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Nonnatural Amino Acid Synthesis by Using Carbon-Hydrogen Bond Functionalization Methodology

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Keywords

palladium; C-H activation; amino acids; C-C coupling

During the last years, transition-metal-catalyzed carbon-hydrogen bond functionalization has witnessed an explosive growth.[1] The use of C-H bond as a functional group is appealing because of shortening of reaction pathways and simplification of retrosynthetic analyses. However, most of the reports that deal with carbon-hydrogen bond conversion to carbon-carbon bonds involve either methodology development or mechanistic investigations. The applications in synthesis of natural products or their analogues are rare.[2] The limited use may be explained by the following issues. First, methods that result in functionalization of alkane C-H bonds are relatively rare.[3] Second, harsh reaction conditions are typically used that may be incompatible with sensitive functionalities. Third, methods often lack generality and require non-removable directing groups.

We have reported the β-arylation of carboxylic acid and γ-arylation of amine derivatives by employing an 8-aminoquinoline or picolinic acid auxiliary, catalytic $Pd(OAc)_2$, and an aryl iodide coupling partner (Scheme 1).[4a] Subsequently, several other auxiliaries were investigated for carboxylic acid β-arylation.[4b] Use of 2-thiomethylaniline auxiliary affords selective monoarylation of methyl groups. In contrast, use of 8-aminoquinoline auxiliary allows either diarylation of methyl or monoarylation of methylene groups. The arylation regioselectivity is determined by formation of double five-membered chelate **1**.

Several other groups have recently used these directing groups in synthesis of natural products.[5] Corey has used the 8-aminoquinoline auxiliary to arylate sp^3 C-H bonds in amino acid derivatives.[5a] However, monoarylation of alanine derivatives was not demonstrated and stereochemical integrity of arylation products as well as directing group removal was not reported. Developing new methodology for unnatural amino acid synthesis is important since they are used in drug discovery, protein engineering, peptidomimetics, glycopeptide synthesis, and click chemistry in biologically relevant systems.[6–7] Methods for preparation of chiral nonracemic unnatural α-amino acids involve synthesis of racemates followed by resolution, use of chiral auxiliaries, asymmetric hydrogenation, and biological approaches.[8] A general method for unnatural amino acid synthesis from chiral pool would expand the toolbox that is available for their preparation. We report here a method of

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palladium-catalyzed synthesis of protected unnatural amino acids by C-H bond functionalization that employs readily available starting materials derived from chiral pool.

The functionalizaton of amino acid C-H bonds requires installation of a directing group and protection of the amino group. Phthaloyl group was chosen for protection of the amino functionality.[9] Directing group was installed by reacting phthaloylamino acid chlorides[10] with 8-aminoquinoline or 2-thiomethylaniline. *N*-Phthaloylalanine derivative **2** was arylated by PhI in the presence of a palladium catalyst and base. Subsequently, directing group was removed by treatment with BF_3*Et_2O in methanol at 100 °C (Table 1).[11] Nearly identical enantiomeric excess of **4** was observed by employing AgOAc, $AgOCOCF_3$, or CsOAc bases at 60–70 °C (entries 3–8). Higher reaction temperatures resulted in erosion of product enantiomeric excess (entries 1, 4, 9), as did addition of pivalic acid (entry 2). The optimal combination of yield and enantiomeric excess was obtained by employing palladium acetate catalyst in combination with AgOAc at 60 °C (entry 5).

Use of 2-thiomethylaniline derivative allows for a selective monoarylation of methyl group in **2** (Scheme 2). Arylation of **2** by iodobenzene affords **3** in 78% yield. 4-Methoxyiodobenzene is reactive and the arylation product **5** was isolated in 68% yield. 2-Iodonaphthalene and 2-iodobenzothiophene afforded the products in good yields. β-(2-Naphthyl)alanine-containing peptides are highly specific Pin1 inhibitors.[12] Interestingly, 3-iodo-1-methylindole can be coupled with **2** to give an *N*-methylated tryptophan derivative **8** in 61% yield. An azido functionality is tolerated and 3-azidophenylalanine derivative **9** was obtained in 81% yield. Thus, a wide variety of substituted phenylalanines can be made from a readily available, single starting material **2** in a convergent fashion. Two of the arylated derivatives were subjected to cleavage of directing group. *N*-Phthaloylphenylalanine methyl ester **4** was obtained in 87% yield and 90% ee. The benzothiophene derivative **10** was obtained in 80% yield.

