Formation of Fused Ring Junction \(N\)-Heterocycles via Cp*Rh(III) Imidoyl C–H Activation

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Synthesis of 5,6 Fused \(N\)-Heterocycles

Three Component Annulation: Aldehyde Scope

Hydrazoyl Annulation: \(R^2\) Scope

Hydrazoyl Annulation: Tethered Substrates

Proposed Mechanism for Three Component Annulation

Paradigm Shift – Small Molecule mRNA Targeting

mRNA Targeting Molecules Synthesized

Acknowledgements

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Sulfoxonium Ylides are Practical and Versatile Inputs

- Crystalline and shelf stable carbene precursors
- Prepared in one step from carboxylic acids and their derivatives
- >10 available from Sigma – Technology Spotlight by Streit et. al.

Three Component Annulation: Ylide and Amine Scope

Proposed Mechanism for Hydrazoyl Annulation

Three Component Annulation: Formyl Ylide

Hydrazoyl Annulation: Pyrrole and Azole Scope

Hydrazoyl Annulation: Alkyne Scope

Isolated yields of pure material, \(100\text{ M concentration}\)

First chemical transformation of formyl ylide

Compatible with halide, acidic, and basic functionalities

Isolated yields of pure material, \(0.5\text{ M concentration}\)

Isolated yields of pure material, \(0.2\text{ M concentration}\)

Isolated yields of pure material, \(0.1\text{ M concentration}\)

Isolated yields of pure material

Paradigm Shift – Small Molecule mRNA Targeting

- Risdiplam – first FDA approved drug to target mRNA
- Collaboration with the Simon lab – Yale Molecular Biophysics and Biochemistry
- Studying how small-molecules interact with the entire mRNA transcriptome

mRNA Targeting Molecules Synthesized

- Negative control, no binding within the transcriptome
- Positive control, Risdiplam-like molecule, binds to ~400 transcripts

Key Risdiplam-like core assembled using three-component Cp*Rh(III) catalysis

Intermediate resubmitted to reaction conditions and found to be competent catalyst

\(13C\)–Rh coupling visible for two C–Rh bonds

Characterization by HRMS, \(\text{\textit{H}},\) and \(13C\) NMR

\(C–H\) activation intermediate prepared and isolated in quantitative yield

- Characterization by HRMS, \(\text{\textit{H}},\) and \(13C\) NMR
- \(13C\)-Rh coupling visible for two C–Rh bonds
- Intermediate resubmitted to reaction conditions and found to be competent catalyst

Access to more complex three-ring products with substituted central pyridazine ring

Isolated yields of pure material. \(5\text{ M concentration}\)

Isolated yields of pure material. \(2\text{ M concentration}\)

Isolated yields of pure material. \(2\text{ M concentration}\)

Isolated yields of pure material. \(2\text{ M concentration}\)

Isolated yields of pure material. \(2\text{ M concentration}\)

Isolated yields of pure material. \(2\text{ M concentration}\)

Isolated yields of pure material. \(2\text{ M concentration}\)

Isolated yields of pure material. \(2\text{ M concentration}\)

Isolated yields of pure material. \(2\text{ M concentration}\)

Isolated yields of pure material. \(2\text{ M concentration}\)

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