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Palladium-Catalyzed Decarboxylative Benzylation of Diphenylglycinate Imines

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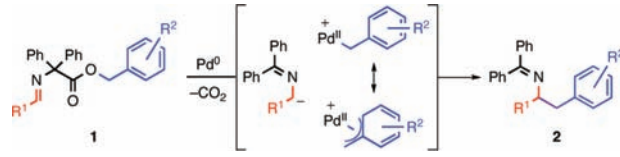
ABSTRACT

General reaction conditions for the Pd-catalyzed decarboxylative benzylation of benzyl diphenylglycinate imines are described. The overall procedure requires a simple catalyst/ligand combination to form a new Csp^3-Csp^3 bond. Microwave irradiation greatly accelerated the transformation. Moreover, various heteroaromatic moieties are tolerated in both the imine and ester components.

Transition-metal-mediated pathways for the formation of Csp^3-Csp^3 bonds have received substantial attention.[1] Pd-catalyzed decarboxylative alkylation (Tsuji−Trost reaction), in particular, has emerged as a versatile and efficient strategy for the construction of these bonds.[1b,2] Despite the rapidly growing interest in this arena, the reaction scope remains generally limited to allylation of enolate nucleophiles[3] with π-allylPd(II) species generated via insertion of a Pd(0) catalyst into an allyl ester or carbonate C−O bond. We recently reported that α-imino anions (2-azaallyl anions) also can be generated and alkylated via Pd-catalyzed decarboxylative allylation of allyl diphenylglycinate imines.[2d,4] Inspired by reports that *benzyl* esters and carbonates are viable substrates for Pd(0)-catalyzed nucleophilic alkylations,[5] we envisioned advancing a similar strategy for the benzylation of α-imino anions. Herein, we report general reaction conditions for the decarboxylative benzylation of benzyl diphenylglycinate imines **1** into the corresponding homobenzylic imines **2** (Scheme 1). Heterocyclic functionalities, e.g., furan, indole, thiazole, and pyridine, on either the imine or ester groups are well tolerated by the reaction conditions. To the best of our knowledge, this represents the

Scheme 1. Decarboxylative Formation and Benzylation of α-Imino Anions



(1) (a) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067. (b) Trost, B. M.; VanVranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (c) Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 6694. (d) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482. (e) Smith, S. W.; Fu, G. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 9334. (f) Dai, X.; Strotman, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 3302. (g) Bi, H.-P.; Zhao, L.; Liang, Y.-M.; Li, C.-J. *Angew. Chem., Int. Ed.* **2009**, *48*, 792. (h) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (i) Li, C.-J.; Li, Z. *Pure Appl. Chem.* **2006**, *78*, 935.

(2) Representative examples: (a) Burger, E. C.; Tunge, J. A. *Org. Lett.* **2004**, *6*, 4113. (b) Imao, D.; Itio, A.; Yamazaki, A.; Shirakura, M.; Ohtoshi, R.; Ogata, K.; Ohmori, Y.; Ohta, T.; Ito, Y. *J. Org. Chem.* **2007**, *72*, 1652. (c) Trost, B. M.; Bream, R. N.; Xu, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3109. (d) Yeagley, A. A.; Chruma, J. J. *Org. Lett.* **2007**, *9*, 2879. (e) Enquist, J. A., Jr.; Stoltz, B. M. *Nature* **2008**, *453*, 1228. (f) White, D. E.; Stewart, I. C.; Grubbs, R. H.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 810.

(3) For some notable exceptions: (a) Burger, E. C.; Tunge, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 10002. (b) Weaver, J. D.; Tunge, J. A. *Org. Lett.* **2008**, *10*, 4657. (c) Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 4138. (d) Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 14860.

(4) (a) Yeagley, A. A.; Lowder, M. A.; Chruma, J. J. *Org. Lett.* **2009**, *11*, 4022. (b) Fields, W. H.; Khan, A. K.; Sabat, M.; Chruma, J. J. *Org. Lett.* **2008**, *10*, 5131.

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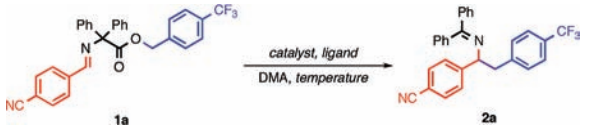
first example of a Pd-catalyzed decarboxylative benzylation involving a nonenolate C-centered nucleophile.

