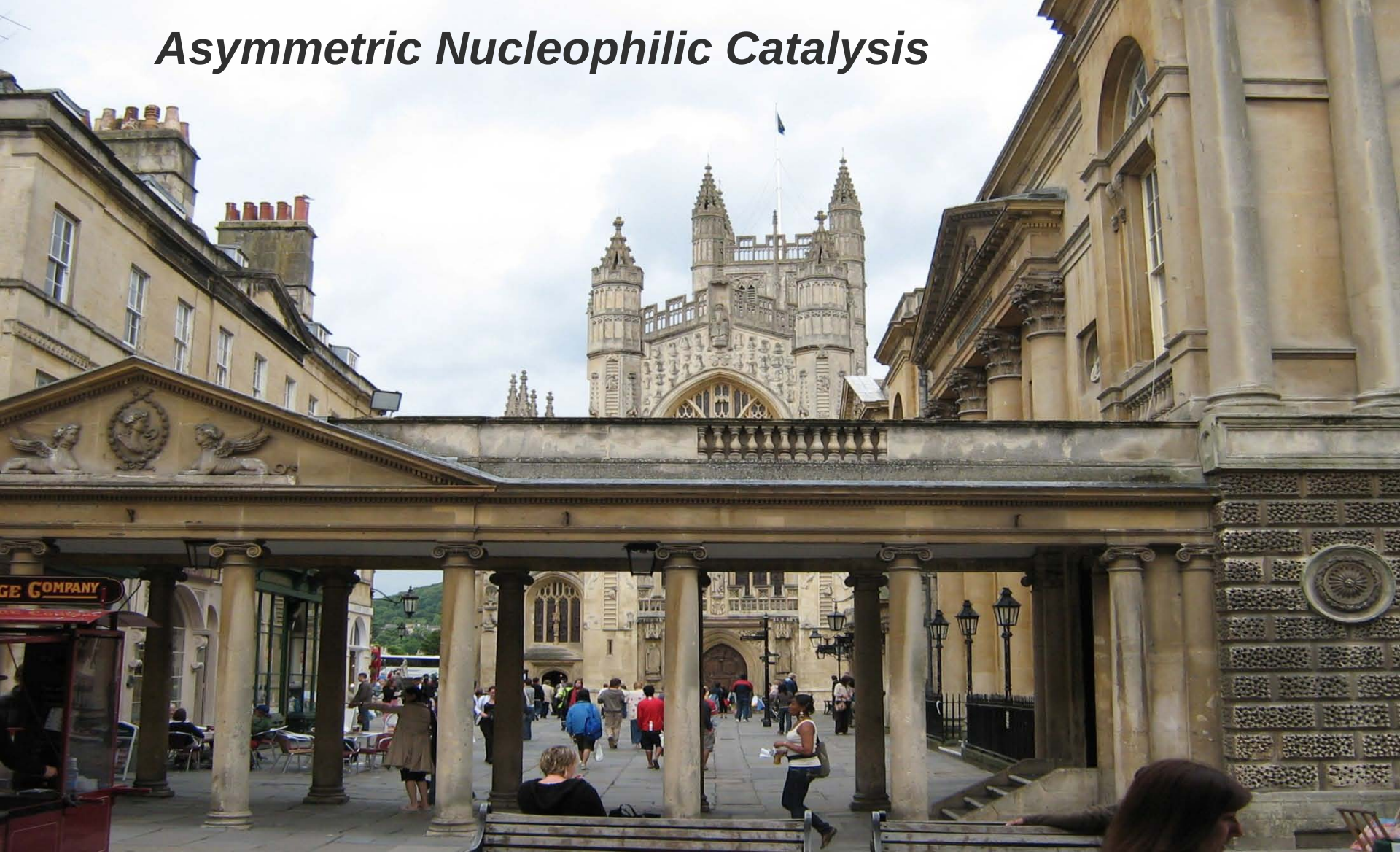
Asymmetric Nucleophilic Catalysis



Young Chemist's Panel - Review Meeting 2012

26thth November 2012

Dr. Dave Carbery, Department of Chemistry, University of Bath

Setting the Context – Catalysing Acyl Transfer with Pyridines

- The term “nucleophilic catalysis” is arguably most associated with pyridines.
- More specifically, 4-dimethylaminopyridine (DMAP) is the catalyst most associated with “nucleophilic catalysis.”
- Pyridine demonstrated to promote acetylation of alcohols and phenols by Einhorn and Hollandt (Munich, 1898).
- In 1967, Litvinenko and Kirichenko (USSR) systematically study the benzoylation of anilines catalysed by structurally diverse pyridines. The presence of DMAP leads to a rate enhancement of x150,000 against the analogous use of Et_3N, and x6000 compared to pyridine.
- In 1969, Steglich and Höfle (Munich) independently demonstrate the catalytic activity of DMAP and soon after, 4-pyrrolidinopyridine.

