

JOSE LLOREDA CAMACHO & CO.

ABOGADOS

Calle 72 No. 5-83 Piso 5, Bogotá, D.C. Tel: 6069700 Fax 6069701

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-106847- -00007-0000

Fecha: 2012-08-28 16:24:04 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 444 RESPUESTAREQUE Folios: 17

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Re: PI.-**ABBOTT LABORATORIES**.-Solicitud de Patente de Invención en Fase Nacional PCT para "**PROCESO PARA LA PREPARACIÓN DE INDAZOLIL UREAS QUE INHIBEN RECEPTORES VANILOIDE DEL SUPTIPO 1(VR1)**".-Clase **A61K 31/416**.-Expediente número **08-106.847**.-

1. Me refiero al auto dictado por ese Despacho notificado mediante fijación en lista de 1 de Junio de 2012.

2. De acuerdo con el Concepto Técnico se tiene que:

"Como resultado de la búsqueda de anterioridades de materia relacionada con la de la presente solicitud, se determinó que existe en el estado de la técnica los siguientes documentos que eventualmente afectaría los requisitos de patentabilidad de esta solicitud:

- GURAM, A.; BUCHWALD. S.; Palladium-Catalyzed Aromatic Aminations with in situ Generated Aminostannanes; J. Am. Chem. Soc, 1994, 116, 7901;
- OLD, D. W.; WOLFE, J.; BUCHWALD. S.: A Highly Active Catalyst for Palladium-Catalyzed Cross-Coupling Reactions; Room-Temperature Suzuki Couplings and Amination of Unactivated Aryl Chlorides; J. Am. Chem. Soc. 1998, 120, 9722-9723;
- HAMANN, B., HARTWIG, J. Sterically Hindered Chelating Alkyl Phosphines Provide Large Rate Accelerations in Palladium-Catalyzed Amination of Aryl Iodides, Bromides, and Chlorides, and the First Amination of Aryl Tosylates J. Am. Chem. Soc. 1998, 120, 7368-7370;
- KAWATSURA M.; HARTWIG, J.; Simple, Highly Active Palladium Catalysts for Ketone and Malonate Arylation: Dissecting the importance of Chelation and steric Hindrance, J. Am. Chem. Soc, 1999, Vol. 121, 1473-1478;
- YIN, J. BUCHWALD, S. J. Am Chem Soc.; Pd-Catalyzed Intermolecular Amidation of Aryl Halides. The Discovery that Xantphos Can Be Trans-chelating in a Palladium Complex. 2002, Vol. 124, 6043-6048;
- WOLFE, J. AHMAN, J.: SADIGHI, J.: SINGER R.; BUCHWALD, S. An Ammonia Equivalent for the Palladium-Catalyzed Amination of Aryl Halides and Triflates, Tet. Lett. 1997. Vol. 38, 6367-6370;
- VOGL E. BUCHWALD. S.; Palladium-Catalyzed Monoarylation of Nitroalkanes; J. Org. Chem 2002, Vol. 67, pages 106-111; y
- LLOYD-JONES G.; ACIEE, 2002, 41, 953.

JOSE LLOREDA CAMACHO & CO.

Calle 72 No. 5-83 Piso 5, Bogotá, D.C. Tel: 6069700 Fax 6069701

3. Para responder a los requerimientos del señor Examinador de conformidad con el Artículo 46 de la Decisión Andina 486 de 2000, anexo me permito presentar a ese Despacho copia de los siguientes documentos solicitados:

- ♦ **GURAM, A.; BUCHWALD. S.; Palladium-Catalyzed Aromatic Aminations with in situ Generated Aminostannanes; J. Am. Chem. Soc, 1994, 116, 7901;**
- ♦ **OLD, D. W.; WOLFE, J.; BUCHWALD. S.; A Highly Active Catalyst for Palladium-Catalyzed Cross-Coupling Reactions; Room-Temperature Suzuki Couplings and Amination of Unactivated Aryl Chlorides; J. Am. Chem. Soc. 1998, 120, 9722-9723;**
- ♦ **HAMANN, B., HARTWIG, J. Sterically Hindered Chelating Alkyl Phosphines Provide Large Rate Accelerations in Palladium-Catalyzed Amination of Aryl Iodides, Bromides, and Chlorides, and the First Amination of Aryl Tosylates J. Am. Chem. Soc. 1998, 120, 7368-7370;**
- ♦ **KAWATSURA M.; HARTWIG, J.; Simple, Highly Active Palladium Catalysts for Ketone and Malonate Arylation: Dissecting the importance of Chelation and steric Hindrance, J. Am. Chem. Soc, 1999, Vol. 121, 1473-1478;**
- ♦ **YIN, J. BUCHWALD, S. J. Am Chem Soc.; Pd-Catalyzed Intermolecular Amidation of Aryl Halides. The Discovery that Xantphos Can Be Trans-chelating in a Palladium Complex. 2002, Vol. 124, 6043-6048;**
- ♦ **WOLFE, J. AHMAN, J.; SADIGHI, J.; SINGER R.; BUCHWALD, S. An Ammonia Equivalent for the Palladium-Catalyzed Amination of Aryl Halides and Triflates, Tet. Lett. 1997. Vol. 38, 6367-6370;**
- ♦ **VOGL E. BUCHWALD. S.; Palladium-Catalyzed Monoarylation of Nitroalkanes; J. Org. Chem 2002, Vol. 67, pages 106-111; y**
- ♦ **LLOYD-JONES G.; ACIEE, 2002, 41, 953.**

4. En vista de lo anterior, ruego a usted tomar atenta nota y proceder de conformidad.

Señor Superintendente,



ALICIA LLOREDA RICAURTE

T.P. 53.215

Dirección para Notificaciones: notificacionespatentes@lloredacamacho.com

Palladium-Catalyzed Aromatic Aminations with in Situ Generated Aminostannanes

Anil S. Guram and Stephen L. Buchwald*

Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

Received May 23, 1994

The arylamine moiety is a structural component in a variety of synthetic and naturally occurring biologically active compounds. Many synthetic methods for the construction of an aryl–nitrogen bond have been reported, but in general these methods suffer from severe reaction conditions and/or are applicable only for activated substrates.¹ Research efforts in our laboratory directed toward the synthesis of arylamine-containing biologically active compounds² necessitated the exploration of newer methods. We were attracted to the critical although inconclusive report by Migita and co-workers describing the preparation of (*N,N*-diethylamino)benzenes from the PdCl₂(P(*o*-tolyl)₃)₂-catalyzed reactions of aryl bromides and (*N,N*-diethylamino)tributyltin.^{3–5} The lack of demonstrated applicability of this route in the general synthesis of arylamines was particularly surprising, but could be attributed in part to the high reactivity/instability⁶ of the aminostannanes which hinder their efficient isolation and further manipulations.⁷ Herein we describe our initial findings on a transamination/Pd-catalysis protocol which provides a fairly general and attractive route to arylamines.

The PdCl₂(P(*o*-tolyl)₃)₂-catalyzed reaction of 3-bromoanisole with (*N,N*-diethylamino)tributyltin (toluene, ~105 °C, ~4 h) afforded 3-(*N,N*-diethylamino)anisole (**1**) (83% isolated yield).^{8,9} Preliminary studies of catalyst and reaction conditions indicate that the P(*o*-tolyl)₃ ligand and higher temperatures are desirable.¹⁰

(1) (a) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992. For recent reports on nucleophilic aromatic substitution reactions of *N*-nucleophiles with activated aromatic substrates, see: (b) Hattori, T.; Sakamoto, J.; Hayashizaka, N.; Miyano, S. *Synthesis* 1994, 199. (c) Semmelhack, M. F.; Rhee, H. *Tetrahedron Lett.* 1993, 34, 1395. (d) Abdel-Aziz, A. S.; Lee, C. C.; Piorko, A.; Sutherland, R. G. *J. Organomet. Chem.* 1988, 348, 95. For synthesis of arylamines via Cu-mediated Ullmann condensation, see: (e) Paine, A. J. *J. Am. Chem. Soc.* 1987, 109, 1496 and references therein.

(2) Tidwell, J. H.; Buchwald, S. L. *J. Org. Chem.* 1992, 57, 6380.

(3) Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* 1983, 927.

(4) Related research was recently described while this work was in progress: Hartwig, J. F.; Patt, J.; Paul, F.; Driver, M. S. *Abstracts of Papers*, 207th National Meeting of the American Chemical Society, San Diego, CA; American Chemical Society: Washington, DC, 1994; INOR 235.

(5) Related intramolecular aromatic aminations using stoichiometric amounts of Pd(PPh₃)₄ have been described: Boger, D. L.; Duff, S. R.; Panek, J. S.; Yasuda, M. *J. Org. Chem.* 1985, 50, 5782.

(6) Leading references: (a) Jones, K.; Lappert, M. F. *Organomet. Chem. Rev.* 1966, 1, 67 and references therein. (b) Chandra, G.; George, T. A.; Lappert, M. F. *J. Chem. Soc. C* 1969, 2565 and references therein.

(7) In contrast, thioannanes are very robust and have been more generally employed in related Pd-catalyzed reactions; see: (a) Dickens, M. J.; Gilday, J. P.; Mowlem, T. J.; Widdowson, D. A. *Tetrahedron* 1991, 47, 8621. (b) Kosugi, M.; Ogata, T.; Terada, M.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn.* 1985, 58, 3657.

(8) A byproduct (anisole, <5% by GC) resulting from reduction of the starting aryl bromide was also formed. Reduction may occur from β-hydride elimination followed by reductive elimination of the intermediate Pd(NEt₂)(*m*-C₆H₄OMe)L_n species (see ref 15). Alternatively, β-hydride and reductive elimination of a Pd(*n*-Bu)(*m*-C₆H₄OMe)L_n species, generated via *n*-Bu transfer from *n*-Bu₃SnX (X = Br, NEt₂) to the Pd(Br)(*m*-C₆H₄OMe)L_n species, is also possible. Such *n*-Bu ligand transfer reactions from *n*-Bu₃SnCl are precendented (see: Pri-Bar, I.; Stille, J. K. *J. Org. Chem.* 1982, 47, 1215) and are anticipated to be relatively more facile in *n*-Bu₃SnNEt₂. Studies to elucidate the reduction mechanism are currently underway.

(9) Analogous reactions of (*N,N*-diethylamino)tributyltin with aryl iodides were less efficient (6–38% variable yields of the desired arylamine) and primarily afforded the reduced product. However, satisfactory yields (>60% isolated) of the desired arylamine were obtained in the presence of ammonium salts. Thus, the reaction of (*N,N*-diethylamino)tributyltin with *p*-iodotoluene in the presence of *N*-benzyltriethylammonium chloride (toluene, 100 °C) afforded 3-(*N,N*-diethylamino)toluene (63% isolated yield, unoptimized).

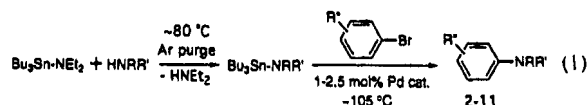
Table 1. Pd-Catalyzed Aromatic Aminations with in Situ Generated Aminostannanes

R ¹ R ²	Amine	Work-up ^a	Aryl Amine	Yield(%) ^b
<i>p</i> -CO ₂ Et	HN(Ph) ₂	B	EtO ₂ C-C ₆ H ₄ -N(Ph) ₂ 2	88
<i>p</i> -NMe ₂	HN(Ph) ₂	A	Me ₂ N-C ₆ H ₄ -N(Ph) ₂ 3	81
<i>m</i> -Me	HN(CH ₂) ₁₁ CH ₃	B	CH ₃ -C ₆ H ₄ -N(CH ₂) ₁₁ CH ₃ 4	79
<i>p</i> -Me	HN(CH ₂) ₁₁ CH ₃	A	CH ₃ -C ₆ H ₄ -N(CH ₂) ₁₁ CH ₃ 5	55
<i>m</i> -OMe	HN(Ph) ₂	A	MeO-C ₆ H ₄ -N(Ph) ₂ 6	79
<i>m</i> -OMe	HN(CH ₂) ₁₁ CH ₃	A	MeO-C ₆ H ₄ -N(CH ₂) ₁₁ CH ₃ 7	84
<i>m</i> -Me	H ₂ N-C ₆ H ₄ -OMe	B	CH ₃ -C ₆ H ₄ -N(CH ₂) ₁₁ CH ₃ 8	66
<i>m</i> -Me	H ₂ N-C ₆ H ₄ -OMe	B	CH ₃ -C ₆ H ₄ -N(CH ₂) ₁₁ CH ₃ 9	64
<i>p</i> -Me	Me-N(Ph) ₂	B	Me-C ₆ H ₄ -N(Ph) ₂ 10	73
<i>p</i> -CO ₂ Et	Me-N(Ph) ₂	B	EtO ₂ C-C ₆ H ₄ -N(Ph) ₂ 11	83

^a Workup A: The product was extracted with 4 N HCl, followed by neutralization of the aqueous fraction with 4 N NaOH and extraction with Et₂O. Workup B: The organics were washed with aqueous KF solution to remove the organostannane as an insoluble *n*-Bu₃SnF polymer. Details are provided in the supplementary material. ^b Yields reported correspond to analytically pure, isolated compounds.

Related PdCl₂L₂ catalysts (L₂ = (PPh₃)₂; DPPF; Ph₂P(CH₂)₃-PPh₂) containing ligands other than P(*o*-tolyl)₃ are not effective, affording only trace amounts of the desired arylamine.

Initial experiments to generalize this reaction to include other higher aminostannane derivatives via in situ generation of aminostannanes by the conventional reaction of lithium amides with *n*-Bu₃SnCl (in ether) were not successful, presumably due to deactivation of the active reagents by either the LiCl salt or residual BuLi or ether solvent. Indeed, the reaction of 3-bromoanisole with (*N,N*-diethylamino)tributyltin in the presence of LiCl (~1 equiv) (toluene, ~105 °C, ~4 h) is not efficient (~20% conversion by GC). These difficulties were overcome by in situ generation of aminostannanes from the reaction of an aminostannane derived from a volatile amine with a higher boiling amine (in toluene), concomitantly with removal of the volatile amine.¹¹ This efficient transamination reaction coupled with Pd catalysis provides a general access to a variety of arylamines (eq 1 and Table 1).



A typical experimental procedure involved in situ generation of the aminostannanes from the transamination reaction (toluene, ~80 °C, argon purge) of (*N,N*-diethylamino)tributyltin (~1.37

(10) The reaction takes ca. 12 h to reach completion at 80 °C (82% isolated yield of **1**). The catalyst system Pd(dba)₂/2P(*o*-tolyl)₃ is equally effective (81% isolated yield of **1**).

equiv) with primary and secondary amines (~1.45 equiv), followed by reaction with aryl bromides (1.0 equiv) at 105–110 °C in the presence of 1–2.5 mol % of $\text{PdCl}_2(\text{P}(o\text{-tolyl})_3)_2$.¹² The reactions were monitored by GC/TLC for the complete conversion of the starting aryl bromide, and the analytically pure arylamines were isolated in good yields by column chromatography on silica gel following either an extractive acidic or aqueous KF workup.

As illustrated in Table 1, the Pd-catalyzed aromatic aminations are fairly general for a variety of in situ generated aminostannanes. Aminostannanes derived from both aliphatic and aromatic amines including aniline undergo Pd-catalyzed reactions with aryl bromides substituted with either electron-withdrawing or electron-donating substituents to afford the desired arylamines in good yields. In general, aryl bromides substituted with a para electron-donating substituent reacted more slowly than those with a para electron-withdrawing substituent (~18 h for 4-bromo-*N,N*-dimethylaniline vs. ~1–2 h for ethyl 4-bromobenzoate). Slower reaction was also observed in the case of an aminostannane derived from aniline (~30–40 h). However, *p*-methoxyaniline (*p*-anisidine) and *N*-methylaniline reacted significantly faster (~12 and ~8 h, respectively). To date, aminostannanes derived from *n*-hexylamine and *N*-methylcyclooctylamine were found to be unreactive under similar conditions.¹³

The Pd-catalyzed aromatic amination most likely proceeds via initial aminostannane-induced reduction of Pd(II) complex to a Pd(0) species, followed by an oxidative addition, transmetalation, and reductive elimination sequence typical of Pd catalysis.^{4,14}

(11) This transamination reaction was originally reported by Jones and Lappert. Secondary amines and primary aromatic amines (e.g., aniline and derivatives) form aminostannanes, whereas primary aliphatic amines form aminodistannanes; see: Jones, K.; Lappert, M. F. *J. Chem. Soc.* 1965, 1944.

(12) (*N,N*-Dimethylamino)tributyltin can also be used in the transamination reaction. Detailed experimental procedures and complete characterization data are provided in the supplementary material. Typical reaction procedure, 3-(*N*-(3,4-dimethoxyphenethyl)-*N*-methylamino)aniline (7): A solution of 3,4-dimethoxy-*N*-methylphenethylamine (349 mg, 1.79 mmol) and (*N,N*-diethylamino)tributyltin (600 mg, 1.66 mmol) in toluene (2 mL) was heated at 85 °C under argon purge for 1 h. 3-Bromoanisole (221 mg, 1.12 mmol), $\text{PdCl}_2(\text{P}(o\text{-tolyl})_3)_2$ (10 mg, 0.02 mmol), and toluene (8 mL) were added and the reaction mixture heated under argon at ~105 °C overnight. The reaction mixture was cooled, diluted with Et_2O (20 mL), and extracted with 4 N HCl solution (2 × 10 mL) (workup A). The aqueous fraction was cooled to 0 °C, made alkaline with 4 N NaOH solution (25–30 mL), and extracted with Et_2O (2 × 15 mL). The organic fraction was dried with MgSO_4 , concentrated in vacuo, and subjected to column chromatography on silica gel using hexane- EtOAc (10:1, 4:1) to afford compound 7 as a light pink oil (301 mg, 84%). ¹H NMR (300 MHz, CDCl_3): δ 7.16 (t, *J* = 8 Hz, 1H, ArH), 6.82–6.70 (m, 3H, ArH), 6.36 (d, *J* = 8 Hz, ArH), 6.30 (obs, 1H, ArH), 6.27 (br s, 1H, ArH), 3.86 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.54 (t, *J* = 8 Hz, NCH_2), 2.86 (s, 3H, NCH_3), 2.80 (t, *J* = 8 Hz, CH_2Ar). ¹³C NMR (75 MHz, CDCl_3): δ 160.8, 150.2, 148.9, 147.4, 132.4, 129.9, 120.6, 112.1, 111.1, 105.3, 100.8, 98.7, 55.9, 55.8, 55.1, 54.8, 38.6, 32.6. Anal. Calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_3$: C, 71.73; H, 7.69. Found: C, 71.88; H, 7.56.

Experimental results indicate that, in general, transmetalation to form the Pd–N bond¹⁵ is influenced by both the steric and electronic properties of the amine. Larger aminostannanes derived from *n*-hexylamine (aminodistannane is formed in this case)¹¹ and *N*-methylcyclooctylamine are unreactive presumably because the increased steric interactions with $\text{P}(o\text{-tolyl})_3$ ligands on palladium preclude transmetalation. This is consistent with the relatively higher reactivity (~1.8 times faster) exhibited by (*N,N*-dimethylamino)tributyltin compared to its homolog (*N,N*-diethylamino)tributyltin in the reaction with 3-bromoanisole at 80 °C.¹⁶ The lower reactivity of aminostannane derived from aniline can be ascribed to its decreased nucleophilicity.

In summary, we have demonstrated that a range of aminostannanes, generated in situ via a simple transamination reaction, undergo Pd-catalyzed reactions with aryl bromides substituted with either electron-withdrawing or electron-donating substituents. Overall, the transamination/Pd-catalysis sequence provides a fairly general and attractive approach to arylamines. Efforts to clarify the reaction mechanism, modify the reaction conditions, broaden the scope, and develop synthetic applications of these and related reactions are currently in progress.

Acknowledgment. This work was supported by the National Science Foundation (CHE-9000482) and the National Institutes of Health (GM34917). A.S.G. is a Postdoctoral Trainee supported by NIH Cancer Training Grant CT32CA09112. We also thank Professor John F. Hartwig for discussions of related results prior to publication.

Note Added in Proof: A related communication by Hartwig and co-workers has recently appeared.¹⁷

Supplementary Material Available: Details of experimental procedures and spectroscopic and analytical data for compounds 1–11 (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(13) The aryl bromide reactant also remained mostly unreacted in these reactions.

(14) For a general review on transition metal catalyzed coupling reactions, see: Tamao, K. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press, Inc., New York, 1991; Vol. 3, p 435.

(15) Complexes containing a Pd–N bond are rare and presumably decompose via β -hydride elimination: (a) Murahashi, S.-I.; Yoshimura, N.; Tsumiyama, T.; Kojima, T. *J. Am. Chem. Soc.* 1983, 105, 5002. (b) Bryndza, H. E.; Tam, W. *Chem. Rev.* 1988, 88, 1163.

(16) A 1.0:1.0:0.7 mixture of (*N,N*-dimethylamino)tributyltin, (*N,N*-diethylamino)tributyltin, and 3-bromoanisole, respectively, was heated at 80 °C and monitored by GC.

(17) Paul, F.; PaH, J.; Hartwig, J. F. *J. Am. Chem. Soc.* 1994, 116, 5969.

A Highly Active Catalyst for Palladium-Catalyzed Cross-Coupling Reactions: Room-Temperature Suzuki Couplings and Amination of Unactivated Aryl Chlorides

David W. Old, John P. Wolfe, and Stephen L. Buchwald*

 Department of Chemistry
 Massachusetts Institute of Technology
 Cambridge, Massachusetts 02139

Received June 29, 1998

Palladium-catalyzed C–N bond-forming reactions have evolved into a versatile and efficient synthetic transformation.¹ However, the lack of a general palladium-based catalyst for aryl chloride substitution reactions,^{2,3} as well as the elevated reaction temperatures often required, prompted us to search for new, more active ligands.

¹H NMR studies in our laboratories of the amination reactions of aryl bromides catalyzed by BINAP/Pd(OAc)₂ suggested that oxidative addition was rate limiting.⁴ For aryl chlorides, oxidative addition can be anticipated to be even more sluggish. To facilitate this slow step, we began to explore the use of electron-rich phosphine ligands.^{2,3c,5a} After some experimentation, we focused our efforts on the preparation of electron-rich bidentate phosphines.⁴ We first prepared the known 2,2'-bis(dicyclohexylphosphino)-1,1'-binaphthyl (1)⁶ and found that 1/Pd(0) constituted a reasonably effective catalyst for the coupling of pyrrolidine with 4-chlorotoluene. This important result, taken together with our experience with bidentate monophosphines PPF-OMe and PPFA^{1b} prompted us to prepare aminophosphine ligand 2 (Table 1).⁷ In comparison to 1, use of ligand 2 is generally superior and significantly expands the scope of palladium-catalyzed aryl chloride transformations. Herein, we demonstrate that the 2/Pd(0) catalyst system is highly active and allows for the room-temperature amination of aryl bromides and the first example of a room-temperature amination of an aryl chloride. Moreover, this system functions as the first general catalyst for room-temperature Suzuki coupling reactions of aryl chlorides.

(1) (a) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215–7216. (b) Marcoux, J.-F.; Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1568–1569. (c) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 6066–6068. (d) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.*, in press. (e) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217–7218. (f) Hartwig, J. F. *Synlett* **1997**, 329–340.

(2) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047–1062.

(3) For existing protocols for the amination of aryl chlorides, see ref 4 and: (a) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054–6058. (b) Riermeier, T. H.; Zapf, A.; Beller, M. *Top. Catal.* **1997**, *4*, 301–309. (c) Reddy, N. P.; Tanaka, M. *Tetrahedron Lett.* **1997**, *38*, 4807–4810. (d) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617–620. (e) Yamamoto, T.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 2367–2370.

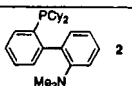
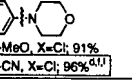
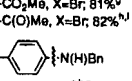
(4) Hartwig and Hamann have recently reported similar NMR experiments. They have also shown that electron-rich bidentate bis-phosphines can be used for the Pd-catalyzed amination of aryl chlorides and room-temperature aminations of aryl bromides and iodides: Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369–7370.

(5) (a) Shen, W. *Tetrahedron Lett.* **1997**, *38*, 5575–5578. (b) Beller, M.; Fischer, H.; Herrmann, W. A.; Öfele, K.; Brossmer, C. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1848–1849. (c) Bumagin, N. A.; Bykov, V. V. *Tetrahedron* **1997**, *53*, 14437–14450. (d) Mitchell, M. B.; Wallbank, P. J. *Tetrahedron Lett.* **1991**, *32*, 2273–2276. (e) Firooznia, F.; Gude, C.; Chan, K.; Satoh, Y. *Tetrahedron Lett.* **1998**, *39*, 3985–3988. (f) Cornils, B. *Org. Process Res. Dev.* **1998**, *2*, 121–127. (g) Indolese, A. F. *Tetrahedron Lett.* **1997**, *38*, 3513–3516. (h) Saito, S.; Oh-tani, S.; Miyaura, N. *J. Org. Chem.* **1997**, *62*, 8024–8030.

(6) Zhang, X.; Mashima, K.; Koyano, K.; Sayo, N.; Kumabayashi, H.; Akutagawa, S.; Takaya, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2309–2322.

(7) (a) Ligand 2 was prepared in three steps from *N,N*-dimethyl-2-bromoaniline. It is obtained as a crystalline solid and is stored and handled in the air without any special precautions. (b) See Supporting Information for complete experimental details.

