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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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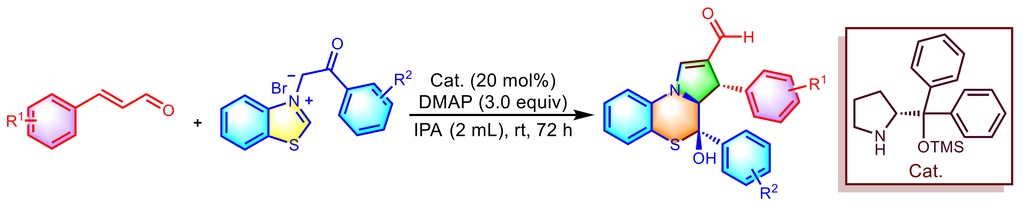
Introduction

1,4-Thiazine, benzo[1,4]thiazine, pyrrolo[1,4]thiazine and their polyhydro derivatives are privileged N, S-containing heterocyclic forms of the core present in many bioactive and pharmacological reagents.[1,2] Over the past decades, many discoveries in the medicinal chemistry, organic synthesis, and catalysis have led to new synthetic methods for various 1,4-thiazine derivatives. Several methods have been developed over the past decades to construct pyrrolo[1,4]thiazine derivatives.[3] In comparison to racemic compounds synthesis, the synthesis of enantioenriched pyrrolo[1,4]thiazine and its derivatives received much less attention. Recently, Feng *et al.* reported the synthesis of chiral thiazoles and [1,4]thiazine derivatives via catalytic asymmetric [3+2] cycloaddition and rearrangement of benzothiazloium salt with various dienophiles using chiral *N*, *N*´-dioxide/metal complex catalysts.[4] Herewith we report the development of an organocatalytic system for the synthesis of new chiral pyrrolo[1,4]thiazine core via highly stereoselective consecutive [3+2] cycloaddition followed by rearrangement between benzothiazolium salt and cinnamaldehyde. The synthesis of chiral pyrrolo[1,4]thiazine carbaldehyde core with three contiguous stereogenic center and one quaternary carbon center was carried out at room temperature utilizing chiral proline derived organocatalytic system as catalyst and DMAP as a base. The desired products were achieved with good to excellent yields with excellent enantio- and diastereoselectivity.

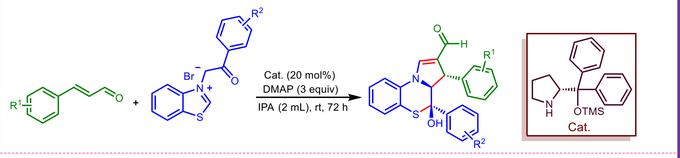


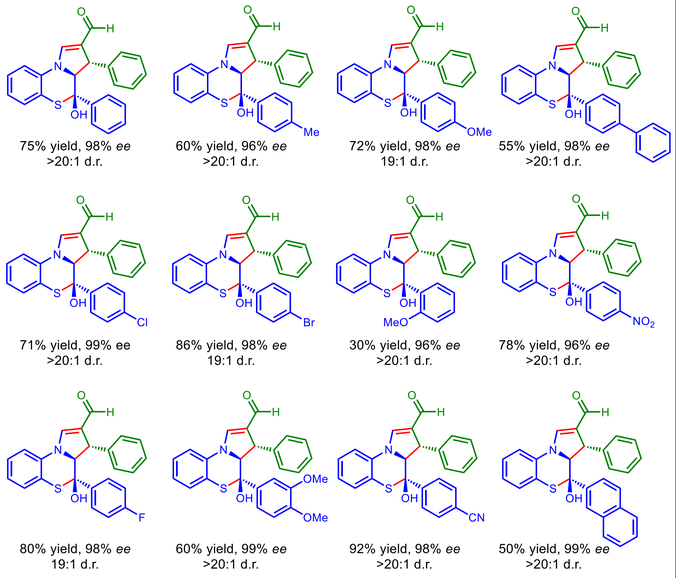
R^1 = alkyl, aryl, heterocycle, halogens
R^2 = alkyl, aryl, halogens

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

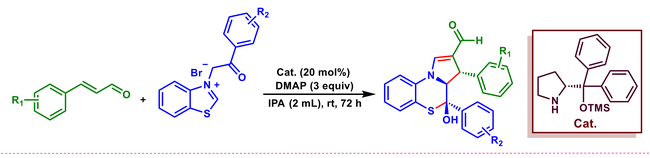
- First organocatalytic reactions of cinnamaldehyde with thiazolium salts
- Mild reaction conditions
- Good functional group tolerance
- Consecutive reaction sequence
- High enantio-and diastereoselectivity
- Fluroresent active chiral molecule
- 25 examples