Lewis Base Catalysis

- The chemistry that grew from the original acylation synthetic methodology work concerned pyridine acting as a *nucleophilic* additive.
- However, the nucleophilic catalyst functions by forming an acylating species, which has enhanced *electrophilicity*.
- In more general terms, DMAP acts as a “Lewis basic catalyst”, reacting with electrophiles. (Denmark discusses in some detail: *Angew. Chem. Int. Ed.* **2008,** *47,* 1560.)

- More generally, Jansen has discussed 9 possible Lewis acid/base combinations based on the nature of the electron pair donator and acceptor:

Donor	Acceptor		
	n*	σ*	π*
n	n→n*	n→σ*	**n→π***
σ	σ→n*	σ→σ*	σ→π*
π	π→n*	π→σ*	π→π*

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Strategies for Stereoselective Synthesis via Acyl Transfer

- Contextualise common stereocontrol strategies used in asymmetric nucleophilic catalysis by alcohol acylation.

$$C = \frac{ee}{ee + ee'} 100 \qquad S = \frac{k_{fast}}{k_{slow}} = \frac{\ln[(1 - C)(1 - ee)]}{\ln[(1 - C)(1 + ee)]}$$

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Strategies for Stereoselective Synthesis via Acyl Transfer

- Contextualise common stereocontrol strategies used in asymmetric nucleophilic catalysis by alcohol acylation.

DMAP-Catalysed Acyl Transfer

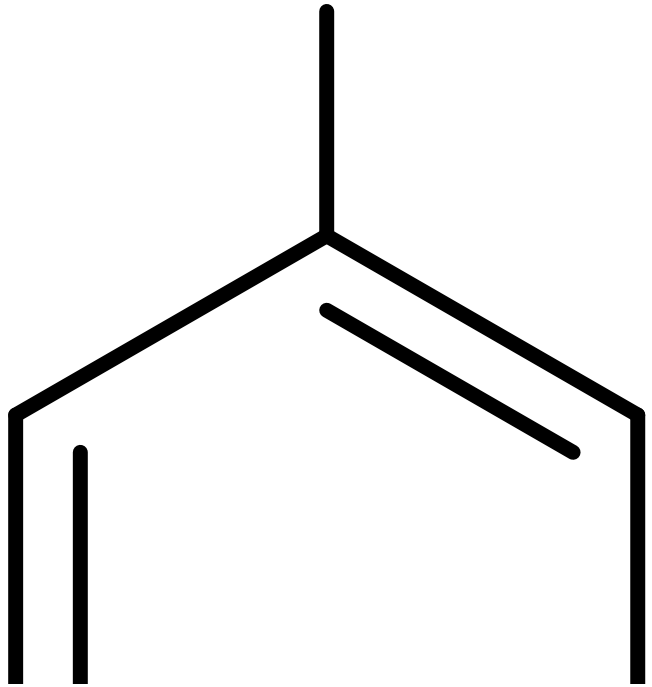
- Consider the DMAP-catalysed reaction of an acid anhydride and an alcohol.
- Equilibrium formation of a highly electrophilic *N*-acylpyridinium salt.
- Donation of electron density from substituent is crucial (no catalysis with pyridine C-2 substituents).
- Reaction of nucleophile at *N*-acyl pyridinium, carboxylate acts as base.

Chiral Aminopyridines – Structure/Activity

Chiral Aminopyridines – Structural Challenges

- The powerful catalysts DMAP and PPY are highly symmetrical with two planes of symmetry.
- Reactive site is pyridine nitrogen (N-1)
- No catalytic activity if substituted at C-2
- How does one effectively desymmetrize a distant lone pair?

