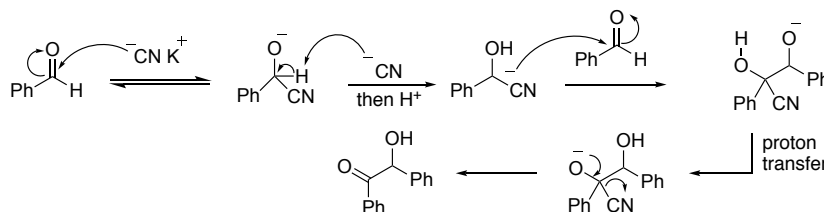


Benzoin and Related Reactions (Lecture 3)

1 Benzoin Reaction

The benzoin reaction is a cyanide ion catalyzed reaction between two aldehydes. It was the first organic reaction for which the mechanism was fully elucidated. The key step is the deprotonation of the cyanohydrin intermediate, which effects a polarity change of the aldehyde - the formerly electrophilic carbonyl carbon becomes nucleophilic. This concept is called "Umpolung" (Seebach *ACIE* **1979**, 18, 239).



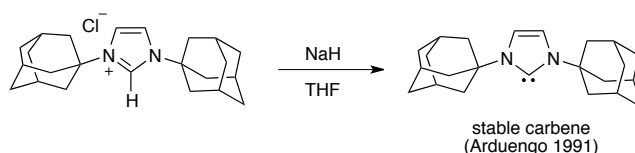
For mechanism: Lapworth, *J. Chem. Soc., Trans.* **1903**, 83, 995 & **1904**, 85, 1206

2 N-heterocyclic Carbenes

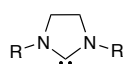
N-heterocyclic carbenes (NHCs) are a unique class of carbenes and have applications for example in catalyzing benzoin and related reactions, or umpolung in general.

2.1 History

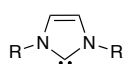
The first applications of thiazolydenes in organocatalytic umpolung were reported as early as 1943 (*J. Pharm. Soc. Jpn.* **1943**, 63, 296) and metal complexes of NHCs were already reported in the late 1960s. However, it is only in the last two decades (milestone: 1991, Arduengo, first X-ray structure of a carbene) that NHCs have become ubiquitous both as **ligands** in organometallic chemistry and as **organocatalysts**.



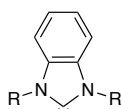
2.2 Examples of Common NHCs and their Nomenclature



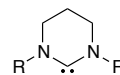
Imidazolylidene



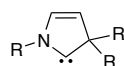
Imidazolylene



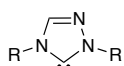
Benzimidazolylene



Tetrahydropyrimidinylene



Pyrrolidinylene



Triazolylene



Thiazolidene

To fine-tune the chemical behavior of the NHC, the R-group can be modified (e.g. R = alkyl or aryl).





2.3 Properties

2.3.1 NHCs are stable singlet carbenes

Unlike other carbene or carbenoid species, which are high-energy intermediates, N-heterocyclic carbenes are very stable. This is because the lone pair of the heteroatom adjacent to the carbene carbon donates electrons into the empty p-orbital of the carbene carbon. Additionally, the *N*-substitution provides kinetic stability.

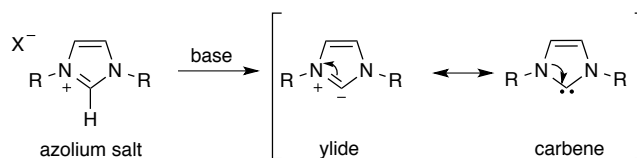
For NHCs, the singlet state is lower in energy than the triplet state. The reason for this is π -donation from the heteroatoms adjacent to the carbene into the carbon p-orbital.

In summary, NHC are electron rich and particularly stable singlet carbenes. Their stability arises from:

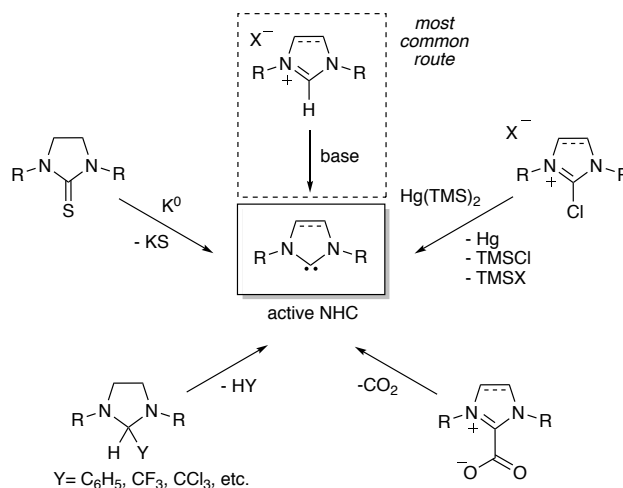
- **shielding effects** by sterically demanding substituents (minor effect)
- **electronic stabilization** (mesomeric interaction of the lone pairs on the nitrogen atoms with the adjacent, empty p-orbital of the sp^2 -hybridized carbene)

2.4 Synthesis / Generation

The **proton** at the 2-position of imidazolium salts is **very acidic** (pK_a value ranges from 16 to 23 in DMSO).



