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Novel Acetoxylation and C–C Coupling Reactions at Unactivated Positions in α-Amino Acid Derivatives

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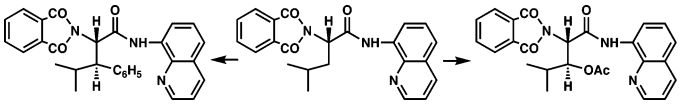
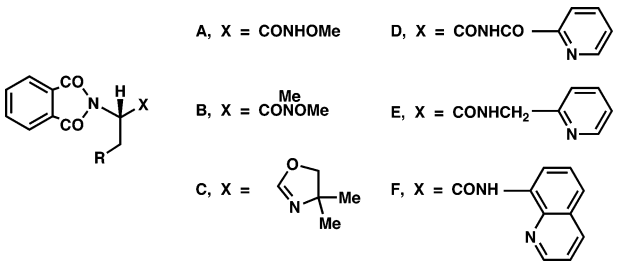
ABSTRACT



Under special conditions, *N*-phthaloyl-α-amino acid amides of 8-aminoquinoline can be either acetoxylated or arylated selectively at the *β*-carbon. In certain cases, arylation can be effected at the *γ*-carbon.

We recently described a method for the selective functionalization of various α-amino acids at the *δ*-carbon that is very useful because it provides rapid and efficient access to many useful chiral unnatural α-amino acids.[1] In that study, we utilized the α-*amino* function to direct the replacement of *δ*-C−H by *δ*-C−Br. Encouraged by the success of this approach, we turned our attention to the possibility of using the *carboxyl* function to direct replacement of a *β*-C−H atom of an α-amino acid by a *β*-C−OAc or *β*-C−OH group. *β*-Hydroxy-α-amino acids are important naturally occurring compounds. In addition to the two genetically coded proteinogenic amino acids serine and threonine, members of the *β*-hydroxy-α-amino acid class occur as constituents of many bioactive natural compounds. *β*-Hydroxyleucine is especially prominent as a building block for lactacystin, salinosporamide A, and various cyclodepsipeptides, including azinothricin, papuamides, and polyoxypeptins.[2] Although there have been several syntheses of *β*-hydroxyleucine, none of these have used the conceptually simplest route, *β*-hydroxylation of leucine.[2] We report herein the development of such a process. The approach used was the carboxamide-directed $Pd(OAc)_2$-catalyzed oxidative conversion of *β*-CH_2 to *β*-CHOAc. This transformation has not previously been applied to α-amino acid derivatives as far as we are aware. The specific substrates employed in this research were amide derivatives of *N*-phthaloyl-protected leucine, alanine, *β*-methylalanine, *β*-ethylalanine, and *β*-phenylalanine. It should be noted that the overwhelming number of examples of sp^3-C−H functionalization using $Pd(OAc)_2$ catalysis involves insertion into methyl groups;[3] insertion into methylene groups generally does not occur under the conditions that suffice for CH_3 insertion.[3f]



In our initial studies, a number of *N*-phthaloylamino acid amides of types **A**−**F** were screened using the *t*-BuOOH−Ac_2O−$Pd(OAc)_2$ system in toluene (C_7H_8) at 110 °C. Of

(1) Reddy, L. R.; Reddy, B. V. S.; Corey, E. J. *Org. Lett.* **2006**, *8*, 2819.

(2) For synthesis of *β*-hydroxyleucines, see: (a) Schollkopf, U.; Groth, U.; Gull, M.-R.; Nozulak, J. *Liebigs Ann. Chem.* **1983**, 1133. (b) Jung, M. E.; Jung, Y. H. *Tetrahedron Lett.* **1989**, *30*, 6637. (c) Caldwell, C. G.; Bondy, S. S. *Synthesis* **1990**, 34. (d) Blaser, D.; Seebach, D. *Liebigs Ann. Chem.* **1991**, 1067. (e) Sunazuka, T.; Nagamitsu, T.; Tanaka, H.; Omura, S.; Sprengleler, P. A.; Smith, A. B., III. *Tetrahedron Lett.* **1993**, *34*, 4447. (f) Panek, J. S.; Masse, C. E. *J. Org. Chem.* **1998**, *63*, 2382. (g) Horikawa, M.; Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 3843. (h) MacMillan, J. B.; Molinsky, T. F. *Org. Lett.* **2002**, *4*, 1883. (i) Saravanan, P.; Corey, E. J. *J. Org. Chem.* **2003**, *68*, 2760. (j) Makino, K.; Hamada, Y. *J. Synth. Chem. Jap.* **2005**, *63*, 1198.

