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Enolizable Ketones as Activators of Palladium(II) Precatalysts in Amine Arylation Reactions

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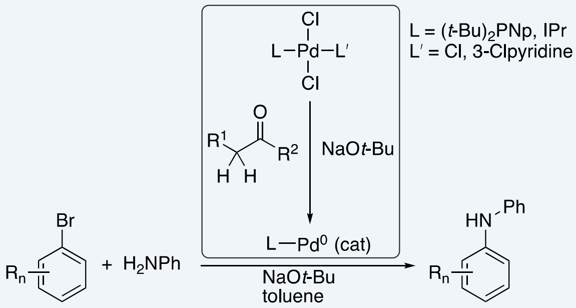
ABSTRACT: Enolizable ketones have been identified as effective activators for palladium(II) precatalysts in the coupling of aryl bromides and aniline. N-arylation reactions catalyzed by $[(DTBNpP)PdCl_2]_2$ (DTBNpP = (bis(*tert*-butyl)neopentylphosphine) and PEPPSI-IPr precatalysts are activated by the addition of acetone, mesityl oxide, and 3-pentanone. 3-Pentanone was the most effective activator. Mechanistic studies show that acetone, 3-pentanone, and mesityl oxide reduce $[(DTBNpP)PdCl_2]_2$ in the presence of NaO-*t*-Bu to $Pd^0(DTBNpP)_2$.



KEYWORDS: *cross-coupling, palladium, phosphine, N-heterocyclic carbene, amination, precatalyst*

INTRODUCTION

Palladium-catalyzed cross-coupling reactions have become ubiquitous methods for the construction of C−C and C−heteroatom bonds in both academic and industrial syntheses. Significant effort has been devoted to the development of optimized supporting ligands that provide highly active catalysts across a broad range of substrates, including sterically demanding trialkylphosphines,[1] 2-biarylphosphines,[2] and N-heterocyclic carbenes.[3] Many synthetic protocols rely on generating the active catalyst species under the reaction conditions (in situ) through the combination of a ligand, or ligand precursor, and a palladium source. Although the choice of ligand often plays a critical role in the success of a particular coupling reaction, recent research has shown that the choice of catalyst precursor can also be critical in particularly challenging cross-coupling reactions.[4]

With current-generation ligands, the active catalyst is a monodentate LPd^0 species.[5] The LPd^0 species is unstable and must be generated from catalyst precursors, although it has been observed under catalytically relevant conditions.[6] In situ generation of the active species from a ligand and a palladium source in a 1/1 ratio is a common strategy, but this approach provides limited control over the formation of the LPd^0 complex. Improved performance can often be achieved by using a palladium(0, I, or II) precatalyst containing one supporting ligand that will remain bound upon activation and additional neutral or anionic ligands that will be lost during the activation process. Successful precatalysts include $(LPd)_2(\mu\text{-cod})$ (**1**),[7] $[((t\text{-Bu})_3P)Pd(\mu\text{-X})]_2$ (**2**),[8] (allyl)Pd(L)X (**3** and **4**),[9] the Buchwald palladacycle precatalysts (**5**),[10] and the PEPPSI complexes (**6**).[3b,c,11]

Palladium(0) precatalysts do not require reduction under the reaction conditions but are typically air-sensitive. Palladium(II) precatalysts are typically air stable, which simplifies their handling. A palladium(II) precatalyst requires a reduction process to form the active palladium(0) species, however. The palladium allyl (**3** and **4**) and palladacyclic catalysts (**5**) are designed to undergo base-promoted reductive elimination under catalytic conditions to generate the LPd^0 species. In contrast, the PEPPSI complexes do not contain ligands primed for reductive elimination upon exposure to base. The PEPPSI precatalyst can be reduced to Pd(0) under a variety of conditions depending on the nature of the coupling partners. With organometallic coupling partners, such as in a Negishi, Kumada, or Suzuki coupling, homocoupling of the organometallic species provides the reduction route.[12] In coupling with alkylamines, reduction can occur by β-hydride elimination of the coordinated amine. In the case of arylamine or thiolate coupling partners, these pathways are unavailable. Organ showed that additives, such as Bu_2Mg, morpholine, and KO-*i*-Pr, activated the PEPPSI precatalyst in the arylation of arenethiols.[13] In the case of isopropoxide, acetone was detected under the reaction conditions, which is consistent with an activation pathway involving β-hydride elimination of a Pd isopropoxide complex.[14]

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Our group has reported the use of halide-bridged monophosphine palladium complexes ($[(R_3P)PdCl_2]_2$, PR_3 = DTBNpP (**7a**), TNpP (**7b**); Figure 1) as stable and effective precatalysts for the Suzuki coupling reaction.[15] Similar to the PEPPSI precatalyst, complexes **7a**,**b** require reduction to the LPd^0 species. Under Suzuki coupling conditions, the arylboronic acid serves as the reductant. We sought to extend the use of these precatalysts to the arylation of aniline derivatives. We expected that a reducing additive would be necessary to activate precatalysts **7a**,**b**. Here we report the use of enolizable ketones as effective activators for **7a** and the PEPPSI-IPr precatalysts in the coupling of aryl bromides and aniline.

