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Amine Directed Palladium Catalyzed C-H Halogenation of Phenylalanine Derivatives

Alexia Ville, [a,c] Julien Annibaletto, [a,c] Sébastien Coufourier, [a,b] Christophe Hoarau, [a] Rodolphe Tamion, [b] Guillaume Journot, *[b] Cédric Schneider, *[a] Jean-François Brière*[a]

Dedication ((optional))

- [a] Dr. A. Ville, Dr. J. Annibaletto, Dr. S. Coufourier, Prof. C. Hoarau, Dr. C. Schneider and Dr. J.-F. Brière Normandie Univ, UNIROUEN, INSA Rouen, CNRS, COBRA, 76000 Rouen, France. E-mail: cedric.schneider@univ-rouen.fr and jean-francois.briere@insa-rouen.fr Internet site: www.lab-cobra.fr/equipes/heterocycles/
- [b] Dr. G. Journot, Dr. R. Tamion Industrial Research Centre–Oril Industrie, CS 60125, 76210 Bolbec, France Email: guillaume.journot@servier.com
- [c] These authors contributed equally to this work.

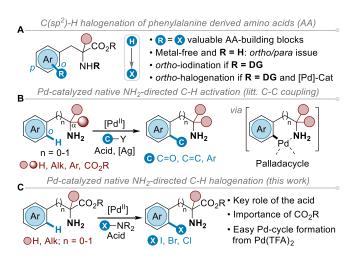
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Abstract: An efficient primary amine-directed palladium catalyzed C-H halogenation (X = I, Br, CI) of phenylalanine derivatives is reported on a range of quaternary amino acid (AA) derivatives thanks to suited conditions employing trifluoroacetic acid as additive. The extension of this original native functionality-directed *ortho*-selective halogenation was even demonstrated with the more challenging native phenylalanine as tertiary AA.

Given the widespread use of non-proteinogenic amino acid (AA) within bioactive molecules, the diversification of α-AA backbone represents an active research field in medicinal chemistry and in the development of synthetic methodologies. [1,2] Beside numerous investigations of directing-group (DG) site-selective metal-catalyzed C(sp3)-H activation of AAs,[2] the analogous C(sp²)-H functionalization of phenylalanine (Phe) derivatives has grown more recently as a powerful strategy for the regioselective C-C and C-heteroatom bonds construction.^[2,3] In this context, the halogenated Phe derivatives are valuable building blocks and versatile platforms for cross-coupling reactions allowing to transform the C-X (X = I, Br, CI) bonds into a myriad of useful functionalities (Scheme 1A).[4] Based on the design of suited Ndirecting-groups (DG) on Phe esters, [5] Yu[5a] and Correa[5b] successfully applied the Pd-catalyzed ortho-iodination (triflimide as DG) and bromination (picolinamide as DG) of Phe derivatives.^[6,7] On the other hand, Barluenga demonstrated the metal-free ortho-iodination of Phe esters based on electrophilic aromatic substitution (S_EAr) using trifluoroacetamide as DG.[8] This strategy overcomes the established moderate ortho-versus para-regioselectivity issues from native-NH2 Phe upon usually substrate-controlled pathways (depending on electronic and steric factors).[9]

In line with atom- and step-economical strategies, exploiting native-functional group (FG) as DG, the unprotected NH $_2$ -directed palladium catalyzed C(sp 2)-H activation emerged as a straightforward C-C bond formation method. [10] Beside the original exploitation of thermodynamically favored five-membered palladacycle intermediates from benzylamine precursors (Scheme 1B, n = 0), [11] Garcia and Granell pioneered the

