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Palladium(II)-Catalyzed Cross-Dehydrogenative Coupling (CDC) of *N*-Phthaloyl Dehydroalanine Esters with Simple Arenes: Stereoselective Synthesis of *Z*-Dehydrophenylalanine Derivatives

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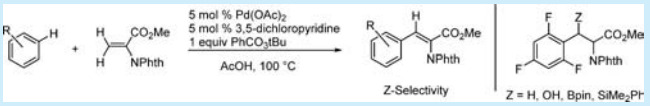
Supporting Information

ABSTRACT: Pd(II)-catalyzed cross-dehydrogenative coupling (CDC) of methyl *N*-phthaloyl dehydroalanine esters with simple aromatic hydrocarbons is reported. The reaction, which involves the cleavage of two sp^2 C−H bonds followed by C−C bond formation, stereoselectively generates highly valuable *Z*-dehydrophenylalanine skeletons in a practical, versatile, and atom economical manner. In addition, a perfluorinated product was expediently converted into important nonproteinogenic amino acid building blocks through copper-catalyzed conjugate additions of boron, silicon, and hydride moieties.



α,β-Dehydroamino acids are nonproteinogenic residues that occur in both natural and synthetic peptides; they are known to introduce side-chain and backbone conformational constraints within peptides, thus enhancing the proteolytic stability.[1] The *β*-unsubstituted, dehydroalanine derivatives are useful building blocks to design novel *α*-amino acids and heterocycles,[2] and their importance as synthetic intermediates for labeling and post-translational modification of proteins and peptides is also well documented.[3] Trisubstituted alkenes containing at least one (large) aromatic ring at the *β* carbon, known as dehydrophenylalanine derivatives, have been well-studied, resulting in peptides with increased rigidity due to high levels of 1,3A-strain; design rules governing their inclusion in secondary structures have been established.[4] Recent discoveries of bioactive natural products containing these residues (Figure 1) combined with the structural/chemical features they impart to peptides provide ample justification for searching for new methods for their efficient synthesis and synthetic modification.[5]

Although classic Mizoroki−Heck type arylation of dehydroalanine derivatives with aryl halides or triflates has been reported,[2] to the best of our knowledge, a similar type of arylation of dehydroalanine with ArH, the Fujiwara−Moritani reaction,[6] and more generally cross-dehydrogenative coupling (CDC)[7] have been much less documented.[8] Although CDC is sometimes also called an oxidative or dehydrogenative Heck reaction,[9] its mechanism is very different because it involves C−H activation of ArH. In fact, CDC reactions allow for more efficient ways to construct carbon−carbon (C−C) bonds by the connection of two different C−H bonds under oxidative conditions. In contrast to traditional cross-coupling reactions, CDC bypasses the need for prefunctionalized coupling partners, reduces the number of steps to the target molecule, and produces, in theory, only water as a byproduct. Despite these apparent advantages, challenges still remain with regard to reactivity, practicality, and scope. In recent years, much effort has been made toward the palladium(II)-catalyzed oxidative coupling of arenes and alkenes,[10] in particular simple acrylates.[11] Although these studies showcase the ability of palladium to perform arene alkenylation, only a few examples of successful arylation have been reported using di- (in particular 1,1-disubstituted) or trisubstituted olefins.[12] The problems with the latter reaction can be rationalized by the low reactivity, probably due to steric congestion around the olefin, and/or the fact that they are not accessible enough to undergo the required *syn*-addition carbopalladation. In addition, even after 1,2-migratory insertion of the Pd−aryl moiety into the olefin, the resulting intermediate, containing a palladium on a quaternary center, is conformationally restricted from undergoing subsequent *β*-hydride elimination with the benzylic hydrogen atoms, rendering uncertain the stereochemical outcome of the C═C bond of the isolated coupling product. Therefore, there is a significant need to develop systems to facilitate the direct coupling of an arene to multisubstituted, functionalized alkenes.

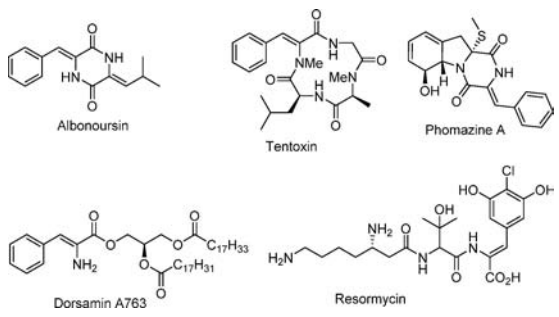


Figure 1. Some examples of natural products containing dehydrophenylalanine.