We initially rationalized that incorporation of an electron-withdrawing group into the benzyl ester would facilitate insertion of Pd(0) into the ester C−O bond.[5] Similarly, based on our previous experience,[2d,4] we predicted that electron-withdrawing substituents on the imine component would accelerate decarboxylation and predispose the resonance-stabilized α-imino anion intermediate toward benzylation at the least substituted carbon. Accordingly, our initial investigations began with (4-trifluoromethyl)benzyl ester **1a**. In accord with related studies by Kuwano and coworkers,[5e,f] only bidentate ligands proved effective in catalyzing the decarboxylative benzylation (Table 1). Moreover, the bite angle of the bidentate ligands demonstrated a significant impact on both the rate of reaction and the relative percentage of side products generated.[6] Extensive screening of reaction conditions identified microwave irradiation of a 0.1 M solution of imine **1a** in dimethylacetamide (DMA) with 3 mol % $Pd(OAc)_2$ and 20 mol % *rac*-BINAP to be optimal, affording the desired decarboxylative benzylation product **2a** in high yield.[7] This high ligand-to-Pd ratio (~6.7 vs 2.0 for conventional heating) proved critical for the success of the microwave-accelerated conditions, presumably by encouraging the formation of the requisite Pd(0)−ligand complex within the relatively short time frame of the reaction. Side products emanating from decarboxylative protonation (**3**)[8] and acetate serving as a competitive nucleophile for the benzyl−Pd(II) intermediate (**4**) comprised the majority of the remaining mass balance (Figure 1). Replacing $Pd(OAc)_2$ with $Pd(O_2CCF_3)_2$ did not afford a notable reduction in the amount of side products from protonation (**3**) or (trifluoro)acetylation.

Table 1. Reaction Optimization[a]



Pd source (mol %)	ligand (mol %)	temp (°C)	time	yield (%)[b]
$Pd(PPh_3)_4$ (10)	—	110[c]	20 h	0[e]
$Pd(PPh_3)_2Cl_2$ (10)	—	110[c]	20 h	0[e]
$Pd(OAc)_2$ (10)	P(*o*-tol)$_3$ (20)	110[c]	20 h	0[e]
$Pd(OAc)_2$ (10)	dppe (20)	110[c]	20 h	0[e]
$Pd(OAc)_2$ (10)	xantphos (20)	110[c]	20 h	37[e]
$Pd(OAc)_2$ (10)	dppf (20)	110[c]	20 h	49
$Pd(OAc)_2$ (10)	*rac*-BINAP (20)	110[c]	20 h	61
$Pd(OAc)_2$ (10)	*rac*-BINAP (20)	150[c]	20 h	60
$Pd(OAc)_2$ (10)	*rac*-BINAP (50)	150[d]	15 min	70
$Pd(OAc)_2$ (3)	**rac-BINAP (20)**	**150[d]**	**15 min**	**78**
$Pd(OAc)_2$ (3)	*rac*-BINAP (6)	150[d]	15 min	0[e]
$Pd(O_2CCF_3)_2$ (10)	*rac*-BINAP (50)	200[d]	45 min	60

[a] Reaction conditions: imine (0.05 mmol), Pd catalyst, and ligand in DMA (0.1 M). Unless otherwise noted, all reactions were run to complete conversion of imine **1a**. [b] Isolated yield. [c] Conventional heating. [d] Microwave heating (CEM Discover, 300 W maximum power). [e] Starting material recovered.

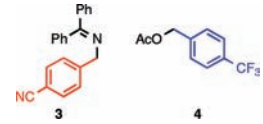


Figure 1. Major side products for the decarboxylative benzylation of imino ester **1a**.

To evaluate the scope of this decarboxylative benzylation reaction, the imine and ester moieties were varied (Table 2). While ideal reaction temperatures/times were substrate specific, heating to 150 °C for as little as 5 min afforded complete conversion of imino ester **1a** and typically provided some conversion for all other substrates investigated. The electronic composition of the benzyl ester significantly impacted product distribution, with electron-withdrawing groups reducing the preference for desired imines **2** (entries 1−8). As an extreme comparison, 4-methoxybenzyl ester **1c** afforded 85% of the desired product **2c**, whereas 4-nitrobenzyl ester **1f** was converted almost exclusively to **3** (32%), 4-nitrobenzyl acetate (10%), and other unidentified side products (cf. entries 3 and 6). Gratifyingly, heteroaromatic benzyl esters proved to be viable substrates for the decarboxylative benzylation protocol (entries 7 and 8), suggesting potential application toward the synthesis of 2-aryl-*β*-carboline alkaloid analogues.[9] To the best of our knowledge, this represents the first example of the formation of a catalytically relevant Pd(II)-3-methylindole species via insertion into the corresponding ester as well as the first example of an indole participating in a Pd-catalyzed decarboxylative alkylation.

