# ORGANOCATALYSIS BY NUCLEOPHILIC HETEROCYCLIC CARBENES

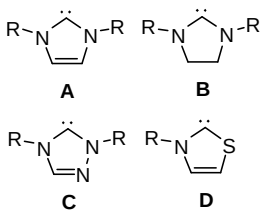
Reported by: Dale Pahls March 16, 2010

## INTRODUCTION

### Nucleophilic Heterocyclic Carbenes and Umpolung

Since the isolation of the first stabilized carbenes by Bertrand in 1988[1] and Arduengo in 1991,[2] nucleophilic heterocyclic carbenes (NHCs) have generated great interest in the chemical community. Due to their singlet carbene nature, NHCs possess both a carbon-centered electron pair and an empty carbon p-orbital. The empty p-orbital can accept electron density and stabilize the accumulation of negative charge at an adjacent atom, while the lone pair is both highly electron donating and nucleophilic.[3] This combination of properties is rare and is what makes NHCs attractive as organocatalysts and as ligands in organometallic catalysis.[4]

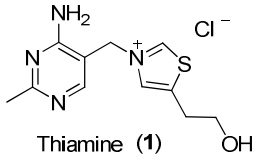
The electronic properties of NHCs can be used to achieve reactivity umpolung[4] of aldehydes and related electrophiles. Reactivity umpolung describes a situation in which a moiety is engendered to react in a manner opposite to its normal reactivity. In the case of NHC adducts of aldehydes, the carbonyl carbon becomes nucleophilic, so the adduct can be considered an acyl anion synthon. This reactivity umpolung can be extended to α,β-unsaturated aldehydes to effect nucleophilic reaction at the β-position of the aldehyde.[4] Although not strictly a reactivity umpolung, NHCs can also catalyze transesterification reactions or ring-opening polymerization of polyesters[4] as well as activate carbon dioxide, via a betaine intermediate,[5-6] towards further functionalization, such as oxygen transfer.[6]




Four classes of NHCs are common in organocatalysis:[4] the imidazol-2-ylidenes (**A**), imidazolin-2-ylidene (**B**), triazol-5-ylidenes (**C**), and thiazol-2-ylidenes (**D**). These catalysts can be added to a reaction as the free carbene, but the azolium salt precursor is more commonly used. Chiral, nonracemic thiazolium salts are the most common catalyst for enantioselective catalysis by NHCs.

## REACTIONS VIA REACTIVITY UMPOLUNG

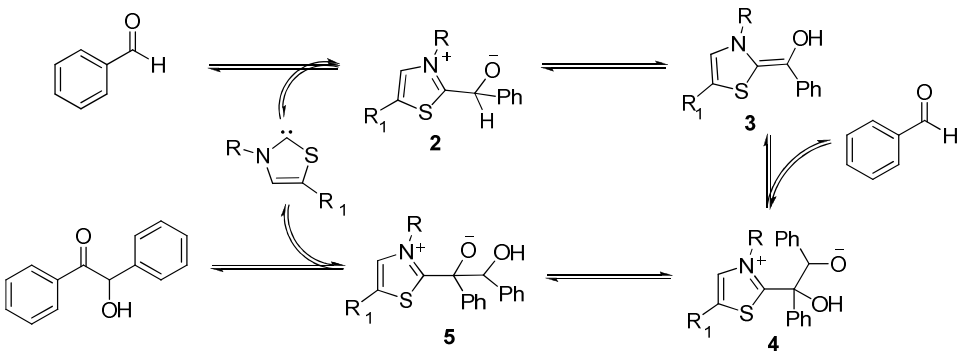
### Benzoin Condensation



Thiamine (**1**)

