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Sulfur-Containing Palladacycles as Catalyst Precursors for the Heck Reaction

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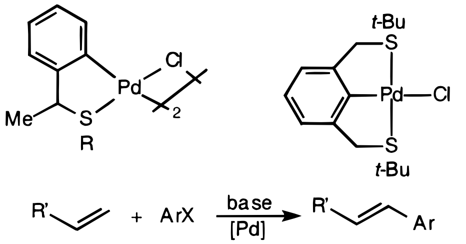
ABSTRACT



The air, water, and highly thermally stable sulfur-containing palladacycles, mainly derived from the ortho-palladation of benzylic thioethers, are exceptional catalyst precursors for the Heck reaction. The reaction can be performed with aryl iodides, bromides, and chlorides, with acrylic esters and styrene, leading to turnover numbers up to 1 850 000.

Heck type reactions are one of the most important transition-metal-catalyzed C−C bond-forming reactions.[1] Although these reactions can be mediated by a variety of Pd(0) and Pd(II) compounds, phosphorus-[2] or nitrogen-containing[3] palladacycles are among the most active catalyst precursors reported to date.[4] Indeed, the advent of these catalyst precursors allowed the Heck reaction to be performed with activated and nonactivated aryl halides using very low catalyst concentrations (down to ppm's in the case of aryl iodides).[2,3] Two of most intriguing aspects of the use of palladacycles in the Heck reaction are the probable involvement of Pd(IV) species and that the Pd(II) catalyst precursors are recovered unchanged after catalysis. This latter aspect is quite surprising since it is well-known that the Pd−C bond of palladacycles is generally reactive toward various electrophilic and nucleophilic substrates, and depalladation processes are usually observed.[5] These highly active catalyst precursors are among the most thermally stable palladacycles known.[6] Since sulfur-containing palladacycles[7] possess one of the most stable Pd−C bonds in this class of organopalladium compounds, they should be potential candidates to mediate the Heck reaction. We report here that, indeed,

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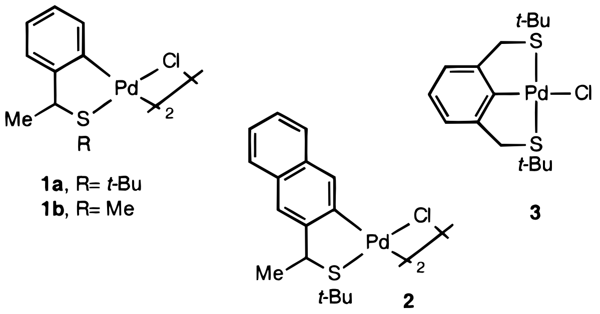
Table 1. Results of the Heck Reaction Mediated by Palladacycle Catalyst Precursors **1**−**3** in DMA under Various Reaction Conditions

