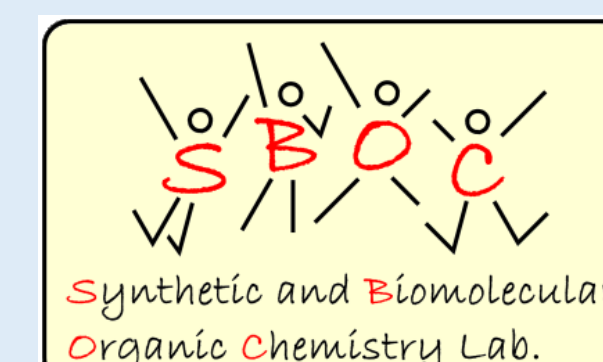
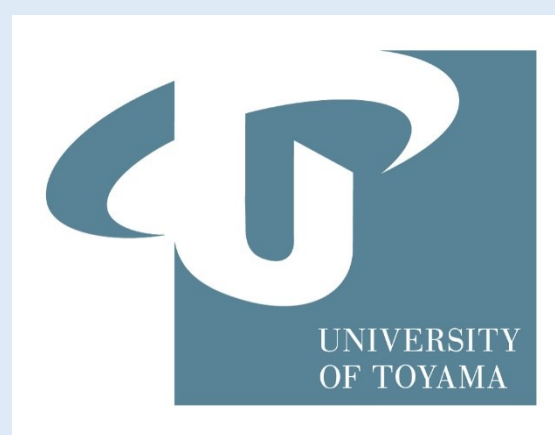


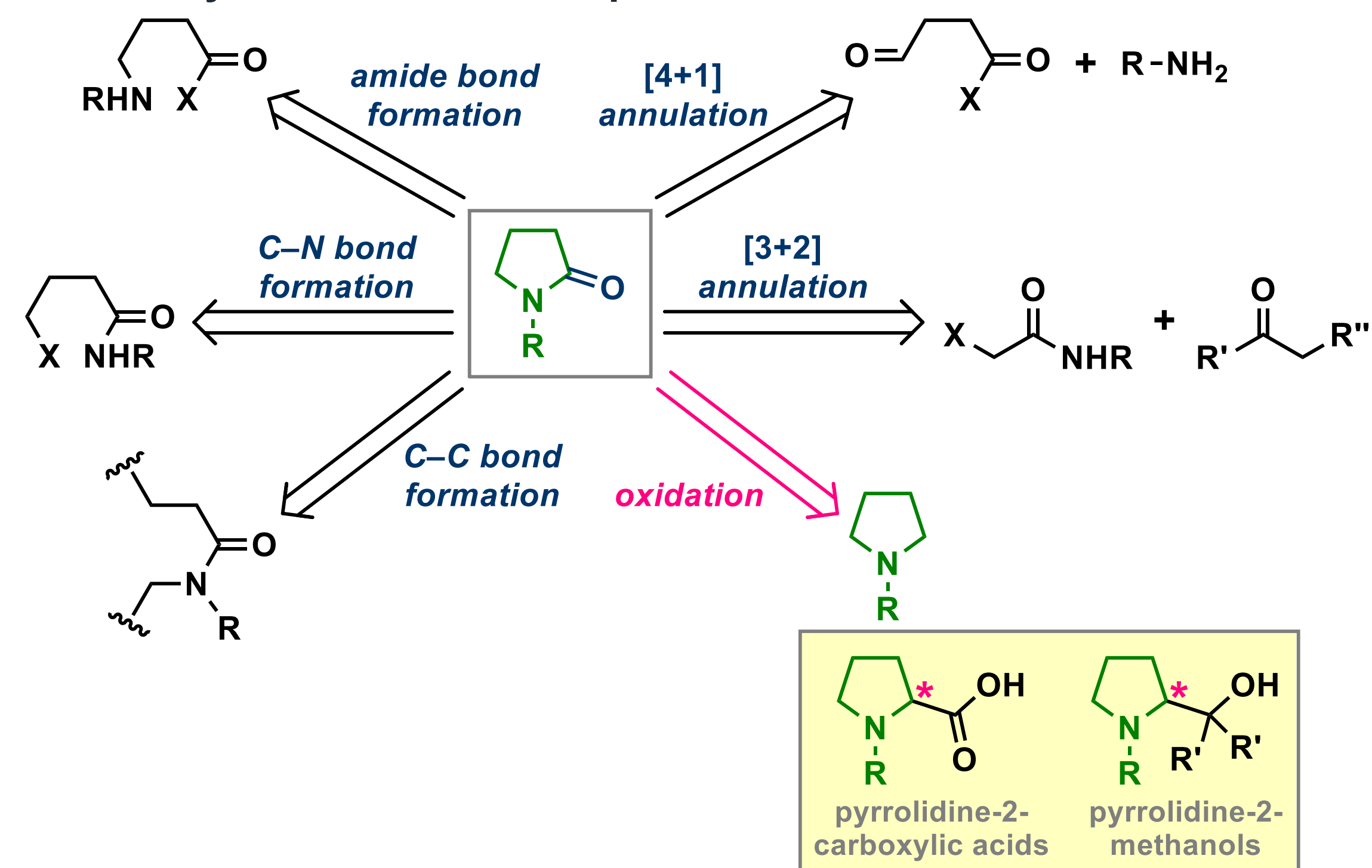
# Synthesis of $\gamma$ -lactams by oxidative cleavage of pyrrolidine-2-methanols using 2-iodobenzamide catalyst

Faculty of Pharmaceutical Sciences, University of Toyama

Hema Naga Lakshmi Perumalla, Maki Okada, Hisanori Nambu, Tomoya Fujiwara, Takayuki Yakura

