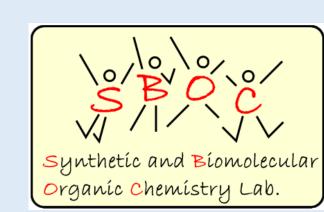
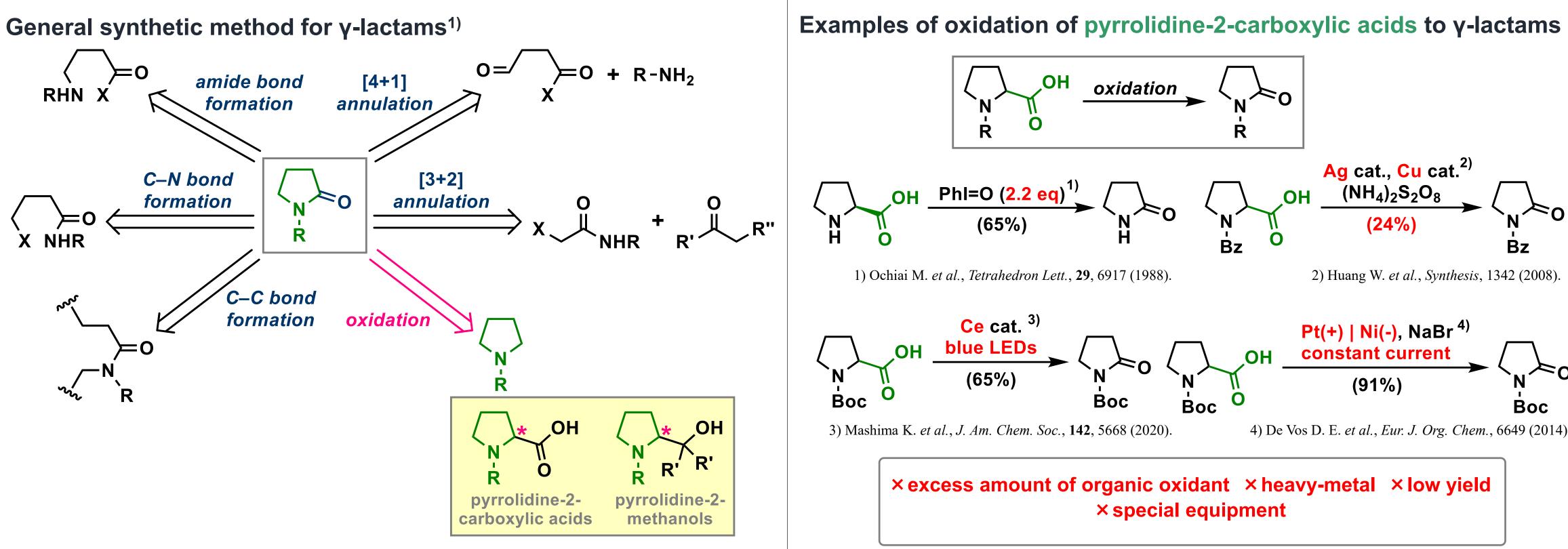
## Synthesis of y-lactams by oxidative cleavage of pyrrolidine-2methanols using 2-iodobenzamide catalyst

Faculty of Pharmaceutical Sciences, University of Toyama





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



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.

1) Robiette R. et al., Org. Biomol. Chem., 14, 10134 (2016)

Ag cat., Cu cat.<sup>2</sup> Pt(+) | Ni(-), NaBr 4 × excess amount of organic oxidant × heavy-metal × low yield

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.

× special equipment

Examples of oxidation of pyrrolidine-2-methanols to γ-lactams × heavy-metal × low yield × multistep × harsh conditions

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

Oxidative cleavage reaction of tetrahydrofuran-2-methanols to γ-lactones using 2-iodobenzamide catalyst (I-cat)<sup>1)</sup>

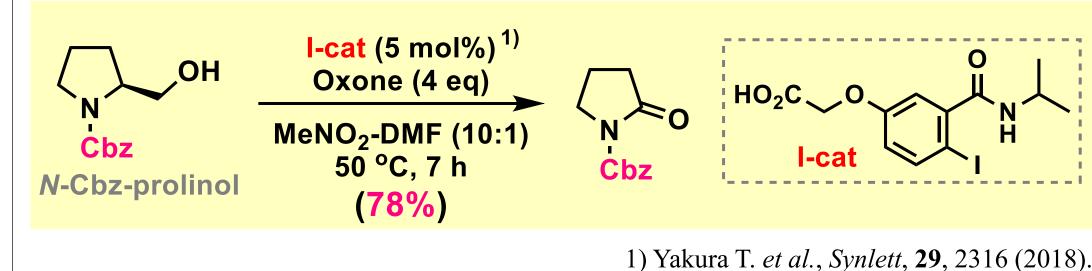
**Oheavy-metal free Oorganic catalyst Oinorganic oxidant** Ono special equipment Oone-step Ohigh yield

We recently developed the oxidative cleavage reaction of tetrahydrofuran-2-methanol to  $\gamma$ -lactone using highly active

Present study: Development of oxidative cleavage reaction of pyrrolidine-2-methanols to γ-lactams using 2-iodobenzamide catalyst (I-cat)

We believe that the application of this reaction to pyrrolidine-2- methanol will result in the formation of  $\gamma$ -lactams.

