Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: J. Dai, W. Ren, H. Wang and Y. Shi, *Org. Biomol. Chem.*, 2015, DOI: 10.1039/C5OB01304F.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

View Article Online
DOI: 10.1039/C5OB01304F

Journal Name

COMMUNICATION

A Facile Approach to β-Amino Acid Derivatives via Palladium-Catalyzed Hydrocarboxylation of Enimides with Formic Acid

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

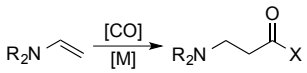
www.rsc.org/

Jie Dai,[a] Wenlong Ren,[a] Haining Wang,[a] and Yian Shi*[a,b,c]

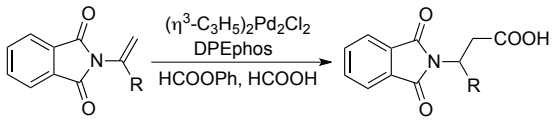
Abstract: An effective Pd(0)-catalyzed hydrocarboxylation of enimides with formic acid in the presence of catalytic amount of HCOOPh is described. A variety of β-amino acid derivatives are obtained in good yields with high regioselectivities without using external toxic CO gas .

β-Amino acids are important functional moieties present in various peptides, peptidomimetics, and biologically active compounds.[1] A variety of effective methods have been developed for the synthesis of this class of compounds.[2] The hydrocarbonylation of enamines and related compounds would provide an attractive approach to β-amino acids and their derivatives (Scheme 1).[3] Thus far, a number of such processes have been reported primarily with *N*-ethenylphthalimide as substrate.[4-7] Developing a reaction process with a broad substrate scope is highly desirable. During our continuing studies on the hydrocarbonylation of olefins without using external CO gas,[8-11] we have recently found that carboxylic acids can be obtained from olefins with HCOOH and HCOOPh in the presence of Pd(0) catalyst.[12] Our further studies show that this system is also highly effective for various substituted *N*-vinylphthalimides, giving the corresponding β-amino acid derivatives in good yields and high regioselectivities (Scheme 2). Herein, we wish to report our preliminary results on this subject.

Scheme 1. Hydrocarbonylation with CO



Scheme 2. Hydrocarboxylation with HCOOH



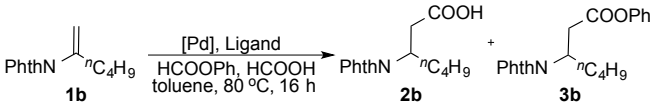
N-Vinylphthalimide **1b** was used as the test substrate for initial studies. Only trace amount of acid **2b** was formed when **1b** was treated with 5 mol % $Pd(PPh_3)_4$, 1.2 equiv HCOOPh, and 1 equiv HCOOH in toluene at 80 °C for 16 h (Table 1, entry 1). The reaction was subsequently examined with several Pd catalysts in the presence of PPh_3 (Table 1, entries 2-5). The best yield was obtained with $(\eta^3\text{-}C_3H_5)_2Pd_2Cl_2$ (APD). Further studies showed that the ligand had a profound impact on the reaction (Table 1, entries 6-14). The best results were obtained with P(*p*-tolyl)$_3$ and DPEphos (**L3**) (Table 1, entries 7 and 14). Acid **2b** was obtained in 93% yield with ligand **L3** when 2 equiv HCOOH was used (Table 1, entry 15). In this case, little ester **3b** was observed from the crude reaction mixture by ^{1}H NMR. A high yield (93%) was still obtained with less amount of the catalyst (0.5 mol %) and catalytic amount of HCOOPh (Table 1, entry 16).[12] The reaction also proceeded efficiently at lower temperature (60 °C) (Table 1, entry 17). Ester **3b** was isolated in good yield when the reaction was carried out in the absence of HCOOH (Table 1, entry 18).

