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Palladium-Catalyzed Nitromethylation of Aryl Halides: An Orthogonal Formylation Equivalent

Ryan R. Walvoord, Simon Berritt, and Marisa C. Kozlowski*

Penn Merck High Throughput Experimentation Laboratory, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323, United States

marisa@sas.upenn.edu

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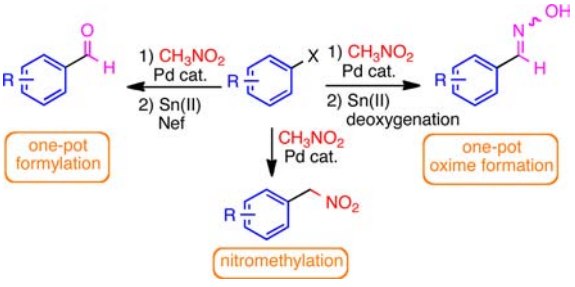
ABSTRACT



An efficient cross-coupling reaction of aryl halides and nitromethane was developed with the use of parallel microscale experimentation. The arylnitromethane products are precursors for numerous useful synthetic products. An efficient method for their direct conversion to the corresponding oximes and aldehydes in a one-pot operation has been discovered. The process exploits inexpensive nitromethane as a carbonyl equivalent, providing a mild and convenient formylation method that is compatible with many functional groups.

Nitroalkanes are compounds of unique and versatile reactivity.[1] Their ability to undergo powerful stereoselective carbon−carbon bond formation[2] in addition to numerous functional group transformations[3] makes them highly desirable synthetic intermediates. Despite this utility, access to nitroalkanes remains synthetically challenging.[1a,4] The coupling of aryl halides with nitromethane, an inexpensive and readily available solvent, would represent an ideal method to prepare a wide variety of arylnitromethanes, precursors to an array of valuable compounds (Scheme 1). In particular, we envisaged that by exploiting the conversion of the nitro to carbonyl group, the Nef reaction, this method would represent a novel, mild formylation orthogonal to Friedel−Crafts and lithiation/formylation transforms.[5] Furthermore, nitromethane is more easily deployed as a formyl equivalent on a small scale compared to carbon monoxide, a toxic gas that requires tanks and often high temperatures and pressures.[6] Herein, we describe the Pd-catalyzed coupling of aryl halides with nitromethane to afford arylnitromethanes and subsequent Sn(II)-mediated Nef reaction to provide aryl oximes or aryl aldehydes.

Our primary challenge lay in developing a facile, robust method to access arylnitromethanes. As observed in recent

(1) (a) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001. (b) Feuer, H., Nielsen, A. T., Eds. In *Nitro Compounds: Recent Advances in Synthesis and Chemistry*; VCH Publishers: New York, 1990; Chapters 1−2. (c) Rosini, G.; Ballini, R. *Synthesis* **1988**, 833–847.

(2) For recent reviews on C−C bond formation with nitroalkanes, see: (a) Marques-Lopez, E.; Merino, P.; Tejero, T.; Herrera, R. P. *Eur. J. Org. Chem.* **2009**, 2401–2420. (b) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933–971. (c) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915–945.

(3) (a) Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *Chimia* **1979**, *33*, 1–18. (b) Ballini, R.; Palmieri, A.; Righi, P. *Tetrahedron* **2007**, *63*, 12099–12121.

(4) Greger, J. G.; Yoon-Miller, S. J. P.; Bechtold, N. R.; Flewelling, S. A.; MacDonald, J. P.; Downey, C. R.; Cohen, E. A.; Pelkey, E. T. *J. Org. Chem.* **2011**, *76*, 8203–8214.

(5) For reviews on aromatic formylation, see: (a) Olah, G. A.; Ohannesian, L.; Arvanaghi, M. *Chem. Rev.* **1987**, *87*, 671–686. (b) Kantlehner, W. *Eur. J. Org. Chem.* **2003**, 2530–2546 and references therein. (c) Wakefield, B. J. *Organolithium Methods*; Academic Press: San Diego, CA, 1988.

(6) (a) Shoenberg, A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 7761–7764. (b) Klaus, S.; Neumann, H.; Zapf, A.; Strübing, D.; Hübner, S.; Almena, J.; Riermeier, T.; Gross, P.; Sarich, M.; Krahnert, W.-R.; Rossen, K.; Beller, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 154–158. (c) Sergeev, A. G.; Spannenberg, A.; Beller, M. *J. Am. Chem. Soc.* **2008**, *130*, 15549–15563.

