2nd NATIONAL CONFERENCE ON CONTEMPORARY FACETS IN ORGANIC SYNTHESIS (CFOS-2022)

Organocatalytic Enantio- and Diastereoselective Construction of Pyrrolo[1,2-*d*][1,4]thiazine-2-Carbaldehydes Core via Consecutive [3+2] Cycloaddition and Rearrangement

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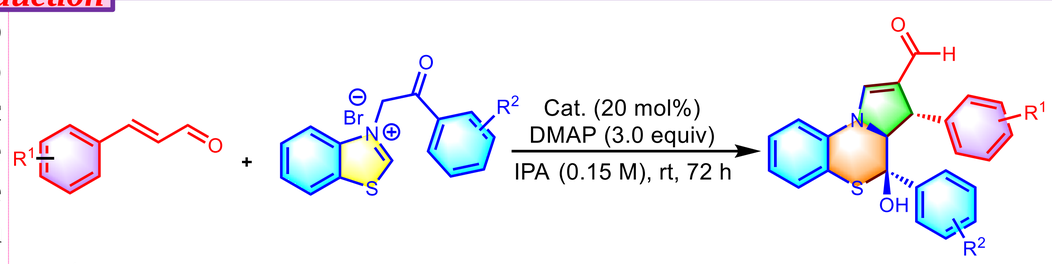
Introduction

1,3-Dipolar cycloaddition reaction of azomethine ylide and dienophile is a quick way to produce N, S containing heterocycles[1] such as thiazoles, 1,4-thiazines, and their polyhydro derivatives, which are found in many medicinal compounds.[2-4] Despite their interest, catalytic asymmetric variants of this process is still in their infancy. There is no report in the literature about the use of benzothiazolium salt reacting with α,β-unsaturated aldehyde. Herein, we describe the first catalytic asymmetric [3+2] cycloaddition/rearrangement that occurs when a benzothiazolium salts and α,β-unsaturated aldehyde are combined to produce pyrrolo[1,2-*d*][1,4]thiazine-2-carbaldehydes with high enantio- and diastereoselectivity (up to 99% *ee*, and >20:1 dr) using proline derived R-diphenylprolinol trimethylsilyl ether. It enables the formation of three contiguous stereocenters as well as one quaternary chiral carbon in a single step. The detailed mechanism is further investigated by DFT calculation, and the enantioselectivity is rationalized.

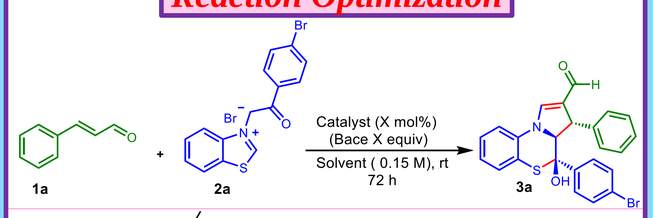


R^1 = alkyl, aryl, heterocycle, halogens, polycyclic
R^2 = alkyl, aryl, halogens, polycyclic

up to 92% yield
up to 99% *ee*, >20:1 d.r.

- First organocatalytic reactions of cinnamaldehyde with thiazolium salts
- Mild reaction conditions
- Good functional group tolerance
- Consecutive reaction sequence
- High enantio-and diastereoselectivity
- Fluroresent active chiral molecule
- 25 examples

