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Alkyne Hydrothiolation Catalyzed by a Dichlorobis(aminophosphine) Complex of Palladium: Selective Formation of *cis*-Configured Vinyl Thioethers

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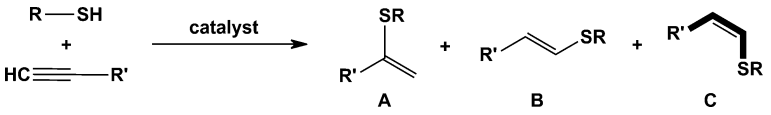
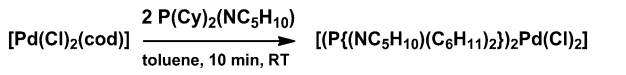
Vinyl sulfides are very important synthetic intermediates in total syntheses and as precursors to a wide range of functionalized molecules. Furthermore, sulfur-containing organic compounds commonly exhibit biological activity, and hence are frequently found in naturally occuring compounds. Moreover, these compounds have found applications in materials science,[1–5] and thus are valuable synthetic targets. The increasing demand for vinyl thioethers expedited the development of new synthetic methods for these target compounds. The most attractive process for their preparation is the (100% atom efficient) alkyne hydrothiolation reaction (Scheme 1).



Scheme 1. General scheme for the transition-metal-catalyzed hydrothiolation of a terminal alkyne with a thiol.

Although few specific cases of selective transformations have been reported for this process under transition-metal-free reaction conditions,[6] the addition of thiols to alkynes (under photochemical or basic conditions) usually lacks stereocontrol of the double-bond geometry, resulting in mixtures of *cis* and *trans anti*-Markovnikov adducts of type **B** and **C** and/or, with specific substrates, proceeding very slowely (even at high reaction temperatures). This means that these reactions are only of very limited practicability. In contrast, transition-metal-catalyzed versions of alkyne hydrothiolation processes often exhibit excellent selectivity, and thus have been successfully applied for selective product formation.[7] For example, whereas the Markovnikov-type vinyl sulfides **A** were selectively formed when alkyne hydrothiolations were catalyzed by $[Pd(OAc)_2]$,[7c,e] [CpNi(NHC)(Cl)] (Cp = cyclopentadienyl; NHC = N-heterocyclic carbene),[7q] oligomeric nickel dithiolate complexes of the form $[\{Ni(SAr)_2\}_n]$,[7r] or $[Tp^*Rh(PPh_3)_2]$ (Tp^* = hydrotris(3,5-dimethylpyrazolyl)borate),[7i–l] selective formation of the *anti*-Markovnikov adducts with a *trans*-configuration (type **B**) has been obtained when $[Rh(Cl)(PPh_3)_3]$[7g,m] or N-heterocyclic carbene based Au^I complexes were applied.[7] However, although desirable, a generally applicable alkyne hydrothiolation catalyst for the high-yielding synthesis of *cis*-configured *anti*-Markovnikov adducts of type **C** has not yet been reported, and hence is the subject of intense investigation within this field of research.[8]

We report herein the catalytic activity of dichloro{bis[1-(dicyclohexylphosphanyl)piperidine]}palladium (**1**),[9] a generally applicable C–C bond-forming catalyst, in the hydrothiolation of alkynes with thiols. $[(P\{(NC_5H_{10})(C_6H_{11})_2\})_2Pd(Cl)_2]$ (**1**) is the first generally applicable alkyne hydrothiolation catalyst that selectively generates *cis*-configured *anti*-Markovnikov adducts of type **C**. The addition products were obtained in excellent yields within a few minutes at 120 °C with *N,N*-dimethylpyrrolidone (NMP) and NaOH as the solvent and base in the presence of only 0.05 mol% of the catalyst, that is, at far lower catalyst loadings than typically applied for this type of reaction. The catalyst was quantitatively prepared within a few minutes by treatment of suspensions of $[Pd(Cl)_2(cod)]$ (cod = cycloocta-1,5-diene) in toluene with two equivalents of 1-(dicyclohexylphosphanyl)piperidine under N_2 at 25 °C (Scheme 2).[9a]



Scheme 2. Synthesis of dichlorobis[1-(dicyclohexylphosphanyl)piperidine]palladium (**1**; Cy = cyclohexyl).