carbonylation reaction of α,α-disubstituted R-NH2 quaternary Phe (n = 1). This catalytically more challenging $C(sp^2)$ -H activation sequence, through the formation of a less favored six-membered NH₂-bond palladacycle, [13,14] was subsequently developed to the coupling reactions of allenes,[13b] alkenes[13c] as well as aryl partners,[13f,13h] and extended to the native Phe (amonosubstituted) in few cases.[13a,13d,13e,13g] During these achievements, long-standing challenges were addressed to overcome both the formation of stable (and poorly reactive) bisamino-Pd^{II} complexes and competitive β-H elimination events.^[13] These issues turned out to be intimately linked to the αsubstitution pattern of the amine substrate and the steric hindrance of this native FG (usually beneficial to the process), [15] while silver and acid reagents turned out to be key additives for securing a successful transformation.[12,13] However, in spite of previously reported insightful halogenation reactions of preformed (stepwise and stoichiometric) six-membered ring NH₂bond palladacycle like pioneered investigations by Vicente and Saura-Llama (n = 1),[14,16] to the best of our knowledge, the Pdcatalyzed NH₂-directed C-H halogenation remains to be achieved.



Scheme 1. NH₂-directed C-H halogenation.

We are pleased to report herein an *ortho*-selective $C(sp^2)$ -H halogenation (X = I, Br, Cl) of Phe derivatives, highlighting the key role of the amine topology and acid additive to achieve a catalytic process while preventing the non-regioselective halogenation of both the amine and arene moieties (Scheme 1C).

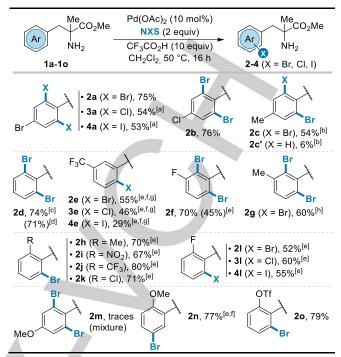
Table 1. Proof of principle and optimization.

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|--------------------|--|----------------------|
| Entry | Deviation from the standard conditions | Yield [%] 2a', 2a |
| 1 | None | 0, 78 |
| 2 | Use of 1.1 equiv of NBS | 22, 37 |
| 3 | Without palladium complex | 0, 0 |
| 4 | Without CF ₃ CO ₂ H ^[a] | 0, 0 |
| 5 | AcOH, HCl, PivOH, PhCO $_2$ H instead of CF $_3$ CO $_2$ H $^{[b]}$ | 0, 0 |
| 6 | Tf ₂ NH or TfOH, instead of CF ₃ CO ₂ H ^[b] | ≈16, 0 |
| 7 | 40 °C instead of 50 °C | 17, 28 |
| 8 | Pd(OAc) ₂ (5 mol%) instead of 10 mol% | 11, 55 |
| 9 | Pd(TFA) ₂ instead of Pd(OAc) ₂ | 14, 64 |
| 10 | In CF ₃ CO ₂ H as solvent instead of CH ₂ Cl ₂ | 0, 42 |
| 11 | In AcOH as solvent instead of CH ₂ Cl ₂ | 0, 64 |
| 12 | In PhCF ₃ as solvent instead of CH ₂ Cl ₂ | 14, 65 |
| 13 | In CPME or AcOEt as solvent instead of CH ₂ Cl ₂ | <26, 0 |
| | | |

Reaction conditions: carried out with **1a-TFA** (0.3 mmol) at CH_2CI_2 as solvent (0.1 M). Yields determined by ¹H NMR with an internal standard. [a] Same outcome in $CH_2CI_2/HFIP$ (1:1). [b] Carried out from the free amine **1a**.

Our investigation commenced with para-bromo-α-methyl phenylalanine ester 1a as an ammonium trifluoroacetate 1a-TFA, because no background halogenation took place in the presence of N-bromosuccinimide (NBS) in CH2Cl2 at 50 °C (Table 1, entry 3).[17] To our delight the major ortho-dibrominated product 2a was formed in 37% NMR yield along with 22% of the mono-brominated counterpart 2a' (entry 2) in the presence of 10 equivalents of trifluoroacetic acid (CF₃CO₂H) and 1.1 equivalent of NBS, while 2 equivalents of NBS furnished exclusively 2a in an excellent 78% yield (entry 1). In general, an excess of NBS led to lower yields.[17] The key role of the acid additive is worthy of note (10 equivalents is the optimal amount),[18] as no reaction took place in the absence of CF₃CO₂H (entry 4), and other acids turned out to be ineffective (entry 5) or to afford traces of 2a' (like TfOH or Tf2NH, entry 6). The amount of Pd(OAc)2 could be decreased to 5 mol % (entry 8), and Pd(TFA)2 (entry 9) could be used instead to furnish the dibrominated product 2a (55-64%, entries 8-9), although the obtained mono-brominated compound 2a' (11-14%) was not completely consumed in these conditions, likewise the reaction temperature at 40 °C (entry 7). A screening of solvents showed that the reaction could be carried out in pure CF₃CO₂H or acetic acid (42% and 64% of 2a, entries 10-11), and in non-coordinating solvents such as PhCF₃ (2a'-14% and 2a-65% yields entries 12-13), but none of them surpassed dichloromethane in the soft 50 °C conditions.

