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Very Important Publication

Chemoselective Peptide Backbone Diversification and Bioorthogonal Ligation by Ruthenium-Catalyzed C–H Activation/Annulation

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Abstract: The field of peptide derivatization by metal-catalyzed C–H activation has been mostly directed to modify the side chains, but poor attention has been given to the peptide backbone. Here we report a ruthenium-catalyzed C–H activation/annulation process that can chemoselectively modify the peptide backbone producing functionalized isoquinolone scaffolds with high regioselectivity in a rapid and step-economical manner. This strategy is characterized by racemization-free conditions and the production of fluorescent peptides, and peptide conjugates to drugs, natural products and other peptide fragments, providing a chemical approach for the construction of novel peptide-pharmacophore conjugates. Mechanistic studies suggest that amide bonds of peptide backbone act as the bidentate directing group to promote the C–H activation/annulation process. This report provides an unprecedented example of peptide backbone diversification and bioorthogonal ligation exploiting the power of ruthenium-catalyzed C–H activation.

Keywords: Peptides; C–H Activation; Metal catalysis; Ruthenium; Annulation

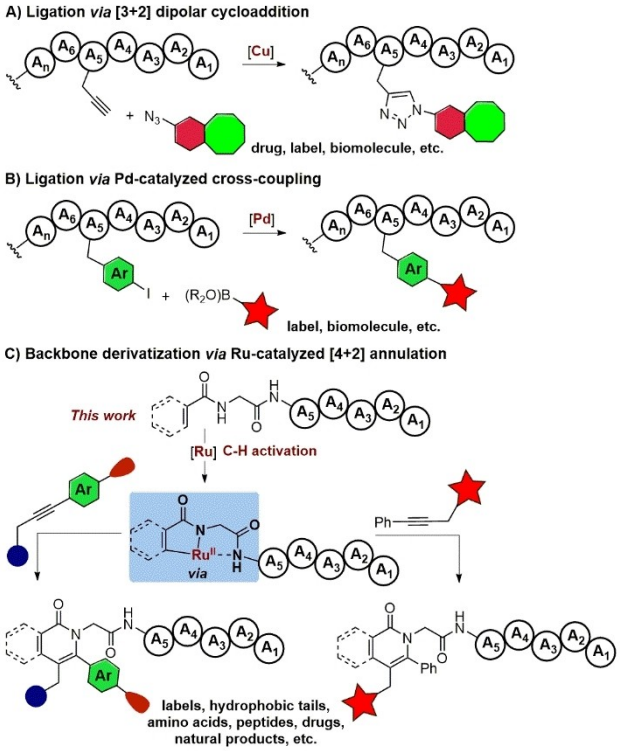
Introduction

The chemo- and regioselective derivatization of peptides is a key synthetic transformation in modern chemistry,[1–5] mainly because of its ability to fine-tuning structural features that help modulate physicochemical and biological properties. Peptide conjugation to other bioactive molecules such as drugs, lipids, carbohydrates and proteins are common derivatizations when seeking applications such as directed cancer therapy or vaccine development.[6–9] Similarly, ligation to synthetic polymers (e.g., PEGs) and fluorescent labels[10–13] are predominant modifications for improving pharmacokinetics and enabling realtime tracking under physiological conditions, respectively. However, many of these covalent modifications are carried out at the peptide side chains and not tend to modify the peptide backbone.

On the other hand, the development of peptide pharmaceuticals[14–17] very often focuses on derivatizing the peptide backbone seeking to modulate pharmacological properties. Thus, the most common approaches are directed toward amide *N*-alkylation and backbone macro- and hetero-cyclization,[18–25] thus aiming at tuning the bioactive conformation and/or improving

metabolic stability (i.e., resistance to peptidases) and membrane permeability.[14–25]

