ORGANIC LETTERS

2009
Vol. 11, No. 17
4022−4025

Tandem C−C Bond-Forming Processes: Interception of the Pd-Catalyzed Decarboxylative Allylation of Allyl Diphenylglycinate Imines with Activated Olefins

Andrew A. Yeagley, Melissa A. Lowder, and Jason J. Chruma*

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22904-4319

jjc5p@virginia.edu

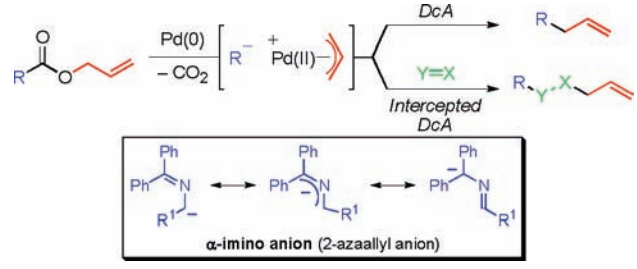
Received July 29, 2009

ABSTRACT

Interception of the Pd-catalyzed decarboxylative allylation of allyl diphenylglycinate imines with appropriately functionalized Michael acceptors, followed by Heck cyclization, allows for the efficient construction of relatively complex organoamine frameworks in one reaction vessel. The initial intercepted decarboxylative allylation is remarkably insensitive toward solvent and catalyst, typically proceeding under ambient conditions.

Since the pioneering work of Tsuji,[1] Saegusa[2] and Trost,[3] Pd-catalyzed decarboxylative allylations (DcAs) have emerged as mild and versatile procedures for rapidly constructing complex molecular frameworks.[4,5] Each DcA transformation proceeds through the intermediacy of an electrophilic π-allyl-Pd(II) species and a corresponding N-, O-, or C-centered nucleophilic anion counterpart (R^-, Scheme 1). Yamamoto[6] and others[7] have demonstrated that activated Michael acceptors and related electrophiles (Y═X, Scheme 1) can intercept the nucleophilic intermediates prior to allylation and regeneration of the Pd(0) catalyst. Reports of C-centered anions participating in such intercepted Pd-catalyzed DcA transformations typically have been limited to enolates.[8] We recently introduced the α-imino anion (2-azaallyl anion) as a viable intermediate for the aldehyde-intercepted Pd-catalyzed DcA of allyl diphenylglycinate imines.[7c] Herein, we report that alkene derivatives of malononitrile (**2**)[9] and Meldrum's acid (**4**) are potent electrophiles for the intercepted DcA of allyl diphenylglycinate imines.[10] The resulting products are appropriately functionalized for a variety of further transformations, for example, Heck cyclization,[11]

Scheme 1. Decarboxylative Allylation (DcA) and Intercepted DcA



(1) (a) Shimizu, I.; Yamada, T.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 3199. (b) Shimizu, I.; Tsuji, J. *J. Am. Chem. Soc.* **1982**, *104*, 5844.
(2) Tsuda, T.; Chujo, Y.; Nishi, S.-i.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 6381.
(3) (a) Trost, B. M. *Tetrahedron* **1977**, *33*, 2615. (b) Trost, B. M.; Hung, M. H. *J. Am. Chem. Soc.* **1984**, *106*, 6837.

10.1021/ol901745x CCC: $40.75
Published on Web 08/06/2009

allowing for the efficient construction of relatively complex organoamine frameworks in as few as one reaction vessel. Our results emphasize that Pd-mediated decarboxylation is a mild and versatile strategy for the generation and derivatization of stabilized α-imino anions.

As an initial assessment of the capability of arylidene malononitriles to act as electrophilic interceptors in the DcA of allyl diphenylglycinate imines, a solution of imine **1a** (1.0 equiv) and alkene **2a** (1.1 equiv) was subjected to our standard DcA reaction conditions (10 mol % $Pd(PPh_3)_4$, MeCN, 20 °C).[7c] Gratifyingly, the intercepted DcA product **3aa** was generated quantitatively as a roughly 1:1 ratio of diatereomers (Table 1, entry 1). The transformation proved

