Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 2923–2926
Tetrahedron Letters

First use of a palladium complex with a thiosemicarbazone ligand as catalyst precursor for the Heck reaction

Dimitra Kovala-Demertzi,[a,*] Paras N. Yadav,[a] Mavroudis A. Demertzis,[a] Jerry P. Jasiski,[b] Fotini J. Andreadaki[c] and Ioannis D. Kostas[c,*]

[a]*University of Ioannina, Department of Chemistry, Sector of Inorganic and Analytical Chemistry, 45110 Ioannina, Greece*
[b]*Department of Chemistry, Keene State College, 229 Main Street, Keene, NH 03435-2110, USA*
[c]*National Hellenic Research Foundation, Institute of Organic and Pharmaceutical Chemistry, Vas. Constantinou 48, 116 35 Athens, Greece*

Received 9 December 2003; revised 4 February 2004; accepted 13 February 2004

Abstract—A novel palladium complex with salicylaldehyde *N*(4)-ethylthiosemicarbazone has been synthesized and according to its crystal structure the ligand is bound to the metal in an O, N, S-terdentate coordination mode. This phosphorus-free system efficiently catalyzes the Heck reaction of aryl bromides (from electron-rich to electron-poor) with styrene under argon, with turnover numbers of up to 43,000, at 150 °C after 24 h, and with a selectivity toward *trans*-stilbenes ranging from 92 to 96%. In air, for activated aryl bromides and for a palladium concentration of 1 mM, the yields are essentially the same as those obtained when the reaction was performed under argon.

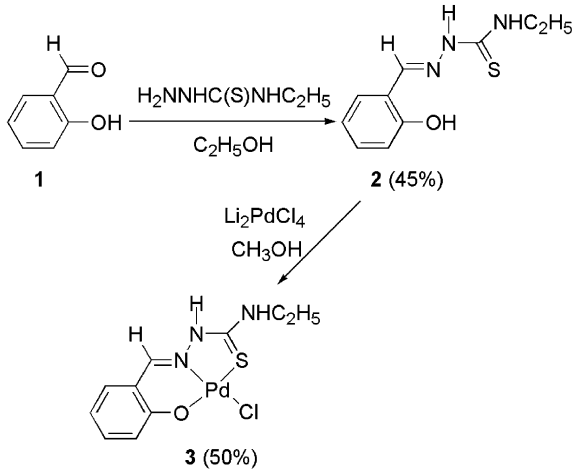
The palladium-catalyzed arylation of alkenes, known as the Heck reaction, represents one of the most powerful tools in organic synthesis for carbon–carbon bond formation.[1] The complexes used as catalysts are usually based on phosphorus ligands.[2] These catalysts are often water- and air-sensitive.[3] Therefore, catalysis under phosphine-free conditions is a challenge of high importance, and a number of phosphine-free ligands[4] as well as ligand-free palladium catalysts[5] for the Heck reaction have been reported. In our attempts to evaluate phosphine-free systems in the Heck reaction, a substituted salicylaldehyde thiosemicarbazone was chosen for this purpose. The chemistry of thiosemicarbazones has been an extremely active area of research primarily because of the beneficial biological (viz. antiviral and antitumor) activities of their transition-metal complexes.[6] Salicylaldehyde thiosemicarbazone is a multidentate ligand with five potential coordination sites: three N, one O, and one S atoms. Usually, it is bonded to a transition-metal leaving some potential donor sites unused, and it could play a constructive role for specific purposes, for example, the construction of heteropolynuclear complexes.[7] This phosphine-free system attracted our attention due to the presence of additional potential N-donors, since it is known that an additional coordination site as a stabilizing group during the course of a metal-mediated reaction could improve the catalytic efficiency of the complex.[2l,4e,8]

Recently, our groups have published several papers concerning the coordination chemistry of thiosemicarbazones[9] and transition-metal homogeneous catalysis employing phosphorus ligands with additional potential donors, such as N, O, S, the constructive role of which in catalysis is decisive, even though the additional donor is not bound to the metal.[2l,10] In the present work, we report the synthesis and crystal structure of a palladium complex with salicylaldehyde *N*(4)-ethylthiosemicarbazone. This phosphine-free system was applied to the Heck reaction of aryl bromides with styrene. To our knowledge, this paper represents the first study concerning the evaluation of a thiosemicarbazone ligand in the Heck reaction.

