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CALCIUM-CATALYZED CHEMOSELECTIVE AND REGIOSELECTIVE EPOXIDE RING-OPENING WITH NH SULFOXIMINES¹

Nicolas George,* Marharyta Kosiuha, Alexandre Moquette, Christophe Parsy

Oncodesign SA. Business Unit Service, 25-27 avenue du Québec, 91140 Villebon-sur-Yvette, France.
ngeorge@oncodesign.com

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OBJECTIVES & OPTIMIZATION

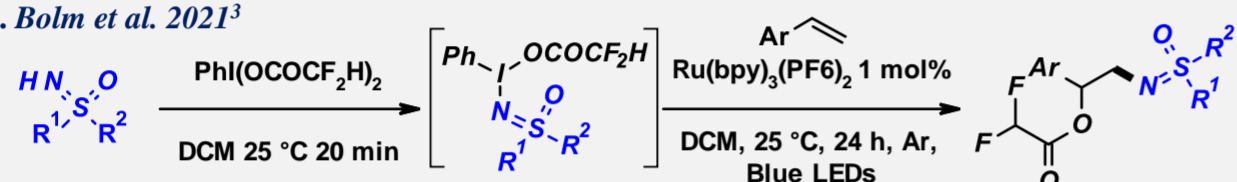
Sulfoximines have received increasing attention in medicinal chemistry through the last decade. With the help of entries into clinical trials of several drug candidates disclosing this moiety, their utility as sulfones aza-analogues is now established. One of the great advantages of NH sulfoximines compared to sulfones is the additional substitution point brought by the nitrogen atom allowing for instance *N*-functionalizations.²



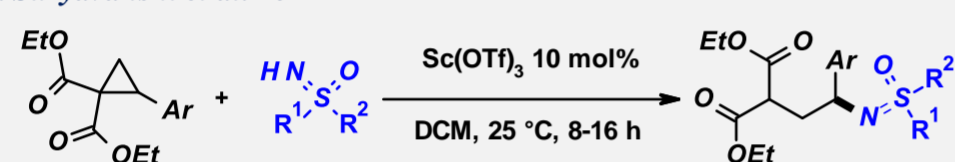
Our aim was to study the ability of NH sulfoximines to perform epoxide ring-opening producing 1,2-sulfoximidoyl ethanol synthons in eco-friendly conditions with low risks in the lab.

Recent examples of *N*-functionalization of NH sulfoximines.