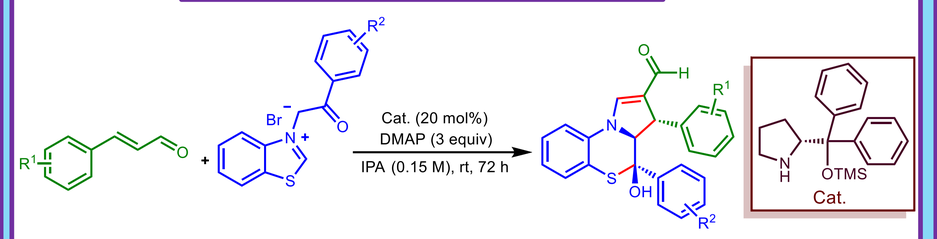
Reaction Optimization

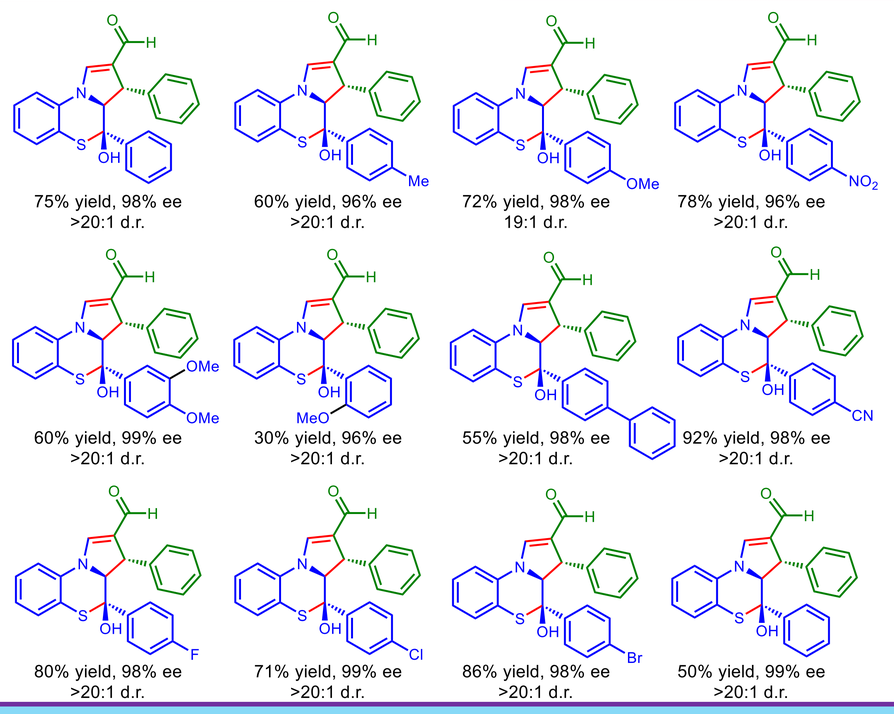


entry	Cat. (mol%)	Base (equiv)	Solvents (mL)	Yield (%)[c]	*ee* (%)[d]	d.r. ratio[e]
1	I (10)	NEt_3 (1)	EtOH	24	16	>20:1
2	I (20)	NEt_3 (2)	EtOH	60	24	>20:1
4	II (20)	NEt_3 (3)	EtOH	10	6	>20:1
5	III (20)	NEt_3 (3)	EtOH	41	28	>20:1
6	IV (20)	NEt_3 (3)	EtOH	32	28	>20:1
7	V (20)	NEt_3 (3)	EtOH	37	68	>20:1
8	VI (20)	NEt_3(3)	EtOH	52	90	>20:1
9	VI (20)	Diethylamine (3)	EtOH	30	50	>20:1
10	VI (20)	DMAP (3)	EtOH	72	98	>20:1
11	VI (10)	DABCO (3)	EtOH	63	97	>20:1
12	VI (15)	Dibutyl amine (3)	EtOH	95	10	>20:1
13	VI (25)	NaOAc (3)	EtOH	24	98	>20:1
14	VI (20)	K_2CO_3 (3)	EtOH	20	60	>20:1
15	VI (20)	DMAP (3)	MeOH	48	74	>20:1
16	VI (20)	DMAP (3)	DCM	65	98	>20:1
17	VI (20)	DMAP(3)	IPA	75	99	>20:1
18	VI (20)	DMAP (3)	Toluene	55	98	>20:1
19	VI (20)	DMAP (3)	CH_3CN	48	98	>20:1
16	VI (20)	DMAP (3)	1,4-Dioxane	44	98	>20:1
17	VI (20)	DMAP (3)	HFIP	55	22	>20:1
18	VI (20)	DMAP (3)	Et_2O	62	98	>20:1

