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Selective Pd^0-Mediated C–C Bond Constructions on the Imidazole Ring of L-Histidine: A Practical Approach to the Synthesis of Diphthamide and Related Histidine Analogues**

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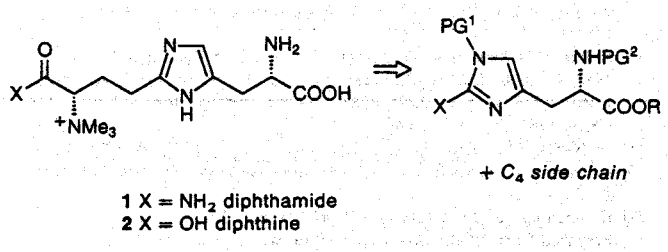
Dedicated to Professor Reinhard W. Hoffmann on the occasion of his 60th birthday

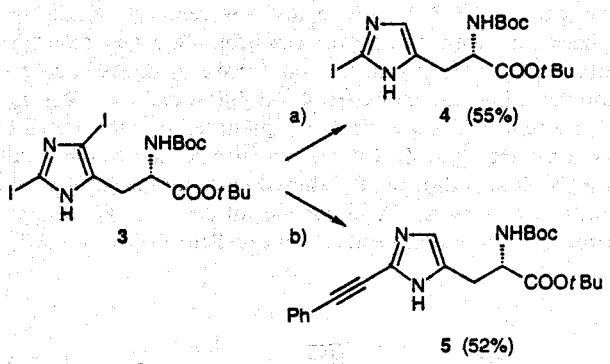
The unique amino acid diphthamide **1**, the target of diphtheria toxin-catalyzed ADP-ribosylation in elongation factor 2 (EF-2) has raised much scientific interest, in particular concerning its role in protein biosynthesis.[1] In our efforts to devise a practical synthesis of diphthamide,[2] we were attracted to the prospect of utilizing L-histidine as one of the principal building blocks for this amino acid (Scheme 1). In particular, the idea of introducing the methionine-derived, C_4 side chain late, and possibly fully functionalized, in the synthesis led us to consider mild Pd-catalyzed coupling reactions[3] for the decisive C–C bond formation. The weakness in this synthetic strategy was associated with the fact that there are few suitable literature procedures available for the regioselective functionalization of histidine at the C2 position of the imidazole nucleus. Of the various reactions reported,[4] only the reactions with diazonium salts proceed with high selectivity at C2.[5] On the other hand, histidine can be converted selectively into 4-iodo[6] or 2,4-diiodo derivatives[7] depending upon the iodine/substrate ratio. Accordingly, with the potential availability of diiodohistidine derivatives such as **3**,[8] we entertained the prospect of carrying out C2 selective Pd^0-catalyzed reactions with substituted alkynes and other organometallic reagents. In spite of the discouraging literature precedent,[9] we thought that selective cross coupling might be achieved at the more sterically accessible, electronically deficient C2 position of the imidazole nucleus.



1 X = NH_2 diphthamide
2 X = OH diphthine

Scheme 1. PG^1, PG^2 = protecting group.

Surprisingly, phenylacetylene, in the presence of Pd^0, functioned as a reducing agent to afford, by a selective H–I exchange (ca. 3/1) at the C4 atom, the monoiodide **4**, which was readily obtained in isomerically pure form by flash chromatography (Scheme 2). In addition to **4**, 1,4-diphenylbutadiyne was isolated as the major by-product of the reaction. If the same reaction is carried out in the presence of phosphane ligands, the Heck coupling[10] product **5** is obtained in 52% yield in high enantiomeric purity [>95% *ee* as determined by NMR analysis of the derivatives with (+)- and (−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride]. This pivotal reaction thus solves the dual problem of the dehalogenation at the C4 atom and the bond construction at the C2 atom in a single operation. Although a concise mechanism cannot be established at the present time, it seems likely that the proximity of a comparably acidic NH-proton facilitates an intramolecular proton transfer to a Pd–C intermediate, initially formed by oxidative addition. Indeed, simple 5-alkyl-substituted diiodoimidazoles underwent sluggish, poorly selective dehalogenations under identical conditions.



Scheme 2. Deiodination and coupling reactions of compound 3. Reagents and conditions: a) 3 equiv PhCCH, 0.05 equiv $[Pd(dba)_2]$ (dba = dibenzylidenacetone), 0.07 equiv CuI in NEt_3; 65 °C; 5 h. b) 3 equiv PhCCH, 0.1 equiv $[PdCl_2(PPh_3)_2]$, 0.05 equiv CuI in NEt_3; 65 °C; 12 h.

The extension of the C2 coupling process with representative alkynes was then investigated. *N*-Protection of **4** (Boc_2O, NEt_3 in CH_2Cl_2; 97%) yielded the monoiodohistidine derivative **6** which proved to be a versatile substrate for Pd-catalyzed coupling reactions (Table 1).

