

Sequential Allylic C–H Amination/Vinylic C–H Arylation: A Strategy for Unnatural Amino Acid Synthesis from α -Olefins

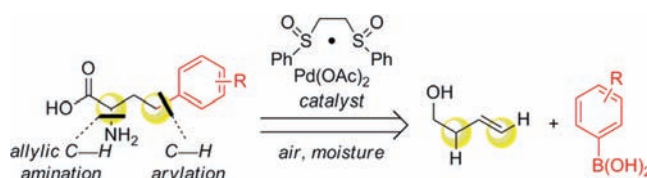
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ABSTRACT



Tandem reaction sequences that selectively convert multiple C–H bonds of abundant hydrocarbon feedstocks to functionalized materials enable rapid buildup of molecular complexity in an economical way. A tandem C–H amination/vinylic C–H arylation reaction sequence is described under Pd(II)/sulfoxide-catalysis that furnishes a wide range of α - and β -homophenylalanine precursors from commodity α -olefins and readily available aryl boronic acids. General routes to enantiopure amino acid esters and densely functionalized homophenylalanine derivatives are demonstrated.

Selective methods for C–H oxidation,^{1,2} amination,^{1,3} alkylation,^{1,4} and dehydrogenation^{1,5} make the direct installation of functional groups into preassembled hydrocarbon frameworks possible. Such reactions enable orthogonal routes to complex molecules from those that rely upon C–C bond forming reactions between preoxidized fragments and provide opportunities to use simple

hydrocarbons as starting materials.^{2e–g,n} Of these, α -olefins are among the most abundant and inexpensive feedstock commodity chemicals. Methods that selectively functionalize one or more of the three distinct types of C–H bonds present in α -olefins (i.e., aliphatic, allylic, and vinylic) enable the rapid buildup of molecular complexity from inert functional groups with minimal manipulations. Herein, we report a one-pot allylic C–H amination/vinylic C–H arylation of α -olefins to furnish unnatural amino

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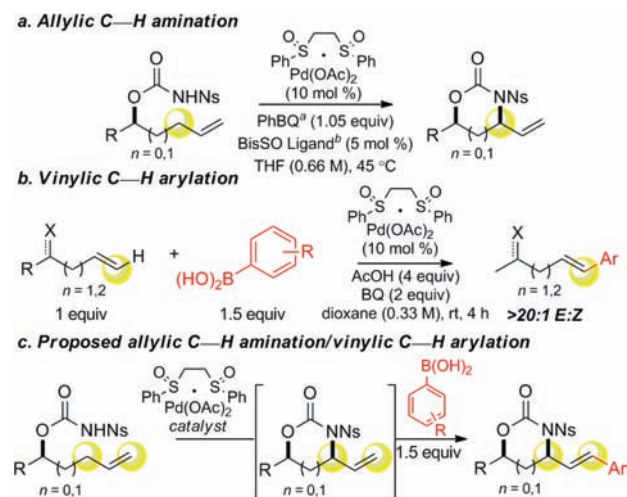
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acid precursors rapidly that has been achieved using Pd(II)/sulfoxide-catalysis.

Within recent years, our laboratory has introduced electrophilic Pd(II)/sulfoxide catalysis as a general platform for allylic C–H activation that enables direct and selective allylic esterification,^{2a–h} amination,^{3b–g} alkylation⁴ and dehydrogenation⁵ of α -olefins. Additionally, we have demonstrated that sulfoxide ligands promote highly selective Pd(II)-mediated vinylic C–H arylations (Heck-type coupling) under analogous oxidative conditions.^{2d,6,7} Exploiting these parallel conditions, we invented a sequential, one-pot Pd(II)-sulfoxide-catalyzed allylic esterification/vinylic arylation of α -olefins (Scheme 1).^{2d} We postulated that analogous sequential reactions would be possible with allylic C–H amination reactions, thus facilitating a rapid and diversifiable route to densely functionalized carbon skeletons such as those found in α - and β -amino acids from simple α -olefin starting materials. Herein, we report a one-pot Pd(II)/sulfoxide-catalyzed allylic C–H amination/vinylic C–H arylation that starts with commodity chemical 3-butenol to access a wide range of homophenylalanine (hPhe) derivatives rapidly. Additionally, by switching to 4-pentenol, analogous β -amino acid precursors may be obtained.

