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Palladium-Catalyzed Regioselective C-5 Arylation of Protected L-Histidine: Microwave-Assisted C−H Activation Adjacent to Donor Arm

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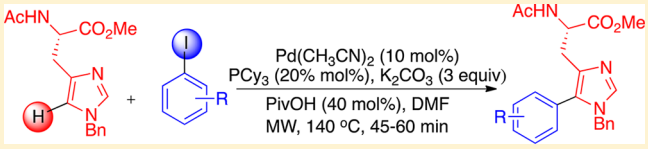
Supporting Information

ABSTRACT: An efficient, microwave-assisted direct C−H arylation at the C-5 position of fully protected L-histidine has been achieved via a palladium-catalyzed transformation reaction. This highly regioselective reaction has been applied to synthesize a series of protected 5-aryl-L-histidines using aryl iodides as coupling partners, in good to excellent yields. The reaction is compatible with substrates possessing electron-donating or electron-withdrawing substituents and offers high reactive functional group tolerance.



INTRODUCTION

Arylated amino acids are vital scaffolds for diverse biologically active compounds.[1] Incorporation of these modified amino acids in peptides results in a broad spectrum of biological activity with enhanced proteolytic stability and activity.[2] Despite the significance of biaryl motifs in drug discovery, regioselective modification of amino acids remains a synthetic challenge.[3] A limited number of C-arylation reports are available for α-amino acids, such as phenylalanine (Phe),[4] tyrosine (Tyr),[5] and histidine (His),[6] but alternative synthetic strategies are required, as known methods are not straightforward. The arylation of Phe and Tyr proceeds through a Suzuki cross-coupling reaction on their iodinated counterparts,[4,5] whereas 5-arylhistidines were synthesized from their 5-bromo counterpart using arylboronic acids in several steps.[6] In recent times, a perceptible reduction has been observed in the application of traditional Suzuki-, Negishi-, Hiyama-, and Kumada-like conventional cross-coupling reactions to form carbon−carbon bonds.[7] Although useful, these C-arylation cross-coupling reactions are limited due to the use of prefunctionalized starting materials, limited coupling partner scope, and low to moderate yields of the product.

Direct C−H functionalization is a much-practiced chemistry of recent times for diverse substitutions in almost all aromatics and heteroaromatics.[8] It overcomes the drawbacks of conventional cross-coupling reactions (the use of activated and prefunctionalized starting materials), thereby increasing atom economy. Nowadays, transition-metal-catalyzed activation of inert C−H bonds with Rh, Ru, Pd, and Cu forms an important reaction type, owing to the regioselective nature of the transformation.[9]

RESULTS AND DISCUSSION

Due to our longstanding interest in developing short cationic antimicrobial peptides (CAPs)[10] as future lead molecules, we required a library of amphiphilic amino acids. In search of amphiphilic amino acids, we observed that modified histidine analogues can provide both cationicity and hydrophobicity. The ring nitrogen of the imidazole nucleus provides cationic character, and modifications on the ring, such as alkylation,[11] halogenation,[12] and arylation,[13] can serve as the hydrophobic part. In our continuing efforts to develop ring-modified histidines, we recently disclosed a method for the regioselective direct C-2 arylation of histidine using arylboronic acids.[14]

Herein, we report an efficient microwave-assisted palladium-catalyzed direct regioselective C-5 arylation of protected L-histidine using aryl iodides. The scope and limitations of this arylation reaction are favorable, with various aryl iodides containing electron-withdrawing and electron-donating substituents giving access to a wide variety of 5-aryl-L-histidines.

As is evident from the literature, directing group guided approach is of significant use in functionalizing inert C−H bonds.[15] Concerted metalation−deprotonation (CMD) is one of the methods for substitution at electronically rich positions in five-membered rings such as oxazole, thiazole, and imidazole and six-membered aromatics.[16]

Keeping these facts in mind, we initiated the study by examining direct C-5 arylation of the commercially available Ac-His-OMe (**1**). In line with the Fagnou arylation procedure for heterocycles, including imidazole,[17] the direct arylation of **1** with 4-iodobenzotrifluoride (**2a**, 2 equiv) using $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), K_2CO_3 (3 equiv), and pivalic acid (40 mol %) in DMF at 140 °C for 48 h was attempted first.

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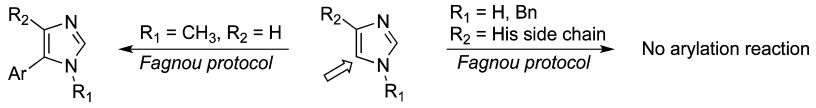
Scheme 1. Arylation of Imidazole and Protected L-Histidine

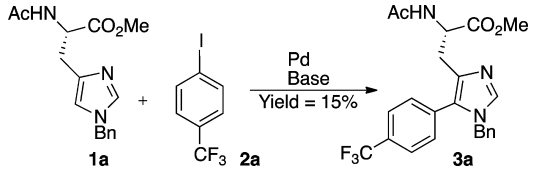


However, to our disappointment, no arylation took place, probably due to the interference of the ring NH group (Scheme 1).

