How to cite: *Angew. Chem. Int. Ed.* **2023,** *62,* e202216661
International Edition: doi.org/10.1002/anie.202216661
German Edition: doi.org/10.1002/ange.202216661

Peptide Modification

Late-stage C–H Functionalization of Tryptophan-Containing Peptides with Thianthrenium Salts: Conjugation and Ligation

*Nikolaos Kaplaneris, Alejandro Puet, Felix Kallert, Julia Pöhlmann, and Lutz Ackermann**

Abstract: Bioorthogonal late-stage diversification of structurally complex peptides bears enormous potential for drug discovery and molecular imaging, among other applications. Herein, we report on a palladium-catalyzed C–H arylation of tryptophan-containing peptides with readily accessible and modular arylthianthrenium salts. Under exceedingly mild reaction conditions, the late-stage diversification of structurally complex peptides was accomplished. The tunability and ease of preparation of arylthianthrenium salts allowed the expedient stitching of tryptophan-containing peptides with drug, natural product, and peptidic scaffolds by forging sterically congested biaryl linkages. The robustness of the palladium catalysis regime was reflected by the full tolerance of a plethora of sensitive and coordinating functional groups. Hence, our manifold enabled efficient access to highly decorated, labelled, conjugated, and ligated linear and cyclic peptides.

Late-stage functionalization of biomolecules has emerged as an efficient method for the expansion of the accessible chemical space, without reliance on cost- and time-intensive de novo manifolds.[1] Thus, the site- and chemoselective diversification of peptides and proteins is of prime importance in academia and pharmaceutical industries. In this context, peptides featuring unnatural amino acids hold a unique conformational space and feature distinct bioactivities, concurrently being more stable towards proteolytic degradation.[2] Efficient late-stage diversification of peptides and proteins, that are not hindered by the myriad of functional groups found on such complex biomolecules, require predictable, robust, and mild methods. Until recently, predominantly classical condensations and (cyclo)additions,[3] or metal-catalyzed cross-couplings[4] have been exploited for the functionalization of peptides. Despite these major advances, palladium-catalyzed cross-couplings require two pre-functionalized substrates, leading to cost- and time-intensive multistep syntheses. During the last decade, C–H activation has been recognized as a transformative platform in molecular syntheses. Thus, late-stage diversification of peptides by noble-metal-catalyzed C–H activation[5] was established by Lavilla/Albericio,[6] Chen,[7] Shi,[8] Ackermann,[9] and Yu,[10] among others[11] and more recently through 3d transition metal catalysis.[12] Among the proteinogenic amino acids, tryptophan is the least abundant residue accounting for only 1–2 % of the amino acids expressed.[13] The indole moiety of tryptophan is the most electron-rich π-system present in amino acids, a property that enables tryptophan to engage in a variety of interactions; thus, tryptophan is generally enriched at centers of biochemical significance.[14] These properties render tryptophan an excellent target for late-stage functionalization as a tool for establishing expedient structure–activity relationships of various peptides and proteins. Thus, significant recent efforts have been devoted to developing mild and chemoselective methods for the functionalization of tryptophan residues, under photochemical[15] and transition metal-catalyzed manifolds.[6,12,16] Among these methods palladium-catalyzed arylation of tryptophan has surfaced for the introduction of various (hetero)aryl moieties utilizing various arylating agents, under distinct reaction conditions (Figure 1a). Among these arylating agents, aryl iodides are the most well-established, yet they typically require stoichiometric amounts of silver salts and elevated reaction temperatures.[6c] To bypass the need for additives and harsh reaction conditions charged electrophiles were utilized, presumably facilitating the oxidative addition, such as aryldiazonium salts[16d] and diaryliodonium salts.[16e] Remarkably, the site- and chemoselective arylation with the diaryliodonium salts was achieved in H_2O at room temperature. In addition, under an oxidative manifold utilizing arylboronic acids, the arylation was achieved by Fairlamb and coworkers under mild reaction conditions, albeit with the requirement of stoichiometric amounts of oxidants.[16f,g] Despite these undisputed advances, the preparation of such arylating agents require rather harsh reaction conditions, thus hindering their use for the merging of structurally

[*] Dr. N. Kaplaneris, A. Puet, F. Kallert, J. Pöhlmann, Prof. Dr. L. Ackermann
Institut für Organische und Biomolekulare Chemie, Georg-August-Universität Göttingen
Tammanstrasse 2, 37077 Göttingen (Germany)
E-mail: Lutz.Ackermann@chemie.uni-goettingen.de
Homepage: http://www.ackermann.chemie.uni-goettingen.de/
Prof. Dr. L. Ackermann
Wöhler Research Institute for Sustainable Chemistry, Georg-August-Universität Göttingen
Tammanstrasse 2, 37077 Göttingen (Germany)
and
German Center for Cardiovascular Research (DZHK)
Potsdamer Strasse 58, 10785 Berlin (Germany)

