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Palladium-catalyzed phosphinylthiolation of terminal alkynes

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ABSTRACT

Phosphinylthiolation of terminal alkynes with $Ph_2P(O)SBu$ or a related compound proceeds in the presence of a palladium–PEt_3 catalyst system. Activity and stereoselectivity are highly dependent on the nature of solvent, ethylbenzene, and *n*-hexanol (or *t*-amyl alcohol) being *E*- and *Z*-selective, respectively.

The addition reaction of inter-element bonds is a research area of vital growth these days. However, as far as P–S and related bonds are concerned, only a limited number of publications have appeared. One of the protocols is based on the radical process as reported for P(O)–SR (R = alkyl) species by Malacria and co-workers[1] and for Ph_2P–SR (R = aryl, alkyl) by Oshima and co-workers.[2] As another protocol, one of us has reported the palladium-catalyzed addition of $(RO)_2P(O)SPh$ and $(RO)_2P(O)SePh$.[3] Attempted reactions starting with $Ph_2P(O)SPh$ aiming at expanding the scope of the protocol did not furnish the desired adducts in appreciable yields.[4] Further attempts, however, have uncovered that the use of alkylthio congeners in the place of $Ph_2P(O)SPh$ does work to give the desired adducts in acceptable yields and that the stereochemistry of the products is highly dependent on the solvents, which will be reported in this Letter.

Since the first several attempts using a catalyst system comprising of CpPd(π-allyl) (5 mol %) and PPh_3 (10 mol %) did not work successfully, a series of trial experiments to search for better phosphine ligands were run at 130 °C for 6 h using diphenyl(butylthio)phosphine oxide (**1a**, 1.0 mmol) and 1-octyne (**2A**, 1.0 mmol) in ethylbenzene (2.0 mL). Under the conditions, strongly electron-donating and sterically less demanding phosphines have proven to be better performing (Table 1). Among the ligands examined, PEt_3 is the ligand of choice, which affords (***E***)-**3aA** in a 70% NMR yield along with the (*Z*)-isomer (8%). Since the related reaction of $(RO)_2P(O)SPh$ with terminal alkynes results in *cis*-addition giving (*Z*)-isomers as the major products, the predominant formation of (***E***)-**3aA** is entirely unexpected. It is also interesting to note from the mechanistic viewpoint (vide infra) that 1-octyn-1-yldiphenylphosphine oxide (**4aA**; 7%) and 2-butylthio-1-octene (**5aA**; 13%) were also found in the reaction mixture. The structures of (***E***)-**3aA** and other products obtained in other reactions were characterized spectroscopically and confirmed unambiguously by X-ray diffraction in two cases, (***E***)-**3aA** and (***Z***)-**3aH**.[5]

Choice of the solvent has proved to be another important factor that affects the reactivity, the stereochemistry in particular. Under the same conditions using PEt_3, the yield ratio of the *Z*/*E* products observed with various solvents increased as follows; ethylbenzene (dielectric constant $\varepsilon = 2.4$) 8%/70% < methyl isobutyl ketone ($\varepsilon = 13.1$) 17/57 < *n*-octane ($\varepsilon = 2.0$) 16/44 < THF ($\varepsilon = 7.58$) 26/45 < chlorobenzene ($\varepsilon = 5.6$) 25/5 < butyronitrile ($\varepsilon = 20.7$) 22/1 < DMF ($\varepsilon = 37.6$) 33/trace < *n*-hexanol ($\varepsilon = 13.3$) 83/trace. Thus, the reaction is *Z*-selective in *n*-hexanol, unlike the *E*-selectivity observed in ethylbenzene (Scheme 1). It is also interesting to note that other alkanols, sterically more demanding and less nucleophilic ones in particular, are more advantageous over *n*-hexanol in the high yielding formation of *Z*-isomers, as exemplified by the reaction of 5-hexynenitrile (Table 2).[6] However, we are unable to find any correlation between the selectivity and the dielectric constant of the solvent.

