Highly Active and Selective Catalysts for the Formation of α-Aryl Ketones

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Abstract: Bulky, electron-rich phosphine ligands with a biphenyl backbone, when combined with $Pd(OAc)_2$, give highly active catalysts for the α-arylation of ketones. The ligand 2-methyl-2′-dicyclohexylphosphinobiphenyl is particularly effective, and with 0.1−1.0 mol % Pd, a large variety of aryl halides and ketones react efficiently and with high selectivity. For two types of substrates, the ligands BINAP and Xantphos are more effective than the biphenyl-based ligands. It is also shown that K_3PO_4 can be used as the base in these reactions, and that base-sensitive functional groups are better tolerated if this is used instead of NaO^{t}Bu or NaHMDS. In some cases, α-aryl ketones can be produced without adding a ligand to the reaction. Although the substrate scope of the ligandless conditions is limited, some combinations react in high yield, and in one case, 100 000 turnovers were obtained. The results of experiments on the Pd-catalyzed arylation of diethyl malonate, cyclic 1,3-diketones, and nitroalkanes are also reported.

Introduction

Finding an efficient and reliable method that forms a bond between an arene and the carbon positioned α- to a carbonyl is a challenging problem in organic synthesis. While it has been known for many years that such bonds can be formed by the nucleophilic aromatic substitution (S_NAR) reaction of a stabilized enolate with an aryl halide,[1] these reactions have a serious limitation, as one or more electron-withdrawing groups are required as substituents on the arene.[2] The reaction of an enolate with a derivative of benzyne is an alternative to the S_NAR reaction.[3] However, intermolecular reactions of substituted benzynes with nucleophiles are often not regioselective,[3] and when the nucleophile is an enolate, intramolecular rearrangement of the resulting α-(2-lithiophenyl)ketone can occur faster than protonolysis.[4] More recently discovered[5] was the $S_{RN}1$ reaction,[6,7] in which an aryl halide reacts with an electron donor to produce an aryl radical that subsequently combines with a nucleophile. When an enolate is the nucleophile, the product is an α-aryl ketone. A merit of this reaction is that electronically neutral aryl halides, as well as those bearing electron-withdrawing or -donating substituents, can be used.[8] However, only a limited number of solvents are suitable, as they cannot possess hydrogen atoms that can be abstracted by an aryl radical.[9] Selectivity is also a concern. While the preference for arylation at a methyl instead of a methine carbon (for ketones such as 3-methyl-2-butanone) is good (≥5:1),[9b,10] the selectivity for ketones that have both enolizable methylene and methyl carbons (such as 2-butanone) is significantly worse (1.3−3.2:1, in favor of substitution at the secondary carbon).[10a,d,f] An additional problem is that hydrogens positioned *β*- to an enolate can be abstracted by aryl radicals, thus converting the aryl halide to the corresponding arene instead of the desired α-aryl ketone.[9b,11]

The lack of a general way to make α-aryl carbonyl compounds prompted the development of a number of reagents for that purpose.[12,13] While many of these are quite effective, their practicality is diminished by the time and cost needed to prepare them in stoichiometric amounts. Furthermore, many of these procedures do not use a carbonyl compound, but instead a less readily available derivative (such as an α-halo ketone).[12g−n,r−t,13b] Catalytic methods that form such bonds are less common,[14−21] and many of these require a Reformatsky reagent, α-halo carbonyl compound, silyl enol ether, or enol acetate.[14,15] There are relatively few catalytic transformations that, without special reagents, directly arylate the position α- to a carbonyl,[16,17] and until recently, there was only one report that described an intermolecular ketone arylation—the Pd-catalyzed reaction of

(1) Heckmann, J. *Ann.* **1883**, *220*, 128.

(2) (a) Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273. (b) Paradisi, C. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: New York, 1991; Vol. 4, Chapter 2.1.

(3) Kessar, S. V. In *Comprehensive Organic Synthesis*: Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: New York, 1991; Vol. 4, Chapter 2.3.

(4) Caubere, P.; Guillaumet, G. *Bull. Soc. Chim. Fr.* **1972**, *12*, 4643.

(5) Kim, J. K.; Bunnett, J. F. *J. Am. Chem. Soc.* **1970**, *92*, 7463.

(6) (a) Rossi, R. A.; Pierini, A. B.; Peñéñory, A. B. In *Supplement D2: The Chemistry of Halides, Pseudo-halides and Azides*; Patai, S., Rappoport, Z., Eds.; Wiley & Sons: Chichester, 1995, Chapter 24. (b) Norris, R. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: New York, 1991; Vol. 4, Chapter 2.2.

(7) For related reactions that are believed to involve aryl radicals as intermediates, see: (a) Sakakura, T.; Hara, M.; Tanaka, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1545. (b) Dell'Erba, C.; Novi, M.; Petrillo, G.; Tavani, C. *Tetrahedron* **1993**, *49*, 235. (c) Kende, A. S.; Koch, K.; Smith, C. A. *J. Am. Chem. Soc.* **1988**, *110*, 2210.

(8) For a tabular survey, see ref 6b, page 464.

(9) Anhydrous ammonia, DMSO, and acetonitrile are commonly used solvents in the $S_{RN}1$ reaction. For illustrative examples of solvent effects, see ref 6b and (a) Moon, M. P.; Wolfe, J. F. *J. Org. Chem.* **1979**, *44*, 4081. (b) Semmelhack, M. F.; Barger, T. *J. Am. Chem. Soc.* **1980**, *102*, 7765.

(10) (a) Rossi, R. A.; Bunnett, J. F. *J. Org. Chem.* **1973,** *38*, 3020. (b) Hay, J. V.; Wolfe, J. F. *J. Am. Chem. Soc.* **1975**, *97*, 3702. (c) Komin, A. P.; Wolfe, J. F. *J. Org. Chem.* **1977**, *42*, 2481. (d) Beugelmans, R.; Ginsburg, H. *J. Chem. Soc., Chem. Commun.* **1980**, 508. (e) Bard, R. R.; Bunnett, J. F. *J. Org. Chem.* **1980**, *45*, 1546. (f) Beugelmans, R.; Boudet, B.; Quintero, L. *Tetrahedron Lett.* **1980**, *21*, 1943. (g) Beugelmans, R.; Ginsburg, H. *Heterocycles* **1985**, *23*, 1197. (h) Beugelmans, R.; Bois-Choussy, M. *Synthesis* **1981**, 729.

(11) Wolfe, J. F.; Moon, M. P.; Sleevi, M. C.; Bunnett, J. F.; Bard, R. R. *J. Org. Chem.* **1978**, *43*, 1020.

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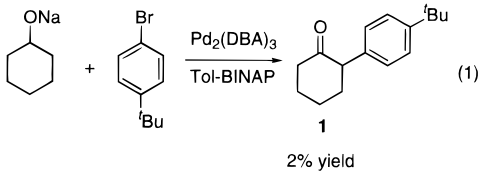
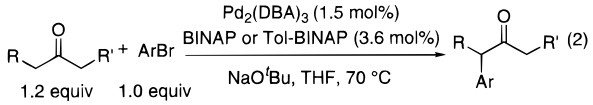
β-tetralone with 2-chloro-5-bromoanisole, for which no yield was reported.[18] Thus, it was of considerable interest when, in the course of our studies on carbon−oxygen bond formation,[22] an α-aryl ketone was formed in small amounts when the sodium salt of cyclohexanol was combined with an aryl bromide and a $Pd_2(DBA)_3$/Tol-BINAP[23] catalyst (eq 1).[19]



Presumably, in the reaction shown in eq 1, cyclohexanone is formed by a Pd-catalyzed oxidation, deprotonated by unreacted sodium alkoxide, and subsequently transformed to **1** by a Pd-catalyzed arylation. It was hoped that, if cyclohexanone was used instead of cyclohexanol and its enolate was formed in situ, conditions otherwise similar to those in eq 1 would produce **1** efficiently. Indeed, this goal was achieved, and a simple protocol was developed that produced a variety of α-aryl ketones by simply heating a THF solution of an aryl bromide and a ketone with sodium *tert*-butoxide, $Pd_2(DBA)_3$, and Tol-BINAP or BINAP[23] (eq 2)[19]



An important feature of this reaction is the selectivity that is observed for ketones with two enolizable positions. Thus, for 2-methyl-3-pentanone, arylation occurs exclusively at the methylene carbon. For 2-hexanone, arylation at the methyl carbon is preferred, with only very minor amounts of arylation at the methylene (selectivity ≥16:1). Also noteworthy is that, for the 12 substrate combinations reported, diarylation was only observed in five cases, and in no case was the ratio of mono: diarylation less than 7:1.

Nearly concurrent with this work, Hamann and Hartwig reported that $Pd(DBA)_2$ and 1,1′-bis(di-*o*-tolylphosphino)ferrocene catalyzed the reaction of aryl bromides or iodobenzene with aromatic ketones or pinacolone,[20] and Miura and co-workers reported that $PdCl_2$ and Cs_2CO_3 converted 1,3 diphenylacetone and iodobenzene to 1,1,3,3-tetraphenylacetone.[21a] A subsequent report by the latter group showed that their procedure was useful for the reactions of aryl iodides or bromobenzene with benzyl ketones, but that arylations of 3-pentanone failed.[21b,24] An extension of these methods was recently reported by Shaughnessy, Hamann, and Hartwig, who found that conditions

(12) Reagents that produce α-aryl ketones: Diaryliodonium salts: (a) Varvoglis, A. *Synthesis* **1984**, 709 and references therein. (b) Iwama, T.; Birman, V. B.; Kozmin, S. A.; Rawal, V. H. *Org. Lett.* **1999**, *1*, 673. (c) Chen, K.; Koser, G. F. *J. Org. Chem.* **1991**, *56*, 5764. (d) Ryan, J. H.; Stang, P. J. *Tetrahedron Lett.* **1997**, *38*, 5061. Organobismuth reagents: (e) Finet, J.-P. *Chem. Rev.* **1989**, *89*, 1487 and references therein. (f) Abramovitch, R. A.; Barton, D. H. R.; Finet, J.-P. *Tetrahedron* **1988**, *44*, 3039 and references therein. Organoboron reagents: (g) Brown, H. C.; Nambu, H.; Rogic, M. M. *J. Am. Chem. Soc.* **1969**, *91*, 6852 and references therein. Tricarbonylcyclohexadienylium iron salts: (h) Kelly, L. F.; Narula, A. S.; Birch, A. J. *Tetrahedron Lett.* **1980**, *21*, 2455. (π-Chlorobenzene)-chromium tricarbonyl: (i) Mino, T.; Matsuda, T.; Maruhashi, K.; Yamashita, M. *Organometallics* **1997**, *16*, 3241. Copper reagents: (j) Rathke, M. W.; Vogiazoglou, D. *J. Org. Chem.* **1987**, *52*, 3697. (k) Marino, J. P.; Jaén, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 3165 and references therein. (l) Sacks, C. E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1975**, *97*, 7372. (m) Sakurai, H.; Shirahata, A.; Araki, Y.; Hosomi, A. *Tetrahedron Lett.* **1980**, *21*, 2325. Aryldiazonium salts with catalytic CuCl: (n) Al Adel, I.; Adeoti Salami, B.; Levisalles, J.; Rudler, H. *Bull. Soc. Chim. Fr.* **1976**, 930. Aryl lead reagents: (o) Pinhey, J. T. In *Comprehensive Organometallic Chemistry II*; McKillop, A., Ed.; Pergamon: Oxford, 1995; Vol. 11, Chapter 11 and references therein. (p) Pinhey, J. T. *Pure Appl. Chem.* **1996**, *68*, 819 and references therein. (q) Morgan, J.; Pinhey, J. T.; Rowe, B. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1005. π-(2-Methoxyallyl)nickel bromide: (r) Hegedus, L. S.; Stiverson, R. K. *J. Am. Chem. Soc.* **1974**, *96*, 3250. Grignard reagents with α-bromoketones: (s) Newman, M. S.; Farbman, M. *J. Am. Chem. Soc.* **1944**, *66*, 1550. Organocadmium reagents: (t) Jones, P. R.; Young, J. R. *J. Org. Chem.* **1968**, *33*, 1675.