8-Aminoquinoline directing group can be used for diarylation of methyl and monoarylation of methylene functionalities (Scheme 3). Diarylation of **11** was accomplished by 3,4-dimethyl-1-iodobenzene and 4-iodobenzoic acid ethyl ester and the products **12** and **13** were isolated in excellent yields. Interestingly, arylation of methylene groups occurs with high diastereoselectivity favoring the anti diastereomers. Protected phenylalanine can be arylated by 4-iodoanisole to give 91% of the product **14** with crude diastereomer ratio 24:1. Similarly, arylation by 2-iodothiophene results in formation of a single diastereomer **15** in 95% yield. Protected lysine can be arylated by 4-iodoanisole and 2-iodothiophene in high yields and diastereoselectivities. Arylation of a leucine derivative affords products **18** and **19** in high yields. The reactions were typically run on a 0.5 mmol scale. A 5.55 mmol scale *p*-methoxyphenylation of the leucine derivative afforded **18** in 67% yield. Cleavage of directing group was investigated for **12** and **18**. Methyl esters **20** and **21** were obtained in 80 and 58% yields, respectively. Compound **21** was produced in 86% ee that could be upgraded to 95% ee (85% recovery) by one recrystallization. Additionally, relative stereochemistry of **21**, which is a derivative of highly constrained β-isopropyltyrosine,[13] was verified by X-ray crystallography.

Preliminary results in alkylation and acetoxylation of amino acid C-H bonds are reported in Scheme 4. Thus, alanine derivative **11** was alkylated by 1-iodooctane affording **22** in 42% yield. Compound **22** is a derivative of a lipidic amino acid which has shown tumor cell growth inhibitor activity.[14] Acetoxylation of **23** gave **24** in 53% yield.[15–16]

The arylation diastereoselectivity is set either at the C-H activation or, less likely, at reductive elimination step.[17] The H/D exchange in **23** was examined by heating the substrate with catalytic $Pd(OAc)_2$ in CD_3CO_2D-toluene-d_8 mixture. (Scheme 5). After 5

hours at 100 °C, 64% of deuterium incorporation was observed at 3S position with minimal (<10%) incorporation at 3R position. A generalized reaction mechanism can be proposed. Formation of a palladium amide **23a** is followed by the C-H activation that affords **23b**. The complex **23b** then can be protonated or deuterated leading to **25**. Since protonation likely occurs with retention of configuration,[18] it can be assumed that **23b** has a trans arrangement of phthaloyl and phenyl groups and that the diastereoselectivity of the arylation is set at the stage of palladation. Oxidative addition to give a high-valent[19] Pd intermediate **26** is followed by reductive elimination that proceeds with retention of configuration. Oxidative addition of aryl iodides to palladium(II) may be facilitated by the silver salts since they are known to complex aryl iodides.[20] Ligand exchange affords **27** and regenerates **23a**.

In conclusion, we have shown that synthesis of a number of substituted phenylalanine derivatives is possible by using C-H bond functionalization methodology. The syntheses are highly convergent and employ *N*-phthaloylalanine possessing a 2-thiomethylaniline directing group. The use of 8-aminoquinoline directing group allows for the diarylation of methyl and diastereoselective monoarylation of amino acid methylene groups. Acetoxylation and alkylation of amino acid derivative C-H bonds is also possible.

