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Highly Enantioselective Addition of Enals to Isatin-Derived Ketimines Catalyzed by N-Heterocyclic Carbenes: Synthesis of Spirocyclic γ-Lactams


NHC-Catalyzed Annulation of Isatin N-Boc Ketimines and Enals

\[ \text{R}^1 = \text{H, Me, OMe, Cl} \quad \text{R}^2 = \text{H, Me, Bn, Ac} \quad \text{R}^3 = \text{Ar, Alk} \]

Selected examples:

\[
\begin{align*}
\text{N} & \text{Me} \quad \text{O} \\
\text{BocN} & \text{Ph} \quad \text{O} \\
83\% \text{ yield} & \text{dr} > 20:1 \quad \text{er} = 99.5:0.5
\end{align*}
\]

\[
\begin{align*}
\text{N} & \text{H} \\
\text{O} & \text{BocN} \quad \text{Ph} \quad \text{O} \\
64\% \text{ yield} & \text{dr} = 17:1 \quad \text{er} = 99.5:0.5
\end{align*}
\]

\[
\begin{align*}
\text{N} & \text{Me} \quad \text{O} \\
\text{BocN} & \text{Me} \quad \text{O} \\
80\% \text{ yield} & \text{dr} > 20:1 \quad \text{er} = 99.5:0.5
\end{align*}
\]

\[
\begin{align*}
\text{N} & \text{Me} \\
\text{O} & \text{BocN} \quad \text{Me} \\
64\% \text{ yield} & \text{dr} = 4:1 \quad \text{er} = 97:3
\end{align*}
\]

Removal of the Boc protecting group:

\[
\begin{align*}
\text{N} & \text{Me} \quad \text{O} \\
\text{BocN} & \text{Ph} \quad \text{TFA} \quad 0\,\text{°C}, 0.5 \text{ h} \\
92\% \text{ yield} & \text{HN} \quad \text{Ph}
\end{align*}
\]

Significance: Chi and co-workers report an N-heterocyclic carbene (NHC)-catalyzed annulation of isatin N-Boc imines with enals, which affords spirocyclic oxindole-γ-lactams bearing one quaternary chiral center in good diastereo- and excellent stereoselectivities (dr up to >20:1 and er > 99.5:0.5). Ketimines and γ-aryl enals with electron-donating substituents lead to better yield and selectivity compared to electron-withdrawing substituents. The presence of a trace of water is beneficial for the conversion of the reaction. The resulting products can be easily deprotected to free γ-lactams in high yield.

Comment: γ-Lactams are privileged scaffolds found in naturally occurring and synthetic biologically active compounds. Herein, the authors have developed a novel NHC-catalyzed annulation methodology, which allows for a rapid construction of spirocyclic oxindole-γ-lactams with high diastereoselectivity and enantioselectivity. More efficient catalysts and the application to more challenging substrates are expected.