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Sulfilimine palladacycles: stable and efficient catalysts for carbon–carbon coupling reactions

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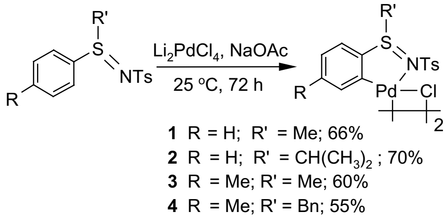
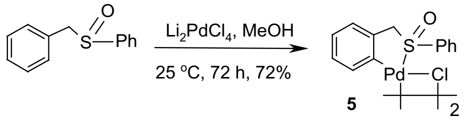
Abstract—A new family of sulfilimine-based palladacycles (**1**–**4**) has been synthesized in high yields from easily accessible starting materials and is found to exhibit high catalytic activities for carbon–carbon bond-formation in Suzuki, Heck, Sonogashira and Ullmann-type reactions, affording coupled products in excellent yields.

Palladium-catalyzed cross-coupling chemistry for the formation of carbon–carbon bonds has recently emerged as a powerful method in organic synthesis.[1] Coupling of organopalladium(II) halide or triflate moieties occurs with a variety of substrates including alkenes (Heck–Mizoroki arylation[2]), organoboron compounds (Suzuki–Miyaura reactions[3]), amines (Hartwig–Buchwald amination[4]) or organotin compounds (Stille coupling[5]). Although these reactions can be mediated by a variety of simple and highly reactive Pd(0) and Pd(II) salts in the presence of various phosphine ligands as well as phosphine-free palladium-carbene catalyst precursors,[6] several challenges remain to be achieved for industrial applications such as the use of aryl chlorides as substrates, the possibility of using aqueous conditions,[7] the recovery of catalyst[8] and the desire to simplify the catalyst by working under phosphine-free conditions.[2h,9] In this context, recent developments for the utilization of aryl chlorides in C–C, C–N and C–O bond-forming reactions have largely focused on Pd-catalysts containing bulky, electron-rich phosphine ligands,[10] the synthesis of which often involves multistep procedures using air-sensitive substances. In order to improve the stability of Pd-based catalysts and to increase their efficiency in coupling reactions, a new family of Pd-based catalyst precursors such as nitrogen-,[11] phosphorus-[12] and sulfur-[13] containing palladacycles[14] have recently been reported. The discovery of these catalyst precursors allows arylation and vinylation reactions to be performed with activated and nonactivated aryl halides using very low catalyst concentrations. In particular, the sulfur- and nitrogen-containing palladacycles are superior to phosphine palladacycles due to their high stability towards moisture, air and high temperature. In this communication, we report, for the first time, a new family of sulfilimine- and sulfoxide-based palladacycles (**1**–**5**), as effective catalyst precursors, for various cross-coupling reactions.

The new sulfilimine- and sulfoxide-based palladacycles (**1**–**5**) were prepared in high yields from the corresponding sulfilimines[15] and a sulfoxide, respectively, through a carbopalladation reaction[16] with lithium tetrachloropalladate in MeOH in the presence of NaOAc as base at 25 °C (Schemes 1 and 2). These complexes were



Scheme 1. Synthesis of sulfilimine palladacycles (**1**–**4**).



Scheme 2. Synthesis of sulfoxide palladacycle **5**.

Keywords: Sulfilimine palladacycle; Suzuki coupling reaction; Heck reaction; Sonogashira reaction.

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Table 1. Suzuki coupling of 4-bromotoluene with phenylboronic acid: screening of palladacycles[a]

No	Cat. (mmol)	Solvent	Yield (%)[b]
1	**1**[c] (0.0005)	Toluene	46.5
2	**1** (0.0025)	Toluene	59.2
3	**1** (0.005)	Toluene	85.6
4	**1** (0.005)	Water	60.1
5	**2**[d] (0.005)	Toluene	75.1
6	**3**[e] (0.005)	Toluene	71.9
7	**4**[f] (0.005)	Toluene	58.7
8	**5**[g] (0.005)	Toluene	54.1

[a] Conditions: 4-bromotoluene (5 mmol), phenylboronic acid (7.5 mmol), K_2CO_3 (10 mmol), solvent (15 ml), 110 °C, 3 h.

[b] Isolated yields after chromatographic purification.

[c] Mp: 135–141 °C (decomp.).

[d] Mp: 96–98 °C (decomp.).

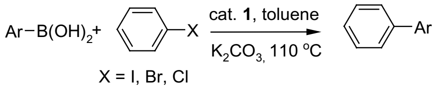
[e] Mp: 78–80 °C (decomp.).

[f] Mp: 156–159 °C (decomp.).

