**N-Heterocyclic Carbenes**

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Scope of Lecture

- transesterification bonding and stability of NHCs
- homoenolates the Wanzlick equilibrium
- the Stetter reaction isolation of stable carbenes
- the benzoin condensation and its mechanism acidity of NHCs

Key Questions

1. Why are NHCs more stable than other carbenes?
2. Do NHCs dimerize?
3. How can NHCs be used to make acyl anion equivalents?

![Chem 106](https://example.com/Chem106.png)

Helpful References


**Introduction**

A carbene is a divalent carbon atom with only six valence electrons. The prototype is methylene, CH$_2$. **N-heterocyclic carbenes** (NHCs) are especially stable carbenes which are flanked by two nitrogens and constrained in a ring.

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

Computations played a crucial role in legitimizing computational chemistry in the 1970s. For the first time, they pointed out some errors in experiments on methylene, in what Schaefer calls the "paradigm of computational chemistry."


There are two possible geometries for methylene, **bent** and **linear**, with accompanying changes in hybridization:

- the bent geometry is isoelectronic to that of water, with a clear $\sigma-\pi$ separation, at least for the isolated molecule

- the linear geometry has two non-bonding $p$-orbitals

Where do the non-bonding electrons go? This determines whether methylene will zero (singlet) or two (triplet) unpaired electrons. For the bent geometry, this means:

Since the two possible singlet electronic configurations are similar in energy (near-degenerate), any reasonable description must include at least a two-reference wavefunction.

In the late 1960s, the consensus was that methylene is linear. This was supported by spectroscopic measurements performed by Herzberg. Foster and Boys had reported very crude computations showing that methylene is bent, but these were dismissed by the theorist Longuet-Higgins.

In 1970, Bender and Schaefer used a CISD/DZ method to compute the structure of methylene and concluded that the H-C-H angle is 135°, and at the very least, not linear. This was soon supported by solid state ESR studies. Herzberg re-examined his UV spectra and condensed that triplet methylene is bent, with an angle of 136°, which is a remarkably close value.

More sophisticated measurements now place the angle at 133.9308° (*J Chem Phys* **1988**, 89, 1327-1332). Hartree-Fock and DFT methods get angles which are within 1-2°; more sophisticated MR-CISD and RCCSD(T) methods get it closer.

**The Singlet-Triplet Gap**

The singlet vs. triplet character of methylene is an organic analog to the high- and low-spin complexes of inorganic chemistry.

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H}
\end{align*}
\]

It turns out that experiments find that methylene has a triplet ground state ($^3B_1$) and a singlet first excited state ($^1A_1$). However, prior to 1972, experimentalists put the gap at either 1-2 kcal/mol or 8-9 kcal/mol. Computations helped resolve this in favor of the latter. Single reference HF and MP2 overestimate this, B3LYP gets it close, and MR-CISD gets it within 0.1 kcal/mol.
N-Heterocyclic Carbenes

Of course, methylene is not a particularly stable carbene. It turns out that the triplet is not always the most stable state, and the properties of the substituents on the carbene can greatly alter the singlet-triplet gap.


In 1895, Nef wrote:
"Now it will be my next task to prepare methylene or derivatives of it which are free of nitrogen; a number of observations already suggest that such substances can exist."

This is pretty remarkable, given that van't Hoff only proposed tetrahedral carbon in 1874. Still, in retrospect, Nef's statement was a bit naive, and ultimately he did not succeed.

It seems that the singlet-triplet energy gap has a lot to do with the separation of the σ and π non-bonding orbitals; the larger the separation, the larger the gap. Hoffmann places the minimum value for a singlet at 2 eV.

Q: How would you rationalize the following data?

| kcal/mol | singlet | triplet | Li=C-Li 180° | singlet | triplet | H=H 134° | triplet | F=F 104° |

(1) The bond angles can be rationalized using Bent's Rule. Fluorine is quite electronegative, so its bonding hybrids have more p-character, and therefore a smaller interhybrid angle. Lithium is quite electropositive, so its bonding hybrids get a lot of s-character, and a larger interhybrid angle. Thus, these cases are controlled by inductive effects.

(2) The larger the X-C-X angle, the more likely it is that the singlet is favored, just based on symmetry and s vs. p energy arguments:

- the non-bonding orbitals are degenerate, so a triplet becomes very likely
- in the bent geometry, symmetry enforces a σ-π separation

What about resonance effects? It turns out that this is a big reason that N-heterocyclic carbenes are especially stable.