Reactions catalyzed by NHCs were known long before the first isolation and characterization of a stabilized carbene.[8] Thiamine, or vitamin B1 (**1**), shown as its chloride salt, has been known as a catalyst for the benzoin reaction for over 50 years and was the first known NHC organocatalyst. The mode of action for thiamine in the benzoin reaction was a topic of much debate until Breslow proposed that a thiazol-2-ylidene intermediate (**D**), present after deprotonation of the parent thiazolium salt, was the active catalyst.[8] Breslow's proposed catalytic cycle was based on analogy to the previously known cyanide-catalyzed synthesis of benzoins (**Scheme 1)**.[9]

**Scheme 1: Mechanism of the Benzoin Reaction**




The mechanism of the benzoin reaction serves as the basis for understanding the mechanism of all subsequent NHC-catalyzed acyl anion additions. The aldehyde first undergoes nucleophilic attack by the NHC, resulting in zwitterionic intermediate **2**, which undergoes proton transfer to give intermediate **3**. The NHC moiety stabilizes the resulting carbanion by accepting electron density, which facilitates the proton transfer. This enamine species, **3**, known as the "Breslow intermediate", is invoked to explain the reactivity umpolung of aldehydes induced by NHC catalysts. A second equivalent of benzaldehyde then undergoes nucleophilic attack by **3** to give intermediate **4**, followed by intermolecular proton transfer between the hydroxyl groups to give **5**. The NHC is eliminated from **5**, regenerating the catalyst and producing the α-hydroxyketone. Importantly, every step in this mechanism is reversible, which allows benzoins to be used as an aldehyde source in other NHC-catalyzed reactions.

The scope of the benzoin reaction is limited to the coupling of an aldehyde with an aldehyde, or in select cases, with a ketone or imine.[4,10] While aliphatic aldehydes do undergo the benzoin reaction,[7]

aromatic aldehydes are the most common substrates for the reaction. Ketones are less reactive than aldehydes in the benzoin reaction;[11] so aldehyde homocoupling can become competitive with product formation. However, this can be overcome by tethering the ketone to the aldehyde, thereby increasing the effective molarity.[11]

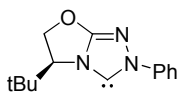
**Stetter Reaction**

Stetter pioneered the extension of the electrophile scope of NHC catalysis to α,β-unsaturated carbonyl compounds.[12] This extension allowed for the synthesis of a variety of molecules containing varied functional groups with a 1,4 substitution pattern. α,β-Unsaturated ketones, esters, amides, phosphonates, acyl imidazoles, and acylimines (generated *in situ* from α-tosyl amides) are all viable as electrophiles in the Stetter reaction.[4]

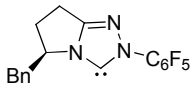
While Stetter improved the electrophile scope, Scheidt expanded the scope of nucleophiles able to form the Breslow intermediate from aldehydes and acyloins[4] to include acylsilanes[13] and pyruvates,[14] both of which can generate acyl anion equivalents.

The addition of acyl anion equivalents generated *in situ* from pyruvates to α,β-unsaturated acyl imidazoles, reported by Scheidt's group, provides an excellent example of several advancements in the Stetter reaction.[14] First, the reaction occurs in buffered aqueous media over a pH range of 4-12. This activity in acidic media is surprising because the thiazolium salt has a pKa of 16.5 in DMSO.[15] Therefore the aqueous media, especially at lower pH values, should be acidic enough to protonate the NHC catalyst and prevent catalysis. Second, the nucleophile is generated *in situ* from a non-aldehyde source.[14] Pyruvates can form the Breslow intermediate (**7**) by decarboxylation after initial attack of the NHC on the ketone (**6**) (**Scheme 2**). This activation precludes the problem of aldehyde dimerization that is often observed. Nucleophilic attack by **7** at the β-position of the carbonyl of the acyl imidizole (**8**) gives a 1,4-dicarbonyl compound (**9**) after subsequent elimination of the carbene catalyst. Further elaboration of the products was accomplished by alkylating the imidazole to form an acylimidazol-2-ylidene (**10**), a species now activated to undergo nucleophilic displacement to form an ester or amide.