(5) (a) Legros, J.-Y.; Fiaud, J.-C. *Tetrahedron Lett.* **1992**, *33*, 2509. (b) Boutros, A.; Legros, J.-Y.; Fiaud, J.-C. *Tetrahedron Lett.* **1999**, *40*, 7329. (c) Legros, J.-Y.; Toffano, M.; Fiaud, J.-C. *Tetrahderon* **1995**, *51*, 3235. (d) Legros, J.-Y.; Primault, G.; Toffano, M.; Rivière, M.-A.; Fiaud, J.-C. *Org. Lett.* **2000**, *2*, 433. (e) Kuwano, R.; Kondo, Y.; Matsuyama, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12104. (f) Kuwano, R.; Yokogi, M. *Org. Lett.* **2005**, *7*, 945. (g) Kuwano, R.; Kondo, Y.; Shirahama, T. *Org. Lett.* **2005**, *7*, 2973. (h) Kuwano, R.; Yokogi, M. *Chem. Commun.* **2005**, 5899. (i) Narahashi, H.; Shimizu, I.; Yamamoto, A. *J. Organomet. Chem.* **2008**, *693*, 283. (j) Miller, K. J.; Abu-Omar, M. M. *Eur. J. Org. Chem.* **2003**, 1294. (k) Kuwano, R. *Synthesis* **2009**, 1049. (l) Liégault, B.; Renaud, J.-L.; Bruneau, C. *Chem. Soc. Rev.* **2008**, *37*, 290.

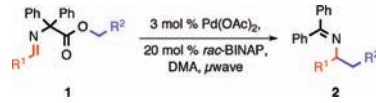
(6) Bite angles in relevant Pd(II) complexes: xantphos = 108.1°, dppf = 102.2°, BINAP = 96.0°, dppe = 86°: (a) Johns, A. M.; Utsunomiya, M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 1828. (b) Steffen, W. L.; Palenik, G. J. *Inorg. Chem.* **1976**, *15*, 2432.

(7) Under these conditions, *R*-BINAP did not confer any enantioselectivity for the conversion of **1a** to **2a**, as monitored by chiral HPLC analysis.

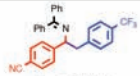
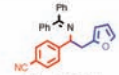
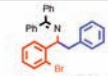
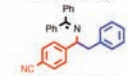
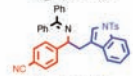
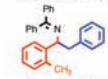
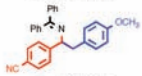
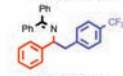
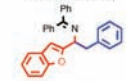
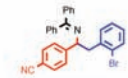
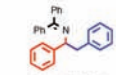
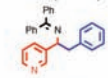
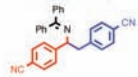
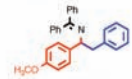
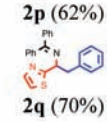
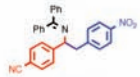
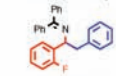
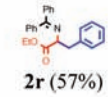
(8) The exact mechanism/source of protonation is unclear and currently under investigation. Stoltz and Tunge have both reported similar difficulty identifying the proton source for related decarboxylative protonation events: Mohr, J. T.; Toyoki, N.; Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 11348, and ref 3b.

(9) (a) Ohmoto, T.; Koike, K. *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1989; Vol. 36, pp 135−150. (b) Love, B. E. *Org. Prep. Proced. Int.* **1996**, *28*, 1.

