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Nitroethylation of Vinyl Triflates and Bromides

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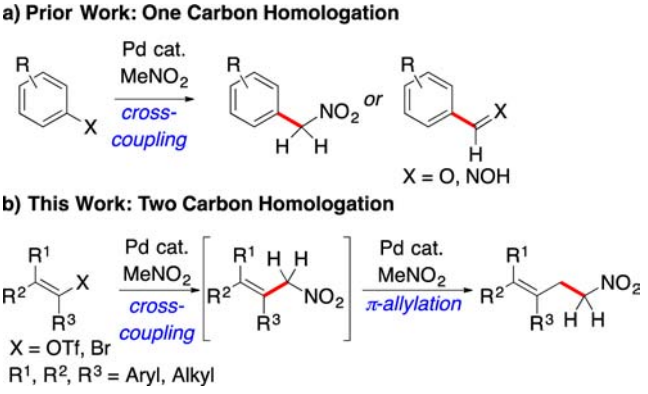
ABSTRACT

A two-carbon homologation of vinyl triflates and bromides for the synthesis of homoallylic nitro products is described. This palladium-catalyzed double coupling of nitromethane exploits the anion stabilizing and leaving group properties of nitromethane, generating the homo allyl nitro products via a tandem cross-coupling/π-allylation sequence. The resultant process provides a mild and convenient entry to nitroethylated products, which are versatile precursors to β,γ-unsaturated carbonyls, homoallylic amines, and nitrile oxides.

Recently, we reported a highly versatile and robust cross-coupling reaction of aryl halides with nitromethane.[1] This work provided simple access to a range of useful arylnitromethane building blocks and exploited nitromethane as a formyl equivalent to directly afford aryl aldehydes or oximes (Scheme 1a). While exploring the use of vinyl bromides to further expand the scope, an unexpected, two-carbon homologated reaction product was encountered. Herein, we communicate the results from this investigation wherein palladium-catalyzed coupling of vinyl halides and enol triflates with nitromethane affords nitroethylated products (Scheme 1b).

Nitromethane has been shown to react as a nucleophile for the Pd-catalyzed substitution reactions with allyl acetates, phenyl ethers, esters, and carbonate derivatives.[2] In addition, allyl nitro compounds have been observed to undergo ionization to form a Pd–π-allyl complex.[3,4] However, accessing homoallylic nitroalkanes directly from vinyl triflates or halides has not been previously reported.[2c,f,5] Such a tandem process provides access to an array of nitroethylated compounds, which are versatile precursors

Scheme 1. Nitromethane Homologation



(1) Walvoord, R. R.; Berritt, S.; Kozlowski, M. C. *Org. Lett.* **2012**, *14*, 4086–4089.

(2) (a) Wade, P. A.; Hinney, H. R.; Amin, N. V.; Vail, P. D.; Morrow, S. D.; Hardinger, S. A.; Saft, M. S. *J. Org. Chem.* **1981**, *46*, 765–770. (b) Wade, P. A.; Morrow, S. D.; Hardinger, S. A. *J. Org. Chem.* **1982**, *47*, 365–367. (c) Deardoff, D. R.; Savin, K. A.; Justman, C. J.; Karanjawala, Z. E.; Sheppeck, J. E., II; Hager, D. C.; Aydin, N. *J. Org. Chem.* **1996**, *61*, 3616–3622. (d) Rieck, H.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *34*, 2687–2689. (e) Giambastiani, G.; Giovanni, P. *J. Org. Chem.* **1998**, *63*, 9608–9609. (f) Trost, B. M.; Surivet, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3122–3124. (g) Uozumi, Y.; Suzuka, T. *J. Org. Chem.* **2006**, *71*, 8644–8646.

(3) (a) Tamura, R.; Hegedus, L. S. *J. Am. Chem. Soc.* **1982**, *104*, 3727–3729. (b) Ono, N.; Hamamoto, I.; Kaji, A. *J. Chem. Soc., Chem. Commun.* **1982**, 821–822.

