ORGANIC LETTERS

2007
Vol. 9, No. 15
2879−2882

C–C Bond-Forming Reactions via Pd-Mediated Decarboxylative α-Imino Anion Generation

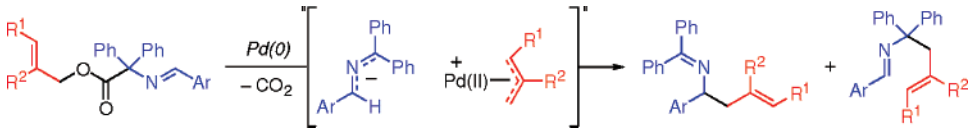
Andrew A. Yeagley and Jason J. Chruma*

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

jjc5p@virginia.edu

Received May 9, 2007

ABSTRACT



α-Imino anions are generated under neutral reaction conditions via a Pd-mediated decarboxylation of allyl diphenylglycinate imines with concomitant formation of a π-allylpalladium species. The resulting delocalized anion can attack the π-allyl-Pd(II) species or be intercepted by aldehydes to afford homoallylic amines or protected 1,2-amino alcohols, respectively.

The α-imino anion (2-azaallyl anion) is a valuable synthon for the construction of organoamines.[1] We were particularly interested in employing an α-imino anion-based protocol toward the synthesis of homoallylic amines, which serve as useful synthetic precursors for aza-heterocycles[2] and alkaloids.[3] Such a strategy would run counter to standard approaches toward homoallylic amines, namely, the addition of allyl organometallics or allylboranes into activated imines.[4] Generation of an α-imino anion typically involves deprotonation of the conjugate acid with a strong base. Herein, we report a "neutral" Pd-mediated decarboxylative method for generating nucleophilic α-imino anions from allyl diphenylglycinate imines. Alkylation of the resulting α-imino anion with the corresponding π-allyl-Pd intermediate establishes the desired homoallylic amine framework. Furthermore, the α-imino anions can be intercepted by aldehydes prior to allylation to afford protected 1,2-amino alcohols.

We were inspired by recent observations that under general acid−base catalysis, diphenylglycine (Dϕg) will readily undergo imine formation with α-ketoacids followed by concomitant decarboxylation and protonation of the resulting α-imino anion to afford the corresponding *N*-(diphenylmethylene)amino acids.[5] To further explore the potential of Dϕg imines as α-imino anion precursors, we sought to separate the imine formation and decarboxylation steps. Allyl esters of Dϕg seemed well-suited for this goal, given that they should not interfere with imine formation and they can be removed readily with Pd(0) catalysts. Upon Pd-mediated deallylation and ensuing decarboxylation, the resulting α-imino anion could then attack the Pd(II)-π-allyl species, affording homoallylic amines (Scheme 1, **1** → **3** + **4**). Shortly after we initiated these investigations, Burger and Tunge reported a complimentary method toward homoallylic amines

(1) For recent examples and reviews: (a) Lee, J.-H.; Jeong, B.-S.; Ku, J.-M.; Jew, S.-s.; Park, H.-g. *J. Org. Chem.* **2006**, *71*, 6690. (b) Nakoji, M.; Kanayama, T.; Okino, T.; Takemoto, Y. *J. Org. Chem.* **2002**, *67*, 7418. (c) O'Donnell, M. J. *Aldrichimica Acta* **2001**, *34*, 3. (d) Pearson, W. H. *Pure Appl. Chem.* **2002**, *74*, 1339. (e) Pearson, W. H.; Stoy, P. *Synlett* **2003**, *7*, 903.

(2) (a) Puentes, C. O.; Kouznetsov, V. *J. Heterocycl. Chem.* **2002**, *39*, 595. (b) Chiou, W.-H.; Mizutani, N.; Ojima, I. *J. Org. Chem.* **2007**, *72*, 1871. (c) Ramachandran, P. V.; Burghardt, T. E.; Bland-Berry, L. *J. Org. Chem.* **2005**, *70*, 7911. (d) Gille, S.; Ferry, A.; Billard, T.; Langlois, B. R. *J. Org. Chem.* **2003**, *68*, 8932.