Table 1. Solvent Studies for the Intercepted DcA

entry	solvent	product	*dr* (*syn*:*anti*)[a]	isolated yield
1	MeCN	**3aa**	1.0:1.2	99%
2	2-Me-THF	**3aa**	1.0:1.4	99%
3	$PhCH_3$	**3aa**	1.0:1.1	89%
4	DMF	**3aa**	1.0:1.1	97%
5	CH_2Cl_2	**3aa**	1.0:1.1	95%
6[b]	$PhCH_3$:H_2O[c]	**3ac**	1.0:1.2	86%[d]

[a] Determined by ^1H NMR analysis of the unpurified reaction mixtures. [b] Alkene **2c** was used. [c] 10 mol % of (−)-*O*-9-allyl-*N*-(9-anthracenylmethyl)cinchondium bromide added as a phase-transfer catalyst. [d] 88% with MeCN as solvent.

highly independent of the reaction medium; nearly identical yields and diastereomeric ratios were obtained employing a variety of solvents (Table 1). Despite the relatively high basicity of the putative α-imino anion intermediate, the presence of water does not significantly impact the transformation (Table 1, entry 6). This stands in marked contrast to the 2-azaallyllithium dipolar nucleophiles described by Kauffmann[12] and Pearson.[13]

Inspired by these results, we next investigated the scope of the electrophiles and imines (**1**, R^1). Arylidene malononitriles bearing electron-rich (**2c** and **2d**) or electron-deficient (**2b** and **2e**) aromatic R^2-groups, as well as heteroaromatics (**2f**), were successfully incorporated into the DcA of imine **1a**, providing the corresponding allylated products **3** in high yield (Table 2, entries 2−6). The branched aliphatic *i*-Pr substituent (**2g**) also was effective (Table 2, entry 7) The bulkier *t*-Bu substrate **2h**, however, was a much poorer intercepting electrophile. Geminal dinitrile **3ah** was isolated in low yield with the *non*-intercepted DcA product **6** (R^1 = 4-CN-Ph, Figure 1) comprising the remainder of converted starting material. For all other alkylidene malononitriles (Table 2, entries 1−7 and 9−12), homoallylic imines **6** were detected in, at most, trace quantities. The results obtained by variation of the imine R^1 group mirrored our previous *non*-intercepted DcA studies.[7c] Specifically, electron-withdrawing aromatic (**1a** and **1b**) and heteroaromatic (**1d**) substituents afforded a single regioisomer. Alternatively, the electron-donating *p*-methoxybenzaldimine **1c** provided a 5:1 ratio of regioisomeric products **3ca**:**7** in 95% combined yield; imine **7** selectively hydrolyzed on silica gel, thus facilitating purification of the other regioisomer (Figure 1). While no diastereoselectivity was observed for the intercepted DcA of imino esters **1** with alkenes **2**, the majority of product (**3**) diastereomeric mixtures could be resolved via standard chromatographic means.

To further explore the electrophile scope, arylidene Meldrum's acid derivatives **4** also were investigated as intercepting agents (Table 2, entries 13−17). Alkenes **4** proved to be weaker electrophiles than their malononitrile counterparts **2**; significant quantities (≤20%) of the homoallylic imine **6** (R^1 = 4-CN-Ph) were produced in competition with interception products **5**. Interestingly, the 2-furanyl alkene **4e** severely deactivated the Pd(0) catalyst, resulting in very slow conversion of imine **1a** to either **5ae** or **6** (Table 2, entry17). Unlike

(4) (a) Tunge, J. A.; Burger, E. C. *Eur. J. Org. Chem.* **2005**, 1715. (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) 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. (e) Waetzig, S. R.; Rayabarapu, D. K.; Weaver, J. D.; Tunge, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4977. (f) Burger, E. C.; Tunge, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 10002. (g) Weaver, J. D.; Tunge, J. A. *Org. Lett.* **2008**, *10*, 4657. (h) Sim, S. H.; Park, H.-J.; Lee, S. I.; Chung, Y. K. *Org. Lett.* **2008**, *10*, 433. Asymmetric variants: (i) Trost, B. M.; Bream, R. N.; Xu, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3109. (j) Burger, E. C.; Tunge, J. A. *Org. Lett.* **2004**, *6*, 4113. (k) Mohr, J. T.; Behanna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924. (l) You, S.-L.; Dai, L.-X. *Angew. Chem., Int. Ed.* **2006**, *45*, 5246.