Experimental Section

(S)-*N*-(3-(Benzothiophene-2-yl)-2-phthalimidopropionyl)-2-methylthioaniline (7)

To a 1-dram vial was added (S)-*N*-(2-phthalimidopropionyl)-2-methylthioaniline (170 mg, 0.5 mmol), $Pd(OAc)_2$ (6 mg, 0.027 mmol), 2-iodobenzothiophene (785 mg, 3.0 mmol), AgOAc (209 mg, 1.25 mmol), and toluene (0.4 mL). The mixture was stirred at 60 °C for 64 h. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 (25 mL) and extracted with brine (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2×15 mL). Combined organic layers were dried over $MgSO_4$. Evaporation to remove the organic solvents followed by purification by flash chromatography in hexanes/EtOAc (100% hexanes to 3:1) and preparative HPLC in hexanes/EtOAc 4:1 gave 175 mg of colorless oil (74%). R_f = 0.45 (SiO_2, 1/2 EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.95 (*s*, 1H) 8.37-8.31 (*m*, 1H) 7.87-7.82 (*m*, 2H) 7.75-7.67 (*m*, 3H) 7.62-7.58 (*m*, 1H) 7.45-7.41 (*m*, 1H) 7.33-7.20 (*m*, 4H) 7.80-7.04 (*m*, 1H) 5.40 (*dd*, 1H, *J*= 5.7, 10.3 Hz) 4.03 (*dd*, 1H, *J*= 5.1, 14.9 Hz) 4.11 (*dd*, 1H, *J*= 10.9, 15.5 Hz) 2.13 (*s*, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) 167.8, 165.8, 140.1, 139.9, 138.0, 134.7, 133.6, 131.5, 129.4, 125.5, 125.0, 124.3, 124.1, 123.9, 123.4, 123.3, 122.3, 120.6, 55.9, 29.7, 19.2 Signal for one carbon could not be located. FT-IR (neat, cm^{-1}) 1715, 1513, 1436, 1380. Calcd for $C_{26}H_{20}N_2O_3S_2$ (472.58 g/mol) C: 66.08; H: 4.27; N: 5.93; Found C: 65.82; H: 4.45; N: 5.72.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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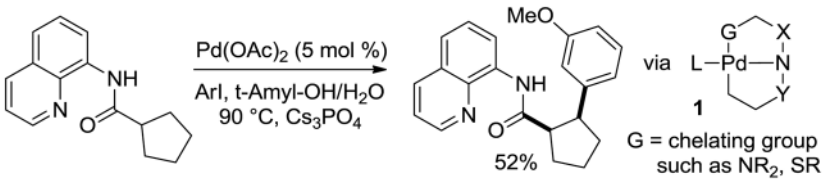
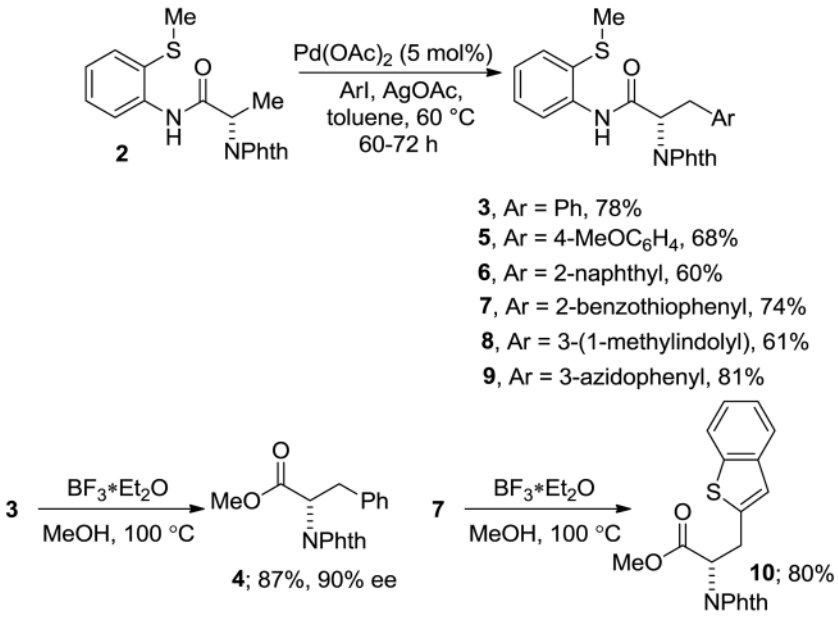
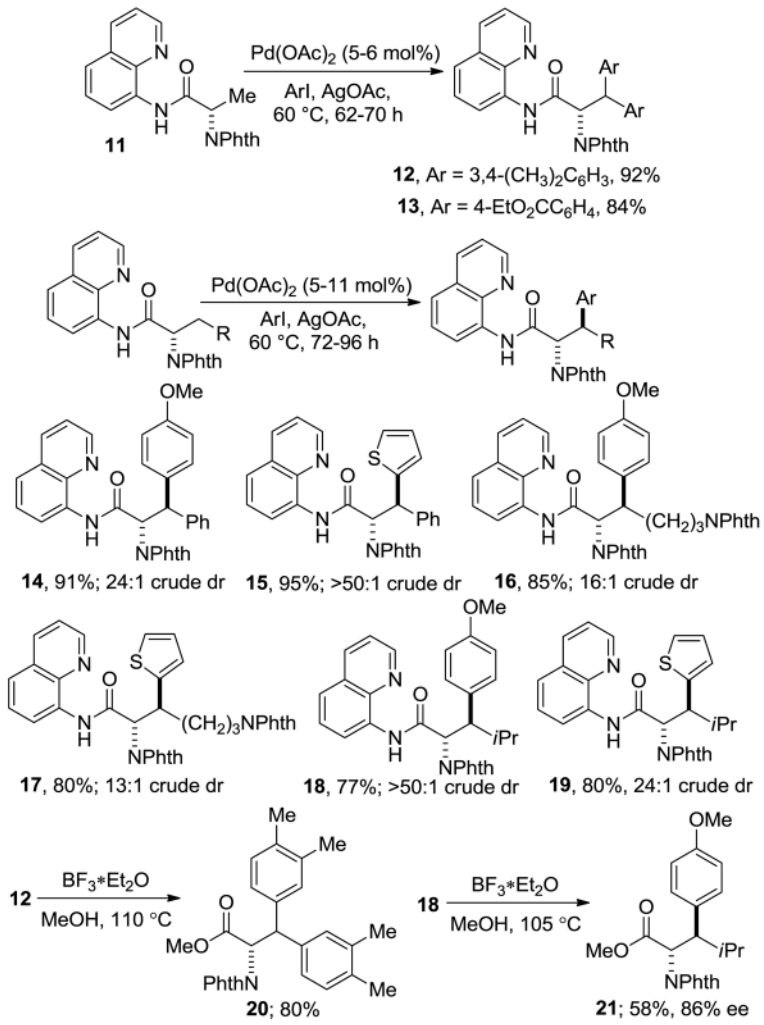


