DOI: 10.1002/ejoc.201000591

Chan–Lam–Evans Coupling of Cbz-Protected Histidines

Christophe DalZotto,[a] Julien Michaux,[a] Elodie Martinand-Lurin,[a] and Jean-Marc Campagne*[a]

Keywords: Copper / Amino acids / Peptidomimetics / Cross-coupling

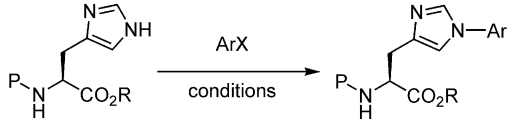
Direct functionalization of protected histidines with arylboronic acids is described under Chan–Lam–Evans conditions to give the corresponding *N*(τ)-arylhistidines in moderate to good yields (12 examples, up to 83 % yield) under mild conditions.

Introduction

The functionalization of amino acids has attracted attention of synthetic chemists due to their chemical and biological stability and pharmacokinetic characteristics upon introduction into peptide-based compounds.[1,2] In living systems, the diversity of amino acid derived products is also greatly extended by further functionalization at various stages of biosynthesis. For example, *N*(τ)-(hetero)arylhistidines are found in the active site of cytochrome c oxidase,[3,4] in natural products (celogentins, moroidin),[5] and have been isolated from liver proteins of rats treated with bromobenzene.[6] Moreover, synthetic *N*-arylimidazoles are found in an increasing number of drugs such as Losartan (antihypertension), Etomidate (hypnotic agent), and Flumazenil (benzodiazepine antagonist).[7]

Among the various strategies described to obtain the *N*(τ)-(hetero)arylhistidine derivatives,[3,8–10] metal-catalyzed direct functionalization of protected histidines has recently been described. To the best of our knowledge, these transformations (Table 1) have been carried out by using Ullmann coupling reactions from aryl iodides in low yields (4 examples, <15% yield)[10] or by using copper catalyzed cross-coupling reactions from aryllead triacetate (4 examples, 48–68% yield),[3] albeit the use of stoichiometric amounts of lead detracts from the attractiveness of the method. In the context of an on-going project on the synthesis of celogentin C,[11] we have been interested in the direct functionalization of such protected histidine derivatives.

Table 1. Direct functionalization of protected histidines.



X	Conditions	Yield	Ref.
I	$Cu(OTf)_2$ (10 mol-%,), Phen (20 mol-%), dba (20 mol-%), Cs_2CO_3 (2 equiv.), DMF, xylene, 120 °C	<15% 4 examples	[10]
$Pb(OAc)_3$	$Cu(OAc)_2$, DCM, r.t.	48–68% 4 examples	[3]
$B(OH)_2$	this work		

Results and Discussion

Starting from commercially available Cbz-His-OMe (**1**), whose protection pattern allows further modification of the cross-coupled product, various condition reactions have thus been undertaken. Despite a mass of different experimental conditions tested, none of the latest versions of the Buchwald–Hartwig[12] and Ullmann[13] conditions proved successful in our hands (yields <10%). Moving to the Chan–Lam–Evans cross-coupling reaction had a dramatic influence on the reaction outcome. The Chan–Lam–Evans coupling has recently emerged as an interesting alternative to the more classical copper-catalyzed Ullmann cross-coupling reactions.[14,15]

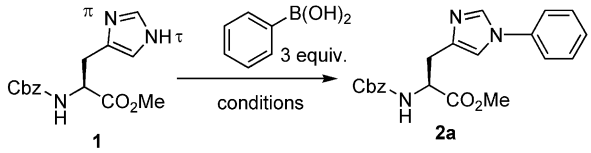
These coupling reactions are compatible with a wide range of heteroatom nucleophiles, including amines, amides, nitrogen heterocycles, alcohols, and phenols to form carbon–heteroatom bonds from arylboronic acids and nitrogen (and oxygen) nucleophiles under mild conditions.[16] Indeed, protected tyrosines have recently been functionalized by using the Chan–Lam–Evans methodology.[17] Moreover, thanks to the success of Suzuki–Miyaura reactions, a large number of arylboronic acids are now commercially available.

[a] Institut Charles Gerhardt, UMR 5253 CNRS-UM2-UM1-ENSCM,
8 Rue de l'Ecole Normale, 34296 Montpellier, France
Fax: +33-4-674322
E-mail: jean-marc.campagne@enscm.fr

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201000591.

