EurJOC
European Journal of Organic Chemistry

Research Article
doi.org/10.1002/ejoc.202201489

Chemistry Europe
European Chemical Societies Publishing

www.eurjoc.org

Palladium-Catalyzed Site-Selective C(sp^2)–H Acetoxylation of Tyrosine-Containing Peptides

Iñaki Urruzuno,[a] Paula Andrade-Sampedro,[a, b] and Arkaitz Correa*[a]

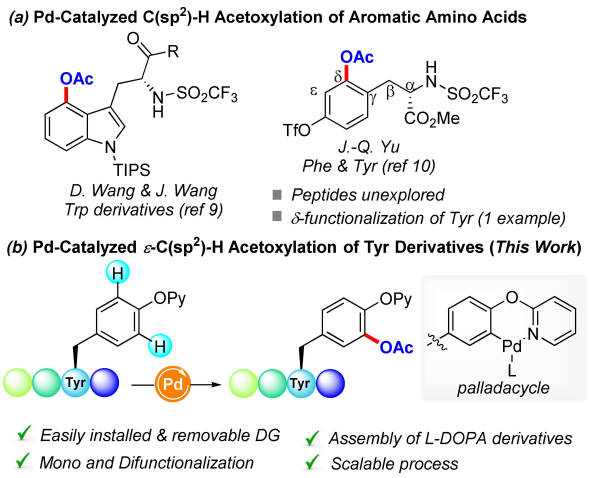
A Pd-catalyzed C(sp^2)–H acetoxylation of Tyr-containing peptides is described. The method relies on the use of a removable 2-pyridyloxy group as directing group and is distinguished by its reliable scalability and easily tuned regioselectivity to perform mono- and diacetoxylation reactions. Remarkably, the assembly of L–DOPA peptidomimetics is beyond reach upon cleavage of the directing group.

Introduction

The development of metal-catalyzed C–H functionalization reactions has arguably changed the landscape of organic synthesis, thereby ushering in a myriad of innovative retrosynthetic disconnections to forge C–C and C–heteroatom linkages.[1] Owing to the presence of oxygenated motifs such as phenols in a wide variety of natural products and industrially relevant compounds,[2] C–O bond-forming reactions are of particular importance in chemical synthesis.[3] Since the seminal works by Crabtree[4] and Sanford,[5] a wide number of directing groups (DGs) as well as metal catalysts and oxidants have been utilized to perform versatile C(sp^2)–H acetoxylation reactions.[6] However, despite the reliability of the existing protocols, they often show a limited substrate scope and the synthetic toolbox remains unexplored in valuable aminoacids and peptides, which house a variety of functional groups. In fact, the latter can deeply compromise the site-selectivity and chemoselectivity of C–H functionalization reactions within a peptide template, hence rendering the direct translation of a given reaction from a simple arene to a peptide compound in a challenging task of utmost synthetic significance.[7]

Whereas the C(sp^3)–H acetoxylation of certain amino acids upon chelation assistance has been elegantly achieved,[8] the parent process within the aromatic side-chain of amino acids is rare. Very recently, the site-selective C4-acetoxylation of a number of tryptophan-containing peptides[9] has been described by Wang and co-workers (Scheme 1, *route a*). Likewise, as part of their work on the C–H functionalization of alkylamines, Yu described the δ-C(sp^2)–H acetoxylation of simple Phe and Tyr residues.[10] In both methods, the incorporation of the trifluoromethylsulfonyl group at the nitrogen atom was required, which resulted in the modification of the corresponding residue at the N-terminal position. Accordingly, a general process for the late-stage and site-selective acetoxylation of versatile tyrosine compounds remains elusive.[11]

In order to complement the method by Yu featuring the oxidation of the δ-C(sp^2)–H bond, we envisaged that the phenol ring within Tyr could be easily transformed into a chelating group to further direct the ensuing acetoxylation at a distal ε-C(sp^2)–H bond upon the formation of a 6-membered palladacycle (Scheme1, *route b*). If successful, our acetoxylation manifold would enable the modification the Tyr unit regardless its position within the peptide sequence.[12] Likewise, further chemical manipulation of the appended oxygenated group and cleavage of the required DG would result in the straightforward assembly of relevant L–DOPA peptidomimetics. In connection with our interest in C–H functionalization,[13] herein we report on the Pd-catalyzed directed C–H acetoxylation of Tyr-contain-



Scheme 1. C–H acetoxylation of amino acid derivatives.

