C–H Bond Functionalization

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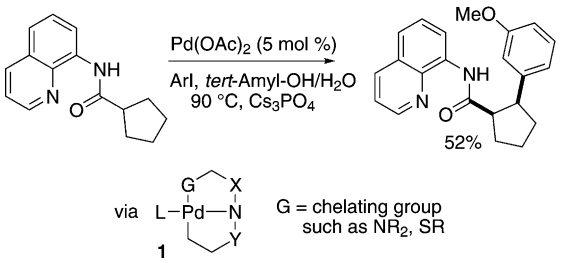
Nonnatural Amino Acid Synthesis by Using Carbon–Hydrogen Bond Functionalization Methodology**

*Ly Dieu Tran and Olafs Daugulis**

During recent years, transition-metal-catalyzed functionalization of carbon–hydrogen bonds has become a rapidly expanding area of research.[1] Functionalization of the C–H bond is appealing, because it allows for shorter and simpler reaction pathways. However, most of the reports that deal with the conversion of carbon–hydrogen bonds into carbon–carbon bonds involve either method development or mechanistic investigations. Their applications in the synthesis of natural products, or their analogues, are rare.[2] The limited use of C–H bond functionalization may be explained by the following issues. First, methods that result in the functionalization of C–H bonds of alkanes are relatively rare.[3] Second, harsh reaction conditions are typically used that may be incompatible with sensitive functionalities. Third, methods are often not broadly applicable and require nonremovable 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, a catalytic amount of $Pd(OAc)_2$, and an aryl iodide coupling partner (Scheme 1).[4a]



Scheme 1. Auxiliaries for C–H bond arylation. L = ligand; X = CH_2, CO, aromatic tether; Y = CH_2, CO; R = alkyl.

Subsequently, several other auxiliaries were investigated for the β arylation of carboxylic acids.[4b] The use of a 2-thiomethylaniline auxiliary results in the selective monoarylation of methyl groups. In contrast, the use of an 8-aminoquinoline auxiliary allows either diarylation of methyl groups or monoarylation of methylene groups. The arylation regioselectivity results from the formation of the double five-membered chelate **1**.

Several other research groups have used these directing groups in the synthesis of natural products.[5] Corey and coworkers have used the 8-aminoquinoline auxiliary to arylate sp^3 C(sp^3)–H bonds in amino acid derivatives.[5a] However, the monoarylation of alanine derivatives was not demonstrated and the stereochemical integrity of the arylation products, as well as removal of the directing group, was not reported. Developing new methods for synthesis of nonnatural amino acids is important, because they are used in drug discovery, protein engineering, peptidomimetics, glycopeptide synthesis, and click chemistry in biologically relevant systems.[6,7] Methods for the preparation of chiral, nonracemic, nonnatural α-amino acids involve the synthesis of racemates followed by resolution, use of chiral auxiliaries, asymmetric hydrogenation, and biological approaches.[8] A general synthesis of nonnatural amino acids from the chiral pool would greatly expand the methods that are available for their preparation. We report herein the palladium-catalyzed synthesis of protected, nonnatural amino acids by C–H bond functionalization, which employs readily available starting materials derived from the chiral pool.

The functionalization of amino acid C–H bonds requires installation of a directing group and protection of the amino group. A phthaloyl group was chosen for protection of the amino functionality.[9] The directing group was installed by treating phthaloylamino acid chlorides[10] with 8-aminoquinoline or 2-thiomethylaniline. The *N*-phthaloylalanine derivative **2** was arylated with phenyl iodide (PhI) in the presence of a palladium catalyst and base. Subsequently, the directing group was removed by treatment with $BF_3{\cdot}Et_2O$ in methanol at 100 °C (Table 1).[11] Compound **4** was obtained in a nearly identical enantiomeric excess when AgOAc, $AgOCOCF_3$, or CsOAc were used as the base at 60–70 °C (entries 3–8). Higher reaction temperatures resulted in a lower enantiomeric excess of **4** (entries 1, 4, and 9), as did the addition of pivalic acid (entry 2). The optimal combination of yield and enantiomeric excess was obtained by employing palladium acetate as the catalyst in combination with AgOAc at 60 °C (entry 5).