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

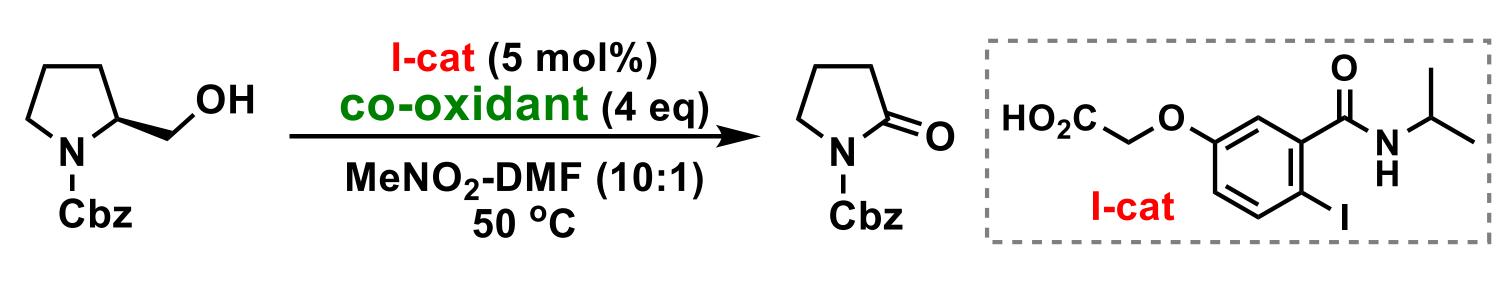


no catalyst Oxone (4 eq) no reaction MeNO<sub>2</sub>-DMF (10:1) 50 °C, 36 h **I-cat** (5 mol%) Oxone (4 eq) Oxone (4 eq) MeNO<sub>2</sub>-DMF (10:1) MeNO<sub>2</sub>-DMF (10:1)

Here we found that the I-catalyst and protecting group are essential for the oxidative cleavage reaction and the carboxylic acids are not suitable for this reaction.

Optimization of reaction conditions: effect of co-oxidant

and easily separable 2-iodobenzamide catalyst and inorganic oxidant oxone.



entry	co-oxidant	time	yield	recovery of SM
1	Oxone (2KHSO <sub>5</sub> ·KHSO <sub>4</sub> ·K <sub>2</sub> SO <sub>4</sub> )	7 h	78%	
2 <sup>a)</sup>	TBA-Oxone (Bu <sub>4</sub> NHSO <sub>5</sub> ) <sup>1)</sup>	36 h	44%	15%
3	powdered Oxone <sup>2)</sup>	5 h	80%	
4	buffered Oxone b)	36 h	80%	

a) 1 eq of KHSO₄ 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.

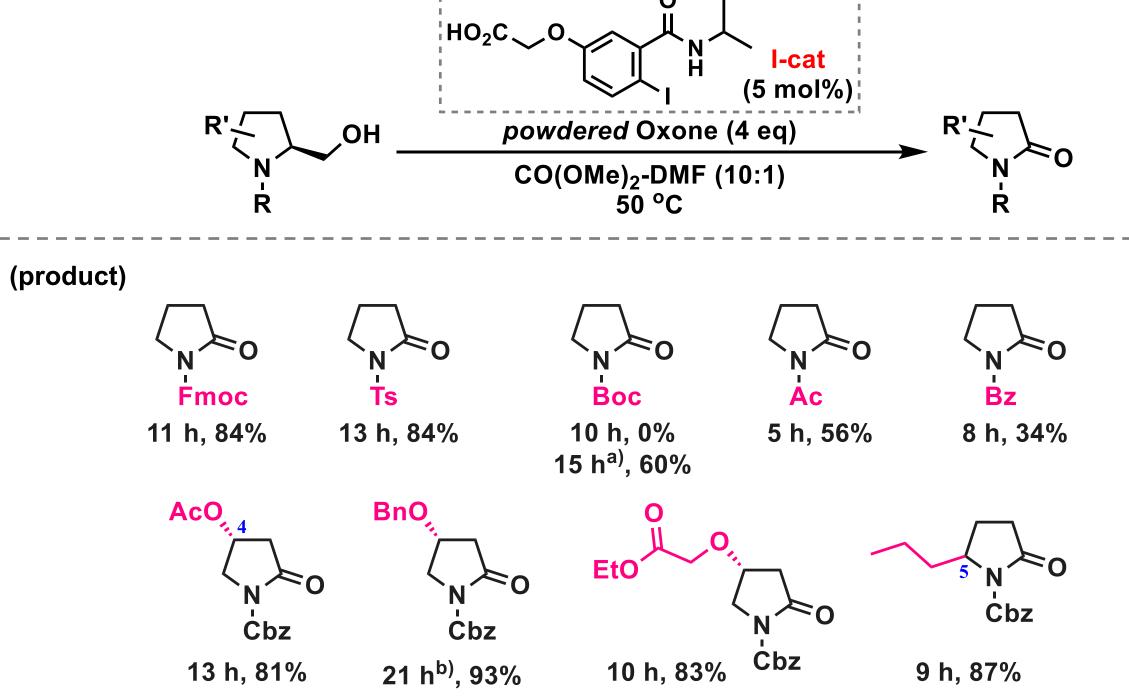
Optimization of reaction conditions: effect of solvent