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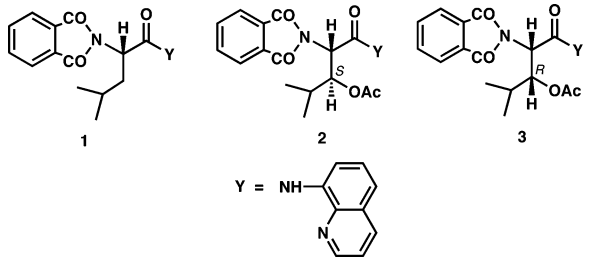
these, only the 8-aminoquinoline derivatives (**F**) appeared to be promising for further study. Even with this most favorable derivative for functionalization, we were not able to obtain useful yields of β-acetoxy-α-phthaloylamino acid 8-aminoquinoline amide products under previously employed conditions for Pd-catalyzed acetoxylation. For instance, when *N*-phthaloyleucine 8-aminoquinoline amide **1** and 0.2 equiv of $Pd(OAc)_2$ were heated with either 2 equiv of $C_6H_5I(OAc)_2$ and Ac_2O in $ClCH_2CH_2Cl$ at 80 °C for 12 h or 5 equiv of *t*-BuOOH and 5 equiv of Ac_2O in C_7H_8 at 110 °C for 8 h, none of the desired β-acetoxylated product **2** could be detected and, in fact, only the starting material **1** was recovered. These conditions have been shown to effect functionalization at β-methyl groups in ketone *O*-methyloximes.[3f,h,j] However, we were pleased to find that treatment of **1** with 20 mol % of $Pd(OAc)_2$, 5 equiv of *t*-BuOOH, and 5 equiv of Ac_2O in benzene at 80 °C in the presence of 1.2 equiv of $Mn(OAc)_2$ gave **2** in 30% yield. This noteworthy acceleration



of reaction rate by Mn(II) has not previously been reported. Although AgOAc has been found to be beneficial to certain $Pd(OAc)_2$-catalyzed C−C couplings with aryl iodides,[4] no reaction was observed when $Mn(OAc)_2$ was replaced by AgOAc in the acetoxylation experiment with **1**. Additional experimentation demonstrated that $Cu(OAc)_2$ and $Co(OAc)_2$ were also ineffective. With $Mn(OAc)_2$ as a promoter, we found that Oxone ($2KHSO_5/KHSO_4/K_2SO_4$) (5 equiv) was superior as an oxidant to *t*-BuOOH and that CH_3NO_2 and $ClCH_2CH_2Cl$ (especially the former) served as the most effective solvents for the β-acetoxylation of the α-phthaloylamino acid amides investigated in the present work. Thus, the reaction of **1** with 20 mol % of $Pd(OAc)_2$, Oxone (5 equiv), acetic anhydride (10 equiv), and $Mn(OAc)_2$ (1.2 equiv) in CH_3NO_2 at 80 °C for 22 h (under air) afforded the crystalline (3*S*)-acetate **2** in 60% isolated yield along with the (3*R*)-diastereomer **3** (ca. 4%). The structure of **2** was confirmed by single-crystal X-ray diffraction analysis (Figure 1).[5] The diastereoselectivity of the reaction was estimated

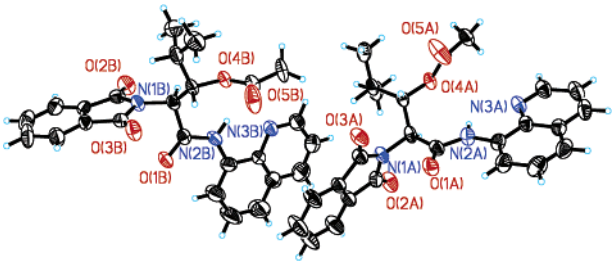
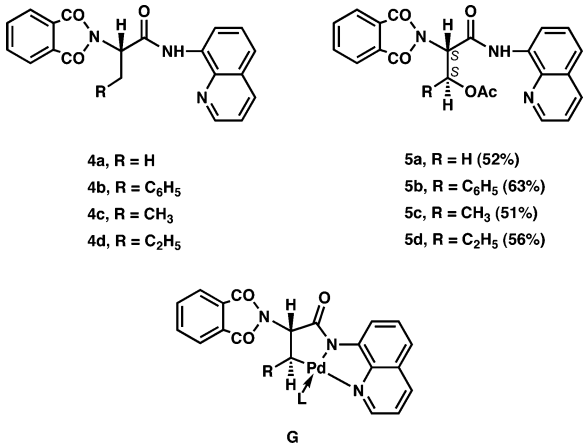


Figure 1. ORTEP representation of **2**.

by ^1H NMR analysis of the total reaction product as 20:1.