 Table 1. Catalytic Amination^a of Aryl Chlorides and Bromides

$\text{R}-\text{C}_6\text{H}_4-\text{X} + \text{HN}(\text{R})\text{R}' \xrightarrow[\text{NaOtBu, toluene, rt-100}^\circ\text{C}]{\text{cat. Pd}_2(\text{dba})_3/\text{Ligand 2}}$		$\text{R}-\text{C}_6\text{H}_4-\text{N}(\text{R})\text{R}'$	
1: R=4-Me, X=Cl; 95% (85%) ^{b,c}	4: R=4-Me, X=Cl; 98%	8: R=4-MeO, X=Cl; 91%	
2: R=4-MeO, X=Cl; 90%	5: R=4-MeO, X=Cl; 95%	9: R=4-CN, X=Cl; 96% ^{d,f}	
3: R=4-Me, X=Br; 96% ^{d,e}	6: R=2,5-Me ₂ , X=Cl; 96%	10: R=2,5-Me ₂ , X=Br; 97% ^{d,g,h}	
	7: R=4-Me, X=Br; 95% ^{d,m}	11: R=4-CO ₂ Me, X=Br; 81% ^g	
13: R=2,5-Me ₂ , X=Cl; 99%	14: R=4-CO ₂ Me, X=Cl; 83% ⁿ	12: R=4-C(O)Me, X=Br; 82% ⁿ	
15: R=2,6-Me ₂ , X=Br; 88% ^{d,f}	16: X=Cl, 93% ^c	17: X=Cl, 89% ^{c,k,n}	

^a Reaction conditions: 1.0 equiv of aryl halide, 1.2 equiv of amine, 1.4 equiv of NaOtBu, 0.5 mol % Pd₂(dba)₃, 1.5 mol % ligand (1.5 L/Pd), toluene (2 mL/mmol halide), 80 °C. Reactions were complete in 11–27 h; reaction times have not been minimized. ^b Reaction run with 0.025 mol % Pd₂(dba)₃. ^c Reaction run at 100 °C. ^d Reaction run at room temperature in DME solvent. ^e Reaction run with 1.5 mol % Pd₂(dba)₃. ^f Reaction run with 2.5 mol % Pd₂(dba)₃. ^g Reaction run using K₃PO₄, DME solvent. ^h Reaction run using Pd(OAc)₂, K₃PO₄, DME solvent. ⁱ One of the two runs only proceeded to 98% conversion. ^j Reaction run with Pd(OAc)₂, ligand 1, Cs₂CO₃ as catalyst, ligand, and base. ^k Using 1 as ligand. ^l [ArBr] = 1 M. ^m [ArBr] = 2 M. ⁿ 1.5 equiv of benzylamine used.

To demonstrate the efficacy of the 2/Pd(0) catalyst system, we have prepared several aniline derivatives from aryl chlorides (Table 1, entries 1, 2, 4–6, 8, 9, 13, and 16). Secondary amines give excellent results in the coupling procedure (Table 1, entries 1, 2, 4–6, 8, and 9), and the arylation of a primary aniline can also be accomplished (Table 1, entry 16). Primary alkylamines are efficient coupling partners provided the aryl chloride is substituted at the ortho position (Table 1, entry 13), or through the use of ligand 1 (Table 1, entries 14 and 17). Catalyst levels as low as 0.05 mol % Pd have been achieved in the reaction of chlorotoluene with di-*n*-butylamine (Table 1, entry 1).

Given the high reactivity of this catalyst, we explored the possibility of carrying out room-temperature aminations. We found that both aryl iodides and aryl bromides (Table 1, entries 3, 7, 10, and 15) reacted readily at room temperature when DME was employed as the solvent. The experimentally simple procedure did not require crown ether or other additives.^{1c,4} Broadly speaking, the room-temperature amination of aryl bromides displays the same scope as the reactions of aryl chlorides at 80 °C. Aryl bromides containing functional groups sensitive to NaOt-Bu could be converted to the corresponding aniline derivative by using K₃PO₄ as the base. In these reactions (Table 1, entries 11 and 12), heating at 80 °C was required due to the decreased basicity and/or solubility of K₃PO₄.

Using 2/Pd(0), the amination of an aryl chloride (albeit an activated one) at room temperature could also be achieved for the first time.⁸ Thus, the coupling of *p*-chlorobenzonitrile and morpholine was catalyzed by 2.5 mol % Pd₂(dba)₃, 7.5 mol % 2, and NaOt-Bu in DME at room temperature to provide the corresponding aniline derivative in 96% yield (Table 1, entry 9).

In light of the high reactivity of this new catalyst system in amination reactions, we proceeded to examine its utility in several different Pd-catalyzed C–C bond-forming reactions. Pd-catalyzed Suzuki coupling reactions⁹ of aryl chlorides are usually inefficient if the aryl halide does not contain electron-withdrawing substituents.^{5a–f} While nickel catalysts are more effective at promoting Suzuki coupling reactions of unactivated aryl chlorides,

(8) Control experiments conducted in the absence of palladium afforded no coupled products after 24 h at room temperature.

(9) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Chapter 2.

Table 2. Suzuki Coupling^a and Ketone Arylation

Entry	Halide	Coupling Partner	Temp	mol% Pd	Yield	Product
1	Me-C ₆ H ₄ -Cl	PhB(OH) ₂	100 °C	0.5	96 ^b	Me-C ₆ H ₄ -Ph
2	Me-C ₆ H ₄ -Cl	PhB(OH) ₂	rt	2.0	94	Me-C ₆ H ₄ -Ph
3	Me-C ₆ H ₄ -Cl	o-MeOPhB(OH) ₂	100 °C	1.0	94 ^c	Me-C ₆ H ₄ -o-MeOPh
4	MeO-C ₆ H ₄ -Cl	PhB(OH) ₂	100 °C	0.5	93 ^b	MeO-C ₆ H ₄ -Ph
5	MeO-C ₆ H ₄ -Cl	PhB(OH) ₂	rt	2.0	92	MeO-C ₆ H ₄ -Ph
6	Me-C ₆ H ₄ -Br	B-n-C ₈ H ₁₃	50 °C	2.0	88 ^c	Me-C ₆ H ₄ -n-C ₈ H ₁₃
7	Me-C ₆ H ₄ -Br	PhB(OH) ₂	rt	1.0	92	Me-C ₆ H ₄ -Ph
8	Me-C ₆ H ₄ -Cl	m-TolB(OH) ₂	rt	2.0	94	Me-C ₆ H ₄ -m-Tol
9	MeO ₂ C-C ₆ H ₄ -Cl	PhB(OH) ₂	rt	2.0	90	MeO ₂ C-C ₆ H ₄ -Ph
10	MeO ₂ C-C ₆ H ₄ -Cl	m-TolB(OH) ₂	rt	2.0	92	MeO ₂ C-C ₆ H ₄ -m-Tol
11	Me-C ₆ H ₄ -Cl	Me-C(=O)-Me	80 °C	3.0	79 ^d	Me-C ₆ H ₄ -C(=O)-Me
12	Me-C ₆ H ₄ -Br	Me-C(=O)-Me	rt	3.0	82 ^e	Me-C ₆ H ₄ -C(=O)-Me

^a Reaction conditions: 1.0 equiv of aryl halide, 1.5 equiv of boron reagent, 3.0 equiv of CsF, 0.5–2.0 mol % Pd(OAc)₂, 0.75–3.0 mol % 2 (1.5 L/Pd), dioxane (3 mL/mmol halide). Reactions were complete in 19–30 h; reaction times have not been minimized. ^b 2.0 equiv of K₃PO₄ used in place of CsF. ^c One of two runs only proceeded to 98% conversion. ^d Pd₂(dba)₃, NaOtBu used as catalyst, base. ^e Pd₂(dba)₃, NaHMDS used as catalyst, base.

sterically hindered substrates are often problematic.^{5a,b} Furthermore, examples of Suzuki coupling reactions that proceed at room temperature are rare¹⁰ and often require stoichiometric amounts of highly toxic thallium hydroxide.^{10b,c} To the best of our knowledge, no examples of room-temperature Suzuki couplings of an aryl chloride have been reported.

Suzuki coupling reactions of both aryl bromides and aryl chlorides proceed in high yield at room temperature using the 2/Pd(0) catalyst system and CsF¹¹ in dioxane solvent (Table 2, entries 2, 5, and 7–10).^{7b,12} These conditions allow for the coupling of both electron-rich and electron-deficient aryl chlorides and tolerate the presence of base-sensitive functional groups. An aryl–alkyl coupling reaction of an aryl chloride using an alkylboron reagent generated in situ from 1-hexene and 9-BBN¹³ was achieved at 50 °C. Suzuki coupling reactions of electron-rich aryl chlorides could also be carried out using inexpensive K₃PO₄ with only 0.5 mol % palladium catalyst, although temperatures of 100 °C were required.

The 2/Pd(0) catalyst system was also effective for the Pd-catalyzed α-arylation of ketones¹⁴ at room temperature using NaHMDS as base (Table 2, entry 12). Interestingly, while the BINAP catalyst system was selective at promoting the mono-arylation of methyl ketones, 2/Pd was selective for the diarylation of methyl ketones (Table 2, entry 11). This may be due to the decreased steric bulk of 2 relative to BINAP.¹⁵

(10) (a) Campi, E. M.; Jackson, W. R.; Marcuccio, S. M.; Naeslund, C. G. *J. Chem. Soc., Chem. Commun.* **1994**, 2395. (b) Anderson, J. C.; Namli, H.; Roberts, C. A. *Tetrahedron* **1997**, *53*, 15123–15134. (c) Uenishi, J.-i.; Beau, J.-M.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4756–4758.

(11) Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095–6097.

(12) Control experiments conducted using dicyclohexylphenylphosphine in place of 2 gave low conversions and low yields of products.^{7b}

(13) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314–321.

(14) (a) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108–11109. (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382–12383.

(15) Other Pd-catalyzed cross couplings of aryl chlorides were surveyed using this catalyst. Stille couplings, Sonogashira couplings, and cross-couplings of aryl halides with organozinc reagents gave no detectable products. The Heck arylation of styrene gave some conversion to product at 110 °C.

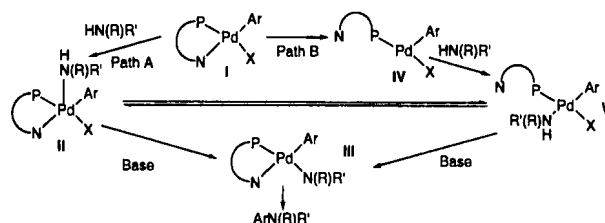


Figure 1.

While the precise mechanistic details of the reactions promoted by the 2/Pd(0) catalyst system remain unknown, we believe that the overall catalytic cycle for the amination reaction is similar to that postulated for the BINAP/Pd-catalyzed amination of aryl bromides.^{1a} However, in reactions catalyzed by 2/Pd, there may be different pathways available for the amine coordination/deprotonation step. Our current view of the course of the reaction involves binding of the amine to four-coordinate complex I, followed by deprotonation of the resulting five-coordinate complex II to give III (Figure 1, path A). Alternatively, coordination of the amine substrate may occur after initial dissociation of the dimethylamino moiety of the ligand, followed by nucleophilic attack of the amine substrate on three-coordinate^{16b} complex IV to give V. Deprotonation of V is followed by rapid recomplexation of the ligand amine group to give III (Figure 1, path B).¹⁶ If path B is operative, the recomplexation of the amine is presumably fast relative to β-hydride elimination since little or no reduced side product is observed. This notion is supported by the fact that Cy₂PPh was not an effective ligand for any of these Pd-catalyzed processes;^{7b,12} amination reactions conducted with electron-rich monodentate phosphines as ligands such as Cy₃P or Cy₂PPh demonstrated that reduction via β-hydride elimination can be a significant problem without a chelating group on the ligand. The relatively small size of the amine group in 2 allows for the efficient coupling of both cyclic and acyclic secondary amines.^{1b} That 2/Pd(0) can be employed in an amination procedure at the 0.05 mol % level (Table 1, entry 1) suggests that the dimethylamino group also contributes to the stability of the catalyst.

Of special importance is that the results presented herein indicate that the reactions of aryl chlorides in Pd-catalyzed processes need not be limited by the rate of the oxidative addition step.² Efforts to design catalysts that maintain this high activity for oxidative addition, but in which the rates of other processes (e.g., transmetalation, reductive elimination, migratory insertion) are enhanced, are currently underway in our laboratories.

Acknowledgment. We thank Amgen, the National Science Foundation, and the National Cancer Institute (Training Grant NCI CI T32CA09112) for financial support. Additional unrestricted support from Pfizer, Merck, and Novartis and fellowships from the Division of Organic Chemistry of the ACS sponsored by Schering-Plough and from Boehringer-Ingelheim are gratefully acknowledged. We also thank Dr. Michael Palucki for his contribution which ultimately led to the preparation of ligand 2. We also thank Professors John F. Hartwig and Greg Fu for sharing related results on aromatic amination and Suzuki coupling processes, respectively, prior to publication.

Supporting Information Available: Complete experimental procedures and characterization data for all new compounds (13 pages, print/PDF). See any current masthead page for ordering and Internet access instructions. See any current masthead page for ordering information and Web access instructions.

JA982250+

(16) (a) It is also possible that reductive elimination occurs from a three-coordinate intermediate^{1f} formed by deprotonation of V. (b) There is precedent for the dissociation of one phosphine of a chelating bis-phosphine.^{1f} (c) In reactions that employ NaOtBu as base, it is possible that complexes shown in Figure 1 may contain X = OtBu: Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109–13110. In reactions that employ Cs₂CO₃ or K₃PO₄ as base, it is unlikely that carbonate or phosphate complexes form due to the low solubility and low nucleophilicity of Cs₂CO₃ and K₃PO₄ relative to NaOtBu.

Sterically Hindered Chelating Alkyl Phosphines Provide Large Rate Accelerations in Palladium-Catalyzed Amination of Aryl Iodides, Bromides, and Chlorides, and the First Amination of Aryl Tosylates

Blake C. Hamann and John F. Hartwig*

Department of Chemistry, Yale University
P.O. Box 208107, New Haven, Connecticut 06520-8107

Received April 20, 1998

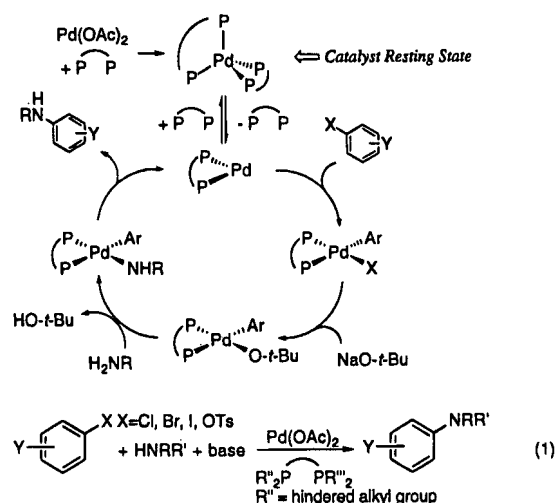
Aromatic phosphines and arsines are typically used as ligands in synthetically valuable palladium-catalyzed cross-coupling processes that include recently developed couplings to form arylamines and aryl ethers from aryl halides and triflates.^{1–3} We have recently sought palladium systems comprised of air stable components that provide faster reaction rates for aryl bromide and iodide amination and allow the amination of less activated and commercially important aromatic substrates such as aryl chlorides and tosylates. Using a mechanistic rationale for the choice of ligands, these goals have now been achieved with sterically hindered chelating alkyl phosphine ligands.^{4,5}

Because our group and Buchwald's have recently showed that chelating phosphine ligands containing aromatic substituents give high selectivity for the amination of aryl halides with primary amines,^{6,7} our studies toward rate acceleration focused on chelating ligands. Mechanistic data^{8–12} on the aryl halide amination reactions catalyzed DPPF (1,1'-bis(diphenylphosphino)ferrocene) or BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) palladium compounds support the mechanism in Scheme 1.

Our studies on rate enhancement began with ³¹P NMR spectroscopic studies to reveal the dominant form of the catalyst in solution. Reactions between *o*-tolyl or *p*-tolyl bromide and *n*-butylamine in the presence of NaO-*t*-Bu were conducted with 20 mol % of several catalysts, including [Pd(BINAP)₂], [Pd(DPPF)₂], [Pd(OAc)₂] with either 1.5 equiv of BINAP or DPPF, and [Pd(DBA)₂] with 1.5 equiv of DPPF. In all cases, the species observed at 80 °C by ³¹P NMR spectroscopy was Pd(0)L₂ (L = BINAP or DPPF).¹³ Thus, oxidative addition of aryl bromide is the likely rate-determining step for the amination reactions catalyzed by DPPF- or BINAP-ligated palladium and more active catalysts must increase the rate of this step.

Increasing the electron density at the metal center by employing chelating alkyl, rather than aryl, phosphine ligands may accelerate reaction rates. However, we have recently shown that oxidative

Scheme 1



addition involves complete dissociation of one of the chelating phosphine ligands to produce a bent Pd(0) chelate complex.¹⁴ Thus, tight binding of alkyl phosphines might, in fact, decelerate the oxidative addition by disfavoring dissociation that generates the active bent Pd(0)L. We, therefore, reasoned that sterically hindered alkylphosphine ligands might provide the required electron rich metal center, while favoring ligand dissociation.

For these reasons we tested the known, but infrequently studied, ligand DB'PF (1,1'-bis(di-*tert*-butylphosphino)ferrocene)^{15,16} (1) in the amination reactions. DB'PF is readily prepared by dilithiation of ferrocene, followed by quenching with ClP(*t*-Bu)₂.¹⁶ It is air sensitive over long periods of time in solution, but can be handled and weighed in air. Table 1 summarizes our results with this ligand and others discussed below in the general reaction presented in eq 1, and these results illustrate (1) remarkable rate enhancements for reactions with sterically hindered alkylphosphine ligands, (2) mild conditions for aminations of aryl chlorides, (3) the first amination of aryl tosylates, and (4) the first preparation of mixed alkyl arylamines in high yields by the metal-catalyzed amination of unactivated aryl chlorides with primary alkylamines. The functional group compatibility of palladium-catalyzed amination chemistry has been discussed previously.¹⁷

DB'PF leads to exceptionally high-yield amination of unactivated aryl chlorides with aniline (entry 1). Reactions were complete after 1 day at 110 °C in toluene solvent, but were complete in only 4 h in dioxane solvent (entry 2). Entry 6 shows that this ligand allows for the palladium-catalyzed amination of aryl chlorides with primary alkylamines in acceptable yields. Diarylation^{7,18} and competing hydrodehalogenation are assumed to be competing reactions in this case. Entries 11 and 12 show that this ligand provides excellent yields of dialkyl anilines from unactivated aryl chlorides under much milder conditions than previous palladium-catalyzed chemistry with unactivated chloroarenes.⁴ Previous unpublished work in our laboratory showed that palladium complexes of 1,1'-bis(dimethylphosphino)ferrocene were ineffective catalysts for the amination chemistry. This result, in combination with those reported here, shows the importance of ligand steric hindrance.

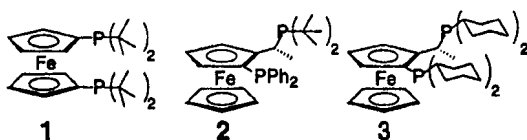
- (1) Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109–13110.
- (2) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10333–10334.
- (3) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 3395.
- (4) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047–1062.
- (5) Portnoy, M.; Milstein, D. *Organometallics* **1993**, *12*, 1665–1673.
- (6) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217–7218.
- (7) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215–7216.
- (8) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 8232–8245.
- (9) Driver, M. S.; Hartwig, J. F. *Organometallics* **1997**, *16*, 5706–5715.
- (10) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 4206–4207.
- (11) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 4708–4709.
- (12) Louie, J.; Paul, F.; Hartwig, J. F. *Organometallics* **1996**, *15*, 2794–3005.
- (13) The fate of the remaining palladium in cases where 1.5 equiv of ligand was added to a catalyst precursor is unclear at this time. However, Pd(OAc)₂ did not catalyze amination, demonstrating that the catalyst is the phosphine-ligated complex.

- (14) Alcazar-Roman, L.; Hartwig, J. F. To be submitted for publication.
- (15) Butler, I. R.; Cullen, W. R.; Kim, T. J.; Rettig, S. J.; Trotter, J. *Organometallics* **1985**, *4*, 972–80.
- (16) Cullen, W. R.; Kim, T. J.; Einstein, F. W. B.; Jones, T. *Organometallics* **1983**, *2*, 714–19.
- (17) Wolfe, J. P.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6359–6362.
- (18) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 3694–3703.

Table 1. Hindered, Chelating Alkylphosphines in the Amination of Aryl Halides and Tosylates^a

	Amine	ArX	Product	Catalyst	Conditions	Yield ^b
1	NH ₂ Ph			3 mol% Pd(dba) ₃ /1	110 °C, 24 h	93%
2	.			3 mol% Pd(dba) ₃ /1	110 °C, 4 h	93% ^c
3	.			2 mol% Pd(dba) ₃ /2	110 °C, 16 h	99%
4	.			1 mol% Pd(OAc) ₂ /2	85 °C, 12 h	92%
5	.			2 mol% Pd(dba) ₃ /3	110 °C, 16 h	96%
6	NH ₂ Bu			1 mol% Pd(dba) ₃ /1	110 °C, 24 h	57%
7	.			1 mol% Pd(OAc) ₂ /2	85 °C, 2 h	89%
8	.			1 mol% Pd(OAc) ₃ /3	85 °C, 2 h	94%
9	NH ₂ Bu			1 mol% Pd(OAc) ₂ /2	85 °C, 2 h	89%
10	.			1 mol% Pd(OAc) ₃ /3	85 °C, 12 h	67%
11				1 mol% Pd(OAc) ₂ /1	100 °C, 10 h	81%
12	NH ₂ Ph			1 mol% Pd(OAc) ₂ /1	100 °C, 12 h	85%
13	NH ₂ Ph			2 mol% Pd(dba) ₃ /2/1	110 °C, 16 h	79%
14	NH ₂ hexyl			2 mol% Pd(OAc) ₂ /2	110 °C, 2 h	83% ^d
15	.			5 mol% Pd(dba) ₃ /2/1	r. t., 20 h	94%
16	NH ₂ Bu			1 mol% Pd(dba) ₃ /2/1	r. t., 24 h	47%
17	NH ₂ Bu			1 mol% Pd(dba) ₃ /2/1	r. t., 7 h	49%
18	NH ₂ Ph			1 mol% Pd(dba) ₃ /2/1	r. t., 24 h	95%

^a Procedures: 1.0 equiv of aryl halide, 1.2 equiv of amine, and 1.2 equiv of NaO^tBu were used along with the specified catalyst in toluene solvent. ^b Yields are for isolated product of >95% purity and are an average of at least 2 runs on a 1 mmol scale with 0.5–1.0 M concentrations. ^c Reaction run in dioxane solvent. ^d NaOC₆H₃-2,4,6-tBu used as base.

**Figure 1.** Ligands employed in the examples of Table 1.**Table 2.** Effect of Ligand on Monoarylation vs Diarylation Selectivity for 4-Chlorotoluene and *n*-Butylamine

ligand	amine (H ₂ NR)	HNArR:NAr ₂ R
1	R = Bu	3.3:1
2	R = Bu	130:1
3	R = Bu	30:1
2	R = Ph	diarylation product not detected

Other chelating ligands with large bite angles created by backbones that are stable to basic conditions, while containing bulky alkyl substituents at the phosphorus, include ligand 2 in Figure 1 used by Lonza for the stereoselective reduction of biotin,¹⁹ and related systems including 3 in Figure 1 reported by Togni et al. for asymmetric hydrogenation.^{20,21} These ligands induced aminations of unactivated aryl chlorides with primary amines under remarkably mild conditions. The ligands 2 and 3 in Figure 1 were evaluated for the amination of hindered and unhindered aryl chlorides with aniline and butylamine. High yields of aryl chloride amination were observed with aniline (entries 3–5). The reaction in entry 4 that employs palladium acetate as catalyst precursor occurs under conditions reminiscent of previous aminations of aryl bromides. Table 2 shows that no diarylation of aniline was observed when ligand 2 was used.

In addition, high yields of mixed alkyl arylamines were obtained by employing these two ligands. Isolated yields between 87% and 94% were obtained when ligand 2 or 3 was used with palladium acetate at only 85 °C for 2–12 h for either hindered or unhindered aryl chlorides. Palladium precursors and ligands

2 and 3 catalyzed the amination of secondary amines only slowly, perhaps due to the exquisite selectivity for monoarylation, as shown in Table 2.⁷ More rapid arylation of secondary amines was observed with 1 in combination of Pd(OAc)₂ providing an excellent catalyst for the arylation of secondary amines as discussed above.

Previous studies on the Pd-catalyzed amination of aryl chlorides using monodentate alkylphosphines required activated aryl chlorides and were limited to secondary amines.^{22,23} Activation of chloroarenes by nickel is well established and Ni-catalyzed amination of aryl chlorides has been reported.²⁴ The work here shows that palladium-catalyzed chemistry, which is often less air sensitive and more general than that of nickel, can lead to amination of unactivated aryl chlorides in toluene solvent and with primary alkylamines.

Entries 13 and 14 show that hindered, chelating alkylphosphine ligands also generate effective catalysts for the amination of aryl tosylates. The reaction yields with unactivated aryl tosylates are remarkable, considering that little palladium-catalyzed cross-coupling with any type of aryl arene sulfonate has been reported.^{25,26} These results illustrate the potential of using chelating alkyl phosphines in chemistry to convert phenols to amines with tosyl chloride instead of triflic anhydride to activate the phenol.

Ligand 1 allowed for aminations of aryl bromides with aniline in excellent yield at room temperature (entry 15). Previous room-temperature palladium-catalyzed amination chemistry required aryl iodides and the addition of crown ethers,²⁷ and aminations with aniline substrates required heating. Entries 16–18 show the room-temperature amination of aryl iodides without additives. In all cases complete consumption of the aryl iodide occurred before 24 h had elapsed. Yields for the amination of aryl iodides with primary alkylamines were acceptable. However, the yields for amination of the unactivated aryl iodide in entry 19 with primary arylamines were excellent.

Our previous studies on the reductive elimination of diarylamine from (DPPF)Pd(Ar)(NHAr) complexes showed that this primary reaction required several hours at room temperature.⁸ We expected the presence of an alkylphosphine ligand to decelerate the reductive elimination of diarylamine, preventing room-temperature chemistry with aniline. Perhaps the size of the DBP-PF ligand compensates for the increased electron density at the metal, maintaining fast rates for reductive elimination.

A general problem in catalysis involves identifying systems that are rapid at both activating and extruding organic molecules. By using sterically hindered alkyl phosphines, it appears that both oxidative addition and reductive elimination are accelerated. This proposal will be tested in future mechanistic work that will accompany studies with dialkylphosphino ligands containing different backbones and the use of these ligands in the α -arylation of ketones and amides.

Acknowledgment. We gratefully acknowledge support from the National Institutes of Health, Boehringer Ingelheim, and the Department of Energy for support.

Supporting Information Available: Reaction procedures and spectroscopic data of ligands and reaction products (7 pages, print/PDF). See any current masthead page for ordering and Web access instructions.

JA981318I

(19) Imwinkelried, R. *Chimia* 1997, 51, 300–302.

(20) Togni, A.; Breutel, C.; Soares, M. C.; Zanetti, N.; Gerfin, T.; Gramlich, V.; Spindler, F.; Rihs, G. *Inorg. Chim. Acta* 1994, 222, 213–24.

(21) Zanetti, N. C.; Spindler, F.; Spencer, J.; Togni, A.; Rihs, G. *Organometallics* 1996, 15, 860–6.

(22) Reddy, N. P.; Tanaka, M. *Tetrahedron Lett.* 1997, 38, 4807–4810.

