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First Evidence for the Use of Organosilver Compounds in Pd-Catalyzed Coupling Reactions; A Mechanistic Rationale for the Pd/Ag-Catalyzed Enyne Synthesis?

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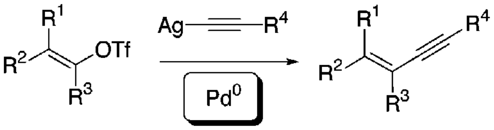
ABSTRACT



Silver acetylides have been prepared and used in Pd-catalyzed coupling reactions. Enynes have thus been obtained in good yields. This work demonstrates that organosilver compounds could enter the Pd catalytic cycle; it also supports the role of silver acetylides as intermediates in the new Pd/Ag-catalyzed coupling reaction.

In connection with the synthesis of enyne natural products,[1,2] especially those bearing ene- and dienediyne moiety such as NCS-Chrom[3] and related members,[4,5] we are currently investigating coupling reactions. We recently demonstrated that a new set of catalysts based on silver and palladium complexes is efficient for the coupling of sensitive vinyl triflates and acetylenes.[6,7] To get a better understanding of this new coupling reaction, we looked for the formation of intermediates in this process. In this communication, we present preliminary results that demonstrate that silver acetylides could be such intermediates. As shown here, silver acetylides can indeed react with in situ formed vinyl-palladium species, yielding substituted enynes.

Sp-sp^2 coupling reactions, the so-called Sonogashira−Linstrumelle reaction, require palladium as catalyst and copper as a cocatalyst.[8] Our use of silver ion as cocatalyst

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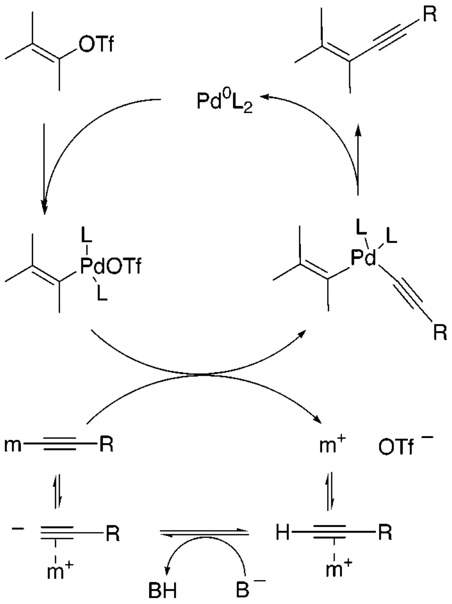
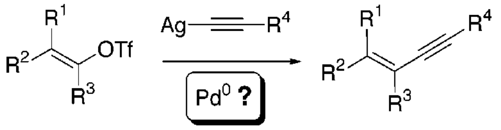
in such coupling reactions was based on the similarities between silver and copper.[6,7,9] We therefore thought that the mechanism of both processes should be closely related. Although some steps remain unclear in the Sonogashira−Linstrumelle reaction, a broad mechanism involving the formation of copper acetylides and then a transmetalation with an organopalladium species is usually proposed[10] for the Pd-catalytic cycle (Scheme 1, top, m = Cu). The copper catalytic cycle is far less known.[11] On the basis of what is known and what we learned from silver and alkyne interactions, the steps depicted in Scheme 1 (bottom, m = Cu or Ag) can nevertheless be proposed for the Cu- or Ag-catalytic cycle. Coordination of alkenes or alkynes to silver is well-known;[12] such coordination activates the alkyne toward nucleophilic addition[13] or deprotonation.[14]

