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Amine Directed Palladium Catalyzed C-H Halogenation of Phenylalanine Derivatives

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Dedication ((optional))

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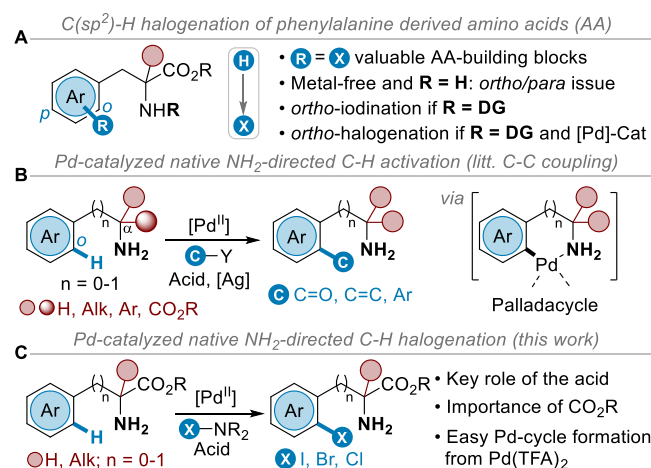
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Abstract: An efficient primary amine-directed palladium catalyzed C-H halogenation (X = I, Br, Cl) of phenylalanine derivatives is reported on a range of quaternary amino acid (AA) derivatives thanks to suited conditions employing trifluoroacetic acid 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(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, 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-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 NH₂-directed palladium catalyzed C(sp²)-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).^[12] This catalytically more challenging C(sp²)-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 (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 NH₂-bond palladacycle like pioneered investigations by Vicente and Saura-Llana (n = 1),^[14,16] to the best of our knowledge, the Pd-catalyzed NH₂-directed C-H halogenation remains to be achieved.



Scheme 1. NH₂-directed C-H halogenation.

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We are pleased to report herein an *ortho*-selective C(sp²)-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 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 CH₂Cl₂ as solvent (0.1 M). Yields determined by ¹H NMR with an internal standard. [a] Same outcome in CH₂Cl₂/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.

 1a-1o	 2-4 (X = Br, Cl, I)	
 2a (X = Br), 75% 3a (X = Cl), 54% ^[a] 4a (X = I), 53% ^[a]	 2b, 76% 2c (X = Br), 54% ^[b] 2c' (X = H), 6% ^[b]	
 2d, 74% ^[c] (71%) ^[d] 2e (X = Br), 55% ^[e,f,g] 3e (X = Cl), 46% ^[e,f,g] 4e (X = I), 29% ^[e,f,g]	 2f, 70% (45%) ^[e] 2g (X = Br), 60% ^[h]	
 2h (R = Me), 70% ^[e] 2i (R = NO ₂), 67% ^[e] 2j (R = CF ₃), 80% ^[e] 2k (R = Cl), 71% ^[e]	 2l (X = Br), 52% ^[e] 3l (X = Cl), 60% ^[e] 4l (X = I), 55% ^[e]	
 2m, traces (mixture)	 2n, 77% ^[e,f]	 2o, 79%

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 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.

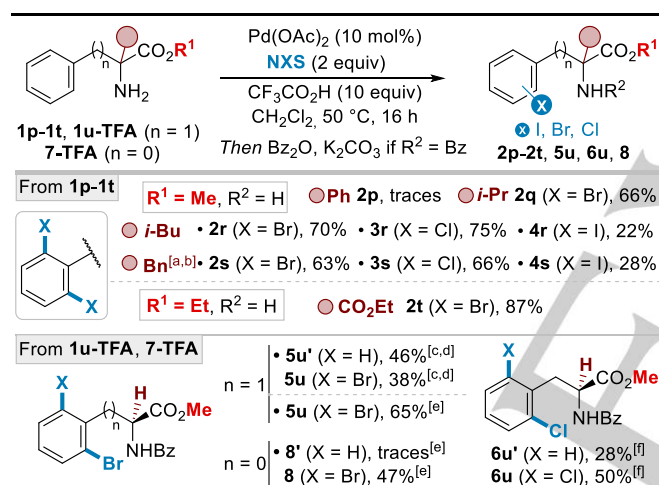
Then, we investigated these soft and *ortho*-selective C–H bromination conditions to α -methyl phenylalanine ester derivatives **1a–1o** as free amine (Table 2). Starting from *para*-substituted **1a–1c** (*para*-Br, Cl and Me) and unsubstituted **1d** precursors, the *ortho*-dibrominated products **2a–c** 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*-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–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

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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 phenomena 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.