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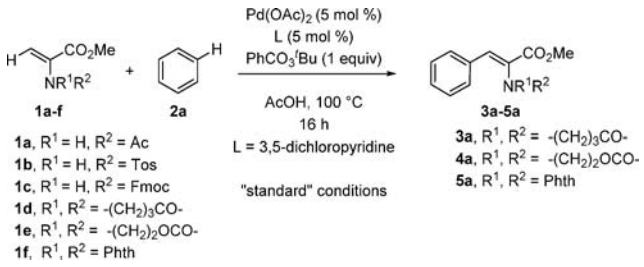
Therefore, we directed our efforts toward the research of a simple, highly reactive catalytic system that can activate the C−H bonds of the arene used, would allow the coordination/insertion to the sterically congested double bond of the dehydroalanine substrate, and would afford the coupled product in a stereoselective manner. The copper-catalyzed conjugate addition of the dehydrophenylalanine product also has been demonstrated to afford functionalized amino acids bearing a hidden reactive center such as silicon or boron.

Our studies began by attempting the proposed stereoselective CDC of benzene (**2a**) with different dehydroalanine substrates (**1a−f**), using previously established catalytic conditions[11] that use $Pd(OAc)_2$ as the catalyst together with inexpensive *tert*-butylperoxybenzoate ($PhCO_3{}^tBu$) as the terminal oxidant, commercially available 3,5-dichloropyridine as the ligand (1:1 with Pd), and acetic acid as the solvent at 100 °C. Initially, *N*-monoprotected dehydroalanines **1a−c** (Table 1, entry 1−3) all failed to give the desired products, while *N*,*N*-disubstituted dehydroalanines **1d** and **1e** afforded the target product albeit in a moderate yield (Table 1, entries 4 and 5). In contrast, the *N*-phthaloyl protected dehydroalanine (**1f**) was successfully coupled with benzene (**2a**) using 5 mol % $Pd(OAc)_2$ to yield (*Z*)-methyl 2-(1,3-dioxoisoindolin-2-yl)-3-phenyl acrylate (**5a**) exclusively, in excellent yield (Table 1, entry 6).[13] No formation of diphenylated was observed, indicating disfavored electronic and steric properties of the product to a second substitution. Resubjecting product **5a** to the reaction conditions did not lead to any further phenylation or change the diastereomeric ratio. No addition products were observed.[14] The alkene geometry of **5a** was confirmed by comparison to the literature.[15] Thus, that a single geometric isomer was obtained is quite reasonable, by the well-accepted mechanism of the Heck reaction, and considering the reaction conditions should favor thermodynamic control.[16] Remarkably, the catalytic system maintained good performance when the reaction temperature was lowered to 50 °C, giving the product in moderate yield (Table 1, entry 7). In the absence of acetic acid and only benzene as the solvent, the conversion of the reaction dropped, although a decent yield was maintained (Table 1, entry 8). The coupling product **5a** was isolated in moderate yield when the sealed reaction vessel was heated under microwave irradiation (Table 1, entry 9). We also examined aerobic C−H arylation reactions using $NaNO_3$ as the redox cocatalyst (Table 1, entry 10).[17] Despite the fact that the product was obtained in moderate yield and the mass recovery of the starting material dehydroalanine **1f** was low, the results showed the possible utilization of dioxygen as the terminal oxidant, redox-active NOx ligands, and Pd catalysis. Finally, in the absence of the 3,5-dichloropyridine ligand, the reaction was much slower and afforded a lower product yield (Table 1, entry 11); whereas in the absence of $Pd(OAc)_2$ or oxidant, the reaction failed to provide **5a**, and **1f** was recovered quantitatively (Table 1, entries 12 and 13).

The new catalytic C−H arylation reaction of *N*-phthaloyl dehydroalanine displayed a broad scope, as demonstrated by successful transformations on substrates containing simple alkyl chains of varying substitution patterns, protected hydroxyl functionalities, carbonyl motifs, and halide-containing aromatics (Scheme 1). Electron-rich arenes such as toluene (**2b**), anisole (**2c**), *p*-xylenes (**2d**), and *p*-methoxyanisole (**2e**) afforded good yields (74−87%) of the corresponding dehydrophenylalanine derivative products (**5b−e**). Also, polyfluoroarenes such as