(13) For reagents that produce 2-aryl-1,3-diketones, α-aryl-β-ketoesters, α-arylmalonate esters, α-aryl cyanoacetates, and α-aryl malononitriles, see refs 12a, e, f, o, p, and (a) Lindley, J. *Tetrahedron* **1984**, *40*, 1433 and references therein. In addition, α-aryl acetates: (b) Brown, H. C.; Nambu, H.; Rogic, M. M. *J. Am. Chem. Soc.* **1969**, *91*, 6855. α-aryl malonate esters: (c) Semmelhack, M. F.; Chong, B. P.; Stauffer, R. D.; Rogerson, T. D.; Chong, A.; Jones, L. D. *J. Am. Chem. Soc.* **1975**, *97*, 2507. (d) Setsune, J.-I.; Matsukawa, K.; Wakemoto, H.; Kitao, T. *Chem. Lett.* **1981**, 367. α-aryl cyanoacetates: (e) Suzuki, H.; Kobayashi, T.; Yoshida, Y.; Osuka, A. *Chem. Lett.* **1983**, 193. α-aryl malononitriles: (f) Suzuki, H.; Kobayashi, T.; Osuka, A. *Chem. Lett.* **1983**, 589. α-aryl phenylsulfonylacetonitriles: (g) Suzuki, H.; Yi, Q.; Inoue, J.; Kusume, K.; Ogawa, T. *Chem. Lett.* **1987**, 887.

(14) Catalytic reactions that form α-arylesters: Pd- and Ni-catalyzed couplings of Reformasky reagents with aryl halides: (a) Fauvarque, J. F.; Jutand, A. *J. Organomet. Chem.* **1979**, *177*, 273. (b) Orzini, F.; Pelizzoni, F.; Vallarino, L. M. *J. Organomet. Chem.* **1989**, *367*, 375. Pd-catalyzed couplings of ethyl-α-tributylstannyl acetate with aryl halides: (c) Kosugi, M.; Negishi, Y.; Kameyama, M.; Migita, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3383. Pd-catalyzed arylations of silylketene acetals with added TlOAc: (d) Carfagna, C.; Musco, A.; Sallese, G.; Santi, R.; Fiorani, T. *J. Org. Chem.* **1991**, *56*, 261. (e) Galarini, R.; Musco, A.; Pontellini, R.; Santi, R. *J. Mol. Catal.* **1992**, *72*, L11. (f) Sakamoto, T.; Kondo, Y.; Masumoto, K.; Yamanaka, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 235. (g) Sakamoto, T.; Kondo, Y.; Masumoto, K.; Yamanaka, H. *Heterocycles* **1993**, *36*, 2509. Pd-catalyzed arylations of silylketene acetals with added Bu_3SnF or CuF: (h) Agnelli, F.; Sulikowski, G. A. *Tetrahedon Lett.* **1998**, *39*, 8807. Ni-catalyzed coupling of aryl-Grignard reagents with α-bromopropionate esters: (i) Amano, T.; Yoshikawa, K.; Sano, T.; Ohuchi, Y.; Manzo, S.; Ishiguro, M.; Fujita, Y. *Synth. Commun.* **1986**, *16*, 499.

(15) Catalytic reactions that form α-aryl ketones: Pd-catalyzed arylations of silyl enol ethers with added Bu_3SnF: (a) Kuwajima, I.; Urabe, H. *J. Am. Chem. Soc.* **1982**, *104*, 6831. Pd-catalyzed arylations of enol acetates with added Bu_3SnOMe: (b) Kosugi, M.; Hagiwara, I.; Sumiya, T.; Migita, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 242. Ni-catalyzed arylations of α-bromosilyl enol ethers: (c) Tamao, K.; Zembayashi, M.; Kumada, M. *Chem. Lett.* **1976**, 1239. Ni-catalyzed electrochemical couplings of aryl halides with α-halo ketones and α-halo esters: (d) Durandetti, M.; Nédélec, J.-Y.; Périchon, J. *J. Org. Chem.* **1996**, *61*, 1748 and references therein.

(16) Ni-catalyzed coupling of a lithium ester enolate: (a) Millard, A. A.; Rathke, M. W. *J. Am. Chem. Soc.* **1977**, *99*, 4833. Cu-catalyzed arylation of β-dicarbonyl compounds with 2-bromobenzoic acids: (b) Bruggink, A.; McKillop, A. *Tetrahedron* **1975**, *31*, 2607 and references therein. Cu-catalyzed reaction of aryliodides with ethyl cyanoacetate, malononitrile, or acetylacetone: (c) Okuro, K.; Furuune, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 7606. Pd-catalyzed reactions of aryl bromides or aryl iodides with alkyl cyanoacetates or malononitrile: (d) Uno, M.; Seto, K.; Takahashi, S. *J. Chem. Soc., Chem. Commun.* **1984**, 932. (e) Sakamoto, T.; Katoh, E.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1988**, *36*, 1664 and references therein.

(17) For catalytic, intramolecular arylations of ketones and 1,3-diketones, see ref 13c and (a) Ciufolini, M. A.; Qi, H.-B.; Browne, M. E. *J. Org. Chem.* **1988**, *53*, 4151. (b) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7577. (c) Muratake, H.; Hayakawa, A.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7581. For a catalytic intramolecular vinylation of a ketone, see: (d) Piers, E.; Renaud, J. *J. Org. Chem.* **1993**, *58*, 11.

(18) Hou, D.; Mas, J. L. U.S. Patent 4,992,591, 1991; *Chem. Abstr.* **1991**, *115*, 28927z.

(19) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108.

(20) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382.

(21) (a) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740. (b) Satoh, T.; Inoh, J.-I.; Kawamura, Y.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239.

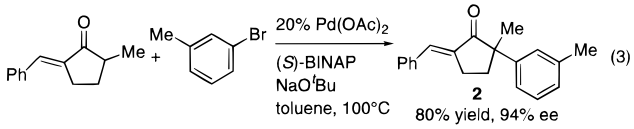
(22) (a) Palucki, M. P.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10333. (b) Palucki, M. P.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *19*, 3395.

(23) DBA = dibenzylidene acetone. Tol-BINAP = 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl. BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

(24) Related work by Miura and co-workers: (a) Terao, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1998**, *39*, 6203. (b) Satoh, T.; Kametani, Y.; Terao, Y.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1999**, *40*, 5345.

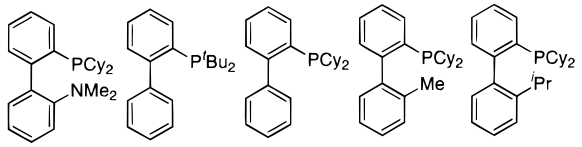
similar to those in eq 2 could be used for the inter- and intramolecular arylations of amides.[25] It has also been shown by Wang and Wu that 4-halophenyl alkyl ketones can be polymerized, and subsequently converted to poly(*p*-phenylenevinylidenes) by reduction with LAH and dehydration with H_3PO_4.[26]

The success of our conditions for the intermolecular α-arylation of ketones inspired the development of asymmetric versions. Indeed, it was found that by using (*S*)-BINAP, and catalytic conditions derived from those in eq 2, compounds that possess an all-carbon quartenary center α- to a carbonyl can be produced enantioselectively (eq 3).[27]



(3)

Recently, our efforts to devise more active catalysts for Pd-catalyzed amination reactions[28] lead to the synthesis of the sterically encumbered, electron rich phosphine ligand **3**.[29] Catalysts derived from **3** were exceptionally effective not only in the amination reactions of aryl chlorides and aryl bromides, but in Suzuki couplings as well.[29] Furthermore, preliminary experiments indicated that Pd catalysts derived from **3** were highly effective for the α-arylation of ketones.[29] Thus, an aryl bromide could be coupled at room temperature, and, for the first time, an aryl chloride was used in a ketone arylation. Subsequently, Kawatsura and Hartwig reported that catalysts derived from the ligands 1,1-bis-(di-*tert*-butylphosphino)ferrocene, P^tBu_3, and PCy_3 were also effective for the α-arylation of ketones.[30] Using these ligands, both aryl chlorides and aryl bromides could be coupled using 1−2 mol % Pd. For one example—the reaction of bromobenzene and propiophenone—a turnover number as high as 20 000 was obtained. They also found that, using a Pd catalyst from the above ligands and NaO^tBu as base, diethylmalonate and di-*tert*-butylmalonate could be arylated by bromo- and chlorobenzene, respectively.

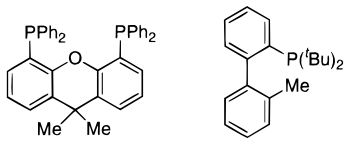


3 **4** **5** **6** **7**

It should be noted that, despite more recent reports on the α-arylation of ketones,[21b,30] our original protocol is the most general with respect to substrate scope.[19] In particular, ours are the only procedures that do not require an aromatic or a benzylic ketone to work well.[19,29] Besides those used in our work, the only aliphatic ketones that have been used are pinacolone (with bromobenzene),[20] 2-methyl-3-pentanone (with 3-chloroanisole),[30] and cyclohexanone (with bromobenzene).[30] In the first case, the yield was only 51%, and in the second case, the selectivity for arylation of the methylene instead of the methine carbon was only 6.7:1.

