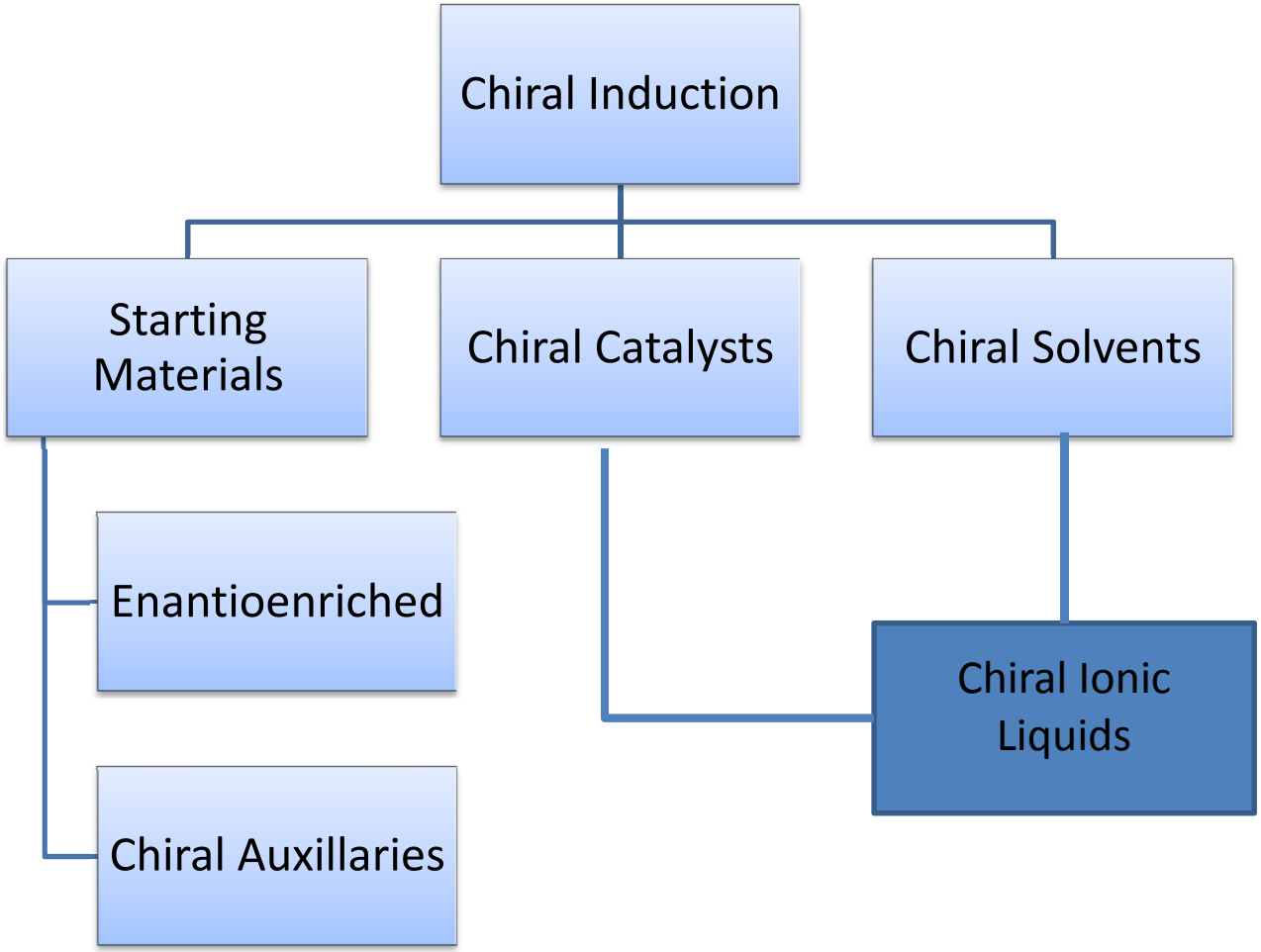
Chiral Ionic Liquids

An Adolescent Technology

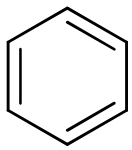
Jeremy Henle 1/24/12

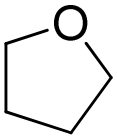
Strategies in Asymmetric Synthesis



Chiral Solvents

- What does the actual solvent look like?





CH_2Cl_2 H_2O

- 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

Seebach, D., et al.,*Organic Syntheses,* Coll. Vol. 7, p.41 (1990); Vol. 61, p.24 (1983).

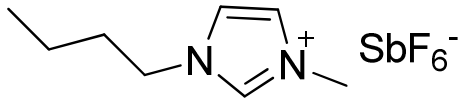
Ionic liquids minimize these disadvantages!

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

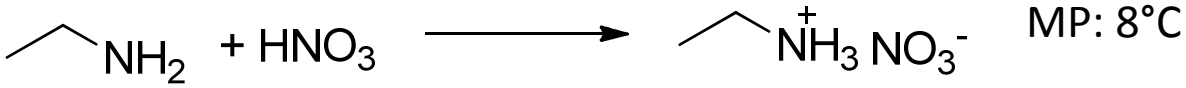
Ionic Liquids



- Low melting points (< 100°C)
  - Many liquid at room temperature
- Variable viscosities
- "Designed" solvent
  - Reactivity also controlled

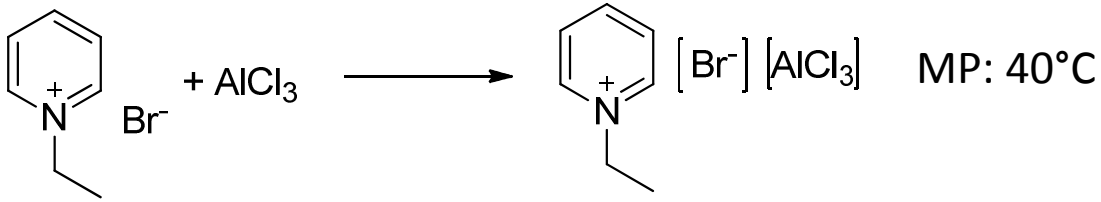
Ionic Liquids

- Known since the 1920s



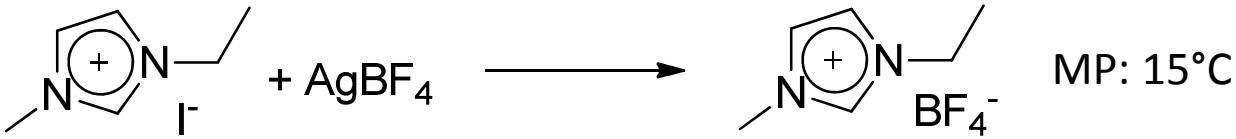
Sugden, S.; Wilkins, H. *JCS*. (1929) 1291.

