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Regiocontrolled palladium-catalyzed and copper-mediated C–H bond functionalization of protected L-histidine†

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We describe the controlled and regioselective transition-metal-catalyzed C–H bond arylation of protected L-histidine with aryl halides as the coupling partner. Using this approach, a large number of C-2 arylated L-histidines have been synthesized with diverse substitutions bearing electron-donating and electron-withdrawing groups, in good to excellent yields. These synthetic amino acids possessing dual hydrophobic–hydrophilic character are important synthons of bioactive peptidomimetics, which are imperative potent inhibitors of *Cryptococcus neoformans*.

Invasive fungal infections, such as *Candidiasis*, *Cryptococcosis* and *Aspergillosis*, have increased considerably over the past few years, and are devastating in humans.[1] These infections mainly develop in immunocompromised patients and affect more than a million people, especially in the resource-limited countries.[2] *Cryptococcus* alone contributes to approximately 625 000 deaths by attacking the CNS system, resulting in death due to cryptococcal meningitis.[3] The seriousness of cryptococcal meningitis can be realized from a recent report released by the Center for Disease Control (CDC) claiming that the mortality from cryptococcal meningitis exceeds the death rate from tuberculosis.[4] Despite extensive efforts to develop new antifungal agents by numerous research groups, the armament of available drugs remains limited.[5] The currently used antimycotic agents target a limited repertoire of fungal-specific cell walls and presents several serious issues such as drug related toxicity, non-optimal pharmacokinetics, poor solubility and serious drug–drug interactions.[6] In our current endeavour to discover a new pharmacophore against deadly *C. neoformans*, we recently disclosed a series of peptidomimetics wherein a number of analogues exhibited activity that was several fold higher than the currently used drug amphotericin B. The peptidomimetics also did not exhibit cytotoxicity when examined in a panel of six mammalian cell lines.[7] Out of all the peptidomimetics tested against *C. neoformans*, the most promising are Arg-His(4-*t*-butylphenyl)-Arg-NHBzl (**NP-2779**) and Arg-His-(biphenyl)-Arg-NHBzl (**NP-2777**) (shown in Fig. 1).

The important structural features of these peptidomimetics are the presence of a free N-terminus and two guanidinium side chains of arginine along with the imidazole ring constituting the indispensable charged moieties of the pharmacophore, whereas the aryl substitution on the L-histidine and benzylamide group at the C-terminus conveys the required lipophilic bulk.

The potent activity exhibited by the above-mentioned peptidomimetics created a greater need for various C-2 arylated histidines. We recently disclosed a method for regioselective direct C-2 arylation of *N*-α-trifluoroacetyl-L-histidine methyl ester using arylboronic acids.[8] The substrate scope for this transformation is quite broad; however, low overall yields (15–55%), more specifically in the case of electron-withdrawing groups containing aryl substituents (15–20%), limits its potential application. Another shortcoming of this method is the use of expensive arylboronic acids and their limited availability. Thus, we set as our goal the quest for an improved method for the regioselective C-2 arylation of histidine, which would be superior in terms of the above-mentioned factors.

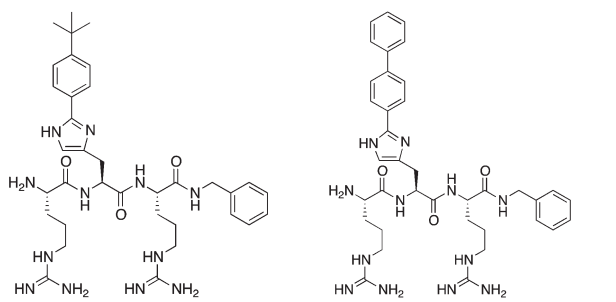

Fig. 1 Structural formula of **NP-2779** and **NP-2777**.