The synthesis of the palladium complex **3** is outlined in Scheme 1.[11] Salicylaldehyde *N*(4)-ethylthiosemicarbazone (H_2Sal4Et) **2**[12] was prepared by treatment of

Keywords: Thiosemicarbazone; O, N, S-ligand; Phosphine-free ligand; Palladium complex; Heck reaction; Homogeneous catalysis.
* Corresponding authors. Tel.: +30-26510-98425; fax: +30-26510-44-831(D.K.-D); tel.: +30-210-7273878; fax: +30-210-7273877 (I.D.K); e-mail addresses: dkovala@cc.uoi.gr; ikostas@eie.gr

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.02.062



Scheme 1.

salicylaldehyde **1** with *N*-ethylthiosemicarbazide in ethanol. The synthesis of complex **3** was achieved by the reaction of ligand **2** with Li_2PdCl_4, prepared in situ from $PdCl_2$ and LiCl. The microanalytical data are consistent with the formula $C_{10}H_{14}ClN_3O_2PdS$, which indicates the structure $[Pd(HSal4Et)Cl]\cdot H_2O$. The presence of lattice water is suggested by the IR spectrum, which revealed the appearance of a strong band at 3494 cm^{-1} consistent with a stretching ν(H–O–H) bond. Also, the low value of ν(Pd–Cl) at 291 cm^{-1} suggests the presence of an inter- or intramolecular halogen hydrogen bond.[13]

Recrystallization of complex **3** from CH_3CN/CH_3OH (1:1) yielded orange prisms suitable for single crystal X-ray analysis. The structure is shown in Figure 1.[14] The presence of lattice water in the complex is obvious as shown in its crystal structure. The monoanionic HSal4Et ligand is coordinated to palladium in a tridentate fashion via the phenoxy oxygen, the azomethine nitrogen N(1), and the sulfur atom, forming one six- and one five-membered chelate ring. The ligand shows a *Z*, *E*, *Z* configuration for the donor centers oxygen, nitrogen, and sulfur, respectively. The S–C(9) bond distance of 1.713(3) Å is consistent with a double-bond character, while both thioamide C–N distances (N(2)–C(9), 1.338(4) Å; N(3)–C(9), 1.331(4) Å) indicate an increased single bond character, in accordance with a molecule

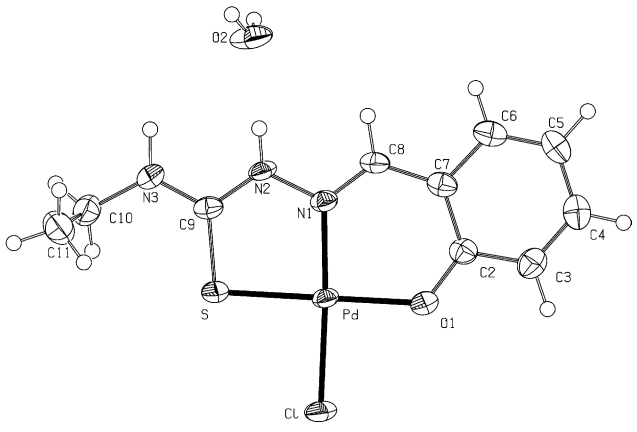
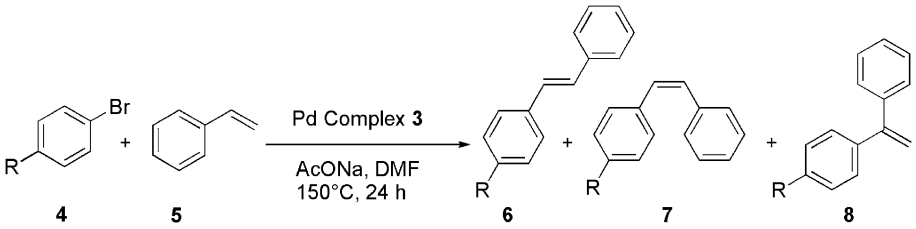


Figure 1. ORTEP drawing of palladium complex **3**.

protonated on N(2).[15] The displacement from coplanarity is indicated by the dihedral angle between the phenol ring and the plane defined by the five-membered chelate ring Pd–S–C(9)–N(2)–N(1) being 3.45(12)°, and the dihedral angle between the phenol ring and the plane defined by the six-membered chelate ring Pd–N(1)–C(8)–C(7)–C(2)–O(1) being 2.21(13)°.