Q: What do the orbitals look like for this NHC?

Let us consider the localized orbitals (i.e., NBOs) for the resonance structure as drawn. The lone pairs on nitrogen are expected to donate into the vacant p-orbital on carbon. This raises the energy of the p-orbital, increasing the singlet-triplet gap. In the limit, we go to this resonance structure:

Now, we have very strong allyl anion-type resonance between the lone pair on nitrogen and the "iminium ion."
**N-Heterocyclic Carbenes**

The p-type non-bonding orbital is such a good acceptor that, in many cases, the right hand resonance structure is best:

\[ \text{Me} - \text{N} \overset{\cdot}{\text{N}} \overset{\cdot}{\text{N}} \overset{\cdot}{\text{N}} \overset{\cdot}{\text{Me}} \quad \text{Me} - \text{N} \overset{\cdot}{\text{N}} \overset{\cdot}{\text{N}} \overset{\cdot}{\text{N}} \overset{\cdot}{\text{Me}} \]

Here are some pictures which demonstrate the complementary roles of inductive and mesomeric stabilization in NHCs:

![N-Heterocyclic Carbenes](image)

In this case, the polarity of the N-C bond suggests that the former interaction is more important.

Phosphinosilylcarbenes are an interesting case where a push-pull mechanism creates a singlet, but linear carbene. In fact, Pauling has suggested that the best way to stabilize a singlet carbene is to maintain the electroneutrality at the carbon center (JCS Chem Comm 1980 688). Here are some pictures:

![Phosphinosilylcarbenes](image)

Donation of the phosphorus lone pair into one vacant p-orbital occurs while a filled carbene lone pair donates into the adjacent C-Si antibond. This breaks the \( p_x, p_y \) degeneracy. As food for thought, diborylcarbenes \( R_2B-C-BR_2 \) are also linear, singlet carbenes!

Bulky substituents favor the triplet state by opening up the X-C-X angle. For example, dimethylmethylenone is a bent ground state singlet (111°), but di-\( \text{tert} \)-butylcarbene is a triplet (143°). In NHCs, the bond angle is constrained to give a bent singlet. Bulky substituents can then protect the carbene center from electrophilic or nucleophilic attack (kinetically).
The Benzoin Condensation
This academic discussion about bond angles and singlet-triplet gaps is all very well and good, but what influence does all this have on reactivity? Ironically, we begin with the cyanide-promoted benzoin condensation, which doesn't involve NHCs:

\[
\text{PhCH} \overset{\text{NaCN}, \text{EtOH, } \Delta}{\xrightarrow{90-92\%}} \text{PhCHOH}
\]

Wohler/Liebig Ann. Pharm. 1832 3 249

This produces a carbonyl anion to make a 1,2-dioxygenated pattern via this "Lapworth mechanism":

\[
\text{PhCHOH} \xrightarrow{-CN} \text{PhCO} \xrightarrow{\text{O}} \text{PhCN} \xrightarrow{\text{OH}} \text{PhCOH}
\]

Lapworth J. Chem. Soc. 1903 83 995

However, the substrate scope of this reaction is quite limited.
By 1954, it was realized that thiamine can catalyze this reaction:

\[
\text{pyruvic acid} \xrightarrow{\text{thiamine}} \text{acetoin}
\]

thiamine (vitamin B₁)

Acidity of NHC Precursors
Here is some evidence for the stability of NHCs:

\[
\begin{align*}
\text{HN} & \overset{\text{pD } 13}{\xrightarrow{\text{D}_2\text{O}}} \text{HN} \\
\text{HN} & \overset{\text{pD } 9}{\xrightarrow{\text{D}_2\text{O}}} \text{HN} \\
\text{HN} & \overset{\text{pD } 9}{\xrightarrow{\text{D}_2\text{O}}} \text{HN}
\end{align*}
\]

- rate varies by less than a factor of 2 for various buffer concentrations and types (Olofson JACS 1964 86 1865)
**Acidity in Water**

- Determined by relating rate of H/D exchange to solvent kinetic isotope effect (Richard JACS 2004 126 4366)
- Kinetic and thermodynamic acidity are correlated

**Mechanism of the Benzoin Condensation**

While the mechanism shown above is now definitive, there have been suggestions of carbene dimers historically:

- **Q1:** Why don't NHCs just dimerize? Or do they?
- **Q2:** What's so special about NHCs?