- Chloroalluminate ILs discovered in the late 1940s



Hurley, F. H.; Wier, Jr., T. P. *J. Electrochem. Soc.* (1951), 98, 207.

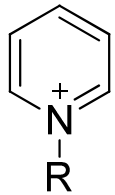
- Did not become widely useful in organic until the 1990s: "neutral" ILs

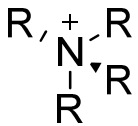


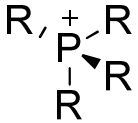
Wilkes, J. S.; Zaworotko, M. J. *JCS CC.* (1992), 965.

Ionic Liquids

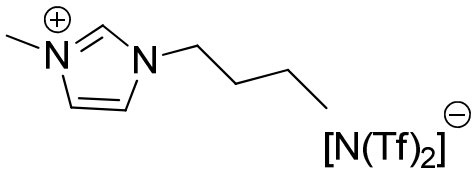
- Common cations







- Common anions
  - Cl^-, Br^-, BF_4^-, PF_6^-, SbF_6^-, NO_3^-, $CH_3CO_2^-$, $CF_3CO_2^-$

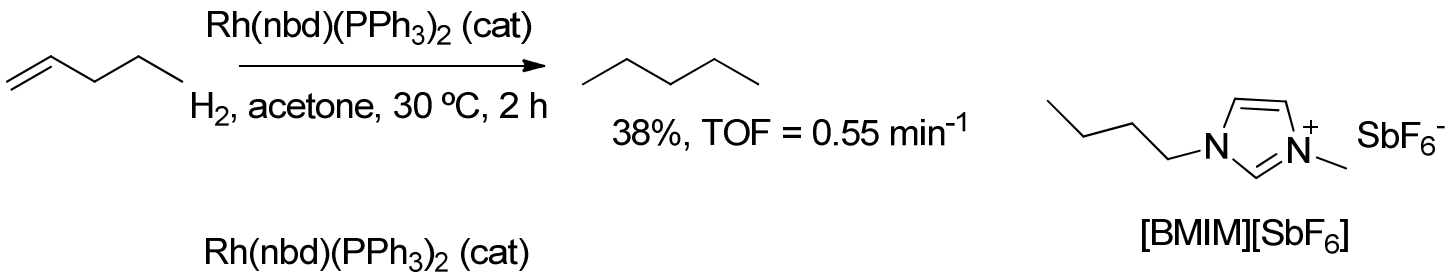


Ionic Liquids as Organic Solvents

- 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

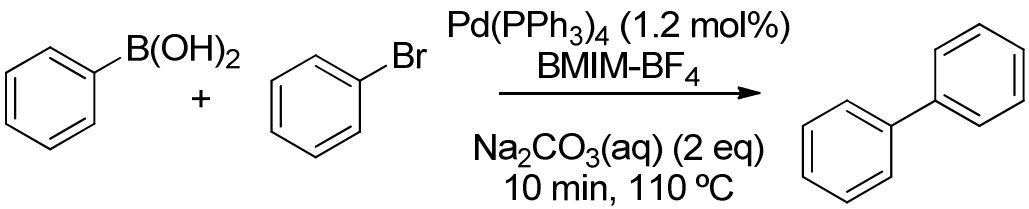
Ionic Liquids in Organic Synthesis

- Hydrogenation



Chauvin, Y., et. al. *ACIEE.* (1995), 34, 2698.

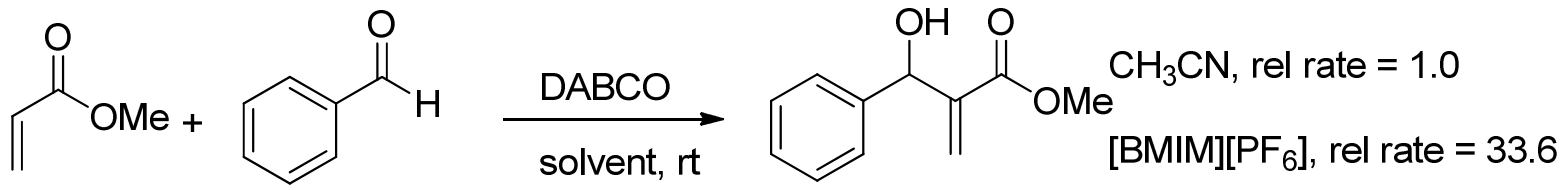
- C-C Coupling



93% yield
Molecular solvent: 88% yield, 6 h
Mathew, C. J.; Smith, P. J.; Welton, T. *Chem. Comm.* 2000, 1249

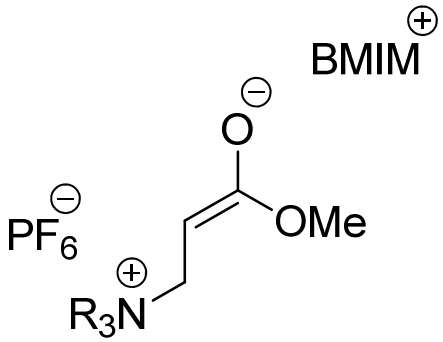
Ionic Liquids in Organic Synthesis

- Baylis-Hillman



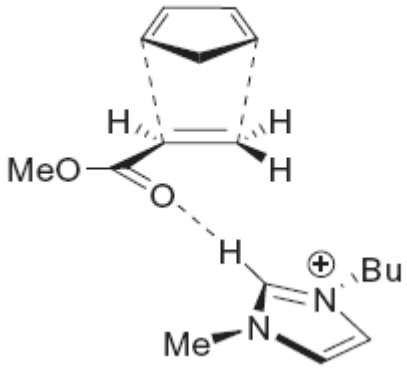
Afonso, A. M., Santos, A. G. *Tetrahedron.* 2001, 57, 4189