As a result, NHCs are most commonly prepared by deprotonating the respective precursor salt.





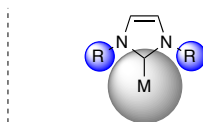
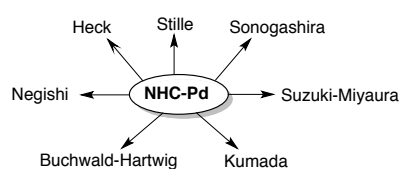
2.5 Application as Ligands

NHC-complexes of almost every transition metal are known. Some frequently used NHC-complexes for organic chemists are listed in the following table.

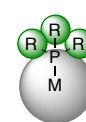
Metal	Class	Example	Catalyst
Ru	Metathesis reactions		<p>Grubbs II</p>
Pd	Cross-coupling reactions	<p><i>Buchwald-Hartwig coupling with hindered substrates</i></p>	<p>Pd-PEPPSI</p>

NHCs behave like phosphines when coordinated to metals (electron donating properties), however they have more influence on the coordination sphere of the metal than phosphines (sterics).

Cross-Coupling Reactions



R groups pointing at the metal "coordination sphere"



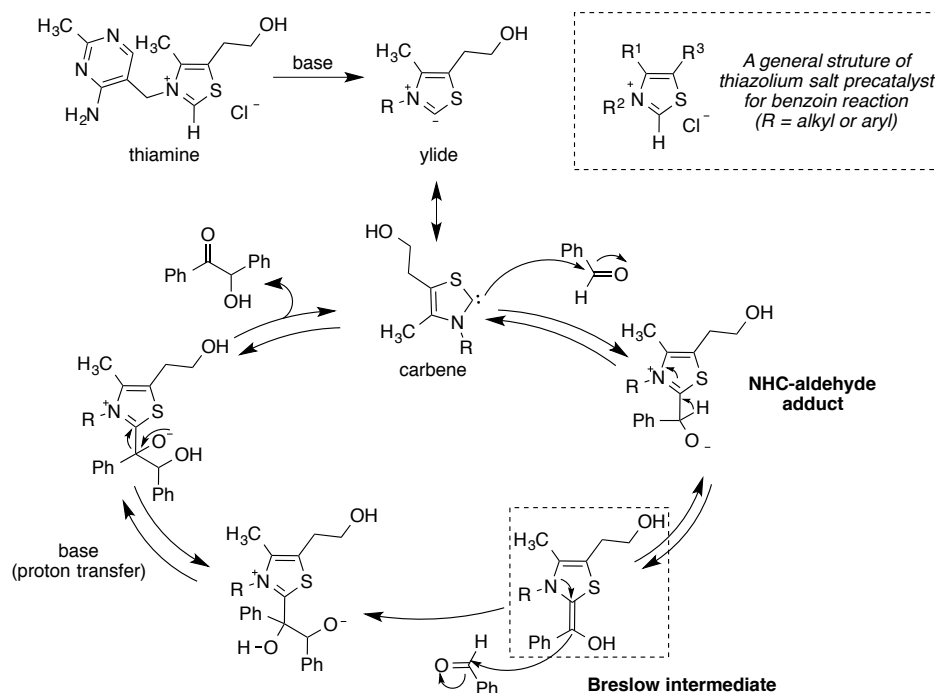
R groups pointing away from the "coordination sphere"