The aminophosphine-based complex **1** was assumed to be an ideal alkyne hydrothiolation catalyst because, in contrast to its phosphine-based analogue, it proved to efficiently promote the formation of palladium nanoparticles. These nanoparticles have been shown to be the catalytically active species in Suzuki, Heck, and cyanation reactions.[9a,c–e] Furthermore, this catalyst can also operate through homogeneous

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mechanisms, as was recently demonstrated to be the case in the Negishi cross-coupling reaction.[9b] Experimental observations clearly indicate that the alkyne hydrothiolation was catalyzed through a molecular mechanism. Consequently, **1** is not only a generally applicable C–C cross-coupling catalyst, but also an efficient catalyst in the hydrothiolation of, for example, acetylenes, providing an initial indication of the general applicability of **1** in C–C and C–X bond-forming reactions.

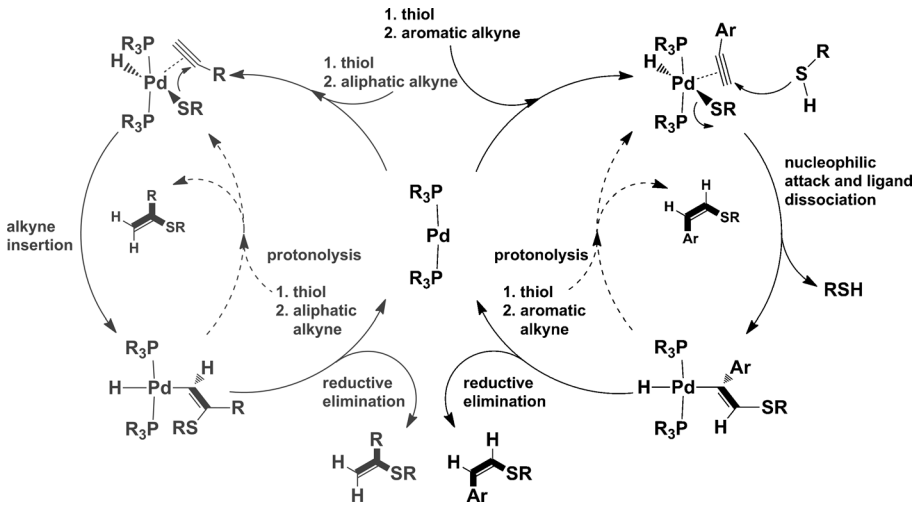
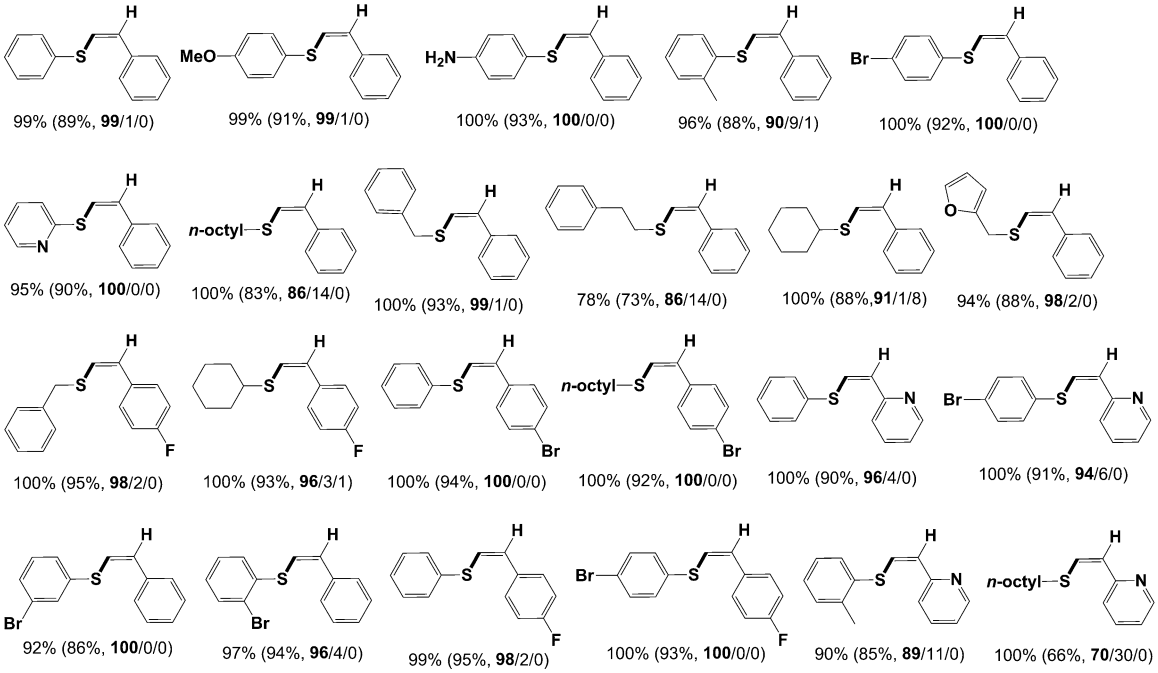


