A Versatile Tandem Catalysis Procedure for the Preparation of Novel Amino Acids and Peptides

Mark J. Burk,* Jeffrey R. Lee, and Jose P. Martinez

P. M. Gross Chemical Laboratory
Department of Chemistry, Duke University
Durham, North Carolina 27706

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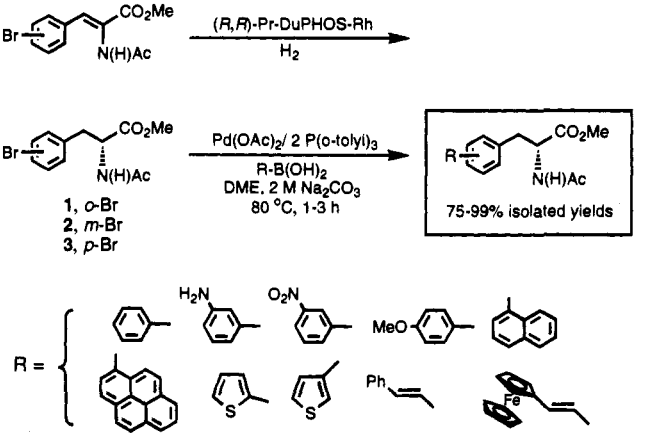
In addition to serving as valuable synthetic intermediates for the preparation of a plethora of biologically active compounds,[1] nonproteinaceous α-amino acids have been found to produce significant improvements in the biological properties of numerous peptide and peptidomimetic drugs.[2,3] Unfortunately, simple access to a broad range of novel α-amino acid derivatives remains limited, thus producing a bottleneck in many vital areas of research. We recently have developed a new class of asymmetric hydrogenation catalysts, DuPHOS-Rh, which provide a convenient route to a wide variety of novel, enantiomerically pure α-amino acid derivatives.[4] In terms of synthetic efficiency, however, asymmetric hydrogenation suffers the drawback that individual enamides must be prepared for each new α-amino acid that is desired. In an effort to further enhance the utility of our asymmetric hydrogenation process, we have developed a new two-step tandem catalysis procedure for the preparation of a diverse range of α-amino acids and peptides.

Our general strategy involves the use of our Et-DuPHOS-Rh- or Pr-DuPHOS-Rh-catalyzed α-enamide hydrogenations to produce functional α-amino acids which can serve as common intermediates from which a wide variety of substituted amino acid derivatives may be readily obtained through a second transition metal-catalyzed reaction. Thus, we initially have prepared enantiomerically pure (*R*)-*N*-acetyl methyl esters of *o*-bromo-, *m*-bromo-, and *p*-bromophenylalanine (**1**−**3**), which subsequently were employed in Pd-catalyzed cross-coupling reactions[5] with a variety of boronic acid derivatives (Scheme 1).[6]

Using standard Suzuki cross-coupling conditions[7] ($Pd(PPh_3)_4$ (5 mol %), 2M Na_2CO_3, C_6H_6, 80 °C, 16−36 h), we found we could introduce several unfunctionalized aromatic substituents such as phenyl, 1-naphthyl, and the fluorescent 9-pyrenyl group into each ring position of phenylalanine. The yields of these reactions were reasonable (60−90%), and no loss of enantiomeric purity was observed under these conditions.

Problems arose, however, in attempted coupling with heteroatom-containing and heterocyclic boronic acids, where yields generally fell to the 0−45% range. Recently, we have found that a catalyst system based on the addition of 2 equiv of tri(*o*-tolyl)phosphine to $Pd(OAc)_2$ appears to be ideal for the present bromophenylalanine/boronic acid couplings. Under these new conditions (5 mol % catalyst, DME, 2 M Na_2CO_3, 80 °C), the reactions outlined in Scheme 1 proceeded much faster (1−3 h) relative to Suzuki conditions, and isolated yields were high (75−99%) for virtually all boronic acids employed to date. In addition to phenyl, naphthyl, and pyrenyl groups, we now have been able to readily incorporate substituents such as 3-aminophenyl, 3-nitrophenyl, 4-methoxyphenyl, 2-thienyl, 3-thienyl, 2-phenylvinyl, and 2-ferrocenylvinyl into each position of the phenylalanine ring (Scheme 1).[8] No detectable racemization of the starting phenylalanine derivatives (**1**−**3**) or products was observed in these reactions. Similarly efficient cross-coupling reactions have been demonstrated with *N*-Boc-bromophenylalanine derivatives.

Scheme 1. Synthesis of Substituted Phenylalanine Derivatives via Tandem Catalysis Procedure



Our ability to prepare, through our hydrogenation reaction, a variety of uncommon (bromoaryl)alanines with high enantiomeric excesses (≥98.5% ee) greatly expands the versatility of our tandem catalysis approach. For example, we have prepared (*R*)-3,5-dibromophenylalanine, (*R*)-3-(4-bromo-2-thienyl)alanine, (*R*)-3-(5-bromo-2-thienyl)alanine, (*R*)-3-(5-bromo-2-furanyl)alanine, and (*S*)-3-(1-bromo-2-naphthyl)alanine derivatives. The availablility of these and similar (bromoaryl)alanine derivatives provides access to a wide range of novel α-amino acids through subsequent palladium-catalyzed cross-coupling reactions. It is important to note that both DuPHOS enantiomers are available[9] and allow the synthesis of either α-amino acid antipodes. Figure 1 shows representative examples that highlight the advantages of our synthetic method. Thus, we have employed the above (bromoaryl)alanines, the $Pd(OAc)_2$/P(o-tolyl)$_3$ catalyst, and previously mentioned boronic acids to prepare the *N*-acetyl methyl esters of 3,5-bis(3-thienyl)phenylalanine (**4**), 4-(2-ferrocenylvinyl)-2-thienylalanine (**5**), 5-(2-thienyl)-2-thienylalanine (**6**), 5-(3-aminophenyl)-2-thienylalanine (**7**), 5-(9-pyrenyl)-2-furanylalanine (**8**), and the interesting 1-(1-naphthyl)-2-naphthylalanine (**9**) (initially obtained as a 4:1 mixture of diastereomers; single diastereomer after a single recrystallization).[8]