3 NHC-Catalyzed Reactions

3.1 Benzoin Reactions

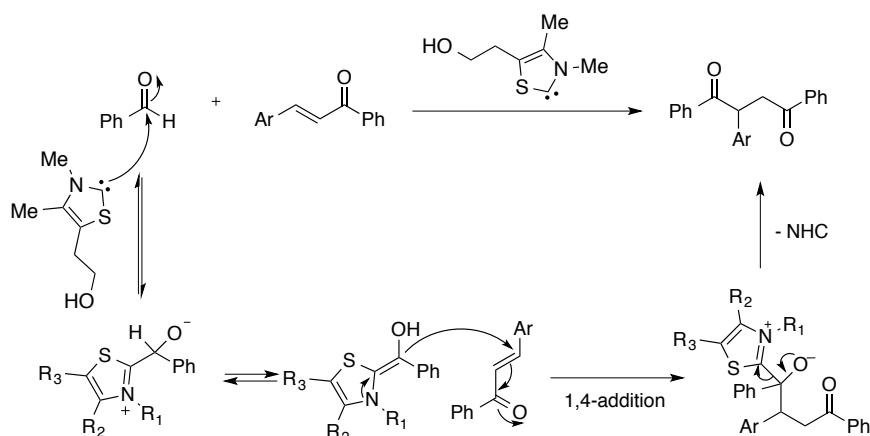
3.1.1 The Thiamine Variant of the Benzoin Reaction

In the benzoin reaction (and many other NHC-catalyzed reactions), the carboxylic carbon of the aldehyde undergoes a reversal in polarity from an electrophilic center to being a nucleophilic center. This concept is called "Umpolung" (Seebach *ACIE* **1979**, *18*, 239).

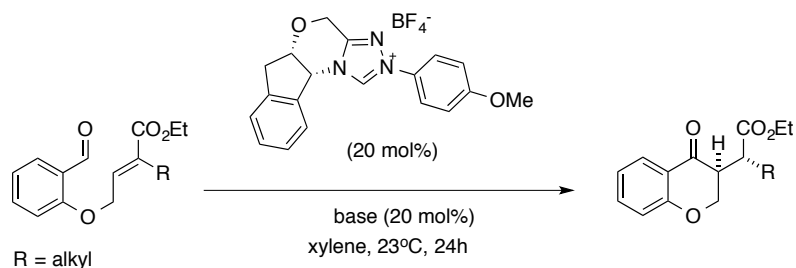




3.2 Stetter Reaction

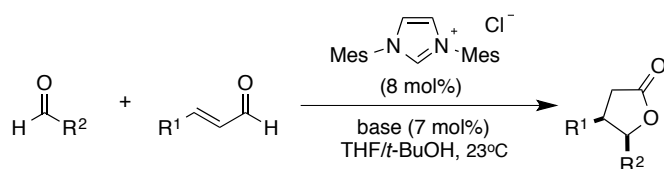


A highly enantio- and diastereoselective catalytic intramolecular Stetter Reaction:

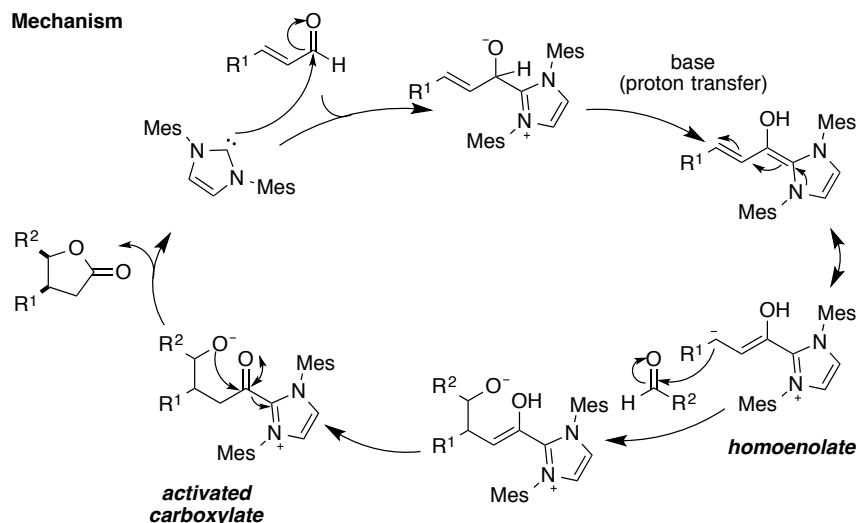


J. Read de Alaniz, T. Rovis, *J. Am. Chem. Soc.*, **2005**, 127, 6284-6289.

3.3 Other NHC-Catalyzed Annulations

3.3.1 Synthesis of γ -Lactones via homoenolate addition

Mechanism

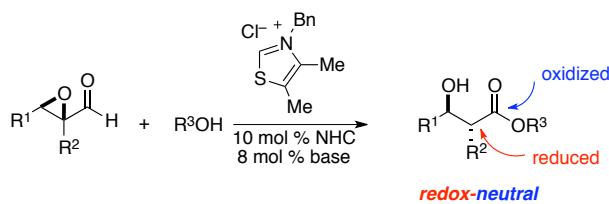


Bode *JACS* **2004**, 126, 8126 & Glorius *ACIE* **2004**, 43, 6205.



