Strategies in Asymmetric Synthesis

- Chiral Induction
  - Starting Materials
    - Enantioenriched
    - Chiral Auxillaries
  - Chiral Catalysts
  - Chiral Solvents
    - Chiral Ionic Liquids
Chiral Solvents

- What does the actual solvent look like?

- What role do solvents play in the course of asymmetric reactions?

- Can solvents convey chiral information?
Molecular Chiral Solvents

**Advantages**
- Hypothesized generality
- Potential for asymmetric unimolecular reactions

**Disadvantages**
- Cost
- Complicated synthesis
- Reusibility issues with molecular solvents
- Separation of products
- Only example: 10-20% ee, 40% in fortuitous cases

Asymmetric Grignard Solvent


Ionic liquids minimize these disadvantages!
**Ionic Liquids**

**Molten Salts**
- NaCl, KCl, etc.
- High melting points
- When liquid, very viscous
  - Corrosive
  - Rarely useful to use 800°C molten salt in organic synthesis

**Ionic Liquids**
- Low melting points (< 100°C)
  - Many liquid at room temperature
- Variable viscosities
- “Designed” solvent
  - Reactivity also controlled
Ionic Liquids

- Known since the 1920s
  \[ \text{NH}_2 + \text{HNO}_3 \rightarrow \text{NH}_3 \text{NO}_3^- \quad \text{MP: 8°C} \]
  Sugden, S.; Wilkins, H. JCS. (1929) 1291.

- Chloroalluminate ILs discovered in the late 1940s
  \[ \text{Br}^- \text{N}^+ + \text{AlCl}_3 \rightarrow \text{Br}^- [\text{AlCl}_3]^+ \quad \text{MP: 40°C} \]

- Did not become widely useful in organic until the 1990s: “neutral” ILs
  \[ \text{I}^- \text{N}^+ + \text{AgBF}_4^- \rightarrow \text{I}^- [\text{BF}_4]^+ \quad \text{MP: 15°C} \]
Ionic Liquids

• Common cations

\[ \text{R-NHN-R} \quad \text{R-NH}_2 \quad \text{R-PN}_2 \]

• Common anions

– Cl\(^-\), Br\(^-\), BF\(_4\)\(^-\), PF\(_6\)\(^-\), SbF\(_6\)\(^-\), NO\(_3\)\(^-\), CH\(_3\)CO\(_2\)\(^-\), CF\(_3\)CO\(_2\)\(^-\)
Ionic Liquids as Organic Solvents

- Substitute for polar/aqueous solvent systems
  - But can be used with water sensitive substrates
  - Stabilize charged intermediates
- Wide liquid phase temperature range
- Non-volatile
- “Designer” solvents
- Ease of product separation
- More expensive, but recyclable
Ionic Liquids in Organic Synthesis

• Hydrogenation

\[
\begin{align*}
\text{Rh(nbd)(PPh}_3\text{)}_2 \text{ (cat)} \quad &\quad \text{H}_2, \text{ acetone, } 30^\circ\text{C}, 2 \text{ h} \\
\implies &\quad 38\%, \text{ TOF } = 0.55 \text{ min}^{-1}
\end{align*}
\]

\[
\begin{align*}
\text{Rh(nbd)(PPh}_3\text{)}_2 \text{ (cat)} \quad &\quad \text{H}_2, \text{ [BMIM][SbF}_6\text{]} \\ &\quad 30^\circ\text{C}, 2 \text{ h} \\
\implies &\quad 85\%, \text{ TOF } = 2.54 \text{ min}^{-1}
\end{align*}
\]


• C-C Coupling

\[
\begin{align*}
\text{PhB(OH)}_2 + \text{PhBr} \quad &\quad \text{Pd(PPh}_3\text{)}_4 \text{ (1.2 mol\%)} \\
&\quad \text{BMIM-BF}_4 \quad \text{Na}_2\text{CO}_3\text{(aq) (2 eq)} \\
&\quad \text{10 min, } 110^\circ\text{C} \\
\implies &\quad 93\% \text{ yield}
\end{align*}
\]

Molecular solvent: 88% yield, 6 h

Mathew, C. J.; Smith, P. J.; Welton, T. Chem. Comm. 2000, 1249
Ionic Liquids in Organic Synthesis

• Baylis-Hillman

\[
\text{CH}_3\text{CN, rel rate} = 1.0
\]

\[
[\text{BMIM}][\text{PF}_6], \text{ rel rate} = 33.6
\]