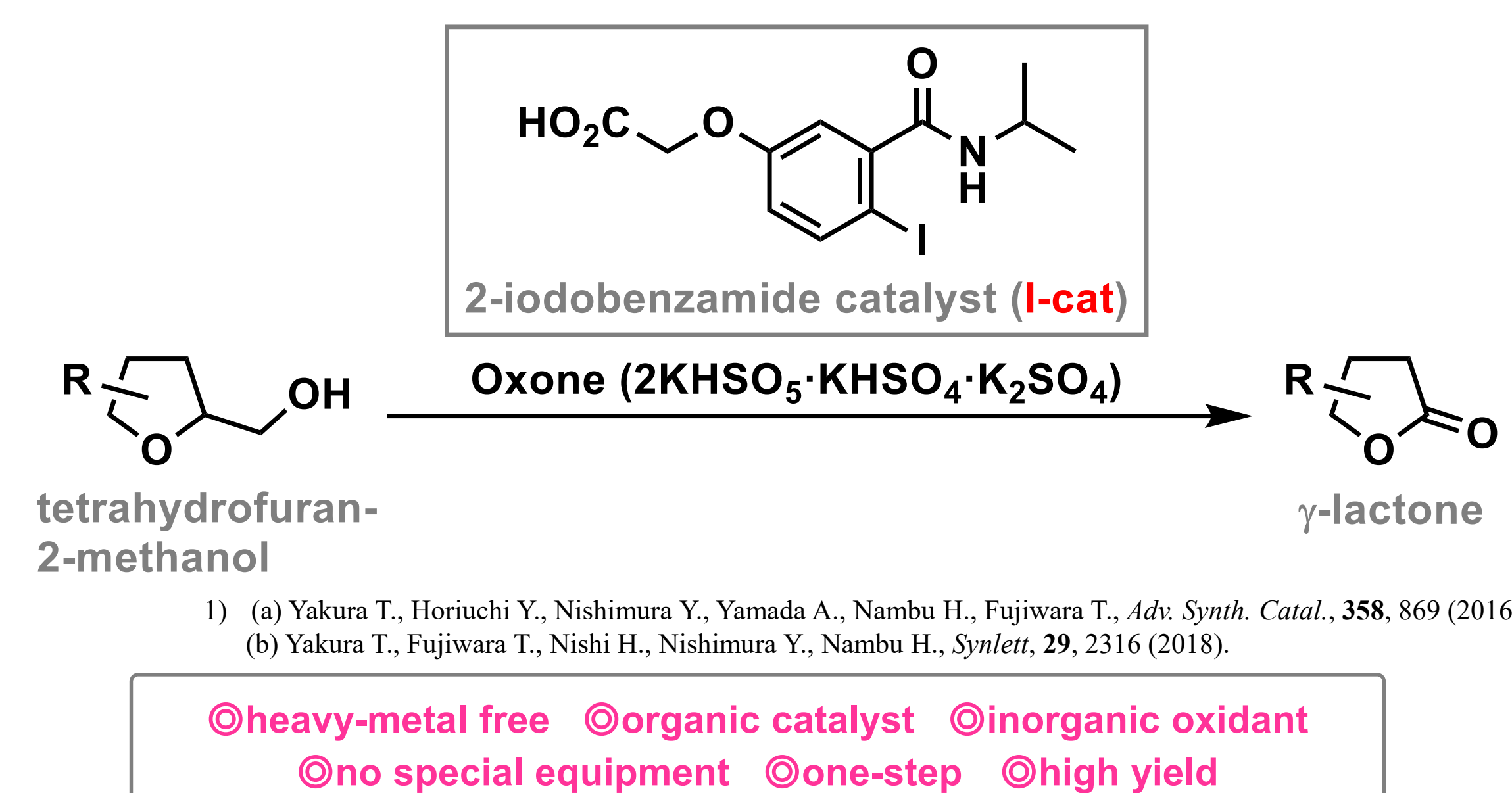


## General synthetic method for $\gamma$ -lactams<sup>1)</sup>



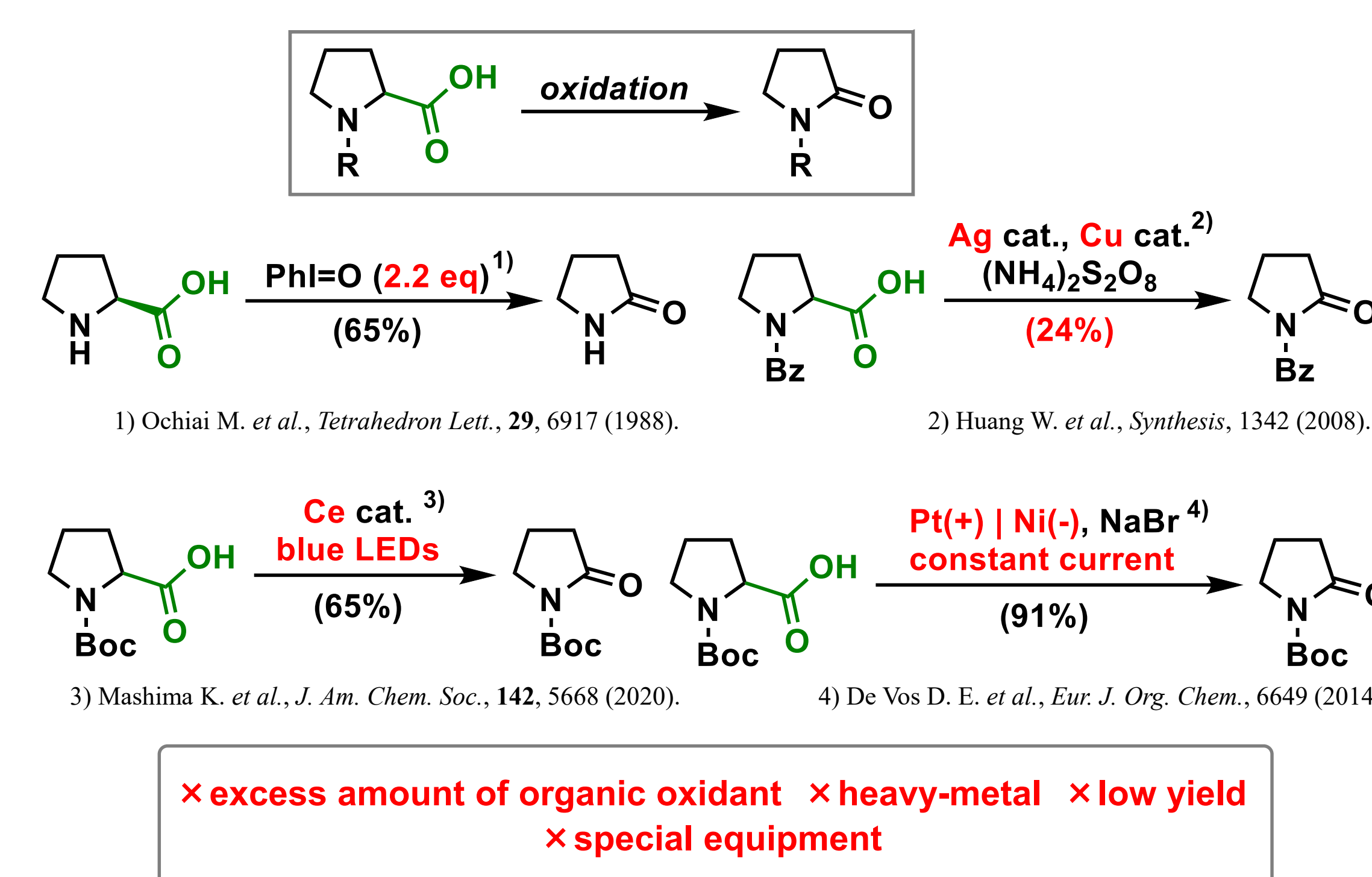
Oxidation of pyrrolidine-2-carboxylic acid and 2-methanol is useful method for the synthesis of optically active  $\gamma$ -lactams because the raw materials are readily available, new chiral carbons can be selectively constructed.