Subsequent experiments in our laboratories have shown that Pd catalysts derived from commercially available, air-stable ligands **4** and **5**,[31] in many cases, are even more active in Suzuki[32,33] and amination[32,34] chemistry than are catalysts from **3**, thus making them the most active catalysts for these reactions to date. In those situations where ligand **3** is more useful, ligands **6** and **7**, which are more easily synthesized than **3**, function equally well. Several other ligands related structurally to **3**−**7** were also synthesized.[35] These, and **4**, gave highly active catalysts for formation of diaryl ethers.[35]

Because ligands **4**−**7** are so effective at promoting the Pd-catalyzed reactions described above, we decided to test their utility in the α-arylation of ketones. We report here that the combination of $Pd(OAc)_2$ and ligand **6** is particularly effective for catalyzing the reaction of many ketones with a variety of aryl chlorides and aryl bromides. Also described are conditions that permit the use of aryl halides that are functionalized with base-sensitive groups, such as esters and nitriles. We describe two situations in which ligands **4**−**7** are not effective, and show that the bidentate ligands BINAP or Xantphos[36] can be used in their place. We further demonstrate that, for a limited number of substrate combinations, it is not necessary to use any ligand in order to catalyze the α-arylation of a ketone. We show that ligand **8**, in combination with $Pd(OAc)_2$ and K_3PO_4, gives a catalyst that is effective for the arylation of diethyl malonate. In addition, we report the first intermolecular Pd-catalyzed arylations of 1,3-diketones,[37] and the first catalytic procedure for the intermolecular arylation of nitroalkanes.[38]



Xantphos **8**

Results

Before determining which ligand was best for reactions that form α-aryl ketones, control reactions were performed, in which $Pd(OAc)_2$ or $Pd_2(DBA)_3$ and no ligand were added. Surprisingly, some substrate combinations could be coupled in good yields and with high efficiency. These results are summarized in Table 1.

(25) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *63*, 6546.

(26) Wang, D.; Wu, Z. *J. Chem. Soc., Chem. Commun.* **1999**, 529.

(27) Åhman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918.

(28) (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (b) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (c) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125.

(29) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722.

(30) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473.

(31) Ligands **4** and **5** are commercially available from Strem Chemical Co.

(32) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413.

(33) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.

(34) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.*, in press.

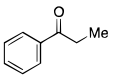
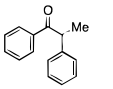
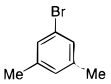
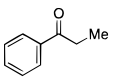
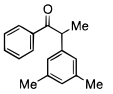
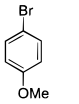
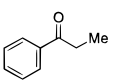
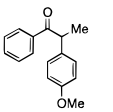
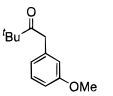
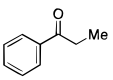
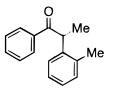
(35) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369.

(36) Xantphos = 9,9-dimethyl-4,6-bis(diphenylphosphino)xanthene. For its preparation, see: (a) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J. *Organometallics*, **1995**, *14*, 3081. For the use of Xantphos in Pd-catalyzed amination reactions, see: (b) Guari, Y.; van Es, D. S.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Tetrahedron Lett.* **1999**, *40*, 3789. For the use of Xantphos in the Pd-catalyzed preparation of *N*-aryl benzophenone hydrazones, and subsequent conversion to indoles, see: (c) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251.

(37) For the Cu-catalyzed, intermolecular reaction of acetylacetone with iodobenzene, see ref 16c. For Cu-catalyzed reactions of 1,3-diketones with *o*-bromobenzoic acid or related derivatives, see refs 13a and 16b.

(38) Intramolecular arylations of nitroalkanes have been described: (a) Muratake, H.; Nakai, H. *Tetrahedron Lett.* **1999**, *40*, 2355. For Pd-catalyzed arylations of 4-alkyl nitrobenzenes, see: (b) Inoh, J. I.; Satoh, T.; Pivsa-Art, S.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1998**, *39*, 4673.

Table 1. Ketone Arylations without an Added Ligand[a]

Entry	Halide	Ketone	Product	Temp	Mol% Pd	Time	Yield
1				120 °C	0.001	24 h	74%
2				80 °C 80 °C	1.0 1.0	2.3 h 14 h	84% 76%[b]
3				80 °C	1.0	3 h	93%
4				80 °C	1.0	6h	68%[c]
5				80 °C	1.0	14h	46%

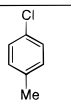
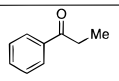
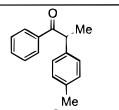
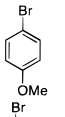
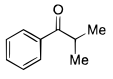
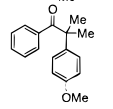
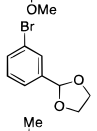
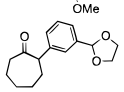
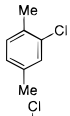
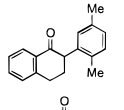
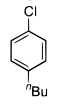
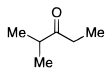
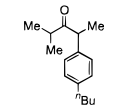
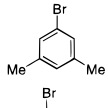
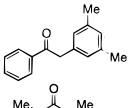
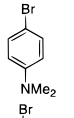
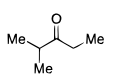
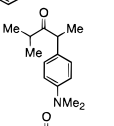
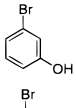
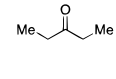
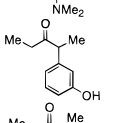
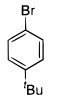
[a] Reaction conditions: 1.0 equiv aryl bromide, 1.2 equiv ketone, 1.3 equiv NaO^{t}Bu, $Pd(OAc)_2$, toluene (1 mL/mmol halide). [b] $Pd_2(DBA)_3$ (0.5 mol %) was used. [c] 2 mL of solvent were added per mmol of aryl halide.

As is shown in Entry 1 of Table 1, the reaction of bromobenzene and propiophenone was especially efficient under these conditions. After 24 h, at 120 °C in toluene, the number of turnovers was 100 000, and the product was isolated in 74% yield. The reaction of 5-bromo-*m*-xylene and propiophenone was conducted at 80 °C, and with either 1 mol % $Pd(OAc)_2$ or 0.5 mol % $Pd_2(DBA)_3$, the α-aryl ketone was obtained in 76−84% yield. A control reaction in which Pd was not added, but was otherwise similar to the ones described in entry 2 of Table 1, gave no product after 17 h. Aryl bromides substituted by methoxyls could also be used under these conditions (Table 1, entries 3 and 4), as could pinacolone (Table 1, entry 4).

Unfortunately, the ligandless reaction conditions were only suitable for a limited number of substrate combinations. For example, cyclohexanone and 4-*tert*-butylbromobenzene, when heated at 70 °C for 14 h in either THF or toluene with NaO^{t}Bu and 1 mol % $Pd_2(DBA)_3$, gave only traces of product. The reaction of 5-bromo-*m*-xylene and 2-methyl-3-pentanone with NaO^{t}Bu and 1 mol % $Pd(OAc)_2$ gave, after heating in toluene at 80 °C for 20 h, xylene and the coupling product in a ∼1:1 ratio, as determined by GC analysis. The yield for the reaction of propiophenone with 2-bromotoluene (46%, Table 1, entry 5) was significantly lower than that obtained when 5-bromo-*m*-xylene was the aryl halide (Table 1, entry 2), and the reaction of propiophenone, 2-bromo-*p*-xylene, and 0.1 mol % $Pd(OAc)_2$ gave, after 21 h, the α-aryl ketone and *p*-xylene in a 1.6:1.0 ratio. Furthermore, it does not appear that these conditions can be extended to aryl chlorides, as 4-chlorotoluene and propiophenone gave, after 24 h in toluene at 80 °C with either 1 mol % $Pd(OAc)_2$ or 0.5 mol % $Pd_2(DBA)_3$, less than 1% of the desired product.

Efforts were thus directed toward finding a catalytic system that would generally and efficiently couple aryl halides with a wide variety of ketones. While the commercially available ligands **4** and **5** promoted the α-arylations of some ketones (Table 2, entries 1−3), in other cases, catalysts from these ligands were not as efficient as those from **3**. For example, while the reaction of α-tetralone with 2-chloro-*p*-xylene using 1.0 mol % **3** gave the desired α-aryl ketone in a yield of 76%, a similar

Table 2. Ketone Arylations Using Ligands **3**−**7**[a]

Entry	Halide	Ketone	Product	Ligand	Temp Solvent	Mol% Pd	Time	Yield
1				**4**	80 °C toluene	1.0	12 h	91%
2				**4**	80 °C toluene	1.0	17 h	72%
3				**5** **6**	60 °C toluene 45 °C toluene	1.0 0.1	18.5 20 h	66%[b,c,d] 80%[b,c]
4				**3** **6**	80 °C toluene 80 °C toluene	1.0 0.1	22 h 5 h	76% 93%
5				**6**	90 °C toluene	0.1	16 h	79%[e,k]
6				**7** **7**	50 °C toluene rt toluene	0.25 1.0	22 h 20 h	74%[f] 88%[f]
7				**6**	85 °C toluene	0.1	24 h	70%[e]
8				**6**	70 °C THF	0.1	24 h	88%[b,g]
9				**6**	85 °C toluene	0.5	24 h	61%
10				**6**	70 °C toluene	0.1	24 h	74%[b,h]
11				**6**	70 °C THF	0.5	17 h	83%
12				**6**	70 °C toluene	0.5	23 h	64%
13				**6**	80 °C toluene	1.0	16 h	91%
14				**7**	80 °C toluene	1.0	18 h	78%[i]
15				**6**	80 °C THF	0.2	24 h	85%[i,j]
16				**7**	80 °C toluene	1.0	6 h	76%[i]

[a] Reaction Conditions: 1.0 equiv aryl halide, 1.2 equiv ketone, 1.3 equiv NaO^{t}Bu. $Pd(OAc)_2$ was the Pd source, and the ratio of ligand/$Pd(OAc)_2$ was 2/1. 1 mL of solvent was added per mmol of aryl halide. [b] 2.0 equiv of ketone were used. [c] 2.2 equiv of NaO^{t}Bu were used. [d] The ratio of mono/diarylation was 13/1. [e] Isolated as a 20:1 mixture of regioisomers. [f] 2.5 equiv of NaO^{t}Bu were used. [g] 2.0 equiv of NaO^{t}Bu were used. [h] The ratio of mono/diarylation was 7/1. [i] NaHMDS (1.1 equiv) was the base. [j] The ratio of ligand/$Pd(OAc)_2$ was 2.2/1. [k] The ratio of mono/diarylation was 21/1.

