Palladium Catalysis

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Palladium-Catalyzed Hydroxylation of Aryl Halides under Ambient Conditions**

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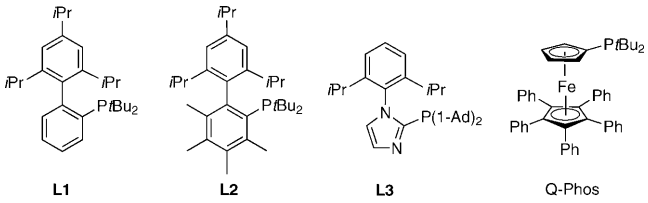
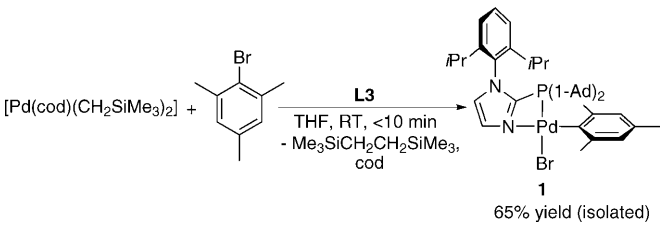
Phenols are found in various natural products ranging from coal tar containing simple phenols to red wine possessing numerous colored polyphenols with antioxidant properties.[1,2] In organic synthesis the development of mild, general, and efficient methods for the preparation of phenols still constitutes a significant challenge. Considering the availability of starting materials, the direct nucleophilic substitution of a halogen atom in aryl halides is an appealing approach to the synthesis of substituted phenols.[3,4] However, reactions of non-activated substrates typically proceed under harsh reaction conditions (200–350 °C).[1] Hence, the development of a milder catalytic phenol synthesis through a two-step coupling procedure by Hartwig and co-workers was an important advancement.[5] Recently, the direct hydroxylation of aryl halides was developed by Buchwald and co-workers as well as by Chan and co-workers using palladium catalysts with bulky tri-*tert*-butylphosphine and biphenylphosphines (**L1**, **L2**).[6,7]



Among the various catalytic systems studied, palladium complexes based on ligands **L1** and **L2** allowed C–O coupling of both activated and non-activated aryl halides at 80–100 °C.[7] Inspired by the efficiency of palladium/biphenylphosphine catalysts, we recently demonstrated the hydroxylation of aryl halides in the presence of imidazole-based ligands.[8] Although progress in palladium-catalyzed C–O bond-forming reactions made it possible to arylate alcohols under milder conditions,[9,10] the coupling using water remained problematic.[4] Indeed, no examples of phenol syntheses from non-activated aryl halides at ambient temperature have been described to date,[11] and the mechanistic understanding of this coupling reaction is limited.

Herein we report the first room temperature palladium-catalyzed hydroxylation of aryl chlorides and bromides as deduced from studies of the elementary steps of the catalytic cycle. In the presence of a novel palladium precursor and the imidazolylphosphine ligand **L3** (Ad = adamantyl), a variety of phenols can be obtained from aryl halides in excellent yield.

Initially, we were interested in the structure and reactivity of palladium complexes of the bulky ligand **L3**, which was previously involved in the hydroxylation of aryl halides. To prepare the corresponding oxidative addition complex, bromomesitylene was reacted with different palladium sources and ligand **L3** in THF at room temperature. Notably, only $[Pd(cod)(CH_2SiMe_3)_2]$ allowed isolation of the desired oxidative addition product in pure form. The oxidative addition of bromomesitylene in the presence of $[Pd(cod)(CH_2SiMe_3)_2]$ and **L3** took place within 10 minutes at room temperature to give complex **1** in 65 % yield (Scheme 1). In contrast, the



Scheme 1. Synthesis of complex **1**. cod = 1,5-cyclooctadiene.

reaction with $[Pd_2(dba)_3]$ (dba = dibenzylideneacetone) proceeded more slowly (14 h) to give the oxidative addition complex in moderate yield (44 %) upon isolation.[12] Recent attempts to synthesize related [Pd(Ar)(X)(L)] (X = halogen) complexes bearing 2-dialkylphosphino-2,4,6-tri*iso*-propylbiphenyl ligands (X-Phos-type phosphines including **L1** and **L2**) were not successful.[13,14] However, the use of a ligand having methoxy groups introduced into the 3,6-positions of X-Phos allowed the synthesis of the stable oxidative addition complexes.[14] Thus, introduction of additional donor atoms may play a profound role in the improved stability of the oxidative addition intermediate.

