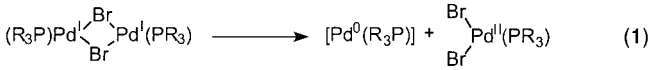
Unparalleled Rates for the Activation of Aryl Chlorides and Bromides: Coupling with Amines and Boronic Acids in Minutes at Room Temperature**

James P. Stambuli, Ryoichi Kuwano, and John F. Hartwig*

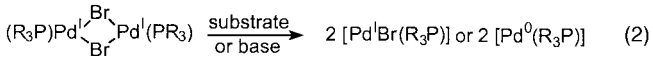
Oxidative addition initiates most palladium-catalyzed cross-couplings[1] and is often rate-limiting for reactions of aryl chlorides[2] and deactivated aryl bromides.[3] This addition usually occurs to an unsaturated complex formed from ligand dissociation or after transformation of a precatalyst to the true catalyst.[4] Although the elementary oxidative addition step could occur to the same Pd^0 intermediate and at the same rate when different catalyst precursors are used, the efficiency with which this Pd^0 intermediate is generated can differ widely. For example, reactions of aryl halides with amines, boronic acids, and olefins occur at elevated temperatures when catalyzed by isolated $[Pd(PtBu_3)_2]$[5–7] but occur at room temperature in some cases when catalyzed by a combination of $[Pd(dba)_2]$ and one equivalent of $PtBu_3$ (dba = (*E*,*E*)-dibenzylideneacetone).[7–10]

Here we describe the catalytic activity of air-stable, readily accessible, alkyl di-*tert*-butylphosphane ligated palladium(I) dimers toward selected couplings of amines with aryl chlorides on the time scale of minutes at room temperature. Furthermore, these dimers catalyze a range of aminations and Suzuki–Miyaura couplings of aryl bromides even more readily. In addition to providing a convenient catalyst for synthetic chemistry, these results indicate that the elementary step of oxidative addition of an aryl chloride to the reactive Pd^0 intermediate ligated by $PtBu_3$ or $P(1\text{-Ad})tBu_2$ (1-Ad = 1-adamantyl) occurs with rates that are unparalleled for this step.[11–14]

We and others have reported several times that the rates for cross-couplings catalyzed by palladium complexes of $PtBu_3$ are faster when a 1:1 ratio of phosphane to palladium is used.[7–10,15] Dimeric $[\{PdBrL\}_2]$ (L = $P(1\text{-Ad})tBu_2$, **1a**; L = $PtBu_3$, **1b**)[16] are formally Pd^I complexes that contain a 1:1 ratio of metal to ligand. They are readily prepared from $[Pd_2(dba)_3]\cdot C_6H_6$, $[PdBr_2(cod)]$, and the corresponding ligand in good yield (cod = (*Z*,*Z*)-cycloocta-1,5-diene). Complex **1a** is air-stable indefinitely as a solid, and **1b** is stable enough to be weighed in air. These dimers could cleave into two different monomeric units, such as a highly reactive monoligated palladium(0) complex and a palladium(II) dibromide [Eq. (1)] or could be reduced to $[Pd^0(PR_3)]$ or $[Pd^0Br(PR_3)]^-$[6,17] [Eq. (2)] by the combination of substrate and base.



1a: $PR_3 = P(1\text{-Ad})tBu_2$
1b: $PR_3 = PtBu_3$



1a: $PR_3 = P(1\text{-Ad})tBu_2$
1b: $PR_3 = PtBu_3$

To evaluate the potential of **1a** and **1b** as catalysts for the aminations of aryl halides, we studied the prototype reaction of *p*-chlorotoluene with dibutylamine in the presence of sodium *tert*-butoxide as base and 0.5 mol% of **1b** in toluene at room temperature. This reaction was complete within 15 min and formed *N*,*N*-dibutyl-*p*-toluidine in 86% yield of isolated product. The reaction occurred at a similar rate and in a higher 95% yield when conducted in THF, most likely because of the greater solubility of **1b** in THF. Although the combination of $[Pd(dba)_2]$ with carbene **2**[18] and the combination of $Pd(OAc)_2$ with biphenylyl phosphane **3**[19] have been used for amination of aryl chlorides at room temperature, reactions catalyzed by these species required longer times at higher catalyst loadings.[20]

2

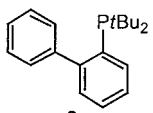


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Table 1 summarizes results on the room-temperature amination of aryl chlorides and bromides catalyzed by palladium(I) dimers **1a** and **1b**. All of these reactions, except that in entry 11, were quenched after 15 min. In some cases, reactions catalyzed by **1a** gave higher conversions with 1 mol% catalyst. For example, the reaction of cyclic secondary amines with *p*-chlorotoluene occurred to only 88% completion after 15 min when catalyzed by **1b**, but to full completion when catalyzed by the **1a** (entry 2). Higher activity of **1a** was also observed for the amination of *o*-substituted aryl chlorides. The reaction of *o*-chlorotoluene with morpholine gave the desired product in 84% yield in the presence of **1a**, but only 68% yield in the presence of **1b** (entries 3 and 4). Most often, additional reaction time at room temperature did not increase conversion when the reactions were incomplete after 15 min. This result implies that high activity of these catalysts is obtained at the expense of stability.

