Requirements for an Effective Chiral Auxiliary Enolate Alkylation

1. $X_c$ must be low cost, and available in both enantiomeric forms
2. The cleavage of $X_c$ from the substrate must occur under mild enough conditions so that racemization is avoided.
3. The pi-facial selectivity of electrophile attack on the enolate will be dictated by steric factors.
4. Either $E$ or $Z$ enolate should be formed exclusively.
5. Metal ion chelation provides a rigid template and a single conformation, so that the steric factors of the auxiliary can enforce facial bias in electrophile attack on the enolate.
Early examples of Chiral auxiliaries for enolate alkylation

2-Oxazolines as Carbonyl Equivalents

phenyl shields top face

\[
\text{Ph} \quad \text{O} \quad \text{N} \\
\text{O} \quad \text{C} \quad \text{H}_3
\]

\[
\text{LDA} \quad \text{EtI}
\]

\[
\text{Ph} \quad \text{O} \quad \text{N} \\
\text{O} \quad \text{C} \quad \text{H}_3
\]


Prolinol amides:

\[
\text{OH} \\
\text{NH}
\]

\[
\text{Cl}
\]

\[
\text{OH} \\
\text{N}
\]

\[
\text{Cl}
\]

\[
\text{OH} \\
\text{N}
\]

\[
\text{Cl}
\]

\[
\text{Ph}
\]

\[
\text{H}
\]

\[
\text{H}
\]

\[
\text{H}
\]

\[
\text{H}
\]

78% ee

76% de

N->O acyl migration, general base cat. hydrolysis

1N HCl/ NaHCO₃

*TL*, 1980, 4233

*JACS*, 1990, 5290.
Enantiocomplementary Reagents:

JACS, 1982, 104, 1737.

Acylaton provides imides, closer to esters in terms of acidity, enolate nucleophilicity, and cleavage chemistry:
Less Reactive Electrophiles: Use sodium enolate

Alternatively, use triflate:

Enolate Oxidation- use Davis Oxaziridine: *JACS*, 1985, 4346

Pseudoephedrine as a Chiral Auxiliary

cheap, commercially available chiral amino alcohols


electrophile enters from the same face as methyl group

epoxides and alkyl halides attack opposite faces of the enolate due to lithium coordination of the epoxide O

Myers, *JOC*, **1996**, 61, 2428
Challenge: Remove Chiral Auxiliary w/o Racemization

Reduction: LiNH₂BH₃
Iterative Synthesis of 1,3 n-Substituted Carbon Chains

Camphor-Based Auxiliaries

Helmchen Chiral Ester Enolate

HMPA breaks up higher order lithium enolate aggregates!

Enolization leakage in the presence of HMPA

ACIEE, 1981, 20, 207
ACIEE, 1984, 23, 60
TL, 1983, 24, 1235
TL, 1983, 24, 3213
Camphor-Based Auxiliaries

Oppolzer Camphorsultam

Oppolzer, *TL*, 1989, 41, 5603

no racemization under these hydrolysis conditions

97% de
Chiral Metalloenamines and Metallated Hydrazones


C-2 Symmetric Amine Auxiliaries

Catalytic Methods for Asymmetric Alkylation

![Chemical structure](image)

**Chiral phase-transfer catalyst**


Ph$_2$N=C=O + R-X $\xrightarrow{\text{1, 10mol\%}}$ Ph$_2$N=C=O$_{\text{tBu}}$

$\begin{array}{c}
\text{R=} \\
\text{\quad -(CH}_2\text{)}_4\text{Cl} \\
\text{\quad -(CH}_2\text{)}_2\text{CO}_2\text{CH}_3 \\
\text{\quad -(CH}_2\text{)}_2\text{COEt} \\
\text{\quad \text{99}} \\
\text{\quad \text{95}} \\
\text{\quad \text{91}} \\
\text{\quad \text{99}}
\end{array}$