Table 2. Scope and limitation.



Reaction conditions: carried out with 1 (0.3 mmol) and NBS (2 equiv). Isolated yields (%) after column chromatography. [a] The presence of starting material (\$\pi\$10%) and mono-halogenated products \$3a'-19% and \$4a'-13% were detected on the crude mixture by \$^1\$H NMR. [b] Inseparable mixture. [c] Without Pd-catalyst a mixture of ortho- and para-brominated products (28% and 29% respectively) was obtained. [d] On 1 mmol scale. [e] With NXS (1.1 equiv). [f] In CH2Cl2/HFIP giving slightly better results. [g] Remaining starting material \$1e\$-10% (X = Br), \$1e\$-13% (X = Cl), \$1e\$-43% (X = I). [h] With NBS (1.1 equiv) 60/40 ratio of mono-Br (5-position) and di-1,5-Br were obtained.

Then, we investigated these soft and ortho-selective C-H bromination conditions to α-methyl phenylalanine ester derivatives 1a-1o as free amine (Table 2). Starting from parasubstituted 1a-1c (para-Br, Cl and Me) and unsubstituted 1d precursors, the ortho-dibrominated products 2a-c and 2d were obtained in isolated yields ranging from 54% to 76%. In the case of para-methyl substrate 1c traces of the mono-brominated 2c' (6%) was also obtained. Interestingly, the α-methyl phenylalanine ester 1d (electron-neutral Ar) furnished a mixture of ortho- and para-brominated products in the absence of palladium. This outcome shows that the Pd-catalyzed C-H halogenation surpasses significantly the rate of the background reaction. Although the sterically hindered meta-CF₃ precursor 1e gave selectively 2-brominated compound 2e in 55% yield (1.1 equiv of NBS), the less sterically encumbered substrates (with m-F and m-Me) led to the di-brominated products 2f and 2g in 70% and 60% yields in the presence of 2 equivalents of NBS. Regardless of the nature of the ortho-substituent on amino esters 1h-I, the corresponding mono-brominated products 2h-2l were isolated in 52-80% yields. As expected, electron-rich methoxy-substituted precursors 1m and 1n underwent a competitive S_EAr-based background pathway e.g. providing the brominated product 2n (77%) at the para-position to the OMe at C2 position. Nonetheless, starting from OTf derivative (10) secured the Pdcatalyzed ortho-bromination reaction to afford 20 in 79% yield. Importantly, although full-conversion was not always reached in similar conditions, the chlorinated (3a-54%, 3e-46%, 3I-60%) and iodinated (4a-53%, 4e-29%, 4I-55%) products were also synthesized by means of NCS and NIS, demonstrating thereby

the versatility of this C-H halogenation sequence towards platforms with orthogonal substitution pattern for further cross-coupling reactions.