– Increased rate explained by association of IL with zwitterionic intermediate
Ionic Liquids in Organic Synthesis

• Diels-Alder Reactions
  – Increased endo:exo selectivity (favoring endo)
    • ILs act as lewis acids
  – Can be used in conjunction with lewis acid additives
Ionic Liquids in Organic Synthesis

• Diels-Alder Selectivity

\[ \text{MeO} + \text{C} \xrightarrow{\text{solvent, rt}} \text{CO}_2\text{Me} + \text{CO}_2\text{Me} \]

- endo:exo = 2.9
- endo:exo = 6.1 [N(Tf)\text{2}]

• Endo:exo ratio similar to polar organic solvents
  - MeOH: 6.7, Acetone: 4.2

Chiral Ionic Liquids

• Ideal candidates for chiral solvent system
  – Easily synthesized, usually using members of the chiral pool of natural products
  – More polymeric/highly ordered than molecular solvents

• Requires interaction for transmission of chiral information

• Consist of at least one chiral ion
  – Chiral Cations
  – Chiral Anion
  – Doubly Chiral CILs
Chiral Cations

- Ammonium Cations

- Imidazolium cations

- Pyridinium cations

Chiral Anions

- Lactate based
- Amino acid based anions

- Tartrates, Sugars, Etc.

Doubly Chiral Ionic Liquids
Current Development Strategies with CILs

• As chiral solvents
  – Achiral catalysts, stoichiometric reactions

• Chiral co-solvents and additives
  – “pockets” of chirality

• Organocatalysts
  – Attach organocatalytic moeities to ILs

• IL supported transition metal ligands
CIL as Chiral Solvent
Initial Examples

- Asymmetric Baylis-Hillman
  - First to achieve higher than 25% ee using chiral solvent
  - 44% ee, 60% yield
  - Demonstrated that OH necessary for induction
    - Hydrogen bonding

CIL as Chiral Solvent
Initial Examples

- Asymmetric Aza-Baylis-Hillman
  - Utilizing chiral anions, achieving up to 84% ee
  - Comparable to contemporary catalysts

\[
\]
CIL as Chiral Solvent

• Origin of Stereoselectivity in Baylis-Hillman
  – Close association of the chiral ionic liquid with the zwitterionic intermediate
CIL as Chiral Co-solvent

- First Michael addition with CIL

\[
\text{PhC} = CH + \text{EtO}_2\text{C} = \text{CO} \cdot \text{Et + } \text{N}^+\text{BzO} \cdot \text{BzO}^{-} \cdot \text{Br}^{-} (10 \text{ eq}) \rightarrow \text{EtO}_2\text{C} = \text{CO} \cdot \text{Et} + \text{PhCH} - \text{NO} \cdot \text{BzO} \cdot \text{Br}^{-} \\
\text{toluene, 10 h, rt} \rightarrow \text{96% yield, 25% ee}
\]

- Further work begins to couple CILs with transition metal catalysis

\[
\text{Cu(OTf)}_2 (3 \text{ mol%}) \rightarrow \text{Et}_2\text{Zn CIL A (35 mol%), -20} \text{C} \rightarrow \text{EtO}_2\text{C} = \text{CO} \cdot \text{Et} + [\text{CIL A}]^{+} \cdot \text{BF}_4^{-}
\]
90% yield, 76% ee
CIL as Chiral Solvent
Transition Metal Catalysis

• Utilizing close ion pairing

\[
\text{[CIL]} + \text{(R)-camphor sulfonate} \xrightarrow{\text{Ru/C, 60 bar H}_2, 60^\circ C} \text{quantitative yield, 80% ee}
\]

\[
\text{[CIL]} + \text{benzaldehyde + camphor sulfonate} \xrightarrow{\text{Ru/C, 60 bar H}_2, 60^\circ C} \text{<5% ee}
\]

CIL as Chiral Solvent
Transition Metal Catalysis

• Extending hydrogenation

\[
\text{ONH} \quad \text{CO}_2\text{Me} \quad \xrightarrow{\text{H}_2, \text{[Rh(cod)_2]BF}_4, \text{ligand, CIL, TEA (20 eq)}} \quad \text{ONH} \quad \text{CO}_2\text{Me} \quad 99\% \text{ yield} \quad 69\% \text{ ee}
\]

• Reused up to 5 times without reloading catalyst/solvent
• Pro-atropoisomeric ligand conveys chiral information from CIL to active complex