Figure 1. Possible catalytic cycles for alkyne hydrothiolation with aromatic and aliphatic thiols.[12] Aminophosphine dissociation (and re-coordination) may be involved at any of the reactions steps.

Catalysis: Complex **1** is a highly active and reliable hydrothiolation catalyst, which efficiently promotes the nucleophilic attack (Figure 1, right) of a wide range of aromatic, benzylic, and aliphatic thiolates on aromatic alkynes (see Tables 1 and 2) to give the *anti*-Markovnikov-type products **C** cleanly (Scheme 1) with excellent regio- and stereoselectivities, conversion rates, and yields. For example, thermal treatment (120 °C) of thiophenol with ethynylbenzene selectively yielded the *anti*-Markovnikov-type addition product phenyl (*Z*)-2-phenylethenyl sulfide almost quantitatively within only a few minutes.[10] The formation of the *cis*-configured vinyl sulfide was confirmed by ^{1}H NMR spectroscopy, and the spectrum showed two doublet signals due to the olefinic protons at $\delta = 6.90$ and 6.52 ppm with coupling constants of $^3J_{HH} = 11.1$ Hz. Similar selectivities, conversion rates, and product yields were obtained for other aromatic thiols, such as 2-methylbenzenethiol, 4-methoxybenzenethiol, 4-aminobenzenethiol, pyridine-2-thiol, 4-bromobenzenethiol, 3-bromobenzenethiol, and 2-bromobenzenethiol, as well as aliphatic thiols, such as octane-1-thiol, cyclohexanethiol, furan-2-ylmethanethiol, phenylmethanethiol, and 2-phenylethanethiol. To expand

Table 1. Hydrothiolation of aromatic alkynes with aliphatic and aromatic thiols, catalyzed by **1**.[a]



[a] Reaction conditions: alkyne (1.3 mmol), thiol (1.0 mmol), NaOH (1.0 mmol), NMP (2 mL), catalyst (0.05 mol%) in solution (THF), at 120 °C. The conversions and product ratios (*cis*/*trans*/*gem*) were determined by GC/MS and are based on the amount of thiol, as well as by NMR spectroscopy. Isolated yields are given in brackets and were obtained after 15 min of reaction time.

