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Efficient Palladium-Catalyzed Cross-Coupling of Highly Acidic Substrates, Nitroacetates

Alison E. Metz,[†] Simon Berritt,[†] Spencer D. Dreher,*[,‡] and Marisa C. Kozlowski*[,†]

Penn Merck High Throughput Experimentation Laboratory, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 1910-6323, United States, and Merck & Co., Inc., Rahway, New Jersey 07065, United States

spencer_dreher@merck.com; marisa@sas.upenn.edu

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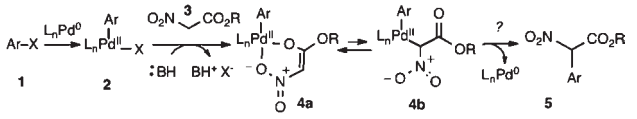
ABSTRACT

Palladium-catalyzed cross-coupling conditions were developed that efficiently afford 2-aryl-2-nitroacetates from aryl bromides and the very acidic nitroacetates.

Formation of C–C bonds via metal-catalyzed cross-couplings has become a broadly useful tool for the construction of organic molecules. In the redox neutral variant (i.e., Stille, Negishi, Kumada, Suzuki, etc.) many nucleophiles have been successfully coupled with a range of halide electrophiles.[1] In addition, numerous obstacles, such as metal coordination and cross-reactivity, have also been overcome in the coupling of nucleophiles generated *in situ* from acidic species. For example, thiolation of aryl halides was one of the first intermolecular cross-couplings involving *in situ* nucleophile formation.[2,3] Subsequently, Hartwig and Buchwald were the first to cross-couple aryl halides with amines and alcohols without the need to preform the corresponding stannyl nucleophiles.[4,5] Concurrently, reductive elimination utilizing softer carbon nucleophiles was being accomplished. Intermolecular cyanoacetate coupling with phenylbromide was first reported in 1985.[5,6] Since then couplings have been expanded to include α-arylation of ketones, azlactones, glycine imines, 1,3-dicarbonyls, sulfones, imines, sulfoximines, and nitroalkanes.[7]

Scheme 1. Nitroacetate Coordination to Palladium



Here, we describe a parallel microscale experimentation (PME) approach to discover suitable conditions for the hitherto unreported coupling of nitroacetates with aryl bromides to generate 2-aryl-2-nitroacetates (Scheme 1). There are few reports[8] on the synthesis of 2-aryl-2-nitroacetates, highlighting a need for development in this area.

[†] The University of Pennsylvania.
[‡] Merck & Co., Inc.

(1) For a recent review refer to: Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417–1492.
(2) For a recent review of cross-coupling to form C–S bonds refer to: Eichman, C. C.; Stambuli, J. P. *Molecules* **2011**, *16*, 590–608.
(3) Kosugi, M.; Shimizu, T.; Migita, T. *Chem. Lett.* **1978**, 13–14.
(4) For a recent review of C–O bond formation via reductive elimination refer to: Enthaler, S.; Company, A. *Chem. Soc. Rev.* **2011**, *40*, 4912–4924.
(5) For select recent reviews of reductive elimination to form a carbon–heteroatom bond refer to: Sadig, J. E. R.; Willis, M. C. *Synthesis* **2011**, *1*, 1–22. Hartwig, J. *Acc. Chem. Res.* **1998**, *31*, 852–860.
(6) Uno, M.; Seto, K.; Ueda, W.; Masuda, M.; Takahashi, S. *Synthesis* **1985**, *5*, 506–508.
(7) For recent reviews refer to: (a) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082–1146. (b) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 676–707.
(8) (a) Lehr, F.; Gonnermann, J.; Seebach, D. *Helv. Chem. Acta* **1979**, *62*, 2258–2275. (b) Ram, S.; Ehrenkaufer, R. E. *Synthesis* **1986**, 133–135. (c) Hugener, M.; Heimgartner, H. *Helv. Chim. Acta* **1995**, *78*, 1490–1498. (d) Kozyrod, R. P.; Pinhey, J. T. *Aust. J. Chem.* **1985**, *38*, 713–721.