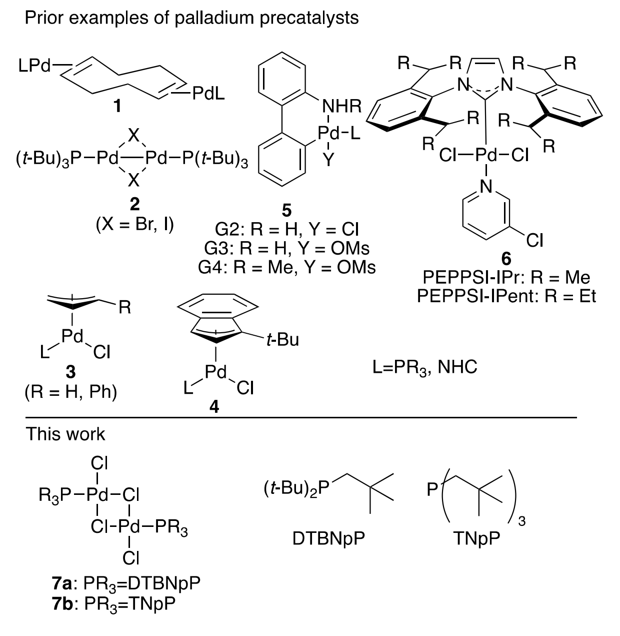
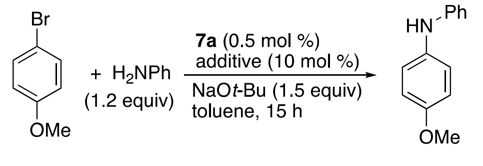


Figure 1. Examples of palladium phosphine and NHC precatalysts.

RESULTS AND DISCUSSION

Ketone Activators in N-Arylation Reactions. We have previously reported that DTBNpP in combination with $Pd_2(dba)_3$ (1 mol % Pd, 1/1 Pd/P) gives complete conversion in the reaction of 4-bromoanisole and aniline in toluene with NaO-*t*-Bu after 1 h at room temperature.[16] The ability of chloride dimer **7a** to catalyze the arylation of aniline was tested under the same conditions using 0.5 mol % **7a** (1 mol % Pd, eq 1). Little conversion was observed after 15 h at ambient temperature or 40 °C (Table 1, entries 1 and 2). Complete conversion was achieved at 80 °C, however. The low activity of **7a** at lower temperature was expected, as there is not an efficient mechanism to convert **7a** to a palladium(0) species. At 80 °C, catalyst activation does occur by an unknown mechanism.



(1)

Additives that can serve as a reductant were explored to improve the activity of **7a** at lower temperatures. Isopropyl alcohol and phenylboronic acid both significantly improved the reaction yield at 40 °C (entries 4 and 5). Surprisingly, acetone, which would be formed upon reduction by isopropyl alcohol, gave complete conversion to product at 40 °C (entry 7) and a 42% yield at room temperature. With the success of acetone, other ketones were tested. 3-Pentanone proved to be more effective than acetone, giving nearly complete conversion at room temperature (entry 8). The more hindered 2,4-dimethyl-3-pentanone gave complete conversion at 40 °C but was less effective than acetone or 3-pentanone at room temperature. Benzophenone, which lacks an enolizable proton, gave the same yields at room temperature or 40 °C (entries 12 and 13) as the additive-free reactions (entries 1 and 2). Aryl alkyl ketones gave somewhat lower conversions in comparison to the symmetric dialkyl ketones but followed the same trend (entries 14–19). Mesityl oxide (4-methylpent-3-en-2-one), which would be the aldol condensation product formed from acetone, also proved to be an effective activator (entries 21 and 22), giving results comparable to those for 3-pentanone.

Table 1. Effect of Additives on the Coupling of 4-Bromoanisole and Aniline Catalyzed by 7a[a]

entry	additive	*T* (°C)	yield (%)[b]
1	none	22	1
2	none	40	16
3	none	80	>99
4	isopropyl alcohol	40	42
5	$PhB(OH)_2$	40	67
6	acetone	22	42
7	acetone	40	>99
8	3-pentanone	22	98
9	3-pentanone	40	>99
10	2,4-dimethyl-3-pentanone	22	28
11	2,4-dimethyl-3-pentanone	40	>99
12	benzophenone	22	2
13	benzophenone	40	16
14	acetophenone	22	38
15	acetophenone	40	98
16	propiophenone	22	80
17	propiophenone	40	98
18	isobutyrophenone	22	18
19	isobutyrophenone	40	55
20	mesityl oxide	22	98
21	mesityl oxide	40	>99

[a]The conditions are depicted in eq 1. [b]Yields determined by GC analysis of reaction mixtures.

The ketone activators used in these reactions are potential substrates for α-arylation reactions in competition with the desired N-arylation reaction. Small amounts of α-arylated products (1–2%) were detected by GC in reactions using acetone, 3-pentanone, acetophenone, and propiophenone as the activators. The larger relative concentration of amine to ketone (12/1) and the increased coordinating ability of the amine results in a preference for N-arylation over α-arylation.

To further evaluate the effectiveness of the ketone activators, reaction profiles were determined for reactions activated by 3-pentanone, mesityl oxide, and acetone (Figure 2). At room temperature, 3-pentanone gave the highest initial reaction rate followed closely by mesityl oxide. At room temperature, acetone gave only 12% conversion after 8 h. At 40 °C, the reaction with acetone was slower than those with 3-pentanone or mesityl oxide but reached 80% conversion after 7 h.

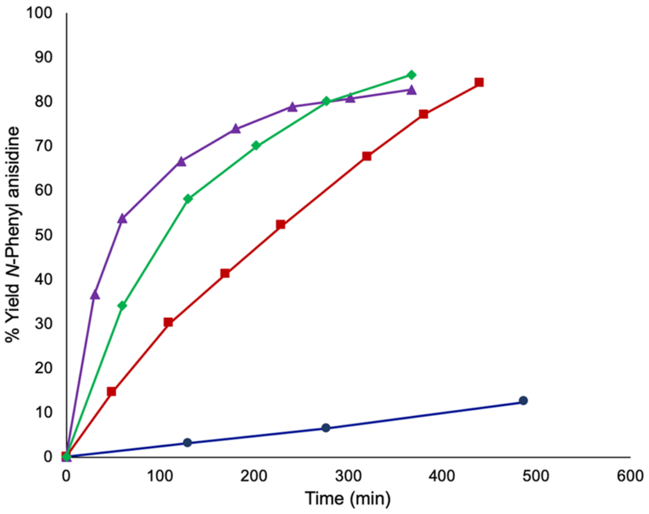


Figure 2. Reaction profile for the reaction of 3-bromoanisole and aniline using **7a** (0.5 mol %) under the conditions of eq 1: 3-pentanone at 22 °C (purple triangles); mesityl oxide at 22 °C (green diamonds); acetone at 40 °C (red squares); acetone at 22 °C (blue circles).

