Selective Functionalization of Amino Acids in Water: A Synthetic Method via Catalytic C−H Bond Activation

Brian D. Dangel, James A. Johnson, and Dalibor Sames*

Department of Chemistry, Columbia University
New York, New York 10027

Received May 25, 2001
Revised Manuscript Received July 2, 2001

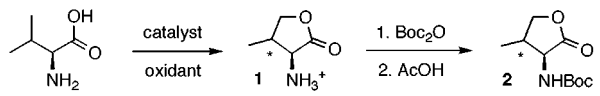
Amino acids are valuable building units and precursors for a variety of organic compounds ranging from small molecules to proteins. In living systems, the diversity of amino acid-derived products is readily expanded by amino acid functionalization at various stages of biosynthesis.[1] Accordingly, a synthetic methodology that would allow for the direct and selective functionalization of available amino acids would be of significant importance. However, most metal reagents and catalysts for C−H activation are sensitive to functional groups or an aqueous environment, two typical features of amino acid chemistry.[2]

Against such odds, there were two seemingly unrelated areas which stimulated our investigation in this direction: first, the original Shilov reaction (Pt(II)/Pt(IV)-mediated oxidation of alkanes) is performed in aqueous acid solution,[3] second, the coordination chemistry of Pt(II) salts with amino acids and proteins has been intensely studied due to the clinical use of cisplatin in tumor therapy.[4] In the process of merging these two fields we discovered that the stoichiometric Shilov reaction was compatible with amino acid substrates, and furthermore, we developed a catalytic system capable of selective functionalization of free α-amino acids in water.

Initial experiments involved submitting L-valine to an aqueous solution of K_2PtCl_4 in the presence of K_2PtCl_6 as the oxidant.[5] Surprisingly, heating the reaction mixture at 100 °C for 12 h yielded two major products identified as diastereomers of γ-hydroxyvaline **1a** and **1b** in 5:1 ratio (anti/syn) (Table 1). Although the conversion was low (<20% yield), this experiment demonstrated that the chelation ability of the amino acid did not inhibit the reaction but may in fact be responsible for the observed regio- and stereoselectivity (see discussion below).

Encouraged by these results we focused our attention toward the development of a catalytic system based on platinum in combination with a practical oxidant. Copper(II) salts have been used to oxidize Pd(0) in the Wacker process,[6] and Pt(0)/Pt(II) in the Shilov and related oxidations.[7] Consequently, we treated L-valine with a catalytic amount of K_2PtCl_4 (1−10 mol %) in the presence of a stoichiometric amount of $CuCl_2$ in water. *Remarkably, at temperatures >130 °C, catalytic turnovers were observed, and the C−H bond functionalization occurred with regio- and stereoselectivity, affording lactones **1a** and **1b** in a 3:1 ratio (anti:syn).* Additionally, only limited racemization of the major products and recovered starting material was found (<5% in 5 h, see Supporting Information).[8]

Table 1. Catalytic Hydroxylation of L-Valine: Optimization



catalyst/oxidant (mol%/equiv)	yield[a] (**1**, %)	anti/syn **1a**/**1b**	TON	isolated yield[b] (**2**, %)	mass balance (%)
K_2PtCl_4/K_2PtCl_6[c]					
16/0.33	21	5:1	0		91
$K_2PtCl_4/CuCl_2$[d]					
1/5	20	3:1	20	14	80
2.5/5	39	3:1	15	20	65
2.5/10	12	3:1	5	10	79
5/3	37	3:1	7	20	80
5/7	56	3:1	11	27	59
5/10	47	3:1	9	22	65
10/10	67	3:1	7	35	55
$Na_2S_2O_8/CuCl_2$[e]	0				

[a] Product/start. material ratio (×100) determined by ^{1}H NMR of the isolated crude mixture. [b] Isolated yields of **2** over three-step sequence including hydroxylation, amino group protection and lactonization. [c] Conditions: L-valine, 0.33 M in H_2O, 100 °C, 10 h. [d] Conditions: L-valine, 0.33 M in H_2O, 160 °C, 10 h. [e] Conditions: L-valine, 0.91 M in H_2O, 1 equiv of $Na_2S_2O_8$ and 1 equiv of $CuCl_2$ (or NaCl), 90 °C (ref 12).

Hitherto, $CuCl_2$ and $CuBr_2$ proved to be the only oxidants capable of regenerating the active platinum species, while other metal salts were ineffective ($CuSO_4$, $Cu(OAc)_2$, $Cu(OTf)_2$, $Cu(OMs)_2$, $Cu(O_3SPh)_2$, $FeCl_3$). Screening the 1−10 mol % range of K_2PtCl_4 in the presence of 1−10 equiv of $CuCl_2$ was conducted (Table 1). In most cases maximum conversion was reached within 10 h at 160 °C, whereas lower temperatures (∼130 °C) required longer reaction times. The highest number of turnovers (20 turnovers based on the crude yield) was achieved in the presence of 1 mol % of K_2PtCl_4 and 5 equiv of $CuCl_2$. After the reaction yield was balanced with the amount of the platinum catalyst required, the most practical conditions were determined to be 5 mol % of platinum catalyst and 7 equiv of copper chloride, to furnish a 56% yield of hydroxyvaline isomers **1a** and **1b**. The products were converted to *N*-Boc-lactones, obtained in 27% overall yield.