(4) Tamura, R.; Kamimura, A.; Ono, N. *Synthesis* **1991**, *6*, 423–434.

(5) Select examples: (a) Aleksandrowicz, P.; Piotrowska, H.; Sas, W. *Tetrahedron* **1982**, *38*, 1321–1327. (b) Maki, K.; Kanai, M.; Shibaski, M. *Tetrahedron* **2007**, *63*, 4250–4257. (c) Grenning, A. J.; Tunge, J. A. *Org. Lett.* **2010**, *12*, 740–742. (c) Grenning, A. J.; Tunge, J. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 1688–1691.

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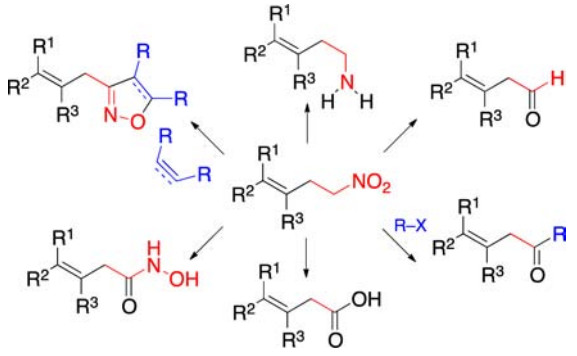
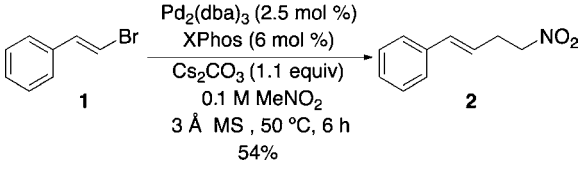
Scheme 2. Utilization of Nitroethylated Products



to β,γ-unsaturated carbonyls, homoallylic amines, and other useful functionality (Scheme 2).

Our studies began with the discovery that the palladium-catalyzed nitromethylation of β-bromostyrene gave rise to an unexpected product (Scheme 3). Instead of obtaining the allylnitro species, the nitroethylated product was isolated in moderate yield (54%).

Scheme 3

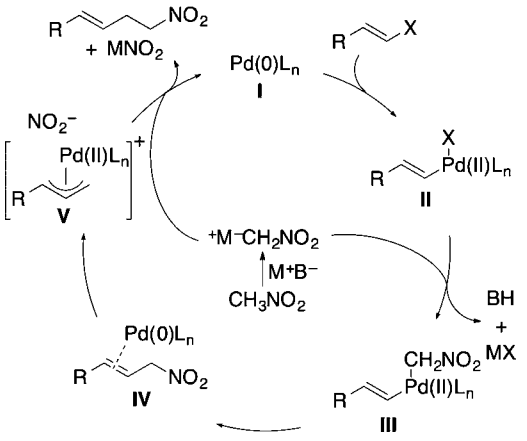


The formation of the nitroethylated product is postulated to arise from a tandem cross-coupling/π-allylation mechanism (Scheme 4). Notably, the intermediate allylnitro compound was never observed in any of the studies conducted, indicating that it undergoes facile oxidative ionization under the reaction conditions. Utilizing nitromethane as a traceless coupling partner to homologate the vinyl moiety by one carbon and to incorporate a leaving group to allow formation of π-allyl intermediate **V** (Scheme 4) and a second homologation is a unique feature of this process.

Notably, the two palladium-catalyzed C−C bond forming events proceed via different mechanisms (oxidative addition/transmetalation/reductive elimination vs oxidative ionization/outer sphere nucleophilic attack), and there is no expectation that a single palladium-ligand species would effectively catalyze both portions.[6] For example, with the exception of CataCXium POMetB, bidentate and bis-*tert*-butyl-ligands performed poorly in the nitromethylation of aryl halides.[1] Indeed, typical π-allylation conditions

(6) For reviews of sequential catalyzed processes, see: (a) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365–2379. (b) Lee, J.; Na, Y.; Han, H.; Chang, S. *Chem. Soc. Rev.* **2004**, *33*, 302–312. (c) Wasilke, J.; Obrey, S. J.; Baker, T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001–1020.