The results in Table 1 and Figure 2 show that the presence of at least one α-proton is necessary to achieve high conversion. The best results were obtained with ethyl ketones having two α-protons (3-pentanone and propiophenone), followed by methyl ketones (acetone and acetophenone). Isopropyl ketones were less effective than acetone yet did have an activating effect. The branched ketones may be less effective as activators due to the increased steric hindrance at the α-position. Mesityl oxide has an activating effect similar to that of 3-pentanone, despite being a methyl ketone.

To determine the optimal loading of the ketone activator, the reaction of 4-bromoanisole and aniline catalyzed by **7a** (0.5 mol %) was performed at room temperature with 3-pentanone loadings ranging from 2 to 20 mol % relative to 4-bromoanisole, which corresponds to 2−20 equiv relative to palladium. The rate of conversion increased on going from 2 to 8 mol % of 3-pentanone (Figure S18, Supporting Information). After 3 h, the reaction with 2 mol % of 3-pentanone had reached 49% conversion, whereas the reaction with 8 mol % had reached 87% conversion (Figure 3). Reactions with 8−14 mol % of 3-pentanone had nearly identical reaction profiles (Figure S18). A further increase in the 3-pentanone loading to 20 mol % resulted in slower conversion (48% after 3 h). After 18 h, the reactions with 5−14 mol % of 3-pentanone gave complete conversion, whereas a 70% conversion was achieved with 2 mol % of ketone and an 80% conversion with 20 mol % of ketone.

These results show that precatalyst **7a** requires at least 5 mol % of 3-pentanone to be efficiently activated. Little change in reaction rate is seen between 5 and 14 mol % ketone, but the catalyst is inhibited at a 20 mol % loading. Although the reaction rate is slower with a 20 mol % loading of the ketone, the reaction still selectively produced the desired amine product. No significant (>1−2%) byproducts are seen by GC in these reactions. The cause of the inhibition at high ketone loading with precatalyst **7a** remains unclear but is not due to competitive arylation of the ketone.

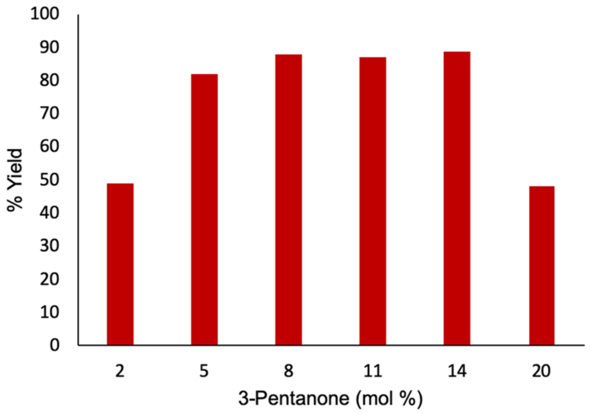
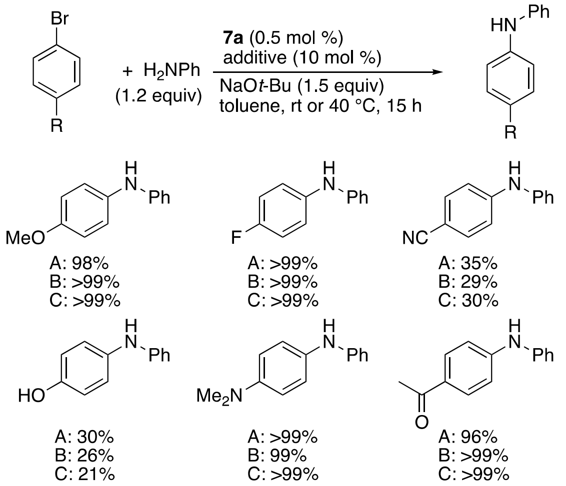


Figure 3. Average yield (three trials) after 3 h for the reaction of 4-bromoanisole and aniline catalyzed by **7a** (0.5 mol %) using NaO-*t*-Bu in toluene at room temperature as a function of 3-pentanone loading.

Scheme 1. Coupling of Aryl Bromides Catalyzed by 7a Using Ketone Activators[a]

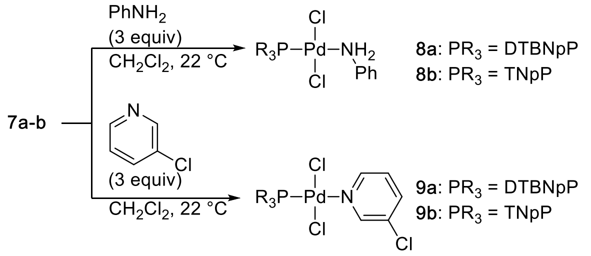


[a]Conditions: (A) 3-pentanone, 22 °C; (B) acetone, 40 °C; (C) mesityl oxide, 22 °C. Yields were determined by GC.

The use of ketone activators with **7a** was tested in the coupling of aniline with a small set of aryl bromides (Scheme 1). Reactions with 3-pentanone (condition A) and mesityl oxide (condition C) were performed at room temperature, whereas those with acetone (condition B) were carried out at 40 °C. High yields were obtained under all three conditions with 4-bromotoluene, 1-bromo-4-fluorobenzene, *N,N*-dimethyl-4-bromoaniline, and 4-bromoacetophenone. These substrates encompass electron-rich and electron-deficient examples. Low yields were obtained with 4-bromobenzonitrile and 4-bromophenol. Although it is electron deficient, 4-bromobenzonitrile can compete with the phosphine ligands to coordinate to palladium. 4-Bromophenol is deprotonated under the reaction conditions to give a very electron rich 4-bromophenoxide substrate.