(23) Beller, M.; Reimer, T. H.; Reisinger, C.; Herrman, W. A. *Tetrahedron Lett.* 1997, 38, 2073–2074.

(24) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* 1997, 119, 6054–6058.

(25) Badone, D.; Cecchi, R.; Guzzi, U. *J. Org. Chem.* 1992, 57, 6321–3.

(26) Kubota, Y.; Nakada, S.; Sugi, Y. *Synlett* 1998, 183.

(27) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* 1997, 62, 6066–6068.

Simple, Highly Active Palladium Catalysts for Ketone and Malonate Arylation: Dissecting the Importance of Chelation and Steric Hindrance

Abbott Laboratory
Exp. 08-106.847
10)

Motoi Kawatsura and John F. Hartwig*

Contribution from the Department of Chemistry, Yale University, P.O. Box 208107, New Haven, Connecticut 06520-8107

Received September 22, 1998

Abstract: A remarkably active catalyst system for α -arylation of ketones and malonates was developed by proposing that sterically hindered alkylphosphines would accelerate the catalytic reaction rates. We initially tested the bisphosphine ligand D'BPF (1,1'-bis-(di-*tert*-butylphosphino)ferrocene) for this palladium-catalyzed chemistry. This catalyst system led to fast reaction rates for reactions of aryl bromides with ketones, including room temperature chemistry in many cases. In some cases turnover numbers were 20 000. The catalyst also gave mild reactions with aryl chlorides with yields that were similar to the chemistry with aryl bromides. Independent synthesis of the arylpalladium enolate complexes with isobutyrophenone enolate showed that only one phosphorus of the bisphosphine ligand D'BPF was coordinated in the enolate complex. Thus, we tested sterically hindered alkylphosphine ligands for the ketone and malonate arylation process and found that P(*t*-Bu)₃ gave exceptionally fast rates and high turnover numbers for these reactions. These results demonstrate several principles for the catalytic chemistry that we did not anticipate: palladium complexes of monophosphine ligands can activate aryl chlorides under mild conditions, and palladium enolates coordinated by certain monophosphines can undergo C–C bond-forming reductive elimination much faster than β -hydrogen elimination.

Introduction

The coupling of enolates with aryl halides, a transformation as fundamental as enolate alkylation, has historically been difficult to conduct.^{1–3} Previously, this reaction was reported with use of tin enolates of methyl ketones in modest yields and in low yields with higher homologs.^{1,4} In addition this reaction was conducted with use of silyl enol ethers in the presence of tin fluoride,² which also uses a stoichiometric amount of tin and presumably generates the same tin enolate. Direct intramolecular reactions of ketones with aryl halides in modest yields was reported many years ago with stoichiometric or high catalyst loadings of Ni(COD)₂.^{3,5} Intramolecular ketone arylation has been recently conducted more successfully with palladium complexes.⁶ Other methods involve the use of electrophilic and often toxic main group aryl reagents.^{7,8} The coupling of malonates with aryl halides is even less common. In some cases these reactions can be conducted with stoichiometric amounts of copper^{9,10} or with catalytic amounts of copper¹¹ most commonly with *o*-halobenzoic acids.^{12,13} However, these mal-

onate arylations require aryl iodides. Similarly, palladium-catalyzed reactions of malononitriles¹⁴ occur in lower yields with bromoarenes and require harsher conditions for hydrolysis than malonic esters.

Recently our group,¹⁵ Buchwald and Palucki,¹⁶ and Satoh et al.¹⁷ showed that palladium complexes catalyzed a simple ketone arylation process. The use of resolved rather than racemic BINAP and substrates that form quaternary carbons allowed this reaction to be conducted asymmetrically.¹⁸ We have sought an understanding of the catalyst properties that are important to develop more active systems for the arylation of carbonyl compounds. We began this effort with several hypotheses that were untested for the ketone arylation. First, oxidative addition of the aryl halides and reductive elimination of product both involve a low-coordinate Pd(0) reactive intermediate. Therefore, steric effects should increase the energy of the more stable high coordinate species, decreasing the relative energy of the reactive intermediate and increasing reaction rates.^{19,20} Second, alkyl-

(1) Kosugi, M.; Hagiwara, I.; Sumiya, T.; Migita, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 242–246.

(2) Kuwajima, I.; Urabe, H. *J. Am. Chem. Soc.* **1982**, *104*, 6831–6833.

(3) Semmelhack, M. F.; Chong, B. P.; Stauffer, R. D.; Rogerson, T. D.; Chong, A.; Jones, L. D. *J. Am. Chem. Soc.* **1975**, *97*, 2507–2516.

(4) Kosugi, M.; Suzuki, M.; Hagiwara, I.; Goto, K.; Saitoh, K.; Migita, T. *Chem. Lett.* **1982**, 939–940.

(5) Millard, A. A.; Rathke, M. W. *J. Org. Chem.* **1977**, *42*, 4833–4835.

(6) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7581–7582.

(7) Barton, D. H. R.; Finet, J. P.; Khamsi, J.; Pichon, C. *Tetrahedron Lett.* **1986**, *27*, 3619–3522.

(8) Barton, D. H. R.; Donnelly, D. M. X.; Finet, J.-P.; Guiry, P. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1365–1375.

(9) Osuka, A.; Kobayashi, S.; Suzuki, H. *SYNTHESIS* **1983**, 67–68.

(10) Setsune, J.-i.; Matsukawa, K.; Wakemoto, H.; Kitao, T. *Chem. Lett.* **1981**, 367–370.

(11) Okuro, K.; Furuune, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 7606–7607.

(12) Bruggink, A.; McKillop, A. *Tetrahedron* **1975**, *31*, 2607–2619.

(13) McKillop, A.; Rao, D. P. *Synthesis* **1977**, 759.

(14) Malononitrile has been shown to react with aryl iodides with palladium catalysts to form the less readily hydrolyzed aryl malononitriles: Uno, M.; Seto, K.; Takahashi, S. *J. Chem. Soc., Chem. Commun.* **1984**, 932–933.

(15) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382–12383.

(16) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108–11109.

(17) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740–1742.

(18) Ahman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918–1919.

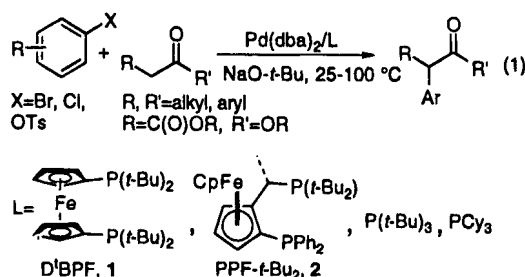
(19) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369–7370.

phosphines should be more resistant toward P–C cleavage processes than arylphosphines, and should provide higher turnover numbers.^{21,22} Third, chelation would prevent the enolate intermediates from undergoing β -hydrogen elimination,^{23,24} which would prevent formation of α -aryl ketone products. Consistent with this third hypothesis, our previous catalysts containing either DPPF or a more sterically hindered *o*-tolyl version of this ligand and the catalyst systems reported by Buchwald involved either bisphosphine ligands or ligands with both phosphorus and nitrogen donor atoms that can chelate to the metal and/or act as hemilabile ligands.^{16,18,25}

For these reasons, we initiated our studies by using palladium complexes of the sterically hindered bisphosphine ligand 1,1'-bis(di-*tert*-butylphosphino)ferrocene (D'BPF, **1**).^{19,26} The high activity of these catalysts confirmed some of our hypotheses, but preliminary mechanistic data disproved the importance of chelation and led us to select simple, sterically hindered alkyl monophosphines as remarkably active catalysts for arylation of both ketones and malonates. These synthetic studies and preliminary mechanistic results are reported here.

Results and Discussion

Synthetic Studies with D'BPF. The overall ketone arylation reaction is shown in eq 1. As shown in Table 1, reactions



employing D'BPF as ligand provided mild arylation of ketones with bromoarenes. Turnover numbers of 20 000 were observed in some cases. Monoarylation of acetophenone was accomplished with 2 equiv of base. Heterocyclic bromides that might displace a hindered phosphine were also suitable substrates. Reactions employing D'BPF as ligand coupled dialkyl ketones with bromoarenes (Entries 11 and 13). Reactions with cyclohexanone selectively gave the monoarylation product. 4-Methyl-3-pentanone reacted with 3-bromoanisole to provide the products from a single α -arylation in 84% yield, with the product formed from arylation of the less hindered alkyl group dominating. The ratio of α -arylation products was 89:11 in the crude reaction mixture (GC analysis).

The catalyst containing D'BPF provided clean chemistry with chloroarenes at only 70 °C. Electron neutral and even electron rich chloroarenes gave the coupled product in high yield, and sterically hindered aryl chlorides were suitable substrates despite the size of the ligand. The use of 2 mol % of Pd(dba)₂ led to

Table 1. Reaction of Ketones and Malonates with ArBr, ArCl, and ArOTs

Entry	ArX	Product	mol% Pd ^a /L	Conditions ^b	Yield ^c
1.	PhBr		2 % A/1	25 °C, 2 h	99%
2.			0.005% A/1	60 °C, 36 h	99%
3.			0.5% B/PBu ₃	25 °C, 2 h	97%
4.			0.005% "	60 °C, <24 h	98%
5.	3-bromopyridine		2 % A/1	50 °C, 5 h	87%
6.	4-MeC ₆ H ₄ OTs		5% B/2	70 °C, 12 h	60%
7.	PhBr		2 % A/1	25 °C, 12 h	90%
8.			1% B/PBu ₃	25 °C, 6 h	96%
9.			R=R'=H, 2 % A/1	50 °C, 6 h	87%
10.			R'=Me, 2 % A/1	50 °C, 12 h	92%
11.	3-MeOC ₆ H ₄ Br		R=H, R'=Me, 2 % A/1	70 °C, 12 h	92% ^d
12.			R'=i-Pr, 1% B/PBu ₃	50 °C, 12h	83% ^e
13.	PhBr		2 % A/1	70 °C, 12 h	70%
14.			1% B/PBu ₃	50 °C, 3 h	73%
15.	PhCl		R=Ph, 2 % A/1	70 °C, 3 h	86%
16.			2% B/PBu ₃	70 °C, 4 h	90%
17.			2% B/PCy ₃	50 °C, 12 h	93%
18.	3-MeOC ₆ H ₄ Cl		R=i-Pr, 2 % A/1	70 °C, 12 h	78% ^f
19.			2% B/PBu ₃	70 °C, 12 h	69% ^g
20.	4-MeOC ₆ H ₄ Cl		2 % A/1	70 °C, 12 h	91%
21.			2% B/PBu ₃	70 °C, 12 h	91%
22.			2% B/PCy ₃	70 °C, 12 h	93%
23.	3-MeOC ₆ H ₄ Cl		2 % A/1	70 °C, 12 h	78%
24.			2% B/PBu ₃	70 °C, 12 h	82%
25.	4-PhC(O)C ₆ H ₄ Cl		2% B/PBu ₃	70 °C, 24 h	95%
26.	2-MeC ₆ H ₄ Cl		2 % A/1	70 °C, 12 h	80%
27.	PhCl		R=i-Bu, 2 % A/1	100 °C, 12 h ^h	78%
28.	PhBr		R=Et, 2% B/PBu ₃	70 °C, 3 h ^h	80%

^a A = Pd(dba)₂; B = Pd(OAc)₂. ^b 1:1.25 ratio of Pd/L for reactions of aryl bromides or for aryl chlorides using monophosphines; 1:0.5 ratio of Pd/L for reactions of aryl chlorides using ligand **1**; 1.5 equiv of NaO-*t*-Bu for all reactions except those for acetophenone that used 2.2 equiv of base, 1.1 equiv of ketone, THF solvent. ^c Yields are an average of two runs on 1 or 2 mmol scale. ^d 89:11 ratio of isomers in crude reaction. ^e 74:26 ratio of isomers in crude reaction. ^f 87:13 ratio of isomers in crude reaction. ^g 76:24 ratio of isomers in crude reaction. ^h Reaction conducted in dioxane solvent using 1.1 equiv of NaO-*t*-Bu.

complete reaction, and 1 mol % ligand was optimal.²⁷ Reactions of chloroarenes with acyclic dialkyl ketones showed similar selectivity to those with bromoarenes. Typical palladium chemistry of aryl chlorides occurs at high temperatures or with electron-poor chloroarenes. These results and others reported recently²⁵ demonstrate that lower temperatures are possible for many coupling processes with palladium complexes.

Ketones did not react with aryl tosylates when using D'BPF as ligand, but a related chelating phosphine with *tert*-butyl substituents 1-diphenylphosphino-2-(di-*tert*-butylphosphino)-ethylferrocene (PPF-*t*-Bu₂, **2**)^{28–30} gave good yields when using 5 mol % catalyst at 70 °C. Little palladium-catalyzed chemistry with aryl tosylates has been reported previously and only one example of cross-coupling.¹⁹ Although **2** is a homochiral ligand in its commercially available form and the product contains a new stereocenter, the basic conditions lead to the formation of racemic product.

(27) Pd(dba)₂ did not catalyze the ketone arylation and slowly gave biaryl product. One can understand the activity of this Pd/bisphosphine ratio in terms of the mechanistic data and results with the 1:1 Pd/monophosphine ratio described below.

(28) This ligand is commercially available from Strem.

(29) Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062–4066.

(30) Togni, A.; Breutel, C.; Soares, M. C.; Zanetti, N.; Gerfin, T.; Gramlich, V.; Spindler, F.; Rihs, G. *Inorg. Chim. Acta* **1994**, *222*, 213–24.

(20) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 3694–3703.

(21) Goodson, F. E.; Wallow, T. I.; Novak, B. M. *J. Am. Chem. Soc.* **1997**, *119*, 12441–12453.

(22) Morita, D. K.; Stille, J. K.; Norton, J. R. *J. Am. Chem. Soc.* **1995**, *117*, 8576–8581.

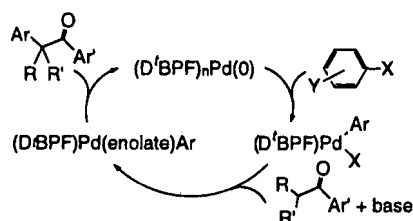
(23) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217–7218.

(24) Hayashi, T.; Knoch, M.; Kumada, M. *Tetrahedron Lett.* **1979**, *21*, 1871–1874.

(25) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722–9723.

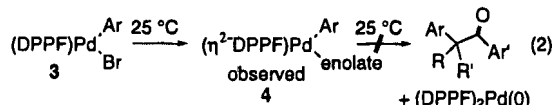
(26) Butler, I. R.; Cullen, W. R.; Kim, T. J.; Rettig, S. J.; Trotter, J. *Organometallics* **1985**, *4*, 972–80.

Scheme 1



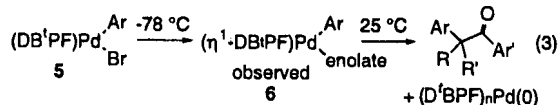
Qualitative Mechanistic Studies. Scheme 1 shows a general mechanism for the ketone arylation. Considering the success of chelating phosphine ligands in previous palladium-catalyzed arylation of ketone enolates that could undergo β -hydrogen elimination, it seemed likely that this ligand property was important to favor reductive elimination over β -hydrogen elimination.^{23,24,31}

Preliminary mechanistic data with D'BPF as ligand cast doubt upon the requirements for chelation. Arylpalladium enolate complexes were generated with both DPPF and D'BPF ligands to evaluate structure/reactivity relationships. Reaction of (DP-PF)Pd(*p*-Tol)(Br) (**3**)¹⁵ with the enolate of isobutyrophenone gave a single set of doublets (δ 29.83, 10.37, J = 34.2 Hz) corresponding to an arylpalladium enolate complex **4** (eq 2).



This enolate was identified as an O-bound enolate due to the two different enolate methyl groups observed in the ^1H NMR spectrum near 2 ppm. This species reacted at room temperature in the presence or absence of added PPh_3 to trap the $\text{Pd}(0)$ product, but gave <10% yield of α -aryl ketone. Biaryls, presumably from disproportionation of the arylpalladium enolate and from P-C cleavage, were the major products.

In contrast, addition of isobutyrophenone enolate to (D'BPF)-Pd(Ph)(Br) (**5**)³² at -78°C (eq 3) generated a single arylpal-



ladium enolate product **6** that underwent reductive elimination in quantitative yield at room temperature (^1H NMR spectroscopy with internal standard). Moreover, the $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of the enolate complex displayed two singlets at 24.8 and 57.2 ppm in a 1:1 ratio. One singlet lay in the region of coordinated ligand and the other in the region near, but not identical with that of free D'BPF (24.6 ppm). We have not yet rigorously determined the geometry and hapticity of the enolate ligand, due to its reactivity at room temperature, its temperature-dependent ^1H NMR spectra, and the overlap of enolate methyl resonances with the *tert*-butyl groups of the ligand. However, the absence of resonances near 2 ppm suggest a different binding mode than for the DPPF complex **4**. Further studies on complex **6** and related palladium enolates will be conducted in the future. For now, it is important to realize that this complex clearly contains a D'BPF ligand that is bound to the metal by only one phosphorus atom as determined by $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy.

From these initial studies, we concluded that sterically hindered monophosphines may be appropriate for this type of cross coupling.

Synthetic Studies Involving Sterically Hindered Alkylphosphines. Considering our mechanistic conclusions concerning the coordination number of D'BPF in the arylpalladium enolate intermediate, we evaluated $\text{PhP}(t\text{-Bu})_2$ as a model for monodentate D'BPF in the ketone arylation. We also evaluated the simple, commercially available monophosphines $\text{P}(t\text{-Bu})_3$ ^{33,34} and PCy_3 . The reactions of aryl bromides with ketones occurred in high yields with these ligands. Reactions with $\text{P}(t\text{-Bu})_3$ were faster than those with $\text{PhP}(t\text{-Bu})_2$, and further chemistry with $\text{PhP}(t\text{-Bu})_2$ was not pursued. Cyclohexanone, 3-methyl-2-propanone, acetophenone, propiophenone, and isobutyrophenone reacted with electron rich, electron neutral, electron poor, sterically hindered, or sterically unhindered aryl bromides and aryl chlorides in high yield when using $\text{P}(t\text{-Bu})_3$ as ligand (Table 1) Turnover numbers for reaction of propiophenone with phenyl bromide were as high as 20 000. Reaction of propiophenone with aryl chlorides also occurred in high yield when using PCy_3 as ligand.

We were able to find conditions that led to monoarylation of all ketones except methyl alkyl ketones. These conditions were developed by considering the acid/base equilibria that result from a more acidic and less nucleophilic reaction product. Reactions of methyl aryl ketones occurred with high selectivity for monoarylation by using 2 equiv of base. If 1 equiv of base is used, the enolate ion of the product is formed in preference to the enolate of the starting ketone and the enolate of the product ketone is an active reagent for the arylation process. Two equivalents of alkoxide base ensures that all ketones exist in their enolate form. The reaction of dialkyl ketones occurred with high selectivity for monoarylation when using 1 equiv of base. In this case, we propose that neither product nor starting ketone is quantitatively deprotonated by the alkoxide base. Further, the enolate of the product is deprotonated at the more acidic tertiary benzylic position, which is sterically hindered and less reactive than the more nucleophilic and less hindered enolate of the starting ketone. Qualitative studies showed that methyl alkyl ketones do undergo formation of diarylation products in good yield, but these reactions were not pursued in detail.

The selectivity for arylation of dialkyl ketones with two enolizable positions is perplexing at this point. Overall, it appears that bisphosphine ligands provide better selectivity than do the ligands in this work that are either monophosphines or bind in a monodentate fashion when the enolate is coordinated. The higher selectivity may, in fact, indicate that the bisphosphines with the smaller aryl substituents generate more sterically demanding enolate complexes. More detailed mechanistic analysis concerning the structures, exchanges, and reductive elimination rates of different enolate complexes are necessary to provide an unambiguous reason for the observed selectivity and a means to combine the high selectivity with high activity in a simple ligand system.

Arylation of Malonates. The arylation of malonates is one of the fundamental reactions of organic chemistry and allows the synthesis of various carboxylic acids. Arylation of malonates is synthetically challenging as discussed in the introduction. However, the use of either D'BPF or P(*t*-Bu)₃ in combination with palladium catalyst precursors led to mild arylation of simple malonates. Reaction of phenyl chloride with di-*tert*-butylma-

(31) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* 1997, 119, 8232–8245.

(32) This complex was prepared by addition of DB'PF to $\{Pd[P(o\text{-tolyl})_3]_2(Ph)Br\}_2$ in toluene and precipitation by addition of pentane. Mann, G.; Hartwig, J.F. To be submitted for publication.

(33) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* 1998, 39, 617-620.

(34) Yamamoto, T.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* 1998, 39, 2367–2370.

lonate in the presence of NaO-*t*-Bu and a combination of D'-BPF and Pd(dba)₂ as catalyst led to the formation of aryl malonate product in high yield at 100 °C. Reactions with this catalyst system did not form useful yields of aryl malonates from diethylmalonate in dioxane solvent. However, reactions between the inexpensive diethyl malonate and phenyl bromide with Pd(OAc)₂ and P(*t*-Bu)₃ as catalyst did cleanly produce the desired aryl malonate product.

Intermolecular reactions of malonates with aryl halides using transition metal catalysts are rare if not unprecedented,¹⁴ and have been conducted intramolecularly only at high temperatures.³⁵ These malonate arylations did not occur in reasonable rates when using DPPF, BINAP, PPh₃, or P(*o*-tolyl)₃ as ligand. In most cases, it is likely that the anions of β -dicarbonyl compounds will form complexes that are stable to reductive elimination. Of course, acetylacetonate complexes are common and are often remarkably stable. In the case of the complexes containing *tert*-butylphosphine ligands, these β -dicarbonylate complexes are more reactive than expected and lead to the formation of aryl malonates. This chemistry is certainly valuable synthetically as a route to α -aryl carboxylic acid derivatives that are a common building block for pharmaceutical materials.

Conclusions

The results presented here suggest several important principles for the palladium-catalyzed arylation of ketones. First, the selectivity for reductive elimination from the enolate intermediate, rather than β -hydrogen elimination, does not require chelation or arylphosphine ligands and is driven toward reductive elimination by steric hindrance. Second, high selectivity for reaction with the less hindered side of a dialkyl ketone may benefit from chelation, and palladium complexes of the simple monophosphines here and complexes of bidentate phosphines^{15,16,18} serve as complementary catalysts. Third, activation of chloroarenes under mild conditions does not require chelation, as one might expect from previous palladium chemistry with chloroarenes.^{36–38} Finally, arylation of simple malonates occurs with catalyst systems containing sterically hindered alkylphosphines, providing a convenient route to α -aryl carboxylic acids. A detailed mechanistic basis for these conclusions will be one subject of future studies in our lab.

Experimental Section

General Methods. Reactions were conducted with standard Schlenk and drybox techniques. ¹H and ¹³C{¹H} NMR spectra were recorded on a Bruker AM 500 MHz spectrometer with TMS (¹H) or residual protiated (¹³C) solvent used as a reference. ³¹P{¹H} NMR spectra were recorded on an Omega 300 MHz spectrometer with shifts reported relative to an external 85% H₃PO₄ standard; resonances downfield of the standard are reported as positive. Low resolution mass spectra were obtained on a Hewlett Packard 5890 series II gas chromatograph interfaced with a Hewlett Packard 5989 A mass spectrometer. Tetrahydrofuran was distilled from sodium and benzophenone and was stored in the drybox. 1,1'-Bis(di-*tert*-butylphosphino)ferrocene³⁹ was prepared by literature procedures and was recrystallized under nitrogen. "[Pd(DBA)₂]" is predominantly a mixture of Pd(dba)₃ and Pd₂(dba)₃ and was obtained by the synthesis reported for [Pd₂(DBA)₃] without

recrystallizing the crude precipitate.⁴⁰ The potassium enolate of isobutyrophenone was prepared by addition of isobutyrophenone to a toluene/pentane solution of potassium hexamethyldisilazide and was recrystallized from THF/ether after isolation by filtration. All other solvents and compounds were used as received.

General Procedure for the Reaction of Ketone with Arylbromide. The reaction conditions and results are shown in Table 1. A typical procedure is given for the reaction in Entry 1.

1,2-Diphenyl-1-propanone:⁴¹ Pd(dba)₂ (23.0 mg, 0.040 mmol), D'-BPF (23.7 mg, 0.050 mmol), and NaO'Bu (288 mg, 3.00 mmol) were suspended in 2 mL of THF in a screw-capped vial. The vial was sealed with a cap containing a PTFE septum and removed from the drybox. Bromobenzene (314 mg, 2.00 mmol) and propiophenone (289 mg, 2.20 mmol) were added to the reaction mixture by syringe. The reaction mixture was stirred at 25 °C and monitored by GC analysis. The crude reaction was diluted with ether and washed with water and brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc = 95/5) to give 396 mg (94%) of 1,2-Diphenyl-1-propanone: ¹H NMR (CDCl₃) δ 7.95 (d, *J* = 7.3 Hz, 2H), 7.48 (t, *J* = 7.3 Hz, 1H), 7.40–7.37 (m, 2H), 7.30–7.29 (m, 4H), 7.23–7.17 (m, 1H), 4.70 (q, *J* = 6.8 Hz, 1H), 1.54 (d, *J* = 6.8 Hz, 3H); ¹³C{¹H} NMR (CDCl₃) δ 200.32, 141.55, 136.53, 132.83, 129.04, 128.82, 128.53, 127.82, 126.95, 47.91, 19.57.

2-Methyl-1,2-diphenyl-1-propanone:⁴² Bromobenzene (157 mg, 1.00 mmol), isobutyrophenone (163 mg, 1.10 mmol), Pd(dba)₂ (11.5 mg, 0.020 mmol), D'BPF (11.8 mg, 0.025 mmol), and NaO'Bu (144 mg, 1.50 mmol) were used. Reaction at 50 °C for 6 h gave 196 mg (87%) of product after silica gel chromatography (hexane/EtOAc = 95/5). ¹H NMR (CDCl₃) δ 7.48 (d, *J* = 7.2 Hz, 2H), 7.38–7.33 (m, 5H), 7.29–7.26 (m, 1H), 7.21 (t, *J* = 7.9 Hz, 2H), 1.62 (s, 6H); ¹³C{¹H} NMR (CDCl₃) δ 203.67, 145.29, 136.25, 131.67, 129.72, 129.02, 127.95, 126.79, 125.72, 51.41, 27.87.