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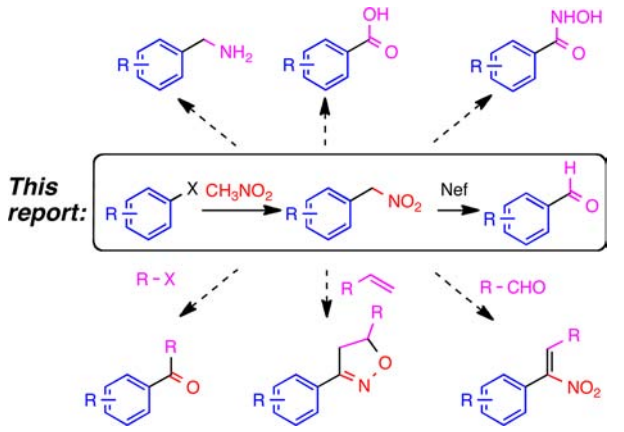
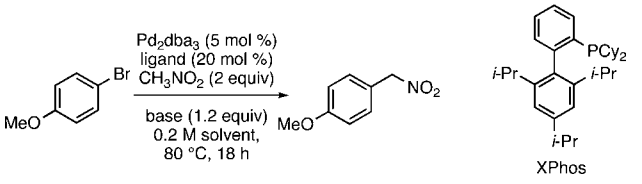
Scheme 1. Utility of the Products from the Coupling of Nitromethane with Aryl Halides



studies utilizing these compounds,[4,7] current methods to generate arylnitromethanes (nitrite displacement of benzylic bromides,[8] oxidation of benzyl amines[9] and oximes[10]) are unsatisfactory,[11] owing to poor efficiency, generality, and availability of the corresponding substrates. We sought to develop a less expensive[12] and more reliable method using nitromethane as a soft nucleophile in a palladium-catalyzed cross-coupling.[13] With the knowledge that this cross-coupling had been described as problematic due to low yields and multiple products,[14] parallel microscale experimentation[15] was implemented to rapidly screen a large number of conditions and draw out trends. Using *para*-bromoanisole as a test substrate, 19 ligands, 4 solvents, and 4 bases were initially assessed using 2 equiv of nitromethane with Pd_2dba_3 at 80 °C.[16] Unlike nitroethane and higher congeners for which tBuMePhos[17] or tBuXPhos[15b] are effective, bis-*tert*-butyl ligands performed poorly here with the exception of cataCXium POMetBu, which was less consistent overall (see below). Rather, the biscyclohexyl ligands XPhos and BrettPhos were superior. These results are surprising since nitromethane is smaller, and it was expected that larger ligands would be needed to force formation of the less favorable C-bound vs O-bound palladium adduct.[18]

A detailed analysis of the HPLC data was crucial to further optimization, revealing the formation of multiple byproducts including debrominated substrate, aldehyde, and decomposition products. Table 1 collects the conversions to the product and all the impurities relative to an internal standard. While cataCXium POMetB gave the highest conversion, there were also large amounts of impurities. Using the difference of the product and impurity conversion (last column, Table 1) as a measure of selectivity to the desired product, further optimization was conducted with XPhos, which is also less costly than the other two candidates.

Table 1. Top Results from the Initial Screen[a]



ligand	solvent	base	prod/IS	impurities/IS	impurities/IS −prod/IS
XPhos	**THF**	**K_3PO_4**	**1.96**	**2.48**	**0.52**
BrettPhos	DME	K_3PO_4	1.75	2.30	0.54
cataXCium POMetB	1,4-dioxane	NaO*t*-Bu	2.40	2.96	0.57
XPhos	1,4-dioxane	K_3PO_4	1.93	2.86	0.93
cataXCium POMetB	1,4-dioxane	K_3PO_4	1.93	3.21	1.28
BrettPhos	THF	Cs_2CO_3	1.66	3.08	1.42
BrettPhos	1,4-dioxane	K_3PO_4	1.82	3.33	1.51
JohnPhos	1,4-dioxane	K_3PO_4	1.87	4.22	2.34

[a] IS = Internal standard.

