

CONSTRUCTION OF FUNCTIONALIZED PYRROLO[3,4-B]INDOLE SCAFFOLDS VIA A SEQUENTIAL INTERRUPTED BARTON–ZARD AND FRIEDEL–CRAFTS ALKYLATION REACTION

Josip Rešetar, Karla Remar, Ana Mikleušević, Josipa Suć Sajko, Ines Bašić, Matija Gredičak

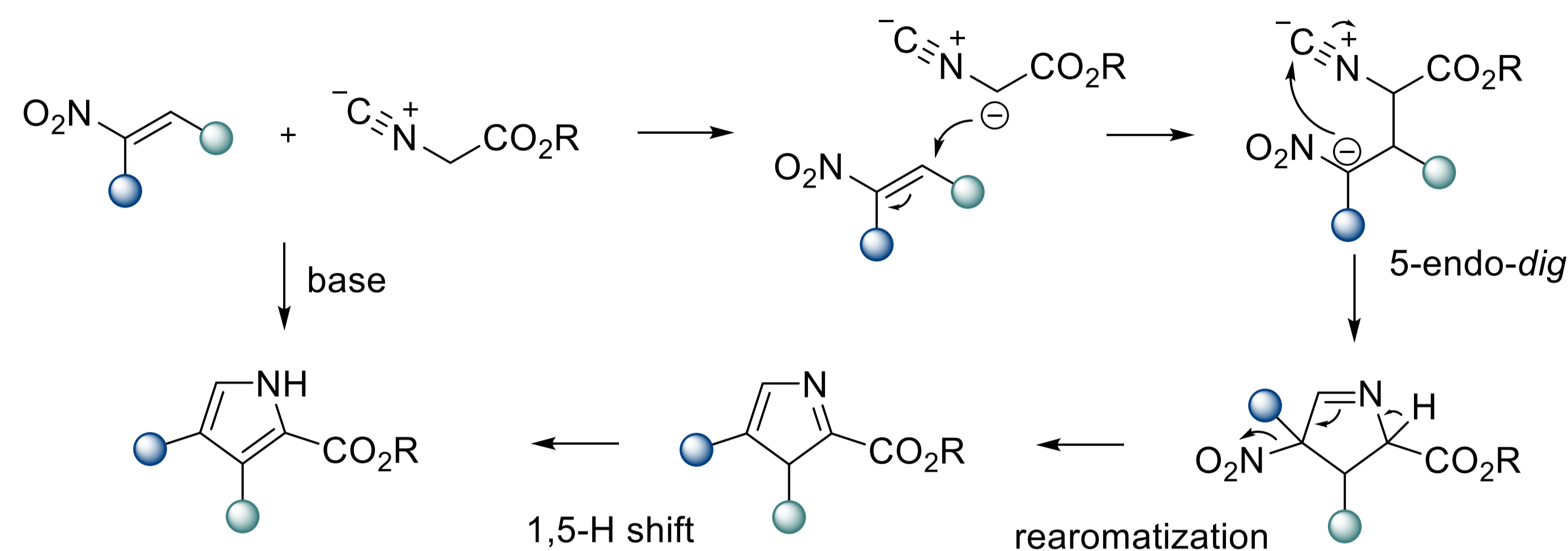
INTRODUCTION

The Barton–Zard reaction offers a direct method for synthesizing aromatic 2-carboxyl-3,4-disubstituted pyrroles from electron-deficient alkenes, nitroarenes, or nitroindoles using α -isocyanoacetates under basic conditions.¹ When α -substituted isocyanoacetates are used, the reaction pathway is altered, preventing rearomatization and resulting in non-aromatic polycyclic products—this is referred to as the interrupted Barton-Zard reaction.²

