Bis(pyrazol-1-yl)acetato-Ruthenium-Complexes: Models for the Active Sites of Enzymes

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Introduction

In recent years protein structures of several mononuclear non heme iron(II) enzymes were solved, such as the deacetoxycephalosporin C synthase (DAOCS) [1], taurine dioxygenase (TauD) [2] and isopenicillin N synthase (IPNS) [3].
In the active site of these enzymes the iron(II) centre is coordinated by two histidines and one aspartate, the so-called facial 2-His-1-carboxylate triad [4].

In a-ketoglutarate dependent enzymes such as DAOCS or TauD the a-ketoglutarate co-substrate is bound via one carboxylate and the

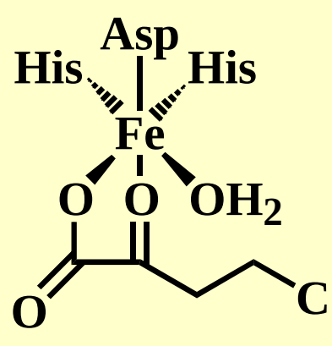


Fig.1: Active site of DAOCS

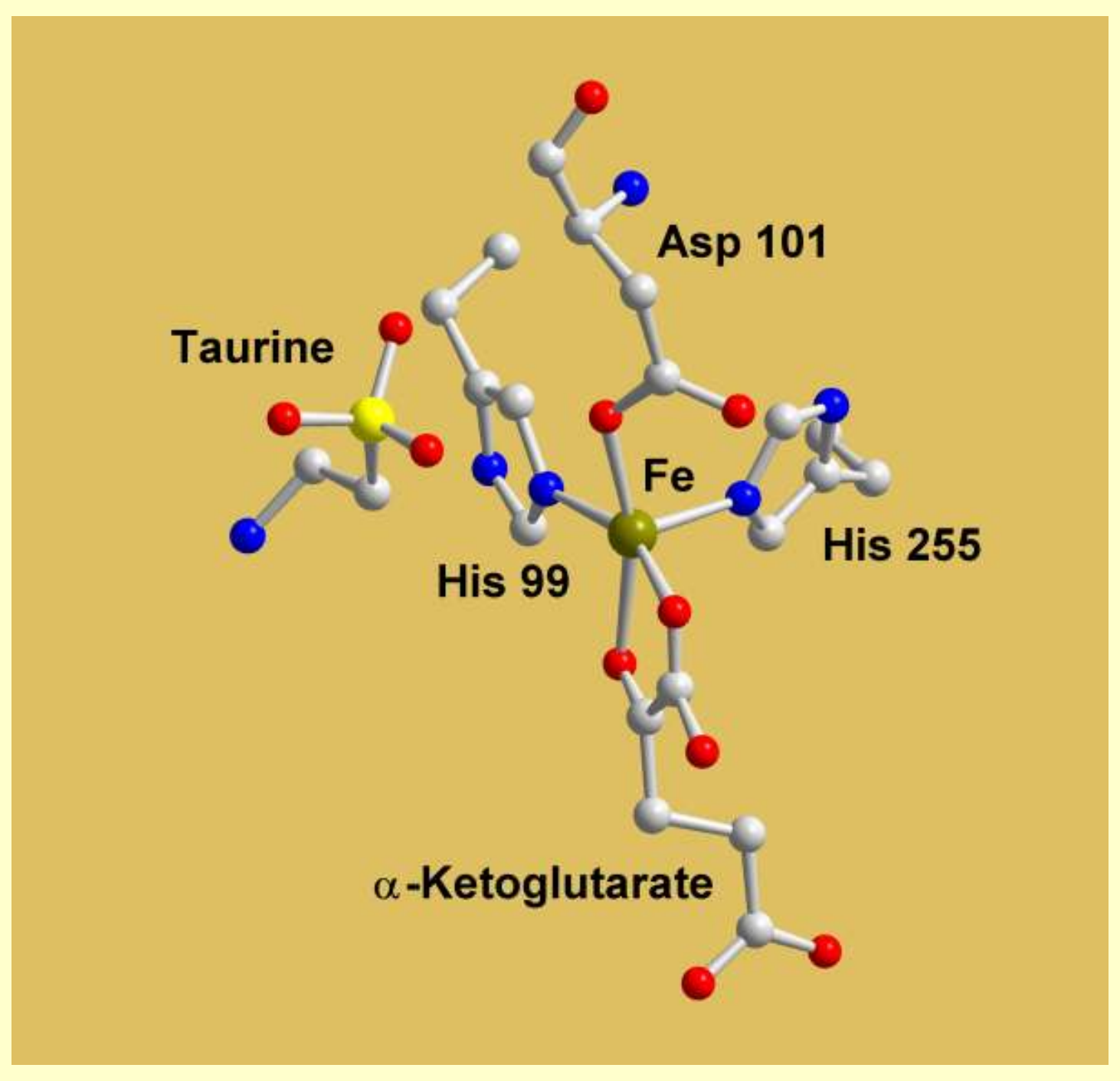


Fig.2: X-ray structure of the active site of TauD (PDB-Code: 1GY9) [2]

