Enantioselective Michael Additions in Natural Products Synthesis

MacMillan Group Meeting
12 December 2001
Julie Y. Park

I. Introduction
II. Early Examples
III. Misc. Auxiliaries
IV. Amide Enolates
V. Chiral Imines and Enamines
VI. Chiral Sulfinyl Imines
VII. Chiral Sulfoxides
VIII. Phase-Transfer Catalysts
IX. Heterobimetallic Catalysts
X. Summary
Introduction

Definition of Michael addition:

\[
\begin{array}{c}
\text{R}^1 \text{Z}^1 \\
\text{R}^2 \text{Z}^2 \\
\rightarrow \\
\text{R}^1 \text{Z}^1 \\
\text{R}^2 \text{Z}^2
\end{array}
\]

- Carbon-carbon bond-forming reaction
- Addition of a compound with an electron-withdrawing group (Z) to an activated C-C multiple bond
- Excludes metal-mediated 1,4-conjugate addition (cuprates, Grignards, lithiates, etc.)
- Excludes heteroatom conjugate addition

Representative Michael donors:

\[
\begin{array}{cccc}
\text{R} \text{O} & \text{R} \text{NR} & \text{R} \text{S} \text{R} & \text{R} \text{NO}_2
\end{array}
\]

Representative Michael acceptors:

\[
\begin{array}{cccc}
\text{O} \text{O} & \text{+NR}_2 & \text{S} \text{R} & \text{NO}_2
\end{array}
\]

- The same functional groups serve to activate either the nucleophile or the electrophile
- A wide variety of functional handles that can be further elaborated in synthesis

Early Examples of Enantioselective Michael Reactions

Synthesis of optically active cyclopropanes:

\[
\begin{array}{c}
\text{OEt} \\
\text{Me}
\end{array}
\quad
\begin{array}{c}
\text{O} \\
\text{Cl}
\end{array}
\quad
\begin{array}{c}
\text{OH}^+ \\
\text{RO}_2 \text{C}
\end{array}
\]


Chiral base catalyzed Michael addition forms chiral quaternary center:

\[
\begin{array}{c}
\text{Me} \\
\text{O}
\end{array}
\quad
\begin{array}{c}
\text{R} \\
\text{Me}
\end{array}
\quad
\begin{array}{c}
\text{R} \text{CO}_2 \text{Me}
\end{array}
\]

optically active product of undetermined stereochemistry

**Auxiliary-Controlled Asymmetric Induction**

Oppolzer's synthesis of (-)-khusimone:

\[
\text{RO}_2C\text{Me} \text{Me} \xrightarrow{\text{LDA, } \text{Br}} \xrightarrow{\text{Mg ene cyclization, Enolate alkylation}} (-)\text{-Khusimone}
\]

63:21:9 dr

**Stereochemical rationale:**

- Alpha face of enolate is shielded by the auxiliary
- Enantiofacial discrimination of the enone determined by sterics and chelating factors which favor model A.


---

**Auxiliary Control: Enantioselective Robinson Annulation**

Taber's synthesis of (+)-o-methyljoubertiamine

\[
\text{OMe} \xrightarrow{\text{MVK, } \text{K}_2\text{CO}_3, \text{CH}_2(\text{OMe})_2/\text{H}_2\text{O}} \xrightarrow{\text{MeOCH=PH}_3, \text{H}_2\text{O}^+} \xrightarrow{\text{NaBH}_4, \text{BnBr, NaH}} \xrightarrow{\text{HgO/}B\text{F}_2\text{OE}_2, \text{p-TSA}} \xrightarrow{\text{Me}_3\text{SiCl/Nal, Me}_2\text{NH}} (+)\text{-o-Methyljoubertiamine}
\]

90% de, 76% yield

Factors in choosing \(\text{K}_2\text{CO}_3\) as base:

- weak base to quench intermediate ketone enolate
- chelating counterion

**Auxiliary Control: RAMP and SAMP Technology**

- (R)- or (S)-1-glycine-2-methoxymethylpyrrolidines
- Developed by Enders and coworkers
- Commercially available or easily prepared from (S)-proline or (R)-glutamic acid
- Form hydrazones in quantitative yield, even from sterically hindered ketones
- Anions are often more reactive than aldehyde or ketone enolates
- Auxiliary is easily cleaved and recycled


