OBC
www.rsc.org/obc

Palladium-catalyzed addition of disulfides and diselenides to alkynes under solvent free conditions†

Valentine P. Ananikov*[a] **and Irina P. Beletskaya***[b]
[a] *Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky Prospect 47, Moscow, 119991, Russia. E-mail: val@ioc.ac.ru; Fax: +007 (095) 1355328*
[b] *Lomonosov Moscow State University, Chemistry Department, Vorob'evy gory, Moscow, 119899, Russia. E-mail: beletska@org.chem.msu.ru; Fax: +007 (095) 9393618*

Received 10th October 2003, Accepted 16th December 2003
First published as an Advance Article on the web 19th December 2003

An efficient methodology was developed for performing palladium-catalyzed E–E (E = S, Se) bond addition to alkynes under solvent free conditions. Compared to reaction in solvent significant enhancement of reaction rate, improved efficiency and remarkable catalyst stability were observed under solvent free conditions. The addition reactions were carried out with high stereoselectivity and yields in a short reaction time.

Nowadays development of organic synthesis is focused on environmentally friendly procedures with fewer toxic substances involved. Special attention is paid to minimize quantity of organic solvents used in the reaction, since very often organic solvents are ecologically harmful and flammable. In addition, using large quantities of solvents gives rise to waste removal concern.

Undoubtedly, solvent free organic synthesis is the best eco-friendly methodology to overcome the above problems.[1] Very often performing the reaction under solvent free conditions requires applying microwaves to bring additional energy to the system. Many examples of microwaves assisted solvent free organic synthesis procedures have already been published.[2] In contrast, transition metal catalyzed solvent free methodology is at the beginning stage of development and encounters several difficulties due to the multicomponent nature of the system. In this case excluding solvents also has an economical benefit, since transition metal catalyzed transformations usually require rigorously dried and purified solvents treated under an inert atmosphere. At the moment solvent free methodology has been successfully applied to cross-coupling reactions: Suzuki coupling,[3] Heck reaction,[4] and C–N bond formation.[5] However, to the best of our knowledge no studies have been published concerning transition metal catalyzed addition reactions to unsaturated species under solvent free conditions.

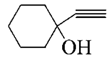
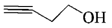
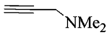
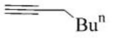
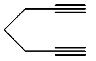
The addition reactions are performed with 100% atom efficiency with no waste materials formed. In particular, E–E bond addition to alkynes is a recognized tool for modern organic and element-organic synthesis.[6] A very efficient palladium catalyzed S–S and Se–Se bond addition reaction to alkynes has been developed leading to *Z*-substituted alkenes with high stereoselectivity.[7] The addition reaction represents a convenient single stage way of two carbon-element bond formations and leads to important products required in synthetic organic chemistry[8] and materials science.[9] Recently we have studied the mechanism of the E–E (E = S, Se) addition reaction to alkynes and have found that the catalytic cycle involves dinuclear palladium complexes (Scheme 1).[10]

Continuing our recent studies we have developed a new synthetic approach to palladium catalyzed S–S and Se–Se bond addition to alkynes under solvent free conditions. Besides economical and ecological advantages the approach is superior in respect of higher reaction rate and better catalyst efficiency.

The present study is the first example of a transition metal catalyzed addition reaction under solvent free conditions.

The key point of the solvent free reaction is the presence of an excess of phosphine ligand (entries 1, 2; Table 1). In the absence of an excess of PPh_3 rapid polymerization of

