (MPPMs) and subsequent thiol-yne coupling with \( \beta \)-D-glucopyranosyl thiol.

In order to prepare carbohydrate-presenting surfaces for studies of lectin–carbohydrate interactions,[42] polystyrene-coated quartz crystals were first functionalized with N-hydroxysuccinimide-derivatized perfluorophenylazide (PFPA-NHS) by irradiation at 254 nm and then allowed to react with the alkynyl-amine linker to give the corresponding amide (Scheme 11).

Scheme 11. Lectin sensors obtained by photoinduced thiol-yne coupling.

Finally, the alkynylated crystals were subjected to TYC with mannose or galactose thiols in water under UV irradiation (\( \lambda _{\text{max}} = 350 \) nm) to afford densely glycosylated surfaces that were used to evaluate the binding affinities toward the specific lectin concanavalin-A and \textit{Ricinus communis} agglutinin I by use of a quartz crystal microbalance (QCM) flow-through system.

A very recent application of TYC in the oligosaccharide mimetics field, reported by Csávás, Herczeg, and Borbás,[43] involved the synthesis of sialylated trisaccharide analogues. The photoinduced double thiosialylation of 6-propargylated galactose derivative \( 22 \) or 3-propargylated \( 24 \) was achieved with the peracetylated methyl 2-thio-neuraminic acid \( 21 \) as the thiol (Scheme 12). Unfortunately, despite the use of an excess of the thiol reagent (4 equiv.), the target compounds \( 23 \) and \( 25 \) were obtained in poor yields (11–12%), with the major product (82%) being, in both cases, the corresponding monosialylated vinyl sulfide, recovered as an inseparable mixture of \( E \) and \( Z \) isomers. The reversibility of the addition of the thiyl radical to the latter intermediates, actually a thiol-ene process, and the steric hindrance of the major, thermodynamically more stable \( (E) \)-vinyl sulfide were suggested as the possible causes of the low yields found in the synthesis of the 1,2-dithioethers \( 23 \) and \( 25 \).
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Scheme 12. Synthesis of sialylated trisaccharide mimetics by TYC.

In 2011, Dondoni, Davis, and their co-workers reported the TYC-based glycoconjugation and fluoresceination of bovine serum albumin (BSA) induced by light at visible wavelength. However, dual labeling with two different fragments (i.e., glucose and fluorescein) occurred not only at the protein’s free cysteine moiety but also at two thiol groups derived from the photoinduced cleavage of a nearby disulfide bond (Scheme 13).

Scheme 13. Glycosylation and fluoresceination of BSA through TYC.

While the relevance of the Dondoni–Davis group’s work in protein dual labeling with two different reagents, an alkyne and a thiol, was duly recognized by Li and co-workers, these authors pointed out a limitation of the above strategy in that the target protein could contain only one free cysteine residue unless labeling at multiple locations was acceptable. Therefore, it appeared necessary to develop an alternative strategy for protein site-specific dual labeling through TYC. Hence, the method of Li consisted of labeling HdeA proteins carrying a single alkyne handle that was incorporated by use of an alkyne-containing l-lysine amino acid (pyrrolysine analogue). Then, the resulting tagged proteins were subjected to a photoinduced thiol-yne reaction with a fluorescent disulfide, \( N,N' \)-bis(dansyl)cystamine, to give proteins labeled with two thiol fragments per alkyne handle (Scheme 14).

Scheme 14. Fluorescent labeling of alkynylated protein HdeA by \( N,N' \)-bis(dansyl)cystamine.

In a very recent paper, Ovaa and co-workers reported that C-terminally propargylated ubiquitin (Ub-Prg) underwent a Markovnikov addition of the cysteine thiol located in the active site of the ubiquitin carboxyl-terminal hydrolase isozyme L3 (UCHL3) to give the corresponding branched vinyl thioether. The actual structure of this unexpected adduct was confirmed by X-ray crystallographic analysis of the complex between another de-ubiquitinating enzyme (vOTU) and the same propargylated ubiquitin. The crystallographic studies unambiguously showed the attachment of the cysteine sulfur atom to the quaternary carbon of the vinyl thioether. The use of various alkynylated ubiquitin derivatives showed that the terminal hydrogen atom was essential for the observed thiol–yne monoaddition. Moreover, the authors demonstrated that the reaction between C-terminal alkynes and active-site cysteine residues could be extended to other classes of enzymes such as proteases (e.g., caspase-1). Because the radical mechanism as well as the formation of an allene intermediate from the alkyne function were ruled out by the authors, it was concluded that the vinyl thioether adduct should form by direct nucleophilic attack on the quaternary propargyl carbon.

