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COMMUNICATION

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Dedication ((optional))

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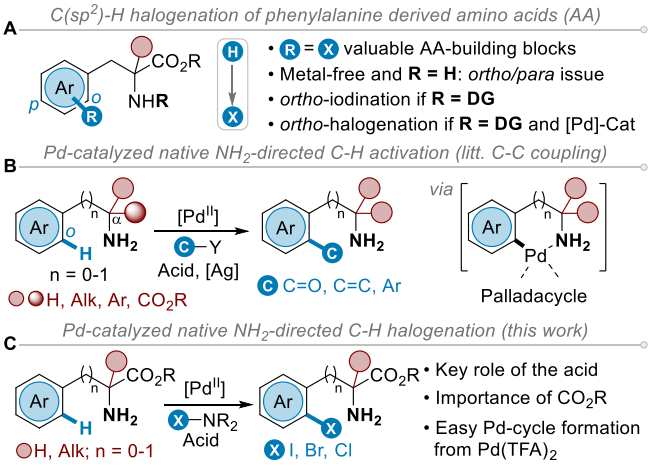
Abstract: An efficient primary amine-directed palladium catalyzed C-H halogenation (X = I, Br, Cl) of phenylalanine derivatives is reported on a range of quaternary amino acid (AA) derivatives thanks to suited conditions employing trifluoroacetic acid as additive. The extension of this original native 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(sp^3)-H activation of AAs,[2] the analogous C(sp^2)-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, Cl) bonds into a myriad of useful functionalities (Scheme 1A).[4] Based on the design of suited *N*-directing-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-NH_2 Phe upon usually substrate-controlled pathways (depending on electronic and steric factors).[9]

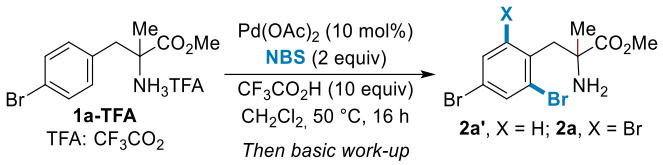
In line with atom- and step-economical strategies, exploiting native-functional group (FG) as DG, the unprotected NH_2-directed palladium catalyzed C(sp^2)-H activation emerged as a straightforward C-C bond formation method.[10] Beside the original exploitation of thermodynamically favored five-membered palladacycle intermediates from benzylamine precursors (Scheme 1B, n = 0),[11] Garcia and Granell pioneered the carbonylation reaction of α,α-disubstituted R-NH_2 quaternary Phe (n = 1).[12] This catalytically more challenging C(sp^2)-H activation sequence, through the formation of a less favored six-membered NH_2-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 (α-monosubstituted) 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) *bis*-amino-Pd^{II} complexes and competitive *β*-H elimination events.[13] These issues turned out to be intimately linked to the α-substitution 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 pre-formed (stepwise and stoichiometric) six-membered ring NH_2-bond palladacycle like pioneered investigations by Vicente and Saura-Llama (n = 1),[14,16] to the best of our knowledge, the Pd-catalyzed NH_2-directed C-H halogenation remains to be achieved.



Scheme 1. NH_2-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.

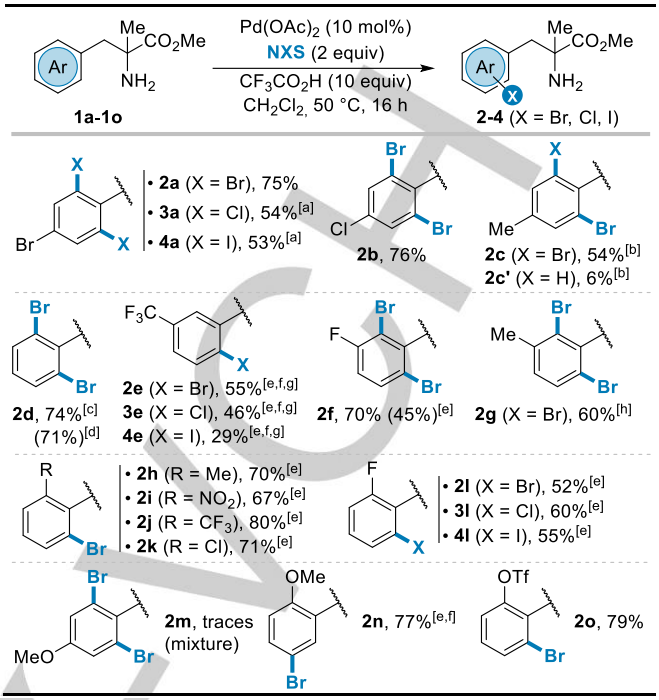


Entry	Deviation from the standard conditions	Yield [%] **2a'**, **2a**
1	*None*	0, 78
2	Use of 1.1 equiv of NBS	22, 37
3	Without palladium complex	0, 0
4	Without CF_3CO_2H[a]	0, 0
5	AcOH, HCl, PivOH, $PhCO_2H$ instead of CF_3CO_2H[b]	0, 0
6	Tf_2NH or TfOH, instead of CF_3CO_2H [b]	≈16, 0
7	40 °C instead 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_3CO_2H as solvent instead of CH_2Cl_2	0, 42
11	In AcOH as solvent instead of CH_2Cl_2	0, 64
12	In $PhCF_3$ as solvent instead of CH_2Cl_2	14, 65
13	In CPME or AcOEt as solvent instead of CH_2Cl_2	<26, 0