The crystal structure of the oxidative addition complex **1** is shown in Figure 1.[15] Complex **1** contains a single phosphine ligand coordinated to the metal through both the phosphorous and nitrogen atoms, thereby forming a four-membered P,N-chelate ring.[16] The additional coordination of the nitro-

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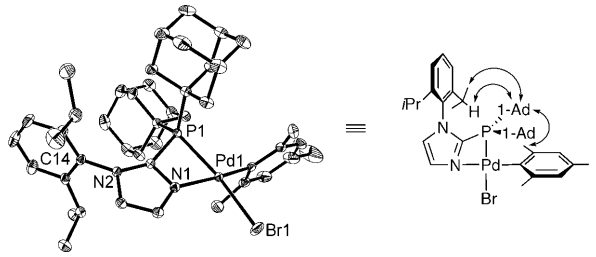
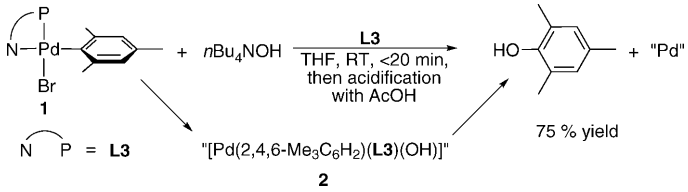


Figure 1. Crystal structure and important through-space interactions in NOESY NMR spectrum of complex **1** (see the Supporting Information for details). The thermal ellipsoids are set at 30% probability.

gen atom "freezes" the rather sterically unfavorable conformation of the coordinated phosphine with bulky di*iso*-propylphenyl and di-1-adamantylphosphino groups facing each other.

Thus, one side of the complex is sterically overcrowded with the phosphine, whereas the opposite side is relatively open for nucleophilic attack. As determined by NOESY NMR experiments **1** exists in a single form in solution,[17] which corresponds to that found in the solid state (Figure 1).[18]

Next, we investigated the preparation of the corresponding hydroxo complex "[Pd(Ar)(OH)(**L3**)]" (**2**), which is the key catalytic intermediate for the formation of phenol. Thus, **1** was reacted with an excess of nBu$_4$NOH·30 H$_2$O in THF at room temperature. The starting complex **1** was completely consumed within less than 20 minutes. To our surprise instead of the desired hydroxo complex **2**, 2,4,6-trimethylphenol was formed in 75% yield (Scheme 2). Apparently, complex **2** immediately underwent C–O bond-forming reductive elimi-

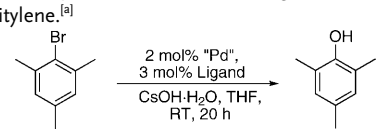


Scheme 2. Reaction of **1** with tetra-*n*-butyl ammonium hydroxide.

nation at room temperature. To the best of our knowledge such direct reductive elimination of phenols from palladium has not been reported until now.[19] It is this step that is considered as the "bottle-neck" of the palladium-catalyzed hydroxylation and which is responsible for rather high reaction temperatures ($\geq$ 80 °C).[6,7]

Apparently, the combination of [Pd(cod)(CH$_2$SiMe$_3$)$_2$]/**L3** allows all steps of the catalytic cycle to proceed at room temperature within minutes. These findings encouraged us to study the corresponding catalytic reaction in the presence of [Pd(cod)(CH$_2$SiMe$_3$)$_2$] and other palladium precursors (Table 1). To our delight the reaction of bromo mesitylene with an excess of CsOH·H$_2$O in the presence of [Pd(cod)(CH$_2$SiMe$_3$)$_2$] and **L3** in THF gave mesitol in nearly quantitative yield (Table 1, entry 2). The oxidative addition complex **1** as catalyst led to the product in identical yield

Table 1: Variation of palladium sources and ligands in the hydroxylation of bromomesitylene.[a]



