Organic Letters

Letter

pubs.acs.org/OrgLett

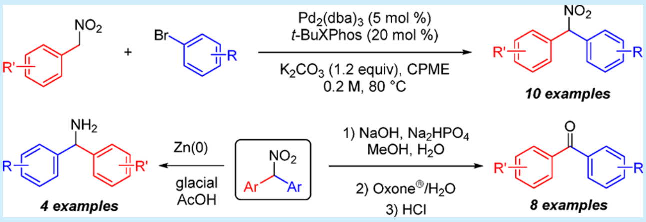
Palladium-Catalyzed α-Arylation of Aryl Nitromethanes

Kelsey F. VanGelder and Marisa C. Kozlowski*

Department of Chemistry, Roy and Diana Vagelos Laboratories, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323, United States

S *Supporting Information*

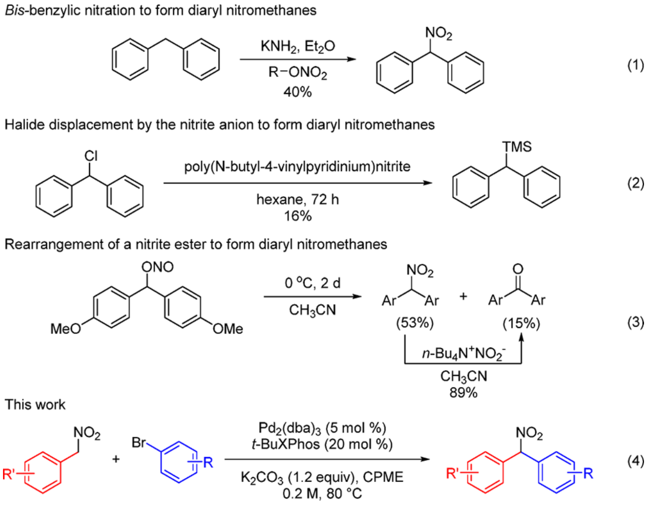
ABSTRACT: Catalytic conditions for the α-arylation of aryl nitromethanes have been discovered using parallel microscale experimentation, despite two prior reports of the lack of reactivity of these aryl nitromethane precursors. The method efficiently provides a variety of substituted, isolable diaryl nitromethanes. In addition, it is possible to sequentially append two different aryl groups to nitromethane. Mild oxidation conditions were identified to afford the corresponding benzophenones via the Nef reaction, and reduction conditions were optimized to afford several diaryl methylamines.



The nitro group is highly versatile, as it can be transformed into a variety of other functional groups.[1] Also, the corresponding nitronate salts can be used as nucleophiles for the formation of carbon−carbon bonds.[1c,2,3] In this letter, conditions for the palladium-catalyzed α-arylation of aryl nitromethanes to afford the diaryl nitromethane products are reported. The resultant products have been applied to the synthesis of both benzophenone and diaryl methyl amine derivatives.

Published methods for diaryl nitromethanes include the *bis*-benzylic nitration (Scheme 1, eq 1),[4] halide displacement by nitrite (Scheme 1, eq 2),[5] and rearrangement of the nitrite ester (Scheme 1, eq 3).[6] The methods are all low yielding, and most afford a mixture of products, as some diaryl nitromethanes have been reported to spontaneously convert to the corresponding benzophenones.[4,6] In addition, the requisite starting materials are often difficult to access.

Scheme 1. Literature Precedent To Form Diaryl Nitromethanes



In 2002, the first catalytic α-arylation of nitroalkanes was reported by Buchwald and co-workers.[7] Under these Pd-catalyzed conditions, further arylation of the product, that is the aryl nitromethane, did not occur. Our laboratory subsequently developed robust conditions for the arylation of more difficult substrates including nitroacetates[8] and nitromethane.[9] A second arylation at the α position was never observed under these conditions, but a preliminary high-throughput experimentation study showed that altering the phosphine ligand could result in the second α-arylation. Studies were then initiated to efficiently accomplish the previously unreported α-arylation of aryl nitromethanes.

