Applications of N-Heterocyclic Carbenes and its Transition metal Complexes in Organic Reactions

Phanindra Gutala
Dr. K. R. Prasad’s Group
Introduction

- Introduction to N-Heterocyclic Carbenes.
- Applications of N-Heterocyclic Carbenes in Organic Reactions.
- Applications of Metal Complexes of N-Heterocyclic Carbenes in Organic Reactions.
- Anionic N-Heterocyclic Carbenes.
Introduction to N-Heterocyclic Carbenes

- Electron withdrawing substituents stabilise S-non bonding orbital by increasing its S-Character and leaves Pπ orbital unchanged, so the S-Pπ gap is increased and singlet state is favoured.

First Synthesis of Crystalline Carbenes

Push-Pull Stabilisation

Electron donation into the carbene out-of-plane p-orbital by the electron-rich system (N-C=C-N) leads to a moderation of the typical electrophilic reactivity of carbenes. In the σ-framework, additional stability for the carbene electron pair may be gained from the σ-electron-withdrawal effects on the carbene center by the more electronegative nitrogens which moderates the nucleophilic reactivity of carbene.

Codes of imidazolium salts with Different Substituents on Nitrogen
Applications of N-Heterocyclic Carbenes in Organic Reactions

N-Heterocyclic Carbenes are the one of the strongest lewis bases known. It can Catalyse many organic reactions reacting with electrophiles.

\[ \text{D=Electron donating group} \]

NHC is such a strong two electron donor that it can donate electrons to almost any element in the periodic table.

Reaction of NHC with Electrophilic reagents
Benzoin Condensation

- Homo condensation between two aromatic aldehydes
- Thiamine is known to catalyse benzoin condensation since long time, actual catalyst is thiazol-ylidine.
- Thiazolium salts can catalyse the benzoincondensation. The mechanism involves the formation of the C-2 anion in the thiazolium ring, which then acts as a pseudo cyanide anion by the normal mechanism.

Stetter reaction

- The benzoin condensation was extended to Michael Acceptors, and this is now a versatile method for the preparation of 1,4-diketones mostly, but also of 4-ketoesters and 4-ketonitriles.

- The importance of the Stetter reaction products as valuable precursors in the synthesis of cyclopentanone derivatives and heterocycles explains its now very common use in total synthesis, in solid-phase organic synthesis, and in the preparation of extended heterocyclic systems.

Extension of Stetter reaction to the Synthesis of Pyrrole derivatives

1,2,3,5-Tetrasubstituted pyrroles can be synthesized in good yields in a one-pot, three-step, four-component process by a coupling-isomerization-Stetter reaction-Paal-Knorr sequence of an electron-poor (hetero)aryl halide, a terminal propargyl alcohol, an aldehyde, and a primary amine.

Activated Carboxylate and Butyrolactone From Homoenoate

N-Heterocycle carbenes generated in situ from imidazolium or triazolium salts and bases react with enals, leading to the catalytic generation of homoenoates.

Strong bases such as tBuOK lead to carbon-carbon bond formation, while weaker bases allow protonation of the homoenoate and subsequent generation of activated carboxylates.

Catalytic Cycle for Catalytic Redox Esterifications of Enals

Weaker bases allow protonation of the homoenolate and subsequent generation of activated carboxylates

The organocatalyzed conjugate umpolung of α,β-unsaturated aldehydes allows the direct, intermolecular, and crossed linking of an α,β-unsaturated aldehyde with another aldehyde or ketone, resulting in a flexible one-step synthesis of substituted γ-butyrolactones.

- Reaction of the NHC with the α,β-unsaturated aldehyde gives rise to a zwitterionic structure.
- Isomerisation of zwitterionic structure by protonation/deprotonation to the conjugated dienamine.
- Nucleophilic attack of the isomer of the dienamine to aldehyde results in the formation of alcoholate, which tautomerises and cyclise to give lactone.

Synthesis of γ-Lactams via Direct Annulations of Enals and N-Sulfonyl imines

Cinnamaldehydes and N-sulfonylimines undergo direct annulations to cis-disubstituted γ-lactams via the intermediacy of catalytically generated homoenolates.

Deprotection and Ring-Opening of Catalytically Prepared N-Sulfonyl Lactams

- The N-sulfonyl protecting group is easily removed under a variety of reductive conditions.
- Alternatively, this moiety activates the lactam toward nucleophilic ring opening by alkoxides and other nucleophiles, leading to γ-amino acid derivatives.

Amidation of Unactivated Esters and Trans esterification

- Functional group tolerance, selectivity, and low catalyst loading are the Advantages.
- Polymerization of cyclic ester monomers is achieved with NHC.

