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One-Pot Tandem Decarboxylative Allylation−Heck Cyclization of Allyl Diphenylglycinate Imines: Rapid Access to Polyfunctionalized 1-Aminoindanes

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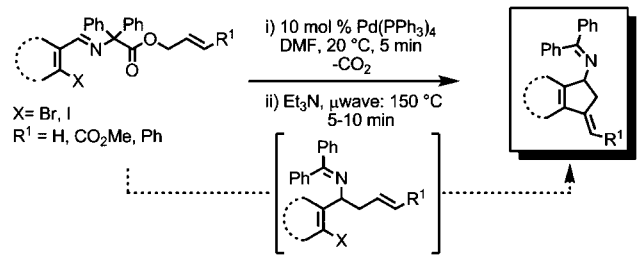
ABSTRACT



1-Aminoindanes are generated from allyl diphenylglycinate imines employing a "one-pot" palladium-catalyzed decarboxylative allylation−Heck cyclization cascade. Variation of both the aryl and allyl moieties leads to a diverse range of polycyclic imines, amenable to the synthesis of natural products and other biologically relevant small molecules.

Palladium-catalyzed decarboxylative coupling reactions, which typically proceed through an η^3 π-allyl palladium intermediate, have emerged as efficient and essentially neutral pathways for carbon−carbon bond formation.[1] A unique value inherent to Pd-catalyzed transformations is the ability to couple them to other powerful carbon−carbon bond-forming events in one reaction vessel.[2] Despite intense interest in Pd-mediated decarboxylative alkylations,[1,3] to the best of our knowledge, very few examples exist that couple this technique with other Pd-catalyzed carbon−carbon bond-forming reactions in one reaction vessel.[4] Herein, we report a two step−one-pot decarboxylative allylation−Heck cyclization to rapidly afford 3-alkylidenyl-1-aminoindanes.

Recent studies have identified the functionalized 1-aminoindane motif as both a unique platform for ventures in diversity-oriented synthesis[5a] and for the construction of potent atypical antipsychotic agents.[5b] We reasoned that the Pd-catalyzed decarboxylative allylation of diphenylglycinate

(1) For recent examples of decarboxylative enolate alkylations, see: (a) Burger, E. C.; Tunge, J. A. *Org. Lett.* **2004**, *6*, 4113–4115. (b) Enquist, J. A., Jr.; Stoltz, B. M. *Nature* **2008**, *453*, 1228–1231. (c) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846–2847. (d) McFadden, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 7738–7739.

(2) (a) Metal Catalyzed Cascade Reactions. *Top. Organomet. Chem.* Müller, T. J. J., Ed. **2006**, *19*, 1−91, 149−205. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442–4489. (c) Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959–5989. (d) de Meijere, A.; Bräse, S. *Organomet. Chem.* **1999**, *576*, 88–110.

(3) (a) Burger, E. C.; Tunge, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 10002–10003. (b) Tunge, J. A.; Burger, E. C. *Eur. J. Org. Chem.* **2005**, *9*, 1715–1726. (c) Rayabarapu, D. K.; Tunge, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 13510–13511. (d) Yamamoto, Y.; Nakamura, H.; Sekido, M.; Ito, M. *J. Am. Chem. Soc.* **1998**, *120*, 6838–6839. (e) You, S.-L.; Dai, L.-X. *Angew. Chem., Int. Ed.* **2006**, *45*, 5246–5248. (f) Tsuji, J. *Pure Appl. Chem.* **1986**, *58*, 869–878. (g) Imao, D.; Itoi, A.; Yamazaki, A.; Shirakura, M.; Ohtoshi, R.; Ogata, K.; Ohmori, Y.; Ohta, T.; Ito, Y. *J. Org. Chem.* **2007**, *72*, 1652–1658.

(4) (a) Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250–11251. (b) Moon, J.; Jeong, M.; Nam, H.; Ju, J.; Moon, J. H.; Jung, H. M.; Lee, S. *Org. Lett.* **2008**, *10*, 945–948. (c) Forgione, P.; Brochu, M. C.; St-Onge, M.; Thesen, K. H.; Bailey, M. D.; Bilodeau, F. *J. Am. Chem. Soc.* **2006**, *128*, 11350–11351. (d) Goossen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662–664.

(5) (a) Kesavan, S.; Panek, J. S.; Porco, J. A. *Org. Lett.* **2007**, *9*, 5203–5206. (b) Graham, J. M.; Coughenour, L. L.; Barr, B. M.; Rock, D. L.; Nikam, S. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 489–493.