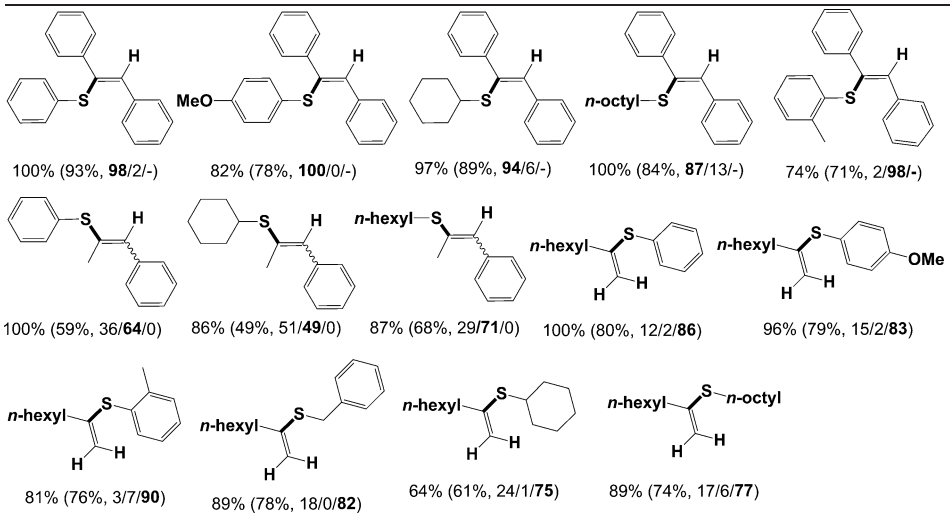
the scope of this process even further, reactions were performed with different aryl-substituted alkynes, including 1-ethynyl-4-fluorobenzene, 1-ethynyl-4-bromobenzene, and 2-ethynylpyridine, for which the *anti*-Markovnikov adducts of type **C** were selectively formed within only 15 min (Table 1) for all of the reactions examined.

Internal alkynes also react with thiols to yield the respective addition products, but require slightly prolonged reaction times (2 h) for high conversions. For example, thermal treatment of 1,1′-ethyne-1,2-diyldibenzene with thiophenol exclusively gave phenyl (*Z*)-2-phenylethenyl sulfide, that is, the addition product with *cis*-configuration, in a yield of 93%. The same stereoselectivity was observed if other thiols were applied in the reaction (Table 2). However, although smooth product formation was noticed, the use of unsymmetrical internal alkynes proceeded with rather modest regioselectivity. For example, thermal treatment of prop-1-yn-1-ylbenzene with thiophenol (or 1-hexanethiol) gave mixtures of phenyl (1*E*)-1-phenylprop-1-en-2-yl sulfide and phenyl (1*Z*)-1-phenylprop-1-en-2-yl sulfide (or hexyl (1*E*)-1-phenylprop-1-en-2-yl sulfide and hexyl (1*Z*)-1-phenylprop-1-en-2-yl sulfide) in a ratio between 1:1 and 2:1, in favor of the less-hindered isomer, most probably due to a change in the mechanism (for details of the formation of different addition products through the alkyne insertion mechanism and the nucleophilic attack, see Figure 1).

On the other hand, if aliphatic alkynes (e.g., 1-octyne) were thermally treated with thiols, the branched Markovnikov-type addition products **A**, which are susceptible to isomerization, were favorably formed (≈80%). The striking difference in product selectivity obtained with aliphatic alkynes is most probably due to their lower ligating tendency, favoring, in contrast to aromatic alkynes, insertion into the Pd–S bond (Figure 1, left) over nucleophilic attack (Figure 1, right).

