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

CiHS Oral Presentation

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Date: 23-08-2023

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Introduction

Asymmetric synthesis?

✓ Asymmetric synthesis is synthesis of optically active compounds, preferability single enantiomers.

Organocatalyst

✓ No air & moister sensitive

✓ Inexpensive

✓ Nontoxic

✓ Easy screening

Transition Metal catalyst

✓ Tedious process

✓ Air and moisture sensitive.

✓ Metal impurity's in final product

Biocatalysts

✓ Limited choice of substrate

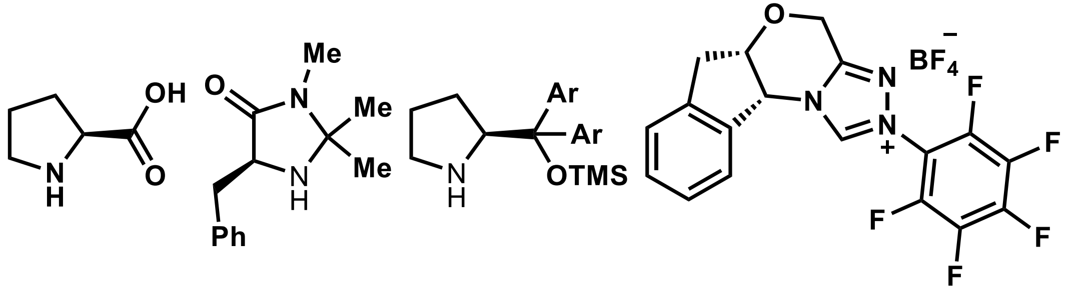
✓ Formation of single enantiomer.

Organocatalyst?

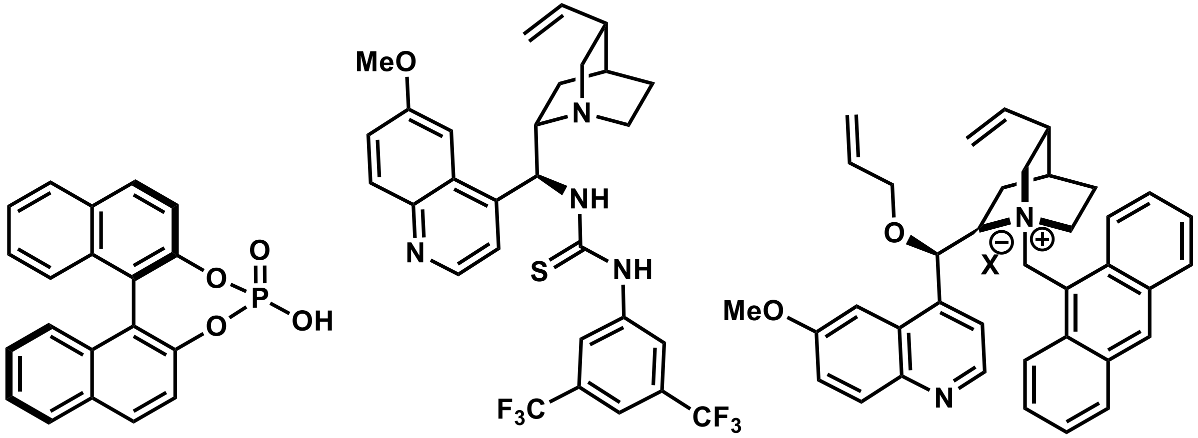
✓ The catalysis with small organic molecules, where an metals is not part of the active principle.

Lewis acid Branstad acid
Lewis base Branstad base

Covalent bond activation



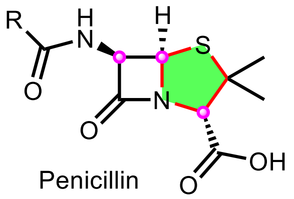
Non-covalent bond activation



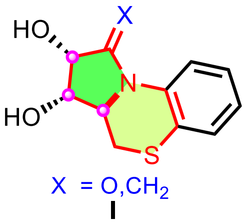
S. Cabrera. *et al, Chem. Soc. Rev.*, **2013,** *42*, 774--793

Literature reports

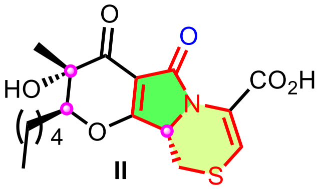
Importance of thiazoles & pyrrolo-thiazines



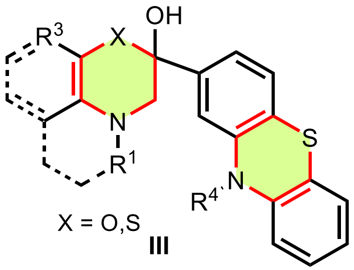
Penicillin



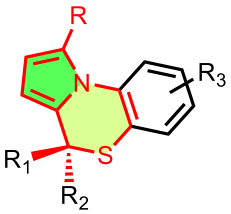
Inhibition of β-Ribosidases



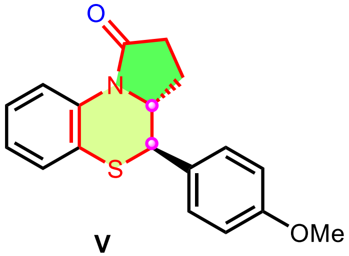
Naturel STAT 3 inhibitor



Antioxidant, anti-inflammatory, (SQS) inhibitory/hypolipidemic activities



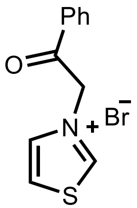
Ca entry blockers inhibtors

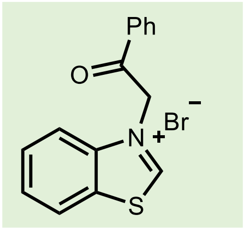


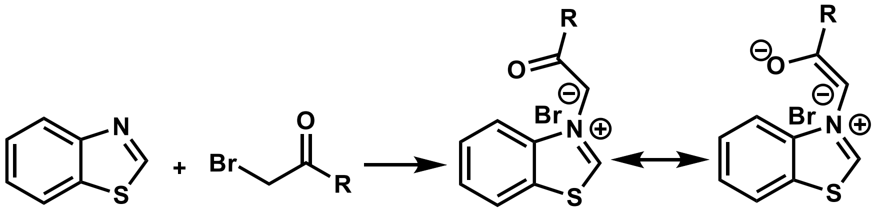
selective myocardial calcium channel modulators

A. Daıch. *et al*, *Chem. Eur. J.* **2019**, *25*, 6113–6118

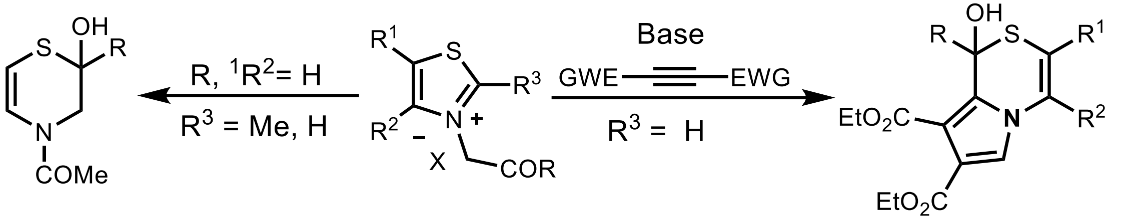
Azomethine ylide



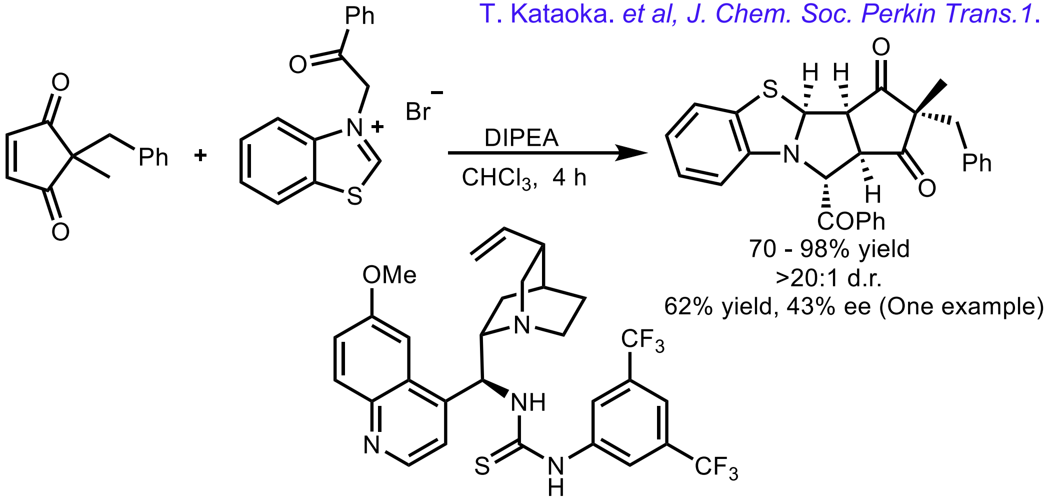




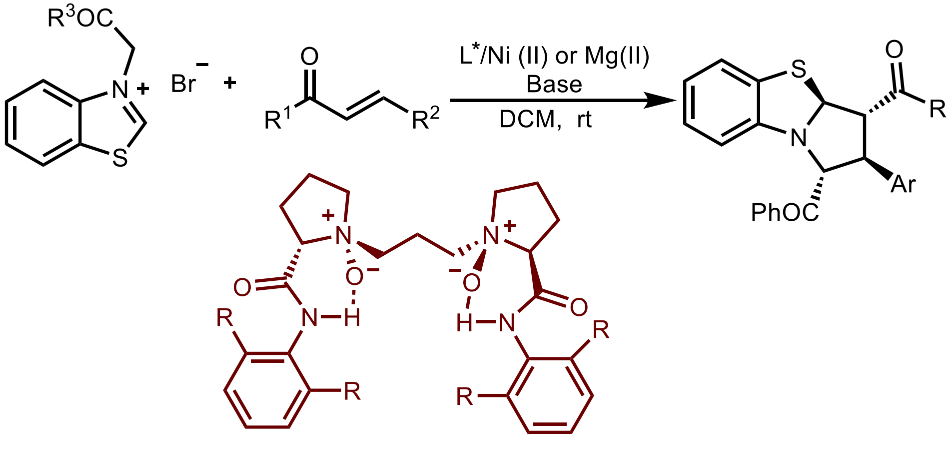
A. Naeem. *et al*, *Molecules*. **2016**, *21*, 1054



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



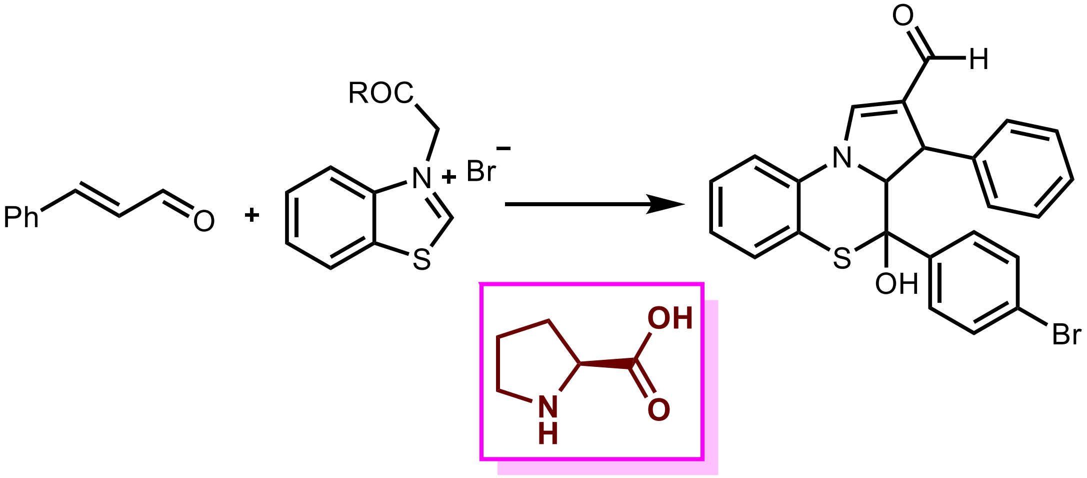
S. C. Pan, *et al*, *J. Org. Chem.* **2017**, *82*, 12763 - 12770

