Direct synthesis of peptidomimetics containing non-coded amino acids via Photocatalytic carbamoylation reaction

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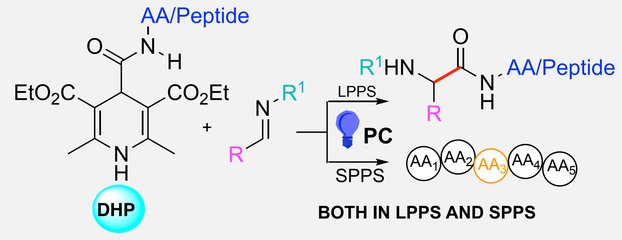
INTRODUCTION AND AIM OF THE WORK

Nowadays, peptidomimetics are widely studied, being useful tools in drug discovery and medicinal chemistry. They are indeed able to mimic the conformation of natural peptides and, thanks to small structural modifications, as the insertion of non-natural amino acids, could present improvements respect to natural peptides, such as higher affinity and selectivity toward a target receptor and an enhanced conformational and metabolic stability.
Here, we present an **innovative photocatalytic approach** for the synthesis of peptidomimetics by using dihydropyridines (DHPs)[1], functionalized with natural amino acids (AAs) or peptides, and imines.[2]

Formation of non-conventional peptidomimetics:

- R^1 could be of biological interest (i.e. sulfonyl group) or a protecting group;
- R (aromatic heterocycle/aryl) is the side chain of the *in situ* generated non-coded amino acid
- the DHP is functionalized with amino acids or peptides

Peptidomimetics Synthesis this work

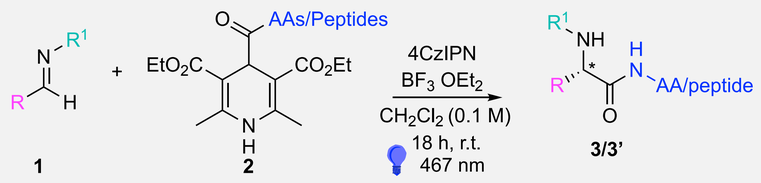


AA_3 = Non-coded amino acid
R = aryl groups
R^1 = sulfonamides or cleavable protecting group

- Green reaction conditions (metal-free approach);
- **Protocol validated also in SPPS**

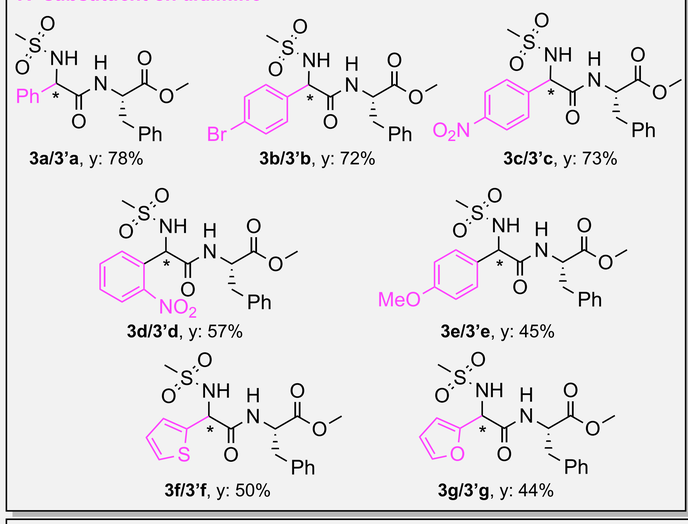
SCOPE OF THE REACTION -LPPS-

N-benzylidenemethanesulfonimide (1) and DHP-Phe (2) were used to optimize the reaction, testing: **PCs (photocatalyst)**, **additives**, **solvents**, **concentrations**, **PC loading** and **LED lamps**.