Application in the synthesis of ant pheromones:

![Chemical diagram for ant pheromone synthesis](attachment:image.png)


---

**Auxiliary Control: Total Synthesis of (−)-Secodaphniphylline**

Asymmetric induction using a C₂-symmetric N-acyl pyrrolidine

![Chemical diagram for total synthesis](attachment:image.png)

- Initial Michael addition–alkylation sets three contiguous stereocenters
- Stereochemistry of substituents on cyclopentane determine stereochemistry of methyl homosecodaphniphyllate


Evans Oxazolidinone

Evans acyl oxazolidone addition to nitroalkenes – α-amino stereocenter:

\[
\begin{align*}
\text{Bn} & \quad \text{Me} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

1) NaHDSM
2) BnO-\text{Me}

\[
\begin{align*}
\text{NO}_2 & \quad \text{Obn} \\
\text{MeO} & \quad \text{OMe} \\
\end{align*}
\]

88% de

(\(\text{R}\))-(-)-Rolipram


\(\text{C}_{26}-\text{C}_{32}\) fragment of calyculin A – 1,4-functionality via Curtius rearrangement:

\[
\begin{align*}
\text{Me} & \quad \text{Bn} \\
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{N} \\
\end{align*}
\]

1) Ti(OiPr)\text{Cl}_3, \text{iPr}_2\text{NEt}

\[
\begin{align*}
\text{CO}_2\text{Bu} & \quad \text{Me} \\
\text{X} & \quad \text{X} \\
\text{CO}_2\text{Me} & \quad \text{OH} \\
\text{BOC} & \quad \text{H} \\
\end{align*}
\]

DPPA, Et\text{3}N

\[
\begin{align*}
\text{tBuOH} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{X} & \quad \text{X} \\
\text{CO}_2\text{Me} & \quad \text{OH} \\
\text{BOC} & \quad \text{H} \\
\end{align*}
\]


Chiral Amide Enolates

Vicinal stereocontrol:

\[
\begin{align*}
\text{N} & \quad \text{OH} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
\]

1) LDA, THF, \(-78{\degree}\text{C}\)

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{CO}_2\text{Et} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{OH} & \quad \text{OH} \\
\end{align*}
\]

(+)\text{-dehydroiridodial}

16% overall yield, 85% ee

\[
\begin{align*}
\text{N} & \quad \text{OH} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
\]

1) LDA, THF, \(-78{\degree}\text{C}\)

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{CO}_2\text{Et} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{OH} & \quad \text{OH} \\
\end{align*}
\]

(+)\text{-isodehydroiridodial}

4.6% overall yield, 79% ee

Model for stereoselectivity:

- Amide enolates prefer (Z) geometry
- Bulky amides prefer TS A, yielding the anti product.

**Chiral Imines and Enamines**

(R)- or (S)-phenethylamine as a source of chiral induction:
- Effects conversion of racemic stereocenters into enantiomerically enriched products.
- Construction of asymmetric quaternary carbon centers.
- Chiral amine is inexpensive (< $1/g).
- Amine is easily recovered with no loss of optical purity.

Regio- and stereoselectivity affected by cyclic transition state – syn approach of substituents:

- Internal proton transfer only allowed for the more substituted enamine:

  ![Regio- and stereoselectivity affected by cyclic transition state](image)

  
  - Only enamine A has syn orientation of enamine and proton


---

**Chiral Imines and Enamines**

Application in the synthesis of (+)-valencenol via Robinson annulation:

![Application in the synthesis of (+)-valencenol via Robinson annulation](image)

- Used as a synthetic equivalent for the unreactive trans-2-pentenone


Application to alkaloid synthesis:

![Application to alkaloid synthesis](image)

  
Chiral Imines and Enamines

Enantioselective route to steroid precursors:

\[
\begin{align*}
\text{HN} & \quad \text{MVK} \quad \text{NaOMe, MeOH} \\
\text{OMe} & \\
\text{HN} & \quad \text{Me} \\
\text{HN} & \quad \text{Me} \\
\text{HN} & \quad \text{Me} \\
\end{align*}
\]