(5) Recent applications in natural product total synthesis: (a) Enquist, J. A., Jr.; Stoltz, B. M. *Nature* **2008**, *453*, 1228. (b) White, D. E.; Stewart, I. C.; Grubbs, R. H.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 810. (c) McFadden, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 7738.

(6) (a) Shim, J.-G.; Nakamara, H.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 8470. (b) Nakumura, H.; Shibata, H.; Yamamoto, Y. *Tetrahedron Lett.* **2000**, *41*, 2911. (c) Aoyagi, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 5977. (d) Shim, J.-G.; Park, J. C.; Cho, C. S.; Shim, S. C.; Yamamoto, Y. *Chem. Commun.* **2002**, 852. (e) Patil, N. T.; Hou, Z.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 6991. (f) Patil, N. T.; Hou, Z.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 2503. (g) Patil, N. T.; Yamamoto, Y. *Synlett* **2007**, 1994. (h) Yoshikawa, E.; Radhakrishnan, K. V.; Yamamoto, Y. *Tetrahedron Lett.* **2000**, *41*, 729.

(7) (a) Nokami, J.; Watanabe, H.; Mandai, T.; Kawada, M.; Tsuji, J. *Tetrahedron Lett.* **1989**, *30*, 4829. (b) Wang, C.; Tunge, J. A. *Org. Lett.* **2005**, *7*, 2137. (c) Yeagley, A. A.; Chruma, J. J. *Org. Lett.* **2007**, *9*, 2879. (d) Wang, C.; Tunge, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 8118. (e) Shintani, R.; Murakami, M.; Hayashi, T. *Org. Lett.* **2009**, *11*, 457.

(8) For a very recent exception: Pi, S.-F.; Tang, B.-X.; Li, J.-H.; Liu, Y.-L.; Liang, Y. *Org. Lett.* **2009**, *11*, 2309.

(9) CAUTION: Many arylidenemalononitriles are powerful irritants and should be handled in a well-ventilated fume hood!

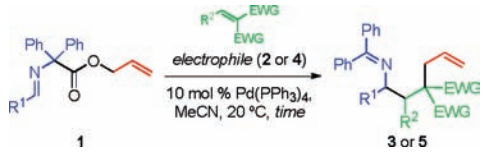
(10) For a related Ru-catalyzed intercepted DcA of β-ketoesters: Wang, C.; Tunge, J. A. *Org. Lett.* **2005**, *7*, 2137.

(11) (a) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146. (b) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.

(12) (a) Kauffmann, T.; Berg, H.; Koppelmann, E.; Kuhlmann, D. *Chem. Ber.* **1977**, *110*, 2659. (b) Kauffmann, T.; Eidenschink, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 739. (c) Kauffmann, T.; Köppelmann, E. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 290. (d) Kauffmann, T.; Busch, A.; Habersaat, K.; Käppelmonn, E. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 568. (e) Kauffmann, T.; Ahlers, H.; Hamsen, A.; Schulz, H.; Tilhard, H.-J.; Vahrenhorst, A. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 119, references therein.

(13) (a) Pearson, W. H.; Stoy, P. *Synlett* **2003**, *7*, 903. (b) Pearson, W. H. *Pure Appl. Chem.* **2002**, *74*, 1339, and references therein.

Table 2. Intercepted DcA of Imines **1** with Activated Alkenes



entry	1 (R^1)	electrophile[a]	time (h)	product (% yield)[b]	entry	1 (R^1)	electrophile[a]	time (h)	product (% yield)[b]
1	**1a** (4-CN-Ph)	**2a**	3	**3aa** (>99)	9	**1b** (2-Br-Ph)	**2a**	3	**3ba** (>99)
2	**1a** (4-CN-Ph)	**2b**	3	**3ab** (99)	10	**1c** (4-MeO-Ph)	**2a**	12	**3ca** (58)[d]
3	**1a** (4-CN-Ph)	**2c**	2.5	**3ac** (88)[c]	11	**1d** (2-thiazolyl)	**2a**	3	**3da** (>99)
4	**1a** (4-CN-Ph)	**2d**	3	**3ad** (77)	12	**1e** (EtO_2C)	**2a**	3	**3ea** (76)
5	**1a** (4-CN-Ph)	**2e**	12	**3ae** (84)	13	**1a** (4-CN-Ph)	**4a**	1	**5aa** (67)[f]
6	**1a** (4-CN-Ph)	**2f**	36	**3af** (98)	14	**1a** (4-CN-Ph)	**4b**	18	**5ab** (68)[f]
7	**1a** (4-CN-Ph)	**2g**	3.5	**3ag** (81)[c]	15	**1a** (4-CN-Ph)	**4c**	18	**5ac** (61)
8	**1a** (4-CN-Ph)	**2h**	7	**3ah** (28)[e]	16	**1a** (4-CN-Ph)	**4d**	19	**5ad** (72)[g]
					17	**1a** (4-CN-Ph)	**4e**	96	**5ae** (14)[f,g]

