

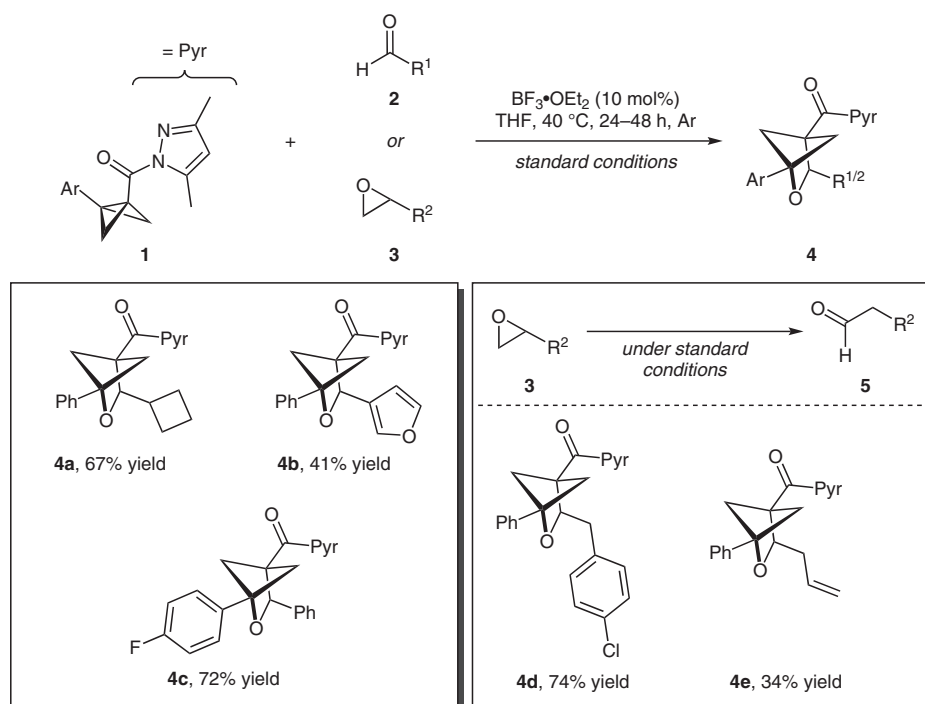
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Catalytic Formal $[2\pi+2\sigma]$ Cycloaddition of Aldehydes with Bicyclobutanes: Expedient Access to Polysubstituted

2-Oxabicyclo[2.1.1]hexanes

Angew. Chem. Int. Ed. 2023, 62, e202305043 DOI: 10.1002/anie.202305043.

Synthesis of Substituted 2-Oxabicyclo[2.1.1]hexanes via $[2\pi+2\sigma]$ Cycloadditions with Bicyclobutanes



Significance: Frequent challenges in medicinal chemistry campaigns revolve around modulating the physicochemical properties of candidate molecules. Such parameters that are of paramount importance to ADME/Tox properties are the solubility/lipophilicity of the molecule, and the fraction of sp^3 -hybridized carbons (F_{sp^3}). Incorporation of 2-oxabicyclo[2.1.1]hexanes (2-oxa-BCHs) as phenyl bioisosteres favorably addresses both the F_{sp^3} , and the solubility (by introducing a polar oxygen atom) of potential drug molecules. Synthetic methods to access these highly substituted 2-oxa-BCHs are thus desirable, as they allow for diverse avenues of discovery towards medicinal agents. Previous synthetic efforts targeting this important structural motif have been limited, and modular access towards these saturated ring systems could prove to be highly beneficial to the chemistry community.

Comment: The authors described an elegant $[2\pi+2\sigma]$ cycloaddition reaction of strained bicyclobutanes (BCBs) **1** and aldehydes **2**. The authors found that a mild Lewis acid (BF₃·OEt₂) is crucial for the transformation, as well as a BCB bearing an acyl pyrazole. (Hetero)aryl and aliphatic aldehydes were tolerated in the reaction, which furnished 2-oxa-BCHs **4a–e** in moderate to good yields. BCBs **1** bearing other Ar groups could be prepared and used efficiently in the reaction (**4c**). The authors also found that epoxides **3** could be used in the reaction instead of aldehydes (**4d,e**). Control reactions indicated that under the standard reaction conditions, epoxides **3** underwent a LA-mediated isomerization to aldehydes **5**, which then participated in the cycloaddition reaction. The authors also demonstrated that the necessary acyl-pyrazole functionality could be used for downstream transformations, which further strengthened the practicality of this method.

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Synfacts 2023, 19(10), 0969 Published online: 14.09.2023
DOI: 10.1055/s-0042-1752219; Reg-No.: V12423SF

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Category

Synthesis of
Heterocycles

Key words

cycloaddition

bicyclobutanes

Lewis acid catalysis

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