[a] I. Urruzuno, P. Andrade-Sampedro, A. Correa
University of the Basque Country (UPV/EHU)
Department of Organic Chemistry I
Joxe Mari Korta R&D Center
Avda. Tolosa 72, 20018 Donostia-San Sebastián (Spain)
E-mail: arkaitz.correa@ehu.eus
https://www.ehu.eus/en/web/qbbm/home
[b] P. Andrade-Sampedro
Donostia International Physics Center (DIPC)
Paseo Manuel de Lardizabal 4
20018 Donostia-San Sebastián (Spain)

Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202201489

Research Article
doi.org/10.1002/ejoc.202201489

ing peptides at a challenging ε-C(sp^2)–H site. This scalable method features the use of a removable DG, thereby representing a powerful late-stage diversification technique to forge phenols in a peptide template.

Results and Discussion

To evaluate the feasibility of our oxygenation manifold, we first selected the fully protected tyrosine derivative **1a** housing a removable 2-pyridyloxy group as DG.[12b–c,e,14] After evaluation of the reaction conditions,[15] we observed that the desired acetoxylation event could occur to provide mixtures of mono- and diacetoxylated compounds **2a** and **2a'**, respectively. Importantly, the selectivity toward the formation of both products could be entirely controlled with the amount of oxidant and temperature. Whereas the use of 1.2 equivalents of PIDA in MeCN at 80 °C provided **2a** in 61% yield (Table 1, entry 2), the performance of the process at 100 °C with 3.0 equivalents of oxidant ushered in **2a'** in 71% yield (Table 1, entry 3).

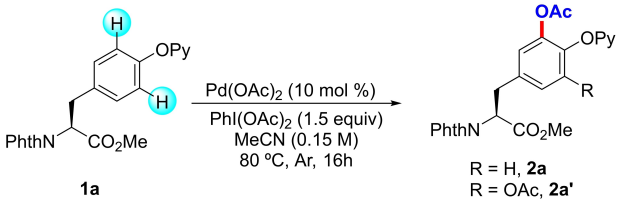
Screening of different solvents evidenced the suitability of MeCN as the ideal solvent (entries 4–5). $Pd(OAc)_2$ exhibited superior efficiency as catalyst than other Pd sources (entries 6–9), and ruthenium salts shown ineffective in these acetoxylation processes (entries 10–11). Other related oxidants such as PIFA resulted in the entire degradation of the starting material (entry 13) and persulfates such as $K_2S_2O_8$ were found inactive (entry 14). As expected, the reaction did not proceed in the absence of either metal or oxidant.[15] Notably, the mono-acetoxylation reaction could be performed at 1.24 mmol with identical results (entry 1).

In order to analyze the role of the DG, other coordinating heterocycles were used (Scheme 2); whereas pyrimidine could also assist the corresponding acetoxylation,[16] pyrazine-containing derivative **1c** remained unreactive. Likewise, the formation of a 6-membered palladacycle was found key for the process to occur as compound **1d** derived from picolinic acid, which would involve the intermediacy of a 7-membered palladacycle, showed no conversion. Other DGs featuring a weak coordination mode such as acetyl (**1f**) and carbamates (**1g–h**) were found unreactive in these reaction conditions. In accordance with the method by Fang,[17] native Tyr residue **1e** underwent undesired oxidative processes instead of the targeted C–H acetoxylation. Therefore, the 2-pyridyl ether easily installed upon a conventional Cu-catalyzed O-arylation reaction posed the most effective DG in these endeavors.