The PEPPSI precatalyst family has a monomeric (NHC)-$PdCl_2$(3-chloropyridine) structure in which the pyridine ligand can be displaced under the reaction conditions to reveal the (NHC)Pd^0 active species.[3b,c,11] No examples of phosphine analogues of the PEPPSI catalysts have been reported. Our group previously reported the structure of (DTBNpP)-$PdCl_2$(4-picoline)[15] but had not explored the catalytic activity of these types of complexes. Aniline (**8a,b**) and 3-chloropyridine (**9a,b**) complexes were readily prepared by reacting the nitrogen ligand with dimer **7a** or **7b** in methylene chloride (Scheme 2).

Scheme 2. Synthesis of Nitrogen Ligand Adducts of 7a,b



The synthesis and crystal structure of **8b** has been previously reported by us.[17] X-ray-quality crystals of **9b** were obtained by slow evaporation from a benzene solution. Complex **9b** adopts a square-planar structure with the 3-chloropyridine ligand trans to the TNpP ligand, which is structurally similar to that of other (TNpP)PdCl$_2$(amine) adducts which we have characterized (Figure 4).[17] The structure of **9b** has the same Pd−N bond length as the PEPPSI-IPr complex,[18] but the palladium square plane is somewhat more distorted to accommodate the TNpP ligand.

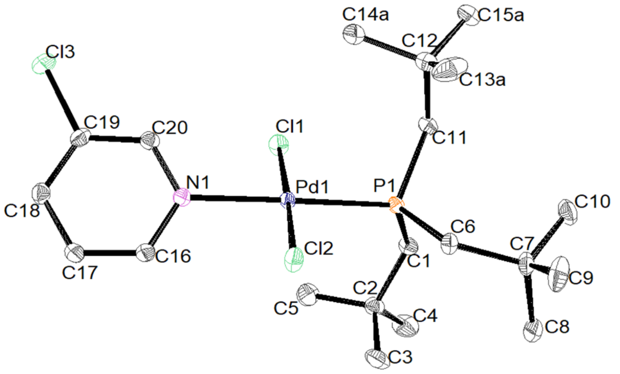


Figure 4. Thermal ellipsoid plot (50% probability) of the molecular structure of **9b**. Hydrogen atoms and disorder are omitted for clarity. Selected bond distances (Å) and angles (deg): Pd1−P1 2.2571(3), Pd1−N1 2.1349(9), Pd−Cl$_{av}$ 2.307, Cl1−Pd1−N1 88.48(1), N1−Pd1−Cl2 89.12(2), Cl2−P1−P1 93.78(1), P1−Pd1−Cl1 88.70(2).

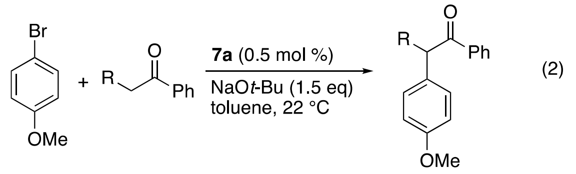
Complexes **8a,b** and **9a,b** were tested in the coupling of bromobenzene and aniline in comparison to the halide dimers **7a,b** at 22 °C (Table 2). In the absence of ketone activator, less than 10% yield was observed for all precatalysts. With 3-pentanone (10 mol %), all three DTBNpP-derived precatalysts (**7a**, **8a**, and **9a**) gave quantitative conversion to product. The TNpP-derived catalysts were less effective. Previous studies have shown that TNpP-derived catalysts generally required higher temperatures in comparison to those derived from DTBNpP.[19] The 3-chloropyridine-derived complex **9b** provided higher yields than **7b**, whereas the aniline complex **8b** was less effective.

Ketone Arylation. Enolate arylation products were observed as minor byproducts in the ketone-activated amination reactions. On the basis of these results, precatalyst **7a** was expected to be an effective precatalyst for the arylation of ketones in the absence of other activators. Coupling of 4-bromoanisole with acetophenone and propiophenone gave over 50% conversion to the α-arylated products after 1 h and complete conversion to product after 5 h (eq 2). Complex **7a** showed activity comparable to that of the catalyst generated in situ from Pd(OAc)$_2$ and DTBNpP.[20]

Table 2. Amine Adducts as Precatalysts for N-Arylation Reactions

		yield of Ph$_2$NH (%)	
entry	precatalyst	condition A[a]	condition B[b]
1	**7a**	4	>99
2	**8a**	6	>99
3	**9a**	5	>99
4	**7b**	0.3	19
5	**8b**	0.3	12
6	**9b**	0.2	27

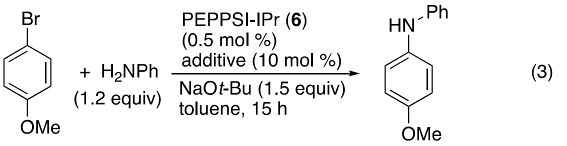
[a]Condition A: precatalyst (1 mol % Pd), phenyl bromide (1 mmol), aniline (1.2 mmol), NaO-*t*-Bu (1.5 mmol), toluene, 22 °C, 3 h. [b]Condition B: same as condition A with the addition of 3-pentanone (0.1 mmol).



(2)

R	1 h	5 h
H	57%	100%
Me	55%	100%

Ketone Activation of the PEPPSI-IPr Precatalyst. The PEPPSI family of precatalysts developed by Organ (**6**; Figure 1) effectively catalyze a wide range of C−C and C−heteroatom coupling reactions.[3b,c] Similar to the case for complex **7a**, the PEPPSI precatalysts must undergo reduction to form the active palladium(0) species. The ability of ketones to promote the coupling of 4-bromoanisole and aniline using the PEPPSI-IPr precatalyst was tested (eq 3). In the absence of any additive, low yields were obtained in the coupling of 3-bromoanisole and aniline using PEPPSI-IPr from room temperature to 60 °C (Table 3, entries 1−3). Significantly higher yields were obtained by the addition of 3-pentanone (entries 4 and 5), although the yields at room temperature and 40 °C were lower than those obtained with precatalyst **7a**. Increasing the temperature to 60 °C and the 3-pentanone loading to 29 mol % increased the yield to 80% (entry 7). The higher ketone loading increased the amount of α-arylated byproducts to 5%. Mesityl oxide also improved the yield of the product, but was less effective than 3-pentanone (entries 8 and 9).