Entry	Ligand	"Pd" source	Yield [%][b]
1	–	**1**	99
2	**L3**	[Pd(cod)(CH$_2$SiMe$_3$)$_2$]	98 (88)[c]
3	**L3**	[Pd$_2$(dba)$_3$]	76 (44)[c]
4	**L3**	[Pd(allyl)(Cp)]	37
5	**L3**	[Pd(TMEDA)(Me)$_2$]	35
6	**L3**	Pd(OAc)$_2$	30
7	**L1**	[Pd(cod)(CH$_2$SiMe$_3$)$_2$]	1
8	**L2**	[Pd(cod)(CH$_2$SiMe$_3$)$_2$]	0
9	PtBu$_3$	[Pd(cod)(CH$_2$SiMe$_3$)$_2$]	0
10	Q-Phos	[Pd(cod)(CH$_2$SiMe$_3$)$_2$]	0
11	**L4**	[Pd(cod)(CH$_2$SiMe$_3$)$_2$]	11

[a] Reaction conditions: bromomesitylene (1 mmol), CsOH·H$_2$O (3 mmol), [Pd(cod)(CH$_2$SiMe$_3$)$_2$] (2 mol%), phosphine ligand (3 mol%), hexadecane (100 μL), THF (2 mL), 24 °C, 20 h. [b] Yields determined by using GC methods. [c] In parentheses: 1 mol% of Pd and 1.5 mol% of a ligand was used. Cp = cyclopentadiene, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

(Table 1, entry 1). Notably, all other palladium precursors tested with **L3** are considerably less efficient (Table 1, entries 3–6). The advantage of [Pd(cod)(CH$_2$SiMe$_3$)$_2$] in the room temperature hydroxylation is explained by the efficient generation of the corresponding palladium (0) complex (PdL) by rapid substitution of 1,5-cyclooctadiene for the bulky phosphine ligand L and a subsequent fast reductive elimination of bis(trimethylsilyl)ethane.[20] As a result, the oxidative addition occurs fast at room temperature. Inferior results with the common palladium(0) precursor, [Pd$_2$(dba)$_3$] in the catalytic reaction (Table 1, entry 3) are attributed to a much slower oxidative addition of the aryl bromide (see below). This deceleration should be caused by the stronger coordination of the electron-poor olefin (dibenzylidenacetone) to the palladium center.[21] Similar unfavorable effects of dba in palladium-catalyzed reactions are well documented in the literature.[22]

Notably, despite applications of [Pd(cod)(CH$_2$SiMe$_3$)$_2$] (R = Me, Ph) in organometallic synthesis,[14,20] these complexes have never been used in catalytic reactions.[23] The ability of [Pd(cod)(CH$_2$SiMe$_3$)$_2$] to generate catalytically active species in situ under mild reaction conditions and in a one-step synthesis from commercially available precursor[20] make this complex an appealing tool for catalysis of cross-coupling reactions at room temperature.[24]

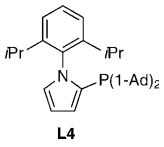
Furthermore, the palladium(0) precursor was tested with other ligands, which were successfully employed for hydroxylation of aryl halides at high temperature (**L1**, **L2**, and PtBu$_3$). For comparison, we also employed Q-Phos which is the unique ligand for arylation of tBuOH and tBuMe$_2$SiOH at room temperature.[10] However, none of these tests led to the product at room temperature, demonstrating the superiority of **L3** for this reaction (Table 1, entries 7–10).

We suppose that the improved activity of the **L3**-based catalyst in the room temperature hydroxylation stems from a

favorable combination of the steric bulk of the biphenyl-type backbone and alkyl substituents bound to the phosphorous center, as well as the ability to coordinate to the metal through the sp^2-nitrogen atom. The favorable effect of increased steric bulk of biphenyl-type ligands has already been highlighted.[8,25] Indeed, in the hydroxylation at elevated temperatures (80–100 °C), the efficiency of the catalysts based on bulky biphenyl ligands (**L1**, **L2**), and their arylimidazolyl congeners with a similar backbone is rather close.[7,8] However, in the room temperature reaction the novel palladium precursor and imidazolyl ligand **L3** exhibits an enormous difference in efficiency relative to reaction runs with the biphenyl phosphines **L1** and **L2** (Table 1, entries 2 and 7–8).