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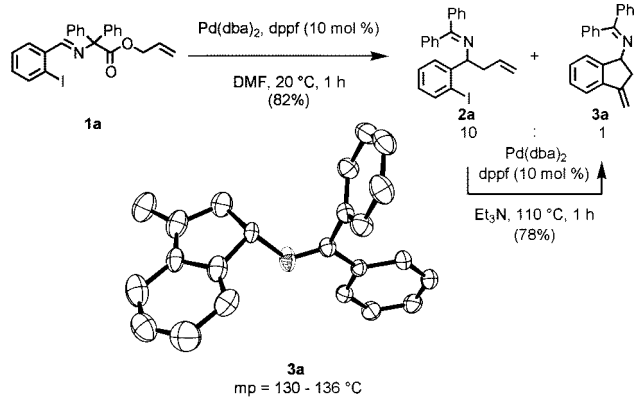
imines recently developed by our group[6] could be coupled to an intramolecular Heck reaction to rapidly generate functionalized 1-aminoindanes. Accordingly, *o*-iodobenzaldimine **1a** was subjected to our standard decarboxylative allylation conditions (10 mol % of $Pd(dba)_2$, dppf, DMF, 20 °C). We were gratified to observe the formation of the cyclized product **3a** in addition to the expected homoallylic imine **2a** in a 1:10 ratio and excellent combined yield (Scheme 1). It is worth noting that **3a** was obtained even

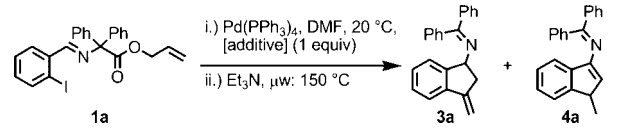
Scheme 1. Two-Step Decarboxylative Allylation−Heck Cascade



without the addition of exogenous base or heat. Subjection of the resulting reaction mixture to typical Heck reaction conditions[7] effected complete conversion to the 3-methylenyl-1-aminoindane **3a**, whose structure was confirmed by X-ray crystallographic analysis (see inset).

Encouraged by these results, we next sought optimal conditions to effect the two-step process in one reaction vessel. Initial attempts employed 10 mol % of $Pd(dba)_2$ and dppf as catalyst, but coelution of the dibenzylidene−acetone ligand during chromatography compromised the purity of the product. Tetrakis(triphenylphosphine)palladium(0), however, provided rapid and effective decarboxylative allylation and subsequent Heck cyclization without introducing intractable purification issues. Furthermore, microwave irradiation rapidly accelerated the Heck reaction,[8] though in some cases an additional isomerized product **4a** was coisolated in unpredictable ratios (Table 1).[5a,9] This result may be attributed to the production of an ephemeral palladium hydride species that can isomerize the double bond to the more substituted position via a series of addition−elimination events.[10] Remarkably, the resulting enimine **4a** was stable to standard flash chromatography through nonbuffered silica gel. We investigated a variety of additives to enhance the selectivity of the Heck cyclizations (Table 1).[10] Tetraalkylammonium salts[10f] did not have an appreciable effect on the reaction rate or alkene isomer ratios (entries 2−4). Alternatively, silver(I) sulfate successfully inhibited isomerization, leading to the exclusive formation of **3a** in excellent isolated yield (entry 5).[10a,e] Similarly, addition of Tl_2CO_3, shown in entry 9, for the tandem reaction led to a significantly improved isomer ratio.[10c] It is worth noting that other silver(I) salts (entries 6−8) completely inhibited the initial decarboxylative allylation; none of the other additives were found to impact this transformation.[11] Van Vranken et al. observed that use of an insoluble base was crucial for inhibiting alkene migration of α,β-unsaturated esters in their tandem carbene insertion−Heck cyclization tactic.[12] For our reaction, however, we obtained a disappointing 2.6:1 ratio of alkenes **3a**:**4a** when triethylamine was replaced with K_2CO_3 as base.