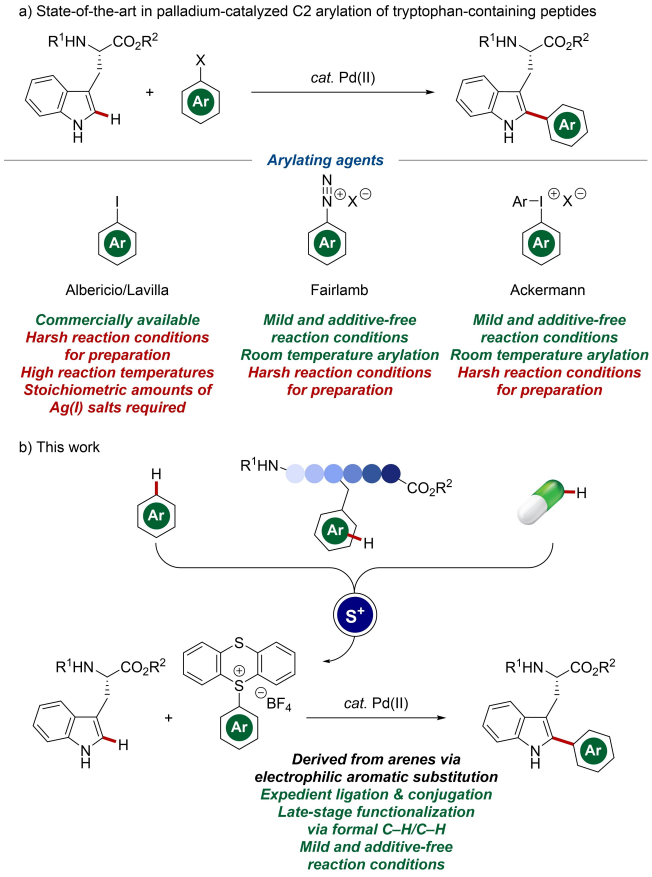
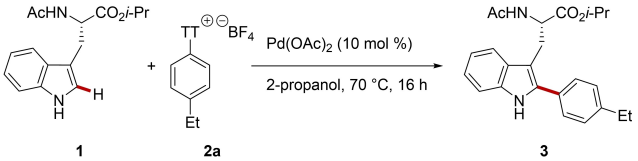


Figure 1. a) Arylating agents for C2 arylation of tryptophan residues. b) Expedient entry to conjugated and ligated peptides by palladium-catalyzed C–H arylation with arylthianthrenium salts.

Table 1: Optimization of the C2 arylation of tryptophan derivative **1** with arylthianthrenium salt **2a**.[a]



1 **2a** **3**

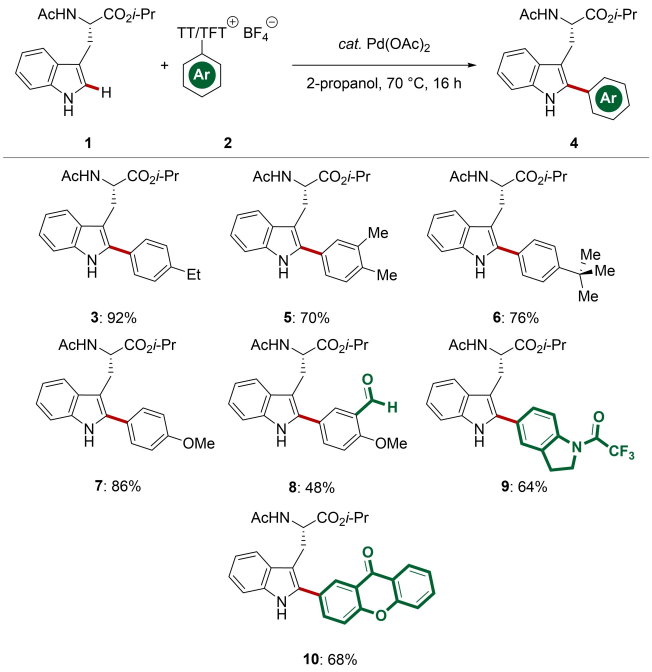
Entry	Deviation from the standard conditions	Yield [%][b]
1	none	92
2	toluene as solvent	52
3	1,4-dioxane/DME as solvent	34/33
4	EtOAc as solvent	42
5	DMA/DMF/MeCN as solvent	nd/nd/nd
6	MeOH/TFE/HFIP as solvent	16/nd/nd
7	at 50 °C	54
8	$Pd(OAc)_2$ (5.0 mol %)	75
9	$MnBr(CO)_5$/$[RuCl_2(p\text{-cymene})]_2$/ $[Cp^*RhCl_2]_2$/$[Cp^*IrCl_2]_2$ as catalyst	nd/nd/nd/nd
10	without $Pd(OAc)_2$	nd
11	Under light irradiation 456 nm/390 nm[c]	54/24
12	Under light irradiation, without $Pd(OAc)_2$ 456 nm/390 nm[c]	nd/nd

[a] Reaction conditions: **1** (0.10 mmol), **2a** (0.15 mmol), $Pd(OAc)_2$ (10 mol %), solvent (1.0 mL), 70 °C, 16 h. [b] Yield of isolated product. [c] Reaction at 25 °C. TT: thianthrene, DME: 1,2-dimethoxyethane, DMA: *N*,*N*-dimethylacetamide, DMF: *N*,*N*-dimethylformamide, TFE: 2,2,2-trifluoroethanol, HFIP: 1,1,1,3,3,3-hexafluoro-2-propanol, Cp*: 1,2,3,4,5-pentamethylcyclopentadienyl.

complex motifs to tryptophan residues. This impediment leads to lengthy and costly multistep de novo approaches. Hence, we probed whether a more versatile arylating agent could be employed to overcome those limitations. Recently, elegant studies by Ritter,[17] Procter,[18] and others[19] showcased that the site- and chemoselective preparation of arylsulfonium salts provides expedient access to structurally complex aryl electrophiles for cross-couplings and photochemical reactions. As part of our program on late-stage functionalization through C–H activation, we now report on the arylation of tryptophan-containing peptides with arylthianthrenium salts without the aid of directing groups (Figure 1b).[20] Salient features of our findings include 1) epimerization-free C–H arylation of structurally complex peptides under additive-free and exceedingly mild reaction conditions, 2) expedient access to peptide/drug conjugates with drug-derived thianthrenium salts and 3) ligation of peptides by the stitching of tryptophan residues with tyrosine or phenylalanine residues to forge sterically demanding biaryl motifs.