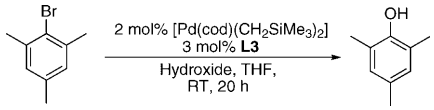
The main reason for this different catalytic behavior is seen in the ability of **L3** to coordinate to the palladium through both the P and N atoms (Figure 1). In agreement with this assumption, the pyrrole-based ligand **L4** which has the same framework as **L3**, but contains no second nitrogen atom available for coordination, provided only 11 % yield of phenol versus 98 % in the presence of **L3** (Table 1, entries 11 and 2).

Next, we optimized the reaction conditions for room temperature hydroxylation of bromomesitylene (Table 2). Among the various hydroxides tested, the best results were obtained in the presence of $CsOH{\cdot}H_2O$ (Table 2, entry 3). The mediocre performance of $n Bu_4NOH{\cdot}30H_2O$ in the catalytic reaction (Table 2, entry 5) compared to the reaction using stoichiometric amounts of $n Bu_4NOH{\cdot}30H_2O$ (Scheme 2) is attributed to the formation of a biphasic mixture resulting from the high water content in the commercial hydroxide.



L4

Table 2: Variation of hydroxides in the hydroxylation of bromomesitylene.[a]

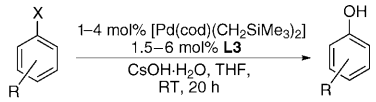


Entry	Hydroxide	Conversion [%][b]	Yield [%][b]
1	LiOH	7	0
2	KOH	37	27
3	$CsOH{\cdot}H_2O$	100	98
4	$Me_4NOH{\cdot}5H_2O$	98	87
5	$n Bu_4NOH{\cdot}30H_2O$	41	36

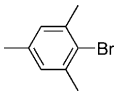
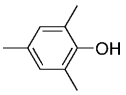
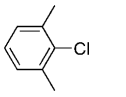
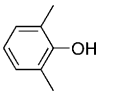
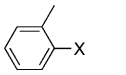
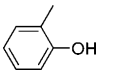
[a] Reaction conditions: bromomesitylene (1 mmol), base (3 mmol), $[Pd(cod)(CH_2SiMe_3)_2]$ (2 mol %), **L3** (3 mol %), hexadecane (100 μL), THF (2 mL), 24 °C, 20 h. [b] Determined by GC methods.

Finally, we applied the optimized reaction conditions to the hydroxylation of various aryl halides at ambient conditions. As shown in Table 3, different aryl bromides and even aryl chlorides are transformed into the corresponding phenols in good to excellent yields (isolated; 67–99 %). In all cases, aryl chlorides were as active as the corresponding bromides and no noticeable amounts of diphenyl ethers were detected. Aryl halides containing electron-withdrawing substituents in the *ortho* and *para* positions reacted smoothly (Table 3, entries 10–16). Functional groups such as cyano, nitro, and

Table 3: Palladium-catalyzed hydroxylation of aryl halides at room temperature.[a]



X = halogen

Entry	Aryl Halide		Product	"Pd" [mol %]	Yield [%][b]
1				1 2	n.d. (88) 93 (98)
2				2	96
3		X = Br		2	92
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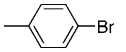
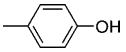
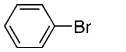
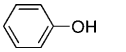
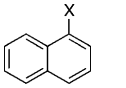
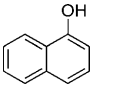
5				4	70[c]
6				2	72 (97)[c,d]
7		X = Br		2	85
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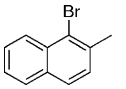
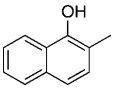
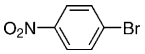
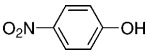
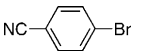
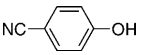
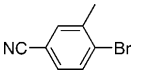
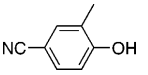
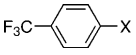
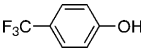
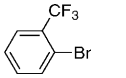
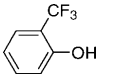
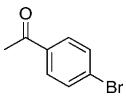
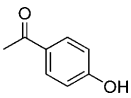
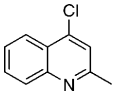
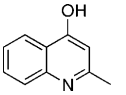
9				2	87
10				2	94
11				4	88
12				1	99
13		X = Br		2	83 (89)[d]
14		X = Cl		2	73 (98)[d]
15				4	67 (72)[d]
16				2	95
17				2	99