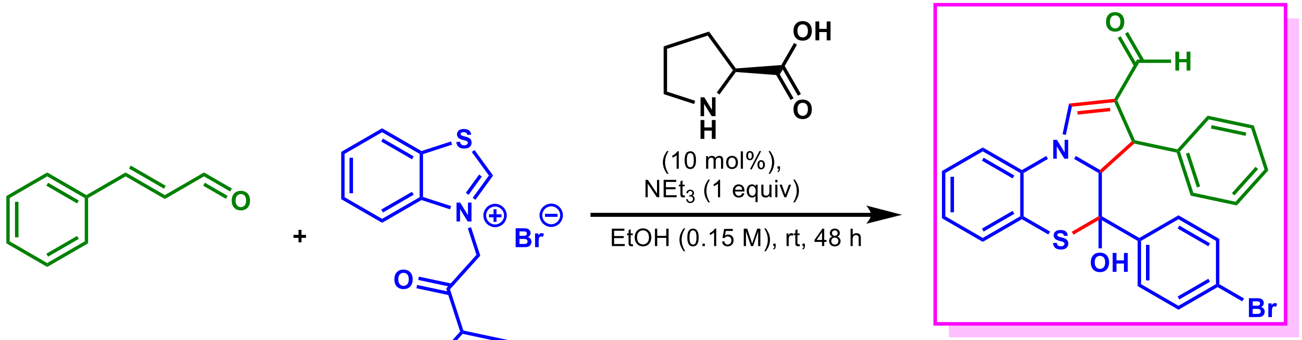


Chiral *N,N'*-dioxide ligand

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

Our methodology

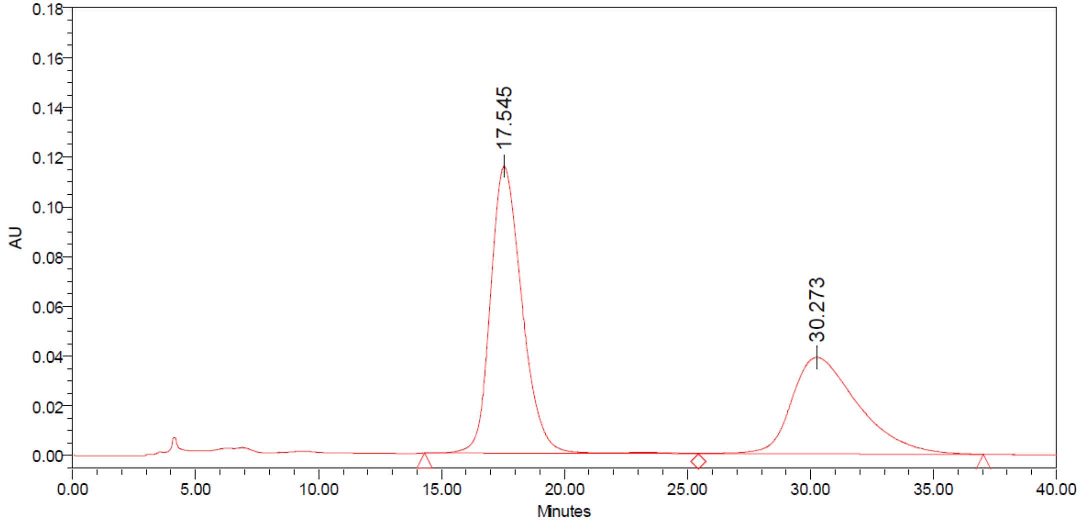




24% yield

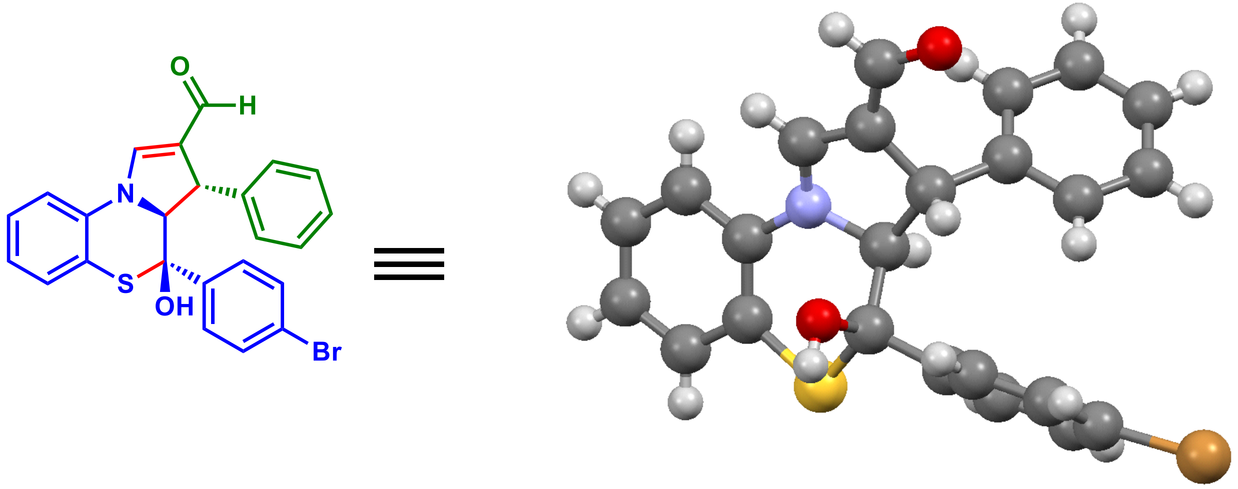
Fluorescent emissive nature

16% ee, >20:1 d.r.

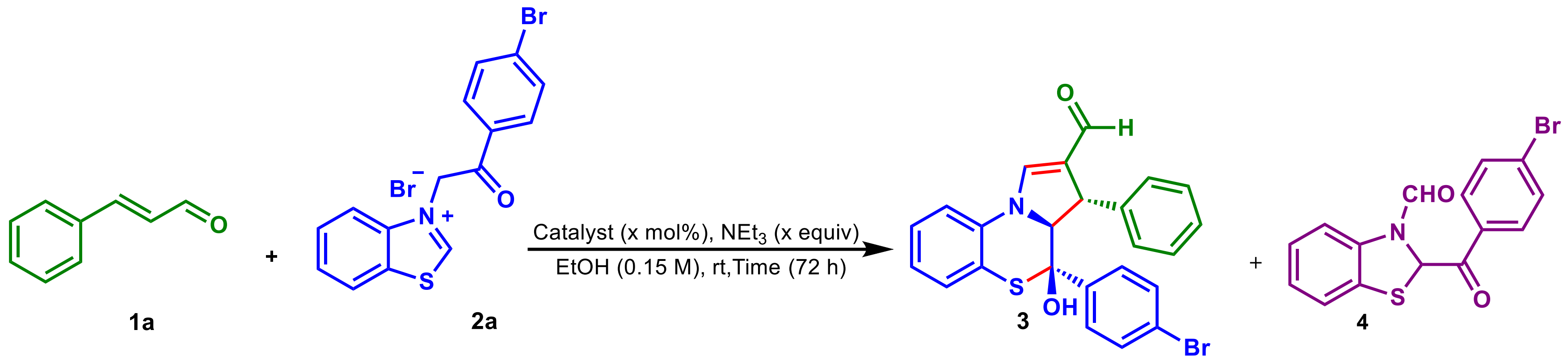


Peak Results

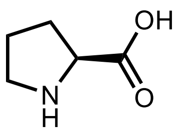
	Name	RT	Area	Height	% Area	% Height
1		17.545	10289469	115420	58.4924	74.8420
2		30.273	7301666	38798	41.5076	25.1580
Sum			17591134.8		100.0000	100.0000



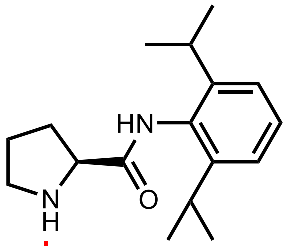
Reaction optimization



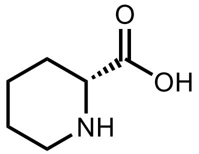
S. No	Base (equiv)	Catalyst (mol%)	Solvents (0.15M)	Yield (%)	ee (%)	d.r.	4 (%)
1	NEt_3 (1)	**L_1** (20)	EtOH	24	24	19.1	10
2	NEt_3 (2)	**L_1** (20)	EtOH	60	16	19.1	5
3	NEt_3 (3)	**L_1** (20)	EtOH	75	16	19.1	trace
4	NEt_3 (3)	**L_4** (20)	EtOH	32	38	19.1	10
5	NEt_3 (3)	**L_5** (20)	EtOH	52	90	19.1	5
6	Dibutyl amine (3)	**L_5** (20)	EtOH	95	10	19.1	-
7	DMAP (3)	**L_5** (20)	EtOH	72	98	19.1	5
8	DMAP (3)	**L_5** (20)	MeOH	48	74	19.1	5
9	DMAP (3)	**L_5** (20)	DCM	65	98	19.1	10
10	DMAP (3)	**L_5** (20)	IPA	87	99	19.1	trace



