Enantioselective Synthesis of 2-Carboxy Cyclic Ethers

**Significance:** The formation of new carbon–heteroatom bonds using transition-metal-catalyzed carbene insertion reactions into X–H bonds (X = O, N, S) is a useful synthetic tool. While highly enantioselective variants of intermolecular O–H insertions are known, selective intramolecular versions have not been developed. Herein, the authors present the first highly enantioselective copper-catalyzed O–H insertion approach used for the preparation of chiral 2-carboxy cyclic ethers of type \( \mathbf{2} \).

**Comment:** Starting from readily available \( \omega \)-hydroxy-\( \alpha \)-diazo esters \( \mathbf{1} \), a number of chiral cyclic ethers of type \( \mathbf{2} \) with various ring sizes could be prepared in good to excellent yields and high enantioselectivities. The combination of CuOTf and the chiral spiro bisoxazoline ligand (\( S_\alpha,S,S \))-\( \mathbf{3} \) in the presence of catalytic amounts of NaBArF in non-coordinating solvents like methylene chloride was found to be crucial to achieve high selectivities. The products formed in this transformation are useful building blocks since the 2-carboxylic cyclic ether substructure can be found in several natural products and pharmaceuticals.

**Selected examples:**

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\begin{align*}
\text{ \( \mathbf{1} \)} & \quad \text{80% yield; 93% ee} \\
\text{ \( \mathbf{2} \)} & \quad \text{77% yield; 88% ee} \\
\text{ \( \mathbf{3} \)} & \quad \text{81% yield; 88% ee} \\
\text{ \( \mathbf{4} \)} & \quad \text{94% yield; 95% ee} \\
\text{ \( \mathbf{5} \)} & \quad \text{79% yield; 97% ee} \\
\text{ \( \mathbf{6} \)} & \quad \text{95% yield; 92% ee}
\end{align*}
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