Chinese Chemical Letters 35 (2024) 108505

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Free amino group-directed C(sp^2)–H arylation of α-amino-β-aryl esters by palladium catalysis

Yue Gao[a,b,c], Yu Du[a,b,c,*], Weiping Su[a,b,c,*]

[a] State Key Laboratory of Structural Chemistry, Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences, Fuzhou 350002, China
[b] Fujian Science & Technology Innovation Laboratory for Optoelectronic Information of China, Fuzhou 350108, China
[c] University of Chinese Academy of Sciences, Beijing 100049, China

ARTICLE INFO

Article history:
Received 23 November 2022
Revised 13 April 2023
Accepted 23 April 2023
Available online 27 April 2023

Keywords:
Native amino-directed
Palladium catalyst
C(sp^2)-H arylation
α-Amino-β-aryl ester
Chiral α-amino acid

ABSTRACT

Native amino-directed palladium-catalyzed C(sp^3)–H activation/functionalization has been developed for modification of α-amino acids and peptides. Herein a palladium(II)-catalyzed C(sp^2)–H arylation of α-amino-β-aryl esters has been disclosed, using the native amino as the directing group. A variety of chiral α-amino-β-aryl esters can be functionalized to give the corresponding *ortho*-substituted mono- and di-arylated products.

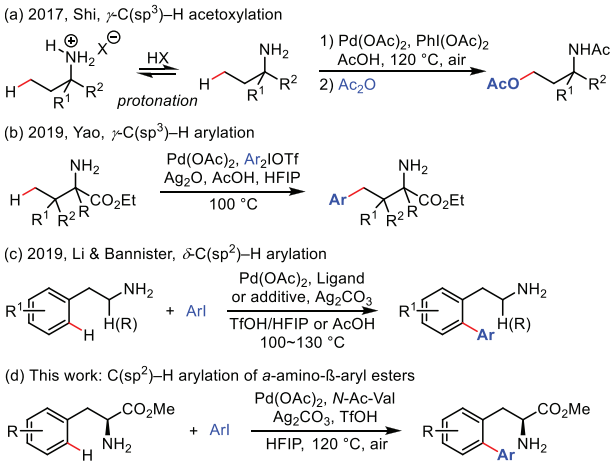
α-Amino acids (α-AAs) are an important class of natural chiral compounds which are essential building blocks of proteins and peptides. The modification of easily available α-AAs that provides new molecules bears great practical potential in chemistry, chemical biology, drug discovery and other disciplines [1–4]. In recent years, C–H activation catalysis has gradually emerged as a powerful tool for α-AAs [5–9] and peptides [10–12] modification in an atom- and step-economical manner. However, the existing methods *via* C–H activation often require installation of either directing auxiliaries or introducing protecting groups to manipulate the reactivity, the development of novel methods using native carboxyl or amino groups as directing groups has attracted substantial attention. In contrast to the steady progress of carboxylate-directed inert C–H activation [13–16] and its application in modifying α-AAs [17–21], free NH_2-directed transformation is less studied [22–23].

In order to suppress the high propensity to form strong binding and less active bis-amine complexes of primary amines with metal catalysts [24], a protonation strategy of using acetic acid as the solvent [25] was employed by Shi to realize the NH_2-directed γ-C(sp^3)–H acetoxylation of aliphatic primary amines (Scheme 1a) [26]. Applying the same strategy to α-AAs modification, an efficient NH_2-directed γ-C(sp^3)–H arylation of α-amino esters was developed by Yao (Scheme 1b) [27,28], and substrates were further expanded to *N*-terminus unprotected oligopeptides [29,30]. Meanwhile, native amino-directed palladium-catalyzed C(sp^2)–H arylation of primary amines had also been developed (Scheme 1c) [31,32]. Aryl substituted α-AAs are an important class of natural α-AAs (*e.g.*, Phe, Trp, Tyr) and derivatives. However, at present, native NH_2-directed C(sp^2)–H functionalization of such α-AAs has rarely been discussed [32]. In this context, herein we report a native amino-directed palladium(II)-catalyzed C(sp^2)–H arylation of α-amino-β-aryl esters with various aryl iodides (Scheme 1d). A variety of chiral α-amino esters could be arylated by this method directly.