Complex **3** was applied to the Heck reaction of styrene with some representative 4-substituted aryl bromides (from electron-rich to electron-poor) in DMF at 150 °C for 24 h, using AcONa as base, and in the absence of any promoting additive (Scheme 2, Table 1).[16] Although the reaction can be performed at lower temperatures, 150 °C is the best reaction temperature for synthetic purposes. Catalysis was performed under an inert atmosphere as well as in air. The reaction was first performed using a 1:1000 catalyst:aryl bromide molar ratio to ensure a higher yield process, and then by decreasing the ratio to 1:100,000. There was good selectivity for formation of *trans*-stilbenes **6**, ranging from 92% to 96%, and it is noteworthy that side-products, other than *cis*-stilbenes **7** and 1,1-diphenylethylenes **8**, were absent or present only in traces. As expected, the catalytic activity depended on the halide, while electron-withdrawing groups on the aryl ring increased the reaction rate. The activity follows in the order NO_2>CHO>H>OMe, suggesting that the rate-determining step in the Heck reaction is the oxidative addition of the aryl bromide to the palladium catalyst. Under argon, the catalyst is thermally stable and the reaction mixture remains yellow or colorless, depending on the palladium concentration. A catalyst:substrate ratio of 1:1000 leads to total yields of 46% and 54% for the very inactive 4-bromoanisole and the relatively inactive bromobenzene, respectively. At lower conversions, for these substrates the reaction proceeds with TONs of up to 17,000 and 18,000, respectively. High activity was observed for the activated 4-bromobenzaldehyde and 1-bromo-4-nitrobenzene. A catalyst:substrate ratio of 1:1000 led to high conversion (95%) of the aryl bromide, and with a ratio of 1:100,000, the reaction proceeded with TONs of up to 43,000. At lower ratios, even higher TONs were possible but these were not optimized. In spite of the thermal stability of the complex under argon, unfortunately, at high temperatures in air, partial decomposition took place, and the reaction mixture turned to dark brown. In air, a catalyst:substrate ratio of 1:1000 led to total yields of 12% and 18% for 4-bromoanisole and bromobenzene, respectively. These yields are significantly lower compared to those obtained under argon. It is obvious, however, that the catalyst remains active in air even for the nonactivated aryl bromides. On the other hand, with a catalyst:substrate ratio of 1:1000, and for the activated aryl bromides, it is noteworthy that the yields were found to be essentially the same as those obtained when the reaction was performed under argon. However, in air and at a very low palladium concentration, for a catalyst:4-bromobenzaldehyde ratio of 1:100,000, the yield was diminished.

In summary, we have synthesized and characterized a chelate palladium complex with salicylaldehyde *N*(4)-



Scheme 2.

Table 1. Heck reaction of aryl bromides with styrene catalyzed by palladium complex **3**

Entry	R	Atmosphere	ArBr/Pd ratio	GC Yield (%)[a]	TON[b]	Selectivity **6**:**7**:**8**
1	OMe	Argon	1000	46	460	95.4:0.5:4.1
2	OMe	Air	1000	12	120	94.1:—:5.9
3	OMe	Argon	100,000	17	17,000	92.0:0.2:7.8
4	H	Argon	1000	54	540	96.4:0.7:2.9
5	H	Air	1000	18	180	95.0:—:5.0
6	H	Argon	100,000	18	18,000	95.3:—:4.7
7	CHO	Argon	1000	95	950	95.1:0.1:4.8
8	CHO	Air	1000	94	940	96.4:0.3:3.3
9	CHO	Argon	100,000	30	30,000	95.1:—:4.9
10	CHO	Air	100,000	14	14,000	95.7:0.7:3.6
11	NO_2	Argon	1000	95	950	95.1:0.7:4.2
12	NO_2	Air	1000	94	940	96.1:0.7:3.2
13	NO_2	Argon	100,000	43	43,000	94.8:0.5:4.7

Reaction conditions: ArBr (1.0 mmol), styrene (1.5 mmol), AcONa (2.0 mmol), Pd complex **3** in DMF (1 mL), 150 °C, 24 h.
[a] Total GC yield of all isomers, based on the aryl bromide using decane as internal standard.
[b] Turnover no (TON) = fraction of products (**6** + **7** + **8**) × substrate/Pd ratio.

ethylthiosemicarbazone, in which, according to its crystal structure, deprotonation from the alcohol function takes place, and the ligand is bound to the metal in an O, N, S-terdentate coordination mode, forming one six- and one five-membered chelate ring. This phosphorus-free complex with additional potential N-donors is thermally stable under argon, and efficiently catalyses the Heck reaction of aryl bromides with styrene, with good turnover numbers, and good selectivity toward *trans*-stilbenes. The catalyst is also active in air, in particular for the activated substrates. This first study of the application of thiosemicarbazone ligands to the Heck reaction provides important information on the catalytic activity of these systems. The development of analogous ligands for the Heck as well as other palladium-catalyzed reactions is currently in progress.