For the N-1 protection of the imidazole ring of histidine, various reported strategies using groups such as phenyl, methyl, SEM, MOM, MEM, TBDMS, TMS, trityl, and benzyl were considered. The methyl and phenyl groups provide permanent protection, whereas SEM, MEM, and MOM groups provide both N-1 and N-3 regioisomers. The silyl-based TBDMS and TMS protecting groups encountered the same problem of regioisomerization. Protection with the trityl group introduced the steric bulk, which interfered in the arylation reaction. The moderate conditions of benzylation and debenzylation favored the benzyl group. The reaction of **1** with benzyl bromide in the presence of silver carbonate led to the regioselective formation of Ac-His(1-Bn)-OMe (**1a**) in 90% yield. Next, we examined the direct arylation of **1a**, while keeping the aforementioned reaction conditions intact. We did not observe an arylation reaction even at 140 °C over a period of 48−72 h (Scheme 1).

We then attempted microwave (MW) irradiation as an alternate energy source in order to provide sufficient activation energy to functionalize the C−H bond. To our delight, C−H activation of **1a** took place under MW irradiation. The arylation reaction of **1a** in the presence of **2a** (2 equiv), $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), K_2CO_3 (3 equiv), and pivalic acid (40 mol %) as an additive in DMF under MW irradiation (140 °C, 45 min, 100 W) afforded **3a** in low 15% yield (Scheme 2).

Scheme 2. Pd-Catalyzed C-5 Arylation of 1a under MW Irradiation[a]



[a]Reaction conditions: **1a** (1.0 equiv), **2a** (2.0 equiv), $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), K_2CO_3 (3.0 equiv), PivOH (40 mol %), DMF, MW (140 °C, 45 min, 100 W).

With these initial results in hand, we screened various palladium catalysts substituted with diverse groups along with phosphine ligands for the arylation of hindered five-membered heteroaromatic at the most nucleophilic center. As summarized in Table 1, **3a** was obtained in 5−7% yield, when $Pd_2(dba)_3$ and $Pd(PPh_3)_4$ were used in the presence of PPh_3 (entries 1 and 2). No reaction was observed when $Pd(OAc)_2$ was used as catalyst in the presence of $P(2\text{-furyl})_3$ (entry 3). Highly satisfying results were obtained by changing the ligand to PCy_3, resulting in higher conversion of **1a** to **3a** with substantially enhanced yield (entry 4). We further optimized the reaction by using palladium catalysts such as $Pd(TFA)_2$ and $Pd(CH_3CN)_2$ having electron-withdrawing substituents and PCy_3 as a ligand. This resulted in even higher conversion and excellent yield (80−85%) (entries 5 and 6). The ligandless reaction with $Pd(CH_3CN)_2$ and $Pd(TFA)_2$ resulted in reduced yield (54−56%) (entries 7 and 8). The screening of $Pd(CH_3CN)_2$ with the sterically encumbered ligands X-Phos, $P^tBu(1\text{-adamantyl})_2$, and $P(^nBu)_2HBF_4$ resulted in no arylation reaction (entries 9−11).

Table 1. Screening of Catalysts and Ligands for the Conversion of 1a to 3a[a]

entry	catalyst	ligand	conversn, %[b]
1	$Pd_2(dba)_3$	PPh_3	30 (5)
2	$Pd(PPh_3)_4$	PPh_3	25 (7)
3	$Pd(OAc)_2$	$P(2\text{-furyl})_3$	30 (0)
4	$Pd(OAc)_2$	PCy_3	60 (30)
5	$Pd(TFA)_2$	PCy_3	85 (80)
6	$Pd(CH_3CN)_2$	PCy_3	90 (85)
7	$Pd(TFA)_2$		68 (54)
8	$Pd(CH_3CN)_2$		70 (56)
9	$Pd(CH_3CN)_2$	X-Phos	
10	$Pd(CH_3CN)_2$	$P^tBu(1\text{-adamantyl})_2$	
11	$Pd(CH_3CN)_2$	$P(^nBu)_2HBF_4$	

[a]Reaction conditions: **1a** (1.0 equiv), **2a** (2.0 equiv), catalyst (10 mol %), ligand (20 mol %), K_2CO_3 (3.0 equiv), PivOH (40 mol %), DMF, MW (140 °C, 45 min, 100 W). [b]Isolated yields (%) in parentheses.

In a nutshell, the $Pd(CH_3CN)_2$−PCy_3 catalytic system offered the best combination for the regioselective arylation reaction. To the best of our knowledge, this is the first report on the use of an electron-withdrawing substituent containing $Pd(CH_3CN)_2$ catalyst in conjuction with PCy_3 for a direct C−H functionalization reaction. With the highly selective catalytic system $Pd(CH_3CN)_2$−PCy_3 in hand, we tried to find an effective medium for the reaction. The use of polar aprotic solvents such as acetonitrile (ACN), 1,2-dichloroethane (DCE), and tetrahydrofuran (THF) offered low conversion (Figure 1). The use of *N*-methyl-2-pyrrolidone (NMP), *N*,*N*-dimethylacetamide (DMA), and dimethyl sulfoxide (DMSO), with higher solubility capacity for heterogeneous base,[18] did not offer any superiority over DMF. The use of stronger bases such as KO-*t*-Bu, KOH, and DBU led to only 20% conversion with traces of **3a**, probably due to the inherent selectivity of these bases for acidic sites in comparison to nucleophilic sites in the ring.