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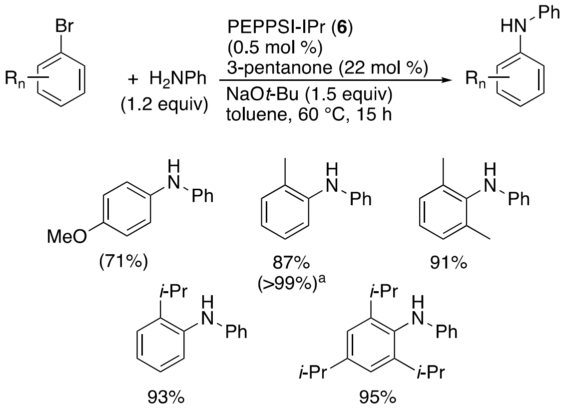
The PEPPSI-IPr precatalyst was used in the coupling of a series of aryl bromides and aniline using 22 mol % of 3-pentanone at 60 °C (Scheme 3). 4-Bromoanisole gave 71% conversion to product under these conditions. Aryl bromides with ortho substituents gave complete conversion to product under these conditions and high isolated yields. Even in the

Table 3. Effect of 3-Pentanone in Activation of PEPPSI-IPr Precatalyst[a]

entry	additive	temp (°C)	yield (%)[b]
1	none	22	0
2	none	40	7
3	none	60	14
4	3-pentanone	22	14
5	3-pentanone	40	61
6	3-pentanone[c]	60	71
7	3-pentanone[d]	60	80
8	mesityl oxide	22	4
9	mesityl oxide	40	43

[a] Conditions are depicted in eq 3. [b] Yields determined by GC analysis of reaction mixtures. [c] 22 mol % of 3-pentanone. [d] 29 mol % of 3-pentanone.

Scheme 3. 3-Pentanone-Activated Coupling of Aryl Bromides and Aniline Using PEPPSI-IPr[b]

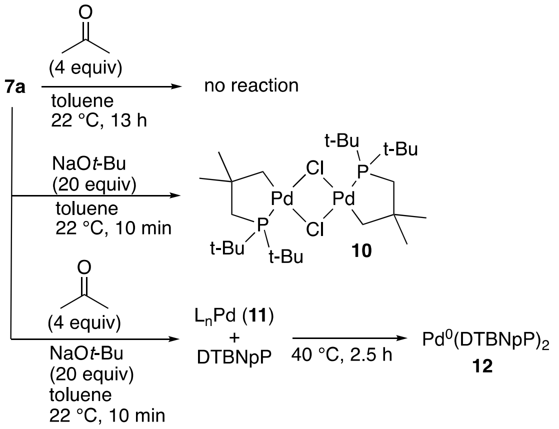


[a] Reaction performed at room temperature. [b] Isolated yields, except for yields in parentheses (GC yields).

presence of a relatively high concentration of 3-pentanone, high selectivity for the N-arylation reaction occurs. The PEPPSI-IPr/3-pentanone system is much more efficient with ortho-substituted aryl bromides than with unhindered cases. Complete conversion of 2-bromotoluene was achieved at room temperature in the presence of 3-pentanone in comparison to a 3% yield in the absence of the ketone activator. In contrast, only 14% conversion to product was achieved at room temperature with 4-bromoanisole under the same conditions.

Mechanism of Ketone Activation. Ketones have not previously been shown to be able to activate palladium(II) precatalysts in cross-coupling reactions, to our knowledge. To better understand this process, the reaction of precatalyst **7a** with ketones under a variety of conditions was analyzed by ^{31}P NMR spectroscopy. Treatment of **7a** with acetone in toluene resulted in no change in the ^{31}P NMR spectrum over 13 h (Scheme 4). When **7a** was reacted with NaO-*t*-Bu in toluene, complete conversion to palladacycle **10** occurred within 10 min. We have previously observed the base-promoted metalation of **7a** to be rapid in the absence of other reactants.[15] When **7a** was treated with acetone and NaO-*t*-Bu in toluene, the only phosphorus species observed after 10 min was free DTBNpP. No change was observed over the course of 14 h. When this reaction was repeated at 40 °C, a 3/1 mixture of free DTBNpP and Pd^0(DTBNpP)$_2$ (**12**) was observed. Over the course of 2.5 h, the remaining free DTBNpP was converted to complex **12**. The results show that, in the presence of acetone and NaO-*t*-Bu, the DTBNpP ligand is rapidly displaced to form a phosphorus-free palladium species (**11**) with an unknown structure. At 40 °C, this species slowly forms Pd^0(DTBNpP)$_2$ without any other phosphorus byproducts. Notably, palladacycle **10** is not formed in the presence of acetone, which suggests that the conversion of **7a** to **11** is much faster than base-promoted ligand metalation to give **10**. Under the catalytic reaction conditions (4-bromoanisole, aniline, NaO-*t*-Bu, acetone, and toluene), only free DTBNpP is observed from 10 min through 13 h at both 22 and 40 °C. In the 40 °C reaction, complete conversion of the aryl bromide occurs after 2.5 h.