Table 1 Catalytic Ar_2E_2 addition to alkynes under solvent free conditions

Entry	Ar_2E_2	Alkyne	Conditions[a]	Yield[b], %
1	Ph_2S_2	**1-A**  **1-A**	80 °C, 8 h	0[c]
2	Ph_2S_2	**1-A**	80 °C, 8 h	99 (90)
3	Ph_2S_2	**1-B**  **1-B**	80 °C, 8 h	99 (90)
4	Ph_2S_2	**1-C**  **1-C**	80 °C, 8 h	98 (85)
5	Ph_2S_2	**1-D**  **1-D**	80 °C, 8 h	97 (80)
6	Ph_2S_2	**1-E**  **1-E**	80 °C, 8 h	96 (85)
7	Ph_2S_2	**1-A**	100 °C, 2 h	99 (90)
8	Ph_2S_2	**1-B**	100 °C, 2 h	99 (90)
9	Ph_2S_2	**1-C**	100 °C, 2 h	99 (85)
10	Ph_2S_2	**1-D**	100 °C, 2 h	98 (80)
11	Ph_2S_2	**1-E**	100 °C, 2 h	97 (85)
12	Ph_2 Se_2	**1-B**	100 °C, 2 h	96 (87)
13	Ph_2Se_2	**1-C**	100 °C, 2 h	97 (80)
14	$(p\text{-MePh})_2Se_2$	**1-B**	100 °C, 2 h	95 (85)
15	$(p\text{-FPh})_2Se_2$	**1-B**	100 °C, 2 h	95 (85)

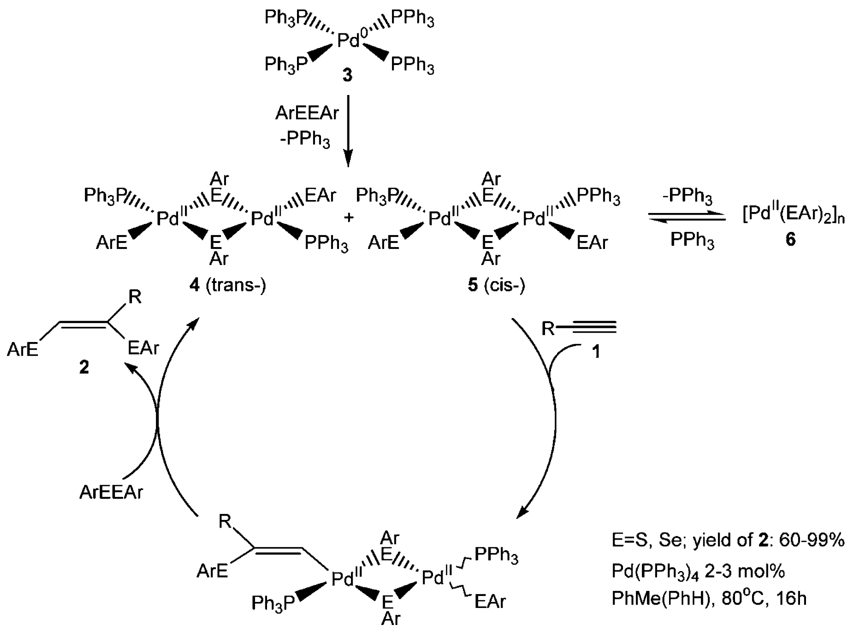
[a] The reactions were performed in 1 mmol scale.[11] [b] Determined with NMR spectroscopy, the isolated yield is given in parentheses;[12] in all cases *Z*/*E* > 97 : 3 was observed. [c] The reaction was carried out with 1 mol% of $Pd(PPh_3)_4$ without addition of PPh_3.

---

† Electronic supplementary information (ESI) available: full experimental details of synthetic procedure, compound separation and purification, details of spectroscopic studies, kinetic measurements and compound characterization. See http://www.rsc.org/suppdata/ob/b3/b312471a/

DOI: 10.1039/b312471a

This journal is © The Royal Society of Chemistry 2004



Scheme 1

the palladium catalyst is observed resulting in a dark brown precipitate insoluble in common organic solvents (**6**, Scheme 1).

Under the reaction conditions at 80 °C (or higher) both Ph_2S_2 and PPh_3 are molten and $Pd(PPh_3)_4$ can be easily dissolved in the Ph_2S_2/PPh_3 melt. An excess of PPh_3 prevents precipitate formation and results in a homogeneous melt. Therefore, stirring is no longer needed for the system. The addition process was performed under very simple reaction conditions in a sealed tube. Excellent yields were obtained for various alkynes (entries 2–5; Table 1). No difference in the product yield was observed in the reactions performed under an inert atmosphere or under air. Due to quantitative conversion and the absence of solvent product separation is much simplified as well. In fact, filtering out palladium complex and PPh_3 on silica or a rapid flash chromatography[13] suits very well for most of the cases studied.

