Cu(I)-BOX Catalyzed Asymmetric 3-Component Reaction for the Synthesis of Trifluoromethylated Propargylic Ethers and Anilines

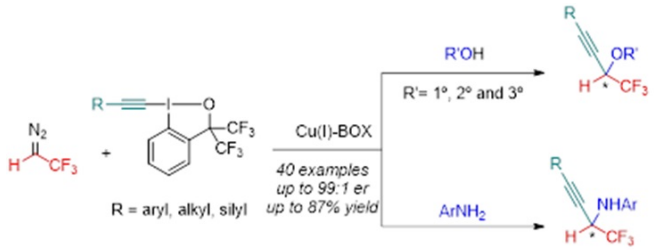
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Chiral trifluoromethylated (CF_3) scaffolds are very important in organic and medicinal chemistry due to their excellent physical and pharmacological properties. Nevertheless, traditional methods often rely on the use of strongly basic reaction conditions, presenting a narrow scope. For this reason, it is important to find alternatives that allow the preparation of enantioenriched CF_3-compounds in a more efficient manner.[1] Propargylic ethers and anilines represent a versatile class of organic compounds in synthetically and medicinal chemistry due to the rigidity, electronic properties and easy post-functionalization of the alkyne group.

Multi-Component Reactions (MCRs) are often employed in medicinal chemistry because they facilitate the synthesis of libraries of compounds starting from easily accessible starting materials. Diazo compounds represent an important example of precursors in MCRs since they can react with both nucleophiles and electrophiles on the same reactive center, allowing the formation of multiple bonds in a single step.

In this context, Hypervalent Iodine Reagents (HIR) have been widely used in organic chemistry for the Umpolung of the reactivity of nucleophiles [2], but barely in MCRs with diazo compounds. In the last years, our group has reported different multi-component reactions with HIR and diazo compounds as starting materials. [3,4] Here, we report the first enantioselective 3-CR reaction between diazo compounds, nucleophiles and HIRs allowing the asymmetric synthesis of trifluoromethylated propargylic ethers or anilines catalyzed by a simple Cu(I)-BOX catalytic system. The reaction proceeds with a broad functional group tolerance, since primary, secondary and tertiary alcohols as well as both electron-rich and electron-poor anilines can be used as nucleophiles. Regarding the electrophilic partner, aryl-, alkyl- and silyl-substituted alkynes can be successfully introduced. In the case of chiral natural alcohols, the reaction proceeds with high catalyst control, achieving the synthesis of the trifluoromethylated propargylic ethers with very high diastereoselectivity [5]



[1] Pavel. K. Mykhailiuk, *Chem. Rev.*, **2020**, 120, 12718-12755.
[2] Jonathan P. Brand, Jerome Waser, *Chem. Soc. Rev.*, **2012**, 41, 4165-4179.
[3] Durga Prasad Hari, Jerome Waser, *J. Am. Chem. Soc.,* **2017**, 139, 8420–8423.
[4] For alcohols see: Guillaume Pisella, Alec Gagnebin, Jerome Waser, *Chem. Eur. J.*, **2020**, 26, 10199-10204. For anilines see: Nieves P. Ramirez, Guillaume Pisella, Jerome Waser, *J. Org. Chem.* **2021**, 86, 10928–10938.
[5] Nieves P. Ramirez, Jerome Waser, https://doi.org/10.26434/chemrxiv-2023-78fk0