

Enolizable ketones as activators of palladium(II) precatalysts in amine arylation reactions

Huaiyuan Hu, Ashley M. Gilliam, Fengrui Qu, and Kevin H. Shaughnessy

ACS Catal., **Just Accepted Manuscript** • DOI: 10.1021/acscatal.0c00221 • Publication Date (Web): 06 Mar 2020

Downloaded from pubs.acs.org on March 9, 2020

Just Accepted

“Just Accepted” manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides “Just Accepted” as a service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. “Just Accepted” manuscripts appear in full in PDF format accompanied by an HTML abstract. “Just Accepted” manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are citable by the Digital Object Identifier (DOI®). “Just Accepted” is an optional service offered to authors. Therefore, the “Just Accepted” Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the “Just Accepted” Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these “Just Accepted” manuscripts.

1
2
3 **Enolizable Ketones as Activators of Palladium(II) Precatalysts in Amine Arylation**
4
5
6 **Reactions**
7

8 Huaiyuan Hu, Ashley M. Gilliam, Fengrui Qu, Kevin H. Shaughnessy*
9

10
11
12
13
14 Department of Chemistry and Biochemistry, The University of Alabama, Box 870336,
15
16 Tuscaloosa, AL 35487-0336, USA
17

18
19 *Email: kshaughn@ua.edu
20
21
22
23
24

25 **Abstract:**
26

27 Enolizable ketones have been identified as effective activators for palladium(II)
28 precatalysts in the coupling of aryl bromides and aniline. *N*-Arylation reactions
29 catalyzed by [(DTBNpP)PdCl₂]₂ (DTBNpP = di-(*tert*-butyl)neopentylphosphine) and
30 PEPPSI-IPR precatalysts are activated by the addition of acetone, mesityl oxide, and 3-
31 pentanone. 3-Pentanone was the most effective activator. Mechanistic studies show
32 that acetone, 3-pentanone, and mesityl oxide reduce [(DTBNpP)PdCl₂]₂ in the presence
33 of NaO*t*-Bu to Pd⁰(DTBNpP)₂.
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48

49 **Keywords:** cross-coupling, palladium, phosphine, *N*-heterocyclic carbene, amination,
50
51 precatalyst
52
53
54
55
56
57
58
59
60

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 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 $(\text{LPd})_2(\mu\text{-cod})$ (**1**),⁷ $[(t\text{-Bu})_3\text{P}]\text{Pd}(\mu\text{-X})_2$ (**2**),⁸ $(\text{allyl})\text{Pd}(\text{L})\text{X}$ (**3-4**),⁹ the Buchwald palladacycle precatalysts (**5**),¹⁰ and the PEPPSI complexes (**6**).^{3b,c,11}

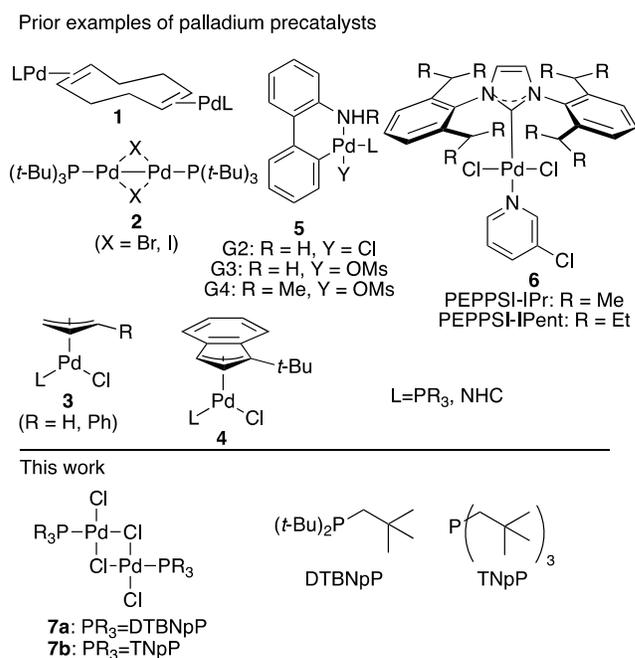


Figure 1. Examples of palladium phosphine and NHC precatalysts

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 (**3-4**) 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

1
2
3 base. The PEPPSI precatalyst can be reduced to Pd(0) under a variety of conditions
4
5 depending on the nature of the coupling partners. With organometallic coupling
6
7 partners, such as in a Negishi, Kumada, or Suzuki coupling, homocoupling of the
8
9 organometallic species provides the reduction route.¹² In coupling with alkyl amines,
10
11 reduction can occur by β -hydride elimination of the coordinated amine. In the case of
12
13 aryl amine or thiolate coupling partners, these pathways are unavailable. Organ
14
15 showed that additives, such as Bu₂Mg, morpholine, and KO*i*-Pr, activated the PEPPSI
16
17 precatalyst in the arylation of arylthiols.¹³ In the case of isopropoxide, acetone was
18
19 detected under the reaction conditions, which is consistent with an activation pathway
20
21 involve β -hydride elimination of a Pd-isopropoxide complex.¹⁴
22
23
24
25
26
27
28
29

30 Our group has report the use of halide-bridged monophosphine palladium
31
32 complexes ($[(R_3P)PdCl_2]_2$, PR₃ = DTBNpP (**7a**), and TNpP (**7b**), Figure 1) as stable and
33
34 effective precatalysts for the Suzuki coupling reaction.¹⁵ Similar to the PEPPSI
35
36 precatalyst, complexes **7a-b** require reduction to the LPd(0) species. Under Suzuki
37
38 coupling conditions, the arylboronic acid serves as the reductant. We sought to extend
39
40 the use of these precatalysts to the arylation of aniline derivatives. We expected that a
41
42 reducing additive would be necessary to activate precatalysts **7a-b**. Here we report the
43
44 use of enolizable ketones as effective activators for **7a** and the PEPPSI-IPr precatalysts in
45
46 the coupling of aryl bromides and aniline.
47
48
49
50
51
52
53

54 Results and Discussion

55
56
57
58
59
60

Ketone activators in *N*-arylation reactions. We have previously reported that DTBNpP in combination with Pd₂(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 hour 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 1-2). 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.

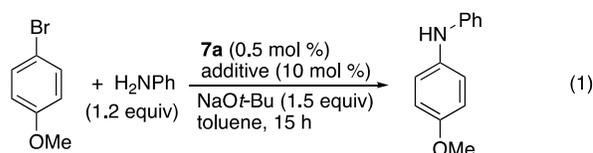


Table 1. Effect of additives on the coupling of 4-bromoanisole and aniline catalyzed by **7a**^a

entry	additive	T (°C)	yield (%) ^b
1	none	22	1
2	none	40	16
3	none	80	>99
4	isopropanol	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 Conditions depicted in equation 1. ^b Yields determined by GC analysis of reaction mixtures.

Additives that can serve as a reductant were explored to improve the activity of **7a** at lower temperatures. Isopropanol and phenylboronic acid both significantly improved the reaction yield at 40 °C (entries 4-5). Surprisingly, acetone, which would be formed upon reduction by isopropanol, 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 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 12-13) as the additive-free reactions (entries 1-2). Aryl alkyl ketones gave somewhat lower conversions compared

1
2
3 to the symmetric dialkyl ketones, but followed the same trend (entries 14-19). Mesityl
4
5
6 oxide (4-methylpent-3-en-2-one), which would be the aldol condensation product
7
8
9 formed from acetone, also proved to be an effective activator (entries 21-22), giving
10
11
12 results comparable 3-pentanone.

13
14 The ketone activators used in these reactions are potential substrates for α -arylation
15
16
17 reactions in competition with the desired *N*-arylation reaction. Small amounts of α -
18
19
20 arylated products (1-2%) were detected by GC in reactions using acetone, 3-pentanone,
21
22
23 acetophenone, and propiophenone as the activators. The larger relative concentration
24
25
26 of amine to ketone (12:1) and the increased coordinating ability of the amine results in a
27
28
29 preference for *N*-arylation over α -arylation.