Enantioselective versions of the Stetter reaction have also been developed.[7] Triazoles are the most common NHC backbones for enantioselective catalysis (**11**,**12**). Chiral NHCs typically have chiral centers incorporated into the backbone rather than possessing chrial R substitutents on nitrogen. In certain cases, erosion of the enantioselectivity was observed with extended reaction times. The racemization was proposed to be



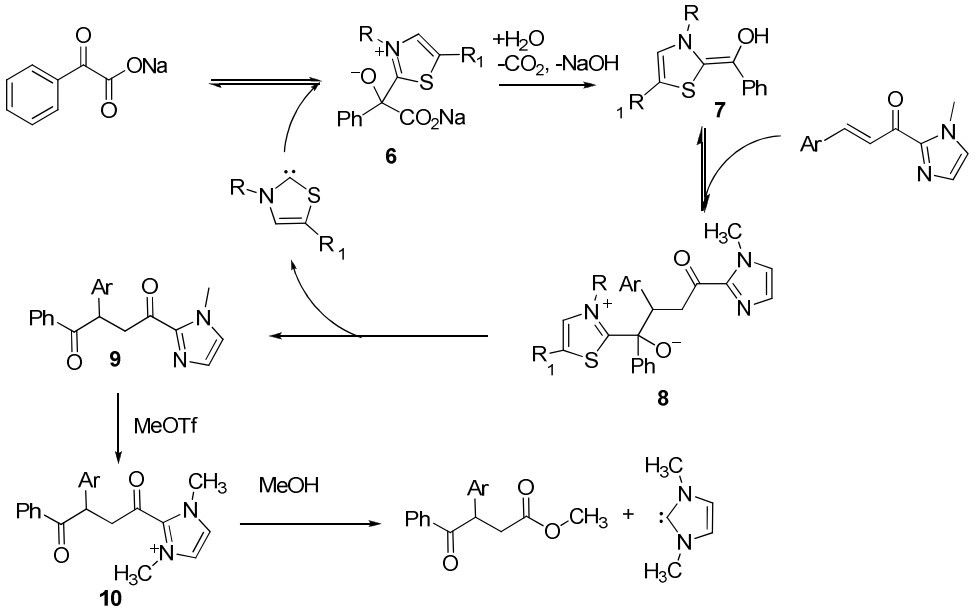
**11**



**12**

caused by deprotonation of the enolizable methine proton by the base additive. A solution was to add the neutral carbene rather than an azolium salt, avoiding the need for the base additive.[16]

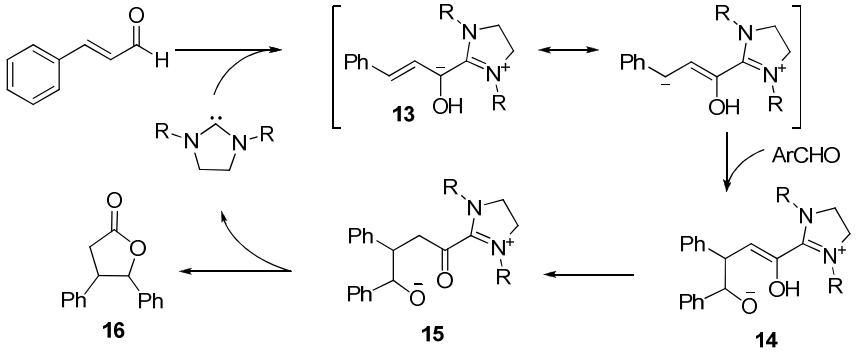
**Scheme 2: The Reaction of Pyruvates with Acylimidazoles and Subsequent Functionalization**




**Reactions of Homoenolates**

Just as the utilization of α,β-unsaturated electrophiles greatly diversified the range of transformations catalyzed by NHCs, modifying the nucleophile precursor from an aldehyde to an α,β-unsaturated aldehyde unlocked new reactivity.[4,17] The Breslow intermediate is now in conjugation with the olefin (**13**) and the reactive carbanion is stabilized at both the carbonyl carbon and the beta carbon by resonance; therefore, the β-carbon is also nucleophilic. (**Scheme 3**).

