Asymmetric Organocatalysis with N-Heterocyclic Carbenes

History and Recent Developments

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Early Developments
The Benzoin Condensation

- 1832: First report of benzoin condensation by Wöhler and Liebig

\[
\text{PhCH}_2\text{CO}_2\text{H} + 2\text{CN}^- \rightarrow \text{PhCH}_2\text{CNPh} + 2\text{H}_2\text{O}
\]

- 1903: Mechanism proposed by Lapworth

\[
\text{PhCH}_2\text{CNPh} + \text{H}_2\text{O} \rightarrow \text{PhCH}_2\text{CNPh} + \text{H}_2\text{O}
\]

Thiamine (Vitamin $B_1$)

Enzymatic Acyl Anion Generation

- Thiamine is responsible for the generation of acyl anion equivalents in a number of biochemical reactions

\[
\begin{align*}
\text{R} & \text{C} & \text{O} & \text{O} & \text{R} \\
\text{O} & \text{N} & \text{H} & \text{M} & \text{e} \\
\text{N} & \text{H} & \text{M} & \text{e} & \text{S} \\
\text{thiamine} & & & & \\
\text{CO}_2
\end{align*}
\]

- Most commonly found as the co-enzyme thiamine diphosphate (TDP)

\[
\begin{align*}
\text{R} & \text{O} & \text{O} & \text{R} & + \\
\text{O} & \text{N} & \text{H} & \text{M} & \text{e} \\
\text{N} & \text{H} & \text{M} & \text{e} & \text{O} \\
\text{thiamine diphosphate (TDP)} & & & & \\
\text{CO}_2
\end{align*}
\]

- Pyruvate decarboxylase
- Pyruvate oxidase
- Pyruvate dehydrogenase
- Transketolase

**Early Developments**

*Thiamine-Catalyzed Benzoin Condensation*

- 1943: Ugai discovered that thiazolium salts could replace cyanide in benzoin condensations

A variety of other thiazolium compounds were also demonstrated to be effective catalysts

1954: Mizuhara demonstrated that thiamine could catalyze a number of reactions that had also been observed in biological systems.

\[ \text{MeCH}_2\text{CHO} + \text{MeCO}_2\text{R} \rightarrow \text{MeCO}_2\text{Me} + \text{MeCHO} + \text{AcOH} \] (for \( R = \text{Me} \))

\[ \text{MeCH}_2\text{CHO} + \text{MeCO}_2\text{R} \rightarrow \text{MeCO}_2\text{Me} + \text{MeCO}_2\text{H} + \text{CO}_2 \] (for \( R = \text{OH} \))

Showed that the thiazolium moiety of thiamine was responsible for the catalytically activity.

Early Developments

Mechanism of the Thiamine-Catalyzed Benzoin Condensation?

Reactions such as pyruvate decarboxylation and benzoin-type condensations catalyzed by thiamine (vitamin B₁) dependent enzymes were considered some of the most "mysterious" transformations.

1958: Breslow demonstrated that the C-2 proton of thiazoliums exchanges rapidly with deuterium.

Breslow, R. J. Am. Chem. Soc. 1958, 80, 3719.
1958: Breslow proposed his mechanism for the thiazolium catalyzed benzoin condensation.

Breslow, R. J. Am. Chem. Soc. 1958, 80, 3719.
From 'Laboratory Curiosities' to Catalysis Mainstays

Synthesis of Stable N-Heterocyclic Carbenes

Since the mechanistic work by Breslow, NHCs were only considered as highly reactive intermediates.

Their high reactivity made the isolation of such species seemingly impossible, with dimerization being a major reaction pathway.

This was the case until 1968, when seminal work by the groups of Wanzlick and Öfele demonstrated that NHCs could be isolated in their metal-ligated forms.
Wanzlick and Öfele

1968: First isolation of ligated NHCs

- Wanzlick et al isolated a mercury complexed NHC

\[
\text{EtO}_2\text{C-N=NS-Ph} \xrightarrow{\text{conc. HCl}} \text{Ph-N=NS-Ph} \xrightarrow{1) \text{HNO}_3, 2) \text{NaClO}_4} \left[\text{Hg(NHC)}\right]^{-}\text{[ClO}_4^-]^{-}
\]

- Isolated as colourless plates
- Structure confirmed by \(^1\text{H NMR}\)

Öfele isolated a chromium NHC complex while trying to generate dehydro-complexes from heterocyclic salts.