**Isolation of Stable Carbenes**


Arduengo knew that imidazolium salts could be converted to thiones, presumably via NHCs:

In 1988, Dupont needed a polymer cross-linker, and these thiones were thought to be useful, since they are relatively nucleophilic, but not very basic. A multicomponent strategy involving multiple condensations was developed:

The availability of a wide range of imidazolium salts allowed Arduengo to examine the properties of a variety of NHC precursors.
Isolation of Stable Carbenes

As might be expected on the basis of the previous arguments, the placement of bulky groups on nitrogen protects the carbene from decomposition. Here is the first crystalline carbene to be isolated (Arduengo, *JACS* 1991, 113, 361; CSD: KAKQMIY): 

![Chemical structure of a crystalline carbene]

What makes this stable?

1. The adamantyl groups make this kinetically stable from steric shielding.
2. The nitrogens give an "allyl anion"-type stabilization:

   ![Chemical structure with N^+ radicals and π*CN]

3. The carbene is confined to a five-membered ring, which enforces a bent geometry. This maintains σ–π separation, and makes the singlet more stable than the triplet. Here, the N-C-N angle is 102°.
4. With the olefin, this is a $6\pi$-aromatic system.

The saturated counterpart has been isolated, but is less stable and requires very bulky mesityl groups to shield it. (Arduengo, *JACS* 1995, 117, 11027; CSD: ZIHXOD):

![Chemical structure of a saturated carbene]

Frenking has compared (*JACS* 1996 118 2039) the stability of the unsaturated, and at least formally aromatic, and saturated NHCs at the MP4/6-311g(d,p)//MP2/6-311g(d,p) level, which is admittedly a single-reference method:

\[
\begin{align*}
\text{NHC} & + \text{H}_2 \rightarrow \text{NHC}^- \quad -20.8 \text{ kcal/mol} \\
\text{NHC} & + \text{H}_2 \rightarrow \text{NHC}^{-} \quad -39.7 \text{ kcal/mol}
\end{align*}
\]

NICS, which has been proposed as a method of assessing the aromaticity of systems, as well magnetic susceptibility calculations confirm this is a partially magnetic system.

The Wanzlick Equilibrium

In 1960, Wanzlick proposed there is a monomer-dimer equilibrium to form tetraaminoethylenes (*ACIE* 1960 72 494):

\[
\begin{align*}
\text{NHC} & \quad \rightleftharpoons \quad \text{NHC} \quad \text{NHC}^{-} \quad \text{NHC}^{-}
\end{align*}
\]
The Wanzlick Equilibrium

Certainly, some carbenes do dimerize. These tetraaminoethylene species are very electron rich and therefore easy to oxidize (Lemal JACS 1962 84 1761):

$$\begin{align*}
\text{ClO}_4^- & \quad \text{MesMgBr} \\
\text{THF} & \\
\text{NHC}^+ & \quad \text{colorless} \\
\text{air} & \quad \text{deep violet}
\end{align*}$$

In fact, Lemal proposed that these dimers might actually be responsible for the chemistry. Of course, this doesn't rule out NHCs, either (ACIE 1962 175, ACIE 1964 86 2518):

$$\begin{align*}
\text{PhCHO} & \quad 130 \degree C \\
\text{NHC} & \quad 90\%
\end{align*}$$

$$\begin{align*}
\text{HCl} & \quad \text{rt} \\
\text{NHC} & \quad 100\%
\end{align*}$$

$$\begin{align*}
\text{NC} \quad \text{CN} & \quad \text{NC} \quad \text{CN} \\
\text{NHC} & \quad 70\%
\end{align*}$$

Wanzlick thought there was a monomer-dimer equilibrium, with the monomer NHC as the active species; Lemal thought the dimer tetraaminoethylene was the sole species, with no monomer-dimer equilibrium.

Q: What do crossover experiments say?

To support this theory, Lemal showed a lack of crossover:

$$\begin{align*}
\text{NHC} \quad \text{NHC} \\
\text{Ar} = o\text{-Tol} \\
\underset{2 \text{h}}{\text{reflux in PhMe}} \\
2 \text{NHC}
\end{align*}$$

Wiberg later confirmed this with alkyl and aryl tetraaminoethylenes (JACS 1965 87 2055). However, things were thrown into disarray in 1999 by Denk, however (TL 1999 40 2057):

$$\begin{align*}
\text{NHC} \quad \text{NHC} \\
\text{R, R'} = \text{Me/Et; Et/iPr; iPr/Me; Ph/pTol} \\
\underset{2}{\text{?}}
\end{align*}$$

A statistical mixture (1:2:1) is formed! So how might one interpret these results?