Table 1. Optimization Studies of One-Pot Reaction



entry	time (i:ii)	additive	isolated yield (%)	isomer ratio (**3a**:**4a**)
1	5 min:5 min	none	≥99	1:1[a]
2	5 min:5 min	TBAC	72	9.4:1
3	5 min:5 min	TBAI	73	2.7:1
4	5 min:5 min	TBAB	65	3.4:1
5	**5 min:5 min**	**Ag_2SO_4**	**91**	**≥20:1**
6	2 h[b]:10 min	$AgNO_3$	NR	
7	2 h[b]:10 min	AgOTf	NR	
8	2 h[b]:10 min	AgO_2CCF_3	NR	
9	5 min:5 min	Tl_2CO_3	72	16:1
10	5 min:5 min	K_2CO_3	70	2.6:1

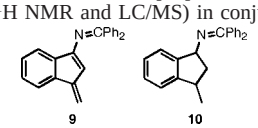
[a] This represents an average ratio; specific ratios per run were highly variable. [b] No conversion to homoallylic imine; subjection to Heck reaction conditions after 2 h led to complete decomposition of **1a**. [c] 2 equiv of K_2CO_3 instead of Et_3N. NR = no reaction. TBAC = tetrabutylammonium chloride. TBAI = tetrabutylammonium iodide. TBAB = tetrabutylammonium bromide.

(6) Yeagley, A. A.; Chruma, J. J. *Org. Lett.* **2007**, *9*, 2879–2882.

(7) (a) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146–151. (b) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581. (c) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066. (d) Daves, G. D.; Hallberg, A. *Chem. Rev.* **1989**, *89*, 1433–144.

(8) (a) Xie, X.; Lu, J.; Chen, B.; Han, J.; She, X.; Pan, X. *Tetrahedron Lett.* **2004**, *45*, 809–811. (b) Declerckz, V.; Ribière, P.; Nédellec, Y.; Allouchi, H.; Martinez, J.; Lamaty, F. *Eur. J. Org. Chem.* **2007**, 201–208. (c) Svennebring, A.; Garg, N.; Nilsson, P.; Hallberg, A.; Larhed, M. *J. Org. Chem.* **2005**, *70*, 4720–4725. (d) Donets, P. A.; Van der Eycken, E. V. *Org. Lett.* **2007**, *9*, 3017–3020.

(9) Small amounts of the alkene disproportionation products **9** and **10** were also observed (^1H NMR and LC/MS) in conjunction to **4a**.



(10) (a) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130–4133. (b) Wheatley, B. M. M.; Keay, B. A. *J. Org. Chem.* **2007**, *72*, 7253–7259. (c) Reetz, M. T. *Angew. Chem., Int. Ed.* **1972**, *11*, 129–130. (d) Grigg, R.; Loganathan, V.; Santhakumar, V.; Sridharan, V.; Teasdale, A. *Tetrahedron Lett.* **1991**, *32*, 687–690. (e) Larock, R. C.; Gong, W. H. *J. Org. Chem.* **1989**, *54*, 2047–2050. (f) Jeffery, T. *Synthesis* **1987**, 70–71.

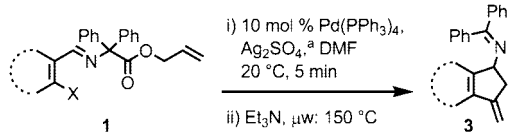
(11) We have observed a similar inhibition of the decarboxylative allylation at rt with ≥10 mol % of other Lewis acids, e.g., LiCl, $ZnCl_2$, or $Sc(OTf)_3$.

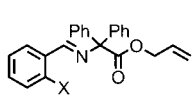
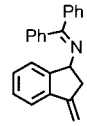
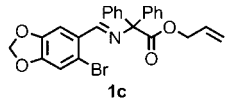
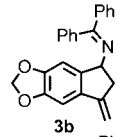
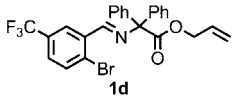
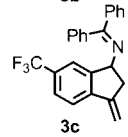
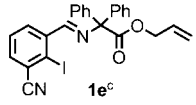
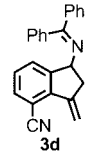
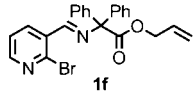
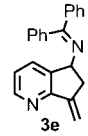
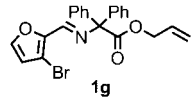
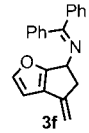
(12) Kudirka, R.; Van Vranken, D. L. *J. Org. Chem.* **2008**, *73*, 3585–3588.

(13) (a) Knowles, J. P.; Whiting, A. *Org. Biomol. Chem.* **2007**, *5*, 31–44. (b) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427–436.