Scheme 4. Proposed Mechanism



employing trialkylphosphine ligands do not catalyze this initial cross-coupling step.[2a]

Further study of the transformation from Scheme 3 revealed that the nitroethylated product decomposed under the reaction conditions over time as observed by GC analysis (see Supporting Information). Additionally, subjecting the nitroethylated product to the reaction conditions for 6 h led to only a 68% mass recovery. The low stability of the product coupled with the potential multiple pathways available from the Pd η^3 π-allyl intermediate (Scheme 5) and the need to simultaneously optimize two very different transformations (cross-coupling vs π-allylation; see above) prompted us to utilize parallel microscale (10 μmol of vinyl halide, 100 μL reaction volume) experimentation to screen conditions. In addition to being able to rapidly assess the impact of different combinations of base, solvent, palladium source, and ligand on product formation, LCMS analysis of the reaction profiles provides insight into which sets of conditions give rise to undesired reaction pathways.

Due to the low stability of β-bromostyrene and its nitroethylated products, the screening focused on the more stable **3a** as a test substrate (Table 1). For a general process, vinyltrifluoromethanesulfonates are also preferred because they are more easily obtained (via enolization of the ketone) than the corresponding vinyl bromides. A variety of bis-*tert*-butyl and biscyclohexyl ligands were selected for screening that are known to promote the first step of the process (nitromethylation of the aryl halide).[1] Based on the efficiency of PPh_3 in the C-alkylation of allylic acetates with (phenylsulfonyl)nitromethane,[2a] the combination of PPh_3 with Xantphos, BINAP, CataCXium POMetB, JohnPhos, BrettPhos, or XPhos was also examined. With these ligands, six different bases (2.4 equiv) were screened.

Select results from this screen are listed in Table 1. In general, K_3PO_4 and Cs_2CO_3 were the most efficient bases (Table 1, entries 5−8). Bis-*tert*-butyl ligands (Table1, entries 1 and 8) and a mixed ligand system (Table 1, entry 11) performed poorly (< 3.0 product/internal standard).

Scheme 5. Potential Reaction Pathways from the π-Allyl Nitro Intermediate

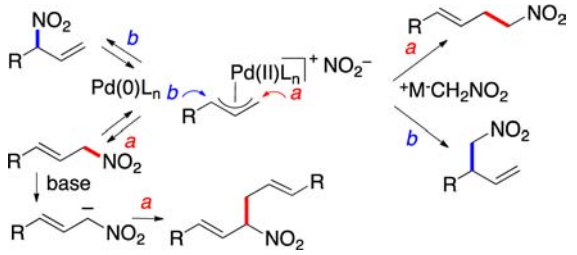
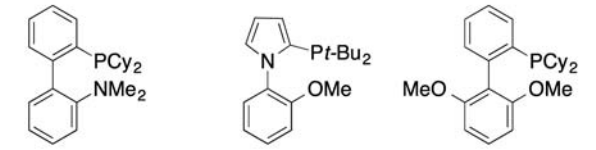