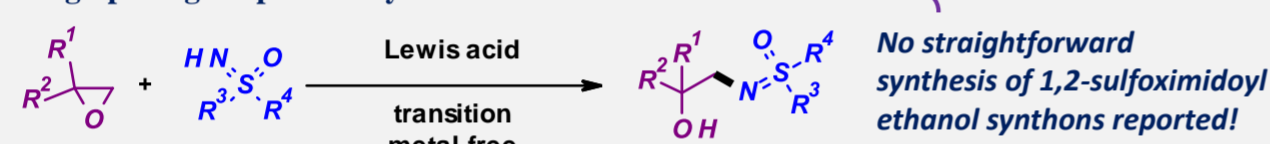
A. Bolm et al. 2021³



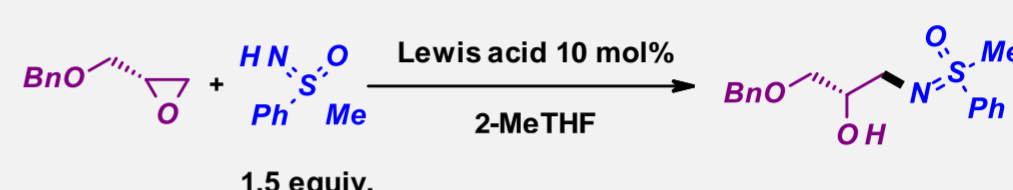
B. Suryavanshi et al. 2022⁴



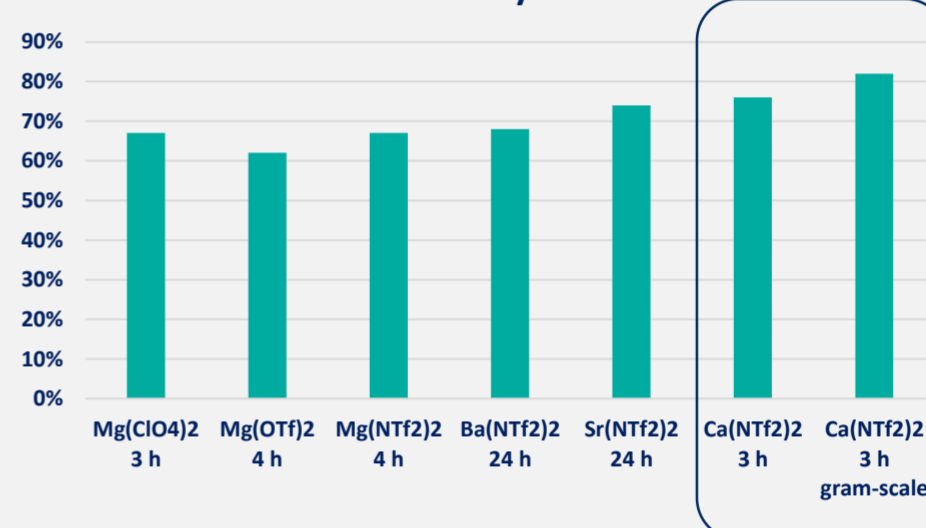
C. Ring-opening of epoxides by NH sulfoximines: *this work*



Optimization of the reaction conditions.



Isolated yield

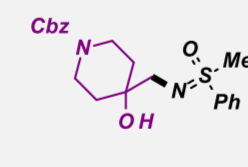
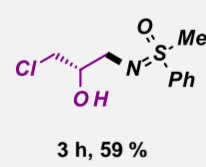
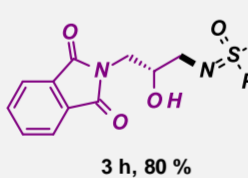
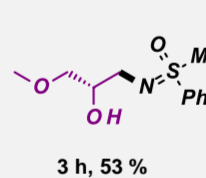
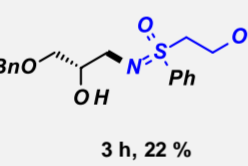
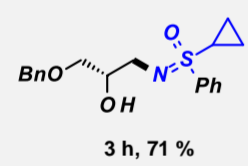
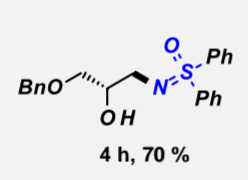
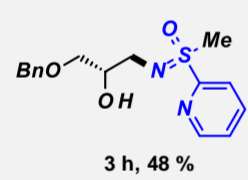
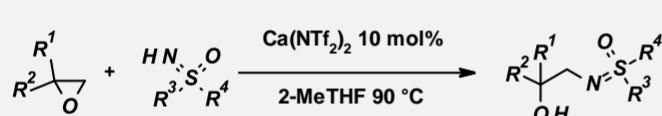


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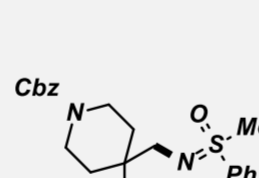
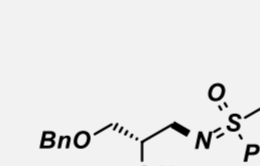
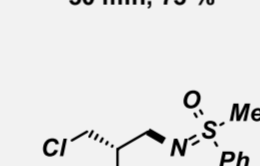
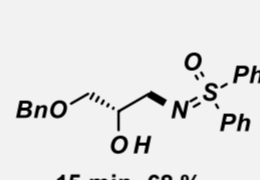
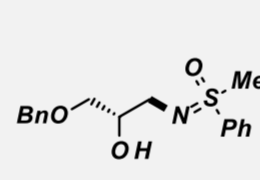
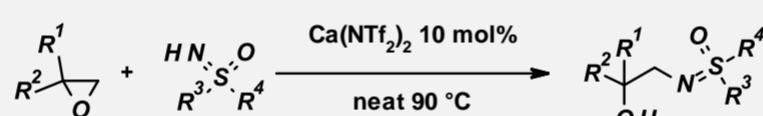