1-Phenyl-2-(3-pyridyl)-1-propanone:⁴³ 3-Bromopyridine (158 mg, 1.00 mmol), propiophenone (148 mg, 1.10 mmol), Pd(dba)₂ (11.5 mg, 0.020 mmol), D'BPF (11.9 mg, 0.025 mmol), and NaO'Bu (144 mg, 1.50 mmol) were used. Reaction at 55 °C for 12 h gave 183 mg (87%) of 1-phenyl-2-(3-pyridyl)-1-propanone after silica gel chromatography (hexane/EtOAc = 80/20). ¹H NMR (CDCl₃) δ 8.61 (s, 1H), 8.47 (d, *J* = 4.8 Hz, 1H), 7.94 (d, *J* = 7.5 Hz, 2H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.23 (dd, *J* = 4.8, 7.9 Hz, 1H), 4.75 (q, *J* = 6.9 Hz, 1H), 1.56 (d, *J* = 6.9 Hz, 3H); ¹³C{¹H} NMR (CDCl₃) δ 199.46, 149.32, 148.13, 136.85, 135.81, 135.04, 133.09, 128.57, 128.54, 123.69, 44.68, 19.20.

2-(3-Methoxyphenyl)-4-methyl-3-pentanone: 3-Bromoanisole (187 mg, 1.00 mmol), 2-methyl-3-pentanone (100 mg, 1.10 mmol), Pd(dba)₂ (11.5 mg, 0.020 mmol), D'BPF (11.8 mg, 0.025 mmol), and NaO'Bu (288 mg, 3.00 mmol) were used. Reaction at 50 °C for 12 h gave 189 mg (92%) of a mixture of 2-(3-methoxyphenyl)-4-methyl-3-pentanone and 2-(3-methoxyphenyl)-2-methyl-3-pentanone after silica gel chromatography (hexane/ether = 95/5). The ratio of isomers was determined by GC analysis in the crude reaction mixture. ¹H NMR (CDCl₃) δ 7.24 (t, *J* = 7.9 Hz, 1H), 6.84–6.78 (m, 2H), 6.76 (s, 1H), 3.89 (q, *J* = 6.9 Hz, 1H), 3.80 (s, 3H), 2.70 (sept, 6.9 Hz, 1H), 1.37 (d, *J* = 6.9 Hz, 3H), 1.08 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H); ¹³C{¹H} NMR (CDCl₃) δ 214.42, 159.93, 142.33, 129.76, 120.35, 113.61, 112.34, 55.16, 39.10, 25.17, 19.23, 18.28, 18.02. MS *m/e* (rel intensity) 206 (42), 135 (100), 120 (12), 105 (34), 91 (38), 77 (24), 71 (55), 51 (6). Anal. Calcd for C₁₃H₁₈O₂: C, 75.69; H, 8.80. Found: C, 75.75; H, 8.71. Selected ¹H NMR of minor isomer: 0.97 (t, *J* = 7.3 Hz, 3H), 1.48 (s, 6H), 2.24 (q, *J* = 7.3 Hz, 2H), 3.81 (s, 3H), aromatic region overlaps with major isomer. MS *m/e* (rel intensity) 206 (41), 149 (100), 135 (9), 121 (56), 109 (31), 91 (28), 77 (12), 65 (6), 57 (6).

(40) Ukai, T.; Kawazura, H.; Ishii, Y.; Bounet, J. J.; Ibers, J. A. *J. Organomet. Chem.* **1974**, *65*, 253.

(41) Yoshida, T.; Matsuda, T.; Okano, T.; Kitani, T.; Otsuka, S. *J. Am. Chem. Soc.* **1979**, *101*, 2027–2038.

(42) Baumstark, A. L.; Vasquez, P. C.; Chen, Y.-X. *J. Org. Chem.* **1994**, *59*, 6692–6696.

(43) Rathke, M. W.; Vogiazoglou, D. *J. Org. Chem.* **1987**, *52*, 3697–3968.

(35) Ciufolini, M. A.; Qi, H. B.; Browne, M. E. *J. Org. Chem.* **1988**, *53*, 4149–4151.

(36) Ben-David, Y.; Portnoy, M.; Milstein, D. *J. Am. Chem. Soc.* **1989**, *111*, 8742–8743.

(37) Ben-David, Y.; Portnoy, M.; Milstein, D. *J. Chem. Soc., Chem. Commun.* **1989**, 1816–1817.

(38) Ben-David, Y.; Portnoy, M.; Gozin, M.; Milstein, D. *Organometallics* **1992**, *11*, 1995–1996.

(39) Cullen, W. R.; Kim, T. J.; Einstein, F. W. B.; Jones, T. *Organometallics* **1983**, *2*, 714–719.

2-Phenyl-1-cyclohexanone:⁴⁴ Bromobenzene (157 mg, 1.00 mmol), cyclohexanone (108 mg, 1.10 mmol), Pd(dba)₂ (11.5 mg, 0.020 mmol), D'BPF (11.8 mg, 0.025 mmol), and NaO'Bu (144 mg, 1.50 mmol) were used. Reaction at 55 °C for 3 h gave 122 mg (70%) of 2-phenyl-1-cyclohexanone after silica gel chromatography (hexane/ether = 90/10). ¹H NMR (CDCl₃) δ 7.35 (t, *J* = 7.2 Hz, 2H), 7.27 (t, *J* = 7.2 Hz, 1H), 7.16 (d, *J* = 7.2 Hz, 2H), 3.62 (dd, *J* = 12.3, 5.4 Hz, 1H), 2.57–2.44 (m, 2H), 2.31–2.27 (m, 1H), 2.18–2.15 (m, 1H), 2.09–1.99 (m, 2H), 1.87–1.59 (m, 2H); ¹³C{¹H} NMR (CDCl₃) δ 210.14, 138.88, 128.557, 128.34, 126.86, 57.34, 42.22, 42.18, 35.13, 27.83, 25.31.

General Procedure for the Reaction of Ketone with Arylchloride. The reaction conditions and results are shown in Table 1. A typical procedure is given for the reaction of Entry 15.

1,2-Diphenyl-1-propanone:⁴¹ Pd(dba)₂ (36.6 mg, 0.064 mmol), D'BPF (23.8 mg, 0.050 mmol), and NaO'Bu (288 mg, 3.00 mmol) were suspended in 2 mL of THF in a screw-capped vial. The vial was sealed with a cap containing a PTFE septum and removed from the drybox. Chlorobenzene (225 mg, 2.00 mmol) and propiophenone (295 mg, 2.20 mmol) were added to the reaction mixture by syringe. The vial was heated at 70 °C and monitored by GC analysis. The crude reaction was diluted with ether and washed with water and brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc = 95/5) to give 365 mg (87%) of 1,2-diphenyl-1-propanone.

2-(3-Methoxyphenyl)-1-phenyl-1-propanone: 3-Chloroanisole (285 mg, 2.00 mmol), propiophenone (295 mg, 2.20 mmol), Pd(dba)₂ (36.6 mg, 0.064 mmol), D'BPF (23.8 mg, 0.050 mmol), and NaO'Bu (288 mg, 3.00 mmol) were used. Reaction at 70 °C for 2 h gave 477 mg (99%) of 2-(3-methoxyphenyl)-1-phenyl-1-propanone after silica gel chromatography (hexane/EtOAc = 95/5). ¹H NMR (CDCl₃) δ 7.96 (d, *J* = 7.5 Hz, 2H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.21 (t, *J* = 7.8 Hz, 1H), 6.88 (d, *J* = 7.8 Hz, 1H), 6.83 (s, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 4.65 (q, *J* = 7.0 Hz, 1H), 3.77 (s, 3H), 1.53 (d, *J* = 7.0 Hz, 3H); ¹³C{¹H} NMR (CDCl₃) δ 200.13, 160.02, 143.05, 136.50, 132.80, 129.99, 128.76, 128.49, 120.20, 113.53, 112.15, 55.15, 47.91, 19.45. MS *m/e* (rel intensity) 240(11), 135 (14), 105 (100), 91 (11), 77 (40), 51 (9). Anal. Calcd for C₁₆H₁₆O₂: C, 79.97; H, 6.71. Found: C, 79.74; H, 6.65.

2-(3-Methoxyphenyl)-2-methyl-1-phenyl-1-propanone: 3-Chloroanisole (143 mg, 1.00 mmol), isobutyrophenone (163 mg, 1.10 mmol), Pd(dba)₂ (18.3 mg, 0.032 mmol), D'BPF (12.0 mg, 0.025 mmol), and NaO'Bu (144 mg, 1.50 mmol) were used. Reaction at 70 °C for 12 h gave 201 mg (79%) of 2-(3-methoxyphenyl)-1-phenyl-1-propanone after silica gel chromatography (hexane/EtOAc = 95/5). ¹H NMR (CDCl₃) δ 7.51 (d, *J* = 8.3 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.29–7.22 (m, 3H), 6.91 (d, *J* = 7.4 Hz, 1H), 6.88 (t, *J* = 2.3 Hz, 1H), 6.81 (dd, *J* = 8.3, 2.3 Hz, 1H), 3.79 (s, 3H), 1.58 (s, 6H); ¹³C{¹H} NMR (CDCl₃) δ 203.51, 160.06, 146.95, 136.24, 131.70, 130.00, 129.66, 127.96, 118.24, 111.90, 111.67, 55.17, 51.38, 27.79. MS *m/e* (rel intensity) 254 (14), 149 (100), 121 (48), 105 (99), 91 (27), 77 (67), 65 (7), 51 (18). Anal. Calcd for C₁₇H₁₈O₂: C, 80.29; H, 7.13. Found: C, 80.50; H, 7.14.

2-(4-Methoxyphenyl)-1-phenyl-1-propanone:⁴⁵ 4-Chloroanisole (284 mg, 2.00 mmol), propiophenone (295 mg, 2.20 mmol), Pd(dba)₂ (36.6 mg, 0.064 mmol), D'BPF (23.8 mg, 0.050 mmol), and NaO'Bu (288 mg, 3.00 mmol) were used. Reaction at 70 °C for 12 h gave 192 mg (92%) of 2-(4-methoxyphenyl)-1-phenyl-1-propanone after silica gel chromatography (hexane/EtOAc = 95/5). ¹H NMR (CDCl₃) δ 7.95 (d, *J* = 8.0 Hz, 2H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.65 (q, *J* = 6.8 Hz, 1H), 3.76 (s, 3H), 1.51 (d, *J* = 6.8 Hz, 3H); ¹³C{¹H} NMR (CDCl₃) δ 200.55, 158.51, 136.53, 133.50, 132.73, 128.80, 128.76, 128.49, 114.40, 55.15, 46.95, 19.55.

2-(4-Methylphenyl)-1-phenyl-1-propanone:⁴⁶ 4-Chlorotoluene (253 mg, 2.00 mmol), propiophenone (295 mg, 2.20 mmol), Pd(dba)₂ (36.6 mg, 0.064 mmol), D'BPF (23.8 mg, 0.050 mmol), and NaO'Bu (288 mg, 3.00 mmol) were used. Reaction at 70 °C for 1 h gave 440 mg

(99%) of 2-(4-methylphenyl)-1-phenyl-1-propanone after silica gel chromatography (hexane/EtOAc = 95/5). ¹H NMR (CDCl₃) δ 7.96 (d, *J* = 8.1 Hz, 2H), 7.47 (t, *J* = 8.1 Hz, 1H), 7.38 (t, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 4.66 (q, *J* = 6.7 Hz, 1H), 2.29 (s, 3H), 1.52 (d, *J* = 6.7 Hz, 3H); ¹³C{¹H} NMR (CDCl₃) δ 200.46, 138.55, 136.82, 136.51, 132.75, 129.74, 128.82, 128.50, 127.68, 47.52, 21.03, 19.58.

2-(2-Methylphenyl)-1-phenyl-1-propanone:⁴⁷ 2-Chlorotoluene (127 mg, 1.00 mmol), propiophenone (148 mg, 1.10 mmol), Pd(dba)₂ (18.3 mg, 0.032 mmol), D'BPF (11.9 mg, 0.025 mmol), and NaO'Bu (144 mg, 1.50 mmol) were used. Reaction at 70 °C for 12 h gave 189 mg (84%) of 2-(2-methylphenyl)-1-phenyl-1-propanone after silica gel chromatography (hexane/EtOAc = 95/5). ¹H NMR (CDCl₃) δ 7.38 (d, *J* = 7.3 Hz, 2H), 7.46 (t, *J* = 7.3 Hz, 1H), 7.36 (t, *J* = 7.3 Hz, 2H), 7.21 (d, *J* = 7.3 Hz, 1H), 7.12 (t, *J* = 7.3 Hz, 1H), 7.09 (t, *J* = 7.3 Hz, 1H), 7.04 (t, *J* = 7.3 Hz, 1H), 4.77 (q, *J* = 6.8 Hz, 1H), 2.51 (s, 3H), 1.48 (d, *J* = 6.8 Hz, 3H); ¹³C{¹H} NMR (CDCl₃) δ 200.97, 140.19, 136.61, 134.57, 132.82, 132.69, 131.02, 128.52, 126.99, 126.90, 126.80, 44.61, 19.63, 18.06.

2-(2-Methylphenyl)-1-phenyl-1-ethanone:⁴⁸ 2-Chlorotoluene (127 mg, 1.00 mmol), acetophenone (132 mg, 1.10 mmol), Pd(dba)₂ (18.3 mg, 0.032 mmol), D'BPF (11.9 mg, 0.025 mmol), and NaO'Bu (144 mg, 1.50 mmol) were used. Reaction at 70 °C for 12 h gave 175 mg (83%) of 2-(2-methylphenyl)-1-phenyl-1-ethanone after recrystallization from *n*-hexane. ¹H NMR (CDCl₃) δ 8.04 (d, *J* = 7.3 Hz, 2H), 7.59 (t, *J* = 7.3 Hz, 1H), 7.50 (t, *J* = 7.3 Hz, 2H), 7.22–7.14 (m, 4H), 4.33 (s, 2H), 2.29 (s, 3H); ¹³C{¹H} NMR (CDCl₃) δ 197.51, 136.95, 133.57, 133.23, 130.42, 133.15, 130.37, 128.73, 128.39, 127.29, 126.18, 43.53, 19.86.

Reactions with Tri-*tert*-butylphosphine as Ligand. The reaction conditions and results are shown in Table 1. A typical procedure is given for the reaction in Entry 8.

1,2-Diphenyl-1-ethanone:⁴⁹ Pd(OAc)₂ (2.3 mg, 0.010 mmol), tri-*tert*-butylphosphine (2.1 mg, 0.010 mmol), and NaO'Bu (211 mg, 2.20 mmol) were suspended in 1 mL of THF in a screw-capped vial. The vial was sealed with a cap containing a PTFE septum and removed from the drybox. Bromobenzene (157 mg, 1.00 mmol) and acetophenone (132 mg, 1.10 mmol) were added to the reaction mixture by syringe. The reaction mixture was stirred at 25 °C and monitored by GC analysis. The crude reaction was diluted with ether and washed with 1 N HCl, water, and brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc = 95/5) to give 188 mg (96%) of 1,2-diphenyl-1-ethanone. ¹H NMR (CDCl₃) δ 8.02 (d, *J* = 7.1 Hz, 2H), 7.58–7.26 (m, 8H), 4.31 (s, 2H); ¹³C{¹H} NMR (CDCl₃) δ 197.52, 136.79, 134.67, 133.09, 129.54, 129.50, 128.64, 128.62, 126.88, 45.50.

2-(4-Benzoylphenyl)-1-phenyl-1-propanone: Pd(OAc)₂ (4.5 mg, 0.020 mmol), tri-*t*-butylphosphine (4.1 mg, 0.020 mmol), NaO'Bu (144 mg, 1.50 mmol), 4-bromobenzophenone (261 mg, 1.00 mmol), and propiophenone (148 mg, 1.10 mmol) were used. Reaction at 70 °C for 12 h gave 304 mg (97%) of 2-(4-benzoylphenyl)-1-phenyl-1-propanone after silica gel chromatography (hexane/EtOAc = 85/15). ¹H NMR (CDCl₃) δ 7.96 (d, *J* = 7.7 Hz, 2H), 7.76–7.75 (m, 4H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.52 (t, *J* = 7.1 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.43–7.40 (m, 4H), 4.79 (q, *J* = 6.9 Hz, 1H), 1.59 (d, *J* = 6.9 Hz, 3H); ¹³C{¹H} NMR (CDCl₃) δ 199.66, 196.14, 146.16, 137.51, 136.23, 133.10, 132.40, 130.82, 129.94, 129.80, 128.75, 128.63, 128.26, 127.79, 47.72, 19.37. MS *m/e* (rel intensity) 314 (10), 105 (100), 77 (38), 51 (13). Anal. Calcd for C₂₂H₁₈O₂: C, 84.05; H, 5.77. Found: C, 83.91; H, 5.88.

Reaction with 0.005 mol% catalyst: Pd(OAc)₂ (0.5 mg, 0.0023 mmol), tri-*tert*-butylphosphine (0.4 mg, 0.0020 mmol), and NaO'Bu (5.80 g, 60.3 mmol) were suspended in 5 mL of THF in a screw-capped test tube. Bromobenzene (6.28 g, 40.0 mmol) and propiophenone (5.90 g, 44.0 mmol) were added to the reaction mixture in the drybox. The

(44) Baradarani, M. M.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* 1980, 72–77.

(45) Morgan, J.; Pinhey, J. T.; Rowe, B. A. *J. Chem. Soc., Perkin Trans. 1* 1997, 1005–1008.

(46) Curtin, D. Y.; Pollak, P. I. *J. Am. Chem. Soc.* 1951, 73, 992–994.

(47) Wagner, P. J.; Zhou, B.; Hasegawa, T.; Ward, D. L. *J. Am. Chem. Soc.* 1991, 113, 9640–9654.

(48) Wagner, P. J.; Meador, M. A.; Zhou, B.; Park, B.-S. *J. Am. Chem. Soc.* 1991, 113, 9630–9639.

(49) Gurudutt, K. N.; Pasha, M. A.; Ravindranath, B.; Srinivas, P. *Tetrahedron* 1984, 40, 1629–1632.

reaction tube was sealed with a cap and the mixture was stirred for 24 h at 60 °C. The reaction was diluted with ether and washed with water and brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc = 95/5) to give 8.2 g (98%) of 1,2-diphenyl-1-propanone.

Reaction of propiophenone with *p*-tolyltosylate: Pd(OAc)₂ (9.0 mg, 0.040 mmol), ligand 2 (27.1 mg, 0.050 mmol), NaO^tBu (144 mg, 1.50 mmol), and 4-methylphenyl-*p*-toluene sulfonate (262 mg, 1.00 mmol) were suspended in 1 mL of dioxane in a screw-capped vial. The vial was sealed with a cap containing a PTFE septum and removed from the drybox. Propiophenone (132 mg, 1.10 mmol) was added to the reaction mixture by syringe. The reaction mixture was stirred at 100 °C and monitored by GC analysis. The crude reaction was diluted with ether and washed with 1 N HCl, water, and brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc = 95/5) to give 135 mg (60%) of 2-(4-methoxyphenyl)-1-phenyl-1-propanone.

Reactions with Tricyclohexylphosphine as ligand. The reaction conditions and results are shown in Table 1. A typical procedure is given for the reaction of Entry 17.

1,2-Diphenyl-1-propanone:⁴⁸ Pd(OAc)₂ (4.5 mg, 0.020 mmol), Tricyclohexylphosphine (5.6 mg, 0.020 mmol), and NaO^tBu (144 mg, 1.50 mmol) were suspended in 1 mL of THF in a screw-capped vial. The vial was sealed with a cap containing a PTFE septum and removed from the drybox. Chlorobenzene (113 mg, 1.00 mmol) and propiophenone (144 mg, 1.10 mmol) were added to the reaction mixture by syringe. The reaction mixture was stirred at 50 °C and monitored by GC analysis. The crude reaction was diluted with ether and washed with water and brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc = 95/5) to give 204 mg (97%) of 1,2-diphenyl-1-propanone²

Reaction of Malonates with Aryl Halides: Phenyl Di-*tert*-butylmalonate:⁵⁰ Pd(OAc)₂ (9.0 mg, 0.040 mmol), D'BPF (23.8 mg, 0.050 mmol), and NaO^tBu (288 mg, 3.00 mmol) were suspended in 2 mL of dioxane in a screw-capped vial. The vial was sealed with a cap containing a PTFE septum and removed from the drybox. Chlorobenzene (225 mg, 2.00 mmol) and di-*tert*-butyl malonate (480 mg, 2.20 mmol) were added to the reaction mixture by a syringe. The reaction was heated at 100 °C and monitored by GC analysis. The reaction mixture was diluted with ether and was washed with water and brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc = 80/20) to give 465 mg (80%) of phenyl di-*tert*-butylmalonate: ¹H NMR (CDCl₃) δ 7.40–7.33 (m, 5H), 4.44 (s, 1H), 1.47 (s, 18H); ¹³C{¹H} NMR (CDCl₃) δ 167.44, 133.51, 129.30, 128.38, 127.83, 81.92, 60.10, 27.87.

(50) Semmelhack, M. F.; Chorg, B. P.; Stauffer, R. D.; Rogerson, T. D.; Chong, A.; Jones, L. D. *J. Am. Chem. Soc.* **1975**, *97*, 2507–2516.

Phenyl diethylmalonate:⁵¹ Pd(OAc)₂ (4.5 mg, 0.020 mmol), P(^tBu)₃ (4.1 mg, 0.020 mmol), and NaO^tBu (100 mg, 1.04 mmol) were suspended in 2 mL of dioxane in a screw-capped vial. The vial was sealed with a cap containing a PTFE septum and removed from the drybox. Bromobenzene (157 mg, 1.00 mmol) and diethyl malonate (176 mg, 1.10 mmol) were added to the reaction mixture by syringe. The reaction was heated at 70 °C and monitored by GC analysis. The reaction mixture was diluted with ether and washed with water and brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc = 80/20) to give 205 mg (86%) of phenyl diethylbutylmalonate: ¹H NMR (CDCl₃) δ 7.42–7.33 (m, 5H), 4.62 (s, 1H), 4.23 (q, *J* = 7.3 Hz, 4H), 1.27 (t, *J* = 7.3 Hz, 6H); ¹³C{¹H} NMR (CDCl₃) δ 168.13, 132.84, 129.25, 128.56, 128.16, 61.75, 57.98, 13.98.

Generation of {Pd(DPPF)(*p*-Tol)[OC(=CMe₂)Ph]}. Into a vial was weighed 8.3 mg (0.01 mmol) of {Pd(DPPF)(*p*-Tol)(Br)},³¹ and into a second vial was weighed 2.6 mg (0.01 mmol) of KOC(=CMe₂)-Ph·THF. The palladium complex was suspended in 0.6 mL of benzene-*d*₆ and the suspension was added to the vial of enolate. The sample was transferred to an NMR sample tube and was shaken for 1–2 min until the palladium complex reacted with the enolate to make an orange solution with a white precipitate (KBr). The sample was then placed into the NMR probe and ¹H and ³¹P{¹H} NMR spectra were recorded at room temperature. ¹H NMR (C₆D₆) δ 8.39 (t, 8.0 Hz, 4H), 7.41 (t, 9 Hz, 4H), 7.2–7.0 (m, 11H), 6.89 (m, 4H), 6.80 (d, 6.6 Hz, 4H), 6.51 (m, 2H), 4.43 (s, 2H), 3.90 (s, 2H), 3.87 (s, 2H), 3.72 (s, 2H), 2.29 (s, 3H), 2.11 (s, 3H), 1.85 (s, 3H); ³¹P{¹H} (C₆D₆) δ 29.83, 10.37 (*J* = 34.2 Hz).

Generation of {Pd(D'BPF)(Ph)[OC(=CMe₂)Ph]}. Into a vial was weighed 7.4 mg (0.01 mmol) of {Pd(D'BPF)(Ph)(Br)},³² and into a second vial was weighed 2.6 mg (0.01 mmol) of KOC(=CMe₂)-Ph·THF. The palladium complex was suspended in 0.6 mL of benzene-*d*₆ and the suspension was added to the vial of enolate. The sample was transferred to an NMR sample tube and was shaken for 1–2 min until the palladium complex reacted with the enolate to make an orange solution with a white precipitate (KBr). The sample was then placed into the NMR probe and ¹H and ³¹P{¹H} NMR spectra were recorded at room temperature. ¹H NMR (toluene-*d*₈, 0 °C) δ 1.18 (d, 10.8 Hz, 18H), 1.23 (s, 3H), 1.24 (s, 3H), 1.32 (d, 14 Hz, 18H), 4.12 (s, 2H), 4.27 (s, 2H), 4.29 (s, 2H), 4.44 (m, 2H), 6.8–7.3 (m, 6H), 7.56 (d, 7.1 Hz, 2H), 7.86 (d, 6.8 Hz); ³¹P{¹H} NMR (C₆D₆) δ 24.8 (s), 57.2 (s).

Acknowledgment. We thank Boehringer Ingelheim for support of this work and Grace Mann for a sample of (D'BPF)-Pd(Ph)(Br). JFH is a recipient of a Camille Dreyfus Teacher Scholar Award and an NSF Young Investigator Award and is an Alfred P. Sloan Fellow.

JA983378U

(51) Robert, A.; Jagueline, S.; Guinamant, J. L. *Tetrahedron* **1986**, *42*, 2275–2282.

Pd-Catalyzed Intermolecular Amidation of Aryl Halides: The Discovery that Xantphos Can Be Trans-Chelating in a Palladium Complex

Jingjun Yin and Stephen L. Buchwald*

Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received November 29, 2001

Abstract: A general method for the intermolecular coupling of aryl halides and amides using a Xantphos/Pd catalyst is described. This system displays good functional group compatibility, and the desired C–N bond forming process proceeds in good to excellent yields with 1–4 mol % of the Pd catalyst. Additionally, the arylation of sulfonamides, oxazolidinones, and ureas is reported. The efficiency of these transformations was found to be highly dependent on reaction concentrations and catalyst loadings. A Pd complex resulting from oxidative addition of 4-bromobenzonitrile, (Xantphos)Pd(4-cyanophenyl)(Br) (II), was prepared in one step from Xantphos, Pd₂(dba)₃, and the aryl bromide. Complex II proved to be an active catalyst for the coupling between 4-bromobenzonitrile and benzamide. X-ray crystallographic analysis of II revealed a rare trans-chelating bisphosphine–Pd(II) structure with a large bite angle of 150.7°.