Table 1. Product/Internal Standard Ratios from Initial Screening

entry	ligand	product:internal standard			
		K_3PO_4	$CsHCO_3$	Cs_2CO_3	NaO*t*-Bu
1	QPhos	0.68	0.39	1.54	0.82
2	*t*-BuMePhos	2.38	0.90	4.00	0.80
3	P(*t*-Bu)$_3$•HBF$_4$	1.24	0.49	0.36	0.61
4	RuPhos	0.52	0.31	0.54	---
5	**SPhos**	4.60	3.24	**5.60**	3.66
6	**DavePhos**	4.28	2.80	**4.39**	2.09
7	**CataCXium-POMetB/PPh$_3$**	4.04	2.67	**5.21**	2.96
8	JohnPhos	2.91	1.81	3.75	1.29
9	BrettPhos	1.08	0.85	1.72	1.04
10	XPhos	2.56	3.34	3.79	0.77
11	XPhos/PPh$_3$	2.35	2.61	1.18	0.79

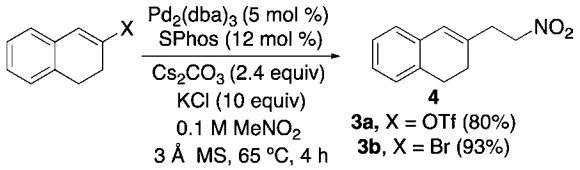


Biscyclohexyl (DavePhos and SPhos) phosphine ligands and CataCXium POMetB were superior (Table 1, entries 5−7), even though they are not highly effective in typical π-allylations. The top three results were scaled up (0.360 mmol scale) using Cs_2CO_3 and afforded the desired product in 51−72% isolated yield (Table 1). Complete conversion was observed with DavePhos and SPhos while incomplete conversion was observed with CataCXium POMetB. The SPhos ligand proved most effective, offering enhanced reactivity and cleaner reaction profiles in comparison to DavePhos and CataCXium POMetB.

(7) Solvation of the metal ion to enhance the nucelophilicity of nitromethane with the use of ethereal solvents did not improve the yield.

The use of chloride ion additives was explored since it is well documented that chloride ions are critical for coupling enol triflates.[7,8] The allylPdOTfL_n intermediate formed after oxidative addition of the enol triflate is proposed to undergo a counterion exchange.[9] Indeed, performing the reaction in the presence of excess chloride ions (10 equiv KCl) led to improved isolated yields and rates providing good results for both vinyl triflates and bromides (Scheme 6).

Scheme 6. Use of KCl in the Nitroethylation



The optimized conditions did not prove to be broadly applicable to other alkene, diene, and β- and α-styrene substrates affording the desired product in < 50% yield (see Supporting Information). Incomplete conversion of starting material and byproducts were observed in most cases. Thus, lead ligands from the initial screen were assessed with a variety of alkene substrates to draw out reactivity trends (Table 2). Indeed, the yields could be improved to a > 50% yield for each substrate class.[10]

Dienes, disubstituted alkenes, and di- and trisubstituted β-bromostryene derivatives fall into class **A** where the XPhos ligand performed best (Table 2). α-Bromostyrenes and α-tetralone substrates comprise class **B**, for which the CataCXium POMetB and DavePhos ligands are superior. SPhos is most effective for β-tetralone substrates (class **C**). As expected, the addition of a potassium chloride additive is most effective for enol triflates derived from β-tetralones and did not improve the outcome for vinyl bromides.

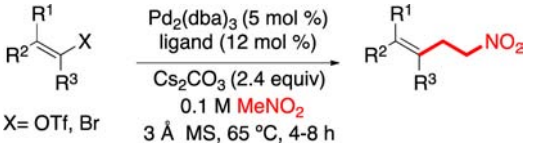
In an effort to understand the discrete reaction steps, the allyl nitro species for the corresponding β-tetralone was synthesized and subjected to the reaction conditions. The desired nitroethylated product was isolated in 14% yield (Scheme 7) suggesting that slow formation of the allyl nitro intermediate is necessary. Oxidative ionization of the allyl nitro ostensibly competes with other pathways such as dimerization, the products from which could be identified in LCMS of the HTE screen. Once the π-allyl species does form, however, nucleophilic attack is highly regioselective for the primary position. The branched product was not observed here (Scheme 7) or with any of the other substrates studied.

