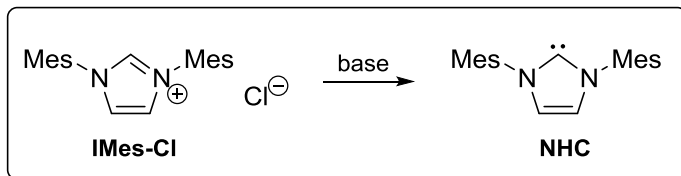


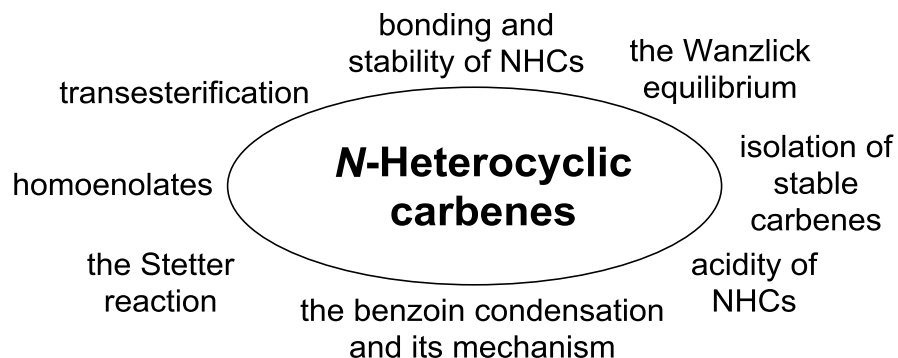
N-Heterocyclic Carbenes

Eugene E. Kwan

November 28, 2011.

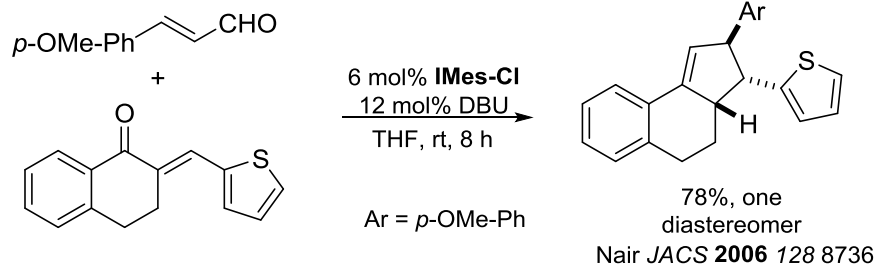


Scope of Lecture



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?

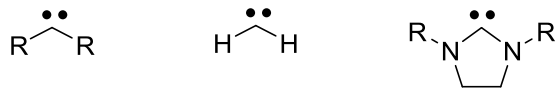


Helpful References

1. **"N-Heterocyclic Carbenes as Organocatalysts."** Marion, N.; Diez-Gonzalez, S.; Nolan, S.P. *Angew. Chem. Int. Ed.* **2007**, *26*, 2988. (general review)
2. **"Stable Carbenes."** Bourissou, D.; Guerret, O.; Gabbai, F.P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39-91. (general review)
3. **"Nucleophilic Carbenes: An Incredible Renaissance."** Regitz, M. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 725-728. (discovery)
4. **"Looking for Stable Carbenes: The Difficulty in Starting Anew."** Ardugengo III, A.J. *Acc. Chem. Res.* **1999**, *32*, 913-921. (discovery)
5. **"Formation and Stability of N-Heterocyclic Carbenes in Water: The Carbon Acid pKa of Imidazolium Cations in Aqueous Solution."** Amyes, T.; Diver, S.T.; Richard, J.P.; Rivas, F.M.; Toth, K. *J. Am. Chem. Soc.* **2004**, *126*, 4366-4374. (pKa of NHCs)
6. **"When and How Do Diaminocarbenes Dimerize?"** Alder, R.W.; Blake, M.E.; Chaker, L.; Harvey, J.N.; Paolini, F.; Schutz, J. *Angew. Chem. Int. Ed.* **2004**, *43*, 5896-5911. (general review)
7. **"Catalyzed Reactions of Acyl Anion Chemistry."** Johnson, J.S. *Angew. Chem. Int. Ed.* **2004**, *43*, 1326-1328. (benzoin, Stetter)
8. **"Nucleophilic Carbenes in Asymmetric Organocatalysis."** Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534-541. (asymmetric benzoin, Stetter)
9. **"Extending Mechanistic Routes in Heterazolium Catalysis--Promising Concepts for Versatile Synthetic Methods."** Zeitler, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 7506-7510. (homoenolates)

Introduction

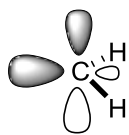
A **carbene** is a divalent carbon atom with only six valence electrons. The prototype is methylene, CH₂. **N-heterocyclic carbenes** (NHCs) are especially stable carbenes which are flanked by two nitrogens and constrained in a ring.



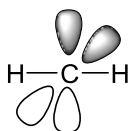
Computations played a crucial role in legitimizing computational chemistry in the 1970s. For the first time, they pointed out some errors in experiments on methylene, in what Schaefer calls the "paradigm of computational chemistry."

refs: Bachrach, Computational Organic Chemistry, Ch. 8
Schaefer III, H.F. *Science* **1986**, 231, 1100-1107.

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

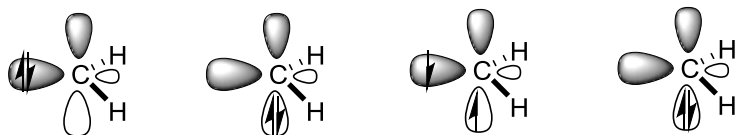


- the bent geometry is isoelectronic to that of water, with a clear σ - π separation, at least for the isolated molecule



- 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.

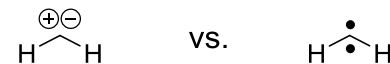
In the late 1960s, the consensus was that methylene is linear. This was supported by spectroscopic measurements performed by Herzberg. Foster and Boys had reported very crude computations showing that methylene is bent, but these were dismissed by the theorist Longuet-Higgins.

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 concluded 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.



It turns out that experiments find that methylene has a triplet ground state (³B₁) and a singlet first excited state (¹A₁).

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.

"Heterocyclic Carbenes." Hahn, F.E.; Jahnke, M.C. *ACIE* **2008**, *47*, 3122-3172.

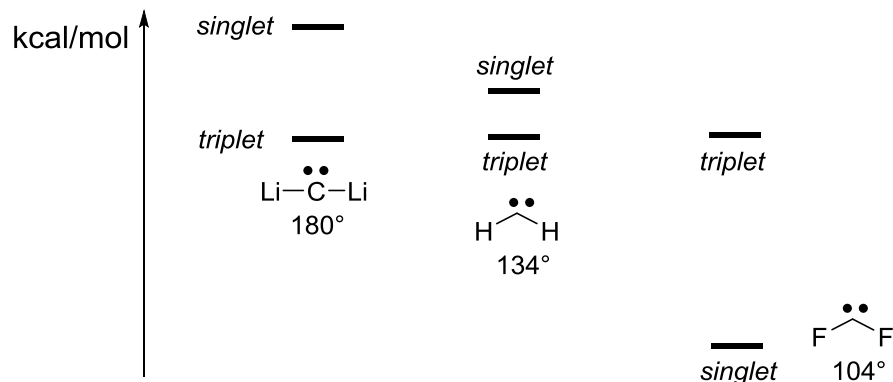
In 1895, Nef wrote:

"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.

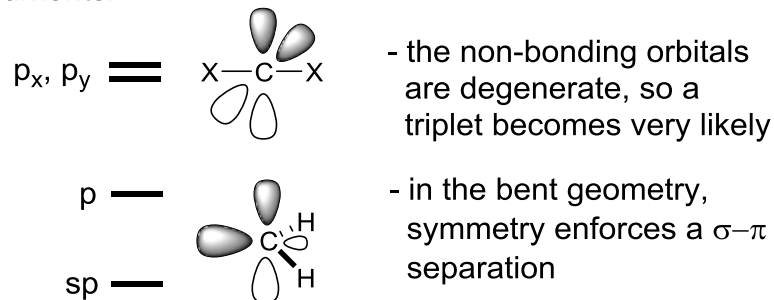
It seems that the singlet-triplet energy gap has a lot to do with the separation of the σ and π non-bonding orbitals; the larger the separation, the larger the gap. Hoffmann places the minimum value for a singlet at 2 eV.

Q: How would you rationalize the following data?



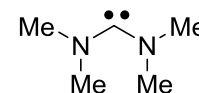
(1) The bond angles can be rationalized using Bent's Rule. Fluorine is quite electronegative, so its bonding hybrids have more p-character, and therefore a smaller interhybrid angle. Lithium is quite electropositive, so its bonding hybrids get a lot of s-character, and a larger interhybrid angle. Thus,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

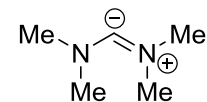


What about resonance effects? It turns out that this is a big reason that N-heterocyclic carbenes are especially stable.