Next, we explored the diversity of the AA backbone (Table 3). The use of the amino ester 1p, having a α -phenyl moiety, led to a mixture likely due to competitive formation and reaction of 5 and 6-membered ring Pd-cycles. These phenomenons have been discussed by Garcia, Granell and Ariza for the carbonylation reaction.[12,13b] However, precursors with more hindered alkyl groups such as i-Pr 1q and i-Bu 1r, and the precursor with ethyl ester moiety 1t gave rise to the corresponding di-bromo compounds 2q, 2r and 2t in respectively 66%, 70% and 87% yields. Note of worthy, the tert-butyl-esters, and even the benzylester derivatives did not completely survive to these acidic conditions. Interestingly, the dibenzyl-glycine precursor 1s yielded uneventfully tetra-ortho-brominated product 2s in 63% (even with less than 4 equivalents of NBS), highlighting an efficient poly-halogenation process. Furthermore, the chlorinated (3r-75% and 3s-66%) and, in lower yields, iodinated (4r-22% and 4s-28%) products were also accessible.

Table 3. Scope and structure-activity relationship.

$$\begin{array}{c} \text{Pd}(\mathsf{OAc})_2 \ (10 \ \mathsf{mol\%}) \\ \text{NXS} \ (2 \ \mathsf{equiv}) \\ \text{CF}_3\mathsf{CO}_2\mathsf{H} \ (10 \ \mathsf{equiv}) \\ \text{CH}_2\mathsf{Cl}_2, \ 50 \ ^\circ\mathsf{C}, \ 16 \ \mathsf{h} \\ \text{Then Bz}_2\mathsf{O}, \ \mathsf{K}_2\mathsf{CO}_3 \ \mathsf{if} \ \mathsf{R}^2 = \mathsf{Bz} \\ \text{Prom 1p-1t} \\ \text{R}^1 = \mathsf{Me}, \ \mathsf{R}^2 = \mathsf{H} \\ \text{Ph 2p, traces} \quad \bullet i\text{-Pr 2q} \ (\mathsf{X} = \mathsf{Br}), \ 66\% \\ \text{Prom 1p-1t} \\ \text{R}^1 = \mathsf{Me}, \ \mathsf{R}^2 = \mathsf{H} \\ \text{Ph 2p, traces} \quad \bullet i\text{-Pr 2q} \ (\mathsf{X} = \mathsf{Br}), \ 66\% \\ \text{Prom 1p-1t} \\ \text{R}^1 = \mathsf{Me}, \ \mathsf{R}^2 = \mathsf{H} \\ \text{Ph 2p, traces} \quad \bullet i\text{-Pr 2q} \ (\mathsf{X} = \mathsf{Br}), \ 66\% \\ \text{Prom 1p-1t} \\ \text{Bn}^{[a,b]} \cdot 2\mathsf{s} \ (\mathsf{X} = \mathsf{Br}), \ 63\% \cdot 3\mathsf{s} \ (\mathsf{X} = \mathsf{Cl}), \ 75\% \cdot 4\mathsf{r} \ (\mathsf{X} = \mathsf{I}), \ 22\% \\ \text{Prom 1p-1t} \\ \text{Prom 1p-1t} \\ \text{Prom 1p-1t} \\ \text{Prom 2p-1t} \\ \text{Prom 2p-1t} \\ \text{Prom 3p-1t} \\ \text{Prom 3p-1t} \\ \text{Prom 3p-1t} \\ \text{Prom 3p-1t} \\ \text{Prom 4p-1t} \\ \text{Pro$$

Reaction conditions: carried out with 1p-1t, 1u-TFA, 7-TFA (0.3 mmol). Isolated yields (%) after column chromatography. [a] Both benzyl moieties were *orthodi*-halogenated with NXS (4 equiv). [b] By ^1H NMR with an internal standard: 2s-95%, 3s-89%, 4s-56%. [c] ^1H NMR yield of monoBr/diBr 2u':2u amines before benzoylation in various solvents gave 28:19 in CH₂Cl₂, 55:33 in CH₂Cl₂/HFIP, 67:34 in CH₂Cl₂/HFIP with Cu(OAc)₂. *Variations of conditions*. [d] NBS (1.5 equiv), Cu(OAc)₂ (1 equiv), CH₂Cl₂:HFIP (1:1), 50 °C, 16 h, and *N*-protection. [e] NBS (1.5 for 8 and 2 equiv for 5u), Pd(OAc)₂ (10 mol% for 8 and 20% mol% for 5u), CF₃CO₂H as solvent. [f] NCS (1.5 equiv) at 60 °C, 24 h; 58% of 6u' and 29% of 6u at 50 °C.