entry	solvent	time	yield	recovery of SM
1	MeNO <sub>2</sub> -DMF (10:1)	5 h	80%	_
2	MeNO <sub>2</sub> -DMF (1:1)	36 h	55%	37%
3	MeNO <sub>2</sub>	36 h	62%	trace
4	DMF	36 h	0%	33%
5	MeCN	9 h	62%	_
6	CO(OMe) <sub>2</sub> <sup>1)</sup>	46 h	95%	_
7	CO(OMe) <sub>2</sub> -DMF (10:1)	9 h	93%	_
8	CO(OMe) <sub>2</sub> -DMF (1:1)	36 h	10%	64%
9	CO(OMe) <sub>2</sub> -DMF (20:1)	13 h	84%	_
10	$CO(OMe)_2$ -MeNO <sub>2</sub> (10:1)	36 h	81%	5%

1) Ishihara K. et al., Angew. Chem. Int. Ed., **56**, 3956 (2017).

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



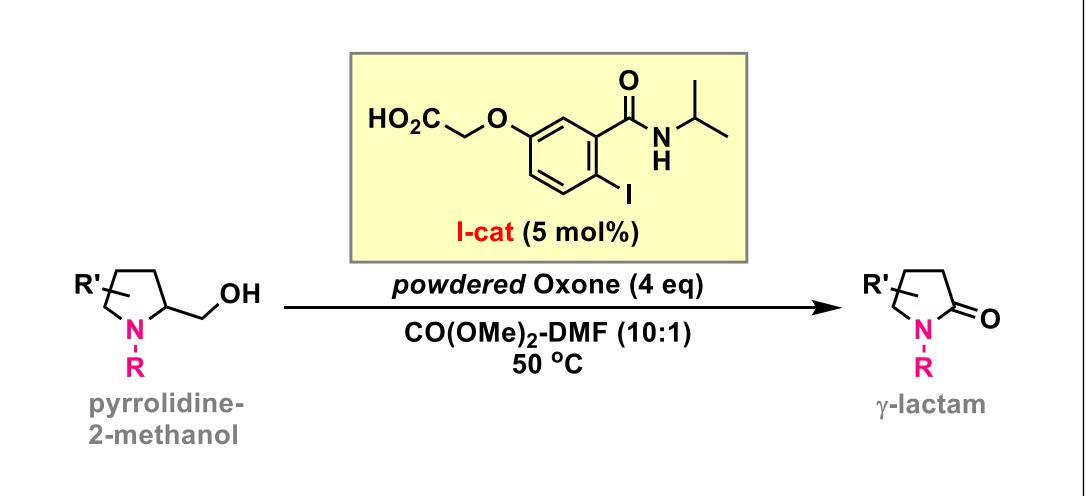
Buffered Oxone was used as a co-oxidant. b) 1 eq of BHT was added.

Oxone (2KHSO<sub>5</sub>·KHSO<sub>4</sub>·K<sub>2</sub>SO<sub>4</sub>) Oxone  $X = 2 O CO_2H$ 

Plausible reaction mechanism of oxidative cleavage reaction

Oxidative cleavage of a variety of pyrrolidine-2-methanols using the optimal conditions were examined. These results | 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

Summary: Oxidative cleavage reaction of pyrrolidine-2-methanols to y-lactams using 2-iodobenzamide catalyst (I-cat)



**Oheavy-metal free Oorganic catalyst Oinorganic oxidant** Ono special equipment Oone-step Ohigh yield

We successfully developed oxidative cleavage reaction of pyrrolidine-2-methanol to γ-lactam using 2iodobenzamide 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.

indicate that carbamate protecting groups and sulfonyl protecting groups are suitable for this 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 again to pentavalent by oxone. oxidation at the benzylic position.