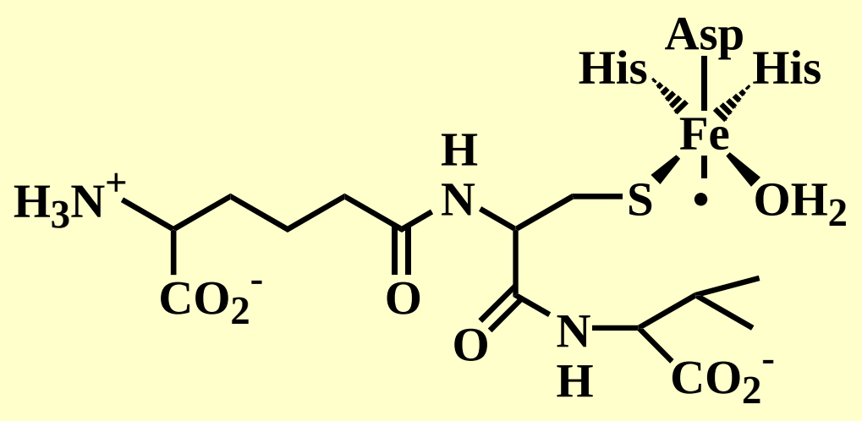


Fig.3: Active site of IPNS with ACV substrate

In IPNS, the key enzyme in the penicillin biosynthesis, the tripeptide substrate ACV (d-(*L*-a-aminoadipoyl)-*L*-cysteinyl-*D*-valine) coordinates in form of a

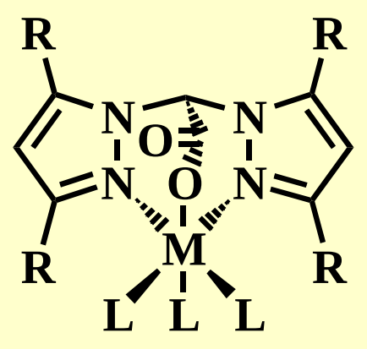
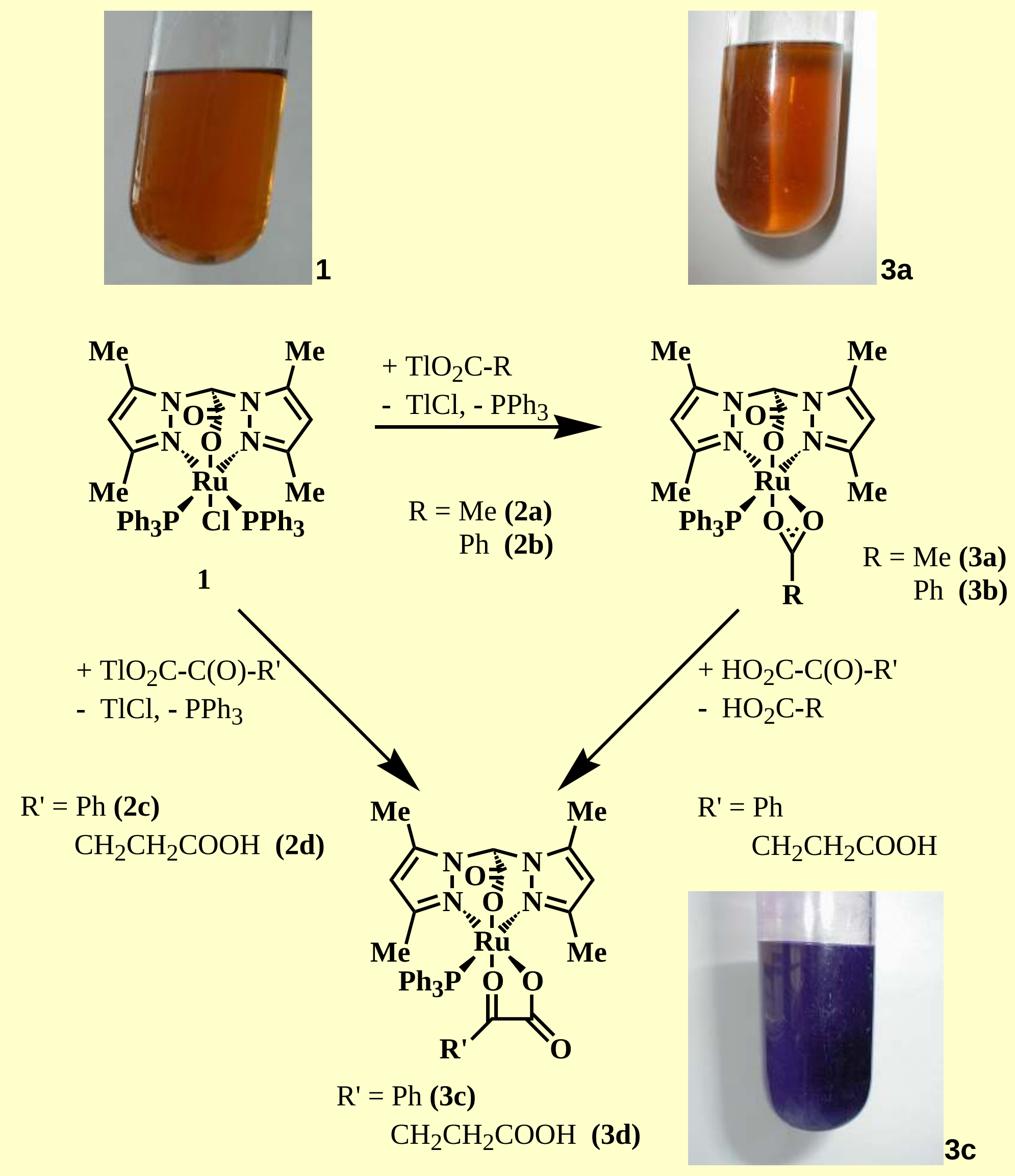