Having demonstrated the viability of labelling a single Tyr residue, we next tackled the modification of more challenging Tyr-containing short peptides possessing multiple competing sites. A collection of dipeptides housing Leu (**3a**), Ala (**3b**), Glu (**3c**), Phe (**3d**), Val (**3e**) and Pro (**3f**) smoothly underwent the acetoxylation reaction in a selective fashion to produce **4a–f** in up to 57% yield (Table 2). The success of the method did not depend on a specific location of the Tyr unit along the peptide sequence as peptides bearing the Tyr both at the N- and C-terminal positions could be accommodated. Likewise, our acetoxylation platform could also be used to tag structurally more complex tri- and tetrapeptides **3g–l** incorporating residues such as Thr or Asp.

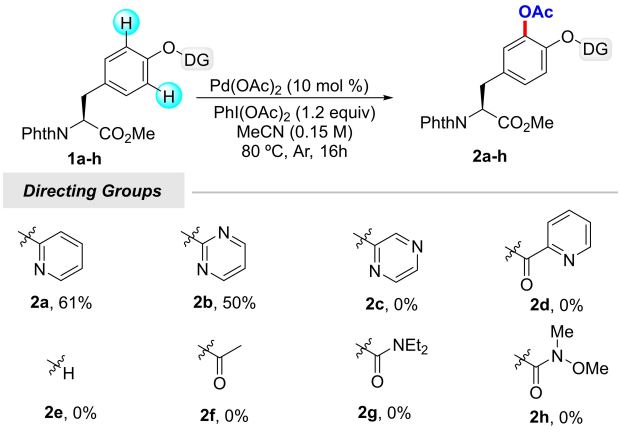
However, when increasing the number of amino acids, an excess of oxidant and a higher temperature was required to reach full conversion, which may be due to the presence of multiple amide bonds within the peptide sequence that could diminish the catalyst efficiency. Remarkably, the acetoxylation of tetrapeptide **3i** could be run at a gram-scale to afford **4i** in 51% yield (Table 2), which underpinned the reliability of this technique. Likewise, a biologically relevant acetoxylated tetra-

Table 1. Optimization for the ε-C–H acetoxylation of **1a**.[a]



Entry	Change from the standard conditions	**2a** (%)[b]	**2a'** (%)[b]
1[c]	none	60	7
2	PIDA (1.2 equiv)	61	2
3	PIDA (3.0 equiv) at 100 °C	0	71
4	water as solvent	0	0
5	THF as solvent	0	0
6	$Pd(OTFA)_2$ as catalyst	35	0
7	$PdCl_2$ as catalyst	43	12
8	$Pd(OPiv)_2$ as catalyst	57	10
9	$PdCl_2(MeCN)_2$ as catalyst	35	10
10	$RuCl_3$ as catalyst	0	0
11	$[RuCl_2(p\text{-cymene})]_2$ as catalyst	0	0
12	at 70 °C	55	8
13	PIFA as oxidant	0	0
14	$K_2S_2O_8$ in AcOH/DCE	0	0

[a] Reaction conditions: **1a** (0.15 mmol), $Pd(OAc)_2$ (10 mol%), PIDA (1.5 equiv.), MeCN (1.0 mL) at 80 °C for 16 h under Ar. [b] Yield of isolated product after column chromatography. [c] Reaction performed at 1.24 mmol scale.