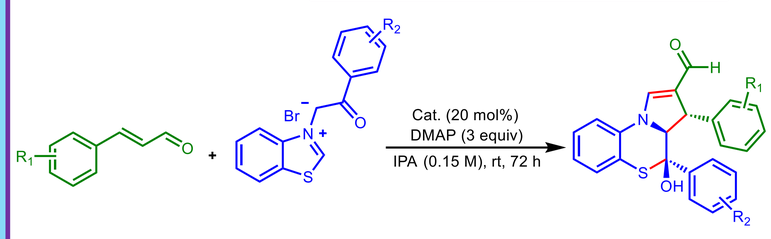
[a]Standared reaction conditions: **1a** (0.3 mmol), **2a** (0.3mmol), Base (1-3 equiv), Catalyst (20 mol%), Solvent (0.15 M), [b]Isolated yield, [c] Enantiomeric excess where determined by chiral HPLC, [d]d.r. where determined by crude reaction mixture.

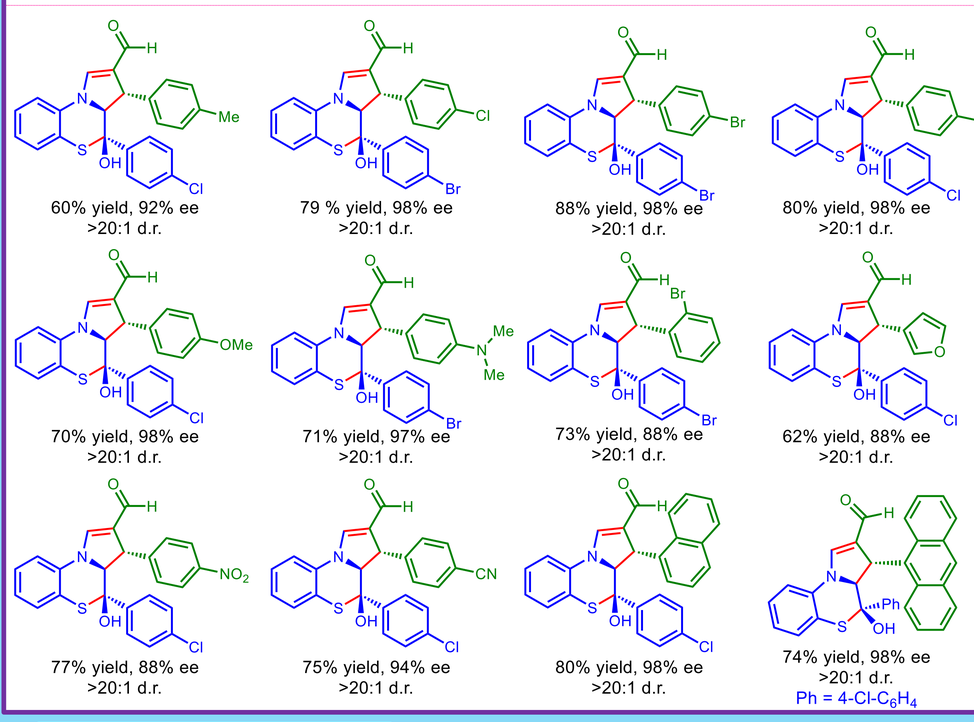
Scope for Benzothiazolium Salt



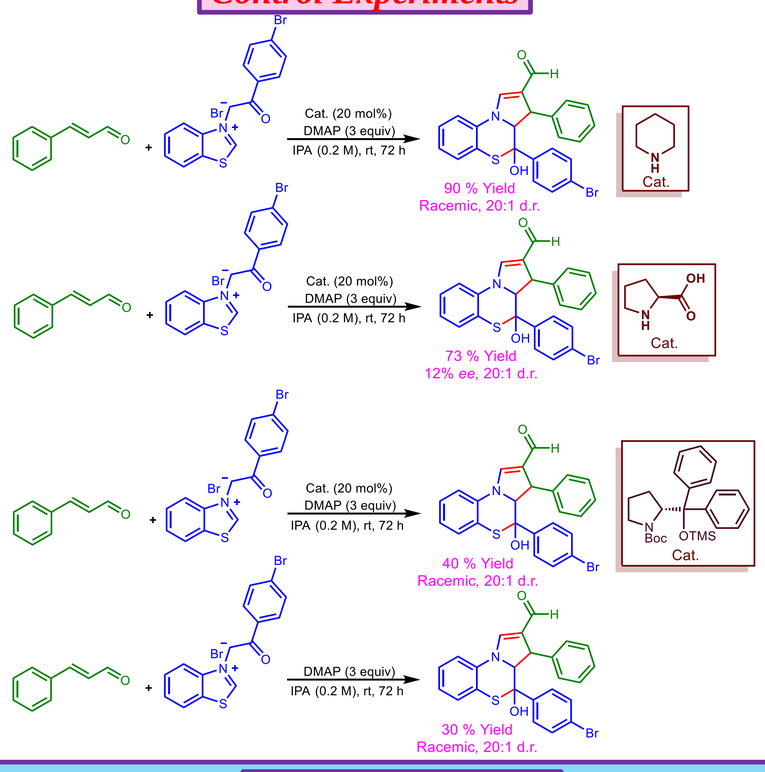


Scope for Cinnamaldehyde

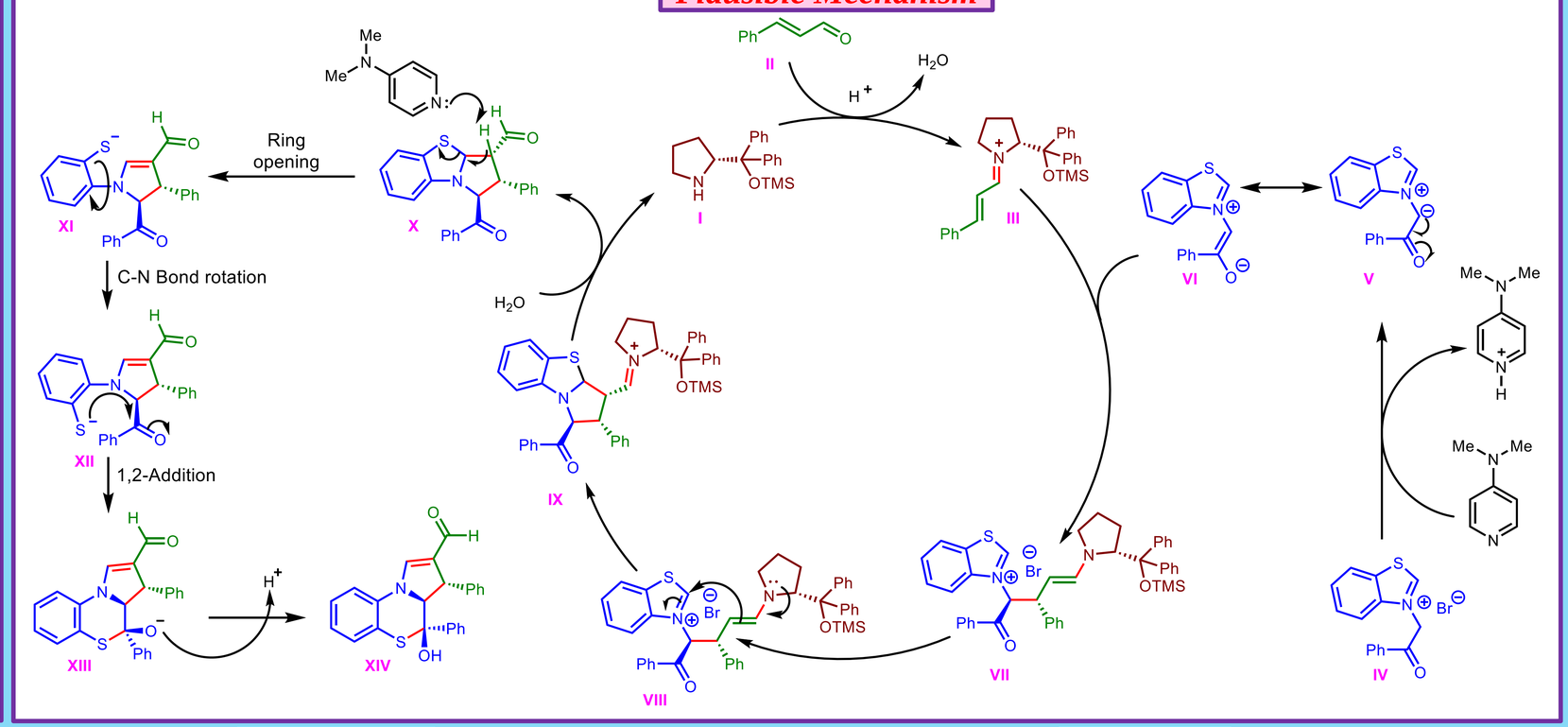




Control Experiments

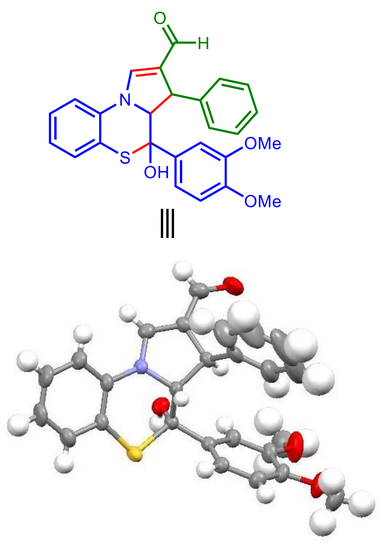


Plausible Mechanism