  – Increased rate explained by association of IL with zwitterionic intermediate



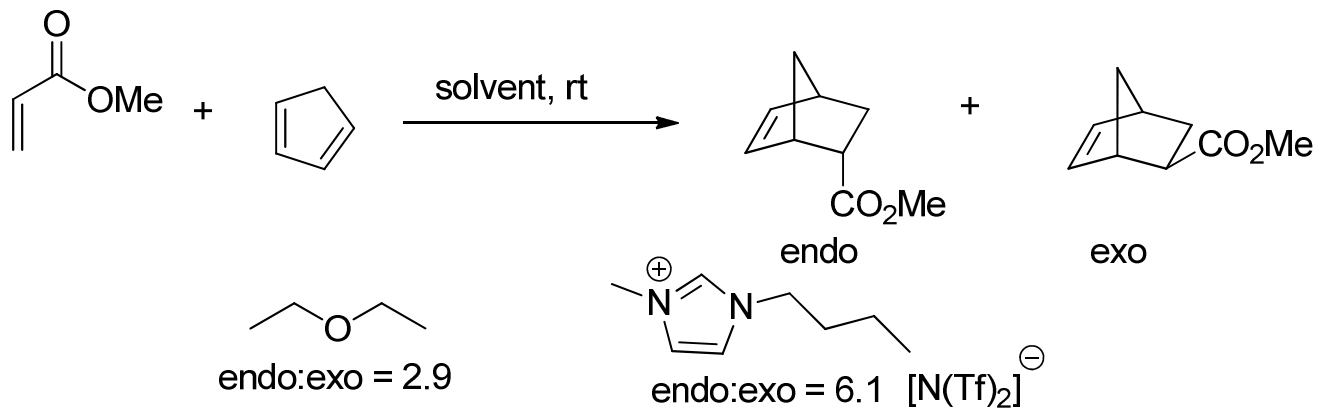
Ionic Liquids in Organic Synthesis

- 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



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

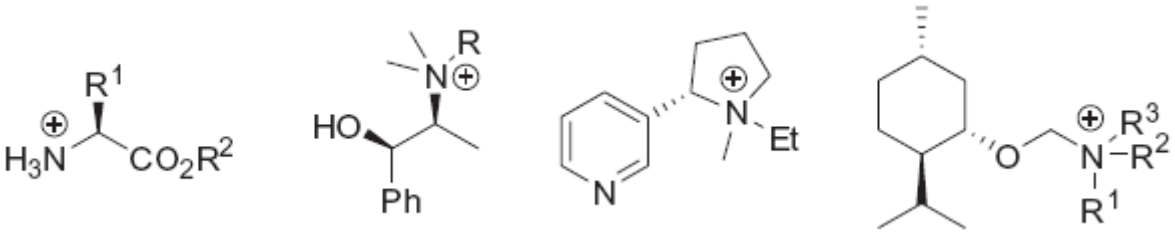
Aggarwal, A., et al. *Green Chem.* 2002, 4, 517-520.

Chiral Ionic Liquids

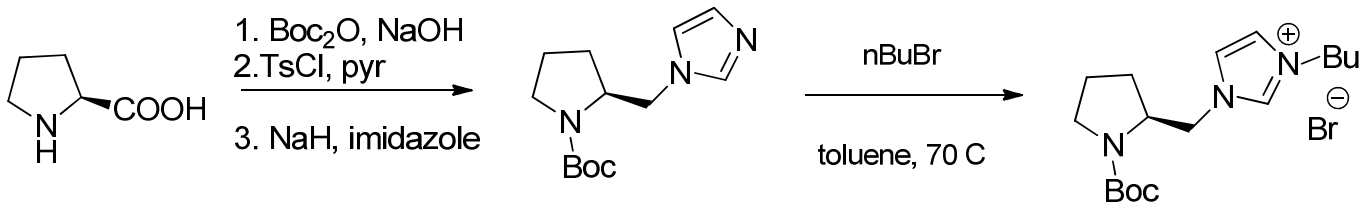
- Ideal candidates for chiral solvent system
  - Easily synthesized, usually using members of the chiral pool of natural products
  - More polymeric/highly ordered than molecular solvents
- Requires interaction for transmission of chiral information
- Consist of at least one chiral ion
  - Chiral Cations
  - Chiral Anion
  - Doubly Chiral CILs

Chiral Cations

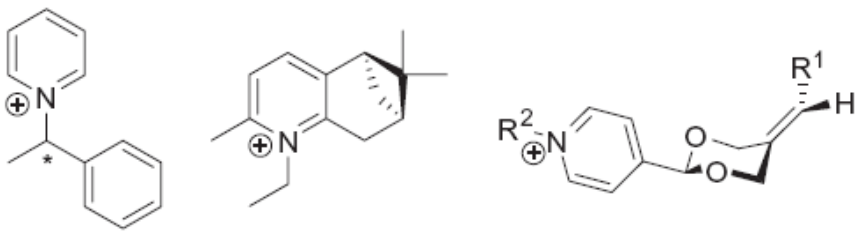
- Ammonium Cations



- Imidazolium cations



- Pyridinium cations

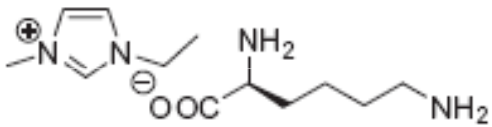


Gaumont, A-C., et al. *Catalytic Methods in Asymmetric Synthesis: Advanced Materials, Techniques, and Applications*. 323-339