30
31 To further evaluate the effectiveness of the ketone activators, reaction profiles were
32
33
34 determined for reactions activated by 3-pentanone, mesityl oxide, and acetone (Figure
35
36
37 2). At room temperature, 3-pentanone gave the highest initial reaction rate followed
38
39
40 closely by mesityl oxide. At room temperature, acetone gave only 12% conversion after
41
42
43 8 hours. At 40 °C, the reaction with acetone was slower than those with 3-pentanone or
44
45
46 mesityl oxide, but reached 80% conversion after 7 hours.
47
48
49
50
51
52
53
54
55
56
57
58
59
60

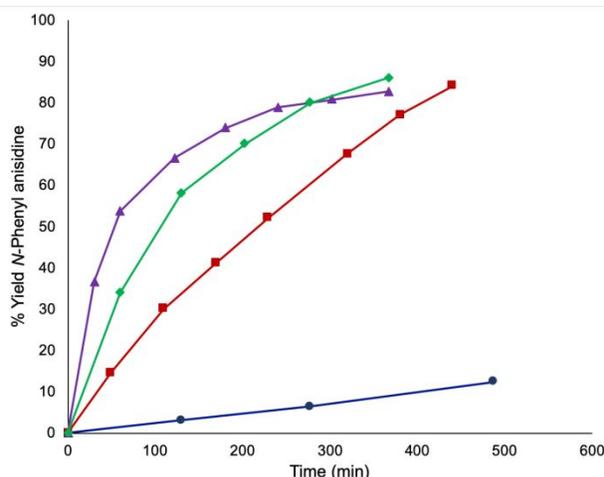
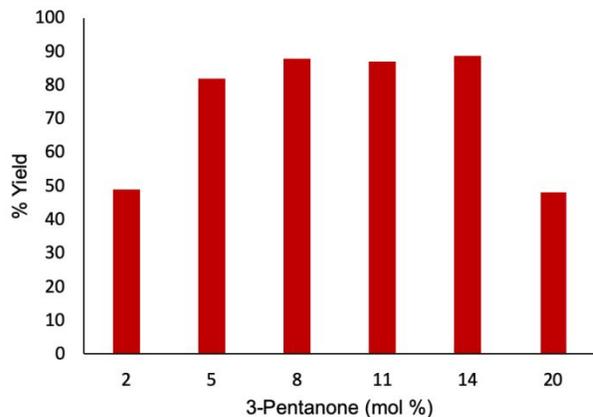


Figure 2. Reaction profile for the reaction of 3-bromoanisole and aniline using **7a** (0.5 mol %) under conditions of equation 1: 3-pentanone at 22 °C (purple triangle), mesityl oxide at 22 °C (green diamond), acetone at 40 °C (red square), acetone at 22 °C (blue circle).

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 a similar activating effect to 3-pentanone, despite being a methyl ketone.

To determine the optimal loading of ketone activator, the reaction of 4-bromoanisole and aniline catalyzed by **7a** (0.5 mol %) was performed at room temperature with 3-

1
2
3 pentanone loadings ranging from 2–20 mol % relative to 4-bromoanisole, which
4
5
6 corresponds to 2–20 equivalents relative to palladium. The rate of conversion increased
7
8
9 on going from 2 to 8 mol % 3-pentanone (Figure S18, Supporting Information). After 3
10
11 hours, the reaction with 2 mol % 3-pentanone had reached 49% conversion, whereas the
12
13 reaction with 8 mol % had reached 87% conversion (Figure 3). Reactions with 8–14
14
15 mol% 3-pentanone had nearly identical reaction profiles (Figure S18). Further
16
17 increasing the 3-pentanone loading to 20 mol%, resulted in slower conversion (48%
18
19 after 3 hours). After 18 hours, the reactions with 5–14 mol % 3-pentanone gave
20
21 complete conversion, whereas a 70% conversion was achieved with 2 mol % ketone and
22
23
24 complete conversion, whereas a 70% conversion was achieved with 2 mol % ketone and
25
26
27 an 80% conversion with 20 mol % ketone.
28
29

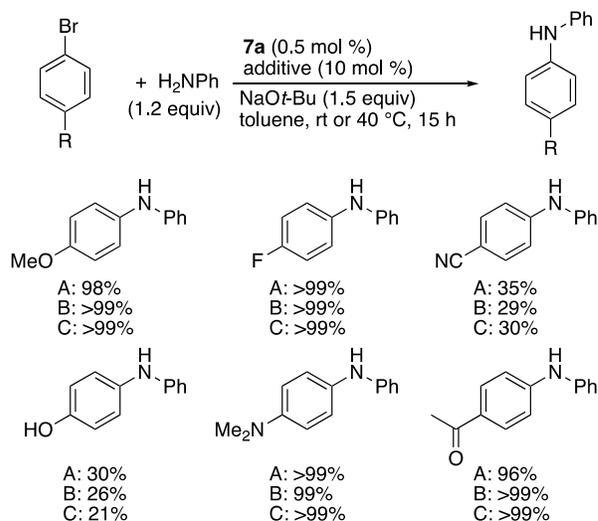


30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45 **Figure 3.** Average yield (3 trials) after 3 hours for the reaction 4-bromoanisole and
46
47 aniline catalyzed by **7a** (0.5 mol %) using NaOt-Bu in toluene at room temperature as a
48
49 function of 3-pentanone loading.
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

These results show that precatalyst **7a** requires at least 5 mol% 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 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.

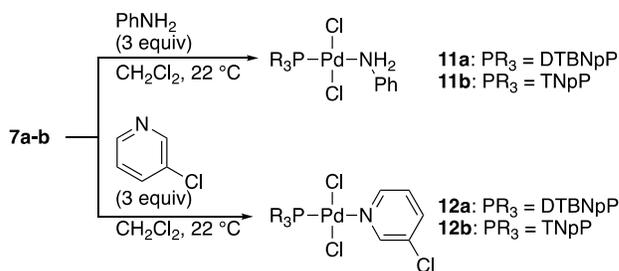
The use of ketone activators with **7a** was tested in the coupling of aniline with a small set of aryl bromides (Scheme 1). Reactions with 3-pentanone (condition A) and mesityl oxide (condition C) were performed at room temperature, whereas those with acetone (condition B) were carried out at 40 °C. 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 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.



21 **Scheme 1.** Coupling of aryl bromides catalyzed by **7a** using ketone activators.

22
23
24 Condition A: 3-pentanone, 22 °C; Condition B: acetone, 40 °C; Condition C: mesityl
25
26 oxide, 22 °C. Yields determined by GC.
27
28
29
30

31
32 The PEPPSI precatalyst family has a monomeric (NHC)PdCl₂(3-chloropyridine)
33
34 structure in which the pyridine ligand can be displaced under the reaction conditions to
35
36 reveal the (NHC)Pd(0) active species.^{3b,c,11} No examples of phosphine analogs of the
37
38 PEPPSI catalysts have been reported. Our group previously reported the structure of
39
40 (DTBNpP)PdCl₂(4-picoline),¹⁵ but had not explored the catalytic activity of these types
41
42 of complexes. Aniline (**8a-b**) and 3-chloropyridine (**9a-b**) complexes were readily
43
44 prepared by reacting the nitrogen ligand with dimers **7a** or **7b** in methylene chloride
45
46 (Scheme 2).
47
48
49
50
51
52
53
54
55
56
57
58
59
60



13
14
15
16
17

Scheme 2. Synthesis of nitrogen ligand adducts of **7a-b**.

18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37

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 that is structurally similar to that of other (TNpP)PdCl₂(amine) adducts that 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.

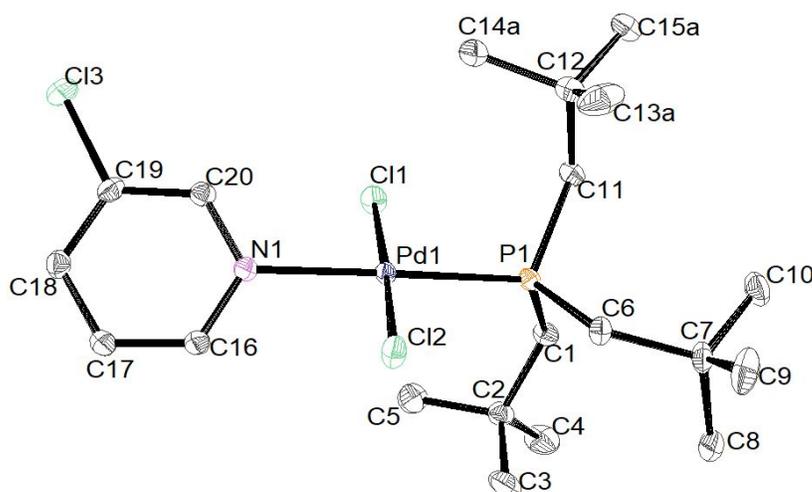


Figure 4. Thermal ellipsoid plot (50% probability) of the molecular structure of **9b**. Hydrogen atoms and disorder are omitted for clarity. Selected bond distances (Å) and angles (°): Pd1-P1 2.2571(3), Pd1-N1 2.1349(9), Pd-Cl_{ave} 2.307, Cl1-Pd1-N1 88.48(1), N1-Pd1-Cl2 89.12(2), Cl2-P1-P1 93.78(1), 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 than those derived from DTBNpP.¹⁹ 3-Chloropyridine-derived complex **9b** provided higher yields than **7b**, whereas aniline complex **8b** was less effective.

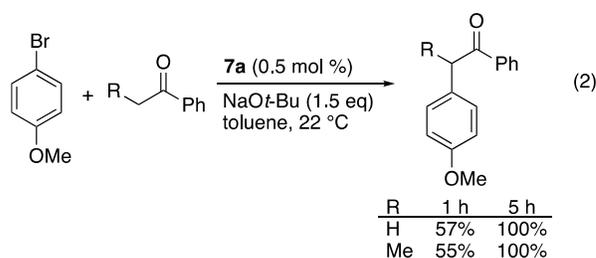
Table 2. Amine adducts as precatalysts for *N*-arylation reactions

entr y	precataly st	yield Ph ₂ NH (%)	
		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

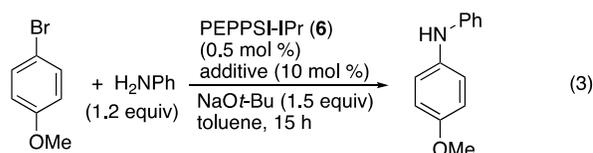
^a Condition A: precatalyst (1 mol % Pd), phenyl bromide (1 mmol), aniline (1.2 mmol), NaOt-Bu (1.5 mmol), toluene, 22 °C, 3 h. ^b Condition B: Same as condition A with the addition of 3-pentanone (0.1 mmol).