[a] 1.1 equiv compared to imine **1**. [b] Isolated yield of diastereomeric mixture after preliminary chromatography. [c] The *dr* was ~2:1 in favor of the *anti* diastereomer. [d] The remaining mass balance corresponded to the regioisomeric product **7**. [e] Only one diastereomer isolated. [f] The *anti* diastereomer was isolated exclusively. [g] Isolated yield after Et_3N-*buffered* SiO_2 chromatography.

malononitriles **2**, the nonplanar cyclic diesters **4** typically demonstrated a subtle diastereoselectivity favoring the *anti*-**5** stereoisomer. Moreover, to varying degrees, the *syn* epimer selectively decomposed upon passage through *nonbuffered* silica gel, allowing for the exclusive isolation of the *anti*-**5** isomer in acceptable yields. This stereoselective decomposition during chromatography was eliminated by addition of 1% Et_3N to the eluent, but the diastereomers typically coeluted.

The presence of catalytic Pd(0), requisite for the intercepted DcA transformation, allows for further C−C bond-forming events in the same reaction vessel. Toward this end,

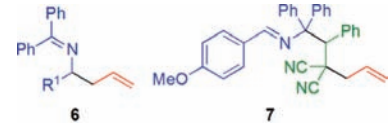
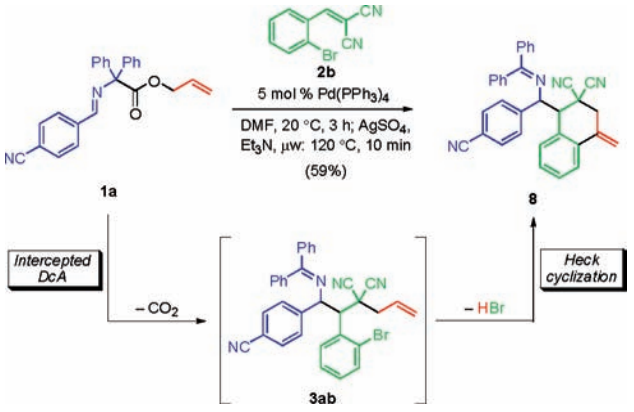


Figure 1. Noteworthy side-products.

(14) Previous DcA-Heck cascade studies from our group: Fields, W. H.; Khan, A. K.; Sabat, M.; Chruma, J. J. *Org. Lett.* **2008**, *10*, 5131.

we successfully coupled the *intercepted* DcA between imine **1a** and alkene **2b** with a microwave-accelerated intramolecular Heck reaction for a two-step, one-pot process to rapidly generate *exo*-methylene **8** (Scheme 2, *dr* 1:1).[14]