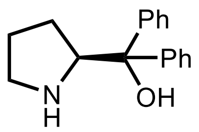
L_1



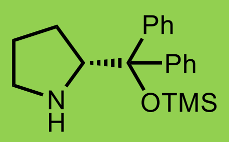
L_2



L_3

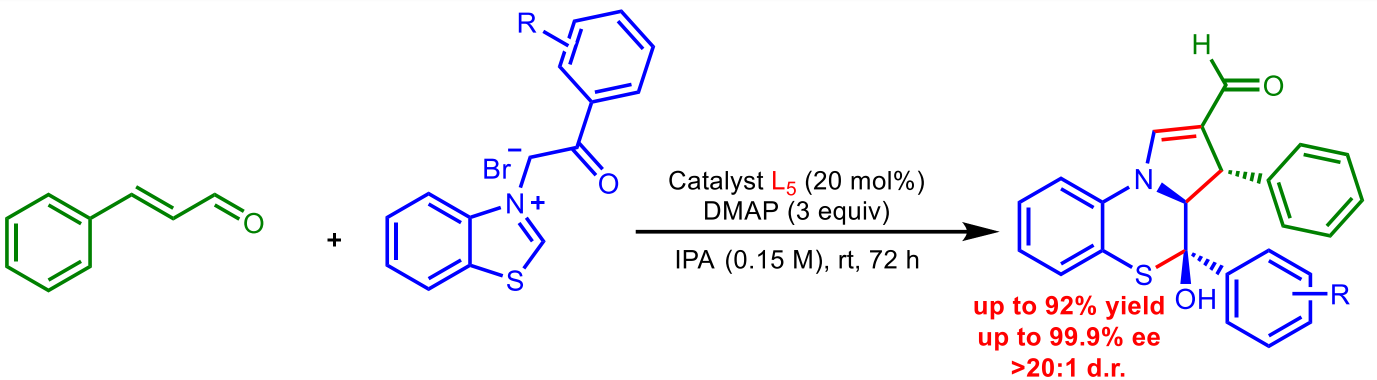


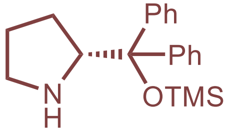
L_4



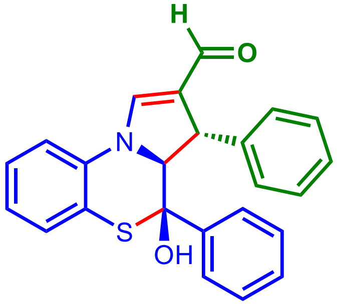
L_5

Scopes of benzothiazolium salts

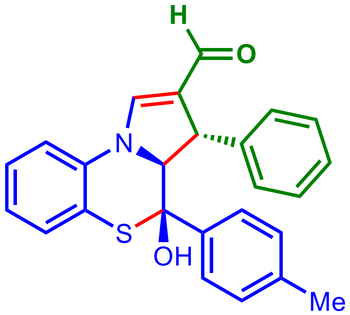




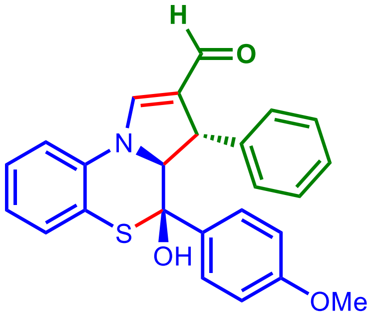
L_5



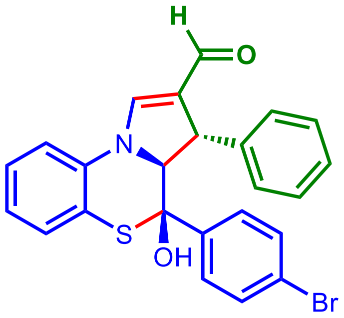
3a; 75%, 98% ee
>20:1 d.r.



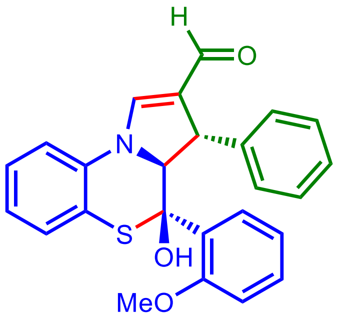
3b; 60%, 96% ee
>20:1 d.r.



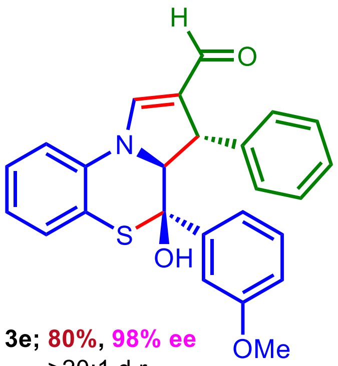
3c; 72%, 98% ee
>19:1 d.r.



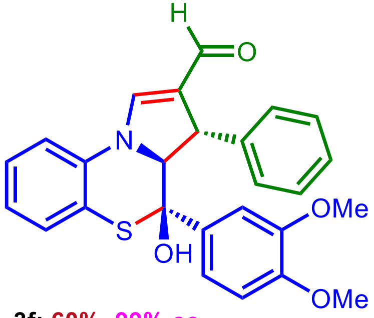
3d; 86%, 98% ee
>19:1 d.r.



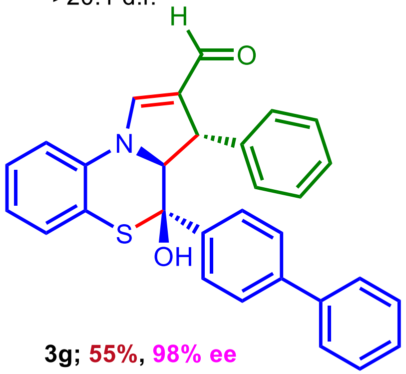
3d; 76%, 98% ee
>20:1 d.r.



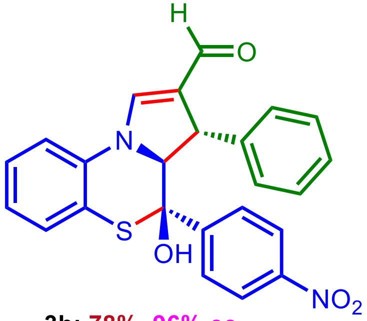
3e; 80%, 98% ee
>20:1 d.r.



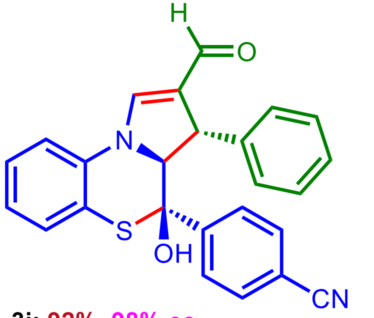
3f; 60%, 99% ee
>20:1 d.r.



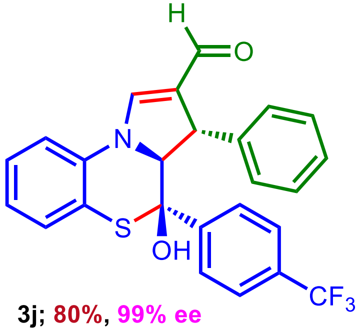
3g; 55%, 98% ee
>20:1 d.r.



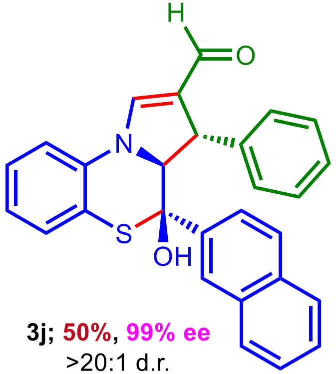
3h; 78%, 96% ee
>20:1 d.r.



3i; 92%, 98% ee
>20:1 d.r.



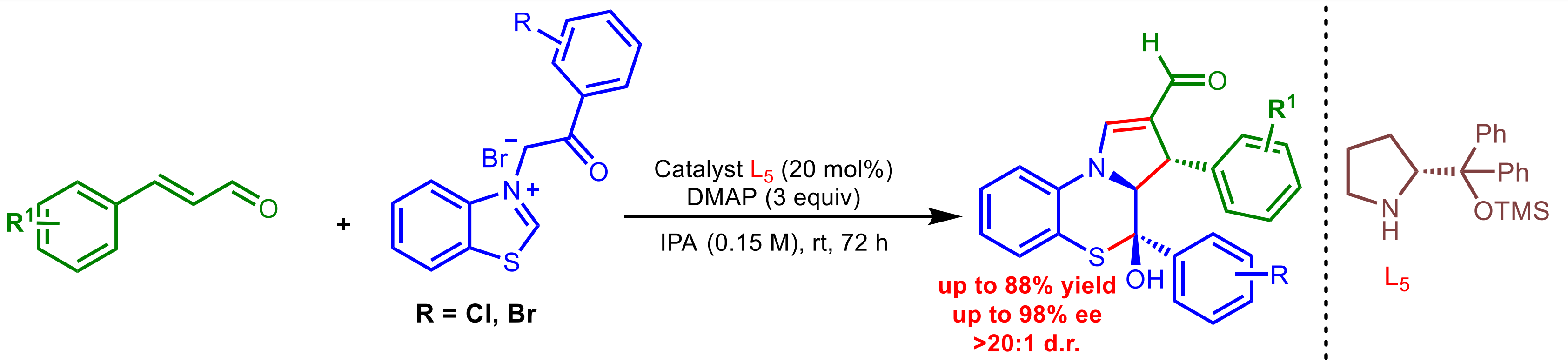
3j; 80%, 99% ee
>20:1 d.r.

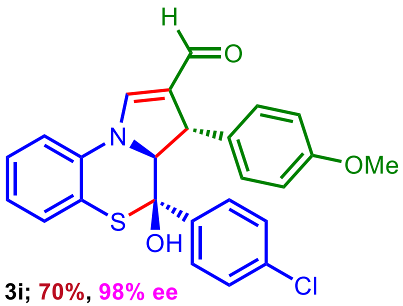


3j; 50%, 99% ee
>20:1 d.r.

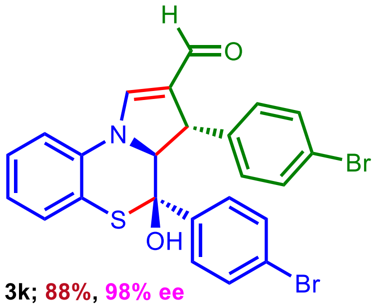
"Manuscript under revision"

Scopes of α,β-unsaturated aldehydes

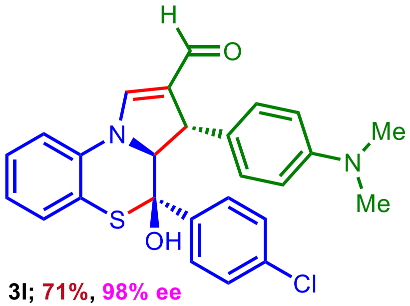




3i; 70%, 98% ee
>20:1 d.r.



3k; 88%, 98% ee
>20:1 d.r.



3l; 71%, 98% ee
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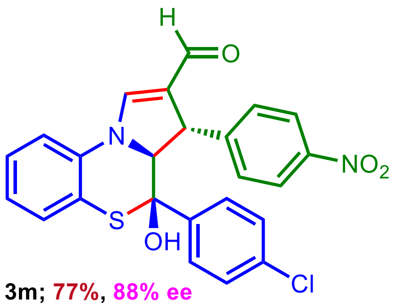

3m; 77%, 88% ee
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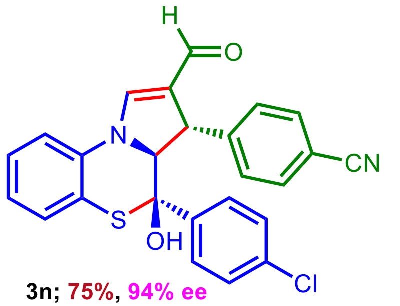
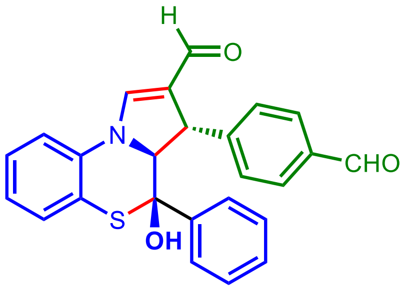


3n; 75%, 94% ee
>20:1 d.r.



3o; 76%, 92% ee
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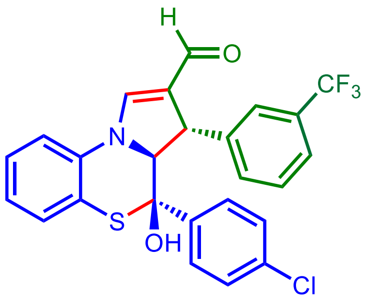
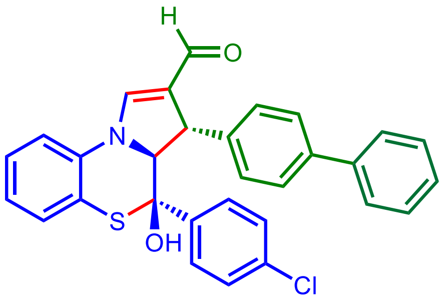
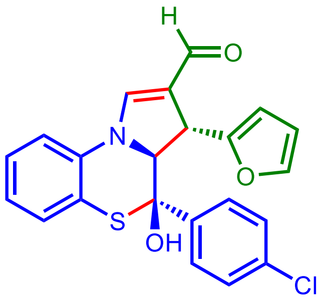


3p; 75%, 94% ee
>20:1 d.r.