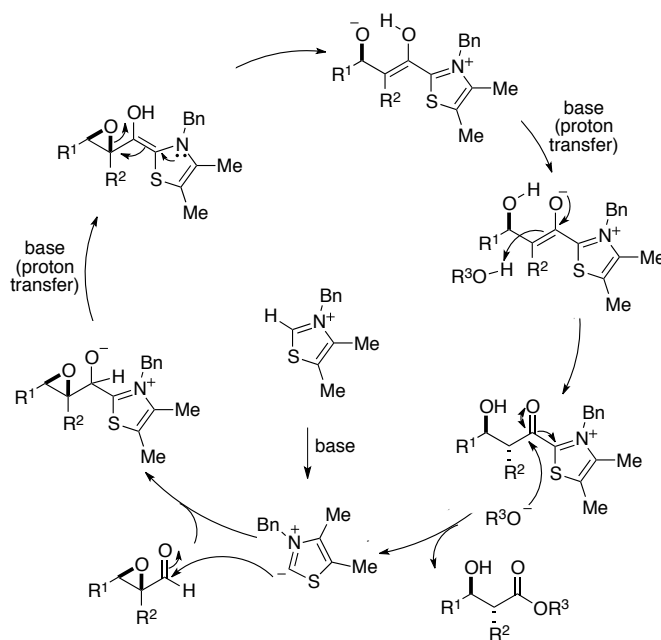
3.3.2 Internal Redox Reactions

Epoxy aldehyde:

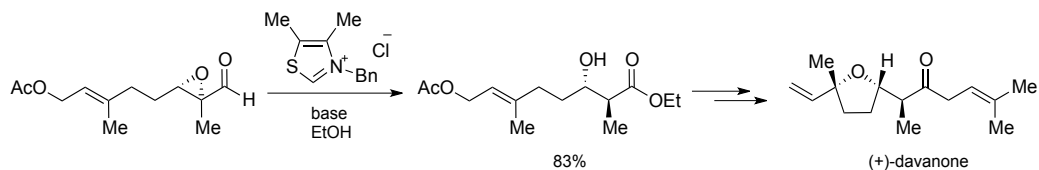


Bode *JACS*, 2004, 126, 8126.

Mechanism:

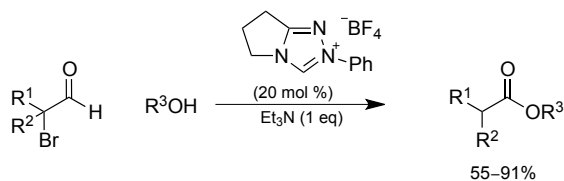


An application to natural product synthesis:



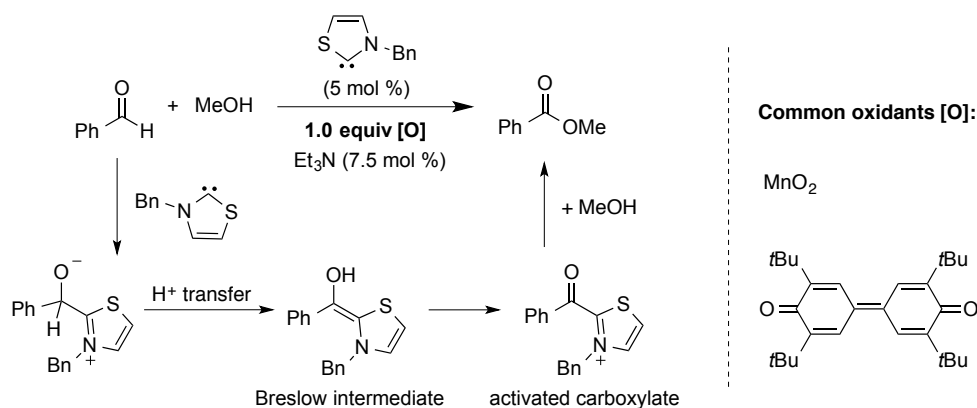
Vosburg *OL*, 2009, 11, 2217.

Redox esterification from α -haloaldehyde was concurrently reported:



Rovis, *JACS*, 2004, 126, 9518.

3.3.3 Oxidation by N-Heterocyclic Carbenes



4 Biological Counterparts

Carbenes play a central role in several biological processes. One of the most important examples is Vitamin B₁ (Thiamine pyrophosphate), a cofactor involved in many metabolic pathways. For instance, the enzyme *pyruvate decarboxylase* is assisted by TPP in catalyzing the transformation of pyruvate into acetaldehyde, which is a key step in anaerobic fermentation. Think about this next time you have a drink!