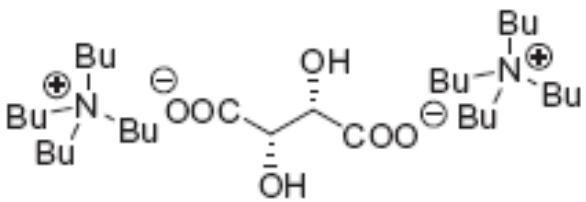
Chiral Anions

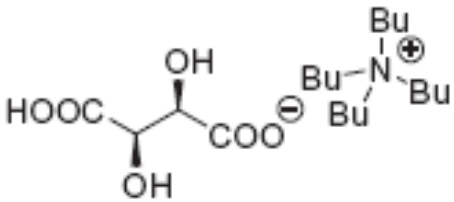
- Lactate based

- Amino acid based anions



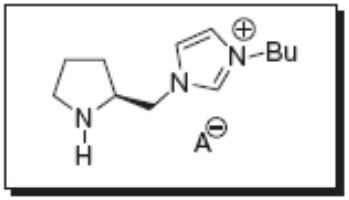
- Tartrates, Sugars, Etc.

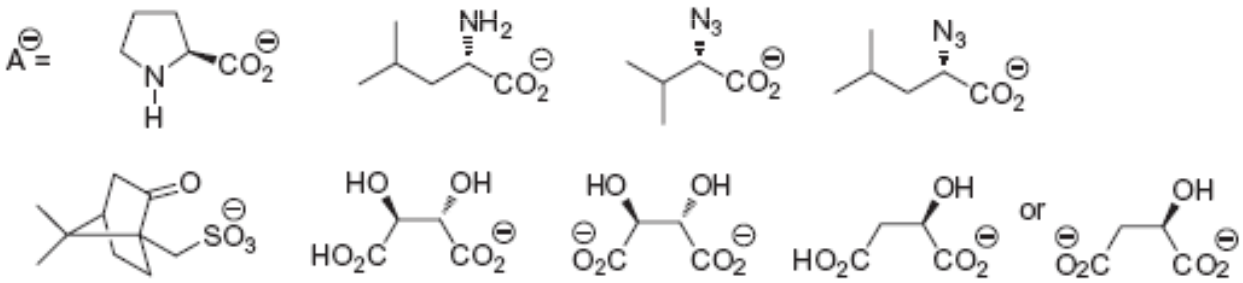




Gaumont, A-C., et al. *Catalytic Methods in Asymmetric Synthesis: Advanced Materials, Techniques, and Applications*. 323-339

Doubly Chiral Ionic Liquids





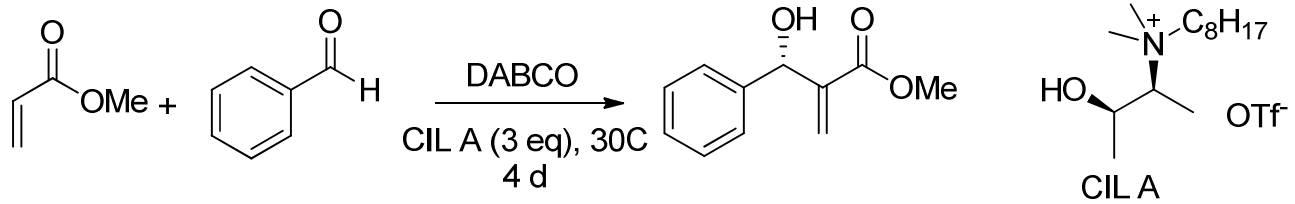
Current Development Strategies with CILs

- 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



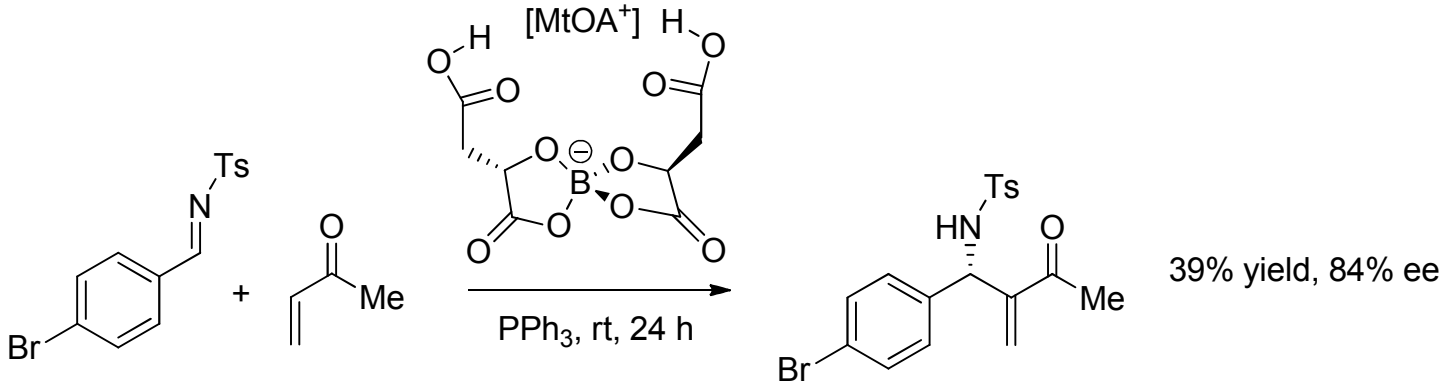
Vo-Thanh, G., et al. *Tetrahedron Lett.* 2004, 45, 6425

  - 44% ee, 60% yield
  - Demonstrated that OH necessary for induction
    - Hydrogen bonding