Reaction conditions: carried out with **1a-TFA** (0.3 mmol) at CH_2Cl_2 as solvent (0.1 M). Yields determined by ^1H NMR with an internal standard. [a] Same outcome in CH_2Cl_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 CH_2Cl_2 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 (CF_3CO_2H) 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 CF_3CO_2H (entry 4), and other acids turned out to be ineffective (entry 5) or to afford traces of **2a'** (like TfOH or Tf_2NH, 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 CF_3CO_2H or acetic acid (42% and 64% of **2a**, entries 10-11), and in non-coordinating solvents such as $PhCF_3$ (**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.



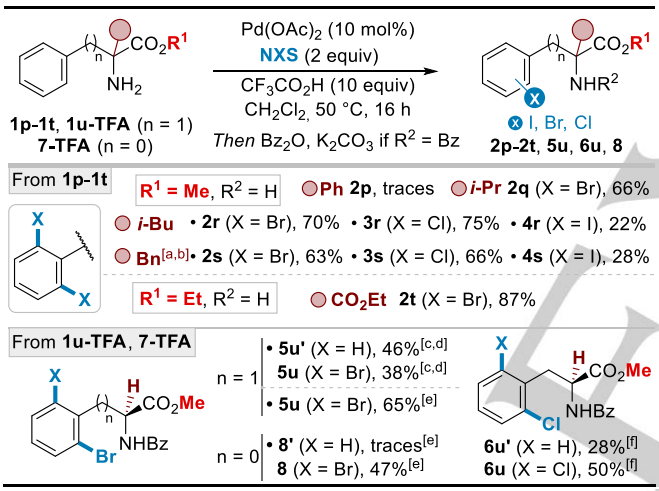
Reaction conditions: carried out with **1** (0.3 mmol) and NBS (2 equiv). Isolated yields (%) after column chromatography. [a] The presence of starting material (≈10%) and mono-halogenated products **3a'**-19% and **4a'**-13% were detected on the crude mixture by ^1H NMR. [b] Inseparable mixture. [c] 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 CH_2Cl_2/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 *para*-substituted **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*-CF_3 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**-**l**, 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 (**1o**) secured the Pd-catalyzed *ortho*-bromination reaction to afford **2o** in 79% yield. Importantly, although full-conversion was not always reached in similar conditions, the chlorinated (**3a**-54%, **3e**-46%, **3l**-60%) and iodinated (**4a**-53%, **4e**-29%, **4l**-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.

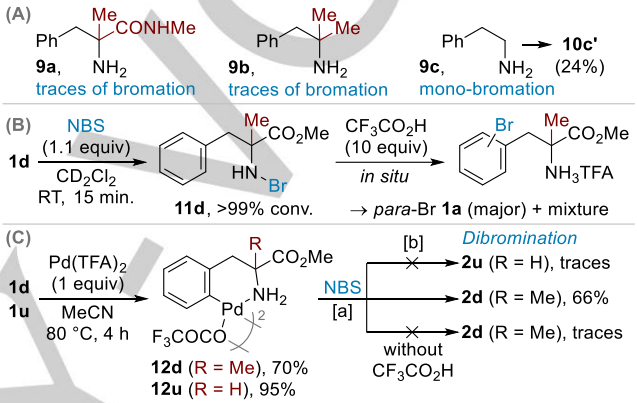
Next, we explored the diversity of the AA backbone (Table 3). The use of the amino ester **1p**, having a α-phenyl moiety, led to a mixture likely due to competitive formation and reaction of 5 and 6-membered ring Pd-cycles. These phenomenons have been discussed by Garcia, Granell and Ariza for the carbonylation 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 benzyl-ester 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.



Reaction conditions: carried out with **1p**-**1t**, **1u-TFA, 7-TFA** (0.3 mmol). Isolated yields (%) after column chromatography. [a] Both benzyl moieties were *ortho*-di-halogenated with NXS (4 equiv). [b] By ^{1}H NMR with an internal standard: **2s**-95%, **3s**-89%, **4s**-56%. [c] ^{1}H NMR yield of monoBr/diBr **2u'**:**2u** amines before benzoylation in various solvents gave 28:19 in CH_2Cl_2, 55:33 in CH_2Cl_2/HFIP, 67:34 in CH_2Cl_2/HFIP with $Cu(OAc)_2$. *Variations of conditions.* [d] NBS (1.5 equiv), $Cu(OAc)_2$ (1 equiv), CH_2Cl_2: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**), CF_3CO_2H as solvent. [f] NCS (1.5 equiv) at 60 °C, 24 h; 58% of **6u'** and 29% of **6u** at 50 °C.