An interesting application of TYC in bioconjugation was reported in 2012 by the group of Davidson and Levkin.
Given the importance of delivery of nucleic acids such as plasmid DNA and siRNA into cells for medical therapeutics and the limitation on the use of non-viral lipid-based vectors due to difficulties in their synthesis, these researchers reported a facile modular and scalable approach employing TYC for the parallel synthesis of a library of cationic thioether lipids. These new biomimetic lipids each featured two hydrophobic tails of variable length and a linker group structurally mimicking the glycerol core of the phospholipids (Scheme 15). More than 100 new lipids were synthesized by this approach, and some of them (10%) showed highly efficient transfection in different cell types, surpassing the efficiency of several commercial transfection reagents.

Thiol radical addition to alkenes and alkynes was also applied to the synthesis of sugar-based non-ionic surfactants that featured either a carbohydrate unit at each end of a hydrocarbon chain (bolaform derivatives) or two sugars at one extremity of the chain (double-headed derivatives). Along with a series of mannose-based surfactants prepared by thiol-ene coupling, Debuigne and co-workers described[48] the synthesis of a double-headed derivative by TYC ligation. Compound 27 was isolated in 78% yield by column chromatography after coupling of 6-O-(3-mercaptopropanoyl)-d-mannopyranose (26, 2.4 equiv.) with tetradec-1-yne in the presence of the photoiniator DPAP (Scheme 16). The new surfactant showed a critical micellar concentration (CMC) significantly lower than that observed for the bolaform analogue. This behavior indicated that the presence of the sugars at each extremity rather than at the same end of the hydrocarbon chain leads to higher water solubility.

Another area of research in which the potential of TYC was exploited as a ligation tool was that of surface modification. In fact, once again several advantages were associated with the use of TYC, such as the absence of the nos-ious copper metal involved as catalyst in copper-catalyzed alkynie-azide cycloaddition (CuAAC) and the lack of reduced surface coverage occurring in the strain-promoted alkynie-azide cycloaddition (SPAAC) due to the steric bulk of cyclooctyne moieties.[49] An important feature of TYC was that in principle it allowed the binding of two different groups onto the surface-terminal group, thus enabling surfaces with complex surface requirements to be obtained. Based on these premises, Zuilhof and co-workers investigated TYC chemistry for the modification of alkyne-terminated monolayers on oxide-free Si(111) surfaces.[50] To this end a wide range of thiols, including 9-fluorenylmethoxy-carbonyl cysteine, 1-thio-β-D-glucose tetraacetate, thioacetic acid, thiglycerol, and thioglycolic acid, were immobilized by TYC under photochemical conditions and all modified surfaces were characterized by suitable spectroscopic means. Thus, it was found that TYC chemistry afforded high surface coverage for all investigated thiols and that this was consistently higher than that obtained by thiol-ene chemistry previously reported by the same group. This result was simply attributed to the double addition of thiols to the alkyne-terminated monolayers. Notably, the formation of mixed monolayers with high coverage of two different thiols was also carried out, this result being in line with the stepwise mechanism of TYC. This double hydrothiolation with different thiols indicated the possibility of easily constructing complex surface architectures.

A further demonstration of the convenient use of TYC in materials science was provided by the group led by Carbonnier.[51] These researchers reported on the surface immobilization of gold nanoparticles (GNPs) on the porous monolith surface of poly(NAS-co-EDMA) (NAS = N-acyloxy succinimide, EDMA = ethylene dimethylacrylate) in which the key reaction was the photoinitiated biad-dition of cysteamine to the propargyl groups attached to the copolymer surface through amidic linkages. This led to a homogeneous dispersion of NH₂ groups on the monolithic pore surface, onto which the adsorption of GNPs was simply performed by dynamic loading of a commercial red colloidal solution containing a known amount of GNPs (Scheme 17). Control experiments demonstrated the specific role of the amine surface functionality installed by TYC in the immobilization of the GNPs. This method was consid-ered to offer great promise for the controlled design of microdevices based on nanostructured polymer hybrids.

An elegant application of TYC in materials science, dealing with graphene post-functionalization, was reported in 2013 by a French–Polish–Chinese group led by Bouker-rouh and Szunerits.[52] In this work, graphene oxide (GO)
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Scheme 17. Immobilization of GNPs on the poly(NAS-co-EDMA) interface. Key step is the photoinduced bis-cysteamine addition to the alkyne units.

was simultaneously exfoliated and reduced (i.e., almost completely liberated from the oxygen functionalities while the sp² network was re-established[53]) by using alkynyl dopamine under sonication to give rGO/alkynyl-dopamine nanosheets. Thus, alkynyl-dopamine was at the same time installed onto the graphene network, very likely owing to strong π–π interactions between the hexagonal cells of graphene and the aromatic ring of dopamine. In turn, these modified graphene sheets were treated with two special thiols – namely a ferrocenyl-based thiol and a perfluorinated alkanethiol – under photochemical conditions (Scheme 18). The double addition of the ferrocenethiol to each alkynyl group of rGO/alkynyl-dopamine was confirmed by X-ray photoelectron spectroscopy (XPS), whereas the perfluorinated alkanethiol gave rise preferentially to the formation of a monoaddition product.

