CARBOXYLATION OF PHENOLS AND ASYMMETRIC NUCLEOPHILE ADDITION ACROSS C=C BOND

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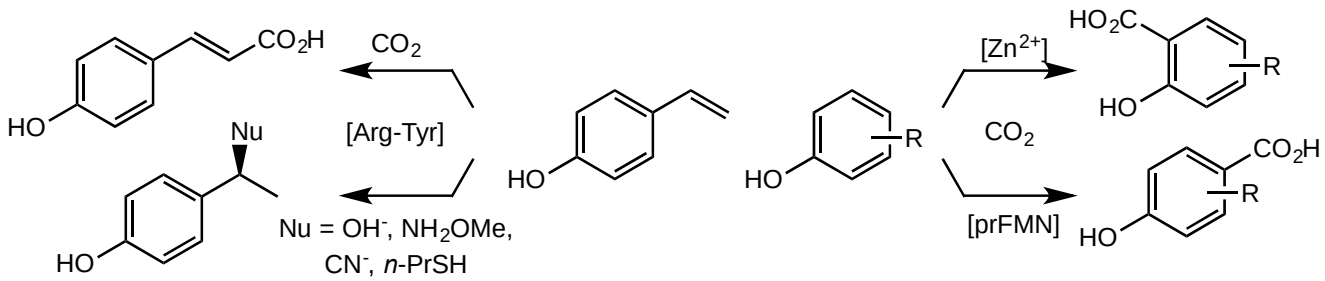
The regioselective carboxylation of electron-rich (hetero)aromatics employing decarboxylases in the redox-neutral (reverse) carboxylation reaction using bicarbonate or $CO_{2(g)}$ is currently exploited for the biocatalytic synthesis of carboxylic acids.[1] Three enzyme classes exert complementary regioselectivities through diverse mechanisms: (i) Whereas the *o*-carboxylation of phenols (an equivalent to the Kolbe-Schmitt reaction) is mediated by Zn^{2+}-dependent *o*-benzoic acid (de)carboxylases,[2] (ii) the □-carboxylation of hydroxystyrenes is catalysed by phenolic/ferulic acid (de)carboxylases acting via a pair of Tyr-Arg residues.[3] (iii) Surpringly, these enzymes also exhibit a catalytic promiscuity for the nucleophile addition of H_2O,[4] NH_2-OMe, cyanide and *n*-Pr-SH across the vinyl C=C bond via a quinone-methide intermediate, which yields the corresponding (*S*)-configurated adducts in up to 91% e.e.[5] (iv) In search of ATP-independent regio-complementary *p*-benzoic acid (de)carboxylases, we discovered that 3,4-dihydroxybenzoic acid decarboxylase from *Enterobacter cloacae*[6] (DHBDC_*Ec*) surprisingly depends on prenylated FMN[7] as cofactor. In an attempt to propose a mechanism for the carboxylation of catechol by DHBDC_*Ec*, QM calculations revealed that the transient formation of a 1,3-dipolar cycloaddition product (as suggested for the decarboxylation of cinnamic acid with ferulic acid decarboxylase from *S. cerevisiae*[8]) was highly disfavored (>30 kcal/M). As an alternative, we propose a mono-covalent nucleophile adduct involving a prFMN iminium electrophile (~14 kcal/M).



Regio-complementary carboxylation and asymmetric nucleophile addition.

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