Negative Crossover = Definitely no equilibrium
Positive Crossover = Might be an equilibrium

Why do I say "might"? One can't rule out a [2+2] cycloaddition/ [2+2] cycloreversion process:

$$\begin{align*}
\text{A=A} & \quad \underset{\text{B=B}}{\text{A-B}} & \quad \text{A} & \quad \text{B} \\
\text{B=B} & \quad \underset{\text{A=A}}{\text{A-B}} & \quad \text{A} & \quad \text{B}
\end{align*}$$

Although the concerted process is thermally forbidden, it is conceivable a non-concerted pathway is possible. Additionally, when the experiment is performed under very rigorous conditions, crossover is eliminated (Lemal TL 2000 41 599):

$$\begin{align*}
\text{NHC} \quad \text{NHC} & \quad \text{C}_6\text{D}_6 \quad 100 \degree C \\
\text{Ar = p-Tol} & \quad 2 \text{NHC}
\end{align*}$$

as drawn: 19% crossover after 6 h
with KH: no crossover product
**The Wanzlick Equilibrium**

This raises the real possibility that contamination led to the crossover results. The original experiments were prepared via triphenylcarbinol oxide, rather than heating with trimethyl orthofomate. In fact, adding acid catalyzes the equilibrium (Hu *J Mol Phys* 2004 102 2617).

Benzo-fused NHCs are less stable, as the penalty for dearomatizing the NHC is less. In this case, an equilibrium is observable by NMR:

- bulky R favors carbene (R=Pr, neopentyl)
- for R=Et, $\Delta H^\circ = 13.7 \pm 0.6$ kcal/mol, $\Delta S^\circ = 30.4 \pm 1.7$ eu
- at 25 °C, this corresponds to $\Delta G = 5$ kcal/mol

For now, it seems the evidence leans against the Wanzlick equilibrium, but it's still controversial. But most people draw the NHC as a monomeric carbene.

Lemal *JACS* 1999 121 10626  Hahn *ACIE* 2000 112 541  
**Summary:** Herrmann *ACIE* 2000 39 4036

**Asymmetric Benzoin Condensations**

NHCs have allowed inverted polarity transformations to be rendered asymmetric and synthetically useful. An early attempt by Sheehan showed this was possible (*JACS* 1974 39 1196):

10 mol% NHC  
10 mol% Et$_3$N  
1:2 MeOH/H$_2$O  
30 °C, 24 h

- aldehyde: 78%, 8% ee

So how do these reactions work? Enders proposes this dual H-bond/p-p stacking model (*ACIE* 2004 37 534):

The idea is that the aldehyde approaches opposite the bulky tert-butyl group, and that the benzaldehyde is able to π-stack with the phenyl of the substrate. Both geometric isomers are accessible, but only the one drawn avoids a π–π interaction.
Asymmetric Benzoin Condensations

In contrast, Houk has used B3LYP (PNAS 2004 101 5770):

favored transition state (+0.0 kcal/mol)

(1) Agreement between experimental and predicted ee's is only moderate.
(2) The B3LYP method is not supposed to work very well for π–π stacking.
(3) Why the triazolium catalysts are more enantioselective than the thiazolium catalysts is unclear:

favored transition state (+0.0 kcal/mol)

disfavored transition state (+2.8 kcal/mol)

disfavored transition state (+0.8 kcal/mol)
**Crossed Benzoin Condensations**

These are now possible in an intramolecular format (Enders *ACIE* 2006 45 1463; *Synlett* 2006 15 2431):

These are becoming useful in synthesis (Suzuki *ACIE* 2006 45 3492; *OL* 2007 9 2713):

Miller has used this sort of methodology to make acyloin-type products (*JOC* 2007 72 5260). Once again, imidazolium salts are not active. Here, the yields are low due to product instability.

**Tip:** this generates an anion, which then participates in a pericyclic reaction.
Crossed Benzoin Condensations
The proposed mechanism involves an initial crossed-benzoin addition, followed by an anion-accelerated oxy-Cope reaction:

\[
\text{PhCHO} + \text{MeO}_2\text{C-Ph} \xrightarrow{\text{cross-benzoin}} \text{PhCHO} + \text{MeO}_2\text{C-Ph}
\]

(reversible)

\[
\text{PhCO} + \text{MeO}_2\text{C-Ph} \xrightarrow{\text{oxy-Cope}} \text{PhCO} + \text{MeO}_2\text{C-Ph}
\]

(irrev.)