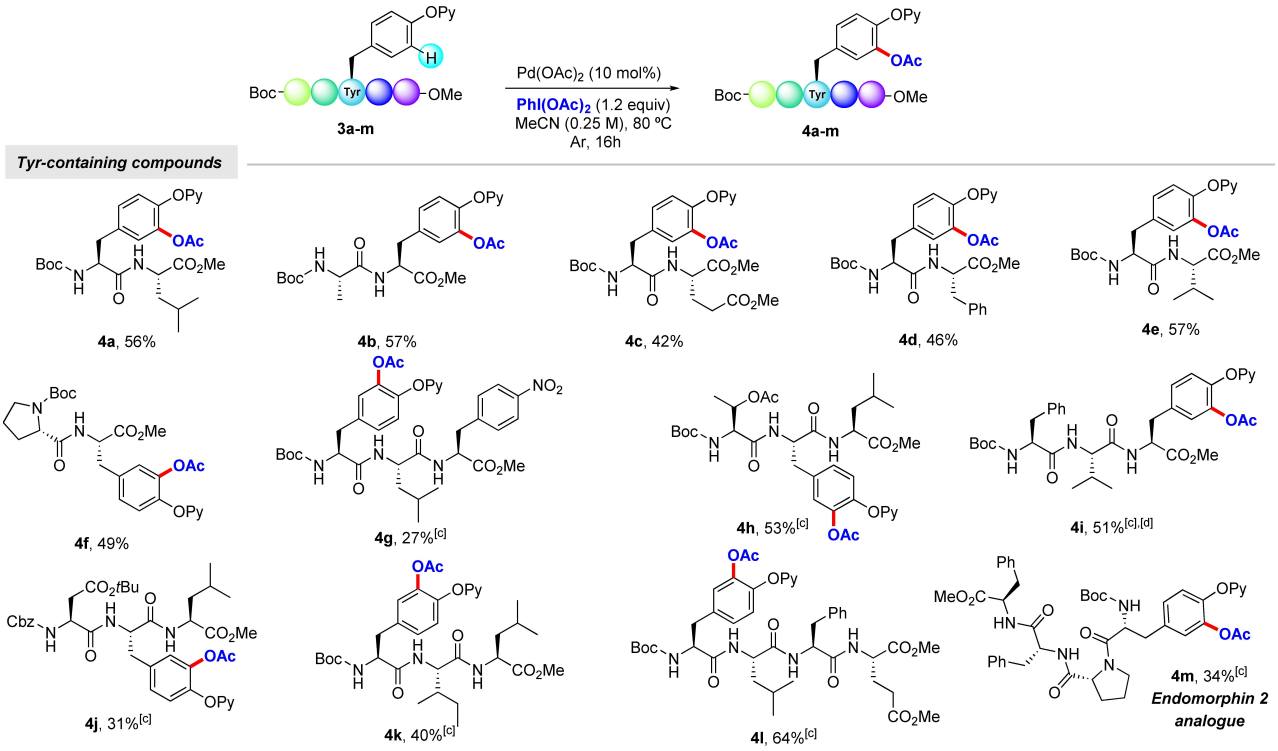


Scheme 2. Influence of the directing groups.

Research Article
doi.org/10.1002/ejoc.202201489

Chemistry Europe
European Chemical Societies Publishing

Table 2. ε-C–H monoacetoxylation of Tyr-containing peptides.[a,b]



[a] Reaction conditions as for Table 1, entry 2. [b] Yield of isolated product after column chromatography, average of at least two independent runs with a variable yield of no more than 5% between runs. [c] Reaction conditions as for Table 1, entry 3. [d] Reaction performed at gram-scale.

peptide such as endomorphin 2 analogue **4m** was beyond reach, albeit in moderate yields.

Importantly, the diacetoxylation of dipeptides was efficiently achieved to produce fully decorated Tyr-containing compounds **4a'–f'** in good yields (Table 3). As previously anticipated, not only the 2-pyridyl unit but also the 2-pyrimidyl group could assist the difunctionalization process and **2b'** was formed in 53% yield. As expected, the dipeptide containing two Tyr units **1n** could undergo a selective diacetoxylation of the residue housing the 2-pyridyl ether, thereby preferentially delivering **4n'** and enabling ample opportunities for further manipulation at the pivalate motif.

