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 p-carboxylation of hydroxystyrenes is catalysed by phenolic/ferulic acid (de)carboxylases acting via a pair of Tyr-Arg residues.\(^3\) (iii) Surprisingly, these enzymes also exhibit a catalytic promiscuity for the nucleophile addition of H$_2$O,\(^4\) NH$_2$-OMe, cyanide and n-Pr-SH across the vinyl C=C bond via a quinone-methide intermediate, which yields the corresponding (S)-configured 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 monocovalent nucleophile adduct involving a prFMN iminium electrophile (~14 kcal/M).

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\text{HO}_2\text{C} \quad \text{CO}_2\text{H} \quad [\text{Arg-Tyr}] \quad \text{Nu} \quad \text{CO}_2
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\text{HO} \quad \text{HO} \quad \text{Nu} = \text{OH}^-, \text{NH}_2\text{OMe}, \text{CN}^-, \text{n-Pr-SH}
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\text{Regio-complementary carboxylation and asymmetric nucleophile addition.}
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References