## Oxidative cleavage reaction of tetrahydrofuran-2-methanols to $\gamma$ -lactones using 2-iodobenzamide catalyst (**I-cat**)<sup>1)</sup>



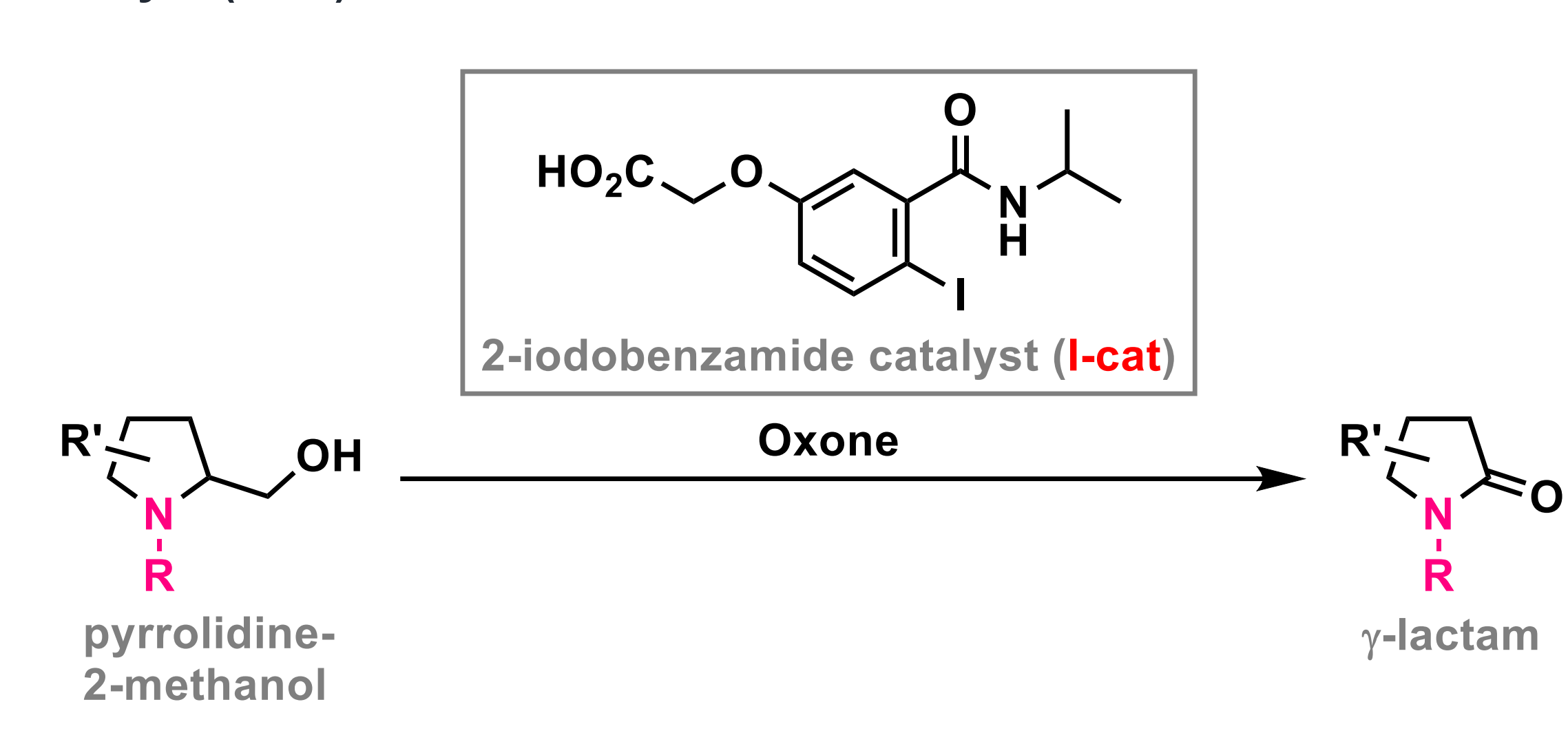
We recently developed the oxidative cleavage reaction of tetrahydrofuran-2-methanol to  $\gamma$ -lactone using highly active and easily separable 2-iodobenzamide catalyst and inorganic oxidant oxone.