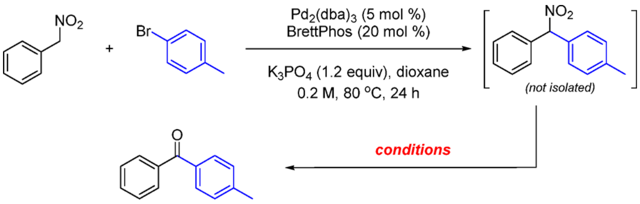
Initial studies revealed that both the diaryl nitromethane and benzophenone products were produced. As reported by Mayr and co-workers,[6] some diaryl nitromethanes spontaneously convert under air to the corresponding benzophenone. This reactivity is primarily dictated by the electronic effects imparted by the substituents on the aryl rings. In order to fully capture all of the material that successfully underwent cross-coupling, we elected to convert the initially formed diaryl nitromethane to the benzophenone. Thus, preliminary efforts focused on the second step of a two-step process, wherein the diaryl nitromethanes were transformed via the Nef reaction to the corresponding benzophenones (Table 1).

Upon increasing the concentration from 0.1 to 0.2 M, it was quickly found that the concentration of the cross-coupling reaction was extremely important, as the Nef screening (Table 1) displayed higher overall yields with the higher concentration. Using unoptimized cross-coupling conditions at 0.2 M, eight conditions for the Nef reaction were screened. The most effective version was a mild, oxidative method utilizing Oxone (Table 1, entry 1).[10,14]

Received: September 25, 2015

DOI: 10.1021/acs.orglett.5b02793
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Optimization of Conditions for the Nef Reaction

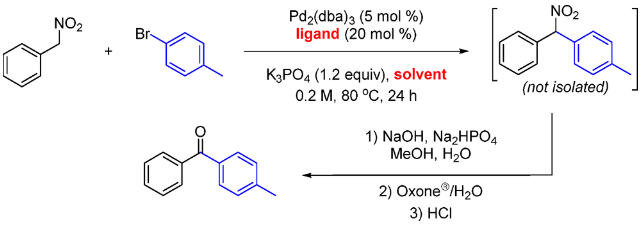


entry[a]	conditions	isolated yield (%)[b]
1[10]	(1) NaOH, Na_2HPO_4, MeOH; (2) Oxone/H_2O; (3) 5 M HCl	44
2[11]	(1) TMSCl, DBU, CH_2Cl_2; (2) *m*CPBA	40
3[8b]	TBAF, KF, MeOH, MeI	40
4	(1) 5 M KOH, Et_2O; (2) 5 M HCl, Et_2O	36
5[12]	(1) KOH, MeOH; (2) $KMnO_4$, $MgSO_4$; (3) 5 M HCl	34
6	(1) SiO_2, MeOH, $CDCl_3$, air; (2) KOH	34
7[13]	(1) 2.0 M NaOH, MeOH; 5 M HCl	32
8[6]	$Bu_4N^+NO_2^-$, benzene, MeOH	14

[a] Conditions shown for the cross-coupling are unoptimized. [b] Isolated yields are for the two-step formation of the benzophenone.

After the Nef reaction was optimized, high-throughput experimentation (HTE) was undertaken to optimize the conditions of the first step, the coupling reaction. Twelve ligands and eight solvents were examined with $Pd_2(dba)_3$ and K_3PO_4 (Table 2). This screen resulted in three optimal ligands and three optimal solvents, which were utilized in a lab scale validation of the two-step process.

Table 2. Optimization of Ligand and Solvent for the Cross-Coupling Reaction

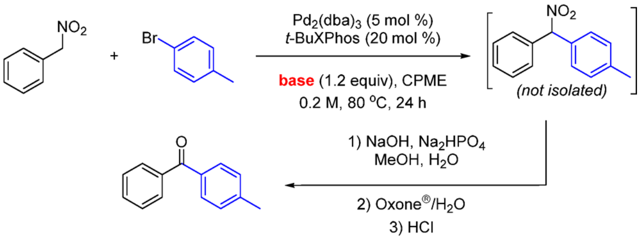


entry	ligand	solvent	HTE sum of products/IS[a]	isolated yield (%)[b]
1	*t*-BuXPhos	CPME	8.50	80
2	CataCXium POMetB	CPME	7.85	55
3	Brett Phos	CPME	7.60	49
4	*t*-BuXPhos	benzene	7.11	42
5	BrettPhos	benzene	6.61	41
6	*t*-BuXPhos	dioxane	8.38	38

[a] IS = internal standard. *P* = sum of diaryl nitromethane and benzophenone products. High-Throughput Experimentation (the) was performed using 4-bromoanisole. [b] Isolated yields are for the two-step formation of the benzophenone on larger scale experiments than the HTE.