Despite these advances, the field remained relatively inactive for 23 years until a breakthrough discovery by the group of Arduengo.

Öfele, K. J. Organomet. Chem. 1968, 12, 42.
Arduengo

1991: First isolation of a stable crystalline NHC

- Isolated the free carbene by deprotonation of a bis-adamantyl imidazolium chloride

\[
\begin{align*}
\end{align*}
\]

- The structure was unequivocally established by single-crystal X-ray analysis
  - Thermally stable in the absence of oxygen and moisture

- The synthesis of isolable NHCs was instrumental in causing the explosion in interest in *stable carbene chemistry*
Isolable NHCs

Explosion in the Number of Reported Isolations

After the first report from Arduengo in 1991, many other groups reported successful syntheses of a variety of new NHCs.

- Arduengo et al. 1992
- Enders et al. 1995 (first commercially available carbene)
- Herrmann et al. 1996
- Arduengo et al. 1997

- Arduengo et al. 1992
- Arduengo et al. 1995
- Herrmann et al. 1996

Isolable NHCs

Stability

- Original reports suggested that isolation was due to sterics preventing dimerization.

- The isolation of the carbene from 1,3,4,5-tetramethylimidazolium chloride suggested that electronic factors may have greater impact on the stability of carbenes than sterics.

**Isolable NHCs**

**Stability**

- Electronic factors operating in both the $\pi$ and $\sigma$ frameworks result in a "push-pull" synergistic effect to stabilize the carbene.

- $\pi$ donation into the carbene from the out-of-plane $\pi$ orbital stabilizes electrophilic reactivity

- $\sigma$ withdrawal by electronegative atoms stabilizes nucleophilic reactivity

- The combined effect is to increase the singlet-triplet gap and stabilize the singlet-state carbene over the more reactive triplet-state carbene


Isolable NHCs

Reactivity: Why are they so useful?

- NHCs are exceptionally good $\sigma$ donors so form strong metal–carbon bonds:

- Compared to phosphines, NHCs form complexes that:
  - are more straightforward to prepare (due to in situ NHC formation)
  - show greater air and thermal stability
  - often have catalytic activities 100 to 1000 times greater

 Singlet carbenes of NHCs are distinct Lewis bases that show both $\sigma$ basicity and $\pi$ acidity:

 - Allows for the generation of a second nucleophile during a reaction (e.g. Breslow intermediate)
 - This unique "doubly" nucleophilic aspect allows NHCs to react as powerful organocatalysts

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Isolable NHCs

Reactivity: Why are they so useful?

- These factors have resulted in a huge increase in interest in NHCs over the past 70 years
**N-Heterocyclic Carbenes In Enantioselective Organocatalysis**

*Modes of Reactivity*

**Acyl Anions**

\[
\begin{align*}
\text{R} & \text{O} \\
\text{R} \text{CH} & \text{H} \\
\text{R} \text{N} \text{N} \\
\end{align*}
\]

\[
\begin{align*}
\rightarrow \\
\text{R} \text{N} \text{N} \\
\text{R} \text{N} \text{N} \\
\text{O} \\
\text{R} \\
\end{align*}
\]

\[
\begin{align*}
\text{R} \text{N} \text{N} \\
\text{R} \text{N} \text{N} \\
\text{O} \\
\text{R} \\
\rightarrow \\
\text{R} \text{O} \\
\end{align*}
\]

**Homoenolates**

\[
\begin{align*}
\text{R} & \text{O} \\
\text{R} \text{CH} & \text{H} \\
\text{R} \text{N} \text{N} \\
\end{align*}
\]

\[
\begin{align*}
\rightarrow \\
\text{R} \text{N} \text{N} \\
\text{R} \text{N} \text{N} \\
\text{O} \\
\text{R} \\
\end{align*}
\]

\[
\begin{align*}
\text{R} \text{N} \text{N} \\
\text{R} \text{N} \text{N} \\
\text{O} \\
\text{R} \\
\rightarrow \\
\text{R} \text{O} \\
\end{align*}
\]