## Examples of oxidation of pyrrolidine-2-carboxylic acids to $\gamma$ -lactams

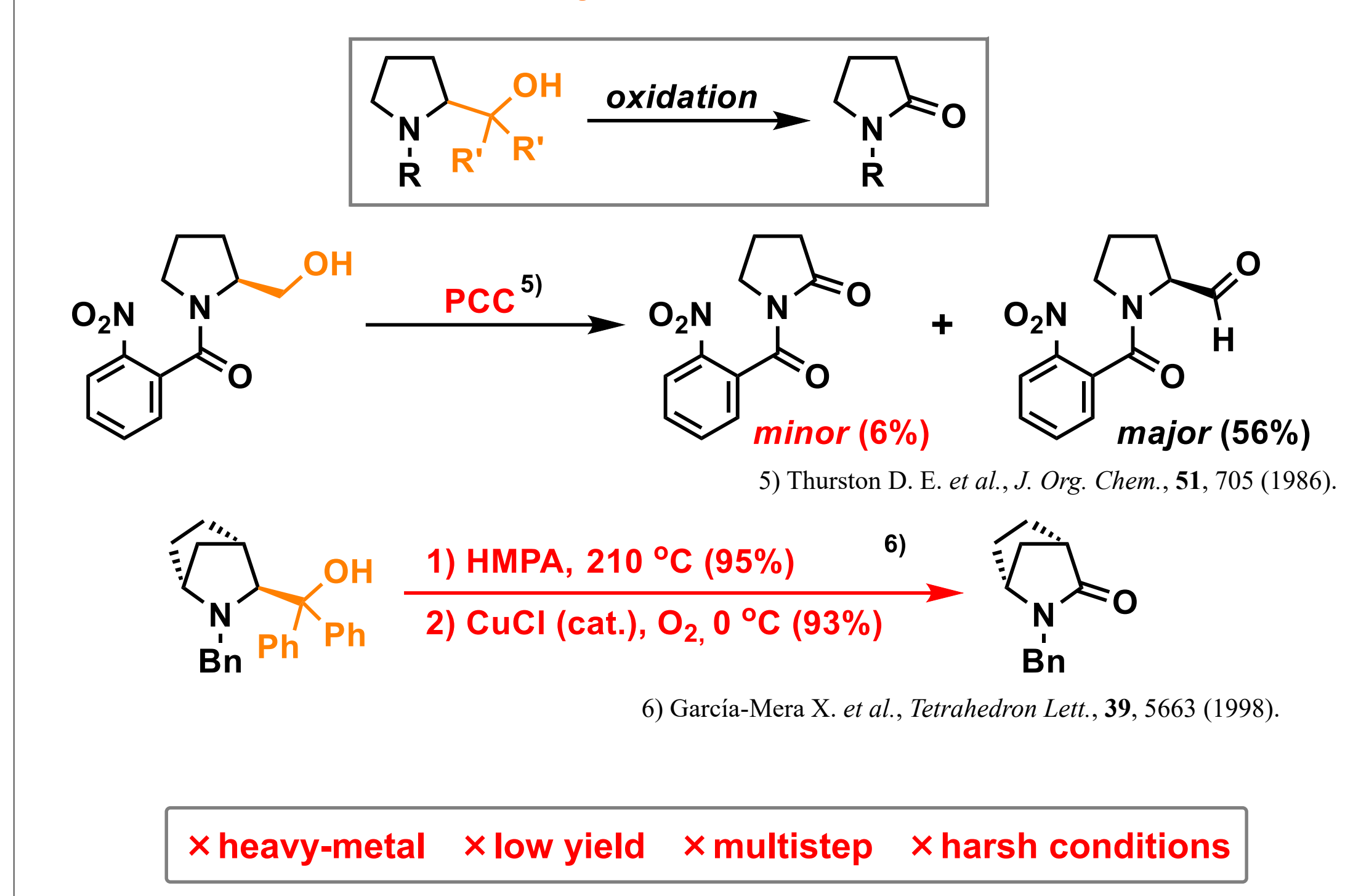


Synthesis of  $\gamma$ -lactams by decarboxylation of pyrrolidine-2-carboxylic acids have some problems such as usage of organic reactants and heavy metals, low yields, special reaction conditions.

## Present study: Development of oxidative cleavage reaction of pyrrolidine-2-methanols to $\gamma$ -lactams using 2-iodobenzamide catalyst (**I-cat**)