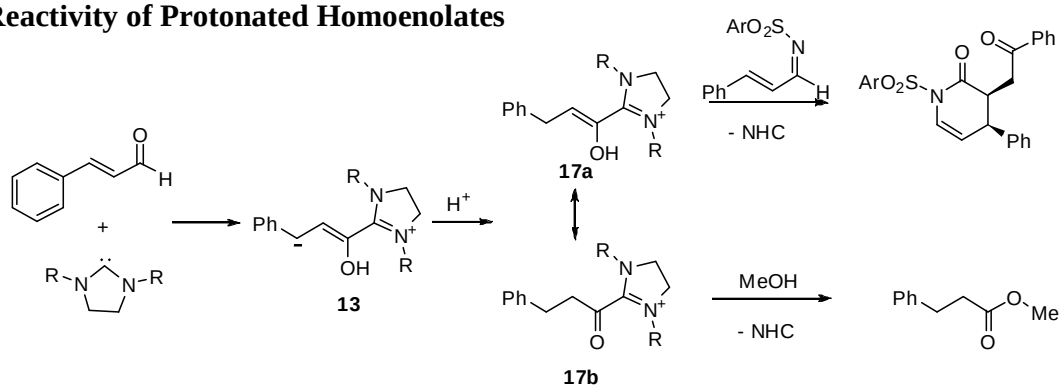
**Scheme 3: Homoenolate annulations to form gamma butyrolactones**



This reactive species, known as a homoenolate, enables the synthesis of 1,4-di-substituted products with different connectivity than the Stetter reaction. The R groups on NHCs catalysts used for homoenolate reactions are usually bulky and are designed to minimize reactivity at the former carbonyl carbon. Nucleophilic attack of **13** upon a ketone, aldehyde, or imine generates an alkoxide or amide intermediate (**Scheme 3, 14**). After tautomerization of the resulting enol to the acylimidizolium species (**15**), nucleophilic attack of the pendant alkoxide or amide moeity forms a lactone (**16**) or lactam and releases the NHC catalyst.

An interesting subset of reactivity comes from using a proton as the electrophile (**Scheme 4**).[4] The resulting enol (**17a**) is stabilized by the NHC and has been used as an electron-rich dieneophile for Diels-Alder reactions. Tautomerization to the acylimidizolium species (**17b**), followed by nucleophilc attack at the carbonyl carbon by an alcohol, leads to saturated ester products.[18] The overall transformation is an oxidation of the aldehyde and concomitant reduction of the olefin, an internal deprotonation that proceeds without the need for any external oxidants or reductants. Neither of these reactions is available to traditional Breslow intermediates.

**Scheme 4: Reactivity of Protonated Homoenolates**




## OTHER REACTIONS CATALYZED BY NHC ORGANOCATALYSIS

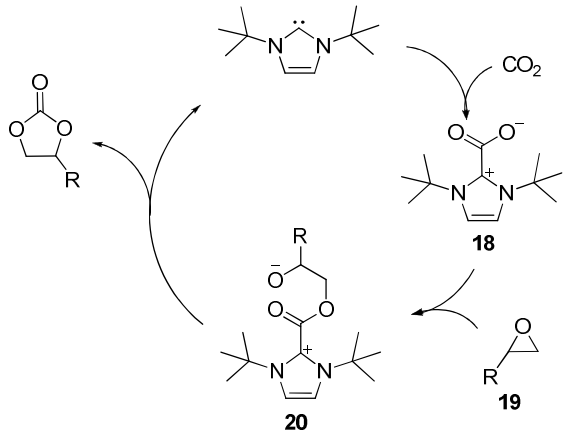
### Reactions of Carbon Dioxide

Nucleophilic heterocyclic carbenes are nucleophilic enough to react with carbon dioxide to form a stabilized betaine structure, a novel species that affords previously unattainable reactivity. Two such reactions are the carboxylative cyclization of carbon dioxide with propargylic alcohols and the oxidation of aromatic aldehydes by carbon dioxide.[5-6]