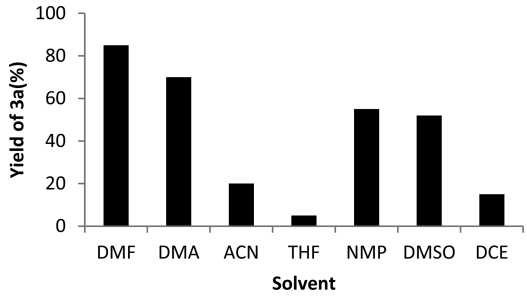


Figure 1. Comparison of solvents.

With the successful demonstration of a regioselective palladium-catalyzed arylation reaction of **1a** with **2a**, the generality of the reaction with a range of aryl iodides was

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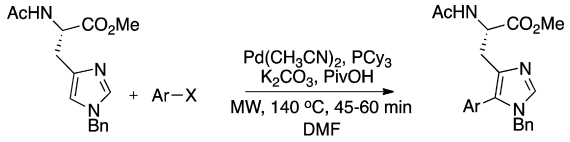
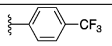
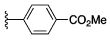
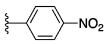
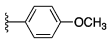
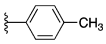
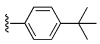
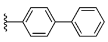
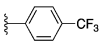
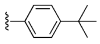
evaluated. The results of arylation reactions are shown in Table 2. As is evident, a reaction time from 45 to 60 min was required, depending on the aryl iodide used. Both electron-rich and electron-deficient aryl iodides reacted with **1a** to give good isolated yields of **3**. A sterically hindered aryl iodide (entry 3) also readily reacted to provide the desired product in good yield. Importantly, these reaction conditions proved compatible in the presence of reactive functional groups such as ester, cyano, nitro, and chloro on the aromatic ring. The successful functionalization with 4-iodobiphenyl and 2-naphthyl iodide showed the wide applicability of the reaction (entries 9 and 13, respectively, Table 2). It is also remarkable that the reaction also proceeds with aryl bromides as coupling partners under similar conditions, but with much lower yields of the product (entries 14 and 15, respectively, Table 2).

Table 2. Direct C-5 Arylation of 1a with Aryl Halides 2a−o under MW Irradiation[a]



Entry	X	Ar	Product	Time (min)	Yield (%)
1	I		3a	45	85
2	I		3b	60	70
3	I		3c	60	72
4	I		3d	45	75
5	I		3e	45	71
6	I		3f	60	64
7	I		3g	60	62
8	I		3h	60	61
9	I		3i	45	78
10	I		3j	45	76
11	I		3k	45	78
12	I		3l	45	86
13	I		3m	45	70
14	Br		3a	60	18
15	Br		3h	60	10

[a]Reaction conditions: **1a** (1.0 equiv), **2** (2.0 equiv), $Pd(CH_3CN)_2$ (10 mol %), PCy_3 (20 mol %), K_2CO_3 (3.0 equiv), PivOH (40 mol %), DMF, MW (140 °C, 45−60 min, 100 W).

On the basis of some earlier reports,[16−19] a mechanism for the Pd-catalyzed direct C-5 arylation can be postulated (Figure 2). The regioselective transformation of **1a** to **3a** possibly

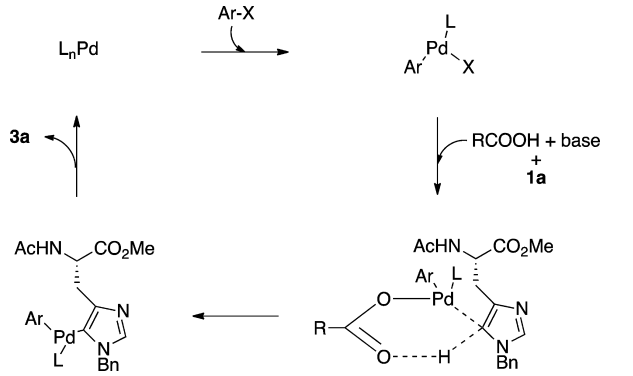


Figure 2. Plausible mechanism for C-5 arylation of **1a** through the CMD pathway.

proceeds through a CMD pathway. The catalytic cycle begins with the insertion of active Pd(0) into the aryl halide, generating ArPdX as a coupling partner. Electrophilic palladation at the nucleophilic site is the rate-determining step of the proposed cyclic pathway, resulting in the formation of a carbon−metal bond. The use of the more highly electrophilic $Pd(CH_3CN)_2$ as the catalyst precursor results in the selective attachment of the aryl group at the nucleophilic C-5 position. Reductive elimination leads to the generation of the arylated histidine, and Pd(II) converted into catalytically active Pd(0) presumably by the PCy_3 ligand. The use of K_2CO_3 over the bases such as KO-*t*-Bu, DBU, and KOH and the use of PivOH stregthens the proposed CMD-based mechanistic pathway.