The use of a 2-thiomethylaniline derivative allows for a selective monoarylation of the methyl group in **2** (Scheme 2). Arylation of **2** with iodobenzene affords **3** in 78% yield. 4-Methoxyiodobenzene is also reactive and the arylation product **5** was isolated in 68% yield. 2-Iodonaphthalene and 2-iodobenzothiophene afforded the products **6** and **7**, respectively, in good yields. β-(2-Naphthyl)alanine-containing peptides are highly specific Pin1 (peptidyl prolyl

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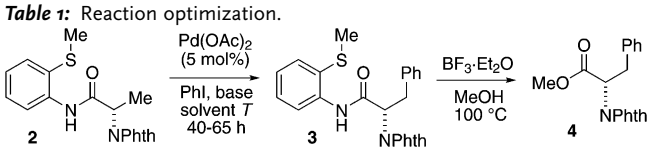
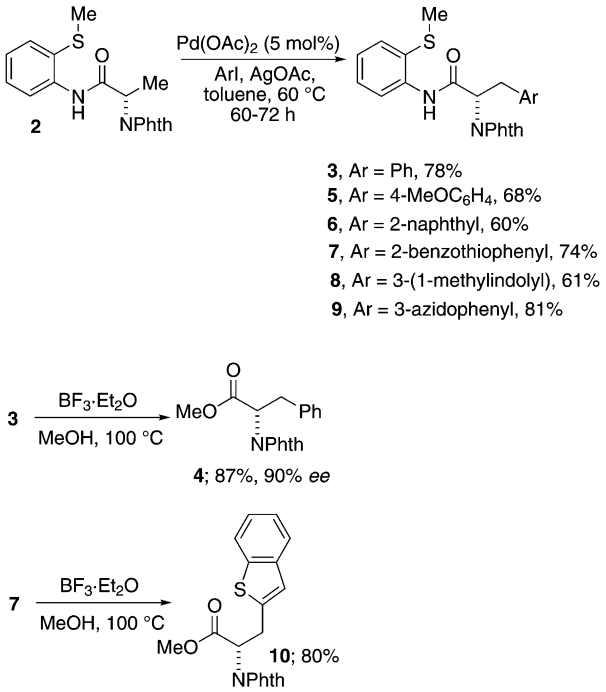
Table 1: Reaction optimization.



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

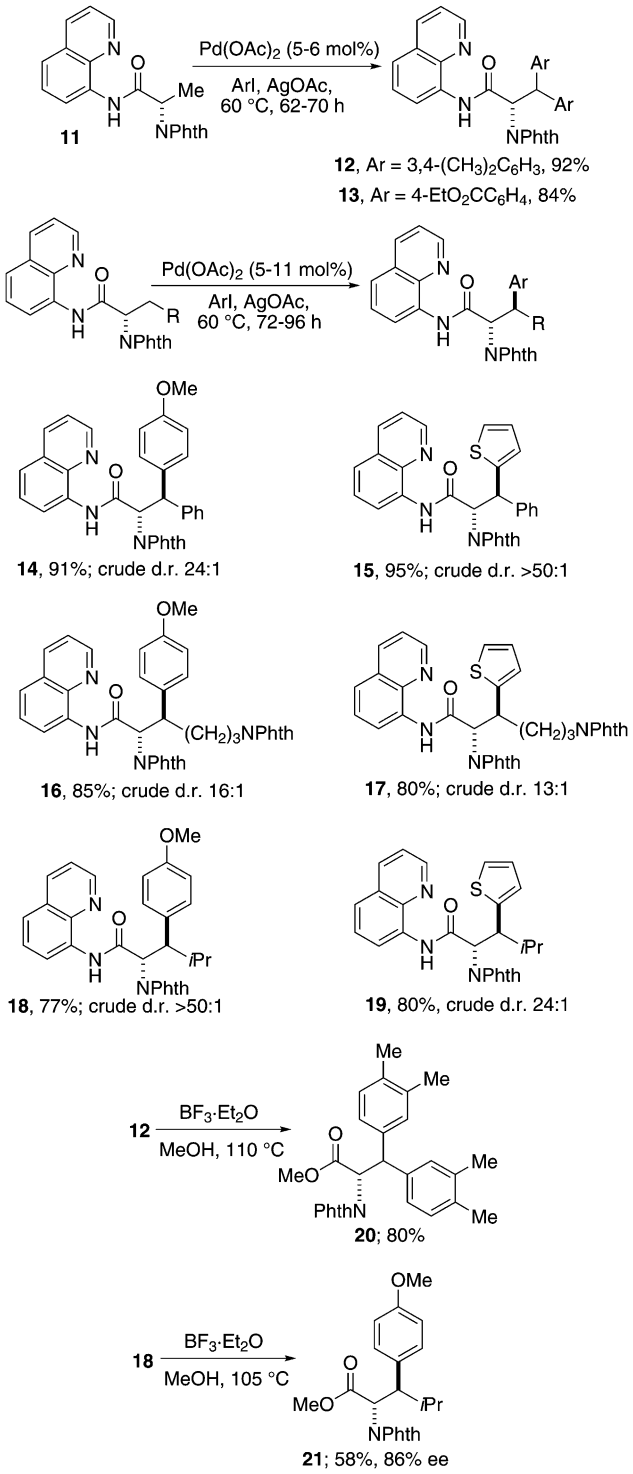
[a] Toluene as solvent. [b] Pivalic acid added. [c] Yield of isolated product. [d] No solvent. [e] $Pd(OCOCF_3)_2$ as catalyst. [f] Reaction time 12 h. See the Supporting Information for details. Phth = phthaloyl.