SCOPE & APPLICATIONS

Scope of the reaction:^a selected examples

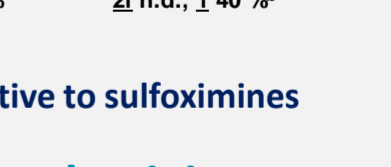
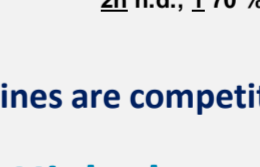
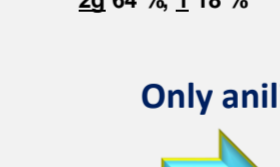
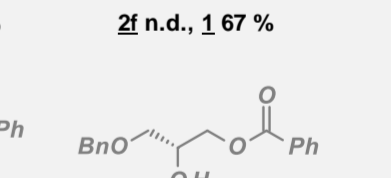
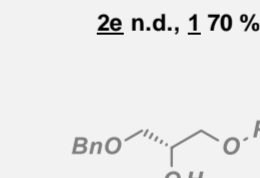
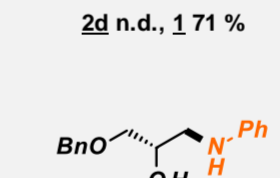
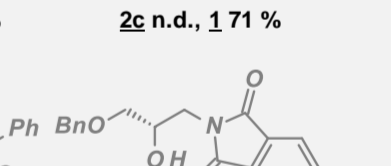
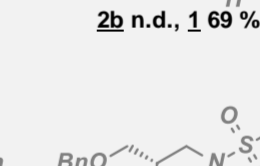
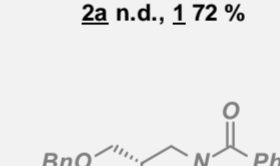
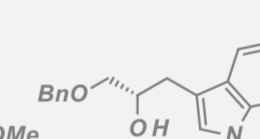
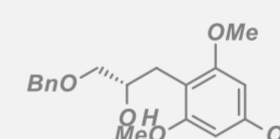
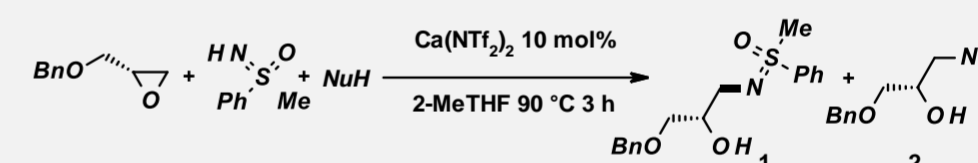


Solvent-free reaction^a



Solvent-free conditions reduced the reaction time

Chemoselectivity assessment by competitive reactions with other nucleophiles^a



Only anilines are competitive to sulfoximines

High chemoselectivity

^a Standard conditions: 0.609 mmol of epoxide, 0.914 mmol of sulfoximine, 10 mol% of Ca(NTf₂)₂ in 2-MeTHF (3 mL) at 90 °C. Yields refer to isolated yields after flash column chromatography.

^a Standard conditions: 0.609 mmol of epoxide, 0.914 mmol of sulfoximine, 10 mol% of Ca(NTf₂)₂ in 3 mL of 2-MeTHF at 90 °C. Yields refer to isolated yields after flash column chromatography.

^a Standard conditions: 100 mg (0.609 mmol) of benzyl (S)-glycidyl ether, 142 mg (0.914 mmol) of methyl phenyl sulfoximine, 0.914 mmol of competitor nucleophile, 10 mol% of Ca(NTf₂)₂ in 2-MeTHF (3 mL) at 90 °C, 3 h of reaction time. Yields refer to isolated yields after flash column chromatography. n.d. = not detected. ^b reaction not completed after 3 h.

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CONCLUSION

- Efficient chemoselective and regioselective methodology of epoxide ring-opening by NH sulfoximines.
- Mild and eco-friendly catalytic conditions: no transition metals, strong Brønsted/Lewis acids or strong bases needed. 2-MeTHF in 3-13 h and solvent-free conditions in 15-30 min produced the same results.
- Very good chemoselectivity. Could be used as late-stage functionalization.
- First straightforward synthesis of 1,2-sulfoximidoyl ethanol synthons to be used as original synthons, further transformed or used as metal ligand in asymmetric catalysis.
- Ca(NTf₂)₂ is known to activate alcohols, alkenes, ketones, ester, cyclopropanes and sulfonyl fluorides.⁵ To our knowledge, this is the first example of epoxides activation with Ca(NTf₂)₂.

4



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