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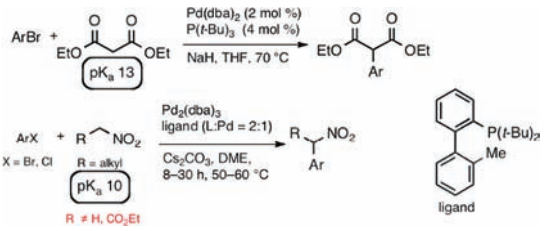
Scheme 2. Hartwig's Coupling of Malonates and Buchwald's Coupling of Nitroalkanes

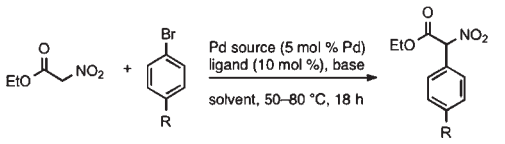


The higher acidity of nitroacetates (pK_a 5.8)[9] combined with a disposition toward chelation poses a new set of challenges in cross-coupling with aryl halides compared to similar activated methylene compounds such as acyclic 1,3-dicarbonyls (pK_a 9−13) and nitroalkanes (pK_a 10) (Scheme 2).[10−12] This high acidity would lead to the expectation that only a very mild base would be needed. However, the resultant anion is a very poor nucleophile and is poised to form highly favorable O,O′-bound intermediates such as **4a** (Scheme 1). Rearrangement to the C-bound form **4b**, a prerequisite for C−C reductive elimination and formation of **5**,[11] would require considerable reorganization and potentially a second ligand. Initial trials utilizing conditions reported for the related malonates[10a] (Scheme 2) were unsuccesful (Table 1, entry 1). Reasoning that milder bases could be used, a range of alternate bases were examined to no avail (entries 2−5). To determine if the reductive elimination step was problematic, a more electron-rich aryl bromide was utilized, but no improvement was seen (entries 6−7). Finally, the optimal ligand for nitroalkanes[12a] (Scheme 2) was studied with similar poor results (entry 8).

While the preliminary results secured that conversion of **2** to **5** is achievable, it was clear that the conditions highly effective for malonates and nitroalkanes were not translatable to nitroacetates. Since our understanding of how the reaction variables effect the mechanism was incomplete, a range of Pd sources, ligands, and bases needed to be examined. To effectively complete this study, parallel microscale experimentation was utilized.[13] By using 1-mL vials with 100 μL reaction volumes at a 0.2 M concentration (4.4 μL of nitroacetate per vial), it was straightforward to undertake 96 reactions very quickly in a single plate (3 d for setup, reaction, and analysis).

Based upon the results in Table 1 an unbiased screen of various phosphines was undertaken at 75 °C with two Pd sources and four bases spanning a broad pK_a range

Table 1. Initial Benchtop Results (eq 1)[a]



entry	R	base	solvent	ligand	conversion[b] (%)
1	H	NaH	THF	P(t-Bu)$_3$	0
2	H	Cs_2CO_3	THF	P(t-Bu)$_3$	0
3	H	Cs_2CO_3	DME	P(t-Bu)$_3$	7
4	H	$CsHCO_3$	DME	P(t-Bu)$_3$	2
5	H	NaOAc	DME	P(t-Bu)$_3$	4
6	OMe	$CsHCO_3$	toluene	P(t-Bu)$_3$	3
7	OMe	NaOAc	toluene	P(t-Bu)$_3$	7
8	H	Cs_2CO_3	toluene	t-BuMePhos	6

[a] Reaction conditions: Pd_2dba_3 (2.5 mol %), nitroacetate (2 equiv), aryl bromide (1 equiv), base (1.2 equiv), and solvent (0.2 M). [b] Determined by ^{1}H NMR with respect to ethyl nitroacetate starting material.

(Figure 1). The conversion as indicated by the product/internal standard ratio is illustrated in the 3-D plot in Figure 1. Table 2 lists the top screening results along with selected isolated yields when performed on a larger scale.

This screen revealed that only three ligands, BrettPhos **L10**, Me$_4$ *t*-BuXPhos **L15**, and *t*-BuXPhos **L14** (Figure 1), provided *any* product with the latter two proving superior. Di-*tert*-butyl substituted biphenylphosphine ligands seem to be superior for cross-couplings of weak nucleophiles as seen here and in other reports.[14,15] In this case, this narrow window suggests that the biphenyl η-1 coordination[15] is critical to forming a reactive species. In addition, blocking of palladacycle formation with the isopropyl groups is necessary.[16] Most surprising was the narrow range of sterically acceptable ligands with the smaller XPhos **L9** failing while the two methoxy groups of BrettPhos **L10** offset the smaller phosphine cyclohexyl substituents (**L9** < **L10** ≪ **L15** < **L14**). On the other end, Me$_4$ *t*-BuXPhos **L15** appears too large.