Thus, starting from protected histidine **1** and phenylboronic acid, different copper sources were first tested (Table 2, Entries 1–3). As no reaction was observed with $Cu(OTf)_2$, the reaction in the presence of CuBr or $Cu(OAc)_2{\cdot}H_2O$ was next tested, leading to desired coupling product **2a** in moderate 26 and 31% yield, respectively. Using the reaction conditions described by Yu and Xie,[18] in methanol in an opened-air vessel, compound **2a** was obtained in a moderate 44% yield. To improve the yields, the use of various additives was next investigated (Table 2, Entries 5–7).[19] Additives such as KF or molecular sieves were not efficient (Table 2, Entries 6 and 7), whereas the use of 3 equiv. of NaOAc increased the yield to 62% (Table 2, Entry 5). The presence of oxygen[18] is crucial in the catalytic process (Scheme 2, Entry 8), as no reaction was observed under inert atmosphere.

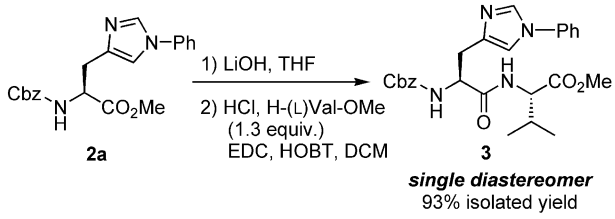
Table 2. Direct functionalization of **1** under Chan–Lam–Evans coupling conditions.



Entry	Catalyst (10 mol-%)	Conditions (50 °C, 24 h)	Additives	Isolated yield [%]
1	$Cu(OTf)_2$	DCM, air	–	NR
2	CuBr	DCM, air	–	26
3	$Cu(OAc)_2{\cdot}H_2O$	DCM, air	–	31
4	$Cu(OAc)_2{\cdot}H_2O$	MeOH, air	–	44
5	***$Cu(OAc)_2{\cdot}H_2O$***	***MeOH, air***	***NaOAc (3 equiv.)***	***62***
6	$Cu(OAc)_2{\cdot}H_2O$	MeOH, air	KF (3 equiv.)	40
7	$Cu(OAc)_2{\cdot}H_2O$	MeOH, air	4 Å MS	27
8	$Cu(OAc)_2{\cdot}H_2O$	MeOH, N_2	NaOAc (3 equiv.)	NR

Moreover, compound **2a** was obtained as a single regioisomer (to the less-hindered τ nitrogen atom as previously observed by Konopelski[3] and Hanzlik[10] by comparison with the previously described NMR spectroscopic data[3]) and in the absence of racemization. A racemization-free process is indeed essential when dealing with epimerizable amino acid derivatives. To check its stereogenic integrity, **2a** was first saponified in the presence of LiOH and then coupled to H-(L)-Val-OMe (Scheme 1). The absence of racemization could be observed by comparing the ^1H and ^{13}C NMR spectra and the HPLC chromatograms (see the Supporting Information) of crude **3** to a diastereomeric mixture obtained from **2a** and racemic H-(DL)Val-OMe. Compound **3b** was observed as a single diastereomer (>98:2 by ^1H NMR spectroscopy and HPLC, see the Supporting Information), confirming the stereochemical integrity of **2a**, and thus that the Chan–Lam–Evans protocol proceeds without racemization under these reaction conditions.[20]

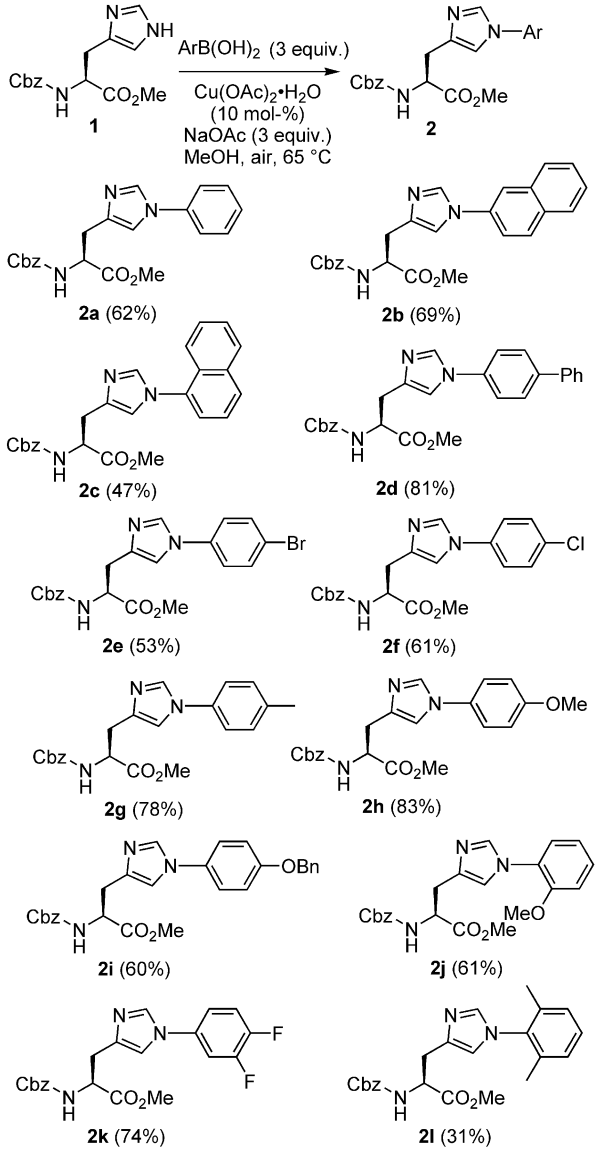
With these optimized reaction conditions in hand, we next employed a variety of arylboronic acids in this cross-coupling reaction. As illustrated in Scheme 2, the reaction tolerated a variety of functional groups.[20] In the presence



