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Regiospecific Decarboxylative Allylation of Nitriles

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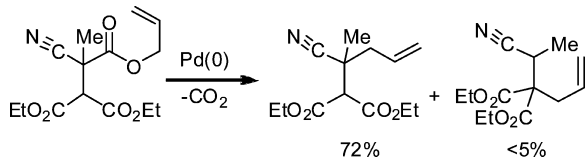
ABSTRACT



Palladium-catalyzed decarboxylative α-allylation of nitriles readily occurs with use of $Pd_2(dba)_3$ and *rac*-BINAP. This catalyst mixture also allows the highly regiospecific α-allylation of nitriles in the presence of much more acidic α-protons. Thus, the reported method provides access to compounds that are not readily available via base-mediated allylation chemistries. Lastly, mechanistic investigations indicate that there is a competition between *C*- and *N*-allylation of an intermediate nitrile-stabilized anion and that *N*-allylation is followed by a rapid [3,3]-sigmatropic rearrangement.

Decarboxylative allylation reactions are a powerful method for the allylation of a wide variety of nucleophiles under neutral conditions.[1−3] While the decarboxylative allylation of enolates has received the most attention, relatively little attention has been paid to nitrogen-containing carbon nucleophiles.[2,3] Given the prevalence of nitrogen in biologically active molecules, we are interested in extending decarboxylative couplings to allow facile incorporation of nitrogen. In Tsuji's pioneering work on decarboxylative allylation, he showed that α-allylation of a nitrile could occur at 100 °C in dioxane, albeit with substantial amounts of undesirable decarboxylative protonation.[3a] That said, Tsuji provided the proof-of-principle that we have chosen to build upon to develop milder, regiospecific allylation of nitriles that we report herein.

The work of Tsuji,[3a] Saegusa,[3b] Darensbourg,[4] and Shibasaki[3d] has shown that the decarboxylation of α-cyano acetates can provide access to metalated nitriles[5] without the need for strongly basic reagents. We posited that the absence of basic proton shuttles would allow us to generate nitrile-stabilized carbanions regiospecifically in the presence of more acidic functional groups.[6] Before we could approach that problem it was critical that we optimize the reaction conditions to promote allylation and prevent unwanted protonation. Toward this end, a variety of catalyst/ligand combinations were evaluated for their

(1) (a) Shimizu, I.; Yamada, T.; Tsuji, J. *Tetrahedron Lett.* **1980**, 3199. (b) Rayabarapu, D. K.; Tunge, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 13510. (c) Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 4138. (d) Weaver, J. D.; Tunge, J. A. *Org. Lett.* **2008**, *10*, 4657. (e) Mohr, J. T.; Behenna, D. C.; Harned, A. W.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924. (f) Trost, B. M.; Bream, R. N.; Xu, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3109. (g) Singh, O. V.; Han, H. *J. Am. Chem. Soc.* **2007**, *129*, 774. (h) Wang, C.; Tunge, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 8118.

(2) (a) Burger, E. C.; Tunge, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 10002. (b) Yeagley, A. A.; Chruma, J. J. *Org. Lett.* **2007**, *9*, 2879. (c) Bi, H.; Chen, W.; Liang, Y.; Li, C. *Org. Lett.* **2009**, *11*, 3246.

(3) For decarboxylative couplings of nitrile-stabilized anions see: (a) Tsuji, J.; Yamada, T.; Minami, I.; Yuhara, M.; Nisar, M.; Shimizu, I. *J. Org. Chem.* **1987**, *52*, 2988. (b) Tsuda, T.; Chujo, Y.; Nishi, S.-i.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 6381. (c) Waetzig, S. R.; Rayabarapu, D. K.; Weaver, J. D.; Tunge, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4977. (d) Yin, L.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 9610.

(4) (a) Darensbourg, D. J.; Longridge, E. M.; Holtcamp, M. W.; Klausmeyer, K. K.; Reibenspies, J. H. *J. Am. Chem. Soc.* **1993**, *115*, 8839. (b) Darensbourg, D. J.; Longridge, E. M.; Holtcamp, M. W.; Khandelwal, B.; Klausmeyer, K. K.; Reibenspies, J. H. *J. Am. Chem. Soc.* **1995**, *117*, 318. (c) Pletnev, A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9438.