This is poised for an aldol addition, the product of which can acylate the alkoxide. This regenerates the NHC. Finally, decarboxylation occurs:

\[
\text{PhCO} \xrightarrow{-\text{CO}_2} \text{PhCO}
\]

Evidence for the anion-accelerated oxy-Cope reaction:

\[
\text{PhCHO} + \text{MeO}_2\text{C-Ph} \xrightarrow{10 \text{ mol}\% \text{NHC}} \text{PhCHO} + \text{MeO}_2\text{C-Ph}
\]

15 mol\% DBU,

1,2-DCE/EtOH,

rt, 24 h

Initial oxy-cope rearrangement generates a formally zwitterionic species. The nucleophilically activated carbonyl can expel the NHC to generate a ketene, which can acylate ethanol (hence, the ethyl ester).

The Stetter Reaction
While the benzoin condensation delivers umpolung 1,2-dioxy fragments, the Stetter reaction gives 1,4-dioxy fragments:

\[
\text{RCHO} + \text{R'C} \xrightarrow{\text{benzoin}} \text{ROH} + \text{R'C}
\]

acyl anion  aldehyde  a-hydroxy ketones

\[
\text{RCHO} + \text{R'C} \xrightarrow{\text{Stetter}} \text{RKY} + \text{R'C}
\]

acyl anion  Michael acceptor  1,4-dicarbonyl compounds

So the Stetter reaction is a vinylogous benzoin condensation and the Stetter is to benzoin as Michael is to aldol. The NHC-catalyzed process provides alternatives to radical reactions.


The original reaction was reported in 1973 by Stetter:

\[
\text{PhCHO} + \text{MeO}_2\text{C-Ph} \xrightarrow{\text{NaCN, DMF, rt}} \text{PhCO} \xrightarrow{33\%}
\]

Nowadays, asymmetric variants are possible. Here is an early example from the Enders group (Helv. Chim. Acta. 1996 79 1899):

\[
\text{RCHO} + \text{ClO}_4^- \xrightarrow{20 \text{ mol}\% \text{NHC}} \text{PhC} \xrightarrow{44-73\%, 56-74\% \text{ ee}} \text{PhC}
\]

K$_2$CO$_3$

THF, rt, 24 h
The Stetter Reaction

The Rovis group has developed some nice asymmetric Stetter reactions as well (JACS 2002 12410298; Synlett 2003 12 1934):

$$\text{CHO} \quad \text{20 mol\% NHC} \quad \text{20 mol\% KHMDS} \quad \text{xylenes, rt, 24 h}$$

$$\text{NHC} = \begin{array}{c}
\text{O} \\
\text{N} \\
\text{N} \\
\text{BF}_4^- \\
\text{OMe}
\end{array}$$

- significantly improved yields and ee's
- Z enoates do not react
- $\alpha,\beta$-unsaturated aldehydes, carboxamides, and nitro compounds are inactive
- $\alpha,\beta$-unsaturated ketones react more rapidly than corresponding esters

This has been extended to aliphatic tethers, but six-membered rings cannot be formed. Note the high catalyst loadings:

$$\text{CHO} \quad \text{20 mol\% NHC} \quad \text{20 mol\% KHMDS} \quad \text{xylenes, rt, 24 h}$$

With $\alpha,\alpha$-disubstituted acceptors, an enantioselective Stetter reaction can be followed by a diastereoselective protonation:

Rovis JACS 2005 127 6284

NHC = $\begin{array}{c}
\text{N} \\
\text{N} \\
\text{BF}_4^- \\
\text{CF}_3
\end{array}$

94%, 95% ee, dr 30:1

What is the origin of diastereoselectivity? Note that E and Z acceptors behave differently:

80%, 93% ee, dr 42:1

70%, 38% ee, dr 6:1

However, quaternary stereocenters can be formed (Rovis JACS 2004 126 8876):
**The Stetter Reaction**
Rovis and co-workers propose the following model:

**E enoate** (high ee and dr)
Here, addition of the acyl anion equivalent occurs opposite to the bulky substituent on the NHC. The product ester enolate is protonated intramolecularly (aryl group abbreviated to olefin):

- 
- 
- A(1,3) min.

**Z enoate** (low ee and dr)
Here, adding to the side opposite the bulky NHC substituent incurs developing A(1,3) strain. The proton is still delivered from the same face. However, flipping the olefin geometry results in the opposite epimer. Thus, this is mismatched:

- 
- 
- not A(1,3) min.