**Azolium Enolates / Acyl Azoliums**

\[
\begin{align*}
\text{X} & \text{O} \\
\text{R} \text{CH} & \text{H} \\
\text{R} \text{N} \text{N} \\
\end{align*}
\]

\[
\begin{align*}
\rightarrow \\
\text{R} \text{N} \text{N} \\
\text{R} \text{N} \text{N} \\
\text{O} \\
\text{R} \\
\end{align*}
\]

\[
\begin{align*}
\text{R} \text{N} \text{N} \\
\text{R} \text{N} \text{N} \\
\text{O} \\
\text{R} \\
\rightarrow \\
\text{R} \text{O} \\
\end{align*}
\]

\[
\begin{align*}
\text{R} & \text{O} \\
\text{R} & \text{CH} \\
\text{R} \text{N} \text{N} \\
\end{align*}
\]

\[
\begin{align*}
\rightarrow \\
\text{R} \text{N} \text{N} \\
\text{R} \text{N} \text{N} \\
\text{O} \\
\text{R} \\
\end{align*}
\]

\[
\begin{align*}
\text{R} \text{N} \text{N} \\
\text{R} \text{N} \text{N} \\
\text{O} \\
\text{R} \\
\rightarrow \\
\text{R} \text{O} \\
\end{align*}
\]
**N-Heterocyclic Carbenes In Enantioselective Organocatalysis**

*Modes of Reactivity*

**Acyl Anions**

\[
\begin{align*}
\text{RCHO} & \xrightarrow{\text{R-N=N-R}} \left[ \begin{array}{c}
\text{R} \\
\text{R} \\
\text{R} \\
\text{R}
\end{array} \right] \\
& \equiv \text{R}^- \text{O}
\end{align*}
\]

- Benzoin Condensations
- Stetter Reactions
- Hydroacylations
The Use of NHCs for the Generation of Acyl Anion Equivalents

Early Developments

- 1943: Ugai discovered the thiazolium-catalyzed benzoin condensation

The Use of NHCs for the Generation of Acyl Anion Equivalents

The First Asymmetric Examples

- 1966: Sheehan described the first asymmetric benzoin condensations catalyzed by chiral thiazolium salts

\[
\begin{align*}
\text{PhCHO} & \quad \xrightarrow{\text{Et}_3\text{N}(10 \text{ mol\%})} \quad \text{PhCO} \\
\text{PhCHO} & \quad \xrightarrow{\text{Et}_3\text{N}(10 \text{ mol\%})} \quad \text{PhCO}
\end{align*}
\]

Precipitate: 50%, 0.8% ee
Filtrate: 9% yield, 22% ee

- 1974: Sheehan reported slight improvements to enantioselectivity but still low yield

\[
\begin{align*}
\text{PhCHO} & \quad \xrightarrow{\text{Et}_3\text{N}(10 \text{ mol\%})} \quad \text{PhCO} \\
\text{PhCHO} & \quad \xrightarrow{\text{Et}_3\text{N}(10 \text{ mol\%})} \quad \text{PhCO}
\end{align*}
\]

6% yield, 52% ee

The Use of NHCs for the Generation of Acyl Anion Equivalents

The First Asymmetric Examples

Following the work of Sheehan, a number of other groups reported the use of similar NHCs to catalyze benzoin condensations.

- 20%, 35% ee
  Takagi et al, 1980

- 47-57%, 20-30% ee
  Zhao et al, 1988

- 21%, 26% ee
  López-Calahora et al, 1993

- 66%, 75% ee
  Enders et al, 1996

Bicyclic triazoliums are key!

- 50%, 21% ee
  Leeper et al, 1997

- 45%, 80% ee
  Leeper et al, 1998

The Use of NHCs for the Generation of Acyl Anion Equivalents

The First Asymmetric Examples

The initial development of N-aryl-bicyclic triazoliums led the way to improved catalyst efficiency

The Use of NHCs for the Generation of Acyl Anion Equivalents

Bicyclic Triazolium Salts Give High Enantioselectivities

Modification of Leepers bicyclic triazoliums allowed Enders to develop a highly efficient NHC catalysts

\[
\text{PhCHO} \quad \text{KOT-Bu (10 mol%) THF} \quad \text{PhCO-Ph} \quad 83\% \text{ yield}, \ 90\% \text{ ee}
\]

Connon et al demonstrated the NHCs bearing alcohol directing groups can give exceptional levels of enantioinduction.

