

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

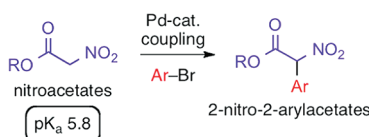
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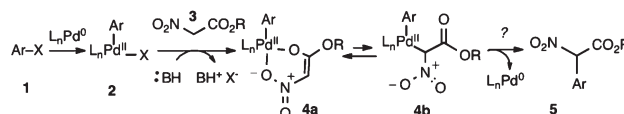
ABSTRACT



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

Scheme 1. Nitroacetate Coordination to Palladium



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

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 reports⁸ on the synthesis of 2-aryl-2-nitroacetates, highlighting a need for development in this area.

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(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.

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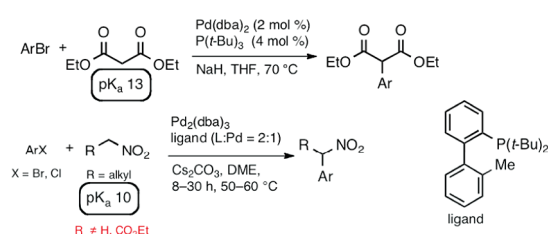
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Scheme 2. Hartwig's Coupling of Malonates and Buchwald's Coupling of Nitroalkanes

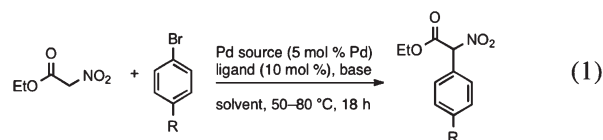


The higher acidity of nitroacetates (pK_a 5.8)⁹ combined with a disposition toward chelation poses a new set of challenges in cross-coupling with aryl halides compared to similar activated methylene compounds such as acyclic 1,3-dicarbonyls (pK_a 9–13) and nitroalkanes (pK_a 10) (Scheme 2).^{10–12} This 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 unsuccessful (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 μ L reaction volumes at a 0.2 M concentration (4.4 μ L 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 ₂ CO ₃	THF	P(t-Bu) ₃	0
3	H	Cs ₂ CO 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 ₂ CO ₃	toluene	<i>t</i> -BuMePhos	6

^a Reaction conditions: Pd₂dba₃ (2.5 mol %), nitroacetate (2 equiv), aryl bromide (1 equiv), base (1.2 equiv), and solvent (0.2 M). ^b Determined by ¹H 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**, Me₄ *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 coordination¹⁵ 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, Me₄ *t*-BuXPhos **L15** appears too large.

With the *t*-BuXPhos (**L14**) ligand and the CsHCO₃ 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, Pd₂dba₃·CHCl₃ and a preformed palladacycle containing the optimal *t*-BuXPhos ligand¹⁷ gave consistent results, whereas [(allyl)PdCl]₂ and Pd(OAc)₂ were less consistent. Upon scale up, Pd₂dba₃·CHCl₃ provided high isolated yields (93%) with the

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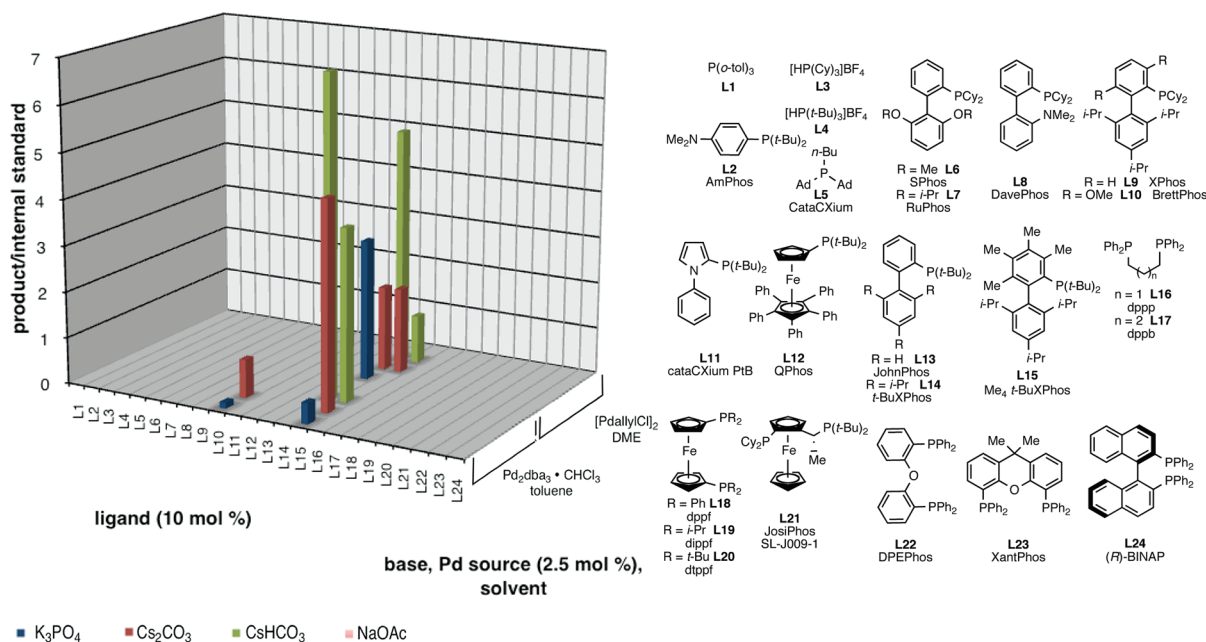


Figure 1. Graphical summary of PME screen #1 (eq 1, R = H, T = 75 °C) (Ad = adamantyl).