CIL as Chiral Solvent

Initial Examples

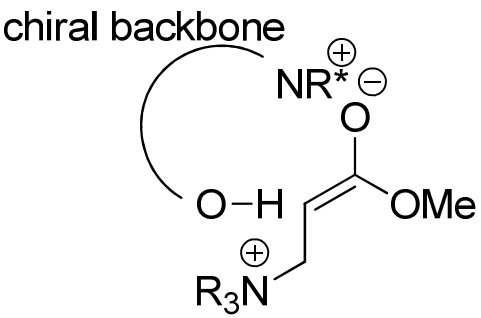
- Asymmetric Aza-Baylis-Hillman
  - Utilizing chiral anions, achieving up to 84% ee
  - Comparable to contemporary catalysts

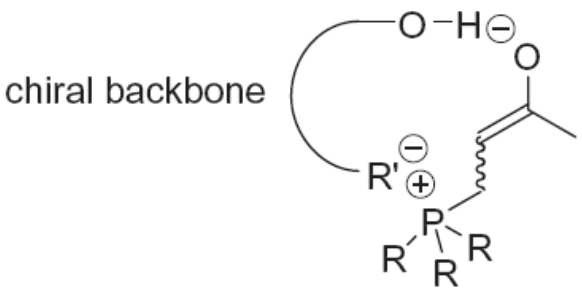


Leitner, et al. *Angew. Chem. Int. Ed.* 2006, 45, 2689

CIL as Chiral Solvent

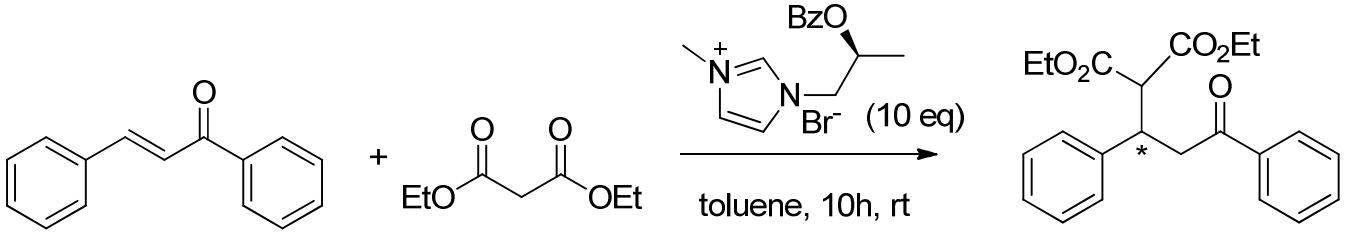
- Origin of Stereoselectivity in Baylis-Hillman
  - Close association of the chiral ionic liquid with the zwitterionic intermediate





CIL as Chiral Co-solvent

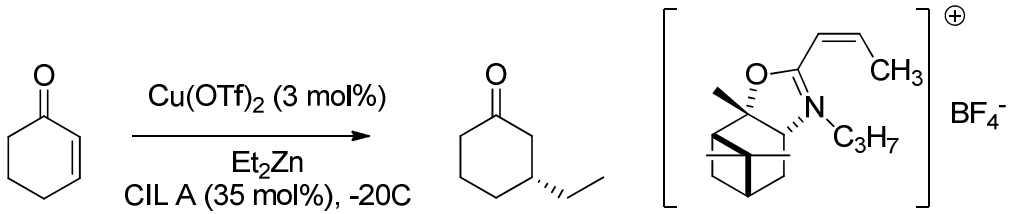
- First Michael addition with CIL



96% yield, 25% ee

Bao, W., et al. *Tetrahedron Lett.* 2005, 46, 4657.

- Further work begins to couple CILs with transition metal catalysis

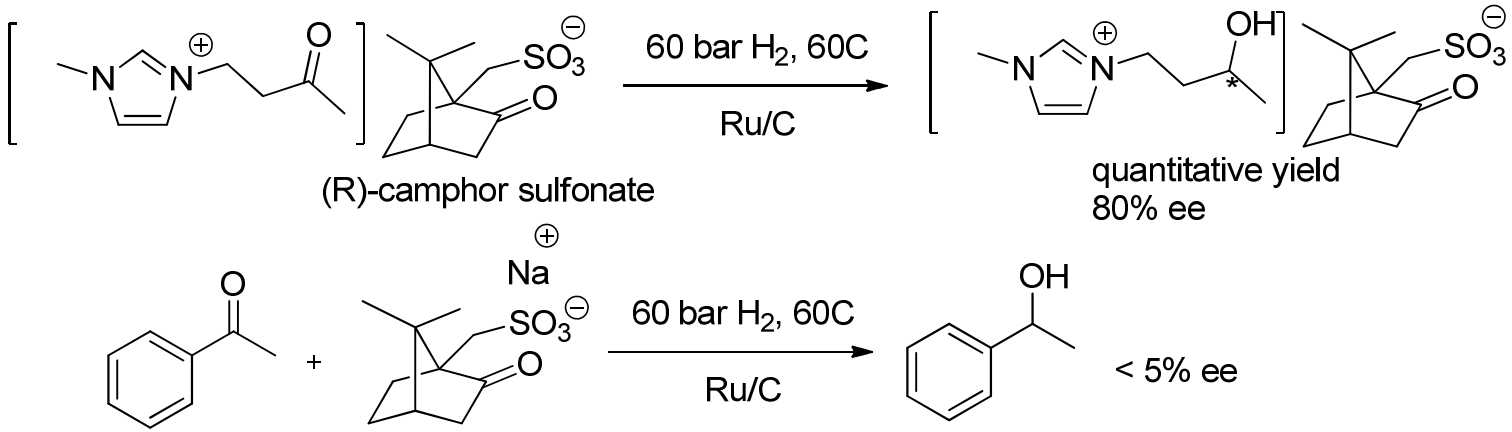


90% yield
76% ee

Malhotra, S. V. *Tetrahedron: Asymmetry*. 2006, 17, 1032

CIL as Chiral Solvent
Transition Metal Catalysis

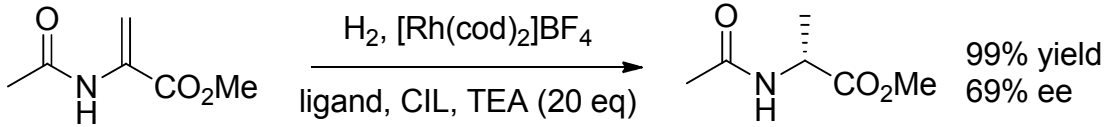
- Utilizing close ion pairing

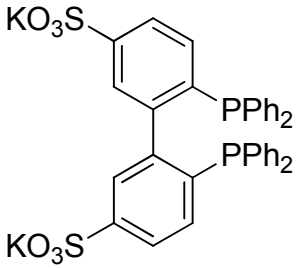


Wasserscheid, et. al. *Angew. Chem.* 2007, 119, 1315.