The Use of NHCs for the Generation of Acyl Anion Equivalents
Bicyclic Triazolium Salts Give High Enantioselectivities

Connon et al demonstrated the NHCs bearing alcohol directing groups can give exceptional levels of enantioinduction.

The Use of NHCs for the Generation of Acyl Anion Equivalents

Early Developments

■ 1943: Ugai discovered the thiazolium-catalyzed benzoin condensation

1974: Stetter reported the 1,4-addition variant = The Stetter Reaction

The Use of NHCs for the Generation of Acyl Anion Equivalents

Intramolecular Stetter Reactions

In 1996 Enders et al. reported the first asymmetric Stetter Reaction

The Use of NHCs for the Generation of Acyl Anion Equivalents

Intramolecular Stetter Reactions

Following the original report by Enders, Rovis et al. developed the first highly enantioselective intramolecular Stetter reactions.

Development of asymmetric intermolecular Stetter reactions still remains a formidable challenge. This is due to the diminished reactivity of Michael acceptors containing a β-substituent.

Enders et al. developed a high yielding protocol taking advantage of the higher reactivity of chalcones, although the enantioselectivities were only moderate.

\[
\begin{align*}
\text{Ar}^1\text{H} & \quad \text{Ar}^2\text{Ar}^3 \\
\text{Ar}^2 & \quad \text{Ar}^3 \\
\end{align*}
\]

\[
\begin{array}{c}
\text{TBDPSO-} \\
\text{N} \\
\text{N} \\
\text{Ph} \\
\text{BF}_4^- \\
(10 \text{ mol%})
\end{array}
\]

\[
\begin{array}{c}
\text{Cs}_2\text{CO}_3 (10 \text{ mol%}) \\
\text{THF}
\end{array}
\]

49-98% yield, 58-78% ee

The Use of NHCs for the Generation of Acyl Anion Equivalents

**Intermolecular Stetter Reactions**

In the same year Rovis et al. reported a highly enantioselective intermolecular Stetter reaction of glyoxamides a number of Michael acceptors

![Chemical diagram showing the reaction]

A limitation was the need for highly activated alkylidene dicarboxyls

*A general strategy for asymmetric intermolecular Stetter reactions has not yet been developed!*

The Use of NHCs for the Generation of Acyl Anion Equivalents
Hydroacylation of Unactivated Double Bonds

- In 2008, She et al. reported the intramolecular hydroacylation of enol ethers

\[
\begin{align*}
\text{Ph} & \quad \text{R} \\
\text{O} & \quad \text{Ar} \
\end{align*}
\]

\[
\begin{align*}
\text{HO} & \quad \text{Me} \\
\text{Me} & \quad \text{I} \\
\end{align*}
\]

\[
\begin{align*}
\text{DBU} & \quad (70 \text{ mol\%}) \\
xylene, \text{ reflux} & \\
\end{align*}
\]

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

66-99%

- In 2011, Glorius et al. reported a highly asymmetric variant

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

\[
\begin{align*}
\text{DBU} & \quad (10 \text{ mol\%}) \\
dioxane, \text{ 80 °C} & \\
\end{align*}
\]

28-99% yield, 96-99% ee

He, J.; Tang, S.; Liu, J.; Su, Y.; Pan, X.; She, X. *Tetrahedron* 2008, 64, 8797.
The Use of NHCs for the Generation of Acyl Anion Equivalents

Hydroacylation of Unactivated Double Bonds

- The mechanism was investigated by Glorius and Grimme and found to likely proceed via a concerted but highly asynchronous transition state.