Fig.4: Structure of a bis(pyrazol-1-yl)acetato complex

A new class of scorpionate ligands, the bis(pyrazol-1-yl)-acetato ligands, reflects a good structural mimic for the facial 2-His-1-carboxylate triad of iron(II) enzymes [5].

Results

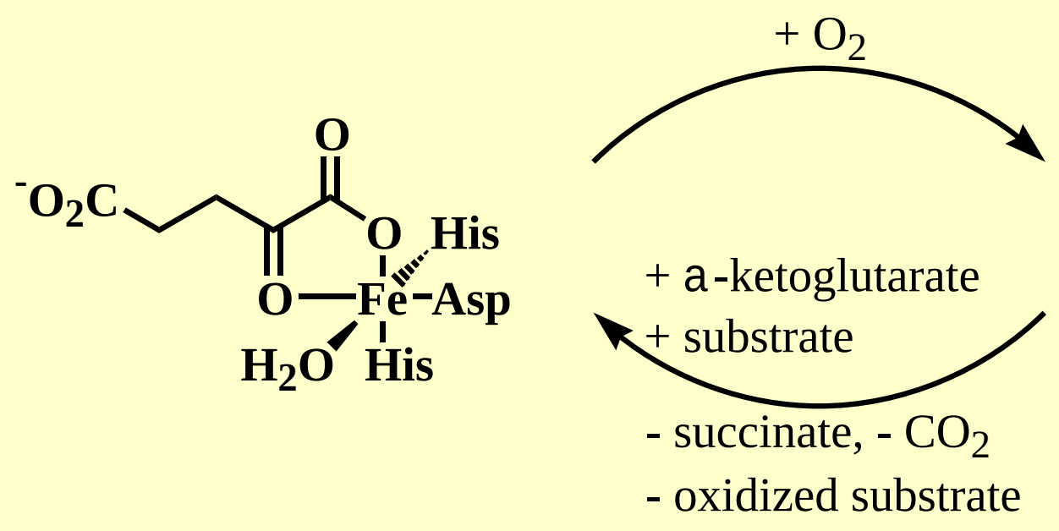


Scheme 1: Synthesis of carboxylato complexes

Carboxylato and keto carboxylato complexes are obtained by reaction of the recently reported bis(3,5-dimethyl-pyrazol-1-yl)-chloro-bis(triphenylphosphine)ruthenium(II) complex $[(bdpmza)RuCl(PPh_3)_2]$ [6] with the corresponding thallium carboxylates (Scheme 1).