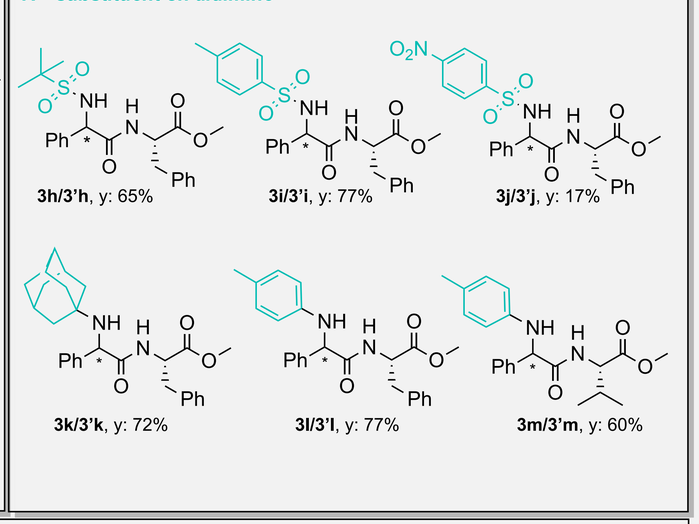


Imine scope

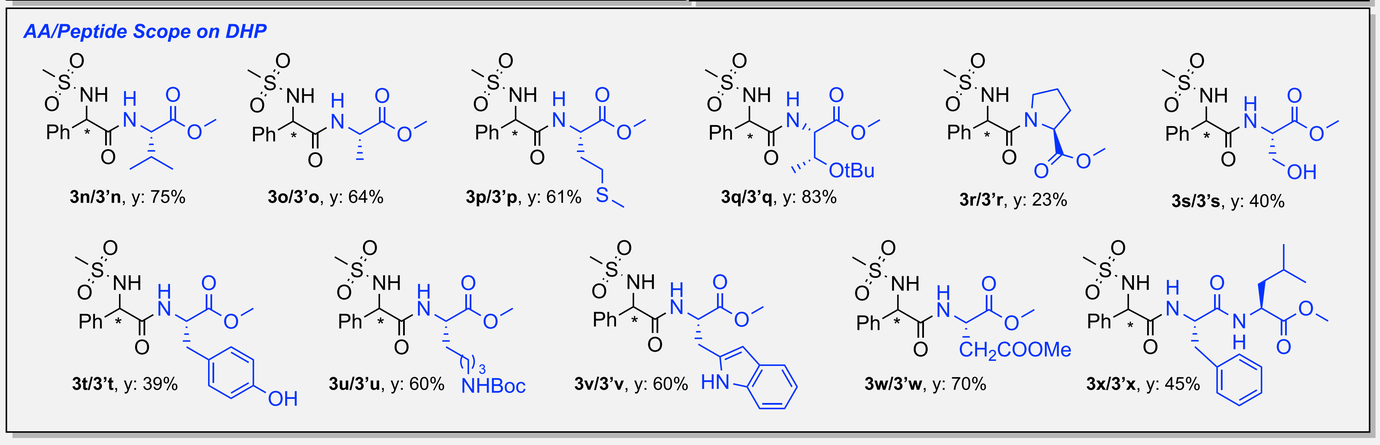
R- substituent on aldimine



R^1- substituent on aldimine



AA/Peptide Scope on DHP

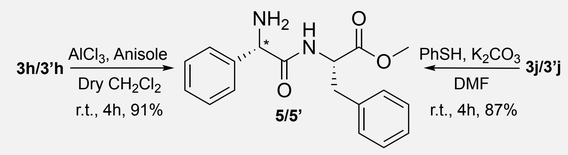


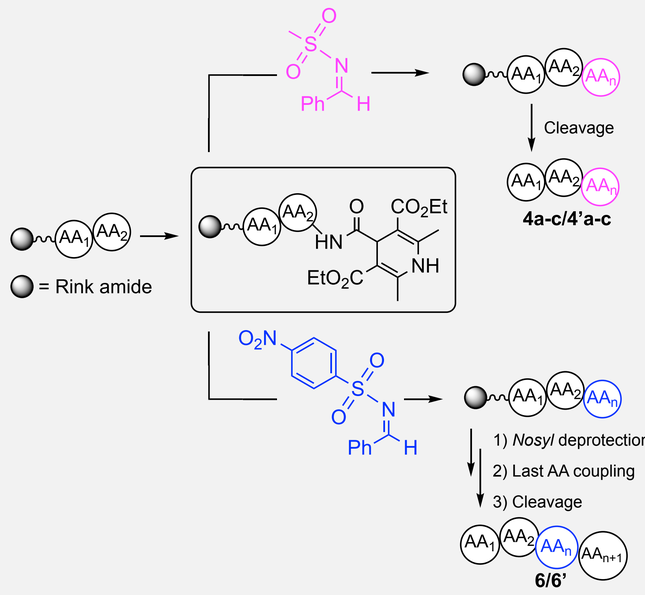
Scope of our carbamoylation reaction. y = yield. Reaction conditions: Imine **1** (1.0 equiv.), DHP-AA/Peptide **2** (1.3 equiv.), 4CzIPN (0.025 equiv.), BF_3OEt_2 (1.0 equiv.) in dry CH_2Cl_2 (3.0 mL, 0.1 M)

SYNTHESIS OF 4a-c/4'a-c and 6/6' -SPPS-

To further demonstrate the versatility of our method, we explored the deprotection of the sulfonamide moieties. Envisaging the possibility