N-Heterocyclic Carbenes In Enantioselective Organocatalysis

Modes of Reactivity

**Acyl Anions**

\[
\text{RCHO} \quad \underbrace{\begin{array}{c}
\text{R-N-N-R}
\end{array}}_\text{NHC}
\rightarrow \begin{array}{c}
\text{RCH(OH)NR}_2
\end{array} = \text{RCO}^-
\]

**Homoenolates**

\[
\begin{array}{c}
\text{RCH(OH)NR}_2
\end{array} \quad \underbrace{\begin{array}{c}
\text{R-N-N-R}
\end{array}}_\text{NHC}
\rightarrow \begin{array}{c}
\text{RCH(OH)C(OH)NR}_2
\end{array} = \text{RCH(OH)}^-
\]

**Azolium Enolates / Acyl Azoliums**

\[
\begin{array}{c}
\text{RCO}_x
\end{array} \quad \underbrace{\begin{array}{c}
\text{R-N-N-R}
\end{array}}_\text{NHC}
\rightarrow \begin{array}{c}
\text{RCO}_x
\end{array} = \text{RCO}^-
\]
N-Heterocyclic Carbenes In Enantioselective Organocatalysis

Modes of Reactivity

Homoenolates

- Cyclopentene Synthesis
- Spiroannulations
- Lactam/Lactone Synthesis
- Conversion of Enals to Saturated Esters
The Use of NHCs for the Generation of Homoenolates

The First Examples

In 2004, the groups of Bode and Glorius reported the use of NHC-catalyzed homoenolate formation for the synthesis of γ-butyrolactones.

Bode:

\[
\begin{align*}
\text{Ar}^1 & \quad \text{Ar}^2 \\
\text{O} & \quad \text{O}
\end{align*}
\]

\[\text{NHC} \quad \text{Cl}^- \]

DBU (7 mol%)

THF/t-BuOH

41-87%, 3:1-7:1 cis:trans

Glorius:

\[
\begin{align*}
\text{Ar}^1 & \quad \text{Ar}^2 \\
\text{O} & \quad \text{O}
\end{align*}
\]

\[\text{NHC} \quad \text{Cl}^- \]

KOT-Bu (10 mol%)

THF

33-70%, up to 4:1 cis:trans


The Use of NHCs for the Generation of Homoenoates

The First Examples

- Proposed mechanism for the NHC-catalyzed formation $\gamma$-butyrolactones


The Use of NHCs for the Generation of Homoenoates

Many Asymmetric Examples Followed

- Bode et al. demonstrated a variety of highly enantioselective transformations of homoenoates

The Use of NHCs for the Generation of Homoenoates

Many Asymmetric Examples Followed

- Bode et al. demonstrated a variety of highly enantioselective transformations of homoenoates

![Diagram showing chemical reactions and structures involving NHCs]
The Use of NHCs for the Generation of Homoenoates

Many Asymmetric Examples Followed

Recently, Chi et al. demonstrated a homoenoate coupling with benzodi(enone)s for the synthesis of complex tricyclic structures.

\[ \begin{align*}
\text{R}^1\text{O} & \text{H} \\
\text{R}^2\text{O} & \text{R}^3\text{O} \\
\text{O} & \text{N} \\
\text{N} & \text{Cl}^{-} \\
\text{Mes} &
\end{align*} \]

(20 mol%) 

DBU (30 mol%) 

THF 

53-84% yield 

96-99% ee 

10-20:1 dr
Recently, Chi et al. demonstrated a homoenolate coupling with benzodi(ene)one)s for the synthesis of complex tricyclic structures.
N-Heterocyclic Carbenes As Enantioselective Organocatalysts

Alternative Applications of Homoenolates

Homoenolates

\[
\begin{align*}
R^1 & \text{OH} \\
R^2 & \text{H}
\end{align*}
\]

"Redox Relay"
The Use of NHCs for the Generation of Homoenoates
Alternative Applications of Homoenoates

Using this ester formation reaction they could perform desymmetrizations of meso diols and enantioselective protonations of $\beta,\beta$-disubstituted enals.

The Use of NHCs for the Generation of Homoeno\textit{lates}

Alternative Applications of Homoeno\textit{lates}

The group of Chi has reported the reversed process for the generation of homoeno\textit{lates} from saturated esters, allowing for direct $\beta$-substitution.

![Chemical diagram]

The group of Chi has reported the reversed process for the generation of homoenolates from saturated esters, allowing for direct $\beta$-substitution.

