

# Organocatalyzed Enantioselective Synthesis of Chiral Heterocyclic Compounds using Domino Cycloaddition/Rearrangement

**XVIII J-NOST Oral Presentation**



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**Research supervisor : Prof. G. Sekar**

**12-10-2023**

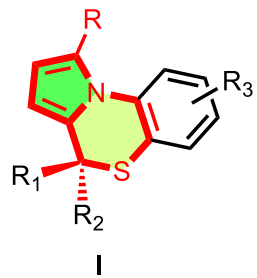
**Department of Chemistry**

**Indian Institute of Technology Madras**

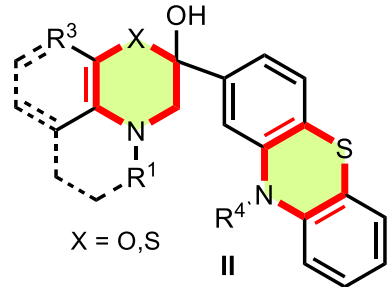


# Introduction

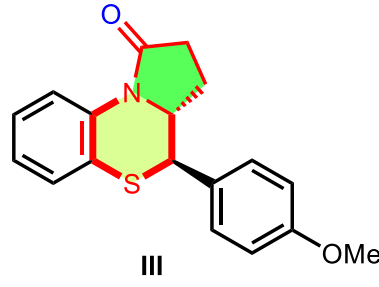
## Importance of pyrrolo-thiazines and dihydropyrroles



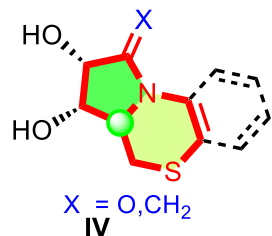
I  
Ca entry blockers inhibitors



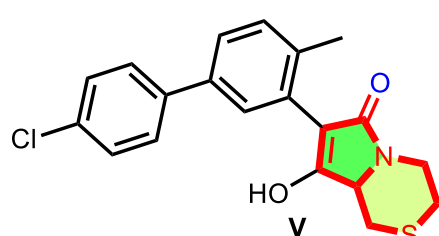
II  
X = O, S  
Antioxidant, anti-inflammatory, (SQS) inhibitory/hypolipidemic activities



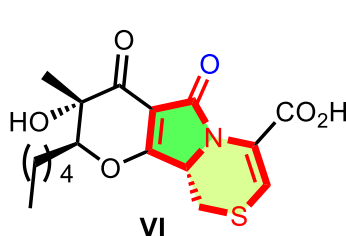
III  
selective myocardial calcium channel modulators



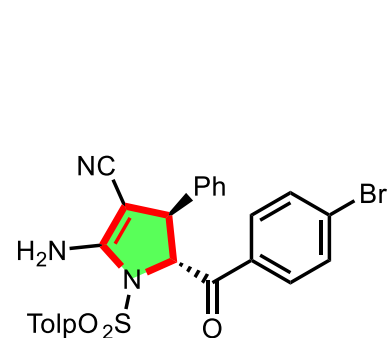
IV  
X = O, CH<sub>2</sub>  
Inhibition of  $\beta$ -Ribosidases