Scheme 1. Epimerization studies.

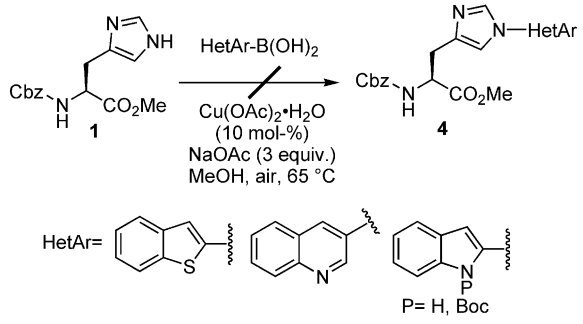
of further aryl groups such as 1- and 2-naphthalenes (i.e., **2b** and **2c**) and *p*-phenyl groups (i.e., **2d**) the products were obtained in 69, 47, and 81% yield, respectively.

Halogens in the *para* position (i.e., **2e** and **2f**), which potentially allow further functionalization of the aromatic ring, are well tolerated: 53 and 61% yield, respectively. Electron-rich (i.e., **2g–j**) and electron-poor (i.e., **2k**) aromatics were next successfully tested (60–83% yield). Finally and



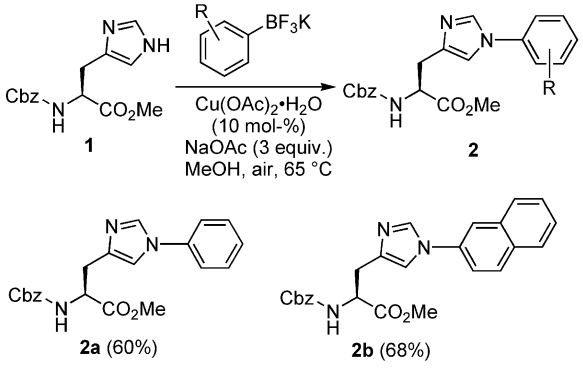
Scheme 2. Scope of the Chan–Lam coupling of **1** with various boronic acids.

not surprisingly,[13b] in the presence of the sterically hindered 2,6-dimethylphenyl boronic acid, compound **2l** was obtained in lower yield (31%). Next, in light of the synthesis of celogentin C,[11] various heteroaromatic boronic acids were tested in this reaction. However, a heteroatom on the boronic acid was found to be detrimental to efficiency, and no cross-coupling product could be observed from benzothiophene, (Boc- and unprotected) indoles, and quinoline derivatives (Scheme 3). Because histidine itself is heteroaromatic, such a behavior is puzzling. However heterocyclic boronic acids are known to be poorly active in Chan–Lam coupling reactions.[14f,15g]



Scheme 3. Chan–Lam–Evans coupling reactions with heteroaromatic boronic acids.

Finally, the use of potassium organotrifluoroborates was next tested in these reactions (Scheme 4).[21] However, no real improvement was observed (Scheme 4) in these transformations and compounds **2a** and **2b** were obtained in 60 and 68% yield, respectively (62 and 69% yield, respectively, from the corresponding boronic acid).



Scheme 4. Chan–Lam–Evans coupling reactions with organotrifluoroborates.