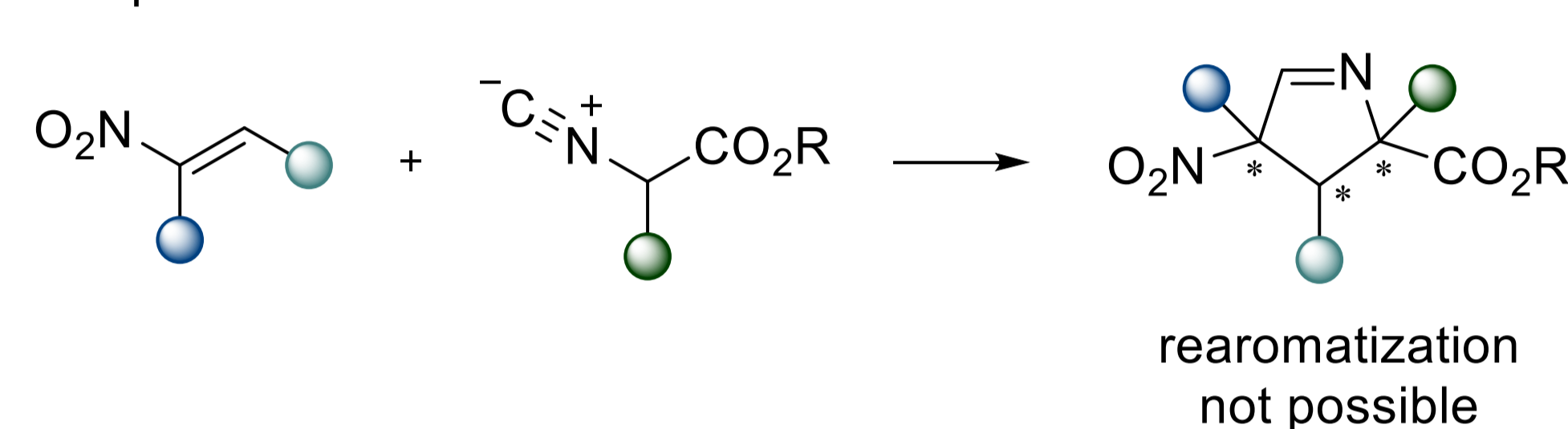
RESULTS AND DISCUSSION

Notably, only one example of such 3,3-diaryl-substituted polycyclic systems has been previously reported, and only as a postmodification.³ In this work, we present a telescoped interrupted Barton-Zard/Friedel-Crafts alkylation sequence for synthesizing hexahydropyrrolo[3,4-*b*]indole cores with multiple aryl substituents. Using Brønsted base-mediated phase-transfer conditions, 3-nitroindoles (**1a–p**) react with benzophenone-derived isocyanides (**2a–c**) to form pyrrolo[3,4-*b*]indole intermediates, which undergo *in situ* alkylation with aromatic and heteroaromatic nucleophiles under acidic conditions.

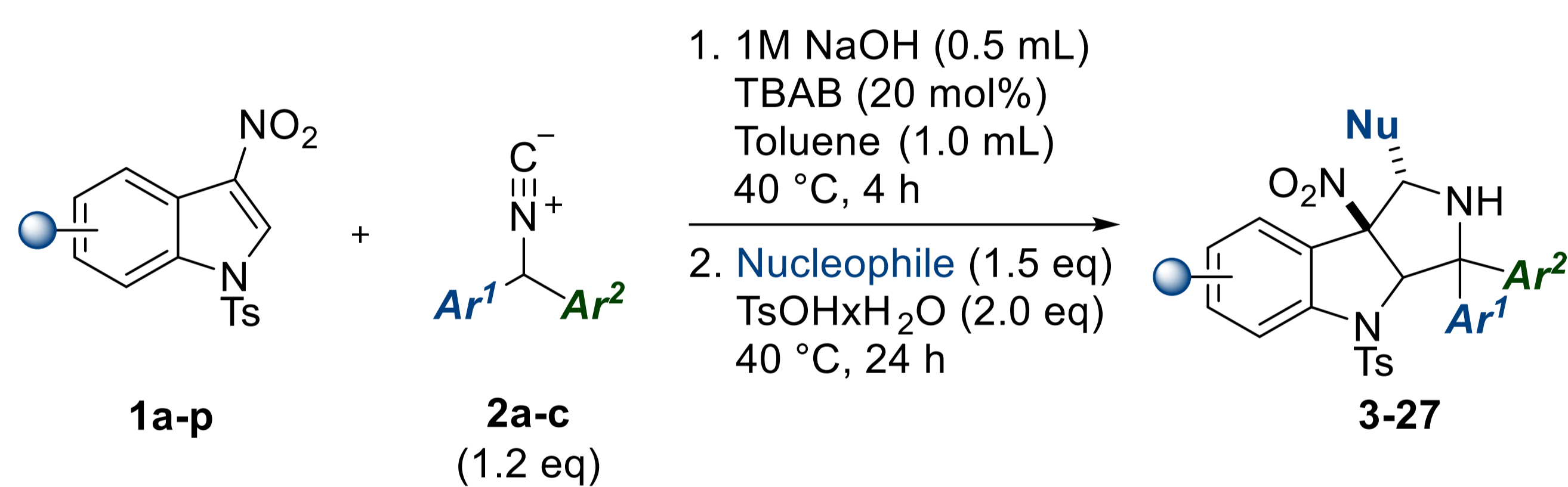
A) Classical Barton-Zard reaction^[1]