We established the debenzylation procedure of **3l** by a procedure reported earlier.[20] A suspension of **3l** in 10% Pd−C in methanol was treated with ammonium formate, and the mixture was refluxed for 18 h to afford **4a** in 90% yield. Finally, the removal of protecting groups of **4a** was achieved by refluxing in 6 N HCl for 24 h. 5-Phenyl-L-histidine·2HCl (**5a**) was obtained by evaporation of the solution (Scheme 3).

To confirm the chiral integrity of the synthesized C-5 arylated amino acids, chiral HPLC analysis of **5a** was performed on a ChiralPak-WH column. We have also synthesized 5-phenyl-D-histidine·2HCl to differentiate between the retention times of enantiomers of 5-phenylhistidine·2HCl. It was clear from the HPLC chromatograms of the enantiomers that chiral integrity was well maintained in this reaction.

In summary, we have developed an efficient, rapid, and regioselective direct C−H arylation of Ac-His(Bn)-OMe followed by deprotection to afford 5-aryl-L-histidines. This reaction is catalyzed by the $Pd(CH_3CN)_2$−PCy_3 system and proceeds under MW irradiation. Important features of this method are identification of a new catalytic system for the direct C−H functionalization reaction, use of microwave energy, short reaction time, high yield, reactive functional

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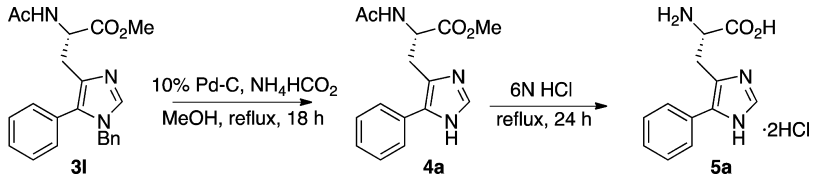
Scheme 3. Deprotection of Benzyl and Side Chain Protecting Groups



group tolerance, absolute regioselectivity, and chiral integrity of the modified amino acids.

EXPERIMENTAL SECTION

General Considerations. All arylation reactions were carried out under an argon atmosphere, unless otherwise stated. All starting materials were commercially purchased and used further without any additional purification. Analytical thin-layer chromatography (TLC) was performed using aluminum plates precoated with silica gel (0.25 mm, 60 Å pore size) impregnated with a fluorescent indicator (254 nm). Visualization on TLC was achieved by the use of UV light (254 nm), treatment with 10% ninhydrin in ethanol, or straining with iodine. Flash column chromatography was undertaken on silica gel (400−630 mesh). Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a 400 MHz NMR instrument. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent (DMSO-d_6, δ 2.50). A drop of D_2O was added to shift the peak of moisture in the case of spectra recorded in DMSO-d_6. The following abbreviations were used to describe peak patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quadraplet, m = multiplet. Coupling constants, J, are reported in hertz (Hz). Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were recorded on a 100 MHz NMR instrument and were fully decoupled by broad-band decoupling. Chemical shifts str reported in ppm referenced to the center line of a miltiplet at 39.52 ppm for DMSO-d_6. High-resolution mass spectra were taken using the ESI-TOF method. Infrared (IR) spectra are reported in frequencies of the absorption (cm^{-1}).

Synthesis of *N*-α-Acetyl-1-benzyl-L-histidine Methyl Ester (1a). A mixture of *N*-α-acetyl-L-histidine methyl ester (**1**; 1, equiv, 2.37 mmol), benzyl bromide (1.5 equiv, 3.55 mmol), and silver carbonate (1.5 equiv, 3.55 mmol) in DMF (2 mL) was stirred at ambient temperature for 4 h. The solvent was removed under reduced pressure, and the residue was purified on an automated flash column chromatography system to afford **1a**: yield 642 mg (90%); ^{1}H NMR (CD_3OD) δ 8.37 (s, 1H), 7.38−7.43 (m, 3H), 7.31−7.37 (m, 2H), 7.15 (s, 1H), 5.29 (s, 2H), 4.69−4.72 (m, 1H), 3.69 (s, 3H), 3.12−3.18 (m, 1H), 2.96−3.02 (m, 1H), 1.88 (s, 3H); ^{13}C NMR (CD_3OD) δ 172.0, 171.0, 147.3, 141.6, 133.7, 129.5, 127.8, 117.4, 52.0, 51.6, 26.4, 21.5; IR (KBr) 2937, 1784, 1326, 1235, 1180, 1150, 1126 cm^{-1}; HRMS (ESI-TOF) m/z [M + H$^+$] calculated for $C_{16}H_{20}N_3O_3$ 302.1504, found 302.1504.