Introduction

Palladium-catalyzed C–N bond-forming reactions between aryl halides and amines have been extensively studied in the past few years.¹ These amination reactions can be carried out under mild conditions. Such processes enjoy excellent functional group tolerance and wide substrate scope. The analogous Pd-catalyzed C–N cross-coupling reactions with amides or sulfonamides, however, have been less generally successful.^{2–11} Although it has been well-known that aryl halides react with various amides under Ullmann-type conditions (the Goldberg reaction), stoichiometric amounts of copper salts, high temperatures (> 150 °C), and polar solvents such as DMF, collidine,

and pyridine are usually required.^{2,3} The substrate scope of these copper-mediated amidations has traditionally been quite limited as well. Recently, we described an improved copper-based system that is able to effect the coupling of aryl iodides and amides, as well as several nitrogen heterocycles, using 0.2–10 mol % of CuI.⁴

One of our initial forays into Pd-catalyzed C–N bond-forming reactions included the investigation of intramolecular couplings of aryl bromides and amides to form five- to seven-membered rings,^{5a} and subsequent work in our group has allowed for the extension of this chemistry to carbamate and sulfonamide substrates.^{5b} These transformations can be accomplished with P(*o*-Tol)₃, P(2-furyl)₃, BINAP, or other chelating phosphines as the ligand and K₂CO₃ or Cs₂CO₃ as the base.⁵

Other groups have reported Pd-catalyzed C–N bond-forming reactions involving amides and related nitrogen nucleophiles. For example, Shakespeare found that intermolecular reactions between lactams and aryl bromides could be effected with a DPPF-based catalyst system.⁶ Skerlj described the arylation of *tert*-butylcarbazate with a DPPF/Pd(OAc)₂ catalyst,⁷ and Arterburn recently extended this method to the reaction of halopyridines.⁸ In a related process, Hartwig has reported that aryl bromides and chlorides can be effectively coupled with *tert*-butyl carbamate by using P(*t*-Bu)₃ as ligand and sodium phenoxide as base.⁹ Using an electron-rich, hindered biaryl-based phosphine, Edmondson effected the intermolecular coupling between aryl halides and vinylogous amides.¹⁰ Additionally, Bolm and Harmata have reported the Pd-catalyzed *N*-arylation of sulfoximines,¹¹ while Beletskaya and co-workers have recently described the use of ureas as substrates in Pd-catalyzed C–N bond-forming processes.¹² Last year, we reported a reasonably general Pd-based catalyst for the inter-

* Corresponding author. E-mail: sbuchwal@mit.edu.

- (1) (a) Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2046–2067. (b) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575–5580. (c) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125–146. (d) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144–1157. (e) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158–1174 and references therein.
- (2) For a review on Cu-catalyzed cross-coupling reactions, see: Lindley, J. *Tetrahedron* **1984**, *40*, 1435–1456.
- (3) Examples of CuI-mediated intramolecular amidations under relatively mild conditions have been reported: Kametani, T.; Ohsawa, T.; Ihara, M. *Heterocycles* **1980**, *14*, 277–280.
- (4) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727–7729.
- (5) (a) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *21*, 7525–7546. (b) Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35–37.
- (6) Shakespeare, W. C. *Tetrahedron Lett.* **1999**, *40*, 2035–2038.
- (7) Wang, Z.; Skerlj, R. T.; Bridger, G. J. *Tetrahedron Lett.* **1999**, *40*, 3543–3546.
- (8) Arterburn, J. B.; Rao, K. V.; Ramdas, R.; Dible, B. R. *Org. Lett.* **2001**, *3*, 1351–1354.
- (9) Hartwig, J. F.; Kawatsura, M.; Hauck, S. L.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575–5580.
- (10) Edmondson, S. D.; Mastracchio, A.; Parmee, E. R. *Org. Lett.* **2000**, *2*, 1109–1112.
- (11) (a) Bolm, C.; Hildebrand, J. P. *Tetrahedron Lett.* **1998**, *39*, 5731–5734. (b) Harmata, M.; Pavri, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2419–2421. (c) Bolm, C.; Hildebrand, J. P.; Rudolph, J. *Synthesis* **2000**, 911–913. (d) Bolm, C.; Hildebrand, J. P. *J. Org. Chem.* **2000**, *65*, 169–175.

Table 1. Pd-Catalyzed Amidation of Activated and Unactivated Aryl Halides^a

Xantphos

Entry	ArX	Amide	Product	mol% Pd	T (°C)	t (h)	Yield (%)
1 (X=Br)				1	45	19	93 ^{a,b}
2 (X=I)				1	45	18	98 ^{a,b}
3				1	45	42	97 ^{a,b}
4				1	100	35	78 ^{a,d}
5				2	110	44	66 ^{a,d}
6				1	80	16	74 ^a
7				2	100	22	87 ^a
8 (X=OTf)				4	100	16	94 ^{d,e}
9 (X=I)				2.5	100	16	89 ^{d,e}
10 (X=Br)				2.5	100	16	91 ^{d,e}
11				1	100	16	99 ^a
12 (n=1)				1	100	16	93 ^d
13 (n=2)				1	100	16	96 ^d
14 (n=3)				1	100	32	92 ^d
15 (n=4)				1	100	22	90 ^d

^a Reaction conditions: 1.0 equiv of aryl halide/triflate, 1.1–1.2 equiv of amide/carbamate/sulfonamide, Xantphos/Pd(OAc)₂ = 1.5/1, 1.4–1.5 equiv of Cs₂CO₃, 1,4-dioxane ([halide/triflate] = 1 M). Yields refer to isolated yields (average of two runs) of compounds estimated to be >95% pure as determined by ¹H NMR and GC analysis or combustion analysis. ^b THF as solvent. ^c 1.2 equiv of aryl bromide and 1.0 equiv of sulfonamide were used. ^d Reaction conditions: 1.0 equiv of the aryl halide/triflate, 1.2 equiv of amide, Xantphos/Pd₂(dba)₃ = 3/1 (L/Pd = 1.5/1), 1 mol % Pd refers to 0.5 mol % Pd₂(dba)₃, 1.4 equiv of Cs₂CO₃, 1,4-dioxane ([halide/triflate] = 1 M); 100 °C. ^e [halide/triflate] = 2 M.

molecular coupling of aryl halides and amides.¹³ In this paper, we disclose in full the results of this investigation as well as the discovery of a surprising trans-chelating bis(phosphine) Pd(II) complex that was demonstrated to be a competent catalyst in the amide arylation reaction.

Results and Discussion

To establish the viability of the amide coupling process, we undertook an intensive screening of a variety of ligands and reaction variables. We found that a Pd catalyst using Xantphos, a ligand developed by van Leeuwen,¹⁴ with Cs₂CO₃ as the base and THF or 1,4-dioxane as the solvent provided the most generally successful catalyst for the coupling of amides with activated (electron deficient) as well as electronically neutral aryl halides.

During the study of various reaction variables, we found that Pd(OAc)₂ was the Pd source of choice in reactions involving

electron-deficient aryl halides. Representative results are summarized in Table 1 (entries 1–7). Activated aryl bromides, iodides, and triflates could be cleanly coupled. Electron-withdrawing groups such as nitriles (entries 1–3), esters (entries 4, 5, and 7), and nitro groups (entry 7) were well tolerated.

For electronically neutral and electron-rich aryl halides, the desired C–N bond formation was less straightforward. For example, under the conditions used for the successful reaction between 4-bromobenzonitrile and benzamide, the coupling between 4-*tert*-butylbromobenzene and benzamide afforded none of the desired product. Subsequent screening of reaction conditions revealed that by using Pd₂(dba)₃ as the palladium

(12) Artamkina, G. A.; Sergeev, A. G.; Beletskaya, I. P. *Tetrahedron Lett.* **2001**, *42*, 4381–4384.

(13) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101–1104.

(14) (a) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **1995**, *14*, 3081–3089. Previous uses of Xantphos in C–N bond-forming reactions: (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*, 3789–3790. (c) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251–10263. (d) Harris, M. C.; Geis, O.; Buchwald, S. L. *J. Org. Chem.* **1999**, *64*, 6019–6022. For a kinetic study of Xantphos/Pd-catalyzed amine arylation reactions, see: (e) Guari, Y.; van Strijdonck, G. P. F.; Boele, M. D. K.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Chem. Eur. J.* **2001**, *7*, 475–482.

source and Xantphos as the ligand, the amidation of unactivated aryl halides could be efficiently carried out (entries 8–15). Electronically neutral or slightly electron-rich aryl halides or triflates reacted efficiently with both aromatic and aliphatic primary amides, *N*-methylformamide (entries 12), and lactams (entries 12–15) at 100 °C. It is worth mentioning that couplings between bromobenzene and four- to seven-membered-ring lactams could generally be realized with as little as 1 mol % of Pd at 100 °C. Notably, under these basic conditions, none of the product resulting from ring opening was observed.

When less reactive aryl halides were used, small amounts (2–8%) of *N*-phenylated amides were detected as the byproducts in crude reaction mixtures (GC and GC-MS analysis); removal of these side products was straightforward with flash chromatography. Increasing the Xantphos:Pd ratio usually resulted in increased amounts of the *N*-phenylamide. These byproducts are likely formed via exchange between the aryl group bound to Pd(II) and the phenyl group of the phosphine ligand;¹⁵ Hartwig and co-workers have observed similar aryl group exchange processes in Pd-catalyzed aminations.^{15a}

During the course of these studies, we found an unusual dependence of catalyst loading on the reaction efficiency. For example, using 5 mol % of Pd (as Pd₂dba₃)/7.5 mol % of Xantphos in the coupling of 4-*tert*-butylbromobenzene and benzamide, a product:ArBr ratio of 1:5 was obtained as compared to 1.1:1 with 2 mol % of Pd, implicating the possibility of an unknown catalyst decomposition pathway occurring at higher catalyst concentrations. Notably, higher amounts of *N*-phenylated side products were observed at higher catalyst loadings as well (~1 M in ArBr).

At this point in our investigations, the amidations of activated aryl halides were fairly general, but the scope of the amidation involving unactivated aryl halides was still limited. For example, acyclic secondary amides as well as sulfonamides were unreactive, and sterically hindered or electron-rich unactivated aryl halides were not viable substrates under the optimized conditions shown above. Additionally, aryl group exchange became more problematic in these challenging couplings, and increasing amounts of the phenylated byproduct was observed. Generally, higher catalyst loadings may be used to accelerate a reaction; however, for these amidation processes, additional catalyst often led to an increase in aryl group exchange product and faster decomposition of the catalyst. Unfortunately, replacement of the phenyl groups on Xantphos with *o*-tolyl groups to suppress aryl group exchange yielded an inefficient amidation catalyst. A detailed examination of the reaction parameters led to the discovery that careful control of catalyst loading and the reaction concentration was key to the successful amidation of less reactive substrates.

A substrate concentration of 1 M was suitable for most cases reported in Table 1; however, lower concentrations (0.125 to 0.5 M) and higher palladium catalyst loadings were required for these more challenging reactions to proceed efficiently. Lower concentrations may decrease the rate of catalyst decomposition, particularly when more catalyst was used.

With a better understanding of the reaction variables important to the success of these couplings, we sought to extend the

methodology to more challenging substrate combinations (Table 2). Thus, with 4 mol % of Pd and a concentration of 0.5 M, 2-bromotoluene reacted with benzamide in 98% yield (entry 1). The lactam 2-pyrrolidinone was also coupled with sterically hindered 2-bromo-*p*-xylene at 0.25 M (88% yield, entry 2). Electron-rich aryl halides such as 2-bromoanisole and 2-iodoanisole both underwent amidations in good yields (entries 3 and 4). Previously extremely inactive amides such as *N*-methylacetamide (an acyclic secondary amide), as well as a primary or secondary sulfonamide, also reacted with unactivated aryl bromides under these more controlled conditions (entries 5–7). It is interesting to note that although dioxane has been the solvent of choice for most amidations, toluene proved to be the preferred solvent for the coupling of the secondary sulfonamide *N*-methyl *p*-tolylsulfonamide (entry 6).

We also examined the C–N bond-forming reactions using other amide analogues such as cyclic carbamates^{7–9} and ureas.¹² With K₃PO₄ as base, 2-oxazolidone reacted with 4-chlorobromobenzene in 87% yield (entry 8). Both five- and six-membered cyclic ureas were doubly arylated with 3-bromoanisole with as little as 1 mol % of the palladium catalyst (entries 9 and 10). In the latter two cases, increasing the loading of the palladium catalyst and Xantphos ligand resulted in an increase of the aryl group exchange byproducts.

The Pd-catalyzed amidations of aryl halides described above have shown very good substrate scope and functional group compatibility. Aryl halides bearing electron-withdrawing groups at ortho, meta, or para positions underwent C–N bond formation reactions generally with primary and secondary amides, carbamate, and sulfonamides. Unactivated or deactivated aryl halides also coupled with various amides under more carefully controlled conditions. However, a few classes of substrate combinations still remain challenging for this Pd–catalyst system. Amidations of aryl halides bearing a ketone functional group suffered from a competitive ketone arylation processes. Additionally, amidation reactions involving aryl halides that possess a para-electron-donating group or acyclic secondary amides were usually sluggish and yielded large amounts (>20%) of aryl group exchange products (*N*-phenyl amides).

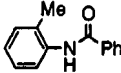
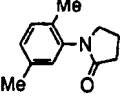
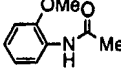
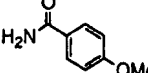
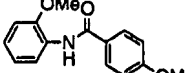
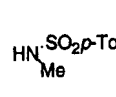
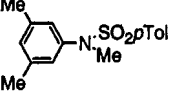
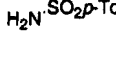
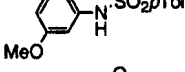
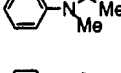
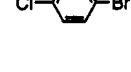
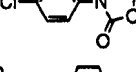
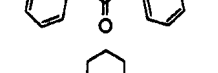
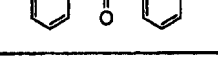
The fact that only Xantphos worked efficiently for amidation reactions prompted us to study the mechanism of the reaction in greater detail. To this end, we first tried to isolate the oxidative addition product from 4-bromobenzonitrile, Pd₂(dba)₃, and Xantphos. (Bisphosphine)Pd(Ar)X complexes have been prepared from their monophosphine complex dimers [(P(*o*-Tol))₃Pd(Ar)X]₂¹⁶ (I) or [(PPh₃)Pd(Ar)X]₂.¹⁷ Following a procedure used to prepare (BINAP)Pd(4-cyanophenyl)(Br) in our laboratories,¹⁶ complex I underwent ligand exchange when treated with Xantphos in methylene chloride at room temperature to afford the corresponding Xantphos complex, (Xantphos)Pd(4-cyanophenyl)(Br) (II), which is air-stable and can be stored in a vial on the bench for over a year without noticeable decomposition, as judged by NMR (Scheme 1). We subsequently found that complex II could be prepared in 80% yield by simply stirring 4-bromobenzonitrile, Pd₂(dba)₃, and Xantphos in benzene at room temperature for 22 h. To our surprise, complex II showed only one singlet in ³¹P NMR at +9.3 ppm, compared to a pair

(15) (a) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* 1998, 120, 3694–3703. For a mechanistic study, see: (b) Goodson, F. E.; Wallow, T. I.; Novak, B. M. *J. Am. Chem. Soc.* 1997, 119, 12441–12453.

(16) (a) Widenhoefer, R. A.; Zhong, H. A.; Buchwald, S. L. *J. Am. Chem. Soc.* 1997, 119, 6787–6795. (b) Widenhoefer, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* 1998, 120, 6504–6511.

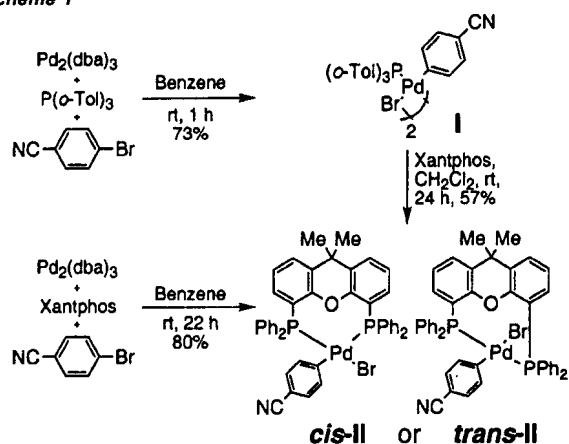
(17) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* 1997, 119, 8232–8245.

Table 2. Pd-Catalyzed Amidation of Less Reactive Substrates^a

Entry	Halide	Amide	Product	mol% Pd	conc (M)	t (h)	Yield (%)
1				4	0.5	15	98
2				4	0.25	15	88
3				2	0.5	15	97
4				4	0.25	46	72 ^b
5				1	0.125	38	82 ^{c,d}
6				4	0.25	47	56 ^e
7				4	0.25	37	73
8				2	0.125	16	87 ^f
9				1	0.25	44	92 ^g
10				1	0.5	44	97 ^g

^a Reaction conditions: 1.0 equiv of the aryl halide/triflate, 1.2 equiv of amide, Xantphos/Pd₂(dba)₃ = 3/1 (L/Pd = 1.5/1), 1 mol % of Pd refers to 0.5 mol % of Pd₂(dba)₃, 1.4 equiv of Cs₂CO₃, 1,4-dioxane, 100 °C. Yields refer to isolated yields (average of two runs) of compounds estimated to be >95% pure as determined by ¹H NMR, and GC analysis or combustion analysis. ^b 95% conversion. ^c Run in toluene at 120 °C. ^d 0.5 mmol of sulfonamide and 0.6 mmol of bromide were used. ^e Run at 120 °C. ^f K₃PO₄ as base. ^g 0.5 mmol of urea, 1.4 mmol of bromide, and 1.4 mmol of Cs₂CO₃ were used.

Scheme 1



of doublets ($J = 38.4$ Hz) at +27.9 and +12.9 ppm of the (BINAP)Pd(4-cyanophenyl)(Br), which has a normal cis-chelating structure. The corresponding iodide complex, (Xantphos)-Pd(4-cyanophenyl)I, was prepared in a similar fashion and also displayed one singlet at +9.9 ppm by ³¹P NMR. These data

suggested the possibility of a trans-chelating structure (*trans*-II). Van Leeuwen has previously reported a cis-chelating Xantphos-Pd(0) tetracyanoethylene complex as well as a *cis*-Xantphos-Pd(II) allyl complex,^{18,19} and after the completion of our work, he very recently has reported a trans-chelated Xantphos-Pd(Me)Cl complex, which was characterized crystallographically.²⁰

The unambiguous assignment of the structure of complex II was possible through X-ray crystallography. As shown in Figure 1, the complex features a rare trans-chelating structure.^{20,21} The aryl group (4-cyanophenyl) and the bromide are trans to each

- (18) 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**, 1839–1849.
- (19) van Haaren, R. J.; Goubitz, K.; Fraanje, F.; van Strijdonck, G. P. F.; Oevering, H.; Coussens, B.; Reek, J. N. H.; van Leeuwen, P. W. N. M. *Inorg. Chem.* **2001**, *40*, 3363–3372.
- (20) Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Acc. Chem. Res.* **2001**, *34*, 895–904.
- (21) *trans*-Pd complexes have been observed with Transphos and long-chain bisphosphines: (a) Bachechi, F.; Zambonelli, L.; Venanzi, L. M. *Helv. Chim. Acta* **1977**, *60*, 2815–2823. (b) March, F. C.; Mason, R.; Thomas, K. M.; Shaw, B. L. *Chem. Commun.* **1975**, 584. (c) Alcock, N. W.; Brown, J. M.; Jeffery, J. C. *Chem. Commun.* **1974**, 829.

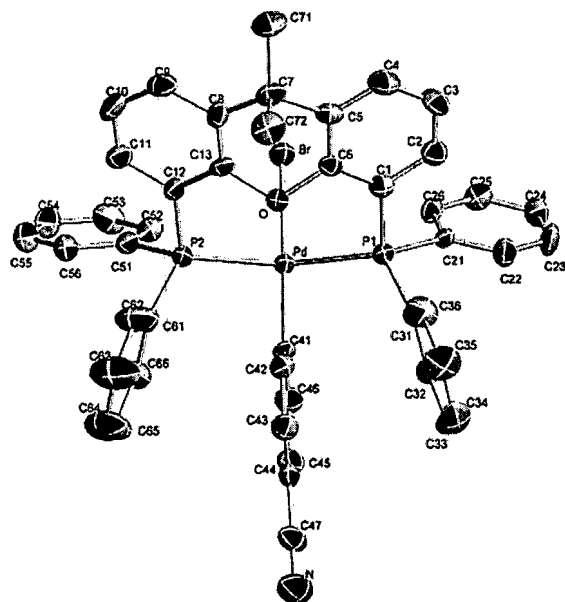


Figure 1. ORTEP structure of II.

other, with a C–Pd–Br angle of 176.4° in the distorted square-planar Pd complex. The two phosphorus atoms are trans to each other with a bite angle²² (P–Pd–P) of 150.7° , much larger than 104.6° observed by van Leeuwen in the *cis*-(Xantphos)Pd-(TCNE) complex and closer to the 153° bite angle measured in the *trans*-(Xantphos)Pd(Me)Cl crystal structure.²³ Notably, the observed angle is also beyond the calculated flexible bite angle range of Xantphos (97 – 135°) and much larger than the bite angles (72 – 131°) of most commonly used bidentate phosphine ligands. This unusually large bite angle might be a result of the weak interaction of the oxygen atom with the Pd (Pd–O distance = $2.697 \text{ \AA}$).^{23,24} Although the Pd–P bond lengths of complex II (2.304 and $2.311 \text{ \AA}$) are even slightly shorter than those seen in the (Xantphos)Pd(TCNE) (A) (2.356 and $2.352 \text{ \AA}$), the P1–P2 bond length of complex II is much longer ($4.466 \text{ \AA}$ compared to $3.726 \text{ \AA}$ of A and $4.080 \text{ \AA}$ of free Xantphos²⁵) due to the large bite angle.

Complex II proved to be a competent precatalyst for the amidation of 4-bromobenzonitrile with benzamide that was comparable to the in situ generated $\text{Pd}_2(\text{dba})_3$ /Xantphos complex. With $1 \text{ mol } \%$ of complex II, the reaction between 4-bromobenzonitrile and benzamide went to completion in 23 h at 45°C to provide the desired product in 96% yield. The *trans*-chelating structure of complex II raises the question of how the reductive elimination occurs from such a *trans*-Pd complex.²⁶

Presumably, dissociation of one of the coordinating phosphine groups with reductive elimination from a three-coordinate intermediate²⁷ or isomerization to the *cis* isomer followed by reductive elimination takes place.^{26b} Unfortunately, attempts to prepare the analogous Pd(II) amide complex, the proposed intermediate formed prior to reductive elimination, have been unsuccessful.

Conclusions

The first general intermolecular cross-coupling between aryl halides or triflates and amides, sulfonamides, and carbamates has been developed by using a Xantphos/Pd catalyst, Cs_2CO_3 as the base, and dioxane (or THF) as the solvent. This amidation protocol enjoys a reasonably broad substrate scope and good functional group compatibility. Activated aryl halides that bear electron-withdrawing groups at ortho, meta, or para positions efficiently underwent C–N bond formation with primary and secondary amides, as well as carbamates and sulfonamides. Unactivated or deactivated aryl halides also reacted with various amides under more carefully controlled conditions to prevent unwanted side reactions such as aryl exchange with the phosphine or catalyst deactivation. During our studies, we prepared a rare *trans*-chelating palladium(II) complex, (Xantphos)-Pd(4-cyanophenyl)(Br) (II), which was readily prepared from Xantphos, $\text{Pd}_2(\text{dba})_3$, and 4-bromobenzonitrile. Complex II proved to be an effective catalyst for the coupling of 4-bromobenzonitrile and benzamide whose activity was comparable to the catalyst generated in situ from $\text{Pd}_2(\text{dba})_3$ and the ligand.

Experimental Section

General Procedure for Pd-Catalyzed Couplings of Aryl Halides or Triflates and Amides, Carbamates, or Sulfonamides (Tables 1 and 2). The reactions in Table 1 were performed on a 1.0 mmol scale unless mentioned otherwise, and those in Table 2 were all performed on a 0.5 mmol scale. A flame-dried resealable Schlenk tube was charged with $\text{Pd}(\text{OAc})_2$ or $\text{Pd}_2(\text{dba})_3$ (NOTE: $0.5 \text{ mol } \%$ $\text{Pd}_2(\text{dba})_3$ refers to $1 \text{ mol } \%$ of Pd) as indicated in the tables, Xantphos ($\text{L}/\text{Pd} = 1.5$), the solid reactant(s) (1.0 equiv of the aryl halide/triflate and 1.2 equiv of the amide, carbamate, or sulfonamide), and Cs_2CO_3 (1.4 equiv). The Schlenk tube was capped with a rubber septum, evacuated, and backfilled with argon twice. The liquid reactant(s) and anhydrous 1,4-dioxane ($1 \text{ mL}/\text{mmol}$ aryl halide or triflate or according to the concentration indicated in the table) were then added by syringe through the septum. The septum was replaced with a Teflon screwcap. The Schlenk tube was sealed, and the mixture was stirred at the indicated temperature (45 – 120°C) for the times indicated in the table (6 – 46 h) until the starting aryl halide or triflate had been completely consumed as judged by GC analysis. The reaction mixture was then allowed to cool to room temperature, diluted with dichloromethane (10 mL), filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel.

Synthesis of the Oxidative Addition Pd Complex II. A solution of Xantphos (128 mg , 0.22 mmol , 1.1 equiv), $\text{Pd}_2(\text{dba})_3$ (92 mg , 0.10 mmol , 0.20 mmol Pd, 1.0 equiv), and 4-bromobenzonitrile (168 mg , 0.92 mmol , 4.6 equiv) in benzene (6 mL) was stirred at room temperature for 22 h . The mixture was then filtered through a pad of Celite and concentrated in vacuo. Ether (6 mL) was then added to the residue and yellow crystalline solid was allowed to form upon standing for 1 h . The solid was then filtered, washed with ether, and dried under vacuum to give 140 mg (80%) of complex II: mp $>195^\circ\text{C}$ dec; ^1H NMR (300 MHz , CDCl_3) δ 7.64 (dd, $J = 6.8, 2.4 \text{ Hz}$, 2 H), 7.29 –

- (22) (a) Dierkes, P.; van Leeuwen, P. W. N. M. *J. Chem. Soc., Dalton Trans.* **1999**, 1519–1529. For an excellent review on ligand bite angle effects, see: (b) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741–2769.
(23) A weak interaction of a third atom with Pd could lead to large bite angles. See (a) ref 18. Complex $[(\text{DPPF})\text{Pd}(\text{PPh}_3)](\text{BF}_4)_2$ also shows a big bite angle of 155.9° with an Fe–Pd bond: (b) Sato, M.; Shigeta, H.; Sekino, M. *J. Organomet. Chem.* **1993**, *458*, 199–204.
(24) Pd–O distances observed in a few Pd complexes range from 2.02 to $2.14 \text{ \AA}$. See: (a) Alsters, P. L.; Boersma, J.; Smeets, W. J. J.; Spek, A. V.; van Koten, G. *Organometallics* **1993**, *12*, 1639–1647. (b) Alsters, P. L.; Baesjou, P. J.; Janssen, M. D.; Kooijman, H.; Sicherer-Roertman, A.; Spek, A. V.; van Koten, G. *Organometallics* **1992**, *11*, 4124–4135.
(25) The distance was reported to be $4.045 \text{ \AA}$ by Haenel. See: Hillebrand, S.; Bruckmann, J.; Krüger, C.; Haenel, M. W. *Tetrahedron Lett.* **1995**, *36*, 75–78.
(26) For discussions of reductive elimination from Pd, see: (a) Gillie, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4933–4941 (b) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852–860.