Iron oxide nanoparticles were functionalized by TYC as well. As a part of their research on the development of multimodal nanoplatforms for biomedical and catalysis applications, Guénin and co-workers used TYC for the functionalization of γ-Fe₂O₃ nanoparticles.[54] The nanoparticles were coated by a bifunctional molecule from the bisphosphonic acid family, called BPheptyne. Hence, the new γ-Fe₂O₃@BPheptyne nanoplatfrom had alkyne groups on its surface, on which it was possible to carry out photochemical coupling of various thiols (e.g., N-acetylcysteine and glutathione) that differed in their molecular weight and functionalities (Scheme 19). The coating and functionalization yields were deduced from energy-dispersive X-ray (EDX) analysis, with measurement of the ratio of iron to phosphorus and sulfur signals. Thus it was evaluated that the numbers of molecules of thiols that were grafted were in the range of 100–200 per nanoparticle. Only one thiol, namely hexane-1,6-dithiol, showed an abnormal increase in the grafting (i.e., 860 molecules per nanoparticle), and this result was explained as due to the formation of disulfide bonds between several molecules and/or nanoparticles. In comparison with the same authors’ previous work on a similar nanoplatform using CuAAC chemistry, the use of TYC for functionalization of nanoparticles turned out to be more efficient. Because the nanoplatform was also compatible with the CuAAC procedure, sequential click reactions were carried out on the nanoparticle surface. In a first step, an azido-rhodamine B derivative was grafted by CuAAC, thus inducing a low loading of rhodamine B (about ten molecules per nanoparticle). The second step consisted of the thiol-yne coupling of HS-PEG-COOH onto the remaining alkyne groups. The grafting of this thiol, as evaluated by FTIR and EDX analysis, indicated that approximately 150 molecules per nanoparticle were grafted. It was noted that the presence of the carboxylic group on the surface of the nanoparticle would allow a further functionalization step by, for example, carbodiimide coupling.

Scheme 18. TYC on graphene platform.
A final contribution of TYC to the field of polymer chemistry has to be mentioned before closing this section. In mid-2013 Serrano and Omenat and co-workers reported[55] the preparation of a polymer network by photocrosslinking of a low-molecular-weight thiol-based reagent (i.e., a tetrathiol) with a liquid crystalline dendrimer functionalized with terminal O-propargyl groups. The network obtained showed a liquid crystalline phase at room temperature; it was characterized by optical microscopy, differential scanning calorimetry, and X-ray diffraction.

Conclusions

From the above survey it appears that alkyne hydrothiolation is an effective process for carbon-sulfur bond formation in a completely atom-economical manner. The metal-catalyzed approach offers many options for the formation of valuable intermediates such as vinyl sulfides with high regio- and stereoselectivity. Although this approach has been studied by many groups in very recent years, there is still an ongoing interest in discovering new and simple organometallic complexes as catalysts that can make the process of practical synthetic value and attractive even to researchers who are non-expert in the field. The free-radical approach, however, appears to be of broader scope and utility, because it turned out to be a powerful metal-free tool for bioconjugation and introduction of biomolecule pairs in rigid scaffolds or in functionalized surfaces. The operative simplicity of the photoinduced radical process and the use of simple apparatus are two main features that make this approach of wide application in the fields both of polymer chemistry and bioorganic synthesis. It should be also mentioned that this approach features a wide orthogonality with a multitude of other chemistries, thus making its application possible in the most disparate areas of organic synthesis. In that respect it appears that TYC nicely complements CuAAC as a ligation tool with alkynes (Scheme 20) with the advantage of being a metal-free process exploiting the greenest of all catalysts, such as visible light, and establishing flexible, robust and biologically stable, sterically non-demanding thioether linkages. The only point of TYC that has not so far been considered is the formation of a stereocenter in the final dithioether, which therefore results in a mixture of stereoisomers in 1:1 ratio. Whereas this situation should not affect the properties of a large molecular construction such as a protein or a polymer, it constitutes a limitation on the use of small molecules prepared in this way.

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Metal-catalyzed approaches for the selective preparation of vinyl thioethers (top) and free-radical approaches for the assembly of multifunctionalized constructions (bottom) are surveyed.

Keywords: Alkynes / Hydrothiolation / Radical reactions / Click chemistry / Regioselectivity / Atom economy