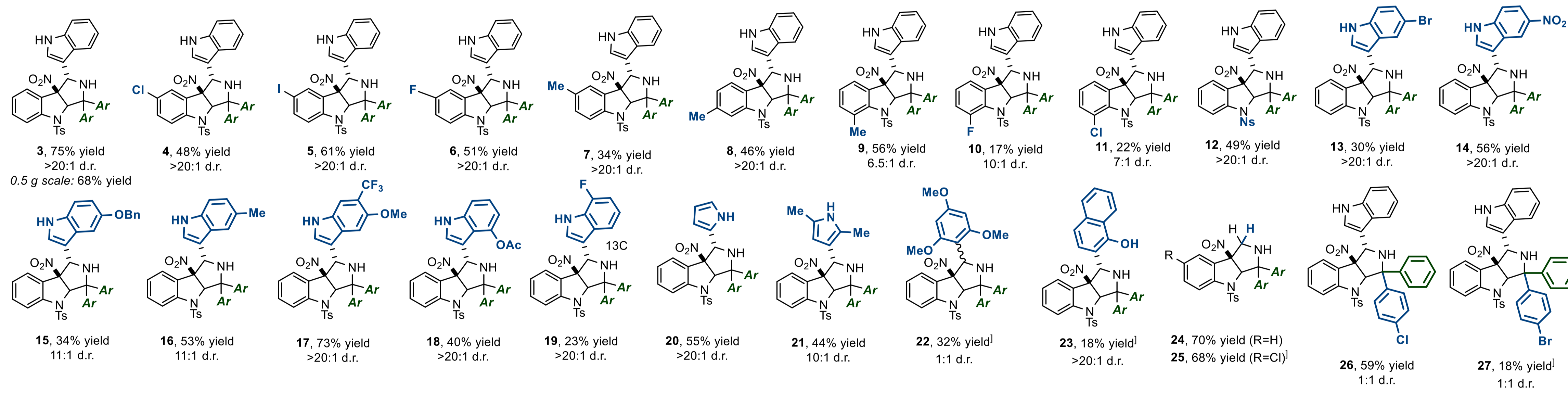
B) Interrupted Barton-Zard reaction



Scheme 1. Classical vs. Interrupted Barton-Zard reaction



Scheme 2. Developed cascade reaction for the synthesis of polycyclic pyrrolo[3,4-*b*] indole cores



CONCLUSION

The reaction of 3-nitroindoles with α,α -diaryl-substituted methyleneisocyanides, followed by *in situ* addition of an aryl nucleophile, generally afforded the desired products as single diastereomers in moderate to good yields.⁴ While the process tolerates most electron-deficient indoles and nucleophiles, it is highly sensitive to the structure of the isocyanide derivatives, with the dearomatization step representing the limiting stage of the cascade. Preliminary attempts under asymmetric conditions yielded racemic products in low yields; further optimization in this direction is currently underway in our group.



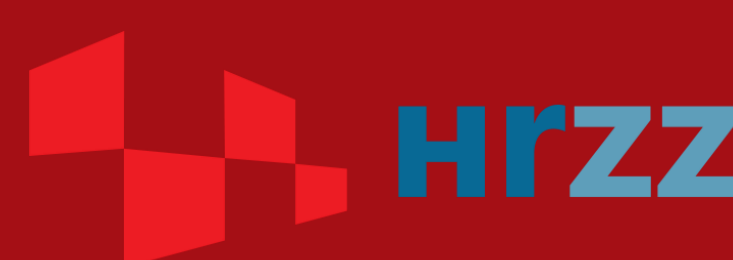
Synthetic Methodologies in Organic Chemistry
Division of Organic Chemistry and Biochemistry
Ruđer Bošković Institute
Zagreb, Croatia

Contact: jresetar@irb.hr

Our research group



Funding



IP-2022-10-5184

References

- [1] D. H. R. Barton and S. Z. Zard, *J. Chem. Soc., Chem. Commun.* (1985) 1098–1100.
- [2] Q. Wan, J. H. Xie, C. Zheng, Y. F. Yuan and S. L. You, *Angew. Chem. Int. Ed.* 60 (2021) 19730–19734.
- [3] R. Dong, T. J. Han, L. Huang, G. J. Mei, *Org. Chem. Front.* 11 (2024) 3624–3629.
- [4] J. Rešetar, K. Remar, A. Mikleušević, J. Suć Sajko, I. Bašić and M. Gredičak, *Asian. J. Org. Chem.* (2025), e00261.