We commenced our studies towards the desired C2 arylation of directing group-free tryptophan derivative **1** with arylthianthrenium salt **2a** and $Pd(OAc)_2$ by probing various solvents under additive-free reaction conditions (Table 1). Among the solvents that were tested, 2-propanol provided the desired product in 92 % at 70 °C (entry 1). Interestingly, typical solvents, such as EtOAc, DMF, and DMA, utilized for the C2 arylation of tryptophan derivatives with other arylating agents, led to significantly lower yields (entries 4 and 5). Furthermore, other alcoholic solvents, such as MeOH, TFE, and HFIP, resulted in complete suppression of the reaction (entry 6). Lowering the reaction temperature to 50 °C or the catalyst loading led to slightly diminished yields of the isolated product (entries 7 and 8). Interestingly, various transition-metal catalysts that have been utilized in the C2 functionalization of tryptophan residues proved completely inefficient in the directing-group-free C–H arylation (entry 9). A control experiment demonstrated the essential nature of the palladium catalyst (entry 10). While arylthianthrenium salts have previously been employed as aryl radical precursors under photochemical conditions,[21] reactions promoted solely by light irradiation were not viable (entries 11 and 12).

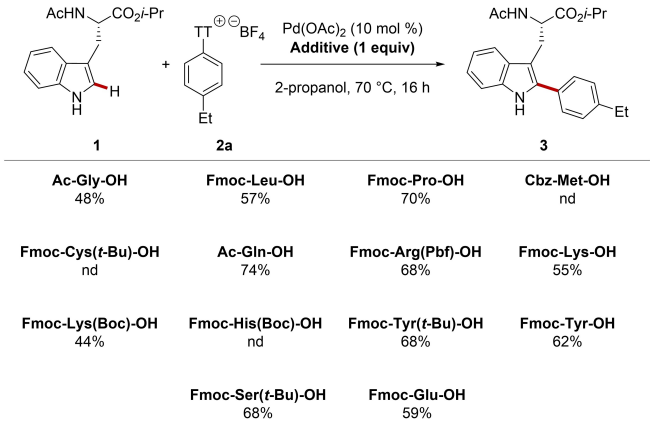
Having optimized the conditions for the palladium-catalyzed C2 arylation of tryptophan residues, we explored the generality of our methodology by probing various arylthianthrenium salts **2** (Scheme 1). Alkyl and alkoxy substituents on the arene moiety of the arylthianthrenium salt **2** were well tolerated leading to the desired arylated tryptophan derivatives **5**–**7** in good to excellent yields. The electrophilic aldehyde functional group on the arylthianthrenium salt **2e** was well tolerated, leading to the functionalized tryptophan derivative **8**, destined



Scheme 1. Chemoselective palladium-catalyzed arylation of tryptophan **1** with arylthianthrenium salts. TFT: tetrafluorothianthrene.

for further condensation-based post-synthetic manipulations. Furthermore, protected indoline derived thianthrenium salt **2f** enabled the efficient construction of the biaryl indole/indoline motif in **9**. The facile preparation of the labeled tryptophan derivative **10**, featuring the fluorescent xanthone scaffold, was also achieved with high efficacy. Under otherwise identical reaction conditions, pyridine- or benzothiophene-derived thianthrenium salts did thus far lead to less satisfactory results.

After having established the initial reaction scope with respect to the arylthianthrenium salts, we conducted an expedient chemoselectivity test[16c] with various amino acid additives (Scheme 2). Thus, hydrophobic amino acids, such as glycine, leucine and proline, were well



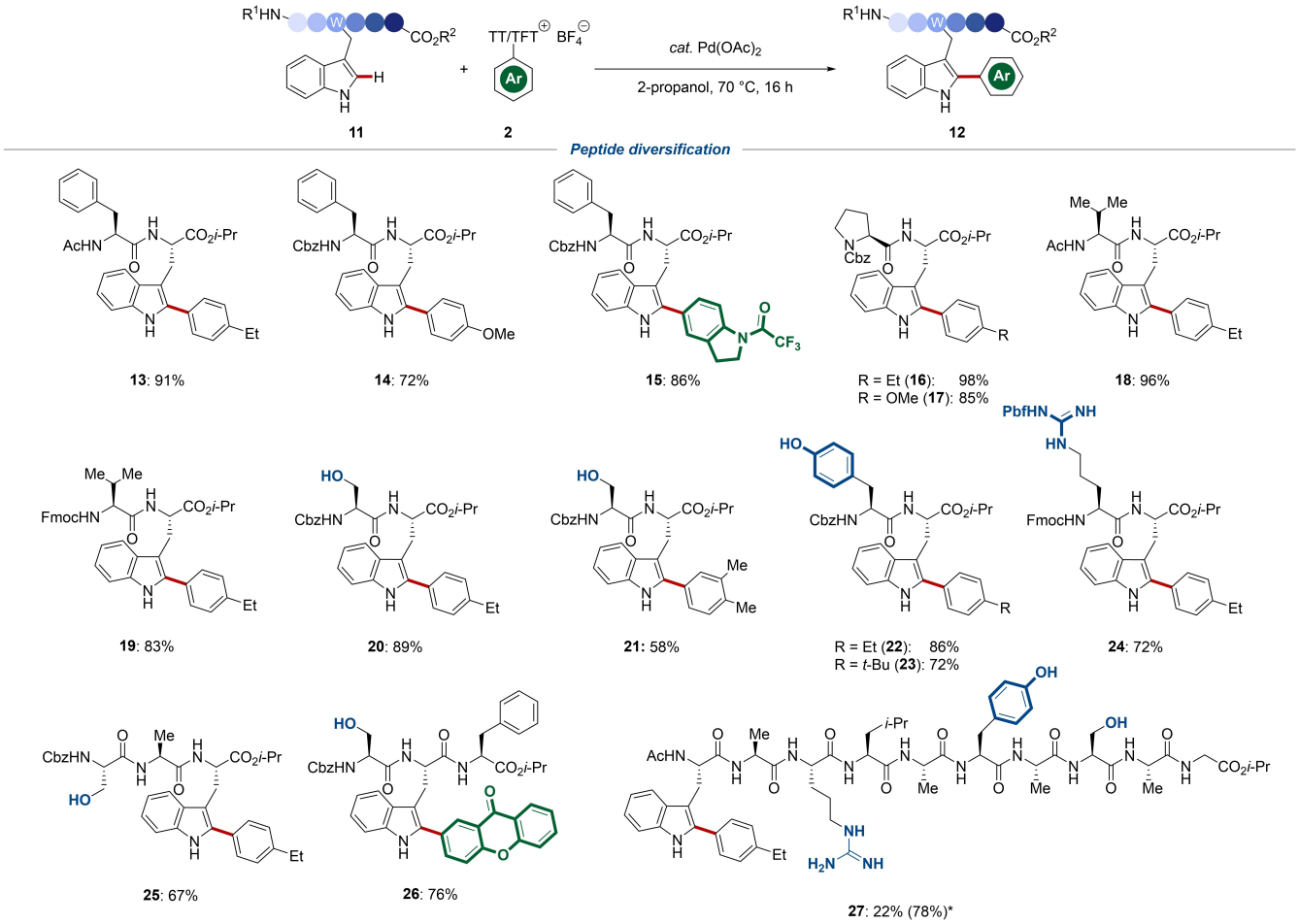
Scheme 2. Chemoselectivity test for palladium-catalyzed C–H arylation of tryptophan **1**.