We subsequently tackled the even more challenging phenylalanine ester 1u, as an ammonium salt 1u-TFA which is much easier to handle (Table 3). As a rule of thumb, the less hindered secondary amines are more prone to both competitive β-H elimination and pre-formation of unreactive *bis*-amino-Pd^{II} complexes. [13a,13d,13e,13g] Although, the previously developed conditions furnished a promising formation of mono- and dibrominated amines 2u' and 2u in 28% and 19% yields (determined by ¹H NMR with 1.5 equiv of NBS), [19] the use of hexafluoroisopropanol (HFIP)[20] as solvent and copper additive led to improved conversions (see Table 3). These conditions allowed to isolate the corresponding products 5u' and 5u in respectively 46% and 38% yields, after the *N*-benzoylation

protection. Interestingly, by carrying out the reaction in trifluoroacetic acid as solvent (2 equiv of NBS and without copper), a smooth dibromination occurred to provide exclusively product **5u** in 65% yield, showing that the second bromination is even faster in this case. ^[21] These conditions were compatible with phenylglycine precursor **7** (*via* a 5-membered Pd-cycle) furnishing the dibrominated compound **8** in a descent yield of 47%. ^[6] Eventually, the successful chlorination reaction of **1u-TFA** was also proven in CH₂Cl₂/HFIP solvent conditions at 60 °C for 24 h giving a mixture of monochlorinated **6u'** (28%) and dichlorinated **6u** (50%) products. This temperature secures a complete consumption of the starting material while giving predominantly the dichlorinated product **6u**, contrariwise to the outcome at 50 °C in 16 h (58% of **6u'** and 29% of **6u**).

$$(A) \begin{tabular}{ll} Me \\ Ph \begin{tabular}{ll} Me \\ Me \begin{tabular}{ll} CO_2Me \\ Me \begin{tabular}{ll} Me \\ Ph \begin{tabular}{ll} Me \\ Me \begin{tabular}{ll} CO_2Me \\ Me \begin{tabular}{ll} Me \\ Ph \begin{tabular}{ll} Me \\ Me \begin{tabular}{ll} Me \begin{tabular}{ll} Me \\ Ph \begin{tabular}{ll} Me \\ Me \begin{tabular}{ll} Me \begin{tabular}{ll} Me \\ Ph \begin{tabular}{ll} Me \\ Me \begin{tabular}{ll} Me \begin{tabular}{ll} Me \\ Ph \be$$

Scheme 2. Reactivity investigation. Reaction conditions: [a] NBS (2 equiv/[Pd]), CF $_3$ CO $_2$ H (10 equiv) in CH $_2$ CI $_2$, 50 °C, 16 h. 1 H NMR yield determined with an internal standard. [b] Same outcome in optimized conditions A in Table 3.

As long as the substrate topology is concerned, the replacement of the CO_2R by an amide function (9a) or the use of the $\alpha_1\alpha_2$ dimethyl amine 9b led to traces of products (unclean reaction, Scheme 2A). Next, an unsubstituted phenethylamine 9c proved to be moderately suited for these conditions giving the monobrominated product 10c' in 24% yield (See SI for details), which shed light on the ester moiety as key element for the C-H halogenation sequence. We also initiated some model testreactions (Scheme 2B). Although a slow background bromination of the aryl moiety was observed for the ammonium salt 1d-TFA, the free amine 1d underwent a rapid transformation in the presence of NBS at room temperature, by forming a priori the N-Br product 11d (structure observed in a NMR tube and analyzed by MS-analysis). The subsequent addition of CF₃CO₂H triggered the halogenation of the phenyl part (via a supposed -NH2+Br species)[22] to afford a mixture of starting material 1d and several derivatives from which the para-bromo 1a was the major product. Actually, this product 1a was hardly observed in the optimized Pdcatalyzed conditions. In line with our previous observation with phenylalanine ester 1u (giving 12u, Scheme 2C),[23] a straightforward synthesis and isolation of the palladacycle 12d as a solid, likely as a dimeric species, was achieved from the freeamine 1d in the presence of Pd(TFA)₂ (likewise from 1d-TFA and Pd(OAc)₂).[17,24] This protocol conveniently complement the seminal investigation of Vicente and Saura-Llama who observed the facile palladation of triflate ammonium salt of phenylalanine esters thanks to the electron-poor (and poorly coordinating) triflate anion. ^[16b] To our surprise, no bromination took place on the palladacycle **12u** (R = H), even in optimized conditions (see Table 3). Contrariwise, the bis-bromination (66% of **2d**) occurred on the more hindered analogue **12d** by NBS, but only in the presence of CF_3CO_2H .

