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Enantioselective Copper-Catalyzed Intramolecular O–H Insertion: An Efficient Approach to Chiral 2-Carboxy Cyclic Ethers

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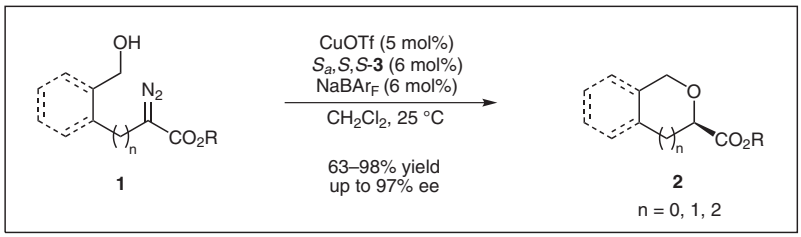
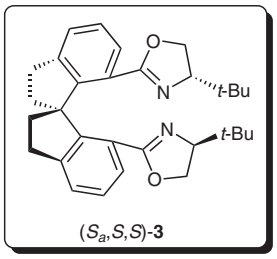
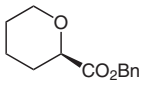
Enantioselective Synthesis of 2-Carboxy Cyclic Ethers

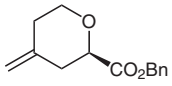




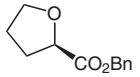
Selected examples:



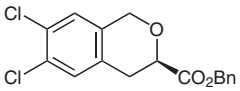
80% yield; 93% ee



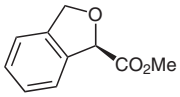
77% yield; 88% ee



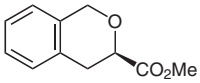
81% yield; 88% ee



94% yield; 95% ee



79% yield; 97% ee



95% yield; 92% ee

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 **2**.

Comment: Starting from readily available ω-hydroxy-α-diazo esters **1**, a number of chiral cyclic ethers of type **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_a,*S*,*S*)-**3** in the presence of catalytic amounts of $NaBAr_F$ 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.

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