(5) (a) Fleming, F. F.; Zhang, Z.; Liu, W.; Knochel, P. *J. Org. Chem.* **2005**, *70*, 2200. (b) Okugawa, S.; Masu, H.; Yamaguchi, K.; Takeda, K. *J. Org. Chem.* **2005**, *70*, 10515. (c) Fleming, F. F.; Liu, W.; Ghosh, S.; Steward, O. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 7098. (d) Yasui, H.; Yorimtsu, H.; Oshima, K. *Chem. Lett.* **2007**, *36*, 32. (e) Gaudin, J.; Millet, P. *Chem. Commun.* **2008**, 588. (f) Fleming, F. F.; Liu, W.; Ghosh, S.; Steward, O. W. *J. Org. Chem.* **2008**, *73*, 2803.

(6) (a) Darvesh, S.; Grant, A. S.; MaGee, D. I.; Valenta, Z. *Can. J. Chem.* **1991**, *69*, 712.

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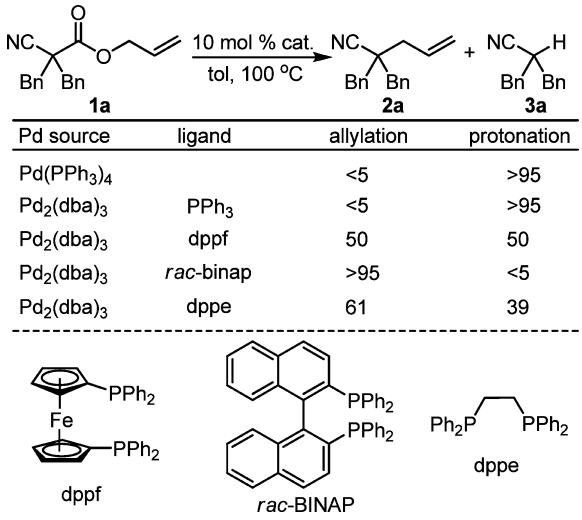
ability to promote decarboxylative allylation of **1a** at the expense of protonation. As can be seen from Table 1, ^{1}H

Table 1. Results of Ligand Screen



Pd source	ligand	allylation	protonation
$Pd(PPh_3)_4$		<5	>95
$Pd_2(dba)_3$	PPh_3	<5	>95
$Pd_2(dba)_3$	dppf	50	50
$Pd_2(dba)_3$	*rac*-binap	>95	<5
$Pd_2(dba)_3$	dppe	61	39

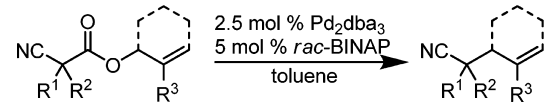
NMR spectroscopic analysis of the crude reaction mixtures shows that the monodentate ligand, triphenylphosphine, produces only protonation product **3a** even in thoroughly dried toluene.[7] The palladium dppe complex employed by Tsuji also generates substantial protonation product.[3a] In contrast, the *rac*-BINAP ligated palladium catalyst produced allylation product **2a** exclusively. This observation is in line with our previous observation that *rac*-BINAP minimized protonation products in the decarboxylative allylation of α-sulfonyl anions.[1d]

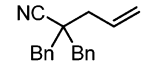
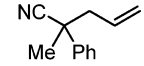
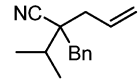
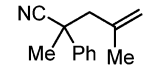
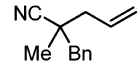
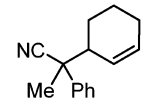
Having identified *rac*-BINAP as the optimal ligand for decarboxylative allylation of nitriles, we proceeded to investigate the scope of substrates that were compatible reaction partners. Simple α,α-dialkyl nitriles undergo allylation in good yield at 100 °C in toluene (**2a**−**c**, Table 2). The α-aryl nitriles **2d**−**f** undergo decarboxylative coupling at room temperature since they are more activated toward decarboxylation. Thus, the qualitative rates of the reaction correlate with the pK_a values of putative nitrile-stabilized carbanions; such a correlation typically suggests that decarboxylation is rate limiting.[1d]

Next, we turned our attention to the investigation of the regiospecificity of the allylation when it is conducted in the presence of adjacent acidic α-hydrogens. Since decarboxylation allows the kinetic, site-specific generation of carbanion equivalents, we were curious whether we could generate and allylate nitrile-stabilized carbanions in the presence of more acidic functional groups. To do so would require that we circumvent the thermodynamically favored proton shift to form the more stable carbanion (Scheme 1).