As shown in Table 2, the hydrocarboxylation reaction can be extended to various substituted *N*-vinylphthalimides, giving the corresponding carboxylic acids in 60-98% yield (the X-ray structure of acid **2a** is shown in Figure 1). The R group can be both alkyl and aromatic groups. The alkyl groups can be linear (**2b-e**) or branched (**2f**) alkanes. The phenyl groups can have various substituents (**2h-l**). In all cases, the hydrocarboxylation proceeded highly regioselectively. As illustrated in the case of **2c**, the phthalimide was readily hydrolyzed to the corresponding β-amino acid (**3c**) in 98% yield with hydrazine hydrate in ethanol (Scheme 3).[13]

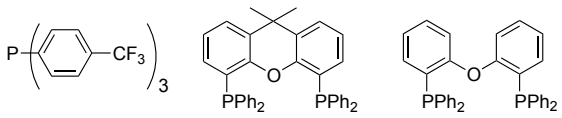
[a] *State Key Laboratory of Coordination Chemistry, Collaborative Innovation Center of Chemistry for Life Sciences, Center for Multimolecular Organic Chemistry, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing, 210093, China;*
[b] *Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China;*
[c] *Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, United States. E-mail: Yian.Shi@colostate.edu*

† We gratefully acknowledge the National Natural Science Foundation of China (0205131566) and Nanjing University for the financial support. Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Table 1. Optimization of the reaction conditions[a]



entry	[Pd] (mol %)	ligand (mol %)	HCOOH (equiv)	yield (%)[b] 2b	3b
1	$Pd(PPh_3)_4$ (5)	-	1	trace	0
2	$Pd(OAc)_2$ (5)	PPh_3 (20)	1	28	0
3	$Pd(dba)_2$ (5)	PPh_3 (20)	1	29	0
4	$Pd(acac)_2$ (5)	PPh_3 (20)	1	32	0
5[c]	APD (2.5)	PPh_3 (20)	1	68	0
6	APD (2.5)	P(*o*-tolyl)$_3$ (20)	1	0	0
7	APD (2.5)	P(*p*-tolyl)$_3$ (20)	1	81	0
8	APD (2.5)	**L1** (20)	1	trace	0
9	APD (2.5)	dppe (10)	1	0	0
10	APD (2.5)	dppp (10)	1	27	0
11	APD (2.5)	dppb (10)	1	65	12[d]
12	APD (2.5)	dppf (10)	1	51	15[d]
13	APD (2.5)	**L2** (10)	1	58	17[d]
14	APD (2.5)	**L3** (10)	1	77	14[d]
15	APD (2.5)	**L3** (10)	2	93	0
16[e,f]	APD (0.5)	**L3** (2)	2	93	0
17[e,g]	APD (0.5)	**L3** (2)	2	93	0
18[h]	APD (2.5)	**L3** (10)	0	0	86



L1 **L2** **L3**

[a]The reactions were carried out with **1b** (0.50 mmol), [Pd] (0.0050 mmol), ligand (0.050 mmol or 0.10 mmol, P/Pd = 4/1), HCOOPh (0.60 mmol), and HCOOH (0.50-1.0 mmol) in toluene (0.50 mL) at 80 °C for 16 h unless otherwise stated. [b]Isolated yield. [c]APD = $(\eta^3\text{-}C_3H_5)_2Pd_2Cl_2$. [d]The yield was determined from the crude reaction mixture by ^{1}H NMR with $BnOCH_3$ as an internal standard. [e]With 0.10 mmol of HCOOPh. [f]At 80 °C for 24 h. [g]At 60 °C for 24 h. [h]In toluene (0.2 mL) at 80 °C for 24 h.