With 1 mol% of the catalyst and 15 mol% of PPh_3 heating at 80 °C for 8 h results in quantitative product yields for several alkynes with various functional groups (entries 2–5; Table 1). Under these conditions two equivalents of Ph_2S_2 can be added to hepta-1,6-diyne with 96% product yield (entry 6; Table 1). A significant acceleration of the reaction under solvent free conditions makes it possible to achieve quantitative yields with 1 mol% of catalyst in 8 h (entries 2–6; Table 1), while the same reaction in solvent requires 12–16 h of heating and 2–3 mol% of the catalyst.[7,10] Increasing the temperature to 100 °C allows quantitative yields to be achieved after 2 h of reaction time. We have shown that Se–Se is less reactive toward alkynes in the palladium catalyzed reaction in solvent compared to the S–S bond.[10] However, the difference in reactivity is less apparent under solvent free conditions, both S–S (entries 7–11) and Se–Se bonds (entries 12–15, Table 1) quantitatively adding to alkynes. In all cases studied, the addition proceeds in a *syn*-manner with high stereoselectivity leading to *Z*-configuration of the products (entries 2–15; Table 1).[14]

For complete utilization of sulfur- and selenium-containing species Ar_2E_2 : alkyne = 1 : 1.5 ratio should be used. Changing the color of reaction mixture from dark-brown to orange or yellow indicates the completion of the reaction. In this case $Pd(PPh_3)_4$ is released at the end of the addition process.

A detailed NMR study of the catalytic reaction has shown a significant acceleration of Ph_2S_2 addition to the triple bond of **1-B** in the solvent free conditions (Table 2).

Table 2 Catalytic Ph_2S_2 addition to **1-B** under solvent free conditions and in solvent[a]

Entry	Total reaction volume, ml	Solvent added,[b] ml	Yield,[c] %	$t_{1/2}$,[d] h
1	0.6	—	66	1.5
2	2.0	1.4	25	4.2
3	5.0	4.4	14	7.6

[a] The reactions were performed in 1 mmol scale at 80 °C with 1 mol% of $Pd(PPh_3)_4$ and 15 mol% PPh_3. [b] Toluene was used as a solvent. [c] Measured with NMR spectroscopy after 2 h of reaction. [d] Time needed for 50% conversion of Ph_2S_2.

Table 3 Temperature dependence of the yields of **2-B** under solvent free conditions[a]

Entry	Temperature, °C	Time, min	Yield,[b] %
1	80	120	66
2	80	270	91
3	80	450	99
4	100	15	63
5	100	30	92
6	100	60	99
7	120	5	99
8	140	<3	99

[a] The reactions were performed in 1 mmol scale with 1 mol% of $Pd(PPh_3)_4$ and 15 mol% of PPh_3. [b] Measured with NMR spectroscopy; in all cases $Z/E > 97 : 3$ was observed.

A typical 1 mmol scale setup[11] results in a reaction volume of about 0.6 ml under the solvent free conditions (entry 1; Table 2). Adding as little as 1.4 and 4.4 ml of solvent dramatically decreases the reaction rate by factors of approximately 3 and 5, respectively (entries 2, 3; Table 2). Obviously, reaction rate enhancement under solvent free conditions originates from the concentration effect.

The rate of catalytic Ar_2E_2 addition to alkynes in solvent cannot be substantially improved at higher temperatures due to rapid catalyst decomposition. We found that the palladium catalyst is much more stable in the solvent free conditions. For the Ph_2S_2 addition across a triple bond in **1-B** increasing the temperature to 100 °C allows the reaction time to be shortened to 1 h (Table 3). With the temperature increased to 120 °C or higher no longer than 5 min of reaction time is required (Table 3).