When seeking chemoselective peptide derivatization, transition metal catalysis offers great opportunities for innovation and achieving the desired bioorthogonality in the process. Traditionally, alkyne-azide dipolar cycloadditions[26–28] (metal-catalyzed or not) and palladium-catalyzed cross-couplings[29–31] have been the most widely employed methods for the bioorthogonal peptide derivatization – including cyclization – and ligation to other molecules or labels (Scheme 1A,B). Although classical reactions and cross-couplings have been employed for the chemoselective diversification and bioorthogonal ligation of peptides, they largely rely on prefunctionalizations, leading to lengthy synthetic procedures and undesired byproducts as well as the racemization of the peptidic scaffold. Recently, this field has been moving towards approaches focusing on transition metal-catalyzed C–H activation processes in an atom- and step-economical manner.[32–36] A variety of elegant transition metal-catalyzed methods have been successfully employed in the late-stage derivatization of peptides, including C–H arylation,[37–43] alkynylation,[44,45] olefination,[46,47] allylation[48,49] and alkylation.[50–52] Despite the indisputable advances, in addition to being used mostly for the modification of the side chains, they also show limitations such as *a*) the dependence on exogenous monodentate or bidentate auxiliaries, which requires the multi-step introduction and subsequent removal of the directing group, and *b*) the predominance of one-step cross-coupling processes, which restrains the structural complexity and diversity that can be achieved in the peptide structure.



Scheme 1. Metal-catalyzed chemoselective approaches for the peptide derivatization (e.g., labeling) and ligation to drugs or other bioactive molecules.

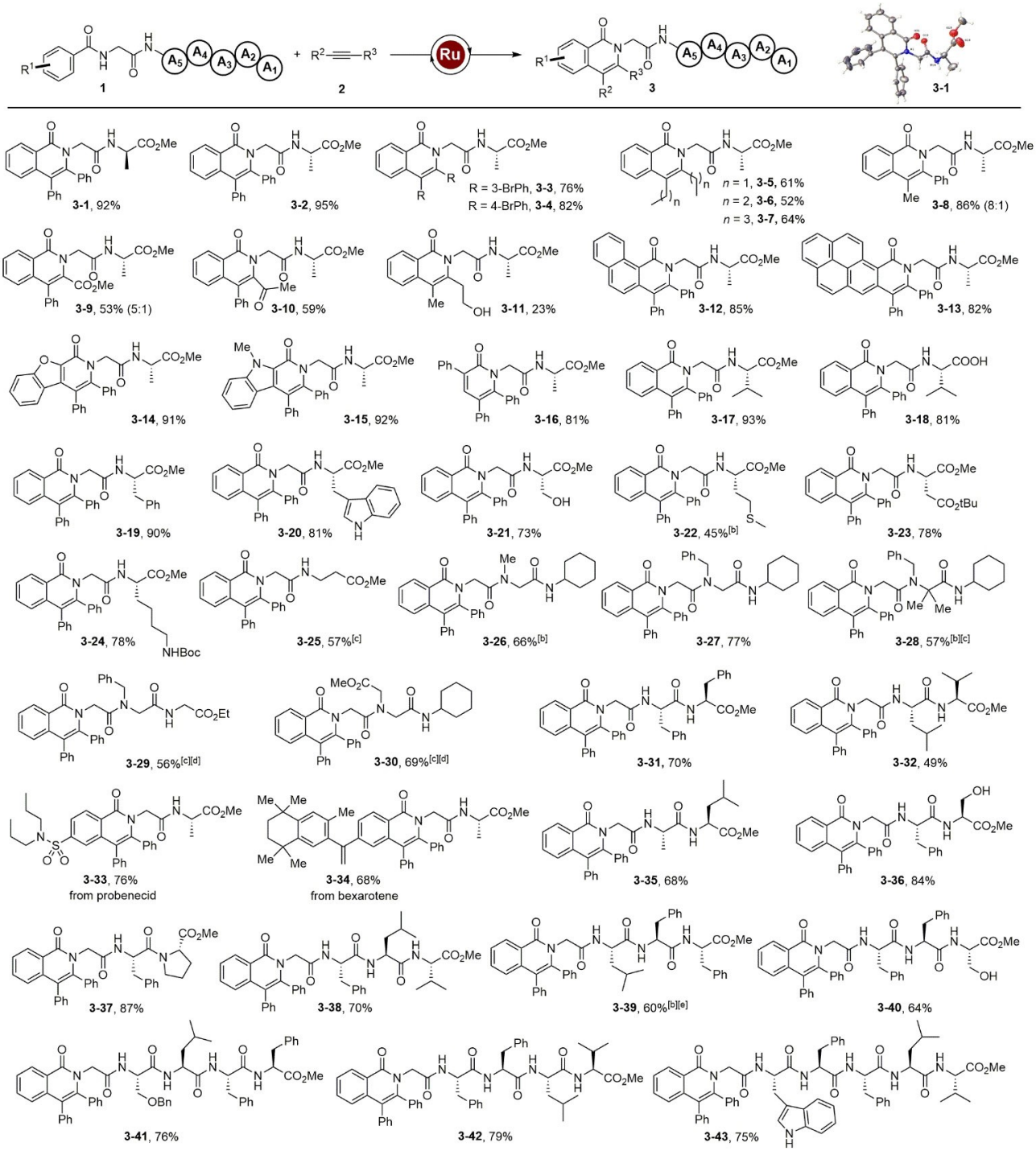
Herein we report a ruthenium-catalyzed C–H activation/annulation[21,24,53] as a versatile procedure for the structural diversification and bioorthogonal ligation of structurally complex peptides (Scheme 1C). Interesting features of our approach are *a*) the chemoselectivity of the C–H activation/annulation at the benzoylated *N*-terminal residue in the presence of other aromatic (Phe, Trp) and functionalized (Lys, Met, Ser) amino acids, *b*) the racemization-free C–H activation/annulation for the efficient synthesis of fluorescent peptides, *c*) the utilization of the peptide backbone as bidentate directing group, *d*) the bioorthogonal ligation to amino acids, other peptides, drugs and natural products in an efficient way, and *e*) the rapid access to dimeric peptide-drug conjugates through twofold C–H activation/annulation.