Acknowledgements

This investigation was supported in part by the Research Committee of the University of Ioannina, Project S. Dakaris, and in part by the General Secretariat of Research and Technology of Greece. P.N.Y. thanks IKY for a scholarship.

References and notes

1. Recent leading monographs and reviews: (a) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons: Chichester, 1995; (b) Reetz, M. T. In *Transition Metal Catalysed Reactions*; Davies, S. G., Murahashi, S.-I., Eds.; Blackwell Science: Oxford, 1999; (c) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066; (d) Whitecombe, N. J.; Hii, K. K. (Mimi); Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449–7476; (e) Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 4176–4211; (f) Tucker, C. E.; de Vries, J. G. *Top. Catal.* **2002**, *19*, 111–118; (g) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2963.
2. Recent selected papers: (a) Stambuli, J. P.; Stauffer, S. R.; Shaughnessy, K. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 2677–2678; (b) Feuerstein, M.; Doucet, H.; Santelli, M. *J. Org. Chem.* **2001**, *66*, 5923–5925; (c) Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem.* **2001**, *66*, 8677–8681; (d) Schnyder, A.; Indolese, A. F.; Studer, M.; Blaser, H.-U. *Angew. Chem. Int. Ed.* **2002**, *41*, 3668–3671; (e) Imbos, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 184–185; (f) Morales-Morales, D.; Redón, R.; Zheng, Y.; Dilworth, J. R. *Inorg. Chim. Acta* **2002**, *328*, 39–44; (g) Kondolff, I.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2003**, *44*, 8487–8491; (h) Tu, T.; Hou, X.-L.; Dai, L.-X. *Org. Lett.* **2003**, *5*, 3651–3653; (i) Hierso, J.-C.; Fihri, A.; Amardeil, R.; Meunier, P.; Doucet, H.; Santelli, M.; Donnadieu, B. *Organometallics* **2003**, *22*, 4490–4499; (j) Imbos, R.; Minnaard, A. J.; Feringa, B. L. *J. Chem. Soc., Dalton Trans.* **2003**, 2017–2023; (k) Catsoulacos, D. P.; Steele, B. R.; Heropoulos, G. A.; Micha-Screttas, M.; Screttas, C. G. *Tetrahedron Lett.* **2003**, *44*, 4575–4578; (l) Kostas, I. D.; Steele, B. R.; Terzis, A.; Amosova, S. V. *Tetrahedron* **2003**, *59*, 3467–3473.
3. For air-stable phosphine catalysts, see for example Refs. 2c,f.
4. Recent selected papers: (a) Tulloch, A. A. D.; Danopoulos, A. A.; Tooze, R. P.; Cafferkey, S. M.; Kleinhenz, S.; Hursthouse, M. B. *Chem. Commun.* **2000**, 1247–1248; (b) Albéniz, A. C.; Espinet, P.; Martín-Ruiz, B.; Milstein, D.

J. Am. Chem. Soc. **2001**, *123*, 11504–11505; (c) Peris, E.; Loch, J. A.; Mata, J.; Crabtree, R. H. *Chem. Commun.* **2001**, 201–202; (d) Selvakumar, K.; Zapf, A.; Beller, M. *Org. Lett.* **2002**, *4*, 3031–3033; (e) Jung, I. G.; Son, S. U.; Park, K. H.; Chung, K.-C.; Lee, J. W.; Chung, Y. K. *Organometallics* **2003**, *22*, 4715–4720; (f) Díez-Barra, E.; Guerra, J.; Hornillos, V.; Merino, S.; Tejeda, J. *Organometallics* **2003**, *22*, 4610–4612; (g) Consorti, C. S.; Zanini, M. L.; Leal, S.; Ebeling, G.; Dupont, J. *Org. Lett.* **2003**, *5*, 983–986; (h) Nájera, C.; Gil-Moltó, J.; Karlström, S.; Falvello, L. R. *Org. Lett.* **2003**, *5*, 1451–1454; (i) Masllorens, J.; Moreno-Mañas, M.; Pla-Quintana, A.; Roglans, A. *Org. Lett.* **2003**, *5*, 1559–1561; (j) Park, S. B.; Alper, H. *Org. Lett.* **2003**, *5*, 3209–3212; (k) Mazet, C.; Gade, L. H. *Eur. J. Inorg. Chem.* **2003**, 1161–1168.