of using our protocol for longer peptide sequences with orthogonal protecting groups on AA side chains, we investigated on both acid and basic condition for the *N*-terminus sulfonamide deprotection.

Thus, starting from **3h/3'h** using acid conditions and from **3j/3'j** with basic ones, we succeeded in obtaining compound **5/5'** with high yield.

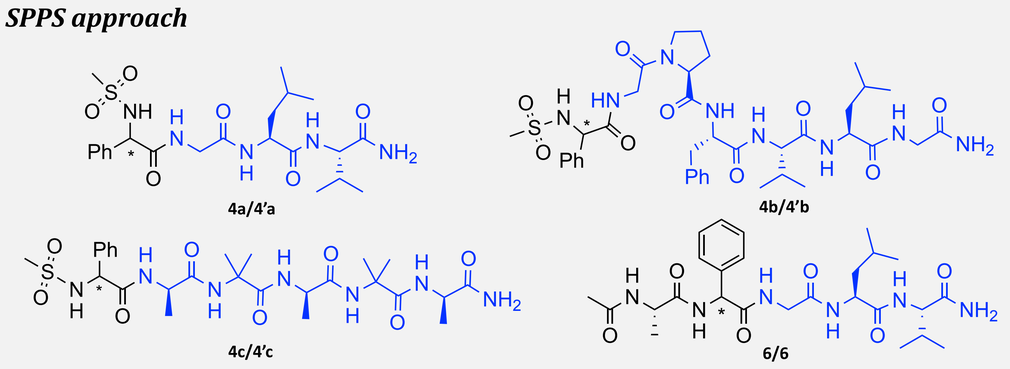




Experimental setup in solid phase.

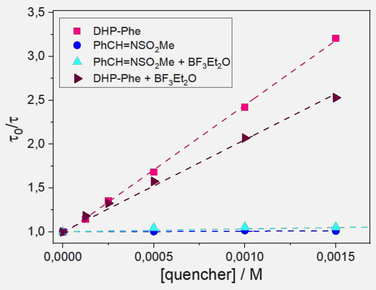
The reaction on peptides with different lenght and conformations was studied to demonstrate its feasibility regardless from the **steric hindrance** and **peptide secondary structure**