The reaction mechanisms described herein are assumed to operate in these reactions. Both, the alkyne insertion mechanism and the nucleophilic attack are initiated by the oxidative addition of a thiol to the metal center of bis[1-(dicyclohexylphosphanyl)piperidine]palladium(0) (**2**), which is generated by the reaction of **1** with OH^-.[11] This results in the formation of the respective thiolate hydride complexes, and is followed by alkyne coordination. Whereas a subsequent nucleophilic attack affords the palladium hydride vinyl sulfide intermediate when aromatic alkynes were used, migration into the Pd–S bond is favored for aliphatic alkynes. Reaction steps involving *cis*/*trans* isomerization of vinyl sulfides, however, have been excluded because the transformation of phenyl (*Z*)-2-phenylethenyl sulfide into its *E* isomer by thermal treatment (under the reaction conditions applied for the catalysis) was not observed. Reductive elimination (or an eventual protonolysis) yields the addition products and regenerates the catalyst for both mechanisms. Although not explicitly mentioned, aminophosphine dissociation and re-coordination may be involved at any of the reaction steps. However, initial formation of complex **2** by reaction of **1** with OH^- gained strong experimental support: whereas the conversion rates and product selectivities remain the same for all types of substrate when alkyne hydrothiolation reactions are catalyzed by **1** in the presence of only 10 mol% of the base, mixtures of all possible addition products and their isomers are formed with aliphatic alkynes in the absence of base. This is most probably due to product formation by both the alkyne insertion mechanism and the nucleophilic attack mechanism.[12] Even more importantly, complex **2** is an excellent alkyne hydrothiolation catalyst, showing the same catalytic activity and product selectivity with both aliphatic and aromatic substrates as complex **1**, even in the absence of base. Furthermore, treatment of **2** with phenylmethanethiol, for example, instantly yielded the respective hydride thiolate palladium(II) complex $[(P\{(NC_5H_{10})(C_6H_{11})_2\})_2Pd(H)(SCH_2C_6H_5)]$ (**3**) at 25°C as proposed in the catalytic cycle. Significantly, complex **3** also shows the same catalytic performance and product selectivity, in the presence and absence of base, as **1** and **2**.[13] Finally, molecular mechanisms do indeed operate, as the involvement of palladium nanoparticles has been excluded (see below).

Table 2. Hydrothiolation of aliphatic (terminal), as well as internal alkynes with thiols, catalyzed by **1**.[a]



[a] Reaction conditions: alkyne (1.3 mmol), thiol (1.0 mmol), NaOH (1.0 mmol), NMP (2 mL), catalyst (0.05 mol%) in solution (THF), at 120°C. The conversions and product ratios (*cis*/*trans*/*gem*) were determined by GC/MS and are based on the amount of thiol, as well as by NMR spectroscopy. Isolated yields are given in brackets and were obtained after 15 min when the reactions were performed with terminal alkynes and after 2 h with internal alkynes.

Mechanistic investigations: The following experimental observations clearly indicate that a molecular mechanism operates in this reaction:[14] 1) Neither sigmoidal-shaped kinetics with induction periods, which are characteristic of metallic particle formation, nor autocatalytic surface growth that can lead to soluble monodisperse nanoclusters (or insoluble bulk-metal formation) have been observed.[15] In contrast, approximately 70% of the product formation was typically observed within one minute. 2) The presence of a large excess of metallic mercury in reaction mixtures of the thiol, alkyne, and catalyst had no effect either on the rate of conversion or on the product yields. The same observations were made if poly(4-vinylpyridine) (PVPy; 2% cross-linked with divinylbenzene) was added instead.[16] 3) No effect on the conversion rates or on the product yields was observed if 0.1 or 0.5 equivalents (relative to the catalyst) of thiophene, CS_2 or PPh_3 were present in the reaction mixtures. 4) No evidence of the presence of palladium nanoparticles was obtained from UV/Vis spectra of the reaction mixtures.[17] Lastly, 5) The catalytic activities of the aminophosphine-based complexes $[(P\{(NC_5H_{10})_{3-n}(C_6H_{11})_n\})_2Pd(Cl)_2]$ (with $n=0$–2) are comparable, whereas a slightly lower level of activity was found for their phosphine-based analogue, providing a very strong indication that a molecular mechanism operates.[18]