entry	[Pd]	[Pd] (M)	ArX	R	base	*T* (°C)	*t* (h)	TON[a]	TOF[b] (min^{-1})	yield[c] (%)
1	**1a**	2×10^{-5}	C_6H_5I	CO_2Me	NEt_3	140	1	47 000	783.0	94
2[e]	**1a**	2×10^{-5}	C_6H_5I	Ph	NEt_3	140	18	50 000	46.3	100
3	**1b**	2×10^{-5}	C_6H_5I	CO_2Me	NEt_3	140	15	42 500	47.2	85
4[e]	**1b**	2×10^{-5}	C_6H_5I	Ph	NEt_3	140	18	50 000	46.3	100
5	**2**	2×10^{-5}	C_6H_5I	CO_2Me	NEt_3	140	18	31 500	29.0	63
6[e]	**2**	2×10^{-5}	C_6H_5I	Ph	NEt_3	140	39	50 000	21.4	100
7	**3**	2×10^{-5}	C_6H_5I	CO_2Me	NEt_3	140	24	45 000	31.2	90
8[e]	**3**	2×10^{-5}	C_6H_5I	Ph	NEt_3	140	43	48 500	18.8	97
9	**1a**	2×10^{-7}	C_6H_5I	CO_2Me	NEt_3	140	38	1 850 000	811.0	37
10	**1a**	1×10^{-2}	C_6H_5Br	CO_2Me	NaOAc	140	2	60	0.5	60
11	**1a**[f]	2×10^{-5}	C_6H_5Br	CO_2Me	NaOAc	140	28	23 500	14.0	47
12[g]	**1a**[f]	2×10^{-5}	C_6H_5Br	Ph	NaOAc	140	28	28 000	16.7	56
13	**1a**[d]	2×10^{-5}	C_6H_5Br	CO_2Bu	NaOAc	170	8	37 500	78.0	75
14	**1a**	2×10^{-5}	$4\text{-CHO-}C_6H_4Br$	CO_2Me	NEt_3	140	56	21 500	6.4	43
15	**1a**[d]	2×10^{-5}	$4\text{-CHO-}C_6H_4Br$	CO_2Me	NaOAc	140	2.5	33 000	220.0	66
16	**3**[d]	2×10^{-5}	$4\text{-CHO-}C_6H_4Br$	CO_2Me	NEt_3	140	24	13 500	9.4	27
17	**1a**[d]	2×10^{-5}	$4\text{-CHO-}C_6H_4Br$	Ph	NEt_3	140	90	5000	0.9	10
18	**1a**[f]	2×10^{-5}	$3\text{-CF}_3\text{-}C_6H_4Br$	CO_2Me	NaOAc	140	4	35 000	145.8	70
19	**1a**[f]	2×10^{-5}	$4\text{-Me-}C_6H_4Br$	CO_2Me	NaOAc	140	26	21 000	13.5	42
20	**1a**[d]	2×10^{-5}	$4\text{-MeO-}C_6H_4Br$	CO_2Bu	NaOAc	170	6	30 500	84.7	61
21	**1a**[d]	1×10^{-3}	PhCH═CHBr	CO_2Me	NaOAc	140	1	400	6.7	40
22	**1a**[d]	2×10^{-5}	PhCH═CHBr	CO_2Me	NaOAc	140	8	9000	18.8	18
23	**1a**[d]	1×10^{-3}	$4\text{-NO}_2\text{-}C_6H_4Cl$	CO_2Bu	NaOAc	170	2	490	4.0	49
24	**1a**[d]	2×10^{-5}	$4\text{-NO}_2\text{-}C_6H_4Cl$	CO_2Bu	NaOAc	170	2	5000	41.7	10
25[h]	**1a**[d]	1×10^{-3}	$4\text{-NO}_2\text{-}C_6H_4Cl$	Ph	NaOAc	170	5	410	1.4	41

[a] TON: turnover number (mol product/mol catalyst). [b] TOF: turnover frequency (mol product/mol catalyst × time. [c] Total GC yield of all isomers (undecane as internal standard). [d] Addition of 20% of $N(n\text{-Bu})_4Br$. [e] *trans*-Stilbene/*cis*-stilbene = 6. [f] Addition of 1 mmol of $N(n\text{-Bu})_4Br$. [g] *trans*-Stilbene/*cis*-stilbene = 9. [h] *trans*-Stilbene almost exclusively.

the air, water, and thermally stable sulfur-containing palladacycles (Figure 1) are highly active catalyst precursors for the Heck reaction.



1a, R= *t*-Bu
1b, R= Me

2

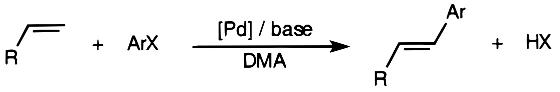
3

Figure 1. Sulfur-containing palladacycles used as catalyst precursors for the Heck reaction.

The new sulfur-containing palladacycles **1** and **2** have been prepared according to procedures similar to those described in the literature using palladium acetate as the metalation agent.[7a] These complexes were fully characterized by means of combustion analysis, IR, and ^1H and ^{13}C NMR spectroscopy. Moreover, the molecular structure of an acetato-bridged derivative of **1a** was determined by X-ray diffraction analysis.[8] Complex **3** was prepared as described previously.[9]

The complexes **1**−**3** show moderate to exceptional catalyst activity for the arylation and vinylation of olefins with aryl iodides, bromides, and chlorides (Scheme 1 and Table 1).