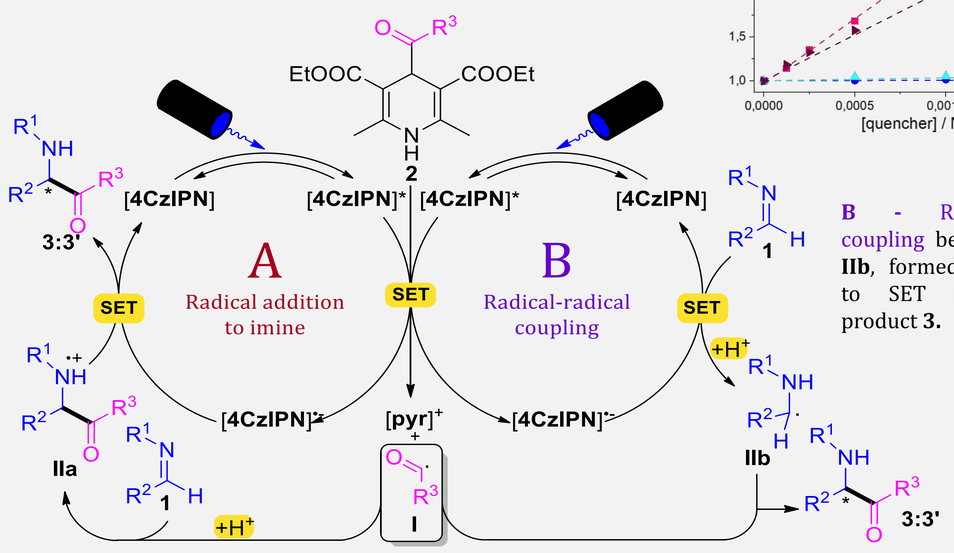
SPPS approach



PROPOSED MECHANISM

Stern-Volmer analyses suggest two reductive quenching mechanisms both starting with the formation of radical intermediate **I**, formed thanks to the reduction of the photocatalyst from its excited state to its radical-anion form ($4CzIPN^{\bullet-}$)[3,4].





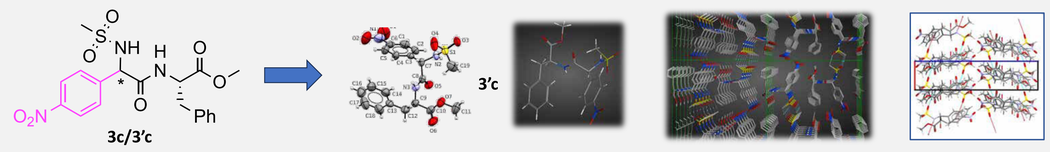
A - Radical addition of **I** to imine **1** facilitated by the presence of a Lewis acid additive to form **IIa**, leads to the product **3** upon SET event with **$4CzIPN^{\bullet-}$**.

B - Radical-radical coupling between **I** and **IIb**, formed subsequent to SET event gives product **3.**

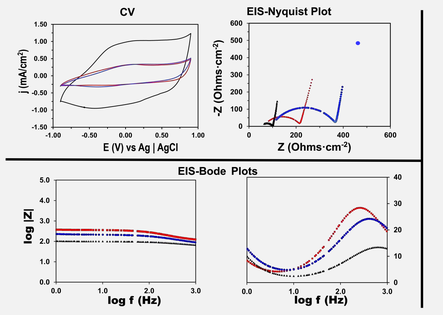
ELECTROCHEMICAL CHARACTERIZATION

When separated, the diastereomers were fully characterized by NMR and similar behaviour in terms of chemical shift and protons patterns were observed for **3** and **3'** series.

X-Ray analysis



Electrochemical Characterization



- **3'c**, with a more favourable spatial disposition, **exhibits better electron transfer efficiency, resulting in lower charge transfer resistance** and a more stable phase angle
- **3c** shows **higher resistance and more capacitive behavior**.

For more information go to *Dulce Quintana Romero*'s poster

FUTURE PERSPECTIVES

- To improve the atom economy of the reaction;
- To develop a methodology for peptidomimetics diastereoselective synthesis.
- To investigate the electrochemical behaviour of **3/3'** compounds

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[4] H.-H Zhang, S. Yu, *J. Org. Chem*. **2017**, *82*, 9995-10006.