With the foregoing results of trial experiments in hand, we ran a series of reactions of **1a** with various alkynes (Table 3). Aliphatic alkynes, inclusive of those substituted by polar functional groups, afford the desired products in acceptable yields of either (*Z*)- or (*E*)-adducts depending on the solvent. However, *t*-butylacetylene (**2C**) and 3-phenyl-1-propyne (**2F**), which produce (*Z*)-adducts in a rather high yield in an alcoholic solvent, mainly afford the same stereoisomer in very low yields in ethylbenzene, partially because of intrinsic low reactivity. Moreover, the reaction of **2F** also formed (*E*)-1-phenyl-2-butylthio-3-diphenylphosphinyl-1-pro-

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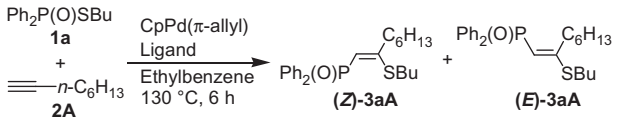
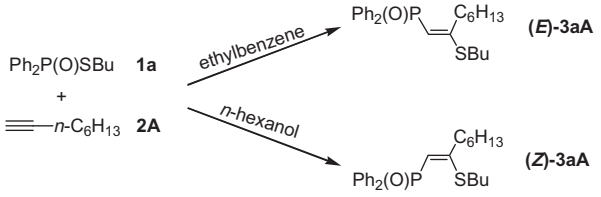
Table 1
Ligand effects on the reaction of **1a** with **2A**[a]



Entry	Ligand	Conversion of **1a**[b] (%)	Yield[c] (%)	
			(*Z*)-**3aA**	(*E*)-**3aA**
1	PMe_3	90	11	31
2	PEt_3	98	8	70
3	PPr_3	51	28	9
4	PBu_3	58	34	15
5	P(*t*-Bu)$_3$	42	0	0
6	Ph-SMAP[d]	93	11	51
7	$P(CH_2O)_3CCH_3$	49	1	8
8	$P(OCH_2)_3CEt$	4	~0	0
9	PCy_3	66	16	16
10	PPh_3	28	8	3
11	P(*p*-An)$_3$	51	12	19
12	$P(OEt)_3$	6	6	Trace
13	dmpe	64	5	9
14	dppe	88	Trace	13
15	dppp	51	0	Trace
16	dppb	43	7	15
17	dcpe[e]	57	Trace	6
18	dppf	38	Trace	8
19	Xantphos	63	7	2

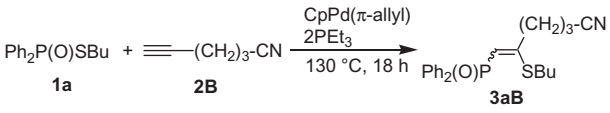
[a] Reaction conditions: $Ph_2P(O)SBu$ (**1a**) (1.0 mmol), 1-octyne (**2A**) (1.0 mmol), CpPd(π-allyl) (0.05 mmol), ligand (P/Pd = 2.0), ethylbenzene (2.0 mL), 130 °C for 6 h.
[b] Determined by GC. Conversion of **2A** was not determined due to peak overlapping with the solvent.
[c] Determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard.
[d] 4-Phenyl-1-phospha-4-silabicyclo[2.2.2]octane.
[e] 1,2-Bis(dicyclohexylphosphino)ethane.