tolerated, while sulfur-containing amino acids proved to be more challenging. Notably, basic free amino NH_2-groups in lysine and free hydroxyl-groups were found to be fully compatible.

Next, the late-stage arylation of larger peptides **11** using arylthianthrenium salts **2** was probed under our optimized reaction conditions (Scheme 3). Various dipeptides featuring hydrophobic amino acids, such as phenylalanine, proline and valine, were readily arylated providing the desired functionalized dipeptides **13**–**19** in good to excellent yields. The site- and chemoselectivity of the palladium-catalyzed C–H arylation was reflected by complete tolerance of nucleophilic, coordinating functional groups, such as free alcohols, phenols and guanidino groups found in serine-, tyrosine- and arginine-containing dipeptides **20**–**24** leading to the desired products in good to excellent yields. In addition, serine-containing tripeptides **11i** and **11j** were chemoselectively functionalized in good yields, leading to the arylated peptide **25** and labeled peptide **26**. Furthermore, arylated decapeptide **27**, featuring unprotected arginine, tyrosine and serine, was obtained with good efficiency.

The mild and selective route for the formation of the arylthianthrenium salts led us to probe whether thianthrenium salts derived from drug scaffolds and natural products could likewise be employed to our C–H arylation manifold, resulting in unprecedented peptide/drug and peptide/natural product conjugates (Scheme 4). Thus, drugs featuring electron-rich phenol scaffolds, such as gemfibrozil, bezafibrate, clofibrate, and fenofibrate, were readily stitched to the indole moiety of the tryptophan derivative **1**. Furthermore, the highly decorated indole scaffold of indometacin was efficiently utilized leading to the formation of hybrid architecture **35**, featuring the indole/indole biaryl motif. Furthermore, the salicin-derivative, featuring glucose, was smoothly employed leading to the desired amino acid/sugar conjugate **36** in good yield. Encouraged by the efficiency of the stitching between amino acid derivative **1** and drug-derived thianthrenium salt **29** we advanced on the stitching of larger peptides to drug scaffolds. Gratifyingly, dipeptides featuring unprotected alcohols embedded in serine residues, were efficiently conjugated with various drug scaffolds. In addition, tetrapeptide **11k** was stitched to clofibrate leading to conjugate **40** in a chemoselective manner.

Peptide ligation represents a strategy towards large peptides without the need for lengthy de novo syntheses. Hence, we explored whether thianthrenium salts derived from amino acids and peptides could be readily accessed and whether they would be suitable partners for our palladium-catalyzed C–H arylation. Tyrosine and phenylalanine were selected as the most suitable residues, owing to their electron-rich arene moieties. Gratifyingly, both amino acid derivatives and peptides possessing such residues delivered the desired thianthrenium salts **42**[17c] suitable for further late-stage manipulation. Under our standard reactions conditions we established a convergent method for the assembly of complex peptides