Scheme 1. Heck Arylation Reaction



In a typical experiment, 1.2 equiv of methyl acrylate or styrene was added to a solution of the aryl halide or the vinyl bromide (1 mmol) in 5 mL of dimethylacetamide (DMA) followed by the addition of a 40% excess of base (triethylamine or sodium acetate) and undecane as the internal standard. After the addition of the palladacycle in dimethylacetamide, the reaction mixture is stirred at 140 °C for the desired time. The reaction mixture was analyzed by gas chromatography, and the yield was determined using unde-

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(8) Gruber, A. S.; Fonseca, G. S.; Ebeling, G.; Burrow, R.; Dupont, J. Manuscript in preparation.

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cane as internal standard.[10] The products were identified by GC-MS and by comparison of their retention times (GC) with those of authentic samples. Selected results are summarized in Table 1.

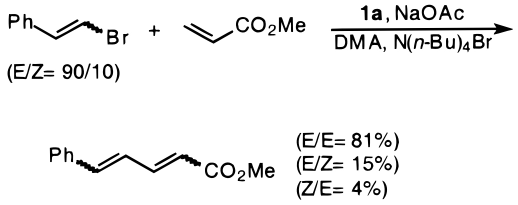
As shown in Table 1, all palladacycles **1**−**3** are active in the arylation of methyl acrylate and styrene (entries 1−8). However, complexes **1** are by far the most active, particularly in the reaction of methyl acrylate with iodobenzene where ppm's of the palladacycle **1a** can be used. In this system, a TOF of 811 min^{-1} (TON up to 1.8×10^6, Table 1, entry 9) was achieved; this TOF value is among the highest reported to date.[2,3] The use of sodium acetate[11] as a base gave generally better reaction rates than triethylamine in particular in the case of the vinyl bromide (see later). In all cases investigated there was no noticeable formation of metallic palladium and the final reaction mixture was pale yellow or almost colorless when very low catalyst concentrations (ppm) were used. These catalyst systems are not sensitive to oxygen and water, and the reaction can be carried out in air, with no change in efficiency. Only in cases where catalyst concentrations are lower than 2×10^{-5} should the purified aryl halides and the olefins be used and the reaction conducted in an inert atmosphere (N_2 or Ar). Although the Heck reaction can be performed at lower temperatures (down to 90 °C), 140 °C is the best reaction temperature for synthetic purposes (in the case of aryl iodides). Screening the solvents we found that DMA is clearly superior, in terms of reaction rates, to toluene, dioxane, DMF, and acetonitrile using the reactions conditions described in Table 1 (entry 1).

The catalytic activity, as expected, depends on the halide and on the olefin substituents. Methyl acrylate gave generally better reaction rates than styrene regardless of the aryl halide employed. Electron-withdrawing groups on the aryl ring increase the reaction rate. For example, in a competitive experiment mediated by **1a** (2×10^{-5} M) the reaction of 4-acetyliodobenzene, iodobenzene, and 4-methoxybenzene (1:1:1) with 0.33 equiv of methyl acrylate and 1.4 equiv of triethylamine in DMA at 140 °C gave after 15 h (100% conversion based on the methyl acrylate) affords the substituted *trans*-methyl cinnamates (4-acetylphenyl, phenyl, 4-methoxyphenyl) in a proportion of 7:2:1, respectively.

Bromobenzene, a relatively inactive halide, gave a 60% yield of *trans*-methyl cinnamate after reaction with methyl acrylate for 2 h at higher catalyst concentration (1%, entry 10). However, the use of $N(n\text{-}Bu)_4Br$[12] as promoter increases the reaction rate and a TON of 23 500 is achievable (entry 11).[13] Moreover, increasing the reaction temperature to 170 °C (entry 13) affords *trans*-*n*-butyl cinnamate in a 75% yield after 4 h (TOF = 78 min^{-1}). Bromobenzenes substituted with electron-withdrawing or electron-donating groups also give good to exceptional TOF's (entries 14−20). These TOF's with aryl bromides and acrylic esters are by far the highest observed so far.[2,3] For example, nitrogen-[3] and phosphorus-containing[14] palladacycles gave TOF's up to 17 and 35 min^{-1}, respectively, in the reaction of methyl acrylate with bromobenzene.

