Intramolecular Hydroacylation of Unactivated Alkenes by NHC Catalysis

X = (CH$_2$)$_n$, O
R^1 = Alk, alkenyl, Ar, HetAr
R^1 = Alk

1

A (2–20 mol%)
DBU (4–40 mol%)

1,4-dioxane, 80 °C, 16 h

2
20 examples
14–99% yield
er from 90.5:9.5 to 99.5:0.5

Selected examples:

99% yield
er = 99.5:0.5
(2 g scale)

88% yield
er = 92.5:7.5

92% yield
er = 99:1

61% yield
er = 95:5

89% yield
er = 99:1

77% yield
er = 98.5:1.5

71% yield
racemic

70% yield
er = 99:1
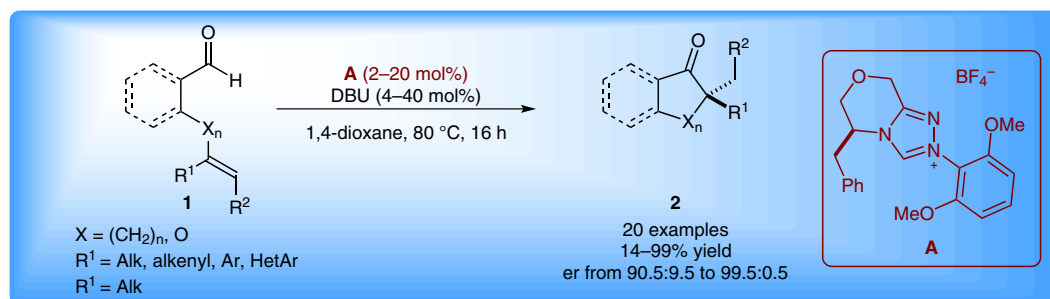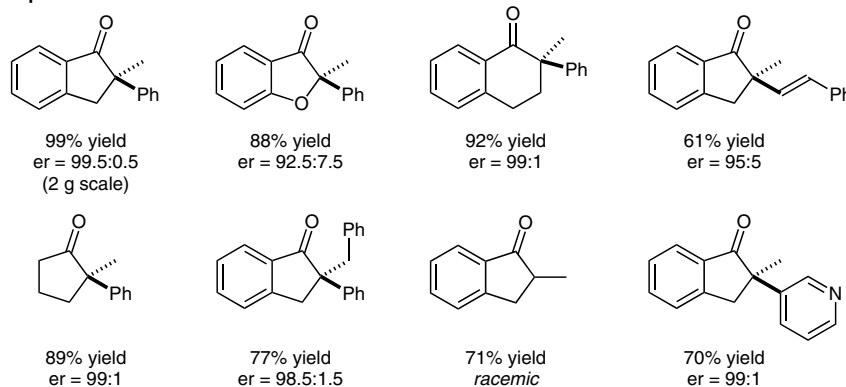
Significance: Glorius and co-workers report a highly enantioselective intramolecular N-heterocyclic carbene catalyzed hydroacylation of unactivated alkenes **1** to afford ketones **2** which bear an α-quaternary stereocenter. By employing pre-catalyst **A**, both aliphatic and aromatic aldehydes reacted smoothly to afford the desired products, by 5- or 6-*exo*-trig cyclization, in good to excellent yields and enantioselectivities. The scalability of the reaction was also proven by running the reaction on a two-gram scale (99% yield, er = 99:1).

Comment: Enantiopure ketones bearing an α-quaternary stereocenter (**2**) are important motifs in biologically active molecules. The authors report an asymmetric approach to synthesize these compounds by employing simple unactivated olefins as starting materials. The methodology shows a strong functional group tolerance, proven by a 'robustness screening' and a broad substrate scope. A current limitation of the protocol is represented by the instability of products bearing an α-tertiary stereocenter; they racemize under the basic reaction conditions. Previous mechanistic studies (*Angew. Chem. Int. Ed.* **2011**, *50,* 4983) from the same group on salicaldehyde-derived substrates suggest a protonation of the alkene from the Breslow intermediate followed by C–C bond formation.