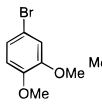
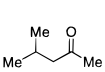
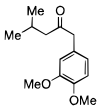
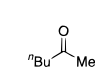
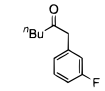
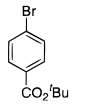
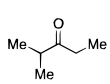
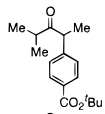
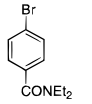
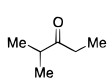
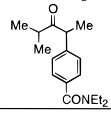
reaction that used the ligand **4** produced substantial amounts of *p*-xylene (the ratio of product: *p*-xylene was 3:1). To see if these differences resulted from the ability of the dimethylamino group of **3** to coordinate to Pd, the ligand **6** was tested, because it is sterically more similar to **3** than is **4** or **5**. The reaction in entry 4 did indeed occur smoothly when **6** was the ligand, and only 0.1 mol % Pd was needed in order to obtain the product in 93% yield. The result implied that Pd-catalysts derived from **6** might be highly active for the α-arylation of ketones. The combination of $Pd(OAc)_2$/**6** was therefore tested for a number of arylation reactions, and Table 2 shows that this was extremely effective. Many substrates could be coupled using only 0.1 mol % $Pd(OAc)_2$ and 0.2 mol % **6**, and no more than 1 mol % Pd was required for any of the transformations in Table 2. The reactions described in entries 3, 4, 7−9, 11, and 12 were also run using commercially available ligands **4** and **5**, under conditions that were otherwise identical, except that higher catalyst loadings were sometimes used. Compared to the reactions catalyzed by $Pd(OAc)_2$/**6**, the yields and/or the turnover numbers were lower.

Table 2 shows that a diverse group of aryl halides and ketones can be coupled successfully. Examples include those in which aryl halide is substituted by an alkyl, methoxyl, hydroxyl, dimethylamino, 1,3-dioxolano, nitrile, and ester functions. Also included are examples in which the arene has either one (Table 2, entry 4) or two (Table 2, entry 12) methyl groups, or a methoxyl group (Table 2, entry 13), positioned *ortho* to the halogen. Both aliphatic and aromatic ketones can be used, and these can either be acyclic or cyclic. Table 2 also shows that secondary, tertiary, and quartenary centers can be prepared, that a methoxyl group can be positioned α- to the carbonyl (Table 2, entry 11), and that five-, six-, and seven-membered ring ketones can be used successfully. We note, however, that cyclopentanone was not coupled successfully under these conditions, as this ketone was consumed too quickly in a competing aldol condensation.

In reactions of 2-methyl-3-pentanone, two regioisomers can be formed. In the reaction of this ketone with either 4-*n*-butylchlorobenzene or *N*,*N*-dimethyl-4-bromoaniline, the preference for arylation at the methylene instead of the methine carbon is 20:1 (Table 2, entries 5 and 7). Selectivity for monoarylation instead of diarylation is also high. The least selective case is that of 4-chloroanisole and 3-pentanone (Table 2, entry 10), for which the ratio of mono/diarylation was 7:1 when 2 equiv of ketone are used. For the other substrate combinations in Table 2, the selectivity for monoarylation was greater than 20:1. In the reaction of acetophenone and 5-bromo-*m*-xylene (Table 2, entry 6), no diarylated product was observed when the recommendation of Kawatsura and Hartwig—the use of 2 equiv of NaO^tBu per equiv of ketone[30]—was followed. This reaction was cleanest at room temperature, using 1 mol % Pd and 2 mol % **7**. A similar reaction using ligand **6** gave, in addition to the desired product, products derived from aldol condensation of the ketone (∼5% as estimated by GC). At 50 °C, acetophenone and 5-bromo-*m*-xylene could be coupled in 74% yield using 0.25 mol % $Pd(OAc)_2$/ 0.5 mol % **7**.

For the reactions in entries 14−16 of Table 2, the choice of base was important. When NaO^tBu was used, the major products, as determined by GC/MS, were those from Claisen-type condensations of the ketone enolate with the ester or nitrile functions of the aryl halides. Also, when NaO^tBu was the base for the reactions in entries 15 and 16, significant amounts of ethyl and methyl benzoate were formed, respectively, presumably because the condensation reactions produce sodium ethoxide and sodium methoxide, which are known to reduce arylhalides under Pd catalysis.[39] These undesired products were not observed, however, when NaHMDS was the base, provided that it was not used in an excess and that, for the reaction of 4-chlorobenzonitrile with propiophenone (Table 2, entry 14), the base and the ketone were mixed prior to adding the aryl halide.

Table 3. Ketone Arylations in Which Bidentate Ligands Are Used[a]

Entry	Halide	Ketone	Product	Ligand	Temp Solvent	Mol% Pd	Time	Yield
1				BINAP	70 °C THF	3.0	16 h	72%[b,c]
				Xantphos	70 °C THF	0.5	17.5 h	72%[b]
2				Xantphos	70 °C THF	1.0	12 h	74%[d]
3				Xantphos	80 °C toluene	0.2	16 h	67%[e,f,g]
4				Xantphos	80 °C toluene	0.2	15 h	74%[f,h]

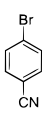
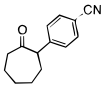
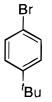
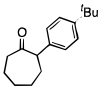
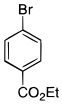
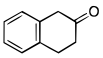
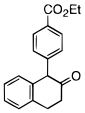
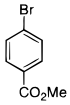
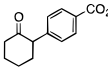
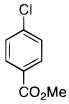
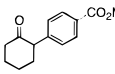
[a] Reaction conditions: 1.0 equiv aryl halide, 1.2 equiv ketone, 1.3 equiv NaO^tBu. $Pd_2(DBA)_3$ was the Pd source, and the ratio of ligand/$Pd_2(DBA)_3$ was 2.4/1 (i.e., ligand/Pd ratio = 1.2/1). 1 mL of solvent was added per mmol of aryl halide. [b] The ratio of mono/diarylation was 12/1. [c] 6 mL of solvent were added per mmol of aryl halide. [d] The ratio of mono/diarylation was 25/1. [e] NaHMDS (2.0 equiv) was the base. 4 mL of solvent were added per mmol of arylhalide. [f] The ratio of ligand/$Pd_2(DBA)_3$ was 2.2/1 (i.e., ligand/Pd ratio = 1.1/1). [g] Regioisomers were formed in a 50/1 ratio. [h] NaO^tBu (2.0 equiv) was the base.

Despite the usefulness of the ligands **3**−**7** for the preparation of many α-aryl ketones, not all types of substrates react effectively. The arylation reactions of ketones that have both enolizable methyl and methylene groups (e.g., 2-hexanone) are not selective. Furthermore, the conditions of entries 14−16 of Table 2, which allow aryl halides with ester or nitrile functions to be coupled with aromatic ketones, fail to give product when applied to aliphatic ketones and give complex mixtures instead.

As was noted in the Introduction, 2-hexanone can be coupled with *N*-(4-bromophenyl)-benzophenone imine if a BINAP/$Pd_2(DBA)_3$ catalyst is used.[19] Because this is the only reported example in which a ketone with both an enolizable methyl and methylene group is selectively arylated by Pd catalysis, we tested to see if these conditions were general for other such combinations of substrates. As is shown in entry 1 of Table 3, 4-bromoveratrole and 4-methyl-2-pentanone react under these conditions to give in 72% yield the product of arylation at the methyl group, and the selectivity for substitution at that position instead of the methylene was 12/1. A survey of other bidentate ligands indicated that high selectivities could also be obtained when $Pd_2(DBA)_3$/Xantphos was the catalyst, and that, compared to reactions that use BINAP as the supporting ligand, a relatively low catalyst loading can be used. Thus, the coupling product of 4-methyl-2-pentanone and 4-bromoveratrole was obtained in 72% yield when 0.5 mol % Pd/0.6 mol % Xantphos was used (Table 3, entry 1). In contrast, a similar reaction that used 0.5 mol % Pd and 0.6 mol % BINAP gave significant amounts of

(39) For the reduction of aryl halides by methanol and catalytic amounts of $Pd(PPh_3)_4$, see: Zask, A.; Helquist, P. *J. Org. Chem.* **1978**, *43*, 1619.

Table 4. α-Arylations of Ketones that Use K_3PO_4 as the Base[a]

Entry	Halide	Ketone	Product	Ligand	Temp Solvent	Mol% Pd	Time	Yield
1				Xantphos	THF 80 °C	1.0	16 h	72%[b]
2				**6**	THF 80 °C	1.0	17 h	81%[c,d]
3				**6**	toluene 100 °C	0.2	23 h	91%[c,e]
4				Xantphos	toluene 80 °C	1.0	15 h	74%[f]
5				**6**	toluene 80 °C	1.0	15 h	70%[g]

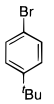
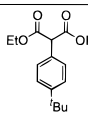
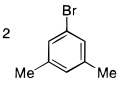
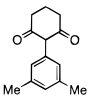
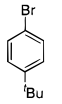
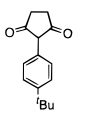
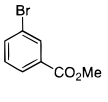
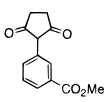
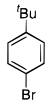
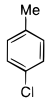
[a] Reaction conditions: 1.0 equiv aryl halide, 2.0 equiv ketone, 2.3 equiv K_3PO_4. 1 mL of solvent was added per mmol of aryl halide. $Pd_2(DBA)_3$ was the Pd source, and the ratio of ligand/$Pd_2(DBA)_3$ was 2.2/1 (i.e., ligand/Pd ratio = 1.1/1). [b] The ratio of mono/diarylation was 8/1. [c] $Pd(OAc)_2$ was the Pd source, and the ratio of ligand/$Pd(OAc)_2$ was 2.2/1. [d] The ratio of mono/diarylation was 15/1. [e] 1.2 equiv of ketone were used. [f] The ratio of mono/diarylation was 6.5/1. [g] The ratio of mono/diarylation was 4.9/1.

products from the aldol condensation of 4-methyl-2-pentanone. The reaction of 2-hexanone with 3-fluoro-bromobenzene, when catalyzed by 1.0 mol % Pd/ 1.2 mol % Xantphos, proceeded in 74% yield, and the preference for monoarylation instead of diarylation was 25/1 (Table 3, entry 2). The regioisomer of the product, that would have been produced if substitution at the methylene carbon had occurred, was not detected. A similar reaction in which BINAP was used instead of Xantphos gave the product in only ~25% yield, as estimated by GC. Again, the major contaminants were derived from the competing aldol condensation of the ketone.

