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Palladium-Catalyzed Decarboxylative sp^3-sp^3 Coupling of Nitrobenzene Acetic Esters

Shelli R. Waetzig and Jon A. Tunge*

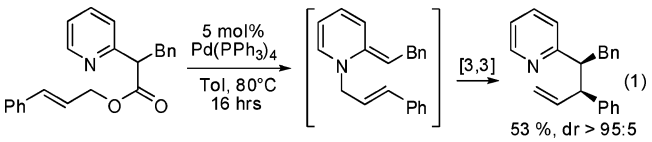
Department of Chemistry, The University of Kansas, 2010 Malott Hall, 1251 Wescoe Hall Drive, Lawrence, Kansas 66045

Received September 12, 2007; E-mail: tunge@ku.edu

Nitroarenes are important intermediates in the synthesis of polymers, azo dyes, and pharmaceuticals such as Viagra, Zyvox, and Angerase.[1] Thus, it is expected that the development of new methods for the cross-couplings of nitroarenes will facilitate synthesis of heterocycles that are prevalent in pharmaceuticals.

Recently, interest in the area of decarboxylative coupling has grown, in part because these reactions occur under neutral conditions and avoid the use of reagents that are typically necessary for transmetalation.[2] For example, Goo*β*en and co-workers have reported a Pd(II)-catalyzed coupling of nitrobenzoic acids with haloaromatics to generate biaryl products.[3] Furthermore, Myers has shown a Pd(II)-catalyzed decarboxylative variant of the Heck reaction.[4] While these advancements represent significant accomplishments in the field of palladium-catalyzed coupling of sp^2-hybridized carbons, catalysis of the decarboxylative coupling of sp^3-hybridized carbons remains a significant challenge. Current methods for sp^3-sp^3 coupling are limited by the requirement for a stoichiometric organometallic that is necessary to effect transmetalation.[5]

We recently demonstrated the Pd-catalyzed decarboxylative benzylic coupling of nitrogen-containing heteroaromatics with allyl electrophiles (eq 1).[6] This reaction proceeded by a unique allylation/aza-Cope rearrangement that did not translate to more general benzylic couplings. Herein, we report a new method for the decarboxylative coupling of nitrobenzene acetic esters.



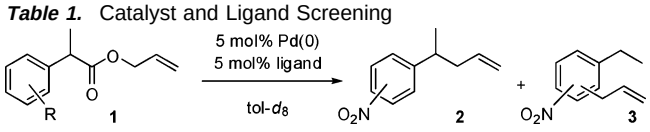
To begin, both *o*- and *p*-nitrophenylacetic esters were synthesized to screen different catalyst/ligand combinations for activity (Table 1).

Although the reaction failed to produce any product at ambient temperature, increasing the temperature to 110 °C readily promoted decarboxylation in the presence of the palladium catalysts; however, products of aromatic allylation were prevalent. Ultimately, *rac*-BINAP proved to be the most selective ligand for benzylic allylation of both *o*- and *p*-nitro benzyl derivatives (entries 3 and 4).

Once standard conditions were determined, a variety of *o*-nitro- and *p*-nitro-substituted aryl substrates were tested (Table 2). All terminally unsubstituted allyl esters gave clean conversion to the desired products in high yield. It is noteworthy that functional groups, such as esters and ketones (**1b**, **1c**), were tolerated and no products arising from allylation of enolates were observed.[7] Furthermore, addition of electron-donating methoxy substituents did not affect reaction time or yield (Table 2, entry 4).

The fact that α-mono- and α,α-disubstituted *p*-nitrophenyl acetic esters (**1f**−**h**) underwent facile decarboxylative coupling indicates that decarboxylation must precede C−C bond formation.[8] Interestingly, decarboxylative coupling of *o*-nitrophenyl acetic esters is limited to substrates that are α-monosubstituted; treatment of **1i** to

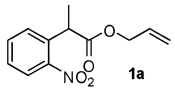
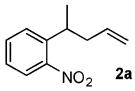
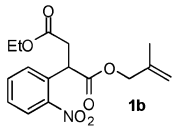
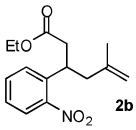
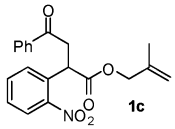
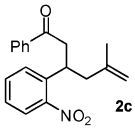
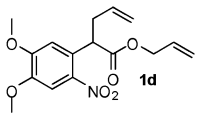
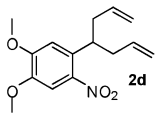
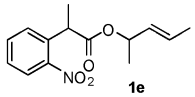
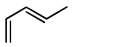
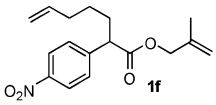
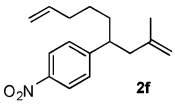
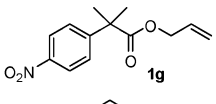
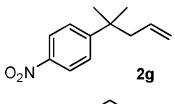
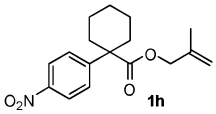
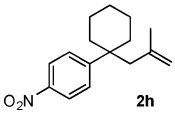
Table 1. Catalyst and Ligand Screening