3q; 78%, 94% ee
>20:1 d.r.



3r; 62%, 88% ee
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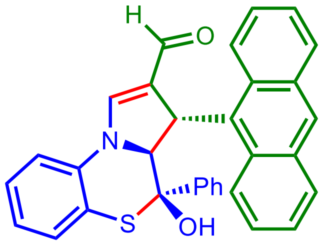

3s; 74%, 98% ee
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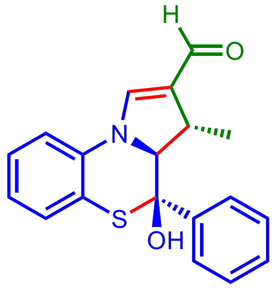

3t; 56%, 80% ee
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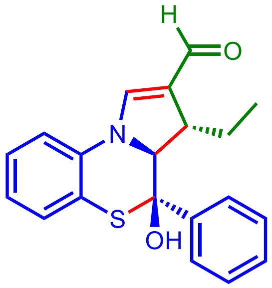
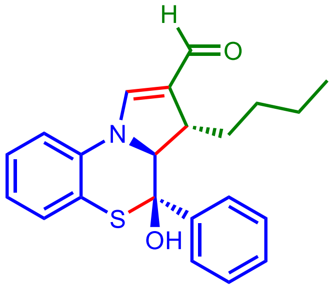
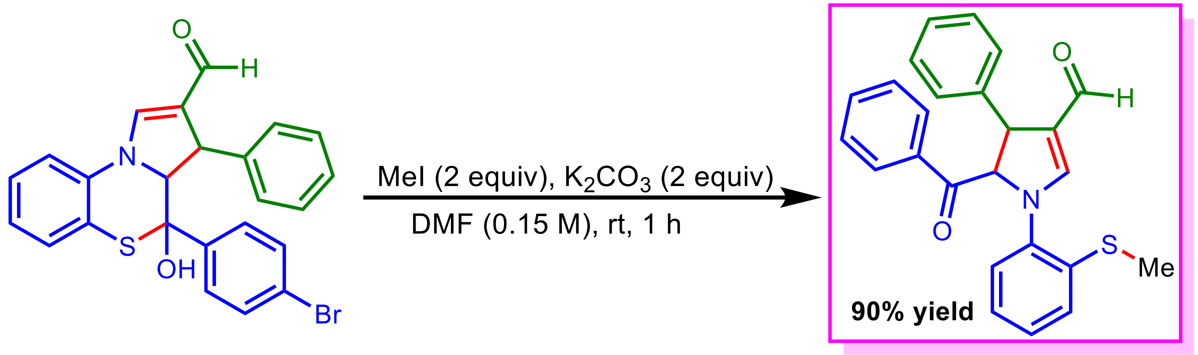


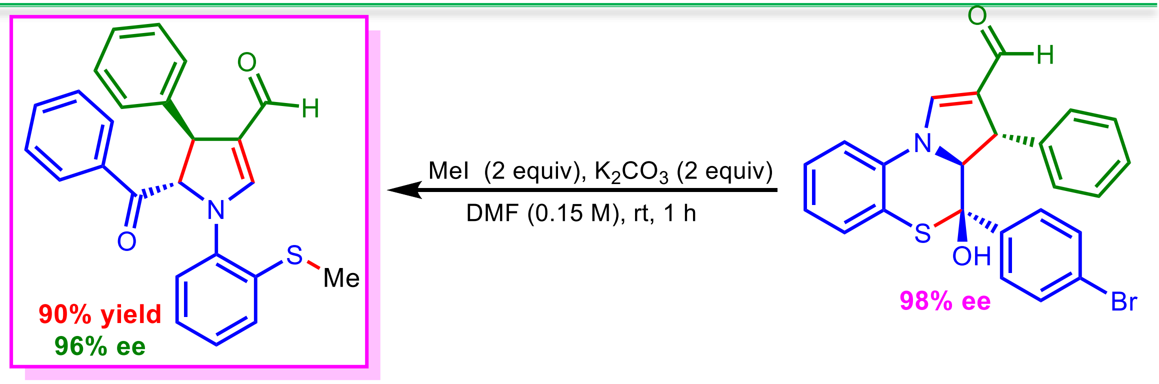
3u; 20%, 92% ee
>20:1 d.r.

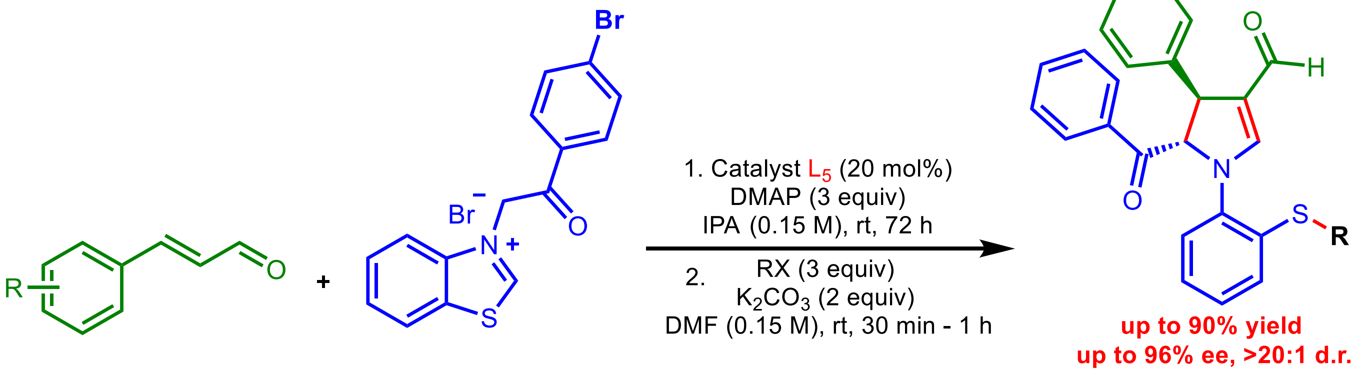


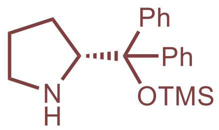
3v; 45%, 96% ee
>20:1 d.r.

"Manuscript under revision"

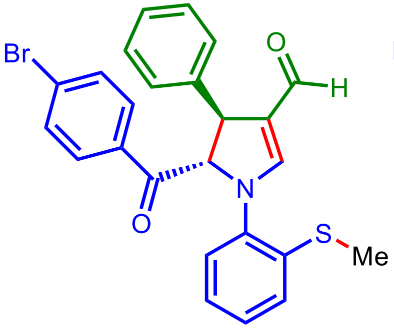




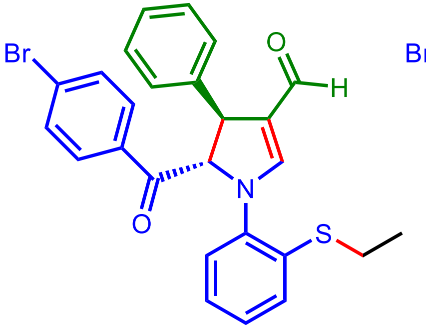




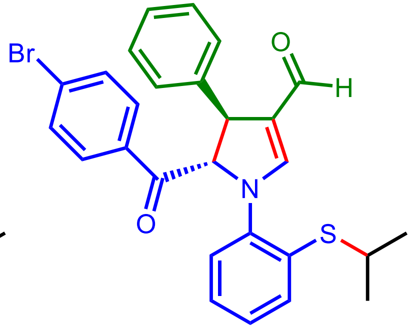
L_5



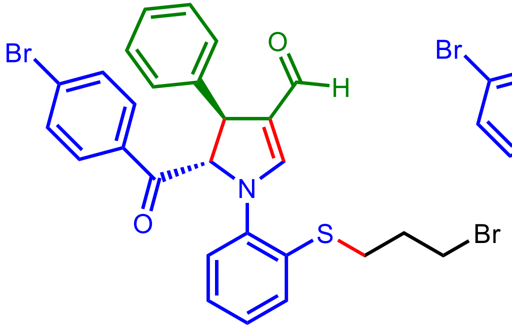
4a; 75%, 98% ee
>20:1 d.r.
72 h + 30 min



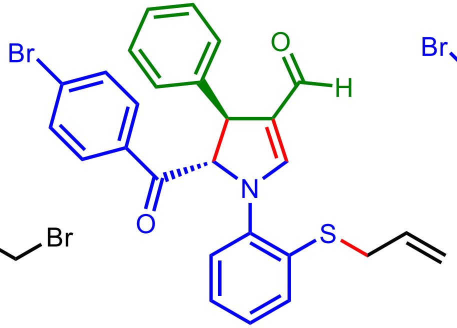
4b; 86%, 88% ee
>20:1 d.r.
72 h + 30 min



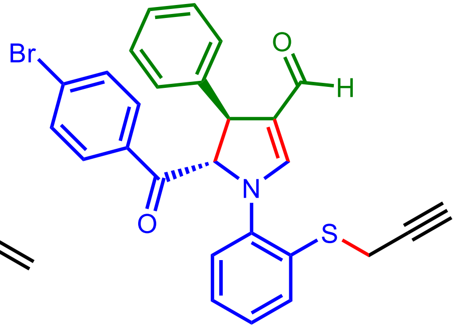
4c; 80%, 86% ee
>20:1 d.r.
72 h + 30 min



4d; 52%, 84% ee
>20:1 d.r.
72 h + 30 min

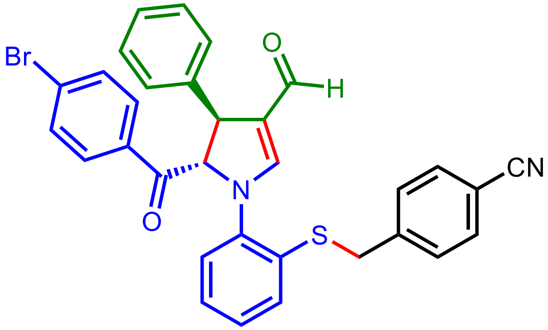


4e; 88%, 80% ee
>20:1 d.r.
72 h + 1 h

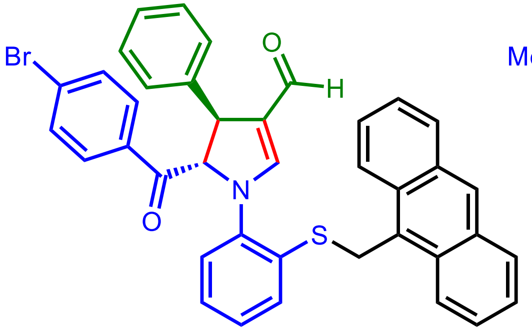


4f; 80%, 82% ee
>20:1 d.r.
72 h + 1 h

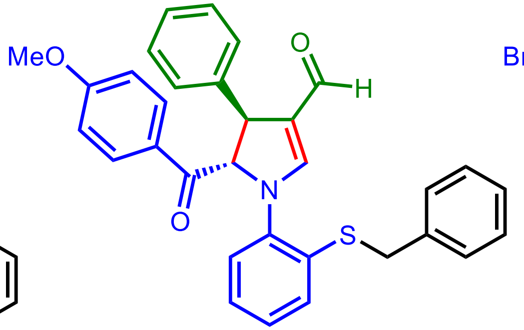
Scopes of pyrrole-3-carbaldehyde



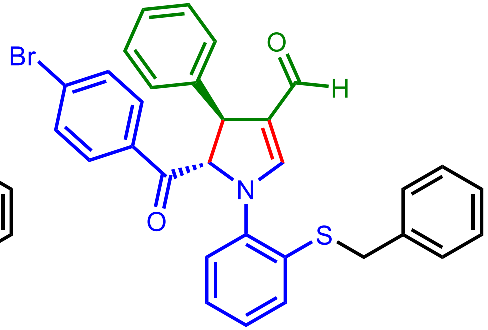
4l; **70%**, **96% ee**
>20:1 d.r.
72 h +1 h