Unnatural homophenylalanine (hPhe) amino acids are important building blocks for pharmaceutical research as exemplified by the commercial angiotensin-converting

Scheme 1. C–H Amination Route to Homophenylalanines^a



^a PhBQ = phenyl-benzoquinone; BisSO ligand = 1,2 bis(phenyl-sulfinyl)ethane (refs 3b and 3c).

enzyme inhibitors (“ACE inhibitors”) benazepril,⁸ enalapril,⁹ imidapril,¹⁰ lisinopril¹¹ and temocapril.¹² Although a variety of chemical methods exist for the synthesis of hPhe derivatives that include Suzuki coupling,¹³ diastereoselective Michael addition¹⁴ and asymmetric hydrogenation reactions,¹⁵ these known routes generally rely upon lengthy reaction sequences from chiral pool materials and often suffer limited scope. We herein report the use of readily available, commercial α -olefins and arylboronic acids as suitable starting materials for the rapid synthesis of a wide range of unnatural homophenylalanine (hPhe) amino acids.

While it was known that palladium bis-sulfoxide catalyst **1** could separately catalyze both the desired allylic C–H amination and vinylic C–H arylation reactions, it was unclear if: (1) such a sequence would proceed with high yields without requiring additional Pd(II)/sulfoxide catalyst **1** loadings, and (2) allylic oxazolidinones would serve as nonresonance directing groups to promote high regio- and *E:Z* stereoselectivities for vinylic arylation. Palladium(II)-Pd(0) catalytic cycles generally suffer from rapid catalyst decomposition through Pd(0)-aggregation pathways because soft donor ligands (e.g., phosphines) that are typically used to prevent aggregation are incompatible with oxidative conditions.¹⁶ It was therefore critical to minimize reaction times for the first step of the proposed tandem

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sequence so that enough active palladium catalyst remained to promote the vinylic C–H arylation. We had previously shown that by switching from *N*-tosyl- to more acidic *N*-nosylcarbamate nucleophiles, reactivity for intramolecular allylic C–H aminations could be significantly enhanced.^{3c,g} We were delighted to find that using 10 mol % Pd(II)/sulfoxide catalyst **1** the *N*-nosylcarbamate substrate **2** reached complete conversion in 5 h versus incomplete conversion (80%) in 72 h for the analogous *N*-tosylcarbamate. Subsequent addition of phenylboronic acid at fragment coupling quantities (1.5 equiv), with no additional catalyst, afforded styryl-oxazolidinone **3** in good yield (79%) and outstanding regio- and *E:Z* selectivities (> 20:1, Scheme 2).

Further exploration of scope revealed that a sequential allylic C–H amination/vinylic C–H arylation reaction could be realized using just 10 mol % **1** with *N*-nosylcarbamate **2** substrate and a wide range of arylboronic acids to afford styryl-oxazolidinones in good yields (65–87%) and outstanding regio- and *E:Z* selectivities (> 20:1, Scheme 2). Methyl- and methoxy substituted homophenylalanine (hPhe) precursors could be accessed in consistently high yield independent of the site of substitution on the aromatic ring (compounds **3–8**). Importantly, these substituted hPhe derivatives are intermediates en route to