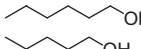
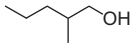
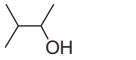
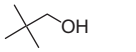
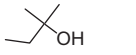


Scheme 1. Solvent dependence on the stereoselectivity.

pene [(*E*)-**3aF′**], an isomer of **3aF**, in a 9% yield (both entries 11 and 12).[7] On the other hand, the reaction of phenylacetylene (**2H**) is somewhat slow as compared with aliphatic alkynes and less selective, ending up with the yield of the desired adduct lower than 50%. Detailed analysis of entries 15 and 16 has revealed that the low yield is due to the more extensive formation of byproducts such as 1-(butylthio)styrene (13% and 21% in entries 15 and 16, respectively), 1,2-di(butylthio)styrene (8% and 4%), and oligomers of **2H** (11% and 15%).[8] In agreement with aliphatic alkynes being more reactive and more selective, *p*-anisylacetylene (**2J**) substituted with an electron-releasing methoxy group is better performing than the parent phenylacetylene, although the reaction of *p*-fluorophenylacetylene (**2K**) cannot be understood in the same line. The stereochemical preference is solvent-dependent as found with aliphatic alkynes. However, the dependence is not as distinct and, subjected to the substituent bound to the phenyl ring, both *n*-hexanol and ethylbenzene afford the same stereoisomer as a major product, as exemplified by the reaction of *p*-methoxyphenylacetylene and *p*-fluorophenylacetylene.

Table 2
Effect of alcohol solvent in the reaction of 5-hexynenitrile[a]



Solvent	Yield of (*Z*)-**3aB**[b] (%)	Yield of (*E*)-**3aB**[b] (%)
	40	Trace
	45	3
	64	8
	67	11
	74	4

[a] Reaction conditions: $Ph_2P(O)SBu$ (**1a**) (1.0 mmol), 5-hexynenitrile (**2B**) (1.5 mmol), CpPd(π-allyl) (0.05 mmol), PEt_3 (0.10 mmol), solvent (2.0 mL), 130 °C for 18 h.
[b] Determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard.

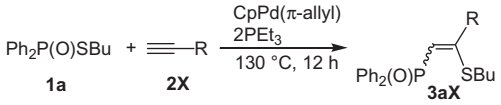
Besides diphenyl(butylthio)phosphine oxide (**1a**), diphenyl(*t*-butylthio)phosphine oxide (**1b**) also reacts smoothly with **2A** to preferentially form (*E*)- and (*Z*)-**3bA** in ethylbenzene and *n*-hexanol, respectively, although the solvent dependence of the stereochemistry is not as distinct as that observed with **1a** (Scheme 2).

Although we assume that the oxidative addition of the P–S bond triggers the catalysis,[3] attempted isolation of intermediates to propose the mechanism has been unsuccessful.[9,10] However, following observation merits consideration of the origin of the solvent-dependent stereoselectivity. Figure 1a illustrates the time course of the reaction in *n*-hexanol, which displays a monotonous increase of the yield of (*Z*)-**3aA**. On the other hand, Figure 1b illustrating the reaction in ethylbenzene indicates that (*Z*)-**3aA** is formed only in the beginning stage. In addition, **4aA** is also formed as another major product in the beginning stage. However, the quantities of (*Z*)-**3aA** and **4aA** start decreasing slightly and instead (*E*)-**3aA** shows a somewhat sigmoidal increase to eventually be the major product. These observations appear to suggest that (*Z*)-**3aA** isomerizes to (*E*)-**3aA** in ethylbenzene.

To substantiate the possibility of the isomerization, an ethylbenzene (5.0 mL) solution of (*Z*)-**3aA** (0.5 mmol) was heated in the presence of CpPd(π-allyl) (0.025 mmol) and PEt_3 (0.05 mmol) at 130 °C for 6 h (Scheme 3). Analysis of the resulting mixture revealed that (*E*)-**3aA** was indeed formed in a 23% yield,[11] although the isomerization was not sufficiently rapid to rationalize that the isomerization is a major provenance of (*E*)-**3aA**.[12]