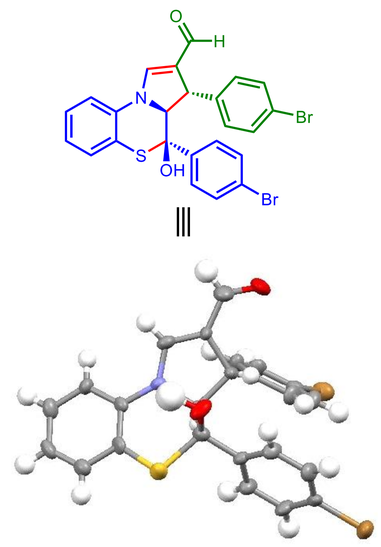


Single crystal XRD

Racemic



Chiral



Conclusion

We have developed a chiral proline derived organocatalytic system for an efficient synthesizing new chiral pyrrolo[1,4]thiazine core highly stereoselective manner *via* consecutive [3+2] cycloaddition followed by rearrangement between benzothiazolium salt and cinnamaldehyde. The protocol worked well for a wide range of functional group in good to excellent yield, with excellent enantio- and diastereoclectivity. The synthesis of new chiral pyrrolo[1,4]thiazine carbaldehyde core are fluorescent active with three contiguous stereogenic center and one quaternary carbon in a single step carried out at room temperature.

References

[1]. a) R. Narayan, M. Potowski, Z.-J. Jia, A. P. Antonchick, H. Waldmann, *Acc. Chem. Res.*, 2014, **47,** 1296-1310; b) B. Bdiri, B.-J. Zhao, Z.-M. Zhou, *Tetrahedron: Asymmetry.*, 2017, **28**, 876-899.

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[3]. a) A. N. Matralis, A. P. Kourounakis, J. *Med. Chem.*, 2014, **57**, 2568-2581; b) L. Gao, R. I. Hollingsworth, *J. Org. Chem.*, 2005, **70**, 9013-9016;

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