Asymmetric Catalysis for Fine Chemical Synthesis

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A Desilylative Approach to Alkyl Substituted C(1)-Ammonium Enolates: Application in Enantioselective [2+2] Cycloadditions

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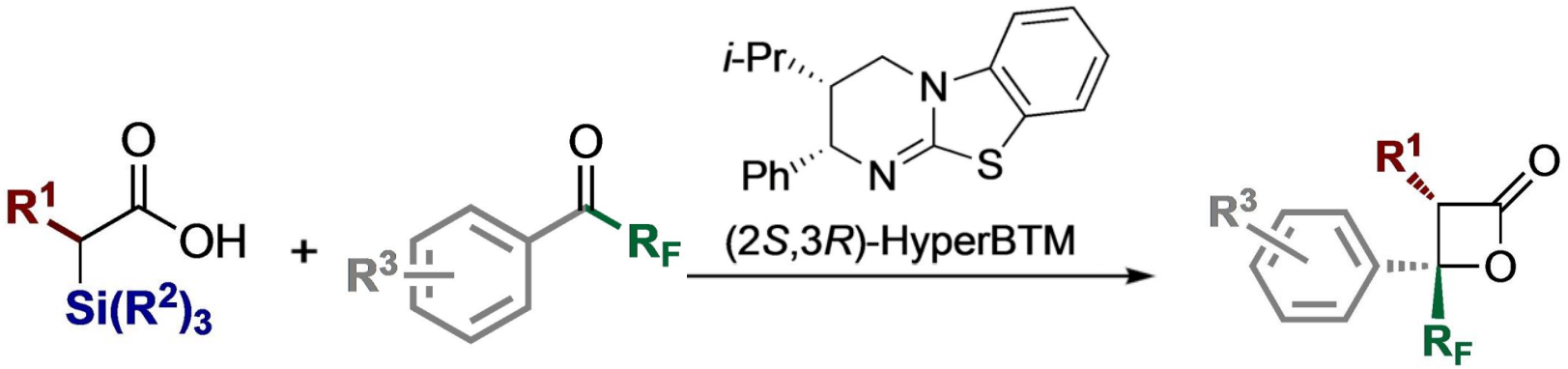
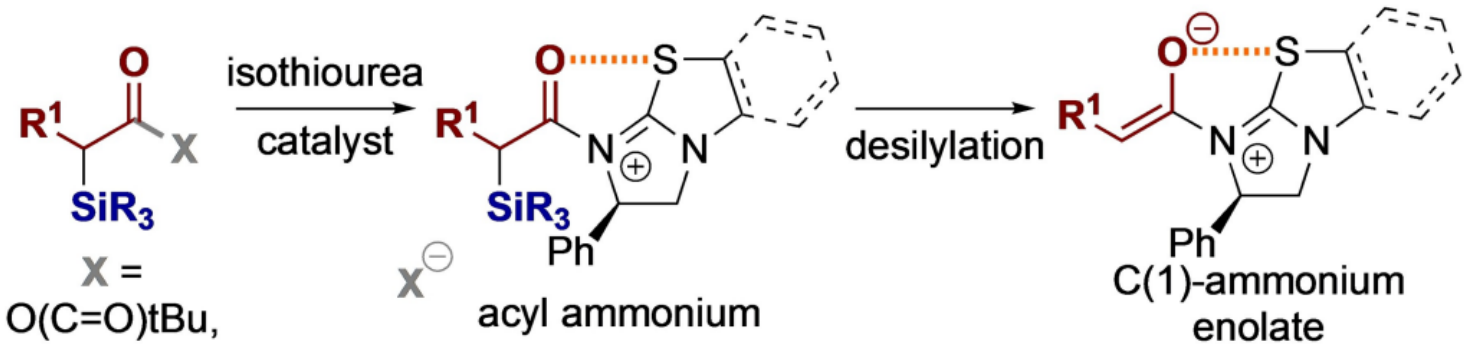
Introduction: Reaction and Reactivity

Desilylative Asymmetric [2+2] Cycloaddition via C(1)-Ammonium Enolates



- **This reaction is :** Desilylation + Tandem Aldol-Lactonization
- **Nucleophile**: C(1)-Ammonium enolate
- **Electrophile**: Perfluoroalkyl ketone
- **Catalyst**: Isothiourea (2S,3R)-HyperBTM
- **Bond formation**: C-C and C-O bonds in a [2+2] formal cycloaddition to form β-lactones

Principle of activation



HOMO activation involves the formation of a mixed anhydride, followed by isothiourea-catalyzed enolate generation via desilylation.