Scheme 2. Tandem Intercepted DcA-Heck Cyclization

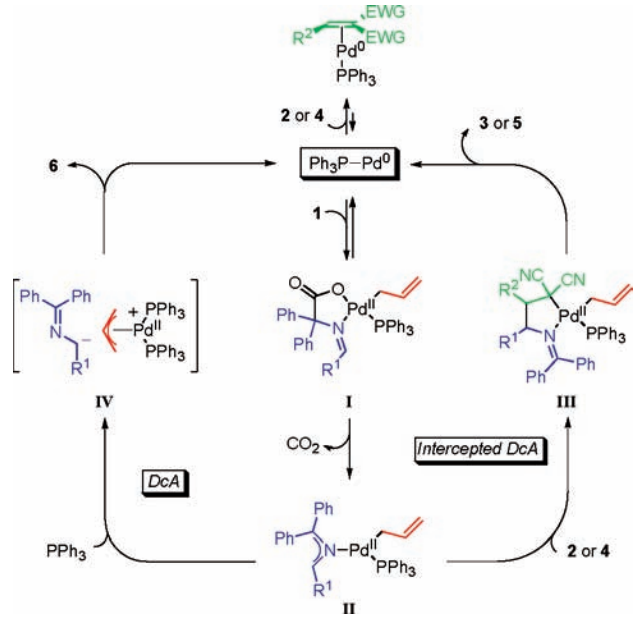


A catalytic cycle for the formation of intercepted DcA products **3** and **5** is proposed in Figure 1. The intercepted DcA process required significantly longer (≥30 times) reaction times in comparison to the corresponding *non*-intercepted DcA, that is, **1**→**6**.[7c] Presumably, the electron-deficient alkenes compete for a coordination site on the π-basic Pd(0) catalyst requisite for either oxidative addition into the allyl ester C−O bond or decarboxylation.[15] Following oxidative addition, intermediate **I** quickly undergoes decarboxylation to yield the *N*-ligated 2-azaallylPd(II) species **II**.[16] The lack of any protonated products by the addition of water to the reaction mixture suggests that an α-imino anion stays in close contact with the Pd(II) metal center. Accordingly, direct nucleophilic attack of Michael acceptors **2** or **4** by intermediate **II** leads to the 5-membered palladacycle **III**. Reductive elimination then affords the corresponding intercepted products **3**/**5** while regenerating the active Pd(0) catalyst. In the absence of activated olefin or with sterically encumberred Michael acceptors (e.g., **2h**), the α-imino anion can be displaced from the metal by a phosphine ligand to afford the tight ion pair complex **IV** which rapidly goes on to produce homoallylic imine **6**.

(15) Experimental and computational studies both suggest that the monophosphine-Pd(0) complex is the active catalyst for oxidative addition: (a) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6353. (b) Ahlquist, M.; Fristrup, P.; Tanner, D.; Norrby, P.-O. *Organometallics* **2006**, *25*, 2066. (c) Li, Z.; Fu, Y.; Guo, Q.-X.; Liu, L. *Organometallics* **2008**, *27*, 4043. (d) Li, Z.; Zhang, S.-L.; Fu, Y.; Guo, Q.-X.; Liu, L. *J. Am. Chem. Soc.* **2009**, *131*, 8815.

(16) The intermediacy of a *bis*-π-allylPd(II) species cannot be ruled out at this point: (a) Nakamura, H.; Shim, J. G.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 8113. (b) Nakamura, H.; Aoyagi, K.; Shim, J.-G.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 372. (c) Solin, N.; Narayan, S.; Szabó, K. J. *J. Org. Chem.* **2001**, *66*, 1686.

Scheme 3. Proposed Catalytic Cycle for the Decarboxylative Allylation (DcA) and Olefin-Intercepted DcA of Imino Esters **1**



In conclusion, we describe a mild and efficient method for generating and functionalizing α-imino anions. The resulting Pd(II)-α-imino anion intermediates are substantially more resistant to aqueous protonation than to their Li(I) counterparts. The olefin-intercepted DcAs employ readily obtainable starting materials and occur at ambient temperature in a variety of solvents at the sole expense of one equivalent of CO_2. These substrates can be further transformed in the same reaction vessel into relatively complex organoamine frameworks via additional Pd(0)-catalyzed C−C bond-forming reactions. Efforts to apply this cascade process toward the total synthesis of alkaloid natural products, particularly karachine,[17] are currently underway and will be reported in due course.

Acknowledgment. Partial financial support provided by the Thomas F. and Kate Miller Jeffress Memorial Trust. We thank M. Sabat (Director, UVA Small Molecule X-ray Facility) for obtaining X-ray crystallographic data for *syn*-(±)-**3ab**.

Supporting Information Available: Experimental procedures, characterization data including X-ray crystallographic data and cif file for *syn*-(±)-**3ab**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL901745X

(17) (a) Blaskó, G.; Murugesan, N.; Freyer, A. J.; Shamma, M.; Ansari, A. A.; Rahman, A.-v. *J. Am. Chem. Soc.* **1982**, *104*, 2039. (b) Stevens, R. V.; Pruitt, J. R. *J. Chem. Soc., Chem. Commun.* **1983**, 1425.