Scheme 2. Synthesis of modified phenylalanine derivatives.

cis/trans isomerase) inhibitors.[12] Interestingly, 3-iodo-1-methylindole can be coupled with **2** to give *N*-methylated tryptophan derivative **8** in 61% yield. An azido functionality is tolerated on the aryl iodide, and the 3-azidophenylalanine derivative **9** was obtained in 81% yield. Thus, a wide variety of substituted phenylalanines can be made in a convergent fashion from a readily available, single starting material **2**. The directing group in two of the arylated derivatives was cleaved, with *N*-phthaloylphenylalanine methyl ester **4** being obtained in 87% yield and 90% *ee*, and the benzothiophene derivative **10** in 80% yield.

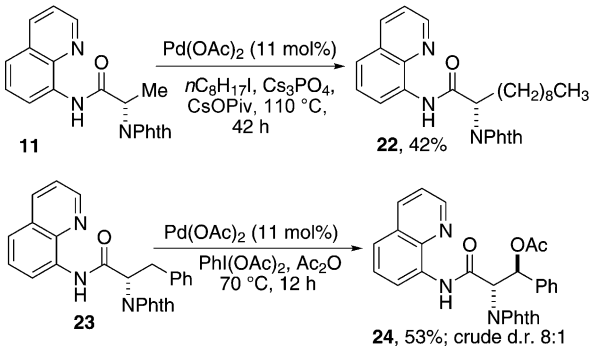
An 8-aminoquinoline directing group can be used for the diarylation of methyl and monoarylation of methylene functionalities (Scheme 3). The diarylation of **11** was accomplished with 3,4-dimethyl-1-iodobenzene to give **12** and 4-iodobenzoic acid ethyl ester to give **13,** with both the products being isolated in excellent yields. Interestingly, the arylation of methylene groups occurs with high diastereoselectivity, in favor of the *anti* diastereomers. Protected phenylalanine can also be arylated with 4-iodoanisole to give **14** in 91% yield, with a crude diastereomer ratio of 24:1. Similarly, the arylation with 2-iodothiophene results in the formation of



Scheme 3. Aminoquinoline auxiliary.

the single diastereomer **15** in 95% yield. Protected lysine can be arylated with 4-iodoanisole and 2-iodothiophene to give **16** and **17** in high yields and diastereoselectivities. The arylation of a leucine derivative affords products **18** and **19** in high yields. The reactions were typically run on a 0.5 mmol scale, but 5.55 mmol scale *p*-methoxyphenylation of the leucine derivative afforded **18** in 67% yield. Cleavage of the directing group was investigated for **12** and **18**. Methyl esters **20** and **21** were obtained in yields of 80 and 58%, respectively. Compound **21** was produced with 86% *ee*, but could be increased to 95% *ee* (85% recovery) by one recrystallization. Additionally, the relative stereochemistry of **21**, which is a derivative of highly-constrained β-isopropyltyrosine,[13] was verified by X-ray crystallography (see Supporting Information).