Scheme 1



In the latter, a zwitterion should be formed, but it would rapidly rearrange to the more stable silver acetylide. Once formed, copper acetylides are known to enter the palladium catalytic cycle at the transmetalation step as other organometallics. However, as far as we are aware of, nothing is known about the ability of silver acetylides to be involved into the palladium catalytic cycle. To check this assumption, we prepared several silver acetylides and attempted to have them react with vinyl triflates in the presence of a palladium source. Various attempts to obtain the silver derivative of 1-hexyne gave white-gray solids,[15] the spectroscopic data of which indeed corresponded to the acetylide. However, elemental analysis revealed the actual formation of complexes between silver *n*-butylacetylide and the salt used for its formation (e.g., **1a**, Table 1).[16] The use of these complex silver acetylides did not allow for coupling with vinyl triflates whatever the conditions used (e.g., Table 1, entries 1 and 2). Using a slight modification of a reported procedure,[15] pure silver *n*-butylacetylide **2**[17,18] was obtained as a stable gray solid soluble in organic solvents. This acetylide is not able by itself to induce any coupling reaction with 4-*tert*-butylcyclohex-1-enyl triflate (entry 3); however, put in the presence of $Pd(PPh_3)_4$, it underwent a smooth transformation giving the expected 4-*tert*-butyl-1-(hex-1′-ynyl)cyclohex-1-ene **6**[7] (entries 4−7).[19]

Scheme 2



The conversion and the yield of coupling product proved to be very sensitive to the relative amount of reagents used. A quantity of 0.1 equiv of $Pd(PPh_3)_4$ gave a modest yield (entry 4) even after prolonged time, while the reaction became nearly quantitative and exceedingly rapid with 0.5 equiv (entry 5). From the other sources of palladium

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(8) Sonogashira, K. In *Comprehensive Organic Chemistry*; Fleming, I., Trost, B. M., Eds; Pergamon: Oxford, 1991; Vol. 3, pp 521−549.

(9) The occurrence of copper acetylides has been suggested as in situ formed intermediates in Sonogashira−Linstrumelle reactions. We thus looked for less nucleophilic intermediates in order to avoid side reactions observed with sensitive triflates and acetylenes; see refs 6 and 17.

(10) A simplified version of the Pd-catalytic cycle has been drawn for convenience. Cationic palladium species having the triflate as counterion and/or anionic pentacoordinated palladium complexes are probably involved in this cycle. For more details, see: Amatore, C.; Jutand, A.; Suarez, A. *J. Am. Chem. Soc.* **1993**, *115*, 9631−9641. Jutand, A.; Mosleh, A. *Organometallics* **1995**, *14*, 1810−1817.

(11) To our knowledge, no details are so far available for the mechanism of the copper catalysis in these reactions.

(12) Noltes, J. G.; Van Koten, G. In *Comprehensive Organometallic Chemistry I*; Wilkinson, G., Abel, E. W., Stone, F. G. A., Eds; Pergamon: Oxford, 1982; Vol. 2, p 709. Van Koten, G.; James, S. L. Jastrzebski, J. T. B. H. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds; Pergamon: Oxford, 1995; Vol. 3, p 57.

(13) (a) Pale, P.; Chuche, J. *Tetrahedron Lett.* **1987**, *28*, 6447−6448. (b) Dalla, V.; Pale, P. *Tetrahedron Lett.* **1994**, *35*, 3525−3528. (c) Dalla, V.; Pale, P. *New J. Chem.* **1999**,*23*, 803−805. (d) Pale, P.; Chuche, J. *Eur. J. Org. Chem.* **2000**, 1019−1025.

(14) Lewandos, G. S.; Maki, J. W.; Ginnebaugh, J. P. *Organometallics* **1982**, *1*, 1700. In situ formed silver acetylides can also be trapped by halogen; see: Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 727−728.

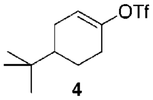
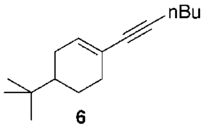
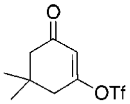
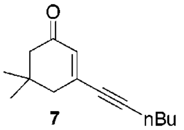
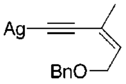
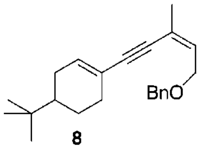
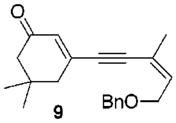
(15) Travkin, I. *J. Gen. Chem. USSR (Engl. Transl.)* **1976**, *46*, 1081. Davis, R. B.; Scheiber, D. H. *J. Am. Chem. Soc.* **1956**, *78*, 1675−1678.