Conclusions

In conclusion, we have developed a regioselective, racemization-free, and efficient functionalization of protected histidines with various aromatic boronic acids. Under Chan–Lam–Evans conditions, using a modified and improved Yu/Xie protocol [air, $Cu(OAc)_2·H_2O$, MeOH, 50 °C] in the presence of NaOAc (3 equiv.), the cross-coupling products were isolated in moderate to good yields (12 examples, 31–83% yield) without epimerization. The use of these mild reaction conditions for the synthesis of pharmacologically active *N*(τ)-(hetero)arylhistidines is currently under progress.

Experimental Section

General Protocol for the Chan–Lam Coupling: To a solution of Z-Hist(OMe) (1 equiv.), NaOAc (3 equiv.), and $Cu(OAc)_2·H_2O$ (0.1 equiv.) in MeOH (0.4 M) was added arylboronic acid (3 equiv.). The mixture was heated in an open-air vessel at reflux for 24 h. The mixture was concentrated under vacuum, and the crude material was loaded on to a silica gel column and purified by chromatography with a mixture of cyclohexane/AcOEt.

Supporting Information (see footnote on the first page of this article): Characterization data of the prepared compounds, HPLC traces, copies of the ^1H and ^{13}C NMR spectra.

Acknowledgments

We are grateful to the Centre National de la Recherche Scientifique (CNRS) for financial support (ATIPE jeune équipe) and the Institut de Chimie des Substances Naturelles (ICSN), Gif sur Yvette, for PhD grants (C. D. Z. and J. M.).

[1] R. B. Herbert, *Nat. Prod. Rep.* **1999**, *16*, 199–208.
[2] A. Grauer, B. König, *Eur. J. Org. Chem.* **2009**, 5099–5111.
[3] a) G. I. Elliott, J. P. Konopelski, *Org. Lett.* **2000**, *2*, 3055–3057; b) J. A. Cappuccio, I. Ayala, G. I. Elliott, I. Szundi, J. Lewis, J. P. Konopelski, B. A. Barry, O. Einarsdottir, *J. Am. Chem. Soc.* **2002**, *124*, 1750–1760; c) K. N. White, I. Sen, I. Szundi, Y. R. Landaverry, L. E. Bria, J. P. Konopelski, M. M. Olmstead, O. Einarsdottir, *Chem. Commun.* **2007**, 3252–3254; d) Y. R. Landaverry, K. N. White, M. M. Olmstead, O. Einarsdottir, J. P. Konopelski, *Heterocycles* **2006**, *70*, 147–152.
[4] M. A. Halcrow, *Angew. Chem. Int. Ed.* **2001**, *40*, 346–349; *Angew. Chem.* **2001**, *113*, 358–362.
[5] a) J. Kobayashi, H. Suzuki, K. Shimbo, K. Takeya, H. Morita, *J. Org. Chem.* **2001**, *66*, 6626–6633; b) T.-W. Leung, C. Williams, J. C. J. Barna, S. Foti, P. B. Oelrichs, *Tetrahedron* **1986**, *42*, 3333–3348; c) S. D. Kahn, P. M. Booth, J. P. Waltho, D. H. Williams, *J. Org. Chem.* **1989**, *54*, 1901–1904; d) B. Ma, D. N. Litvinov, L. He, B. Banerjee, S. L. Castle, *Angew. Chem.* **2009**, *121*, 6104–6107; *Angew. Chem. Int. Ed.* **2009**, *48*, 6220–6223.
[6] R. B. Bambal, R. P. Hanzlik, *Chem. Res. Toxicol.* **1995**, *8*, 729–735.
[7] M. A. Bonin, D. Giguère, R. Roy, *Tetrahedron* **2007**, *63*, 4912–4917 and refs cited.
[8] a) K. S. Feldman, S. Quideau, H. M. Appel, *J. Org. Chem.* **1996**, *61*, 6656–6665; b) X. Huang, R. Xu, M. D. Hawley, K. J. Kramer, *Bioorg. Chem.* **1997**, *25*, 179–202; c) S. Deechonqkit, S. You, J. W. Kelly, *Org. Lett.* **2004**, *6*, 497–500.
[9] R. Bambal, R. P. Hanzlik, *J. Org. Chem.* **1994**, *59*, 729–732.
[10] W. Yue, S. I. Lewis, Y. M. Koen, R. P. Hanzlik, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1637–1640.
[11] J. Michaux, P. Retailleau, J. M. Campagne, *Synlett* **2008**, 1532–1536.
[12] M. W. Hooper, M. Utsnomiya, J. F. Hartwig, *J. Org. Chem.* **2003**, *68*, 2861–2873.
[13] a) A. Kiyomori, J. F. Marcoux, S. L. Buchwald, *Tetrahedron Lett.* **1999**, *40*, 2657–2660; b) E. Alcalde, I. Dinares, S. Rodriguez, C. Garcia de Miguel, *Eur. J. Org. Chem.* **2005**, 1637–1643; c) R. A. Altman, S. L. Buchwald, *Org. Lett.* **2006**, *8*, 2779–2782; d) H. Zhang, Q. Cai, D. Ma, *J. Org. Chem.* **2005**, *70*, 5164–5173; e) R. A. Altman, E. D. Koval, S. L. Buchwald, *J.*