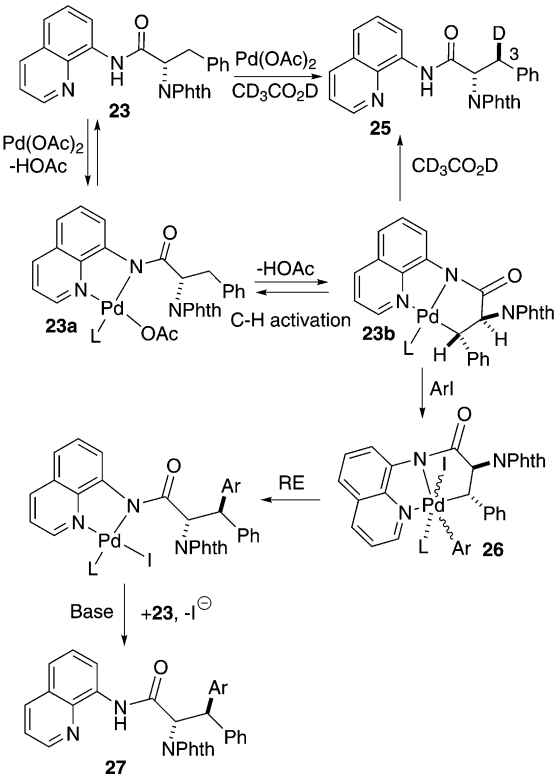
Preliminary results on the alkylation and acetoxylation of C–H bonds of amino acid are reported in Scheme 4. Thus, alanine derivative **11** was alkylated with 1-iodooctane to



Scheme 4. Alkylation and acetoxylation.

afford **22** in 42% yield. Compound **22** is a derivative of a lipidic amino acid, which has been shown to inhibit the growth of tumor cells.[14] Acetoxylation of **23** gave **24** in 53% yield.[15,16]

The diastereoselectivity of the arylation occurs either at the C–H activation step or, less likely, at the reductive elimination step.[17] The H/D exchange in **23** was examined by heating the substrate with a catalytic amount of $Pd(OAc)_2$ in a $CD_3CO_2D/[D_8]$toluene mixture (Scheme 5). After 5 h at 100 °C, 64% of deuterium incorporation was observed at 3*S* position with minimal (< 10%) incorporation at 3*R* position. From this information, a generalized reaction mechanism can be proposed. Formation of a palladium amide **23a** is followed by the C–H activation that affords **23b**. Complex **23b** can then 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 the phthaloyl and phenyl groups and that the diastereoselectivity of the arylation is established at the palladation step. Oxidative addition to give a high-valent[19] Pd intermediate **26** is followed by a reductive elimination that proceeds with retention of configuration. Oxidative addition of aryl iodides to palladium(II) centers may be facilitated by the silver salts, because they are known to complex aryl iodides.[20] Ligand exchange affords **27** and regenerates **23a**.



Scheme 5. Mechanistic considerations. RE = reductive elimination.

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

Experimental Section

7: (*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) were added to a 1-dram vial. The mixture was stirred at 60 °C for 64 h, then cooled to room temperature and diluted with CH_2Cl_2 (25 mL). The reaction mixture was then extracted with brine (15 mL), and the aqueous layer extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried over $MgSO_4$. Evaporation to remove the organic solvents, followed by purification by flash chromatography with hexanes/EtOAc (100% hexanes to 3:1), and preparative HPLC with hexanes/EtOAc 4:1 gave 175 mg of **7** as a colorless oil (74%). $R_f = 0.45$ (SiO_2, 2:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.95$ (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 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 167.8$, 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 ppm; the signal for one carbon

atom could not be located; FTIR (neat): 1715, 1513, 1436, 1380 cm^{-1}. Elemental analysis calcd (%) for $C_{26}H_{20}N_2O_3S_2$ (472.58 $g\,mol^{-1}$): C 66.08, H 4.27, N 5.93, found: C 65.82, H 4.45, N 5.72.

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Communications

C–H Bond Functionalization

L. D. Tran, O. Daugulis* ____ ▮▮▮▮–▮▮▮▮

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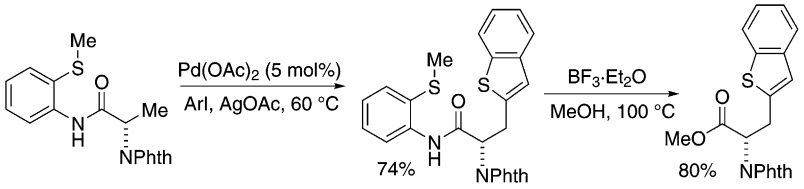

Taking direction well: Substituted phenylalanine derivatives were prepared by C–H bond functionalization (see scheme). The syntheses are highly convergent and employ an *N*-phthaloylalanine with a 2-thiomethylaniline directing group. The use of an 8-aminoquinoline directing group allows for the diarylation of methyl and the diastereoselective arylation of methylene groups.