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More recently, we published the microwave (MW)-assisted direct C–H arylation at the C-5 position of fully protected L-histidine *via* a palladium-catalyzed transformation reaction.[9] This is the first catalytic example on histidine to construct a C–C bond with aryl halides as the coupling partner. In recent years, researchers have started searching for novel approaches to develop clean and efficient synthetic methods based on C–H activation to construct useful scaffolds, which can be incorporated into the lead molecules to optimize their activity.[10] The other methods for C–C bond construction include the renowned conventional Suzuki-, Negishi-, Hiyama-, and Kumada-cross-coupling reactions.[11] The advantages of C–H activation over cross-coupling reactions are the exclusion of pre-activated substrates and elimination of undesired by-products. Thus, the ideal organic transformations would be initiated from the easily available and inexpensive chemicals. In this context, the direct transformation of the C–H bond, a ubiquitous group in the organic world, into desired functionalities has drawn much attention and interest.[12]

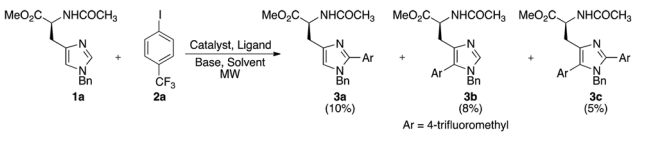
Herein, we report the regiocontrolled C–H bond functionalization of protected L-histidine using inexpensive aryl halides as the coupling partner. This arylation reaction is proficient with various aryl iodides containing both electron-withdrawing and electron-donating substituents to give access to a diverse library of 2-aryl-L-histidine analogues.

A number of reports involving C–H activation have been reported in a wide range of substrates, including heterocyclic scaffolds.[13] In these heterocyclic scaffolds, the selectivity among the electron-deficient and electron-rich sites is always a dubious question. A limited number of regioselective direct arylation reports have been available over the past few years,[14] but regioselective arylation of amino acids has received much less attention.[15] In the year 2007, Bellina and Rossi published regioselective Pd- and Cu-mediated reactions on a large variety of π-electron-deficient heteroarenes.[16] In another report, Fagnou and his co-workers described Pd-catalyzed direct arylation of a wide range of heterocycles with aryl halides.[17] In subsequent years, Sames and other research groups published a number of research articles on the direct C–H activation.[18] After taking clues from several earlier reports, we first attempted the direct arylation of commercially available Ac-His-OMe (**1**) with 4-iodobenzotrifluoride (**2a**, 2 equiv.) using $Pd(OAc)_2$ (20 mol%), PPh_3 (40 mol%), K_2CO_3 (3 equiv.), CuI (2 equiv.) and pivalic acid (40 mol%) in DMF at 140 °C for 72 h. But to our disappointment no arylation took place, probably due to the interference of the reactive imidazole ring NH group. In our earlier work on the regioselective Pd-catalyzed direct C-5 arylation of protected histidine, we discussed the merits and demerits of various NH protecting groups.[9] A careful examination of various protective groups resulted in the observation that the benzyl group is most suitable for the reaction. The use of the benzyl group is not only favoured by the moderate conditions of its incorporation and removal, but also favoured by the fact that its presence introduces more lipophilicity into the histidine, a critical requirement for the antifungal peptides, where it is essential for potent activity against *C. neoformans*.

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**). Next, C–H arylation of **1a** keeping the above reaction conditions was examined. We did not observe the arylation reaction at 140 °C over a period of 48–72 h. In order to provide sufficient energy to activate and subsequently functionalize the C–H bond, we then used MW irradiation. We observed arylation of **1a** in the presence of **2a** (2 equiv.) using $Pd(OAc)_2$ (20 mol%), PPh_3 (40 mol%), K_2CO_3 (3 equiv.), CuI (2 equiv.) and pivalic acid (40 mol%) in DMF under MW irradiation (140 °C, 45 min, 100 W) to provide overall low yield of a mixture of fully protected arylated L-histidines [2-aryl (**3a**, 10%), 5-aryl (**3b**, 8%) and 2,5-diaryl (**3c**, 5%)] (Scheme 1).