Reaction of the carboxylato complexes with a-keto acids also yields the keto carboxylato complexes. This reaction can be compared with the regeneration of a-ketoglutarate dependent enzymes (Scheme 2).

Future work needs to establish a functional model with the focus on the formation of a Ru(IV)=O species starting from



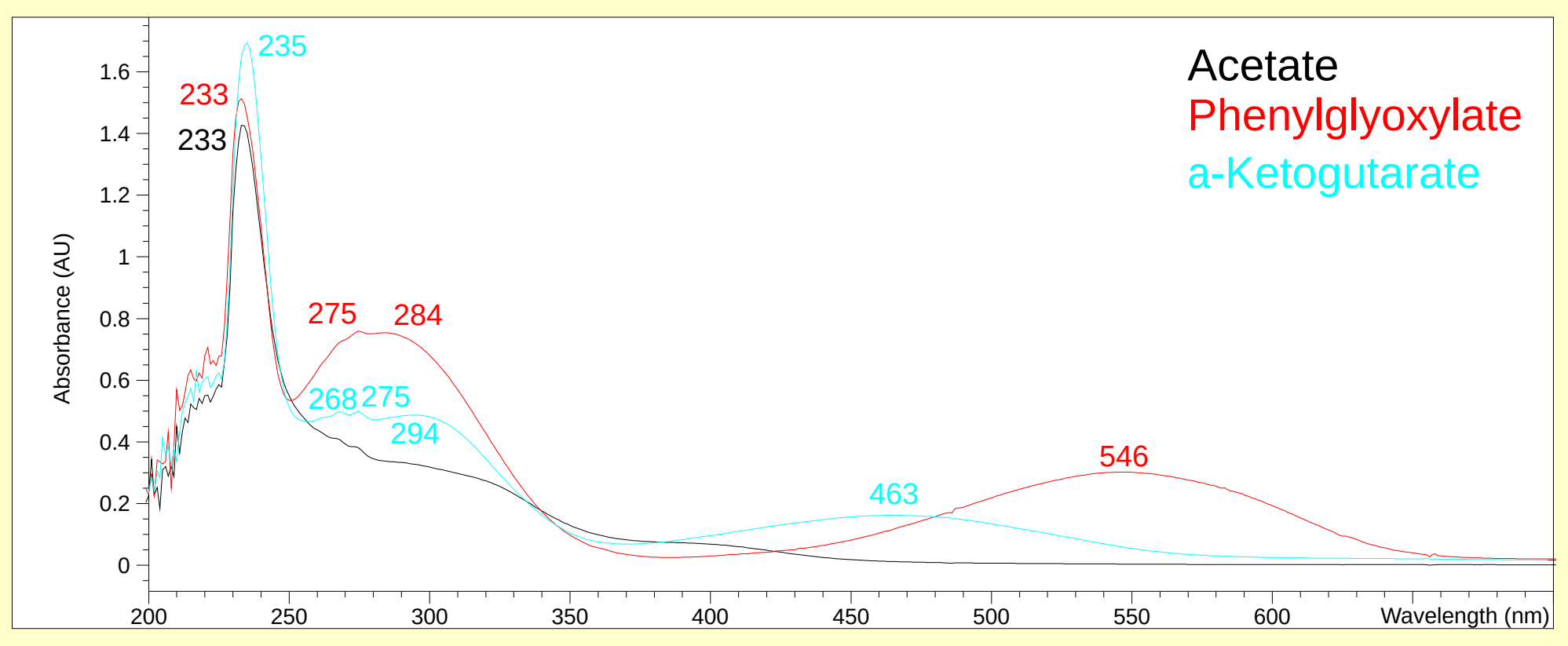


Fig.5: UV spectra of carboxylato and keto carboxylato complexes

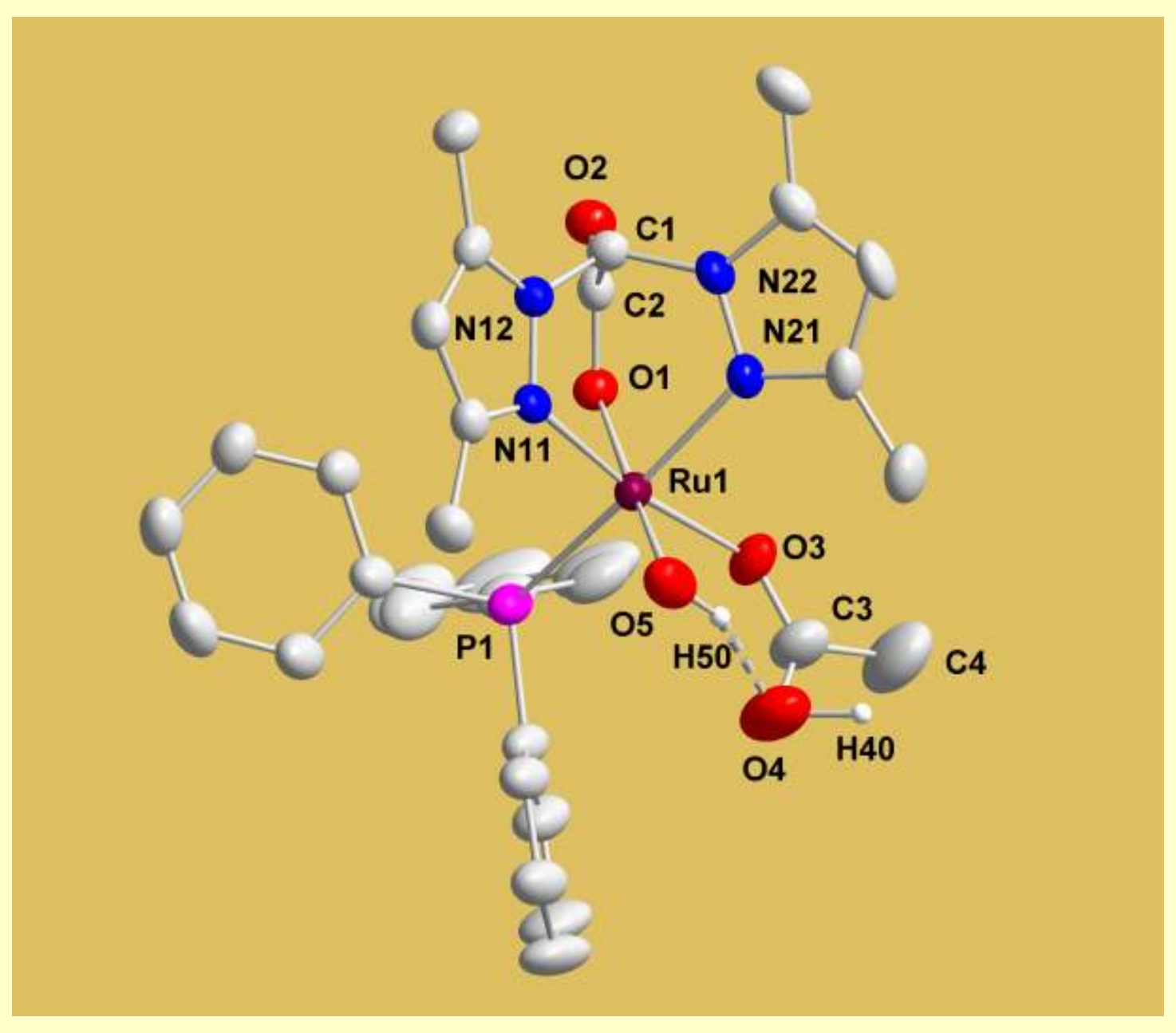
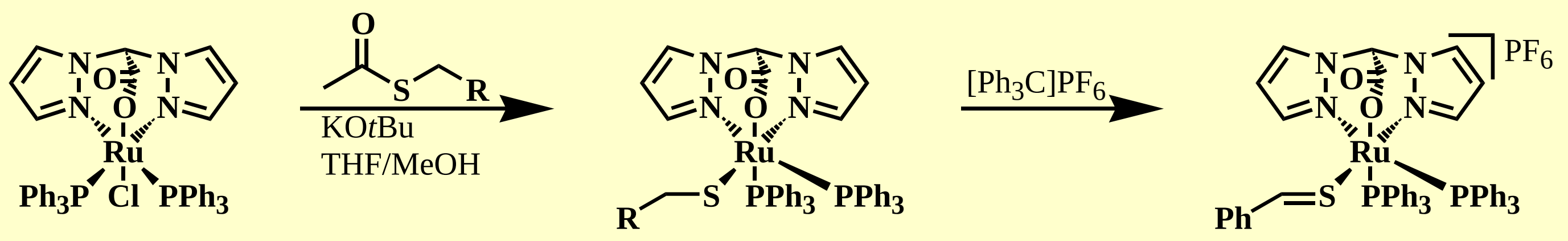