Mechanism proceeds through a Carbene Alcohol complex which rearranges to Aminoester which on acyl transfer gives amide.

Enantioselective Azadiene Diels-Alder Reactions

The selectivity is rationalized by the high preference for an endo transition state, and in the NHC-catalyzed system, this reaction mode is reinforced by the presence of the bulky triazolium moiety in the active dienophile. The cis-stereoselectivity would arise from a (Z)-enolate reacting as the dienophile.

Cyanosilylation of Carbonyl Compounds

In benzoin condensation, the nucleophilic addition of the NHC to a carbonyl carbon atom of an aldehyde produces an intermediate. Its tautomer is an acyl anion equivalent, which reacts with another aldehyde to produce benzoin. Here the intermediate reacts with TMS-CN to produce cyanosilyl ethers and the NHCs to catalyze the cyanosilylation reaction.

NHC-catalyzed 1,2-addition reactions

Applications of Metal Complexes of N-Heterocyclic Carbenes in Organic Reactions

Stabilisation of the organometallic Species by NHC ligands

- Stabilisation of the various coordinatively unsaturated metal centres through the incorporation of NHC ligands is the recent advance.

- Although NHCs can be considered as phosphane mimics it has become apparent that there are substantial differences between the two ligand families.

- Many of these carbene species show high catalytic activity in many metal-mediated organic transformations, e.g. ruthenium-mediated olefin metathesis, iridium catalyzed hydrogenation and hydrogen transfer, hydrosilylation, and palladium C-C coupling reactions.

- the strong s-donor nature of the ligands often results in more stable catalysts than analogous phosphane-based systems.
Comparison between NHC ligand and trialkyl Phosphane

A number of studies have suggested that as ligands, nucleophilic carbenes have advantages over electron rich trialkylphosphanes (strong s donors).

Phosphane ligands suffer from significant P–C bond degradation at elevated temperatures, while NHCs have been shown to possess greater thermal stability in addition to stronger donating ability.

Already, the easily modified NHC ligands are highly acclaimed affording more stable, yet highly reactive metal catalysts, where phosphane analogues have been found less effective or ineffective.

\[
[Cp^*RuCl]_4 + 4L \xrightarrow{\text{THF, r.t.}} \text{Cp}^*\text{Ru(L)}\text{Cl}
\]

<table>
<thead>
<tr>
<th>L</th>
<th>R</th>
<th>$\Delta H_{\text{rxn}}$ (kcal/mol)</th>
<th>relative BDE (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>cyclohexyl</td>
<td>ICy: 85.0(0.2)</td>
<td>21.2</td>
</tr>
<tr>
<td></td>
<td>4-methylphenyl</td>
<td>ITol: 75.3(0.4)</td>
<td>18.8</td>
</tr>
<tr>
<td></td>
<td>4-chlorophenyl</td>
<td>lPCl: 74.3(0.3)</td>
<td>18.6</td>
</tr>
<tr>
<td></td>
<td>2,4,6-trimethylphenyl</td>
<td>IMes: 62.6(0.2)</td>
<td>15.6</td>
</tr>
<tr>
<td></td>
<td>adamantyl</td>
<td>lAd: 27.4(0.4)</td>
<td>6.8</td>
</tr>
<tr>
<td>PCy$_3$;</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PiPr$_3$;</td>
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The reactions with NHC ligands were more exothermic and quantitative than trialkylphosphane Ligands.

These enthalpy values can be converted into relative bond dissociation enthalpies (BDE) which clearly indicate that NHCs are better donor ligands.

Comparison between NHC ligand and trialkyl Phosphane

\[
\text{Cp}^*\text{Ru(PCI}_3\text{)Cl} + \text{NHC} \xrightarrow{\text{THF}} \text{Cp}^*\text{Ru(NHC)Cl} + \text{PCI}_3
\]

NHC = IMes, ICy

Ligand exchange reactions between \([\text{Cp}^*\text{Ru(PCI}_3\text{)Cl}]\) and IMes or ICy were examined, Which confirms NHC is a good donar.


Spectroscopic studies showed significant back-bonding to the olefin from the Pd center suggesting that the carbene ligands are strongly donating.

Cavell, J. K.; Mc Guinness, S. D. *Organometallics* 1999, 18, 1596.
Stereo and electronic effects of the bulky ligands on nitrogen atoms in NHC ligands

Mechanism for the Organometallic catalysed reactions

The steric bulk of the most common carbenes such as IMes and SIMes facilitate reductive elimination by increasing the steric bulk around the metal.

Cavell has reported a number of cases in which reductive elimination occurs quite readily between $N$-heterocyclic carbenes and cis-disposed ligands.