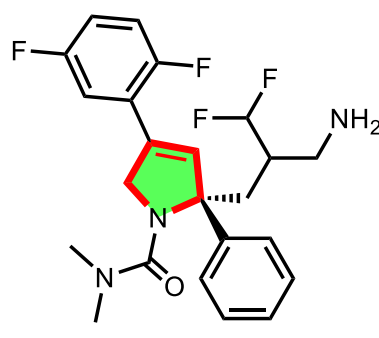
V  
Anti-tumor disorders



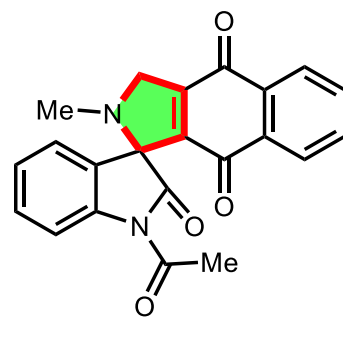
VI  
Naturel STAT<sub>3</sub> inhibitor



VII  
Antiproliferative



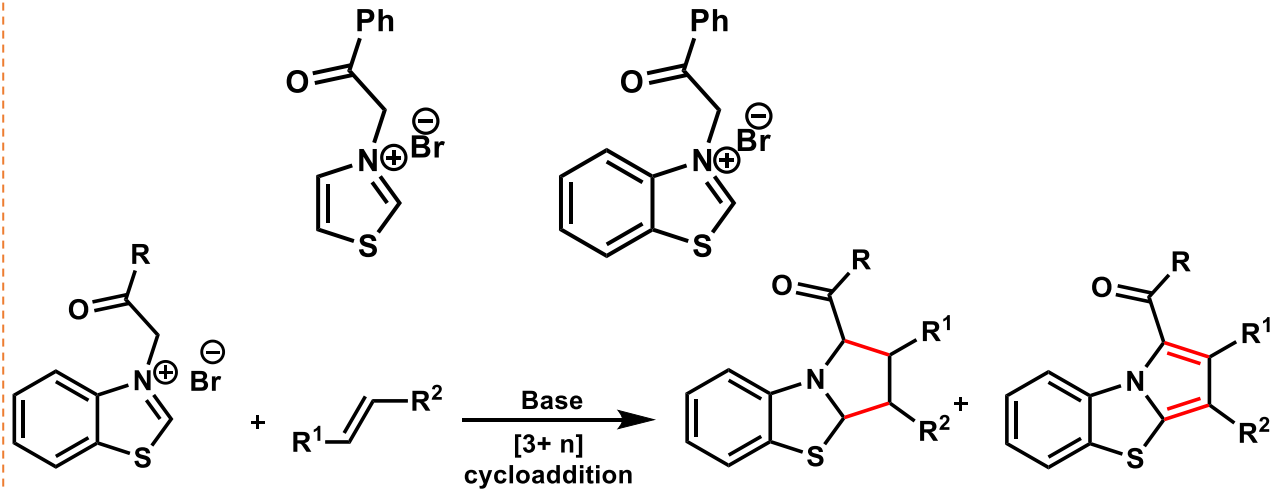
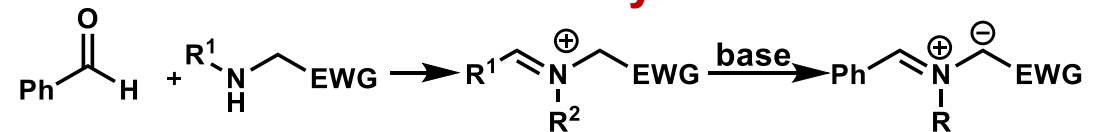
VIII  
Kinesin spindle protine inhibitory effects



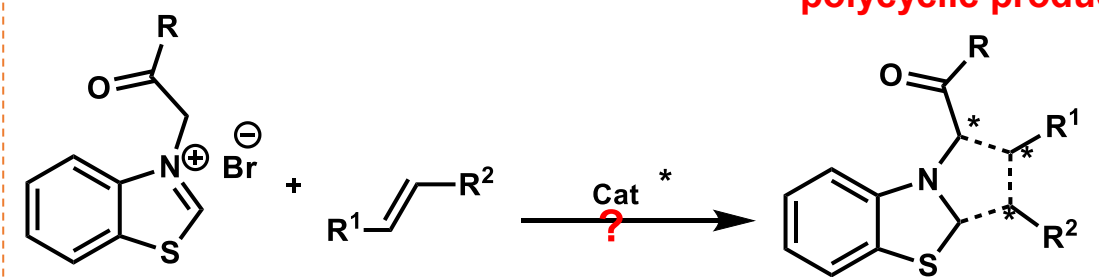
IX  
Antifungal activity

A. Daich et al. *Chem. Eur. J.* **2019**, *25*, 6113 - 6118

## Azomethine ylide



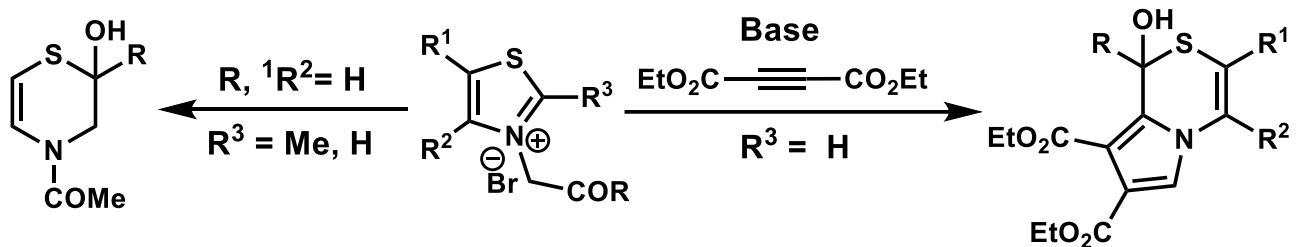
## Rearranged achiral and polycyclic product



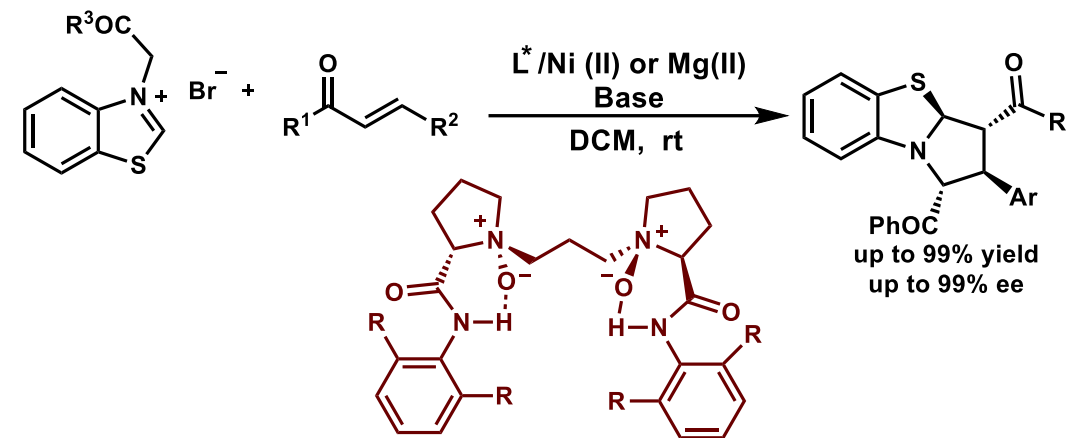
## Challenges:

Control the reactivity, regio, enantio-and diastereoselectivity

# Previous literature reports

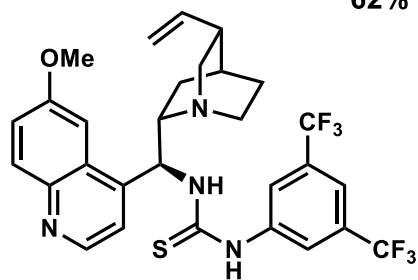
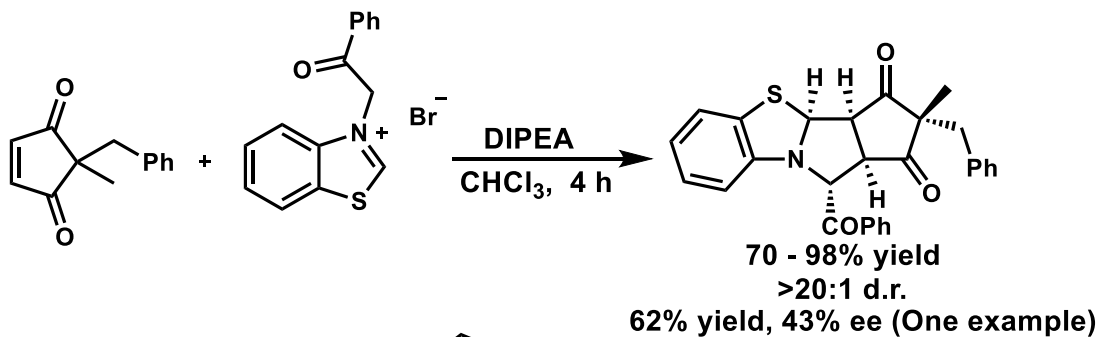


T. Kataoka et al. *J. Chem. Soc. Perkin Trans.1.* **1996**, 629 - 635

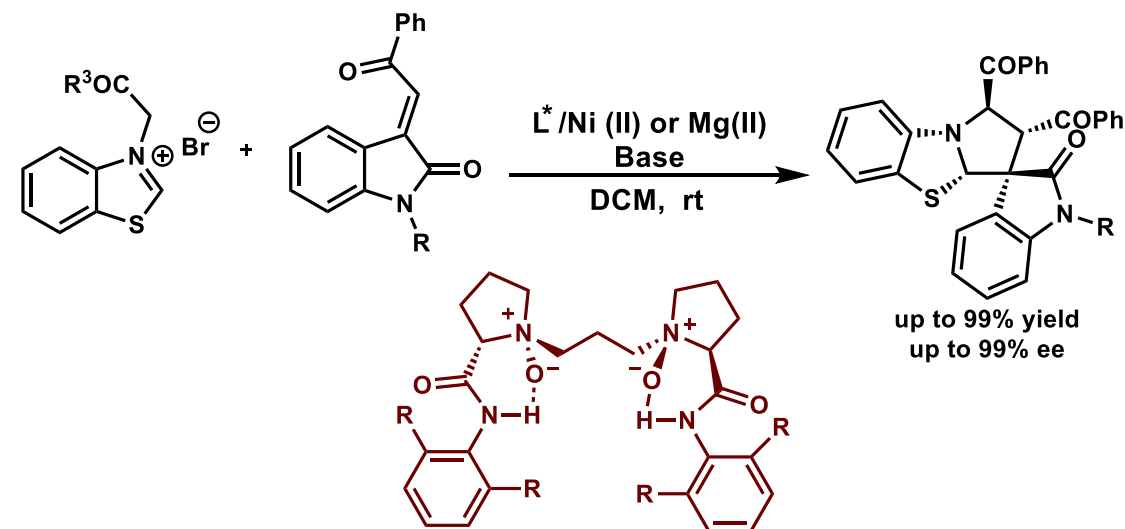


Chiral *N,N*-dioxide ligand

X. Feng et al. *Org. Chem. Front.* **2018**, 5, 2126 - 1231



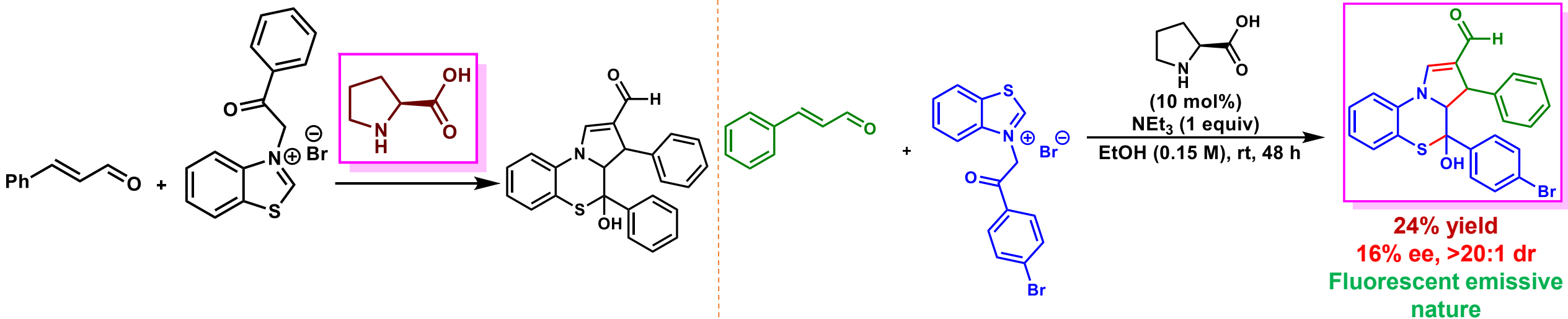
S. C. Pan et al. *J. Org. Chem.* **2017**, 82, 12763 - 12770