With the *t*-BuXPhos (**L14**) ligand and the $CsHCO_3$ base held constant, further parallel microscale experimentation was undertaken (Figure 2). On the whole, lower temperatures (75 vs 110 °C) provided better results, presumably due to product decomposition at the higher temperature. With every solvent combination, $Pd_2dba_3 \cdot CHCl_3$ and a preformed palladacycle containing the optimal *t*-BuXPhos ligand[17] gave consistent results, whereas $[(allyl)PdCl]_2$ and $Pd(OAc)_2$ were less consistent. Upon scale up, $Pd_2dba_3 \cdot CHCl_3$ provided high isolated yields (93%) with the

(9) Adolph, H. G.; Kamlet, M. J. *J. Am. Chem. Soc.* **1966**, *88*, 4761–4763.

(10) (a) Beare, N. A.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 541–555. (b) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360–1370.

(11) Hartwig, J. F.; Culkin, D. A. *Acc. Chem. Res.* **2003**, *36*, 234–245.9.

(12) (a) Vogl, E. M.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 106–111. (b) Muratake, H.; Nakai, H. *Tetrahedron Lett.* **1999**, *40*, 2355–2358.

(13) Dreher, S. D.; Dormer, P. G.; Sandrock, D. L.; Molander, G. A. *J. Am. Chem. Soc.* **2008**, *130*, 9257–9259.

(14) Rosen, B. R.; Ruble, J. C.; Beauchcamp, T. J.; Navarro, A. *Org. Lett.* **2011**, *13*, 2564–2567.

(15) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696.

(16) (a) Burgos, C. H.; Barder, T. E.; Huang, X.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 4321–4326. (b) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 676–707.

(17) Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 6686–6687.

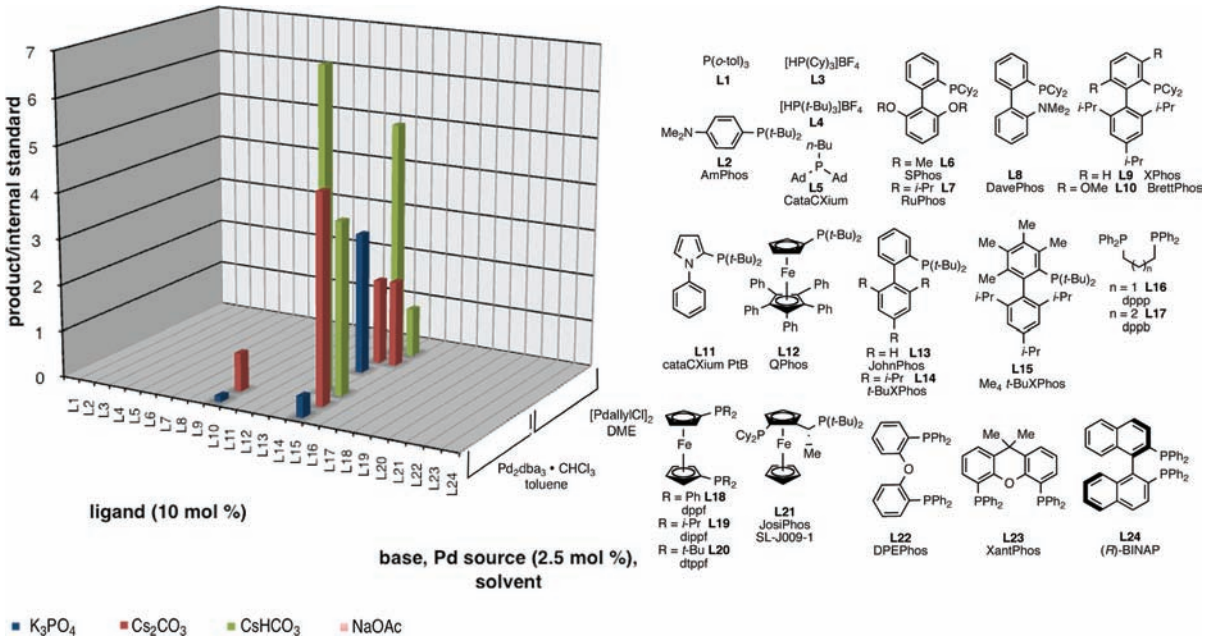


Figure 1. Graphical summary of PME screen #1 (eq 1, R = H, T = 75 °C) (Ad = adamantyl).