Ketone arylation. Enolate arylation products were observed as minor byproducts in the ketone-activated amination reactions. Based on 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 hour and complete conversion to product after 5 hours (eq 2). Complex **7a** showed comparable activity to the catalyst generated in situ from Pd(OAc)₂ and DTBNpP.²⁰



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 complex **7a**, the PEPPSI precatalysts must undergo reduction to form the active palladium(0) species. The ability of ketones to

1
2
3 promote the coupling of 4-bromoanisole and aniline using the PEPPSI-IPr precatalyst
4
5
6 was tested (eq 3). In the absence of any additive, low yields were obtained in the
7
8
9 coupling of 3-bromoanisole and aniline using PEPPSI-IPr from room temperature to 60
10
11 °C (Table 3, entries 1-3). Significantly higher yields were obtained by the addition of 3-
12
13
14 pentanone (entries 4-5), although the yields at room temperature and 40 °C were lower
15
16 than those obtained with precatalyst **7a**. Increasing the temperature to 60 °C and the 3-
17
18
19 pentanone loading to 29 mol % increased the yield to 80% (entry 7). The higher ketone
20
21
22 loading increased the amount of α -arylated byproducts to 5%. Mesityl oxide also
23
24
25 improved the yield of product, but was less effective than 3-pentanone (entries 8-9).
26



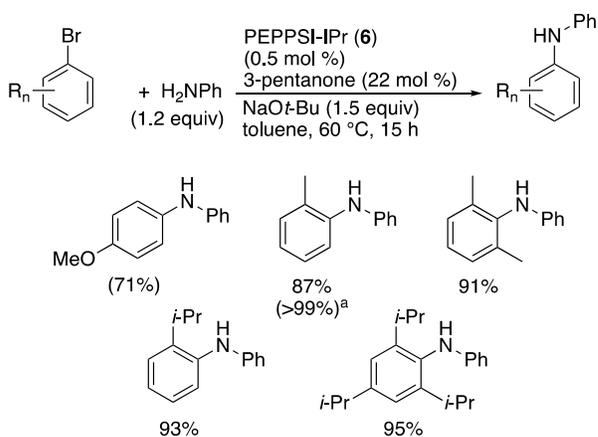
34 **Table 3.** Effect of 3-pentanone in activation of PEPPSI-IPr precatalyst^a

35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50

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

51 ^a Conditions depicted in equation 3. ^b Yields determined by GC analysis of reaction
52
53
54 mixtures. ^c 22 mol % 3-pentanone ^d 29 mol % 3-pentone
55
56
57
58
59
60

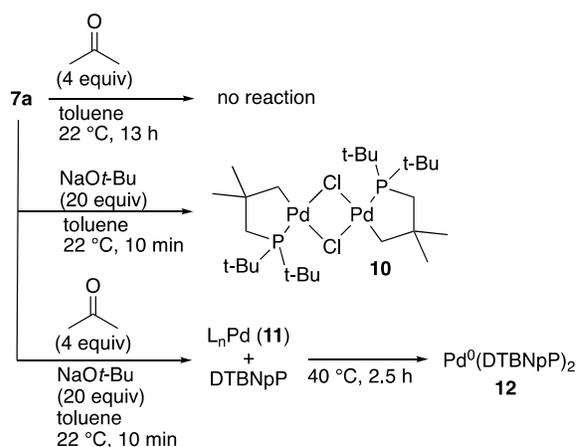
1
2
3
4
5
6 The PEPPSI-IPr precatalyst was used in the coupling of a series of aryl bromides and
7
8 aniline using 22 mol % 3-pentanone at 60 °C (Scheme 3). 4-Bromoanisole gave 71%
9
10 conversion to product under these conditions. Aryl bromides with ortho-substituents
11
12 gave complete conversion to product under these conditions and high isolated yields.
13
14 Even in the presence of a relatively high concentration of 3-pentanone, high selectivity
15
16 for the *N*-arylation reaction occurs. The PEPPSI-IPr/3-pentanone system is much more
17
18 efficient with the ortho-substituted aryl bromides than unhindered cases. Complete
19
20 conversion of 2-bromotoluene was achieved at room temperature in the presence of 3-
21
22 pentanone compared to 3% yield in the absence of the ketone activator. In contrast,
23
24 only 14% conversion to product was achieved at room temperature with 4-
25
26 bromoanisole under the same conditions. In contrast,
27
28 only 14% conversion to product was achieved at room temperature with 4-
29
30 bromoanisole under the same conditions.
31
32
33
34
35



1
2
3 **Scheme 3.** 3-Pentanone-activated coupling of aryl bromides and aniline using
4
5
6 PEPPSI-IPr. Isolated yields, except yields in parentheses (GC yields). ^a Reaction
7
8 performed at room temperature.
9

10
11
12
13
14 **Mechanism of ketone activation.** Ketones have not previously been shown to be
15
16 able to activate palladium(II) precatalysts in cross-coupling reactions, to our knowledge.
17
18 To better understand this process, the reaction of precatalyst **7a** with ketones under a
19
20 variety of conditions was analyzed by ³¹P NMR spectroscopy. Treatment of **7a** with
21
22 acetone in toluene resulted in no change in the ³¹P NMR spectrum over 13 hours
23
24 (Scheme 4). When **7a** was reacted with NaO*t*-Bu in toluene, complete conversion to
25
26 palladacycle **10** occurred within 10 minutes. We have previously observed the base
27
28 promoted metalation of **7a** to be rapid in the absence of other reactants.¹⁵ When **7a** was
29
30 treated with acetone and NaO*t*-Bu in toluene, the only phosphorus species observed
31
32 after 10 minutes was free DTBNpP. No change was observed over the course of 14
33
34 hours. When this reaction was repeated at 40 °C, a 3:1 mixture of free DTBNpP and
35
36 Pd⁰(DTBNpP)₂ (**12**) was observed. Over the course of 2.5 hours, the remaining free
37
38 DTBNpP was converted to complex **12**. The results show that in the presence of acetone
39
40 and NaO*t*-Bu, the DTBNpP ligand is rapidly displaced to form a phosphorus-free
41
42 palladium species (**11**) with an unknown structure. At 40 °C, this species slowly forms
43
44 Pd⁰(DTBNpP)₂ without any other phosphorus byproducts. Notably, palladacycle **10** is
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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, NaOt-Bu, acetone, and toluene), only free DTBNpP is observed from 10 minutes through 13 hours at both 22 and 40 °C. In the 40 °C reaction, complete conversion of the aryl bromide occurs after 2.5 hours.



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 NaOt-Bu and 3-pentanone, complete conversion to $Pd(DTBNpP)_2$ (**12**) occurs within 10 minutes, 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 NaOt-

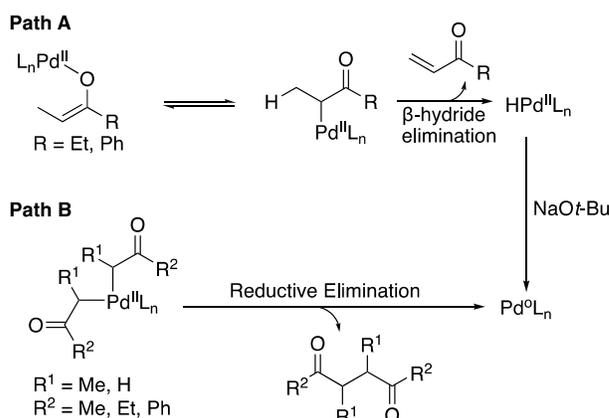
1
2
3 Bu. In the mesityl oxide-promoted coupling reaction, only complex **12** is observed after
4
5
6 10 minutes, with no further change in the ^{31}P NMR spectrum over several hours.
7

8
9 These studies show that the tested ketones are capable of reducing **7a** to
10
11 palladium(0) complex **12**. This reaction occurs slowly in the case of acetone, through a
12
13 phosphine-free palladium intermediate. In the cases of 3-pentanone and mesityl oxide,
14
15 this reduction occurs rapidly (< 10 minutes) at room temperature without observing
16
17 free phosphine. It is possible that these reactions also proceed through intermediate **11**,
18
19 but that the resulting intermediate rapidly is converted to palladium(0) complex **12**.
20
21
22 The efficiency of the catalytic reaction correlates with rapid formation of **12** in the
23
24 presence of ketone and base. Both 3-pentanone and mesityl oxide are effective
25
26 activators of precatalyst **7a**, whereas acetone is less effective at ambient temperature and
27
28 provides a less active catalyst at 40 °C. Although the rapid formation of **12** correlates
29
30 with efficient catalysis, complex **12** is not seen under catalytic conditions when 3-
31
32 pentanone is used as the activator. It is possible that the formation of **12** in the absence
33
34 of aryl bromide and aniline indicates efficient Pd(0) formation, but that under the
35
36 catalytic condition the amine or other ligands are coordinated to the active species. In
37
38 contrast to these results, we do observe either **12** or the oxidative addition product
39
40 derived from **12** ($[(\text{DTBNpP})\text{Pd}(\text{Ar})\text{Br}]_2$) under Suzuki coupling conditions.¹⁵
41
42
43
44
45
46
47
48
49
50

51
52 Analysis of the reaction of **7a** with 3-pentanone (4 equiv) and NaO*t*-Bu (20 equiv) by
53
54 ^1H NMR spectroscopy showed a broad peak at approximately 4 ppm. This resonance is
55
56
57
58
59
60

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 $[\text{Pd}(\text{enolate})_2]_n$ or $[\text{ClPd}(\text{enolate})]_n$ species. This species then would undergo a reductive process to form Pd(0), which can re-coordinate the phosphine ligands. A plausible mechanism in the case of 3-pentanone would 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.