Results and Discussion

Assessment of the chemoselectivity and substrate scope. As shown in Table 1, our study on peptide C–H activation/annulation was initiated using standard reaction conditions[21,24,53] with dipeptide **1–1**, bearing a D-Ala residue, and the commercially available diphenylacetylene **2–1**. To our delight, **1–1** was fully consumed in just 1 h and the annulation product **3–1** was obtained in 92% yield.[54] A dipeptide bearing an L-Ala residue worked equally well, giving product **3–2** in 95% yield in 1 h. Then symmetrical diaryl- and dialkyl-substituted alkynes were utilized, leading to products (**3–3** to **3–7**) in 52–82% yield. We were pleased to observe that unsymmetrical disubstituted alkynes (**3–8** to **3–10**) and especially dialkyl-substituted alkynes (**3–11**), were well tolerated to yield the desired products (23–86%) with excellent regioselectivity in the annulation process. Dipeptides with various benzamides, such as naphthalene, pyrene, benzofuran, indole and acrylamide reacted smoothly to deliver the desired products (**3–12** to **3–16**) in 81–92%.

To address the influence of the peptide sequence on the reaction outcome, a variety of dipeptides having functionalized amino acids were evaluated. Thus, dipeptides bearing a free C-terminal carboxylic group (Val, **3–18**), a deprotected indole (Trp, **3–20**), a free hydroxyl (Ser, **3–21**), a Boc-protected amine (Lys, **3–24**) and a thioether (Met, **3–22**) afforded the isoquinolone-decorated peptides (**3-17** to **3–24**) in 45–93%. This approach also displayed the capability to efficient synthesis of decorated peptide involving both α- and β-amino acids (**3–25**). These examples proved the

Table 1. Evaluation of the substrate scope and chemoselectivity of the ruthenium-catalyzed C–H activation/annulation of *N*-terminal benzoyl peptides.[a]



[a] **1** (0.3 mmol), **2** (0.36 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (0.015 mmol), NaOAc (0.15 mmol), $Cu(OAc)_2$ (0.6 mmol) and *t*-AmOH (3.0 mL), 120 °C, 1 h.
[b] 2 h.
[c] *t*-AmOH/DMF (1:1).
[d] 12 h.
[e] *t*-AmOH/DMF (3:1). The regioisomeric ratios are shown in parenthesis.