Under the same conditions as those described just above for the transformation of **1** to **2**, the alanine derivative **4a** was converted into the serine derivative **5a** in 52% yield. These conditions also resulted in the analogous conversion with the β-phenylalanine series of **4b** to **5b** (63%). In the case of reactant **4b**, the reaction was completely diastereoselective for **5b**, whereas for **4c** and **4d** diastereoselectivities were on the order of 5:1 and 8:1, respectively, favoring in each case the (3*S*)-diastereomers (**5c** and **5d**). The observed stereochemistry of the β-functionalization can be understood in terms of a preference for forming the sterically more favored intermediate *trans*-palladacycle **G**.



The palladacycle **G**, R = *i*-Pr, could be generated, trapped, and defined structurally by the reaction of **1** with *p*-iodoanisole (4 equiv), $Pd(OAc)_2$ (20 mol %), and AgOAc (1.5 equiv, to remove HI) at 110 °C for 30 min (without solvent) which afforded the crystalline 2*S*,3*S*-3-*p*-anisyl derivative **6** in 95% yield.[6] The structure of **6** was verified by single-crystal X-ray diffraction analysis (Figure 2).[5]

Our results are generally supportive of the most recent mechanistic discussions of Pd(II)-mediated sp^3-C−H inser-

(3) (a) Constable, A. G.; McDonald, W. S.; Sawkins, L. C.; Shaw, B. L. *J. Chem. Soc., Chem. Commun.* **1978**, 1061. (b) Carr, K.; Sutherland, J. K. *J. Chem. Soc., Chem. Commun.* **1984**, 1227. (c) Baldwin, J. E.; Nájera, C.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1985**, 126. (d) Jun, C.-H. *Chem. Soc. Rev.* **2004**, 610. (e) Jun, C.-H.; Moon, C. W.; Lee, D.-Y. *Chem.−Eur. J.* **2002**, *8*, 2423. (f) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542. (g) Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112. (h) Giri, R.; Liang, J.; Lei, J.-G.; Li, J.-J.; Wang, D.-H.; Naggar, I. C.; Guo, C.; Foxman, B.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420. (i) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300. (j) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141. (k) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (l) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790.

(4) The use of AgOAc in Pd-catalyzed C−C bond formation with aryl iodides has been reported; see: Shabashov, D.; Daugulis, O. *Org. Lett.* **2005**, *7*, 3657.

(5) Carried out by Dr. Richard Staples; see Supporting Information for details.

(6) For precedent, see ref 3k.

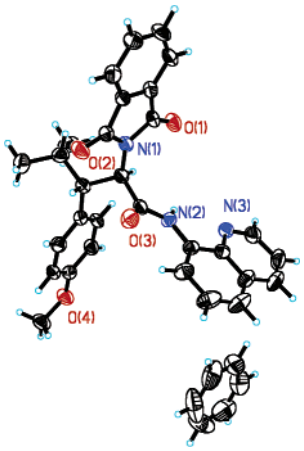
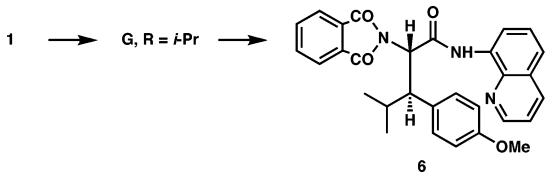