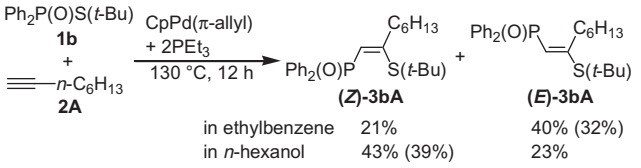
Another interesting observation that merits further mechanistic consideration is that 1-octyn-1-yldiphenylphosphine oxide (**4aA**) and 2-butylthio-1-octene (**5aA**) were formed as byproducts in the reaction of **2A** run in ethylbenzene (vide supra). The formation of **4aA** may have come from the metathetical reaction of **1a** and **2A**, which is envisioned to generate butane-1-thiol as a coproduct. Although butane-1-thiol is not found in the reaction mixture, the formation of **5aA** is rationalized by assuming that butane-1-thiol generated during the catalysis has added across the triple bond of 1-octyne.[13] This assumption is supported by the reaction of **2A**-d_1 with **1a** forming **5aA** (20% NMR yield),[14] in which the D content at the methylene carbon estimated by ^{1}H NMR spectroscopy was higher than 90% both at *syn* and *anti* positions (Scheme 4). A similar observation has been reported by Ogawa and co-workers in the mechanistic study on the palladium-catalyzed hydrophosphination of alkynes with tetraphenyldiphosphine.[15]

Table 3
Phosphinylthiolation of terminal alkynes with $Ph_2P(O)SBu$[a]



Entry	Alkyne **2**, R=	Solvent[b]	Conversion of **1a**[c] (%)	Yield of (***Z***)-**3aX**[d] (%)	Yield of (***E***)-**3aX**[d] (%)
1[e]	**2A**, *n*-hexyl	*t*-AA	98	89 (81)	~0
2[e]	**2A**, *n*-hexyl	EB	98	8	70 (60)
3[f]	**2B**, 3-cyanopropyl	*t*-AA	93	74 (68)	4
4[f]	**2B**, 3-cyanopropyl	EB	95	13	64 (41)
5[f]	**2C**, *t*-Bu	H	93	61 (46)	~0
6[f]	**2C**, *t*-Bu	EB	38	3	~0
7	**2D**, 3-(carbomethoxy)propyl	*t*-AA	97	73 (70)	3
8	**2D**, 3-(carbomethoxy)propyl	EB	79		63 (61)
9	**2E**, 3-hydroxylpropyl	*t*-AA	99	76 (71)	0
10	**2E**, 3-hydroxylpropyl	EB	51	9	17 (16)
11[f]	**2F**, benzyl	*t*-AA	96	71 (70)[g]	~0
12[f]	**2F**, benzyl	EB	38	7[g]	4
13	**2G**, 1-cyclohexenyl	H	85	38	22
14	**2G**, 1-cyclohexenyl	EB	43	3	36 (20)
15	**2H**, phenyl	H	81	47 (36)	8
16	**2H**, phenyl	EB	65	trace	37 (34)
17	**2I**, *p*-tolyl	H	81	47	8
18	**2I**, *p*-tolyl	EB	65	~0	37 (35)
19	**2J**, *p*-methoxyphenyl	H	99	31	46
20	**2J**, *p*-methoxyphenyl	EB	89	18	51
21	**2K**, *p*-fluorophenyl	H	86	25 (21)	1
22	**2K**, *p*-fluorophenyl	EB	81	27	12

[a] Reaction conditions: **1a** (1.0 mmol), **2X** (1.5 mmol), CpPd(π-allyl) (0.05 mmol), PEt_3 (0.10 mmol), solvent (2.0 mL), 130 °C for 12 h.
[b] *t*-AA = *t*-amyl alcohol, EB = ethylbenzene, H = *n*-hexanol.
[c] Determined by GC.
[d] Determined by ^1H NMR spectroscopy. The figures in parentheses are isolated yields.
[e] Quantity of **2A** = 1.0 mmol, reaction time = 6 h.
[f] Reaction time = 18 h.
[g] A double bond isomer was also formed in a 9% yield. See the text.



Scheme 2. Phosphinylthiolation with diphenyl(*t*-butylthio)phosphine oxide (figures in parentheses are isolated yields).