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:



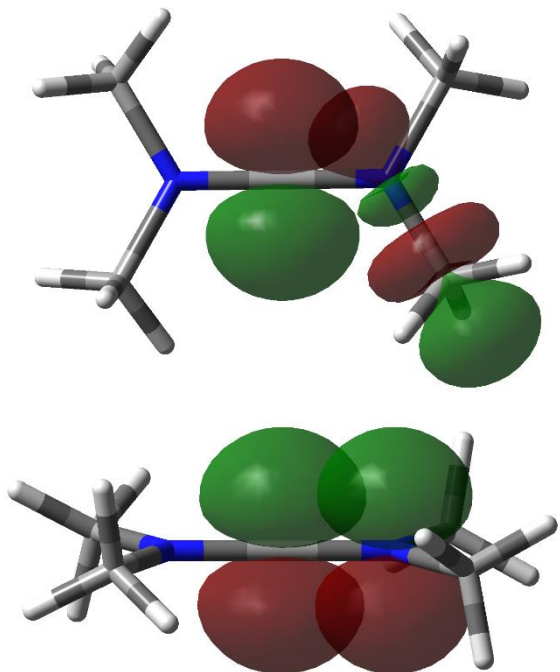
Now, we have very strong allyl anion-type resonance between the lone pair on nitrogen and the "iminium ion."

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:

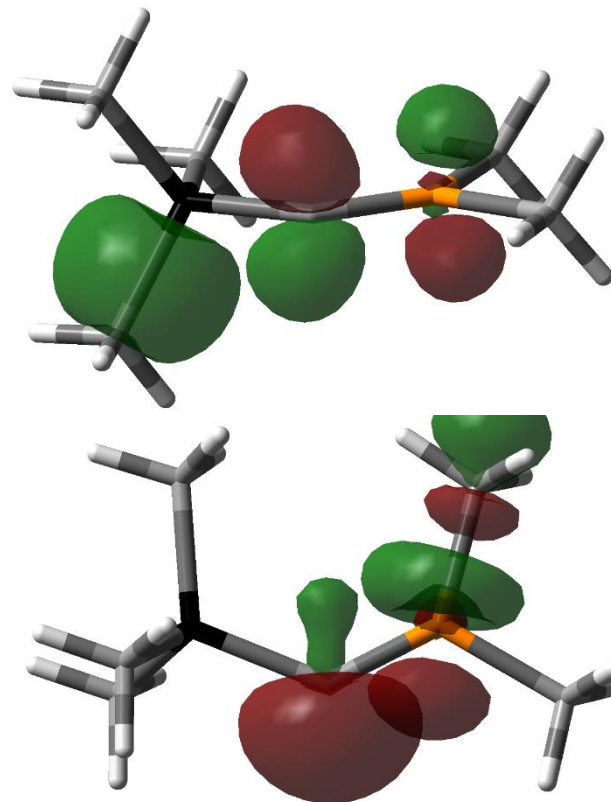


Here are some pictures which demonstrate the complementary roles of inductive and mesomeric stabilization in NHCs:



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:

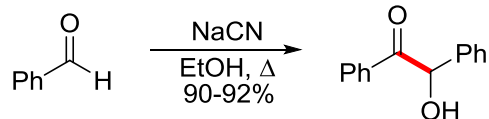


Donation of the phosphorus lone pair into one vacant p-orbital occurs while a filled carbene lone pair donates into the adjacent C-Si antibond. This breaks the p_x , p_y degeneracy. As food for thought, diborylcarbenes $R_2B-C-BR_2$ are also linear, singlet carbenes!

Bulky substituents favor the triplet state by opening up the X-C-X angle. For example, dimethylmethylene is a bent ground state singlet (111°), but di-*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).

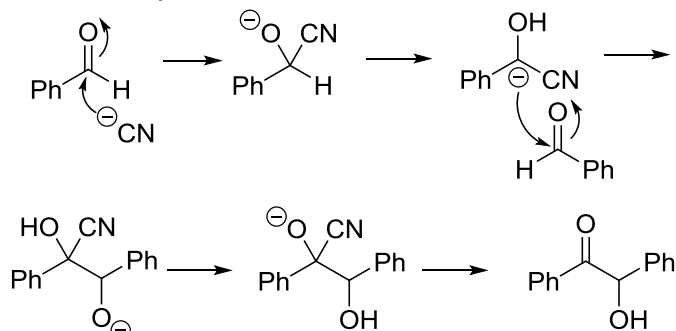
The Benzoin Condensation

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:

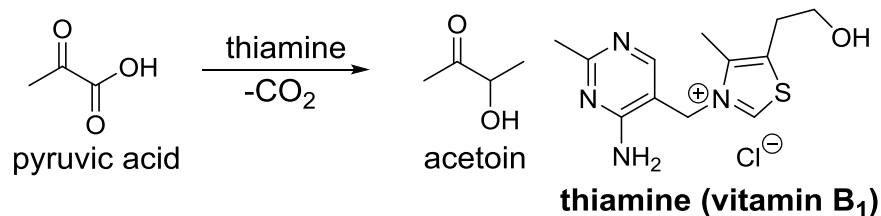


Wohler/Liebig *Ann. Pharm.* **1832** 3 249
 Adams *Org. Syn. Coll. Vol. 1* **1941** 94

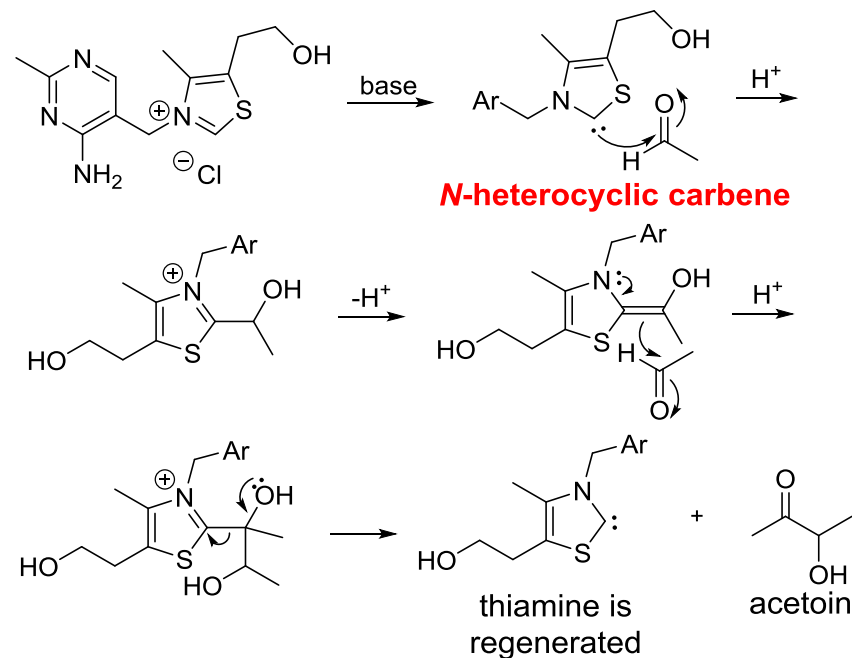
This produces a carbonyl anion to make a 1,2-dioxygenated pattern via this "Lapworth mechanism":



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

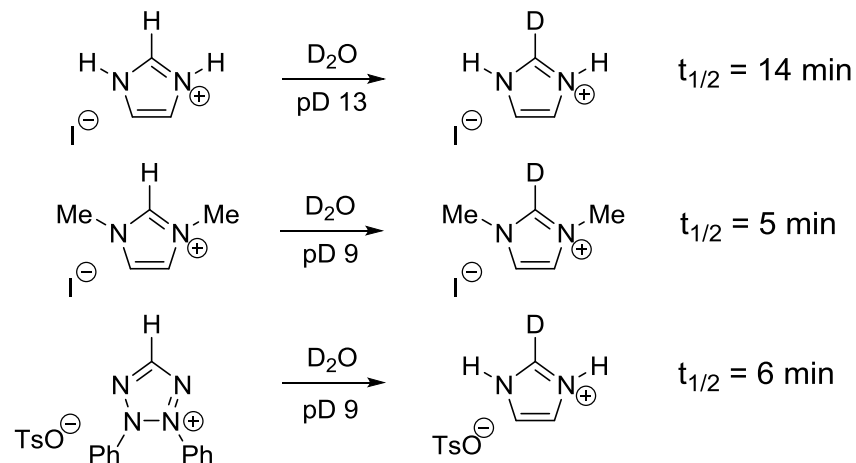


How does this work? Clearly, thiamine has the trappings of an NHC, albeit with one sulfur and one nitrogen instead of two nitrogens. Breslow studied this reaction and suggested the mechanism shown below (*JACS* **1958**, 80, 3719):



Acidity of NHC Precursors

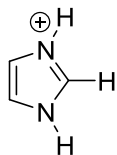
Here is some evidence for the stability of NHCs:



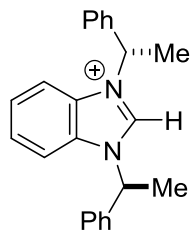
- rate varies by less than a factor of 2 for various buffer concentrations and types (Olofson *JACS* **1964** 86 1865)

acidity in water

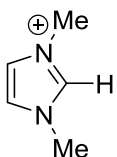
rate of deprot. ($M^{-1} s^{-1}$) /
relative rate



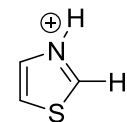
1.54×10^1 (1)
 $pK_a = 23.8$



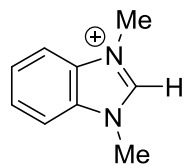
6.17×10^3 (400)
 $pK_a = 21.2$



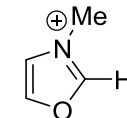
1.03×10^2 (7)
 $pK_a = 23.0$



1.3×10^5 (8 400)
 $pK_a = 19.9$



2.39×10^3 (150)
 $pK_a = 21.6$

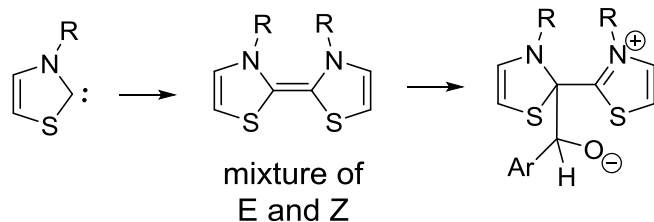


3.0×10^7 (1 900 000)
 $pK_a = 16.9$

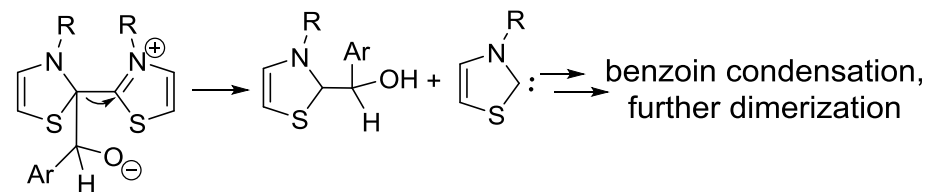
- determined by relating rate of H/D exchange to solvent kinetic isotope effect (Richard *JACS* **2004** 126 4366)
- kinetic and thermodynamic acidity are correlated

Mechanism of the Benzoin Condensation

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



These "bis-enamines" can also be considered to be nucleophilic:



Q1: Why don't NHCs just dimerize? Or do they?