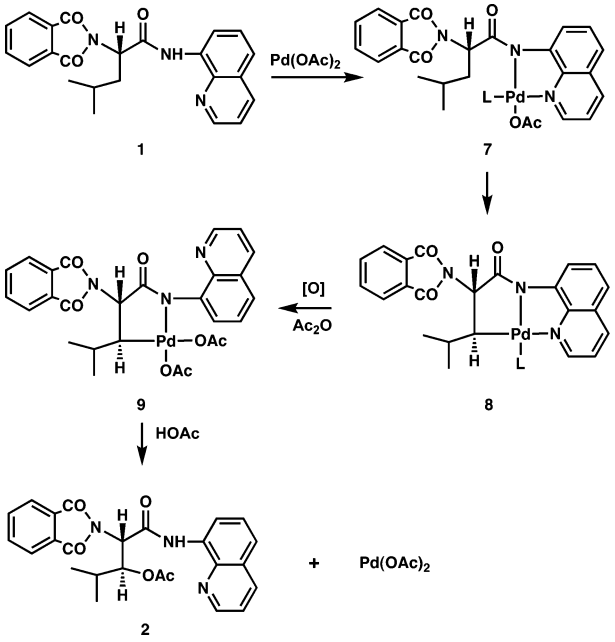
Figure 2. ORTEP representation of **6**.



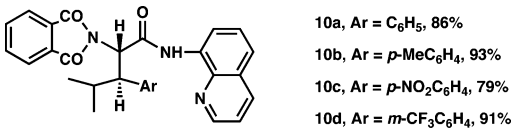
tion and functionalization.[7] In terms of the substrates and conditions involved in the reactions reported herein, any mechanistic proposal needs to take into account the rate (and yield) enhancing effects of the additive $Mn(OAc)_2$ and the solvent CH_3NO_2. One possibility for the role of $Mn(OAc)_2$ is that it undergoes oxidation to $Mn_3O(OAc)_7$ which functions as a Lewis acid to increase the positive charge on Pd in the first reaction intermediate (**7**, in Scheme 1),[8] thereby lowering the barrier for C−H insertion and allowing concerted formation of the palladacycle **8** and HOAc.[9] Successful β-acetoxylation requires that the oxidation of **8** to a Pd(IV) species be rapid so that it can compete with decomposition pathways such as Pd−C homolysis or β-C−H elimination of Pd(0). Oxone appears to be the oxidant that is best suited to this task. A reasonable role of Ac_2O could be its functioning to produce the diacetate **9** by acetylation of the initial Pd(IV) intermediate. This intermediate is the logical precursor of the reaction product **2**, with regeneration of $Pd(OAc)_2$. The efficacy of CH_3NO_2 as solvent is due in part to the fact that it dissolves the various reactants and in part to its noncoordinating, polar nature which maximizes the electrophilicity (δ^+) of the Pd species responsible for C−H insertion.[9]

Although the initial objective of this research was the development of a methodology for the β-acetoxylation of α-amino acid derivatives, the ease and high yield of the conversion of **1** to **6** provided encouragement to examine

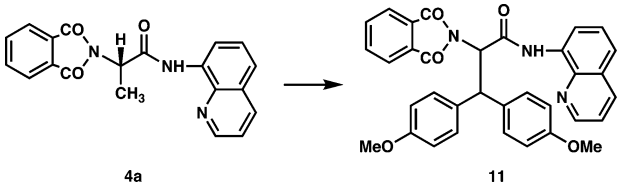
Scheme 1. Possible Pathway for the β-Acetoxylation of *N*-Phthaloyleucine 8-Aminoquinoline Amide (**1**) by Pd(II) Catalysis



this β-arylation reaction to assess scope. With regard to the arylation agent, several other aryl iodides were examined with outstanding results. Thus, the series of β-arylated leucine derivatives **10a**−**d** was readily prepared in the isolated yields indicated.



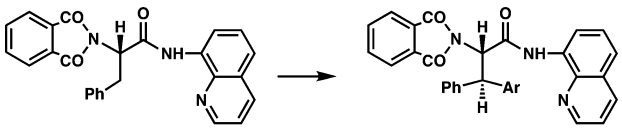
An interesting result was obtained when the alanine 8-aminoquinoline amide **4a** was treated with 20 mol % of $Pd(OAc)_2$ and 1.5 equiv of AgOAc in *p*-iodoanisole (4 equiv) as solvent at 110 °C for 1.5 h. The product was the unusual diarylated alanine **11** (92% yield), which can also be viewed as a β-*p*-anisylated tyrosine derivative.



β-Diarylated alanine derivatives were also made from the *N*-phthaloylated phenylalanine amide **4b**, which was efficiently converted into **12a** (91%) or **12b** (89%) with *p*-iodoanisole or iodobenzene, respectively. Clearly, **12a** would be much more difficult to synthesize stereoselectively by other routes.