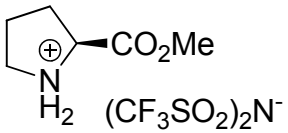
CIL as Chiral Solvent
Transition Metal Catalysis

- Extending hydrogenation





ligand



CIL

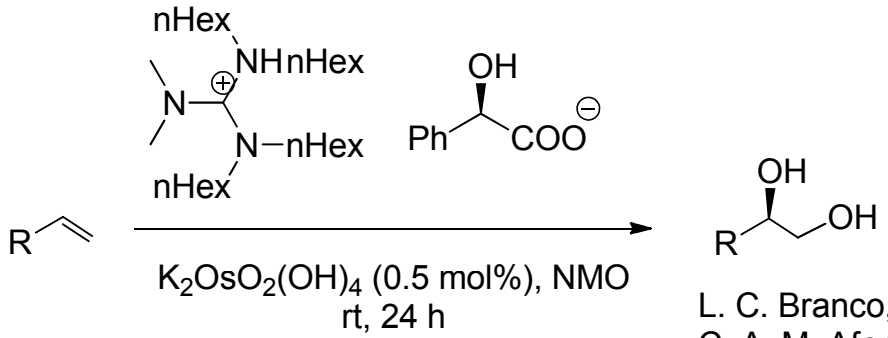
Leitner, W., et al. *Chem. Commun.* 2007, 4012

- 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



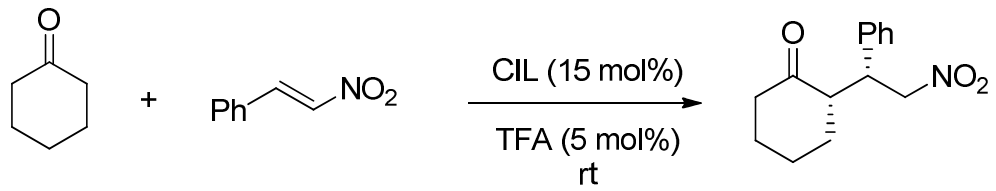
R = n-Bu, yield 95%, 85% ee
R = Ph, yield 92%, 72% ee

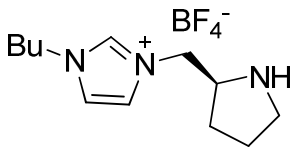
L. C. Branco, P. M. P. Gois, N. M. T. Lourenço, V. B. Kurteva, C. A. M. Afonso. *Chem. Commun*. 2006 , 2371 –2372 .

- Industrial Scalability
  - Reuse Os/CIL solution multiple times without purification

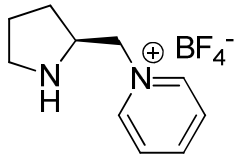
Organocatalysis with CILs

- Proline derived CILs





100% yield, 8h
99% ee, 99:1 dr



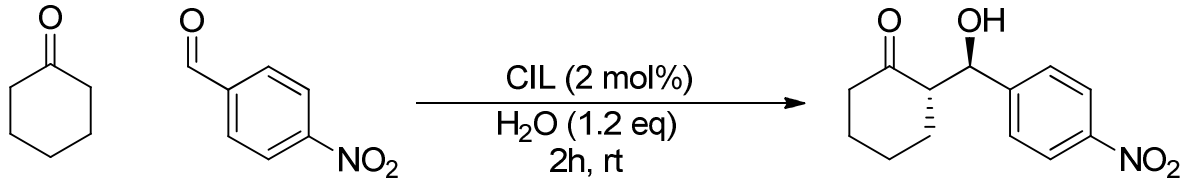
92% yield, 30h
99% ee, >99:1 dr

Luo, et al. *Angew. Chem. Int. Ed.* 2006, 45, 3093.
Headly, A. D., *Green Chem.* 2007, 9, 737.

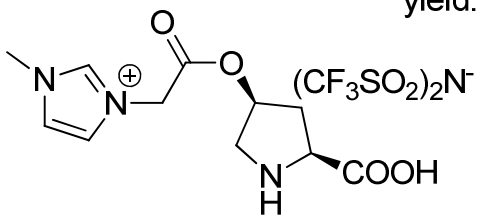
- Initial results only on the model system