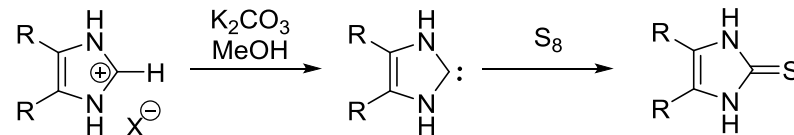
Q2: What's so special about NHCs?

"When and How Do Diaminocarbenes Dimerize?" Alder, R.W.; Blake, M.E.; Chaker, L.; Harvey, J.N.; Paolini, F.; Schutz, J. *ACIE* **2004** 43 5896-5911.

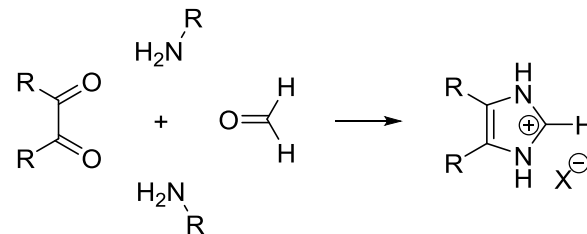
Isolation of Stable Carbenes

"Looking for Stable Carbenes: The Difficulty in Starting Anew." Arduengo III, A.J.

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



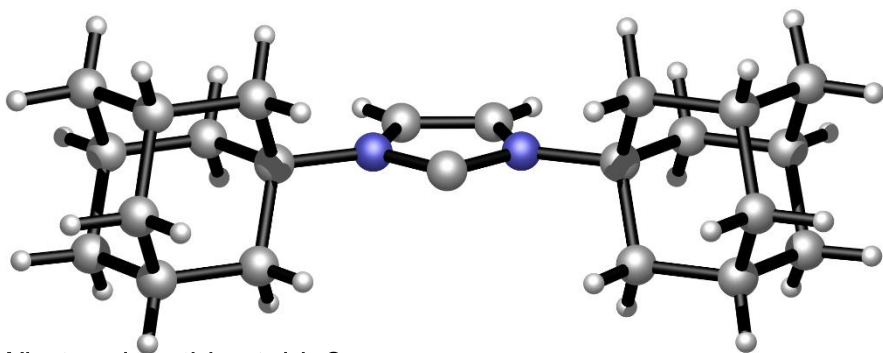
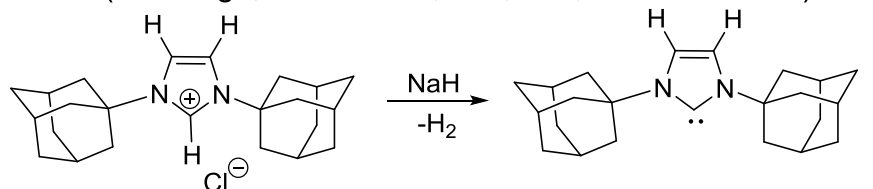
In 1988, Dupont needed a polymer cross-linker, and these thiones were thought to be useful, since they are relatively nucleophilic, but not very basic. A multicomponent strategy involving multiple condensations was developed:



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

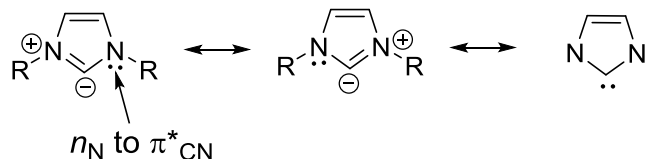
As might be expected on the basis of the previous arguments, the placement of bulky groups on nitrogen protects the carbene from decomposition. Here is the first crystalline carbene to be isolated (Arduengo, *JACS* **1991**, 113, 361; CSD: KAQMIY):



What makes this stable?

(1) The adamantyl groups make this kinetically stable from steric shielding.

(2) The nitrogens give an "allyl anion"-type stabilization:

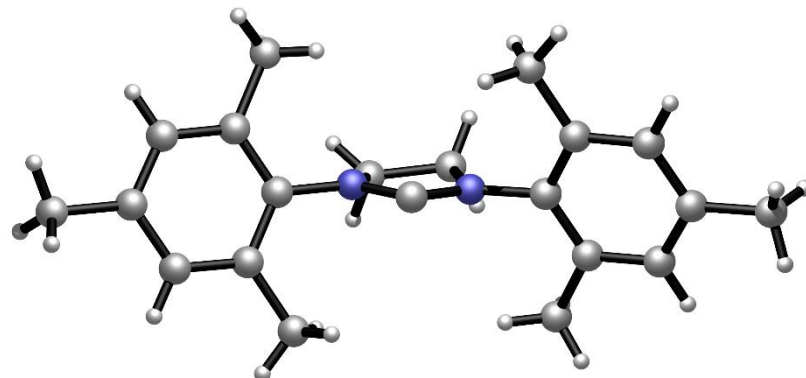


(3) The carbene is confined to a five-membered ring, which enforces a bent geometry. This maintains σ - π separation, and makes the singlet more stable than the triplet. Here, the N-C-N angle is 102° .

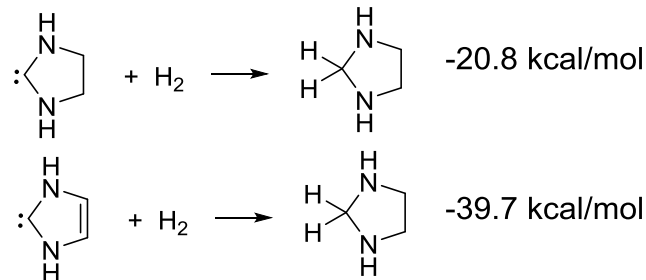
(4) With the olefin, this is a 6π -aromatic system.

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):



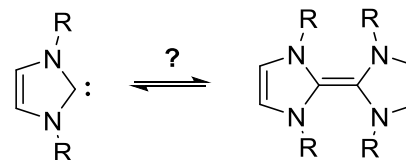
Frenking has compared (*JACS* **1996** 118 2039) the stability of the unsaturated, and at least formally aromatic, and saturated NHCs at the MP4/6-311g(d,p)//MP2/6-311g(d,p) level, which is admittedly a single-reference method:



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

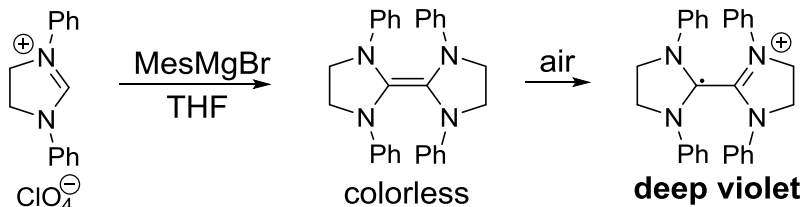
The Wanzlick Equilibrium

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

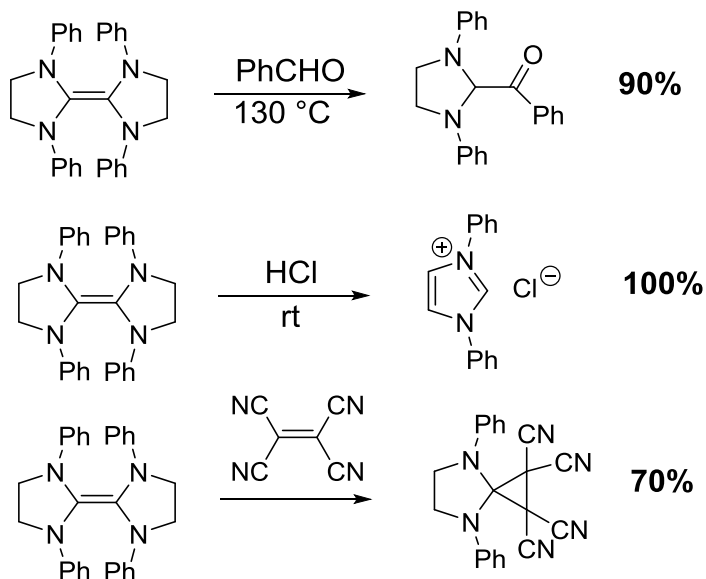


The Wanzlick Equilibrium

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



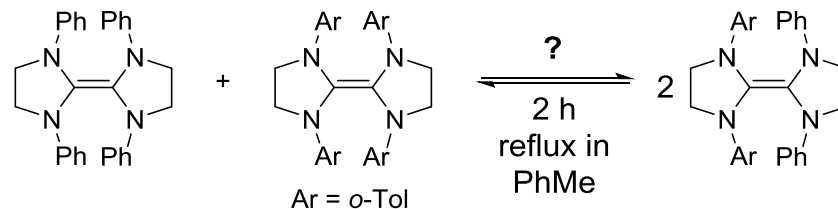
In fact, Lemal proposed that these dimers might actually be responsible for the chemistry. Of course, this doesn't rule out NHCs, either (*ACIE* **1962** 1 75, *ACIE* **1964** 86 2518):