The Use of NHCs for the Generation of Homoenolates

Alternative Applications of Homoenolates

N-Heterocyclic Carbenes In Enantioselective Organocatalysis

Modes of Reactivity

**Acyl Anions**

![Acyl Anions Reaction](image1)

**Homoenolates**

![Homoenolates Reaction](image2)

**Azolium Enolates / Acyl Azoliums**

![Azolium Enolates Reaction](image3)
N-Heterocyclic Carbenes In Enantioselective Organocatalysis

Modes of Reactivity

Azolium Enolates / Acyl Azoliums

- [2+2] Cycloadditions
- [4+2] Cycloadditions
- [3+2] cycloadditions
- Enolate Chemistry
The Use of NHCs for the Generation of Azolium Enolates

The First Examples

The groups of Ye and Smith independently developed formal [2+2] cycloadditions promoted by the addition of NHCs to ketenes

\[
\text{Ar}^1\text{C}=\text{O} \quad \text{N}^\text{Boc}\text{C}(\text{H})\text{Ar}^2
\]

(10 mol%) \quad \text{Cs}_2\text{CO}_3 (10 mol%) \quad \text{THF}

\[
\text{O} \quad \text{N}^\text{Boc}\text{Ar}^2
\]

53-78% yield, 91-99% ee
2.5-99:1 dr

\[
\text{Ph}=\text{C}(\text{Ph})\quad \text{N}^\text{Ts}\text{C}(\text{H})\text{Ar}^1
\]

(10 mol%) \quad \text{KHMDS} (9 mol%) \quad \text{Et}_2\text{O}

\[
\text{O} \quad \text{N}^\text{Ts}\text{Ar}^1
\]

79-96% yield, up to 75% ee
(>99% ee after recryst.)

The Use of NHCs for the Generation of Azolium Enolates

The First Examples

The groups of Ye and Smith independently developed formal [2+2] cycloadditions promoted by the addition of NHCs to ketenes.

The Use of NHCs for the Generation of Azolium Enolates

Expanding the Scope of [2+2] Cycloadditions

Since 2008, Ye et al. have reported numerous other enantioselective [2+2] cycloadditions

The Use of NHCs for the Generation of Azolium Enolates

[3+2] Cycloadditions

The same group also reported an analogous [3+2] cycloaddition using oxaziridines

![Chemical structure image]

up to 78% yield, up to 95% ee
8-15:1 dr

The Use of NHCs for the Generation of Azolium Enolates

[4+2] Cycloadditions

Ye et al. also demonstrated a number [4+2] cycloaddition reactions

\[
\begin{align*}
\text{Ar} & \quad \text{R} & \quad \text{EtO}_2C & \quad \text{N} & \quad \text{CO}_2\text{Et} \\
\text{Ar} & \quad \text{R} & \quad \text{Bz} & \quad \text{N} & \quad \text{N} & \quad \text{Bz} \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{N} & \quad \text{N} & \quad \text{BF}_4^- \\
\text{Ph} & \quad \text{OTMS} & \\
\text{THF} & \\
\end{align*}
\]

\[
\begin{align*}
\text{Cs}_2\text{CO}_3 (10 \text{ mol}%) & \\
\end{align*}
\]

52-95% yield, 33-91% ee

[Reaction Schematic]

The Use of NHCs for the Generation of Azolium Enolates

\[4+2\] Cycloadditions

Ye et al. reported the use of a variety of other 'dienes' in \[4+2\] cycloaddition reactions

\[\begin{align*}
\text{O} & \quad \text{O} & \quad \text{N} & \quad \text{Ph} \\
\text{Ar}^1 & \quad \text{R} & \quad \text{Bz}
\end{align*}\]

\(50-92\%\) yield
\(>90\%\) ee

\(\begin{align*}
\text{O} & \quad \text{O} & \quad \text{Ar}^2 \\
\text{Ar}^1 & \quad \text{R} & \quad \text{CO}_2\text{Et}
\end{align*}\]

\(>80\%\) yield
\(57-93\%\) ee
\(>15:1\) dr

\(\begin{align*}
\text{O} & \quad \text{N} & \quad \text{Ar}^2 \\
\text{Ar}^1 & \quad \text{R} & \quad \text{R}^1 & \quad \text{R}^2
\end{align*}\]