The use of a catalyst based on Xantphos and either NaHMDS or NaO^{t}Bu allows aryl halides that are functionalized by some electron-withdrawing groups to couple with aliphatic ketones. Thus, either *N*,*N*-diethyl-4-bromobenzamide or *tert*-butyl-4-bromobenzoate reacted with 2-methyl-3-pentanone, using only 0.2 mol % Pd/0.22 mol % Xantphos, in 74 and 67% yields, respectively. For the reaction of *tert*-butyl-4-bromobenzoate, the selectivity for arylation at the methylene instead of the methine carbon was 50:1, and for *N*,*N*-diethyl-4-bromobenzamide, only one regioisomer was detected. However, these conditions are not general for aryl halides substituted by all electron-withdrawing groups. Thus, the major product of the reaction of methyl-3-bromobenzoate and 3-methyl-2-pentanone was methyl benzoate. Also, substantial amounts of benzonitrile were formed in the reaction of cyclohexanone and 3-bromobenzonitrile.

We hoped that a wider range of base-sensitive groups could be employed in the ketone arylation reaction if, instead of NaO^{t}Bu or NaHMDS, a mild base was used. After some experimentation, we determined that potassium phosphate, in either THF or toluene solvent, is effective for this purpose. As is shown in entries 1 and 4 of Table 4, aryl bromides react with ketones in good yield when K_3PO_4 is the base and Xantphos/$Pd_2(DBA)_3$ is the catalyst precursor. Table 4 also shows that ligand **6** can be used in conjunction with K_3PO_4. Cycloheptanone

Table 5. Arylations of Malonate Esters, 1,3-Diketones, and Nitroalkanes[a]

Entry	Halide	1,3-Dicarbonyl or Nitroalkane	Product	Ligand Base	Temp Solvent	Mol% Pd	Time	Yield
1				K_3PO_4 **8**	THF 70 °C	1.0	10 h	92%[b]
2				K_3PO_4 **8**	THF 80 °C	1.0	15 h	84%[c]
3				K_3PO_4 **8**	THF 80 °C	1.0	23 h	96%[c]
4				K_3PO_4 **8**	dioxane 100 °C	1.0	19 h	96%[c]
5				K_3PO_4 **8**	dioxane 110 °C	5.0	20 h	73%[d]
				NaO^{t}Bu **4**	dioxane 95 °C	3.0	22 h	80%[e]
6				NaO^{t}Bu **8**	dioxane 120 °C	3.0	20 h	76%[e]

[a] Reaction conditions: 1.0 equiv of aryl halide, 1.2 equiv of the dicarbonyl compound, 2.3 equiv of K_3PO_4. The ratio of ligand/$Pd(OAc)_2$ was 2.2/1. [b] 2 mL of solvent were added per mmol of aryl halide. [c] 3 mL of solvent were added per mmol of aryl halide. [d] 1.0 equiv of aryl halide, 2.0 equiv of nitroalkane, and 1.3 equiv of K_3PO_4 were used. The ratio of ligand/$Pd(OAc)_2$ was 2/1. 1 mL of solvent was added per mmol of aryl halide. [e] 1.0 equiv of aryl halide, 2.0 equiv of nitroalkane, and 1.2 equiv of NaO^{t}Bu were used. The ratio of ligand/$Pd(OAc)_2$ was 2/1. 1 mL of solvent was added per mmol of aryl halide.

and 4-bromo-*tert*-butylbenzene can be coupled in 81% yield when $Pd(OAc)_2$/**6** is the catalyst precursor (Table 4, entry 2). Cyclohexanone reacts with methyl-4-chlorobenzoate to give the product of a single arylation in 70% yield when $Pd(OAc)_2$/**6** is used (Table 4, entry 5). However, under these conditions, the reaction of cyclohexanone with methyl-4-bromobenzoate gives substantial amounts of methyl benzoate and biphenyl-4,4′-dicarboxylic acid dimethyl ester. This reaction is successful if $Pd_2(DBA)_3$/Xantphos is used instead of $Pd(OAc)_2$/**6**—the α-aryl ketone was isolated in 74% yield.

Preliminary investigations, to see if the methods used here to arylate ketones could be extended to other stabilized carbanions, were begun. A Pd catalyst based on **8** and K_3PO_4 was effective for the reaction of diethyl malonate with 4-bromo-*tert*-butylbenzene (Table 5, entry 1). The arylation product was isolated in 92% yield, provided that 2 equiv of K_3PO_4 were used per equiv of malonate. When less base was added, the reaction did not go to completion. The combination of $Pd(OAc)_2$/**8**/2.3 equiv K_3PO_4 was also suitable for the arylations of cyclohexane-1,3-dione and cyclopentane-1,3-dione (Table 5, entries 2−4). However, our initial attempts to use acetylacetone under similar reactions were unsuccessful, and only the starting materials were recovered. The failure may be related to the ability of acetylacetone to form stable complexes with palladium.[40] The reaction of nitroethane and 4-bromo-*tert*-butylbenzene went to completion when K_3PO_4 was the base and a

(40) Complexes of the type (pyridyl)Pd(PPh_3)(acac), and (pyridyl)Pd(PEt_3)(η^1-acac) are stable as solids or in solution at room temperature. See (a) Tanaka, H.; Isobe, K.; Kawaguchi, S.; Okeya, S. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1850 and references therein.

relatively high catalyst loading (5 mol % Pd/10 mol % **8**) was used (Table 5, entry 5). A similar reaction that used ligand **4** did not go to completion, and when ligand **6** was used, no product was formed. A more active system resulted when NaO^{t}Bu was used instead of K_3PO_4—the reaction could be run at 95 °C, only 3 mol % $Pd(OAc)_2$ was needed, and ligand **4** could be used in place of **8**. (Table 5, entry 5). Also, when NaO^{t}Bu is the base, 4-chlorotoluene can be coupled with 1-nitropropane using 3 mol % $Pd(OAc)_2$ and 6 mol % **8** (Table 5, entry 6).

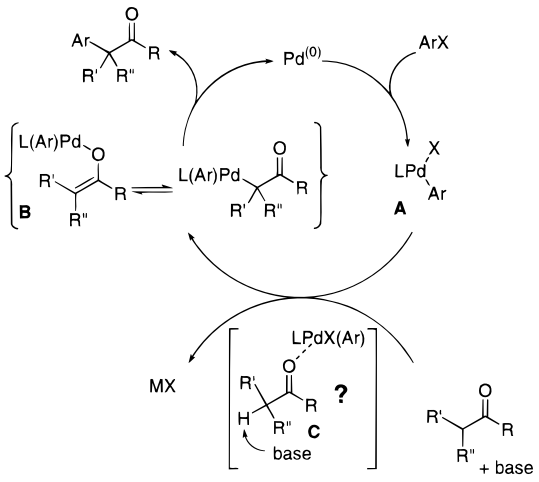
Discussion

The procedures introduced here for the α-arylation of ketones significantly increase the scope of substrates that can be used. The selection of ligand and base is extremely important, and the optimal catalytic system depends both on the nature of the aryl halide and ketone. It is shown that some substrate combinations react even when no ligand is added to the reactions. This procedure has the advantage of simplicity and low cost and should therefore prove useful for a limited class of substrates.

As was noted in the Introduction, Kawatsura and Hartwig found that, for the Pd-catalyzed reaction of propiophenone and bromobenzene, a high number of turnovers (20 000) were obtained when either P(^{t}Bu)$_3$ or 1,1′-bis-(di-*tert*-butylphosphino)ferrocene was used as the supporting ligand.[30] The impressive efficiency and stability of the catalyst was attributed to the use of these ligands, despite the lack of high turnover numbers for other substrate combinations (no less than 1 mol % Pd was used in the other reactions reported). We show here that 100 000 turnovers can be obtained for the reaction of bromobenzene and propiophenone without adding any ligand to the reaction, although a higher temperature (120 °C instead of 60 °C) was used than for reactions in which a ligand is added.[30] These turnover numbers are considerably higher than those obtained for other combinations of substrates. Thus, the reaction of propiophenone and bromobenzene appears to be exceptionally facile, and the high turnover numbers obtained in the absence of a ligand imply that, in this instance, the remarkable efficacy of the catalyst is not derived from the phosphine but is instead related to the properties of the ketone. These results exemplify the danger of drawing conclusions about the activity and stability of a catalytic system when only one reaction is studied at low catalyst loadings. An analogous reaction is the Suzuki coupling of 4-bromoacetophenone with phenylboronic acid: a combination for which turnover numbers as high as 1×10^6 were obtained in the past.[41] We recently reported that 1×10^5 turnovers can be obtained in this reaction when no ligand is added.[33] Although even higher numbers of turnovers (1×10^8) can be obtained when $Pd(OAc)_2$/**4** is used,[33] it is clear that the exceptional effectiveness of the catalyst in this particular reaction is related to the substrates that are used, and that, to truly develop Pd catalysts that are highly active, a wide range of substrates must be studied.

The reaction of propiophenone and bromobenzene excluded, the Pd catalysts based on ligands **3**−**7**, and ligand **6** in particular, are considerably more active for the α-arylation of ketones than the catalytic systems that have been reported previously.[20−22,29,30] Although it is unclear why subtle variances in the structures of these ligands cause significant differences in the effectiveness

Scheme 1



of their catalysts (e.g., the differences between catalysts based on **6** and **5**), we believe that the activity of this class of ligands can be explained as follows: the ligands are electronically rich and sterically encumbered, and these attributes should promote the oxidative addition[42] and reductive elimination steps in the catalytic cycle, respectively. Furthermore, the biphenyl moiety is believed to stabilize Pd-complexes of these ligands, and to further facilitate the reductive elimination step.[33,34] Possibly, the interaction between the biphenyl and the metal center is similar to that between the metal and the binaphthyl components in Pd(II) complexes of MOP and MAP.[43]

A likely catalytic cycle for ketone arylations which use ligands **4**−**7** is shown in Scheme 1. It is possible that two phosphines coordinate to the Pd centers of intermediates **A** and **B**, provided that their substitution is *trans* with respect to the metal.[44] However, a study by Kawatsura and Hartwig suggests that, for bulky, electron-rich phosphines, only one phosphine binds to the metal center of aryl palladium enolate intermediates,[30] and mechanistic studies of the amination reaction using ligand **4** suggest that monophosphine complexes are involved. Analogously, we feel that when ligands **4**−**7** are used, the Pd:phosphine ratio for intermediates **A** and **B** is 1:1.[34] We also believe that a similar mechanism operates when **3** is the ligand. Circumstantial evidence suggests that binding of the dimethylamino group of **3** to Pd is not essential for the catalytic process and, in fact, may not occur at all. This is implied by the similarities between ligands **3**, **6**, and **7** in the Pd-catalyzed ketone arylations reported here, as well as in Suzuki[33] and amination reactions.[34]

For reactions in which either BINAP or Xantphos is the supporting ligand, we believe that the mechanism is similar to that in Scheme 1, except that the ligand bound to Pd in intermediates **A** and **B** is chelating.[45,46] That high selectivity is obtained in the reactions of relatively unhindered aliphatic ketones, such as 2-hexanone, but not with the monodentate

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(42) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047.