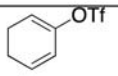
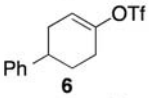
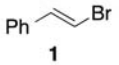
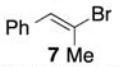
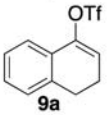
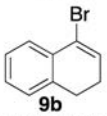
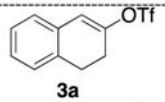
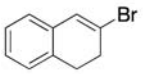
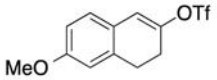
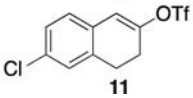
(8) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630–4632.

(9) (a) Jutand, A.; Mosleh, A. *Organometallics* **1995**, *14*, 1810–1817. (b) Jutand, A.; Négri, S. *Organometallics* **2003**, *22*, 4229–4237. (c) Jutand, A. *Appl. Organometal. Chem.* **2004**, *18*, 574–582.

(10) 3 Å MS suppressed aldehyde formation from water. See ref 1.

Table 2. Palladium-Catalyzed Nitroethylation



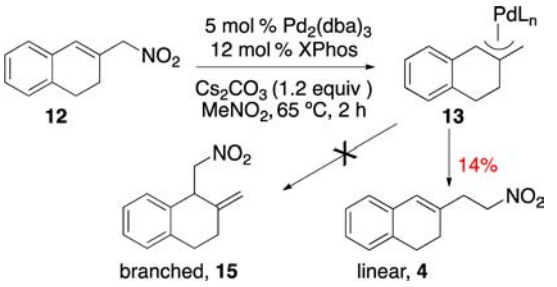
class	substrate	Yield[a] SPhos	XPhos	CataCXium POMetB	DavePhos
A	 5	26%	47%		
	 6	42%[b]	76%	46%	59%
	 1		69%	62%	27%
	 7 Me		64%	47%	
B	 8	47%	43%	60%	33%
	 9a	16%	66%	74%	68%
	 9b				83%
C	 3a	80%[c]			
	 3b	93%[c]			
	 10	67%			
	 11	55%[b]	49%		

[a] Isolated yields. [b] Conversion determined by ^{1}H NMR. [c] 10 equiv of KCl added.

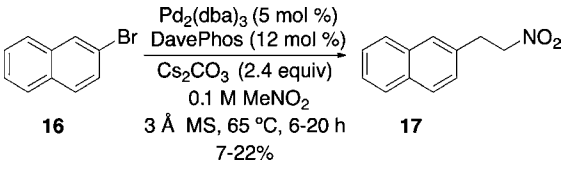
To probe whether a similar reaction pathway is feasible with benzylic[11] vs allylic nitro intermediates,

(11) (a) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9546–9547. (b) Nettekoven, U.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 1166–1167. (c) Johns, A. M.; Utsunomiya, M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 1828–1839. (d) Kuwano, R.; Kondo, Y.; Matsuyama, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12104–12105. (e) Trost, B. M. *J . Am. Chem. Soc.* **2010**, *132*, 15534–15536. (f) Trost, B. M.; Czabaniuk, L. C. *J. Am. Chem. Soc.* **2012**, *134*, 5778–5781.

Scheme 7. One-Carbon Homologation from the Putative Allylnitro Intermediate



Scheme 8. Nitroethylation of an Aryl Halide



2-bromonaphthalene was subjected to the reaction conditions (Scheme 8). Small amounts of the anticipated nitroethylated product were observed indicating the potential of such substrates.

In conclusion, a tandem cross-coupling/π-allylation of alkenyl bromides and triflates with nitromethane has been developed. Examining the reactivity of a variety of alkene substrates with selected conditions obtained from a test substrate proved to be an effective strategy for rapid optimization of different substrate classes. This method allows for facile nitroethylation of both enol triflates, readily available from the corresponding ketones, and bromides to afford versatile homoallylic nitro building blocks.

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Supporting Information Available. Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.