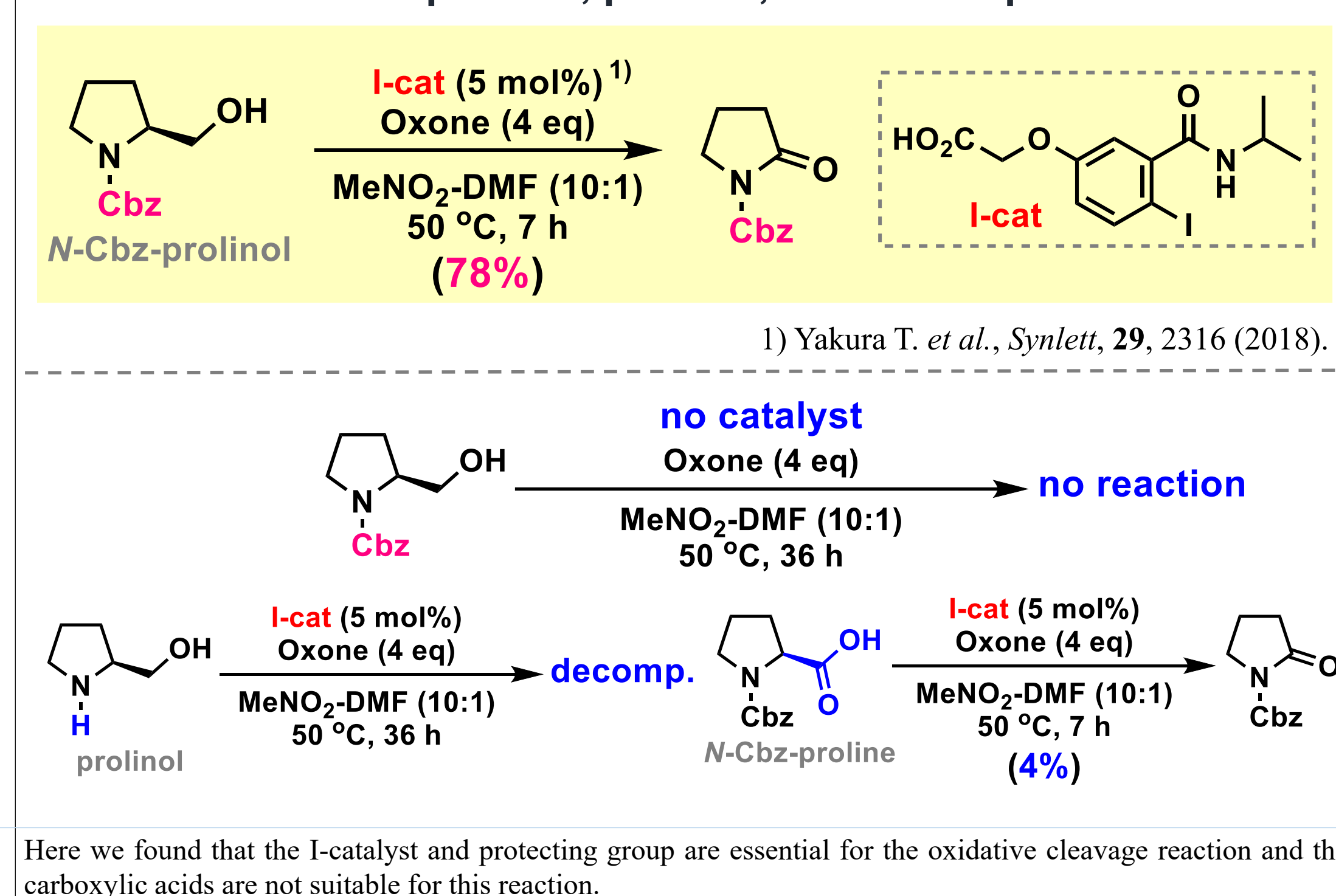


## Examples of oxidation of pyrrolidine-2-methanols to $\gamma$ -lactams

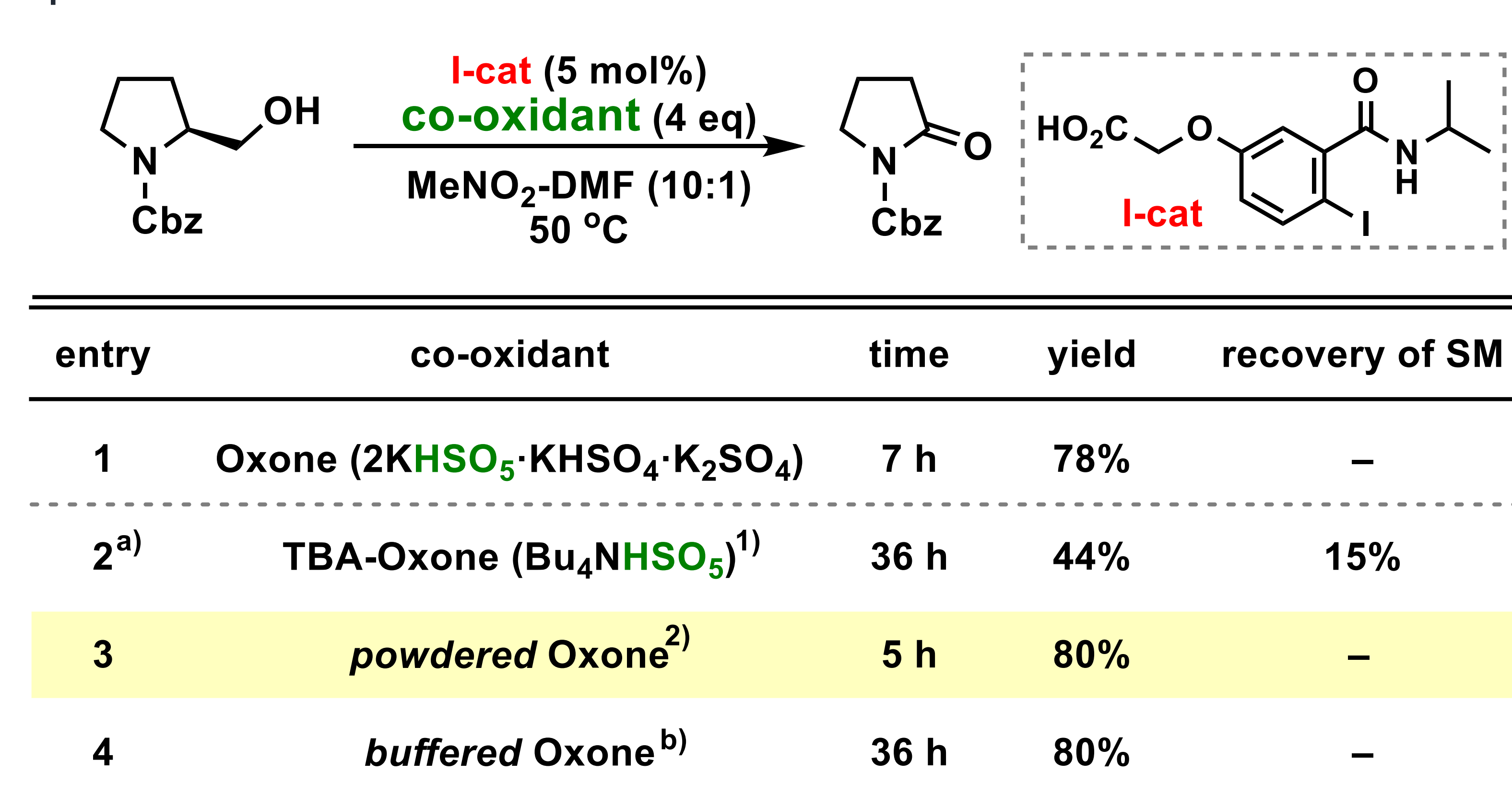


The oxidation of pyrrolidine-2-methanol to  $\gamma$ -lactam is shown here. But the required lactam was obtained by using heavy metals or harsh conditions. Therefore it is desirable to develop a method that does not have these problems.

