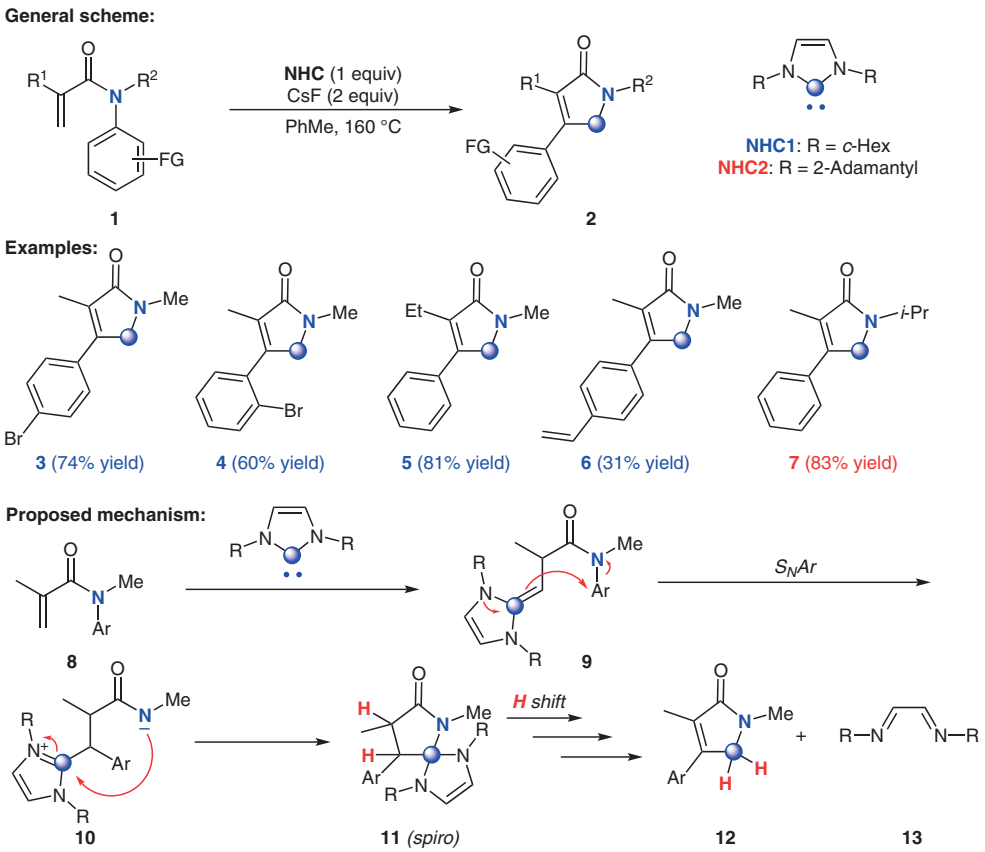
M. KAMITANI, B. NAKAYASU, H. FUJIMOTO, K. YASUI, T. KODAMA, M. TOBISU* (OSAKA UNIVERSITY, JAPAN)

Single–Carbon Atom Transfer to α,β-Unsaturated Amides from N-Heterocyclic Carbenes
Science **2023**, *379*, 484–488, DOI: 10.1126/science.ade5110.

NHC-Mediated Synthesis of γ-Lactams



Significance: While single-carbon homologation reactions are pivotal for the synthesis of numerous natural products and pharmaceuticals, they rely on the availability of a suitable C1 reagent to enable the chemistry. In this respect, atomic carbon represents the simplest C1 source and though able to form four bonds from a single carbon center in a single-carbon atom doping (SCAD) reaction, its use in synthesis is not practical owing to the specialist methods required to generate this species in solution phase. The current report describes the use of a commercially available NHC, which transfers a single-carbon atom in the synthesis of γ-lactams (**2**) from α,β-unsaturated amides (**1**) with the overall transformation featuring the formation of five single bonds (two C–C, two C–H and a C–N bond).

Comment: Key to the success of the transformation is the judicious selection of the NHC employed with model studies demonstrating that either the cyclohexyl- or 2-substituted adamantly variant were optimal (*Org. Lett*. **2021**, *23*, 1572 highlights an alternative reaction course with a different NHC). The reactions could be performed at lower temperatures if the reaction times were extended while use of the NHC labeled with ^{13}C at the C2 position demonstrated unambiguously that this is the carbon incorporated at the C5 position of the lactam. A broad range of functional group tolerance was demonstrated (**3–7**) including application to complex biologically active substrates though terminal and internal alkenes failed to undergo the reaction. Mechanistic studies suggest that the reaction proceeds through a 1,4-aryl migration (to give **10**) followed by formation of a spirocyclic intermediate (**11**).

SYNFACTS Contributors: Paul Richardson (Pfizer)
Synfacts 2023, 19(05), 0435 Published online: 14.04.2023
DOI: 10.1055/s-0042-1752446; **Reg-No.:** V06023SF

Category
Synthesis of Heterocycles

Key words
SCAD
lactams
N-heterocyclic carbenes
single-carbon homologation

Synfact of the Month