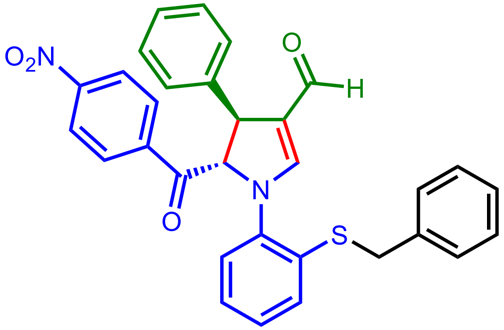
4n; **85%**, **90% ee**
>20:1 d.r.
72 h + 1 h



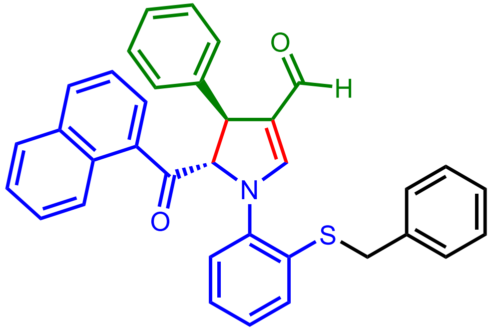
4p; **72%**, **96% ee**
>20:1 d.r.
72 h + 1 h



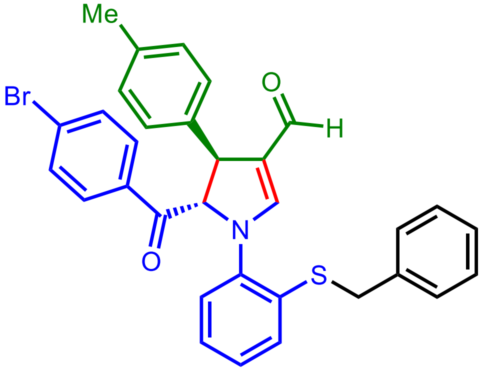
4q; **85%**, **98% ee**
>20:1 d.r.
72 h + 40 min



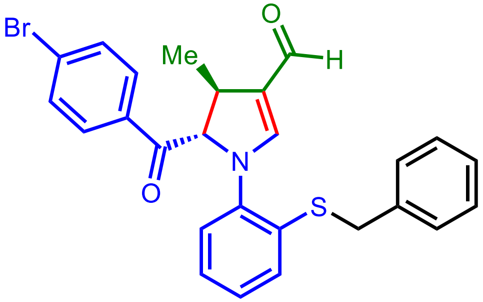
4r; **75%**, **90% ee**
>20:1 d.r.
72 h + 1 h



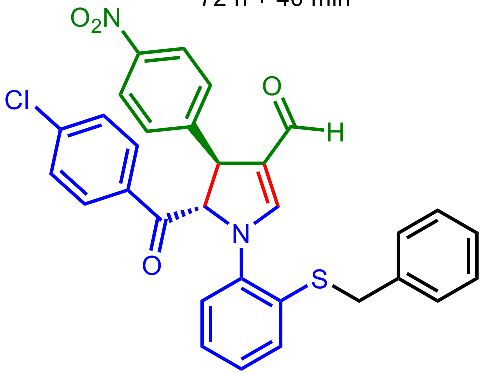
4s; **60%**, **90% ee**
>20:1 d.r.
72 h + 1 h



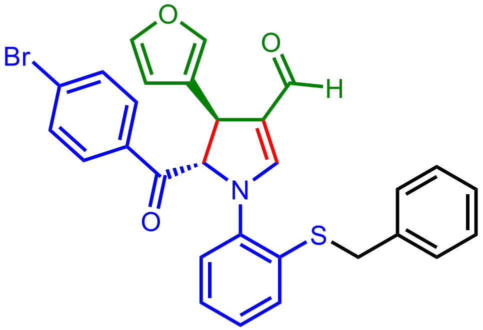
4t; **76%**, **98% ee**
>20:1 d.r.
72 h + 1 h



4u; **48%**, **82% ee**
>20:1 d.r.
72 h + 30 min



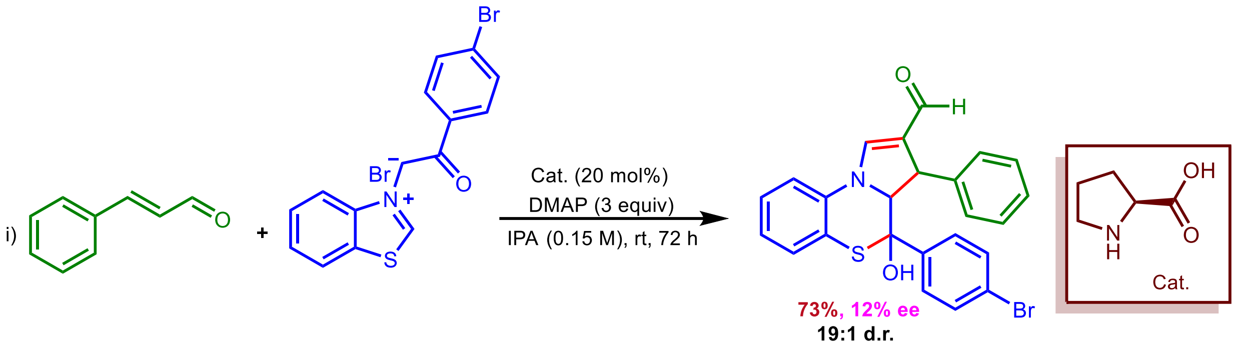
4w; **72%**, **98% ee**
>20:1 d.r.
72 h + 1h

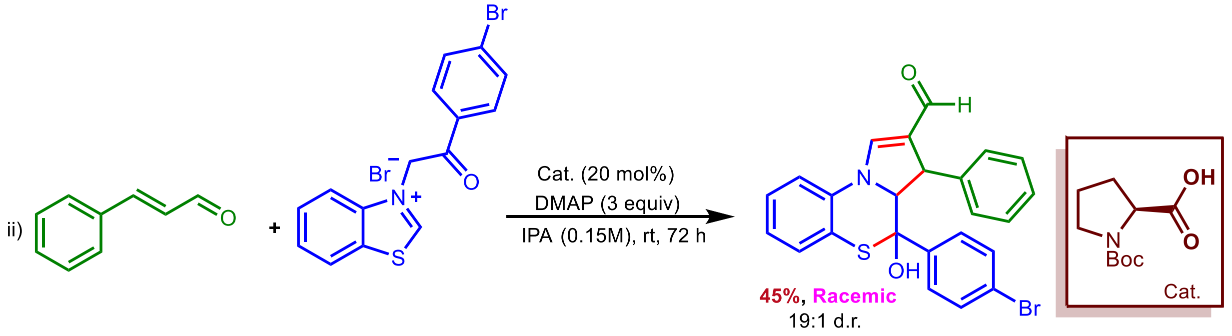


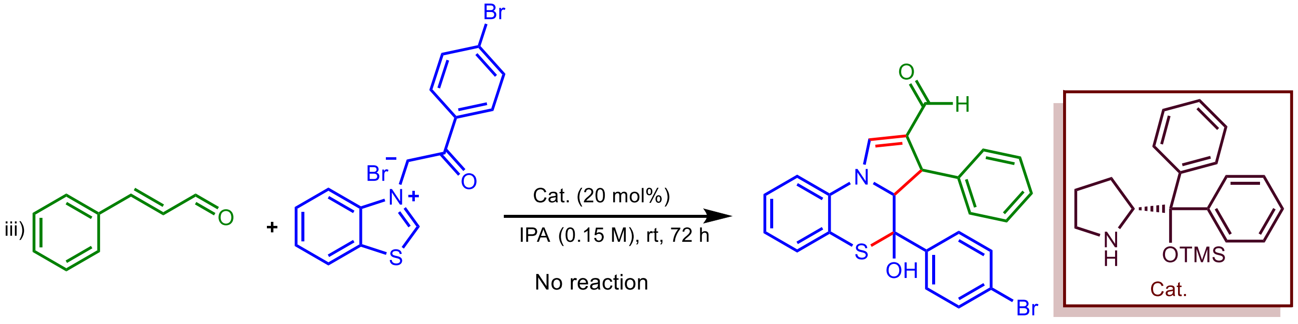
4x; **65%**, **88% ee**
>20:1 d.r.
72 h + 1 h

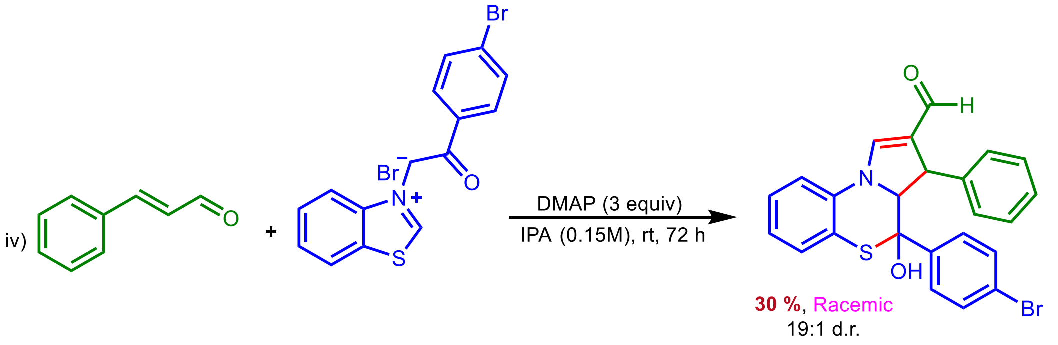
"Manuscript under revision"