Table 2. Top Screening Results from PME Screen #1 and Scale up (eq 1, R = H)

entry	ligand	Pd	base	solvent	product/ IS[a], yield[b]
1	*t*-BuXPhos	$Pd_2dba_3 \cdot CHCl_3$	$CsHCO_3$	toluene	6.9, 93%
2	*t*-BuXPhos	$(allylPdCl)_2$	$CsHCO_3$	DME	5.1, 46%
3	Me_4*t*-Bu XPhos	$Pd_2dba_3 \cdot CHCl_3$	Cs_2CO_3	toluene	4.5, N/A[c]
4	Me_4*t*-BuXPhos	$Pd_2dba_3 \cdot CHCl_3$	$CsHCO_3$	toluene	3.7, N/A[c]
5	*t*-BuXPhos	$(allylPdCl)_2$	K_3PO_4	DME	3.0, N/A[d]
6	Me_4*t*-BuXPhos	$(allylPdCl)_2$	Cs_2CO_3	DME	1.8, N/A[d]
7	*t*-BuXPhos	$(allylPdCl)_2$	Cs_2CO_3	DME	1.8, 53%
8	Me_4*t*-BuXPhos	$(allylPdCl)_2$	$CsHCO_3$	DME	1.04, N/A[d]

[a] Relative conversions from screen (IS = internal standard). [b] Isolated yields upon scale up (0.25 mmol scale). [c] Not isolated because conversion by ^{1}H NMR was low. [d] Not scaled up.

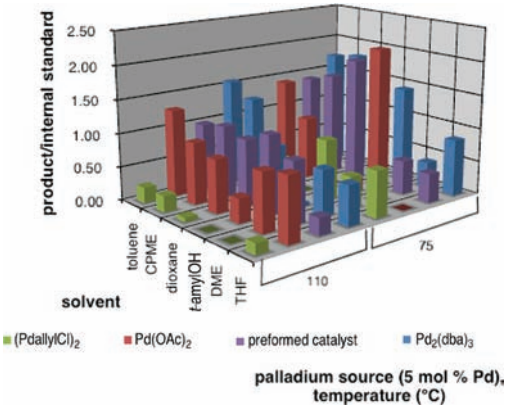


Figure 2. Graphical summary of PME screen #2 results (eq 1, R = H, base = $CsHCO_3$, ligand = *t*-BuXPhos) (CPME = cyclopentyl methyl ether, *t*-amylOH = *tert*-amyl alcohol).

preformed catalyst being less effective (88%). Nonpolar solvents performed better than polar solvents.

Further experiments indicated that a 2:1 ligand/Pd ratio was the most effective, in line with other results with enolates.[10,12] As expected for this reaction where deprotonation of the nitroacetate is a key step, a base was cruical (Table 3, entry 1). An examination of bases (Table 3) found that relative to $CsHCO_3$ (entry 2) stronger bases (K_3PO_4, Cs_2CO_3, Figure 1; CsOH, NaO*t*-Bu, entries 3−4) were not as successful. Presumably, stronger bases generate larger amounts of the nitroacetate anion, which is not very soluble.[10a] Bases with harder cations ($KHCO_3$, $NaHCO_3$, Li_2CO_3, entries 5−7) provided little or no product formation, due to either lower solubility or greater bonding to the nitronate anion, which would impede ligand exchange. On the other end of the spectrum, even softer counterions (Rb_2CO_3, entry 8) performed similarly relative to cesium. CsF (entry 9) with the optimal counterion and a similar pK_a relative to $CsHCO_3$ was effective, but less so, indicating that the fluoride anion may remain involved. Amine bases were ineffective (entries 10−13).

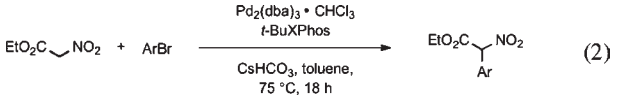
The best reaction conditions were 2.5 mol % $Pd_2dba_3 \cdot CHCl_3$, 10 mol % *t*-BuXPhos, and 1.2 equiv of $CsHCO_3$ in toluene at 75 °C, which afforded the products from various aryl bromides and ethyl nitroacetate in isolated yields of 52−96% (Table 4). Notably, electron-rich and -poor aryl bromides reacted well reinforcing the notion that oxidative addition is not the problematic step. In addition,

Table 3. Benchtop Screen of Bases (eq 1, R = H)[a]

