Asymmetric Catalysis

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Copper-Catalyzed Intramolecular Desymmetric Aryl C–O Coupling for the Enantioselective Construction of Chiral Dihydrobenzofurans and Dihydrobenzopyrans**

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Abstract: *O-Heterocyclic structures such as 2,3-dihydrobenzofurans are key motifs in many natural compounds and pharmaceuticals. Enantioselective formation of chiral dihydrobenzofurans and analogues was achieved through a copper-catalyzed desymmetrization strategy with a chiral cyclic 1,2-diamine. A broad range of substrates are compatible with this Cu^{I}-diamine catalytic system and afford the desired coupling products with chiral tertiary or quaternary carbon centers in high yields and good to excellent enantioselectivities under mild conditions.*

Oxygen-heterocycles such as 2,3-dihydrobenzofurans and chromans are common structures in a variety of naturally occurring and medicinally relevant compounds (Figure 1).[1–3] Although many catalytic systems employing transition-metal-catalyzed coupling reactions, such as couplings of aryl halides with oxygen nucleophiles catalyzed by Pd[4,5] and Cu[6,7], have been developed for the synthesis of such structures, asymmetric synthesis in this area is still a challenge.[2,8,9]

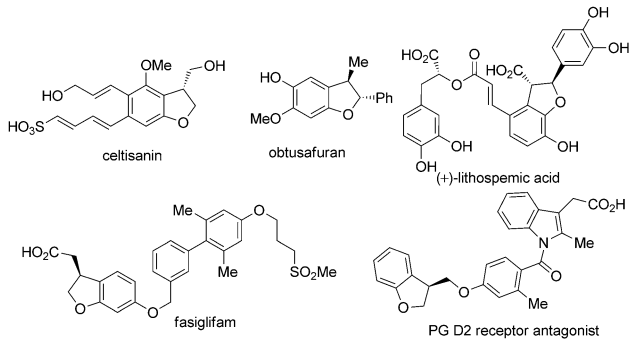

Figure 1. Examples of bioactive natural products or pharmaceuticals with 2,3-dihydrobenzofuran frameworks.

In 2013, we reported the first Pd-catalyzed enantioselective aryl C–O coupling reaction[9a] for the formation of central chirality in chromans through an asymmetric desymmetrization strategy,[10–12] which differentiates the two symmetric hydroxy groups of 2-(2-haloaryl)1,3-diols[13] by intramolecularly reacting with one aryl halide. However, such a method has the following limits to its practical applications: 1) only low to moderate yields were obtained in most cases due to β-H elimination and dehalogenation side reactions; 2) only moderate enantioselectivity was obtained due to the limited availability of chiral ligands; 3) substrates were restricted to those forming six-membered ring chromans. Asymmetric 5-membered cyclization afforded dihydrobenzofurans with only 50% yield and 50% *ee*. Furthermore, substrates were limited to those with tertiary prochiral centers. Substrates with a quaternary prochiral carbon center showed very low reactivity and poor enantioselectivity; and 4) the reaction conditions were relatively harsh.

Although an improved Pd catalytic system was later developed for the asymmetric desymmetrization of 2-(2-halophenoxyl)1,3-diols by employing a SDP(O) ligand,[9b] the efficiency of the system was limited to a narrow range of substrates and still only tertiary chiral carbon centers were formed in these reactions. Thus, it is highly desirable to develop a new catalytic system with a broader substrate scope and with high yield and enantioselectivity.

Copper catalysts have been complementary to Pd catalysts in cross-coupling reactions[14] and copper-catalyzed coupling reactions of aryl halides with alcohols or phenols are important methods for the formation of aryl alkyl ethers or diaryl ethers. Improved protocols for such reactions have been developed in recent years by using appropriate ligands to promote them under relatively mild conditions.[6,7] More importantly, dehalogenation in copper-catalyzed coupling reactions is not as prevalent as in palladium-catalyzed reactions, and this may offer an opportunity to improve the reaction efficiency. However, to the best of our knowledge, only one example of copper-catalyzed enantioselective aryl C–O coupling, generating axial chirality in the intramolecular diaryl ether formation, has been reported[15] and no copper-catalyzed aryl C–O coupling for the enantioselective formation of central chirality has been reported to date. In this communication, we would like to report a copper-catalyzed enantioselective aryl C–O coupling reaction, useful for the formation of 2,3-dihydrobenzofurans and analogues with tertiary and all-carbon quaternary stereochemical centers based on a desymmetrization strategy.

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