Postulating that increasing the effective concentration of the nucleophile might improve rate and minimize decomposition pathways, neat nitromethane was employed to good effect, providing shorter reaction times and cleaner reaction profiles. To further suppress aldehyde formation, which requires water, molecular sieves were added. As a result, the optimal conditions of Pd_2dba_3 with the XPhos ligand, Cs_2CO_3, powdered 3 Å molecular sieves, and 0.1 M nitromethane as solvent were discovered (Table 2).

(7) Davis, T, A.; Johnston, J. N. *Chem. Sci.* **2011**, *2*, 1076–1077.

(8) (a) Kornblum, N.; Taub, B.; Ungnade, H. E. *J. Am. Chem. Soc.* **1954**, *76*, 3209–2111. (b) Kornblum, N.; Larson, H. O.; Blackwood, R. K.; Mooberry, D. D.; Oliveto, E. P.; Graham, G. E. *J. Am. Chem. Soc.* **1956**, *78*, 1497–1501. (c) Ballini, R.; Barboni, L.; Giarlo, G. *J. Org. Chem.* **2004**, *69*, 6907–6908.

(9) (a) Emmons, W. D. *J. Am. Chem. Soc.* **1957**, *79*, 5528–5530. (b) Rozen, S.; Kol, M. *J. Org. Chem.* **1992**, *57*, 7342–7344.

(10) (a) Emmons, W. D.; Pagano, A. S. *J. Am. Chem. Soc.* **1955**, *77*, 4557–4559. (b) Bose, D. S.; Vanajatha, G. *Synth. Commun.* **1998**, *28*, 4531–4535.

(11) Independent work in our lab also showed that the $AgNO_2$ or $NaNO_2$ methods provided the arylnitromethanes in low to moderate yields (30−50%) for typical cases [BnBr, *p*-$ClC_6H_4CH_2Br$, *p*-(*t*-Bu)-$C_6H_4CH_2Br$, *m*-$CF_3C_6H_4CH_2Br$] and purification was difficult due to multiple byproducts. Activated or hindered systems (*p*-MeOBnBr, 1-NapCH_2Br, 2-NapCH_2Br) gave little (<20%) or no product. We found that oxidation of the corresponding aryl oximes was also low yielding (<20%).

(12) Superstoichiometric $AgNO_2$ ($48/10 g via Sigma-Aldrich) is typically employed.

(13) Prim, D.; Campagne, J.-M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, *58*, 2041–2075.

(14) Vogl, E. M.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 106–111.

(15) (a) Dreher, S. D.; Dormer, P. G.; Sandrock, D. L.; Molander, G. A. *J. Am. Chem. Soc.* **2008**, *130*, 9257–9259. (b) Metz, A. E.; Berritt, S.; Dreher, S. D.; Kozlowski, M. C. *Org. Lett.* **2012**, *14*, 760–763.

(16) See the Supporting Information for additional details regarding the high-throughput experimentation.

(17) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360–1370.

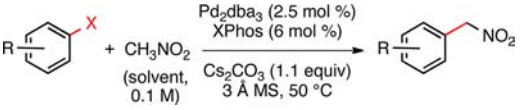
(18) Liao, X.; Weng, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 195–200.

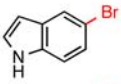
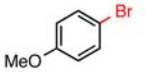
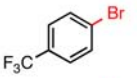
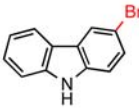
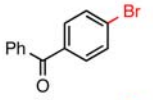
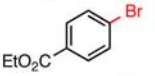
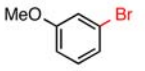
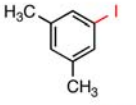
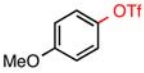
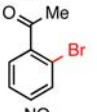
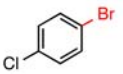
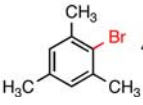
These optimized conditions were effective with substrates possessing electron-donating and -withdrawing groups (Table 2, entries 1–9), *ortho*-substituents (entries 7–9), and even highly sterically encumbered substrates (entry 10). Ketones bearing acidic protons were well tolerated and did not exhibit competitive coupling or reaction with nitromethane under the basic reaction conditions (entry 8). As formation of *ortho*-substituted or electron-rich arylnitromethanes via S_N2 displacement of the corresponding benzyl bromides has been shown to be a poor process,[19] this report allows greatly improved access to a range of novel arylnitromethanes. Heteroaryls were also well tolerated, although higher reaction temperatures (70–80 °C) were needed (entries 11–14). In addition to bromides, aryl iodides and triflates could be coupled effectively (entries 15–16). On the other hand, chlorides undergo reaction more slowly and require higher temperatures (80 °C, entry 17). Since the rate with aryl bromides was much faster relative to that of aryl chlorides, chloro-substituted aryl bromides could be selectively coupled (entries 18–19).