Control experiments

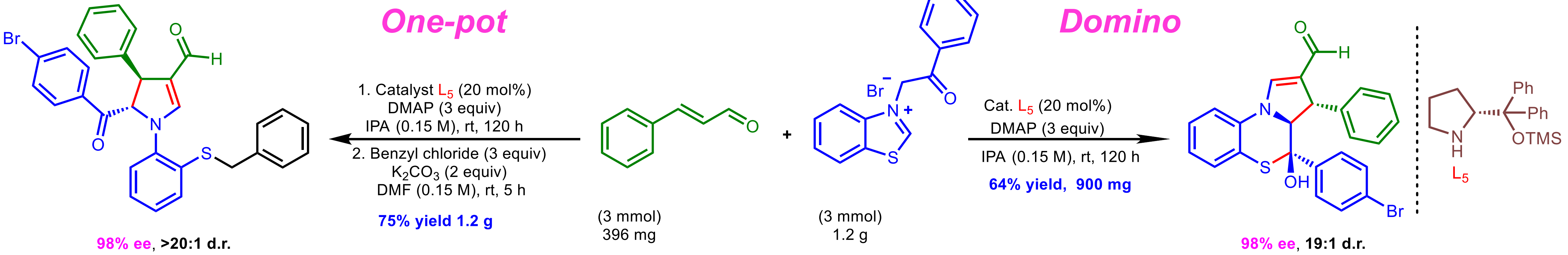




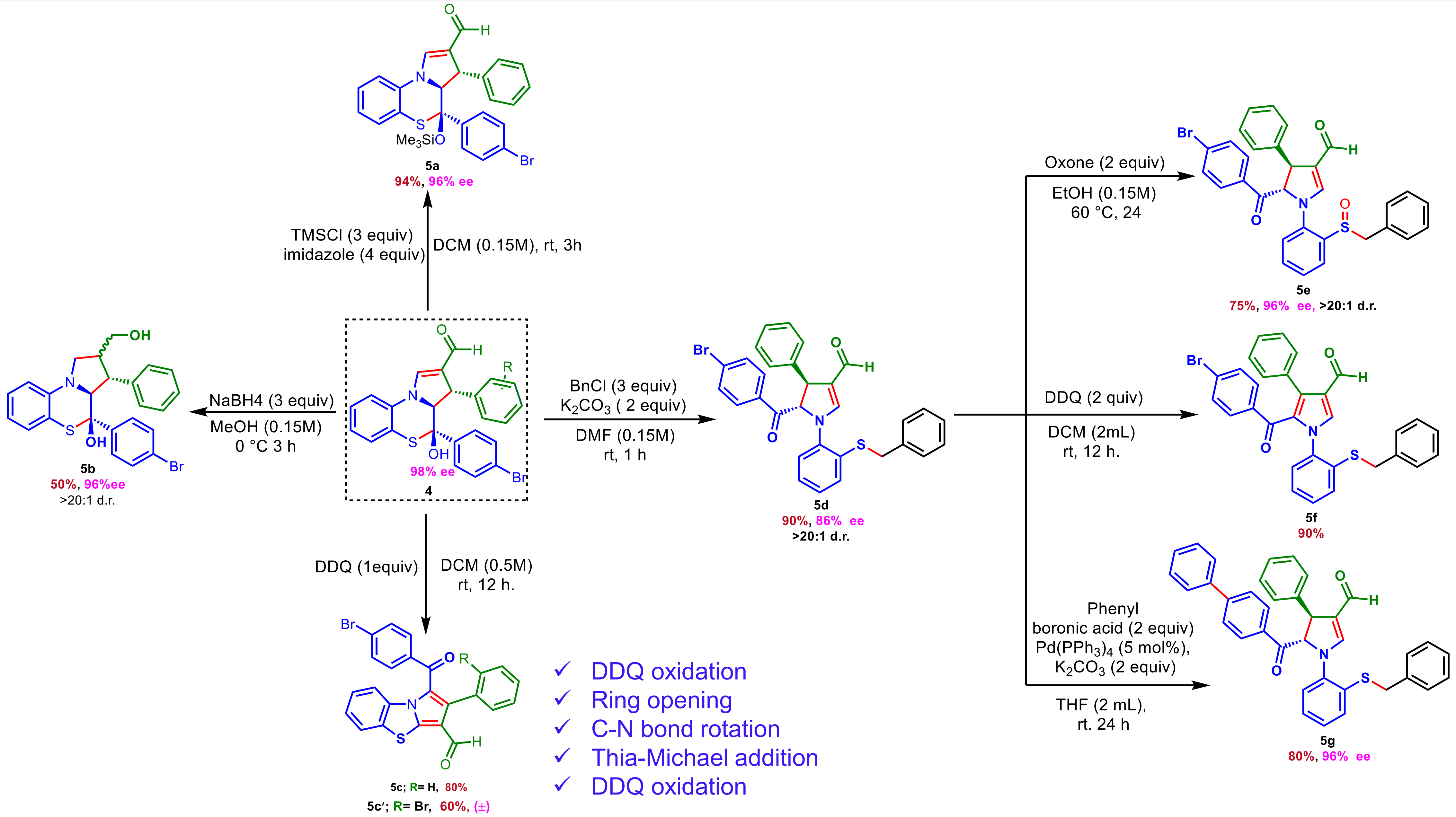




Gram scale synthesis

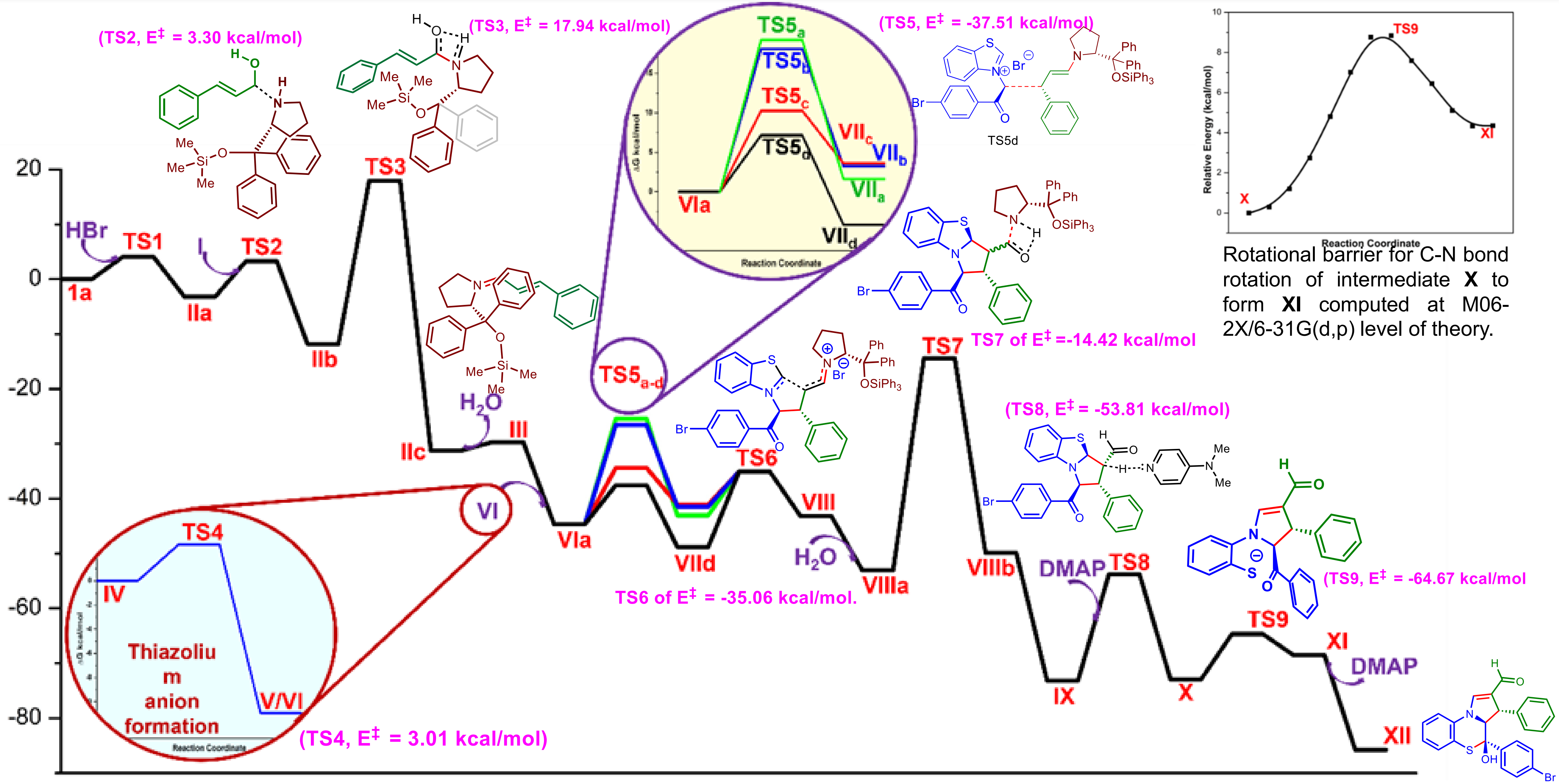


Synthetic utility



- ✓ DDQ oxidation
- ✓ Ring opening
- ✓ C-N bond rotation
- ✓ Thia-Michael addition
- ✓ DDQ oxidation

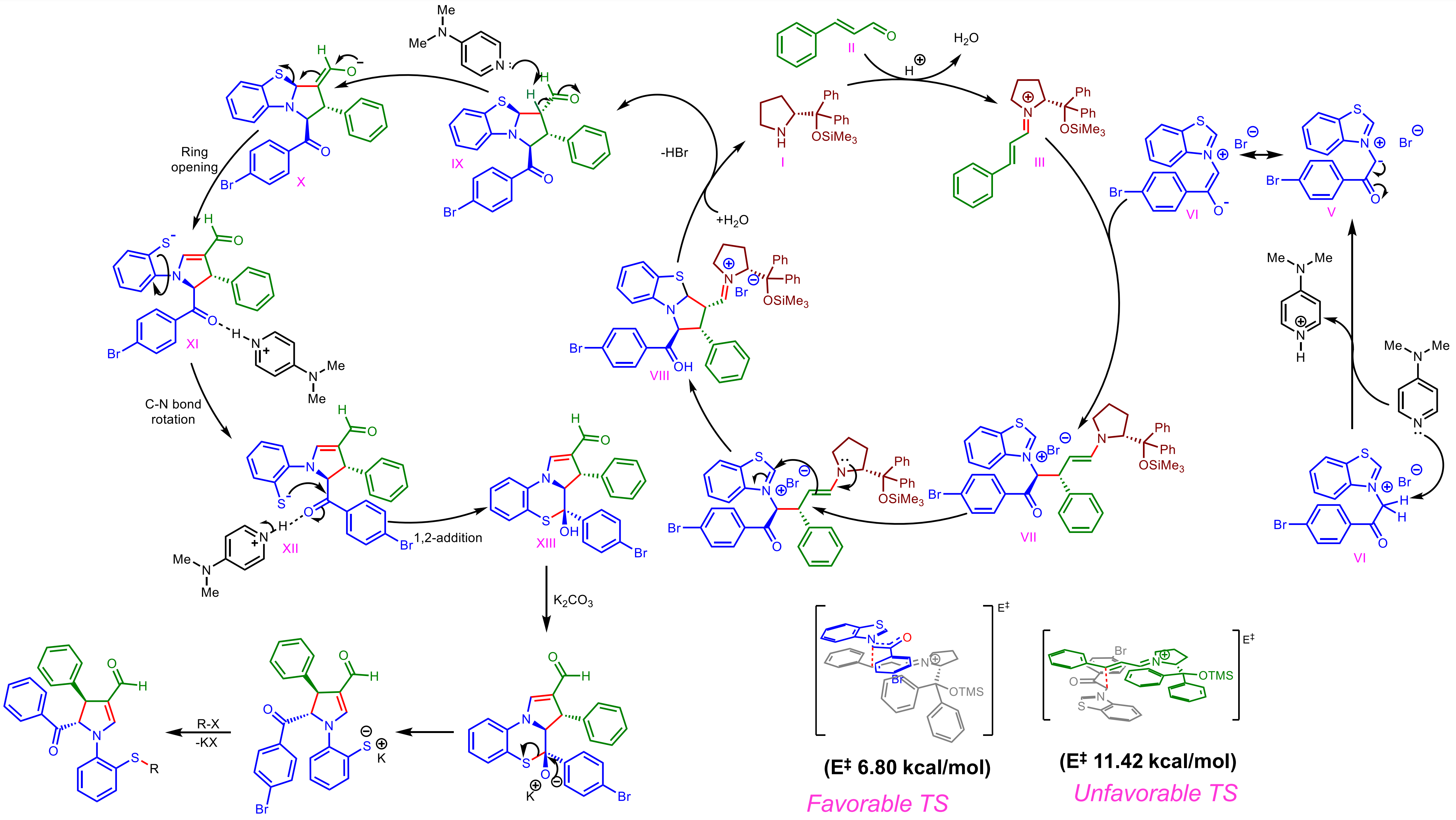
Computational study



Rotational barrier for C-N bond rotation of intermediate **X** to form **XI** computed at M06-2X/6-31G(d,p) level of theory.