## Oxidation of *N*-Cbz-prolinol, prolinol, and *N*-Cbz-proline



## Optimization of reaction conditions: effect of co-oxidant



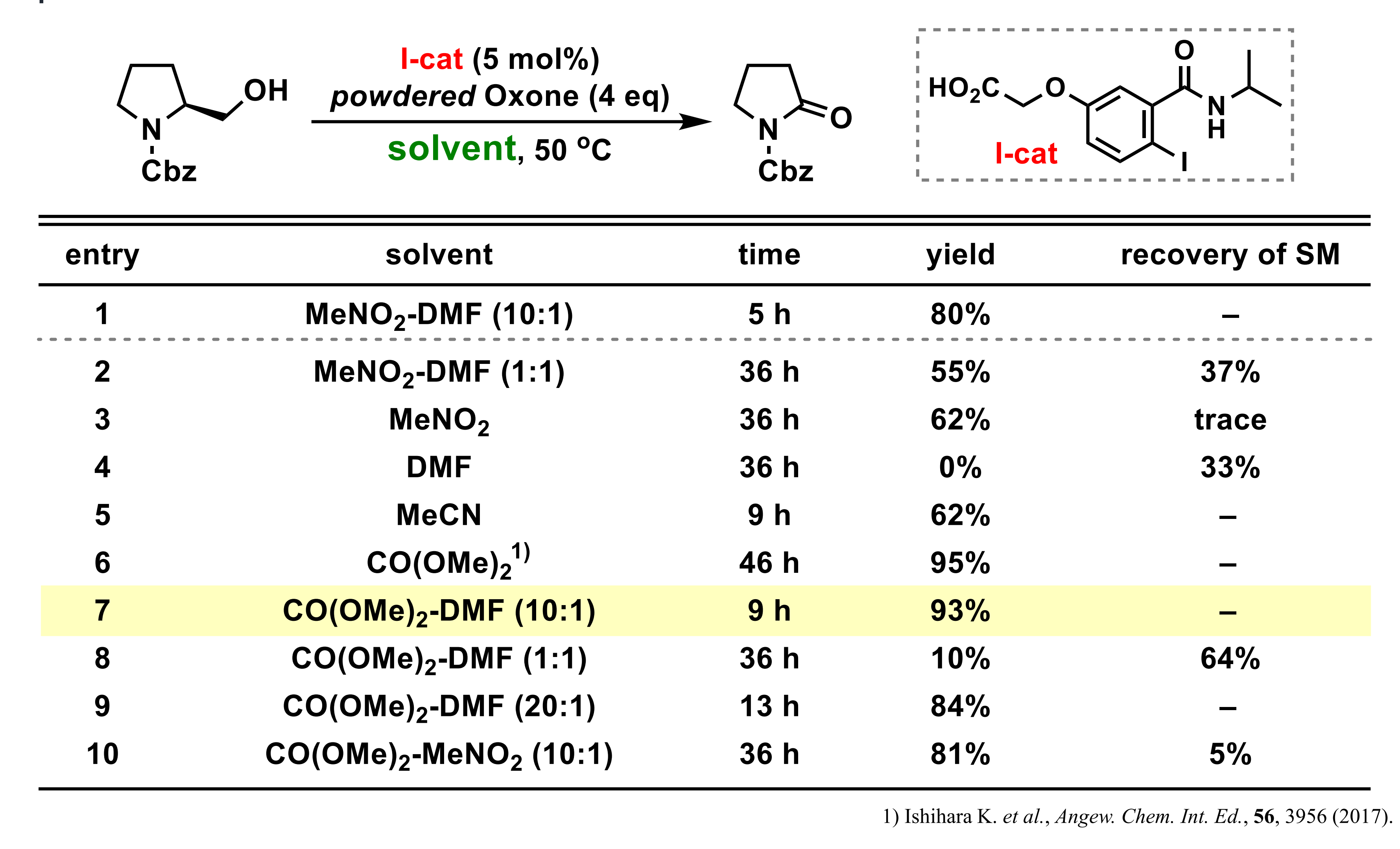
a) 1 eq of KHSO<sub>4</sub> was added as an acid after stirring for 5 h.

b) buffered Oxone<sup>3)</sup>: a 2:1 mixture of powdered Oxone and K<sub>2</sub>CO<sub>3</sub>

- 1) Trost B. M. *et al.*, *J. Org. Chem.*, **53**, 532 (1988).  
2) Ishihara K. *et al.*, *J. Am. Chem. Soc.*, **131**, 251 (2009).  
3) Ishihara K. *et al.*, *Angew. Chem. Int. Ed.*, **56**, 3956 (2017).