entry	R	catalyst/Ln	temp (°C)	**2**/**3**[a]
1	*o*-NO_2	$Pd(PPh_3)_4$	25	NR
2	*o*-NO_2	$Pd(PPh_3)_4$	110	1.8:1
3	*o*-NO_2	Pd_2dba_3/rac-BINAP	110	100:0
4	*p*-NO_2	Pd_2dba_3/rac-BINAP	110	4.9:1
5	*p*-NO_2	Pd_2dba_3/dppe	110	2:1
6	*p*-NO_2	Pd_2dba_3/dppf	110	1.6:1

[a] Ratios determined by ^1H NMR spectroscopy of crude reaction mixtures.

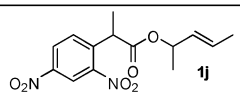
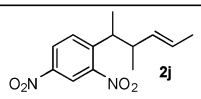
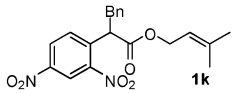
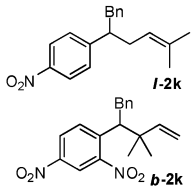
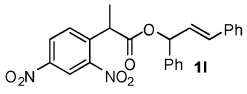
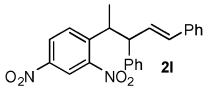
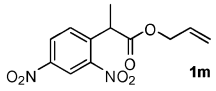
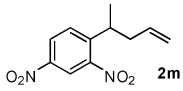
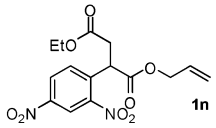
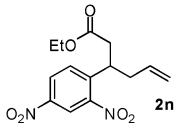
Table 2. Decarboxylative Coupling of Substituted Nitrophenylacetic Esters[a]

Entry	Substrate	Product	Yield **2** (%)
1	 **1a**	 **2a**	86
2	 **1b**	 **2b**	85
3	 **1c**	 **2c**	77
4	 **1d**	 **2d**	94
5[b]	 **1e**		<5
6	 **1f**	 **2f**	77
7	 **1g**	 **2g**	96
8	 **1h**	 **2h**	94

[a] Conditions: 0.3 mmol substrate, 0.0075 mmol Pd_2dba_3, 0.015 mol *rac*-BINAP, 3 mL toluene, 110 °C, 1−3 h. [b] $Pd(PPh_3)_4$ used as catalyst.

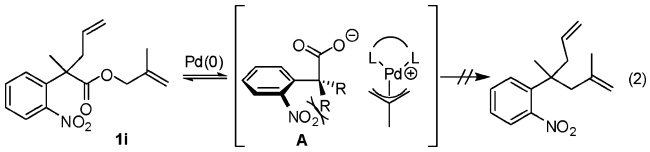
10.1021/ja077070r CCC: $37.00

Table 3. Decarboxylative Coupling of Dinitrophenyl Acetic Esters[a]

Entry	Substrate	Product	% Yield **2** (*dr*)
1	 **1j**	 **2j**	95 (1.2:1)
2	 **1k**	 ***l*-2k** + ***b*-2k**	26[b]
3	 **1l**	 **2l**	84 (1.4:1)
4	 **1m**	 **2m**	91
5	 **1n**	 **2n**	88

[a] Conditions: 0.3 mmol substrate, 0.015 mol $Pd(PPh_3)_4$, toluene, room temp, 1−3 h. [b] Linear/branched ratio = 1.5:1.

the standard conditions of catalysis produced no product nor degradation of starting material (eq 2).[9]

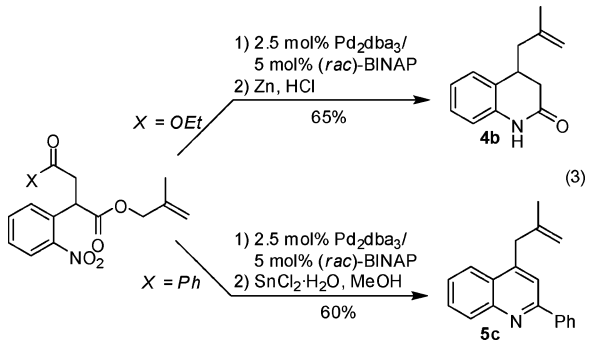


(2)

It can be reasoned that for decarboxylation to occur, the carboxylate must align perpendicular to the electron-accepting arene. This results in a high energy conformation where there is significant A-strain (**A**), thus precluding decarboxylation. Since this steric hindrance is not present when the *p*-nitro group is employed, decarboxylation of those substrates can be achieved.

