The Importance of *N*-Heterocyclic Carbene Basicity in Organocatalysis

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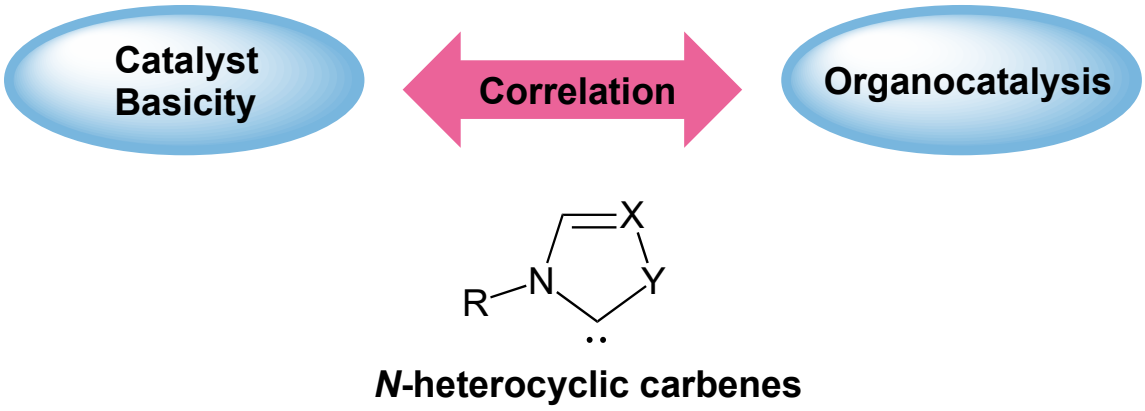
TOC graphic



***N*-heterocyclic carbenes**

TOC graphic text: This review highlights the importance of N-heterocyclic carbene (NHC) basicity for transformations in which NHCs are used as catalysts.

Abstract

N-Heterocyclic carbenes (NHCs) are versatile species that figure prominently as catalysts. Despite their widespread use in organocatalysis, studies of the relationship between the basicity of NHCs and their catalytic ability are limited. Herein we review work on both the examination of NHC basicity as well as its impact on organocatalysis. The review is divided into three main parts: an overview of NHC basicity studies, both in solution and in the gas phase; the role of basicity in *Umpolung*-type catalysis; and the relationship between NHC basicity and its growing role as a Brønsted base catalyst. This review is not an exhaustive catalog of all NHC catalysis, but rather focuses on work that specifically examines and discusses the effect of NHC basicity on catalyst function.

1. Introduction.

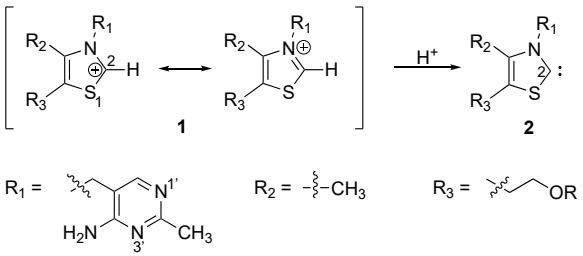
Since the first reports of isolable, stable *N*-heterocyclic carbenes (NHCs) nearly three decades ago, these intriguing species have come to the forefront as important players in organic catalysis.[1,2] NHCs serve as both ligands for organometallic catalysts as well as catalysts in their own right, more prominently as nucleophilic species in *Umpolung* chemistry, but also as Brønsted bases in organic transformations.

Despite the importance of NHCs in catalysis, the measurement and study of NHC properties, to achieve an improved understanding of these species, as well as to increase understanding of catalytic mechanisms and to produce better catalysts, are surprisingly limited.

In this review, we focus on the importance of carbene basicity for NHC-catalyzed reactions. We review what is known, and what the future may hold.

2. Carbene basicity (acidity of protonated carbene)

Solution phase acidity (pK_a). The measurement of the thermodynamic basicity of NHCs is most often discussed as the acidity of the conjugate acid, the protonated NHC. Interest in the acidity of protonated NHCs was first sparked in 1958, when Breslow made the novel proposal that the thiamin conjugate base **2**, generated by deprotonation of the conjugate acid **1** at C(2), was the active catalytic species in biochemical and organic transformations in which thiamin is involved (Scheme 1).[3]

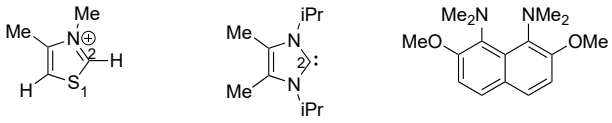


Scheme 1. Breslow's work.