Table 4 Catalytic Ph_2S_2 addition to alkynes with different reaction scale and amount of catalyst used[a]

Entry	Alkyne	Reaction scale, mmol	$Pd(PPh_3)_4$, mol %	Time, min	Yield,[b] %
1	**1-A**	1	1.0	<3	97
2	**1-A**	1	0.1	30	97
3	**1-A**	10	0.1	30	97
4	**1-A**	10	0.01	60	97
5	**1-A**	10	0.001	300	70
6	**1-B**	1	0.1	30	98
7	**1-B**	10	0.1	30	98

[a] The reactions were performed at 140 °C with 15 mol% of PPh_3. [b] Measured with NMR spectroscopy.

To check the scope of the catalytic reaction at high temperature we have repeated Ph_2E_2 addition to alkynes **1-A**–**1-D** at 140 °C (entries 2–12, Table 1). In all cases after 5 min of heating 96–99% product yields were obtained with high stereoselectivity ($Z/E > 97/3$). It is known that long heating at high temperatures could lower overall stereoselectivity of E–E addition due to noncatalytic thermal reaction or double bond isomerisation.[6] However, this was not the case for the studied solvent free system, since reaction time at high temperature is very short.

Reaction rate enhancement and remarkable catalyst stability at high temperature give an opportunity to perform addition reactions with a rather small amount of catalyst (entries 1–5, Table 4). Particularly, 97% product yield was observed with only 0.01 mol% of catalyst (entry 4, Table 4). Even with as low as 0.001 mol% of catalyst a 70% yield was observed after 5 h of reaction at 140 °C (entry 5, Table 4).

Performing reactions with 0.1 mol% of catalyst requires about 1 mg of $Pd(PPh_3)_4$ for the synthesis of ~3 g of the addition products (entries 3, 7; Table 4).

The developed solvent free methodology provides the same quantitative yields for 1 and 10 mmol of reaction scale (entries 2–3 and 6–7; Table 4). For the alkyne **1-A** this corresponds to 0.33 and 3.32 g of the final product, respectively (**2-A**).

Recently we have shown that the mechanism of $Pd(PPh_3)_4$ catalyzed Ar_2E_2 (E = S, Se) addition to alkynes in toluene or benzene solutions involves dinuclear complexes[10] formed after the E–E bond oxidative addition to zero valent palladium (**4**, **5**; Scheme 1).[15] It was shown that the concentration of dinuclear complexes in solution is increased in the presence of excess of PPh_3.[10] Most likely, triphenylphosphine prevents catalyst polymerization leading to insoluble $[Pd(EAr)_2]_n$[16] (**6**) and ensures homogeneous reactions conditions.

To clarify the reaction mechanism under solvent free conditions we have performed a $^{31}P\{^1H\}$ NMR study directly in the molten Ph_2S_2/PPh_3. Adding $Pd(PPh_3)_4$ to the melted Ph_2S_2/PPh_3 at 80 °C results in the appearance of two major resonances at δ = 30.4 and 29.0 ppm (Fig. 1A) corresponding to dinuclear complexes **4** and **5** (Scheme 1).[17] Similar complexes were detected in toluene in the oxidative addition reaction of Ph_2S_2 to $Pd(PPh_3)_4$ (δ = 30.8 and 29.4 ppm).[10,15] The small difference in the chemical shifts of dinuclear complexes in the molten Ph_2S_2/PPh_3 and in the toluene solution indicates rather similar solvation properties of both media. This is one of the key factors for developing a successful synthetic procedure under solvent free conditions.

$^{31}P\{^1H\}$ NMR monitoring of the catalytic reaction in the molten Ph_2S_2/PPh_3 confirmed the presence of the dinuclear complexes **4**, **5** (Fig. 1A). The observation indicates that the catalytic process under solvent free conditions, involves dinuclear complex $[Pd_2(EAr)_4(PPh_3)_2]$ (**4**, **5**) formation. The present study suggests the same mechanism of the catalytic reaction under solvent free conditions and in solvent.