Complexes bearing only one NHC ligand showed significantly higher activity compared to bis-NHC systems. Mechanistically, since the $M\text{--NHC}$ bond is a stronger bond than the $M\text{--PR}_3$ bond, the mixed $\text{PR}_3$/NHC ligand system would proceed by phosphane ligand displacement via dissociative-type pathway, leading to the active catalyst, at play.

Reactions Catalysed by Metal-NHC Complexes
Suzuki, Sonagashira, Heck Couplings

Heck reaction
Alkyne coupling
Suzuki reaction

Mixed catalyst has Highest activity

Sonagashira Coupling

Fu, C. G.; Eckhardt, M. J. Am. Chem. Soc. 2003, 125, 13642.
Arylation of amines

The palladium-catalyzed amination of aryl halides

Modifications in Grubbs catalyst

- The activity of \((\text{PCy}_3)_2\text{Cl}_2\text{RuCHPh}\) is highly dependent.
- Catalyst activity increases with larger and more electron-donating ligands.
- The steric bulk of the ligands may also contribute to phosphine dissociation by destabilizing the crowded bis(phosphine) olefin complex.

The key insight was that \((\text{PCy}_3)_2\text{Cl}_2\text{RuCHPh}\) forms a highly active mono(phosphine) intermediate during the catalytic cycle. As a design motif, this intermediate became a starting point for the development of improved catalysts.

Modifications in Grubbs catalyst

The idea of mixing NHC and trialkyl- or triarylposphines for catalysis was based on the idea to merge the strengths of both ligand systems: High stability of the NHC-palladium bond, combined with easy dissociation of the phosphine ligands. Mixed NHC-phosphine complexes trigger both stability and activity.

During an attempted synthesis of a Ru IMes hydride species, from \([\text{Ru(H)}_2(\text{PPh}_3)_3(\text{CO})]\) with free IMes, yielded the bis NHC-substituted complex, Continued heating led to C-C activation.

- Protolytic elimination of methane
- C–H insertion into the cyclohexyl substituent and loss of methane
- Finally, β-hydride elimination


The increased electron density on the metal as a result of the strongly electron donating carbene and the fact that C–H and C–C bonds are forced into close contact with the metal because of the steric bulk of the NHC.
Anionic N-Heterocyclic Carbene-Silver complex

The efficient synthesis of a N-benzoyliminoimidazolium ylide provides access to a new type of N-heterocyclic anionic carbene.

N-amination methodology to N-mesityl imidazole to obtain the corresponding N-aminoimidazolium salt. Treatment of imidazolium with benzoyl chloride then deprotonation of the salt afforded the desired N-benzoyliminoimidazolium ylide. Deprotonation affords a bidentate NHC.

Anionic N-Heterocyclic Carbene-Silver complex

To test the carbene transferability, it was treated with CuCl$_2$·2H$_2$O, in THF at room temperature.

Application

Complex was shown to be catalytically active in the arylation of aldimines with arylboronic acids

σ-Donor with a Planar Six-π-Electron B₂N₂C₂ Framework: Anionic Carbene

The reaction of the corresponding trimethylsilyl formamidinate with 1,1-bis(methylchloroboryl)ethane in the presence of trimethylsilyl triflate yielded the zwitterion, which gives anionic carbene.

Six π electrons appear to be distributed over two allyl-like fragments (B₂C⁻ and N₂C⁺) to form a zwitterionic structure, rather than delocalized over the entire ring framework.

Total donation of s electrons to Li complexes is 0.484, 0.566, According to DFT.

Anionic N-Heterocyclic Carbenes-Zwitterionic Complex

Pyrimidinium betaïnes constitute precursor for anionic carbene by a classical double peptide-type coupling between a formamididine and a monosubstituted malonic acid.

Carbene generated in situ and reacted with 0.5 equiv of $[\text{RhCl}(1,5-\text{COD})]_2$ and produced the zwitter ionic complex $\text{Rh(maloNHC)(COD)}$.

First Rhodium Complex of anionic NHC

Donar properties of anionic NHC

Reacting anionic NHC with a series of simple basic transition-metal complexes produced zwitter ionic complexes.

Estimating the donor properties of anionic NHC compared with those of a “normal” NHC by using CO stretching frequencies as a probe.

\[
\text{NHC} = \text{IMes (CO)}: 2050, 2006 \text{ cm}^{-1} \\
\text{NHC} = \text{SIMes (CO)}: 2049, 2005 \text{ cm}^{-1}.
\]

IR values indicate that the anionic \textit{maloNHC} is a better donor than IMes or SIMes.

Summary

- Organo catalytic properties of N-Heterocyclic Carbenes were described.
- Modifications of various catalytic systems with NHC ligands are described.
- Anionic N-Heterocyclic Carbenes and their donating properties are described.
Thank you