Although the removal of the OPy group has been successfully accomplished in simple aryl systems upon treatment with methyl triflate followed by an alcoholic solution of sodium, its application in a peptide setting ushered in mixtures of various products. Notably, the cleavage of the DG was efficiently performed through a methylation/hydrogenation sequence[12b] to easily produce peptides housing a diphenol unit derived from a concomitant hydrolysis of the acetyl group. In this manner, L–DOPA (**5a**) and its peptidomimetics derivatives (**5b–c**) could be prepared in a reliable manner in up to 60% yields (Scheme 3). Likewise, the selective cleavage of the appended oxygenated group could be performed upon treatment of **4i** with ammonium acetate to deliver hydroxylated tripeptide **6** in 58% yield, thereby complementing our previously described Ru-catalyzed hydroxylation protocol occurring upon weak chelation assistance with carbamates.[12a]

Based on the extensive knowledge in the field,[4–6] the described acetoxylation reaction is assumed to happen through a Pd(II)/Pd(IV) regime (Scheme 4). Initial metalation of the Tyr unit assisted by the OPy group would provide a 6-membered palladacycle intermediate **I**[18] prone to undergo a subsequent oxidation to its high valent Pd(IV) analogue. Eventually, the desired acetoxylated product would be obtained upon a C–O bond-forming reductive elimination event.

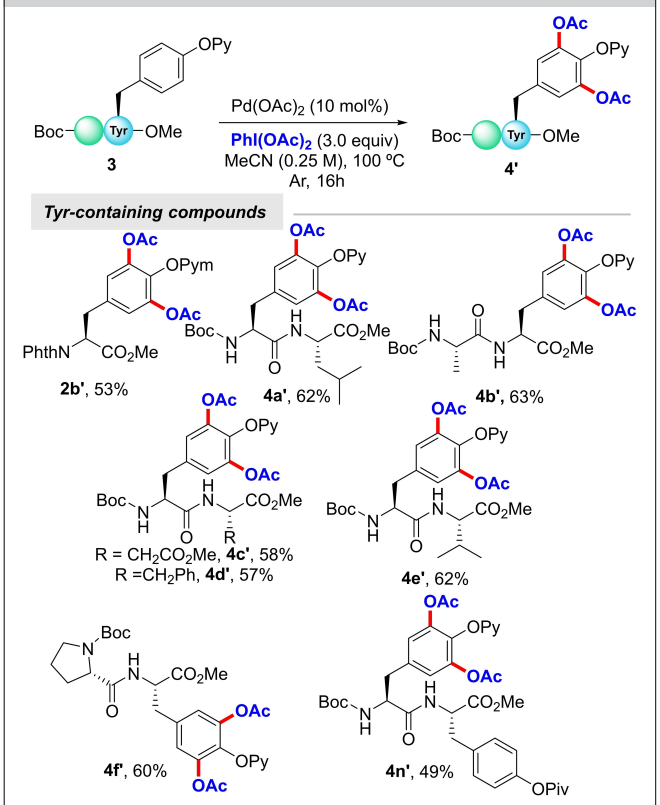
Conclusion

In summary, we have performed a Pd-catalyzed C–H acetoxylation process within a Tyr-containing template featuring the use of a removable 2-pyridyl or pyrimidyl unit. Salient features of this method are the controlled regioselectivity toward the mono- and difunctionalization, the scalability and the easy installation and cleavage of the DG to deliver high-value L–DOPA mimetics in a practical fashion. As a result, this oxygenation manifold represents a versatile tool for the selective modification of biomass compounds and creating molecular diversity within the landscape of peptide and medicinal chemistry.