- (27) This is consistent with our work involving bulky, electron-rich ligands which are believed to yield L–Pd complexes after their reaction.

Table 3. Selected Bond Lengths (Å) and Angles (deg) for Complex II

Pd–P(1)	2.3114(16)	Pd–P(2)	2.3042(16)
Pd–Br	2.5324(19)	Pd–C(41)	1.996(5)
C(41)–Pd–P(2)	90.35(16)	C(41)–Pd–P(1)	89.64(16)
P(2)–Pd–P(1)	150.70(6)	C(41)–Pd–Br	176.44(17)
P(2)–Pd–Br	89.62(4)	P(1)–Pd–Br	92.12(4)
C(1)–P(1)–Pd	104.11(19)	C(12)–P(2)–Pd	104.78(19)

6.75 (m, 36 H), 6.33 (br s, 2 H), 1.81 (br s, 6 H); ^{13}C NMR (75 MHz, CDCl_3) δ 170.2, 155.5, 155.4, 155.3, 134.92, 134.89, 134.86, 131.88, 131.1, 130.81, 130.5, 130.1, 128.5, 128.1, 127.5, 124.62, 124.58, 121.7, 121.4, 121.1, 120.5, 103.8, 36.42, 36.40, 36.37 (observed complexity due to P–C splitting); ^{31}P NMR (121 MHz, C_6D_6) δ +9.3; IR (neat, cm^{-1}) 3053, 2971, 2218, 1571, 1434, 1399, 1211, 745, 695. Anal. Calcd for $\text{C}_{46}\text{H}_{36}\text{BrNOPd}$: C, 63.85; H, 4.18. Found: C, 63.67; H, 4.12.

Amidation with Complex II as the Catalyst. A flame-dried Schlenk tube was charged with complex II (4.3 mg, 0.005 mmol, 1%), 4-bromobenzonitrile (91 mg, 0.50 mmol, 1.0 equiv), benzamide (67 mg, 0.55 mmol, 1.1 equiv), and Cs_2CO_3 (245 mg, 1.5 mmol, 1.5 equiv),

evacuated, and backfilled with argon. THF (0.5 mL) was then added through syringe. The Schlenk tube was sealed and heated at 45 °C for 23 h when GC analysis revealed complete conversion of the aryl bromide. The mixture was then diluted with methylene chloride (10 mL), filtered, concentrated, and purified by flash column chromatography (silica gel) to give 108 mg (97%) (second run gave 105 mg, 95%) of *N*-(4-cyanophenyl)benzamide as a white solid.

Acknowledgment. We thank NIH (GM58160) for support of this work. We are also grateful to Pfizer and Merck for additional unrestricted support. We thank Dr. William M. Davis (MIT) for the X-ray crystal structure of complex II, and Dr. Alexander Muci for assistance in preparing this manuscript.

Supporting Information Available: Characterization data for all new products and details of the X-ray structure of complex II (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA012610K

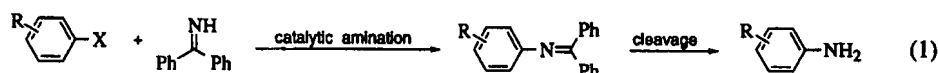
An Ammonia Equivalent for the Palladium-Catalyzed Amination of Aryl Halides and Triflates

John P. Wolfe, Jens Åhman,[§] Joseph P. Sadighi, Robert A. Singer and Stephen L. Buchwald*

Department of Chemistry,
 Massachusetts Institute of Technology,
 Cambridge, MA 02139

Abstract. Commercially available benzophenone imine serves as a convenient ammonia equivalent in the palladium-catalyzed amination of aryl halides and triflates. The benzophenone imine adducts can be cleaved directly to the corresponding primary anilines by catalytic hydrogenation or treatment with hydroxylamine hydrochloride or a catalytic amount of HCl in wet THF. © 1997 Elsevier Science Ltd.

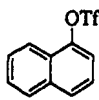
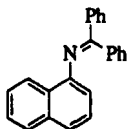
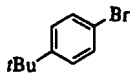
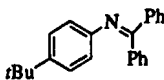
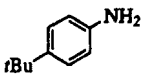
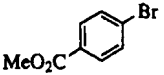
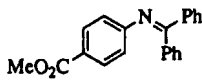
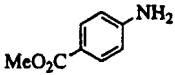
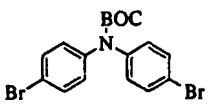
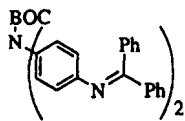
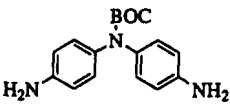
A number of useful protocols for the palladium- and nickel-catalyzed conversion of aryl bromides,^{1a, b} chlorides,^{1c} iodides^{1d} and triflates^{1e, f} to the corresponding aniline derivatives have been recently reported. While these procedures are effective for the preparation of substituted anilines, no simple means for the preparation of the unsubstituted primary anilines has been described. We now have found that commercially available benzophenone imine serves as a convenient surrogate for ammonia in these coupling procedures (Eq 1). The benzophenone imines formed can be isolated in pure form or can be converted under a variety of conditions to the corresponding anilines in a straightforward manner.²



During the course of our work on the synthesis of oligoaniline derivatives for study as conducting and sensor materials we had reason to employ a protecting group for a primary aniline. We found that benzophenone imines served this role in a convenient manner; they were easily formed,³ stable to base and mild acid, and cleaved under a variety of conditions. It occurred to us that the protected anilines might be directly accessible using our previously reported methods for the amination of aryl halides and triflates.

In general, we found that the coupling reactions with benzophenone imine were efficient. Shown in Table 1, are four examples of substrates which were converted to benzophenone imines.⁴ The diphenyl ketimine moiety instilled or enhanced crystallinity in the products which allowed for facile purification by recrystallization from MeOH. Subsequent cleavage to the primary aniline was effected by acidic hydrolysis, hydrogenolysis, or

Table 1: Palladium-Catalyzed Amination of Aryl Bromides and Triflates

Entry	Substrate	Product	Yield (%)	Cleavage Conditions	Product	Yield (%) ^e
1			85% ^{a, ref. 5}	cat. HCl wet THF rt		98%
2			90% ^b	NH ₄ ⁺ HCO ₂ ⁻ cat Pd/C MeOH/60° C		84%
3			75% ^c	NH ₂ OH·HCl NaOAc MeOH/rt		88%
4			91% ^d	NH ₄ ⁺ HCO ₂ ⁻ cat Pd/C MeOH/60° C		95%

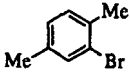
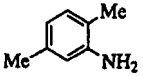
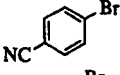
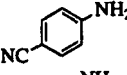
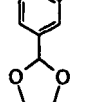
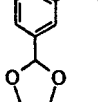
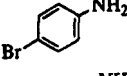
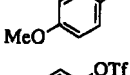
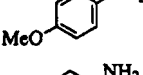
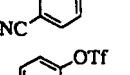
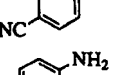
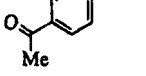
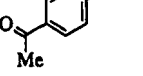
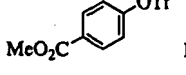
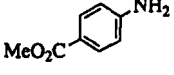
(a) 1 mol% Pd(OAc)₂, 1.5 mol% BINAP, 1.4 eq Cs₂CO₃, THF, 65 °C, 16 h. (b) 0.25 mol% Pd₂(dba)₃, 0.75 mol% BINAP, 1.4 eq NaOtBu, toluene, 80 °C, 13 h. (c) 2 mol% Pd(OAc)₂, 3 mol% BINAP, 1.4 eq Cs₂CO₃, toluene, 100 °C, 5 h. (d) 0.25 mol% Pd₂(dba)₃, 0.75 mol% BINAP, 1.4 eq NaOtBu, toluene, 80 °C, 6 h. (e) Isolated yields reported are an average of two runs.

transamination with hydroxylamine.⁶ In many cases it may be advantageous to retain the imine moiety after coupling for use as a protecting group of the primary aniline because of its robust nature⁷ and facile removal.²

Catalytic amination was carried out on additional substrates using benzophenone imine as shown in Table 2. The yields reported correspond to isolation of the primary aniline for the two step sequence of amination and imine cleavage. The methodology is effective with aryl chlorides, bromides, iodides and triflates. Couplings involving aryl triflates employed Cs₂CO₃ in place of NaOtBu to avoid hydrolysis of the triflate.^{1e, 8} Benzophenone imine serves as an ideal coupling partner since it is relatively unhindered, the nitrogen is sp² hybridized,⁸ and can not undergo palladium-catalyzed β-hydride elimination. Due to the variety of methods available for imine cleavage, conditions were found for selective diphenyl ketimine removal in products containing a benzylic acetal (entry 4), a methyl ester (entries 8 and 10), or a benzylic ketone (entry 9).

In summary, we have demonstrated the utility of employing benzophenone imine as a substitute for ammonia in the palladium-catalyzed amination of aryl halides and triflates. The couplings and subsequent deprotections proceed in uniformly high yields. When it is desirable to retain the imine as a means of masking the primary amine, the diphenyl ketimine adducts may be isolated as crystalline solids or purified by chromatography on silica gel in high yield.

Table 2: Palladium-Catalyzed Amination and Subsequent Imine Cleavage

Entry	Substrate	Product	Time	Cleavage ^{ref. 6}	Yield (%) ^a
1			5 h ^a	B	87
2			19 h ^a	B	77
3			1.5 h ^a	A	97
4			1.5 h ^a	A	89
5			48 h ^b	C	91
6			14 h ^b	A	88
7			4.5 h ^c	A	84
8			20 h ^c	A	80
9			4 h ^c	C	83
10			5 h ^c	A	89
11			16 h ^d	A	81

(a) 0.25 mol% Pd₂(dba)₃, 0.75 mol% BINAP, 1.4 eq NaOtBu, toluene, 80 °C. (b) 1.0 mol% Pd₂(dba)₃, 3.0 mol% BINAP, 1.4 eq NaOtBu, 1.4 eq 18-Crown-6, THF, rt. (c) 3 mol% Pd(OAc)₂, 4.5 mol% BINAP, 1.4 eq Cs₂CO₃, THF, 65 °C. (d) 5 mol% Ni(COD)₂, 10 mol% DPPF, 1.4 eq NaOtBu, toluene, 100 °C.^{ref. 1f} (e) Isolated yields reported are an average of two runs. All compounds were characterized by NMR (¹H, ¹³C), and IR. All aniline products are commercially available except for entry 4 in Table 1 and entry 4 in Table 2.^{ref. 9} Combustion analyses were obtained for all imine and aniline products which were not commercially available.

Acknowledgments. We thank the National Science Foundation, the Office of Naval Research, Pfizer, Kodak and the Wallenberg Foundation for support of this research.

References and Footnotes

§ Wallenberg Foundation Postdoctoral Fellow

- (1) (a) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215. (b) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217. (c) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.*, in press. (d) Wolfe, J. P.; Buchwald, S. L. Manuscript submitted. (e) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1264 and references cited therein. (f) Louie, J.; Driver, M. S.; Hamann, B.C.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 1268 and references cited therein. (g) Åhman, J.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, accompanying paper in this issue.
- (2) (a) Wessjohann, L.; McGaffin, G.; de Meijere, A. *Synthesis*, **1989**, 359. (b) Fasth, K.-J.; Antoni, G.; Långström, B. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3081. (c) O'Donnell, M. J.; Boniece, J. M.; Earp, S. E. *Tetrahedron Lett.* **1978**, 2641.
- (3) Taguchi, K.; Westheimer, F. H. *J. Org. Chem.* **1971**, *36*, 1570.
- (4) Representative Procedure: An oven-dried Schlenk tube was charged with Pd₂(dba)₃ (0.00125 mmol) and BINAP (0.00375 mmol), and purged with argon. To the flask was added 4-*t*-butylbromobenzene (1.00 mmol), benzophenone imine (1.20 mmol), NaOtBu (1.40 mmol) and toluene (4 mL), and the mixture was heated to 80 °C with stirring until the starting material had been consumed as judged by GC analysis. The mixture was cooled to room temperature, diluted with ether (10 x volume of toluene), filtered, and concentrated. The crude product was then recrystallized from MeOH. Yellow crystals of the diphenyl ketimine adduct were isolated in 90% yield.
- (5) The imine product has been previously prepared: Seno, M.; Shirashi, S.; Suzuki, Y.; Asahara, T. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1413. It was found that DBU could be used in place of Cs₂CO₃ to carry out the Pd-catalyzed (3 mol%) coupling of α -naphthyltriflate and benzophenone imine in 82% yield at 110 °C in toluene (24 h). Utilizing DBU as a base has not been found to be general in scope.
- (6) General Procedures for Imine Cleavage:

Method A (Transamination with Hydroxylamine) To a solution of the imine adduct in MeOH (0.1 M) at rt was added NaOAc (2.4 eq) and hydroxylamine hydrochloride (1.8 eq). Oxime formation was usually complete in 15 to 30 minutes. The solution was then partitioned between 0.1 M NaOH and CH₂Cl₂. The organic layer was dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The product was purified by chromatography on silica gel.

Method B (Hydrogenolysis) A solution of the imine adduct, ammonium formate (15 eq) and 5% Pd/C (10 mol%) were heated to 60 °C in MeOH (0.2 M in imine). After 2 h reduction was usually complete. The solution was cooled to rt and diluted with CH₂Cl₂ (5 x volume MeOH) to be passed through a plug of celite. The organic solution was washed with 0.1 M NaOH, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The product was purified by chromatography on silica gel.

Method C (Acidic Hydrolysis) To a solution of the imine adduct in THF (0.3 M) was added aqueous 2.0 M HCl (added 5% by volume of THF). After 5-20 minutes hydrolysis was complete and the reaction mixture was partitioned between 0.5 M HCl and 2:1 hexane/EtOAc. The aqueous layer was separated and made alkaline. The product aniline was extracted with CH₂Cl₂, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*.
- (7) The imine adducts are stable to purification by chromatography on silica gel. As a further demonstration of the stability of the diphenyl ketimine, we have found that it was possible to carry out halogen metal exchange (*n*-BuLi, THF, -78 °C) on the benzophenone imine protected 4-bromoaniline without substantial (<5 %) addition to the imine.
- (8) Reductive elimination from palladium should be more facile (electronically) for an imine than an amine.
- (9) Manecke, G.; Vogt, H. G. *J. Solid-Phase Biochem.* **1979**, *4*, 233.

(Received in USA 27 May 1997; accepted 8 July 1997)

Palladium-Catalyzed Monoarylation of Nitroalkanes

Erasmus M. Vogl[†] and Stephen L. Buchwald*Expt. 08-106.947
vii)

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

sbuchwal@mit.edu

Received September 26, 2001

A general protocol for the Pd-catalyzed-arylation of nitroalkanes is described. Substituted aryl bromides as well as aryl chlorides can be coupled efficiently with a variety of nitroalkanes under mild conditions to selectively yield the monoarylated products. This method tolerates a number of functional groups including ketones, esters, and olefins. Notably, the arylation of nitroalkanes can be effected chemoselectively over ketone and ester arylation.

Introduction

Several procedures for the Pd-catalyzed α -arylation of ketones with a variety of aryl bromides, chlorides, and triflates have recently been reported.¹ These methods have also been extended to other carbonyl substrates including esters and amides.² Additionally, we have reported that catalysts based on 2-di-*tert*-butylphosphino-2'-methylbiphenyl (**1**) and Pd(OAc)₂ were particularly efficient in the arylation of malonate esters, 1,3-diketones, and in isolated cases, nitroalkanes.^{1e} Herein, we report in full the protocol for the arylation of nitroalkanes.³ This method allows for the selective monoarylation of nitroalkanes under mild conditions that tolerate several functional groups including ethers, esters, ketones, and olefins. Additionally, the arylation of nitroalkanes can be performed chemoselectively in the presence of enolizable esters and ketones.⁴

Results and Discussion

Our initial studies were performed using bromobenzene or 4-chlorotoluene and nitroethane as coupling partners. After screening a variety of reaction conditions, we found that Cs₂CO₃ was effective as base, although K₃PO₄ was sometimes suitable. Stronger bases such as metal alkoxides were not as effective. It was readily apparent that catalysts based on di-*tert*-butyl-substituted phosphine ligands yielded significant amounts of products while the dicyclohexyl- or diphenyl-substituted ligands did not promote nitroalkane arylation at all. Of

the biaryl ligands screened, **1** proved most effective, although commercially available 2-di-*tert*-butylphosphino-biphenyl generally gave satisfactory yields.⁵ In addition, we found that catalysts based on Pd₂dba₃ were more active than catalysts based on Pd(OAc)₂; presumably the in situ reduction of the Pd(II) is inefficient under the reaction conditions.

As shown in Table 1, a variety of aryl bromides and aryl chlorides can be efficiently coupled with nitroalkanes. Electron-withdrawing aryl bromides react cleanly to furnish the desired nitroalkanes in good yield. For example, 4-bromomethylbenzoate reacts with nitroethane to furnish the desired product in 85% yield (entry 6). Electronically neutral aryl bromides are also good substrates for the reaction; 4-*tert*-butylbromobenzene is efficiently coupled with nitroethane and nitropropane to give the arylated products in 95 and 81% yields, respectively (entries 3, 11). Although the reaction is more practical when performed at elevated temperatures (45–60 °C), the arylation also proceeds at room temperature, albeit very slowly (entry 11). Aryl bromide substrates with electron-donating groups (e.g., OMe) in the *ortho* or *para* position of the aryl bromide are transformed in high yield as well (entries 5, 12). Additionally, aryl chlorides can be used with this catalyst system; electron-withdrawing substituents on the aryl chloride allow for an efficient transformation (entries 10, 14, 16). In addition, the reaction of *m*-chloroanisole with nitropropane afforded the desired nitroalkane in 68% isolated yield (entry 13). Double arylation of the nitroalkane was not observed in any of the examples studied. In fact, subjecting phenyl nitromethane to the arylation protocol resulted in no reaction. Reactions with nitromethane yielded the desired arylated compounds; however, yields were low and multiple products were observed.

The arylation of carbonyl-derived enolates has been demonstrated to be an efficient process.^{1,2} Moreover, the Heck arylation of terminal alkenes has proven to be one of the most powerful transformations in modern organic synthesis.⁶ We queried whether coupling partners containing enolizable ketones and esters, as well as terminal olefins, would be suitable in the nitroalkane arylation reaction. In the cases studied, we found that the desired arylation α to the nitro group was observed; no ketone arylation products were detected (Table 2,

[†] Present address: Bayer AG, Central Research–Synthesis Research, 51368 Leverkusen, Germany.

(1) (a) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* 1997, 119, 11108. (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* 1997, 119, 12382. (c) Ahman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* 1998, 120, 1918. (d) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* 1999, 121, 1473. (e) Fox, J. M.; Huang, X. H.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* 2000, 122, 1360 and references therein.

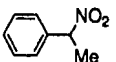
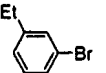
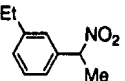
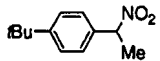
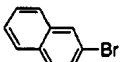
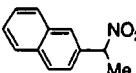
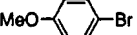
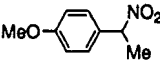
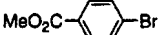
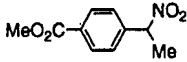
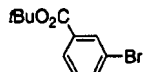
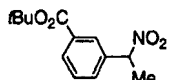
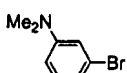
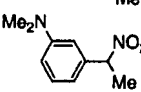
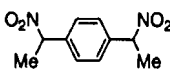
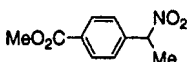
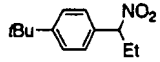
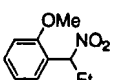
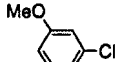
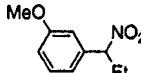
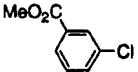
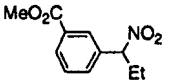
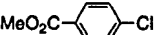
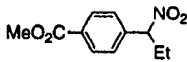
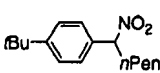
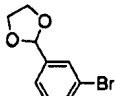
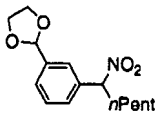
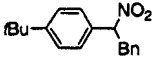
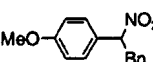
(2) (a) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* 1998, 63, 6546. (b) Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* 2001, 123, 7996. (c) Lee, S.; Beare, N. A.; Hartwig, J. F. *J. Am. Chem. Soc.* 2001, 123, 8410.

(3) The Pd-catalyzed intramolecular α -arylation of nitroalkanes has been reported: Muratake, H.; Nakai, H. *Tetrahedron Lett.* 1999, 40, 2355–2358.

(4) For other methods for the α -arylation of nitroalkanes, see: (a) Aleksandrowicz, P.; Piotrowska, H.; Sas, W. *Tetrahedron* 1982, 38, 1321–1327. (b) Kozyrod, R. P.; Pinhey, J. T. *Tetrahedron Lett.* 1981, 22, 783–784. (c) Kornblum, N.; Taylor, H. J. *J. Org. Chem.* 1963, 28, 1424–1425. (d) Park, K. P.; Clapp, L. B. *J. Org. Chem.* 1964, 29, 2108–2109.

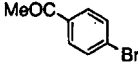
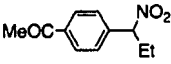
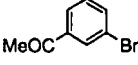
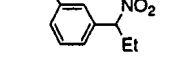
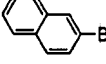
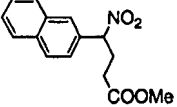
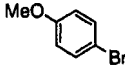
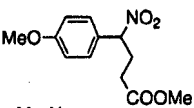
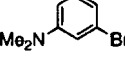
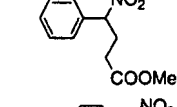
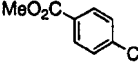
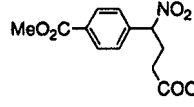
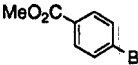
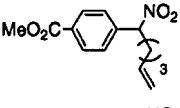
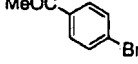
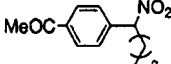
(5) For the synthesis of these ligands, see: Tomori, H.; Fox, J. M.; Buchwald, S. L. *J. Org. Chem.* 2000, 65, 5334–5341.

Table 1. Pd-Catalyzed α -Arylation of Nitroalkanes

$ \begin{array}{c} \text{R}-\text{C}_6\text{H}_4-\text{X} \\ \text{1 equiv} \end{array} + \begin{array}{c} \text{R}'-\text{CH}_2-\text{NO}_2 \\ \text{2 equiv} \end{array} \xrightarrow[\text{Cs}_2\text{CO}_3 \text{ (1.1 equiv), DME}]{\text{Pd}_2(\text{dba})_3, \text{ 1 (1:Pd = 2:1)}} \begin{array}{c} \text{R}-\text{C}_6\text{H}_4-\text{CH}(\text{NO}_2)-\text{R}' \\ \text{8 - 30 h} \end{array} $						
Entry	Halide	Nitroalkane	Product	T [°C]	Mol% Pd	% Yield ^a
1		Et-NO ₂		50	3	90
2		Et-NO ₂		50	3	95
3		Et-NO ₂		50	1.5	95
4		Et-NO ₂		50	3	96
5		Et-NO ₂		50	3	94
6		Et-NO ₂		50	2	85
7		Et-NO ₂		50	3	82
8		Et-NO ₂		50	1.5	98
9 ^b		Et-NO ₂		50	10	62
10		Et-NO ₂		50	3	71
11		<i>n</i> Pr-NO ₂		<i>rt</i> ^c	2	81
12		<i>n</i> Pr-NO ₂		50	10	95
13		<i>n</i> Pr-NO ₂		55	1.5	68
14		<i>n</i> Pr-NO ₂		55	1.5	65
15		<i>n</i> Pr-NO ₂		60	2	86
16 ^d		<i>n</i> Hex-NO ₂		50	2	92
17		<i>n</i> Hex-NO ₂		55	5	85
18 ^d		Bn-CH ₂ -NO ₂		50	5	65
19 ^d		Bn-CH ₂ -NO ₂		50	5	62

^a Isolated yields are an average of two runs. All compounds >95% pure as determined by ¹H NMR, GC, or combustion analysis. ^b 4 equiv of nitroalkane and 2.2 equiv of base were used. ^c Reaction performed for 96 h. ^d 1 equiv of nitroalkane and 1.1 equiv of base was used.

Table 2. Chemoselective Pd-Catalyzed α -Arylation of Nitroalkanes

Entry	Halide	Nitroalkane	Product	T [°C] / t [h]	Mol% Pd	% Yield ^a
1		$n\text{Pr}-\text{NO}_2$		45/35	3	80
2		$n\text{Pr}-\text{NO}_2$		45/33	3	63
3		$\text{MeO}_2\text{C}-\text{CH}_2-\text{CH}_2-\text{NO}_2$		50/22	5	78
4		$\text{MeO}_2\text{C}-\text{CH}_2-\text{CH}_2-\text{NO}_2$		50/22	5	72
5		$\text{MeO}_2\text{C}-\text{CH}_2-\text{CH}_2-\text{NO}_2$		50/24	5	75
6		$\text{MeO}_2\text{C}-\text{CH}_2-\text{CH}_2-\text{NO}_2$		50/24	5	67
7		$\text{CH}_2=\text{CH}-\text{CH}_2-\text{NO}_2$		50/18	2	67
8 ^b		$\text{CH}_2=\text{CH}-\text{CH}_2-\text{NO}_2$		rt/60	3	64

^a Isolated yields are an average of two runs. All compounds >95% pure as determined by ¹H NMR, GC, or combustion analysis. 1 equiv of nitroalkane and 1.1 equiv of base were used. ^b 1.5 equiv of nitroalkane and 1.1 equiv of base were used.

entries 1–3). This chemoselective arylation could also be effected with an activated aryl chloride (entry 4). It should be noted that di-*tert*-butylphosphino-derived ligands such as 1 are not efficient supporting ligands for ketone arylation.^{1e} Olefins were also tolerated under the reaction conditions; no Heck-type addition across the olefin was observed, and the desired nitroalkanes were isolated in moderate yield (entries 5, 6).