Scheidt as shown that acylsilanes are competent acyl anion equivalents when paired with NHCS (*JACS* 2004 126 2314):

![Chem 106](image)

- an analogue of thiamine diphosphate
- this sequence incorporates a Brook rearrangement (*JOC* 2006 71 5715)

Decarboxylative addition is possible (*JACS* 2005 127 14675):

- 
- 
- 92%

Enantioselective desymmetrizations are also possible (Rovis *JACS* 2006 128 2552, *OPRD* 2007 11 598):

- 86%, >99% ee
- one diastereomer
Homoenolates
How would you generate the homoenolate synthon?

Addition of NHCs to α,β-unsaturated aldehydes:

This can undergo reactions at its d3 terminus (homoenolate reactivity) or its d1 terminus (acyl anion reactivity). Here are the initial reports of homoenolate benzoin reactions (Glorius ACIE 2004 43 6205; Bode JACS 2004 126 14370 - simultaneous):

representative examples: Bode

These make γ-butyrolactones, which are valuable pharmacophores.

Dimerization is also possible:

conditions:
- 8 mol% IMes-Cl, 7 mol% DBU
- 2 equiv electrophilic aldehyde
- rt, 15 h, 10:1 THF/tBuOH

- aliphatic aldehydes are not effective
- slow addition of enal increases yields
- performing the reaction with cis-p-anisaldehyde still leads to the cis adduct
- if reaction is performed with t-BuOD, D is incorporated exclusively at the α-position (no quenching of homoenolate by solvent)

Homoenolate Michael Additions
If homoenolate benzoin condensations are possible, are homoenolate Stetter reactions possible? Scheidt has reported (ACIE 2007 46 3107) precisely this:
Homoenolate Michael Additions

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Chemical Structure]</td>
<td>[Chemical Structure]</td>
<td>59</td>
<td>99</td>
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<tr>
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<td>[Chemical Structure]</td>
<td>52</td>
<td>62</td>
</tr>
</tbody>
</table>

- the product acyl-NHC is quenched by methanol
- primary or secondary amides are accessed if amines are used instead of MeOH

NHC = \[
\begin{array}{c}
\text{N} \\
\text{N}
\end{array} \quad \text{BF}_4
\]

What if the NHC attacks the β-carbon of the acceptor instead of the homoenolate? This becomes possible if the aldehyde is deleted. Here is an example (Fu JACS 2006 128 1472):

isotopic scrambling

- 90%
- 48%

proposed catalytic cycle

when Nu PbU, this step is not possible and there is <3% D incorporation at the β-carbon
Transesterification

In addition for carbon-carbon bond formation, NHCs are also useful for transesterification. There are different protocols, depending on whether you want to transesterify to a primary or secondary alcohol (Waymouth/Hendrick *OL* 2002 4 3587; Nolan *OL* 2002 4 3583; Nolan *JOC* 2003 68 2812):

**primary alcohols**

\[
\text{RO} \text{OR'} \xrightarrow{1 \text{ mol% IMes or ICy, 4A MS}} \text{RO}'' \text{OH} \quad \text{R}'' = \text{Me, Et, vinyl}
\]

95-100%

**secondary alcohols** (Nolan *JOC* 2004 69 209)

\[
\text{OEt} \xrightarrow{5 \text{ mol% ICy, 4A MS}} \text{O} \quad \text{ROH}
\]

68-98%

These reactions are no doubt driven by an excess of the primary alcohol and possibly also by a mass-action effect of the molecular sieves. The direct amidation of esters is also possible (Movassaghi *OL* 2005 7 2453):

\[
\text{RO} \text{OR'} \xrightarrow{6.5 \text{ mol% IMes-Cl, 5 mol% tBuOK}} \text{R} \text{N} \text{OH} \quad \text{R} = \text{alkyl, aryl, heterocyclic}
\]

- enantiopurity unchanged

\[ \text{R} = \text{Me or lactone} \]

\[ \text{R}' \text{OH} \]

**typical yields 90%**

One possibility is that the ester gets acylates by the NHC in a 4-DMAP-type fashion:

 Movassaghi suggests that this is general base catalysis instead:

\[
\text{Mes} \xrightarrow{\text{N to O acyl transfer}} \text{R} \text{NH} \text{OH}
\]

He notes that an equimolar mixture of IMes: and MeOH in deuterated benzene produces a visible IMes-MeOH complex. ReactIR shows the transient O-acyl intermediate.

The IMes-MeOH complex is isolable (CSD keyword: JAPDEK) and seems to be a donor-acceptor complex (C...H distance: 1.96 A):