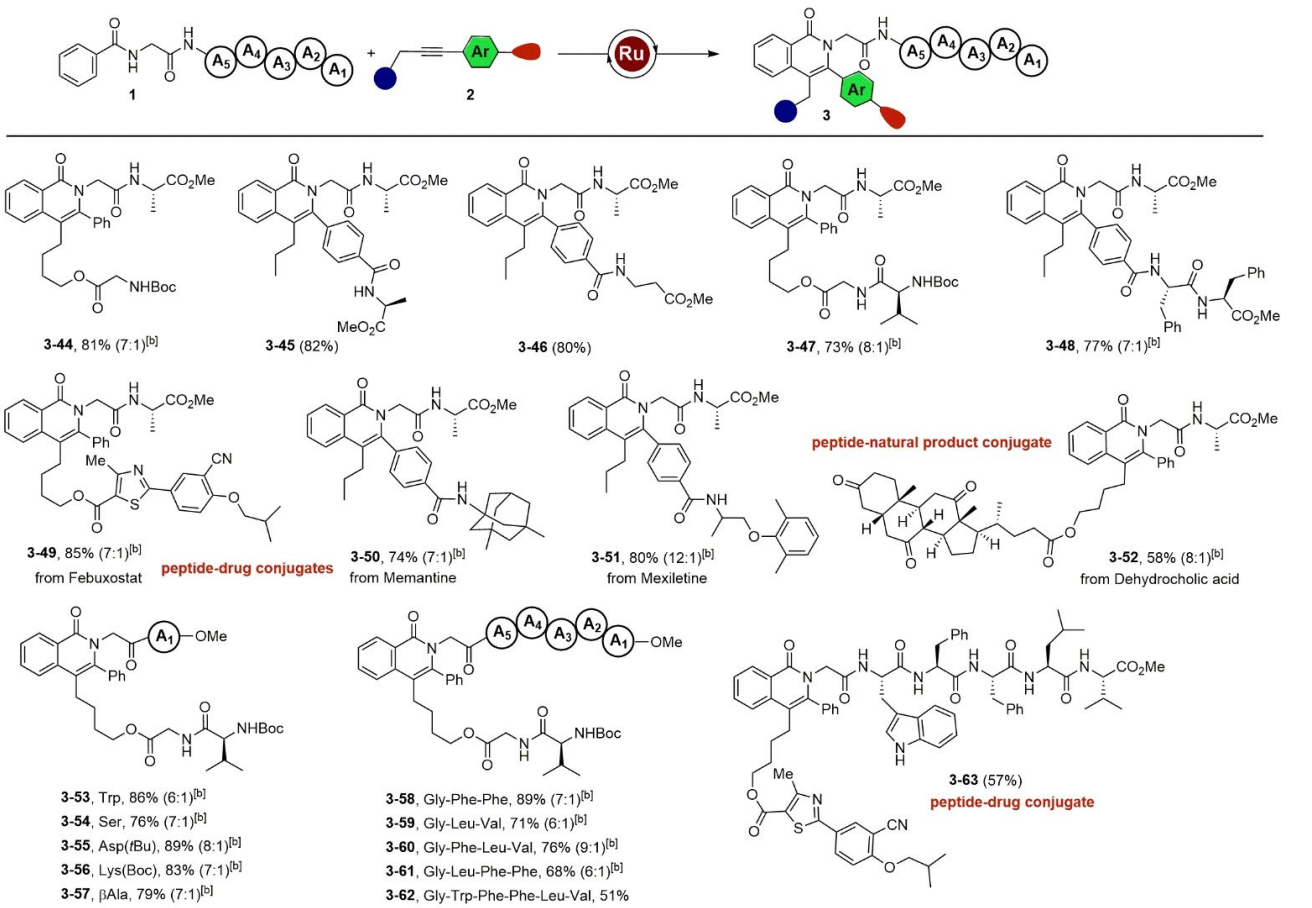
excellent chemoselectivity of this ruthenium-catalyzed C–H activation/annulation strategy and its potential for the derivatization of more complex architectures.

We were also interested in evaluating the efficacy of this process with peptides having an *N*-alkylated amide in the second position. To achieve this, we employed the Ugi four-component reaction to assemble peptides having *N*-alkylated amides[55,56] and these compounds were submitted to the ruthenium(II)-catalyzed reaction to furnish the isoquinolone-peptide hybrids **3–26** to **3–30** in good to excellent yields. The good results obtained in the synthesis of these compounds – especially **3–28** that includes a sterically congested *N*-benzyl α-disubstituted residue – confirm the robustness of this protocol.