Figure 2. X-ray structure of compound 2a

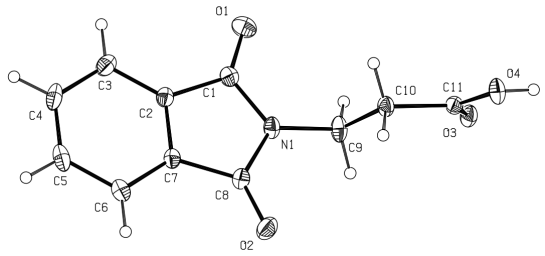
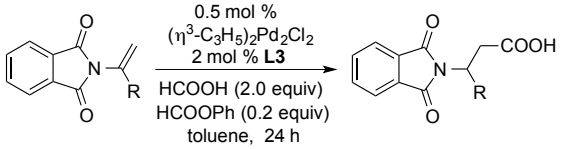
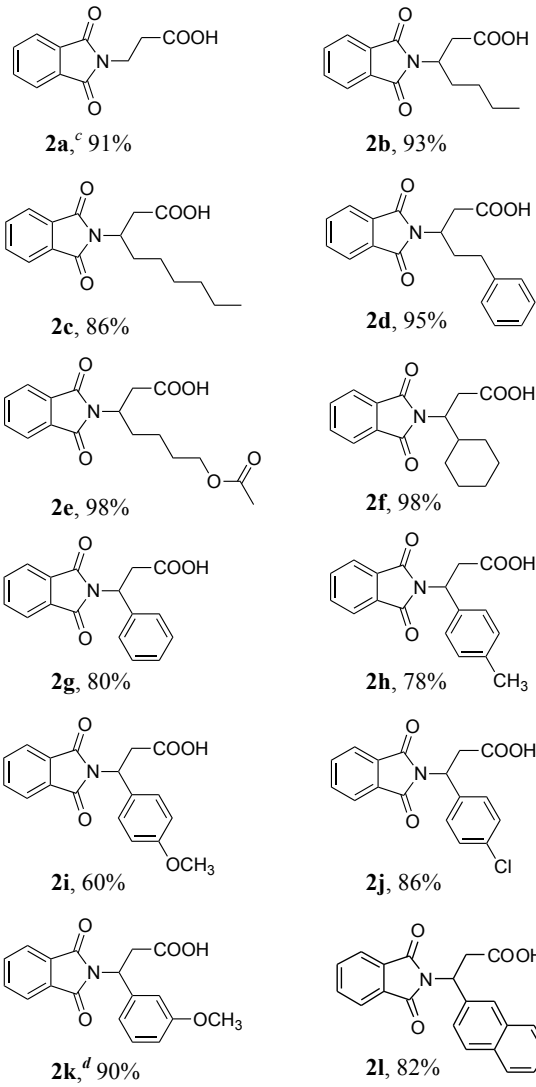


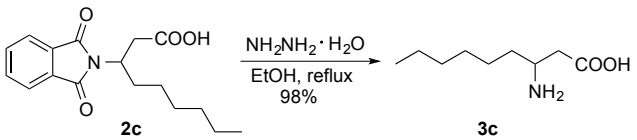
Table 2. Hydrocarboxylation of enimides[a,b]





[a]The reactions were carried out with **1** (0.50 mmol), $(\eta^3\text{-}C_3H_5)_2Pd_2Cl_2$ (0.0025 mmol), **L3** (0.010 mmol), HCOOPh (0.10 mmol), and HCOOH (1.0 mmol) in toluene (0.50 mL) at 80 °C for 24 h unless otherwise stated. [b]Isolated yield. [c]In 0.2 mL of toluene. [d]At 60 °C for 24 h.

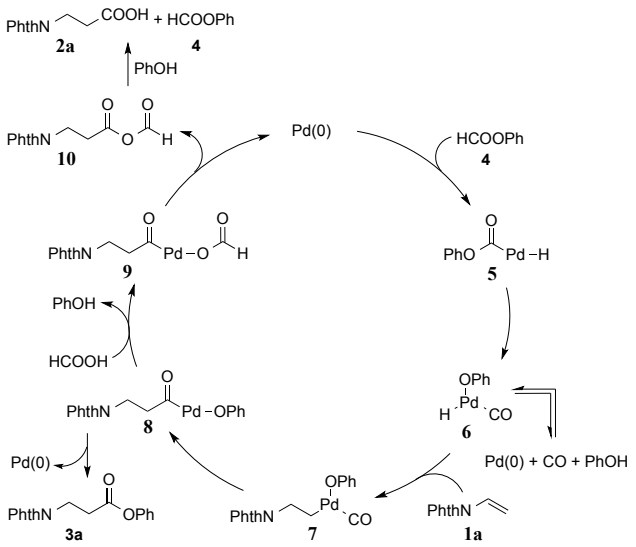
Scheme 3. Hydrolysis of phthalimide



2c **3c**

A precise understanding of the reaction mechanism awaits further study. A catalytic cycle analogous to the previously proposed pathway is shown in Scheme 4.[12] The oxidative addition of Pd(0) to HCOOPh gave palladium hydride complex **5**, which rearranged to complex **6**. The hydropalladation of the enimide (**1a**) by **6** generated alkyl palladium complex **7**, which gave acylpalladium complex **8** after a migratory insertion. The PhO group of **8** was subsequently replaced by the formate to give complex **9**, which underwent a reduction elimination to form mixed anhydride **10** with regeneration of the Pd(0) catalyst. Anhydride **10** was converted to carboxylic acid **2a** by reacting with PhOH and/or via decomposition under the reaction conditions. In the absence of HCOOH, acylpalladium complex **8** can undergo a reductive elimination to an ester (**3a**).