(43) Kočovský, P.; Vyskočil, Š.; Císařová, I.; Sejbal, J.; Tišlerová, I.; Smrčina, M.; Lloyd-Jones, G. C.; Stephen, S. C.; Butts, C. P.; Murray, M.; Langer, V. *J. Am. Chem. Soc.* **1999**, *121*, 7714.

(44) A modeling study showed that intermediates of the structure $LPdX_2$ (L = **4**) are already sterically crowded, and further inspection suggests that the *cis*-coordination of a second phosphine would be highly congested.[34] For the complex $(PCy_3)_2Pd(Ph)(Cl)$, the substitution of the phosphines is *trans*. See: Huser, M.; Youinou, M.-T.; Osborn, J. A. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1386.

(45) In palladium aryl halide and palladium aryl alkoxide complexes with BINAP, the ligand is chelating. See: Widenhofer, R. A.; Zhong, H. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6787.

phosphines **3**−**7**, is likely a consequence of the increased steric congestion around the Pd-center when these ligands are used.

For the first time, it was shown that a weak base (K_3PO_4) can be used in Pd-catalyzed ketone arylations and that the use of this base expands the scope of substrates that can be coupled. The effectiveness of K_3PO_4 is somewhat surprising, since the pK_a of K_2HPO_4 (∼12)[47] is considerably lower than that of an aliphatic ketone (the pK_a of cyclohexanone is 16.7),[48] and because K_3PO_4 does not completely dissolve in the reaction media (THF or toluene). Thus, the concentration of the free enolate is expected to be low. A possiblity is that, before deprotonation, the ketone coordinates to the Pd center, as represented by intermediate **C** in Scheme 1. Thus, the acidity of the proton situated α- to the carbonyl would be increased, and subsequent deprotonation and formation of intermediate **B** would be facile.

Preliminary results show that Pd catalysts based on **8** can be used to arylate diethyl malonate, cyclic 1,3-diketones, and nitroalkanes. A merit of the procedure reported here for malonate arylation is that K_3PO_4 is used instead of an alkoxide base,[30] and problems that could result from alcoholysis of the product should therefore be avoided.[49] A catalytic method for the intermolecular arylation of nitroalkanes has not been reported previously,[38] and Pd-catalysis has not been used previously for the intermolecular arylation of cyclic 1,3-diketones. The only precedents for the catalytic intermolecular arylation of 1,3-diketones use a copper catalyst,[13a,16b,c] and there is only one example in which a carboxylic acid function is not required to be positioned *ortho*- to the halogen on the arene.[16c] Further development of the arylations of these and other carbanions will be the subject of a future study.

The arylation procedures introduced here are easy to carry out. All of the ligands used in this study can be weighed and stored in the air, and the only precaution taken is to store the ligands in a desiccator. A glovebox was used only for reactions in which NaHMDS was the base.[50] Despite the high utility of ligands **3**, **6**, **7**, and **8** in the arylations of ketones and other carbanions, these ligands have the disadvantage that, unlike **4** and **5**, they are not commercially available,[31] and their syntheses require 2−4 steps. New one-step methods for the synthesis of these ligands are currently under development in our laboratories[51] and will be the subject of a future publication.

Conclusions

Several procedures for the Pd-catalyzed α-arylation of ketones are described. A protocol in which no ligand is added to the reaction mixture is suitable for a limited class of substrates, and for one substrate combination, remarkably high turnover numbers are obtained. Catalysts based on ligands **3**−**7**, and ligand **6** in particular, are highly active for ketone arylations and have a substrate scope that is large. For two classes of substrates, catalysts derived from **3**−**7** are less effective than those from the bidentate ligands BINAP and Xantphos. Of these, the catalysts based on Xantphos are more active. Procedures in which K_3PO_4 is the base are described, and these conditions were more generally compatible with base sensitive functional groups, such as esters and nitriles. Also described is a procedure for the arylation of diethyl malonate, the first intermolecular Pd-catalyzed protocol for the arylation of 1,3-diketones, and the first catalytic procedure for the arylation of nitroalkanes. For these reactions, catalysts based on **4** and **8** are found to be effective.

Experimental Section

General Considerations All reactions were carried out in glassware that was flame-dried under vacuum, and cooled under argon. Elemental analyses were performed by Atlantic Microlabs, Inc, Norcross GA. THF was distilled from benzophenone ketyl under an atmosphere of argon. Toluene was distilled from molten sodium under an atmosphere of nitrogen. Ketones and aryl halides were purchased from commercial sources and used without purification. Ligands **3**,[29] **4**,[34,35] **5**−**7**,[34] and Xantphos[36a] were prepared as described previously. Racemic BINAP, palladium acetate, tris(dibenzylideneacetone)dipalladium (0), and sodium hexamethyldisilazane (NaHMDS) were purchased from Strem Chemical Company. Sodium *tert*-butoxide was purchased from Aldrich Chemical Co., and the bulk of the material was stored under nitrogen in a Vacuum Atmospheres glovebox. Small portions (∼1−2 g) were removed from the glovebox and stored in glass vials, and then kept in the air in desiccators filled with anhydrous calcium sulfate. Tribasic potassium phosphate was purchased from Fluka Chemical Company. All materials were weighed in the air, except for NaHMDS, which was weighed and added to the reaction flask in a glovebox. IR spectra reported in this paper were obtained by placing neat samples directly on the DiComp probe of an ASI REACTIR in situ IR instrument. Yields in Tables 1−5 refer to isolated yields (average of 2 runs) of compounds estimated to be ≥95% pure as determined by ^{1}H NMR, GC, and combustion analysis. Compounds that are described more than once in the same table were completely characterized once. Other samples of these compounds were characterized by comparing their ^{1}H NMR spectra to those of the fully characterized product, and their purity was confirmed by GC analysis. The procedures described in this section are representative, and thus the yields may differ from those in Tables 1−5.

2-(Di-*tert*-butylphosphino)-2′-methylbiphenyl (8). A dry 50 mL flask with a sidearm adapter was evacuated, backfilled with argon, and charged with magnesium turnings (164 mg, 6.75 mmol). Under a flow of argon, the tube was then capped with a septum, and THF (7.0 mL) was injected. 2-Bromo-2′-methylbiphenyl[34] (1.50 g, 6.07 mmol) was dissolved in 1 mL of THF, and it was transferred via cannula to the flask containing the Mg. Additional THF (∼1 mL) was used to rinse the flask that contained the 2-bromo-2′-methylbiphenyl. The mixture was then stirred and heated in an oil bath at 65 °C for 4.5 h. The reaction was cooled to room temperature; as the flask was flushed with argon, the septum was removed, and CuCl (661 mg, 6.68 mmol) was added. The septum was replaced, and chloro-di-*tert*-butylphosphine (1.38 mL, 7.28 mmol) was injected. The flask was then heated at 65 °C for 16 h. After cooling to room temperature, the mixture was diluted with ∼10 mL of a 1:1 mixture of ethyl acetate/hexane, filtered on a Buchner funnel, and rinsed with 240 mL of 1:1 ethyl acetate/hexane. Ether (50 mL) and concentrated NH_4OH were sequentially added to the filtrate, which was stirred for 1 h at room temperature, and then transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted twice with additional ether. The organics were combined, washed sequentially with concentrated NH_4OH and brine, dried (Na_2SO_4), filtered, and concentrated. Crystallization of the residue gave 314 mg of the title compound as white crystals, mp = 86−87 °C. Chromatography of the mother liquor (the eluant was 98:2 hexane: ethyl acetate) provided an additional 319 mg of the title compound. The combined yield for the crystallization and the chromatography was 33%. ^{1}H NMR (C_6D_6, 300 MHz) δ 7.77−7.82 (m, 1H), 7.34−7.28 (m, 2H), 7.22−7.12 (m, 6H), 2.18 (s, 3H), 1.14 (d, 18H, J_{H-P} = 11.4 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 150.3 (d, J_{C-P} = 33.1 Hz), 142.8 (d, J_{C-P} = 6.9 Hz), 136.1 (d, J_{C-P} = 27.5 Hz), 135.5, 135.5 (d, J_{C-P}

(46) For crystal structures of Xantphos/Pd complexes, see: Kranenburg, M.; Delis, J. G. P.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Vrieze, K.; Veldman, N.; Spek, A. L.; Goubitz, K.; Fraanje, J. *J. Chem. Soc., Dalton Trans.* **1997**, *11*, 1839.

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(48) Bell, R. P.; Smith, P. W. *J. Chem. Soc. (B)* **1966**, 241.

(49) Ethanolic sodium ethoxide is known to convert diethyl α-phenylmalonate to ethyl phenylacetate. See: Connor, R. *J. Am. Chem. Soc.* **1933**, *55*, 4597.

(50) NaHMDS can also be purchased in either THF or toluene solution from Aldrich Chemical Co. These solutions can be handled without using a glovebox.

(51) Tomori, H.; Buchwald, S. L., unpublished results.

= 11.5 Hz), 131.6 (d, J_{C-P} = 3.4 Hz), 130.8 (d, J_{C-P} = 6.9 Hz), 129.5, 128.3, 126.9, 125.7, 124.2, 33.1 (d, J_{C-P} = 24.0 Hz), 32.4 (d, J_{C-P} = 25.3 Hz), 31.2 (d, J_{C-P} = 14.6 Hz), 30.8 (d, J_{C-P} = 14.7 Hz), 20.8 (d, J_{C-P} = 3.4 Hz) ppm. ^{31}P NMR (C_6D_6, 121 MHz) δ 20.0 (s) ppm. IR (neat, cm^{-1}) 2981, 2960, 2941, 2890, 2856, 1463, 1459, 1360, 1171. Calcd for $C_{21}H_{29}P$: C, 80.73; H, 9.36. Found: C, 80.62; H, 9.46.

General Procedure A: Ketone Arylations without Ligand. An oven-dried, resealable Schlenk tube containing a stirbar was capped with a rubber septum, flame-dried under vacuum, and then backfilled with argon and cooled to room temperature. The tube was then charged with sodium *tert*-butoxide (125 mg, 1.3 mmol) and $Pd(OAc)_2$ (2.2 mg, 0.01 mmol). The septum was replaced, and the tube was again evacuated and backfilled with argon. Toluene (1 mL), aryl halide (1.0 mmol), and ketone (1.2 mmol) were sequentially injected, and under a flow of argon, the septum was replaced by a Teflon screw cap. The tube was sealed, and the mixture was stirred and heated in an oil bath at 80 °C for the time specified. The contents of the tube were then partitioned between ether and water. The aqueous layer was separated and extracted three times with additional ether. The organics were then combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure, and the residue was chromatographed on silica gel.