General Procedure for the Synthesis of *N*-α-Acetyl-5-aryl-1-benzyl-L-histidine Methyl Esters (3a−m). All microwave irradiation experiments were performed using a CEM Discover microwave reactor. Reaction times refer to the hold time at the desired set temperature and not to the total irradiation time. The reaction mixture temperature during microwave heating was measured by using an internal probe. Reaction cooling was performed by compressed air automatically after the heating period had elapsed. All of the solid reagents were weighed in air and placed in a 10 mL microwave vial equipped with a magnetic stir bar.

In a 10 mL capacity microwave vial, K_2CO_3 (3.0 equiv, 4.98 mmol), $Pd(CH_3CN)_2$ (10 mol %, 0.17 mmol), PCy_3 (20 mol %, 0.33 mmol), PivOH (40 mol %, 0.66 mmol) and **1a** (1 equiv, 1.66 mmol) were added, and it was purged with argon. The appropriate aryl iodide **2a** (2 equiv, 3.32 mmol) or aryl bromide (2 equiv) were added at this point if solids. The vial was purged with argon, and DMF (2 mL) was added. The aryl iodide (2 equiv) was added at this point, if a liquid. Addition of solvent was done under positive argon pressure with stirring. The sealed reaction vial was then placed in the microwave reactor and stirred at 140 °C over the indicated time (see Table 2). The solution was then cooled to room temperature, diluted with EtOAc, washed with H_2O (three times), dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The reaction mixture was purified on an automated flash column chromatography system to give **3a−m**.

*N-α-Acetyl-5-(4-trifluoromethylphenyl)-1-benzyl-L-histidine methyl ester (**3a**):* R_f = 0.5 (MeOH/$CHCl_3$, 1/9); yield 628 mg (85%); yellow liquid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (d, J = 7.8 Hz, 1H), 7.86 (s, 1H), 7.73 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.3 Hz, 2H), 7.19−7.21 (m, 3H), 6.81−6.83 (m, 2H), 5.16 (s, 2H), 4.55 (d, J = 6.5 Hz, 1H), 3.45 (s, 3H), 2.84 (d, J = 6.3 Hz, 1H), 2.82 (d, J = 7.5 Hz, 1H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.5, 169.6, 139.0, 137.8, 136.1, 134.1, 130.9, 129.0, 128.2, 128.0, 126.9, 125.8, 123.9, 52.4, 52.1, 48.5, 29.5, 22.7; IR (ν_{max}) 1325, 1275, 1260, 764, 750 cm^{-1}; HRMS (ESI-TOF) m/z [M + H$^+$] calculated for $C_{23}H_{23}F_3N_3O_3$ 446.1691, found 446.1697.

*N-α-Acetyl-5-(3-trifluoromethylphenyl)-1-benzyl-L-histidine methyl ester (**3b**):* R_f = 0.5 (MeOH/$CHCl_3$, 1/9); yield 517 mg (70%); yellow liquid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (d, J = 7.5 Hz, 1H), 7.89 (s, 1H), 7.69 (d, J = 7.7 Hz, 1H), 7.62 (d, J = 7.7 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.37 (s, 1H), 7.20 (d, J = 6.4 Hz, 3H), 6.80 (d, J = 7.3 Hz, 2H), 5.11 (s, 2H), 4.55 (d, J = 7.0 Hz, 1H), 3.45 (s, 3H), 2.79 (dd, J = 7.0, 9.8 Hz, 2H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 172.6, 169.6, 138.9, 137.8, 136.0, 134.5, 130.9, 130.1, 128.9, 128.2, 127.9, 126.9, 52.4, 52.0, 48.6, 29.5, 22.7; IR (ν_{max}) 2924, 1745, 1326, 1275, 1260, 1166, 1126, 764, 750 cm^{-1}; HRMS (ESI-TOF) m/z [M + H$^+$] calculated for $C_{23}H_{23}F_3N_3O_3$ 446.1691, found 446.1720.

*N-α-Acetyl-5-(2-trifluoromethylphenyl)-1-benzyl-L-histidine methyl ester (**3c**):* R_f = 0.5 (MeOH/$CHCl_3$, 1/9); yield 531 mg (72%); yellow liquid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.87 (s, 1H), 7.67 (d, J = 7.9 Hz, 1H), 7.57−7.61 (m, 1H), 7.44 (d, J = 7.7 Hz, 1H), 7.25 (s, 1H), 7.15−7.17 (m, 3H), 6.72−6.74 (m, 2H), 5.07 (s, 2H), 4.41−4.44 (m, 1H), 3.38 (s, 3H), 2.78 (d, J = 2.0 Hz, 1H), 2.77 (d, J = 1.8 Hz, 1H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.3, 170.6, 138.8, 137.4, 135.3, 134.4, 130.4, 130.2, 128.9, 128.4, 128.0, 126.8, 52.6, 52.2, 48.7, 29.0, 22.4; IR (ν_{max}) 2924, 1275, 1260, 1166, 1126, 764, 750 cm^{-1}; HRMS (ESI-TOF) m/z [M + H$^+$] calculated for $C_{23}H_{23}F_3N_3O_3$ 446.1691, found 446.1700.