At the time, no stable NHC had been isolated (and would not be for more than thirty years), but Breslow recognized the importance of the deprotonated "carbene", or "ylide" form of thiamin. The earliest measurement of protonated NHC acidity in aqueous solution is attributable to Washabaugh and Jencks who, in 1988, examined C2-proton exchange for a series of thiazolium ions, including thiamin **1**, *N*(1')-methylthiamin, and several 3-substituted-4-methylthiazoliums.[4] They determined that the pK_a values for the thiazolium ions studied fell between 17-19, in water. This work was motivated by an interest in enzymes that are thiamin-dependent. This seminal measurement both debunked an earlier report

of 12.7 for the thiamin pK_a and also lent quantitative support for several earlier estimates of thiamin pK_a of 17-20.[5-9] Since this early work, careful and important measurements of the acidity of imidazolium and triazolium cations in water have been carried out by the groups of Amyes and Diver, and O'Donoghue and Smith.[10-14]

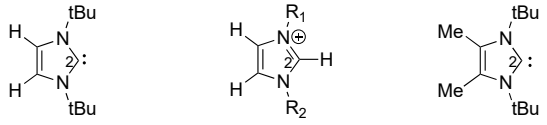
Because the measurement of the acidity of a substrate that is less acidic than water precludes a direct equilibrium acidity measurement, aqueous measurements utilize a kinetic method. Direct measurement of NHC pK_a in an aprotic solvent was first accomplished by Bordwell and Satish in 1991.[15] Their measurement of the pK_a of the thiamin analog 3,4-dimethylthiazolium cation in DMSO (**3**) was estimated to be greater than 16, consistent with the kinetic acidity measurements in water noted above (Scheme 2). Soon thereafter, Alder measured the pK_a of the conjugate acid of a particularly basic stable carbene, 1,3-diisopropyl-4,5-dimethylimidazol-2-ylidene (**4**) in deuterated DMSO, finding it to be a stronger base than DBU, DBN, and the proton sponge **5**, with a pK_a of 24 (Scheme 2).[16]



3 **4** **5**

Scheme 2. Structures studied in early NHC pK_a work.

Kim and Streitwieser tackled a highly basic stable carbene, 1,3-di-*tert*-butylimidazol-2-ylidene **6**, measuring the pK_a in THF (Scheme 3).[17] They found that the carbene is more basic in DMSO than THF by several pK_a units. This 2002 study was followed by that of Cheng and coworkers, who examined a series of 1,3-dialkylimidazolium salts **7** in DMSO (Scheme 3).[18] They found that counterions do not affect acidity, but that ring substitution, as expected, does. A pK_a span of 19.7-23.4 was observed for this series. In 2011, Grishina and coworkers measured the DMSO pK_a for 1,3-di-*tert*-butyl-4,5-dimethylimidazolylidene **8** to be 24.8, making it the strongest imidazol-2-ylidene base reported at that time (Scheme 3).[19] Very recently (2017), Dunn *et al.* and Li *et al.* conducted systematic studies of the pK_a values of imidazolium and triazolium salts in DMSO.[20,21] Both studies delved into the effect of varying substituents on acidity, finding a relationship between pK_a and Hammett parameters. Last, Xue, Ji and coworkers have just published a series of calculations of the pK_a values of ionic liquids in DMSO, including some 1,3-dialkyl imidazoliums.[22]

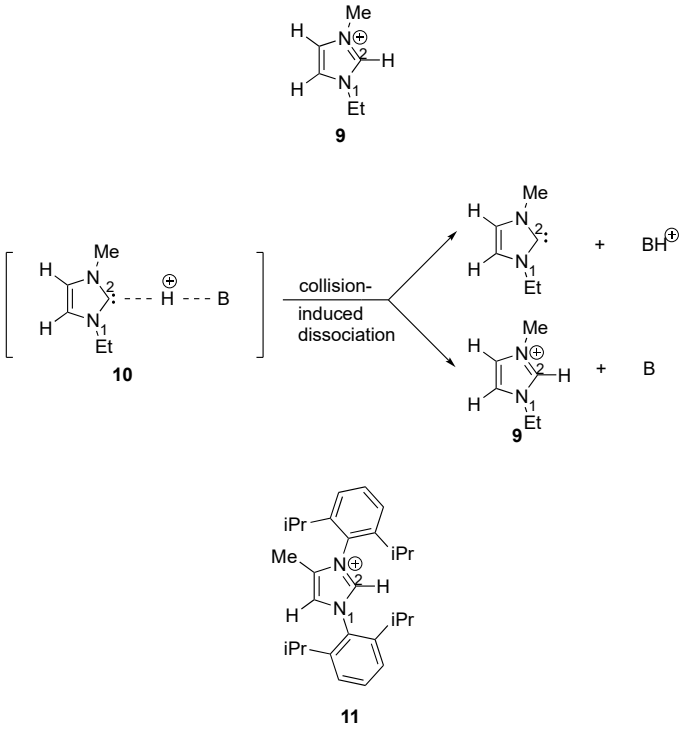


Scheme 3. NHCs studied in DMSO.

More methodology details as well as compilations of aqueous NHC pK_a data may be found in a fine review published in 2014 by O'Donoghue and Massey.[23]

Gas phase acidity. The examination of the properties of organic species in the gas phase has the advantage of revealing inherent reactivity, in the absence of solvent. Historically such measurements have utilized mass spectrometry. The limitation for many years was that the species of interest had to be easily volatilized. This posed a fairly substantial barrier, since many organic compounds of interest are not volatile. The development of electrospray ionization coupled to mass spectrometry was first reported by Yamashita and Fenn in 1984, and opened the door to the examination of nonvolatile species that were previously inaccessible in the gas phase.[24,25] While various gas phase calculations of protonated NHC acidity have been reported over the years, experimental measurements have been more recent.[23] No review of the gas phase measurements of NHC basicity has been yet compiled, so in this section we will focus on some of the details of these experiments.