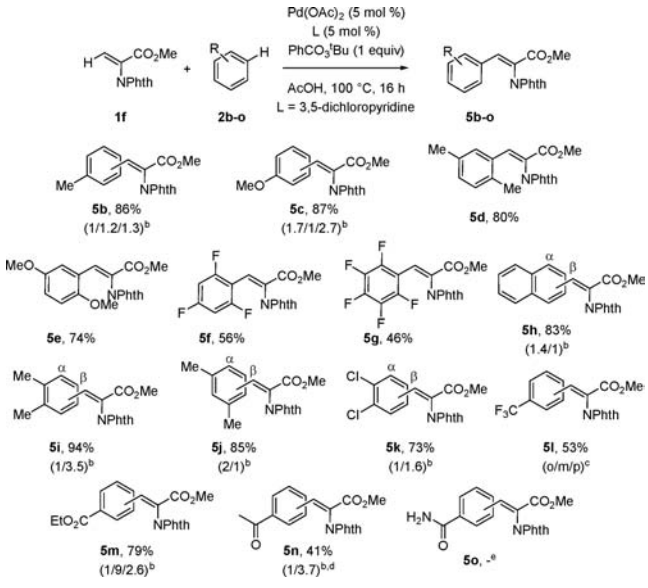
Table 1. Cross-Dehydrogenative Coupling of Benzene with *N*-Protected Dehydroalanine (DHA) Derivatives (1a−f): Effect of Reaction Parameters[a]



entry	DHA	variation from the "standard" conditions	conversion (%)	yield **5a** (%)[b]
1	**1a**	none	100	–[c]
2	**1b**	none	100	–[c]
3	**1c**	none	100	–[c]
4	**1d**	none	100	**3a** (66)[d]
5	**1e**	none	100	**4a** (35)[d]
6	**1f**	none	100	(95)[d]
7	**1f**	50 °C instead of 100 °C	55	41
8	**1f**	no AcOH	67	65
9	**1f**	MW instead of 100 °C	79	(46)[d]
10	**1f**	0.3 equiv of $NaNO_3/O_2$ instead of $PhCO_3{}^tBu$	55	15
11	**1f**	no 3,5-dichloropyridine	55	50
12	**1f**	no $Pd(OAc)_2$	5	–[c]
13	**1f**	no $PhCO_3{}^tBu$	10	7

[a]Reaction conditions: DHA (**1a−f**) (0.3 mmol), benzene (**2a**) (0.3 mL). [b]Determined by ^1H NMR analysis of the crude reaction mixture. [c]No formation of product was observed. [d]Value in parentheses represents isolated yields.

Scheme 1. Scope of Cross-Dehydrogenative Coupling of *N*-Phthaloyl Dehydroalanine Methyl Ester (1f) with Arene Derivatives (2b−o)[a]



[a]Reaction conditions: **1f** (0.3 mmol), for arenes **2b−k** (0.3 mL), for arenes **2l−o** (1.1 mL). [b]Product ratios were determined from isolated mixtures. The ratio is reported as *o*/*m*/*p* or *α*/*β*. [c]Indistinguishable mixture. [d]The ratio is reported as *o*/*m*. [e]No product formation was observed.

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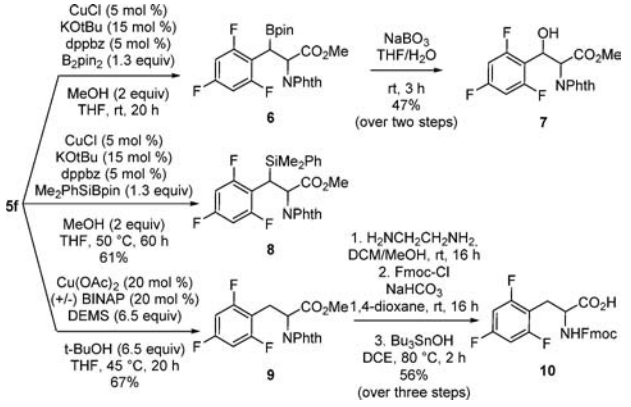
1,3,5-trifluorobenzene (**2f**) and pentafluorobenzene (**2g**) furnished the perfluorated dehydroamino acid coupling products (**5f**, **g**) in decent yields. Naphthalene (**2h**) and other disubstituted arenes (**2i**–**k**) also provided good results; however, a mixture of isomeric products (**5h**–**k**) in 73–94% yield and a ratio from 2:1 to 1:3.5 resulted. Finally, challenging substrates for C–H olefination such as electron-deficient aromatics such as trifluorotoluene (**2l**), ethyl benzoate (**2m**), and acetophenone (**2n**) proceeded in moderate to good yields (41–79%), preferentially affording the meta-olefinated product, in agreement with other studies.[10,11] Interestingly, the reaction of benzamide (**2o**) completely consumed the starting dehydroalanine **1f**, but with no formation of coupled products; whereas with 2-phenylpyridine and acetanilide (data not shown), the two most used/popular aryl-containing directing groups to achieve proximity-driven C–H olefination, a very low conversion and no formation of the desired product resulted when treated with **1f** under standard reaction conditions.[18]