In this initial assessment of the annulation reaction, we also carried out the derivatization of dipeptides derived from the commercial drugs probenecid and bexarotene, resulting in the chimeric products **3–33** (76%) and **3–34** (68%). Finally, we derivatized a number of tri-, tetra-, penta- and hexapeptide substrates, which again included Ser (**3–36** and **3–40**), Trp (**3-43**) and Pro (**3–37**) residues, as well as several others having Phe at different positions. In none of the cases did we detect side reactions involving the modification of the peptide side chains, thus proving broad substrate scope and excellent functional-group tolerance regardless the peptide length and sequence. It is particularly noteworthy that the racemization of peptidic backbone did not occur under the standard conditions from NMR spectra.

After proving the success of this C–H activation/annulation strategy in the chemoselective derivatization of varied peptide sequences, we were encouraged to further investigate the bioorthogonal ligation of peptides to α- and β-amino acids, other peptides, drugs and bioactive natural products. As depicted in Table 2, besides the variation of the peptide sequence, two additional diversification sites are available at the isoquinolone ring, thus enabling to use either the substituted phenyl ring or the aliphatic tail for the ligation to the molecule of interest. In this sense, the

Table 2. Peptide ligation to drugs, other peptides and natural products by ruthenium-catalyzed C–H activation/annulation.[a]



[a] **1** (0.3 mmol), **2** (0.36 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (0.015 mmol), NaOAc (0.15 mmol), $Cu(OAc)_2$ (0.6 mmol) and *t*-AmOH (3.0 mL), 120 °C, 1 h.

[b] The regioisomeric ratios are shown in parenthesis.

short dipeptide *N*-benzoyl-Gly-Ala-OMe was subjected to a variety of annulation/ligation procedures using the alkyne functionalized peptides, the drugs febuxostat, memantine, mexiletine and the natural product derivative dehydrocholic acid. To our delight, all these substrates were efficiently ligated to the peptide forming the isoquinolone scaffold and leading to hybrids **3**–**44** to **3**–**52** in good to excellent yields.

Subsequently, the bioorthogonal ligation of diverse oligopeptides to the alkynyl dipeptide Val-Gly-OMe was examined, furnishing the conjugated peptides **3**–**53** to **3**–**62** in excellent yields, with complete chemoselectivity regarding the peptide side chains. The good regioselectivity of the annulation process when using asymmetric alkynes bearing an aliphatic and aromatic substituent validates our hypothesis that the two appendages are equally useful diversification points of the isoquinolone-peptide hybrid. Finally, the drug febuxostat was conjugated to a complex hexapeptide to render the conjugate **3**–**63** in a very good yield.

Due to the formation of the pyridone moiety conjugated to other aromatic rings, we envisioned that this could be a useful method for accessing fluorescent peptide derivatives. Figure 1 illustrates the fluorescence spectra of selective decorated peptides with maximum emission wavelengths ranging from 392 to 479 nm. This proves the capacity of this covalent modification to modulate the electronic properties of decorated peptides at the same time that the medicinally relevant moieties are attached to the peptide backbone.

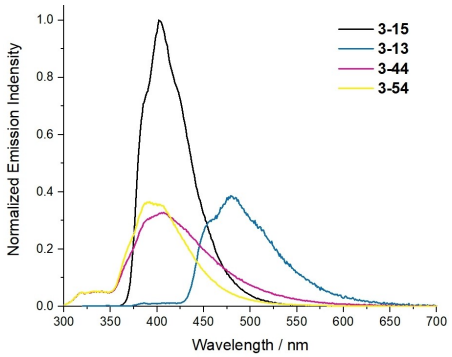
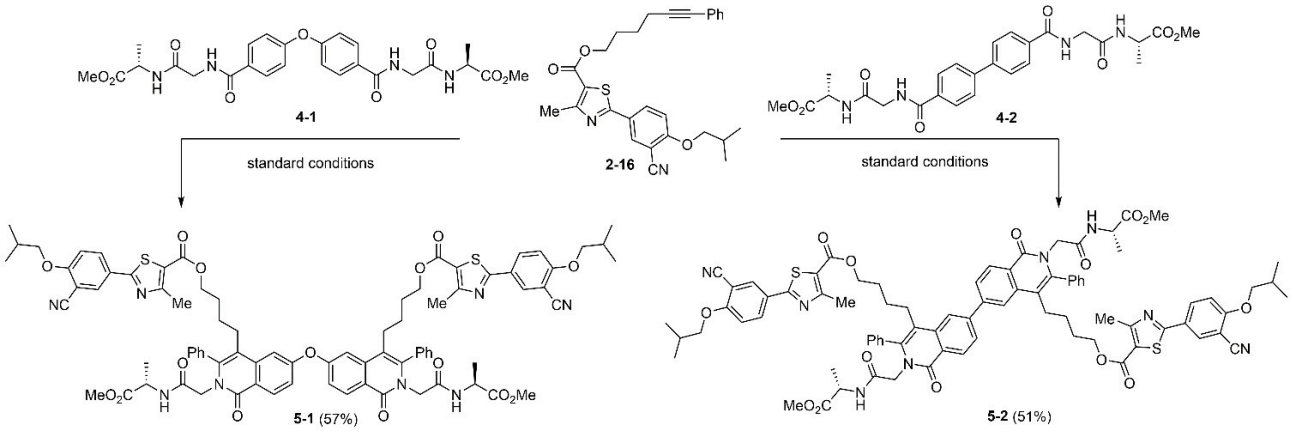