Scheme 4. Reaction of Precatalyst 7a with Reaction Components



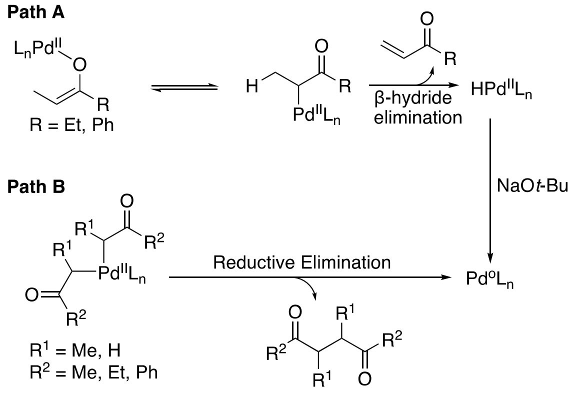
The reaction of **7a** with 3-pentanone and mesityl oxide was explored in a similar fashion. No reaction is seen with **7a** and 3-pentanone. In the presence of NaO-*t*-Bu and 3-pentanone, complete conversion to Pd(DTBNpP)$_2$ (**12**) occurs within 10 min, without formation of palladacycle **10**. Unlike acetone, no free DTBNpP is observed. In contrast, under the full catalytic conditions, only free DTBNpP is seen during the course of the coupling reaction, as was the case for acetone. Mesityl oxide is also unreactive with **7a** in the absence of base but gives clean conversion to **12** in the presence of NaO-*t*-Bu. In the mesityl oxide promoted coupling reaction, only complex **12** is observed after 10 min, with no further change in the ^{31}P NMR spectrum over several hours.

These studies show that the tested ketones are capable of reducing **7a** to palladium(0) complex **12**. This reaction occurs slowly in the case of acetone, through a phosphine-free palladium intermediate. In the cases of 3-pentanone and mesityl oxide, this reduction occurs rapidly (<10 min) at room temperature without free phosphine being observed. It is possible that these reactions also proceed through intermediate **11** but that the resulting intermediate rapidly is converted to palladium(0) complex **12**. The efficiency of the catalytic reaction correlates with rapid formation of **12** in the presence of ketone and base. Both 3-pentanone and mesityl oxide are effective activators of precatalyst **7a**, whereas acetone is less effective at ambient temperature and provides a less active catalyst at 40 °C. Although the rapid formation of **12** correlates with efficient catalysis, complex **12** is not seen under catalytic conditions when 3-pentanone is used as the activator. It is possible that the formation of **12** in the absence of aryl bromide and aniline indicates efficient Pd(0) formation but that under the catalytic condition the amine or other ligands are coordinated to the active species. In contrast to these results, we do observe either **12** or the oxidative addition product derived from **12** ([(DTBNpP)Pd(Ar)Br]$_2$) under Suzuki coupling conditions.[15]

Analysis of the reaction of **7a** with 3-pentanone (4 equiv) and NaO-*t*-Bu (20 equiv) by ^{1}H NMR spectroscopy showed a broad peak at approximately 4 ppm. This resonance is consistent with an O-bound metal enolate,[21] although it is not possible to determine if the coordinated metal is sodium, palladium, or a mixture of the two. No other new resonances consistent with possible byproducts of the palladium reduction reaction were observed.

The nature of the phosphine-free palladium complex (**11**) is unknown. We hypothesize that complex **11** may be a [Pd(enolate)$_2$]$_n$ or [ClPd(enolate)]$_n$ species. This species then would undergo a reductive process to form Pd(0), which can recoordinate the phosphine ligands. A plausible mechanism in the case of 3-pentanone would be formation of a C-bound palladium enolate followed by *β*-hydride elimination (Scheme 5, path A). This sequence has been proposed for the palladium-catalyzed oxidation of ketones to *α*,*β*-unsaturated ketones.[22] An alternative possibility available to methyl ketones would be reductive elimination from a dienolate complex (path B). Oxidative coupling of enolates by one-electron oxidants, such as ferrocenium,[23] TiCl$_4$,[24] and CuCl$_2$,[25] have been reported, but to our knowledge there are no examples of enolate homocoupling by a reductive elimination process using palladium.

Scheme 5. Possible Reduction Pathways from a Pd(II)-Bound Enolate



The *β*-hydride elimination pathway should result in the formation of 1-penten-3-one from 3-pentanone or 1-phenyl-2-penten-1-one from propiophenone. Analysis of the reduction of palladium by 3-pentanone (4 equiv) and NaO-*t*-Bu (20 equiv) shows no evidence of the *β*-hydride elimination products by ^{1}H NMR spectroscopy or GC-MS analysis. The expected products of enolate homocoupling, for example hexane-2,5-dione from acetone, have also not been observed by GC-MS or ^{1}H NMR analysis. Therefore, the mechanism by which complex **7a** is reduced to palladium(0) in the presence of ketones and base remains unclear.

Amination reactions activated by acetone and 3-pentanone appear to involve a phosphine-free species (**11**) as the potential active catalyst. To determine whether the phosphine is necessary, (MeCN)$_2$PdCl$_2$ was explored as a precatalyst (Table 4). Using (MeCN)$_2$PdCl$_2$ in place of **7a** with acetone (40 °C) or 3-pentanone (22 °C) gave no conversion to product. When DTBNpP was used in combination with (MeCN)$_2$PdCl$_2$, no yield was obtained at 22 °C in the absence of a ketone activator. Addition of acetone at 40 °C gave a modest yield of the arylated product, but the (MeCN)$_2$PdCl$_2$/DTBNpP catalyst system was less effective than **7a**. The use of 3-pentanone with (MeCN)$_2$PdCl$_2$/DTBNpP at room temperature gave no conversion. It appears that the prior coordination of DTBNpP to the palladium is critical to the success of the precatalyst under these conditions.

Table 4. Aniline Arylation Using (MeCN)$_2$PdCl$_2$ as the Precatalyst[a]

entry	ligand	additive	*T* (°C)	yield (%)
1	none	acetone	40	0
2	none	3-pentanone	22	0
3	DTBNpP	none	22	0
4	DTBNpP	acetone	40	35
5	DTBNpP	3-pentanone	22	0

[a] Reaction conditions: 4-bromoanisole (1 mmol), aniline (1.2 mmol), NaO-*t*-Bu (1.5 mmol), (MeCN)$_2$PdCl$_2$ (0.01 mmol), DTBNpP (0 or 0.01 mmol), ketone (0.1 mmol), in toluene at the indicated temperature. Yields were determined by GC analysis.