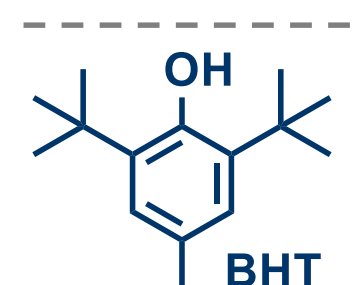
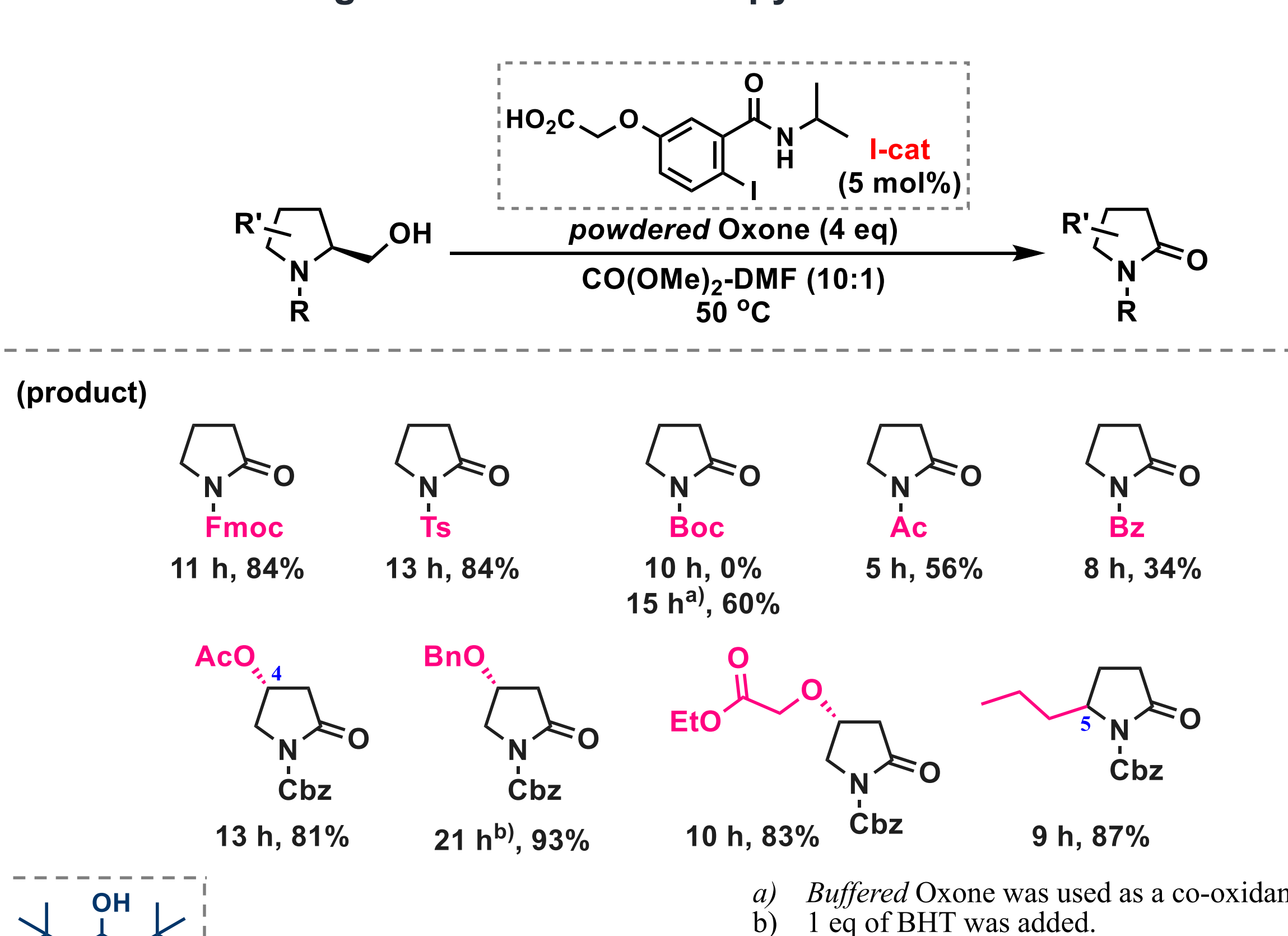
We explored the reaction conditions using Cbz-prolinol. The investigation of effect of co-oxidant using Cbz-prolinol indicates that acid is necessary to proceed the reaction and powdered oxone is the best co-oxidant.

## Optimization of reaction conditions: effect of solvent



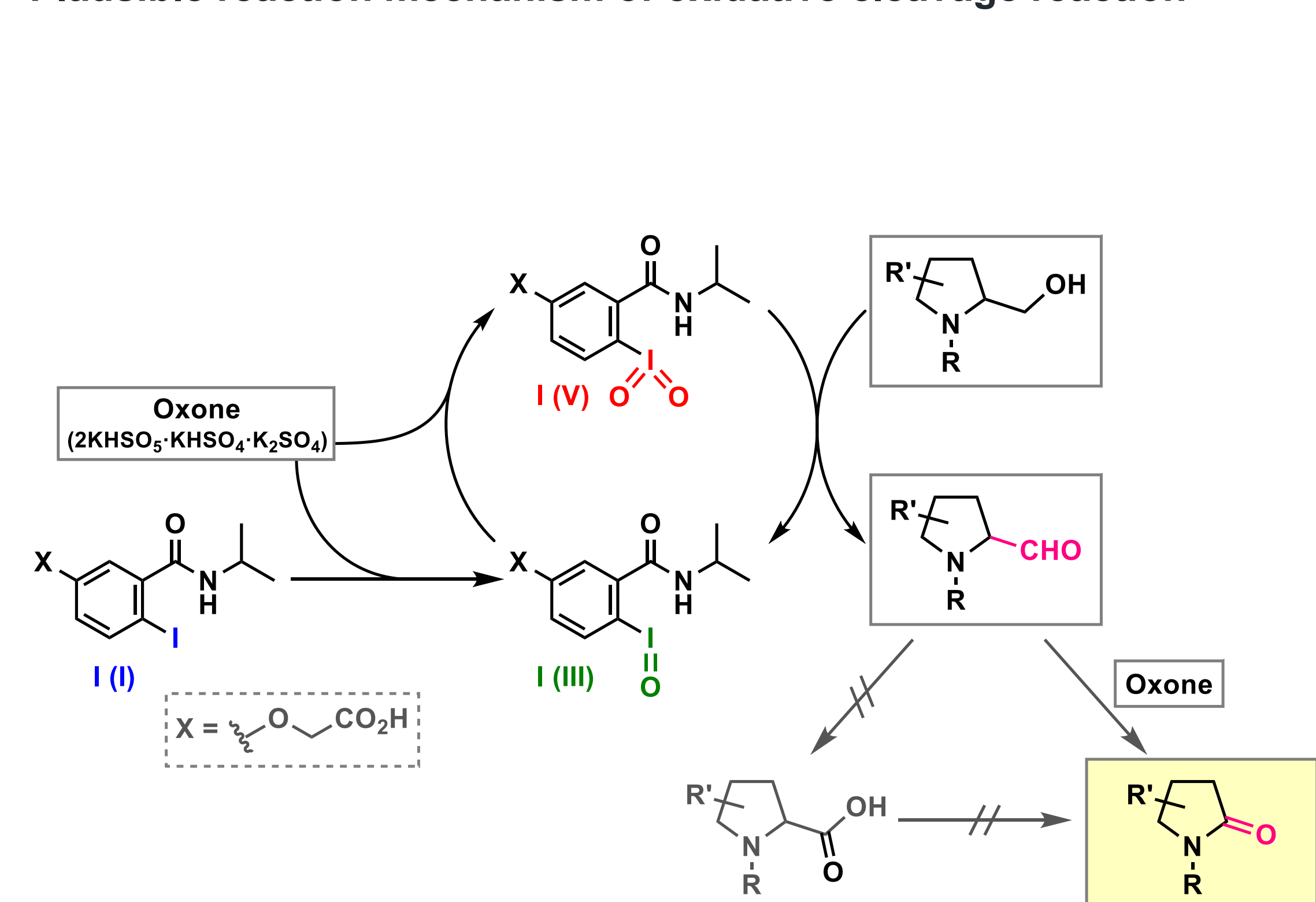
The effect of solvent on the reaction were investigated using powdered oxone and found that the 5 mol% catalyst and 4 equivalents of powdered oxone in a 10:1 mixture of dimethyl carbonate-DMF at 50 °C were the optimal conditions for the reaction.