With **6** in hand we turned our attention towards reactions that might lead to the incorporation of functionalized car-

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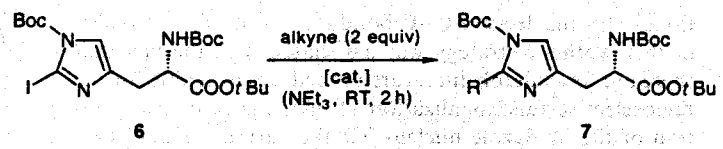

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Table 1. Pd-catalyzed coupling of alkynes with **6**.

Alkyne	Catalyst	Equiv	Yield [%]	Product
Bu—≡—H	$[PdCl_2(PPh_3)_2]/CuI$	0.05/0.1	91	**7a**
Ph—≡—H	$[PdCl_2(PPh_3)_2]/CuI$	0.05/0.1	98	**7b**
tBu—≡—H	$[PdCl_2(PPh_3)_2]/CuI$	0.05/0.1	96	**7c**
Me_3Si—≡—H	$[PdCl_2(PPh_3)_2]/CuI$	0.05/0.1	83	**7d**
HO— —≡—H	$[PdCl_2(PPh_3)_2]/CuI$	0.05/0.1	94	**7e**
Ph—≡—$SnBu_3$	$[PdCl_2(PPh_3)_2]$	0.1	97 [a]	**7b**

[a] Conditions: THF, reflux, 4 h.

bon chains at C2. In this regard, the reaction of alkylzinc compounds with iodoarenes has been shown to tolerate a high degree of functionalization.[11] We therefore sought to employ a homoserine-based 4-iodobutanoic acid ester as a C_4 precursor. These esters were quantitatively metalated by using an activated Zn/Cu couple.[12] Addition of the resulting alkylzinc iodide in *N,N*-dimethylacetamide (DMA) to a solution of **6** in DMA under the influence of Pd catalysis afforded the desired products in excellent yields (Table 2).

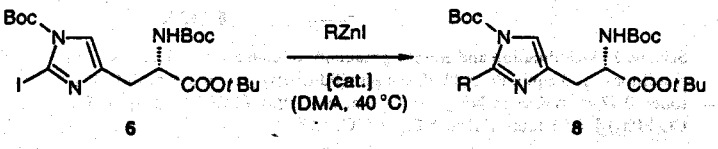

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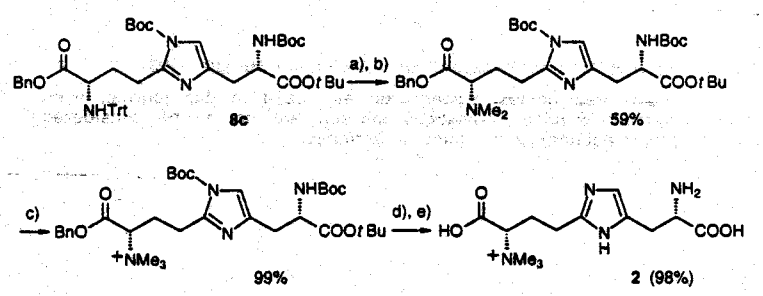
Table 2. Pd-catalyzed coupling of functionalized alkylzinc iodides with **6**.

RZnI	Equiv	Catalyst	Equiv	Yield [%]	Product
EtO(O)C—ZnI	2	$[PdCl_2(PPh_3)_2]$	0.1	84	**8a**
BnO(O)C—CH(NHBoc)—ZnI	4	$[PdCl_2(PPh_3)_2]$	0.1	65	**8b**
BnO(O)C—CH(NHTrt)—ZnI	3	$[PdCl_2(PPh_3)_2]$	0.1	79	**8c**

The required amino acid esters were prepared stepwise from L-homoserine by standard methods.[13] The coupling reaction proceeded smoothly without detectable epimerization, which was demonstrated by comparison of **8c** with its diastereomer, obtained from *rac*-homoserine. The practicability of this route was finally illustrated in the completion of a total synthesis of diphthine **2**, the most important degradation product of diphthamide[14] (Scheme 3). The trityl group (Trt) in **8c** was selectively cleaved by titration with 0.1 N HCl in 90% aqueous trifluoroethanol (TFE) without loss of the Boc-protecting groups.[15] Subsequent reductive elimination, quaternization, and deprotection led to (*S,S*)-diphthine **2**. Other analogues and diphthamide itself should be equally well accessible by combining this coupling sequence with previously described methods.[2]



Scheme 3. Completion of the total synthesis of (*S,S*)-diphthine **2**. Reagents and conditions: a) 0.1 N HCl in TFE (aq, 90%), pH > 4; room temperature (RT). b) CH_2O, NaOAc in $HOAc/H_2O/MeOH$; $NaCNBH_3$; RT. c) 25 equiv MeI in MeOH; RT; 2 d. d) H_2 (500 psi), Pd/C (100% w/w) in $HOAc/H_2O/MeOH$ (1/1/3); RT; 14 h. e) 2 N HCl (aq); RT; 14 h.

In conclusion, the preceding study establishes the first reliable methodology for the selective carbofunctionalization of the imidazole moiety at the C2 atom in L-histidine. An extension of the Pd-catalyzed transformations to related, simpler imidazole derivatives appears possible.

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