The substrate scope of the reaction was first evaluated through variation of the imine moiety. Accordingly, imines **1** were subjected to our optimized two-step, one-pot reaction conditions to afford the corresponding cyclic products **3** (Table 2). A variety of aryl and heteroaryl functionalities

Table 2. Tandem Decarboxylative Allylation−Heck Cyclization



entry	imine	μwave time (min)	product	isolated yield
				
1	**1a** X = I	5	**3a**	91%
2	**1a** X = I	5	**3a**	71%[e]
3	**1b** X = Br	5	**3a**	85%
4	 **1c**	10	 **3b**	58%
5	 **1d**	10	 **3c**	81%[b]
6	 **1e**[c]	10	 **3d**	76%
7	 **1f**	10	 **3e**	74%
8	 **1g**	10	 **3f**	n.d.[d]

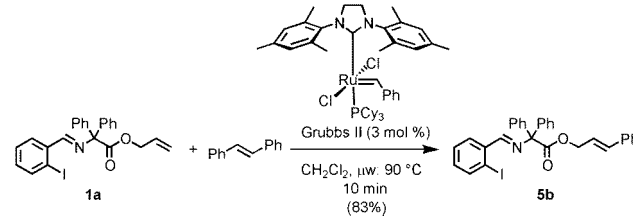
[a] 1.0 equiv of Ag_2SO_4 added to inhibit double-bond migration. [b] Ag_2SO_4 omitted. [c] Compound **1e** was a 4.6:1 ratio of aryl iodide and aryl bromide. [d] 100% conversion to homoallylic imine as a 9.3:1 ratio of regioisomers; no cyclized product (**3f**) was observed. [e] Et_3N added prior to decarboxylative allylation.

successfully underwent the tandem reaction process. In accord with our previous decarboxylative allylation studies and the accepted mechanism of the Heck reaction,[13] electron-deficient *o*-halobenzaldimines provided superior yields and rates versus electron-rich counterparts (compare entries 5 and 4). In an extreme case, the electron-rich furanyl bromide **1g** did not undergo Heck cyclization, halting at the intermediate homoallylic imine as a 9.3:1 ratio of regioisomers (entry 8).[6]

The relatively electron-deficient pyridinyl heterocycle **1f**, however, smoothly converted to the corresponding tandem decarboxylative allylation−Heck cyclization product **3e** (entry 7). As demonstrated in entry 2, combining all reagents at once, including the amine base, followed by immediate microwave irradiation, also produced the desired 1-iminoindane, though in a lower isolated yield versus the two-step, one-pot process (entry 1).

Diversification of the allyl ester was achieved by microwave-accelerated olefin cross-metathesis either prior to or after imine formation.[14] For example, subjection of alkene **1a** and stilbene to Grubbs' second-generation catalyst[15] under microwave heating (90 °C, 10 min) rapidly afforded the corresponding imine **5b** in high isolated yield (Scheme 2).

Scheme 2. Diversification of the Allyl Ester Moeity Employing Olefin Cross-Metathesis



The resultant α-imino esters **5** were subjected to our optimized tandem decarboxylative allylation−Heck cyclization conditions (Table 3). For the methyl acrylate substrate **5a**, the ratio of resultant isomers **6a** and **7a** proved to be extremely variable, though combined yields were typically high (entries 1 and 2). In contrast to allyl ester **1a**, Ag_2SO_4 did not consistently improve the ratio of products in favor of dihydrobenzofulvene **6a**. Surprisingly, addition of Tl_2CO_3 to the reaction mixture resulted in the predominant formation of the isomerized product **7a**. Preferential formation of the internalized alkene was unique to substrate **5a**; cinnamyl ester **5b** and furanyl imine **5c** consistently afforded the corresponding exomethylenes **6b** and **6c**, respectively, as the exclusive cyclization products. The successful Heck cyclization of the election-rich furanyl substrate **5c** is noteworthy, given that the related allyl ester **1g** did not proceed past

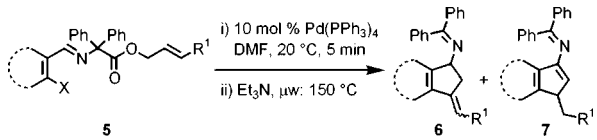
(14) For examples of microwave-accelerated olefin cross-metathesis reactions, see: (a) Coquerel, Y.; Rodriguez, J. *Eur. J. Org. Chem.* **2008**, 1125–1132. (b) Gebauer, J.; Arseniyadis, S.; Cossy, J. *Eur. J. Org. Chem.* **2008**, 2701–2704. (c) Aitken, S. G.; Abell, A. D. *Aust. J. Chem.* **2005**, *58*, 3–13.

(15) (a) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110. (b) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **1995**, *34*, 2039–2041.