C(1)-ammonium enolate formation is favoured by the O-S interaction and stabilize the structure of the active species

Asymmetric induction arises from the planar symmetry imposed by the O-S interaction, which restricts C-N bond rotation, combined with the steric hindrance of the aryl group.

Catalytic Cycle and Enantioselectivity

0) In situ formation of silylated anhydride.

1) **HOMO activation** in two steps

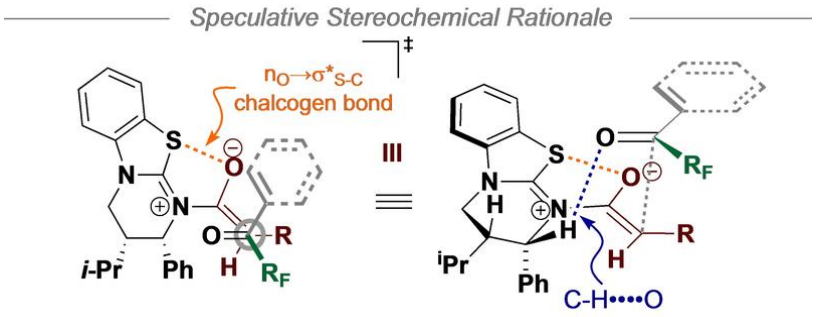
1.1) Preferencial N-acylation with (R)-enantiomer.

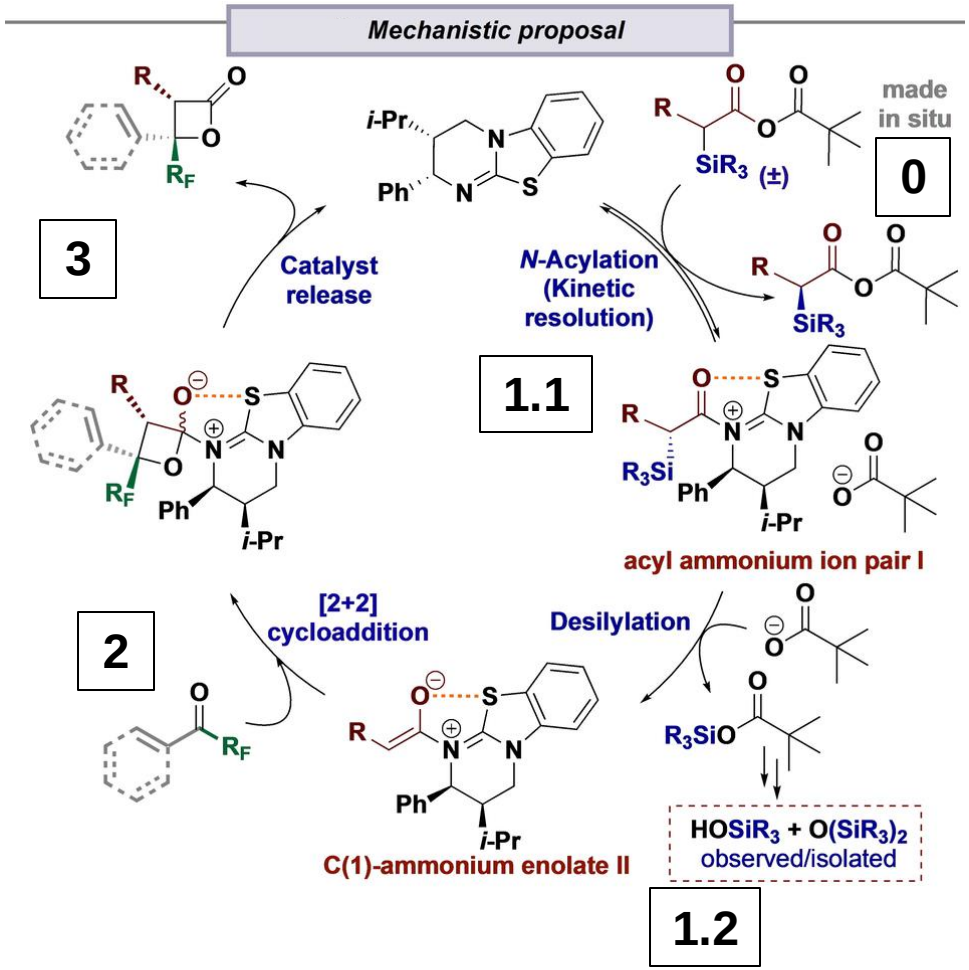
1.2) Desilylation to form (Z)-enolate via substitution or Brook rearrangement.

2) **Bond formation** by *intramolecular* formal [2+2] tandem aldol-lactonization.