*N-α-Acetyl-5-[(4-carboxymethylester)phenyl]-1-benzyl-L-histidine methyl ester (**3d**):* R_f = 0.5 (MeOH/$CHCl_3$, 1/9); yield 542 mg (75%); brownish yellow liquid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, J = 8.0 Hz, 2H), 7.84 (s, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 4.3 Hz, 3H), 6.73−6.75 (m, 2H), 5.12 (s, 2H), 4.42 (t, J = 6.8 Hz, 1H), 3.80 (s, 3H), 3.38 (s, 3H), 2.80−2.84 (m, 2H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.4, 170.7, 166.7, 139.0, 137.4, 135.5, 134.4, 130.4, 129.8, 129.3, 128.9, 128.9, 128.0, 126.8, 55.0, 52.8, 52.7, 52.2, 48.6, 29.1; IR (ν_{max}) 2924, 1721, 1436, 1275, 1260, 1026, 764, 750 cm^{-1}; HRMS (ESI-TOF) m/z [M + H$^+$] calculated for $C_{24}H_{26}N_3O_5$ 436.1872, found 436.1876.

*N-α-Acetyl-5-(4-nitrophenyl)-1-benzyl-L-histidine methyl ester (**3e**):* R_f = 0.5 (MeOH/$CHCl_3$, 1/9); yield 497 mg (71%); dark brown liquid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (d, J = 8.0 Hz, 2H), 7.88 (s, 1H), 7.43 (d, J = 8.2 Hz, 2H), 7.14 (s, 3H), 6.74 (d, J = 4.0 Hz, 2H), 5.15 (s, 2H), 4.40−4.44 (m, 1H), 3.39 (s, 3H), 2.86 (d, J = 7.0 Hz, 1H), 2.83 (d, J = 7.3 Hz, 1H), 1.72 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.3, 170.9, 147.1, 139.5, 137.1, 136.4, 136.3, 131.1, 129.0, 128.1, 126.9, 124.1, 52.6, 52.4, 48.8, 29.0, 22.3; IR (ν_{max}) 2925, 1735, 1519, 1338, 1275, 1260, 1025, 855, 764, 750 cm^{-1}; HRMS

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(ESI-TOF) m/z [M + H$^+$] calculated for $C_{22}H_{23}N_4O_5$ 423.1668, found 423.1668.

*N-α-Acetyl-5-(4-methoxyphenyl)-1-benzyl-L-histidine methyl ester (**3f**):* R_f = 0.5 (MeOH/$CHCl_3$, 1/9); yield 433 mg (64%); dark yellow liquid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (s, 1H), 7.18−7.24 (m, 3H), 7.06 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 6.81−6.79 (m, 2H), 5.04 (s, 2H), 4.41−4.44 (m, 1H), 3.42 (s, 3H), 2.74−2.77 (m, 1H), 2.49−2.50 (m, 1H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.5, 170.2, 159.5, 138.0, 137.7, 134.3, 132.0, 131.8, 129.6, 128.9, 127.9, 126.8, 121.4, 114.4, 55.5, 52.7, 52.1, 48.2, 29.2, 22.6; IR (ν_{max}) 3407, 1639, 1275, 1260, 1024, 994, 764, 750 cm^{-1}; HRMS (ESI-TOF) m/z [M + H$^+$] calculated for $C_{23}H_{26}N_3O_4$ 408.1923, found 408.1933.

*N-α-Acetyl-5-(4-methylphenyl)-1-benzyl-L-histidine methyl ester (**3g**):* R_f = 0.5 (MeOH/$CHCl_3$, 1/9); yield 403 mg (62%); yellow liquid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (s, 1H), 7.16−7.20 (m, 5H), 7.01 (d, J = 4.8 Hz, 2H), 6.77 (d, J = 7.6 Hz, 2H), 5.04 (s, 2H), 4.39 (t, J = 7.0 Hz, 1H), 3.39 (s, 3H), 2.78 (d, J = 5.5 Hz, 1H), 2.76 (d, J = 5.5 Hz, 1H), 2.26 (s, 3H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.5, 170.7, 138.3, 137.8, 134.1, 130.2, 130.0, 129.7, 129.1, 129.0, 128.0, 126.8, 126.7, 126.1, 54.9, 52.9, 52.2, 48.2, 29.0, 22.4; IR (ν_{max}) 2924, 1735, 1661, 1436, 1275, 1260, 1026, 764, 750 cm^{-1}; HRMS (ESI-TOF) m/z [M + H$^+$] calculated for $C_{23}H_{26}N_3O_3$ 392.1974, found 392.1971.