■ CONCLUSION

Enolizable ketones have been demonstrated to be effective activators of palladium(II) precatalysts in the arylation of aniline using both phosphine and NHC-derived precatalyst species. 3-Pentanone was identified as the most effective activator. Mechanistic studies indicate that palladium(II) complex **7a** is reduced to palladium(0) in the presence of ketone and base. The rate of the reduction correlates with the activity of the catalyst formed upon ketone activation. 3-Pentanone and mesityl oxide, which give rapid conversion to palladium(0) complex **12**, also provide the most active **7a**-derived catalysts. Acetone gives slow reduction of **7a** to **12** and also provides a less active catalyst. The mechanism of the reduction process remains unclear, however. We hypothesize that a palladium enolate species is the key intermediate. In the case of 3-pentanone, a likely activation pathway would be *β*-hydride elimination to give a palladium hydride that could be deprotonated to afford the palladium(0) active species. The expected byproducts of this pathway have not been observed, however. Therefore, an as yet undetermined mechanism is possible. Efforts to determine the reduction mechanism are ongoing.

■ EXPERIMENTAL SECTION

General Procedure. Reagents were purchased from commercial suppliers and used as received, except as noted. [(DTBNpP)PdCl$_2$]$_2$ (**7a**),[15] [(TNpP)PdCl$_2$]$_2$ (**7b**),[15] and (TNpP)Pd(aniline)Cl$_2$ (**8b**)[17] were prepared according to previously reported methods. Toluene was refluxed over sodium for 1 h and freshly distilled before use. Reactions were conducted with nitrogen double-manifold inert-atmosphere techniques, unless noted otherwise. GC analysis was performed using a Shimadzu gas chromatograph (GC-2014) outfitted with a Alltech EC-5 column (30 m × 0.32 mm i.d. × 0.25 *μ*m film thickness) and FID detector. Chromatograms were run with an initial oven temperature of 150 °C, increasing to 250 °C at a rate of 10 °C/min. NMR spectra were obtained on a Brüker 500 MHz spectrometer. ^{31}P NMR spectra were acquired using the gated decoupling mode.

General Procedure for Ketone-Activated N-Arylation Reactions. A screw-capped vial with **7a** (0.5 mol %) was put into the glovebox. NaO-*t*-Bu (1.5 equiv) was added. The vial was sealed with a septum cap and taken out of the glovebox. Aryl halide (1 mmol), ketone (10 mol %), aniline (1.2 mmol), and toluene (3 mL) were added, and the reaction mixture was stirred at room temperature or placed in an oil bath preheated to the desired temperature. After 15 h, the reactions were analyzed by GC.

(DTBNpP)Pd(aniline)Cl$_2$ (8a). [(DTBNpP)PdCl$_2$]$_2$ (**7a**, 100 mg, 0.128 mmol) was dissolved in methylene chloride (8 mL). Then aniline (35.1 μL, 0.384 mmol) was added into the solution. After the mixture was stirred for 1 h, the volatiles were removed under vacuum to provide **8a** as an air-stable orange solid (116.7 mg, 94%). ^{1}H NMR (500 MHz, C_6D_6, 295 K): δ 7.28 (d, J = 7.8 Hz, 2H), 6.96 (t, J = 7.8 Hz, 2H), 6.82 (t, J = 7.3 Hz, 1H), 3.90 (s, 2H), 2.08 (d, J = 12.8 Hz, 2H), 1.43 (d, J = 12.8 Hz, 18H), 1.33 (s, 9 H). ^{13}C NMR (125 MHz, C_6D_6, 295 K): δ 140.95, 124.72, 121.36, 107.98, 37.23 (d, J_{C-P} = 6.4 Hz), 34.26 (d, J_{C-P} = 25.2 Hz), 33.59 (d, J_{C-P} = 6.4 Hz), 31.21 (d, J_{C-P} = 4.3 Hz), 30.86 (d, J_{C-P} = 4.3 Hz). ^{31}P{^{1}H} NMR (202.5 MHz, C_6D_6, 295 K): δ 63.0.

(DTBNpP)Pd(3-chloropyridine)Cl$_2$ (9a). [(DTBNpP)-PdCl$_2$]$_2$ (**7a**, 100 mg, 0.128 mmol) was dissolved in methylene chloride (8 mL) under nitrogen. Then 3-chloropyridine (36.5 μL, 0.384 mmol) was added to the solution. After the mixture was stirred for 1 h, the volatiles were removed under vacuum to provide **9a** as an air-stable orange solid (120.2 mg, 93%). ^{1}H NMR (500 MHz, C_6D_6, 295 K): δ 9.11 (s, 1H), 8.71 (s, 1H), 6.55 (d, J = 7.3 Hz, 1H), 6.02 (s, 1H), 2.28 (d, J = 12.8 Hz, 2H), 1.59 (d, J = 12.8 Hz, 18H), 1.50 (s, 9 H). ^{13}C NMR (125 MHz, C_6D_6, 295 K): δ 150.57, 149.51, 137.15, 131.97, 124.27, 37.86 (d, J_{C-P} = 6.4 Hz), 34.48 (d, J_{C-P} = 25.2 Hz), 33.81 (d, J_{C-P} = 6.4 Hz), 31.351 (d, J_{C-P} = 4.3 Hz), 31.16 (d, J_{C-P} = 4.3 Hz). ^{31}P{^{1}H} NMR (202.5 MHz, C_6D_6, 295 K): δ 62.0.