## Oxidative cleavage reaction of various pyrrolidine-2-methanols



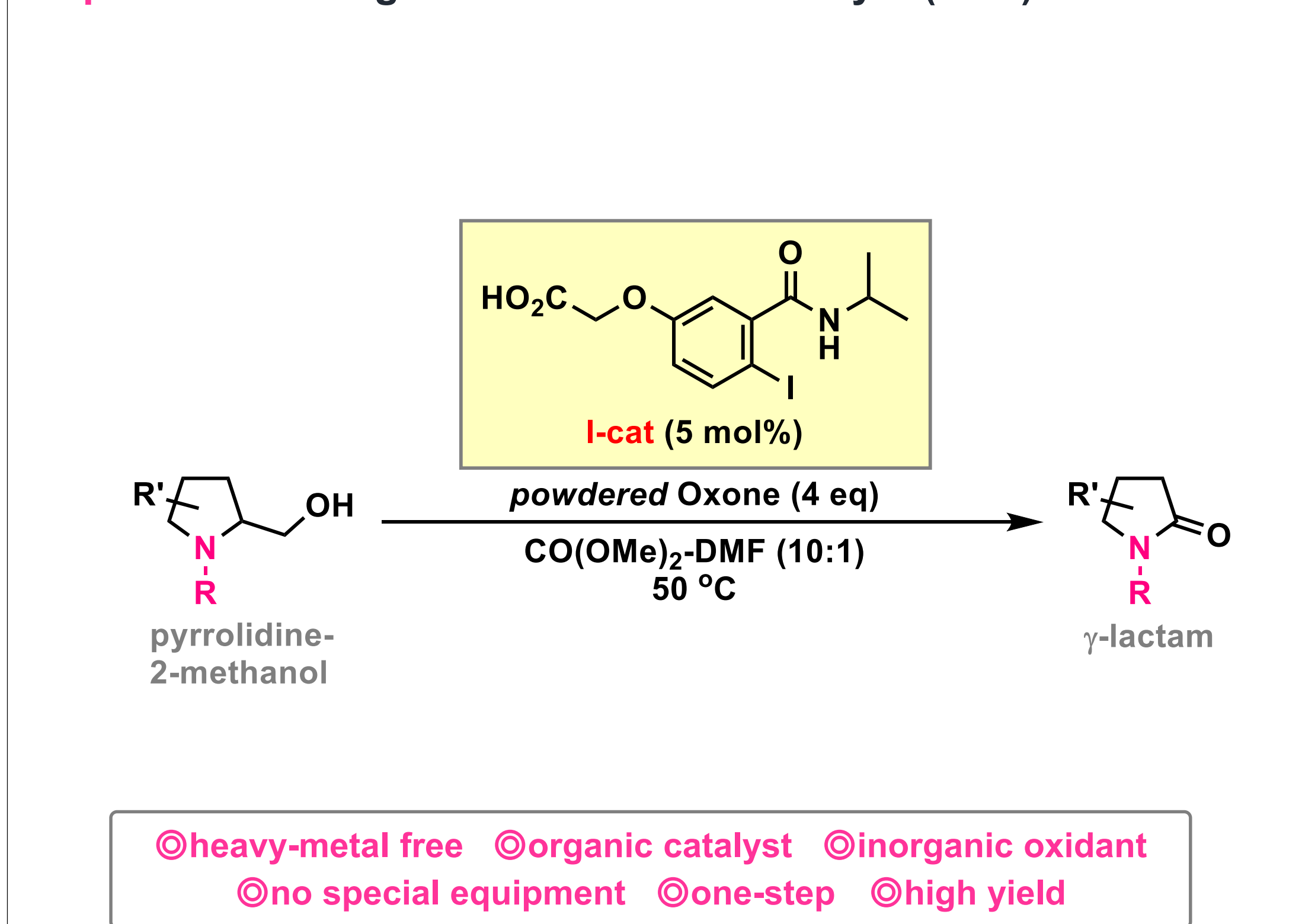
Oxidative cleavage of a variety of pyrrolidine-2-methanols using the optimal conditions were examined. These results indicate that carbamate protecting groups and sulfonyl protecting groups are suitable for these reactions. Furthermore, lactams were obtained in high yields from the reaction of substrates with substituents at the 4 and 5 positions on the pyrrolidine ring. However, for substrates with benzyloxy groups, the addition of BHT was necessary to prevent the oxidation at the benzylic position.

## Plausible reaction mechanism of oxidative cleavage reaction



Reaction mechanism: Oxone oxidizes monovalent iodobenzamide to pentavalent iodine, which in turn oxidizes pyrrolidine-2-methanols to aldehyde which undergoes rapid oxidative cleavage by oxone to lactam. On the other hand, the pentavalent hypervalent iodine that oxidized pyrrolidine-2-methanol was reduced to trivalent and oxidized again to pentavalent by oxone.

## Summary: Oxidative cleavage reaction of pyrrolidine-2-methanols to $\gamma$ -lactams using 2-iodobenzamide catalyst (**I-cat**)



We successfully developed oxidative cleavage reaction of pyrrolidine-2-methanol to  $\gamma$ -lactam using 2-iodobenzamide catalyst. The reaction can be proceeded without the use of any heavy metals and also does not require any special equipment, only by using organocatalysts and inorganic oxidants. Since lactams can be efficiently obtained from various substrates in a single step, it is superior to the oxidative conversion reactions developed so far.