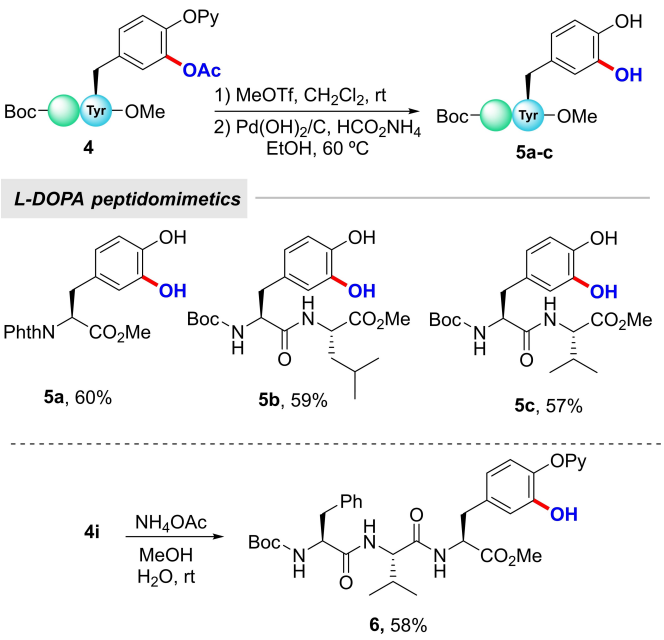
Research Article
doi.org/10.1002/ejoc.202201489

Chemistry Europe
European Chemical Societies Publishing

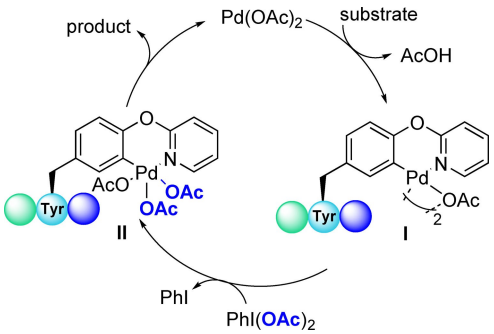
Table 3. Diacetoxylation of Tyr-containing peptides.[a,b]



[a] Reaction conditions as for Table 1, entry 3. [b] Yield of isolated product after column chromatography, average of at least two independent runs with a variable yield of no more than 5% between runs.



Scheme 3. Assembly of L–DOPA peptidomimetics.



Scheme 4. Plausible reaction pathway.

Experimental Section

General procedure for the Pd-catalyzed acetoxylation of 3a: A reaction tube containing a stirring bar was charged with the peptide derivative **3a** (0.25 mmol, 122 mg), PIDA (0.30 mmol) and $Pd(OAc)_2$ (10 mol%). The reaction tube was then evacuated and back-filled with dry argon (this sequence was repeated up to three times). Then, acetonitrile (1.0 mL) was added by syringe under argon atmosphere. The reaction tube was next warmed up to 80 °C in a heating block and stirred for 16 h. The mixture was then allowed to cool down to room temperature and evaporated under vacuum. The resulting crude was then purified by column chromatography to afford 75 mg (56% yield) of **4a** as a white solid. Mp 164–165 °C. Column chromatography (Hex/EtOAc 1:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (dd, J=5.1, 2.0 Hz, 1H), 7.68 (ddd, J=8.4, 7.2, 2.0 Hz, 1H), 7.19–7.06 (m, 3H), 6.99 (ddd, J=7.3, 5.0, 0.9 Hz, 1H), 6.91 (d, J=8.3 Hz, 1H), 6.40 (d, J=8.2 Hz, 1H), 5.12 (d, J=8.2 Hz, 1H), 4.56 (td, J=8.6, 4.9 Hz, 1H), 4.35 (q, J=7.3 Hz, 1H), 3.69 (s, 3H), 3.13–3.03 (m, 2H), 2.04 (s, 3H), 1.68–1.48 (m, 3H), 1.43 (s, 9H), 0.90 (dd, J=6.1, 3.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 170.8, 168.5, 163.0, 155.5, 147.6, 144.3, 142.3, 139.7, 134.4, 128.0, 124.8, 123.2, 118.8, 111.1, 80.5, 55.6, 52.4, 50.9, 41.5, 37.3, 28.4, 24.8, 22.9, 22.0, 20.6. IR (cm^{-1}): 3305, 1766, 1740, 1678, 1655, 1212. HRMS (ESI) m/z: (M^+) *calcd.* for ($C_{28}H_{37}N_3O_8$): 543.2581, *found* 543.2590.