While the previous examples have focused on terminally unsubstituted allyl electrophiles, the coupling of alkyl-substituted allyl groups is also desirable. Unfortunately, when ester **1e** was synthesized and subjected to the standard reaction conditions, the reaction did not proceed (Table 1). The reaction did proceed when $Pd(PPh_3)_4$ was employed as the catalyst; however, elimination to form 1,3-pentadiene was prevalent.

The hypothesis that elimination was favored because the intermediate benzylic anion was too basic led us to believe that dinitroarene substrates would be suitable for coupling with substituted allyl electrophiles (Table 3). While the previously optimized reaction conditions failed to produce clean reaction mixtures with the dinitroarene substrates, $Pd(PPh_3)_4$ was found to be a very efficient catalyst. Under these conditions, alkyl- and aryl-substituted allyl electrophiles (**1j**, **1l**) undergo smooth decarboxylative coupling with the dinitroarene reactants. For example, when employing **1j**, no elimination products were observed and a 95% yield was obtained; no decarboxylative coupling product was observed with the related mononitrobenzyl ester (**1e**). Unfortunately, the coupling of a prenyl-substituted allyl ester still led to low yields owing to competing elimination (entry 2). However, functional group compatibility similar to that observed for the mononitroarene complexes was maintained (entry 5). Moreover, the reactions were facile at ambient temperature; all starting material was consumed within 3 h. The fact that the rate of the reaction increases with increased stability of the benzylic anion suggests that the rate-limiting step of catalysis is decarboxylation.



(3)

The utility of nitroarenes in pharmaceutical synthesis lies in their facile reduction to anilines. For example, decarboxylative coupling can be followed by reductive cyclization to afford dihydroquinolones or quinolines (eq 3). Thus, the coupling of decarboxylative allylation with nitro reduction allows the synthesis of alkylated heterocycles that are common in biologically active molecules.

In conclusion, a new method for catalytic sp^3-sp^3 coupling has been developed that is based on the facile decarboxylative coupling of nitrobenzene acetic esters. The process occurs under neutral conditions and does not require reagents that are typically needed for transmetalation.

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

References

(1) (a) *The Nitro Group in Organic Synthesis;* Ono, N., Ed.; Wiley-VCH: New York. 2001. (b) Hoogenraad, M.; van der Linden, J. B.; Smith, A. A. *Org. Proc. Res. Dev.* **2004**, *8*, 469.
(2) Rayabarapu, D. K.; Tunge, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 13510.
(3) (a) Goo*β*en, L. J.; Rodriguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824. (b) Goo*β*en, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662.
(4) (a) Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250. (b) Tanaka, D.; Romeril, S. P.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323.
(5) (a) Fu, G.; Saito, B. *J. Am. Chem. Soc.* **2007**, *129*, 9602. (b) Dongol, K. G.; Koh, H.; Sau, M.; Chai, C. L. L. *Adv. Synth. Catal.* **2007**, *349*, 1015. (c) Frisch, A. C.; Beller, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 674. (d) Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Org. Lett.* **2005**, *7*, 3805.
(6) Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 4138.
(7) (a) Burger, E. C.; Tunge, J. A. *Org. Lett.* **2004**, *6*, 4113. (b) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924. (c) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 17180. (d)You, S-L.; Dai, L-X. *Angew. Chem, Int. Ed.* **2006**, *45*, 5246. (e) Waetzig, S. R.; Rayabarapu, D. K.; Weaver, J. D.; Tunge, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4977.
(8) Protodecarboxylation of nitrobenzene acetic acids: (a) Bull, D. J.; Fray, M. J.; Mackenny, M. C.; Malloy, K. A. *Synlett* **1996**, 647. (b) Ioussaini, O.; Capedevielle, P.; Maumy, M. *Tetrahedron* **1984**, *40*, 3229. (c) *J. Chem. Soc.* **1938**, 1186.
(9) A similar effect on the decarboxylation of nitroarenes was recently observed, but not explained. Imao, D.; Itoi, A.; Yamazaki, A.; Shirakura, M.; Ohtoshi, R.; Ogata, K.; Ohmori, Y.; Ohta, T.; Ito, Y. *J. Org. Chem.* **2007**, *72*, 1652.

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