Conclusions

In summary, we have developed a general protocol for the Pd-catalyzed monoarylation of nitroalkanes. Using a catalyst based on 1 and Pd₂dba₃, this transformation may be carried out under mild conditions. The nitroalkane can be chemoselectively arylated in the presence of enolizable ketone and ester groups, and an olefin-substituted nitroalkane was also tolerated under the reaction conditions.

Experimental Section

General. Reactions were carried out in a dried resealable Schlenck tube purchased from Kontes. Flash chromatography was performed on Silicycle ultrapure silica gel (230–400 mesh). Elemental analyses were performed by Atlantic Mi-

crolabs, Inc, Norcross GA. Dimethoxyethane and dodecane (used as internal standard) were purchased in small SureSeal bottles from Aldrich Chemical Co. and used as received. Tris-(dibenzylideneacetone)dipalladium was purchased from Strem Chemical, Inc. Sodium *tert*-butoxide (NaOt-Bu), nitroethane, 1-nitropropane, 1-nitrohexane, and 6-nitro-1-hexene were purchased from Aldrich Chemical Co. K₃PO₄ was purchased from Fluka. Cs₂CO₃ was purchased from Chemetall. Moisture sensitive bases were stored under nitrogen in a Vacuum Atmospheres glovebox, and small samples were taken out, stored in a desiccator on the bench, and replaced every 2 weeks. All materials were weighed in the air. 2-Di-*tert*-butylphosphino-2'-methylbiphenyl (1),⁵ 2-phenylnitroethane,⁷ 4-nitrobutyric acid methyl ester,⁸ and *tert*-butyl-3-bromobenzoate⁹ were synthesized as described the literature. IR spectra were obtained by placing neat samples directly on the DiComp probe of an ASI REACTIR in situ IR instrument. Yields in tables refer to isolated yields (average of two runs) of compounds estimated to be ≥95% pure as determined by ¹H NMR, GC, and combustion analysis. Melting points were taken with a MEL-TEMP apparatus. 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 ¹H and ¹³C NMR spectra to those of the fully characterized product, and their purity was confirmed by GC analysis. Compounds previously described in the literature were characterized only by ¹H and ¹³C NMR.

General Reaction Procedure for the Arylation of Nitroalkanes, Method A. A dried resealable Schlenk tube

(6) For reviews on the Heck arylation, see: (a) Brase, S.; deMeijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; pp 99–166. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* 2000, 100, 3009–3066.

(7) Gilbert, K. E.; Borden, W. Y. *J. Org. Chem.* 1979, 44, 659.

(8) Chasar, D. W. *Synthesis* 1982, 841.

(9) Taylor, E. C.; Ray, P. S. *J. Org. Chem.* 1988, 53, 35.

containing a stir bar was charged with 1.0 mmol of the aryl bromide or aryl chloride, the appropriate amount of $\text{Pd}(\text{dba})_3$ and 2-(di-*tert*-butylphosphinyl)-2'-methylbiphenyl (**1**) as indicated, and 1.2 equiv of Cs_2CO_3 . The reaction vessel was capped with a rubber septum, evacuated, and backfilled with argon three times, and dimethoxyethane (5 mL) and 1.0–2.0 equiv of the appropriate nitroalkane were added via syringe under argon. After the mixture was stirred vigorously for 1 min at room temperature, the Schlenk tube was sealed and placed in a preheated oil bath at the given temperature for the time indicated. After the reaction was complete, as judged by either GC or TLC analysis, the reaction mixture was allowed to cool to ambient temperature. The unpurified mixture was quenched with a solution of sat. aqueous NH_4Cl (2 mL, two times), the aqueous phase was extracted with ether (2 mL), and the combined organic phases were washed with brine. The solvent was then removed, and the remaining oil was purified by flash column chromatography.

Method B. A dried resealable Schlenk tube containing a stir bar was charged with the appropriate amount of $\text{Pd}_2(\text{dba})_3$ and 2-(di-*tert*-butylphosphinyl)-2'-methylbiphenyl (**1**) as indicated and 1.2 equiv of Cs_2CO_3 . The reaction vessel was capped with a rubber septum, evacuated, and backfilled with argon three times, and 1.0 mmol of the aryl bromide or aryl chloride, dimethoxyethane (5 mL), and 1.0–2.0 equiv of the appropriate nitroalkane were added sequentially via syringe under argon. The mixture was stirred vigorously for 1 min at room temperature, the Schlenk tube was sealed and placed in a preheated oil bath at the given temperature for the time indicated. After the reaction was complete, as judged by either GC or TLC analysis, the reaction mixture was allowed to cool to ambient temperature. The unpurified mixture was quenched with a solution of sat. aqueous NH_4Cl (2 mL, two times), the aqueous phase was extracted with ether (2 mL), and the combined organic phases were washed with brine. Then the solvent was removed, and the remaining oil was purified by flash column chromatography.

(1-Nitroethyl)benzene (Table 1, entry 1). The reaction was carried out according to general procedure, method B. Flash column chromatography (diethyl ether:hexanes 1:20) yielded the known compound^{10,11} as a volatile (removal of solvent by a stream of air) colorless oil (0.136 g, 0.90 mmol, 90%). ^1H NMR (CDCl_3 , 300 MHz) δ : 7.48–7.40 (m, 5H), 5.62 (q, 1H, $J = 6.9$ Hz), 1.89 (d, 3H, $J = 6.9$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 135.7, 129.9, 129.1, 127.5, 86.3, 19.5 ppm.

3-(1-Nitroethyl)ethylbenzene (Table 1, entry 2). The reaction was carried out according to general procedure, method B. Flash column chromatography (diethyl ether:hexanes 1:20) yielded a colorless oil (0.170 g, 0.95 mmol, 95%). ^1H NMR (CDCl_3 , 300 MHz) δ : 7.36–7.20 (m, 4H), 5.60 (q, 1H, $J = 7.2$ Hz), 2.67 (q, 2H, $J = 7.6$ Hz), 1.89 (d, 3H, $J = 7.2$ Hz), 1.25 (t, 3H, $J = 7.6$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 145.4, 135.8, 129.5, 129.2, 127.1, 124.8, 86.5, 28.9, 19.7, 15.6 ppm; IR (neat, cm^{-1}) ν : 2968, 2935, 2875, 1549, 1453, 1385, 1360, 1165, 1065, 893, 853, 807, 712, 699. Anal. Calcd for $\text{C}_{10}\text{H}_{13}\text{NO}_2$: C, 67.02; H, 7.31. Found: C, 66.85; H, 7.43.

4-*tert*-Butyl-(1-nitroethyl)benzene (Table 1, entry 3). The reaction was carried out according to general procedure, method B. Flash column chromatography (diethyl ether:hexanes 1:20) yielded the known compound¹¹ as a colorless oil (0.197 g, 0.95 mmol, 95%). ^1H NMR (CDCl_3 , 300 MHz) δ : 7.41 (m, 4H), 5.61 (q, 1H, $J = 7.2$ Hz), 1.89 (d, 3H, $J = 7.2$ Hz), 1.32 (s, 9H); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 153.2, 132.8, 127.4, 126.2, 86.2, 34.9, 31.5, 19.6 ppm.

2-(1-Nitroethyl)naphthalene (Table 1, entry 4). The reaction was carried out according to general procedure, method A. Vigorous stirring is important due to the reaction heterogeneity. Additionally, 10 mL of DME were used. Flash column chromatography (diethyl ether:hexanes 1:10) yielded a crystalline solid; mp 51 °C (0.193 g, 0.96 mmol, 96%). ^1H NMR (CDCl_3 , 300 MHz) δ : 7.94–7.84 (m, 4H), 7.60–7.53 (m,

3H), 5.80 (m, 1H), 2.01 (m, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 133.9, 133.2, 133.0, 129.2, 128.5, 127.9, 127.5, 127.3, 127.0, 124.3, 86.5, 19.7 ppm; IR (neat, cm^{-1}) ν : 3060, 2977, 2869, 1549, 1385, 1355, 1281, 1115, 824, 785, 745, 697. Anal. Calcd for $\text{C}_{12}\text{H}_{11}\text{NO}_2$: C, 71.63; H, 5.51. Found: C, 71.73; H, 5.46.

4-(1-Nitroethyl)methoxybenzene (Table 1, entry 5). The reaction was carried out according to general procedure, method B. Flash column chromatography (diethyl ether:hexanes 1:20) yielded the known compound¹¹ as an oil (0.170 g, 0.94 mmol, 94%). ^1H NMR (CDCl_3 , 300 MHz) δ : 7.41 (m, 2H), 6.92 (m, 2H), 5.58 (q, 1H, $J = 6.9$ Hz), 3.82 (s, 3H), 1.88 (d, 3H, $J = 6.9$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 160.8, 129.1, 127.8, 114.4, 85.9, 55.5, 19.5 ppm.

4-(1-Nitroethyl)benzoic Acid Methyl Ester (Table 1, entry 6 and entry 10). The reaction was carried out according to general procedure, method A. Flash column chromatography (toluene 100%) yielded the known compound¹¹ as a pale yellow oil which solidified to a crystalline solid; mp 49 °C (0.178 g, 0.85 mmol, 85%). ^1H NMR (CDCl_3 , 300 MHz) δ : 8.08 (m, 2H), 7.54 (m, 2H), 5.67 (q, 1H, $J = 6.9$ Hz), 3.94 (s, 3H), 1.93 (d, 3H, $J = 6.9$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 166.5, 140.1, 131.6, 130.5, 127.7, 85.9, 52.6, 19.7 ppm.

3-(1-Nitroethyl)benzoic Acid *tert*-Butyl Ester (Table 1, entry 7). The reaction was carried out according to general procedure, method B. Flash column chromatography (diethyl ether:hexanes 1:8) yielded a colorless oil (0.206 g, 0.82 mmol, 82%). ^1H NMR (CDCl_3 , 300 MHz) δ : 8.07–8.02 (m, 2H), 7.64 (m, 1H), 7.48 (m, 1H), 5.66 (q, 1H, $J = 6.9$ Hz), 1.93 (d, 3H, $J = 6.9$ Hz), 1.61 (s, 9H); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 165.1, 135.8, 133.1, 131.4, 131.0, 129.2, 128.8, 85.9, 81.9, 28.4, 19.6 ppm; IR (neat, cm^{-1}) ν : 2979, 2935, 1711, 1551, 1385, 1368, 1297, 1256, 1160, 1115, 849, 753, 731, 689; Anal. Calcd for $\text{C}_{13}\text{H}_{17}\text{NO}_4$: C, 62.14; H, 6.82. Found: C, 62.22; H, 6.97.

3-(1-Nitroethyl)dimethylaminobenzene (Table 1, entry 8). The reaction was carried out according to general procedure, Method B. Flash column chromatography (diethyl ether:hexanes 1:20 to 1:10) yielded a yellow oil (0.190 g, 0.98 mmol, 98%). ^1H NMR (CDCl_3 , 300 MHz) δ : 7.29–7.23 (m, 1H), 6.80–6.72 (m, 3H), 5.57 (q, 1H, $J = 6.9$ Hz), 2.98 (s, 6H), 1.89 (d, 3H, $J = 6.9$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 150.9, 136.7, 129.8, 115.0, 113.6, 111.0, 86.9, 40.6, 19.7 ppm; IR (neat, cm^{-1}) ν : 2989, 2894, 2809, 1603, 1546, 1503, 1441, 1383, 1358, 1231, 1063, 994, 961, 851, 756, 702, 691. Anal. Calcd for $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}_2$: C, 61.84; H, 7.27. Found: C, 61.94; H, 7.33.

1,4-Bis(1-nitroethyl)benzene (Table 1, entry 9). The reaction was carried out according to general procedure, method A (but on a 0.5 mmol scale). 4-Dibromobenzene was purified by column chromatography (SiO_2 , 100% hexanes) prior to use. Flash column chromatography (diethyl ether:hexanes 1:4 to 1:2) yielded a crystalline solid (presumably as a mixture of isomers); mp 63 °C (0.069 g, 0.31 mmol, 62%). ^1H NMR (CDCl_3 , 300 MHz) δ : 7.52 (s, 4H), 5.64 (q, 2H, $J = 6.6$ Hz), 1.91 (d, 6H, $J = 6.9$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 137.2, 128.3, 85.8, 19.6 ppm; IR (neat, cm^{-1}) ν : 2995, 2944, 2900, 1683, 1546, 1385, 1356, 1295, 1063, 1000, 864, 847, 697. Anal. Calcd for $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_4$: C, 53.57; H, 5.39. Found: C, 53.82; H, 5.48.

4-*tert*-Butyl-(1-nitropropyl)benzene (Table 1, entry 11). The reaction was carried out according to general procedure, method B. Flash column chromatography (diethyl ether:hexanes 1:50) yielded a colorless oil (0.179 g, 0.81 mmol, 81%). ^1H NMR (CDCl_3 , 300 MHz) δ : 7.42 (m, 4H), 5.37 (dd, 1H, $J = 9.0$ Hz, 6.3 Hz), 2.52 (m, 1H), 2.11 (m, 1H), 1.33 (s, 9H), 1.00 (t, 3H, 7.5 Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 153.1, 131.7, 127.6, 126.1, 93.0, 34.9, 31.4, 27.4, 10.9 ppm; IR (neat, cm^{-1}) ν : 2966, 2906, 2873, 1549, 1461, 1364, 1270, 1108, 1019, 805, 672. Anal. Calcd for $\text{C}_{13}\text{H}_{19}\text{NO}_2$: C, 70.56; H, 8.65. Found: C, 70.64; H, 8.78.

2-Methoxy-(1-nitropropyl)benzene (Table 1, entry 12). The reaction was carried out according to general procedure, method B. Flash column chromatography (diethyl ether:hexanes 1:10) yielded a colorless oil (0.185 g, 0.95 mmol, 95%). ^1H NMR (CDCl_3 , 300 MHz) δ : 7.45 (m, 1H), 7.37 (m, 1H), 7.02 (m, 1H), 6.93 (m, 1H), 5.91 (dd, 1H, $J = 8.4$ Hz, 6.6 Hz), 3.86 (s, 3H), 2.48 (m, 1H), 2.11 (m, 1H), 1.02 (d, 3H, $J = 7.2$ Hz);

(10) Bose, D. S.; Vanajatha, G. *Synth. Commun.* 1998, 28, 4531.

(11) Baruah, A.; Kalita, B.; Barua, N. C. *Synlett* 2000, 1064.

^{13}C NMR (CDCl_3 , 75 MHz) δ : 157.2, 130.9, 127.7, 123.2, 121.0, 111.0, 85.8, 55.8, 26.7, 11.0 ppm; IR (neat, cm^{-1}) ν : 2975, 2941, 2883, 2842, 1603, 1547, 1493, 1465, 1368, 1248, 1027, 812, 753. Anal. Calcd for $\text{C}_{10}\text{H}_{13}\text{NO}_3$: C, 61.53; H, 6.71. Found: C, 61.76; H, 6.76.

3-Methoxy-(1-nitropropyl)benzene (Table 1, entry 13). The reaction was carried out according to general procedure, method B. Flash column chromatography (diethyl ether:hexanes 1:8) yielded a colorless oil (0.133 g, 0.68 mmol, 68%). ^1H NMR (CDCl_3 , 300 MHz) δ : 7.31 (t, 1H, $J = 8.1$ Hz), 7.05–6.91 (m, 3H), 5.33 (m, 1H), 3.82 (s, 3H), 2.49 (m, 1H), 2.10 (m, 1H), 0.98 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 160.1, 136.0, 130.2, 120.2, 115.3, 113.5, 93.1, 55.5, 27.5, 10.8 ppm; IR (neat, cm^{-1}) ν : 2975, 2941, 2840, 1602, 1547, 1492, 1457, 1368, 1264, 1162, 1046, 787, 689. Anal. Calcd for $\text{C}_{10}\text{H}_{13}\text{NO}_3$: C, 61.53; H, 6.71. Found: C, 61.55; H, 6.81.

3-Methoxycarbonyl-(1-nitropropyl)benzene (Table 1, entry 14). The reaction was carried out according to general procedure, method B. Flash column chromatography (diethyl ether:hexanes 1:8 to 1:5) yielded a pale yellow oil (0.145 g, 0.65 mmol, 65%). ^1H NMR (CDCl_3 , 300 MHz) δ : 8.14 (s, 1H), 8.09 (d, 1H, $J = 7.5$ Hz), 7.68 (d, 1H, $J = 7.8$ Hz), 7.50 (t, 1H, $J = 7.8$ Hz), 5.43 (dd, 1H, $J = 8.4$ Hz, 6.3 Hz), 3.94 (s, 3H), 2.53 (m, 1H), 2.16 (m, 1H), 1.00 (t, 3H, $J = 7.5$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 166.5, 135.0, 132.3, 131.2, 131.1, 129.4, 129.2, 92.7, 52.6, 27.5, 10.8 ppm; IR (neat, cm^{-1}) ν : 2977, 2954, 2883, 1721, 1549, 1434, 1368, 1285, 1200, 1109, 735, 691. Anal. Calcd for $\text{C}_{11}\text{H}_{13}\text{NO}_4$: C, 59.19; H, 5.87. Found: C, 59.40; H, 5.86.

4-Methoxycarbonyl-(1-nitropropyl)benzene (Table 1, entry 15). The reaction was carried out according to general procedure, method A. Flash column chromatography (diethyl ether:hexanes 1:8) yielded a colorless oil (0.191 g, 0.86 mmol, 86%). ^1H NMR (CDCl_3 , 300 MHz) δ : 8.08 (d, 2H, $J = 8.7$), 7.55 (d, 2H, $J = 8.4$ Hz), 5.42 (dd, 1H, $J = 9.0$ Hz, 6.3 Hz), 3.93 (s, 3H), 2.53 (m, 1H), 2.15 (m, 1H), 1.00 (t, 3H, $J = 7.5$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 166.5, 139.1, 131.7, 130.4, 128.0, 92.7, 52.6, 27.6, 10.8 ppm; IR (neat, cm^{-1}) ν : 2977, 2956, 2885, 1721, 1549, 1436, 1368, 1279, 1185, 1113, 1021, 731. Anal. Calcd for $\text{C}_{11}\text{H}_{13}\text{NO}_4$: C, 59.19; H, 5.87. Found: C, 59.48; H, 5.95.

4-*tert*-Butyl-(1-nitrohexyl)benzene (Table 1, entry 16). The reaction was carried out according to general procedure, method B. Flash column chromatography (diethyl ether:hexanes 1:100, the column was twice as long as for the other separations, toluene:hexane 1:3 can be better if starting material is left) yielded a colorless oil (0.242 g, 0.92 mmol, 92%). ^1H NMR (CDCl_3 , 300 MHz) δ : 7.41 (s, 4H), 5.44 (dd, 1H, $J = 9.0$ Hz, 6.3 Hz), 2.49 (m, 1H), 2.05 (m, 1H), 1.32 (s, 15H), 0.89 (m, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 153.1, 131.9, 127.6, 126.1, 91.6, 34.9, 34.0, 31.4, 31.3, 26.0, 22.5, 14.1 ppm; IR (neat, cm^{-1}) ν : 2960, 2933, 2871, 1551, 1465, 1364, 1270, 1109, 828, 774. Anal. Calcd for $\text{C}_{16}\text{H}_{25}\text{NO}_2$: C, 72.97; H, 9.57. Found: C, 72.97; H, 9.59.

2-[3-(1-nitrohexyl)phenyl]-[1,3]dioxolane (Table 1, entry 17). The reaction was carried out according to general procedure, method B. Flash column chromatography (diethyl ether:hexanes 1:8) yielded a yellow oil (0.237 g, 0.85 mmol, 85%). ^1H NMR (CDCl_3 , 300 MHz) δ : 7.60–7.40 (m, 4H), 5.82 (s, 1H), 5.47 (dd, 1H, $J = 9.0$ Hz, 6.3 Hz), 4.17–4.03 (m, 4H), 2.50 (m, 1H), 2.05 (m, 1H), 1.33 (s, 6H), 0.88 (m, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 139.0, 135.0, 129.3, 128.6, 128.2, 126.1, 103.3, 91.6, 65.6, 34.2, 31.3, 25.9, 22.5, 14.1 ppm; IR (neat, cm^{-1}) ν : 2958, 2931, 1549, 1364, 1165, 1079, 969, 700. Anal. Calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_4$: C, 64.50; H, 7.58. Found: C, 64.59; H, 7.70.

1-(4-*tert*-Butyl-phenyl)-2-phenylnitroethane (Table 1, entry 18). The reaction was carried out according to general procedure, method B. Flash column chromatography (diethyl ether:hexanes 1:10; no starting material should be left prior to purification) yielded a pale yellow oil (0.184 g, 0.65 mmol, 65%). ^1H NMR (CDCl_3 , 300 MHz) δ : 7.49–7.18 (m, 9H), 5.70 (dd, 1H, $J = 5.1$ Hz, 9.9 Hz), 3.81 (dd, 1H, $J = 9.9$ Hz, 14.5 Hz), 3.31 (dd, 1H, $J = 5.1$ Hz, 14.5 Hz), 1.33 (s, 9H); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 153.4, 135.9, 131.5, 129.1, 129.0, 127.6, 127.6, 126.2, 92.7, 40.2, 34.9, 31.4 ppm; IR (neat, cm^{-1}) ν : 3033,

2964, 2906, 2869, 1551, 1364, 1270, 1111, 1019, 855, 745, 699. Anal. Calcd for $\text{C}_{18}\text{H}_{21}\text{NO}_2$: C, 76.30; H, 7.47. Found: C, 76.16; H, 7.44.

1-(4-Methoxy-phenyl)-2-phenylnitroethane (Table 1, entry 19). The reaction was carried out according to general procedure, method B. Flash column chromatography (diethyl ether:hexanes 1:20) yielded a crystalline solid; mp 79 °C (0.129 g, 0.50 mmol, 50%). ^1H NMR (CDCl_3 , 300 MHz) δ : 7.45 (m, 2H), 7.30–7.15 (m, 5H), 6.93–6.90 (m, 2H), 5.66 (dd, 1H, $J = 6.0$ Hz, 9.3 Hz), 3.82 (s, 3H), 3.77 (dd, 1H, $J = 9.3$ Hz, 14.4 Hz), 3.33 (dd, 1H, $J = 6.0$ Hz, 14.4 Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 160.9, 135.7, 129.4, 129.1, 129.0, 127.5, 126.5, 114.5, 92.3, 55.5, 40.2 ppm; IR (neat, cm^{-1}) ν : 3012, 2904, 2834, 1609, 1546, 1513, 1455, 1366, 1254, 1177, 1028, 836, 735, 699. Anal. Calcd for $\text{C}_{15}\text{H}_{15}\text{NO}_3$: C, 70.02; H, 5.88. Found: C, 70.11; H, 5.80.

4-Acetyl-(1-nitropropyl)benzene (Table 2, entry 1). The reaction was carried out according to general procedure, method A. Flash column chromatography (diethyl ether:hexanes 1:5) yielded a pale yellow oil which solidifies upon standing; mp 39 °C (0.166 g, 0.80 mmol, 80%). ^1H NMR (CDCl_3 , 300 MHz) δ : 7.98 (d, 2H, $J = 6.8$ Hz), 7.56 (d, 2H, $J = 6.8$ Hz), 5.42 (dd, 1H, $J = 8.7$ Hz, 6.6 Hz), 2.61 (s, 3H), 2.51 (m, 1H), 2.12 (m, 1H), 0.99 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 197.5, 139.1, 138.2, 129.1, 128.2, 92.6, 27.6, 26.9, 10.7 ppm; IR (neat, cm^{-1}) ν : 2977, 2941, 2883, 1684, 1609, 1547, 1416, 1360, 1266, 959, 805. Anal. Calcd for $\text{C}_{11}\text{H}_{13}\text{NO}_3$: C, 63.76; H, 6.32. Found: C, 64.03; H, 6.40.

3-Acetyl-(1-nitropropyl)benzene (Table 2, entry 2). The reaction was carried out according to general procedure, method B. Flash column chromatography (diethyl ether:hexanes 1:5) yielded a pale yellow oil (0.131 g, 0.63 mmol, 63%). ^1H NMR (CDCl_3 , 300 MHz) δ : 8.05 (s, 1H), 8.00 (d, 1H, $J = 7.8$ Hz), 7.71 (d, 1H, $J = 7.8$ Hz), 7.53 (t, 1H, $J = 7.8$ Hz), 5.44 (dd, 1H, $J = 8.7$ Hz, 6.3 Hz), 2.63 (s, 3H), 2.55 (m, 1H), 2.14 (m, 1H), 1.00 (t, 3H, $J = 6.9$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 197.5, 137.9, 135.2, 132.3, 129.9, 129.6, 127.8, 92.7, 27.6, 26.9, 10.8 ppm; IR (neat, cm^{-1}) ν : 2977, 2941, 2883, 1686, 1547, 1360, 1272, 1189, 1084, 799, 764, 691. Anal. Calcd for $\text{C}_{11}\text{H}_{13}\text{NO}_3$: C, 63.76; H, 6.32. Found: C, 64.10; H, 6.38.

4-(Naphthalene-2-yl)-4-nitrobutyric Acid Methyl Ester (Table 2, entry 3). The reaction was carried out according to general procedure, method A. Flash column chromatography (diethyl ether:hexanes 1:3) yielded a viscous oil which solidified upon storage; mp 37 °C (0.218 g, 0.80 mmol, 80%). ^1H NMR (CDCl_3 , 300 MHz) δ : 7.95–7.85 (m, 4H), 7.60–7.52 (m, 3H), 5.78 (m, 1H), 3.70 (s, 3H), 2.97–2.82 (m, 1H), 2.62–2.50 (m, 1H), 2.41 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 172.5, 134.0, 133.1, 131.3, 129.4, 128.5, 128.2, 127.9, 127.4, 127.1, 124.2, 90.3, 52.2, 30.2, 29.0 ppm; IR (neat, cm^{-1}) ν : 3058, 2954, 1735, 1549, 1511, 1437, 1360, 1200, 1177, 1129, 909, 861, 818, 749, 731. Anal. Calcd for $\text{C}_{15}\text{H}_{15}\text{NO}_4$: C, 65.92; H, 5.53. Found: C, 65.98; H, 5.59.