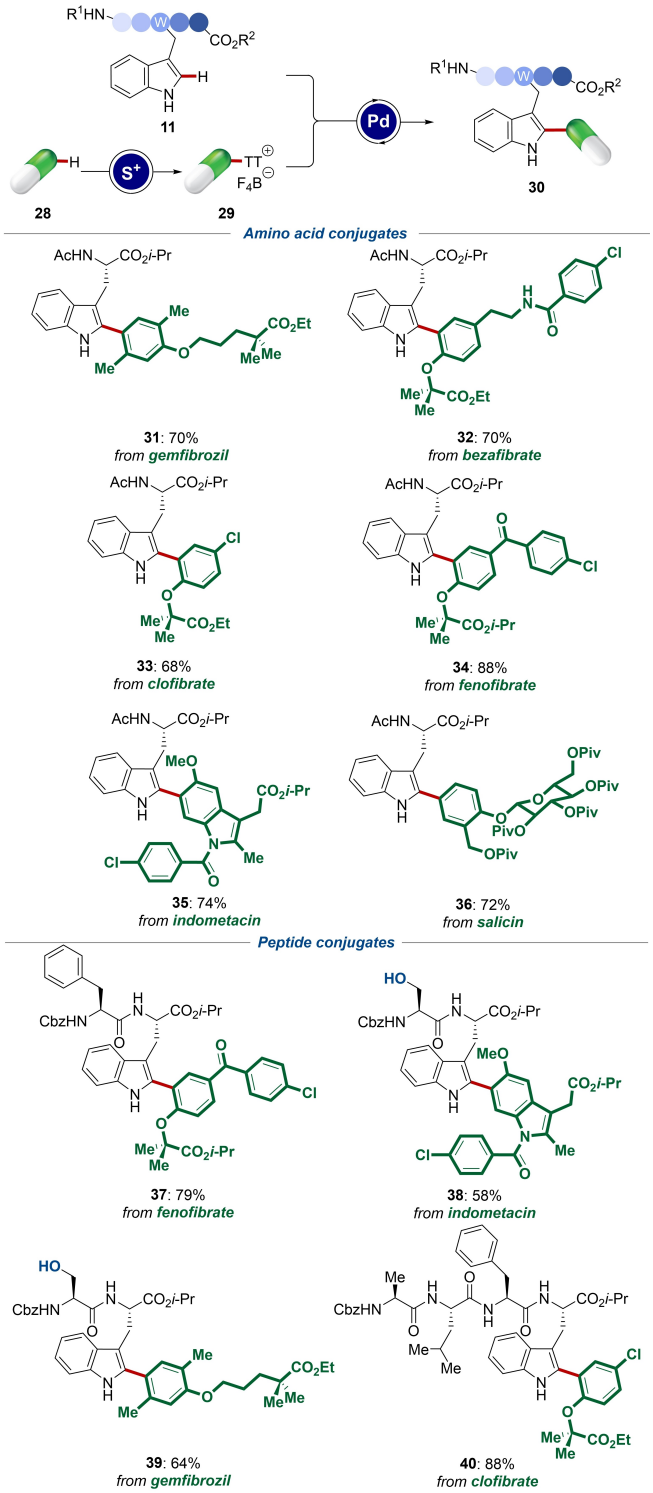


Scheme 3. Site- and chemoselective arylation of linear tryptophan-containing peptides with arylthianthrenium salts. Cbz: benzyloxycarbonyl, Fmoc: fluorenylmethoxycarbonyl, Pbf: 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl. *In parentheses UPLC conversion.

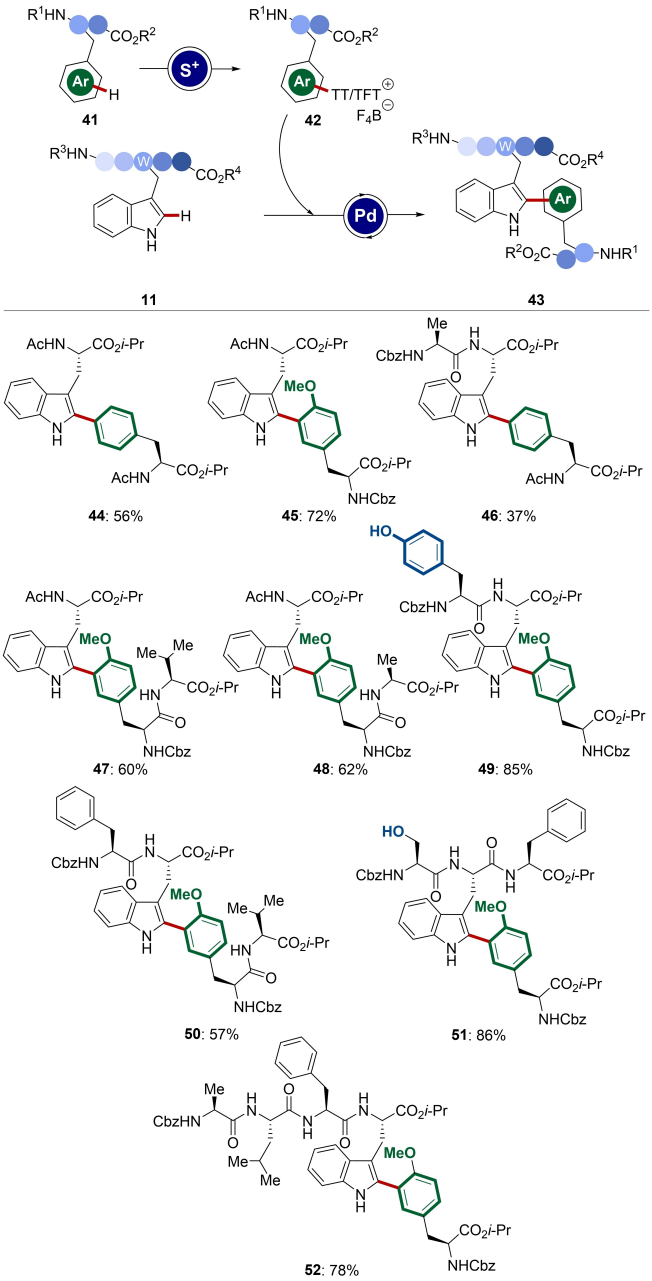
featuring unnatural linkages (Scheme 5). More precisely, unnatural dipeptides Trp-Phe **44** and Trp-Tyr **45** were obtained in moderate to good yields. Then, various tripeptides, featuring unprotected alcohols and phenols, were smoothly assembled in moderate to excellent yields through either a [2+1] or a [1+2] approach. Likewise, tetra- and pentapeptides **50**–**52** were obtained in a site- and chemoselective manner through our convergent approach.