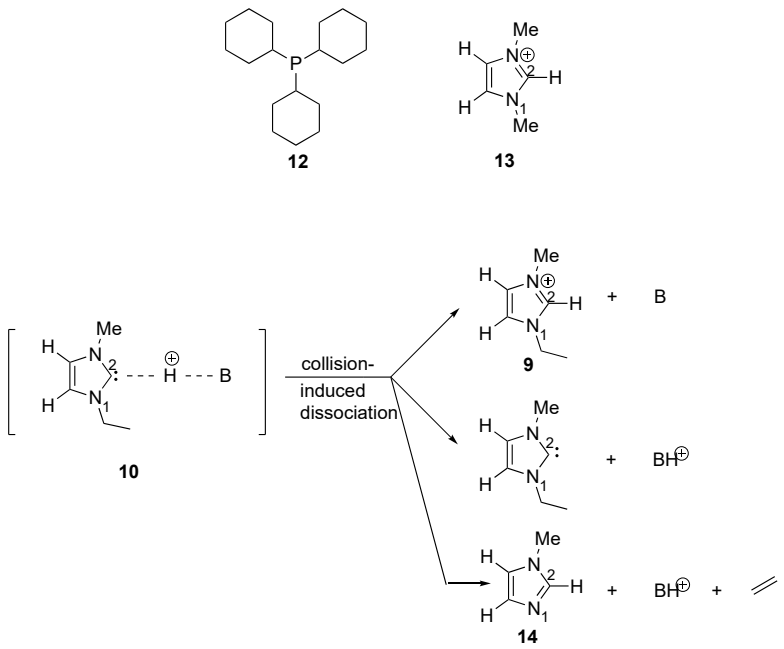
The first measurement of NHC basicity was accomplished by Cooks and coworkers, who examined the gas phase acidity of imidazolium cation **9** using the "Cooks kinetic method" in 2005 (Scheme 4).[26] In the Cooks kinetic method, a proton bound dimer of the species of interest and a reference compound is isolated via mass spectrometry. So in the case of the imidazolium cation **9**, a proton-bound dimer of **9** and a reference base B was generated (**10,** Scheme 4). The reference base B has a known proton affinity. The dimer was then subjected to collision-induced dissociation; the resultant ratio of the two ions -- **9** and BH^+ -- can be then translated to relative proton affinities.[27-29] Use of this method placed the proton affinity of this carbene at 251.3 ± 4 kcal/mol, which is a very high gas phase basicity. Calculations at B3LYP/6-31+G(d) yielded a computed PA that was even higher, by 9.5 kcal/mol (260.8 kcal/mol). These authors also examined 1,3-di-*tert*-butylmizadol-2-ylidene **6** and 1,3-di-(2,6-isopropylphenyl)imidazole-2-ylidene) **11** and found that the relative proton affinities of the three carbenes studied was **9** < **6** < **11**; that is, larger substituents appeared to stabilize the imidazolium ion.



Scheme 4. NHCs studied by Cooks.

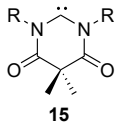
This early measurement was followed up by work from our group, in 2010 and 2011.[30,31] The motivation for our studies was the comparison of properties of *N*-heterocyclic carbenes and tricyclohexylphosphine (PCy_3, **12,** Scheme 5). Both NHCs and PCy_3 are ligands for ruthenium catalysts used in the Grubbs olefin metathesis. First generation catalysts utilized PCy_3 as ligands; second generation catalysts with NHC ligands are more effective.[32] The increased effectiveness of the catalysts with NHC ligands intrigued us, and we sought to compare the proton affinities of NHCs and PCy_3.

Initial studies of the protonated NHC **9** were consistent with the prior Cooks studies.[26] However, we subsequently utilized an alternative method for measuring gas phase basicity, called bracketing.[33] These studies revealed that the acidity of protonated imidazoliums **13** and **9** are quite consistent with calculations at B3LYP/6-31+G(d). For **9**, we cannot differentiate between simple deprotonation and elimination, to yield **14** (Scheme 5). However, we are able to establish that the basicity of the two carbenes are higher than the early Cooks measurements, and that the carbenes are more basic than tricyclohexylphosphine. Further studies indicate that the measurements obtained by us and by Cooks, using the Cooks kinetic method, probably suffered from well-known technical issues associated with that type of experiment.[34]



Scheme 5. Gas phase studies of NHCs by Lee and coworkers.

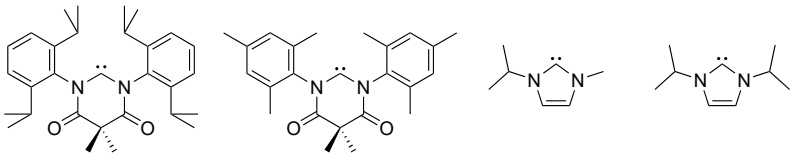
The next measurements of the gas phase proton affinities of NHC-type structures were accomplished by our group (in collaboration with the Bielawski group), on *N,N′*-diamidocarbenes (DACs).[35] Traditional carbenes such as methylene are not isolable, and display characteristic reactivity that is largely electrophilic, such as the ability to insert into C-H bonds, cyclopropanate olefins, and couple with carbon dioxide. The most commonly utilized NHCs, whether imidazolylidene, thiazolylidene, or triazolylidene, are relatively stable, and, compared to traditional carbenes, are found to be much more nucleophilic. DACs were developed by Bielawski and coworkers to be stable, like NHCs, yet also display electrophilic reactivity, like the traditional carbenes. Such a combination was cleverly achieved through strategically placed carbonyl groups that draw electron density away from the carbene center (structures **15,** Scheme 6). These DACs are able to participate in C-H insertion, CO fixation and NH_3 activation, unlike typical NHCs. Because the DACs are more electrophilic than the typical NHCs, we wondered whether they would also be less basic.