Scheme 4. Proposed catalytic cycle for hydrocarboxylation



In summary, we have developed an efficient Pd-catalyzed hydrocarboxylation of enimides with HCOOH and catalytic amount of HCOOPh. A variety of β-amino acid derivatives have been obtained in 60-98% yields with high regioselectivities. The reaction is operationally simple and requires no handling of toxic CO gas. The current process provides a potentially useful method for the synthesis of β-amino acids and their derivatives. Further efforts will be devoted to better understanding the reaction mechanism, further expanding the substrate scope, and developing the asymmetric process for the hydrocarboxylation reaction.

Notes and references

1 For a leading review, see: F. von Nussbaum and P. Spiteller, in *Highlights in Bioorganic Chemistry*: *Methods and Applications*, C. Schmuck and H. Wennemers, Ed.; Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2004, pp. 63-89.

2 For leading reviews, see: (a) M. Liu and M. P. Sibi, *Tetrahedron,* 2002, **58**, 7991; (b) J. Ma, *Angew. Chem. Int. Ed.*, 2003, **42**, 4290; (c) B. Weiner, W. Szymanski, D. B. Janssen, A. J. Minnaard and B. L. Feringa, *Chem. Soc. Rev.*, 2010, **39**, 1656; (d) L. Kiss and F. Fulop, *Chem. Rev.*, 2014, **114**, 1116.

3 For leading reviews on metal-catalyzed hydrocarboxylation, see: (a) G. Kiss, *Chem. Rev.*, 2001, **101**, 3435; (b) B. E. Ali, H. Alper*,* in *Transition Metals for Organic Synthesis*, Vol. 1, 2nd Edition; M. Beller, C. Bolm, Ed., John Wiley & Sons, Inc.: New York, 2004, pp 113-132; (c) C. Godard, B. K. Munoz, A. Ruiz, C. Claver, *Dalton Trans*., 2008, 853; (d) A. Brennfuhrer, H. Neumann, M. Beller, *ChemCatChem.*, 2009, **1**, 28.

4 For leading references on hydroformylation of phthalimide with CO, see: (a) Y. Becker, A. Eisenstadt, J. K. Stille, *J. Org. Chem.,* 1980, **45**, 2145; (b) G. Parrinello, R. Deschenaux and J. K. Stille, *J. Org. Chem.,* 1986, **51**, 4189; (c) G. Parrinello, and J. K. Stille, *J. Am. Chem Soc.,* 1987, **109**, 7122; (d) K. Nozaki, N. Sakai, T. Nanno, T. Higashijima, S. Mano, T, Horiuchi, H. Takaya, *J. Am. Chem Soc.,* 1997, **119**, 4413; (e) O. Saidi, J. Ruan, D.Vinci, X. Wu, J. Xiao, *Tetrahedron Letters,* 2008, **49**, 3516; (f) R. Jennerjahn, I. Piras, R. Jackstell, R. Franke, K. D. Wiese, and M. Beller, *Chem. Eur. J.*, 2009, **15**, 6383; (g) R. I. McDonald, G. W. Wong, R. P. Neupane, S. S. Stahl and C. R. Landis, *J. Am. Chem. Soc.*, 2010, **132**, 14027; (h) I. Piras, R. Jennerjahn, R. Jackstell, W. Baumann, A. Spannenberg, R. Franke, K. D. Wiese, M. Beller, *J. Organomet. Chem.*, 2010, **695**, 479; (i) C. Cai, S. Yu, B. Cao and X. Zhang, *Chem. Eur. J.,* 2012, **18**, 9992.