With a robust method for accessing arylnitromethanes in hand,[20] we next elected to examine the Nef disproportionation[21] to produce the aryl aldehydes. Conventional Nef conditions,[22] which proceed by hydrolysis of the requisite primary aryl nitronic acid, are problematic for the formation of aryl aldehydes.[23] Indeed, exhaustive attempts at utilizing hydrolytic Nef conditions failed on these substrates, providing only recovered substrate. Use of commonly employed $KMnO_4$ yielded significant amounts of oxidatively coupled dimers,[24] even when conducted under extremely dilute conditions. We discovered that a modified procedure using tin(II) chloride[25] was most effective and permitted a far wider range of functional groups to be employed (Table 3). In this one-pot reaction, aryl aldehydes with electron-donating (entries 1–2) and electron-withdrawing groups (entries 3–7) were readily produced. Notably, yields are high for the ketone and ester (entries 5–6), which cannot be generated directly via Friedel–Crafts or lithiation/formylation chemistry. Synthesis of heteroarylaldehydes was also demonstrated (entry 8), although incomplete conversion of the oxime intermediate was observed in this unoptimized reaction.

The overall process, aryl halide to aryl aldehyde, represents a process complementary to Friedel–Crafts reactions,[26] which is restricted to arenes with electron-donating substituents at the *ortho*- or *para*-positions, and lithiation/formylation,[27] which is not compatible with many functional groups. In addition, nitromethane is easier to employ as a formylation equivalent relative to carbon monoxide.

Table 2. Scope of Palladium-Catalyzed Nitromethane Coupling



entry	substrate	time (h)	yield (%)[a]	entry	substrate	time (h)	yield (%)[a]
1		3.5	77	11[b]		2	76
2		5	93	12[c]		1.5	83
3		5	87	13[b]		2	48
4		6	77	14[c]		2.5	77
5		6	61				
6		5	93	15		6	70
7		3.5	93	16		4	78
8		4	91	17[c]		1	44
9		4	89	18		7	69
10		4.5	97	19[d]		12	58

[a] Isolated yield after column chromatography. [b] Unoptimized. Conducted at 70 °C. [c] Conducted at 80 °C with 5 mol % Pd_2dba_3 and 12 mol % XPhos. [d] Conducted at 50 °C with 5 mol % Pd_2dba_3 and 12 mol % XPhos.

(19) (a) Kornblum, N.; Smiley, R. A.; Blackwood, R. K.; Iffland, D. C. *J. Am. Chem. Soc.* **1955**, *77*, 6269–6280. (b) Kupchan, S. M.; Wormser, H. C. *J. Org. Chem.* **1965**, *30*, 3792–3800. (c) Cameron, D. W.; Crosby, I. T.; Feutrill, G. E.; Pietersz, G. A. *Aust. J. Chem.* **1992**, *45*, 2003–2024.

(20) After completion of this work, we discovered a related reaction (only in the Supporting Information of: Burkhard, J. A.; Tchitchanov, B. H.; Carreira, E. M. *Ang. Chem. Int. Ed.* **2011**, *50*, 5379–5382). The conditions described therein [10 equiv of $MeNO_2$, 1.5 mol % Pd_2dba_3, 6 mol % tBuMePhos, 1.1 equiv of Cs_2CO_3, DME, 50 °C, 16.5 h] provided lower yields over longer reaction times (16.5 vs 5 h) with *p*-bromoanisole (74% vs 93% from Table 2, entry 2) and much lower yields with 2-bromomesitylene (< 17% vs 97% Table 2, entry 9).

(21) For a review of recent Nef reactions, see: Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017–1047.

(22) Nef, J. U. *Liebigs Ann. Chem.* **1894**, *280*, 263–291.

