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Homologation reaction to synthesize benzylic quaternary centers

A novel method for the synthesis of tertiary and quaternary benzylic stereocenters from benzyl halides and diazo compounds, with only dinitrogen as a byproduct.

IP Status: Provisional Patent Application Filed

Applications

- Pharmaceuticals
- Pesticide and Agricultural Chemicals

Key Benefits & Differentiators

- Allows the installation of two substituents simultaneously
- Does not use precious transition metal catalysts
- Dinitrogen is the only by-product

Technology Overview

Synthesis of complex chemicals is critical for discovery and development of active molecules in several areas, including pharmaceuticals, agrochemicals, and consumer products. However, some natural products with 3 or 4 unique side chains attached to one carbon center (tertiary or quaternary carbon centers) are highly difficult to synthesize with high purity or yield. While there are some methods in literature that are capable of generating quaternary stereocenters, they predominantly require metal catalysts and require simultaneous steps to add unique side chains.

Prof. Nicholas Race's research group at the University of Minnesota has developed a novel method for the synthesis of compounds with a tertiary or quaternary benzylic center. This method presents a method for the insertion of diazo compounds into the "unactivated" C–C bond of benzyl bromide derivatives catalyzed by a simple Lewis acid. This reaction adds two substituents simultaneously, making it more efficient, and doesn't require precious transition metal catalysts, which can be expensive. Moreover, this method is free of transition-metal and produces dinitrogen as the sole stoichiometric byproduct.

This method employs commonly used reagents (diazo derivatives and benzyl halides), and is complexity-generating (benzylic tertiary and quaternary center). As benzylic tertiary and quaternary stereocenters are important motifs present in drug and drug-like molecules, this technology could enable synthesis of novel drugs and drug derivatives with enhanced properties and functionalities. This technology could also be used for synthesizing agrochemical products with superior properties. Ultimately, this method is simpler and more efficient than current methods and minimizes risks associated with potentially dangerous byproducts, reactants, or buffers.

Applicable list of compounds (sample):

Technology ID
2021-258

Category
Engineering & Physical Sciences/Chemicals
Engineering & Physical Sciences/Processes
Life Sciences/Biochemicals & Small Molecules
Life Sciences/Industrial Biotech

Learn more

- Verapamil
- Fenbuconazole
- 5HT1A antagonist
- (-)-mesenbrine

Phase of Development

TRL: 3
Proof of concept

Desired Partnerships

This technology is now available for:

- License
- Sponsored research
- Co-development

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Researchers

- **Nicholas '"Nick" J. Race, PhD,** Assistant Professor, Department of Chemistry

References

1. Modak, Atanu, Juan V. Alegre-Requena, Louis de Lescure, Kathryn J. Rynders, Robert S. Paton, and Nicholas J. Race. , https://doi.org/10.1021/jacs.1c11503, Journal of the American Chemical Society (2021)