1
2
3 **Scheme 5.** Possible reduction pathways from a Pd(II)-bound enolate
4
5
6
7

8
9 The β -hydride elimination pathway should result in the formation of 1-penten-3-one
10
11 from 3-pentanone or 1-phenyl-2-penten-1-one from propiophenone. Analysis of the
12
13 reduction of palladium by 3-pentanone (4 equivalents) and NaOt-Bu (20 equiv) shows
14
15 no evidence of the β -hydride elimination products by ^1H NMR spectroscopy or GC-MS
16
17 analysis. The expected products of enolate homocoupling, for example hexane-2,5-
18
19 dione from acetone, have also not been observed by GC-MS or ^1H NMR analysis.
20
21 Therefore, the mechanism by which complex **7a** is reduced to palladium(0) in the
22
23 presence of ketones and base remains unclear.
24
25
26
27
28
29

30 Amination reactions activated by acetone and 3-pentanone appear to involve a
31
32 phosphine-free species (**11**) as the potential active catalyst. To determine whether the
33
34 phosphine is necessary, $(\text{MeCN})_2\text{PdCl}_2$ was explored as a precatalyst (Table 4). Using
35
36 $(\text{MeCN})_2\text{PdCl}_2$ in place of **7a** with acetone (40 °C) or 3-pentanone (22 °C) gave no
37
38 conversion to product. When DTBNpP was used in combination with $(\text{MeCN})_2\text{PdCl}_2$,
39
40 no yield was obtained at 22 °C in the absence of ketone activator. Addition of acetone at
41
42 40 °C gave a modest yield of the arylated product, but the $(\text{MeCN})_2\text{PdCl}_2$ /DTBNpP
43
44 catalyst system was less effective than **7a**. The use of 3-pentanone with
45
46 $(\text{MeCN})_2\text{PdCl}_2$ /DTBNpP at room temperature gave no conversion. It appears that the
47
48
49
50
51
52
53
54
55
56
57
58
59
60

prior coordination of DTBNpP to the palladium is critical to the success of the precatalyst under these conditions.

Table 4. Aniline arylation using $(\text{MeCN})_2\text{PdCl}_2$ 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), $\text{NaO}t\text{-Bu}$ (1.5 mmol), $(\text{MeCN})_2\text{PdCl}_2$ (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

1
2
3 catalyst. The mechanism of the reduction process remains unclear, however. We
4
5
6 hypothesize that a palladium enolate species is the key intermediate. In the case of 3-
7
8
9 pentanone, a likely activation pathway would be β -hydride elimination to give a
10
11
12 palladium-hydride that could be deprotonated to afford the palladium(0) active species.
13
14 The expected byproducts of this pathway have not been observed, however. Therefore,
15
16
17 an as yet undetermined mechanism is possible. Efforts to determine the reduction
18
19
20 mechanism are ongoing.
21
22
23
24

25 Experimental

26
27 **General Procedure.** Reagents were purchased from commercial suppliers and used
28
29
30 as received, except as noted. [(DTBNpP)PdCl₂]₂ (**7a**),¹⁵ [(TNpP)PdCl₂]₂ (**7b**),¹⁵ and
31
32
33 (TNpP)Pd(aniline)Cl₂ (**8b**)¹⁷ were prepared according to previously reported methods.
34
35
36 Toluene was refluxed over sodium for an hour and freshly distilled before use.
37
38
39 Reactions were conducted under nitrogen double-manifold inert-atmosphere
40
41
42 techniques, unless noted otherwise. GC analysis was performed using a Shimadzu gas
43
44
45 chromatograph (GC-2014) outfitted with a Alltech EC-5 column (30 m X 0.32 mm ID X
46
47
48 0.25 μ m film thickness) and FID detector. Chromatograms were run with an initial
49
50
51 oven temperature of 150 °C increasing to 250 °C at a rate of 10 °C/min. NMR spectra
52
53
54 were obtained on a Brüker 500 MHz spectrometer. ³¹P NMR spectra were acquired
55
56
57 using gated decoupling mode.
58
59
60

1
2
3 **General procedure for ketone-activated N-arylation reactions.** A screw-capped
4 vial with **7a** (0.5 mol%) was put into the glovebox. NaOt-Bu (1.5 equiv) was added. The
5
6 vial was sealed with a septum cap and taken out of the glove box. Aryl halide (1 mmol),
7
8
9 ketone (10 mol%), aniline (1.2 mmol), and toluene (3 ml) were added and the reaction
10
11
12 was stirred at room temperature or placed in an oil bath preheated to the desired
13
14
15 temperature. After 15 h, the reactions were analyzed by GC.
16
17
18

19 **(DTBNpP)Pd(aniline)Cl₂ (8a).** [(DTBNpP)PdCl₂]₂ (**7a**, 100 mg, 0.128 mmol) was
20
21 dissolved in methylene chloride (8 mL). Then aniline (35.1 μ L, 0.384 mmol) was added
22
23 into the solution. After stirring for one hour, the volatiles were removed under vacuum
24
25 to provide **8a** as an air-stable orange solid (116.7 mg, 94%). ¹H NMR (500 MHz, C₆D₆, 295
26
27 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),
28
29 2.08 (d, *J* = 12.8 Hz, 2H), 1.43 (d, *J* = 12.8 Hz, 18H), 1.33 (s, 9 H), ¹³C NMR (125 MHz,
30
31 C₆D₆, 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
32
33 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). ³¹P{¹H} NMR
34
35 (202.5 MHz, C₆D₆, 295 K): δ 63.0.
36
37
38
39
40
41
42
43

44 **(DTBNpP)Pd(3-chloropyridine)Cl₂ (9a).** [(DTBNpP)PdCl₂]₂ (**7a**, 100 mg, 0.128
45
46 mmol) was dissolved in methylene chloride (8 mL) under nitrogen. Then 3-
47
48 chloropyridine (36.5 μ L, 0.384 mmol) was added to the solution. After stirring for one
49
50 hour, the volatiles were removed under vacuum to provide **9a** as an air-stable orange
51
52 solid (120.2 mg, 93%). ¹H NMR (500 MHz, C₆D₆, 295 K): δ 9.11 (s, 1H), 8.71 (s, 1H), 6.55
53
54
55
56
57
58
59
60

(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, $J_{\text{C-P}} = 6.4$ Hz), 34.48 (d, $J_{\text{C-P}} = 25.2$ Hz), 33.81 (d, $J_{\text{C-P}} = 6.4$ Hz), 31.351 (d, $J_{\text{C-P}} = 4.3$ Hz), 31.16 (d, $J_{\text{C-P}} = 4.3$ Hz). $^{31}\text{P}\{^1\text{H}\}$ NMR (202.5 MHz, C_6D_6 , 295 K): δ 62.0.