Org. Chem. **2007**, *72*, 6190–6199; f) D. Ma, Q. Cai, H. Zhang, *Org. Lett.* **2003**, *5*, 2453–2455; g) F. Monnier, M. Taillefer, *Angew. Chem. Int. Ed.* **2009**, *48*, 6954–6971; *Angew. Chem.* **2009**, *121*, 7088–7105.

[14] a) D. M. T. Chan, K. L. Monaco, R. P. Wang, M. P. Winters, *Tetrahedron Lett.* **1998**, *39*, 2933–2936; b) D. A. Evans, J. L. Katz, T. R. West, *Tetrahedron Lett.* **1998**, *39*, 2937–2940; c) P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, M. P. Winters, D. M. T. Chan, A. Combs, *Tetrahedron Lett.* **1998**, *39*, 2941–2944; d) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054–3131; e) S. V. Ley, A. W. Thomas, *Angew. Chem. Int. Ed.* **2003**, *42*, 5400–5449; *Angew. Chem.* **2003**, *115*, 5558–5607; f) D. Chan, K. Monaco, R. Li, D. Bonne, C. Clark, P. Lam, *Tetrahedron Lett.* **2003**, *44*, 3863–3865.

[15] Review: a) D. M. T. Chan, P. Y. S. Lam in *Boronic Acids: Preparation, Applications in Organic Synthesis and Medicine* (Eds.: D. G. Hall), Wiley-VCH, Weinheim, **2005**, pp. 205–240; for selected recent examples: b) S. Bénard, L. Neuville, J. Zhu, *J. Org. Chem.* **2008**, *73*, 6441–6444; c) B. Sreedhar, G. T. Venkana, K. B. S. Kumar, V. Balasubrahmanyam, *Synthesis* **2008**, 795–799; d) Y. Zhu, S. H. Olson, A. Hermanowski-Vosatka, S. Mundt, K. Shah, M. Springer, R. Thieringer, S. Wright, J. Xiao, H. Zokian, J. M. Balkovec, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3405–3411; e) J. Liu, Y. Naruta, F. Tani, *Chem. Eur. J.* **2007**, *13*, 6365–6378; f) M. T. Wentzel, J. B. Hewgley, R. M. Kamble, P. D. Wall, M. C. Kozlowski, *Adv. Synth. Catal.* **2009**, *351*, 931–937; g) B. K. Singh, P. Appukkuttan, S. Claerhout, V. S. Parmar, E. Van der Eycken, *Org. Lett.* **2006**, *8*, 1863–1866; for mechanistic studies, see: h) A. E. King, T. C. Brunold, S. S. Stahl, *J. Am. Chem. Soc.* **2009**, *131*, 5044.

[16] During the preparation of this manuscript, one example of a Chan–Lam reaction on a protected histidine was described: M. E. Mahoney, A. Oliver, O. Einarsdottir, J. P. Konopelski, *J. Org. Chem.* **2009**, *74*, 8212–8218.

[17] B. Kilitoglu, H. Arndt, *Synlett* **2009**, 720–723.

[18] a) J. Lan, L. Chen, X. Yu, J. You, R. Xie, *Chem. Commun.* **2004**, 188–189; b) M. L. Kantam, B. Neelima, C. V. Reddy, V. Neeraja, *J. Mol. Catal. A* **2006**, *249*, 201–206.

[19] In the presence of lower quantities of boronic acid derivatives (<3 equiv.), lower conversions were usually observed.

[20] By analogy with **2a** (Scheme 3) and due to their structural similarities, an epimerization-free synthesis of **2b**–**l** is anticipated.

[21] a) T. D. Quach, R. A. Batey, *Org. Lett.* **2003**, *5*, 4397–4400; b) S. Darses, S. J.-P. Genet, *Chem. Rev.* **2008**, *108*, 288–325.

Received: April 28, 2010
Published Online: June 8, 2010