[g] Mp: 143–146 °C (decomp.).

fully characterized by means of C, H, N, S analysis, IR and ^{1}H and ^{13}C NMR spectroscopy.[†] Unsymmetrical biaryl units[17] are found in a range of pharmaceuticals, herbicides and natural products as well as in conducting polymers and liquid-crystalline materials. Recent research has been focused on the development of improved conditions for the Suzuki reaction for the synthesis of such biaryl units. We have systematically studied the Suzuki coupling reaction of 4-bromotoluene with phenylboronic acid using sulfilimine- and sulfoxide-palladacycles (**1**–**5**) and the results are summarized in Table 1. As can be seen, palladacycle **1** shows the highest catalytic activity in terms of conversion. While the reactions could be conducted with various bases (Et_3N, Cs_2CO_3, etc.) or solvents (THF, dioxane) the best results were obtained with K_2CO_3 as base and toluene as solvent. Remarkably, even water could be employed as solvent to obtain biaryls in 60% yield. However sulfoxide-based palladacycle **5** was generally found to show low catalytic activity in the coupling reaction resulting in moderate yields.

Table 2. Suzuki coupling of aryl halides with aryl boronic acids catalyzed by palladacycle **1**[a]



No	Ar	Aryl halide	*t* (h)	Yield (%)[b]	TON[c]
1	Ph	C_6H_5I	2	96	960
		C_6H_5Br	3	88	880
		C_6H_5Cl	8	20	200
		4-MeC_6H_4Br	3	86	860
		4-FC_6H_4Br	3	90	900
		4-$MeOC_6H_4I$	2	92	920
		4-$MeOC_6H_4Br$	3	80	800
2	3-ClC_6H_4	C_6H_5I	2	93	930
		C_6H_5Br	3	85	850
		4-$O_2NC_6H_4I$	2	85	850
3	2-Naphthyl	C_6H_5I	2	95	950
		C_6H_5Br	3	85	850
		C_6H_5Cl	8	30	300

[a] Conditions: aryl halide (5 mmol), aryl boronic acid (7.5 mmol), palladacycle **1** (0.005 mmol), substrate/ cat. = 1000, K_2CO_3 (10 mmol), toluene (15 ml), 110 °C.

[b] Isolated yields after chromatographic purification.

[c] TON = mmol of product/mmol of Pd.

Table 2 shows the results of Suzuki coupling of various aryl halides with a variety of aryl boronic acids catalyzed by palladacycle **1**.[‡] It is remarkable that complete conversion with high isolated yields of biaryls was achieved for the electron-rich substrates such as 4-bromotoluene and 4-bromoanisole. However, reduced yields (20–30%) of coupling reactions were observed for aryl chlorides as substrates.

We also examined the Heck arylation and vinylation of olefins with various aryl iodides and bromides using sulfilimine-based palladacycles (Table 3). The palladacycle **1** was found to catalyze the Heck reaction of aryl iodides containing either electron-rich or electron-withdrawing functional groups with high TONs. For example, when 4-nitroiodobenzene was subjected to arylation with ethyl acrylate a high TON (594,000) and excellent yield (99%) was obtained using palladacycle **1** (entry 4). However, no reaction took place when chlorobenzene and 4-nitrochlorobenzene were used as substrates.

In efforts to reduce the amount of diacetylene formation in the Sonogashira reaction, various copper-free condi-

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[†] General experimental procedure for the preparation of palladacycles **1**–**4**: A two-necked 25 ml round bottomed flask was charged with $PdCl_2$ (0.177 g, 1 mmol), LiCl (0.100 g, 2.4 mmol) and MeOH (2 ml) and the resulting reaction mixture was stirred under an argon atmosphere at 25 °C for 2.5 h. Then, NaOAc (0.123 g, 1.5 mmol) and a solution of sulfilimine[15] (1 mmol) in MeOH (2 ml) were added. The resulting reaction mixture was stirred at 25 °C for 72 h. Distilled water (6 ml) was added and the resulting solid was filtered using a sintered funnel, washed with water and dried under reduced pressure (5 mm) for 3 h to afford palladacycles **1**–**4** as brown colored solids. Spectral data for palladacycle **1**: Yield: 66%; mp: 135–141 °C (decomp.); IR (KBr, cm^{-1}): 547, 576, 688, 746, 825, 933, 1087, 1141, 1280, 1296, 1446, 1539, 1595, 2866, 2922, 3024; ^{1}H NMR (DMSO-d_6): δ 2.32 (s, 3H), 2.95 (s, 3H), 7.23 (d, $J = 8.1$ Hz, 2H), 7.60–7.78 (m, 6H); ^{13}C NMR (DMSO-d_6): δ 20.88, 37.42, 125.79, 126.15, 129.28, 129.83, 132.22, 136.22, 141.23, 141.30; Analysis: $C_{14}H_{14}ClNS_2O_2Pd$ requires C, 38.72; H, 3.25; Cl, 8.16; N, 3.23; S, 14.77%; found C: 38.68; H, 3.50; Cl, 8.24; N, 3.34; S, 14.77%.