Figure 1. Complete reaction profile diagram of the reaction of cinnamaldehyde 1a and benzothiazolium salt 2f with (*R*)-diphenylprolinol trimethylsilyl ether L3, computed at M06-2X/6-31G(d,p) level of theory.

Plausible mechanism



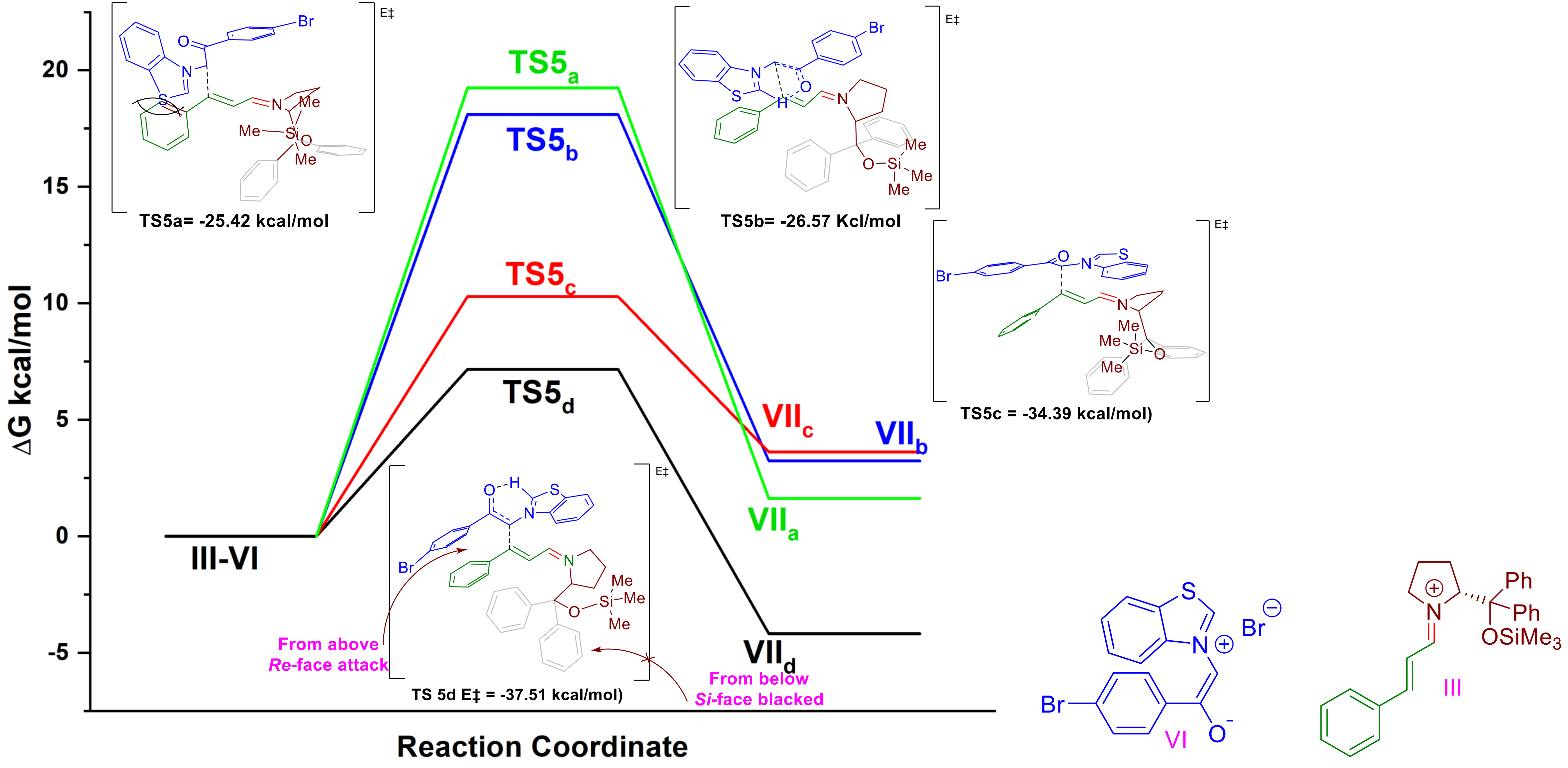
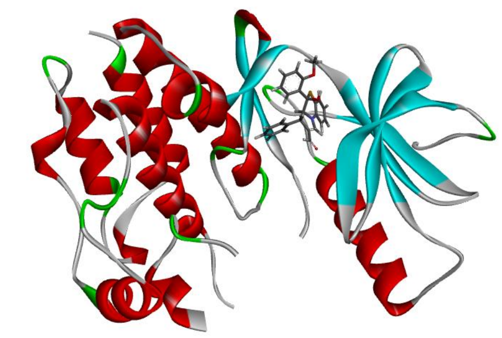
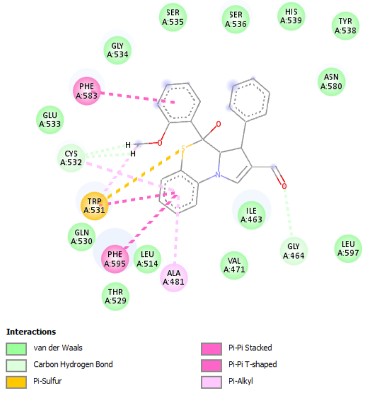
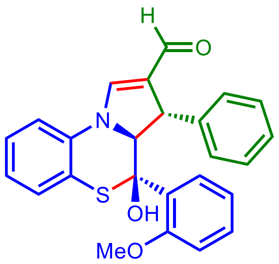


Figure 2. Transition state for C-C bond formation the intermediates **III** and **VI** to combine to produce intermediate **VII** computed at M06-2X/6-31G(d,p) level of theory

Molecular docking study







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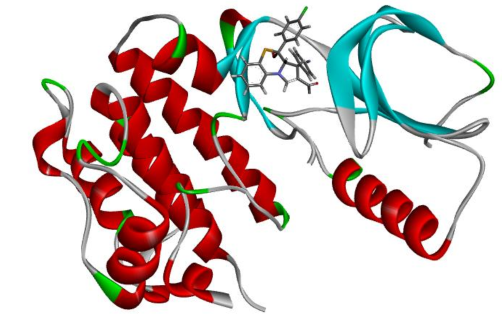

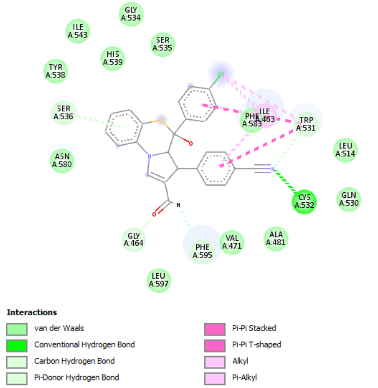

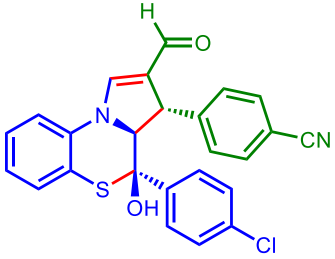

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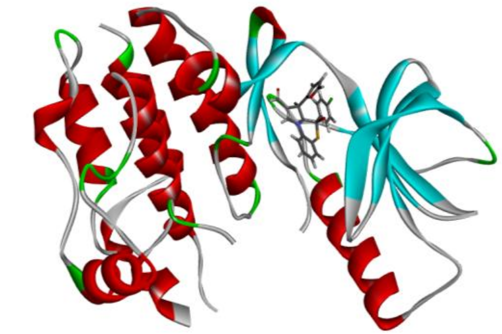

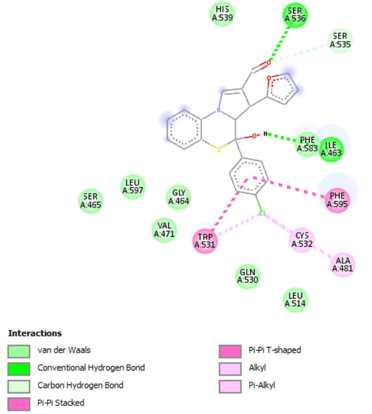

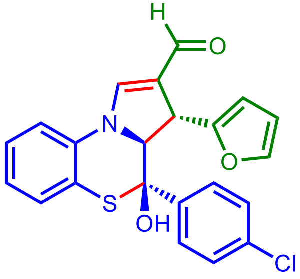

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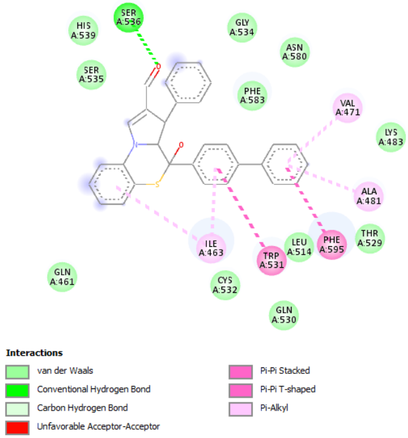

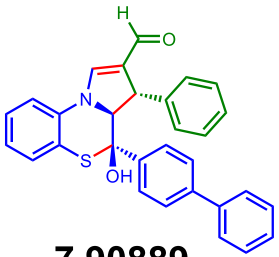

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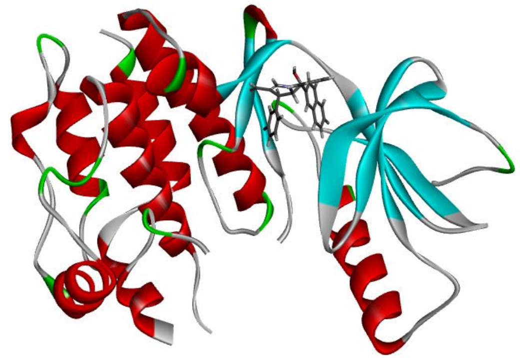