Traditionally, C−H bond functionalization has been achieved via radical processes where regioselectivity in complex substrates has often been controlled through intramolecular abstraction of a hydrogen atom by a proximal nitrogen or oxygen-centered radical (e.g., Hoffmann−Löffler−Freytag reaction,[9] Barton reaction,[10] Breslow remote oxidation[11]). As an important control experiment, we submitted L-valine to conditions known to generate a carboxyl-centered radical ($Na_2S_2O_8$, $CuCl_2$ or NaCl).[12] It was determined that no hydroxyvaline **1** was formed, while simple carboxylic acids yielded γ-lactones in moderate yields (Table 1)! This experiment strongly suggested that the catalytic process developed herein did not proceed via a free radical mechanism, and it

(1) (a) Herbert, R. B. *Nat. Prod. Rep*. **1999**, *16*, 199−208. (b) Sahl, H.-G.; Jack, R. W.; Bierbaum, G. *Eur. J. Biochem*. **1995**, *230*, 827−853.

(2) Jones, W. D. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: Berlin, 1999; pp 9−46.

(3) Shilov, A. E.; Shul'pin, G. B. *Activation and Catalytic Reactions of Saturated Hydrocarbons in the Presence of Metal Complexes*; Kluwer Academic Publishers: Dordrecht, 2000.

(4) (a) Appleton, T. G. *Coord. Chem. Rev*. **1997**, *166*, 313−359. (b) Reedijk, J. *Chem. Rev*. **1999**, *99*, 2499−2510.

(5) (a) Labinger, J. A.; Herring, A. M.; Lyon, D. K.; Luinstra, G. A.; Bercaw, J. E.; Horváth, I. T.; Eller, K. *Organometallics* **1993**, *12*, 895−905. (b) Kao, L.-C.; Sen, A. *J. Chem. Soc., Chem. Commun*. **1991**, 1242−1243.

(6) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley and Sons: Chichester, 1995; pp 19−124.

(7) (a) Lin, M.; Shen, C.; Garcia-Zayas, E. A.; Sen, A. *J. Am. Chem. Soc*. **2001**, 123, 1000−1001. (b) VanKoten, G.; Terheijden, J.; van Beek, J. A. M.; Wehman-Ooyevaar, I. C. M.; Muller, F.; Stam, C. H. *Organometallics* **1990**, *9*, 903−912.

(8) Smith, G. G.; Khatib, A. Reddy, G. S. *J. Am. Chem. Soc*. **1983**, *105*, 293−295.

(9) (a) Corey, E. J.; Hertler, W. R. *J. Am. Chem. Soc*. **1958**, *80*, 2903−2904. (b) Buchschacher, P.; Kalvoda, J.; Arigoni, D.; Jeger, O. *J. Am. Chem. Soc*. **1958**, *80*, 2905−2906.

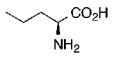
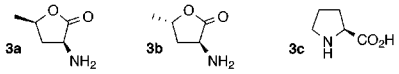
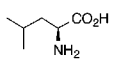
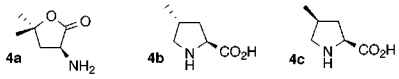
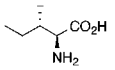
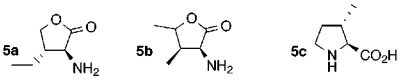
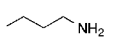
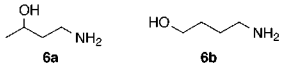
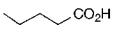
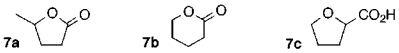
(10) Barton, D. H. R.; Beaton, J. M. *J. Am. Chem. Soc*. **1961**, *83*, 4083−4089.

(11) Breslow, R.; Baldwin, S.; Flechtner, T.; Kalicky, P.; Liu, S.; Washburn, W. *J. Am. Chem. Soc*. **1973**, *95*, 3251.

(12) (a) Nikishin, G. I.; Svitanko, I. V.; Troyansky, E. I. *J. Chem. Soc., Perkin Trans, II* **1983**, 595−601. For photochlorination and photobromination of amino acids: (b) Kollonitsch, J.; Scott, A. N.; Doldouras, G. A. *J. Am. Chem. Soc*. **1966**, *88*, 3624−3626. (c) Easton, C. J.; Hutton, C. A.; Tan, E. W.; Tiekink, E. R. T. *Tetrahedron Lett*. **1990**, *31*, 7059−7062.