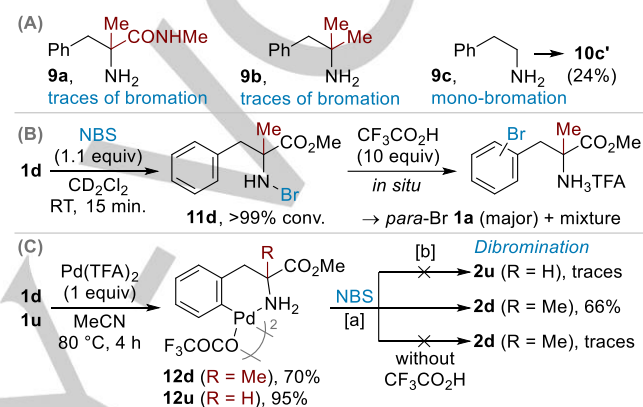
Table 3. Scope and structure-activity relationship.



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 ^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 CH_2Cl_2 , 55:33 in $\text{CH}_2\text{Cl}_2/\text{HFIP}$, 67:34 in $\text{CH}_2\text{Cl}_2/\text{HFIP}$ with $\text{Cu}(\text{OAc})_2$. **Variations of conditions**. [d] NBS (1.5 equiv), $\text{Cu}(\text{OAc})_2$ (1 equiv), $\text{CH}_2\text{Cl}_2/\text{HFIP}$ (1:1), 50 °C, 16 h, and *N*-protection. [e] NBS (1.5 for **8** and 2 equiv for **5u**), $\text{Pd}(\text{OAc})_2$ (10 mol% for **8** and 20% mol% for **5u**), $\text{CF}_3\text{CO}_2\text{H}$ 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

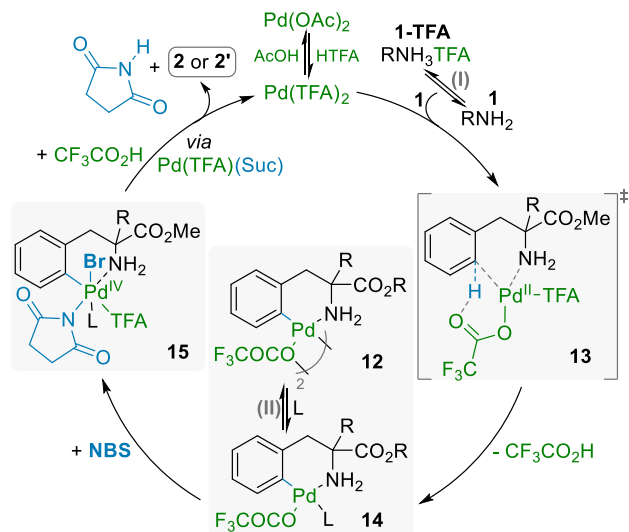
protection. Interestingly, by carrying out the reaction in trifluoroacetic acid as solvent (2 equiv of NBS and without copper), a smooth dibromination occurred to provide exclusively product **5u** in 65% yield, showing that the second bromination is even faster in this case.^[21] These conditions were 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 $\text{CH}_2\text{Cl}_2/\text{HFIP}$ 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]), $\text{CF}_3\text{CO}_2\text{H}$ (10 equiv) in CH_2Cl_2 , 50 °C, 16 h. ^1H 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 $\text{CF}_3\text{CO}_2\text{H}$ triggered the halogenation of the phenyl part (via a supposed $-\text{NH}_2^+\text{Br}$ 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 $\text{Pd}(\text{TFA})_2$ (likewise from **1d-TFA** and $\text{Pd}(\text{OAc})_2$).^[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 CF₃CO₂H.



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 di-halogenation 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 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 = 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(sp²)-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-NH₂ as a DG, preventing thereby any N-(de)protection sequences. The exploitation of this strategy to introduce other functionalities is under investigation.

Acknowledgements

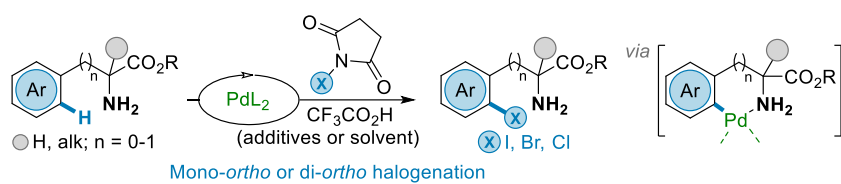
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Keywords: CH functionalization • halogenation • amino acids • palladium • homogenous catalysis

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Entry for the Table of Contents



A site-selective primary amine (as native NH₂-functionality) directed palladium catalyzed C(sp²)-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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