4-(4-Methoxy-phenyl)-4-nitrobutyric Acid Methyl Ester (Table 2, entry 4). The reaction was carried out according to general procedure, method B. Flash column chromatography (diethyl ether:hexanes 1:3) yielded a yellow oil (0.179 g, 0.79 mmol, 71%). ^1H NMR (CDCl_3 , 300 MHz) δ : 7.39 (m, 2H), 6.92 (m, 2H), 5.54 (m, 1H), 3.82 (s, 3H), 3.69 (s, 3H), 2.82–2.70 (m, 1H), 2.50–2.32 (m, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 172.5, 161.0, 129.3, 126.1, 114.6, 89.7, 55.5, 52.1, 30.3, 28.9 ppm; IR (neat, cm^{-1}) ν : 2956, 2842, 1737, 1611, 1549, 1515, 1439, 1360, 1308, 1254, 1179, 1117, 1030, 913, 834, 733. Anal. Calcd for $\text{C}_{12}\text{H}_{15}\text{NO}_5$: C, 56.91; H, 5.97. Found: C, 56.94; H, 5.90.

4-(3-Dimethylamino-phenyl)-4-nitrobutyric Acid Methyl Ester (Table 2, entry 5). The reaction was carried out according to general procedure, method B. Flash column chromatography (diethyl ether:hexanes 1:3) yielded a yellow oil (0.192 g, 0.72 mmol, 72%). ^1H NMR (CDCl_3 , 300 MHz) δ : 7.24 (m, 1H), 6.77–6.70 (m, 3H), 5.51 (dd, 1H, $J = 6.5$ Hz, 8.6 Hz), 3.68 (s, 3H), 2.95 (s, 6H), 2.80–2.69 (m, 1H), 2.50–2.32 (m, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 172.6, 151.0, 135.0, 129.9, 115.2, 113.8, 111.2, 90.7, 52.1, 40.6, 30.3, 29.0 ppm; IR (neat, cm^{-1}) ν : 2954, 2894, 2811, 1737, 1603, 1547, 1503, 1439,

1360, 1233, 1200, 1171, 1063, 996, 849, 764. Anal. Calcd for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81. Found: C, 58.93; H, 6.80.

4-(4-Methoxycarbonylphenyl)-4-nitrobutyric Acid Methyl Ester (Table 2, entry 6). The reaction was carried out according to general procedure, method A. Flash column chromatography (diethyl ether:hexanes 1:3) yielded a pale yellow oil (0.187 g, 0.67 mmol, 67%). ^1H NMR ($CDCl_3$, 300 MHz) δ : 8.06 (d, 2H, $J = 8.3$ Hz), 7.52 (d, 2H, $J = 8.3$ Hz), 5.65 (m, 1H), 3.91 (s, 3H), 3.67 (s, 3H), 2.85–2.70 (m, 1H), 2.50–2.32 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ : 172.3, 166.3, 138.5, 131.8, 130.5, 127.9, 89.6, 52.6, 52.2, 30.0, 29.0 ppm; IR (neat, cm^{-1}) ν : 3002, 2956, 2448, 1725, 1613, 1551, 1437, 1360, 1279, 1185, 1111, 1021, 731. Anal. Calcd for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.38. Found: C, 55.47; H, 5.53.

6-(4-Methoxycarbonylphenyl)-6-nitro-1-hexene (Table 2, entry 7). The reaction was carried out according to general procedure, method A. Flash column chromatography (diethyl ether:hexanes 1:15) yielded a colorless oil (0.176 g, 0.67 mmol, 67%, some mixed fractions had to be purified by prep. TLC otherwise the yield is slightly lower). ^1H NMR ($CDCl_3$, 300 MHz) δ : 8.08 (d, 2H, $J = 8.4$ Hz), 7.55 (d, 2H, $J = 8.1$ Hz), 5.75 (m, 1H), 5.50 (dd, 1H, $J = 8.7$ Hz, 6.3 Hz), 5.07–4.99 (m, 2H), 3.94 (s, 3H), 2.50 (m, 1H), 2.12 (m, 3H), 1.42 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ : 166.5, 139.1, 137.4, 131.7, 130.5, 128.0, 116.0, 91.1, 52.6, 33.5, 33.1, 25.3 ppm; IR (neat, cm^{-1})

ν : 2954, 1723, 1551, 1436, 1279, 1185, 1111, 917, 731; Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51. Found: C, 63.65; H, 6.53.

6-(4-Acetylphenyl)-6-nitro-1-hexene (Table 2, entry 8). The reaction was carried out according to general procedure, method B. Flash column chromatography (diethyl ether:hexanes 1:5) yielded a pale yellow oil (0.158 g, 0.64 mmol, 64%). ^1H NMR ($CDCl_3$, 300 MHz) δ : 7.97 (d, 2H, $J = 8.1$ Hz), 7.55 (d, 2H, $J = 8.4$ Hz), 5.70 (m, 1H), 5.50 (dd, 1H, $J = 8.4$ Hz, 6.3 Hz), 5.06–4.97 (m, 2H), 2.60 (s, 3H), 2.50 (m, 1H), 2.11 (m, 3H), 1.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ : 197.5, 139.2, 138.3, 137.3, 129.1, 128.2, 116.0, 91.0, 33.5, 33.0, 26.9, 25.3 ppm; IR (neat, cm^{-1}) ν : 2933, 1686, 1609, 1549, 1360, 1266, 917, 834, 778. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93. Found: C, 68.16; H, 6.97.

Acknowledgment. We gratefully acknowledge the National Institutes of Health (GM 46059) for funding as well as Merck and Pfizer for unrestricted support. We are also grateful to Prof. H. Hugel and Bayer AG for financial support for E.M.V. We thank Dr. Alex R. Muci for help with this manuscript.

JO010953V

Abstract (laboratory)
Exp. 03-106.847
VIII)

Palladium-Catalyzed α -Arylation of Esters: Ideal New Methodology for Discovery Chemistry**

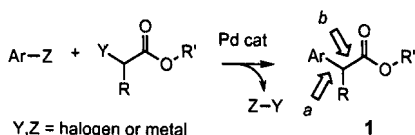
Guy C. Lloyd-Jones*

" α -Aryl carboxylic acids and α -aryl amino acids are amongst the most important carbonyl compounds."^[1]

"The synthesis of α -aryl esters and their derivatives is of interest in organic chemistry."^[2]

"Methylenecarboxy groups are key functionalities in many biologically active compounds."^[3]

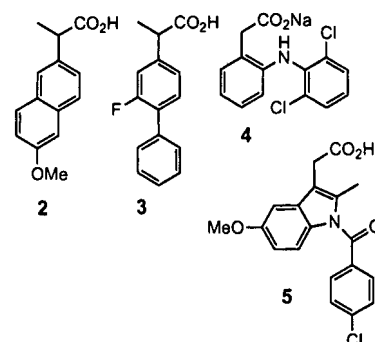
These are the opening statements from Hartwig et al.,^[1] Buchwald et al.,^[2] and Gooßen^[3] in their recent disclosures of new methods for generating $\text{Ar}-\text{C}(\text{R})\text{H}-\text{CO}_2\text{R}'$ units **1** by palladium-catalyzed formation of the $\text{Ar}-\text{C}_\alpha$ bond (bond 'a', Scheme 1).



Scheme 1. A useful route to α -arylated esters and amino acids ($\text{R} = \text{NH}_2$), by formation of bond *a*. Most current synthetic methods involve formation of bond *b*.

These overtures are justified: a wide range of substituted arylacetic acids are of significant commercial importance as 'NSAIDs'.^[4] Examples include naproxen (**2**), flurbiprofen (**3**), dichlofenac (**4**), and indomethacin (**5**).

The majority of synthetic routes to α -aryl acetic acids **1**^[5] and α -aryl α -amino acids^[6] involve construction of the 'b' bond (Scheme 1). Consequently, arylation-type routes (constructing bond *a*, Scheme 1) should be valuable weapons in the synthetic chemists' armory. However, the few examples



that are known^[7] have not been widely adopted; this may be for a variety of reasons including expense, lack of generality, or operational complexity.

Palladium-Catalyzed α -Arylation Reactions

In contrast to other α -arylation routes, the novel methodologies recently reported by the Hartwig, Buchwald, and Gooßen groups are likely to become popular: they proceed in high yield, under simple conditions, and employ readily available substrates and reagents (Scheme 1; $\text{Z} = \text{BR}_2$ or halide, $\text{Y} = \text{Br}$ or H); this Highlight focuses on these important developments.

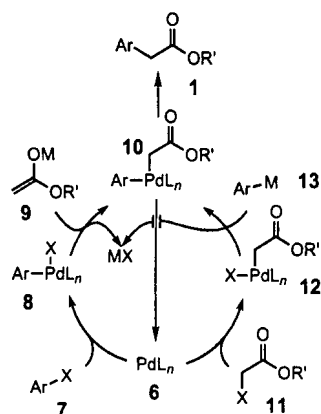
The approach of Hartwig et al., and Buchwald et al. for the generation of **1** is essentially identical and involves the Pd-catalyzed reaction of an aryl halide (**7**) with an ester enolate (**9**; Scheme 2, left-hand half of the catalytic cycle). Common ground with the Gooßen approach (right-hand half) is found in the Pd^0 complex **6** and the proposed palladium-enolate^[8] intermediate **10**, generated in an alternative fashion from a bromoacetate (**11**) and an aryl boronate (**13**). In either procedure, reductive elimination in **10** forms the *a* bond of **1** and regenerates the Pd^0 species **6** to facilitate further turnover of the catalytic cycle.

On first inspection, both routes appear simple and promising. However, as is often the case in the rather subtle science of catalysis, both systems presented a number of obstacles that needed to be overcome.

In the Hartwig–Buchwald system, the requisite enolate **9** is generated by deprotonation of the corresponding ester. This

[*] Dr. G. C. Lloyd-Jones
School of Chemistry
University of Bristol
Cantock's Close, Bristol BS8 1TS (UK)
Fax: (+44)117-929-8611
E-mail: Guy.Lloyd-Jones@bris.ac.uk

[**] Dr. Lukas J. Gooßen (MPI, Mülheim) kindly provided details of attempted α -bromo propionate arylation. I thank the RSC (Hickinbottom Fellowship), Pfizer Ltd, and AstraZeneca for generous and unrestricted research support.

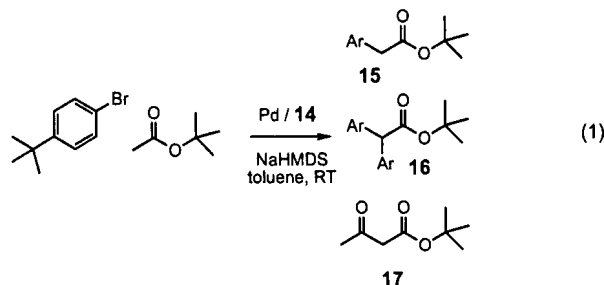


Scheme 2. Potential Pd-catalyzed routes to α -arylated esters **1**. Left-hand of cycle: Hartwig and Buchwald's arylation via enolate ($M = \text{Na}, \text{Li}$) trapping of Ar-Pd intermediate (**8**, $X = \text{Br}, \text{Cl}$); right-hand of cycle: Gooßen's route involving arylative transmetalation (with **13**, $M = \text{B}(\text{OR})_2$) of a Pd -enolate (**12**, $X = \text{Br}$).

method opens the door to an undesired reaction between enolate and ester resulting in Claisen products (acetoacetates). Accordingly, hindered *tert*-butyl esters were employed to suppress nucleophilic attack at the carbonyl carbon atom. As with aryl amination, the choice of ligand and base^[9] is crucial and since Na-derived bases had earlier proved superior in amination reactions, NaHMDS (HMDS = 1,1,1,3,3,3-hexamethylidisilazane) was the first choice.

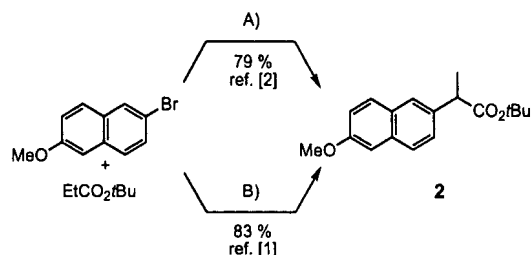
The Buchwald Approach

The Buchwald group employed their biaryl ligand **14** and obtained a 46% yield of mono- and diarylated acetates (**15** and **16**) together with competing Claisen product **17**, on reaction of *tert*-butyl acetate with *p*-*tert*-butyl bromobenzene [Eq. (1)].



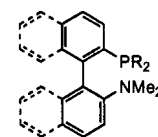
The mixture of mono- and diarylation represents the second problem: the primary product (here, **15**) is more acidic than the *tert*-butyl acetate and thus the acid-base equilibrium will facilitate a second arylation leading to **16**. This problem was controlled by switching from an Na to an Li counterion (LiHMDS),^[10] by using this method a wide range of aryl bromides underwent coupling with *tert*-butyl acetate in toluene at ambient temperature, in yields that ranged from 71–90%. Importantly, the extensively competing Claisen reaction required the use of a large excess of enolate (2.3 equivalents of *tert*-butyl acetate and 2.5 equiv-

alents of LiHMDS) and thus yields based on ester are significantly lower. Propionates and higher homologues also reacted smoothly, although, again a large enolate excess is required. The procedure is very versatile, for example, the *tert*-butyl ester of racemic naproxen (**2**) is obtained in 79% yield after 15 h at ambient temperature (Scheme 3 A).

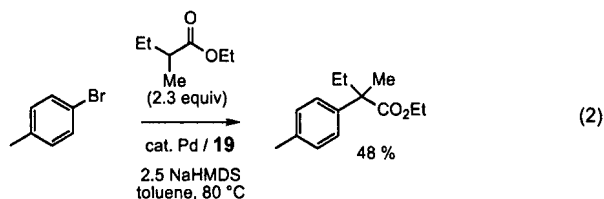


Scheme 3. Buchwald (A) and Hartwig (B) routes to the *tert*-butyl ester of naproxen (**2**). Conditions A) 2.3 equivalents EtCO_2tBu ; 2.5 equivalents NaHMDS ; 3 mol % $\text{Pd}(\text{OAc})_2$; 6 mol % **19**; toluene, RT, 15 h. B) 1.1 equivalents EtCO_2tBu ; 2.3 equivalents NaHMDS ; 1 mol % $\text{Pd}(\text{dba})_2$; 1 mol % **20**; toluene, RT, 12 h; dba = *trans,trans*-dibenzylideneacetone.

Often unpredictably, the choice of ligand in Pd-catalyzed reactions can make surprisingly little difference or can open up new avenues. In the current case, the latter situation prevails. There has recently been much attention given to finding methods for the use of cheaper aryl chlorides in place of bromides or iodides in Pd-catalyzed couplings. Using the ligand **14**, poor results were obtained with 4-chloro-aromatics in the ester arylation reaction, but on switching to the $t\text{Bu}_2\text{PAr}$ analogue (**18**) the reaction proved feasible. Furthermore, with the binaphthyl-based ligand **19**, even α -dialkylated acetates could be arylated (albeit only using aryl bromides) so as to generate quaternary carbon centers [Eq. (2)].

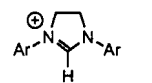


14 benzo, $R = \text{Cy}$
18 benzo, $R = t\text{Bu}$
19 naphtho, $R = t\text{Bu}$



The Hartwig Approach

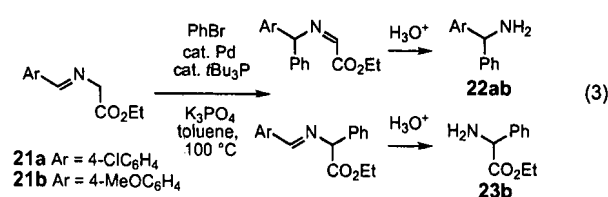
In contrast to the P,C -based ligands (**14**, **18**, and **19**) employed by the Buchwald group, Hartwig et al., chose to use a carbene ligand^[11] generated in situ from hindered dihydroimidazolium **20**. Furthermore, they employed an excess of base. In fact a whole extra equivalent of base (Li- or NaHMDS) was added to only 1.1 equivalents of ester so as to deprotonate the product as it is generated. This cunningly solves three problems: first, the Claisen reaction is sup-



20 $\text{Ar} = 2,6\text{-}i\text{Pr}_2\text{C}_6\text{H}_3$

pressed since this requires non-enolized ester coreactant; second, the more reactive (but less acidic) ester reagent can now compete effectively with the product for arylating agent and thus double arylation is suppressed; third, the reaction no longer requires an excess of ester reagent and thus the yields are good based upon both components. The choice of base again proved important: LiHMDS functioned well with acetates whilst NaHMDS worked well with propionates.^[12] In both cases, excellent yields (75–98%) were obtained with a range of aryl bromides (Scheme 3B).

By slightly modifying the conditions (employing *t*Bu₃P as ligand and K₃PO₄^[13] as base) *N*-protected glycinate undergo analogous arylation. Benzophenone imine proved a suitable protecting group and allowed a large range of glycinate to be arylated. The products are readily hydrolyzed on work-up and thereby facilitate direct access to C-protected α -aryl amino acids. However, the expensive nature of benzophenone imine led Hartwig et al. to explore the use of arylaldimines (**21**). *N*-(4-chlorobenzylidene) glycinate (**21a**) is 'conveniently crystalline', however, reaction with bromobenzene gave two arylated products. The α -aryl-benzylamine (**22a**) was reasoned to arise from arylation of the "wrong" tautomeric enolate, [Eq. (3)]. Electronic tuning of the protecting group (using 4-methoxybenzylidene, see **21b**) shut down this pathway and thus provides, via **23b**, a general route to C-protected α -aryl glycines.^[14]

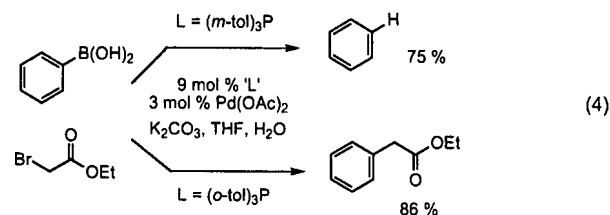


The Gooßen Approach

The switching of electrophile with nucleophile and vice versa, defines the Gooßen approach. Oxidative addition of a α -halo ester to a Pd⁰ species (see 6 in Scheme 1) should generate a neutral Pd^{II}-enolate species **12** bearing a coordinated halide counterion. Transmetalation with aryl–metal compound **13** then generates the requisite aryl–Pd enolate **10** primed for reductive elimination to yield the desired α -aryl ester **1**.

No complications because of acid–base equilibria are expected, a range of aryl boronic acids and α -halo esters are available and thus, in principle, this method appears advantageous. However, there are two problems that are apparent on further consideration. First, competing Pd⁰–Pd^{II}–Pd^{IV} cycles are known to facilitate reduction and reductive coupling of aryl boronic acids under analogous conditions^[15] and thus Ar–H and Ar–Ar are likely by-products. Second, palladium enolates of esters in which there is a β -hydrogen atom (i.e. propionates) are likely to undergo β -H elimination faster than they transmetallate and thus generate acrylates. The former, but not the latter, turned out to be readily solved by ligand tuning. Relatively bulky triaryl phosphanes facilitate the desired reaction and inhibit biaryl formation. Comparison of

the results obtained employing isomeric *meta*- and *ortho*-tritolyphosphane ligands illustrates the case rather well [Eq. (4)].



Ultimately, the best conditions were found to involve tri- α -naphthylphosphane as the ligand, with THF as solvent, K₃PO₄ as base, and water (2 equiv.) as coadditive (to facilitate boronate formation). Using these conditions, a wide range of aryl boronic acids were coupled in high yield with ethyl bromoacetate. Pd-catalyzed Suzuki–Miyaura type reactions of aryl halides with diboronates (R₂B–BR₂) or boranes (R₂B–H) have recently emerged as useful routes to aryl boronic acid derivatives.^[16] By connecting the two reactions, Gooßen went on to develop a very effective strategy for the formal hetero-coupling of aryl halides (or pseudohalides) with bromoacetates. The only current limitation with the Gooßen system is the restriction to bromoacetate. As expected, propionates divert by β -H elimination to yield acrylate esters.^[17] However, recent results from Fu et al.^[18] suggest that these problems may not be insurmountable.

Summary and Outlook

Two new methods have been recently disclosed for α -arylation of esters. One route also provides ready access to α -arylated amino acids. Both methods are based on Pd catalysis and the choice of ligand is crucial. The two approaches are complementary with regard to electrophile and nucleophile pairings.

Unless the catalyst efficiencies are increased phenomenally, the current price of Pd will preclude these methods from commercial production processes. Nonetheless, their generality and operational simplicity makes them ideal for discovery chemistry or lead development in the pharmaceutical or agrochemical industries. Since the requisite substrates (acetates and homologues, iminoacetates, aryl halides, and aryl boronates) are often items of commerce or very readily prepared, it should be anticipated that these new synthetic methods will find extensive application in combinatorial-type screening processes.

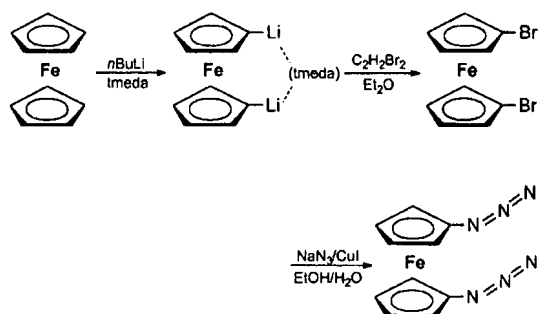
- [1] S. Lee, N. A. Beare, J. F. Hartwig, *J. Am. Chem. Soc.* **2001**, *123*, 8410–8411.
- [2] W. A. Moradi, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 7996–8002.
- [3] L. J. Gooßen, *Chem. Commun.* **2001**, 669–670.
- [4] NSAID = Non-steroidal anti-inflammatory drug. These compounds are cyclooxygenase inhibitors and thus affect prostaglandin synthesis.
- [5] For example by the Willgerdt reaction on the corresponding acetophenone.
- [6] For example by Strecker synthesis from the corresponding benzaldehyde.

- [7] For an example and for leading references, see: F. Agnelli, G. A. Sulikowski, *Tetrahedron Lett.* **1998**, 39, 8807–8810.
- [8] The coordination in Pd-enolate complex is likely to be by the carbon atom (rather than by the oxygen atom). For stoichiometric studies involving analogous intermediates and leading references see: D. A. Culkin, J. F. Hartwig, *J. Am. Chem. Soc.* **2001**, 123, 5816–5817.
- [9] Note that the base employed must not bear a β -hydrogen (because of the potential for undesired Pd^{II} reduction by β -H transfer). *tert*-Butoxide bases proved sluggish whereas hexamethyldisilazide compounds proved useful.
- [10] It is not evident why this works, although there is some discussion of M–O (M = Na, Li) covalency. Perhaps surprisingly, given the reduction of diarylation on switching from NaHMDS to LiHMDS, ethyl phenylacetate can be α -arylated in good yield (based on arylating agent) at 80 °C under essentially the same conditions.
- [11] With very hindered aryl substrates, Hartwig et al., found that *t*Bu₃P proved to be better than the carbene ligand.
- [12] With hindered propionates (those with branching at the α - or β -positions) or glycinate, the ethyl, or methyl ester was preferred over the *tert*-butyl ester.
- [13] The higher C–H acidity of ketimine and aldimine derivatives of glycinate allows the weaker base K₃PO₄ to be employed.
- [14] Homologues (which require generation of a quaternary center) have not yet been successfully prepared by this method.
- [15] M. Moreno-Mañas, M. Pérez, R. Pleixats, *J. Org. Chem.* **1996**, 61, 2346–2351.
- [16] See: M. Murata, T. Oyama, S. Watanabe, Y. Masuda, *J. Org. Chem.* **2000**, 65, 164–168, and references therein.
- [17] L. J. Gooßen, personal communication.
- [18] M. R. Netherton, C. Dai, K. Neuschütz, G. C. Fu, *J. Am. Chem. Soc.* **2001**, 123, 10099–10100.

1,1'-Ferrocenedi(amido) Chelate Ligands in Titanium and Zirconium Complexes

Max Herberhold*

Although known for more than four decades,^[1,2] the sandwich compound [Fe(C₅H₄-NH₂)₂] (**1**) ([fc(NH₂)₂]; fc = ferrocene-1,1'-diyl),^[2,3] has not really been used either as a building block in polymers or as a chelate ligand in transition metal complexes. Recently, however, an improved synthesis—via 1,1'-di(azido)ferrocene ([fc(N₃)₂],^[2] Scheme 1)—has been worked out and the molecular structure of **1** has been determined.^[3]



Scheme 1. Synthesis of 1,1'-di(azido)ferrocene; tmeda = tetramethylethylenediamine.

According to the crystal structure analysis of **1**, the lattice contains two (ecliptic) rotamers, that is the 1,1' and the 1,2' isomer.^[3] The diamine **1** can be protonated, or oxidized (at the iron atom; Scheme 2) to give a green, paramagnetic cation **1a**

($\mu_{\text{eff}} = 2.1 \mu_B$), of which salts of the type [fc(NH₂)₂]⁺A[−] (anion A[−] = PF₆[−], OTf[−] or TCNE[−] (TCNE = tetracyanoethylene) were obtained.^[3]

Starting from the primary diamine **1**, the silylated derivative [fc(NH-SiMe₃)₂] (**2**) can be prepared,^[5] while condensation with benzaldehyde and subsequent hydrogenation generates 1,1'-di(benzylamino)ferrocene, [fc(NH-CH₂Ph)₂] (**3**).^[6]

Titanium and Zirconium Complexes

With regard to the development of new catalysts for the olefin polymerization, during the last few years an increasing number of complexes of the electron-poor transition metals titanium and zirconium with di(amido) chelate ligands has been investigated^[5–8] instead of the highly reactive di(cyclopentadienyl)titanium and -zirconium complexes ("metallocene catalysts"). The doubly deprotonated derivatives of the secondary diamines **2–4** serve as examples for 1,1'-ferrocenedi(amido) ligands (Scheme 2 and 5).

The use of amino-functionalized 1,1'-ferrocenedi(amido) sandwich compounds as chelate ligands provides two particular advantages:

- 1) Owing to the rotational mobility of the two cyclopentadienyl rings around the axis which is defined by the ring centers and the iron atom, the bidentate 1,1'-ferrocenedi(amido) ligand can easily adapt to the steric situation in the coordination sphere of the central metal,—as known for [fc(PPh₂)₂].^[4b]
- 2) Owing to the relatively high charge density in the electron-rich ferrocene sandwich, the iron center can be readily oxidized which may also be controlled by cyclovoltammetry.^[3, 7]

[*] Prof. Dr. M. Herberhold
Laboratorium für Anorganische Chemie
der Universität Bayreuth
Universitätsstrasse 30, 95440 Bayreuth (Germany)
Fax: (+49) 921-55-2540
E-mail: max.herberhold@uni-bayreuth.de