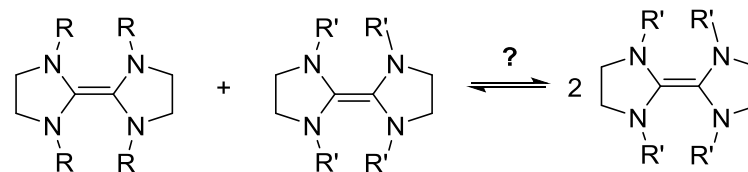
Wanzlick thought there was a monomer-dimer equilibrium, with the monomer NHC as the active species; Lemal thought the dimer tetraaminoethylene was the sole species, with no monomer-dimer equilibrium.

Q: What do crossover experiments say?

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



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):

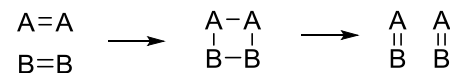


R, R' = Me/Et; Et/*i*Pr; *i*Pr/Me; Ph/*p*Tol

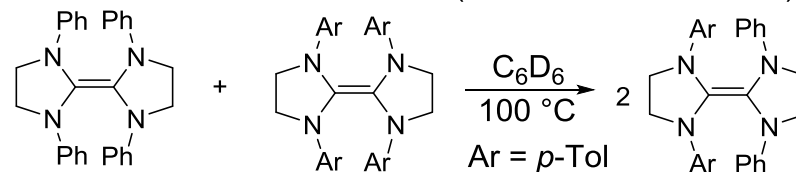
A statistical mixture (1:2:1) is formed! So how might one interpret these results?

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:



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):

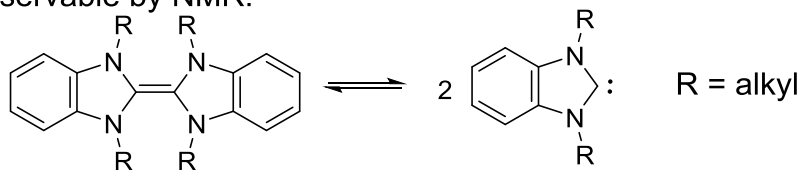


as drawn: 19% crossover after 6 h
with KH: no crossover product

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 orthoformate. 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=*i*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

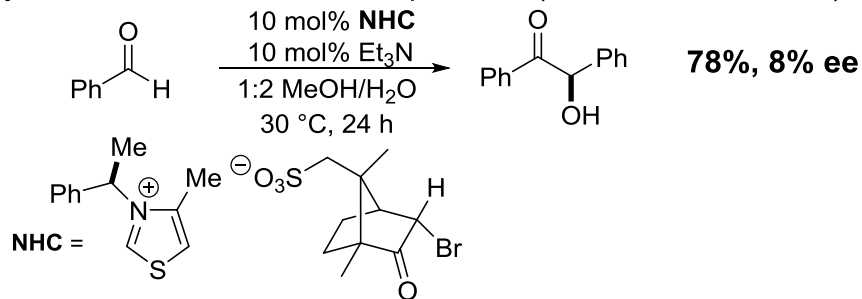
For now, it seems the evidence leans against the Wanzlick equilibrium, but it's still controversial. But most people draw the NHC as a monomeric carbene.

Lemal *JACS* **1999** 121 10626 Hahn *ACIE* **2000** 112 541

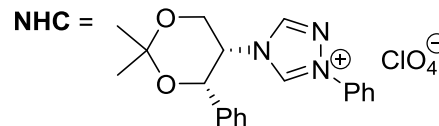
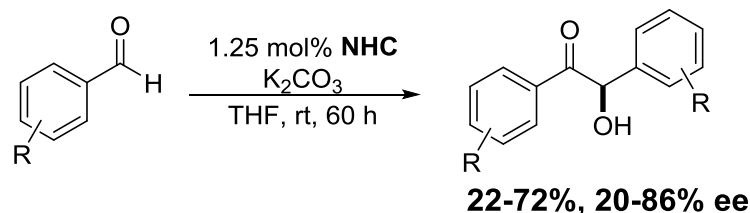
Summary: Herrmann *ACIE* **2000** 39 4036

Asymmetric Benzoin Condensations

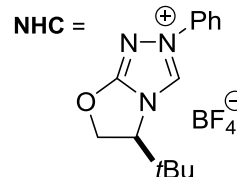
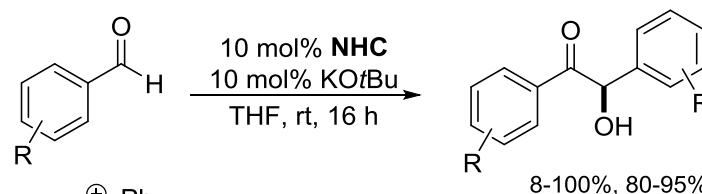
NHCs have allowed inverted polarity transformations to be rendered asymmetric and synthetically useful. An early attempt by Sheehan showed this was possible (*JACS* **1974** 39 1196):



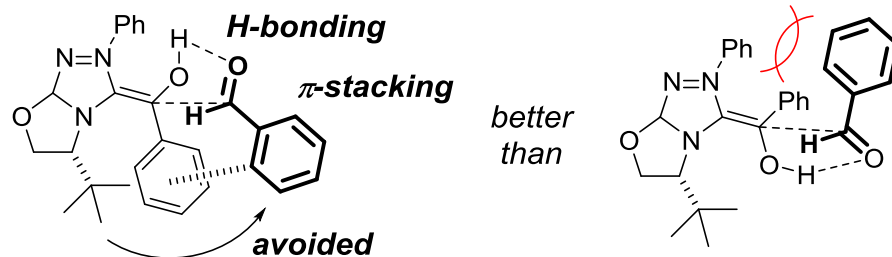
Enders developed this into a useful system (*Helv Chim Acta* **1996** 79 1217; *ACIE* **2002** 41 1743):



Now it works really well:



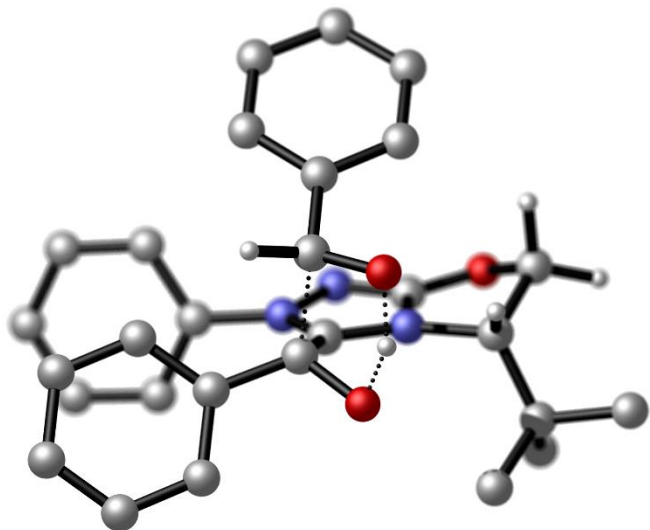
So how do these reactions work? Enders proposes this dual H-bond/ π - π stacking model (*ACIE* **2004** 37 534):



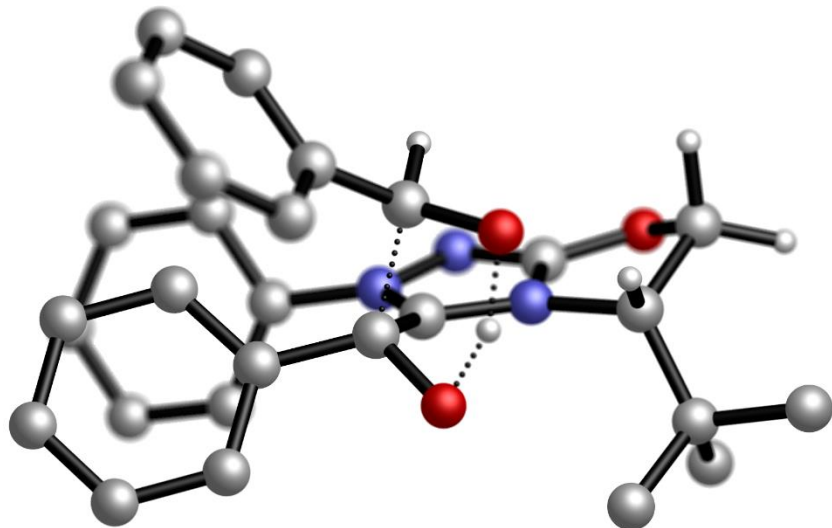
The idea is that the aldehyde approaches opposite the bulky *tert*-butyl group, and that the benzaldehyde is able to π -stack with the phenyl of the substrate. Both geometric isomers are accessible, but only the one drawn avoids a π - π interaction.