We then set as our goal to identify the catalytic system combination required for the regiocontrolled formation of C-2 arylated products. The reactivity at different positions of L-histidine is governed by different factors, thereby creating an underlying problem associated with the direct arylation of the imidazole ring of histidine. In general, nucleophilicity at the C-5 and the acidic nature of C–H at the C-2 positions have been documented in the past.[19] In order to provide a method for regioselective arylation of the five-membered imidazole ring containing histidine residue at the most electron-deficient center, we screened various palladium catalysts substituted with diverse groups along with phosphine ligands.

As shown in Table 1, all possible regioisomers (**3a**, **3b** and **3c**) formed when $Pd(OAc)_2$ was used in the presence of PPh_3, PCy_3 and P(2-furyl)$_3$ (entry no. 1, 2 and 3). Changing the ligand to P(*n*-Bu)(1-adamantyl)$_2$ while keeping the catalyst intact resulted in substantially higher conversion of **1a** to **3a** (75%) with enhanced yield (52%), and absolute regioselectivity (entry no. 4). The change of the ligand to P(*t*-Bu)$_3$HBF$_4$ produced a significant amount of C-2 arylated product (42%), but not complete regioselectivity (entry no. 5). To confirm the role of CuI in the C-2 arylation, we also performed a reaction while keeping the catalytic system intact [$Pd(OAc)_2$–P(*n*-Bu)-(1-adamantyl)$_2$], but excluded CuI (entry no. 6). The predominance of C-5 arylation confirms the formation of a π-complex of Cu with a C–H bond at the C-2 position and its conversion into a C–Cu bond followed by a transmetallation reaction with the palladium catalyst. No reaction was observed when $Pd_2(dba)_3$ was used as a catalyst in the presence of P(*n*-Bu)-(1-adamantyl)$_2$ (entry no. 7). We further tried to enhance the yield by using various palladium catalysts such as $Pd(PPh_3)_2Cl_2$ and $Pd(CH_3CN)_2Cl_2$ possessing electron-withdrawing substituents, and P(*n*-Bu)(1-adamantyl)$_2$ as a ligand. However, these catalytic combinations under the reaction conditions also gave a mixture of **3a**, **3b** and **3c** (entry no. 8, 9 and



Scheme 1 MW-assisted direct arylation of **1a** with **2a**.

Table 1 Screening of catalysts and ligands for the conversion of **1a** to **3a**[a]

S. no.	Catalyst	Ligand	CuI	C-2	C-5	C-2 and C-5	Conv. (%)
1.	$Pd(OAc)_2$	PPh_3	CuI	10	8	5	45
2.	$Pd(OAc)_2$	PCy_3	CuI	38	15	8	70
3.	$Pd(OAc)_2$	P(2-furyl)$_3$	CuI	20	18	12	55
4.	$Pd(OAc)_2$	P(*n*-Bu)(1-adamantyl)$_2$	CuI	52	—	—	75
5.	$Pd(OAc)_2$	P(*t*-Bu)$_3$HBF$_4$	CuI	42	5	2	60
6.	$Pd(OAc)_2$	P(*n*-Bu)(1-adamantyl)$_2$	—	2	38	3	58
7.	$Pd_2(dba)_3$	P(*n*-Bu)(1-adamantyl)$_2$	CuI	—	—	—	—
8.	$Pd(PPh_3)_2Cl_2$	P(*n*-Bu)(1-adamantyl)$_2$	CuI	26	6	3	70
9.	$Pd(CH_3CN)_2Cl_2$	P(*n*-Bu)(1-adamantyl)$_2$	CuI	30	2	3	55
10.	$Pd(TFA)_2$	P(*n*-Bu)(1-adamantyl)$_2$	CuI	40	—	—	65
11.	$PdCl_2(dppf)_2$	P(*n*-Bu)(1-adamantyl)$_2$	CuI	23	2	2	40

[a] Reaction conditions: **1a** (1 equiv.), **2a** (2 equiv.), CuI (2 equiv.), catalyst (20 mol%), ligand (40 mol%), K_2CO_3 (3 equiv.), PivOH (40 mol%), DMF (2 mL), 140 °C, 45 min, MW.