Fig.6: X-ray structure of $[(bdmpza)Ru(OH)(HOAc)(PPh_3)]$

Models for the Isopenicillin N Synthase (IPNS)



4 R = Ph **(5a)**, CH_2Ph **(5b)** R = Ph **(6a)**, CH_2Ph **(6b)** **7a**

Scheme 3: Thiolate and thioaldehyde complexes

Thiolate complexes are synthesized by reaction of the bis(pyrazol-1-yl)-chloro-bis(triphenylphosphine)ruthenium(II) complex [6] with thioacetic acid esters. The resulting complexes have the same asymmetric structure as the active site of IPNS (Fig.3). The corresponding thioaldehyde complex is achieved by using the method of Schenk *et al.* by formal hydride abstraction [7].
Using a suitable ACV analogous thiolate, it might be possible to mimic the b-lactam formation of the

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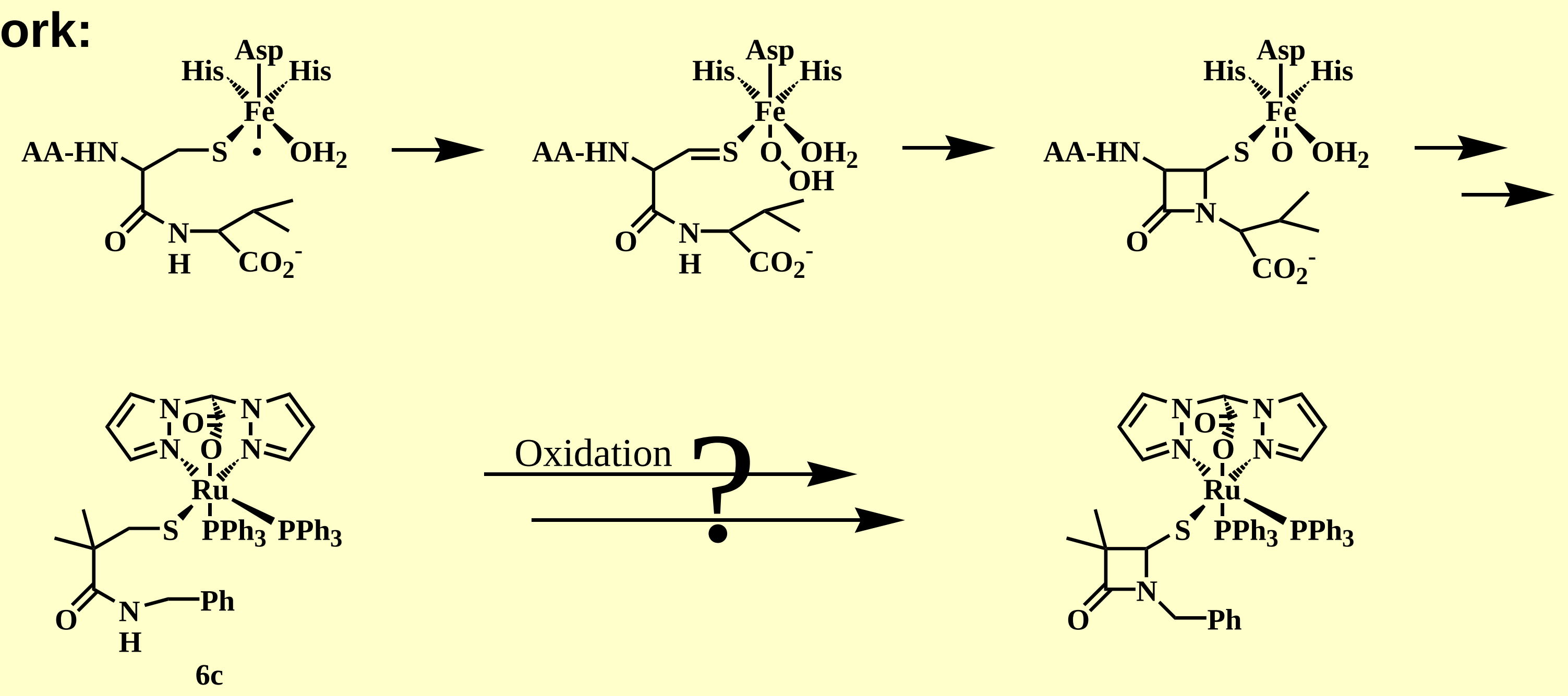

Scheme 4: Biomimetic synthesis in analogy to the reaction pathway of IPNS

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