*N-α-Acetyl-5-(4-tert-butylphenyl)-1-benzyl-L-histidine methyl ester (**3h**):* R_f = 0.5 (MeOH/$CHCl_3$, 1/9); yield 439 mg (61%); yellow liquid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 (s, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.16−7.18 (m, 3H), 7.07 (d, J = 8.3 Hz, 2H), 6.76 (d, J = 4.0 Hz, 2H), 5.04 (s, 2H), 4.41−4.42 (m, 1H), 3.37 (s, 3H), 2.78−2.81 (m, 2H) 1.76 (s, 3H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.4, 170.6, 151.3, 137.9, 137.8, 134.1, 123.0, 129.3, 128.9, 128.1, 127.9, 126.8, 126.3, 125.8, 52.8, 52.1, 48.3, 34.7, 31.4, 31.3, 29.1; IR(ν_{max}) 2925, 1275, 1260, 764, 750 cm^{-1}; HRMS (ESI-TOF) m/z [M + H$^+$] calculated for $C_{26}H_{32}N_3O_3$ 434.2443, found 434.2447.

*N-α-Acetyl-5-biphenyl-1-benzyl-L-histidine methyl ester (**3i**):* R_f = 0.5 (MeOH/$CHCl_3$, 1/9) yield 587 mg (78%); brownish yellow liquid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 (s, 1H), 7.66 (dd, J = 5.5, 7.5 Hz, 4H), 7.45 (t, J = 7.7 Hz, 2H), 7.33−7.37 (m, 1H), 7.25 (d, J = 8.3 Hz, 2H), 7.18−7.23 (m, 3H), 6.80−6.82 (m, 2H), 5.11 (s, 2H), 4.46 (t, J = 7.0 Hz, 1H), 3.41 (s, 3H), 2.84−2.86 (m, 1H), 2.82−2.84 (m, 1H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.4, 170.5, 140.1, 139.6, 138.3, 137.8, 134.7, 130.9, 129.6, 129.0, 128.4, 128.3, 128.0, 127.1, 127.0, 126.8, 52.8, 52.2, 48.4, 31.9, 29.2; IR (ν_{max}) 3784, 2924, 2854, 1752, 1752, 1402, 1275, 1260, 1038, 764, 750 cm^{-1}; HRMS (ESI-TOF) m/z [M + H$^+$] calculated for $C_{28}H_{28}N_3O_3$ 454.2130, found 454.2139.

*N-α-Acetyl-5-(4-chlorophenyl)-1-benzyl-L-histidine methyl ester (**3j**):* R_f = 0.5 (MeOH/$CHCl_3$, 1/9); yield 519 mg (76%); dark yellow liquid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 (s, 1H), 7.40 (d, J = 8.4 Hz, 2H), 7.18−7.20 (m, 3H), 7.14−7.17 (m, 2H), 6.75−6.77 (m, 2H), 5.07 (s, 2H), 4.41 (t, J = 6.9 Hz, 1H), 3.40 (s, 3H), 2.76−2.80 (m, 1H), 2.49−2.50 (m, 1H), 1.75 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.4, 170.6, 138.4, 137.5, 134.9, 133.5, 132.1, 129.1, 128.9, 128.7, 128.2, 128.0, 126.8, 55.0, 52.7, 52.2, 48.4, 29.0; IR (ν_{max}) 3785, 1402, 1275, 1260, 764, 749 cm^{-1}; HRMS (ESI-TOF) m/z [M + H$^+$] calculated for $C_{22}H_{23}ClN_3O_3$ 412.1428, found 412.1430.

*N-α-Acetyl-5-(4-cyanophenyl)-1-benzyl-L-histidine methyl ester (**3k**):* R_f = 0.5 (MeOH/$CHCl_3$, 1/9); yield 521 mg (78%); brownish yellow liquid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (s, 1H), 7.78 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.3 Hz, 2H), 7.15−7.16 (m, 3H), 6.73−6.75 (m, 2H), 5.13 (s, 2H), 4.44 (t, J = 6.9 Hz, 1H), 3.40 (s, 3H), 2.83 (d, J = 7.0 Hz, 1H), 2.80 (d, J = 7.0 Hz, 1H), 1.72 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.3, 170.5, 139.3, 137.2, 135.9, 134.5, 132.8, 130.9, 129.0, 128.3, 128.0, 126.8, 119.1, 110.9, 52.6, 52.2, 48.6, 29.0, 22.4; IR (ν_{max}) 3784, 2925, 1740, 1275, 1260, 1025, 764, 750 cm^{-1}; HRMS (ESI-TOF) m/z [M + H$^+$] calculated for $C_{23}H_{23}N_4O_3$ 403.1770, found 403.1778.