Acknowledgements

We are grateful to Ministerio de Ciencia e Innovación (RTI2018-093721-B-I00, MCI/AEI/FEDER, UE) and Basque Government (IT-1741-22) for financial support. We thank for the technical and human support provided by Central Service of Analysis-SGIker of UPV/EHU and European funding (ERDF and ESF).

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: acetoxylation · amino acid · C–H functionalization · palladium catalysis · peptides

[1] a) L. Zhang, T. Ritter, *J. Am. Chem. Soc.* **2022**, *144*, 2399; b) U. Dutta, S. Maiti, T. Bhattacharya, D. Maiti, *Science* **2021**, *372*, eabd5992; c) B. Liu, A. M. Romine, C. Z. Rubel, K. M. Engle, B.-F. Shi, *Chem. Rev.* **2021**, *121*, 14957; d) S. Rej, Y. Ano, N. Chatani, *Chem. Rev.* **2020**, *120*, 1788.
[2] K. A. Scott, P. B. Cox, J. T. Njardarson, *J. Med. Chem.* **2022**, *65*, 7044.
[3] a) J. Park, J. Son, *Eur. J. Org. Chem.* **2022**, e202200465; b) S. Enthaler, A. Company, *Chem. Soc. Rev.* **2011**, *40*, 4912; c) D. A. Alonso, C. Nájera, C. I. M. Pastor, M. Yus, *Chem. Eur. J.* **2010**, *16*, 5274.
[4] T. Yoneyama, R. H. Crabtree, *J. Mol. Catal. A* **1996**, *108*, 35.
[5] A. R. Dick, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2004**, *126*, 2300.
[6] For selected C(sp^2)–H acetoxylations: a) X. Wang, H. Wang, C. Zhou, L. Yang, L. Fu, G. Li, *Chem. Commun.* **2022**, *58*, 4993; b) Y. Wu, B. Zhou, *Org. Lett.* **2017**, *19*, 3532; c) T. Okada, K. Nobushige, T. Satoh, M. Miura, *Org. Lett.* **2016**, *18*, 1150; d) G. Li, L. Wan, G. Zhang, D. Leow, J. Spangler, J.-Q. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 4391; e) A. V. Gulevich, F. S. Melkonyan, D. Sarkar, V. Gevorgyan, *J. Am. Chem. Soc.* **2012**, *134*, 5528; f) D. C. Powers, M. A. L. Geibel, J. E. M. N. Klein, T. Ritter, *J. Am. Chem. Soc.* **2009**, *131*, 17050; g) L. V. Desai, K. J. Stowers, M. S. Sanford, *J. Am. Chem. Soc.* **2008**, *130*, 13285.
[7] a) N. L. Kjærsgaard, T. B. Nielsen, K. V. Gothelf, *ChemBioChem* **2022**, *23*, e202200245; b) S. Sen, J. Das, D. Maiti, *Tetrahedron Chem.* **2022**, *1*, 100005; c) B.-B. Zhan, M.-X. Jiang, B.-F. Shi, *Chem. Commun.* **2020**, *56*, 13950; d) H.-R. Tong, B. Li, G. Li, G. He, G. Chen, *CCS Chem* **2020**, *2*, 1797; e) W. Wang, M. Lorion, J. Shah, A. R. Kapdi, L. Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 14700; *Angew. Chem.* **2018**, *130*, 14912; f) M. San Segundo, A. Correa, *Synthesis* **2018**, *50*, 2853.