5. Recent selected papers: (a) Reetz, M. T.; Westermann, E. *Angew. Chem. Int. Ed.* **2000**, *39*, 165–168; (b) Gruber, A. S.; Pozebon, D.; Monteiro, A. L.; Dupont, J. *Tetrahedron Lett.* **2001**, *42*, 7345–7348; (c) Yao, Q.; Kinney, E. P.; Yang, Z. *J. Org. Chem.* **2003**, *68*, 7528–7531; (d) Schmidt, A. F.; Smirnov, V. V. *J. Mol. Catal. A: Chem.* **2003**, *203*, 75–78; (e) de Vries, A. H. M.; Mulders, J. M. C. A.; Mommers, J. H. M.; Henderickx, H. J. W.; de Vries, J. G. *Org. Lett.* **2003**, *5*, 3285–3288; (f) Willans, C. E.; Mulders, J. M. C. A.; de Vries, J. G.; de Vries, A. H. M. *J. Organomet. Chem.* **2003**, *687*, 494–497.
6. Recent selected papers: (a) Quiroga, A. G.; Perez, J. M.; López-Solera, I.; Masaguer, J. R.; Luque, A.; Román, P.; Edwards, A.; Alonso, C.; Navarro-Ranninger, C. *J. Med. Chem.* **1998**, *41*, 1399–1408; (b) Kovala-Demertzi, D.; Demertzis, M. A.; Varagi, V.; Papageorgiou, A.; Mourelatos, D.; Mioglou, E.; Iakovidou, Z.; Kotsis, A. *Chemotherapy* **1998**, *44*, 421–426; (c) Varadinova, T.; Kovala-Demertzi, D.; Rupelieva, M.; Demertzis, M.; Genova, P. *Acta Virologica* **2001**, *45*, 87–94; (d) Iakovidou, Z.; Papageorgiou, A.; Demertzis, M. A.; Mioglou, E.; Mourelatos, D.; Kotsis, A.; Yadav, P. N.; Kovala-Demertzi, D. *Anticancer Drugs* **2001**, *12*, 65–70; (e) Jouad, E. M.; Thanh, X. D.; Bouet, G.; Bonneau, S.; Khan, M. A. *Anticancer Res.* **2002**, *22*, 1713–1716.
7. (a) Pal, I.; Basuli, F.; Mak, T. C. W.; Bhattacharya, S. *Angew. Chem. Int. Ed.* **2001**, *40*, 2923–2925; (b) Dutta, S.; Basuli, F.; Peng, S.-M.; Lee, G.-H.; Bhattacharya, S. *New J. Chem.* **2002**, *26*, 1607–1612.
8. Reetz, M. T.; Waldvogel, S. R.; Goddard, R. *Tetrahedron Lett.* **1997**, *38*, 5967–5970.
9. (a) Kovala-Demertzi, D.; Kourkoumelis, N.; Demertzis, M. A.; Miller, J. R.; Frampton, C. S.; Swearingen, J. K.; West, D. X. *Eur. J. Inorg. Chem.* **2000**, 727–734; (b) Kovala-Demertzi, D.; Demertzis, M. A.; Miller, J. R.; Papadopoulou, C.; Dodorou, C.; Filousis, G. *J. Inorg. Biochem.* **2001**, *86*, 555–563; (c) Yadav, P. N.; Demertzis, M. A.; Kovala-Demertzi, D.; Castineiras, A.; West, D. X. *Inorg. Chim. Acta* **2002**, *332*, 204–209; (d) Kovala-Demertzi, D.; Demertzis, M. A.; Filiou, E.; Pantazaki, A. A.; Yadav, P. N.; Miller, J. R.; Zheng, Y. F.; Kyriakidis, D. A. *Biometals* **2003**, *16*, 411–418.
10. (a) Kostas, I. D.; Screttas, C. G. *J. Organomet. Chem.* **1999**, *585*, 1–6; (b) Kostas, I. D. *J. Chem. Res. (S)* **1999**, 630–631; (c) Kostas, I. D. *J. Organomet. Chem.* **2001**, *626*, 221–226; (d) Kostas, I. D. *J. Organomet. Chem.* **2001**, *634*, 90–98; (e) Kostas, I. D. *Inorg. Chim. Acta* **2003**, *355*, 424–427.