Scheme 6. *N, N′* - diamidocarbene structure.

We first attempted the measurement of DACs **16** and **17** and NHCs **18** and **19 (**Scheme 7). Interestingly, despite the difference in reactivity of DACs versus

NHCs, the PAs of **16** and **17** are calculated to be 258.1 and 257.8 kcal/mol, while those of NHCs **18** and **19** are 262.9 and 265.6 kcal/mol, respectively (at B3LYP/6-31+G(d)). The NHCs are slightly more basic but perhaps not as much as one might expect given the markedly different electrophilic reactivity of the DACs.



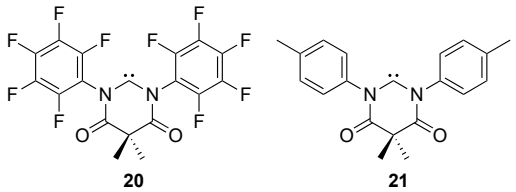
16 **17** **18** **19**

Scheme 7. DACs and NHCs studied by Lee, Bielawski and coworkers.

Despite the computed values of **16** and **17** being under 260 kcal/mol, we found that even bases as strong as 2-tertbutylimino- 2-diethylamino-1,3-dimethylperhydro-1,3,2 diazaphosphorine (BEMP; PA = 263.8 kcal/mol) cannot deprotonate **16H$^+$** and **17H$^+$**. However, BEMP readily deprotonates **18H$^+$**. (BEMP does not deprotonate **19H$^+$**, which is consistent with the calculated acidity of 265.6 kcal/mol).

As noted earlier, protonated NHCs **9** and **13**, as well as **18H$^+$** and **19H$^+$**, have calculated acidities that agree with experiment. But, for the DACs **16** and **17**, the calculations and experiments are not in agreement; the protonated substrates are much more difficult to deprotonate than computationally predicted. The puzzle is, are the calculations or experiments inaccurate? Because we had successfully bracketed the NHC PAs, we suspected that steric inhibition might be playing a role in the deprotonation of DACs **16H$^+$** and **17H$^+$**. The carbene basicity measurement involves deprotonation of the protonated DAC, so we hypothesized that the bulky mesityl and diisopropylphenyl groups were blocking that deprotonation.

To test whether sterics are an issue, we synthesized the hydrated precursor to DAC **20** (Scheme 8). We hypothesized that this substrate would suffer from less steric inhibition, as the perfluorophenyl groups are not as bulky as mesityl and diisopropylphenyl; also, **20** is less basic than **16** and **17**, and the reference bases in that basicity range are also less bulky. Indeed, we were able to bracket the PA of **20** to be 233 kcal/mol, in agreement with the calculated value of 233.0 kcal/mol. We also synthesized a DAC with comparable basicity to, but less steric hindrance than, **16** and **17,** tolyl derivative **21** (calculated PA = 256.3 kcal/mol). We find that the PA of **21** is under 260.6 kcal/mol, consistent with calculations.



20 **21**

Scheme 8. Less sterically hindered DACs.

This study showed that the DACs, despite their more electrophilic behavior (as compared to NHCs), are still quite basic. Also our results highlighted some of the caveats associated with gas phase measurements of carbene basicity, particularly those with bulky substituents (which are common in NHCs and DACs as bulky substituents tend to be stabilizing).

In the next section, we will focus on some examples of how carbene basicity relates to reactivity, focusing on catalysis.

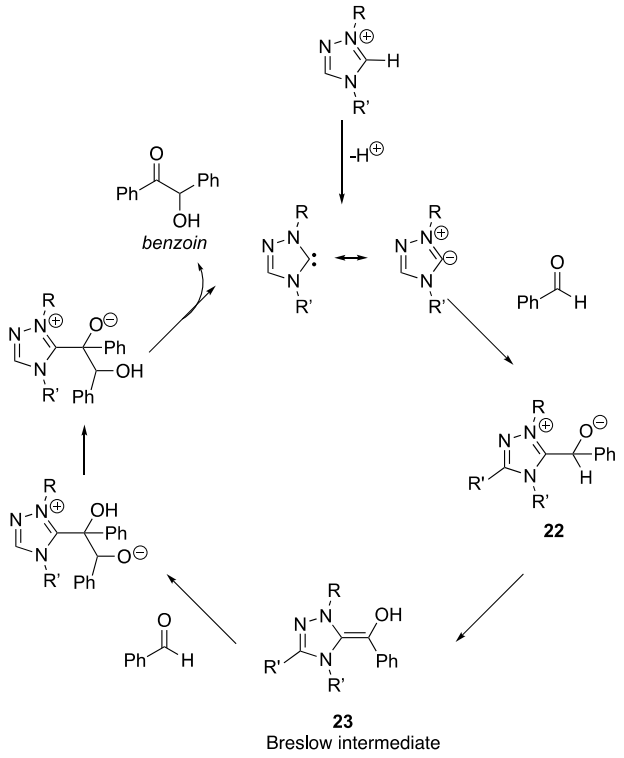
3. Carbene basicity and catalysis.