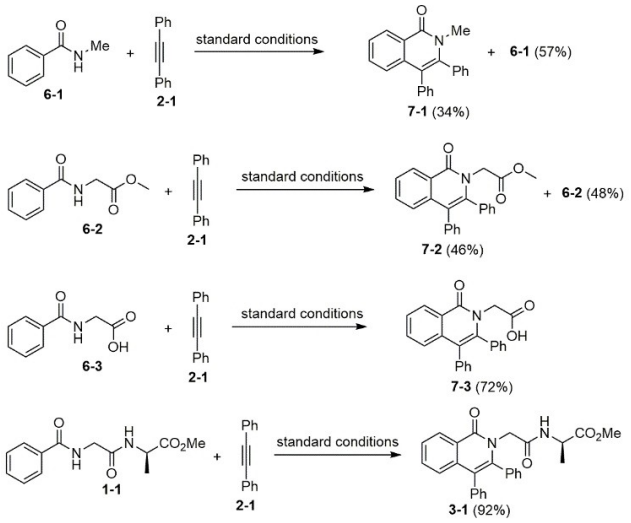
Figure 1. Fluorescent properties of some isoquinolone-peptide hybrids **3**.

Scheme 2 shows a final synthetic approach in which we investigate the possibility to accomplish a double C–H activation/annulation process leading to biaryl and biaryl-ether dimeric peptide conjugates. The syntheses of the chimeric polyheterocyclic-peptide-drug conjugates **5**–**1** and **5**–**2** in good yields confirmed the robustness of this ruthenium(II)-catalyzed procedure to generate molecular complexity in a short sequence. As proven, the rigid bisisoquinolone cores resulting from this dual approach can be used not only for the assembly of multimeric drugs, but also for the multimerization of longer bioactive peptide chains.

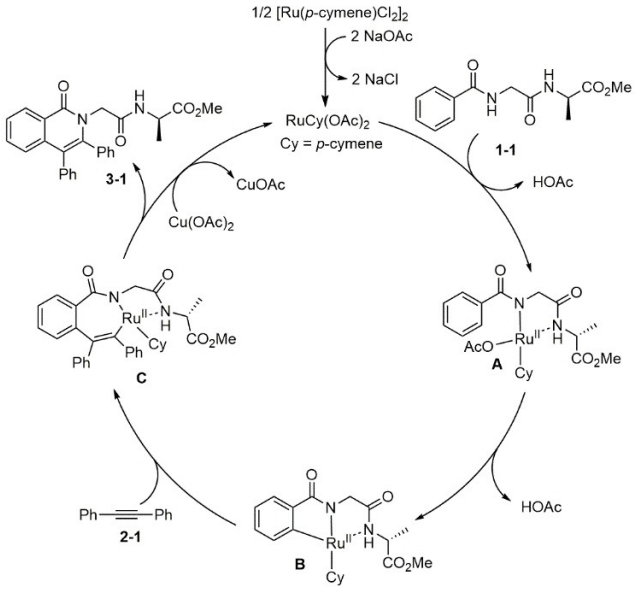
Mechanistic studies. One of the positive aspects that we noted during the C–H activation/annulation process with peptides is that the reaction proceeds in a much shorter time as compared with simpler benzamides not having the peptidic backbone. This implies that the peptide backbone assists the C–H activation/annulation reaction participating as a bidentate ligand, something impossible, for example, in simpler *N*-alkyl benzamides. As a result, we sought to carry out comparative experiments under the standard conditions used in this work (i.e., 5 mol% of $[Ru(p\text{-cymene})Cl_2]_2$, additives, 120 °C, 1 h) to gain more mechanistic insights into the ruthenium-catalyzed C–H activation/annulation reaction. As shown in Scheme 3, *N*-methylbenzamide (**6**–**1**) was initially submitted to the standard conditions with diphenylacetylene **2**–**1**, resulting in the annulation product (**7-1**) and the unreacted substrate in 34% and 57% yield respectively. In parallel, methyl benzoylglycinate (**6**–**2**) furnished the