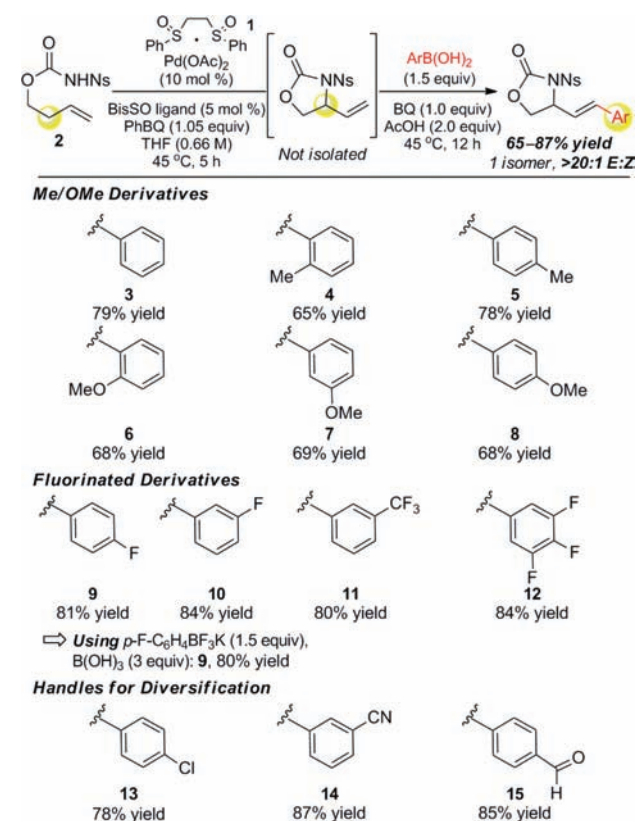
compounds found in metalloproteinase inhibitor (for compounds **4** and **6**)¹⁷ and ACE inhibitor programs (for compound **8**).¹⁸ This method also enabled the rapid synthesis of fluorinated styryl-oxazolidinones **9–12**. Structurally diverse fluorinated compounds are valuable building blocks for medicinal chemistry research,¹⁹ for example, hPhe analogs that may be derived from compounds **9**, **10**, **11** have been used on β -secretase inhibitor programs,²⁰ and to prepare immunosuppressive adjuncts.²¹ In addition, this method allows access to novel hPhe compounds that have not yet been reported, such as compounds derived from **12**.

Functional groups that can be used as handles for further diversification (compounds **13–15**) are also tolerated, most notably the aryl chloride and bromide in compounds **13** and **21** (Scheme 5) which would be incompatible with traditional Pd(0) based Heck methods. Additionally, robust organotrifluoroborates can be employed as alternatives to boronic acids²² in this reaction with the use of B(OH)₃ as an activator (compound **9**).⁶ Notably, the Pd/sulfoxide-catalyzed allylic C–H amination/vinylic C–H arylation reaction is operationally simple, proceeding under ambient atmosphere with no precautions taken to exclude moisture.

We were further delighted to find that this tandem process could be extended to our previously developed 1,3-amination system, thus enabling the synthesis of β -amino acids through this same strategy (Scheme 3). Due to the higher kinetic barrier for 6- versus 5-membered ring formation, the amination step took 13 h (rather than 5 h) to reach complete conversion. Key to maintaining good catalyst regeneration under prolonged reaction times was the addition of catalytic *p*-nitrobenzoic acid, which we have previously shown to promote Pd(0) oxidation.^{3c} Subsequent addition of 4-formylphenylboronic acid, with no additional catalyst, afforded styryl-oxazolidinone **17** in good yield (73%) and outstanding regio- and *E:Z* selectivities (> 20:1).

With the ability to access a variety of homophenylalanine core structures efficiently through a novel C–H amination strategy, we next sought to establish a route to transform the key oxazolidinones into the desired amino acid products in high enantiomeric excess (Scheme 4). Thus, the nosyl group in **18** was first removed under mildly nucleophilic conditions with potassium thiophenolate (Scheme 4). The olefin was then hydrogenated (H₂, Pd/C), the amino alcohol unmasked under basic conditions (LiOH), and the amine protected to furnish intermediate **19** in 76% yield over 4 steps. Pyridinium dichromate (PDC) oxidation of the primary alcohol to the acid, followed by Boc removal

Scheme 2. Scope of the Sequential Allylic C–H Amination/Vinylic C–H Arylation Reaction^a



^a Yields reported are isolated, and the average of at least 2 independent runs. All products were isolated as a single regio- and olefin *E:Z* isomer.