(23) (a) Kornblum, N.; Brown, R. A. *J. Am. Chem. Soc.* **1965**, *87*, 1742–1747. (b) Kornblum, N.; Grahem, G. E. *J. Am. Chem. Soc.* **1951**, *73*, 4041–4043. (c) Semmelhack, M. F.; Keller, L.; Sato, T.; Speiss, E. J.; Wulff, W. *J. Org. Chem.* **1985**, *50*, 5566–5574.

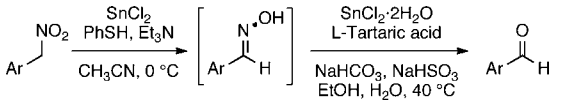
(24) (a) Shechter, H.; Williams, F. T., Jr. *J. Org. Chem.* **1962**, *27*, 3699–3701. (b) Zhang, Z.; Yu, A.; Zhou, W. *Bioorg. Med. Chem.* **2007**, *15*, 7274–7280.

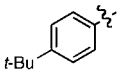
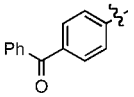
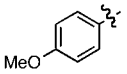
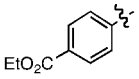
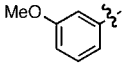
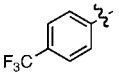
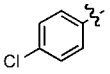
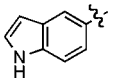
(25) (a) Urpi, F.; Vilarrasa, J. *Tetrahedron Lett.* **1990**, *31*, 7499–7500. (b) Bartra, M.; Romea, P.; Urpi, F.; Vilarrasa, V. *Tetrahedron* **1990**, *46*, 587–594.

(26) Martinez, A. G.; Alvarez, R. M.; Barcina, J. O.; Cerero, S. M.; Vilar, E. T.; Fraile, A. G.; Hanack, M.; Subramanian, L. R. *J. Chem. Soc., Chem. Commun.* **1990**, 1571–1572.

(27) Sicé, J. *J. Am. Chem. Soc.* **1953**, *75*, 3697–3700.

Table 3. Sn(II)-Mediated Nef Reaction



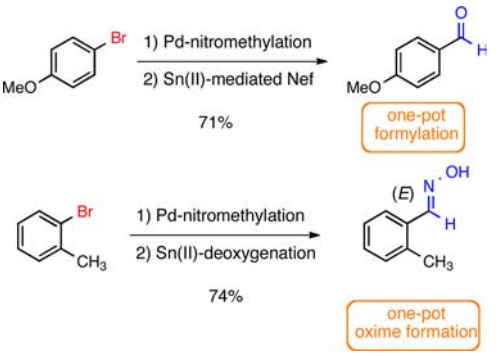
entry	Ar	yield (%)[a]	entry	Ar	yield (%)[a]
1		69	5		87
2		67	6		79
3		68	7		41
4		70	8[b]		58

[a] Isolated yield after column chromatography. [b] Incomplete conversion of the intermediate oxime was observed.

Reasoning that the nitromethane coupling and the Nef reaction could be combined into a convenient, one-pot process, *para*-bromoanisole was subjected to the coupling conditions. Upon consumption of the starting material, the solvent was removed, and the arylnitromethane was directly subjected to the Nef conditions, generating the aryl aldehyde (Scheme 2, top reaction) in good yield in a one-pot process. Similarly, the one-pot process could be halted at the oxime stage with the hindered substrate *ortho*-bromotoluene in good yield (Scheme 2, bottom reaction). Notably, this latter transformation provides a different synthetic disconnection for generating oximes.

In conclusion, a highly selective monocoupling of nitromethane to aryl halides has been developed. The key to developing this useful transformation was the recognition of the unique reactivity of both nitromethane and the reaction product under basic conditions. This study illustrates that selection of a system for further optimization by relying on a singular outcome (e.g., product conversion) is not the most advantageous. Rather, to optimize the formation of product and simultaneously suppress the formation of multiple byproducts, parallel microscale

Scheme 2. One-Pot Formylation and Oxime Formation



experimentation proved useful to examining many variables in concert. The resultant mild method allows for facile synthesis of a range of arylnitromethanes, a class of useful materials that is difficult to obtain efficiently through reported methods. A subsequent highly selective Nef procedure provides easy access to the corresponding oximes or aldehydes. A one-pot protocol telescoping the cross-coupling and Nef reactions provides a mild, useful alternative to formylation with carbon monoxide as well as an expeditious entry to oximes. Additional efforts to explore these processes and understand the key role of the ligand are currently underway.

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

The authors declare no competing financial interest.