Having established a robust protocol for the diversification, labeling, conjugation and ligation of linear tryptophan-containing peptides we examined the late-stage functionalization of 2,5-diketopiperazines and cyclic peptides (Scheme 6). Thus, the palladium-catalyzed C–H arylation of conformationally rigid tryptophan-containing 2,5-diketopiperazines was realized, enabling access to, among other products, brevianamide F (cyclo-[Trp-Pro]) analogue **58**. Furthermore, cyclo[Trp-Val] (**53c**) was efficiently stitched to a tyrosine residue, resulting in the Trp-Tyr unnatural linkage. Moreover, cyclic penta- and hexapeptides **53e** and **53f** were also site- and chemoselectively arylated, giving access to peptides **60** and **61**, featuring serine, threonine and unprotected arginine residues. In addition, lysine-containing cyclic pentapeptide **53g** was merged in a bioorthogonal manner with the salicin moiety leading to the glycopeptide **62**.

In summary, we have developed an efficient palladium-catalyzed C–H arylation of structurally complex peptides with modular and readily available arylthianthrenium salts. The site- and chemoselective peptide arylation was characterized by excellent functional-group compatibility, tolerating a plethora of sensitive and coordinating groups, under mild and epimerization-free reaction conditions. The tunable nature of arylthianthrenium salts allowed the efficient assembly of peptide/drug conjugates and ligated peptides featuring unnatural biaryl motifs, without the need for lengthy and costly prefunctionalization. This robust method paves the way for the development of a bioorthogonal convergent approach to peptide synthesis.



Scheme 4. Palladium-catalyzed assembly of peptide/drug conjugates. Piv: pivaloyl.



Scheme 5. Palladium-catalyzed convergent assembly of complex peptides.

Acknowledgements

We gratefully acknowledge support from the DFG Gottfried-Wilhelm-Leibniz award (L.A.) and Ceindo Santander (mobility fellowship to A.P.). Open Access funding enabled and organized by Projekt DEAL.

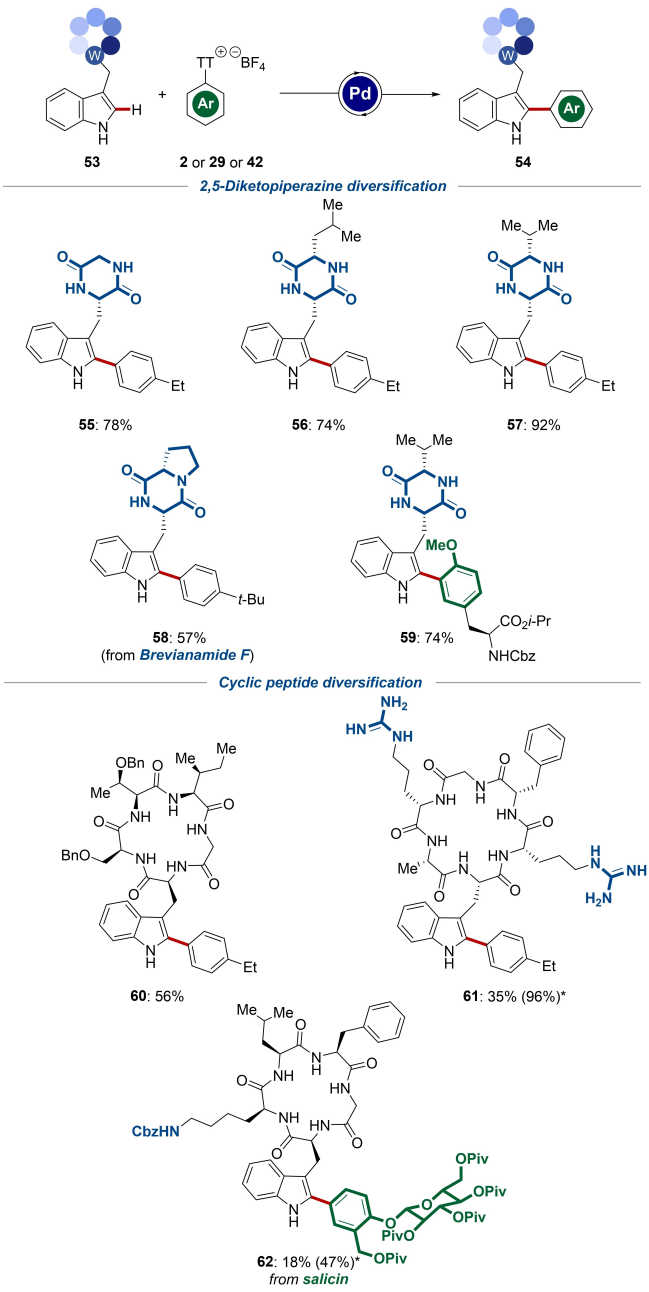
Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: C–H Activation · Late-Stage Functionalization · Ligation · Palladium · Peptides



Scheme 6. Late-stage functionalization of 2,5-diketopiperazines and cyclic peptides. *In parentheses UPLC conversions.

