Quaternary stereocentres via an enantioconvergent catalytic SN1 reaction

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Quaternary Stereocenter

- Formation
  - Carbonyl \(\alpha\)-functionalization
  - Alkene cross coupling
  - Conjugate addition
  - Rearrangement or Sn2’ reaction
  - Cycloaddition

- Downsides: requires the preparation of stereochemically well-defined starting materials (such as trisubstituted olefins) and subsequent enantioselective bond formation
Previous Studies

Previous Studies

\[ \text{rac-1a} \xrightarrow{3 \ (1.0 \text{ equiv})} \text{Me} \xrightarrow{\text{MeOH}} \text{SiMe}_3 \xrightarrow{(S)-2 \ 94\% (81\% \text{ ee})} \]

\[ \text{rac-1b} \xrightarrow{3 \ (0.1 \text{ equiv})} \text{Me} \xrightarrow{\text{MeOSiMe}_3} \xrightarrow{-\text{Me}_3\text{SiOSiMe}_3} \text{Me} \xrightarrow{(S)-2 \ 96\% (98.9\% \text{ ee})} \]

Previous Studies

\[
\text{MeO} \quad \text{OH} \quad \text{Ph} \quad \text{Me indole (2a; 2.0 equiv) cat. (10 mol\%)} \quad \text{solvent (0.1 M)} \quad \text{RT, 12 h} \quad \text{MeO} \\
1a \text{ (racemic)} \quad \xrightarrow{\text{3a} / 4a[^a]} \quad 3a \quad + \quad 4a \\
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>Solvent</th>
<th>(3a / 4a[^a])</th>
<th>(3a) Yield [%][^a]</th>
<th>ee [%][^b]</th>
</tr>
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<tbody>
<tr>
<td>9</td>
<td>B5</td>
<td>CH(_2)Cl(_2)</td>
<td>&gt; 20:1</td>
<td>87</td>
<td>80</td>
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</table>

(R)-B5: R = 9-phenanthryl

Lewis acid enhancement HBD for asymmetric catalysis

Jacobsen’s approach from SN1 reaction

b. The SN1 approach to the construction of quaternary stereocentres described here. c, Enantioselective allylation of propargyl acetates using chiral squaramide catalysts and TMSOTf as a promoter. LG, leaving group; Np, naphthyl; TMS, trimethylsilyl.
Reaction Optimization

\[
\begin{align*}
\text{AcO} & \quad \text{Me} & \quad \text{TMS} \\
\text{Ar} & \quad \text{Me} & \quad \text{TMS} \\
(\pm)-2a, \text{Ar} = 1-\text{Np} \quad \text{Catalyst (10 mol\%)} \quad \text{TMSOTf (1.0 equiv.)} \\
\text{Et}_2\text{O} (0.1 \text{ M}), -78 ^\circ \text{C}, 18 \text{ h} \quad \text{Me} & \quad \text{Ar} & \quad \text{TMS} \\
3a & \quad + & \quad 4a \\
\text{1a: } R = \text{H} & \quad \text{1b: } R = \text{Me} \\
\text{1c: } X = \text{S} & \quad \text{1d: } X = \text{O} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>3a:4a</th>
<th>e.e. 3a (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>1:1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>40:1</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>1b</td>
<td>3.4:1</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>1c</td>
<td>2.9:1</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>1d</td>
<td>3.3:1</td>
<td>-3</td>
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</table>
Substrate Scope

![Chemical reactions and structures showing substituent effects and polarizability of aromatic rings.](image)
SN1-type ionization mechanism
Substrate Scope

- Stabilizing aromatic interactions are likely to serve as a contributing factor in enantiodifferentiation.
- Steric congestion near the reaction site also correlates with enantioselectivity.
Substrate Scope

Heterocyclic substrates

95%, 92% e.e.  
>100:1 (3l:4l)

88%, 94% e.e.  
>100:1 (3m:4m)

85%, 93% e.e.  
>100:1 (3n:4n)
Mechanistic studies

- Monitoring disappearance of 2b using in situ infrared spectroscopy reaction obeys a first-order rate
- Reaction has dependence on the concentration of 2b and has no rate dependence on the concentration of allyltrimethylsilane
Mechanistic studies

sub-first-order dependence of the reaction rate on the concentration of TMSOTf, and a first-order dependence of the reaction rate on the concentration of 1a
Proposed catalytic mechanism
Elimination by-product was irreversible
Enantioselective
Enantiodetermining Step

the first C–C bond-forming step is irreversible and therefore enantiodetermining.
Conclusion

• Cooperative effect of chiral squaramides and TMSOTf generates tertiary carbocations that lack heteroatom stabilization from racemic precursors
• Controls enantioselectivity in additions of a carbon-centred nucleophile, and attenuates undesired elimination pathways.