NHC basicity and reactivity are inevitably linked. In developing his ruthenium catalysts that use NHCs as ligands, for example, Grubbs noted that "both σ basicity and π acidity of the ligands play a role in catalyst activity."[32] Herein we highlight studies where NHC basicity is studied in conjunction with catalysis. We divide this section into two main parts: NHCs as catalysts for *Umpolung* reactions and NHCs as Brønsted base catalysts.[36]

NHCs and Umpolung.

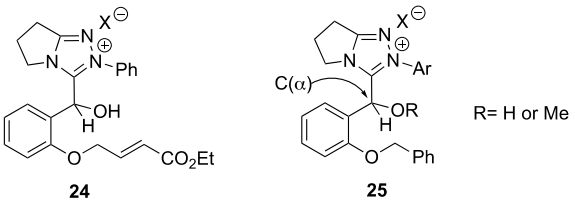
NHC acidity and Umpolung kinetics.

In 2013, O'Donoghue, Smith and coworkers examined triazolylidene-catalyzed Stetter and benzoin reactions.[37] These reactions demonstrate classic NHC *Umpolung* chemistry, where the NHC triggers a reversal of polarity at a carbonyl center. In the proposed mechanism for the benzoin condensation (Scheme 9), the NHC attacks benzaldehyde, forming intermediate **22**, which through proton transfer transforms into the well-known Breslow intermediate **23**. The initial benzaldehyde center is now nucleophilic, and can attack a second benzaldehyde. Subsequent proton transfer and release of catalyst yields the product benzoin. The Stetter reaction has the same first step (NHC attack of a carbonyl center), but the second addition is a 1,4 conjugate addition, to an enone. The mechanism of the Stetter, while assumed to be similar to that of the benzoin, is actually not well studied.[38]



Scheme 9. Benzoin condensation, showing NHC *Umpolung* chemistry.

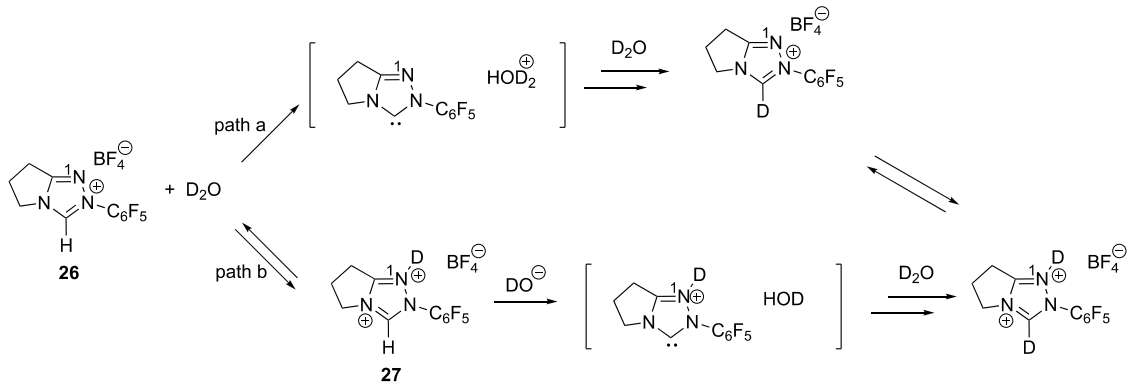
O'Donoghue, Smith and coworkers isolated intermediate 3-(hydroxybenzyl)azolium salts **24** resulting from triazolylidene-catalyzed Stetter reactions (Scheme 10). These intermediates are reversibly formed and proceed onward slowly to yield the Stetter product.



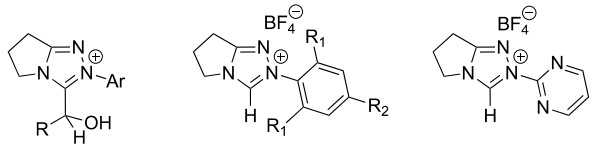
Scheme 10. Substrates studied by O'Donoghue, Smith and coworkers.

Although this group did not study the acidity of the NHC itself, they did examine the relative acidities, through H/D exchange experiments, of the intermediate salts. They synthesized a series of 3-(hydroxy) and 3-(methoxybenzyl)azolium salts with varying *N*-aryl substituents (**25,** Scheme 10). They found that catalysts with electron withdrawing *N*-aryl substituents yielded 3-(oxybenzyl)azolium salts that were more acidic and proceeded more rapidly to the Stetter product. They hypothesized, based on both their results and previous studies by Rovis, that the deprotonation at the C(α) site is rate determining, so the more acidic that site is, the more rapidly forward reaction occurs.[38]

O'Donoghue, Smith and coworkers followed up this work with studies focused on triazolylidenes whose aryl groups have ortho substituents.[11] The authors proposed that for triazolium **26**, under acidic conditions, deuterium exchange might occur via a dicationic intermediate (path b rather than path a, Scheme 11). They postulate that path b, where the N1 is protonated, might be favored by an interaction between the proton at N1 and the ortho fluorines on the *N*-aryl substituent. Thus, while one might expect a C_6F_5 substituent to be electron withdrawing and disfavor protonation of **26** (to form **27**), the authors suggest that protonation is actually favored due to a stabilizing ortho N1-H---F interaction. In terms of NHC catalysis, the authors proposed that the intermediate in a benzoin or Stetter reaction (**28**) could be stabilized by an O-H---X interaction where "X" is an ortho substituent on the *N*-aryl. This hypothesis is supported by their observation that *N*-aryl-ortho-X-heteroatom substituents increase rate and equilibrium constants for formation of **28**, relative to other catalysts that lack such substituents (Scheme 12).