CIL as Chiral Solvent
Transition Metal Catalysis

• Sharpless Dihydroxylation

\[ \text{R} \xrightarrow{\text{K}_2\text{OsO}_2(\text{OH})_4 (0.5 \text{ mol\%}), \text{NMO}} \text{rt, 24 h}} \text{OH} \]

\[ \text{R} = \text{n-Bu, yield 95\%, 85\% ee} \]
\[ \text{R} = \text{Ph, yield 92\%, 72\% ee} \]


• Industrial Scalability
  – Reuse Os/CIL solution multiple times without purification
Organocatalysis with CILs

- Proline derived CILs

\[
\text{CIL (15 mol\%) + TFA (5 mol\%)} \\
\text{rt}
\]

- Initial results only on the model system

Headly, A. D., Green Chem. 2007, 9, 737.
Organocatalysis with CILs

• Asymmetric Aldol

\[
\text{yield: 98\%, ee: >99\% dr: 93:7}
\]

Organocatalysis with CILs
CIL/IL solvent systems

• Extending 1,4 addition scope

\[
\begin{align*}
\text{R}^1\text{R}^2\text{C} = \text{Ph} & \quad \text{CIL B (20 mol%)} \\
\text{H} & \quad \text{[BMIM][BF4]} \\
\text{CIL B} & \quad \text{rt} \\
\text{R}^1\text{R}^2\text{C} = \text{NO}_2 & \quad \text{yields: 81-99%} \\
\text{H} & \quad \text{79-97% ee} \\
\end{align*}
\]

• Innovation is using ionic liquid as solvent with CIL as the catalyst

\[
\begin{align*}
\text{C} & \quad \text{NO}_2 \quad \text{CIL B (20 mol%)} \\
\text{Cl} & \quad \text{[BMIM][BF4]} \\
\text{rt} & \quad \text{100% yield, 97% ee} \\
\end{align*}
\]

• Broad range of ketones and nitroalkenes (15 examples)
Case Study: Diels-Alder

- Already known that ILs can enhance rate/selectivity of Diels-Alder reactions
Case Study: Diels-Alder

- First attempts yield poor enantioselectivity
  - $< 5\%$ ee observed

\[
\text{Me}CH=CHCHO + \text{H}
\xrightarrow{\text{DCM, 48h, -25C}}
\begin{align*}
\text{CHO} & \quad \text{yield: 37\%, } < 5\% \text{ ee, 95:5 endo:exo} \\
\end{align*}
\]
Case Study: Diels-Alder

90% yield, 78:21 dr, 0% ee

60% de, 0% ee

68% de, 0% ee
Case Study: Diels-Alder

- Combining technologies
  - Combining ILs with chiral transition metal ligands

\[ \text{Cu(TfO)}_2 (10 \text{ mol\%}) \]
\[ \text{CIL (10 mol\%)} \]
\[ [\text{EMIM}][\text{NTf}_2], 2 \text{ min} \]

100% yield
88:12 (endo:exo)
95% ee (endo)

Case Study: Diels-Alder

- Aza-Diels-Alder

\[
\text{R = H, solvent = DMSO: 75\% yield, 84:16 endo:exo, 98\% ee (endo)} \\
\text{R = Me, solvent = DCM: 72\% yield, >99:1 endo:exo, >99\% (endo)}
\]


11 Examples with 6, and 7 membered rings, yields 40-90\%, ee 92- >99\%

- Catalyst reusable up to 6 times before any loss of enantioselectivity
Unimolecular Reactions

- Low enantioselectivity, but proof of concept


- Enantioselectivity observed when R = H
  - Ion pairing required for chiral induction
Advantages of CIL as Chiral Source

• Can be used as a chiral solvent source for certain transformations
• When paired with metal catalysts, decrease metal loading amounts
• Remove volatile solvents
• Ease of product separation/Recyclability
• Industrial scalability
• Can use CIL within an IL system
Future Directions

• Asymmetric organocatalysis has become main focus
  – However, chiral solvent systems still being investigated
    • PTC solvents, homogenous cosolvents
    • To date, no reasonable improvements over those reported
• Developing reusable CIL/IL systems
• Broadening the scope of known transformations
• Resolving techniques utilizing CIL systems
Conclusions

• Over the past decade, CILs have become more useful in organic synthesis
• As chiral solvents, systems still require improvements in practicality
• However, CILs have been shown to be effective catalysts and additives, warranting consideration in industrial applications