α-Phenylpropiophenone (Table 1, Entry 1). An oven-dried, resealable Schlenk tube containing a stirbar was capped with a rubber septum, flame-dried under vacuum, and then backfilled with argon and cooled to room temperature. The tube was then charged with sodium *tert*-butoxide (125 mg, 1.3 mmol), the septum replaced, and the tube again evacuated and backfilled with argon. One milliliter of a solution of $Pd(OAc)_2$ (1×10^{-5} M in toluene), bromobenzene (157 mg, 1.0 mmol), and propiophenone (161 mg, 1.2 mmol) were sequentially injected, and under a flow of argon, the septum was replaced with a Teflon screw cap. The tube was sealed and heated in an oil bath at 120 °C, with stirring, for 24 h. The reaction was worked up as in general procedure A. Chromatography (the eluant was 4:1 toluene:hexane) gave 151 mg (72%) of the title compound.

α-(3,5-Dimethylphenyl)propiophenone (Table 1, Entry 2). General procedure A was followed. The yield was 198 mg (83%). A similar reaction, in which $Pd_2(DBA)_3$ (4.6 mg, 0.005 mmol) was used in place of $Pd(OAc)_2$ gave 185 mg (78%) of the title compound.

α-(4-Methoxyphenyl)propiophenone (Table 1, Entry 3). General procedure A was followed. The yield was 216 mg (90%).

α-(3-Methoxyphenyl)pinacolone (Table 1, Entry 4). General procedure A was followed. The yield was 146 mg (71%).

α-(2-Methylphenyl)propiophenone (Table 1, Entry 5). General procedure A was followed. The yield was 100 mg (44%).

General Procedure B: Ketone Arylations with Ligands 3−7. An oven-dried, resealable Schlenk tube containing a stirbar was capped with a rubber septum, flame-dried under vacuum, and then backfilled with argon and cooled to room temperature. The tube was then charged with sodium *tert*-butoxide (125 mg, 1.3 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), and the specified ligand (0.02 mmol). The septum was replaced with a Teflon screw cap, and the tube was again evacuated and backfilled with argon. The solvent (1 mL), aryl halide (1.0 mmol), and ketone (1.2 mmol) were sequentially injected, and under a flow of argon, the septum was replaced by a Teflon screw cap. The tube was sealed, and the mixture was stirred and heated for the time specified in Table 2. The reaction was worked up as in general procedure A.

General Procedure C: Ketone Arylations at Low Catalyst Loadings with Ligand 6. An oven-dried, resealable Schlenk tube containing a stirbar was capped with a rubber septum, flame-dried under vacuum, and then backfilled with argon and cooled to room temperature. The tube was then charged with sodium *tert*-butoxide (125 mg, 1.3 mmol), the septum was replaced, and the tube was again evacuated and backfilled with argon. In a separate flask, a solution of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) and ligand **6** (7.3 mg, 0.02 mmol) in 10 mL of the specified solvent was prepared and heated for several minutes at 60 °C to completely dissolve the $Pd(OAc)_2$. This solution (1 mL), the aryl halide (1.0 mmol), and the ketone (1.2 mmol) were sequentially injected into the tube, and under a flow of argon, the septum was replaced by a Teflon screw cap. The tube was sealed, and the mixture was stirred and heated for the time specified in Table 2. The mixture was worked up as in general procedure A.

α-(4-Methylphenyl)propiophenone (Table 2, Entry 1). General procedure B was followed. The ligand was **4**, and the yield was 216 mg (96%).

α-(4-Methoxyphenyl)isobutyrophenone (Table 2, Entry 2). General procedure B was followed, except that 2.5 mL of solvent was used. The ligand was **4**, and the yield was 194 mg (76%).

α-(3-(1,3-Dioxolan-2-yl)-phenyl)cycloheptanone (Table 2, Entry 3). General procedure C was followed, except that 2.0 mmol of cycloheptanone and 2.2 mmol of NaO^{t}Bu were used. The yield was 200 mg (77%). A similar experiment, using 2 mol % **5**/1 mol % $Pd(OAc)_2$ gave 178 mg (68%) of the title compound.

***β*-(2,5-Dimethylphenyl)-α-tetralone (Table 2, Entry 4).** General procedure C was followed. The yield was 239 mg (96%). A similar experiment, using 2 mol % **3**/1 mol % $Pd(OAc)_2$ gave 200 mg (80%) of the title compound.

2-(4-*n*-Butylphenyl)-4-methyl-3-pentanone (Table 2, Entry 5). General procedure C was followed. The yield was 181 mg (81%) of an oil. ^{1}H NMR, GC/MS, and GC analysis showed this to be a 20:1 mixture of regioisomers— the title compound being the major constituent.

α-(3,5-Dimethylphenyl)acetophenone (Table 2, Entry 6). General procedure B was followed, except that ligand **7** was used instead of **6**, and 2.5 mL of toluene and 2.5 equiv of NaO^{t}Bu were used. The yield was 200 mg (89%). If general procedure C was followed, using 2.5 equiv of NaO^{t}Bu, and 2.5 mL of a toluene solution that was 0.1 M in $Pd(OAc)_2$ and 0.2 M in **7**, 165 mg (74%) of the title compound was obtained.

2-(4-*N*,*N*-Dimethylaminophenyl)-4-methyl-3-pentanone (Table 2, Entry 7). General procedure C was followed. The yield was 156 mg (71%). ^{1}H NMR, GC/MS, and GC analysis showed this to be a 20:1 mixture of regioisomers—the title compound was the major constituent.

2-(3-Hydroxyphenyl)-3-pentanone (Table 2, Entry 8). An oven-dried, resealable Schlenk tube containing a stirbar was capped with a rubber septum, flame-dried under vacuum, and then backfilled with argon and cooled to room temperature. The tube was then charged with sodium *tert*-butoxide (125 mg, 1.3 mmol), the septum was replaced, and the tube was again evacuated and backfilled with argon. In a separate flask, a solution of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) and ligand **6** (7.3 mg, 0.02 mmol) in 5 mL of the THF was prepared and heated for several minutes at 60 °C to completely dissolve the $Pd(OAc)_2$. This solution (0.5 mL), a solution of 3-bromophenol in THF (0.5 mL of a 2.0 M solution), and 3-pentanone (2.0 mmol) were sequentially injected, and under a flow of argon, the septum was replaced. The tube was sealed, and the mixture was stirred and heated for 24 h at 70 °C. The mixture was worked up as in general procedure A. Chromatography gave 157 mg (88%) of the title compound.

2,4-Dimethyl-2-(4-*tert*-butylphenyl)-3-pentanone (Table 2, Entry 9). General procedure B was followed, except that 0.005 mmol of $Pd(OAc)_2$ and 0.01 mmol of **6** were used. The yield was 150 mg (61%).

2-(4-Methoxyphenyl)-3-pentanone (Table 2, Entry 10). General procedure C was followed, except that 2.0 equiv of ketone were used. The yield was 144 mg (75%).

α-Methoxy-α-(4-*tert*-butylphenyl)acetophenone (Table 2, Entry 11). General procedure B was followed, except that 0.005 mmol $Pd(OAc)_2$ and 0.01 mmol of **6** were used. The yield was 239 mg (85%).

2,2-Dimethyl-5-(2,6-dimethylphenyl)cyclopentanone (Table 2, Entry 12). General procedure B was followed, except that 0.005 mmol $Pd(OAc)_2$ and 0.01 mmol of **6** were used. The yield was 145 mg (67%).

α-(2-Methoxyphenyl)-2,5-dimethoxyacetophenone (Table 2, Entry 13). General procedure B was followed. The ligand was **6**, and the yield was 263 mg (92%).

α-(4-Cyanophenyl)propiophenone (Table 2, Entry 14). An oven-dried, resealable Schlenk tube containing a stirbar was capped with a rubber septum, evacuated, and cooled under argon. The tube was then charged with $Pd(OAc)_2$ (2.3 mg, 0.01 mmol) and **7** (8.0 mg, 0.02 mmol). The tube was sealed and transferred to a glovebox. Propiophenone (160 μL, 1.2 mmol) was then injected, followed by the addition of NaHMDS (208 mg, 1.1 mmol) and 2 mL of toluene. After stirring at room temperature for 20 min, the screw cap was replaced with a septum, a solution of 4-chlorobenzonitrile (138 mg, 1.0 mmol) in toluene (1 mL) was injected, and the septum was replaced by a Teflon screw cap. The

tube was then sealed and heated in an oil bath for 18 h at 80 °C. Chromatography gave 192 mg (82%) of the title compound.

α-(4-Carboxyphenyl)-*β*-tetralone ethyl ester (Table 2, Entry 15). In a glovebox, a resealable Schlenk tube was charged with NaHMDS (213 mg, 1.1 mmol). The tube was sealed with a Teflon screw cap and brought out of the box. Under a flow of argon, the screw cap was replaced by a septum. In a separate flask, a solution of $Pd(OAc)_2$ (2.3 mg, 0.01 mmol) and ligand **6** (8 mg, 0.022 mmol) in 5 mL of the toluene was prepared, and stirred for 10 min at room temperature to dissolve the $Pd(OAc)_2$. This solution (1 mL), ethyl 4-bromobenzoate (1.0 mmol) and *β*-tetralone (1.2 mmol) were sequentially injected into the tube, and under a flow of argon, the septum was replaced by a Teflon screw cap. The tube was sealed, and the mixture was stirred and heated for 24h. The mixture was worked up as in general procedure A. Chromatography gave 250 mg (85%) of the title compound as a white solid.

α-(4-Carboxyphenyl)propiophenone methyl ester (Table 2, Entry 16). General procedure B was followed, except that NaHMDS (1.1 equiv), which was added to the Schlenk tube in the glovebox, was used instead of NaO^{t}Bu. The ligand was **7**, and the yield was 220 mg (82%).

General Procedure D: Ketone Arylations with Either *rac*-BINAP or Xantphos An oven-dried, resealable Schlenk tube containing a stirbar was capped with a rubber septum, flame-dried under vacuum, and then backfilled with argon and cooled to room temperature. The tube was then charged with sodium *tert*-butoxide (125 mg, 1.3 mmol), $Pd_2(DBA)_3$, and either *rac*-BINAP or Xantphos. The septum was replaced, and the tube was again evacuated and backfilled with argon. Solvent (1 mL), aryl halide (1.0 mmol), and ketone (1.2 mmol) were sequentially injected, and under a flow of argon, the septum was replaced by a Teflon screw cap. The tube was sealed, and the mixture was stirred and heated for the time specified in Table 3. The mixture was worked up as in general procedure A.