10.1021/ja016280f CCC: $20.00
Published on Web 07/31/2001

Table 2. Catalytic Functionalization of Selected Substrates

entry	substrate	products	a : b : c	ratio(crude yield)[a]	γ- / δ- products	isolated yield[b]
1 L-Norvaline		 **3a** **3b** **3c**	2 : 1 : 1	50(43)	4 : 1[c]	21
2 L-Leucine		 **4a** **4b** **4c**	22 : 4 : 1	46(38)	4.5 : 1	15
3 L-Isoleucine		 **5a** **5b** **5c**	2 : 1 : 3	63(57)	1 : 1[d]	23
4 n-Butylamine		 **6a** **6b**	1 : 3	61	1 : 3	24
5 Valeric acid		 **7a** **7b** **7c**	2 : 1 : 2	28	2 : 3	
6 L-Proline		no reaction		0		

[a] Product to starting material ratio (×100), determined by ^{1}H NMR of isolated crude mixtures. Crude yields were determined by NMR and recovered crude mass. [b] Combined isolated yields of Boc-lactones (a three-step sequence including functionalization, amino group protection, and lactonization), and Boc-pyrrolidines (two steps). [c] γ-ketone was also formed in 7% crude yield. [d] **5b** is a 1:1 mixture of two stereoisomers.

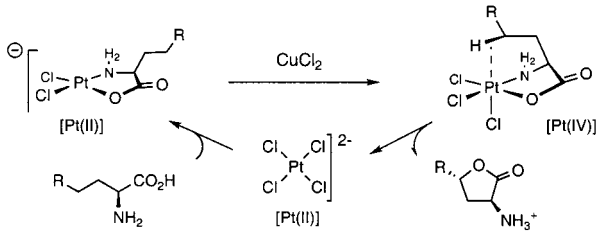


Figure 1. Chelate-directed C−H bond functionalization. Proposed catalytic cycle.

highlighted the use of transition metal catalysts as a favorable alternative to free radical reagents.

To gain more insight into this catalytic process in terms of generality and mechanism, we applied the selected conditions (5 mol % of K_2PtCl_4, 7 equiv of $CuCl_2$) to other amino acid substrates (Table 2). In the case of L-norvaline, oxidation of the γ-methylene unit was the predominant pathway yielding γ-lactones **3a** and **3b** in 32% crude yield and 2:1 ratio, as well as γ-ketone in 7% crude yield. The minor δ-selective pathway provided L-proline, presumably originating from chlorination of the terminal methyl group, followed by intramolecular substitution of the chloride by the amino group. L-Leucine also provided γ-lactone **4a** as the major product (γ-/δ-products, 4.5:1) together with methylpyrrolidines **4b** and **4c** as the minor component (**4b**/**4c**, 4:1). L-Isoleucine provided three major products, **5a** and **5b** from hydroxylation of the γ-methyl and γ-methylene group, respectively, while pyrrolidine **5c** was formed through functionalization of the δ-methyl group. The γ- and δ-functionalized products were obtained in an approximately 1:1 ratio. Simple aliphatic amines were also hydroxylated under the catalytic conditions. In sharp contrast to L-norvaline, *n*-butylamine showed preference for δ-hydroxylation, yielding products **6a** and **6b** in a 1:3 ratio. In the case of valeric acid, the δ-position was hydroxylated with minor preference (3:2) over the γ-position, affording three products, namely, lactones **7a** and **7b**, and the unexpected 2-oxolanecarboxylic acid **7c**.[13]

The results described herein uncovered regioselectivity trends for α-amino acids that were distinctly different from those for simple aliphatic amines and carboxylic acids. Therefore, *we propose that functionalization of α-amino acids proceeds via a mechanism based on chelate-directed C−H bond activation (Figure 1).* The resistance of proline to oxidation under these conditions supports the proposed hypothesis, as its cyclic nature prevents an intramolecular collision between the Pt(IV) metal and a C−H bond.

In summary, we have developed a catalytic process for the selective functionalization of α-amino acids in water. Although catalytic directed functionalization of arene rings has previously been achieved, the discovery of the corresponding process for unactivated alkane segments has been prevented owing to the greater difficulty of metal-mediated cleavage of alkane C−H bonds.[14] This report has demonstrated a very rare, if not the first, example of catalytic heteroatom-directed functionalization of remote alkyl groups in complex substrates.

Acknowledgment. We dedicate this paper to Professor Ronald Breslow on the occasion of his 70th birthday. D. S. is a Cottrell Scholar of Research Corporation and a recipient of the Camille and Henry Dreyfus New Faculty Award. J. A. J. received the BMS Fellowship in Synthetic Chemistry. We thank Dr. L. J. Williams for stimulating discussions and Dr. J. B. Schwarz for editorial assistance.

Supporting Information Available: Detailed experimental procedures, spectral characterization of products (PDF). This material is available free of charge via the Internet at http://pubs.acs.

JA016280F

(13) The product **7c** was generated by copper chloride-mediated oxidation of δ-lactone **7b**, γ-lactone **7a** was resistant to this oxidative process (see Supporting Information).

(14) (a) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698−1712. (b) Catalytic N-directed functionalization of activated sp^3 C−H bonds: Murahashi, S.-I.; Hirano, T.; Yano, T. *J. Am. Chem. Soc.* **1978**, *100*, 348−350. Chatani, N.; Asaumi, T.; Ikeda, T.; Yorimitsu, S.; Ishii, Y.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2000**, *122*, 12882−12883.