Asymmetric Benzoin Condensations

In contrast, Houk has used B3LYP (*PNAS* 2004 101 5770):
 favored transition state (+0.0 kcal/mol)

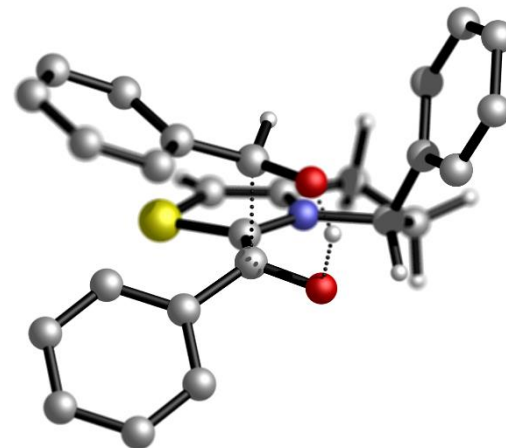


disfavored transition state (+2.8 kcal/mol)

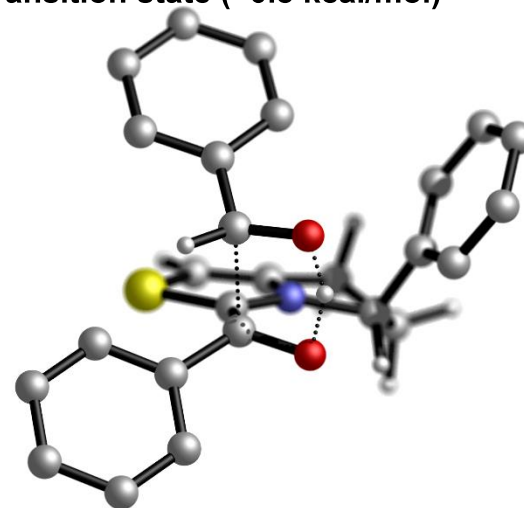


- (1) Agreement between experimental and predicted ee's is only moderate.
- (2) The B3LYP method is not supposed to work very well for π - π stacking.
- (3) Why the triazolium catalysts are more enantioselective than the thiazolium catalysts is unclear:

favored transition state (+0.0 kcal/mol)

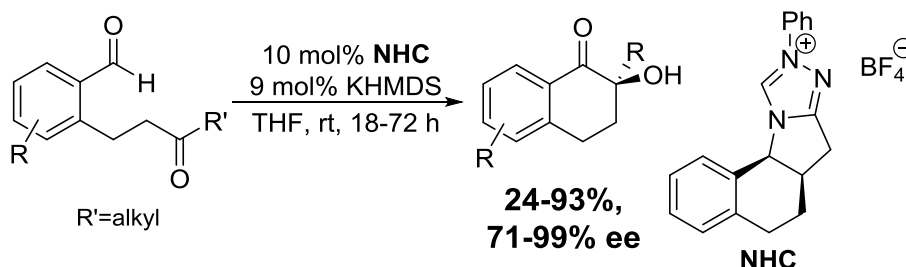


disfavored transition state (+0.8 kcal/mol)

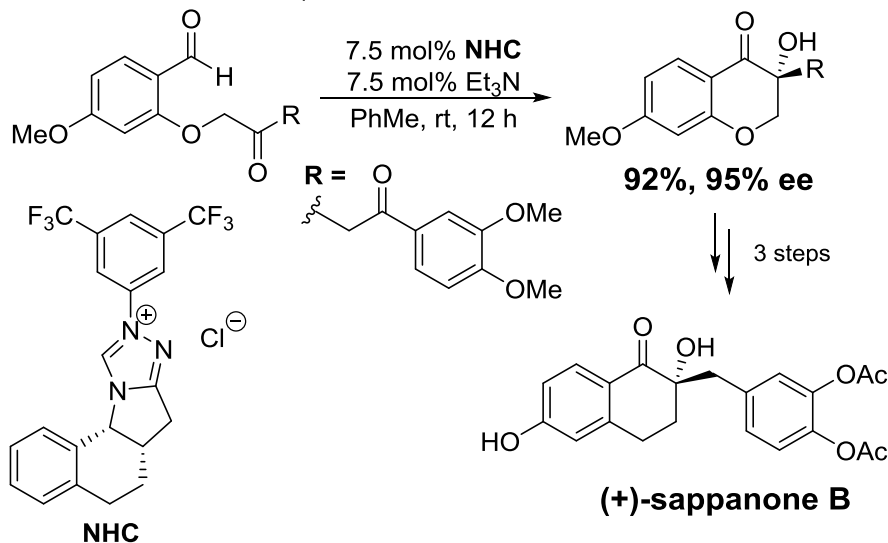


Crossed Benzoin Condensations

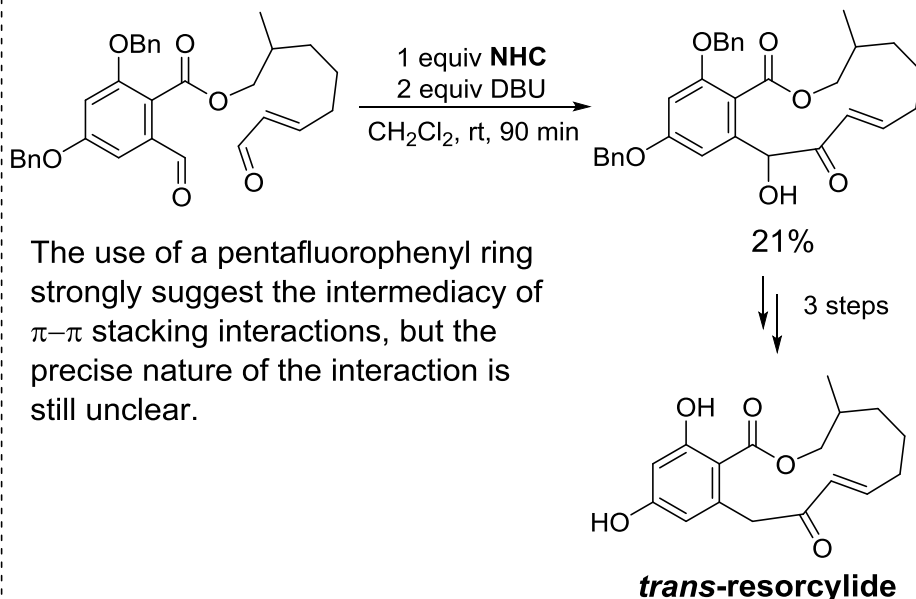
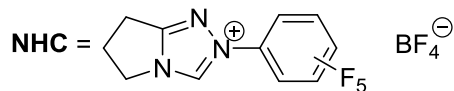
These are now possible in an intramolecular format (Enders *ACIE* **2006** 45 1463; *Synlett* **2006** 15 2431):



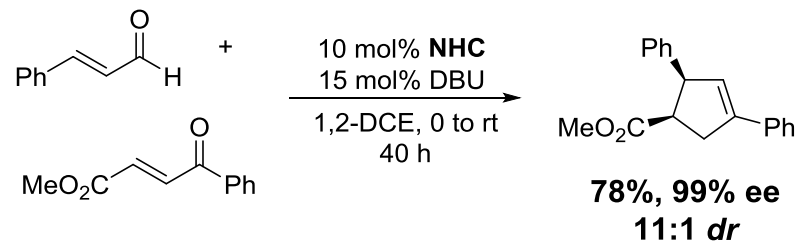
These are becoming useful in synthesis (Suzuki *ACIE* **2006** 45 3492; *OL* **2007** 9 2713):



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.



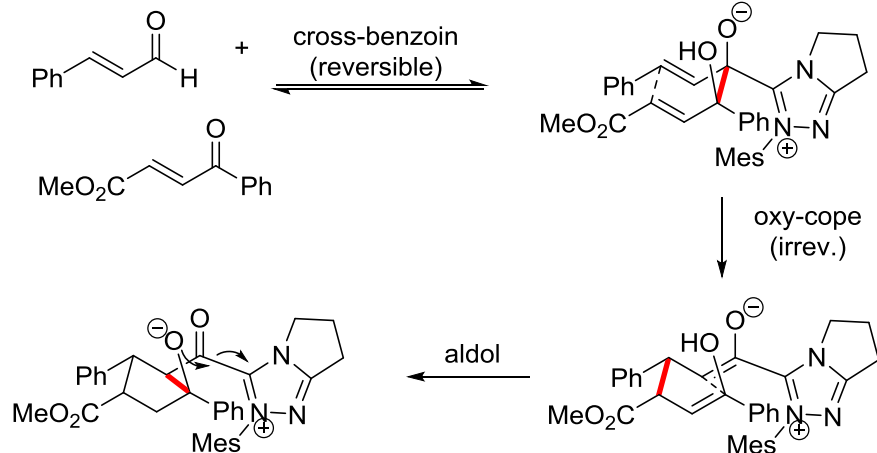
More complicated sequences are possible (Bode *JACS* **2007** 129 3520). What do you think happens in this reaction?



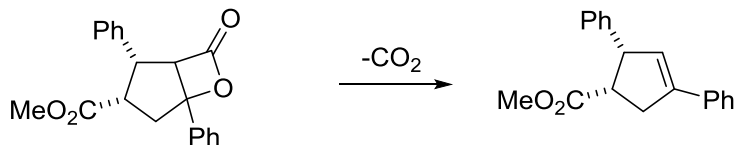
Hint: this generates an anion, which then participates in a pericyclic reaction.