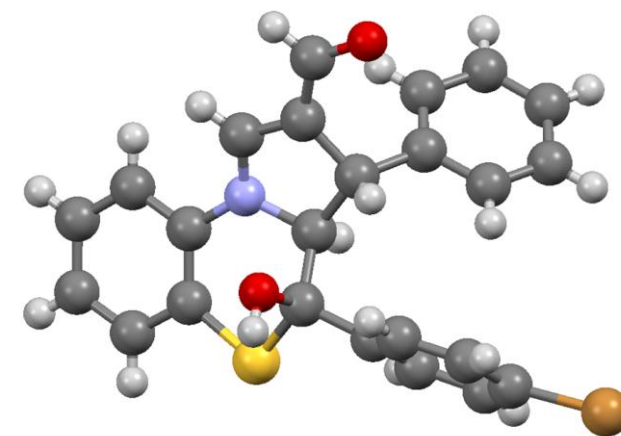
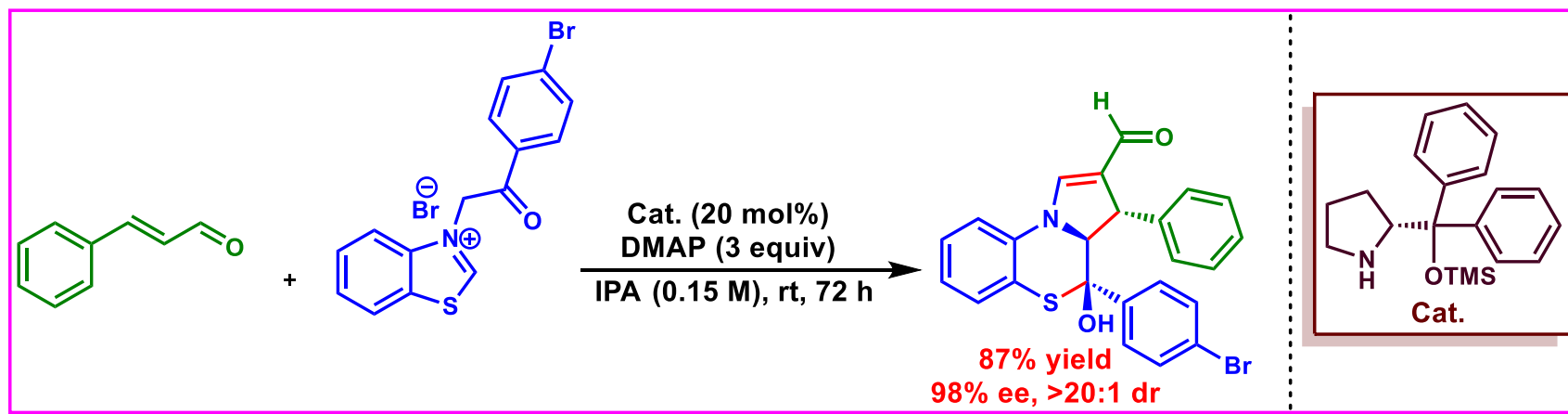
Chiral *N,N*-dioxide ligand

X. Feng et al. *Org. Chem. Front.* **2018**, 5, 2126 - 1231

# Our hypothesis

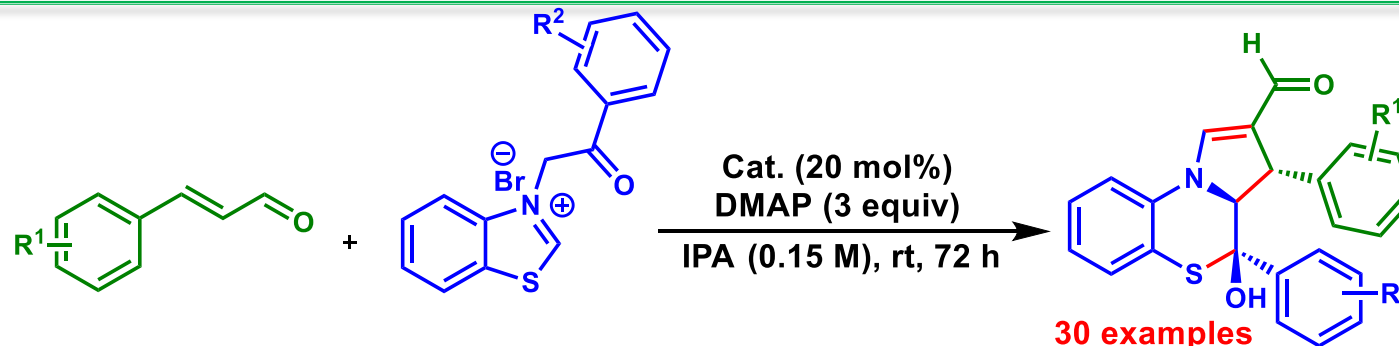


# Optimized condition

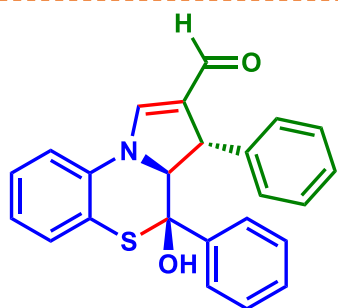
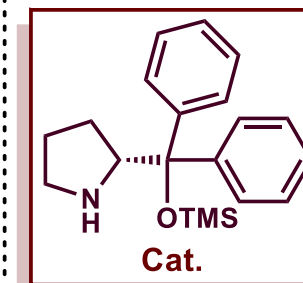