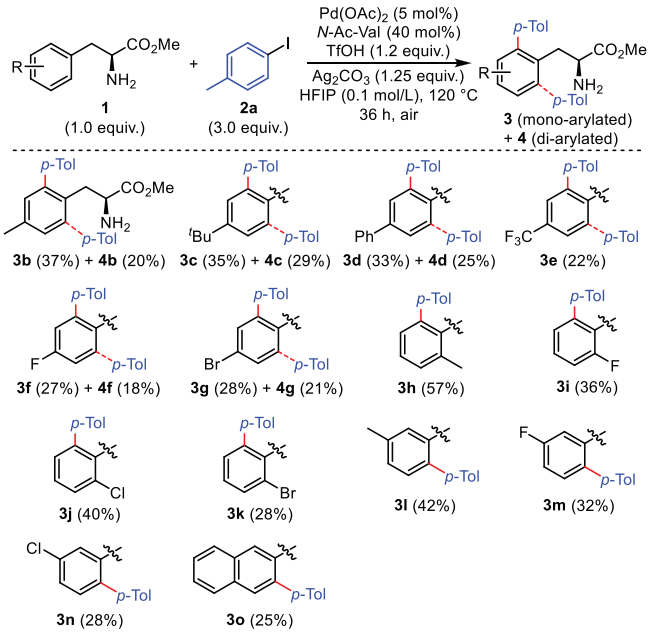
As shown in Table 1, the research was commenced with exploring the coupling reaction of model substrates (*S*)-phenylalanine methyl ester **1a** and 4-methyliodobenzene **2a** in the presence of palladium acetate ($Pd(OAc)_2$, 5 mol%) and *N*-acetyl-glycine (*N*-Ac-Gly, 40 mol%) as a ligand, along with 1.2 equiv. of trifluoromethanesulfonic acid (TfOH) as the proton source and 1.25 equiv. of silver carbonate (Ag_2CO_3), warmed at 120 °C for 24 h in hexafluoroisopropanol (HFIP) under air. The desired *ortho*-arylated products **3a** (mono-arylated) and **4a** (di-arylated) were obtained in yields of 48% and 25% separately (entry 1). Then lots of control experiments were performed to find the optimal conditions (see Supporting information for more reaction conditions evaluation). Various mono-*N*-protected amino acids (MPAAs) [1,33] were examined (entries 1–5), *N*-acetyl-valine (*N*-Ac-Val) is the superior one that affords the highest yields of **3a** and **4a** (entry 3). The screening of

* Corresponding authors.
E-mail addresses: duyu@fjirsm.ac.cn (Y. Du), wpsu@fjirsm.ac.cn (W. Su).

https://doi.org/10.1016/j.cclet.2023.108505
1001-8417/



Scheme 1. NH_2-directed C–H functionalization of primary amines.

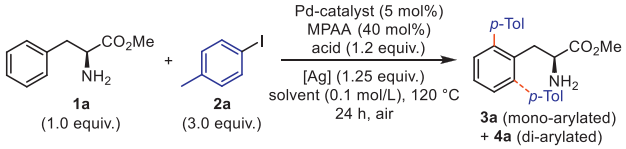


Scheme 2. Scope of α-amino-β-aryl esters. Reactions were performed on a 0.4 mmol scale. Yields are isolated yields.

acid additives showed that TfOH is the best choice (entries 6–8). It should be noteworthy that no target molecules were obtained without the addition of acid, suggesting the critical role of acid in inhibiting the strong binding of the amino group with palladium. A survey of inorganic bases revealed that Ag_2CO_3 significantly outperform others in promoting the reaction (entries 9–11), and silver salts play an irreplaceable role as iodide scavenger [34]. Other polar or nonpolar solvents were also tested, however, no positive effect was observed (entries 12 and 13). Extending reaction time to 36 h led to a little increase of the combined yields of **3a** and **4a** (entry 14), further extending reaction time to 48 h failed to take effect (entry 15). Besides, the use of other palladium-catalysts instead of $Pd(OAc)_2$ led to an erosion in the yield (entries 16–18). The di-arylation increased significantly (>60% yield) with the catalyst loading of $Pd(OAc)_2$ increased to more than 20 mol%, while the mono-arylation was almost disappeared. The results indicate that the poor selectivity is caused by the lack of activity of the catalytic system.