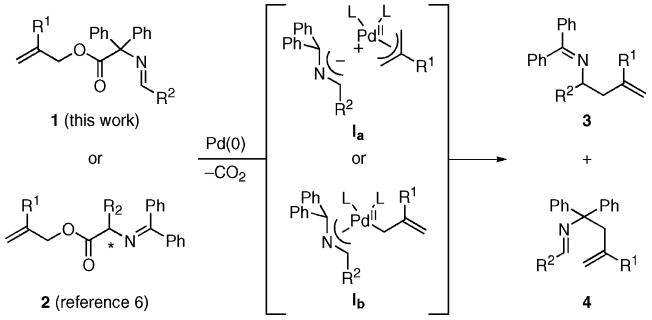
(3) (a) Atobe, M.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **2005**, *46*, 2669. (b) Randl, S.; Blechert, S. *J. Org. Chem.* **2003**, *68*, 8879. (c) Kim, G.; Jung, S.-d.; Lee, E.-j.; Kim, N. *J. Org. Chem.* **2003**, *68*, 5395. (d) Wright, D. L.; Schulte, J. P., II; Page, M. A. *Org. Lett.* **2000**, *2*, 1847. (e) Danieli, B.; Lesma, G.; Passarella, D.; Sacchetti, A.; Silvani, A.; Virdis, A. *Org. Lett.* **2004**, *6*, 493.

(4) (a) Sugiura, M.; Hirano, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 7182. (b) Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687. (c) Friestad, G. K.; Korapala, C. S.; Ding, H. *J. Org. Chem.* **2006**, *71*, 281. (d) Pandey, M. K.; Bisai, A.; Pandey, A.; Singh, V. K. *Tetrahedron Lett.* **2005**, *46*, 5039. (e) Ramachandran, P. V.; Burghardt, T. E. *Pure Appl. Chem.* **2006**, *78*, 1397. (f) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.

(5) (a) Liu, L.; Zhou, W.; Chruma, J.; Breslow, R. *J. Am. Chem. Soc.* **2004**, *126*, 8136. (b) Chruma, J. J.; Liu, L.; Zhou, W.; Breslow, R. *Bioorg. Med. Chem.* **2005**, *13*, 5873.

10.1021/ol071080f CCC: $37.00
Published on Web 06/20/2007

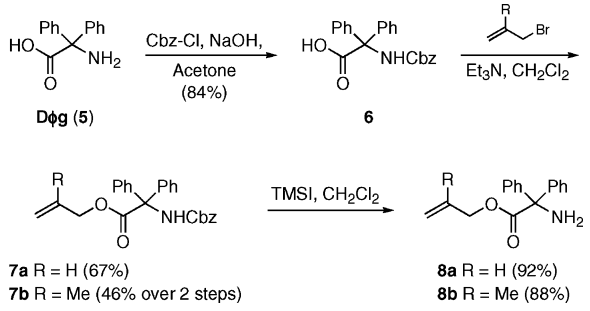
Scheme 1. Complementary Homoallylic Amine Syntheses



employing allyl esters of *N*-(diphenylmethylene)-α-amino acids (Scheme 1, **2** → **3** + **4**).[6] Both strategies should proceed through the same putative intermediates ($\mathbf{I_a}$ or $\mathbf{I_b}$) and thus afford the same products and product ratios. Employing imines **2**, however, necessitates access to the corresponding α-amino acids, which may represent a greater synthetic challenge than the desired products. This requirement is particularly disadvantageous for obtaining complex α-aryl or heteroaryl homoallylic amines.[3] We therefore focused our initial studies with allyl diphenylglycinate imines **1** toward the construction of α-aryl or heteroaryl homoallylic amines.

The required H−Dϕg allyl esters **8a** and **8b** were obtained in three steps and good overall yield on a multigram scale (Scheme 2). Cbz protection of commercially available Dϕg

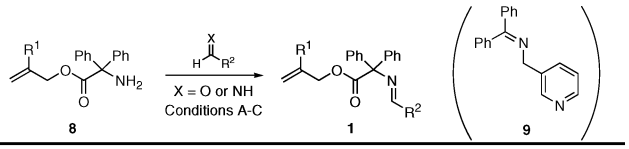
Scheme 2. Synthesis of Dϕg Esters **8**

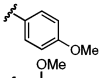
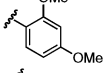


(**5**) proceeded in 84% isolated yield,[7,8] and the resulting carboxylic acid **6** was allylated with allyl bromide or 2-methylallyl bromide to afford esters **7a** and **7b**, respectively. Although the allylation reactions proceeded in modest yield, the remainder of the mass balance was unreacted acid **6**, which was readily recovered by flash chromatography and resubjected to the reaction conditions. Selective deprotection of the Cbz-carbamate over the allyl ester was performed using iodotrimethylsilane,[9] providing amines **8a** or **8b** in excellent yield. Amines **8** were not amenable to long-term storage, but the corresponding acetate salts or Cbz-carbamates **7** can be stored indefinitely at 4 °C.