In the design and optimization of peptide and peptidomimetic therapeutics, numerous variations of a particular amino acid moiety are often necessary in order to obtain optimum activity, bioavailablity, and resistance to metabolic breakdown.[10,11] Moreover, such structure−activity relationship (SAR) studies involving peptides generally require the synthesis of the same

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(8) All new compounds were completely characterized by ^1H and ^{13}C NMR and exhibited the expected C, H, N elemental analyses and/or HRMS.

(9) Both (*R*,*R*)-Et-DuPHOS and (*S*,*S*)-Et-DuPHOS are commercially available from Strem Chemical Co., Newburyport, MA.

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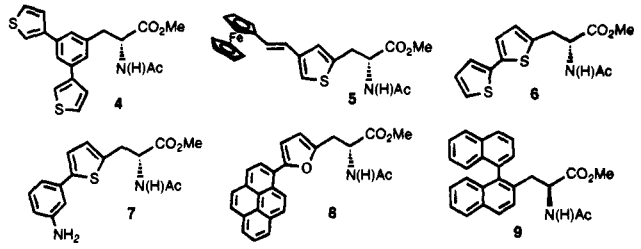


Figure 1. Novel α-amino acid derivatives accessible through tandem catalysis procedure.

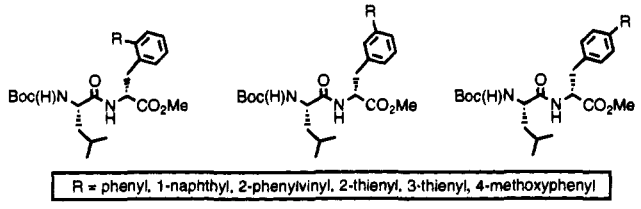


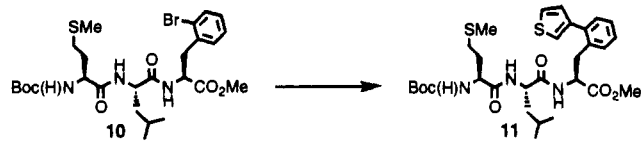
Figure 2. Array of 18 dipeptides prepared through cross-coupling strategy.

large number of individual peptides as α-amino acid variants to be examined. A much more efficient strategy would be to incorporate a functional amino acid residue into a peptide such that a large number of new peptides could be prepared in a multiple, simultaneous fashion from a single peptide intermediate. Toward this goal, we have extended our cross-coupling methodology to peptides.

To demonstrate the principle, initial studies focused on the rapid synthesis of an array of 18 analogous dipeptides from the three intermediates *N*-Boc-(*S*)-Leu-(*R*)-*o*-Br-Phe-OMe, *N*-Boc-(*S*)-Leu-(*R*)-*m*-Br-Phe-OMe, and *N*-Boc-(*S*)-Leu-(*R*)-*p*-Br-Phe-OMe (Figure 2). The dipeptides were prepared through standard solution phase techniques[12] involving DCC/HOBt-mediated coupling between *N*-Boc-(*S*)-Leu and the N-deprotected (*R*)-bromophenylalanine methyl esters. Using the $Pd(OAc)_2/P(o\text{-tolyl})_3$ catalyst for cross-coupling with boronic acids, we readily obtained the desired dipeptide array through introduction of the substituents phenyl, 1-naphthyl, 2-phenylvinyl, 2-thienyl, 3-thienyl, and 4-methoxyphenyl into the ortho, meta, and para positions of the three dipeptides, respectively. These reactions proceeded rapidly (2−4 h) and gave high yields (80−95%) of diastereomerically pure dipeptides.

Finally, we have begun to apply our cross-coupling method to the preparation of new chemotactic peptide analogs. The chemotactic peptide *N*-formyl-Met-Leu-Phe has been found to specifically activate neutrophil leukocytes for chemotaxis and lysosomal enzyme release.[13,14] There currently is great interest in the synthesis of chemotactic peptide analogs for the design of receptor agonists and antagonists.[15,16] Accordingly, we have prepared *N*-Boc-Met-Leu-*o*-Br-Phe-OMe (**10**) using standard solution phase techniques (DCC, HOBt) and subjected it to our cross-coupling conditions. Smooth conversion to the new chemotactic peptide analog **11** was accomplished in 71% isolated yield (Scheme 2).

Scheme 2. Preparation of New Chemotactic Peptide Analog



We have outlined a new two-step tandem catalysis procedure that permits the efficient and rapid synthesis of a wide range of diverse α-amino acids. We also established the viability of peptides as substrates in our cross-coupling reactions and demonstrated tolerance to potentially troublesome residues such as methionine. Extension of this work to other functional amino acids and peptides, as well as to other cross-coupling partners, currently is being pursued. We feel that this new method shows great promise both for the simple introduction of novel pharmacologically active functionality into amino acids and peptides and for the rapid construction of large arrays of analogous peptides for SAR studies.

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Supplementary Material Available: Experimental details, including preparations and spectral and analytical data for all new amino acid and peptide products (16 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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