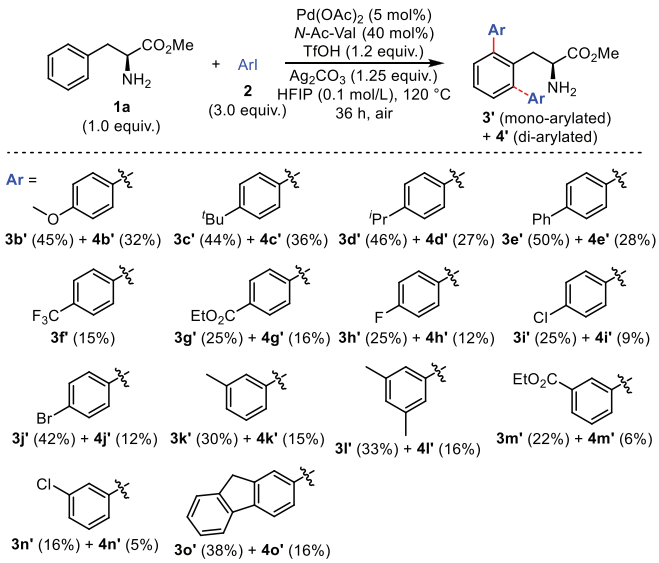
With the optimal conditions (Table 1, entry 14), the generality of this C(sp^2)–H arylated method was first evaluated with various α-amino-β-aryl esters (Scheme 2). In order to ensure the reliability of the yields, all data represent the average of (more than) two independent experiments. A variety of α-amino esters with electron-rich or -deficient aryl groups (**1b**-**1n**), naphthyl (**1o**), could react under the optimal conditions to generate the corresponding arylated products **3** and **4**. Generally, the presence of an electron donating group (**1b**, **1c**, **1h**, **1l**) led to a higher yield than that derived from an electron withdrawing group (**1e**-**1g**, **1i**-**1k**, **1m**-**1n**), which probably because the former can promote the reductive elimination. α-Amino-β-aryl ester bearing a *para*-substituent

Table 1
Optimization of reaction conditions.[a]

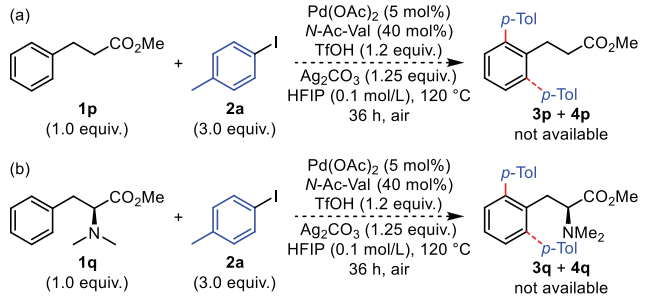


Entry	Pd-catalyst	Ligand	Acid	[Ag]	Solvent	*t* (h)	**3a** Yield (%)[b]	**4a** Yield (%)[b]
1	$Pd(OAc)_2$	*N*-Ac-Gly	TfOH	Ag_2CO_3	HFIP	24	48	25
2	$Pd(OAc)_2$	*N*-Ac-Ala	TfOH	Ag_2CO_3	HFIP	24	40	23
3	$Pd(OAc)_2$	*N*-Ac-Val	TfOH	Ag_2CO_3	HFIP	24	55	35
4	$Pd(OAc)_2$	*N*-Boc-Val	TfOH	Ag_2CO_3	HFIP	24	N.A.	N.A.
5	$Pd(OAc)_2$	*N*-Cbz-Val	TfOH	Ag_2CO_3	HFIP	24	43	29
6	$Pd(OAc)_2$	*N*-Ac-Val	TFA	Ag_2CO_3	HFIP	24	33	16
7	$Pd(OAc)_2$	*N*-Ac-Val	HOAc	Ag_2CO_3	HFIP	24	< 10	trace
8	$Pd(OAc)_2$	*N*-Ac-Val	HBF_4	Ag_2CO_3	HFIP	24	38	37
9	$Pd(OAc)_2$	*N*-Ac-Val	TfOH	AgOAc	HFIP	24	31	9
10	$Pd(OAc)_2$	*N*-Ac-Val	TfOH	Ag_2O	HFIP	24	22	7
11	$Pd(OAc)_2$	*N*-Ac-Val	TfOH	AgOTf	HFIP	24	N.A.	N.A.
12	$Pd(OAc)_2$	*N*-Ac-Val	TfOH	Ag_2CO_3	DCM	24	7	9
13	$Pd(OAc)_2$	*N*-Ac-Val	TfOH	Ag_2CO_3	CH_3CN	24	N.A.	N.A.
14	$Pd(OAc)_2$	*N*-Ac-Val	TfOH	Ag_2CO_3	HFIP	36	59	34
15	$Pd(OAc)_2$	*N*-Ac-Val	TfOH	Ag_2CO_3	HFIP	48	37	28
16	$Pd(TFA)_2$	*N*-Ac-Val	TfOH	Ag_2CO_3	HFIP	36	36	44
17	$PdCl_2(MeCN)_2$	*N*-Ac-Val	TfOH	Ag_2CO_3	HFIP	36	45	30
18	$Pd(acac)_2$	*N*-Ac-Val	TfOH	Ag_2CO_3	HFIP	36	39	19