Dϕg esters **8** were readily converted to the corresponding imines **1**, typically by condensation with the requisite aryl or heteroaryl aldehydes (Table 1).[10] In the case of 3-pyridinecarboxaldehyde, however, heating with amine **8a** in benzene at reflux resulted in imine formation followed unexpectedly by deallylation, decarboxylation, and protonation to afford benzophenone imine **9** in 92% yield. To circumvent this problem, amine **8a** was stirred with 3-pyridinecarboximine at room temperature overnight. Under these milder conditions, transimination proceeded without concomitant decarboxylation, affording imine **1h** in good yield. Imines **1** were purified by flash chromatography using ethyl acetate and hexanes buffered with 1−2% Et_3N as eluent. The noncrystalline electron-rich aldimines (e.g., **1g**) exhibited increased sensitivity toward hydrolysis during chromatography, thus accounting for the corresponding modest isolated yields.

Table 1. Generation of Imines **1**



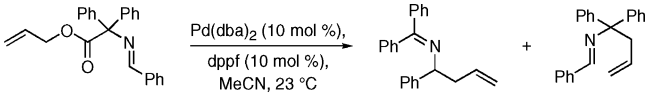
substrate	R^1	R^2	conditions[a]	isolated yield
1a	H		A	95%
1b	H		A	80%
1c	H		A	96%[b]
1d	H		B	63%
1e	H		A	94%[b]
1f	H		A	79%
1g	H		A	53%[b]
1h	H		B	73%
1i	H		C	50%[b]
1j	Me		A	99%[b]

[a] Conditions: A = **8** + aldehyde (1 equiv), PhH, reflux (Dean-Starke), 24 h; B = **8** + imine (1 equiv), CH_2Cl_2, 4 Å MS, 23 °C, 24 h; C = **8** + ethyl glyoxylate (~1 equiv), $PhCH_3$, 4 Å MS, 23 °C, 24 h. [b]Only performed once.

Initial reaction optimization studies were performed on benzaldimine **1a** (Table 2). The ratio of regioisomeric

(6) Burger, E. C.; Tunge, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 10002.
(7) Crisma, M.; Valle, G.; Bonora, G. M.; De Menego, E.; Toniolo, C.; Lelj, F.; Barone, V.; Fraternali, F. *Biopolymers* **1990**, *30*, 1.
(8) Unless otherwise noted, all reported yields represent average isolated yields for at least two runs.
(9) Lott, R. S.; Chauhan, V. S.; Stammer, C. H. *J. Chem. Soc., Chem. Commun.* **1979**, *11*, 495.
(10) Though considerably more sensitive to hydrolysis, imines **1** can also be derived from aliphatic aldehydes (e.g., isobutyraldehyde).

Table 2. Solvent and Catalyst Effects



1a 3a 4

solvent	catalyst	time	isolated yield	ratio (**3a**/**4a**)
toluene[a]	15% $Pd(dba)_2$, 15% dppf	1 h	82%	2.6:1
THF-d_8	10% $Pd(dba)_2$, 10% dppf	15 min[b]	92%	3.8:1
CH_2Cl_2	10% $Pd(dba)_2$, 10% dppf	25 min	94%[d]	5.2:1
dioxane	10% $Pd(dba)_2$, 10% dppf	40 min	83%[d]	5.5:1
MeCN	10% $Pd(dba)_2$, 10% dppf	30 min	96%	6.1:1
THF	10% $Pd(dba)_2$, 10% dppe	1 h	79%[d]	2.5:1
MeCN	10% $Pd(dba)_2$, 20% PPh_3	15 min	89%[d]	4.5:1
MeCN	5% $(PdC_3H_5Cl)_2$, 10% dppf[c]	–	0%	–
MeCN	10% $Pd(OAc)_2$	–	0%	–

[a] Required continuous bubbling of Ar through the reaction mixture. [b]Monitored by ^1H NMR spectroscopy. [c]NaOAc added. [d]Only performed once.

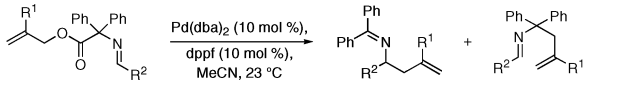
products **3a** and **4a** was determined by ^1H NMR analysis of the unpurified reaction mixture. Employing a Et_3N-buffered eluent, **3a** and **4a** were purified from the reaction mixture by flash chromatography, though they coeluted; the corresponding ^1H NMR spectra typically provided a product ratio similar to the unpurified reaction mixture. Subjection of the mixture of imine products to *nonbuffered* silica gel resulted in preferential hydrolysis of aldimine **4a**, allowing for exclusive isolation of the desired *N*-(diphenylmethylene)-imine **3a** in spectroscopically pure form. This behavior was general for all compounds tested.