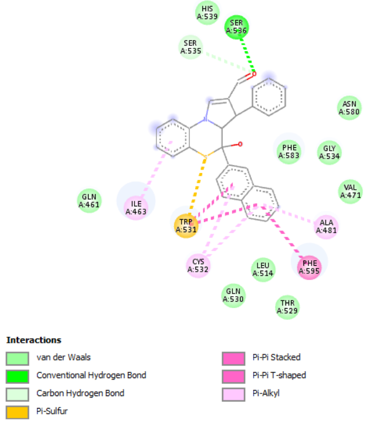

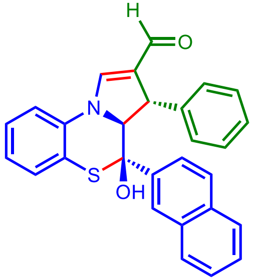

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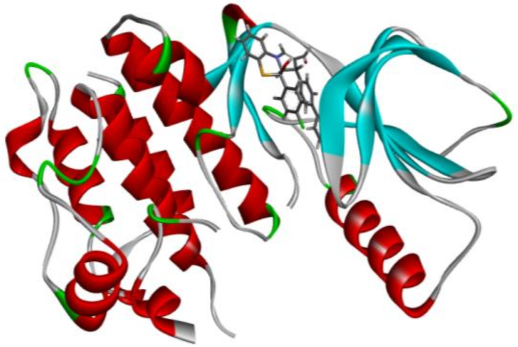
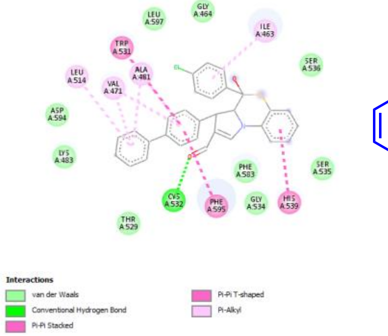
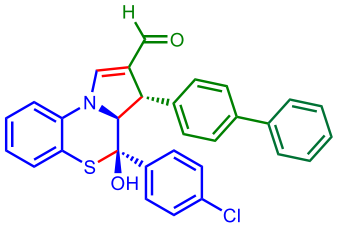


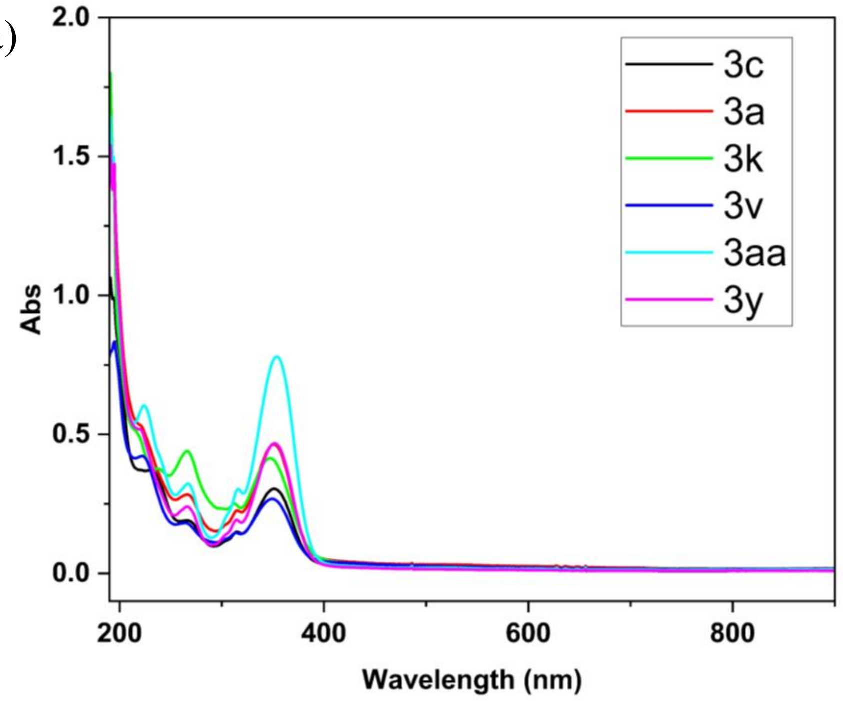




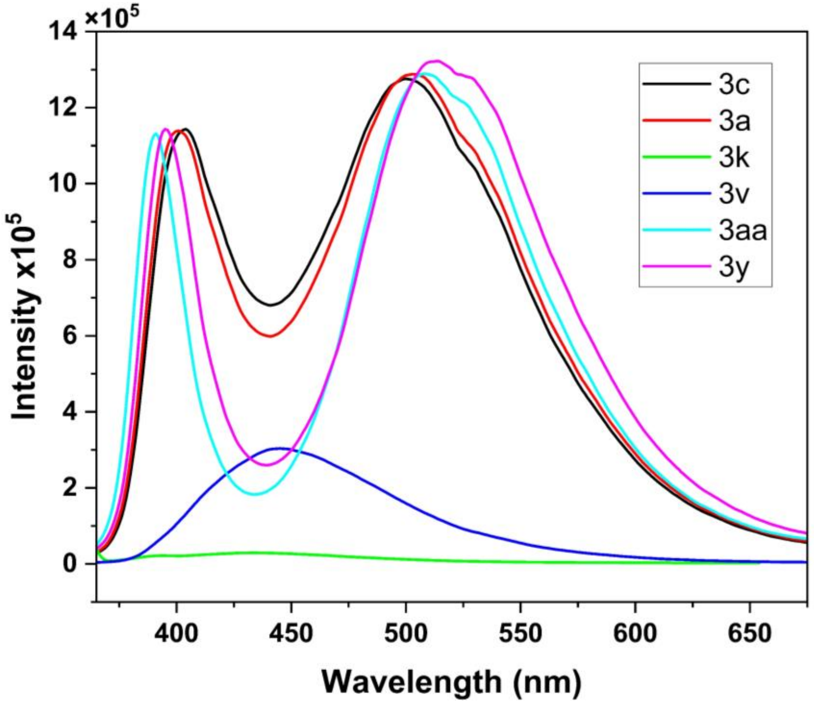
-7.40894

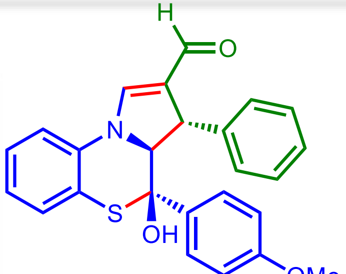
Fluorescent study

a)

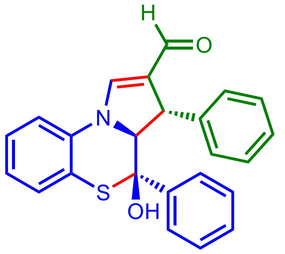


b)

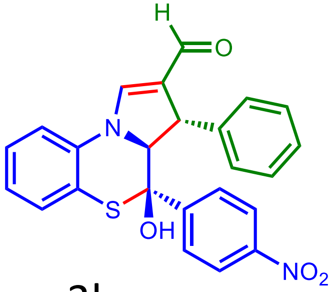




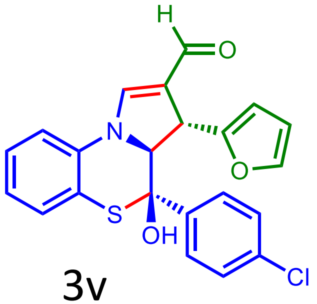
3c



3a

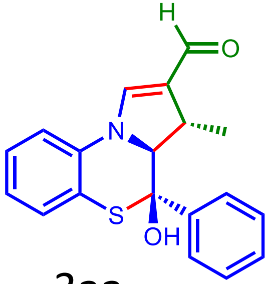


3k

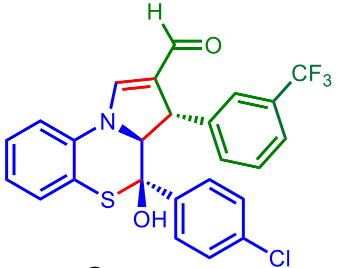


3v

c)



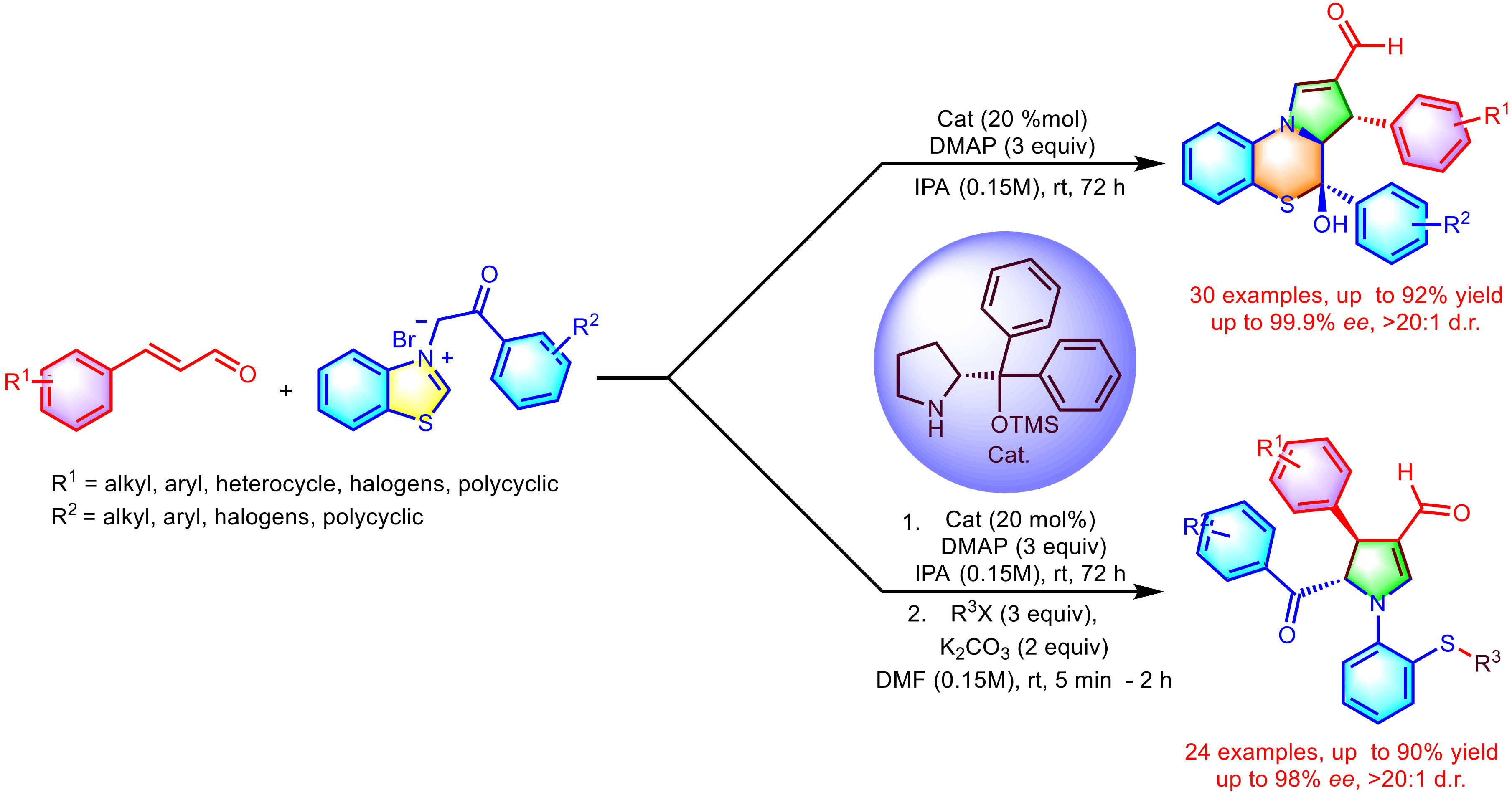
3aa



3y

Figure .1 (a) Absorption spectra in CH_3CN (50 *μ*m) (b) Fluorescence emission spectra in CH_3CN (50 *μ*m) (λ_{ex} = 352 nm). (c) Fluorescence image in CH_3CN (λ_{ex} = 365 nm).

Conclusion



- First asymmetric reaction of α,β- unsaturated aldehyde with benzothiazolium salts
- Transition metal-free organocatalyst
- Domino & one-pot reaction sequence

- High enantio-and diastereoselectivity
- Flurorescent emmisive chiral molecule
- DFT,and molecular docking studies
- Anticancer activity

Thank You