(TNpP)Pd(3-chloropyridine)Cl$_2$ (9b). [(TNpP)PdCl$_2$]$_2$ (**7b**, 100 mg, 0.119 mmol) was dissolved in methylene chloride (8 mL). Then 3-chloropyridine (33.9 μL, 0.357 mmol) was added into the solution. After the mixture was stirred for 1 h, the volatiles were removed under vacuum to provide **9b** as an air-stable orange solid (119.3 mg, 94%). Orange single crystals were formed after slow evaporation of a benzene solution. ^{1}H NMR (500 MHz, C_6D_6, 295 K): δ 9.33 (s, 1H), 8.96 (s, 1H), 6.56 (d, J = 7.3 Hz, 1H), 6.04 (s, 1H), 3.82 (s, 2H), 2.35 (d, J = 12.8 Hz, 6H), 1.35 (s, 27 H). ^{13}C NMR (125 MHz, C_6D_6, 295 K): δ 150.66, 149.65, 137.41, 132.34, 124.54, 39.15 (d, J_{C-P} = 25.2 Hz), 33.41 (d, J_{C-P} = 6.4 Hz), 32.64 (d, J_{C-P} = 4.3 Hz). ^{31}P{^{1}H} NMR (202.5 MHz, C_6D_6, 295 K): δ 15.28.

Crystallographic Analysis of 9b. A suitable crystal of **9b** was selected and mounted on a Mitgen cryoloop in a random orientation on a XtaLAB Synergy R, DW system, HyPix diffractometer. The crystal was kept at 101(2) K during data collection. Using Olex2,[26] the structure was solved with the ShelXT[27] structure solution program using intrinsic phasing and refined with the ShelXL[28] refinement package using least-squares minimization with Olex2,[26] ShelXle,[29] or both. The structure was found to have a rotational disorder on one of the neopentyl ligands. Atoms on the two moieties were restrained to have similar geometries (SAME).

General Procedure for the PEPPSI-IPr-Catalyzed Amination. PEPPSI-IPr (3.4 mg, 5 μmol) was placed in a 3 dram glass vial with a stir bar. The vial was transferred into a nitrogen glovebox, at which point NaO-*t*-Bu (144 mg,1.50 mmol) was added. The vial was sealed with a rubber septum cap and removed from the glovebox. The remaining reagents were placed in the vial in the following order via syringe: dry toluene (3.5 mL), aryl bromide (1.0 mmol), 3-pentanone (23 μL, 0.22 mmol), and aniline (110 μL, 1.20 mmol). The vials were placed in a preheated oil bath at the desired temperature, and the contents were stirred for 24 h. The reaction mixture was quenched with aqueous ammonium chloride and extracted three times with ethyl acetate (ca. 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude products were purified via silica gel chromatography with hexane as eluent.

***N*-Phenyl-2-toluidine.**[30] 2-Bromotoluene (120.4 μL, 1.0 mmol) was coupled with aniline according to the general procedure. GC analysis indicated complete conversion. The reaction mixture was worked up as described in the general procedure. The crude product was purified by column chromatography to afford the product as an oil (148.6 mg, 87%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.24−7.21 (m, 3H), 7.17 (m, 1H), 7.11 (t, J = 7.8 Hz, 1H), 6.94−6.91 (m, 3H), 6.90−6.86 (m, 1H), 5.34 (brs, 1H), 2.22 (s, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 144.0, 141.2, 130.9, 129.3, 128.3, 126.7, 122.0, 120.4, 118.8, 117.4, 17.8.

***N*-Phenyl-2,6-dimethylaniline.**[30] 2-Bromo-1,3-dimethylbenzene (133 μL, 1.0 mmol) was coupled with aniline according to the general procedure. GC analysis indicated 95% conversion. The reaction mixture was worked up as described in the general procedure. The crude product was purified by column chromatography to afford the product as an oil (167.5 mg, 91%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.21−7.10 (m, 5H), 6.78 (tt, J = 7.3 Hz, 1.0 Hz, 1H), 6.55−6.53 (m, 2H), 5.21 (brs, 1H), 2.25 (s, 6H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 146.3, 138.2, 135.9, 129.2, 128.5, 125.8, 118.1, 113.5, 18.3.

***N*-Phenyl-2-isopropylaniline.**[31] 1-Bromo-2-isopropylbenzene (153 μL, 1.0 mmol) was coupled with aniline according to the general procedure. GC analysis indicated complete conversion. The reaction mixture was worked up as described in the general procedure. The crude product was purified by column chromatography to afford the product as an oil (184.6 mg, 93%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.31 (dd, J = 7.7, 1.4 Hz, 1H), 7.24−7.19 (m, 3H), 7.13 (dt, J = 7.6, 1.6 Hz, 1H), 7.06 (dt, J = 7.5, 1.2, 1H), 6.87−6.82 (m, 3H), 5.40 (brs, 1H), 3.15 (sept, J = 6.9 Hz, 1H), 1.24 (d, J = 7.0 Hz, 6H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 145.3, 140.6, 139.5, 129.2, 126.4, 126.0, 123.5, 121.9, 119.7, 116.4, 27.6, 23.0.

***N*-Phenyl-2,4,6-triisopropylaniline.**[32] 1-Bromo-2,4,6-triisopropylbenzene (153 μL, 1.0 mmol) was coupled with aniline according to the general procedure. GC analysis indicated complete conversion. The reaction mixture was worked up as described in the general procedure. The crude product was purified by column chromatography to afford the product as an oil (228.1 mg, 95%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.18 (t, J = 7.3 Hz, 2H), 7.12 (s, 2H), 6.74 (tt, J = 7.3, 1.0 Hz, 1H), 6.54 (d, J = 8.3 Hz, 2H), 5.09 (brs, 1H), 3.25 (sept, J = 6.9 Hz, 2H), 2.99 (sept, J = 6.9 Hz, 1H), 1.35 (d, J = 6.9 Hz, 6H), 1.20 (d, J = 6.9 Hz, 12H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 148.4, 147.4, 147.2, 132.7, 129.1, 121.7, 117.3, 112.8, 34.2, 28.2, 24.1, 23.9.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c00221.

NMR spectra of isolated compounds, X-ray characterization details, and reaction profile as a function of ketone loading (PDF)

Crystallographic data for **9b** (CIF)

Accession Codes

CCDC 1978602 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

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