Previous work by both the Hartwig and Kozlowski laboratories has shown that the proportion of base that was soluble in the reaction medium was also very important in the arylation of acidic substrates.[8a,15] Thus, the top two ligands from Table 2 were screened with 12 different bases. CataCXium POMetB was inferior in this screen, so validation was performed for five different bases with *t*-BuXPhos (Table 3). K_2CO_3 performed significantly better than the control, K_3PO_4. Upon the addition of more equivalents of base, however, the reaction slowed significantly.

Table 3. Optimization of Base for the Cross-Coupling Reaction

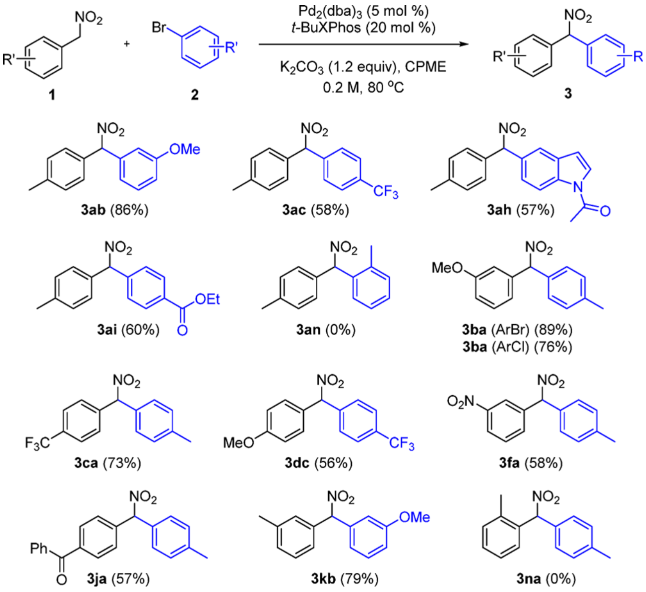


entry	base	HTE sum of products/IS	isolated yield (%)[a]
1	K_2CO_3	1.05	94
4	K_3PO_4	1.00	80
2	KOH	0.96	71
3	$KHCO_3$	1.01	70[b]
5	Cs_2CO_3	0.99	61

[a] Isolated yields are for the two-step formation of benzophenone. [b] The cross-coupling reaction time was 10 h.

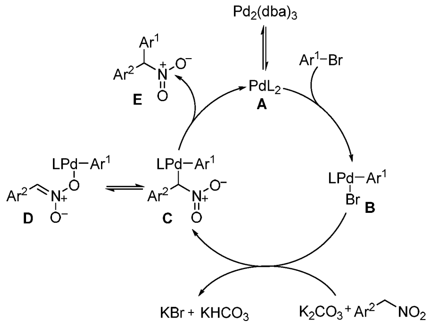
With these optimized conditions in hand, we shifted our focus to the substrate scope of the reaction. However, we discovered that some substrates were resistant to the Nef reaction and gave rise to stable diaryl nitromethanes that could be isolated (Scheme 2). Generally, more electron-poor and electron-neutral diaryl nitromethanes were more stable. Both electron-neutral and electron-poor aryl bromides are coupled effectively. Changing the electronic character of the aryl nitromethane starting material is also well tolerated under the optimized reaction conditions. A heterocyclic aryl halide coupled in moderate yield (**3ah**). Unfortunately, *ortho*-substituted aryl halides proved challenging and could not be coupled. An *ortho*-substituent on the aryl nitromethane starting material also had a deleterious effect. Longer reaction times and higher temperatures proved ineffective for these resistant cases.