11). The use of $Pd(TFA)_2$ in the presence of P(*n*-Bu)(1-adamantyl)$_2$ resulted in lower yield (40%), but with regioselectivity intact (entry no. 10).

Next, we examined the possible influence of some reaction parameters like solvent and base on the outcome of the regioselective C-2 arylation. The use of heterogeneous bases such as Cs_2CO_3, CsF and K_3PO_4 did not offer any advantage over K_2CO_3 (entry no. 2, 3 and 6, Table 2). The use of a homogeneous stronger base such as *t*-BuOK led to higher conversion with enhanced yield of **3a**, probably due to the inherent selectivity of the base for acidic sites within the hetero ring (entry no. 4). Moreover, we observed that no reaction occurred when acetonitrile (ACN), 1,4-dioxane or 1,2-dichloroethane (DCE) was used as a solvent in place of DMF (entry no. 8, 10 and 12). In contrast, the use of a solvent such as DMF, *N*-methyl-2-pyrrolidone (NMP), *N*,*N*-dimethylacetamide (DMA) or dimethyl sulfoxide (DMSO) possessing mildly basic characteristics offered higher yields, with NMP emerging as the solvent of choice (entry no. 7). All these experiments led us conclude that the use of Ar–X (2 equiv.), $Pd(OAc)_2$ (20 mol%), P(*n*-Bu)(1-adamantyl)$_2$ (40 mol%), CuI (2 equiv.), *t*-BuOK (3.0 equiv.), and PivOH (40 mol%), in NMP as a solvent at 140 °C for 45 min under MW irradiation offered the best conditions for the direct regiocontrolled formation of **3a**.

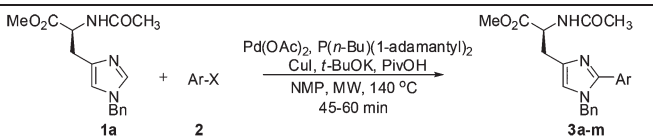
We then applied the newly developed direct arylation conditions to other aryl counterparts to obtain a number of C-2 arylated products with absolute regioselectivity in good to excellent yields. The results of the arylation reaction are given in Table 3. As is evident, a long (45–60 min) reaction time was

Table 2 Screening of bases and solvents for the conversion of **1a** to **3a**[a]

Entry	Base	Solvent	Catalyst/ligand	Conv. (%)
1.	K_2CO_3	DMF	$Pd(OAc)_2$/P(*n*-Bu)-(1-adamantyl)$_2$	75
2.	Cs_2CO_3	DMF	$Pd(OAc)_2$/P(*n*-Bu)-(1-adamantyl)$_2$	45
3.	CsF	DMF	$Pd(OAc)_2$/P(*n*-Bu)-(1-adamantyl)$_2$	46
4.	*t*-BuOK	DMF	$Pd(OAc)_2$/P(*n*-Bu)-(1-adamantyl)$_2$	79
5.	DBU	DMF	$Pd(OAc)_2$/P(*n*-Bu)-(1-adamantyl)$_2$	51
6.	K_3PO_4	DMF	$Pd(OAc)_2$/P(*n*-Bu)-(1-adamantyl)$_2$	32
7.	*t*-BuOK	NMP	$Pd(OAc)_2$/P(*n*-Bu)-(1-adamantyl)$_2$	89
8.	*t*-BuOK	ACN	$Pd(OAc)_2$/P(*n*-Bu)-(1-adamantyl)$_2$	—
9.	*t*-BuOK	DMSO	$Pd(OAc)_2$/P(*n*-Bu)-(1-adamantyl)$_2$	45
10.	*t*-BuOK	1,4-Dioxane	$Pd(OAc)_2$/P(*n*-Bu)-(1-adamantyl)$_2$	—
11.	*t*-BuOK	DMA	$Pd(OAc)_2$/P(*n*-Bu)-(1-adamantyl)$_2$	60
12.	*t*-BuOK	DCE	$Pd(OAc)_2$/P(*n*-Bu)-(1-adamantyl)$_2$	—