An equally fascinating outcome was seen in the reaction of the isoleucine derivative **13** with *p*-iodoanisole under the

(7) See, especially, refs 3h, 3j, and 3k.
(8) This intermediate which is formed by heating **1** with $Pd(OAc)_2$ has been isolated.
(9) The greater the positive charge is on Pd, the lower the energy of the vacant d-orbital that interacts with the C−H σ-bond and the more favorable the agostic interaction leading to C−H insertion.

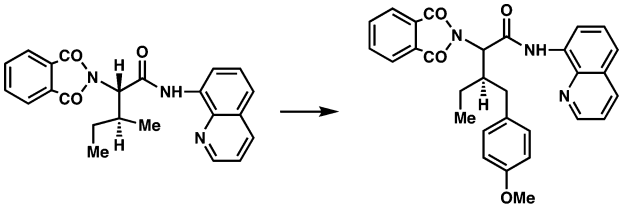


4b

12a, Ar = *p*-MeOC$_6$H$_4$

12b, Ar = C$_6$H$_5$

arylation conditions described just above, but with a modestly longer reaction time (2.5 h at 110 °C). The isoleucine substrate was cleanly transformed into the γ-CH_3 arylation product **14** in 87% yield. This result indicates that when the

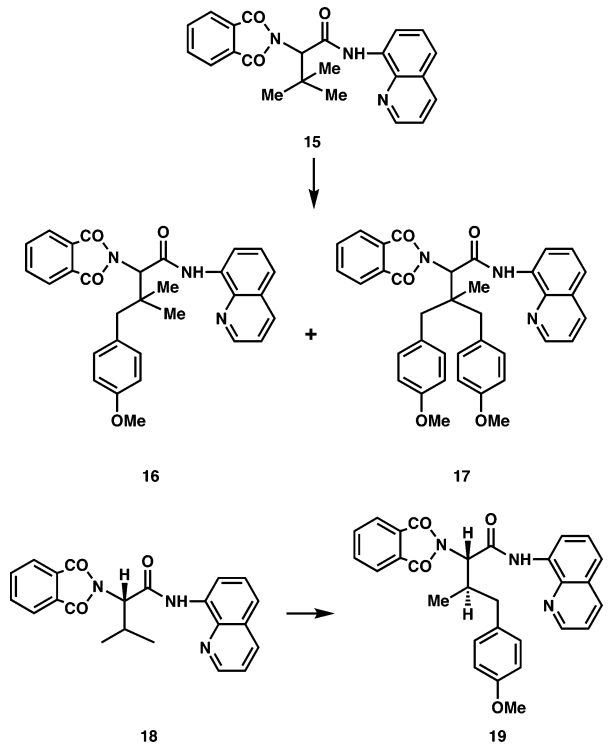


13 14

β-hydrogen is attached to a tertiary carbon the rate of C−H activation (i.e., insertion) by Pd is so attenuated that insertion into a γ-methyl C−H can compete. Obviously, the arylated isoleucine analogue **14** would not be easy to synthesize by other means. In extension of this result, we found that the *t*-leucine derivative **15** was smoothly transformed into a mixture of mono- and diarylated products **16** and **17** with *p*-iodoanisole (4 equiv) under the standard conditions after 3.5 h.

Finally, when the coupling reaction was applied to *N*-phthaloylvaline 8-aminoquinoline amide **18** and *p*-iodoanisole under the standard conditions (1.5 equiv of AgOAc, 20 mol % of $Pd(OAc)_2$, 4 equiv of *p*-iodoanisole at 110 °C for 3.5 h; no solvent), the γ-arylated product **19** was obtained in 85% yield. It is difficult to imagine another synthesis of **19** as simple as this.

The β-acetoxylation and γ-C−C coupling reactions described herein provide easy access to a broad range of



15

16 17

18 19

unnatural (*S*)-α-amino acids using readily available, naturally occurring (*S*)-α-amino acids as starting materials. This methodology and the previously described process of selective δ-halogenation of (*S*)-α-amino acid derivatives[1] open up new avenues of research in synthetic and biological chemistry.

Supporting Information Available: Experimental procedures and characterization data for the new compounds reported herein. X-ray crystallographic data for compounds **2** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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