[a] Unless otherwise noted, reactions were carried out on a 0.4 mmol scale.
[b] Yields were determined by ^1H NMR spectroscopic analysis of crude reaction mixtures using 1,3,5-trimethoxybenzene (22.4 mg, 0.133 mmol) as the internal standard.



Scheme 3. Scope of aryl iodides. Reactions were performed on a 0.4 mmol scale. Yields are isolated yields.



Scheme 4. Additional control experiments.

(**1b**-**1g**) would give a mixture of mono- and di-arylated products (**3b**-**3g** & **4b**-**4g**), while *ortho*- and *meta*-substituted substrates (**1h**-**1o**) led to only mono-arylation (**3h**-**3o**). By now the method appears not applicable for site-selective C–H functionalization of peptides containing Phe as the N-terminus, both C(sp^2)–H and C(sp^3)–H arylation were observed after reactions (details see Supporting information).

Further investigation of coupling reagents, aryl iodides, was carried out under the optimal conditions with (*S*)-phenylalanine methyl ester **1a** (Scheme 3). Various functional groups such as methoxy, alkyl, phenyl, trifluoromethyl, ester and halogen groups at the *para*- or *meta*-position were tolerated, generating mixtures of mono- and di-arylated products (**3b'**–**3n'** & **4b'**–**4n'**). In contrast, *ortho*-substituted iodobenzene doesn't work in this reaction. Fluorenyl derivative (**2o**) also worked well to give the corresponding mono- and di-arylated products (**3o'** & **4o'**) in a moderate combined yield. Regrettably, the method is not applicable to heteroaryl iodides or α-amino-β-heteroaryl esters (*e.g.*, Trp-OMe).

Chiral HPLC analysis of arylated products derived from (*R*)- and (*S*)-phenylalanine methyl esters showed that there is a little erosion in enantiomeric excess (di-arylated product **4a**, 88% *ee*, see Supporting information), revealing that partial racemization occurred during the reaction due to the basicity and high temperature. In order to verify the directing effect of the native NH_2, as shown in Scheme 4, methyl 3-phenylpropanoate **1p** and *N*,*N*-dimethyl-Phe-OMe **1q** were subjected to the reaction, and no observation of the desired C(sp^2)–H arylation. The results exclude the possible ester-directed C–H activation.

In summary, an efficient and practical Pd(II)-catalyzed C(sp^2)–H arylation of α-amino-β-aryl esters with various aryl iodides has been developed, using the native NH_2 as the directing group. A variety of chiral α-amino esters could be functionalized by this method to give the corresponding mono- and di-arylated products with a little erosion in enantiomeric excess. The method features broad substrate scope, excellent functional group tolerance and mild conditions. Further exploration of this protocol for C(sp^2)–H arylation of oligopeptides and structure modification of polypeptide drugs is currently underway in our laboratory.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by the National Key Research and Development Program of China (No. 2018YFA0704502), the National Natural Science Foundation of China (Nos. 21871261, 21931011), and Fujian Science & Technology Innovation Laboratory for Optoelectronic Information of China (No. 2021ZZ105).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2023.108505.