Flack parameter value : 0.001(5)

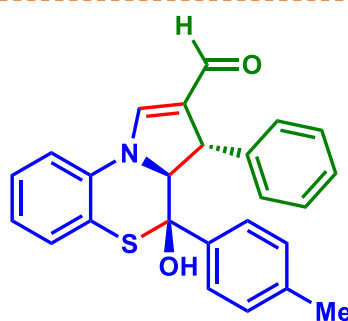
# Substrate Scopes of pyrrolo-thiazine carbaldehydes



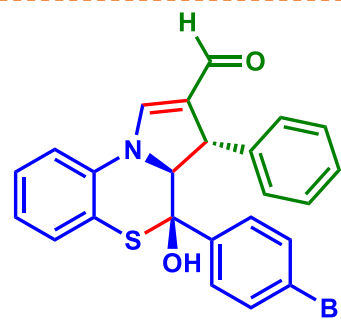
30 examples  
up to 92% yield  
up to 99.9% ee  
>20:1 d.r.



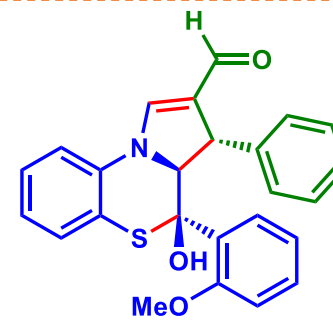
75%, 98% ee  
>20:1 d.r.



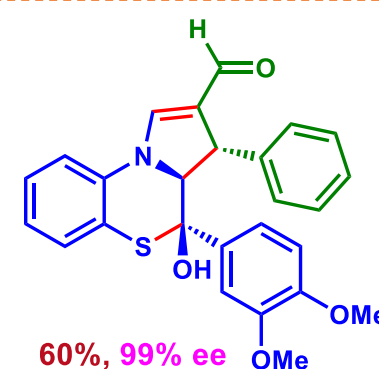
60%, 96% ee  
>20:1 d.r.



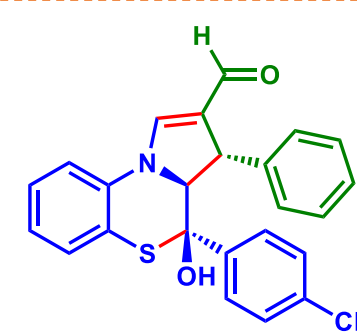
86%, 98% ee  
>19:1 d.r.



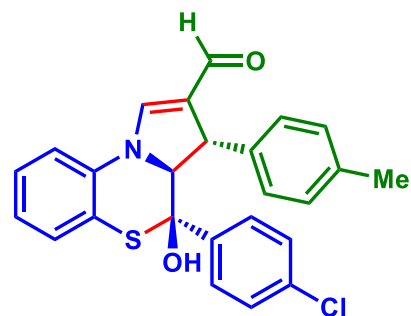
76%, 98% ee  
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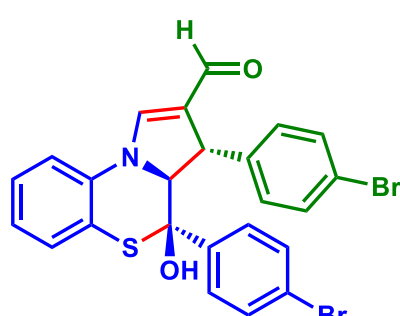
60%, 99% ee  
>20:1 d.r.



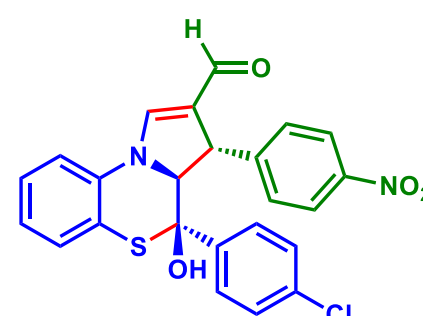
92%, 98% ee  
>20:1 d.r.



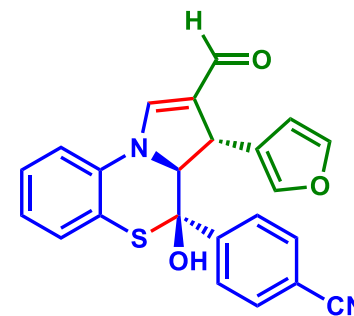
60%, 92% ee  
>20:1 d.r.



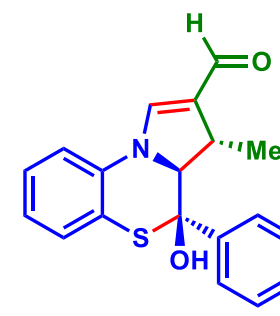
88%, 98% ee  
>20:1 d.r.