Organocatalysis with CILs

- Asymmetric Aldol



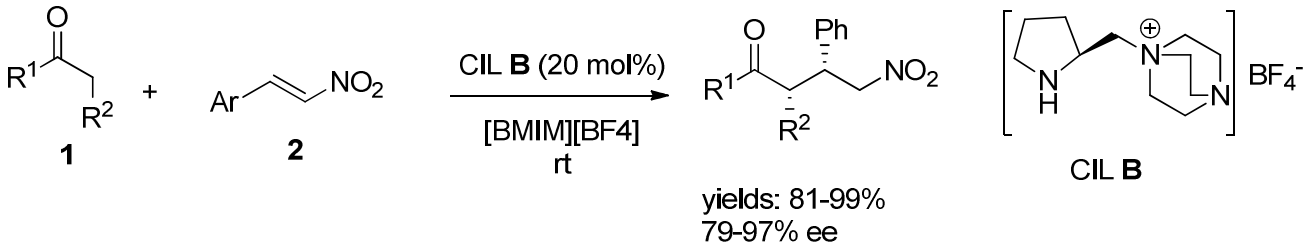
yield: 98%, ee: >99% dr: 93:7

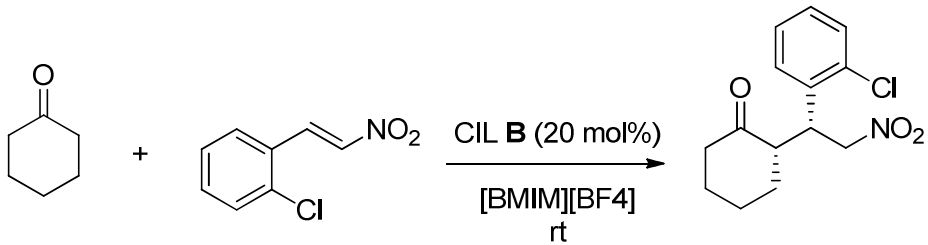


Lombardo, M. *Adv. Synth. Catal.* 2009, 351, 276

Organocatalysis with CILs
CIL/IL solvent systems

- Extending 1,4 addition scope





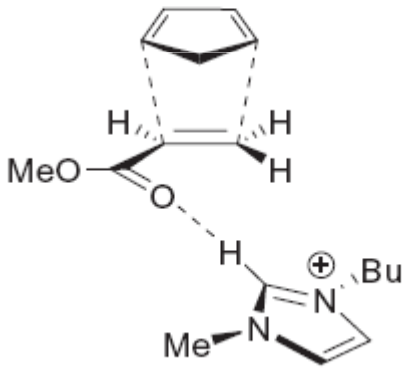
100% yield, 97% ee

Xu, D.Z., et al. *Tetrahedron: Asymmetry*. 2010, 21, 2530.

- Innovation is using ionic liquid as solvent with CIL as the catalyst
- Broad range of ketones and nitroalkenes (15 examples)

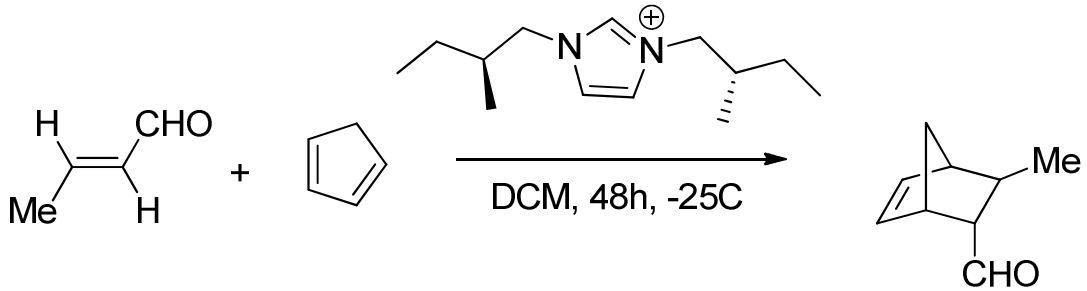
Case Study: Diels-Alder

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



Case Study: Diels-Alder

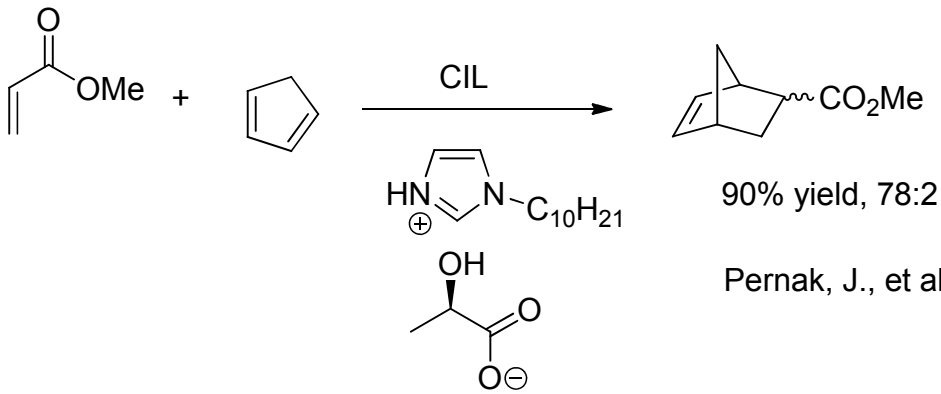
- First attempts yield poor enantioselectivity
  - < 5% ee observed



yield: 37%, < 5% ee, 95:5 endo:exo

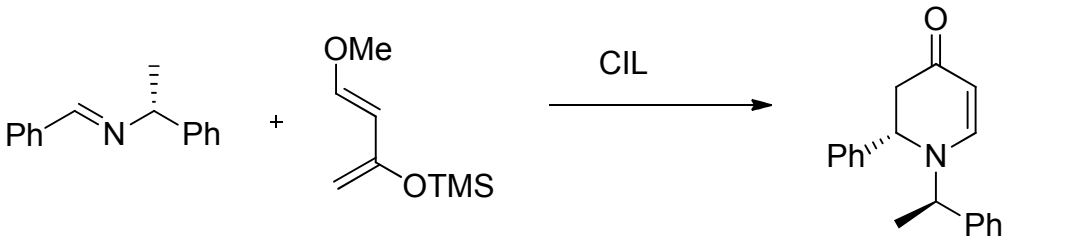
Howarth, J., et al. *Tetrahedron Lett.* 1997, 38, 3097.

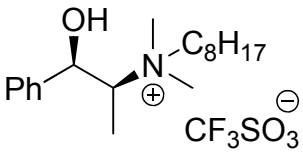
Case Study: Diels-Alder



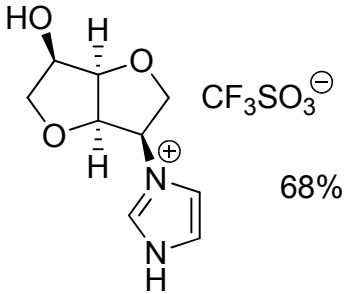
90% yield, 78:21 dr, 0% ee

Pernak, J., et al. *Tetrahedron Lett.* 2006, 47, 4079.