(TNpP)Pd(3-chloropyridine)Cl₂ (9b). [(TNpP)PdCl₂]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 stirring for one hour, 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. ^1H 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, $J_{\text{C-P}} = 25.2$ Hz), 33.41 (d, $J_{\text{C-P}} = 6.4$ Hz), 32.64 (d, $J_{\text{C-P}} = 4.3$ Hz). $^{31}\text{P}\{^1\text{H}\}$ 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 ShelXT²⁷ structure solution program using Intrinsic Phasing and refined with ShelXL²⁸ refinement package using Least Squares minimization using either Olex2²⁶ or ShelXle²⁹ or both. The structure was found to have

1
2
3 a rotational disorder on one of the neopentyl ligand. Atoms on the two moieties were
4
5 restrained to have similar geometries (SAME).
6
7

8 **General procedure for the PEPPSI-IPr-catalyzed amination.** PEPPSI-IPr (3.4 mg, 5
9
10 μmol) was added to a 3 dram glass vial with a stir bar. The vial was transferred into a
11
12 nitrogen glove box, where, NaO-*t*-Bu (144 mg, 1.50 mmol) was added. The vial was
13
14 sealed with rubber septum cap and removed from the glove box. The remaining
15
16 reagents were added to a vial in the following order via syringe: dry toluene (3.5 mL),
17
18 aryl bromide (1.0 mmol), 3-pentanone (23 μL , 0.22 mmol), and aniline (110 μL , 1.20
19
20 mmol). The vials were placed in a preheated oil bath at the desired temperature and
21
22 allowed to stir for 24 hrs. The reaction mixture was quenched with aqueous ammonium
23
24 chloride and extracted three times with ethyl acetate (ca 25 mL). The combined organic
25
26 phases were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure.
27
28 The crude products were purified via silica gel chromatography eluting with hexane.
29
30
31
32
33
34
35
36
37

38 ***N*-Phenyl-2-toluidine.**³⁰ 2-Bromotoluene (120.4 μL , 1.0 mmol) was coupled with
39
40 aniline according to the general procedure. GC analysis indicated complete conversion.
41
42 The reaction mixture was worked up as described in the general procedure. The crude
43
44 product was purified by column chromatography to afford the product as an oil (148.6
45
46 mg, 87%). ¹H NMR (CDCl₃, 500 MHz) δ 7.24–7.21 (m, 3H), 7.17 (m, 1H), 7.11 (t, *J* = 7.8
47
48 Hz, 1H), 6.94–6.91 (m, 3H), 6.90–6.86 (m, 1H), 5.34 (brs, 1H), 2.22 (s, 3H). ¹³C NMR
49
50 (CDCl₃, 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.
51
52
53
54
55
56
57
58
59
60

1
2
3 ***N*-Phenyl 2,6-dimethylaniline.**³⁰ 2-Bromo-1,3-dimethylbenzene (133 μ L, 1.0 mmol)
4
5
6 was coupled with aniline according to the general procedure. GC analysis indicated
7
8 95% conversion. The reaction mixture was worked up as described in the general
9
10 procedure. The crude product was purified by column chromatography to afford the
11
12 product as an oil (167.5 mg, 91%). ¹H NMR (CDCl₃, 500 MHz) δ 7.21–7.10 (m, 5H), 6.78
13
14 (tt, J = 7.3 Hz, 1.0 Hz, 1H), 6.55–6.53 (m, 2H), 5.21 (brs, 1H), 2.25 (s, 6H). ¹³C NMR
15
16 (CDCl₃, 126 MHz) δ 146.3, 138.2, 135.9, 129.2, 128.5, 125.8, 118.1, 113.5, 18.3.
17
18
19
20
21

22 ***N*-Phenyl 2-isopropylaniline.**³¹ 1-Bromo-2-isopropylbenzene (153 μ L, 1.0 mmol)
23
24 was coupled with aniline according to the general procedure. GC analysis indicated
25
26 complete conversion. The reaction mixture was worked up as described in the general
27
28 procedure. The crude product was purified by column chromatography to afford the
29
30 product as an oil (184.6 mg, 93%). ¹H NMR (CDCl₃, 500 MHz) δ 7.31 (dd, J = 7.7, 1.4 Hz,
31
32 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
33
34 (m, 3H), 5.40 (brs, 1H), 3.15 (sept, J = 6.9 Hz, 1H), 1.24 (d, J = 7.0 Hz, 6H). ¹³C NMR
35
36 (CDCl₃, 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,
37
38 23.0.
39
40
41
42
43
44
45

46 ***N*-Phenyl 2,4,6-triisopropylaniline.**³² 1-Bromo-2,4,6-triisopropylbenzene (153 μ L,
47
48 1.0 mmol) was coupled with aniline according to the general procedure. GC analysis
49
50 indicated complete conversion. The reaction mixture was worked up as described in the
51
52 general procedure. The crude product was purified by column chromatography to
53
54
55
56
57
58
59
60

1
2
3 afford the product as an oil (228.1 mg, 95%). ¹H NMR (CDCl₃, 500 MHz) δ 7.18 (t, *J* = 7.3
4 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),
5
6
7
8
9 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* =
10
11 6.9 Hz, 12H). ¹³C NMR (CDCl₃, 126 MHz) δ 148.4, 147.4, 147.2, 132.7, 129.1, 121.7, 117.3,
12
13
14 112.8, 34.2, 28.2, 24.1, 23.9.
15
16
17
18

19 **Supporting Information**

20 Supporting information is available free of charge at <https://xxxx>

21
22
23
24 NMR spectra of isolated compounds, X-ray characterization details, reaction
25
26
27 profile as a function of ketone loading (PDF)
28
29
30
31
32

33 **Accession Codes**

34
35
36 CCDC 1978602 contains the supplementary crystallographic data for this paper.

37
38 These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by
39
40
41 emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge
42
43
44 Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223
45
46 336033.
47
48
49
50
51

52 **Acknowledgements.** H.H. acknowledges support of his post-doctoral associate
53
54 position from the College of Arts & Sciences, The University of Alabama. The structure
55
56
57
58
59
60

1
2
3 of **9b** was obtained on an X-ray diffractometer purchased with support from NSF (CHE
4
5
6 MRI 1828078). Johnson-Matthey is acknowledged for donation of palladium salts.
7
8
9

10 11 **References**

- 12
13
14 1. (a) Fleckenstein, C. A.; Plenio, H., Sterically Demanding Trialkylphosphines for
15
16 Palladium-Catalyzed Cross Coupling Reactions—Alternatives to $PtBu_3$. *Chem. Soc. Rev.*
17
18 **2010**, *39*, 694-711; (b) Shaughnessy, K. H., Monodentate Trialkylphosphines: Privileged
19
20 Ligands in Metal-Catalyzed Cross-Coupling Reactions. *Curr. Org. Chem.* **2020**,
21
22 published online. DOI: 10.2174/1385272824666200211114540.
23
24
25
26
27 2. (a) Surry, D. S.; Buchwald, S. L., Diamine Ligands in Copper-Catalyzed
28
29 Reactions. *Chem. Sci.* **2010**, *1*, 13-21; (b) Surry, D. S.; Buchwald, S. L., Dialkylbiaryl
30
31 Phosphines in Pd-Catalyzed Amination: A User's Guide. *Chem. Sci.* **2011**, *2*, 27-50.
32
33
34
35 3. (a) Fortman, G. C.; Nolan, S. P., *N*-Heterocyclic Carbene (NHC) Ligands and
36
37 Palladium in Homogeneous Cross-Coupling Catalysis: a Perfect Union. *Chem. Soc. Rev.*
38
39 **2011**, *40*, 5151-5169; (b) Valente, C.; Çalimisiz, S.; Hoi, K. H.; Mallik, D.; Sayah, M.;
40
41 Organ, M. G., The Development of Bulky Palladium NHC Complexes for the Most-
42
43 Challenging Cross-Coupling Reactions. *Angew. Chem. Int. Ed.* **2012**, *51*, 3314-3332; (c)
44
45 Valente, C.; Pompeo, M.; Sayah, M.; Organ, M. G., Carbon–Heteroatom Coupling Using
46
47 Pd-PEPSI Complexes. *Org. Proc. Res. Dev.* **2014**, *18*, 180-190; (d) Shi, S.; Nolan, S. P.;
48
49 Szostak, M., Well-Defined Palladium(II)-NHC Precatalysts for Cross-Coupling
50
51
52
53
54
55
56
57
58
59
60

1
2
3 Reactions of Amides and Esters by Selective N-C/O-C Cleavage. *Acc. Chem. Res.* **2018**,
4
5
6 *51*, 2589-2599.

7
8
9 4. (a) Li, H.; Johansson Seechurn, C. C. C.; Colacot, T. J., Development of Preformed
10
11 Pd Catalysts for Cross-Coupling Reactions, Beyond the 2010 Nobel Prize. *ACS Catal.*
12
13 **2012**, *2*, 1147-1164; (b) Hazari, N.; Melvin, P. R.; Beromi, M. M., Well-Defined Nickel and
14
15 Palladium Precatalysts for Cross-Coupling. *Nat. Rev. Chem.* **2017**, *1*, 0025; (c)
16
17 Shaughnessy, K. H., Development of Palladium Precatalysts that Efficiently Generate
18
19 LPd(0) Active Species. *Isr. J. Chem.* **2019**, *59*, published online, DOI:
20
21
22 10.1002/ijch.201900067.
23
24
25

26
27 5. Christmann, U.; Vilar, R., Monoligated Palladium Species as Catalysts in Cross-
28
29
30 Coupling Reactions. *Angew. Chem. Int. Ed.* **2005**, *44*, 366-374.
31
32

33 6. (a) Ortiz, D.; Blug, M.; Le Goff, X. F.; Le Floch, P.; Mézailles, N.; Maître, P.,
34
35 Mechanistic Investigation of the Generation of a Palladium(0) Catalyst from a
36
37 Palladium(II) Allyl Complex: A Combined Experimental and DFT Study.
38
39 *Organometallics* **2012**, *31*, 5975-5978; (b) Zheng, Q.; Liu, Y.; Chen, Q.; Hu, M.; Helmy, R.;
40
41
42
43 Sherer, E. C.; Welch, C. J.; Chen, H., Capture of Reactive Monophosphine-Ligated
44
45 Palladium(0) Intermediates by Mass Spectrometry. *J. Am. Chem. Soc.* **2015**, *137*, 14035-
46
47
48 14038.
49
50

51
52 7. (a) Lee, H. G.; Milner, P. J.; Buchwald, S. L., An Improved Catalyst System for the
53
54 Pd-Catalyzed Fluorination of (Hetero)Aryl Triflates. *Org. Lett.* **2013**, *15*, 5602-5605; (b)
55
56
57
58
59
60

1
2
3 Lee, H. G.; Milner, P. J.; Buchwald, S. L., Pd-Catalyzed Nucleophilic Fluorination of
4 Aryl Bromides. *J. Am. Chem. Soc.* **2014**, *136*, 3792-3795.