Remarkable catalyst stability provides the necessary conditions for recycling. Indeed, we have found that palladium catalyst can be easily separated by flash chromatography after completing the reaction.[18] The $^{31}P\{^1H\}$ NMR spectrum of the isolated compound shows several lines in the region of 29.5–31.0 ppm (Fig. 1D). Adding an excess of PPh_3 increases the intensity of the signals corresponding to dinuclear complexes **4**, **5** (δ = 30.8 and 29.4 ppm) simultaneously decreasing the intensity of the other lines (Fig. 1C). In a 15 fold excess of the ligand only two signals of **4** and **5** are detected (Fig. 1B). The NMR study confirms the suggestion made earlier: an excess of the ligand prevents catalyst oligomerization and shifts the equilibrium toward dinuclear complexes.[19]

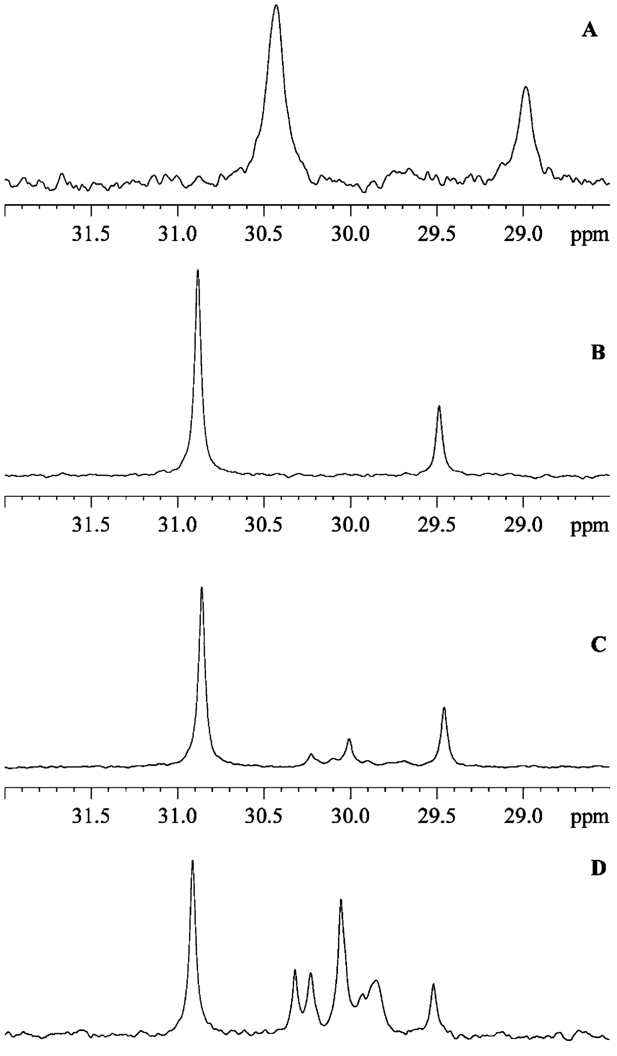


Fig. 1 $^{31}P\{^1H\}$ NMR spectra of the dinuclear complexes *trans*-, *cis*-$[Pd_2(SPh)_4(PPh_3)_2]$ (**4**, **5**): **A** – in the melted Ph_2S_2/PPh_3 without solvent; **B** – in a toluene solution in the presence of a 15 fold excess of PPh_3; **C** – in a toluene solution in the presence of twofold excess of PPh_3; **D** – in a toluene solution.

Recycled catalyst shows the same catalytic activity and stereoselectivity in the Ar_2E_2 addition reaction under solvent free conditions compared to the initial $Pd(PPh_3)_4$. The recycling

Table 5 Catalytic Ph_2S_2 addition to alkynes using recycled catalyst[a]

Cycles	Alkyne	Yield,[a] %
1	**1-A**	98
2	**1-B**	96
3	**1-D**	97

[a] The reactions were performed in 1 mmol scale with 1 mol% of initial $Pd(PPh_3)_4$ and 15 mol% of PPh_3 at 140 °C.[20] [b] Measured with NMR spectroscopy after 8 h.

sequence being repeated three times does not substantially effect the reaction yield (Table 5).

For catalyst recycling the optimal Ar_2E_2 : alkyne ratio is 1 : 1. In this case the dark-brown complex $[Pd_2(EAr)_4(PPh_3)_2]$ is the final form of the catalyst, which can be easily recycled under regular conditions in air. As mentioned above, in the case of an excess of alkyne air-sensitive $Pd(PPh_3)_4$ is formed, which is hardly possible for recycling.