(16) When 1-hexyne is added to a solution of silver nitrate or triflate in acetone−water, a solid rapidly appeared, the elemental and spectroscopic analysis of which corresponded to a mixed silver acetylide−salt complex: $AgNO_3{\cdot}AgC{\equiv}CC_4H_9$ or $AgOTf{\cdot}AgC{\equiv}CC_4H_9$. The silver acetylide−silver nitrate has already been isolated; see: Chevastelon, R. *C. R. Acad. Sci.* **1897**, *124*, 1364.

(17) Bertus, P. thèse de doctorat, Université de Reims-Champagne-Ardenne, Reims, 1997. **General Procedure.** Silver nitrate (2.1 equiv) was suspended in a mixture of water (3 M) and methanol (5 M). To this suspension kept in the dark was dropwise added an aqueous ammoniac solution until the solution was homogeneous, and then the alkyne (1 eq) was added. A white solid rapidly formed, which was filtered off. The solid was then washed with water and dried under vacuum. The solid so obtained (85−95% yield) must be preserved from light but is not air sensitive; it is readily soluble in organic solvents.

(18) Selected data for **2**: NMR ^1H (200 MHz, $CDCl_3$) 0.94 (3H, t, J = 7.2), 1.46 (2H, m), 1.66 (2H, m), 2.48 (2H, t, J = 7.3); NMR ^{13}C ($CDCl_3$) 13.6 (q); 21.7 (t), 22.4 (t), 31.8 (t), 80.2 (s), 129.9 (s); IR (KBr): 2041, 1458, 1290, 1246, 1103, 1032. Anal. Calcd for C_6H_9Ag: C, 38.1; H, 4.7. Found: C, 35.5; H, 4.3; N, 0.5.

Table 1. Coupling of Silver Acetylides

Entry	Silver Acetylide	Triflate	Catalyst	Solvent	Time	Yield	Enyne
1	$AgNO_3.Ag-\equiv-nBu$ **1a**	 **4**	0.1eq $Pd(PPh_3)_4$	DMF	24h	0%	–
2			0.5eq $Pd(PPh_3)_4$	DMF	24h	0%	–
3	$Ag-\equiv-nBu$ **2**	"	none	DMF	24h	0%	–
4	"	"	0.1eq $Pd(PPh_3)_4$	DMF	24h	30%	 **6**
5	"	"	0.5eq $Pd(PPh_3)_4$	DMF	5mn	98%	
6	"	"	0.5eq $Pd(OAc)_2$ + 1eq PPh_3	DMF	40mn	52%	
7	"	"	0.5eq $Pd(PPh_3)_4$	MeCN	1h	15%	
8	"	"	0.5eq $Pd(PPh_3)_4$	Et_2O	4h	37%	
9	"	 **5**	0.1eq $Pd(PPh_3)_4$	DMF	24h	5%	 **7**
10	"		0.5eq $Pd(PPh_3)_4$	DMF	1h	78%	
11	"		0.5eq $Pd(PPh_3)_4$	MeCN	1h	53%	
12	"		0.5eq $Pd(PPh_3)_4$	Et_2O	4h	67%	
13	 **3**	**4**	0.5eq $Pd(PPh_3)_4$	DMF	2h	49%	 **8**
14	"	"	0.5eq $Pd(PPh_3)_4$	MeCN	1.5h	53%	
15	"	"	0.5eq $Pd(PPh_3)_4$	Et_2O	15mn	14%	
16	"	**5**	0.5eq $Pd(PPh_3)_4$	DMF	1h10	44%	 **9**
17	"	"	0.5eq $Pd(PPh_3)_4$	MeCN	15mn	77%	
18	"	"	0.5eq $Pd(PPh_3)_4$	Et_2O	10	66%	

investigated, palladium acetate together with triphenylphosphine, a mixture known to produce an active zerovalent palladium species,[20] is the only one really effective for this coupling. Here again, 0.5 equiv of palladium is required to get an acceptable yield of enyne (entry 6). With $Pd(PPh_3)_4$, changing the solvent dramatically affected the reaction efficiency. In acetonitrile or ether, the formation of coupling product was slower although the starting triflate was consumed in a few hours (entry 7 or 8, respectively). These variations suggest a rather slow transmetalation step since the oxidative addition step with vinyl triflates is known to be a fast process.[21]