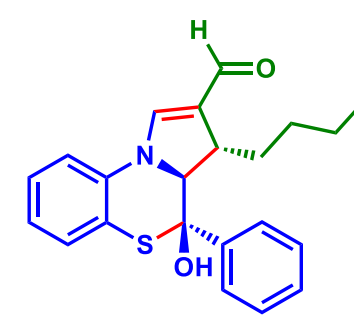
77%, 88% ee  
>20:1 d.r.



92%, 88% ee  
>20:1 d.r.

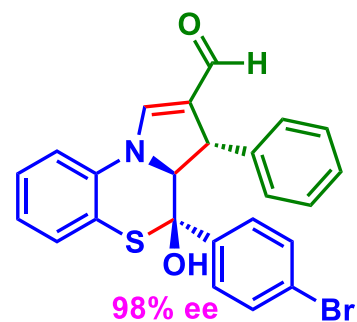


56%, 80% ee  
>20:1 d.r.



45%, 96% ee  
>20:1 d.r.

# Synthesis of dihydropyrrole-3-carbaldehydes

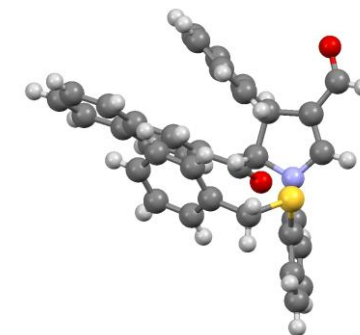
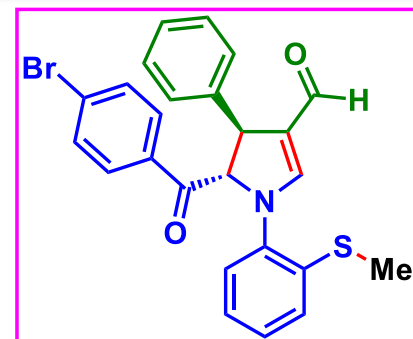


Mel (2 equiv), K<sub>2</sub>CO<sub>3</sub> (2 equiv)

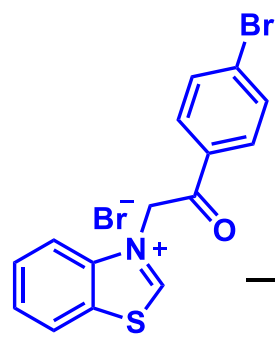
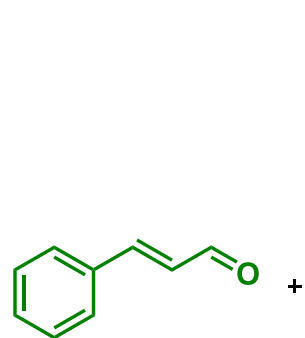
DMF (0.15 M), rt, 1 h

90% yield

96% ee, >20:1 d.r.



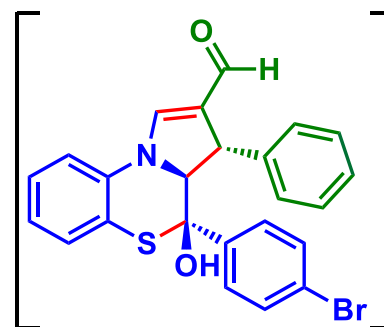
Flack parameter value : - 0.02(3)



Cat. (20 mol%)

DMAP (3 equiv)

IPA (0.15 M), rt, 72 h

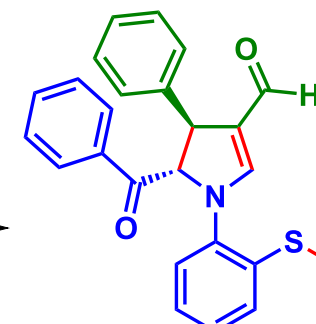


RX (3 equiv)

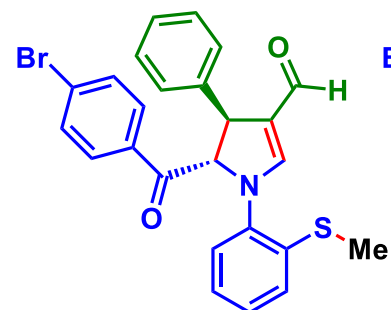
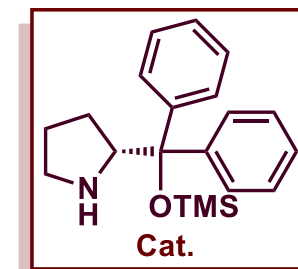
K<sub>2</sub>CO<sub>3</sub> (2 equiv)

DMF (0.15 M)

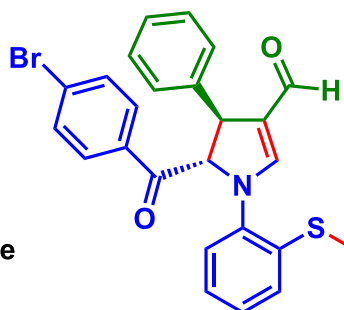
rt, 30 min - 1 h



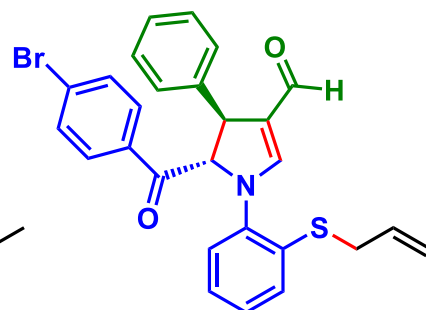
23 examples  
up to 90% yield  
up to 96% ee, >20:1 d.r.