The present article reports the first example of a transition metal catalyzed E–E bond addition reaction to unsaturated molecules in the absence of solvent. Two key-factors are of great importance for the reaction: 1) solvation properties of Ar_2E_2/PPh_3 are similar to those of aromatic solvents; and 2) the excess of PPh_3 ligand effectively blocks polymerization of palladium complexes and keeps the active form of the catalyst in the melt. In the present case the solvent free reaction was performed as a simple thermal process without microwave irradiation.

In the developed solvent free methodology quantitative yields of stereoselective Ar_2E_2 addition to alkynes can be achieved in very simple reaction conditions, followed by a significantly simplified product separation procedure. The developed methodology combines several advantages: 1) atom efficiency of the addition reaction; 2) high stereoselectivity of the transition metal catalyzed transformation; and 3) economical and ecological benefits of the solvent free conditions. In addition, significant acceleration of the reaction was observed, as a result reaction time was decreased from several hours to a few minutes with less catalyst used. An important advantage of the solvent free methodology is the ability for catalyst recycling.

The NMR study has shown the formation of dinuclear intermediate complexes $[Pd_2(EAr)_4(PPh_3)_2]$ in the catalytic reaction performed under solvent free conditions, therefore, suggesting the same catalytic reaction mechanism as in solution.

Acknowledgements

The work was carried out with partial support from the Chemistry and Material Science Branch of the Russian Academy of Sciences (Program: "Theoretical and experimental investigations of the nature of chemical bonding and mechanisms of the most important chemical reactions and processes").

Notes and references

1 For recent reviews on solvent free synthesis see: (*a*) K. Tanaka and F. Toda, *Chem.Rev.*, 2000, **100**, 1025; (*b*) J. O. Metzger, *Angew. Chem., Int. Ed.*, 1998, **37**, 2975.

2 For recent reviews on microwave assisted solvent free synthesis see: (*a*) R. S. Varma, *Pure Appl. Chem.*, 2001, **73**, 193; (*b*) A. Loupy, A. Petit, J. Hamelin, F. Texier-Boullet, P. Jacquault and D. Mathe, *Synthesis*, 1998, 1213; (*c*) R. S. Varma, *Green Chem.*, 1999, **1**, 43; (*d*) S. A. Galema, *Chem. Soc. Rev.*, 1997, **26**, 233.

3 (*a*) G. W. Kabalka, L. Wang, R. M. Pagni, M. C. Hair and V. Namboodiri, *Synthesis*, 2003, 217; (*b*) L. M. Klingensmith and N. E. Leadbeater, *Tetrahedron Lett.*, 2003, **44**, 765; (*c*) C. R. LeBlond, A. T. Andrews, J. R. Sowa and Y. Sun, *Org. Lett.*, 2001, **3**, 1555; (*d*) G. W. Kabalka, V. Namboodiri and L. Wang, *Chem. Commun.*, 2001, 775.

4 (*a*) A. Diaz-Ortiz, A. de la Hoz and F. Langa, *Green Chem.*, 2000, **2**, 165; (*b*) R. J. Morphy, Z. Rankovic and M. York, *Tetrahedron Lett.*, 2002, **43**, 5973; (*c*) A. Diaz-Ortiz, P. Prieto and E. Vasquez, *Synlett*, 1997, 269.

5 (*a*) F. Y. Kwong and S. L. Buchwald, *Org. Lett.*, 2003, **5**, 793; (*b*) B. Basu, S. Jha, N. K. Mridha and M. H. Bhuiyan, *Tetrahedron Lett.*, 2002, **43**, 7967; (*c*) J. P. Wolfe and S. L. Buchwald, *J. Org. Chem.*, 2000, **65**, 1144.