[a] Reaction conditions: aryl halide (1 mmol), $CsOH{\cdot}H_2O$ (3 mmol), $[Pd(cod)(CH_2SiMe_3)_2]$ (1–4 mol %), **L3** (1.5–6 mol %), hexadecane (100 μL), THF (2 mL), 24 °C, 20 h; reaction time is not optimized. [b] Yields for isolated product, and yields given in parentheses were determined by using GC methods. The reported yields refer to independent runs. [c] The reaction was carried out at 50 °C. [d] Volatile compound.

keto substituents are well tolerated. Moreover, the room temperature hydroxylation has a broader functional group scope compared to the reaction run at elevated temperature. For example, at 100 °C, we have observed only limited tolerance to nitriles.[26] In contrast, the present mild protocol enables preservation of nitrile group in all cases. Indeed, hydroxylation of 4-bromo-3-methylbenzonitrile and 4-bromobenzonitrile gave phenols in 88 % and 99 % yields,

respectively, using lower catalyst loadings (Table 3, entries 11 and 12). Previously, all attempts to hydroxylate aryl halides possessing a CF_3 substituent at elevated temperatures failed because of the hydrolysis of the CF_3 group. Under the present set of conditions both *para*- and *ortho*-aryl halides possessing CF_3 groups were coupled successfully at room temperature in good yields (Table 3, entries 13–15). In addition, a heterocyclic derivative, such as 4-chloro-2-methylquinoline, is smoothly transformed into the corresponding phenol in quantitative yield (Table 3, entry 17). With regard to limitations of the present method, we found that CO_2H and OH groups are not tolerated presumably because of the formation poorly soluble salts.

The novel protocol was also successfully applied for the hydroxylation of various non-activated aryl bromides including bromobenzene, *ortho*- and *para*-substituted halobenzenes, and 1-halonaphthalenes to give substituted phenols in 70–93% yields (Table 3, entries 1–9). Bromo- and chloronaphthalenes smoothly reacted at room temperature affording naphthols in 75–87% yields (Table 3, entries 7–9). Bromobenzene and 4-bromotoluene were somewhat less reactive and required a reaction temperature of 50°C (Table 3, entries 5–6). The introduction of one or two methyl groups in *ortho* positions of halobenzenes increased the reactivity of the halides, allowing the reaction again to proceed at room temperature with excellent yields (Table 3, entries 1–4). For example, bromomesitylene and 2-bromotoluene furnished phenols in 93% and 92% yields, respectively. Hydroxylation of similar chloro derivatives also proceeded under the same conditions (Table 3, entries 2 and 4). Acceleration of the reaction by *ortho* substituents in haloarenes, as well as the similar reactivity of aryl bromides and aryl chlorides, makes it likely that reductive elimination is the rate limiting step for this hydroxylation reaction. Indeed, it is known that carbon–heteroatom bond-forming reductive elimination from arylpalladium complexes is accelerated by *ortho* substituents in aryl halides.[27] However, we found that the further increase in the steric bulk of the *ortho* substituents, for example, from methyl to *iso*-propyl decelerates the reaction. Hence, room temperature hydroxylation of 2-bromo-*iso*-propylbenzene proceeded only to 10% conversion, whereas the reaction of 2,4,6-tri*iso*-propylbromobenzene did not occur at all and led to decomposition of the catalyst.

This effect of the different *ortho* substituents on the rate of the hydroxylation may imply a change of the rate-determining step.

In summary, we demonstrated for the first time that all steps of the catalytic cycle of the palladium-catalyzed hydroxylation of aryl chlorides and bromides can proceed at room temperature. Based on these findings, the catalytic synthesis of phenols occurs under unprecedented mild conditions. The key to the success is the combination of the novel palladium precursor $[Pd(cod)(CH_2SiMe_3)_2]$ and the imidazole-based ligand **L3**, which should be useful for numerous other catalytic coupling reactions as well.

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