11. Analytical data. *H_2Sal4Et* **2**: mp 150 °C. IR (KBr): *v* 3355 (OH), 3252 (NH), 3179 (NH), 1618, 1602 (C=N), 958 (N–N), 870 cm^{-1} (C=S); ^{1}H NMR (DMSO-d_6): δ 11.39 (s, 1H), 9.90 (s, 1H), 8.48 (m, 2H), 7.95 (d, $J = 8.0$ Hz, 1H), 7.27 (t, $J = 11.2$ Hz, 1H), 6.89 (m, 2H), 3.66 (m, 2H), 1.18 (t, $J = 9.2$ Hz, 3H). Anal. Calcd for $C_{10}H_{13}N_3OS$: C, 53.8; H, 5.9; N, 18.8; S, 14.4. Found: C, 53.6; H, 6.1; N, 18.6; S, 14.2. *[Pd(HSal4Et)Cl]·H_2O*: mp 279 °C. IR (KBr): *v* 3494 (OH_2), 3279 (NH), 1600 (C=N), 817 cm^{-1} (C=S); FAR-IR (PE): *v* 424 (Pd–N), 392 (Pd–O), 343 (Pd–S), 291 cm^{-1} (Pd–Cl); ^{1}H NMR (DMSO-d_6): δ 8.46 (m, 2H), 7.95 (d, $J = 8.0$ Hz, 1H), 7.24 (t, $J = 11.2$ Hz, 1H), 6.86 (m, 2H), 3.35 (m, 2H), 1.17 (t, $J = 11.2$ Hz, 3H). Anal. Calcd for $C_{10}H_{14}ClN_3O_2PdS$: C, 31.4; H, 3.7; Cl, 9.5; N, 11.0; Pd, 27.9; S, 8.4. Found: C, 31.5; H, 3.7; Cl, 9.3; N, 11.2; Pd, 27.8; S, 8.3.
12. Known compound: (a) Mishra, P.; Chowdhari, D.; Katrolia, S. P.; Agrawal, R. K. *Hind. Antibiot. Bull.* **1988**, *30*, 37–39 [*Chem. Abstr.* **1988**; *109*, 208128]; (b) Yin, D.-D.; Jiang, Y.-L.; Shan, L. *Chin. J. Chem.* **2001**, *19*, 1136–1140 [*Chem. Abstr.* **2003**; *136*, 183890].
13. Kovala-Demertzi, D.; Domopoulou, A.; Demertzis, M. A.; Raptopoulou, C. P.; Terzis, A. *Polyhedron* **1994**, *13*, 1917–1925.
14. Crystallographic data for the structure of **3** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 225257. Crystal data for **3**: Intensity data were collected on a Rigaku AFC6S diffractometer with graphite monochromated Mo-Kα radiation ($\lambda = 0.71069$ Å) at 296 K, using the $\omega - 2\theta$ technique to a maximum 2θ of 54.9°. $C_{10}H_{12}ClN_3OPdS \cdot H_2O$, $M = 382.12$, triclinic, $a = 8.9232(7)$ Å, $b = 9.522$ (1) Å, $c = 8.061$ (2) Å, $\alpha = 103.56$ (1)°, $\beta = 91.99$ (1)°, $\gamma = 92.55$ (1)°, $V = 664.5$ (2) Å^3, space group *P*-1 (no 2), $Z = 2$, $d_{calcd} = 1.751$ g/cm^3, 3245 reflections measured, 3049 reflections [$I > 2\sigma(I)$] were used in all calculations, $R = 0.0635$, $R_w = 0.0262$.
15. Kovala-Demertzi, D.; Miller, J. R.; Kourkoumelis, N.; Hadjikakou, S. K.; Demertzis, M. A. *Polyhedron* **1999**, *18*, 1005–1013.
16. *General experimental procedure for the Heck reaction:* A Schlenk flask equipped with a reflux condenser, was charged under argon or in air with aryl bromide (1.0 mmol), styrene (0.17 mL, 1.5 mmol), AcONa (0.164 g, 2.0 mmol), a stock solution of complex **3** in DMF (1 or 0.01 mM, 1 mL, 0.001 or 0.00001 mmol, respectively), and decane (0.08 mL, 0.4 mmol) as internal standard, stirred in a preheated 150 °C oil bath for 24 h, and then allowed to cool to rt. After addition of aqueous NaOH and extraction with dichloromethane, the organic phase was washed with brine, dried over Na_2SO_4, filtered, passed through Celite, and analyzed by GC and GC–MS. All the Heck products are known compounds.[2l]