In general, the CDC strategy provides a convenient gateway to a wide range of subsequent transformations by manipulation of the intrinsic functionality within the products and can be used to readily access the core framework of various relevant molecules and ligands for biological systems. Typically, dehydroamino acids serve as precursors to saturated amino acids, and increasing the availability of unnatural and unconventional amino acid derivatives remains an important goal. Because of the important role that fluorinated compounds play in pharmaceuticals, agrochemicals, and materials science,[19] we chose compound **5f** for further useful manipulation by the copper-catalyzed conjugate addition reaction (Scheme 2). The preparation of compound **5f** on a larger scale under the above standard conditions afforded 60% of the isolated product with the same complete *Z*-diastereoselectivity.

Scheme 2. Transformations of the Cross-Dehydrogenative Coupling Product 5f



Using conditions reported by us and others,[20] we were able to transfer boron and silicon nucleophiles regioselectively onto fluorinated dehydrophenylalanine **5f** to give *β*-boronated and silylated orthogonally *N*- and *C*-protected amino acids **6** and **8**, as a mixture of diastereomers (2:1). By simple oxidation with Borax, the hydroboration product was expediently converted into a valuable *β*-hydroxy-*α*-amino acid derivative (**7**).

Next, we turned our attention to metal-catalyzed hydrogenation of **5f**. We expected that hydrogenation of this substrate would be exceptionally challenging due to the increased steric bulk around the olefin and the reduced propensity of phthaloyl vs acetyl to associate with the metal catalyst; indeed, subjecting substrate **5f** to the standard conditions for the *N*-acetyl-protected substrates provided no conversion to product.[21] Moreover, the use of Pd/C (75 psi H_2, 35 °C, EtOAc) failed, with the double bond untouched. Given the good propensity of **5f** for conjugate addition, we decided to explore highly regioselective copper-catalyzed conjugate reduction using the copper-hydride catalyst developed by Lipshutz and Buchwald.[22] Although activated olefins, such as enoates, enones, and vinylnitriles, have been thoroughly investigated as substrates for CuH catalysis, dehydrophenylalanine as a substrate has not been reported previously. Treatment of a THF/*t*BuOH solution of **5f** with the active LnCuH species, formed by reacting $Cu(OAc)_2$, racemic BINAP, and a superstoichiometric amount of the hydrosilane DEMS = $(EtO)_2MeSiH$, at 45 °C for 48 h gave the desired reduced product **9** in excellent yield. In response to needs for new unnatural amino acids, the fluorinated saturated bisprotected amino acid **9** was easily converted into an interesting amino acid building block for solid-phase peptide synthesis. The phthalimide group was removed in the presence of ethylenediamine to generate the free amine, which was subsequently converted to the Fmoc-protected amino ester. Finally, the ester was hydrolyzed to give the desired amino acid **10** in 56% overall yield.[23] The convergent nature of this transformation should lend itself to the preparation of unnatural phenylalanine derivatives for use in a broad array of synthetic and biological applications.

In conclusion, we have developed an operationally simple protocol involving a Pd-catalyzed dehydrogenative Heck coupling strategy for the synthesis of a range of highly substituted dehydrophenylalanine derivatives (**5a**–**n**) with complete stereoselectivity around the double bond from unfunctionalized and commercially available starting materials. Importantly, this "green" CDC protocol for the synthesis of dehydrophenylalanine derivatives circumvents the limited availability, problematic synthesis, and higher cost of aryl halide precursors (or their equivalents) and/or stoichiometric waste products. In addition, we anticipate that the distinct reactivity of dehydrophenylalanine revealed in the current reaction manifold, the copper-catalyzed boryl-, silyl-, and hydrocupration followed by protonation, will inspire further advances in a range of functionalization processes using these highly substituted dehydrophenylalanine derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01255.

Experimental procedures, compound characterizations, and copies of $^1H/^{13}C$ NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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