(7) Similar protonation products have been observed in the decarboxylative allylations of enolates: Mohr, J. T.; Nishimata, T.; Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 11348.

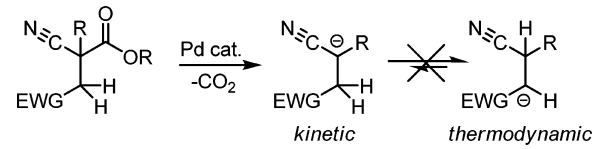
Table 2. Decarboxylative Couplings of Nitriles



entry	product	yield	entry	product	yield
2a		85%	**2d**		80%[b]
2b		71%[a]	**2e**		75%[c]
2c		70%	**2f**		75%[d]

[a] Contains 5% impurity. [b] Reaction performed at 25 °C. [c] Reaction performed at 90 °C. However, ^{1}H NMR analysis reveals smooth reaction at 25 °C. [d] 5 mol % of $Pd(PPh_3)_4$ at 25 °C.

Scheme 1. Regiospecific Nucleophile Generation



To test this idea, a variety of substrates containing moderately acidic C−H bonds were synthesized and subjected to decarboxylative allylation. In short, the anion generation and subsequent allylation reactions are highly regiospecific when pendant aromatic ketones (**2g**−**i**, Table 3), aliphatic ketones (**2k**, **2l**), and esters (**2j**, **2m**) were present; no regioisomeric products were ever observed by ^{1}H NMR spectroscopic analysis of the crude reaction mixtures. Thus, nitrile-stabilized anions (p$K_a \approx 32$ in DMSO) can be generated and selectively allylated in the presence of the more acidic α-hydrogens of ketones (p$K_a \approx 26$ in DMSO) and esters (p$K_a \approx 30$ in DMSO).[8] This suggests that if a nitrile-stabilized carbanion is formed, it is trapped by allylation more rapidly than it undergoes proton transfer to generate the more stable anion.

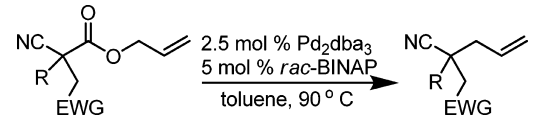
To probe the limits of the regiospecificity of the anion generation and allylation further, a substrate (**1n**) containing a diethylmalonate fragment was synthesized (Scheme 2). Subjecting **1n** to the standard reaction conditions produced the α-allylated nitrile **2n** without any regioisomerization of

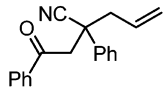
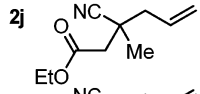
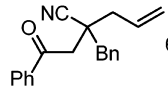
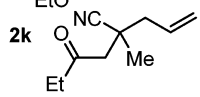
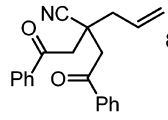
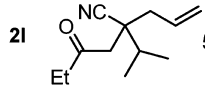
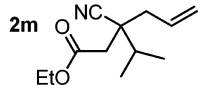
(8) (a) Bordwell, F. G.; Van Der Puy, P.; Vanier, N. R. *J. Org. Chem.* **1976**, *41*, 1885. (b) Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Conforth, F. J.; Drucker, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 7006.

(9) Scheme 3 shows potential mechanistic "cartoons" that ignore the ligation state of palladium. We presume that the bidentate BINAP ligand remains bound throughout the catalysis.

(10) Tsuda, T.; Okada, M.; Nishi, S.-i.; Saegusa, T. *J. Org. Chem.* **1986**, *51*, 421.

Table 3. Regiospecific Decarboxylative Couplings



entry	product	yield	entry	product	yield
2g		85%	2j		74%
2h		63%	2k		74%
2i		83%	2l		53%
			2m		65%

the anion to form the malonate anion. This is remarkable given that the malonate is ca. 10^{15} times more acidic than a typical aliphatic nitrile. Generation of product **2n** via more standard base mediated allylation would be difficult, if not impossible.

