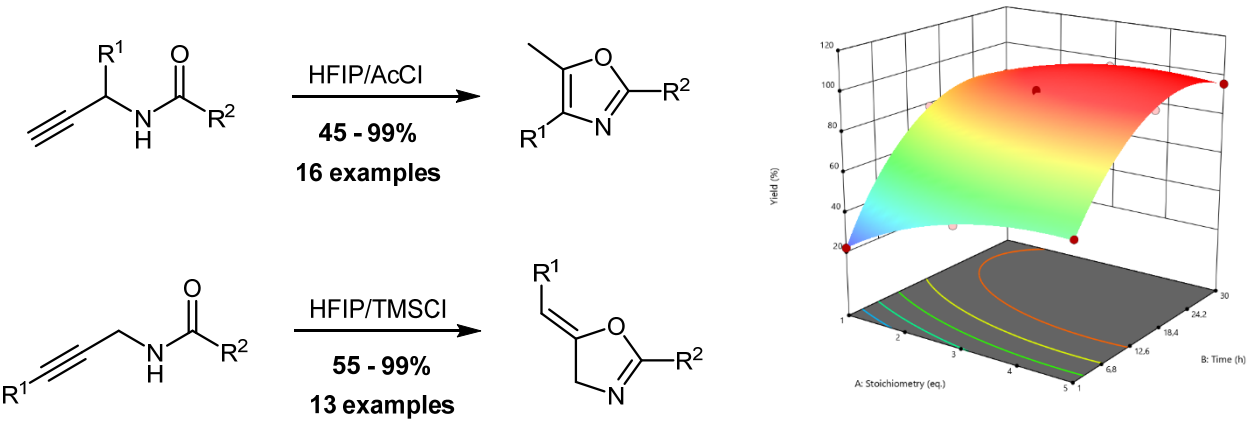
# Transition metal-free synthesis of oxazoles and oxazolines in hexafluoroisopropanol (HFIP)

Norbert Krause,[a] Nicholas Jankowski[a]
TU Dortmund University, Organic Chemistry, D-44227 Dortmund, Germany
norbert.krause@tu-dortmund.de

Oxazoles and oxazolines are five-membered heterocycles which are found in numerous natural products, drug candidates, and even approved drugs. Among different synthetic approaches, the transition metal-catalyzed cycloisomerization of propargylic amides is versatile but suffers from the limited availability and high price of transition metal catalysts, as well as, the contamination of the heterocyclic products. Taking into account that a proton is isolobal to cationic gold(I), we have used HCl generated *in situ* from 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) and acetyl chloride[1] for the cycloisomerization of propargylic amides to oxazoles and oxazolines. Statistical optimization of the reaction conditions using Design of Experiments (DoE)[2] enabled the efficient synthesis of a variety of oxazolium hydrochlorides and oxazoles from propargylic amides with a terminal triple bond.[3] The HFIP/AcCl medium is removed by simple distillation and can be reused several times. By contrast, propargylic amides with an internal triple bond gave unsatisfactory results under these conditions. Fortunately, replacing AcCl by TMSCl allowed an efficient synthesis of numerous oxazolines which were obtained stereoselectively as (Z)-isomers.[4]




1 H. F Motiwala, C.Fehl, S. W. Li; E.Hirt, P.Porubsky, J. Aubé, *J. Am. Chem. Soc.* **2013**, *135*, 9000.
2 Software: *Design-Expert 12* by *Statcon*.
3 N. Jankowski, N. Krause, *Adv. Synth. Catal.* **2022**, *364*, 3404.
4 N. Jankowski, N. Krause, submitted.