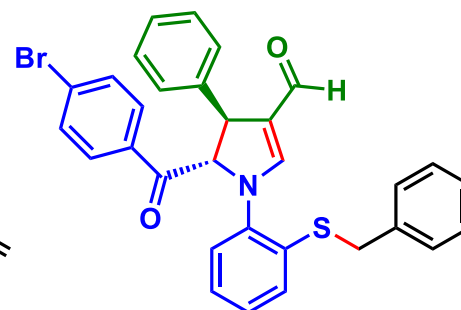
75%, 98% ee  
>20:1 d.r.  
72 h + 30 min



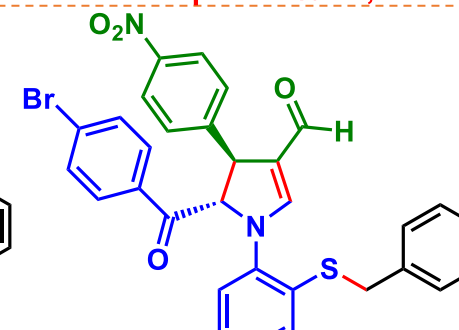
86%, 88% ee  
>20:1 d.r.  
72 h + 30 min



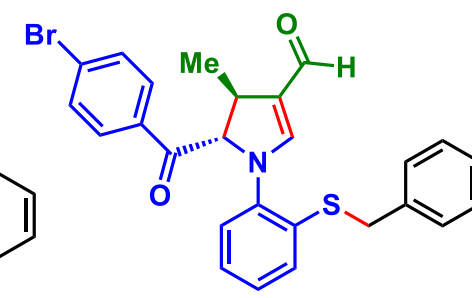
88%, 80% ee  
>20:1 d.r.  
72 h + 1 h



80%, 86% ee  
>20:1 d.r.  
72 h + 30 min

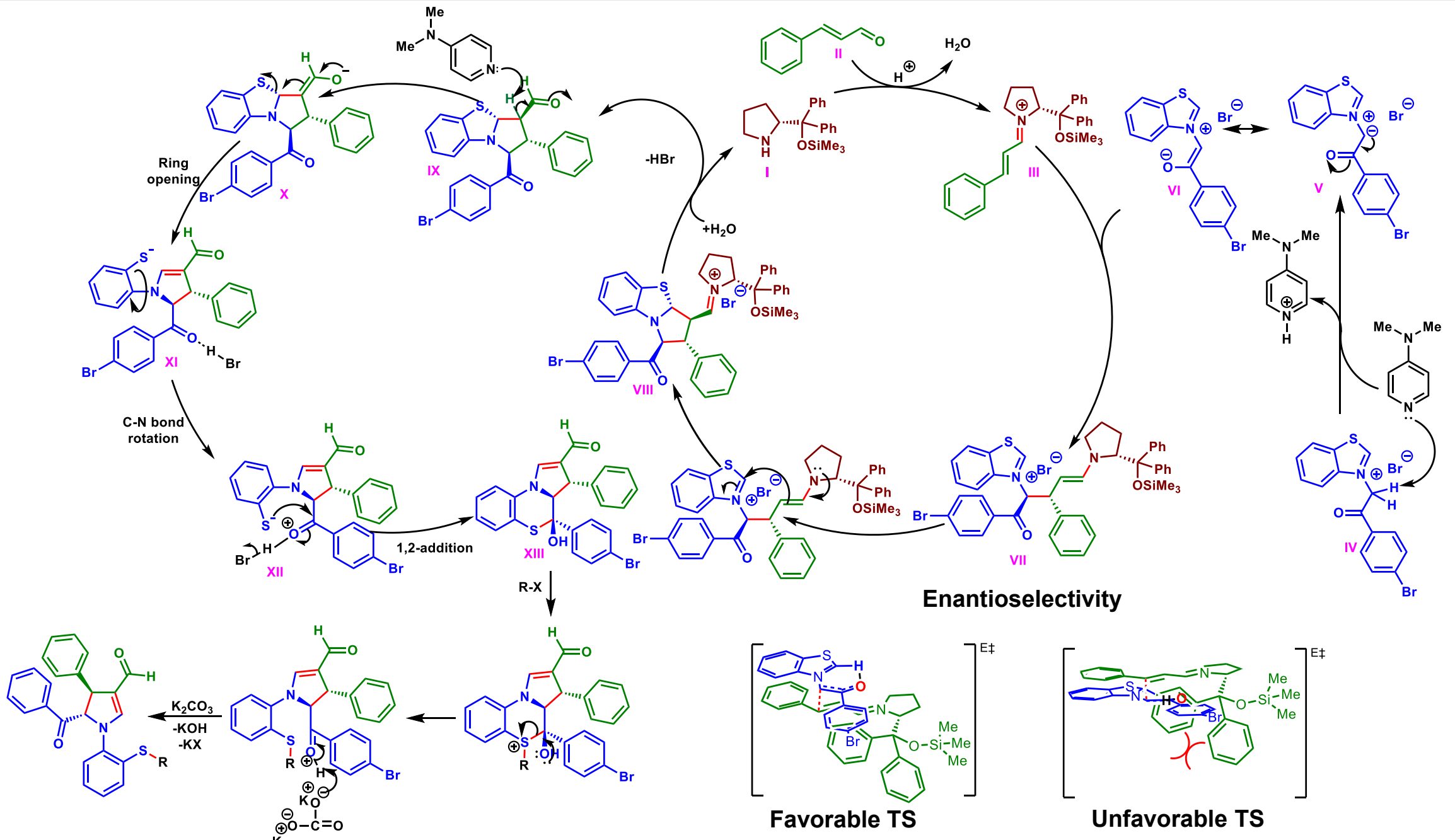


72%, 98% ee  
>20:1 d.r.  
72 h + 1 h

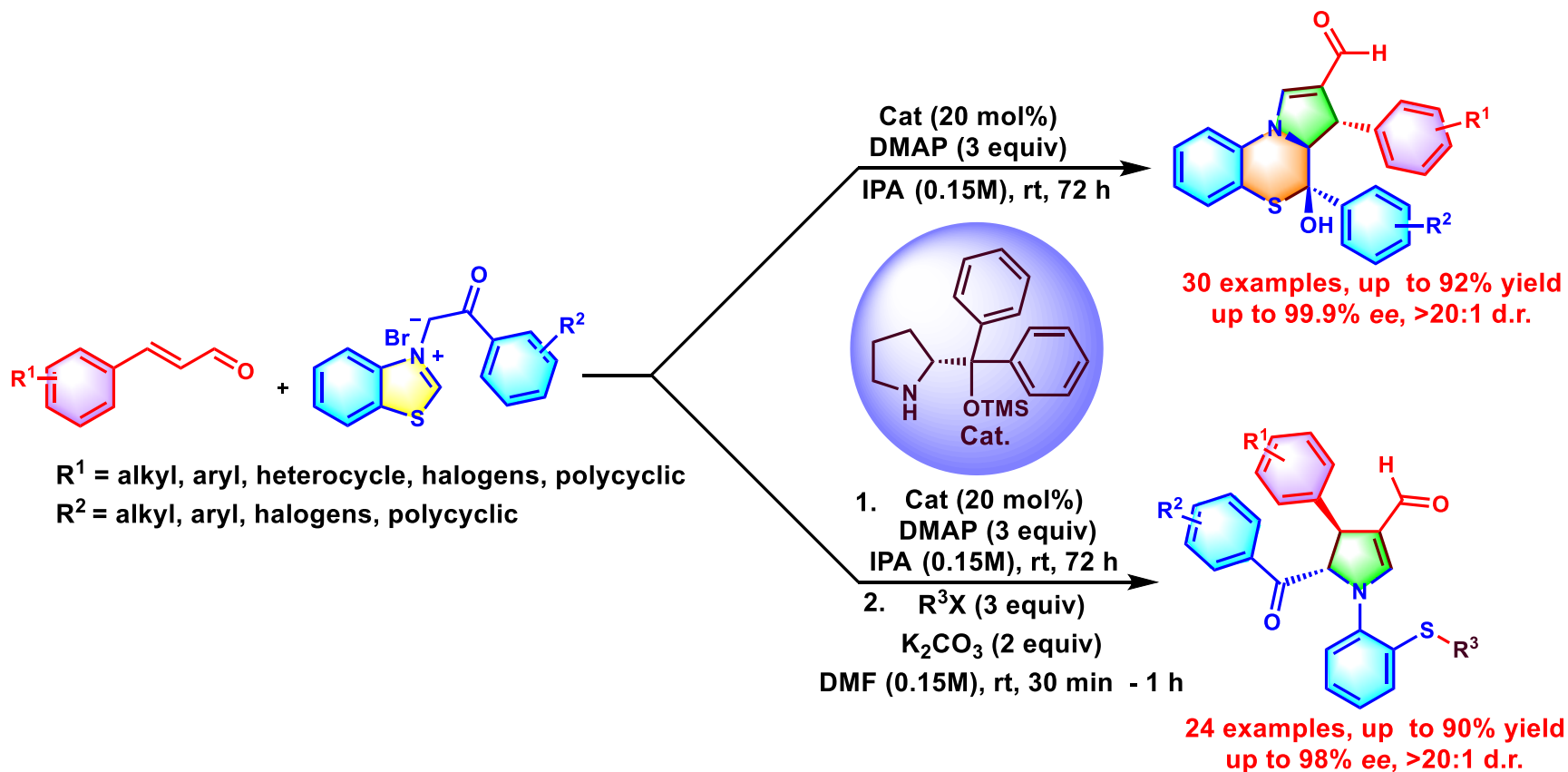


48%, 82% ee  
>20:1 d.r.  
72 h + 30 min

# Plausible mechanism



# Conclusion



- ✓ Transition metal free organocatalyst
- ✓ Domino & one-pot reaction sequence
- ✓ High enantio- and diastereoselectivity
- ✓ Fluorescent emissive chiral molecules
- ✓ DFT and molecular docking studies
- ✓ Anticancer activity

Indian patent application no: **202241065630**  
Patent no: **454952**

“Manuscript under preparation”