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	<i>t</i> -BuXPhos	Pd ₂ dba ₃ • CHCl ₃	CsHCO ₃	toluene	6.9, 93%
2	<i>t</i> -BuXPhos	(allyl)PdCl ₂	CsHCO ₃	DME	5.1, 46%
3	Me ₂ <i>t</i> -Bu XPhos	Pd ₂ dba ₃ • CHCl ₃	Cs ₂ CO ₃	toluene	4.5, N/A ^c
4	Me ₂ <i>t</i> -BuXPhos	Pd ₂ dba ₃ • CHCl ₃	CsHCO ₃	toluene	3.7, N/A ^c
5	<i>t</i> -BuXPhos	(allyl)PdCl ₂	K ₃ PO ₄	DME	3.0, N/A ^d
6	Me ₂ <i>t</i> -BuXPhos	(allyl)PdCl ₂	Cs ₂ CO ₃	DME	1.8, N/A ^d
7	<i>t</i> -BuXPhos	(allyl)PdCl ₂	Cs ₂ CO ₃	DME	1.8, 53%
8	Me ₂ <i>t</i> -BuXPhos	(allyl)PdCl 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 ¹H NMR was low. ^d Not scaled up.

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 crucial (Table 3, entry 1). An examination of bases (Table 3) found that relative to CsHCO₃ (entry 2) stronger bases (K₃PO₄, Cs₂CO₃, 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 (KHCO₃, NaHCO₃, Li₂CO₃, 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

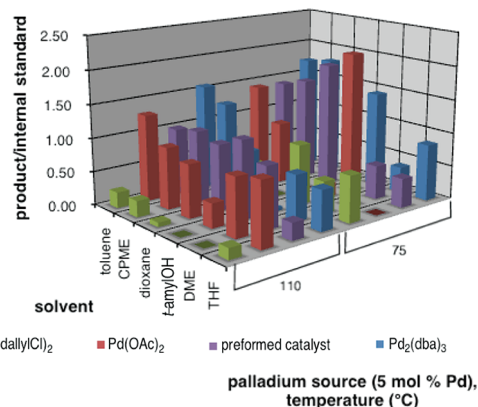


Figure 2. Graphical summary of PME screen #2 results (eq 1, R = H, base = CsHCO₃, ligand = *t*-BuXPhos) (CPME = cyclopentyl methyl ether, *t*-amylOH = *tert*-amyl alcohol).

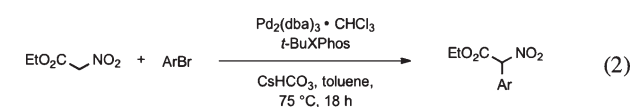
(Rb₂CO₃, entry 8) performed similarly relative to cesium. CsF (entry 9) with the optimal counterion and a similar p*K*_a relative to CsHCO₃ was effective, but less so, indicating that the fluoride anion may remain involved. Amine bases were ineffective (entries 10–13).


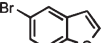




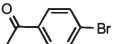
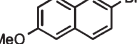
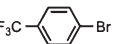
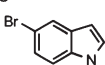
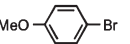

The best reaction conditions were 2.5 mol % Pd₂dba₃ • CHCl₃, 10 mol % *t*-BuXPhos, and 1.2 equiv of CsHCO₃ in toluene at 75 °C, which afforded the products from various aryl bromides and ethyl nitroacetate in isolated yields of 52–96% (Table 4). Notably, electron-rich and -poor aryl bromides reacted 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 ₂ CO ₃	100, 90
2	CsHCO ₃	100, 93	9	CsF	60, 60
3	CsOH	41, N/A ^d	10	(<i>i</i> -Pr) ₃ NEt	0, 0
4	NaO <i>t</i> -Bu	0, 0	11	DMAP	0, 0
5	KHCO ₃	19, N/A ^d	12	2,6-(<i>t</i> -Bu) ₂ -4-MePy	0, 0
6	NaHCO ₃	0, 0	13	DBU	10, N/A ^d
7	Li ₂ CO ₃	0, 0			

^a Reaction conditions: Pd₂(dba)₃•CHCl₃ (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

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), CsHCO₃ (1.2 equiv), and toluene (0.2 M). ^b 20 mol % Pd.

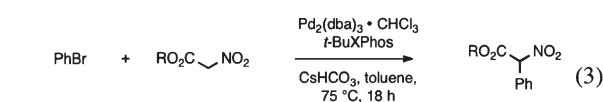
heterocyclic compounds (entries 7 and 11) could be employed. Interestingly, ketones did not undergo a competing reaction with the nitroacetate anion (entry 4). Reaction selectivity for aryl bromides over aryl chlorides was observed (entry 12) with only a small amount of the dicoupled product isolated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

talation 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 ketones¹¹ 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

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

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

^a Reaction conditions: 5 mol % Pd, 10 mol % *t*-BuXPhos, nitroacetate (2 equiv), aryl bromide (1 equiv), CsHCO₃ (1.2 equiv), and toluene (0.2 M).

nitroacetate to hydrolyze and decarboxylate lowers the isolated yield (entry 1).

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.

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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>.

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