5
6
7
8 8. (a) Aufiero, M.; Scattolin, T.; Proutière, F.; Schoenebeck, F., Air-Stable Dinuclear
9 Iodine-Bridged Pd(I) Complex - Catalyst, Precursor, or Parasite? The Additive Decides.
10 Systematic Nucleophile-Activity Study and Application as Precatalyst in Cross-
11 Coupling. *Organometallics* **2015**, *34*, 5191-5195; (b) Bonney, K. J.; Proutiere, F.;
12 Schoenebeck, F., Dinuclear Pd(I) Complexes—Solely Precatalysts? Demonstration of
13 Direct Reactivity of a Pd(I) Dimer With an Aryl Iodide. *Chem. Sci.* **2013**, *4*, 4434-4439; (c)
14 Proutière, F.; Aufiero, M.; Schoenebeck, F., Reactivity and Stability of Dinuclear Pd(I)
15 Complexes: Studies on the Active Catalytic Species, Insights into Precatalyst Activation
16 and Deactivation, and Application in Highly Selective Cross-Coupling Reactions. *J. Am.*
17 *Chem. Soc.* **2012**, *134*, 606-612.

18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35 9. (a) Melvin, P. R.; Nova, A.; Balcells, D.; Dai, W.; Hazari, N.; Hruszkewycz, D. P.;
36 Shah, H. P.; Tudge, M. T., Design of a Versatile and Improved Precatalyst Scaffold for
37 Palladium-Catalyzed Cross-Coupling: $(\eta^3\text{-}1\text{-}t\text{-Bu-indenyl})_2(\mu\text{-Cl})_2\text{Pd}_2$. *ACS Catal.* **2015**, *5*,
38 3680-3688; (b) Hruszkewycz, D. P.; Balcells, D.; Guard, L. M.; Hazari, N.; Tilset, M.,
39 Insight into the Efficiency of Cinnamyl-Supported Precatalysts for the Suzuki-Miyaura
40 Reaction: Observation of Pd(I) Dimers with Bridging Allyl Ligands During Catalysis. *J.*
41 *Am. Chem. Soc.* **2014**, *136*, 7300-7316; (c) Johansson Seechurn, C. C. C.; Parisel, S. L.;
42 Colacot, T. J., Air-Stable Pd(R-allyl)LCl (L= Q-Phos, P(t-Bu)₃, etc.) Systems for C–C/N
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 Couplings: Insight into the Structure–Activity Relationship and Catalyst Activation
4
5
6 Pathway. *J. Org. Chem.* **2011**, *76*, 7918-7932; (d) Marion, N.; Nolan, S. P., Well-Defined N-
7
8 Heterocyclic Carbenes-Palladium(II) Precatalysts for Cross-Coupling Reactions. *Acc.*
9
10
11 *Chem. Res.* **2008**, *41*, 1440-1449.
- 12
13
14 10. (a) Biscoe, M. R.; Fors, B. P.; Buchwald, S. L., A New Class of Easily Activated
15
16 Palladium Precatalysts for Facile C–N Cross-Coupling Reactions and the Low
17
18 Temperature Oxidative Addition of Aryl Chlorides. *J. Am. Chem. Soc.* **2008**, *130*, 6886-
19
20 6887; (b) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L., Design and Preparation of New
21
22 Palladium Precatalysts for C–C and C–N Cross-Coupling Reactions. *Chem. Sci.* **2013**, *4*,
23
24 916-920.
- 25
26
27 11. Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G., Palladium Complexes of N-
28
29 Heterocyclic Carbene as Catalysts for Cross-Coupling Reactions—a Synthetic Chemist's
30
31 Perspective. *Angew. Chem. Int. Ed.* **2007**, *46*, 2768-2813.
- 32
33
34 12. O'Brien, C. J.; Kantchev, E. A. B.; Valente, C.; Hadei, N.; Chass, G. A.; Lough, A.;
35
36 Hopkinson, A. C.; Organ, M. G., Easily Prepared Air- and Moisture-Stable Pd-NHC
37
38 (NHC=N-Heterocyclic Carbene) Complexes: A Reliable, User Friendly, Highly Active
39
40 Palladium Precatalyst for the Suzuki-Miyaura Reaction. *Chem. – Eur. J.* **2006**, *12*, 4743-
41
42 4748.
- 43
44
45 13. (a) Sayah, M.; Organ, M. G., Carbon–Sulfur Bond Formation of Challenging
46
47 Substrates at Low Temperature by Using Pd-PEPPSI-IPent. *Chem. – Eur. J.* **2011**, *17*,
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 11719-11722; (b) Sayah, M.; Lough, A. J.; Organ, M. G., Sulfination by Using Pd-PEPPSI
4
5
6 Complexes: Studies into Precatalyst Activation, Cationic and Solvent Effects and the
7
8 Role of Butoxide Base. *Chem. — Eur. J.* **2013**, *19*, 2749-2756.

9
10
11 14. Sayah, M.; Organ, M. G., Potassium Isopropoxide: For Sulfination It is the Only
12
13 Base You Need! *Chem. — Eur. J.* **2013**, *19*, 16196-16199.

14
15
16 15. Barnett, K. L.; Howard, J. R.; Treager, C. J.; Shipley, A. T.; Stullich, R. M.; Qu, F.;
17
18 Gerlach, D. L.; Shaughnessy, K. H., Air-Stable [(R₃P)PdCl₂]₂ Complexes of
19
20 Neopentylphosphines as Cross-Coupling Precatalysts: Catalytic Application and
21
22 Mechanism of Catalyst Activation and Deactivation. *Organometallics* **2018**, *37*, 1410-1424.

23
24
25 16. Hill, L. L.; Moore, L. R.; Huang, R.; Craciun, R.; Vincent, A. J.; Dixon, D. A.;
26
27 Chou, J.; Woltermann, C. J.; Shaughnessy, K. H., Bulky Alkylphosphines with
28
29 Neopentyl Substituents as Ligands in the Amination of Aryl Bromides and Chlorides. *J.*
30
31 *Org. Chem.* **2006**, *71*, 5117-5125.

32
33
34 17. Hu, H.; Vasiliu, M.; Stein, T. H.; Qu, F.; Gerlach, D. L.; Dixon, D. A.;
35
36 Shaughnessy, K. H., Synthesis, Structural Characterization, and Coordination
37
38 Chemistry of (Trineopentylphosphine)palladium(aryl)bromide Dimer Complexes
39
40
41 [(Np₃P)Pd(Ar)Br]₂. *Inorg. Chem.* **2019**, *48*, 13299-13313.

42
43
44 18. Nasielski, J.; Hadei, N.; Achonduh, G.; Kantchev, E. A. B.; O'Brien, C. J.; Lough,
45
46
47 A.; Organ, M. G., Structure–Activity Relationship Analysis of Pd–PEPPSI Complexes in
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 Cross-Couplings: A Close Inspection of the Catalytic Cycle and the Precatalyst

4
5
6 Activation Model. *Chem. – Eur. J.* **2010**, *16*, 10844-10853.

7
8
9 19. (a) Raders, S. M.; Moore, J. N.; Parks, J. K.; Miller, A. D.; Leißing, T. M.; Kelley, S.
10
11 P.; Rogers, R. D.; Shaughnessy, K. H., Trineopentylphosphine: A Conformationally
12
13 Flexible Ligand for the Coupling of Sterically Demanding Substrates in the Buchwald-
14
15 Hartwig Amination and Suzuki-Miyaura Reaction. *J. Org. Chem.* **2013**, *78*, 4649-4664; (b)
16
17 Hu, H.; Qu, F.; Gerlach, D. L.; Shaughnessy, K. H., Mechanistic Study of the Role of
18
19 Substrate Steric Effects and Aniline Inhibition on the
20
21 Bis(trineopentylphosphine)palladium(0)-Catalyzed Arylation of Aniline Derivatives.
22
23
24
25
26
27
28 *ACS Catal.* **2017**, *7*, 2516-2527.

29
30
31 20. Raders, S. M.; Jones, J. M.; Semmes, J. G.; Kelley, S. P.; Rogers, R. D.;
32
33 Shaughnessy, K. H., Di-*tert*-Butylneopentylphosphine (DTBNpP): An Efficient Ligand
34
35 in the Palladium-Catalyzed A-Arylation of Ketones. *Eur. J. Org. Chem.* **2014**, 7395-7404.

