Asymmetric Synthesis of Trifluoromethylated Propargylic Amines and Ethers through Multi-Component Reactions

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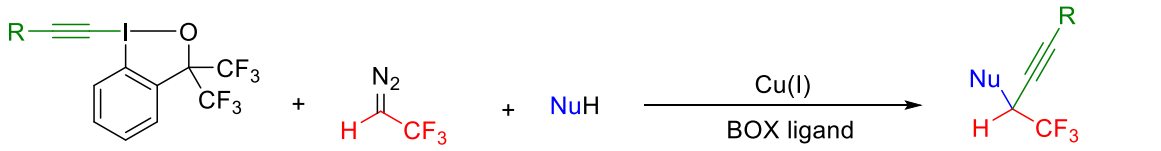
The synthesis of chiral trifluoromethylated compounds is very important in medicinal chemistry due to their excellent pharmacological properties. However, most of the traditional methods to synthesize them require the use of strongly basic conditions and present a narrow scope. For this reason, it is important to find alternatives that allow the preparation of enantioenriched CF_3-compounds in a more efficient manner.[1]

Multi-Component Reactions (MCRs) have emerged as a very convenient approach in medicinal chemistry because they facilitate the synthesis of libraries of compounds starting from easily accessible starting materials. Diazo compounds can react with nucleophiles and electrophiles on the same reactive center allowing the formation of multiple bonds in a single step and are therefore ideally suited for MCRs.

In this context, Hypervalent Iodine Reagents (HIR) have been widely used in organic chemistry for the Umpolung of the reactivity of nucleophiles.[2] However, they have been barely employed 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 reported the first enantioselective 3-CR reaction between diazo compounds, nucleophiles and HIR allowing the synthesis of trifluoromethylated propargylic ethers or anilines (Scheme I).[5]



R = aliphatic, aryl, heteroaromatic, silyl

Nu = alcohols (1º, 2º and 3º) and anilines

40 examples
up to 99:1 er
up to 87% yield

Scheme I.

[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, *Manuscript under preparation.*