On the basis of these considerations, addition of butane-1-thiol across the triple bond of **4aA** appears to be another candidate route to (***E***)-**3aA**. Indeed, when a toluene-d_8 solution of **4aA** (0.07 mmol), butane-1-thiol (0.07 mmol), CpPd(π-allyl) (0.01 mmol), and PEt_3 (0.02 mmol) was heated at 110 °C for 6 h, (***E***)-**3aA** was formed in a 64% yield along with only a trace of (***Z***)-**3aA** (Scheme 5).[16,17] Another reaction without using the palladium complex under otherwise identical conditions afforded a mixture of (***Z***)-**3aA** (24%) and (***E***)-**3aA** (45%).

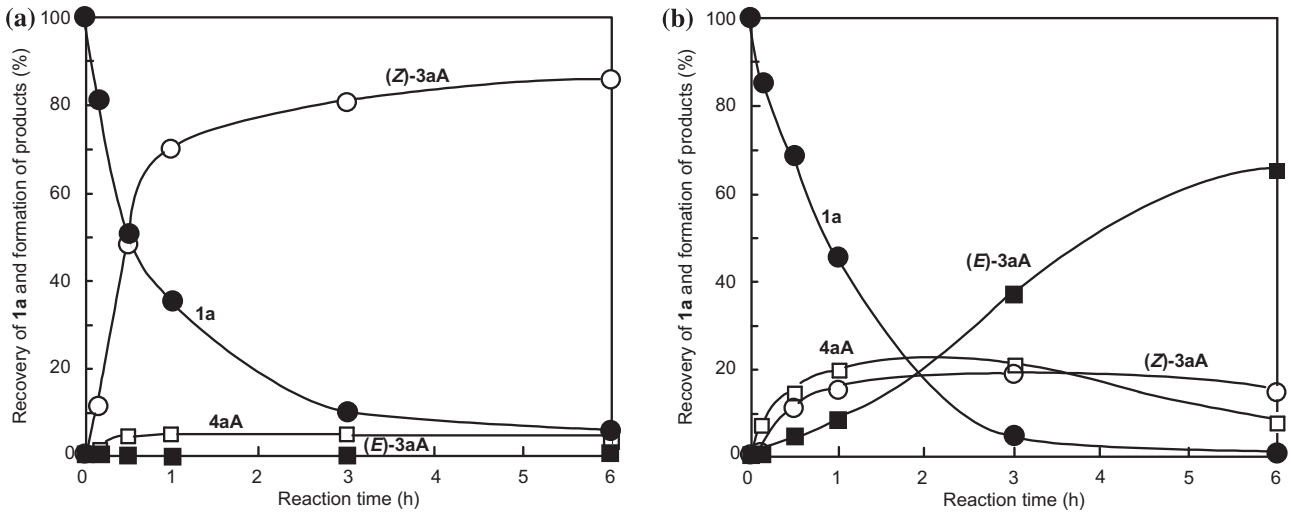
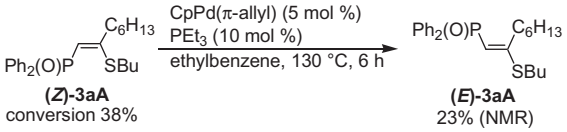
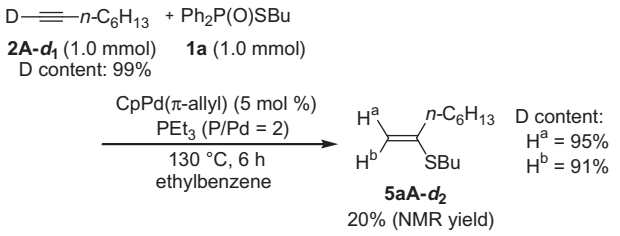


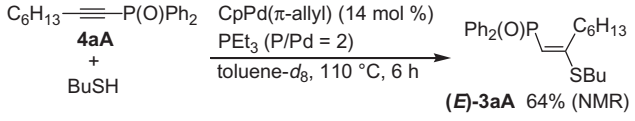
Figure 1. Time course of the reaction of **1a** with **2A** run (a) in *n*-hexanol (left) and (b) in ethylbenzene (right). Conditions are basically the same as those for Table 1.