[1] a) L. Zhang, T. Ritter, *J. Am. Chem. Soc.* **2022**, *144*, 2399–2414; b) F. Berger, T. Ritter, *Synlett* **2021**, *33*, 339–345; c) L. Guillemard, N. Kaplaneris, L. Ackermann, M. J. Johansson, *Nat. Chem. Rev.* **2021**, *5*, 522–545; d) D. C. Blakemore, L. Castro, I. Churcher, D. C. Rees, A. W. Thomas, D. M. Wilson, A. Wood, *Nat. Chem.* **2018**, *10*, 383–394; e) J. N. Degruyter, L. R. Malins, P. S. Baran, *Biochemistry* **2017**, *56*, 3863–3873; f) J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369.

[2] a) E. Lenci, A. Trabocchi, *Chem. Soc. Rev.* **2020**, *49*, 3262–3277; b) M. A. T. Blaskovich, *J. Med. Chem.* **2016**, *59*, 10807–10836.

[3] E. A. Hoyt, P. M. S. D. Cal, B. L. Oliveira, G. J. L. Bernardes, *Nat. Chem. Rev.* **2019**, *3*, 147–171.

[4] a) C. Zhang, E. V. Vinogradova, A. M. Spokoyny, S. L. Buchwald, B. L. Pentelute, *Angew. Chem. Int. Ed.* **2019**, *58*, 4810–4839; *Angew. Chem.* **2019**, *131*, 4860–4892; b) M. Jbara, S. K. Maity, A. Brik, *Angew. Chem. Int. Ed.* **2017**, *56*, 10644–10655; *Angew. Chem.* **2017**, *129*, 10780–10792.

[5] a) H.-R. Tong, B. Li, G. Li, G. He, G. Chen, *CCS Chem.* **2021**, *3*, 1797–1820; b) W. Wang, M. M. Lorion, J. Shah, A. R. Kapdi, L. Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 14700–14717; *Angew. Chem.* **2018**, *130*, 14912–14930; c) A. F. M. Noisier, M. A. Brimble, *Chem. Rev.* **2014**, *114*, 8775–8806.

[6] a) L. Mendive-Tapia, S. Preciado, J. García, R. Ramón, N. Kielland, F. Albericio, R. Lavilla, *Nat. Commun.* **2015**, *6*, 7160; b) S. Preciado, L. Mendive-Tapia, F. Albericio, R. Lavilla, *J. Org. Chem.* **2013**, *78*, 8129–8135; c) J. Ruiz-Rodríguez, F. Albericio, R. Lavilla, *Chem. Eur. J.* **2010**, *16*, 1124–1127.

[7] a) B. Li, X. Li, B. Han, Z. Chen, X. Zhang, G. He, G. Chen, *J. Am. Chem. Soc.* **2019**, *141*, 9401–9407; b) X. Zhang, G. Lu, M. Sun, M. Mahankali, Y. Ma, M. Zhang, W. Hua, Y. Hu, Q. Wang, J. Chen, G. He, X. Qi, W. Shen, P. Liu, G. Chen, *Nat. Chem.* **2018**, *10*, 540–548; c) Y. Feng, G. Chen, *Angew. Chem. Int. Ed.* **2010**, *49*, 958–961; *Angew. Chem.* **2010**, *122*, 970–973.

[8] a) X.-S. Yin, W.-Y. Qi, B.-F. Shi, *Chem. Sci.* **2021**, *12*, 13137–13143; b) L. Liu, Y.-H. Liu, B.-F. Shi, *Chem. Sci.* **2020**, *11*, 290–294; c) B.-B. Zhan, Y. Li, J.-W. Xu, X.-L. Nie, J. Fan, L. Jin, B.-F. Shi, *Angew. Chem. Int. Ed.* **2018**, *57*, 5858–5862; *Angew. Chem.* **2018**, *130*, 5960–5964; d) J.-W. Xu, Z.-Z. Zhang, W.-H. Rao, B.-F. Shi, *J. Am. Chem. Soc.* **2016**, *138*, 10750–10753.

[9] a) J. Wu, N. Kaplaneris, S. Ni, F. Kaltenhäuser, L. Ackermann, *Chem. Sci.* **2020**, *11*, 6521–6526; b) W. Wang, M. M. Lorion, O. Martinazzoli, L. Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 10554–10558; *Angew. Chem.* **2018**, *130*, 10714–10718; c) M. Bauer, W. Wang, M. M. Lorion, C. Dong, L. Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 203–207; *Angew. Chem.* **2018**, *130*, 209–213.

[10] a) T. Liu, J. X. Qiao, M. A. Poss, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2017**, *56*, 10924–10927; *Angew. Chem.* **2017**, *129*, 11064–11067; b) W. Gong, G. Zhang, T. Liu, R. Giri, J.-Q. Yu, *J. Am. Chem. Soc.* **2014**, *136*, 16940–16946.

[11] a) Z. Bai, C. Cai, Z. Yu, H. Wang, *Angew. Chem. Int. Ed.* **2018**, *57*, 13912–13916; *Angew. Chem.* **2018**, *130*, 14108–14112; b) B. Mondal, B. Roy, U. Kazmaier, *J. Org. Chem.* **2016**, *81*, 11646–11655; c) L. D. Tran, O. Daugulis, *Angew. Chem. Int. Ed.* **2012**, *51*, 5188–5191; *Angew. Chem.* **2012**, *124*, 5278–5281.