Crossed Benzoin Condensations

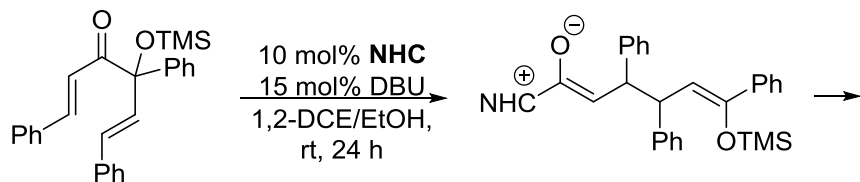
The proposed mechanism involves an initial crossed-benzoin addition, followed by an anion-accelerated oxy-Cope reaction:



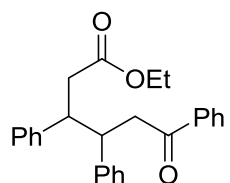
This is poised for an aldol addition, the product of which can acylate the alkoxide. This regenerates the NHC. Finally, decarboxylation occurs:



Evidence for the anion-accelerated oxy-Cope reaction:

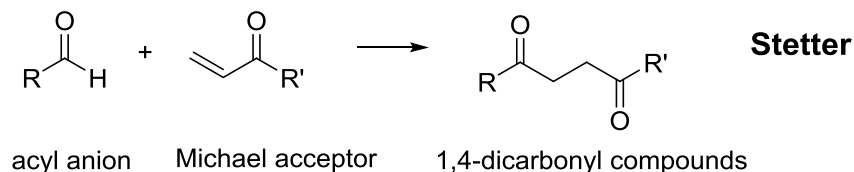
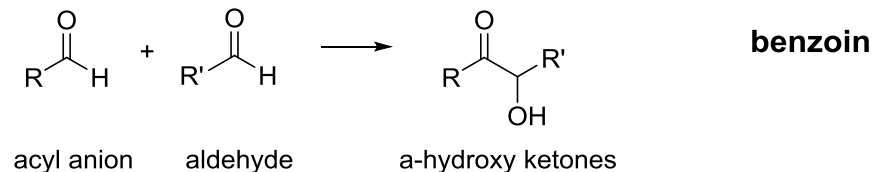


Initial oxy-cope rearrangement generates a formally zwitterionic species. The nucleophilically activated carbonyl can expel the NHC to generate a ketene, which can acylate ethanol (hence, the ethyl ester).



The Stetter Reaction

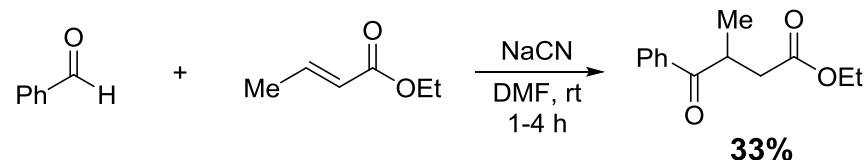
While the benzoin condensation delivers *umpolung* 1,2-dioxy fragments, the Stetter reaction gives 1,4-dioxy fragments:



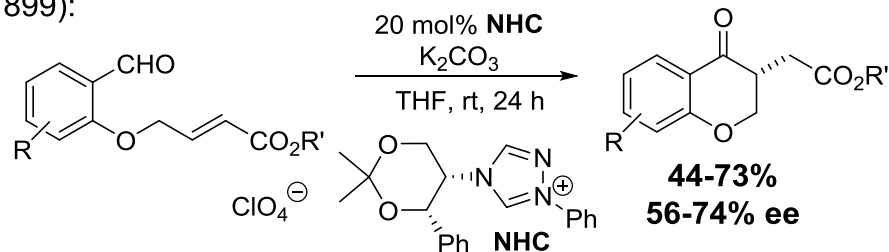
So the Stetter reaction is a vinylogous benzoin condensation and the Stetter is to benzoin as Michael is to aldol. The NHC-catalyzed process provides alternatives to radical reactions.

Useful reviews: Stetter *ACIEE* **1976** 14 639 and Christmann *ACIE* **2005** 44 2632.

The original reaction was reported in 1973 by Stetter:

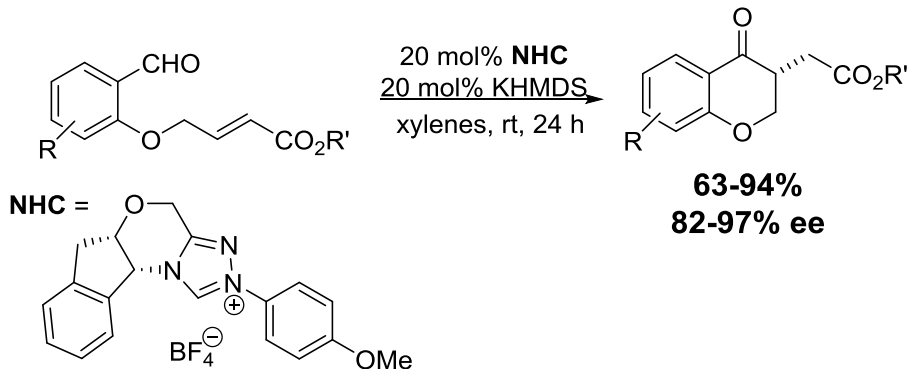


Nowadays, asymmetric variants are possible. Here is an early example from the Enders group (*Helv. Chim. Acta.* **1996** 79 1899):



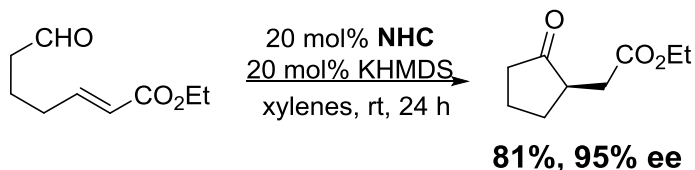
The Stetter Reaction

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

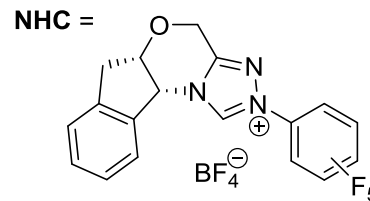
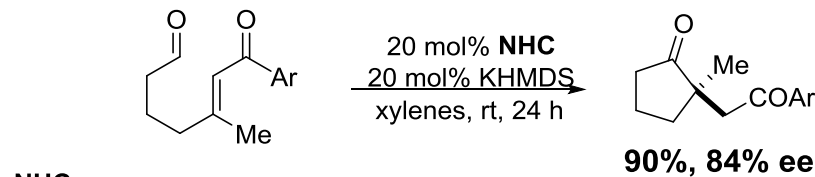
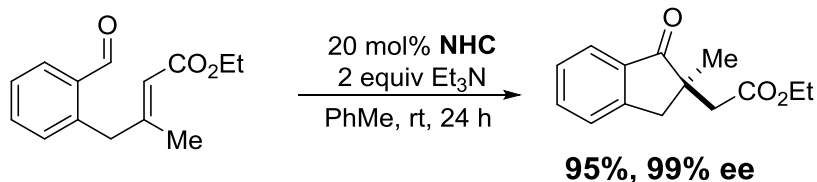


- significantly improved yields and ee's
- *Z* enoates do not react
- α,β -unsaturated aldehydes, carboxamides, and nitro compounds are inactive
- α,β -unsaturated ketones react more rapidly than corresponding esters

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



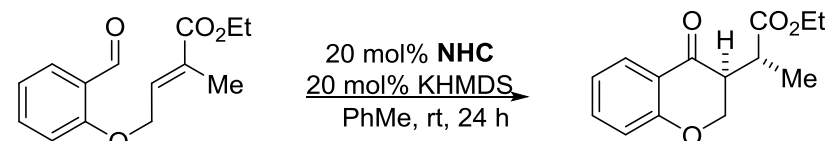
However, quaternary stereocenters can be formed (Rovis *JACS* **2004** 126 8876):



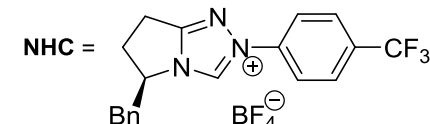
- some kinetic resolution can also be obtained with racemic γ -substituted substrates

ref: Rovis *Tet* **2005** 61 6368

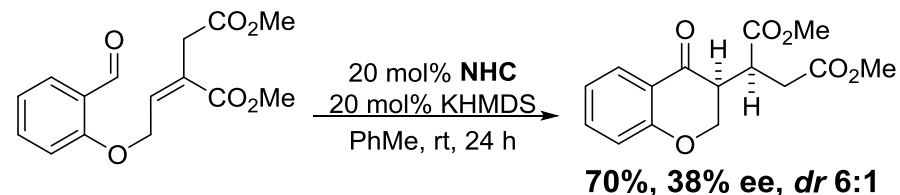
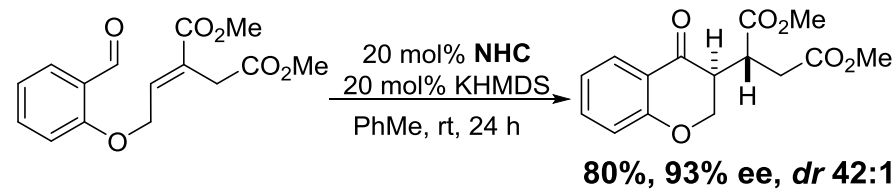
With α,α -disubstituted acceptors, an enantioselective Stetter reaction can be followed by a diastereoselective protonation:



Rovis *JACS* **2005** 127 6284



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

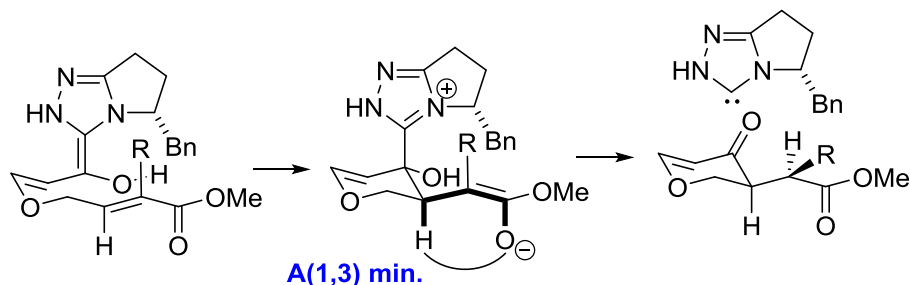


The Stetter Reaction

Rovis and co-workers propose the following model:

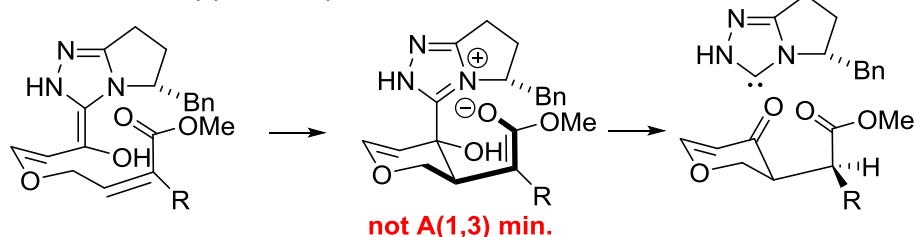
E enoate (high ee and dr)

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):

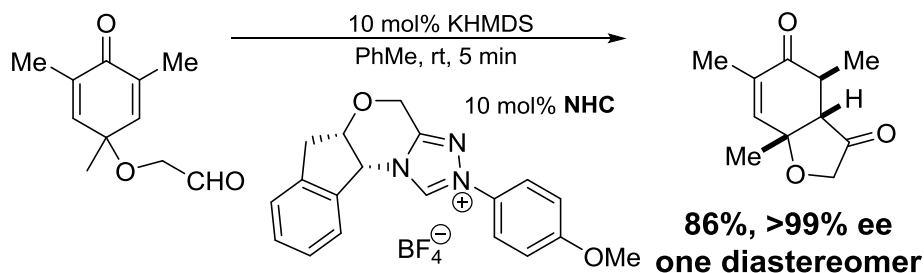


Z enoate (low ee and dr)

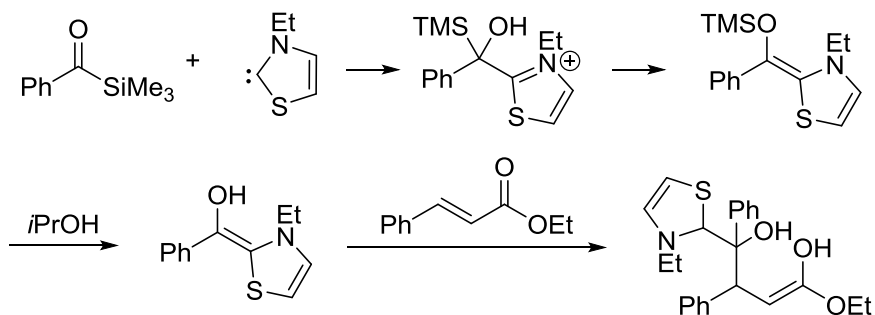
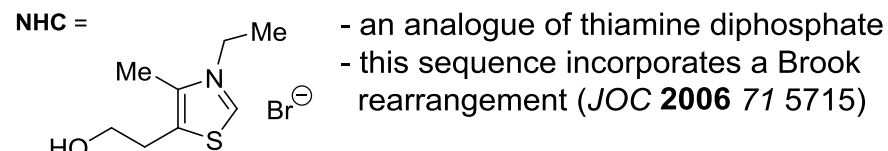
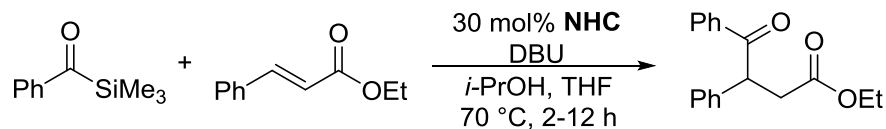
Here, adding to the side opposite the bulky NHC substituent incurs developing A(1,3) strain. The proton is still delivered from the same face. However, flipping the olefin geometry results in the opposite epimer. Thus, this is mismatched:



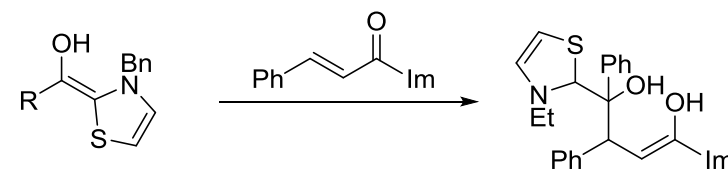
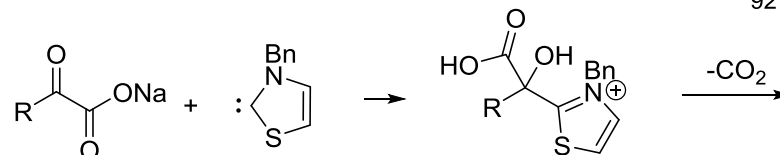
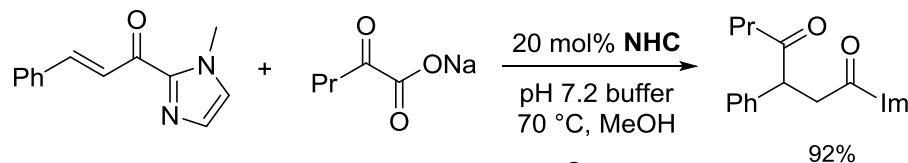
Enantioselective desymmetrizations are also possible (Rovis *JACS* **2006** 128 2552, *OPRD* **2007** 11 598):



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

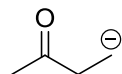


Decarboxylative addition is possible (*JACS* **2005** 127 14675):

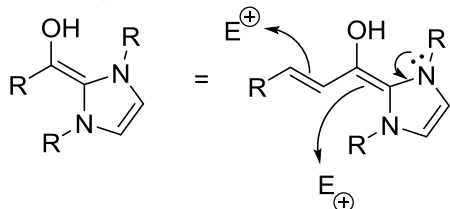


Homoenolates

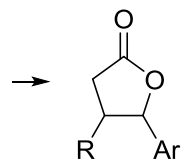
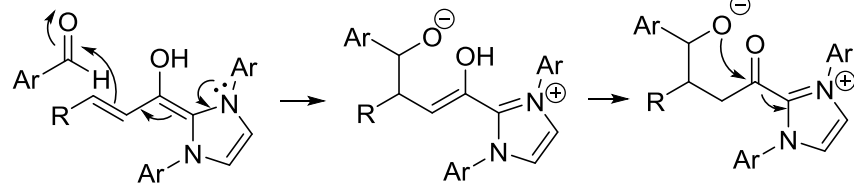
How would you generate the homoenolate synthon?



Addition of NHCs to α,β -unsaturated aldehydes:

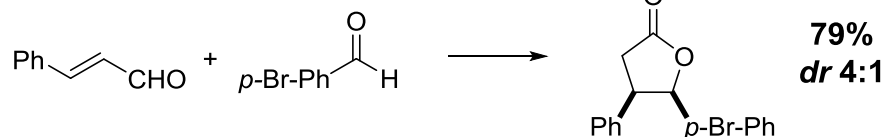


This can undergo reactions at its d^3 terminus (homoenolate reactivity) or its d^1 terminus (acyl anion reactivity). Here are the initial reports of homoenolate benzoin reactions (Glorius *ACIE* **2004** 43 6205; Bode *JACS* **2004** 126 14370 - simultaneous):

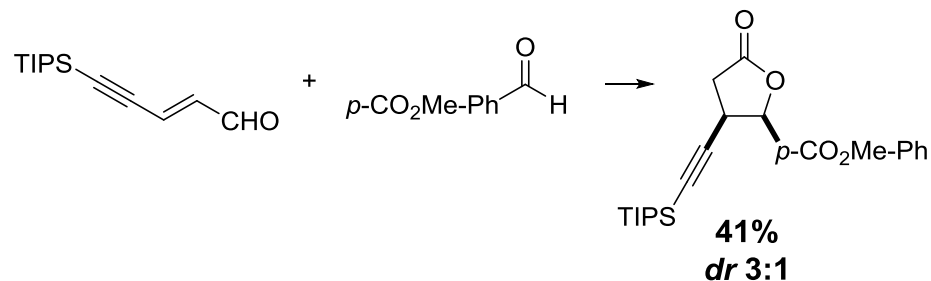


- moderate *cis* selectivity is observed
- steric bulk of NHC catalyst is important to avoid catalyst dimerization

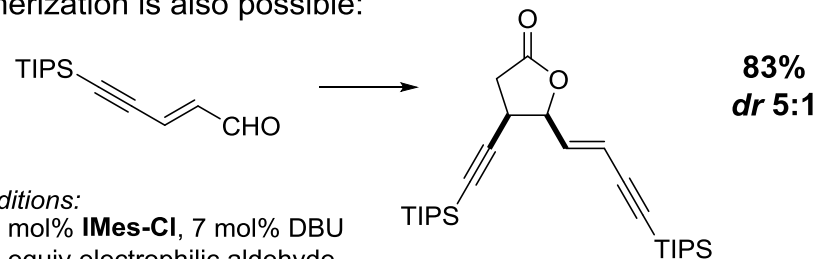
representative examples: Bode



These make γ -butyrolactones, which are valuable pharmacophores.

