

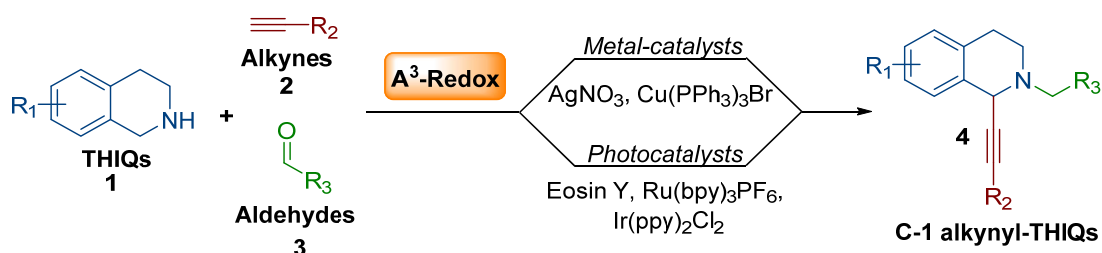
# SYNTHESIS OF C-1 ALKYNYL TETRAHYDROISOQUINOLINE DERIVATIVES THROUGH THE A<sup>3</sup> REDOX-NEUTRAL COUPLING USING COPPER-CATALYSIS AND PHOTOCATALYSIS

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**Introduction.** The biological and pharmacological activities attributed to tetrahydroisoquinolines (THIQs) and their derivatives have boosted the development of new synthetic routes such as the A<sup>3</sup>-coupling.<sup>1</sup> This methodology is very attractive because it allows to do a coupling of three substrates by one-pot synthesis and under the concept of atom economy.<sup>2</sup> In this contribution, we report the syntheses of C-1 alkynyl-THIQs through the A<sup>3</sup>-coupling, testing different reaction conditions under metal-catalysis and photocatalysis. For the first time, we evaluated the effectiveness of catalytic Cu(PPh<sub>3</sub>)<sub>3</sub>Br/PhCOOH system and photocatalysts comparing with that of AgNO<sub>3</sub> catalyst to obtain new C-1 alkynyl-THIQs.

**Results and discussion.** The multicomponent coupling between tetrahydroisoquinolines 1, terminal alkynes 2 and aromatic aldehydes 3 was carried out towards single regioselective THIQ products 4. This was achieved employing AgNO<sub>3</sub>, Cu(PPh<sub>3</sub>)<sub>3</sub>Br and Cu(PPh<sub>3</sub>)<sub>3</sub>Br/PhCOOH with high catalytic potential. The Cu(PPh<sub>3</sub>)<sub>3</sub>Br/PhCOOH-catalyzed A<sup>3</sup> reaction was assisted by microwave for 15 minutes, obtaining THIQs 4 in yields greater than 70 % (Scheme 1). On the other hand, when the same reaction was performed through a photocatalytic approach employing eosin Y, Ru(bpy)<sub>3</sub>PF<sub>6</sub> and Ir(ppy)<sub>2</sub>Cl<sub>2</sub> as photocatalysts, desired products 4 were obtained with yields lower than 50 %. Nevertheless, when combining catalytic Cu(PPh<sub>3</sub>)<sub>3</sub>Br/PhCOOH system with Ir(ppy)<sub>2</sub>Cl<sub>2</sub> or eosin Y photocatalysts, preparation of the THIQ products 4 were easily achieved in good yields (50-70 %) showing an important cooperation of synergistic photocatalytic and copper-catalyzed cycles.



**Scheme 1.** Synthesis of C-1 alkynyl-THIQs through the A<sup>3</sup> redox-neutral coupling reaction using metal-catalysts and photocatalysts

**Conclusion.** Diverse THIQ products 4 were obtained *via* the A<sup>3</sup> redox-neutral coupling reaction by using the new Cu(PPh<sub>3</sub>)<sub>3</sub>Br/PhCOOH catalytic system. In addition, it was demonstrated an efficient synergy between copper-catalysis and photocatalysis.

**Acknowledgments:** This work was financially supported by COLCIENCIAS through the National Program 617 and 727 for CPEG and MCOV. MCOV acknowledges to VIE-UIS for its financial support.

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