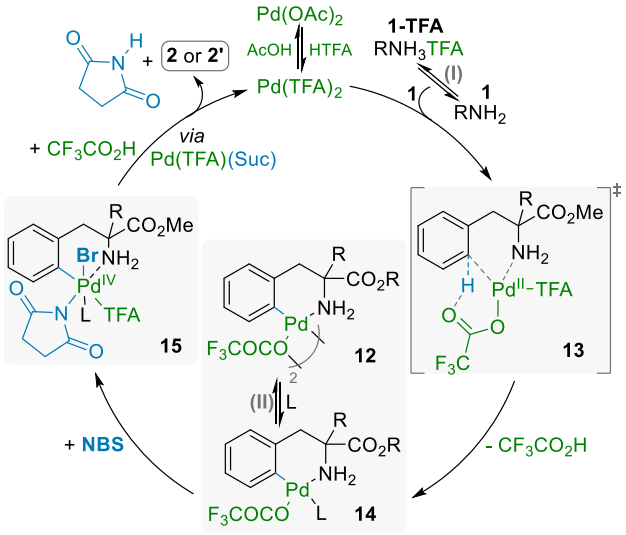
We subsequently tackled the even more challenging phenylalanine ester **1u**, as an ammonium salt **1u-TFA** which is much easier to handle (Table 3). As a rule of thumb, the less hindered secondary amines are more prone to both competitive *β*-H elimination and pre-formation of unreactive *bis*-amino-Pd^{II} 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 ^{1}H 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 CH_2Cl_2/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**).



Scheme 2. Reactivity investigation. Reaction conditions: [a] NBS (2 equiv/[Pd]), CF_3CO_2H (10 equiv) in CH_2Cl_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 α,α-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 test-reactions (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 CF_3CO_2H triggered the halogenation of the phenyl part (via a supposed -NH_2^+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 Pd-catalyzed 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 free-amine **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 CF_3CO_2H to trigger the NH_2-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 di-halogenation of hindered quaternary amino esters (**1**, R ≠ H) or secondary aminoesters **1u** and **7** in CF_3CO_2H as solvent, contrariwise to phenylalanine ester **1u** in $HFIP/CH_2Cl_2$.[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 CF_3CO_2H,[28] through the previously proposed formation of a Pd^{IV} 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 pK_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 = CF_3CO_2H, 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, Cl) of phenylalanine (Phe) platforms. This strategy gives rise to the formation of a large array of original halogenated Phe-derivatives 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.

Acknowledgements

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

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[21] Interestingly, the direct bromination of phenyalanine as amino acid occured (in CF_3CO_2H, $Pd(OAc)_2$ 20 mol%, 50 °C) to give **5u'** and **5u** in 50% and 45% NMR yields after protection, but the purification of **5u'** was not successful due to the coelution of impurities. This is a rare case of amino acid directed C-H functionalization of phenethylamine platform as pioneered by Albericio and Lavilla for C-C bond formation see ref. 13a.

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[24] Although a rather stable solid compound **12d** was obtained after filtration and evaporation, this pallacycle proved to be rather labile in solution (e.g. in the presence of ligands) and was further caracterized by subsequent transformations. In line with previous observations in Phe and Gly series (see references 12 and 25), one set of signals were observed by ^{1}H NMR at room temperature, despite the presence of two enantiomers and the possible formation of cisoid or transoid palladacyles, which tend to show several stereoisomeric species in equilibrium (see SI).

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[29] At that stage, we cannot rule out the formation of a binuclear Pd^{III}-Pd^{III} intermediate from **12** or the Pd^{II}/Pd^{II} redox-neutral electrophilic cleavage sequence of **12** or **14** upon the CF_3CO_2H activation of NBS or with other halogenated reagents, see references 27 for discussion.

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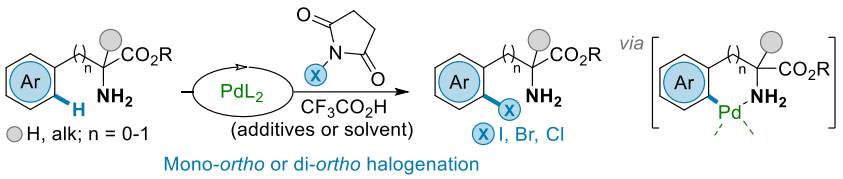
Entry for the Table of Contents



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

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