In conclusion, dichlorobis[1-(dicyclohexylphosphanyl)piperidine]palladium, $[(P\{(NC_5H_{10})(C_6H_{11})_2\})_2Pd(Cl)_2]$ (**1**), a generally applicable C–C bond-forming catalyst is one of the most effective and versatile alkyne hydrothiolation catalysts. Moreover, complex **1** is the first generally applicable system that converts aromatic alkynes and aliphatic or aromatic thiols into *cis*-configured *anti*-Markovnikov-type vinyl thioethers in excellent yields within a few minutes at 120°C, in the presence of only 0.05 mol% of catalyst. In addition, the alkyne hydrothiolation reaction is tolerant of a broad range of functional groups, including ethers, amines, halides, and nitrogen-containing heterocycles. Thus it demonstrates the outstanding catalytic activity, selectivity, and hence, general applicability of complex **1** in this process, making the aminophosphine-based system the catalyst of choice for the high-yielding synthesis of *cis*-configured *anti*-Markovnikov adducts of type **C** through hydrothiolation of aromatic alkynes. On the other hand, branched Markovnikov-type addition products **A** were selectively formed if aliphatic alkynes were applied in the reaction. Mechanistic investigations indicate that a molecular mechanism operatates in the alkyne hydrothiolation with initial formation of bis[1-(dicyclohexylphosphanyl)piperidine]palladium(0), $[(P\{(NC_5H_{10})(C_6H_{11})_2\})_2Pd]$. Moreover, the ligating properties of the alkyne were found to deterime the course of the reaction, that is, whether the alkyne insertion mechanism or the nucleophilic attack operate, and hence, the regio- and stereoselectivity of the addition products.

Acknowledgements

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Keywords: alkynes · aminophosphines · *cis* selectivity · C–S bond formation · hydrothiolation · reaction mechanisms

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[8] To be more precise, some rhodium- and iridium-based complexes have been screened in the hydrothiolation of phenylacetylene with thiophenol, of which some complexes were found to give the *cis*-configured *anti*-Markovnikov adducts (**C**) as the major product (see: S. Burling, L. D. Field, B. A. Messerle, K. Q. Vuong, P. Turner, *Dalton Trans.* **2003**, 4181). In addition, individual reports of related reactions have been published, which selectively yield the *cis*-configured vinyl sulfides **C**: Wang and co-workers, for example, reported the synthesis of (*Z*)-1-alkenyl sufides through copper-catalyzed alkyne hydrothiolation with diaryl disulfides in the presence of large amounts of sodium hydroxymethylsulfinate as a radical initiator (see: Z.-L. Wang, R.-Y. Tang, P.-S. Luo, C.-L. Deng, P. Zhong, J.-H. Li, *Tetrahedron* **2008**, *64*, 10670). Another recently introduced reaction is the copper-catalyzed decarboxylative thiolation of arylpropiolic acids, which selectively gives (*Z*)-vinyl sulfides in high yields after 24 h at 90 °C in NMP and $CsCO_3$ as the solvent and base (see: S. Ranjit, Z. Duan, P. Zhang, X. Liu, *Org. Lett.* **2010**, *12*, 4134).

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[10] It is important to note that although very slow (≈90% conversion after 24 h at 120 °C), the *anti*-Markovnikov addition products of type **C** were selectively formed when phenylacetylene was allowed to react with thiophenol or *n*-octanethiol in the presence of a base under catalyst-free reaction conditions. Moreover, alkyne hydrothiolation reactions (catalyzed by **1**) also proceed at ambient reaction temperatures. For example, the addition of thiophenol to ethynylbenzene was complete after one hour; the product selectivity, however, was significantly lower, with 65% formation of the *anti*-Markovnikov addition product of type **C**, and hence is of very limited practicability.

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[12] This is in contrast to hydrothiolation reactions performed with aromatic alkynes, which are also highly regioselective in the absence of a base and therefore still give the addition products of type **C** as the major product, although with a slightly reduced stereoselectivity. This observation confirms the highly ligating properties of aromatic alkynes and supports a nucleophilic attack mechanism, but also indicates that complex **1** may be involved in the catalytic cycle (at least in the first few cycles) in the absence of base. However, the formation of thiolate complexes of the type $[(P\{(NC_5H_{10})(C_6H_{11})_2\})_2Pd(Cl)(SR)]$ or $[(P\{(NC_5H_{10})(C_6H_{11})_2\})_2Pd(SR)_2]$ (accompanied by HCl liberation), or oligomeric palladium dithiolate complexes cannot be excluded during catalysis.[7g] In contrast, their formation seems possible because it was confirmed that complexes of the type $[(P\{(NC_5H_{10})(C_6H_{11})_2\})_2Pd(SR)_2]$ gave the same catalytic activity, as well as product selectivity, as complex **1**.[13]