Scheme 2. Synthesis of multimeric peptide-drug conjugates by double ruthenium-catalyzed C–H activation/annulation.



Scheme 3. Control experiments using standard conditions (5 mol% $[Ru(p\text{-cymene})Cl_2]_2$, additives, 120 °C, 1 h).



Scheme 4. Proposed mechanism based on experimental evidence.

annulated product **7–2** in 46% yield under the same standard conditions, with a 48% yield recovery of the unreacted substrate. On the other hand, a significant improvement was observed in the reaction of benzoylglycine (**6–3**), which led to the corresponding product **7–3** in almost full conversion and 72% yield. Nonetheless, the efficiency of this transformation for the dipeptidic **1–1** is superior to all previous examples, showing full conversion into product **3–1** just after 1 h, with an isolated yield of 92%.

These results confirm that the peptide backbone serves as a bidentate directing group promoting the ruthenium-catalyzed C–H activation/annulation[57] even to a greater extent than a terminal carboxylate. Based on these results and previous reports, we proposed a plausible mechanism for this transformation (Scheme 4). Initially, the ruthenium(II) catalyst coordinates to the NH-deprotonated **1–1**, resulting in a bidentate coordinated intermediate **A**. Subsequently, **A** undergoes C(sp^2)-H bond cleavage to deliver the intermediate **B**. Alkyne insertion into intermediate **B** generates intermediate **C**, which then undergoes reductive elimination to render the product **3–1**. The resulting ruthenium(0) is next reoxidized by $Cu(OAc)_2$ to regenerate the ruthenium(II) species that enters into the next catalytic cycle.

Conclusion

We have developed a versatile and efficient procedure for the chemoselective and racemization-free diversification of the peptide backbone of amino acids such as Ser, Met, Phe, and Trp. This bioorthogonal derivatization strategy relies on a ruthenium(II)-catalyzed C–H activation/annulation reaction between *N*-benzoyl peptides and functionalized alkynes, affording *N*-terminal isoquinolone-decorated peptides with good to excellent regioselectivity in a rapid and step-economical manner. Through the chelating assistance of amide bonds of the peptide backbone – i.e., bidentate directing group – very complex annulation products are obtained in high yield, including peptide conjugates to drugs, bioactive natural products and other peptide fragments. Some decorated peptides are analyzed for their fluorescent properties, showing that this type of backbone heteroannulation might be useful for labeling/tracking strategies in peptide chemistry. Finally, this straightforward C–H activation/annulation, implemented in a twofold manner, allows for the rapid access to dimeric peptide-drug conjugates, a strategy that shows promise for the multimerization of peptide therapeutics. Overall, we have demonstrated that this robust and versatile C–H activation/annulation method can be implemented for the derivatization of complex peptides and their bioorthogonal ligation to drugs or other biomolecules.

Experimental Section

In a seal capped flask equipped with a stirring bar, the peptide (0.3 mmol), alkyne (0.36 mmol), $Cu(OAc)_2$ (0.6 mmol), NaOAc (0.15 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (0.015 mmol) and 3 mL of *t*-AmOH were added. The reaction mixture was put in an oil bath and heated at 120 °C for 1 h. After the reaction completion (TLC checked), the mixture was diluted with 25 mL of DCM and filtered over a pad of Celite. The remaining organics were dried over anhydrous Na_2SO_4. Then, the organic phase was concentrated in vacuum and the crude was purified by a silica

gel column chromatography (*n*-heptane/ethyl acetate or DCM/MeOH) to afford the product.

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FULL PAPER

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