Solvent appears to play only a minor role in regards to isolated yield and product ratio. In most solvents studied, using 10 mol % of $Pd(dba)_2$ and 10 mol % of diphenylphosphinoferrocene (dppf) at 23 °C, imine **1a** was converted to homoallylic amines **3a** and **4a** in excellent yield and a ~5:1 ratio, respectively. Acetonitrile (MeCN) afforded the best yields and product ratios. Toluene, however, was an exception, in that reaction rates were slow; the product ratio was relatively low; and great care had to be taken to degas the solvent to prevent precipitation of the catalyst. Modification of the palladium source or ligands did not favorably impact yield or product ratio. The ligand diphenylphosphinoethane (dppe) in THF[11] proved inferior to dppf in MeCN in all regards. Likewise, use of triphenylphosphine (PPh_3) as the ligand accelerated the reaction rate but decreased the yield and product ratio. Interestingly, Pd(II) catalysts, including the π-allyl palladium dimer $(PdC_3H_3Cl)_2$, did not effect the desired reaction.

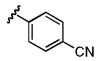
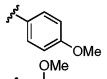
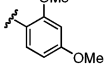
Imines **1b**−**j** were also converted to the corresponding homoallylic amines **3** and **4** under our optimized reaction conditions (Table 3). The electronic character of the imine proved to have a significant impact on the reaction rate, yield, and product ratio. Except for imine **1h**, all imines were converted to the corresponding mixture of homoallylic imines

(11) Poor solubility of the Pd−dppe complex in MeCN resulted in no conversion in that solvent.

Table 3. Pd-Mediated Decarboxylative Allylations



1 3 4

substrate	R^1	R^2	time	isolated yield	ratio (**3**:**4**)[a]
1a	H		0.5 h	96%	6.1:1
1b	H		1 h	97%	5.5:1
1c	H		1 h	91%	•20:1
1d	H		2 h	75%	4.1:1
1e	H		7 h	52%	2.2:1
1f	H		5 h	76%	2.4:1
1g	H		3 h	70%	3.4:1
1h	H		2.5 h[b]	47%	≥20:1
1i	H		1.5 h	91%	≥20:1
1j	Me		2 h[c]	82%[d]	≥20:1[d]

[a] Determined by ^1H NMR spectroscopy of the unpurified reaction mixture. [b]Imine **9** isolated in ca. 50% yield. [c]Reaction heated to 40 °C. [d]Only performed once.

3 and **4** in nearly quantitative yield. The electron-rich aldimines (i.e., **4d**−**g**), however, were particularly sensitive toward hydrolysis during chromatography, even under Et_3N-buffered conditions, resulting in lowered isolated yields for **3** + **4**. Electron-donating substituents also decreased the reaction rate and reduced the ratio of homoallylic imines **3**/**4**.[12] Alternatively, electron-withdrawing groups that can shift the electron density in the intermediate α-imino anion toward the substituent via delocalization (e.g., 4-cyanobenzaldimine **1c** or ethyl glyoximine **1i**) increased the reaction rate and afforded the *N*-(diphenylmethylene)imine **3** as essentially the sole product (≥20:1 product ratio) in excellent yield.

Electronegative substituents that cannot further delocalize the negative charge in the intermediate α-imino anion (e.g., *p*-fluorobenzaldimine **1b**) did not dramatically impact the reaction profile in comparison to benzaldimine **1a**. An apparent exception to these trends is 3-pyridylcarboximine **1h**, in which the benzophenone imine **3h** was the sole homoallylic imine product, though it was isolated in only 47% yield. The remaining mass balance was imine **9**, suggesting that protonation of the intermediate α-imino anion competes with allylation. The strong preference for product **3h** was surprising, given that the 3-pyridyl substituent has

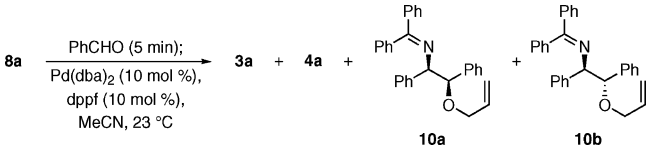
(12) O_2 must be excluded from the reaction mixture with imines **1e**−**g** to prevent precipitation of an organometallic species, presumably arising from imine-directed electrophilic addition of Pd(II) into the electron-rich aromatic rings: Ryabov, A. D. *Synthesis* **1985**, 233.

an electronic profile similar to phenyl (i.e., **1a**). Protonation of the pyridine nitrogen is expected to shift the electron density of the intermediate anion to favor production of **3h** over **4h** as well as to provide an acidic proton source leading to methylene amine **9**; DFT calculations support this hypothesis (see Supporting Information). Alternatively, coordination of the pyridine nitrogen to the Pd(II) intermediate would have a similar effect on the electron density of the anion, but this would not account for the production of the conjugate acid **9**. The source of the acidic proton is currently under investigation.