[a] Reaction conditions: **1a** (1 equiv.), **2a** (2 equiv.), CuI (2 equiv.), PivOH (40 mol%), catalyst (20 mol%), ligand (40 mol%), base (3 equiv.), solvent (2 mL), 140 °C, 45 min, MW.

Table 3 Direct C-2 arylation of **1a** with aryl halides under MW irradiation[a]



Entry	Product no.	Ar–X	R	Yields (%)
1	**3a**	Ar–I	4-Trifluorophenyl	78
2	**3d**	Ar–I	3-Trifluorophenyl	74
3	**3e**	Ar–I	2-Trifluorophenyl	72
4	**3f**	Ar–I	4-Cyanophenyl	76
5	**3g**	Ar–I	4-Chlorophenyl	77
6	**3h**	Ar–I	Phenyl	70
7	**3i**	Ar–I	4-*t*-Butylphenyl	65
8	**3j**	Ar–I	4-Methylphenyl	65
9	**3k**	Ar–I	4-Methoxyphenyl	64
10	**3l**	Ar–I	Biphenyl	69
11	**3m**	Ar–I	2-Naphthyl	69
12	**3a**	Ar–Br	4-Trifluorophenyl	48
13	**3f**	Ar–Br	4-Cyanophenyl	36
14	**3g**	Ar–Br	4-Chlorophenyl	38

[a] Reaction conditions: **1a** (1.0 equiv.), Ar–X (2.0 equiv.), $Pd(OAc)_2$ (20 mol%), P(*t*-Bu)(1-adamantyl)$_2$ (40 mol%), CuI (2 equiv.), *t*-BuOK (3.0 equiv.), PivOH (40 mol%), NMP, MW (140 °C, 45–60 min, 100 W).

required, depending on the aryl iodide used. Both electron-rich and electron-deficient aryl iodides reacted with **1a** to give good isolated yield of **3**. The sterically hindered aryl iodide (entry no. 2 and 3) also produced the desired product in good yield. Importantly, these reaction conditions proved compatible in the presence of reactive functional groups such as cyano and chloro on the aromatic ring, which may be subjected to further synthetic manipulations. The successful coupling reaction with the polyaromatic 4-iodobiphenyl and 2-iodonaphthalene showed the wide range of this transition-metal-catalyzed reaction (entry no. 10 and 11). The reaction was found to also offer products when using aryl bromides as the coupling partner, but in much lower yields (entry no. 12, 13 and 14) when compared to the aryl iodides.

On the basis of experimental observations and earlier reports,[20] a plausible mechanism of the Pd/Cu-catalyzed direct arylation of **1a** might involve a base-assisted cupration of the **1a** to give the aryl-Cu species (**TS-I**, Fig. 2). Subsequently, **TS-I** undergoes transmetallation with an aryl-Pd complex **TS-II** (**TS-II** formed by the oxidative addition of Pd^0 to aryl iodide) to give intermediate **TS-III**, which undergoes reductive elimination to furnish the product **3a** with the concomitant use of both Pd and Cu catalysts.

The protecting groups of **3a** were removed at the very end by using earlier reports.[21] For debenzylation, a suspension of **3a** in 10% Pd–C in methanol was treated with ammonium formate and the mixture was refluxed for 18 h to afford **4** in 85% yield. Finally, the removal of α-amino and α-carboxyl protecting groups in **4** was achieved by refluxing in aqueous 6 N HCl for 24 h. The 2-(4-trifluorophenyl)-L-histidine·2HCl (**5**) was obtained by the evaporation of the acidic solution (Scheme 2).