Table 2. Substrate Scope for the Pd-Catalyzed Decarboxylative Benzylation of Imino Esters **1**[a]



1 **2**

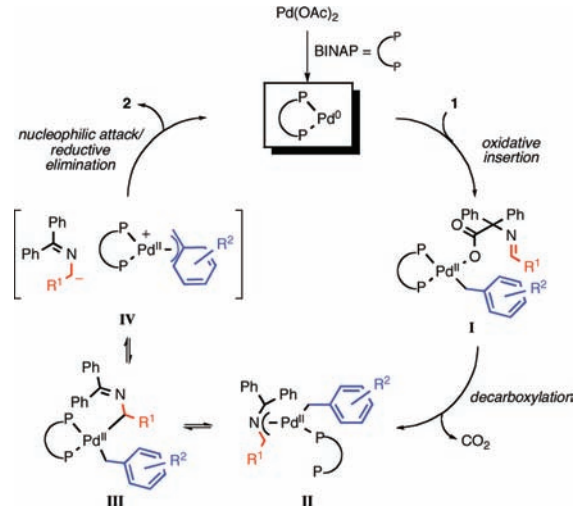
entry	temp (°C)	time (min)	product (yield)[b]	entry	temp (°C)	time (min)	product (yield)[b]	entry	temp (°C)	time (min)	product (yield)[b]
1	150	5	 **2a** (74%)	7	175	5	 **2g** (43%)	13	200	45	 **2m** (36%)
2	175	5	 **2b** (81%)	8	210	5	 **2h** (60%)	14	200	15	 **2n** (26%)
3	150	5	 **2c** (85%)	9	175	5	 **2i** (73%)	15	175	5	 **2o** (43%)
4	210	15	 **2d** (48%)	10	175	5	 **2j** (44%)	16	210	8	 **2p** (62%)
5	175	5	 **2e** (46%)	11	200	5	 **2k** (50%)	17	150	5	 **2q** (70%)
6	200	5	 **2f** (13%)[c]	12	175	5	 **2l** (54%)	18[d]	200	5	 **2r** (57%)

[a] Reaction conditions: imino ester **1** (100 mg), $Pd(OAc)_2$ (3 mol %), and *rac*-BINAP (20 mol %) in DMA (0.1 M), microwave irradiation to the indicated temperature for an indicated time. [b] Isolated yield after chromatographic purification. The remaining mass balance was predominantly the protonation and acetaylation side products, à la **3** and **4**. [c] Determined by ^{1}H NMR spectroscopy of an inseparable mixture of **2f** and **3** with durene as an internal standard. [d] Reaction Conditions: imine (100 mg), $Pd(OAc)_2$ (10 mol %), and *rac*-BINAP (40 mol %) in DMA (0.1 M).

Variation of the imine moiety was also tolerated (entries 9−18), though increasing the size of the *ortho* substituent dramatically impacted the corresponding isolated yields (cf. entries 12−14). It is noteworthy that heteroaryl imines 2-benzofuranyl **1o**, 3-pyridyl **1p**, and 2-thiazolyl **1q** successfully underwent the transformation in moderate to good yields (entries 15−17). Moreover, conversion of α-imino ester **1r** into fully protected phenylalanine **2r** simply required higher catalyst and ligand loading (10 mol % $Pd(OAc)_2$ and 40 mol % *rac*-BINAP), a phenomenon specific to this substrate.

A preliminary mechanistic explanation for the Pd-catalyzed decarboxylative benzylation of imino esters **1** is provided in Scheme 2. Reduction of $Pd(OAc)_2$ with BINAP generates the active BINAP-Pd(0) catalyst.[10] Insertion into the ester C−O bond[5] forms an ephemeral Pd(II)-carboxylate species **I** that undergoes irreversible decarboxylation to the 2-azaallylPd(II) intermediate **II**, which is in equilibrium with the η^1 complex **III** and the tight-ion-paired π-benzylPd(II):α-imino anion species **IV**. Reductive elimination (from **III**) or regioselective nucleophilic attack (from **IV**) then regenerates the Pd(0) catalyst with concomitant formation of homobenzylic imines **2**.

Scheme 2. Possible Mechanism for Decarboxylative Benzylation



In summary, we report general reaction conditions for the Pd-catalyzed decarboxylative benzylation of benzyl diphenylg-

(10) Since the reduction of $Pd(OAc)_2$ with BINAP also results in formation of the corresponding monophosphine oxide (BINPO), the involvement of this species in the catalytic cycle cannot be rigorously excluded at this time: Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, 2177.

lycinate imines. This transformation expands the scope of our previously identified Pd-catalyzed decarboxylative generation and derivatization of stabilized α-imino anions.[2d] Given the broad substrate scope and utility of the Tsuji−Trost decarboxylative *allylation* manifold, our evidence supporting extension to *benzyl* ester substrates is expected to have a significant impact.

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

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