Scheme 3. Proposed catalytic cycle.

In light of these preliminary investigations,[17] the Pd-catalyzed C-H activation process and the subsequent halogenation events seem to be finely balanced between reaction conditions and substrate structure.[18,25,26] Then, we propose a postulated catalytic cycle depicted in Scheme 3, in order to account these outcomes. The more potent Pd(TFA)2 would be formed in situ from Pd(OAc)₂ and CF₃CO₂H to trigger the NH₂-directed palladation to give intermediate 14.[11a],[18] With regard to insightful investigations on phenylglycine esters, [26] a type of concerted metalation-deprotonation (CMD) mechanism would occur. However, the rate of the second metalation significantly depends on the conditions and substrates, leading to a more facile dihalogenation of hindered quaternary amino esters (1, R ≠ H) or secondary aminoesters 1u and 7 in CF₃CO₂H as solvent, contrariwise to phenylalanine ester 1u in HFIP/CH2Cl2. [25] The halogenation of N-bonded Pd-cycle has been well-investigated while revealing complex and various scenarios that also depend on the nature of the halogenated reagent.[27] At that stage, we hypothesize that the monomeric palladium complex 14 is the most reactive species which undergoes a rapid oxidative insertion by NBS, possibly pre-activated by CF₃CO₂H,[28] through the previously proposed formation of a PdIV intermediate 15,[27a,29] prior to the final reductive elimination furnishing the halogenated product 2. Although the key role of reagents and additives requires further investigations, one can suppose that the trifluoroacetic acid additive also possesses the suited p K_a value to maintain the amino acid derivatives essentially in the ammonium salt state (1-TFA). These conditions prevent thereby the otherwise fast and unselective background bromination reaction, while liberating sufficient amount of amine 1 (equilibrated step I) for the subsequent coordination event towards 14 via 13. Next, the equilibrium between dimeric[29,30] palladium complex 12 (supposed less reactive) and monomeric counterpart 14, is driven towards 14 (equilibrated step II) upon the

influence of both (1) steric hindrance (R = H vs Me)^[15] and (2) an external weakly coordinating ligand (L = CF₃CO₂H, NBS, etc.). We assume likewise that the electron-poor and coordinated ester group could balance the *equilibrated steps 1 and 2* favorably in the catalytic cycle.^[13b]

In conclusion, this work reports an efficient and versatile primary amine-directed palladium catalyzed $C(sp^2)$ -H halogenation (X = I, Br, CI) of phenylalanine (Phe) platforms. This strategy gives rise to the formation of a large array of original halogenated Phederivatives as non-proteinogenic-AA and highlights the use of native functionality-NH $_2$ as a DG, preventing thereby any N-(de)protection sequences. The exploitation of this strategy to introduce other functionalities is under investigation.

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Keywords: CH functionalization • halogenation • amino acids • palladium • homogenous catalysis

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Entry for the Table of Contents

Mono-ortho or di-ortho halogenation

A site-selective primary amine (as native NH_2 -functionality) directed palladium catalyzed $C(sp^2)$ -H halogenation (X = I, Br, Cl) of phenylalanine (Phe) platforms was demonstrated and paves the way of the construction of original halogenated Phe-derivatives as non-proteinogenic-AA

Institute and/or researcher Twitter usernames: @Labex_Synorg @CdricSchneider2 @JFBriere76