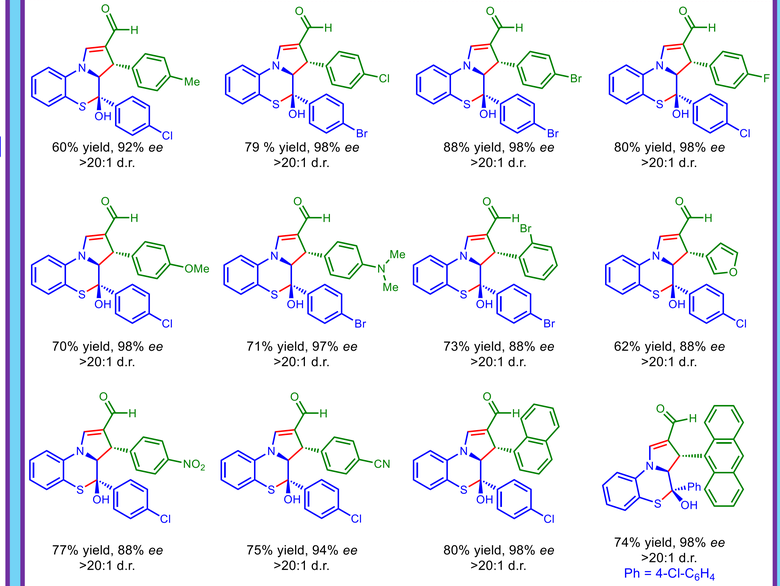
Scope for Benzothiazolium Salt



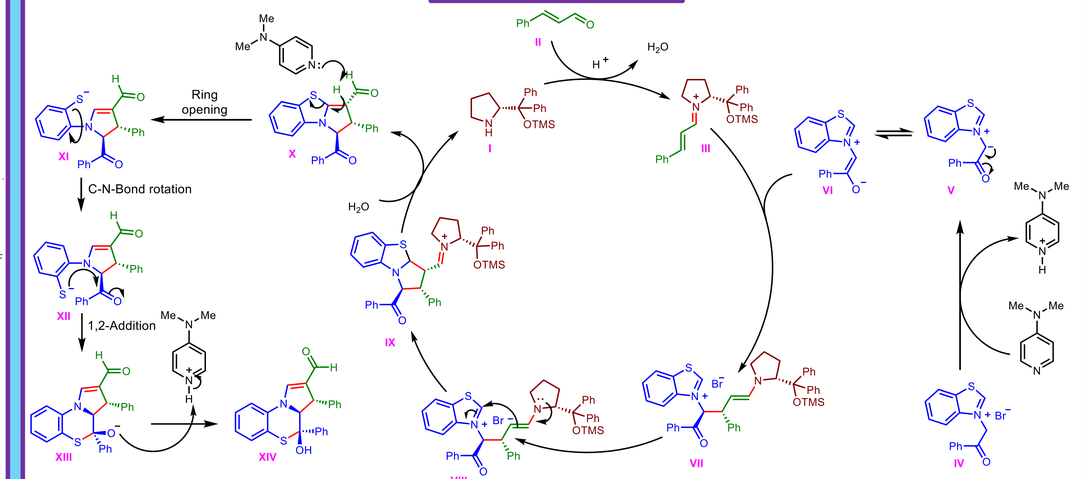


Scope for Cinnamaldehyde

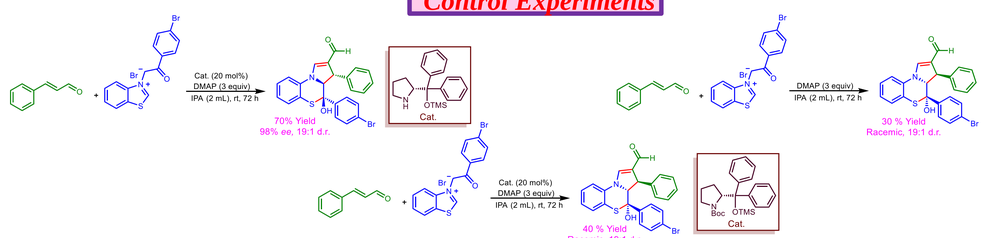




Plausible Mechanism

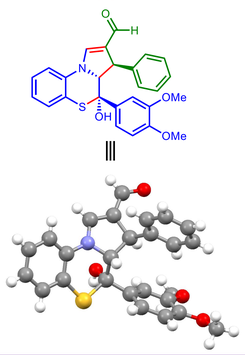


Control Experiments

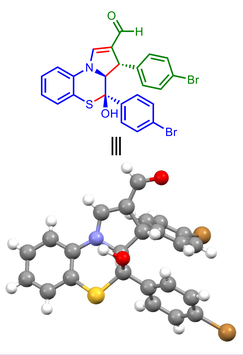


Single crystal XRD

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 with three contiguous stereogenic center and one quaternary carbon center was carried out at room temperature.

References

1. a) Badshah, S. L.; Naeem, A. *Molecules.* **2016,** *21*, 1054/1-1054/20. b) Selvakumar, N.; Reddy, B. Y.; Kumar, G. S.; Khera, M. K.; Srinivas, D.; Kumar, M. S.; Das, J.; Iqbal, J.; Trehan, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4416-4419.
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