Scheme 11. Deuterium exchange mechanisms.



Scheme 12. Catalysts utilized by O'Donoghue, Smith and coworkers.

Studies of **29** and **30** supported this hypothesis, in that deuterium exchange reactions indicate that triazoliums with 2,6 heteroatom substituents have a donor effect on pK_a at N1 (Scheme 12).

Thus, these authors were able to show that *N*-aryl-ortho-X heteroatom substituents on certain triazolium NHCs can stabilize a nearby acidic proton. This result can be extended to explain the acceleration observed in the first step

of NHC-catalyzed *Umpolung* reactions with similar triazolylidenes, in that the *N*-aryl-ortho-X heteroatom substituents might stabilize the OH in the first intermediate (e.g. **28**), driving the reaction forward.

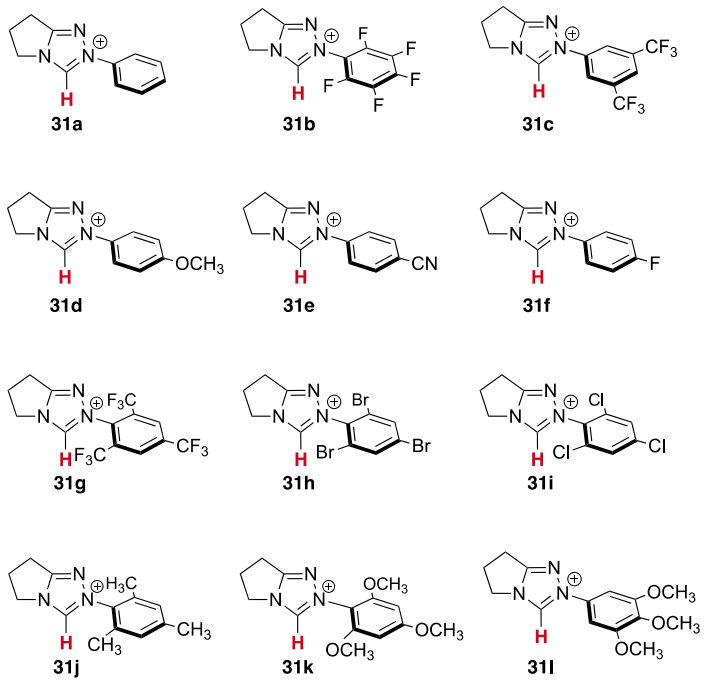
NHC acidity and stereoselectivity.

NHC acidity and diastereoselectivity.

Subsequent to this work, we, in collaboration with the Rovis group, examined a series of *N*-aryl-triazolylidene NHCs in the gas phase.[39] Specifically, we examined the gas phase C3-H acidity of a series of triazolium cations. The motivation lay in the fact that for *Umpolung* reactions catalyzed by NHCs, the carbene is generated by *in situ* deprotonation of the corresponding protonated precatalysts. Thus, the acidity of the protonated NHC and the nucleophilicity of the resulting NHC are of great interest for understanding the catalytic mechanism.

By examining a series of catalytic *N*-aryl-triazolylidene NHCs in the absence of solvent, we hoped to gain insight into the intrinsic reactivity of these species.

We studied the *N*-aryl triazolium cation series **31** (Scheme 13). Our gas phase results (both calculations at B3LYP/6-31+G(d) and experiments), along with known pK_a values, are listed in Table 1.



Scheme 13. Achiral precatalysts examined by Lee, Rovis and coworkers.

Table 1. Calculated (B3LYP/6-31+G(d); 298 K) and experimental data for achiral triazolium cations.[a]

Substrate	Calculated ΔH_{acid}	Experimental ΔH_{acid}[b]	pK_a[c]
31c	242.7	246	
31b	245.1	248	16.5
31e	245.1	248	16.9
31g	248.0		
31f	251.2	252	17.4
31i	252.1	252	
31h	253.0	252	16.7
31a	253.9	252	17.5
31l	255.5	256	
31d	257.1	256	17.8
31j	258.6	259	17.7
31k	267.5		

[a]ΔH_{acid} values are in kcal/mol; [b]Error is ±3-4 kcal/mol; [c]Reference [12]