References

[1] Q. Shao, K. Wu, Z. Zhuang, S. Qian, J.Q. Yu, Acc. Chem. Res. 53 (2020) 833–851.
[2] C.C. Hanna, Y.O. Hermant, P.W.R. Harris, M.A. Brimble, Acc. Chem. Res. 54 (2021) 1878–1890.
[3] B.M. Cooper, J. Iegre, D.H. O'Donovan, M.Ö. Halvarsson, D.R. Spring, Chem. Soc. Rev. 50 (2021) 1480–1494.
[4] E. Rémond, C. Martin, J. Martinez, F. Cavelier, Chem. Rev. 116 (2016) 11654–11684.
[5] M. Zhang, S. Zhong, Y. Peng, et al., Org. Chem. Front. 8 (2021) 133–168.
[6] S. Shabani, Y. Wu, H.G. Ryan, C.A. Hutton, Chem. Soc. Rev. 50 (2021) 9278–9343.
[7] S. Mondal, S. Chowdhury, Adv. Synth. Catal. 360 (2018) 1884–1912.
[8] G. He, B. Wang, W.A. Nack, G. Chen, Acc. Chem. Res. 49 (2016) 635–645.
[9] X. Lu, B. Xiao, R. Shang, L. Liu, Chin. Chem. Lett. 27 (2016) 305–311.
[10] A. Correa, Eur. J. Inorg. Chem. 2021 (2021) 2928–2941.
[11] B.B. Zhan, M.X. Jiang, B.F. Shi, Chem. Commun. 56 (2020) 13950–13958.
[12] W. Wang, M.M. Lorion, J. Shah, A.R. Kapdi, L. Ackermann, Angew. Chem. Int. Ed. 57 (2018) 14700–14717.
[13] J. Das, D.K. Mal, S. Maji, D. Maiti, ACS Catal. 11 (2021) 4205–4229.
[14] A. Das, B. Maji, Chem. Asian J. 16 (2021) 397–408.
[15] A. Uttry, M. van Gemmeren, Synlett 29 (2018) 1937–1943.
[16] J. He, M. Wasa, K.S.L. Chan, Q. Shao, J.Q. Yu, Chem. Rev. 117 (2017) 8754–8786.
[17] G. Chen, Z. Zhuang, G.C. Li, et al., Angew. Chem. Int. Ed. 56 (2017) 1506–1509.
[18] K.K. Ghosh, M. van Gemmeren, Chem. Eur. J. 23 (2017) 17697–17700.
[19] Y. Zhu, X. Chen, C. Yuan, et al., Nat. Commun. 8 (2017) 14904.
[20] P.X. Shen, L. Hu, Q. Shao, K. Hong, J.Q. Yu, J. Am. Chem. Soc. 140 (2018) 6545–6549.
[21] Z. Zhuang, C.B. Yu, G. Chen, et al., J. Am. Chem. Soc. 140 (2018) 10363–10367.
[22] J. Albert, X. Ariza, T. Calvet, et al., Organometallics 32 (2013) 649–659.
[23] B. López, A. Rodriguez, D. Santos, et al., Chem. Commun. 47 (2011) 1054–1056.
[24] A.D. Ryabov, Chew. Rev. 90 (1990) 403–424.
[25] A.P. Smalley, M.J. Gaunt, J. Am. Chem. Soc. 137 (2015) 10632–10641.
[26] K. Chen, D. Wang, Z.W. Li, et al., Org. Chem. Front. 4 (2017) 2097–2101.
[27] P.K. Pramanick, Z. Zhou, Z.L. Hou, B. Yao, J. Org. Chem. 84 (2019) 5684–5694.
[28] P.K. Pramanick, Z. Zhou, Z. Hou, Y. Ao, B. Yao, Chin. Chem. Lett. 31 (2020) 1327–1331.
[29] F. Yuan, Z.L. Hou, P.K. Pramanick, B. Yao, Org. Lett. 21 (2019) 9381–9385.
[30] Z.L. Hou, F. Yuan, B. Yao, Org. Lett. 22 (2020) 8692–8696.
[31] Y. Ding, S. Fan, X. Chen, et al., Org. Lett. 21 (2019) 4224–4228.
[32] H. Lin, X. Pan, A.L. Barsamian, T.M. Kamenecka, T.D. Bannister, ACS Catal. 9 (2019) 4887–4891.
[33] T.G. Saint-Denis, R.Y. Zhu, G. Chen, Q.F. Wu, J.Q. Yu, Science 359 (2018) eaao4798.
[34] N. Zhao, X. Jin, Y. Dang, Chin. Chem. Lett. 32 (2021) 3980–3983.