60% de, 0% ee

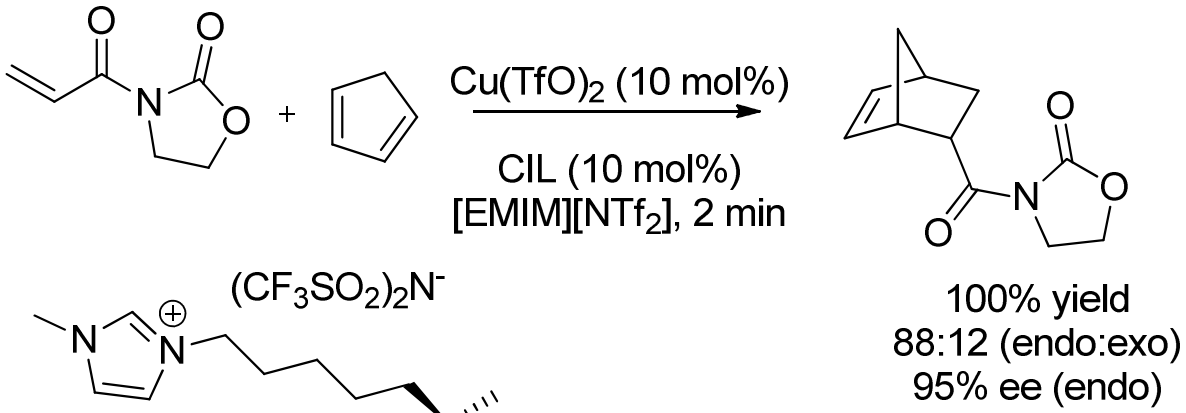


68% de, 0% ee

Vo-Thanh, G., et al. *J. Org. Chem.* 2006, 2, 18.
Vo-Thanh, G., et al. *Tetrahedron.* 2009, 65, 2260.

Case Study: Diels-Alder

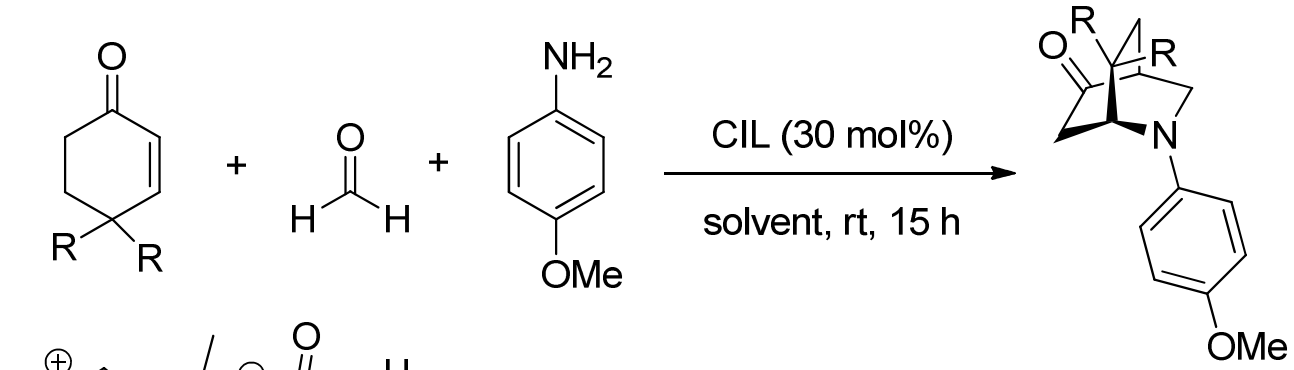
- Combining technologies
  - Combining ILs with chiral transition metal ligands

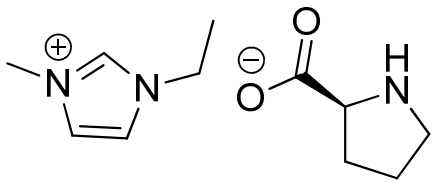


Doherty, S., et al. *Adv. Synth. Catal.* 2007, 349, 951.

Case Study: Diels-Alder

- Aza-Diels-Alder





CIL

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

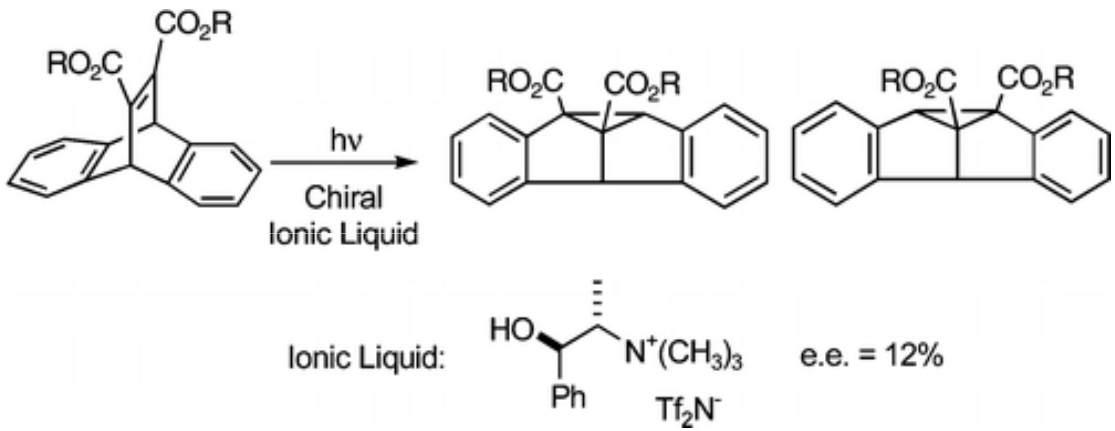
Zheng, X.; Wang, Y. *Catal. Commun.* 2010, 11, 567.

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



Armstrong, D. W., et al. *Org. Lett.* 2005, 7, 335.

- 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