Drug discovery, Chemical process

Development of single-carbon atom doping reactions

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Abstract

Single–carbon atom doping reactions are lacking in organic synthesis, partly because of the absence of atomic carbon sources under standard solution-phase conditions. We found that N-heterocyclic carbenes can serve as atomic carbon donors. This strategy is applicable to single–carbon atom doping to α,β-unsaturated amides, which can be converted into γ-lactams through the formation of four single bonds at one carbon center in one operation.

Background & Results

One-carbon homologation reactions, in which a carbon-chain or a carbon-ring of the starting molecule is expanded by one-carbon unit, represent indispensable methods that underpin the synthesis of natural products, pharmaceuticals, and functional materials. Although a number of C1 reagents for use in homologation reactions have been developed to date, an atomic carbon, the simplest C1 source, has never been employed from the synthetic perspective, clearly due to its instability. We discovered that a class of molecules known as N-heterocyclic carbenes work as a stabilized version of an atomic carbon equivalent. By a straightforward reaction with α,β-unsaturated amides, various homologated γ-lactams were produced via the formation of four new single bonds in one operation. The reaction mechanism by which N-heterocyclic carbenes functions as an atomic carbon equivalent was elucidated by isotope labeling experiments and computational studies. Furthermore, the obtained γ-lactams can be derivatized to the corresponding pyrroles and pyrrolidines.

Significance of the research and Future perspective

While N-heterocyclic carbenes are commonly used as ligands for metal catalysts or as organocatalysts, their use as an atomic carbon equivalent represents a new remarkable application. This study shows that atomic carbon equivalents can be used in organic synthesis under standard solution-phase conditions. Reaction efficiency is an important factor in chemical processes. The strategy of single-carbon atom doping potentially shorten synthetic process to create more elaborate compounds, since the use of atomic carbons allows for the formation of the maximum number of new bonds at one carbon center in a single step.

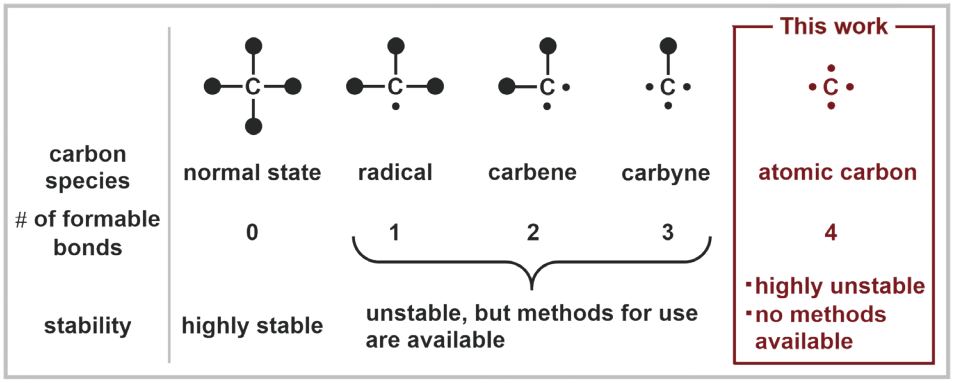

Fig 1

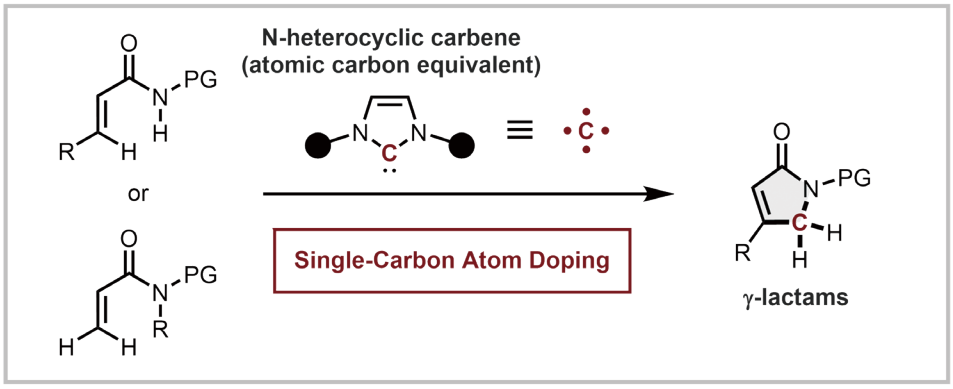

Fig 2

Patent

Treatise Fujimoto, Hayato; Tobisu, Mamoru et al. Single–carbon atom transfer to α,β-unsaturated amides from N-heterocyclic carbenes. Science 2023, 379, 484-488. doi: 10.1126/science.ade5110
Fujimoto, Hayato; Tobisu, Mamoru et al. Synthesis of γ-lactams from acrylamides by single-carbon atom doping annulation. J. Am. Chem. Soc. 2023, 145, 19518-19522. doi: 10.1021/jacs.3c07052

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Keyword organic synthesis, atomic carbon, N-heterocyclic carbene