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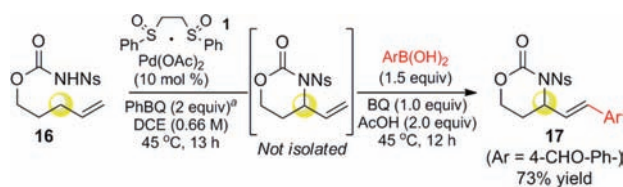
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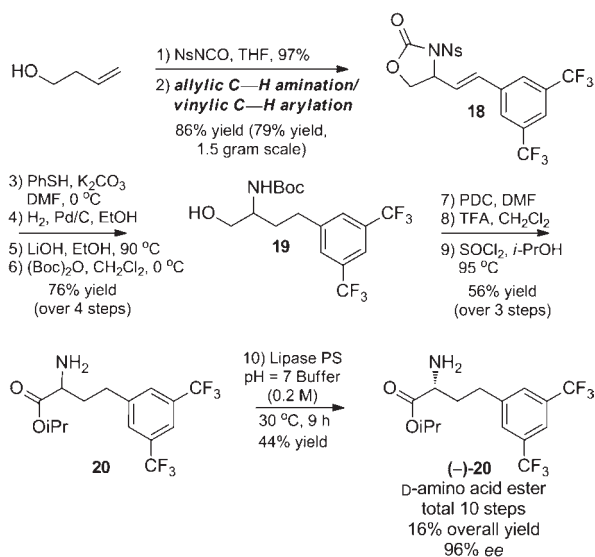
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Scheme 3. Sequential Allylic C–H Amination/Vinylic C–H Arylation Reaction toward β -Amino Acid Motif^a



^a Additives: *p*-nitrobenzoic acid (10 mol %), BisSO ligand (5 mol %).

Scheme 4. Synthesis of Enantiopure Homophenylalanine Derivative



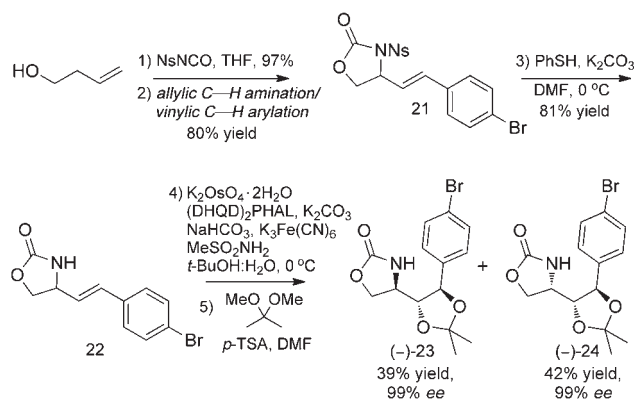
with trifluoroacetic acid (TFA) and formation of the isopropyl ester afforded **20** (56% over 3 steps), a suitable precursor for subsequent enzymatic resolution. Lipase PS mediated kinetic resolution²³ of racemate (\pm)-**20** afforded enantiopure aminoester (–)-**20** in a total of 10 steps and 16% overall yield from the commercially available α -olefin 3-butenol.

While this route provides an efficient means of accessing homophenylalanine derivatives, we recognized that additional structural complexity could be gained by elaborating the internal *E*-olefin functional groups generated via the vinylic C–H arylation. We were pleased to find that the Sharpless asymmetric dihydroxylation (SAD)²⁴ could be used to this end (Scheme 5). In fact, SAD of oxazolidinone **21** followed by protection of the crude mixture of diols afforded the two diastereomers (–)-**23** and (–)-**24** in 39% and 42% isolated yield of each in >99% ee. The absolute stereochemistry of (–)-**23** was confirmed by X-ray crystallography (see Supporting Information). In only four steps from commercial starting material, we are able to forge

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Scheme 5. Access to Functionalized Homophenylalanine Derivatives through Sharpless Asymmetric Dihydroxylation



four new bonds, selectively introducing new functional groups at three of the four carbons of 3-butenol. The ease with which densely functionalized building blocks are constructed from robust, commercial hydrocarbons highlights the power of selective C–H functionalization methods.

In conclusion, we have demonstrated a sequential C–H amination/vinylic C–H arylation reaction proceeding via Pd(II)/sulfoxide catalysis that transforms commodity α -olefins into α - and β -homophenylalanine precursors. This work demonstrates the power of sequential, selective C–H functionalization methods to incorporate functional group handles rapidly onto simple and inexpensive hydrocarbon feedstocks, thereby enabling their use as starting materials for medicinally important compounds.

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Supporting Information Available. ¹H and ¹³C NMR, IR and HRMS data and experimental procedures for compounds **2–24**. X-ray data for compound (–)-**23**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Note Added after ASAP Publication. The version published ASAP on February 24, 2012 contained errors in Scheme 5 and in the Supporting Information. The correct version reposted on February 28, 2012.

The authors declare no competing financial interest.