The carboxylative cyclization of carbon dioxide with propargylic alcohols was first reported by Ikariya using trialkyl phosphines as organocatalysts in supercritical carbon dioxide as solvent.[19] Since NHCs are nucleophilic like phosphines, the Ikariya group decided to test the reactivity of NHC catalysts

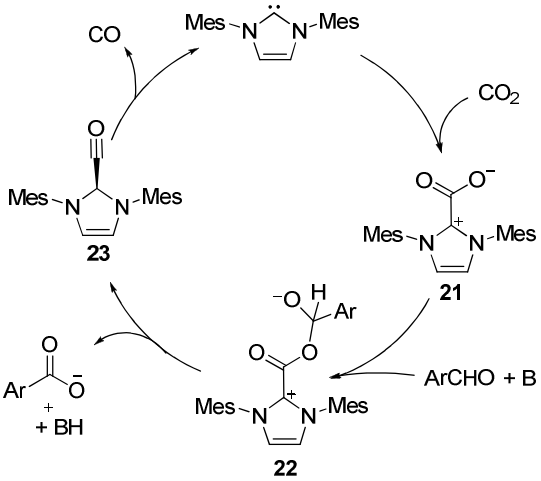
under the same conditions, and found that NHCs also catalyzed the desired transformation.[5] A betaine structure (**18**) was proposed as the activated form of the carbon dioxide. An epoxide (**19**) or propargylic alcohol undergoes nucleophilic attack by **18** (**Scheme 4**). The alkoxide generated (**20a-b**) then attacks the carbonyl carbon, releasing the NHC catalyst and forming a carbonate.

**Scheme 4: Reaction of Carbon Dioxide with Epoxides**




Perhaps even more surprising than the nucleophilicity of the betaine intermediate, is the ability of the betaine to undergo oxygen transfer.[6] Zhang has reported the reaction of carbon dioxide with both benzaldehydes and cinnamaldehydes catalyzed by NHCs to yield carboxylic acids and carbon monoxide. Similar to the mechanism reported by Ikariya, carbon dioxide is first activated by the NHC to form a betaine structure (**Scheme 5, 21**). Then the aldehyde undergoes nucleophilic attack by **21** to yield **22**.

**Scheme 5: Oxidation of Aromatic Aldehydes**

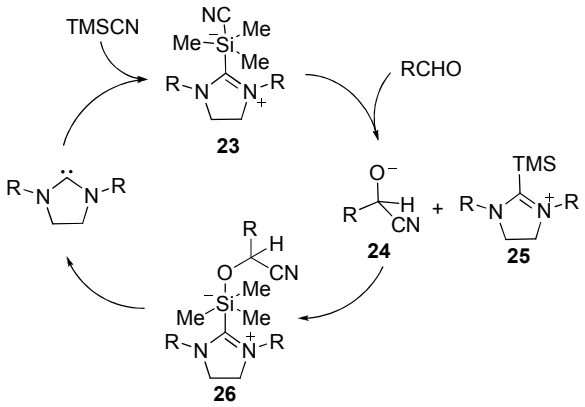


After external deprotonation by base as shown, or a possible intramolecular deprotonation by a nitrogen of the NHC followed by deprotonation by the external base, the benzoic or cinnamic acid is released, and an NHC-CO Lewis pair adduct is formed (**23**). Carbon monoxide is known to bind very weakly to NHCs,[20] and subsequent release of carbon monoxide regenerates the catalyst.