Chiral Aminopyridines – Vedejs Reagent



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Chiral Aminopyridines – Fuji Catalyst

Chiral Aminopyridines – Yamada Catalyst

Chiral Aminopyridines – Yamada Catalyst

Chiral Aminopyridines – Connon Catalyst

Chiral Aminopyridines – Jeong's Kemp Triacid

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Chiral Aminopyridines – Spivey Atropisomeric Catalyst

Chiral Aminopyridines – Spivey Atropisomeric Catalyst Synthesis

Chiral Aminopyridines – Fu Planar Chiral Catalyst

Chiral Aminopyridines – Fu Planar Chiral Catalyst Resolution Examples

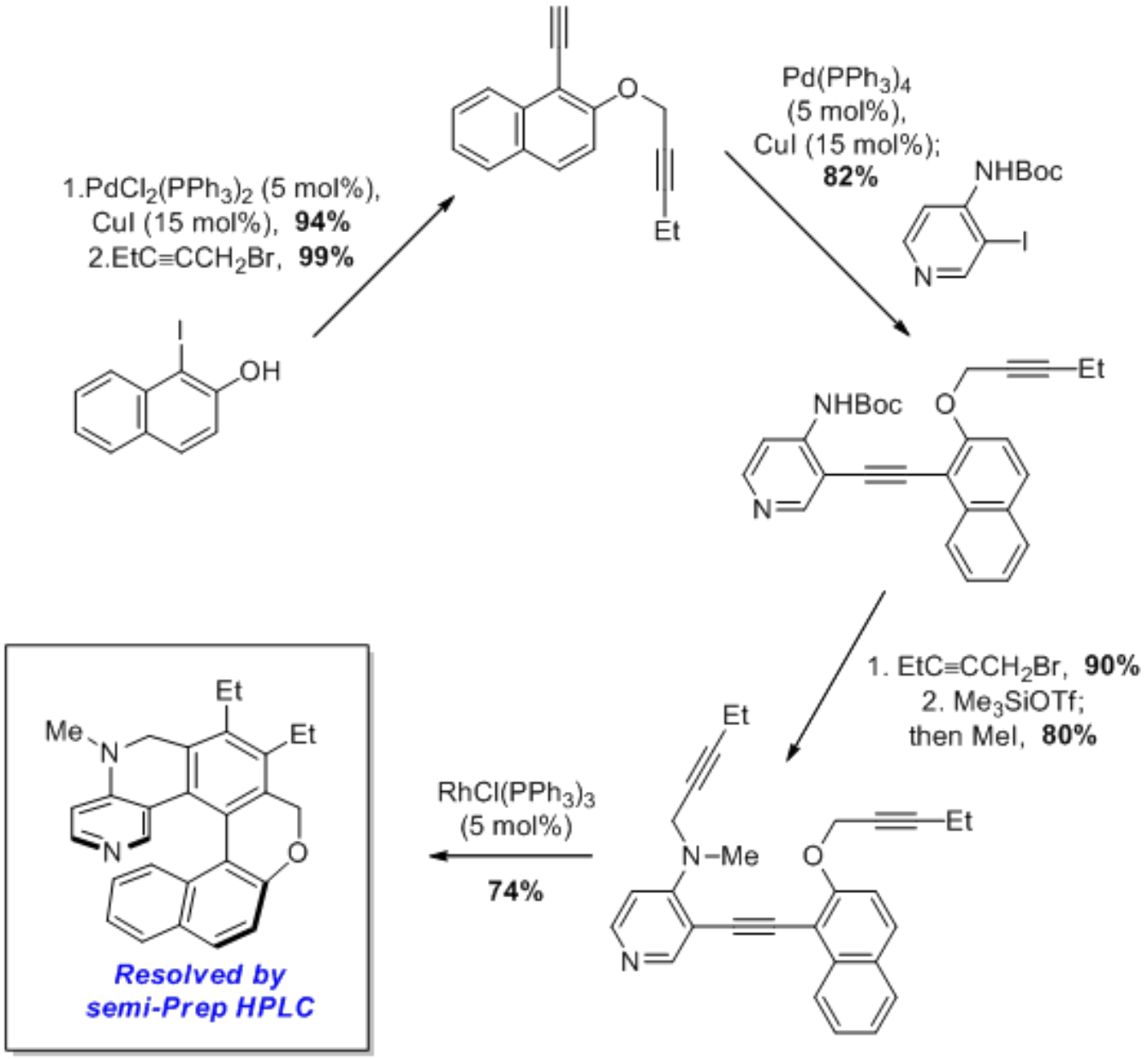
Chiral Aminopyridines – Fu Planar Chiral Catalyst Resolution Examples