[13] It should be noted that the formation of dithiolate–bis(aminophosphine) complexes during catalysis, possibly by reaction of the hydride thiolate complexes with another thiol molecule (accompanied by formation of H_2), is highly probable, given that bis(phenylmethanethiolate){bis[1-(dicyclohexylphosphinyl)piperidine]}palladium(II) (**4**), for example, was found to be an efficient alkyne hydrothiolation catalyst, showing exactly the same activity and product selectivity with aromatic and aliphatic substrates (even in the absence of base) as **1**, (**2**), and **3**. Moreover, whereas H_2 generation was indeed detected by gas chromatography in all reactions tested (with both aliphatic and aromatic alkynes) with **1** in the presence of base, **2**, and **3**, no H_2 formation was detected for reactions with **1** in the absence of base (similar to the mechanism proposed by Ogawa and co-workers).[7g]

[14] For a comprehensive review article about the problem of distinguishing true homogeneous catalysis from soluble or other metallic particle heterogeneous catalysis under reducing conditions, see: J. A. Widegren, R. G. Finke, *J. Mol. Catal. A: Chem.* **2003**, *198*, 317.

[15] For details, see: a) M. A. Watzky, R. G. Finke, *J. Am. Chem. Soc.* **1997**, *119*, 10382; b) J. A. Widegren, M. A. Bennett, R. G. Finke, *J. Am. Chem. Soc.* **2003**, *125*, 10301.

[16] PVPy is a palladium trap that can effectively inhibit catalysis when nanoparticles are the catalytically active form of a catalyst. Nevertheless, it should be mentioned that Pd nanoparticles immobilized on PVPy spheres have also been applied as the catalyst in Heck reactions. Therefore, this test is not definitive and neither conclusively proves nor rules out either catalysis by the surface of Pd nanoparticles or molecular Pd^0 species, but can strongly support the conclusions drawn from other tests. For details, see: K. Yu, W. Sommer, M. Weck, C. W. Jones, *J. Catal.* **2004**, *226*, 101, and references therein.

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[18] The steric bulk of the aminophosphine-based ligands 1,1′,1″-(phosphanetriyl)tripiperidine, 1,1′-(cyclohexylphosphanediyl)dipiperidine, 1-(dicyclohexylphosphanyl)piperidine, and tricyclohexylphosphine is almost identical, as are their σ-donor strengths (as indicated by the CO stretching frequency of complexes of the type *cis*-$[(PR_3)(NC_5H_{10})Mo(CO)_4]$,[19] which is indicative of the electron density at the metal centers).[9e] Thus, similar catalytic activities are expected to be obtained when molecular mechanisms are the mode of action, whereas a dramatic difference in their performance should be obtained when palladium nanoparticles are involved in the catalytic cycle (compare with results obtained for these catalysts in the Heck, Suzuki, and Negishi reactions).[9a,b,e]

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Homogeneous Catalysis

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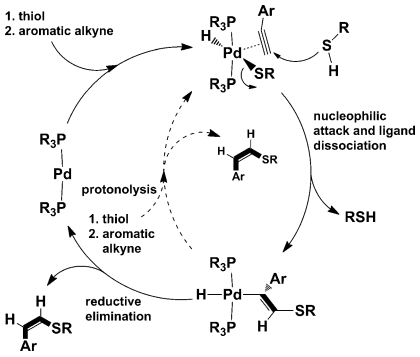
Alkyne Hydrothiolation Catalyzed by a Dichlorobis(aminophosphine) Complex of Palladium: Selective Formation of *cis*-Configured Vinyl Thioethers



***Cis* all round**: Dichlorobis[1-(dicyclohexylphosphanyl)piperidine]palladium, $[(P\{(NC_5H_{10})(C_6H_{11})_2\})_2Pd(Cl)_2]$, is a highly efficient alkyne hydrothiolation catalyst and the first generally applicable system that selectively generates *cis*-configured *anti*-Markovnikov adducts in excellent yields within only a few minutes at 120 °C in the presence of only 0.05 mol % of the catalyst (see scheme).