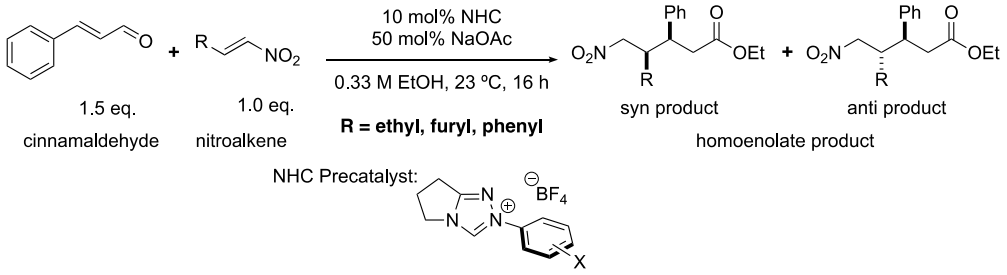
The experimental gas-phase values generally correlate to the computational values, indicating that the DFT method, for these species, calculates acidity with reasonable accuracy. Looking at the computed gas phase values, one observes that more electron withdrawing groups increase acidity, with the exception of **31c** and **31g**. Despite the presence of an additional trifluoromethyl group on the phenyl ring of **31g** versus **31c**, **31g** is *not* more acidic. We attribute this to the diortho placement of the two trifluoromethyl groups in **31g**, which forces the phenyl ring out of planarity, relative to the triazolium ring. Calculations support this change of geometry, which reduces orbital overlap with the azolium, and renders the additional CF_3 groups less effective in influencing the acidity.

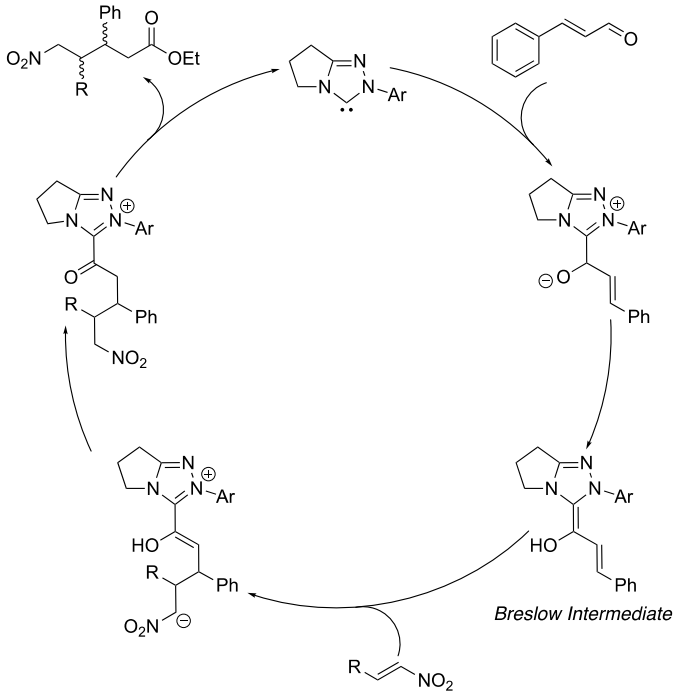
Generally speaking (with the exception of **31h**), the acidity values in both the gas phase and in solution follow a similar trend, decreasing in acidity as one moves down the table. The acidity range is much greater in the gas phase than in solution; comparing the calculated ΔH_{acid} versus pK_a, the span is 11 kcal/mol for the former but just 2 kcal/mol for the latter. There are also some reversals in the gas phase versus solution, such as **31d** being more acidic than **31j** in the gas phase (by 1.5 kcal/mol) but less acidic in water by 0.1 pK_a units. **31h** also has a surprisingly low pK_a as compared to its gas phase acidity. We attribute such reversals to solvent effects; it is not uncommon to see acidity trends differ in the absence of solvent.

The wider range of acidity in the gas phase has a distinct advantage, however, when looking for relationships between acidity and catalysis. Because the

nonpolar environment provides for larger differences among acidity, it would be potentially easier to gauge nuances among catalyst reactivity.

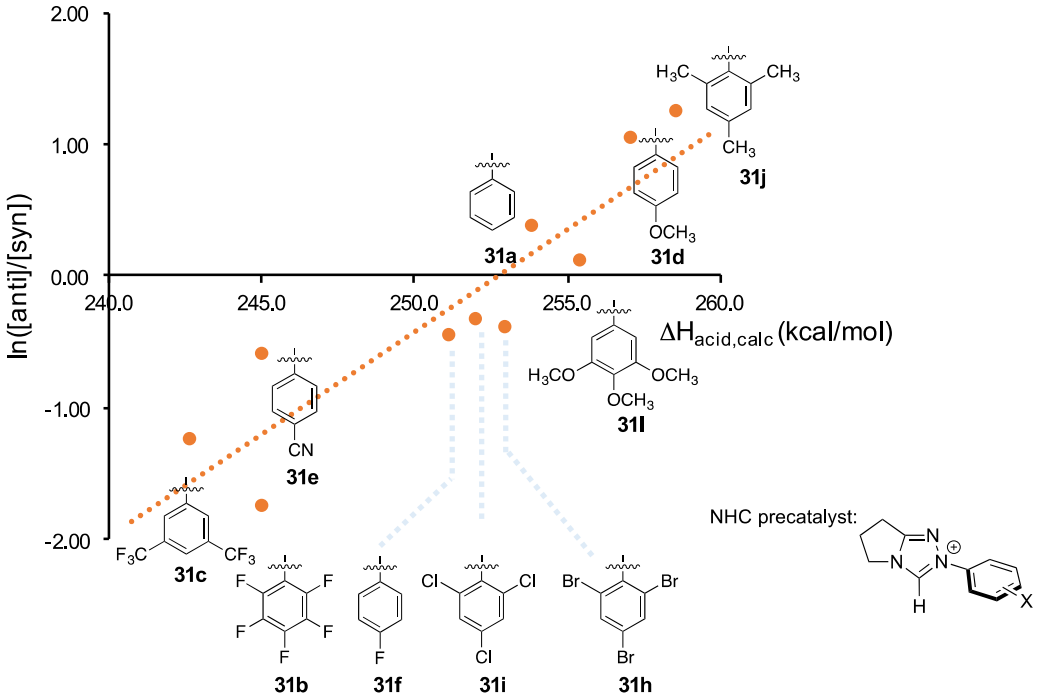
We used several of these triazoliums as precatalysts for an *Umpolung* homoenolate reaction of cinnamaldehyde with nitroalkenes (Scheme 14). The triazolium precatalyst, when deprotonated, yields a triazolylidene that can attack the carbonyl of the cinnamaldehyde. Proton transfer to the Breslow intermediate is followed by addition of the nitroalkene. Two products are possible, a *syn* and an *anti* product (only one of each enantiomer is shown; that is, this is a diastereoselective reaction that yields both enantiomers for *anti* and for *syn*).