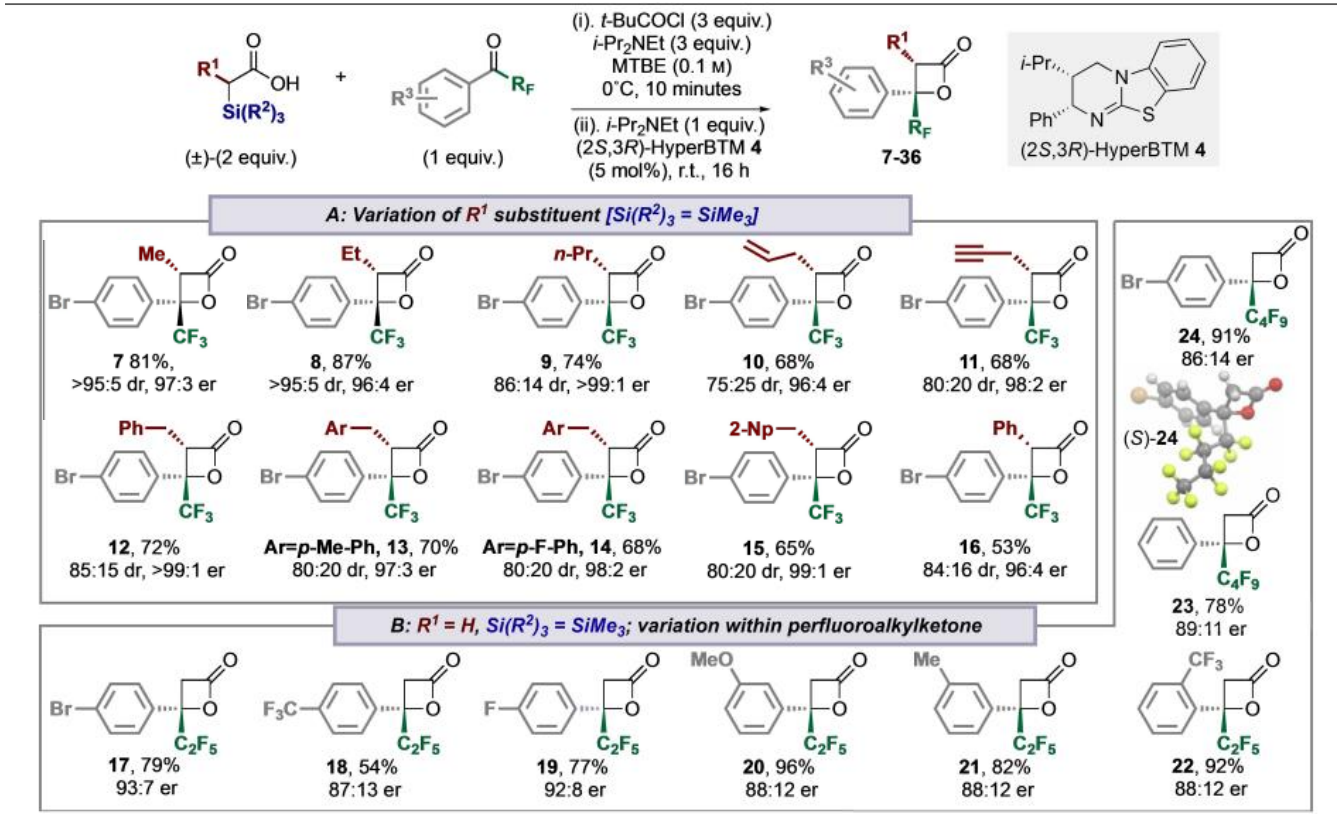
Asymmetric induction at this step.

3) **Catalyst turnover** promoted via β-lactone formation.