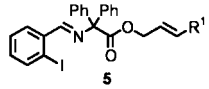
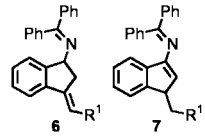
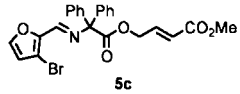
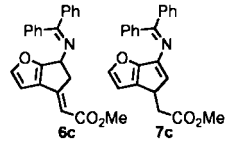
(16) Young and Kerr noted a similar reliance on Ag_2SO_4 for a related Heck cyclization in their total synthesis of nakadomarin A: Young, I. S.; Kerr, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 1465–1469.

(17) (a) Lautens, M.; Fang, Y.-Q. *Org. Lett.* **2003**, *5*, 3679–3682. (b) Andersson, P. G.; Schab, S. *Organometallics* **1995**, *14*, 1–2. (c) Takacs, J. M.; Lawson, E. C.; Clement, F. *J. Am. Chem. Soc.* **1997**, *119*, 5956–5957. (d) Maeda, K.; Farrington, E. J.; Galardon, E.; John, B. D.; Brown, J. M. *Adv. Synth. Catal.* **2002**, *344*, 104–109. (e) Bray, K. L.; Lloyd-Jones, G. C.; Muñoz, M. P.; Slatford, P. A.; Tan, E. H. P.; Tyler-Mahon, A. R.; Worthington, P. A. *Chem.—Eur. J.* **2006**, *12*, 8650–8663. (f) Hudlicky, T.; Olivo, H. F. *J. Am. Chem. Soc.* **1992**, *114*, 9694–9696.

Table 3. Tandem Decarboxylative Allylation−Heck Cyclization of Imines **5**



5 6 7

entry	imine	μwave time (min)	product ratio (6:7)	isolated yield
	 5		 6 7	
1	**5a** $R^1 = CO_2Me$	10	1:2 [a]	77%
2	**5a** $R^1 = CO_2Me$	10	1: ≥20	72% [b]
3	**5b** $R^1 = Ph$	10	≥20 :1	81%
	 5c		 6c 7c	
4		30	≥20:1	88% [c,d]

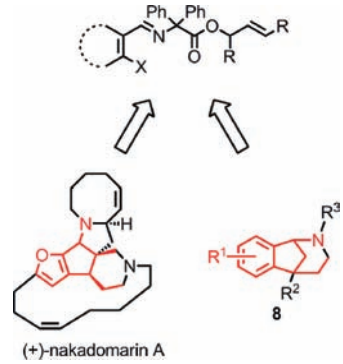
[a] This represents an average ratio; specific ratios are highly variable sometimes with **6a** predominating. [b] 2.0 equiv of Tl_2CO_3 added. [c] Decarboxylative allylation required 15 min. [d] 1.5 equiv of Ag_2SO_4 added.

decarboxylative allylation following our standard reaction conditions (see Table 2). Addition of Ag_2SO_4 to the reaction mixture and longer reaction time, however, were crucial for promoting the Heck cyclization to afford **6c**.[16] These results suggest that successful Heck cyclization under our reaction conditions relies on an intimate and complex interplay between the electronic factors governing the reversible oxidative addition and migratory insertion steps.

Extensive 2D-NMR spectroscopic analysis (NOESY) of alkenes **6** indicated predominant formation of the *E*-alkene geometry, as shown, thus representing a formal *anti*-β-hydride elimination of the Pd(II) intermediate in the Heck cyclization. Although Heck reactions typically require *syn*-β-hydride elimination,[13] several examples suggest the possibility of either an *anti*-β-hydride elimination or an isomerization manifold.[17]

In conclusion, we report a rapid and mild pathway toward the synthesis of complex polycyclic organoamines using a one-pot decarboxylative allylation−Heck reaction cascade. This work stands as a proof-of-principle that decarboxylative allylations can be coupled effectively to other powerful transition-metal-mediated carbon−carbon bond-forming events in one reaction vessel. Future efforts will be directed at the application of this reaction cascade toward the total synthesis of the manzamine-related alkaloid nakadomarin A[18] as well as libraries of B-norbenzomorphans **8**, a conformationally restricted benzazepine scaffold that has provided potent analgesics and acetylcholinesterase inhibitors (Scheme 3).[19]

Scheme 3. Future Targets Acessible via the Pd-Catalyzed Decarboxylative Allylation−Heck Cascade



General Microwave Procedure. The reaction mixtures were heated to the indicated temperatures (300 W maximum power) for the indicated time in a sealed 10 mL CEM IntelliVent microwave tube using a CEM Explorer−Discover microwave reactor with IR temperature probe. Reaction temperature, pressure, and temperature-time profiles were monitored using the associated ChemDriver Explorer Application program.

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Supporting Information Available: Experimental procedures, characterization data, and cif file for compound **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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