Scheme 2. Exploration of Substrate Scope



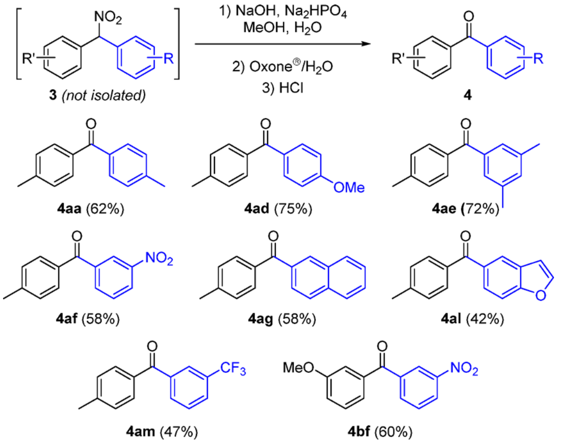
We propose that the reaction proceeds via a mechanism similar to that reported for α-arylations of other acidic species (Scheme 3).[16−18] Furthermore, reactivity is compromised by the presence of the nitro group. Specifically, deprotonation of the acidic aryl nitromethane is likely facile, but the correspondingly low nucleophilicity slows reaction with intermediate **B**. In addition, the palladium can coordinate either the benzylic carbon **C** or the nitro group **D**, but only the former leads to product.[18] Formation of species **C** is disfavorable due to considerable steric hindrance from the Ar^2 group. Bulky *ortho*-substituents on either aryl ring further exacerbate this problem.

Scheme 3. Proposed Mechanism for the α-Arylation of Aryl Nitromethanes



Next, a variety of diaryl nitromethanes were converted to the corresponding benzophenones (Scheme 4), via the optimized Nef conditions from Table 1. This one-pot sequence afforded a diverse array of benzophenones, including a heterocyclic example (**4al**). The reaction tolerated both electron-rich and electron-poor aryl bromides and both electron-rich and electron-neutral aryl nitromethanes.

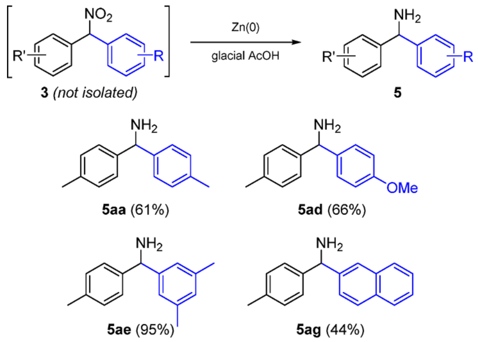
Scheme 4. Nef Reaction of Diaryl Nitromethanes To Afford Corresponding Benzophenones[a]



[a]Yields are for the two-step process from aryl nitromethane **1**.

The diaryl nitromethanes were also subjected to reduction conditions. Of the conditions screened,[8b,19−21] only sequential addition of excess zinc dust resulted in reduction of the nitro group with no over-reduction to the diaryl methane.[8b] Several examples are shown in Scheme 5, including a naphthalenyl diaryl methyl amine **5ag**.

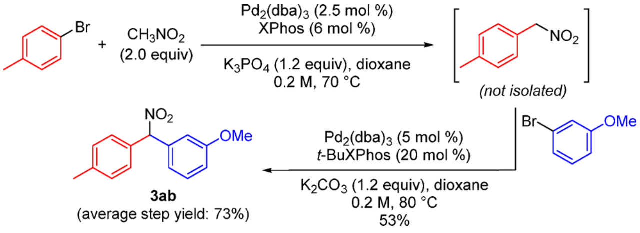
Scheme 5. Reduction of Diaryl Nitromethanes to Diaryl Methylamines[a]



[a]Yields are for the two-step process from aryl nitromethane, **1**.

Finally, a one-pot diarylation of nitromethane was accomplished. As shown in Scheme 6, the first arylation of nitromethane can be accomplished with 2.0 equiv of nitromethane.[9b] The vial was then charged with the reagents for the second arylation that we report herein, without changing solvent. The second coupling can be accomplished efficiently, with an overall yield of 53%, corresponding to an average step yield of 73%.

Scheme 6. One-Pot Diarylation of Nitromethane



In conclusion, the α-arylation of aryl nitromethanes has been accomplished, permitting straightforward access to diaryl nitromethanes. These conditions have the added benefit of starting from widely available and easily differentiated aryl halides. While these compounds can be difficult to work with due to their stability, their high reactivity allows facile generation of benzophenones and diaryl methyl amines.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02793.

Experimental procedures and full characterization of new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: marisa@sas.upenn.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Institutes of Health (GM087605) and the National Science Foundation

(CHE1213230, CHE1464778) for financial support of this research. The NSF provided funding of the High Throughput Laboratory (GOALI CHE-0848460). Partial instrumentation support was provided by the NIH for MS (1S10RR023444), NMR (1S10RR022442), and HTE (S10OD011980). We thank Dr. Simon Berritt (University of Pennsylvania) for his help on high-throughput experimentation. We thank Hulbert Soh (University of Pennsylvania) for his efforts.