Aryl chlorides with varied electronic properties reacted with dialkyl amines to give the coupled product within 15 min. Deactivated (entry 5) and electron-deficient (entries 6–8) chloroarenes were converted to the desired amine in high yield within 15 min. Because of the short reaction time, the process tolerated functional groups, such as nitro groups, that

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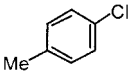
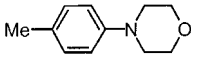
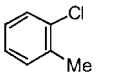
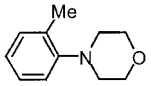
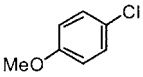
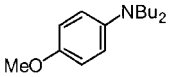
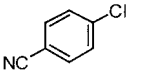
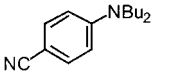
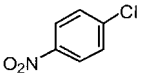
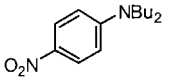
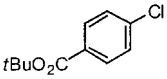
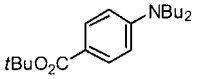
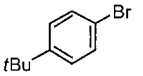
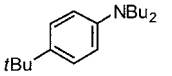
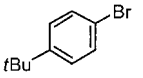
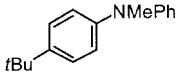
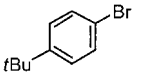
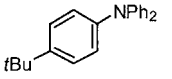
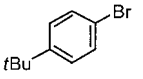
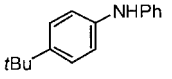
Table 1. Rapid amination of aryl halides with $[\{PdBr(PR_3)\}_2]$ as catalyst.[a]

Entry	Catalyst	Aryl halide	Amine	Product	Yield [%][b]
1	**1b**				88
2	**1a**				92
3	**1a**				84
4	**1b**				68
5	**1b**		$HNBu_2$		87
6	**1a**		$HNBu_2$		93
7	**1b**		$HNBu_2$		97
8	**1b**		$HNBu_2$		> 99
9	**1b**		$HNBu_2$		96
10	**1a**		HNMePh		98
11[c]	**1b**		$HNPh_2$		96
12	**1a**		H_2NPh		89
13	**1b**				82

[a] Reactions were conducted on 1 mmol scale in THF (1 mL) at room temperature for 15 min unless otherwise noted. The relative amounts of aryl halide, amine, NaO*t*Bu, and $[\{PdBr(PR_3)\}_2]$ were 200:210:300:1. [b] Yields of isolated products are an average of two runs. [c] The reaction was conducted for 1 h.

are typically unstable when the aminations are conducted with NaO*t*Bu as base.

Although **1a** and **1b** displayed high activity for the amination of aryl chlorides at room temperature with dialkylamines, the scope of this fast room-temperature chemistry is narrower than the slower room-temperature chemistry with some other catalysts.[11,21] For example, no reaction of *p*-chlorotoluene with diphenylamine or primary amines occurred at room temperature with these dimers as catalyst.

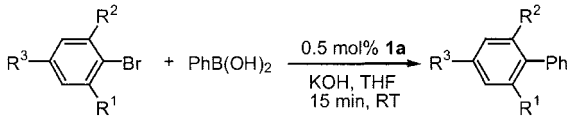
These palladium dimers, **1a** and **1b**, also catalyzed aminations of unactivated aryl bromides (entries 9–13) with remarkable rates. Each reaction that occurred with an aryl chloride substrate also occurred with the corresponding aryl bromide. In addition, reactions of aryl bromides with diarylamines occurred in high yield (entry 11), though these reactions were faster when catalyzed by the combination of $[Pd(dba)_2]$ and P*t*Bu_3.

To explore the versatility of catalysts **1a** and **1b**, we examined their activity toward Suzuki–Miyaura reactions. Catalyst **1a** induced couplings of various aryl bromides, such as *p*-bromotoluene, *o*-cyano-, *o*-trifluoromethyl-, and *o*-methoxybromobenzene, with phenylboronic acid at similarly fast rates at room temperature (Table 2). *o*-Substituted aryl bromides (entries 2–4) were as reactive as *p*-bromotoluene (entry 1) in the presence of dimer **1a**. Even the more hindered 2-bromo-*m*-xylene coupled with phenylboronic acid within minutes in 84% yield (entry 5). Reactions of phenyl boronic acids with deactivated aryl chlorides at room temperature occurred rapidly, but did not exceed 70% conversion.

Preliminary mechanistic studies of amination reactions catalyzed by **1a** suggest that oxidative addition is rate limiting, even with these short reaction times. The rates for reaction of aryl bromides and chlorides were measured at −20 °C and 0 °C, respectively. Loadings of 20 mol% were required to obtain full conversion of aryl chlorides at 0 °C. Catalyst decomposition and the observation of several ^{31}P NMR signals corresponding to palladium complexes we have not been able to identify made detailed kinetic studies unwarranted. However, reactions conducted with varying concentrations of aryl chloride clearly showed the reaction to be first order in this reagent. In contrast to reactions catalyzed by the disphosphane complex $[Pd(PtBu_3)_2]$,[6] the concentration of base did not influence the reaction rate.