*N-α-Acetyl-5-phenyl-1-benzyl-L-histidine methyl ester (**3l**):* R_f = 0.5 (MeOH/$CHCl_3$, 1/9); yield 538 mg (86%); brown-yellow liquid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (s, 1H), 7.34−7.37 (m, 3H), 7.16−7.17 (m, 3H), 7.11−7.13 (m, 2H), 6.75−6.77 (m, 2H), 5.05 (s, 2H), 4.40 (t, J = 6.9 Hz, 1H), 3.38 (s, 3H), 2.80 (d, J = 4.8 Hz, 1H), 2.79 (d, J = 4.8 Hz, 1H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.4, 170.8, 138.0, 137.7, 134.3, 130.3, 130.0, 129.2, 129.1, 128.9, 128.8, 128.0, 126.8, 52.8, 52.2, 48.9, 48.4, 29.0; IR (ν_{max}) 3005, 1735, 1659, 1436, 1275, 1260, 1025, 764, 750, 703 cm^{-1}; HRMS (ESI-TOF) m/z [M + H$^+$] calculated for $C_{22}H_{24}N_3O_3$ 378.1817, found 378.1883.

*N-α-Acetyl-5-(2-naphthyl)-1-benzyl-L-histidine methyl ester (**3m**):* R_f = 0.5 (MeOH/$CHCl_3$, 1/9); yield 496 mg (70%); dark brown liquid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87−7.90 (m, 2H), 7.79−7.83 (m, 2H), 7.66 (s, 1H), 7.50−7.52 (m, 2H), 7.27 (dd, J = 1.6, 8.4 Hz, 1H), 7.13−7.15 (m, 3H), 6.76 (d, J = 4.0 Hz, 2H), 5.14 (s, 2H), 4.46 (t, J = 6.9 Hz, 1H), 3.37 (s, 3H), 2.86 (d, J = 5.6 Hz, 1H), 2.84 (d, J = 5.6 Hz, 1H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.5, 170.3, 138.3, 137.9, 135.0, 133.1, 132.7, 129.8, 129.5, 128.9, 128.5, 128.3, 128.0, 127.9, 127.8, 127.5, 127.1, 126.9, 126.8, 55.1, 52.7, 52.2, 48.5, 29.3; IR (ν_{max}) 3785, 3406, 2924, 1746, 1378, 1275, 1260, 1029, 750 cm^{-1}; HRMS (ESI-TOF) m/z [M + H$^+$] calculated for $C_{26}H_{26}N_3O_3$ 428.1974, found 428.1975.

Synthesis of *N-α*-acetyl-5-phenyl-L-histidine Methyl Ester (4a). We established the debenzylation procedure of **3l** by an procedure reported earlier.[20] A suspension of **3l** (1 equiv, 1.09 mmol) and 10% Pd−C (10 equiv, 10.9 mmol) in methanol (5 mL) was treated with ammonium formate (5 equiv, 5.48 mmol), and the reaction mixture was refluxed for 18 h. The reaction mixture was filtered through a Celite pad, and the solvent was removed under reduced pressure. The resulting residue upon purification on a fully automated flash column chromatography system yielded **4a**: R_f = 0.5 (MeOH/$CHCl_3$, 2:8); yield 282 mg (90%); pale white liquid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63 (s, 1H), 7.46 (d, J = 7.8 Hz, 2H), 7.39 (t, J = 7.7 Hz, 2H), 7.24−7.28 (m, 1H), 4.46−4.49 (m, 1H), 3.40 (s, 3H), 3.12−3.18 (m, 1H), 3.03−3.08 (m, 1H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.3, 170.9, 135.3, 132.5, 129.2, 127.3, 127.0, 52.8, 52.7, 52.3, 28.3; IR (ν_{max}) 2917, 2291, 1733, 1634, 1412, 1163, 1048, 941, 727 cm^{-1}; HRMS (ESI-TOF) m/z [M + H$^+$] calculated for $C_{15}H_{18}N_3O_3$ 288.1348, found 288.1345.

Synthesis of 5-Phenyl-L-histidine·2HCl (5a). A solution of *N-α*-acetyl-5-phenyl-L-histidine methyl ester (**4a**) in 6 N HCl was heated at 100 °C for 24 h. The complete removal of solvent under reduced pressure produced **5a**: yield 382 mg (95%); light colorless liquid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (s, 1H), 7.53 (d, J = 3.0 Hz, 3H), 7.49−7.51 (m, 2H), 4.27−4.31 (m, 1H), 3.38 (s, 1H), 3.36 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.6, 134.3, 130.5, 130.1, 129.8, 128.6, 126.8, 123.5, 51.0, 25.3; IR (ν_{max}) 2934, 2354, 1600, 1350, 1170, 932, 831 cm^{-1}; HRMS (ESI-TOF) m/z [M + H$^+$] calculated for $C_{12}H_{14}N_3O_2$ 232.1086, found 232.1077.

Chiral HPLC Method. To analyze the optical integrity of the established protocol, a representative examples of 5-phenyl-L-histidine·2HCl and 5-phenyl-D-histidine·2HCl were analyzed using a ChiralPak-WH column on HPLC. The mobile phase used in this study was 5 mM copper(II) sulfate in water and 95−5% 2-propanol using a gradient run for 60 min. The flow rate of the mobile phase used was 1.5 mL/min, with a column temperature of 50 °C and detection at 254 nm.

■ ASSOCIATED CONTENT

Supporting Information

Figures giving all spectral data (^{1}H, ^{13}C, chiral HPLC). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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