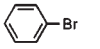
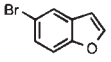
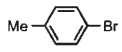
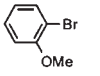
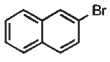
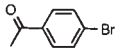
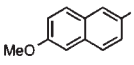
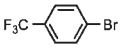
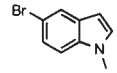
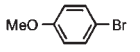
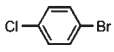
entry	base	conversion[b](%), yield[c](%)	entry	base	conversion[b] (%), yield[c](%)
1	none	0, 0	8	Rb_2CO_3	100, 90
2	$CsHCO_3$	100, 93	9	CsF	60, 60
3	CsOH	41, N/A[d]	10	$(i\text{-Pr})_2NEt$	0, 0
4	NaO*t*-Bu	0, 0	11	DMAP	0, 0
5	$KHCO_3$	19, N/A[d]			
6	$NaHCO_3$	0, 0	12	2,6-(*t*-Bu)$_2$-4-MePy	0, 0
7	Li_2CO_3	0, 0	13	DBU	10, N/A[d]

[a] Reaction conditions: Pd_2dba_3•$CHCl_3$ (2.5 mol %), nitroacetate (2 equiv), aryl bromide (1 equiv), base (1.2 equiv), and toluene (0.2 M) at 75 °C. [b] Conversion by ^1H NMR with respect to remaining ethyl nitroacetate. [c] Isolated yields. [d] Not isolated.

Table 4. Reaction of Ethyl Nitroacetate with ArBr (eq 2)[a]



(2)

entry	aryl bromide	yield (%)	entry	aryl bromide	yield (%)
1		93	7		52
2		79	8		80
3[b]		69	9		77
4		96	10		76
5		71	11		95
6		81	12		61

[a] Reaction conditions: 5 mol % Pd, 10 mol % ligand, ethyl nitroacetate (2 equiv), aryl bromide (1 equiv), $CsHCO_3$ (1.2 equiv), and toluene (0.2 M). [b] 20 mol % Pd.

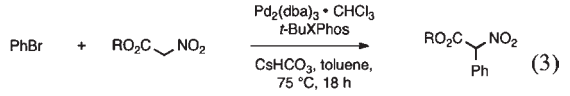
heterocyclic compounds (entries 7 and 11) could be employed. Interestingly, ketones did not undergo a competing reaction with the nitroacetate anion (entry 4). Reaction selectivity for aryl bromides over aryl chlorides was observed (entry 12) with only a small amount of the dicoupled product isolated (16%).

On the other hand, the method was not suitable for aryl iodides, triflates, and chlorides. Since such species undergo oxidative addition under these conditions, the nature of the counterion may be critical to the transmetalation of **3** to **4** (Scheme 1) in line with related reports on other enolates.[18]

While moderately hindered aryl bromides couple (Table 4, entry 3), more hindered compounds such as 1-bromonaphthalene or *ortho*-bromotoluene were not successful. Hartwig and Culkin notice this downfall in the α-arylation of ketones[11] and propose it arises from the inability of the O,O-bound Pd intermediate **4a** to rearrange to the C-bound intermediate **4b**, an already difficult proposition in this system (Scheme 1).

To further probe the reactivity of this system methyl, *tert*-butyl, and benzyl nitroacetates were synthesized.[19] These nitroacetate couplings afforded product in moderate to good yields (Table 5). The increased tendency of methyl nitroacetate to hydrolyze and decarboxylate lowers the isolated yield (entry 1).

Table 5. Reaction of Various Nitroacetates with PhBr (eq 3)[a]



(3)

entry	R	yield (%)
1	Me	53
2	Et	93
3	*t*-Bu	88
4	Bn	95

[a] Reaction conditions: 5 mol % Pd, 10 mol % *t*-BuXPhos, nitroacetate (2 equiv), aryl bromide (1 equiv), $CsHCO_3$ (1.2 equiv), and toluene (0.2 M).

In summary, we have developed conditions for the catalytic cross-coupling of nitroacetates with aryl bromides to generate 2-aryl-2-nitroacetates. A key requirement in the Pd-catalyzed coupling is the use of *t*BuXPhos as a ligand, which is likely a result of the high acidity of the nitroacetate substrate and O,O′-chelation competing with C-coordination to Pd. An improved understanding of ligand requirements is critical to the more rapid development of these important processes.

Acknowledgment. We thank Mr. Trung Cao for training on the Penn Merck PME equipment (NSF GOALI CHE-0848460) and are grateful to the NIH (RO1GM087605) for financial support. Partial instrumentation support was provided by the NIH for MS (1S10RR023444) and NMR (1S10RR022442).

Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(18) Liao, X; Weng, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 195–200.

(19) Vanier, S. F.; Larouche, G.; Wurz, R. P.; Charette, A. B. *Org. Lett.* **2010**, *12*, 672–675.