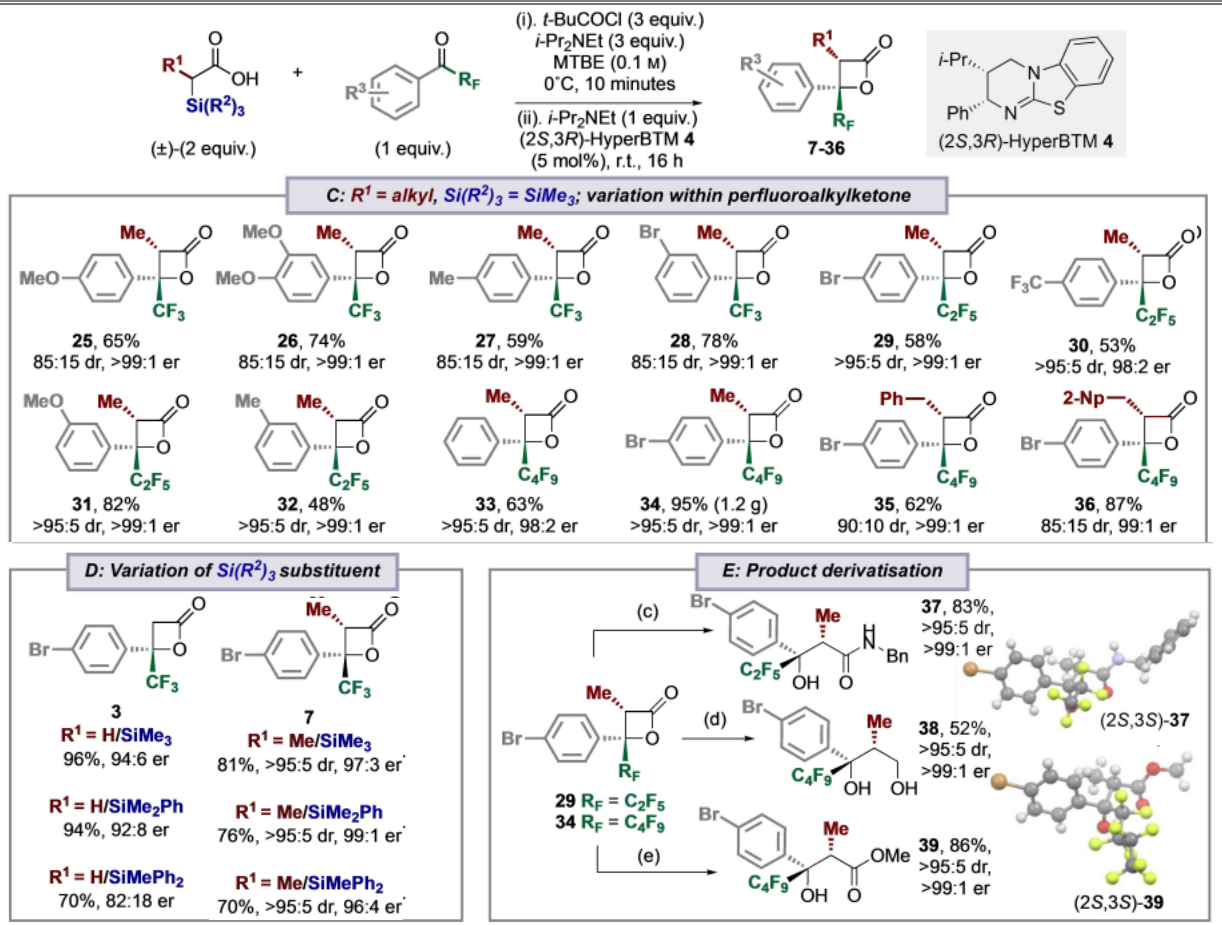


Scope and limitations



- Scope: Broad α-silyl-α-alkyl acid compatibility
- Moderate to excellent yields (53–96%)
- High diastereo- and enantioselectivity across scope
- Benchmark substrate (**compound 7**): 81%, >97:3 er
- Bulky group tolerated (**compound 15**): 65%, >99:1 er

Scope and limitations



- Limitations:
  - **Compound 30** (Br-substituted ketone): 53% yield
  - Possibly due to steric/electronic effects
- Silyl group impact:
  - $SiMe_3$ enhances *er*
  - Bulkier $SiMePh_2$ lowers selectivity (compound 7)
- Stereocontrol maintained across examples

Critical analysis: Novelty

Strong points

- Innovative desilylative access to α-alkyl C(1)-ammonium enolates.
- Avoids limitations of deprotonation methods.
- High stereoselectivity and scalability demonstrated.

Weaker points

- Requires synthesis of α-silyl acids.
- Limited to fluorinated ketones/enones.

Critical analysis: Practicability

Strong points

- Mild conditions (room temperature).
- High selectivity and reproducibility.
- Works on gram scale.
- One-pot reaction

Weaker points

- Substrate synthesis needed (α-silyl acids).
- Limited scope of ketones.
- Use of MTBE, red solvent → bad for people

Critical analysis: Sustainability

Strong points

- Mild temperatures, scalable reaction.
- Low catalyst loading, organocatalysis instead of transition metals.
- Efficient and selective.
- Formation of valuable medchem fluorinated products without excess fluorinated substrate → better environmental compatibility

Weaker points

- MTBE solvent is red → bad for environment
- Loss of the silyl group affects atom economy.
- Extra synthetic steps for substrates.

Thanks for your attention

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Questions

Question 1

What is the role of the Si substituent in the starting material? Why was it needed?

Question 2

What is the advantage of this class of isothiourea catalyst whencompare to imidazole or pyridine-based catalysts?

Question 3

Why was a fluorinated group needed on the ketone?