REFERENCES

(1) (a) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933−971. (b) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001. (c) Rosini, G.; Ballini, R. *Synthesis* **1988**, *1988*, 833−847. (d) Feuer, H., Nielsen, A. T., Eds. *Nitro Compounds: Recent Advances in Synthesis and Chemistry*; VCH Publishers: New York, 1990.

(2) (a) Ballini, R.; Palmieri, A.; Righi, P. *Tetrahedron* **2007**, *63*, 12099−12121. (b) Wade, P. A.; Morrow, S. D.; Hardinger, S. A. *J. Org. Chem.* **1982**, *47*, 365−367. (c) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915−945. (d) Aleksandrowicz, P.; Piotrowska, H.; Sas, W. *Tetrahedron* **1982**, *38*, 1321−1327. (f) Gildner, P. G.; Gietter, A. A. S.; Cui, D.; Watson, D. A. *J. Am. Chem. Soc.* **2012**, *134*, 9942−9945.

(3) (a) Henry, L. *C. R. Acad. Sci. Ser. C* **1895**, *120*, 1265−1268. (b) Henry, L. *Bull. Soc. Chim. France* **1895**, *13*, 999. (c) Adams, H.; Anderson, J. C.; Peace, S.; Pennell, A. M. K. *J. Org. Chem.* **1998**, *63*, 9932−9934.

(4) Feuer, H.; Friedman, H. *J. Org. Chem.* **1975**, *40*, 187−190.

(5) Zarchi, M. A. K.; Zarei, A. *J. Chin. Chem. Soc.* **2005**, *52*, 309−311.

(6) Tishkov, A. A.; Schmidhammer, U.; Roth, S.; Riedle, E.; Mayr, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 4623−4626.

(7) Vogl, E.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 106−111.

(8) (a) Metz, A. E.; Berritt, S.; Dreher, S. D.; Kozlowski, M. C. *Org. Lett.* **2012**, *14*, 760−763. (b) Metz, A. E.; Kozlowski, M. C. *J. Org. Chem.* **2013**, *78*, 717−722.

(9) (a) Walvoord, R. R.; Berritt, S.; Kozlowski, M. C. *Org. Lett.* **2012**, *14*, 4086−4089. (b) Walvoord, R. R.; Kozlowski, M. C. *J. Org. Chem.* **2013**, *78*, 8859−8864.

(10) Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Epifano, F.; Rosati, O. *Synth. Commun.* **1998**, *28*, 3057−3064.

(11) Aizpurua, J. M.; Oiarbide, M.; Palomo, C. *Tetrahedron Lett.* **1987**, *28*, 5361−5364.

(12) Zhang, Z.; Yu, A.; Zhou, W. *Bioorg. Med. Chem.* **2007**, *15*, 7274−7280.

(13) Cameron, D. W.; Hildyard, E. M. *J. Chem. Soc. C* **1968**, 166−169.

(14) A mechanism for the Oxone-mediated Nef reaction is included in ref 10; however, there are other mechanisms that have been reported under basic reaction conditions, with and without the presence of molecular oxygen: (a) Gissot, A.; N'Gouela, S.; Matt, C.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **2004**, *69*, 8997−9001. (b) Umemiya, S.; Nishino, K.; Sato, I.; Hayashi, Y. *Chem. - Eur. J.* **2014**, *20*, 15753−15759.

(15) Beare, N. A.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 541−555.

(16) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 5816−5817.

(17) Wolkowski, J. P.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4289−4291.

(18) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234−245.

(19) Iron reduction conditions: Stamford, A. W.; Zhu, Z.; Mandal, M.; Wu, Y.; Cumming, J. N.; Liu, X.; Li, G.; Iserloh, U. International Patent WO2009/131975.

(20) Conditions for the *in situ* generation of cobalt boride reductant: Davis, T. A.; Johnston, J. N. *Chem. Sci.* **2011**, *2*, 1076−1079.

(21) Pd/C hydrogenation conditions: Borah, J. C.; Gogoi, S.; Boruwa, J.; Kalita, B.; Barua, N. C. *Tetrahedron Lett.* **2004**, *45*, 3689−3691.