### 1,2 Addition Reactions

Another reaction class catalyzed by NHCs is the addition of a nucleophile and an electrophile to an aldehyde in a 1,2 manner.[4] Compounds such as trimethylsilyl cyanide, trifluorylmethyltrimethylsilane, and cyanophosphate esters, which contain both an electrophilic and nucleophilic moiety, can react in this manner. What makes this reaction so intriguing is that although an unprotected aldehyde exists within the reaction mixture, the carbene is proposed to activate the silyl group by forming a pentavalent silicon center (**23**).[21] The cyanide moiety of **23** then attacks the carbonyl, and the resulting alkoxide (**24**) reacts with the silylcarbene (**25**), releasing the carbene catalyst. Kondo and Aoyama do not comment on the mechanism for activation of cyanophosphate esters,[22] but addition of the NHC to the phosphonate ester to release cyanide, nucleophilic attack of the cyanide onto the carbonyl with subsequent attack of the resulting alkoxide on the phosphonate to liberate the NHC catalyst seems plausible.

**Scheme 6: 1,2 Additions to Aldehydes**




## CONCLUSION

The uncommon electronic properties of NHCs make them excellent organocatalysts for generating reactivity umpolung. These properties stem from the nature of NHCs as singlet carbenes. The carbene lone pair is highly nucleophilic, but the empty *p* orbital is able to accept electron density and thereby stabilize a nearby accumulation of negative charge. This combination of properties can

invert the reactivity of aldehydes and carbon dioxide, causing these adducts to act as nucleophiles rather than as electrophiles, greatly expanding the possible transformations of these ubiquitous moieties and diversifying their utility. Presently, however, this reversed reactivity can only be accessed with a few electrophiles: carbon dioxide, aldehydes, pyruvates, and acyl silanes, which markedly limits the scope of this area of chemistry. If the properties of NHCs could be altered to activate more functional groups, then the scope of their application to organocatalysis could see a large growth. Though the reaction currently has some limitations in the scope, within its niche it is unparalleled in its reactivity.

## REFERENCES


1 Igau, A.; Grutzmacher, H.; Baceiredo, A.; Bertrand, G. *J. Am. Chem. Soc.* **1988**, *110*, 6463
2 Arduengo, A. J.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361
3 Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.*, **1999**, *121*, 2674
4 Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 2988
5 Kayaki, Y.; Yamamoto, Masafumi, K.; Ikariya, T. *Angew. Chem. Int. Ed.* **2009**, *48*, 4194
6 Gu, L.; Zhang, Y. *J. Am. Chem. Soc.*, **2010**, *132*, 914
7 Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534
8 Breslow, R. *J. Am. Chem. Soc.*, **1958**, *80*, 3719
9 Lapworth, A. *J. Chem. Soc., Trans.*, **1903**, *83*, 995
10 Li, G.; Dai, L.; You, S.; *Chem. Commun.*, **2007**, 852
11 Hachisu, Y.; Bode, J. W.; Suzuki, K. *J. Am. Chem. Soc.* **2003**, *125*, 8432
12 Stetter, H. *Angew Chem Int Ed*, **1976**, *15*, 639
13 Mattson, A. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 2314
14 Myers, M. C.; Bharadwaj, A. R.; Milgram, B. C.; Schedit, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 14675
15 Bordwell, F. G.; Satish, B. A. V. *J. Am. Chem. Soc.*, **1991**, *113*, 985
16 Read de Alainz, J.; Rovis, T. *J. Am. Chem. Soc.*, **2005**, *127*, 6284
17 Najir, V.; Vellalath, S; Babu, B. P. *Chem. Soc. Rev.*, **2008**, *37*, 2691
18 Chan, A.; Scheidt, K. A., *Org. Lett.* **2005**, *7*, 905
19 Kayaki, Y.; Yamamoto, M.; Ikariya, J. *J. Org. Chem.* **2007**, *72*, 647
20 Lavallo, V.; Canac, Y.; Donnadieu, B.; Scholler, W. W.; Bertrand, G. *Angew. Chem. Int. Ed.* **2006**, *118*, 3568
21 Song, J. J.; Gallou, F.; Reeves, J. T.; Tan, Z.; Yee, N. K.; Senanayake, C. H. *J. Org. Chem.* **2006**, *71*, 1273
22 Fukuda, Y.; Maeda, Y.; Kondo, K.; Aoyama, T, *Chem. Pharm. Bull.*, **2006**, *54*, 397