[12] a) N. Kaplaneris, J. Son, L. Mendive-Tapia, A. Kopp, N. D. Barth, I. Maksso, M. Vendrell, L. Ackermann, *Nat. Commun.* **2021**, *12*, 3389; b) N. Kaplaneris, F. Kaltenhäuser, G. Sirvinskaite, S. Fan, T. De Oliveira, L.-C. Conradi, L. Ackermann, *Sci. Adv.* **2021**, *7*, eabe6202; c) M. M. Lorion, N. Kaplaneris, J. Son, R. Kuniyil, L. Ackermann, *Angew. Chem. Int. Ed.* **2019**, *58*, 1684–1688; *Angew. Chem.* **2019**, *131*, 1698–1702; d) N. Kaplaneris, T. Rogge, R. Yin, H. Wang, G. Sirvinskaite, L. Ackermann, *Angew. Chem. Int. Ed.* **2019**, *58*, 3476–3480; *Angew. Chem.* **2019**, *131*, 3514–3518; e) Z. Ruan, N. Sauermann, E. Manoni, L. Ackermann, *Angew. Chem. Int. Ed.* **2017**, *56*, 3172–3176; *Angew. Chem.* **2017**, *129*, 3220–3224.

[13] C. M. Santiveri, M. A. Jiménez, *Biopolymers* **2010**, *94*, 779–790.

[14] S. Barik, *Int. J. Mol. Sci.* **2020**, *21*, 8776.

[15] a) C. R. Hoopes, F. J. Garcia, A. M. Sarkar, N. J. Kuehl, D. T. Barkan, N. L. Collins, G. E. Meister, T. R. Bramhall, C.-H. Hsu, M. D. Jones, M. Schirle, M. T. Taylor, *J. Am. Chem. Soc.* **2022**, *144*, 6227–6236; b) R. N. Lima, J. A. C. Delgado, D. I. Bernardi, R. G. S. Berlinck, N. Kaplaneris, L. Ackermann, M. W. Paixão, *Chem. Commun.* **2021**, *57*, 5758–5761; c) B. Laroche, X. Tang, G. Archer, R. Di Sanza, P. Melchiorre, *Org. Lett.* **2021**, *23*, 285–289; d) S. J. Tower, W. J. Hetcher, T. E. Myers, N. J. Kuehl, M. T. Taylor, *J. Am. Chem. Soc.* **2020**, *142*, 9112–9118; e) B. Ding, Y. Weng, Y. Liu, C. Song, L. Yin, J.

Yuan, Y. Ren, A. Lei, C.-W. Chiang, *Eur. J. Org. Chem.* **2019**, 7596–7605.

[16] a) Z. Bai, C. Cai, W. Sheng, Y. Ren, H. Wang, *Angew. Chem. Int. Ed.* **2020**, *59*, 14686–14692; *Angew. Chem.* **2020**, *132*, 14794–14800; b) M. J. Terrey, A. Holmes, C. C. Perry, W. B. Cross, *Org. Lett.* **2019**, *21*, 7902–7907; c) A. Schischko, H. Ren, N. Kaplaneris, L. Ackermann, *Angew. Chem. Int. Ed.* **2017**, *56*, 1576–1580; *Angew. Chem.* **2017**, *129*, 1598–1602; d) A. J. Reay, L. A. Hammarback, J. T. W. Bray, T. Sheridan, D. Turnbull, A. C. Whitwood, I. J. S. Fairlamb, *ACS Catal.* **2017**, *7*, 5174–5179; e) Y. Zhu, M. Bauer, L. Ackermann, *Chem. Eur. J.* **2015**, *21*, 9980–9983; f) A. J. Reay, T. J. Williams, I. J. S. Fairlamb, *Org. Biomol. Chem.* **2015**, *13*, 8298–8309; g) T. J. Williams, A. J. Reay, A. C. Whitwood, I. J. S. Fairlamb, *Chem. Commun.* **2014**, *50*, 3052–3054; h) Y. Zhu, M. Bauer, J. Ploog, L. Ackermann, *Chem. Eur. J.* **2014**, *20*, 13099–13102.

[17] a) E. M. Alvarez, T. Karl, F. Berger, L. Torkowski, T. Ritter, *Angew. Chem. Int. Ed.* **2021**, *60*, 13609–13613; *Angew. Chem.* **2021**, *133*, 13721–13725; b) F. Ye, F. Berger, H. Jia, J. Ford, A. Wortman, J. Börgel, C. Genicot, T. Ritter, *Angew. Chem. Int. Ed.* **2019**, *58*, 14615–14619; *Angew. Chem.* **2019**, *131*, 14757–14761; c) R. Sang, S. E. Korkis, W. Su, F. Ye, P. S. Engl, F. Berger, T. Ritter, *Angew. Chem. Int. Ed.* **2019**, *58*, 16161–16166; *Angew. Chem.* **2019**, *131*, 16307–16312; d) F. Berger, M. B. Plutschack, J. Riegger, W. Yu, S. Speicher, M. Ho, N. Frank, T. Ritter, *Nature* **2019**, *567*, 223–228.

[18] M. H. Aukland, M. Šiaučiulis, A. West, G. J. P. Perry, D. J. Procter, *Nat. Catal.* **2020**, *3*, 163–169.

[19] a) K. Kafuta, A. Korzun, M. Böhm, C. Golz, M. Alcarazo, *Angew. Chem. Int. Ed.* **2020**, *59*, 1950–1955; *Angew. Chem.* **2020**, *132*, 1966–1971; b) S. I. Kozhushkov, M. Alcarazo, *Eur. J. Inorg. Chem.* **2020**, 2486–2500.

[20] X. Wang, X. Xun, H. Song, Y. Liu, Q. Wang, *Org. Lett.* **2022**, *24*, 4580–4585.

[21] a) K. Sun, A. Shi, Y. Liu, X. Chen, P. Xiang, X. Wang, L. Qu, B. Yu, *Chem. Sci.* **2022**, *13*, 5659–5666; b) Y. Zhao, C. Yu, W. Liang, F. W. Patureau, *Org. Lett.* **2021**, *23*, 6232–6236.

Manuscript received: November 11, 2022
Accepted manuscript online: December 29, 2022
Version of record online: January 24, 2023