Next, the mechanism of the decarboxylative allylation was briefly probed. While a number of different mechanisms can be formulated to fit the observed reaction, there are two mechanisms that allow us to think about several critical issues.[9] First, the allylation reaction could occur via palladium-catalyzed decarboxylation followed by allylation (Scheme 3, upper path) or by allylation of the nitrile followed by decarboxylation and [3,3]-rearrangement (Scheme 3, lower path). While the latter mechanism can explain the regiospecificity of the allylation, it does not readily explain the competing protonation reaction that is observed with many ligands (Table 1). However, the observation of protonation products is more readily explained through protonation of the more basic intermediates in the top pathway. Thus, the feasibility of the top pathway was investigated by determining whether palladium was a competent catalyst for the decarboxylation of α-cyanoacetates; palladium(II) is known to catalyze decarboxylation of β-ketoacids[3a,10] and propiolates,[1b] but does not influence the rates of decarboxylation of α-sulfonyl acetic esters.[1d]

Toward this end, the acid **4** was heated with and without palladium catalyst (Table 4). The results clearly show that Pd(II)

Scheme 2

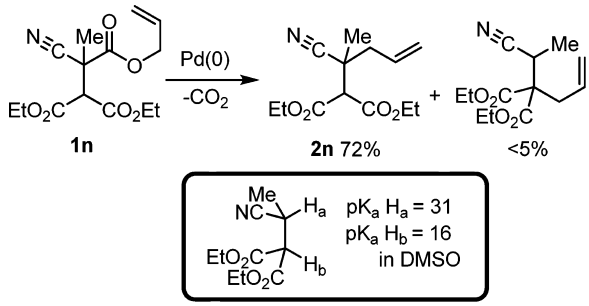
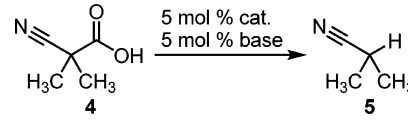


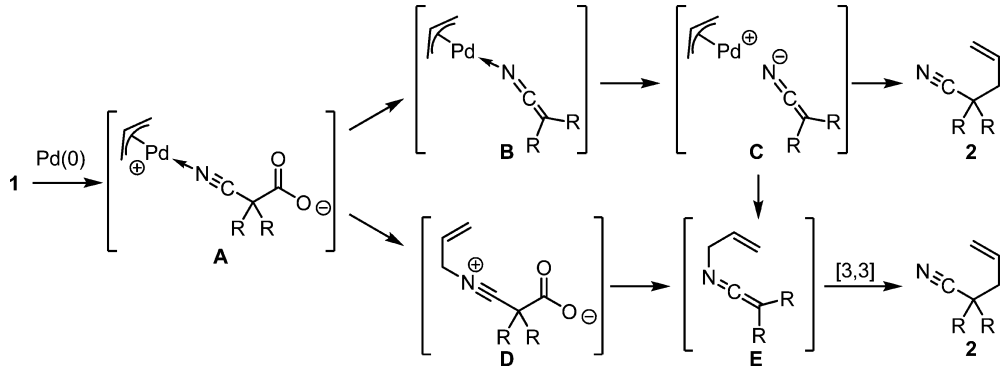
Table 4. Palladium-Catalyzed Decarboxylation



catalyst	base	temp (°C)	time (h)	conversion (%)
none	Et_3N	115	15	<5
$Pd(OAc)_2$	Et_3N	80	5	>95
$Pd(OAc)_2$	none	80	5	55
$Pd(OAc)_2$	none	80	18	>95

is an effective catalyst for the decarboxylation of α-cyano acids. This is not surprising given the elegant mechanistic studies of metal-catalyzed decarboxylations of α-cyanoacetates that were performed by Darensbourg.[4a] Moreover, the palladium-catalyzed decarboxylation is kinetically competent to be taking part in our decarboxylative allylation reaction. Thus, the upper

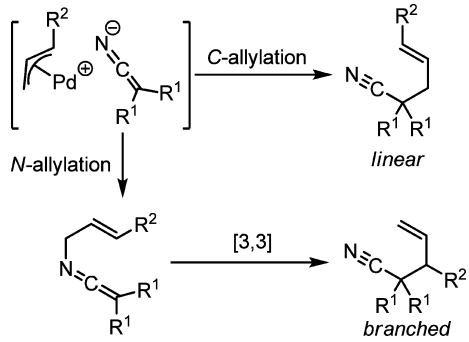
Scheme 3. Potential Mechanisms for Decarboxylative Allylation



mechanistic pathway involving palladium-induced decarboxylation is feasible (Scheme 3).