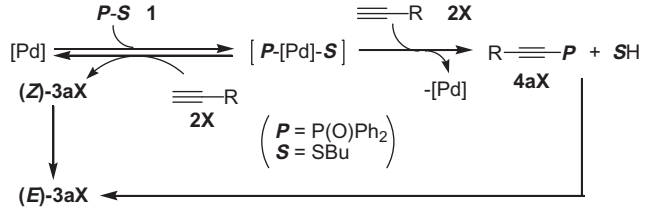
Scheme 3. Isomerization of (***Z***)-**3aA** to (***E***)-**3aA**.



Scheme 4. Formation of 2-butylthio-1-octene-d_2 (**5aA-*d*$_2$**) in the reaction of 1-octyne-d_1 (**2A-*d*$_1$**) with diphenyl(butylthio)phosphine oxide (**1a**).



Scheme 5. Palladium-catalyzed facile addition of butane-1-thiol with 1-octyn-1-yldiphenylphosphine oxide (**4aA**).



Scheme 6. Possible pathways leading to (***E***)-**3aA** and (***Z***)-**3aA**.

To summarize, the possible pathways leading to (***Z***)-**3aA** and (***E***)-**3aA** can be proposed as illustrated in Scheme 6. In alcoholic solvents, the catalysis is carried presumably by the straightforward shuttle between [Pd] and [$Ph_2P(O)$-Pd-SBu] species, which is in good agreement with the stereoselective formation of (***Z***)-**3aA**. In ethylbenzene, on the other hand, (***Z***)-**3aA** formed isomerizes to (***E***)-**3aA**. Moreover, the [$Ph_2P(O)$-Pd-SBu] species somehow reacts with terminal alkynes to generate **4aX** and butane-1-thiol and these two intermediates react together forming mainly (***E***)-**3aA**, along with (***Z***)-**3aA** to a lesser extent.[18] The reason for the lack of isomerization in *n*-hexanol is uncertain at this moment.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.035.