To confirm the chiral integrity of the synthesized C-2 arylated amino acids, chiral HPLC of **5** was performed on a ChiralPak-WH column. We have also synthesized 2-(4-trifluorophenyl)-D-histidine·2HCl to differentiate between the retention times of the enantiomers. It was clear from the HPLC chromatograms of the enantiomers that chiral integrity was well maintained in this reaction (see ESI†).

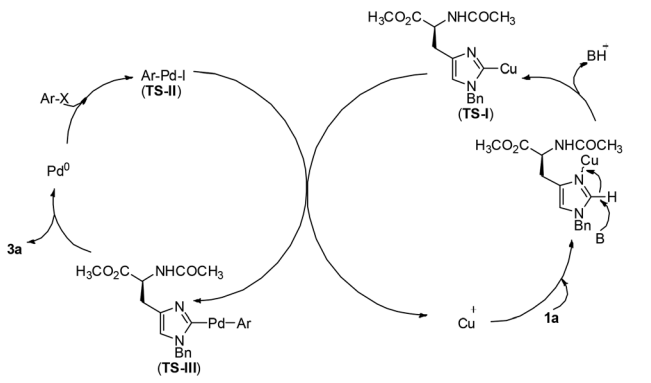
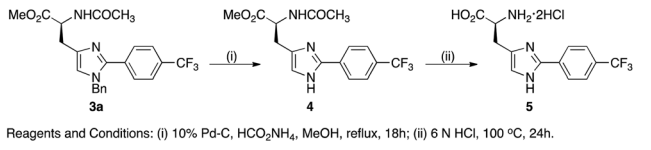


Fig. 2 Plausible mechanism of the direct C-2 arylation.



Scheme 2 Removal of the protecting groups of **3a**.

Conclusions

We have developed an efficient, regioselective and direct C–H arylation reaction of Ac-His(Bn)-OMe effectively catalyzed by the $Pd(OAc)_2$–P(*n*-Bu)(1-adamantyl)$_2$–CuI catalytic system under MW irradiation. The reaction offers high yields and absolute regioselectivity when *t*-BuOK is used as a base in the presence of NMP as the solvent medium. This protocol is equally compatible with electron-deficient and electron-withdrawing aryl partners. The 2-aryl-L-histidines obtained using this versatile procedure are important building blocks of potent and promising antifungal peptides. Further applications of these arylated amino acids in the synthesis of new structural classes of peptides are currently under study.

Experimental section

All arylation reactions were carried out under an argon atmosphere, unless otherwise stated. Reaction times refer to the hold time at the desired set temperature and not to the total irradiation time. Reaction cooling is performed by compressed air automatically after the heating period has elapsed. All the solid reagents were weighed in air and placed in a 10 mL MW vial equipped with a magnetic stir bar. To a 10 mL capacity MW vial, *t*-BuOK (3.0 equiv., 4.98 mmol), $Pd(OAc)_2$ (20 mol%, 0.34 mmol), P(*n*-Bu)(1-adamantyl)$_2$ (40 mol%, 0.66 mmol), CuI (2 equiv., 3.32 mmol) and PivOH (40 mol%, 0.66 mmol) and **1a** (1 equiv., 1.66 mmol) were added and the reaction mixture was purged with argon. The appropriate aryl halide, if solid (**2**, 2 equiv., 3.32 mmol), was added at this point. The reaction mixture was purged with argon and NMP (2 mL) was added. The aryl halide, if liquid (**2**, 2 equiv., 3.32 mmol), is added at this point. Addition of solvent was done under positive argon pressure with stirring. The sealed reaction vial was then placed in the MW reactor (CEM Discover®) and stirred at 140 °C for the indicated time. The solution was then cooled to ambient temperature and diluted with EtOAc, washed with H_2O (3 times), dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The reaction mixture was purified on a Biotage® automated flash column chromatography system to give the desired product.

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