5 For a leading reference on hydroesterification of phthalimide with CO, see: (a) G. Cavinato, L. Toniolo, *J. Organomet. Chem.*, 1982, **229**, 93; (b) B. C. Zhu and X. Z. Jiang, *Appl. Organometal. Chem.,* 2006, **20**, 277.

6 For a leading reference on hydroesterification of phthalimide with HCOOMe, see: I. Fleischer, R. Jennerjahn, D. Cozzula, R. Jackstell, R. Franke, and M. Beller, *ChemSusChem,* 2013, **6**, 417.

7 For a leading reference on aminocarbonylation of phthalimide with CO, see: X. Fang, R. Jackstell and M. Beller, *Angew*. *Chem. Int. Ed.*, 2013, **52**, 14089.

8 For leading reviews on metal-catalyzed hydrocarboxylation with CO surrogates, see: (a) G. Jenner, *App. Catal. A: General,* 1995, **121**, 25; (b) T. Morimoto, K. Kakiuchi, *Angew*. *Chem. Int. Ed.*, 2004, **43**, 5580; (c) L. Wu, Q. Liu, R. Jackstell, M. Beller, *Angew*. *Chem. Int. Ed.*, 2014, **53**, 6310; (d) H. Konishi, K. Manabe, *Synlett*, 2014, **25**, 1971; (e) B. Liu, F. Hu, B. Shi, *ACS Catal*. 2015, **5**, 1863.

9 For leading references on Ru-catalyzed hydroesterification with formates in the absence of CO gas, see: (a) W. Ueda; T. Yokoyama, Y. Morikawa, Y. Moro-oka, T. Ikawa, *J. Mol. Catal.,* 1988, **44**, 197; (b) E. M. Nahmed, G. Jenner, *J. Mol. Catal.,* 1990, **59**, L15; (c) G. Lavigne, N.Lugan, *J. Am. Chem. Soc.,* 1992, **114**, 10669; (d) G. Jenner, A. B. Taleb, *J. Mol. Catal.,* 1994, **91**, 31; (e) C. Legrand, Y. Castanet, A. Mortreux, F. Petit, *J. Chem. Soc., Chem. Commun*., 1994, 1173; (f) S. Fabre, P. Kalck, G. Lavigne, *Angew. Chem. Int. Ed.,* 1997, **36**, 1092; (g) S. Ko, Y. Na, S. Chang, *J. Am. Chem. Soc.,* 2002, **124**, 750; (h) Y. Na, S. Ko, L. K. Hwang, S. Chang, *Tetrahedron Lett*., 2003, **44**, 4475; (i) L. Wang, P. E. Floreancig, *Org. Lett*., 2004, **6**, 4207; (j) E. J. Park, J. M. Lee, H. Han, S. Chang, *Org. Lett*., 2006, **8**, 4355; (k) H. Konishi, T. Ueda, T. Muto, K. Manabe, *Org. Lett.,* 2012, **14**, 4722. (l) I. Profir, M. Beller, I. Fleischer, *Org. Biomol. Chem*., 2014, **12**, 6972; (m) B. Li, S. Lee, K. Shin, S. Chang, *Org. Lett.,* 2014, **16**, 2010.

10 For leading references on Pd-catalyzed hydroesterification with formates in the absence of CO gas, see: (a) J. Grevin, P.

View Article Online
DOI: 10.1039/C5OB01304F

Kalck, *J. Organomet. Chem.,* 1994, **476**, C23; (b) Y. Katafuchi, T. Fujihara, T. Iwai, J. Terao, Y. Tsuji, *Adv. Synth. Catal.,* 2011, **353**, 475; (c) Reference 6.
11 H. Wang, B. Dong, Y. Wang, J. Li, Y. Shi, *Org. Lett.,* 2014, **16**, 186.
12 Y. Wang, W. Ren, J. Li, H. Wang, Y. Shi, *Org. Lett.*, 2014, **16**, 5960.
13 B. Weiner, A. Baeza, T. Jerphagnon, B. L. Feringa, *J. Am. Chem. Soc.,* 2009, **131**, 9473.

Journal Name COMMUNICATION

View Article Online
DOI: 10.1039/C5OB01304F

Table of Contents