36
37
38 21. (a) Lazny, R.; Wolosewicz, K., Expedient Preparation of Amine-Free Lithium
39
40 Enolates Using Immobilized Amide Reagents. *Tetrahedron Lett.* **2013**, *54*, 1103-1106; (b)
41
42
43 Culkin, D. A.; Hartwig, J. F., C-C Bond-Forming Reductive Elimination of Ketones,
44
45 Esters, and Amides from Isolated Arylpalladium(II) Enolates. *J. Am. Chem. Soc.* **2001**,
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
123, 5816-5817; (c) Culkin, D. A.; Hartwig, J. F., Carbon-Carbon Bond-Forming
Feductive Elimination From Arylpalladium Complexes Containing Functionalized

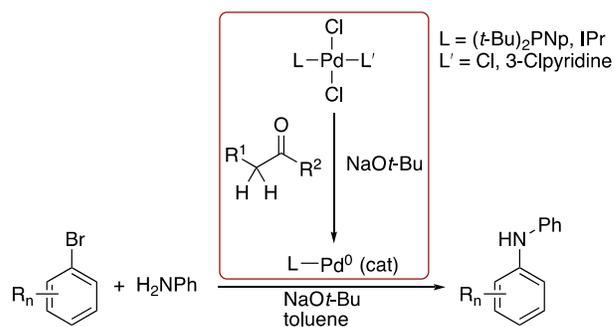
1
2
3 Alkyl Groups. Influence of Ligand Steric and Electronic Properties on Structure,
4
5
6 Stability, and Reactivity. *Organometallics* **2004**, *23*, 3398-3416.

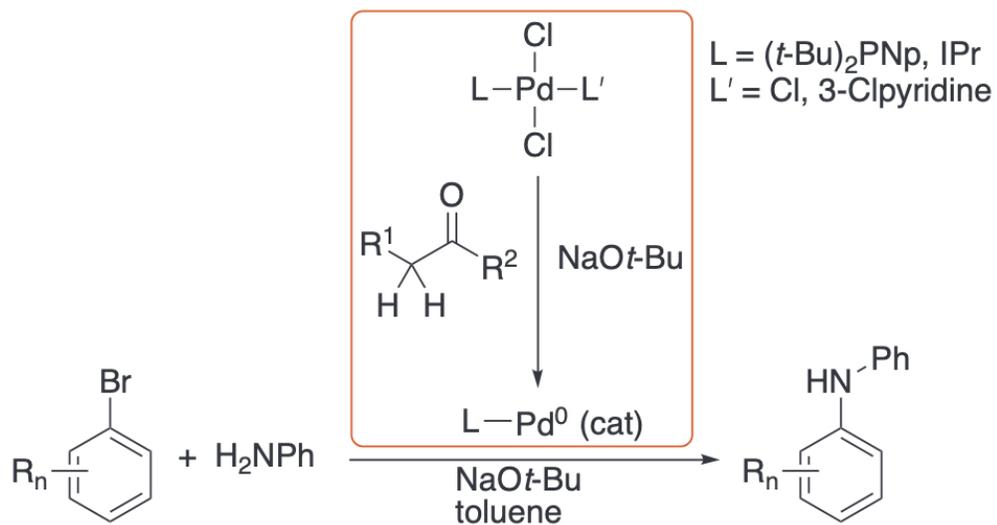
7
8
9 22. (a) Huang, Z.; Dong, G., Catalytic Direct β -Arylation of Simple Ketones with Aryl
10
11 Iodides. *J. Am. Chem. Soc.* **2013**, *135*, 17747-17750; (b) Ito, Y.; Hirao, T.; Saegusa, T.,
12
13
14 Synthesis of α,β -Unsaturated Carbonyl Compounds by Palladium(II)-Catalyzed
15
16 Dehydrosilylation of Silyl Enol Ethers. *J. Org. Chem.* **1978**, *43*, 1011-1013; (c) Muzart, J.,
17
18
19 One-Pot Syntheses of α,β -Unsaturated Carbonyl Compounds through Palladium-
20
21 Mediated Dehydrogenation of Ketones, Aldehydes, Esters, Lactones and Amides. *Eur. J.*
22
23
24
25 *Org. Chem.* **2010**, 3779-3790; (d) Thiessen, R. J., A New Method for the Preparation of α,β -
26
27
28 -Unsaturated Carbonyl Compounds. *J. Org. Chem.* **1971**, *36*, 752-757; (e) Shvo, Y.; Arisha,
29
30
31 A. H. I., Regioselective Catalytic Dehydrogenation of Aldehydes and Ketones. *J. Org.*
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173
174
175
176
177
178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207
208
209
210
211
212
213
214
215
216
217
218
219
220
221
222
223
224
225
226
227
228
229
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
246
247
248
249
250
251
252
253
254
255
256
257
258
259
260
261
262
263
264
265
266
267
268
269
270
271
272
273
274
275
276
277
278
279
280
281
282
283
284
285
286
287
288
289
290
291
292
293
294
295
296
297
298
299
300
301
302
303
304
305
306
307
308
309
310
311
312
313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454
455
456
457
458
459
460
461
462
463
464
465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521
522
523
524
525
526
527
528
529
530
531
532
533
534
535
536
537
538
539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565
566
567
568
569
570
571
572
573
574
575
576
577
578
579
580
581
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599
600
601
602
603
604
605
606
607
608
609
610
611
612
613
614
615
616
617
618
619
620
621
622
623
624
625
626
627
628
629
630
631
632
633
634
635
636
637
638
639
640
641
642
643
644
645
646
647
648
649
650
651
652
653
654
655
656
657
658
659
660
661
662
663
664
665
666
667
668
669
670
671
672
673
674
675
676
677
678
679
680
681
682
683
684
685
686
687
688
689
690
691
692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726
727
728
729
730
731
732
733
734
735
736
737
738
739
740
741
742
743
744
745
746
747
748
749
750
751
752
753
754
755
756
757
758
759
760
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777
778
779
780
781
782
783
784
785
786
787
788
789
790
791
792
793
794
795
796
797
798
799
800
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
825
826
827
828
829
830
831
832
833
834
835
836
837
838
839
840
841
842
843
844
845
846
847
848
849
850
851
852
853
854
855
856
857
858
859
860
861
862
863
864
865
866
867
868
869
870
871
872
873
874
875
876
877
878
879
880
881
882
883
884
885
886
887
888
889
890
891
892
893
894
895
896
897
898
899
900
901
902
903
904
905
906
907
908
909
910
911
912
913
914
915
916
917
918
919
920
921
922
923
924
925
926
927
928
929
930
931
932
933
934
935
936
937
938
939
940
941
942
943
944
945
946
947
948
949
950
951
952
953
954
955
956
957
958
959
960
961
962
963
964
965
966
967
968
969
970
971
972
973
974
975
976
977
978
979
980
981
982
983
984
985
986
987
988
989
990
991
992
993
994
995
996
997
998
999
1000
1001
1002
1003
1004
1005
1006
1007
1008
1009
1010
1011
1012
1013
1014
1015
1016
1017
1018
1019
1020
1021
1022
1023
1024
1025
1026
1027
1028
1029
1030
1031
1032
1033
1034
1035
1036
1037
1038
1039
1040
1041
1042
1043
1044
1045
1046
1047
1048
1049
1050
1051
1052
1053
1054
1055
1056
1057
1058
1059
1060
1061
1062
1063
1064
1065
1066
1067
1068
1069
1070
1071
1072
1073
1074
1075
1076
1077
1078
1079
1080
1081
1082
1083
1084
1085
1086
1087
1088
1089
1090
1091
1092
1093
1094
1095
1096
1097
1098
1099
1100
1101
1102
1103
1104
1105
1106
1107
1108
1109
1110
1111
1112
1113
1114
1115
1116
1117
1118
1119
1120
1121
1122
1123
1124
1125
1126
1127
1128
1129
1130
1131
1132
1133
1134
1135
1136
1137
1138
1139
1140
1141
1142
1143
1144
1145
1146
1147
1148
1149
1150
1151
1152
1153
1154
1155
1156
1157
1158
1159
1160
1161
1162
1163
1164
1165
1166
1167
1168
1169
1170
1171
1172
1173
1174
1175
1176
1177
1178
1179
1180
1181
1182
1183
1184
1185
1186
1187
1188
1189
1190
1191
1192
1193
1194
1195
1196
1197
1198
1199
1200
1201
1202
1203
1204
1205
1206
1207
1208
1209
1210
1211
1212
1213
1214
1215
1216
1217
1218
1219
1220
1221
1222
1223
1224
1225
1226
1227
1228
1229
1230
1231
1232
1233
1234
1235
1236
1237
1238
1239
1240
1241
1242
1243
1244
1245
1246
1247
1248
1249
1250
1251
1252
1253
1254
1255
1256
1257
1258
1259
1260
1261
1262
1263
1264
1265
1266
1267
1268
1269
1270
1271
1272
1273
1274
1275
1276
1277
1278
1279
1280
1281
1282
1283
1284
1285
1286
1287
1288
1289
1290
1291
1292
1293
1294
1295
1296
1297
1298
1299
1300
1301
1302
1303
1304
1305
1306
1307
1308
1309
1310
1311
1312
1313
1314
1315
1316
1317
1318
1319
1320
1321
1322
1323
1324
1325
1326
1327
1328
1329
1330
1331
1332
1333
1334
1335
1336
1337
1338
1339
1340
1341
1342
1343
1344
1345
1346
1347
1348
1349
1350
1351
1352
1353
1354
1355
1356
1357
1358
1359
1360
1361
1362
1363
1364
1365
1366
1367
1368
1369
1370
1371
1372
1373
1374
1375
1376
1377
1378
1379
1380
1381
1382
1383
1384
1385
1386
1387
1388
1389
1390
1391
1392
1393
1394
1395
1396
1397
1398
1399
1400
1401
1402
1403
1404
1405
1406
1407
1408
1409
1410
1411
1412
1413
1414
1415
1416
1417
1418
1419
1420
1421
1422
1423
1424
1425
1426
1427
1428
1429
1430
1431
1432
1433
1434
1435
1436
1437
1438
1439
1440
1441
1442
1443
1444
1445
1446
1447
1448
1449
1450
1451
1452
1453
1454
1455
1456
1457
1458
1459
1460
1461
1462
1463
1464
1465
1466
1467
1468
1469
1470
1471
1472
1473
1474
1475
1476
1477
1478
1479
1480
1481
1482
1483
1484
1485
1486
1487
1488
1489
1490
1491
1492
1493
1494
1495
1496
1497
1498
1499
1500
1501
1502
1503
1504
1505
1506
1507
1508
1509
1510
1511
1512
1513
1514
1515
1516
1517
1518
1519
1520
1521
1522
1523
1524
1525
1526
1527
1528
1529
1530
1531
1532
1533
1534
1535
1536
1537
1538
1539
1540
1541
1542
1543
1544
1545
1546
1547
1548
1549
1550
1551
1552
1553
1554
1555
1556
1557
1558
1559
1560
1561
1562
1563
1564
1565
1566
1567
1568
1569
1570
1571
1572
1573
1574
1575
1576
1577
1578
1579
1580
1581
1582
1583
1584
1585
1586
1587
1588
1589
1590
1591
1592
1593
1594
1595
1596
1597
1598
1599
1600
1601
1602
1603
1604
1605
1606
1607
1608
1609
1610
1611
1612
1613
1614
1615
1616
1617
1618
1619
1620
1621
1622
1623
1624
1625
1626
1627
1628
1629
1630
1631
1632
1633
1634
1635
1636
1637
1638
1639
1640
1641
1642
1643
1644
1645
1646
1647
1648
1649
1650
1651
1652
1653
1654
1655
1656
1657
1658
1659
1660
1661
1662
1663
1664
1665
1666
1667
1668
1669
1670
1671
1672
1673
1674
1675
1676
1677
1678
1679
1680
1681
1682
1683
1684
1685
1686
1687
1688
1689
1690
1691
1692
1693
1694
1695
1696
1697
1698
1699
1700
1701
1702
1703
1704
1705
1706
1707
1708
1709
1710
1711
1712
1713
1714
1715
1716
1717
1718
1719
1720
1721
1722
1723
1724
1725
1726
1727
1728
1729
1730
1731
1732
1733
1734
1735
1736
1737
1738
1739
1740
1741
1742
1743
1744
1745
1746
1747
1748
1749
1750
1751
1752
1753
1754
1755
1756
1757
1758
1759
1760
1761
1762
1763
1764
1765
1766
1767
1768
1769
1770
1771
1772
1773
1774
1775
1776
1777
1778
1779
1780
1781
1782
1783
1784
1785
1786
1787
1788
1789
1790
1791
1792
1793
1794
1795
1796
1797
1798
1799
1800
1801
1802
1803
1804
1805
1806
1807
1808
1809
1810
1811
1812
1813
1814
1815
1816
1817
1818
1819
1820
1821
1822
1823
1824
1825
1826
1827
1828
1829
1830
1831
1832
1833
1834
1835
1836
1837
1838
1839
1840
1841
1842
1843
1844
1845
1846
1847
1848
1849
1850
1851
1852
1853
1854
1855
1856
1857
1858
1859
1860
1861
1862
1863
1864
1865
1866
1867
1868
1869
1870
1871
1872
1873
1874
1875
1876
1877
1878
1879
1880
1881
1882
1883
1884
1885
1886
1887
1888
1889
1890
1891
1892
1893
1894
1895
1896
1897
1898
1899
1900
1901
1902
1903
1904
1905
1906
1907
1908
1909
1910
1911
1912
1913
1914
1915
1916
1917
1918
1919
1920
1921
1922
1923
1924
1925
1926
1927
1928
1929
1930
1931
1932
1933
1934
1935
1936
1937
1938
1939
1940
1941
1942
1943
1944
1945
1946
1947
1948
1949
1950
1951
1952
1953
1954
1955
1956
1957
1958
1959
1960
1961
1962
1963
1964
1965
1966
1967
1968
1969
1970
1971
1972
1973
1974
1975
1976
1977
1978
1979
1980
1981
1982
1983
1984
1985
1986
1987
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
2022
2023
2024
2025
2026
2027
2028
2029
2030
2031
2032
2033
2034
2035
2036
2037
2038
2039
2040
2041
2042
2043
2044
2045
2046
2047
2048
2049
2050
2051
2052
2053
2054
2055
2056
2057
2058
2059
2060
2061
2062
2063
2064
2065
2066
2067
2068
2069
2070
2071
2072
2073
2074
2075
2076
2077
2078
2079
2080
2081
2082
2083
2084
2085
2086
2087
2088
2089
2090
2091
2092
2093
2094
2095
2096
2097
2098
2099
2100
2101
2102
2103
2104
2105
2106
2107
2108
2109
2110
2111
2112
2113
2114
2115
2116
2117
2118
2119
2120
2121
2122
2123
2124
2125
2126
2127
2128
2129
2130
2131
2132
2133
2134
2135
2136
2137
2138
2139
2140
2141
2142
2143
2144
2145
2146
2147
2148
2149
2150