\(>80\%\) yield
\(83-93\%\) ee
\(>10:1\) dr

\(\begin{align*}
\text{O} & \quad \text{O} & \quad \text{Ar}^1 & \quad \text{EtO}_2\text{C} \\
\text{Ar}^1 & \quad \text{R} & \quad \text{Bz}
\end{align*}\]

\(88-99\%\) yield
\(69-90\%\) ee
\(3-10:1\) dr

\(\begin{align*}
\text{O} & \quad \text{O} & \quad \text{Ar}^1 & \quad \text{PMP} \\
\text{R} & \quad \text{CO}_2\text{R}
\end{align*}\]

\(30-96\%\) yield
\(51-99\%\) ee
\(2-9:1\) dr

N-Heterocyclic Carbenes As Enantioselective Organocatalysts

Modes of Reactivity

Azolium Enolates / Acyl Azoliums

- [2+2] Cycloadditions
- [4+2] Cycloadditions
- [3+2] Cycloadditions
- Enolate Chemistry
N-Heterocyclic Carbenes As Enantioselective Organocatalysts

Modes of Reactivity

Azolium Enolates / Acyl Azoliums

Enolate chemistry of α-functionalized aldehydes
The Use of NHCs for the Generation of Azolium Enolates

Utilizing α Functionalized Aldehydes

In 2005, Rovis et al. developed a synthesis of α-chloro esters utilizing an enantioselective protonation of an in situ generated α-chloro enolate.

\[
\begin{align*}
\text{R} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{H} \\
\text{Ar} & \quad \text{OH} & \quad \text{OH} & \quad \text{Cl}
\end{align*}
\]

(10 mol%) \quad (120 mol%)

KH (100 mol%), 18-crown-6 toluene

65-79% yield, 84-93% ee

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Utilizing α-Functionalized Aldehydes

In 2009, Scheidt et al. demonstrated that α-aryloxyacetaldehyde to be competent enolate equivalents in Mannich reactions, giving β-amino amide derivatives

![Chemical Reaction Diagram]

N-Heterocyclic Carbenes In Enantioselective Organocatalysis

Modes of Reactivity

**Acyl Anions**

![Chemical structure](#)

**Homoenolates**

![Chemical structure](#)

**Azolium Enolates / Acyl Azoliums**

![Chemical structure](#)
In 2007 and 2008, Scheidt et al. demonstrated NHCs could catalyze the MnO₂-promoted oxidation of benzylic and vinylic alcohols to esters, and unactivated aldehydes to esters.

**Activated alcohol**

\[ \begin{align*}
R^1\text{OH} \\
\text{MnO}_2, \text{DBU} \\
\text{64-99\% yield}
\end{align*} \]

**Unactivated aldehyde**

\[ \begin{align*}
R^1\text{H} \\
\text{Me} \quad \text{Me} \\
\text{MnO}_2, \text{DBU} \\
\text{64-99\% yield}
\end{align*} \]
Since these reports, Chi et al. have demonstrated the use of oxidative NHC catalysis in a variety of highly enantioselective reactions.

53-98% yield, 70-94% ee
Oxidative NHC Catalysis
Oxidative Functionalization of Aldehydes

Since these reports, Chi et al. have demonstrated the use of oxidative NHC catalysis in a variety of highly enantioselective reactions.

![Chemical structures and reactions](image)

61-89% yield, 84-99% ee

Oxidative NHC Catalysis

Oxidative Functionalization of Aldehydes

Since these reports, Chi et al. have demonstrated the use of oxidative NHC catalysis in a variety of highly enantioselective reactions.

\[
\text{oxidant:}\quad \text{Cs}_2\text{CO}_3 (50\text{ mol\%}), \text{THF}
\]

61-89% yield, 84-99% ee

In 2012, Rovis et al. reported the merger of photoredox and NHC catalysis for the enantioselective α-acylation of tertiary amines

![Chemical structure](image)

Ru(bpy)$_3$Cl$_2$ (1 mol%) 
$m$-dinitrobenzene (120 mol%) 
CH$_2$Cl$_2$, blue LEDs

91% yield, 92% ee