Chiral Aminopyridines – Fu Planar Chiral Catalyst Resolution Examples

Chiral Aminopyridines – Fu Planar Chiral Catalyst
Fu DKR

Chiral Aminopyridines – Carbery Helical Catalyst

Chiral Aminopyridines – Carbery Helical Catalyst



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Chiral Aminopyridines – Carbery Helical Catalyst

Chiral Aminopyridines – Carbery Helical Catalyst – 2nd Generation

Catalyst is Scalable, Selective, Resolution-Free

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Chiral Aminopyridines – Seidel H-Bonding System

Chiral Aminopyridines – Seidel Anion Binding Model

Chiral Imidazoles – Miller's Oligopeptides – Alcohol Resolution

Chiral Imidazoles – Miller's Oligopeptides – Thioamide Resolution

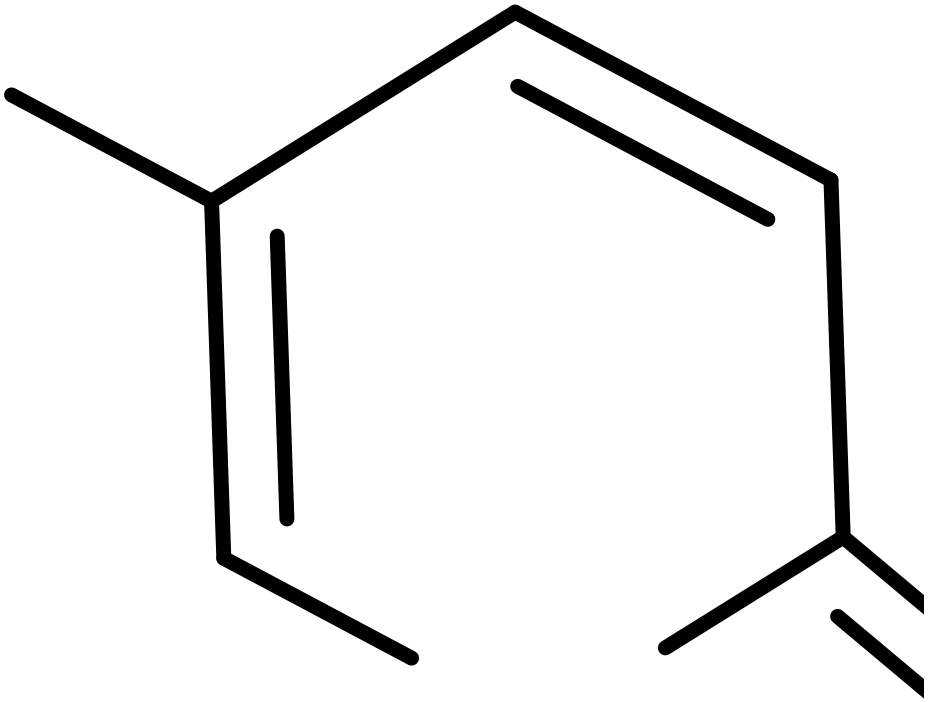
Chiral Imidazoles – Histidinyl Systems

Chiral Amidines – Birman Catalysts

Chiral Amidines – Birman Catalysts

Chiral Amidines – Birman Catalysts

Chiral Amidines – Amidine Catalysts – Structure Variation



Chiral Amidines – Deng/Fossey Amidine

Chiral Vicinal Diamines – Oriyama Catalysts

Chiral Vicinal Diamines – Connon Thiol Resolution

Chiral Phosphines – Vedejs Catalysts

Chiral N-heterocyclic Carbenes

Asymmetric Nucleophilic Catalysis – Outlook and Challenges

Alcohols

Thorough body of work, but, scope for 3° and saturated substrates (alkyl/alkyl 2°).

Amines

Remains a huge challenge. Competitive nucleophilicity. Other elements (P?)

Catalysts

Commercial availability. Multi-functionality/co-operativity. Modelling and understanding.

Reactions

C-C bond formations. Almost all are derived from early DMAP chemistry...creativity.

Electrophiles

E-X..... E = sulfonyl, phosphoryl, silyl etc