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2. Wada, T.; Kondoh, A.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2008**, *10*, 1155.
3. (a) Han, L.-B.; Tanaka, M. *Chem. Lett.* **1999**, *28*, 863; (b) Han, L.-B.; Choi, N.; Tanaka, M. *J. Am. Chem. Soc.* **1996**, *118*, 7000.
4. Tanaka, M. unpublished result.
5. CCDC 863310–863311 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
6. Since the reactions run in *n*-hexanol under the standard conditions formed *n*-hexyl diphenylphosphinate as a byproduct (9–15%), the better performance of *t*-amyl alcohol can be due partially to its low nucleophilicity, which depresses the reactivity in the transesterification (butylthio and alkoxy exchange).
7. Another reaction of **2F** in *n*-hexanol, the formation of (***E***)-**3aF′** was more extensive (36% ^{1}H NMR yield), relative to the formation of (***Z***)-**3aF** (26% ^{1}H NMR yield). Since phenylallene was totally unreactive towards **1a** under the conditions, the formation of (***E***)-**3aF′** is not due to isomerization of **2F** to phenylallene prior to addition of **1a**.
8. To improve the yield, screening of phosphine ligands and solvent effect study were performed for phenylacetylene. However we were unable to find a better ligand than triethylphosphine and a better solvent than *n*-hexanol and *t*-amyl alcohol.
9. One of the species generated in the reaction of **1a** with CpPd(π-allyl) (0.05 mmol) and PMe_3 (0.05 mmol) in benzene-d_6 run at 110 °C for 3 h appeared dimeric such as $[\{Ph_2P(O)\}Pd(\mu\text{-SBu})]_2$, as judged on the basis of ^{31}P NMR, 67.1 ppm (d, J = 37.1 Hz, P═O), −3.7 ppm (d, J = 37.1 Hz, PMe), while the same reaction run in MeOH-d_4 at 60 °C for 3 h appeared to generate, among others, a monomeric species, $Ph_2P(O)Pd\{S(t\text{-Bu})\}(PMe_3)_2$ which displayed ^{31}P NMR signals at 74.0 ppm (t, J = 122.4 Hz) and −29.3 ppm (d, J = 122.4 Hz), indicative of a *trans*-configuration. However, depending on the conditions of these and similar reactions using **1b**, polymeric palladium species also appeared to be formed on the basis of ESI-MS analysis, and we have been unable to further characterize these species due to the complexity of the mixture. For the generation of polymeric and oligomeric palladium sulfide species, see Ref.[10].
10. (a) Ogawa, A. *Top. Organomet. Chem.* doi:10.1007/3418_2011_19.; (b) Stash, A. I.; Levashova, V. V.; Lebedev, S. A.; Hoskov, Y. G.; Mal'kov, A. A.; Romm, I. P. *Russ. J. Coord. Chem.* **2009**, *35*, 136; (c) Stash, A. I.; Perepelkova, T. I.; Noskov, Yu. G.; Buslaeva, T. M.; Romm, I. P. *Russ. J. Coord. Chem.* **2001**, *27*, 585; (d) Higgins, J. D.; Suggs, W. *Inorg. Chim. Acta* **1998**, *145*, 247; (e) Jain, V. K.; Jain, L. *Coord. Chem. Rev.* **2010**, *254*, 2848.
11. The conversion of (***Z***)-**3aA** was 38%, suggesting that other unknown products were also formed during the isomerization.
12. Although diethyl 2-(*p*-tolylthio)ethenylphosphonate, a related compound, is known to undergo a thermal *Z*-to-*E* isomerization, (***Z***)-**3aA** did not isomerize to (***E***)-**3aA** by simple heating with or without PEt_3. See: Acheson, R. M.; Ansell, P. J.; Murry, J. R. *J. Chem. Res., Synop.* **1986**, 378.
13. Palladium-catalyzed addition of thiols across C–C triple bonds is a well established process. See Ref.[10a].
14. In this reaction, **4aA** and (***E***)-**3aA-*d*$_1$** were formed in 9% and 60% yields, respectively. The product distribution in this reaction was basically the same as that found in a reaction using **2A** under otherwise the same conditions, where the yield of **5aA** was 19%.
15. (a) Nagata, S.; Kawaguchi, S.; Matsumoto, M.; Kamiya, I.; Nomoto, A.; Sonoda, M.; Ogawa, A. *Tetrahedron Lett.* **2007**, *48*, 6637; See also: (b) Arisawa, M.; Onoda, M.; Hori, C.; Yamaguchi, M. *Tetrahedron Lett.* **2006**, *47*, 5211.
16. Details will be reported separately. The same reaction of **4aA** and butane-1-thiol run without CpPd(π-allyl) (0.01 mmol) and PEt_3 or in the presence of AIBN did not afford (***E***)-**3aA** at all.
17. Similar reactions of selenols in the presence of the Wilkinson's catalyst have been reported very recently; see: Kawaguchi, S.-i.; Kotani, M.; Atobe, S.; Nomoto, A.; Sonoda, M.; Ogawa, A. *Organometallics* **2011**, *30*, 6766; Palladium-catalyzed anti-hydrothilation of alkynylphosphines was reported; see: Kondoh, A.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 1383.
18. Although less likely, a radical mechanism cannot be rigorously excluded as far as the reaction in ethylbenzene is concerned. When a reaction similar to entry 2, Table 1 was run in the presence of TEMPO (50 mol %) resulted in a 70% conversion of **1a**, giving (***E***)-**3aA** (5% yield), (***Z***)-**3aA** (13%), and **4aA** (42%). On the other hand, another reaction using AIBN (10 mol %) instead of the palladium complex and PEt_3 run at 80 °C for 6 h in benzene did not proceed at all. We presume that the low yield of isomeric **3aA** observed when TEMPO was added is due to the deterioration of the catalyst.