3-(3,4-Dimethoxyphenyl)-4-methyl-2-pentanone (Table 3, Entry 1). General Procedure D was followed, using Xantphos (3.4 mg, 0.006 mmol) and Pd_2DBA_3 (2.3 mg, 0.0025 mmol). The yield was 170 mg (72%). For the reaction in which *rac*-BINAP was used instead of Xantphos, conditions were similar to those above, except that the following amounts were used: 4-methyl-2-pentanone (0.6 mmol), 4-bromoveratrole (0.5 mmol), NaO^{t}Bu (0.65 mmol), *rac*-BINAP (3.6 mmol), $Pd_2(DBA)_3$ (1.5 mmol), and THF (3 mL). The yield of the title compound was 83 mg (70%).

1-(3-Fluorophenyl)-2-hexanone (Table 3, Entry 2). General Procedure D was followed, using Xantphos (6.8 mg, 0.012 mmol) and $Pd_2(DBA)_3$ (4.6 mg, 0.005 mmol). The yield was 136 mg (70%).

α-(4-Carboxyphenyl)-4-methyl-3-pentanone *tert*-butyl ester (Table 3, Entry 3). In a glovebox, a resealable Schlenk tube containing a stirbar was charged with 378 mg (2.0 mmol) of NaHMDS. The tube was then sealed with a Teflon screwcap and taken out of the glovebox, and under a flow of argon, the screwcap was replaced by a septum. Toluene (3 mL) and 2-methyl 3-pentanone (2.2 mmol) were sequentially injected. In a separate flask, a solution of $Pd_2(DBA)_3$ (9.2 mg, 0.01 mmol) and Xantphos (12.7 mg, 0.022 mmol) in 10 mL of toluene was prepared and stirred for 10 min at room temperature to dissolve the $Pd_2(DBA)_3$. This solution (1 mL) and 4-bromo-*tert*-butylbenzoate (200 *μ*L, 1 mmol) were sequentially injected into the tube, and under a flow of argon, the septum was replaced by the Teflon screw cap. The tube was sealed, and the mixture was stirred and heated at 80 °C. The mixture was worked up as in general procedure A. The yield after chromotagraphy was 182 mg (66%).

2-(4-*N*,*N*-Diethylcarbamoylphenyl)-4-methyl-3-pentanone (Table 3, Entry 4). An oven-dried, resealable Schlenk tube containing a stirbar was evacuated and cooled under argon. The tube was then charged with *N*,*N*-diethyl 4-bromobenzamide (256 mg, 1.0 mmol) and NaO^{t}Bu (192 mg, 2.0 mmol), capped with a rubber septum, evacuated, and then backfilled with argon. In a separate flask, a solution of $Pd_2(DBA)_3$ (9.2 mg, 0.01 mmol) and Xantphos (12.7 mg, 0.022 mmol) in 10 mL of toluene was prepared and stirred for 10 min at room temperature to dissolve the $Pd_2(DBA)_3$. 2-Methyl 3-pentanone (2.2 mmol) and the Pd/Xantphos solution (1 mL) were sequentially injected into the tube, and under a flow of argon, the septum was replaced by a Teflon screw cap. The tube was sealed, and the mixture was stirred and heated at 80 °C. The mixture was worked up as in general procedure A. Chromatography gave 201 mg (73%) of the title compound.

General Procedure E: Ketone Arylations with K_3PO_4 as the Base. An oven-dried, resealable Schlenk tube containing a stirbar was charged with $Pd_2(DBA)_3$ (4.6 mg, 0.005 mmol) or $Pd(OAc)_2$ (2.3 mg, 0.01 mmol), Xantphos (6.4 mg, 0.011 mmol) or ligand **6** (8.0 mg, 0.022 mmol), and K_3PO_4 (490 mg, 2.3 mmol). The tube was then capped with a rubber septum, evacuated, and backfilled with argon. Solvent, ketone (1.2 mmol), and aryl halide (1.0 mmol) were sequentially injected. Under a flow of argon, the septum was replaced with a Teflon screw cap. The tube was sealed, and the mixture was stirred and heated for the time specified in Table 4. The mixture was diluted with ethyl acetate, filtered, and concentrated under reduced pressure, and the residue was chromatographed on silica gel.

α-(4-Cyanophenyl)cycloheptanone (Table 4, Entry 1). General procedure E was followed. The Pd source was $Pd_2(DBA)_3$, and the ligand was Xantphos. The yield was 153 mg (72%).

α-(4-*tert*-Butylphenyl)cycloheptanone (Table 4, Entry 2). General procedure E was followed. The Pd source was $Pd(OAc)_2$, and the ligand was **6**. The yield was 190 mg (78%).

α-(4-Carboxyphenyl)-*β*-tetralone Ethyl Ester (Table 4, Entry 3). An oven-dried, resealable Schlenk tube was evacuated and cooled under argon. The tube was then charged with K_3PO_4 (276 mg, 1.3 mmol), capped with a rubber septum, evacuated, and backfilled with argon. In a separate flask, a solution of $Pd(OAc)_2$ (2.3 mg, 0.01 mmol) and ligand **6** (8.0 mg, 0.022 mmol) in 5 mL of toluene was prepared, and stirred for 10 min at room temperature to dissolve the $Pd(OAc)_2$. This solution (1 mL), ethyl 4-bromobenzoate (1.0 mmol), and *β*-tetralone (1.2 mmol) were sequentially injected into the tube, and under a flow of argon, the septum was replaced by a Teflon screw cap. The tube was sealed, and the mixture was stirred and heated for 23h. The mixture was worked up as in general procedure A. The yield after chromotagraphy was 265 mg (90%). Spectral data were identical to those obtained using NaHMDS as the base (Table 2, Entry 15).

α-(4-Carboxyphenyl)cyclohexanone Methyl Ester: From Ethyl 4-Bromobenzoate (Table 4, Entry 4). General procedure E was followed, except that the ethyl 4-bromobenzoate was added to the reaction tube with the other solids, prior to the addition of solvent. The Pd source was $Pd_2(DBA)_3$, and the ligand was Xantphos. The yield was 174 mg (75%).

From Ethyl 4-Chlorobenzoate (Table 4, Entry 5). General procedure E was followed, except that the ethyl 4-chlorobenzoate was added to the reaction tube with the other solids, prior to the addition of solvent. The Pd source was $Pd(OAc)_2$, and the ligand was **6**. The yield was 165 mg (71%).

Diethyl α-(4-*tert*-Butylphenyl)malonate (Table 5, Entry 1). An oven-dried, resealable Schlenk tube containing a stirbar was capped with a rubber septum, evacuated, and cooled under argon. The tube was then charged with $Pd(OAc)_2$ (2.3 mg, 0.01 mmol), ligand **8** (6.9 mg, 0.022 mmol), and K_3PO_4 (490 mg, 2.3 mmol). The septum was replaced, and the tube was again evacuated and filled with argon. THF (2 mL), diethyl malonate (1.2 mmol), and 4-bromo-*tert*-butylbenzene (1.0 mmol) were then injected, and under a flow of argon, the septum was replaced by a Teflon screw cap. The tube was sealed and heated at 70 °C for 10 h. The mixture was then diluted with ethyl acetate and filtered. The filtrate was concentrated and chromatographed to give 266 mg (91%) of the title compound as an oil.

General Procedure F: Arylations of 1,3-Diketones. An oven-dried, resealable Schlenk tube containing a stirbar was capped with a rubber septum, evacuated, and cooled under argon. The tube was then charged with $Pd(OAc)_2$ (2.3 mg, 0.01 mmol), ligand **8** (6.9 mg, 0.022 mmol), the 1,3-diketone (1.2 mmol), and K_3PO_4 (490 mg, 2.3 mmol). The septum was replaced, and the tube was again evacuated and backfilled with argon. Solvent (3 mL) and the aryl bromide (1.0 mmol) were sequentially injected, and the septum was replaced with a Teflon screw cap under a flow of argon. The tube was sealed, and the mixture was stirred and heated for the time specified. The mixture was then diluted with MeOH and filtered. The filtrate was concentrated and chromatographed.

2-(3,5-Dimethylphenyl)-1,3-cyclohexanedione (Table 5, Entry 2). General procedure F was followed. The yield was 184 mg (85%).

2-(4-*tert*−Butylphenyl)-1,3-cyclopentanedione (Table 5, Entry 3). General procedure F was followed. The yield was 220 mg (95%).

2-(3-Carboxyphenyl)-1,3-cyclopentanedione Methyl Ester (Table 5, Entry 4). General procedure F was followed. The yield was 225 mg (97%) of the title compound.

1-(4-*tert*-Butylphenyl)-1-nitroethane (Table 5, Entry 5). An oven-dried Schlenk tube containing a stirbar was capped with a rubber septum, evacuated, and cooled under argon. The tube was then charged with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), **8** (31.2 mg, 0.10 mmol) and K_3PO_4 (276 mg, 1.3 mmol). The septum was replaced, and the tube was evacuated and filled with argon. Dioxane (1 mL), 4-bromo-*tert*-butylbenzene (213 mg, 1.0 mmol), and 1-nitroethane (150 mg, 2.0 mmol) were sequentially added, and under a flow of argon, the septum was replaced by a Teflon screw cap. The tube was sealed and heated in an oil bath at 110 °C for 20 h. The contents of the tube were then partitioned between ether and 1 N HCl. The aqueous layer was extracted three times with ether and washed with water, and the combined organics were dried (Na_2SO_4), filtered, concentrated, and chromatographed to give 153 mg (74%) of the title compound as an oil.

A reaction similar to that above, using NaO^tBu (1.2 mmol) instead of K_3PO_4, **4** (0.06 mmol) instead of **8**, 0.03 mmol of $Pd(OAc)_2$, a temperature of 95 °C, and a reaction time of 22 h, gave 165 mg (80%) of the title compound.

1-(4-Methylphenyl)-1-nitropropane (Table 5, Entry 6). An oven-dried Schlenk tube containing a stirbar was capped with a rubber septum, evacuated, and cooled under argon. The tube was then charged with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), **8** (18.7 mg, 0.06 mmol), and NaO^tBu (115 mg, 1.2 mmol). The septum was replaced, and the tube was evacuated and filled with argon. Dioxane (1 mL), 4-chlorotoluene (127 mg, 1.0 mmol), and 1-nitropropane (178 mg, 2.0 mmol) were sequentially injected, and under a flow of argon, the septum was replaced by a Teflon screw cap. The tube was sealed and heated in an oil bath at 120 °C for 20 h. The contents of the tube were then partitioned between ether and 1 N HCl. The aqueous layer was extracted three times with ether and washed with water, and the combined organics were dried (Na_2SO_4), filtered, concentrated, and chromatographed (eluting with 97:3 hexane:ethyl acetate) to give 142 mg (79%) of the title compound.

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Supporting Information Available: Detailed experimental information and characterization data is provided, as are graphs showing the ^1H and ^{13}C NMR spectra of the compounds described in Table 2, entries 8 and 11, and in Table 5, entries 2−4 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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