6 I. P. Beletskaya and C. Moberg, *Chem. Rev.*, 1999, **99**, 3435.

7 H. Kuniyasu, A. Ogawa, S.-I. Miyazaki, I. Ryu, N. Kambe and N. Sonoda, *J. Am. Chem. Soc.*, 1991, **113**, 9796.

8 (*a*) T. Wirth (Ed), *Organoselenium Chemistry: Modern Developments in Organic Synthesis*, Springer Verlag, Berlin, New York, 2000; (*b*) T. G. Back (Ed), *Organoselenium Chemistry : A Practical Approach*, Oxford University Press, New York, 1999; (*c*) C. Paulmier, *Selenium Reagents and Intermediates in Organic Synthesis*, Pergamon Press, Oxford, 1986; (*d*) S. Patai and Z. Rappoport (Eds), *The Chemistry of Organic Selenium and Tellurium Compounds*, John Wiley & Sons, New York, 1986, Vol. 1–2.

9 (*a*) P. I. Clemenson, *Coord. Chem. Rev.*, 1990, **190**, 171; (*b*) C. Lauterbach and J. Fabian, *Eur. J. Inorg. Chem.*, 1999, 1995 (and references therein).

10 (*a*) V. P. Ananikov, I. P. Beletskaya, G. G. Aleksandrov and I. L. Eremenko, *Organometallics*, 2003, **22**, 1414; (*b*) V. P. Ananikov, D. A. Malyshev, I. P. Beletskaya, G. G. Aleksandrov and I. L. Eremenko, *J. Organomet. Chem.*, 2003, **679**, 162; (*c*) V. P. Ananikov, M. A. Kabeshov, I. P. Beletskaya, G. G. Aleksandrov and I. L. Eremenko, *J. Organomet. Chem.*, 2003, **687**, 451.

11 Typical synthetic procedure was used, see electronic supporting information for details †.

12 Compounds **2-A**–**2-B** were isolated using flash chromatography; **2-D** and **2-E** were isolated with regular column chromatography; **2-C** was isolated as an oxalate salt. A detailed description of separation procedure is given in the electronic supporting information †.

13 (*a*) D. S. Pedersen and C. Rosenbohm, *Synthesis*, 2001, 2431; (*b*) L. M. Harwood, *Aldrichimica Acta*, 1985, **18**, 25.

14 The *Z*-configuration of the products was confirmed with NOESY NMR experiments.

15 For X-ray structures of $[Pd_2(EAr)_4(PPh_3)_4]$ see: (*a*) R. Oilunkaniemi, R. S. Laitinen and M. Ahlgren, *J. Organomet. Chem.*, 2001, **623**, 168; (*b*) R. Oilunkaniemi, R. S. Laitinen and M. Ahlgren, *J. Organomet. Chem.*, 1999, **587**, 200; (*c*) I. Nakanishi, S. Tanaka, K. Matsumoto and S. Ooi, *Acta Crystallogr., Sect. C.*, 1994, **50**, 58.

16 Polymers of general formula $[Pd(ER)_2]_n$ (E = S, Se) were isolated as insoluble dark-brown solids: (*a*) S. Dey, V. K. Jain and B. Varghese, *J. Organomet. Chem.*, 2001, **623**, 48; (*b*) A. Ogawa, *J. Organomet. Chem.*, 2000, **611**, 463.

17 The complexes were identified by comparison with authentic samples synthesized in toluene and dissolved in the molten Ph_2S_2/PPh_3.

18 Flash chromatography was used (see ref. 13). After eluting PPh_3 and product palladium complexes remained adsorbed on the silica (dark brown ring). The complexes were eluted with hexane : EtOAc = 1 : 1 solvents mixture and dried in vacuum (brown oil, estimated yield 90–95% based on initial palladium complex). See electronic supporting information for more details.

19 In the toluene solution increasing PPh_3 concentration results in the appearance of two additional minor resonances at $\delta = 25.0$ and 24.1 ppm. The former was assigned as $O{=}PPh_3$ by comparison with an authentic sample, while the latter could, in principle, be attributed to the mononuclear complex $[Pd(SPh)_2(PPh_3)_2]$. However, at the moment it cannot be unambiguously proved.

20 Typical procedure was followed (see electronic supporting information) except 1 : 1 alkyne : Ph_2S_2 ratio was used.