Synthesis of spirocycles:

\[
\begin{align*}
\text{CH}_3\text{OMe} & \quad 1) \text{AcO-NO}_2 \\
& \quad 2) \text{chromatography} \\
& \quad 1) \text{H}_2\text{O-CHO} \\
& \quad 2) \text{LiAlH}_4 \\
& \quad 3) \text{HCl} \\
\end{align*}
\]

\[(S)-(+)-Polyzonimine \quad 76\% \text{ ee} \]


Chiral Sulfanyl Imines

Asymmetric entry into alkaloid synthesis:

\[
\begin{align*}
\text{1} & \quad \text{LDA} \\
& \quad \text{NaCNBH}_3 \quad \text{AcOH} \\
& \quad 1) \text{Raney Ni} \\
& \quad 2) \text{LiAlH}_4 \\
\end{align*}
\]

Proposed stereochemical rationale for selective reduction:

Factors governing stereoselectivity:

- Hydride delivery occurs from the less hindered face, resulting in overall syn selectivity.
- Delivery of a proton from the coordinated acid creates a stereocenter adjacent to the bulky sulfanyl group.
- Steric interference between aryl protons and vicinal protons favor conformation A.

**Chiral Sulfinyl Imines: Alkaloid Synthesis**

1. \( \text{LDA, } \text{CO}_2\text{Me} \rightarrow 1) \text{LDA, } \text{CO}_2\text{Me} \rightarrow 2) \text{NaCNBH}_3, \text{AcOH} \)

2. 1) Raney Ni, 2) LiAlH₄

3. OTBS

Indolo[2,3-α]-quinolizidine 54% overall yield

4. LDA, \( \text{CO}_2\text{Me} \rightarrow 84:1 \text{dr} \)

5. (-)-Yohimban 18% overall yield


**Chiral Sulfinyl Imines: Functionalized Electrophiles**

1. \( \text{OTBS, NHBoc} \rightarrow \) Raney Ni, 2) BH₃*THF

2. 1) TBAF, 2) Ac₂O, pyr. 3) TMS-I

Methyl α-amidoacrylate does not react with organocuprate reagents.

Poor selectivities limit the utility of this methodology.

Stereochemical rationale:

Chiral Vinylic Sulfoxides

First reported in literature in 1971:


Application in total synthesis:


Chiral Vinyl Sulfoxides: Tandem Hetero-Michael–Michael reaction

A new twist on Posner:

**Chiral Allylic Sulfoxides: Vinylogous Michael Additions**

Camphor-derived chiral sulfoxides:

![Chemical structure of camphor-derived chiral sulfoxides](image)

LDA, THF

Hanessian's chiral phosphonamides:

![Chemical structure of Hanessian's chiral phosphonamides](image)

- Phosphonamide anion adds to a variety of $\alpha,\beta$-unsaturated enones, lactams, lactones and esters

Application to synthesis:

![Chemical reaction scheme](image)

(-)-Methyl Jasmonate
3 steps
26% overall yield
90% ee

**Phase-Transfer Catalysis: Chiral Quaternary Ammonium Salt**

Early example of cinchona alkaloid catalyzed Michael addition:

![Chemical structure of early example of cinchona alkaloid catalyzed Michael addition](image)

100% yield, 25% ee

**Michael addition of an unactivated ketone:**

![Chemical structure of Michael addition of an unactivated ketone](image)

(R)-2

95% yield, 80% ee

- Using an epimeric cinchonidine catalyst, the opposite enantiomer can be obtained, but only with modest selectivity:

![Chemical structure of Michael addition of an unactivated ketone with epimeric catalyst](image)

(S)-2

52% ee

**References**

**Phase-Transfer Catalysis: The Corey Approach**

- Used in enolate alkylations, epoxidations, conjugate additions
- Shielding of three quadrants formed by tetrahedral ammonium ion
- Close ion pairing of the substrate in remaining quadrant provides selectivity
- Limited by strict substrate specificity