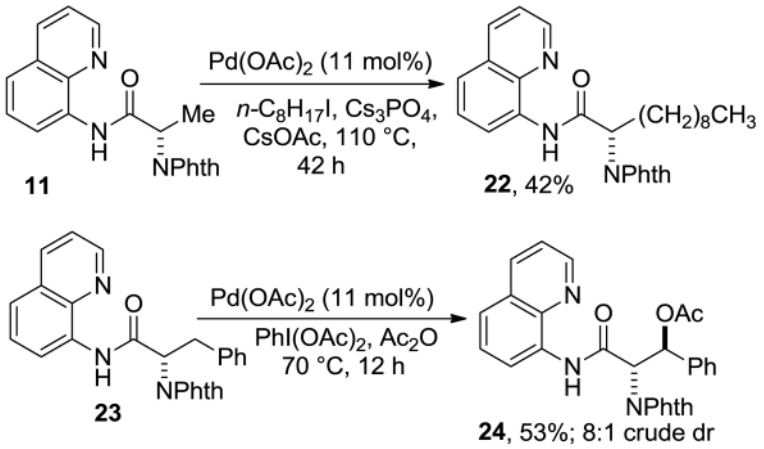
Scheme 1.
Auxiliaries for C-H Bond Arylation



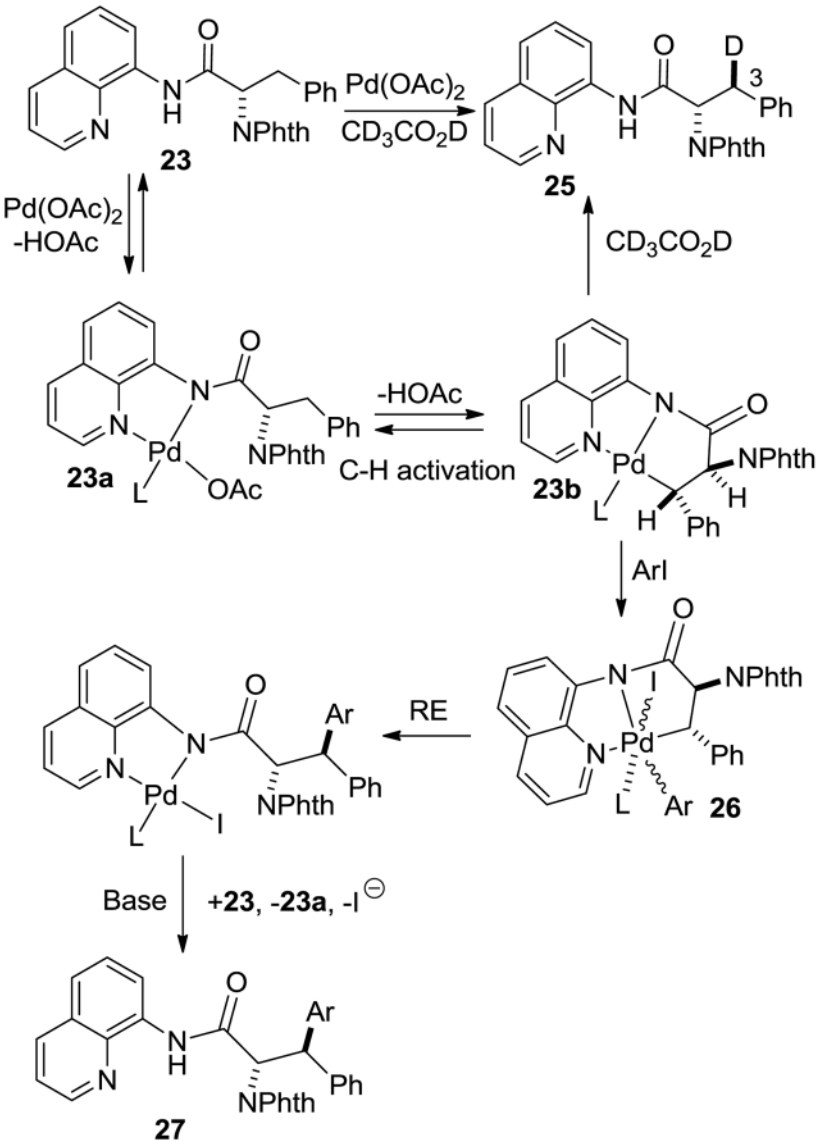
Scheme 2.
Synthesis of Modified Phenylalanine Derivatives.



Scheme 3.
Aminoquinoline Auxiliary.



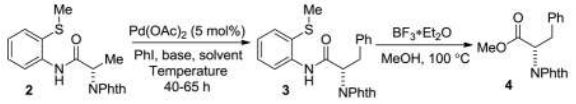
Scheme 4.
Alkylation and Acetoxylation.



Scheme 5.
Mechanistic Considerations.

Table 1

Reaction Optimization.



Entry	Base	Temp, °C	% conv, 3	% ee, 4
1[a]	CsOAc	110	68	77
2[a–c]	CsOAc	90	61	55
3[a]	CsOAc	60	51	92
4[d]	AgOAc	70	90	88
5[b],[d]	AgOAc	60	78	92
6[d]	$AgOCOCF_3$	70	78	91
7[d]	$AgOCOCF_3$	60	77	92
8[d–e]	$AgOCOCF_3$	70	59	93
9[b],[d];[f]	$AgOCOCF_3$	110	82	67

[a] Toluene solvent.

[b] Isolated yield.

[c] Pivalic acid additive.

[d] No solvent.

[e] $Pd(OCOCF_3)_2$ catalyst.

[f] Reaction time 12 h. See supporting information for details.