Similar trends were observed when the same silver acetylide was reacted with the triflate derived from dimedone **5** (entries 9−12). Almost no reaction occurred in the presence of 0.1 equiv of $Pd(PPh_3)_4$ (entry 9), but a rapid reaction and a good yield were observed in the presence of 0.5 equiv of $Pd(PPh_3)_4$ (entry 10). Again, acetonitrile and ether instead of DMF as solvent decreased the efficiency, although less dramatically as in the case of **1** (entries 11 and 12).

It is puzzling that one-half of an equivalent of zerovalent palladium species gives the best results. However, such amount leads to a silver−palladium ratio of 2 to 1, and it is interesting to note that the same ratio between silver and palladium was also found as the best one for optimal results in the catalytic version.[22]

Silver acetylides bearing functional groups behave in the same way. Using the same procedure as for 1-hexyne, benzylated (*Z*)-3-methylpent-2-en-4-ynol could be converted into the corresponding silver acetylide **3**. Submitted to the conditions mentioned above, this acetylide gave the expected coupling products **8**, **9** (entries 13−18). Surprisingly, modest yields were achieved with either unfunctionalized or functionalized triflates when the reaction was conducted in DMF (**4** or **5**; entries 13 and 16, respectively). In ether, quite different results were obtained depending on the triflate nature. A very fast and efficient coupling was achieved with **5** (entry 18), while poor yield was obtained with **4** (entry 15). With the silver acetylide **3**, acetonitrile proved to be the best solvent choice, giving coupling products rapidly and efficiently (entries 14 and 17). These discrepancies may

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(19) **General Procedure.** To a triflate solution (1 equiv, 0.02 M) kept under argon and in the dark were successively added tetrakis(triphenyl) phosphine (0.5 equiv) and the required silver acetylide (1.2 equiv). The resulting solution rapidly darkened. After the disappearance of one of the reagents (see Table 1), ether was added, followed by a saturated aqueous solution of ammonium chloride. The mixture was then filtered, and the two layers were separated. The aqueous layer was extracted three times with ether. The combined organic layers were then washed three times with water, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude enyne was then purified by chromatography.

(20) Amatore, C.; Jutand, A.; Amine M'Barki, M. *Organometallics* **1992**, *11*, 3009−3013.

(21) Stang, P.; Kowalski, M. H.; Schiavelli, M. D.; Longford, D. *J. Am. Chem. Soc.* **1989**, *111*, 3347−3356.

(22) Bertus, P.; Pale, P. Unpublished results, see also refs 6, 7, and 17.

reflect the difference in coordination ability of each solvent, which may affect the reactivity of the organosilver species.

These results clearly show that silver acetylides can enter palladium-catalyzed reactions as various other organometallics do. Such silver organometallics can therefore be intermediates in the palladium/silver-catalyzed coupling reaction we already described.[6,7] Therefore, the present results strongly favor a mechanism in which in situ generated silver acetylides react with organopalladium species in the new Pd/Ag-catalyzed coupling reaction.[6,7]

Together with its relevance to mechanistic studies, the process described here with silver acetylides is interesting because it cleanly yields to sensitive polyunsaturated compounds. This process can thus be helpful for solving synthetic problems occurring with complex or sensitive molecules.

Further works are now in progress to delineate further the in situ formation of silver acetylides and the mechanism of the Pd/Ag-catalyzed coupling reaction. Expanding the scope of silver organometallics in coupling reactions is also under investigations.

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