Asymmetric Michael addition of Schiff base:

\[
\begin{align*}
\text{Ph} & \quad \text{CN} \\
\text{Ph} & \quad \text{OtBu} \\
\text{Ph} & \quad \text{OTs} \\
\end{align*}
\]

10 mol% catalyst 1

50% KOH-CH₂Cl₂

85% yield, 91% ee

\(\text{(S)-Ornithine} \quad 53\% \text{ overall}\)


**Phase-Transfer Catalysis: Robinson Annulation**

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{MeO} & \quad \text{MeO} \\
\end{align*}
\]

10 mol% catalyst

50% KOH, PhMe

72% yield, 80% ee


Stereochemical rationale:

- Enolate is contact ion paired with N⁺
- \(\alpha,\beta\)-enone is wedged between ethyl and quinoline substituents
- Carbonyl poised for ion pairing in enolate transition state

Phase Transfer Catalysis

Synthesis of a chiral γ-amino acid:

![Chemical structures and reactions](image)

- Follows the same model for close ion pairing as the previous two examples


---

Heterobimetallic Catalysts

- Developed by Shibasaki and coworkers
- Catalysts function as both Bronsted base and Lewis acid and can catalyze a variety of reactions
- Complex between alkali metal (Na, Li) and either rare-earth (La, Eu, Pr, Nd) or Group 13 (Al, Ga)

Structures of complexes:

![Complex structures](image)

Acronyms: \(\text{LnMB Ln} = \text{rare-earth metal} \ M = \text{alkali metal} \ B = \text{tris(binaphtoxide)} \ ALB A = \text{Al, L = Li}\)

**Heterobimetallic Catalysts: Asymmetric Michael Reaction**

![Chemical reaction diagram]

- LSB (Lithium sodium tris(binaphthoxide)) is the best complex for these transformations
- Excellent yields and good ee's (74-91%) for a range of substrates
- Proposed catalytic cycle:

![Catalytic cycle diagram]


---

**ALB catalysts in Michael Additions**

- Prepared from BINOL and LiAlH₄:

![Catalytic cycle diagram]

- Electropositive lithium should form lithium enolate preferentially over aluminum enolate
- NMR studies with ALB and 3 equiv. of cyclohexenone show that enones coordinate to aluminum center
- ALB acts as a *multifunctional catalyst*
- Reaction of lithium enolate with enone should generate aluminum enolate – potential for three-component coupling

**ALB: Application to Total Synthesis**

1) LiOH, THF/H2O
2) HOBr, DCC, DMAP, H2N
3) BH3·THF

Key features:
- Regioselective Fischer indole synthesis
- Oxidative formation of tetracycle 1
- Fifth ring closed via thionium ion

20-Deethylrubifolidine

7% overall yield


---

**ALB: Application to Total Synthesis**

Three-component coupling as key step in synthesis of 11-deoxy-PGF1α

| Reaction Steps | 5 mol% (S)-ALB | | 1) MeCl, DMAP, PhMe | | 1) L-selectride | | TBSQ |
|---|---|---|---|---|---|---|
| 1) Rhl(PPh3)3Cl, Et3SiCl | | | 2) TBSOTf | | 2) TBSOTf |
| | 2) HF | | | | 2) TBSOTf |
| | | | | | |
| 1) H2, Pd/C | | | | | |
| 2) Pb(OAc)4 | | | | | |
| 3) K2CO3 | | | | | |

Cyclopentanone 2 was also obtained by Barton deoxygenation of 1 as a single diastereomer in 24% yield.

**Summary**

- The Michael reaction is one of the most powerful carbon-carbon bond-forming reactions in organic synthesis
- Both the Michael donor and Michael acceptor have activating groups that can serve as functional handles
- Asymmetric induction can originate from either the donor or acceptor
- Enolate intermediate opens pathways for tandem Michael–electrophile trapping reactions
- Facile construction of vicinal and quaternary stereocenters, including spirocyclic and polycyclic structures
- Few examples of catalytic asymmetric reactions in total synthesis
- *A great deal of potential remains for the asymmetric Michael reaction to be used as a powerful tool in synthesis*