[‡] General experimental procedure for the Suzuki coupling: A 25 ml two-necked round bottomed flask fitted with a double-walled water condenser was charged with aryl halide (5.0 mmol), aryl boronic acid (7.5 mmol), K_2CO_3 (10 mmol), palladacycle **1** (0.005 mmol) and toluene (15 ml). The reaction mixture was heated in an oil bath at the specified temperature and time (Table 2) (the progress of the reaction was monitored by TLC). The reaction mixture was then allowed to cool to room temperature. The product was isolated by pouring into water (20 ml) followed by extraction with ethyl acetate (3×25 ml). The combined organic extracts were washed with water, brine and dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude product. This was then purified by column chromatography on silica gel using petroleum ether and ethyl acetate as eluent to afford the product in pure form.

Table 3. Heck reaction between alkenes and aryl halides catalyzed by palladacycle **1**[a]

No	Aryl halide	Alkene	Yield (%)[b]	TON[c]
1	C_6H_5I	Styrene	20[d]	80,000
		Styrene	38[e]	153,600
		Styrene	94	392,800
		BA[f]	97	396,000
		MMA[g]	67	269,000
		AN[h]	68	136,000
2	$4\text{-}MeOC_6H_4I$	EA[i]	94	376,000
3	$4\text{-}ClC_6H_4I$	EA	88	528,900[j]
4	$4\text{-}O_2NC_6H_4I$	EA	99	594,000[j]
		Styrene	97	388,000
5	$4\text{-}HOC_6H_4I$	BA	65	260,000
6	$4\text{-}H_2NC_6H_4I$	Styrene	99	397,200
7	C_6H_5Br	MA[k]	21	76,000

[a] Conditions: aryl halide (2 mmol), olefin (2 mmol), Et_3N (4 mmol), palladacycle **1** (5×10^{-6} mmol), NMP (6 ml), substrate/cat. = 0.4×10^6, 140 °C, 12 h.

[b] Isolated yields after chromatographic purification.

[c] TON = mmol of product/mmol of Pd.

[d] K_2CO_3 is used as a base.

[e] NaOAc is used as a base.

[f] *n*-Butyl acrylate.

[g] Methyl methacrylate.

[h] Acrylonitrile.

[i] Ethyl acrylate.

[j] Aryl halide (3 mmol), olefin (3 mmol), Et_3N (6 mmol).

[k] Methyl acrylate.

tions have recently been developed.[18] We also evaluated the effectiveness of palladacycle **1** for Sonogashira and Ullmann-type coupling[19] reactions (Table 4 and Scheme 3). As can be seen from Table 4, very high yields were obtained in the Sonogashira reaction of phenylacetylene with aryl iodides, at 80 °C under copper-free conditions. The reaction also worked well with propargyl alcohol to afford the corresponding coupled product in 50% yield. Finally, moderate yields of symmetrical biaryls were obtained when a variety of substituted aryl iodides were subjected to Ullmann-type coupling (Scheme 3).

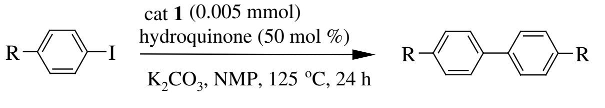
Table 4. Sonogashira coupling between aryl halides and phenylacetylene catalyzed by palladacycle **1**[a]

No	Aryl halide	Yield (%)[b]	TON[c]
1	C_6H_5I	84	336
2	$4\text{-}O_2NC_6H_4I$	88	352
3	C_6H_5Br	25	100
4	C_6H_5Cl	10	40

[a] Conditions: aryl halide (2 mmol), phenylacetylene (3 mmol), Et_3N (6 ml), palladacycle **1** (0.005 mmol), substrate/cat. = 400, 80 °C,12 h.

[b] Isolated yields after chromatographic purification.

[c] TON = mmol of product/mmol of Pd.



R = H; 41%, TON = 164
R = CN; 35%, TON = 140
R = Cl; 44%, TON = 176
R = NO_2; 48%, TON = 192

Scheme 3. Ullmann-type coupling of aryl halides.

In conclusion, a new family of sulfilimine palladacycles has been shown to exhibit high activity in a variety of C–C bond forming reactions using aryl halides (X = I, Br, Cl). The stability of these palladacycles against air, moisture and temperature and the fact that they can be synthesized from inexpensive and readily available starting materials render them very promising catalysts.

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