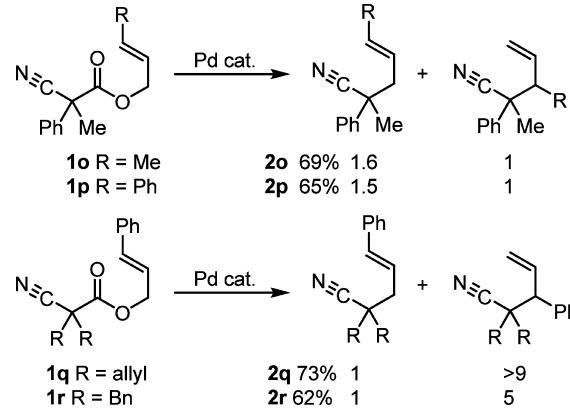
Ultimately, on the basis of Darensbourg's related studies,[4] our working hypothesis is that the formation of intermediate **A** is critical for decarboxylation. After formation of an intermediate like **B**, or its ion-paired isomer **C**, there is another key mechanistic consideration. Does allylation proceed by kinetic *C*-allylation (**C** → **2**) or does it proceed via an *N*-allylation/[3,3]-sigmatropic rearrangement (**C** → **E** → **2**) mechanism?[1c,11] Analogous [3,3]-sigmatropic rearrangements are known to occur rapidly, even at room temperature.[12] These possibilities are most straightforwardly addressed by investigating the linear: branched product selectivity when unsymmetrical allyl alcohol derivatives are utilized. The general preference for nucleophilic attack at the least substituted allyl terminus of palladium−π-allyl complexes suggests that *C*-allylation should give rise to the linear allylated product,[13] whereas the *N*-allylation/sigmatropic rearrangement mechanism should give rise to the branched allylated product (Scheme 4).[1c]

Scheme 4. *C*-Allylation vs. *N*-Allylation



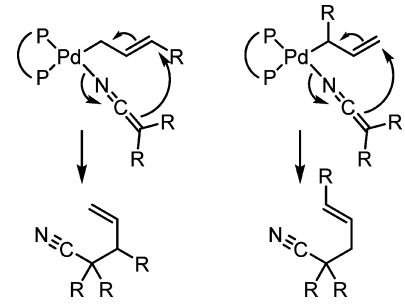
With this in mind, substrates **1o** and **1p** were subjected to our standard conditions for decarboxylative allylation (Scheme 5). In both cases, mixtures of branched and linear regioisomers were obtained, with the linear regioisomers as the major products. However, the amount of branched isomer is much larger than is typically observed in palladium-catalyzed allylations, which suggests competing *C*- and *N*-allylation. Similar treatment of α,α-dialkyl nitriles **1q** and **1r** shows that they undergo decarboxylative allylation with a higher degree of regioselectivity favoring the branched isomer. Thus, we suggest that *C*-allylation and *N*-allylation mechanisms are competing and that *N*-allylation/[3,3] rearrangement is favored by larger,[9] or less stable, nitrile-stabilized anions.

Scheme 5



Alternatively, it is possible that the linear and branched products derive from reductive elimination of σ-allyl palladium complexes (Scheme 6).[14] Such an inner-sphere

Scheme 6



mechanism is expected to proceed via the favored linear σ-allyl complex to favor formation of the branched allyl product.

In conclusion, we have developed a practical ligand/catalyst combination for the decarboxylative allylation of nitriles. In addition, we have shown that the generation of the nitrile-stabilized anion equivalent is regiospecific; no isomerization to more stable carbanions is observed even when much more acidic C−H bonds are present. Mechanistic investigations suggest that palladium is directly involved in the decarboxylation to form a metalated nitrile. Lastly, the product allylated nitriles are formed by competing *C*-allylation and *N*-allylation followed by rapid [3,3]-sigmatropic rearrangement.

Acknowledgment. We the National Institute of General Medical Sciences (1R01GM079644) for financial support of this work.

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.

OL902065P

(11) *C*-allylation vs. *N*-allylation see: (a) Newman, M. S.; Fukunaga, T.; Miwa, T. *J. Am. Chem. Soc.* **1960**, *82*, 873. (b) Clarke, L. F.; Hegarty, A. F. *J. Org. Chem.* **1992**, *57*, 1940.

(12) Walters, M. A.; Hoem, A. B.; McDonough, C. S. *J. Org. Chem.* **1996**, *61*, 55.

(13) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385.

(14) A similar mechanism has been proposed for the decarboxylative allylation of enolates: (a) Keith, J. A.; Behenna, D. C.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Oxgaard, J.; Stoltz, B. M.; Goddard, W. A., III *J. Am. Chem. Soc.* **2007**, *129*, 11876.