- 1
2
3 23. Jahn, U., Highly Efficient Generation of Radicals from Ester Enolates by the
4
5
6 Ferrocenium Ion. Application to Selective α -Oxygenation and Dimerization Reactions of
7
8
9 Esters. *J. Org. Chem.* **1998**, *63*, 7130-7131.
- 10
11 24. Ojima, I.; Brandstadter, S. M.; Donovan, R. J., Oxidative Dimerization of Lithium-
12
13
14 Enolates of Esters Promoted by Titanium Tetrachloride. *Chem. Lett.* **1992**, 1591-1594.
- 15
16 25. Ito, Y.; Konoike, T.; Harada, T.; Saegusa, T., Synthesis of 1,4-Diketones by
17
18
19 Oxidative Coupling of Ketone Enolates with CuCl_2 . *J. Am. Chem. Soc.* **1977**, *99*, 1487-
20
21
22 1493.
- 23
24 26. Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H.,
25
26
27 OLEX2: a Complete Structure Solution, Refinement and Analysis Program. *J. Appl.*
28
29
30 *Cryst.* **2009**, *42*, 339-341.
- 31
32 27. Sheldrick, G. M., SHELXT – Integrated Space-Group and Crystal- Structure
33
34
35 Determination. *Acta Cryst., Sect. A* **2015**, *71*, 3-8.
- 36
37 28. Sheldrick, G. M., Crystal Structure Refinement with ShelXL. *Acta Crystallogr.,*
38
39
40 *Sect. C: Cryst. Struct. Commun.* **2015**, *71*, 3-8.
- 41
42 29. Hübschle, C. B.; Sheldrick, G. M.; Dittrich, B., ShelXle: a Qt Graphical User
43
44
45 Interface for SHELXL. *J. Appl. Cryst.* **2011**, *44*, 1281-1284.
- 46
47
48 30. Kuwano, R.; Utsunomiya, M.; Hartwig, J. F., Aqueous Hydroxide as a Base for
49
50
51 Palladium-Catalyzed Amination of Aryl Chlorides and Bromides. *J. Org. Chem.* **2002**, *67*,
52
53
54 6479-6486.
- 55
56
57
58
59
60

- 1
2
3 31. Matsubara, K.; Ueno, K.; Koga, Y.; Hara, K., Nickel-NHC-Catalyzed α -Arylation
4 of Acyclic Ketones and Amination of Haloarenes and Unexpected Preferential N-
5
6 Arylation of 4-Aminopropiophenone. *J. Org. Chem.* **2007**, *72*, 5069-5076.
7
8
9
10
11 32. Hao, X.; Yuan, J.; Yu, G.-A.; Qiu, M.-Q.; She, N.-F.; Sun, Y.; Zhao, C.; Mao, S.-L.;
12
13 Yin, J.; Liu, S.-H., Air-Stable and Highly Efficient Indenyl-Derived Phosphine Ligand:
14
15 Application to Buchwald-Hartwig Amination Reactions. *J. Organomet. Chem.* **2012**, *706*-
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

TOC Graphic





TOC graphic

80x43mm (301 x 300 DPI)