In conclusion, air-stable palladium dimers $[\{PdBr(PRtBu_2)\}_2]$ are active as catalysts for reactions of various aryl chlorides or bromides and amines that proceed within minutes at room temperature. The fast rates of these reactions show that the proper choice of catalyst precursor can allow the overall rate to approach that for the elementary step of oxidative addition and that the elementary oxidative addition of an aryl chloride can be remarkably fast, even at room temperature. This fast rate for P*t*Bu_3-ligated Pd^0 creates the highest turnover frequencies for cross-couplings of aryl chlorides.

Table 2. Room-temperature Suzuki–Miyaura coupling of hindered aryl bromides catalyzed by **1a**.[a]



Entry	R^1	R^2	R^3	Yield [%][b]
1	H	H	CH_3	95
2	CN	H	H	92
3	CF_3	H	H	90
4	OCH_3	H	H	96
5	CH_3	CH_3	H	84

[a] Reactions were conducted on 1 mmol scale in THF (3 mL) at room temperature for 15 min. The relative amounts of aryl halide, phenylboronic acid, KOH, and **1a** were 200:216:600:1. [b] Yields of isolated products are an average of two runs.

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Experimental Section

1a: $[Pd(dba)_2]$ (288 mg, 0.50 mmol) and P(1-Ad)P*t*Bu_2[22] (560 mg, 2.00 mmol) were stirred in toluene (15 mL) in a vial for 3 h. After this time, $[PdBr_2(cod)]$[23] (378 mg, 1.01 mmol) was added, and the mixture was stirred for an additional 4 h. The reaction volume was concentrated by half, and the contents were filtered through a glass-fritted funnel. The dark-green solid was washed three times with acetone (10 mL) and dried under vacuum. Yield: 498 mg (0.533 mmol, 53.4 %); ^{1}H NMR (400 MHz, C_6D_6): $\delta = 1.39$ (t, 36 H, 6 Hz, *t*Bu), 1.47–1.61 (br m, 12 H, CH_2), 1.77 (br s, 6 H, CH), 2.32 ppm (br s, 12 H, CH_2); ^{13}C NMR (100 MHz, C_6D_6, 40 °C): $\delta = 29.4$ (t, 4.0 Hz, CH_2), 33.0 (br s, CH_2), 36.8 (t, 1.8 Hz, C Ad), 36.9 (s, CH_3), 41.7 (br s, CH), 42.0 ppm (br s, *C*Me_3); ^{31}P NMR (202 MHz, C_6D_6): $\delta = 88.0$ ppm (s); Anal. calcd. for $C_{36}H_{66}Br_2P_2Pd_2$: C 46.32, H 7.13, Br 17.12; found: C 45.94, H 7.03, Br 17.02.

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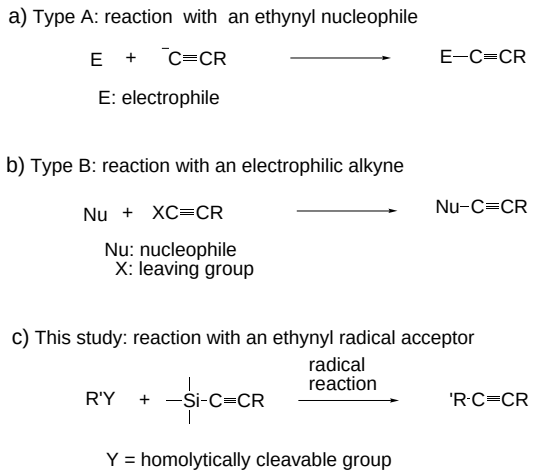
A New Entry to the Stereoselective Introduction of an Ethynyl Group by a Radical Reaction: Synthesis of the Potential Antimetabolite 2′-Deoxy-2′-*C*-ethynyluridine**

Makoto Sukeda, Satoshi Ichikawa, Akira Matsuda, and Satoshi Shuto*

Ethynyl groups are present in many biologically active compounds, including clinically useful drugs,[1] and are also valuable in organic synthesis because the triple bond can be converted into a variety of functional groups.[2] Accordingly, much effort has been expended to develop methods for introducing ethynyl and/or substituted ethynyl groups into compounds to produce alkynes by C–C bond formation.[2] These methods can be generally classified as Type A, reactions of ethynyl nucleophiles such as acetylides or their congeners (Scheme 1 a), and Type B, reactions of electrophilic alkynes bearing a leaving group (Scheme 1 b). Type A includes reactions of alkynyl metals with carbon electrophiles[3] and transition metal catalyzed cross-coupling reactions with alkyne derivatives.[4] Type B is typified by reactions between an alkynyl halide and a carbon nucleophile, which appear to proceed by an addition–elimination mechanism.[5] Although these are very effective, regio- and stereoselective introduction of an ethynyl group at aliphatic carbon centers is sometimes troublesome.



Scheme 1. Methods for introducing ethynyl and substituted ethynyl groups.

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