The reaction also works with vinyl bromides. Thus, the reaction of a mixture of *cis*/*trans* β-bromostyrene with methyl acrylate affords the corresponding dienes (Scheme 2) after 1 h (Table 1, entries 21 and 22). It is interesting to note that when the reaction was performed using triethylamine as a base, only complete isomerization of β-bromostyrene to its *trans* isomer was observed without any coupling products being detected.

Scheme 2. Vinylation of Methyl Acrylate Mediated by Palladacycle **1a**



We were pleased to observe that activated aryl chlorides can also be used (entries 23−25). For example, the reaction of 4-nitrochlorobenzene with *n*-butyl acrylate mediated by **1a** gave *trans*-*n*-butyl cinnamate in 49% yield (entry 23). In opposition, the reaction of chlorobenzene with *n*-butyl acrylate is very slow, giving less than 1.5% of *trans*-*n*-butyl cinnamate after 21 h (TON = 750) at 170 °C using **1a** as a catalyst precursor.

These results suggest that the rate-determining step in the Heck catalysis is the oxidative addition of the aryl halide to the sulfur-containing palladacycle catalyst. Whether this mechanism involves Pd(0)/Pd(II) or Pd(II)/Pd(IV) catalytic cycles is still under debate.[15] The marked differences in the catalytic activity depending on the metalated thioether moiety would suggest Pd(II)/Pd(IV) as the major pathway.

The facility for preparation of the air, water, and thermally stable sulfur-containing palladacycles associated with their excellent catalytic activity on the Heck reaction render them as attractive candidates for other catalytic coupling reactions.[16] Indeed, these sulfur-containing palladacycles also were shown to be excellent catalysts precursors for the Suzuki coupling reaction and telomerization of dienes under

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[10] The products can be easily isolated from the reaction mixture by addition of water and extraction of the organic phase with CH_2Cl_2. Evaporation of the volatiles gave essentially pure compounds (IR, NMR, and GC-MS). For example, the methyl cinnamate was isolated in 90% yield from entry 1 (Table 1). See also the procedure in the Supporting Information.

[11] Spencer, A. *J. Organomet. Chem*. **1983**, *258*, 101.

[12] Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667.

[13] Note that in this case *trans*-*n*-butyl cinnamate (product resulting from the scrambling of *trans*-methyl cinnamate and $N(n\text{-}Bu)_4Br$) is also formed.

[14] Ohff, M.; Ohff, A.; Milstein, D. *J. Am. Chem. Soc.* **1997**, *119*, 11687.

[15] For studies concerning the mechanism of the Heck reaction, see, for example: (a) Amatore, C.; Jutand, A. *J. Organomet. Chem.* **1999**, *576*, 254. (b) Shaw, B. L. *New J. Chem.* **1998**, *22*, 77. (c) Reetz, M. T.; Westermann, E. *Angew. Chem., Int. Ed.* **2000**, *39*, 165.

[16] For other C−C and C−heteroatom coupling reactions mediated by palladacycles, see, for example: (a) Camargo, M.; Dani, P.; Dupont, J.; de Souza R. F.; Pfeffer, M.; Tkatchenko, I. *J. Mol. Catal. A* **1996**, *109*, 127. (b) Hollis, T. K.; Overman, L. E. *Tetrahedron Lett.* **1997**, *38*, 8837. (c) Dani, P.; Dupont, J.; Monteiro, A. L. *J. Braz. Chem. Soc*. **1996**, *7*, 15.

both homogeneous and two-phase conditions. These aspects are currently under investigation in our laboratory, and the results will be published in due course.

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Supporting Information Available: Preparation and characterization of palladacycles **1** and **2** and a representative procedure for the Heck reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

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