Substituents on the 2-position of the allyl ester also favorably impact the product ratio (**3**:**4**). 2-Methylallyl ester **1j** was readily converted to the homoallylic imine **3j** as the sole product in good yield, though the reaction required gentle heating (40 °C). The requirement for elevated reaction temperatures is most likely a result of the higher activation energy required for initial complexation of the Pd(0) catalyst to the less accessible 2-methylallyl substituent.[13,14]

We also investigated combining imine formation and Pd-mediated decarboxylative allylation into one reaction vessel. Our initial attempt at a "one-pot" protocol involved premixing amine **8a** with benzaldehyde in MeCN (5 min), followed by addition of catalytic Pd(0) (Scheme 3). In addition to the

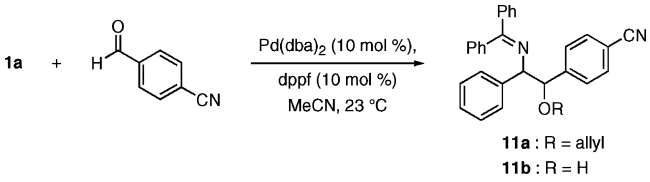
Scheme 3. Attempted "One-Pot" Reaction



expected homoallylic amine products **3a** and **4a**, a diastereomeric mixture of allyl ethers **10a** and **10b** was observed (as determined by ^{1}H NMR spectroscopy and HPLC/MS). Unfortunately, the protected 1,2-amino alcohols **10a** and **10b** coeluted with **3a**, and ^{1}H NMR analysis of the unpurified reaction mixture was not sufficient for determining product and diastereomeric ratios. Production of diastereomers **10** most likely results from interception of the α-imino anion intermediate by unreacted benzaldehyde, followed by allylation of the resulting alkoxide, thus representing a Pd-mediated decarboxylative variant of the Erlenmeyer reaction.[15] Increasing the amine/aldehyde mixing time did not dramatically reduce formation of amino alcohol **10**.

This intriguing reaction pathway can predominate over homoallylic amine synthesis if more electrophilic aldehydes are employed. Specifically, treatment of benzaldimine **1a** with 10 mol % of Pd(dba)$_2$/dppf in the presence of *p*-cyanobenzaldehyde (2 equiv) afforded the allyl ether **11a** in 53% isolated yield as an inseparable mixture of diastereomers (Scheme 4). The remaining mass balance was the 1,2-imino

Scheme 4. Interception of the α-Imino Anion



alcohol **11b**, presumably arising from protonation of the intermediate alkoxide with adventitious water. Importantly, only trace amounts (≤5%) of homoallylic amine products were observed. Optimization of this novel reaction manifold is the subject of current investigation.

In summary, we report the mild conversion of allyl diphenylglycinate imines into α-aryl and heteroaryl homoallylic amines employing a Pd-mediated decarboxylative generation and allylation of α-imino anions. The intermediate anions can be intercepted with aldehydes to afford protected 1,2-amino alcohols. Further investigations will focus on developing asymmetric variants of these efficient C−C bond-forming events.

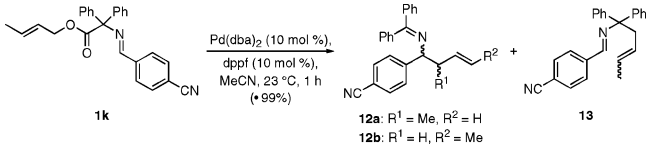
Acknowledgment. Financial support was provided by the U.Va. Dept. of Chemistry and the U.Va. Institute on Aging. DFT calculations were performed by Prof. Carl O. Trindle (U.Va.). We thank Prof. Karl Scheidt (Northwestern U.) for an inspiring conversation.

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

OL071080F

(13) Tsuda, T.; Chujo, Y.; Nishi, S.-i.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 6381.

(14) Subjection of crotyl ester **1k** to our reaction conditions resulted in a complex mixture of inseparable products **12a**, **12b**, and **13**.



(15) Erlenmeyer, E., Jr. *Annalen* **1899**, *307*, 70.