[8] For selected examples, see: a) M. Martínez-Mingo, A. García-Viada, D. S. Prendes, I. Alonso, N. Rodríguez, R. G. Arrayás, J. C. Carretero, *Angew. Chem. Int. Ed.* **2022**, e202209865; b) W.-L. Jia, M. A. Fernández-Ibáñez, *Eur. J. Org. Chem.* **2018**, 6088; c) G. He, Y. Zhao, S. Zhang, C. Lu, G. Chen, *J. Am. Chem. Soc.* **2012**, *134*, 3; d) B. V. S. Reddy, L. R. Reddy, E. J. Corey, *Org. Lett.* **2006**, *8*, 3391.
[9] Q. Zhang, X. Xie, J. Peng, F. Chen, J. Ma, C. Li, H. Liu, D. Wang, J. Wang, *Org. Lett.* **2021**, *23*, 4699.
[10] C. J. Vickers, T.-S. Mei, J.-Q. Yu, *Org. Lett.* **2010**, *12*, 2511.
[11] For selected reviews, see: a) A. Correa, *Eur. J. Inorg. Chem.* **2021**, 2928; b) D. A. Dorta, D. Deniaud, M. Mével, S. G. Gouin, *Chem. Eur. J.* **2020**, *26*, 14257.
[12] For selected metal-catalyzed modifications of Tyr compounds upon chelation assistance, see: a) P. Andrade-Sampedro, J. M. Matxain, A. Correa, *Adv. Synth. Catal.* **2022**, *364*, 2072; b) X. Hou, N. Kaplaneris, B. Yuan, J. Frey, T. Ohyama, A. M. Messinis, L. Ackermann, *Chem. Sci.* **2022**, *13*, 3461; c) I. Urruzuno, P. Andrade-Sampedro, A. Correa, *Org. Lett.* **2021**, *23*, 7279; d) Q.-L. Hu, K.-Q. Hou, J. Li, Y. Ge, Z.-D. Song, A. S. C. Chan, X.-F. Xiong, *Chem. Sci.* **2020**, *11*, 6070; e) M. San Segundo, A. Correa, *Chem. Sci.* **2020**, *11*, 11531.
[13] See, for example: a) M. San Segundo, A. Correa, *Adv. Synth. Catal.* **2022**, *364*, 3161; b) P. Andrade-Sampedro, J. M. Matxain, A. Correa, *Chem. Eur. J.* **2021**, *27*, 5782; c) I. Guerrero, A. Correa, *Org. Lett.* **2020**, *22*, 1754; d) M. San Segundo, A. Correa, *Chem. Sci.* **2019**, *10*, 8872; e) M. San Segundo, A. Correa, *ChemSusChem* **2018**, *11*, 3893; f) A. Goitia, E. Gómez-Bengoa, A. Correa, *Org. Lett.* **2017**, *19*, 962.
[14] For selected C–H oxygenation reactions in simple arenes assisted by *N*-containing heterocycles, see: a) Q. Gou, X. Tan, M. Zhang, M. Ran, T. Yuan, S. He, L. Zhou, T. Cao, F. Luo, *Org. Lett.* **2020**, *22*, 1966; b) Z. Peng, Z. Yu, T. Li, N. Li, Y. Wang, L. Song, C. Jiang, *Organometallics* **2017**, *36*, 15, 2826; c) L. Wang, L. Pan, Y. Huang, Q. Chen, M. He, *Eur. J. Org. Chem.* **2016**, 3113; d) A. Iraztorza, J. M. Aizpurua, A. Correa, *Org. Lett.* **2016**, *18*, 1080.
[15] For further details, see the Electronic Supporting Information.
[16] S. Gu, C. Chen, W. Chen, *J. Org. Chem.* **2009**, *74*, 7203.
[17] P. Wang, Y. Cheng, C. Wu, Y. Zhou, Z. Cheng, H. Li, R. Wang, W. Su, L. Fang, *Org. Lett.* **2021**, *23*, 4137.
[18] a) J.-H. Chu, S.-T. Chen, M.-F. Chiang, M.-J. Wu, *Organometallics* **2015**, *34*, 953; b) D. J. de Geest, B. J. O'Keefe, P. J. Steel, *J. Organomet. Chem.* **1999**, *579*, 97.

Manuscript received: December 22, 2022
Revised manuscript received: December 23, 2022
Accepted manuscript online: December 27, 2022