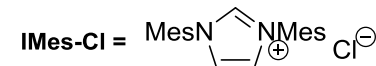


Dimerization is also possible:



conditions:

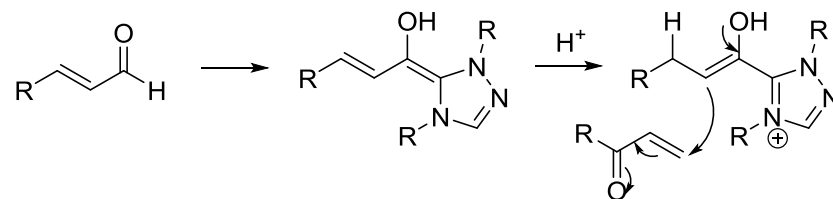
- 8 mol% **IMes-Cl**, 7 mol% DBU
- 2 equiv electrophilic aldehyde
- rt, 15 h, 10:1 THF/*t*BuOH



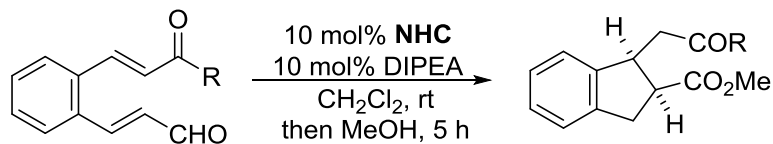
- aliphatic aldehydes are not effective
- slow addition of enal increases yields
- performing the reaction with *cis*-*p*-anisaldehyde still leads to the *cis* adduct
- if reaction is performed with *t*-BuOD, D is incorporated exclusively at the α -position (no quenching of homoenolate by solvent)

Homoenolate Michael Additions

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

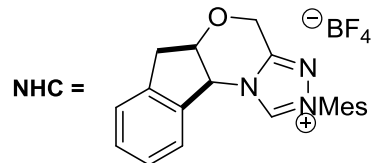


Homoenolate Michael Additions

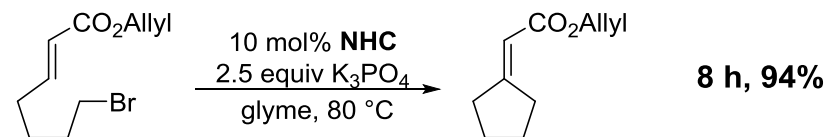


substrate	product	yield	ee
		59	99
		68	99
		66	99
		52	62

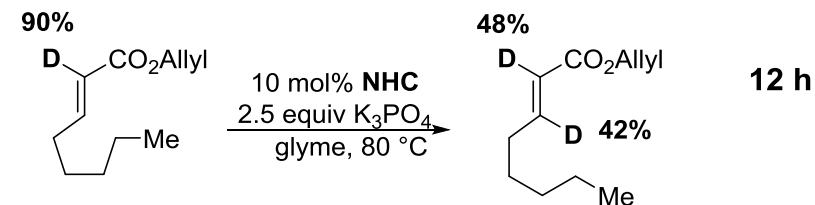
- the product acyl-NHC is quenched by methanol
- primary or secondary amides are accessed if amines are used instead of MeOH



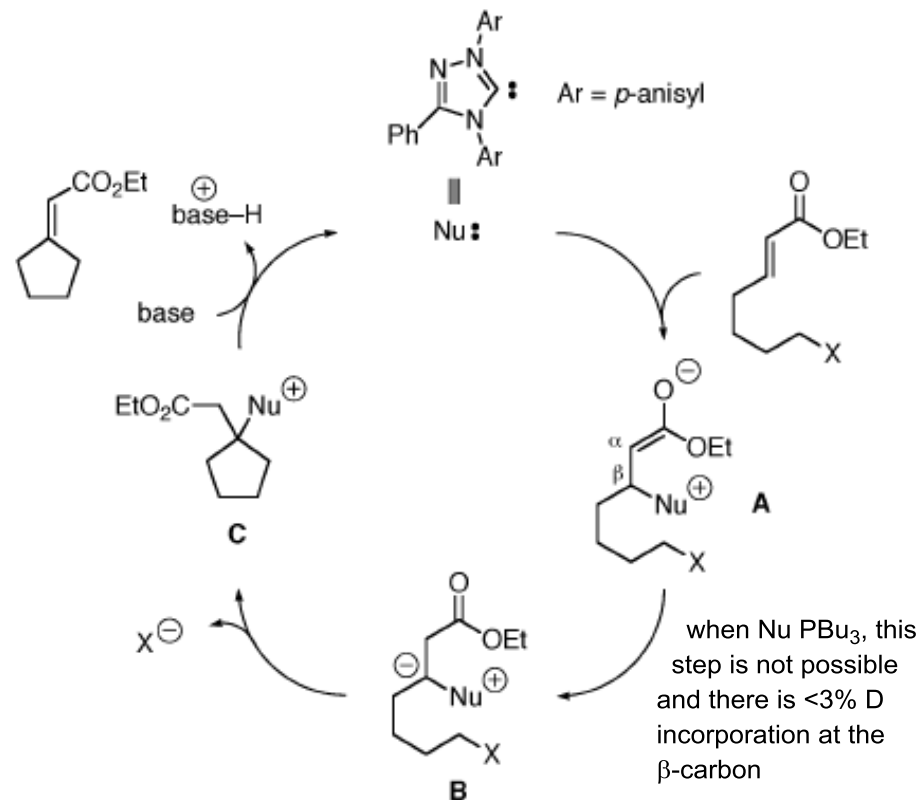
What if the NHC attacks the β -carbon of the acceptor instead of the homoenolate? This becomes possible if the aldehyde is deleted. Here is an example (Fu *JACS* **2006** 128 1472):



isotopic scrambling



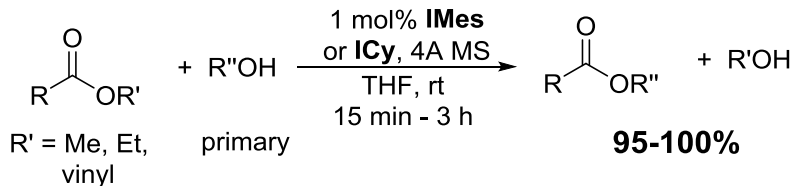
proposed catalytic cycle



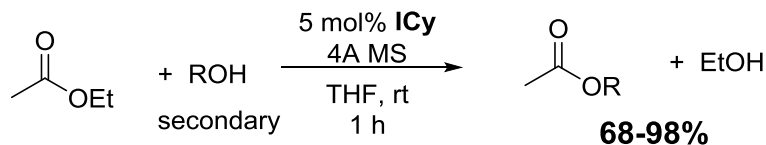
Transesterification

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):

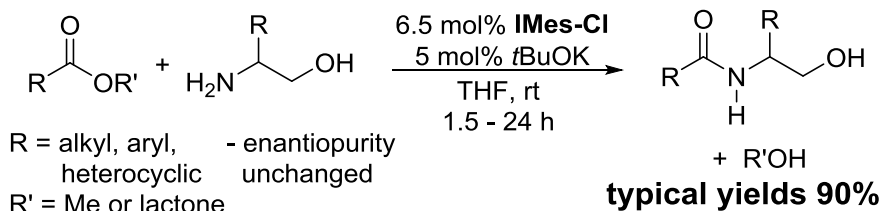
primary alcohols



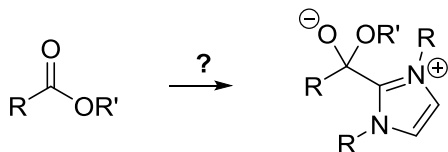
secondary alcohols (Nolan *JOC* **2004** 69 209)



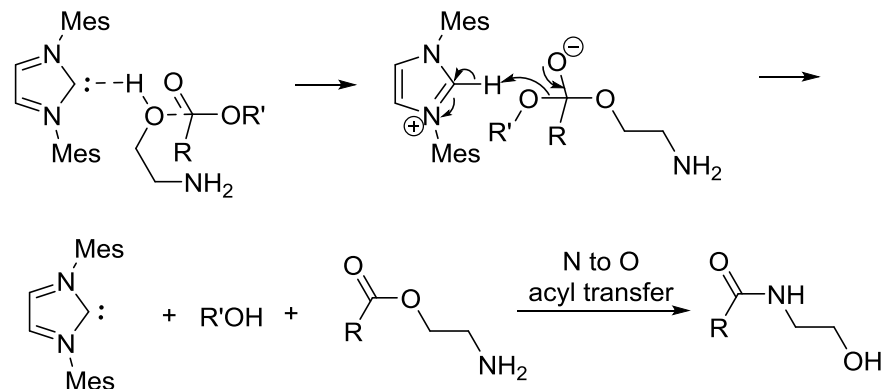
These reactions are no doubt driven by an excess of the primary alcohol and possibly also by a mass-action effect of the molecular sieves. The direct amidation of esters is also possible (Movassaghi *OL* **2005** 7 2453):



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



Movassaghi suggests that this is general base catalysis instead:



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 Å):