Scheme 14. Homoenolate reaction between cinnamaldehyde and nitroalkenes. *Reprinted with permission from the Journal of the American Chemical Society, volume 139, pages 14917-14930, 2017, American Chemical Society.*

We found that acidity of the triazolium precatalyst and diastereoselectivity correlate (Scheme 15). While an overall correlation exists for all the precatalysts, the correlation does improve when precatalysts with diorthoaryl substitution are separated from those without. Clearly, the less acidic the precatalyst, the more favored is the *anti* product.

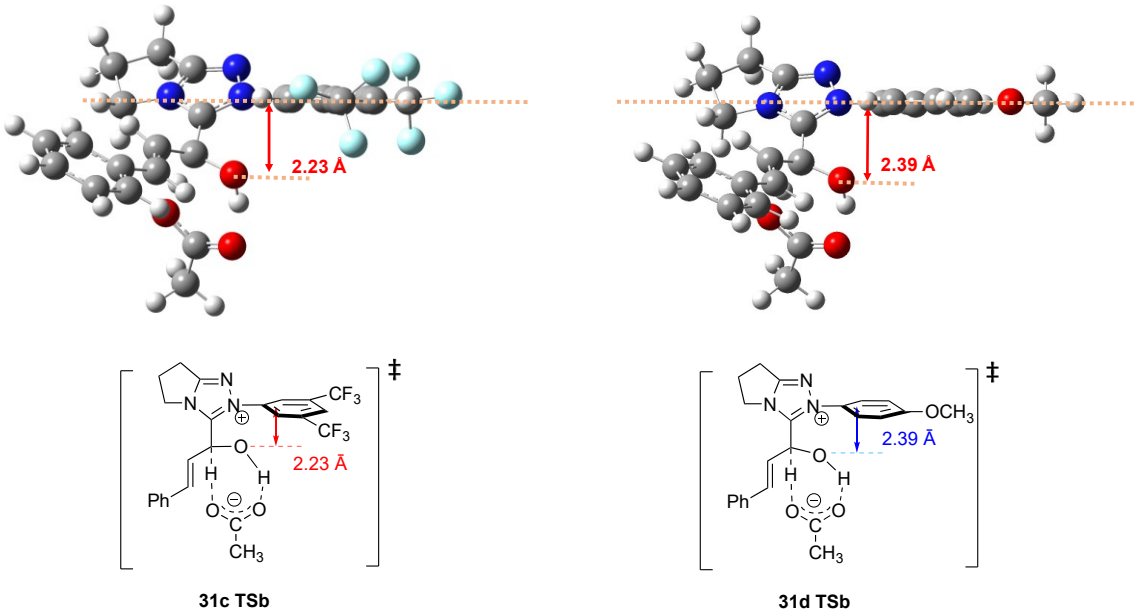


Scheme 15. Diastereoselectivity versus gas phase acidity.

The provenance of this linear correlation is unknown, but we hypothesized that diastereoselectivity might be related to a preference for *E* versus *Z* Breslow intermediate geometry. Prior work by the Liu and Rovis groups, separately, using enantioselective variants of this reaction, implied that *anti* selectivity would arise from a preference for the *E* enol, while *syn* selectivity arises from the *Z* enol.[40,41] Because less acidic triazolium cations (with electron donating substituents) yield more anti selectivity, we therefore postulated that formation of the *E* enol would also be favored for these cations. Conversely, those cations that lead to *syn* selectivity would be more acidic (electron withdrawing substituents) and favor *Z* enol formation. To probe this hypothesis, we calculated the transition states leading to the formation of the *E* versus *Z* enol for a highly acidic triazolium precatalyst (3,5-CF_3) and for a low acidity precatalyst (4-OMe), The calculations support our hypothesis in that the less acidic precatalyst does indeed show a lower barrier for *E* enol formation (than *Z* enol formation), which

by our postulate, also favors the *anti* product, as is experimentally observed. Likewise, the more *acidic* precatalyst has a lower barrier for *Z* enol formation, and experimentally, we do see a *syn* preference.

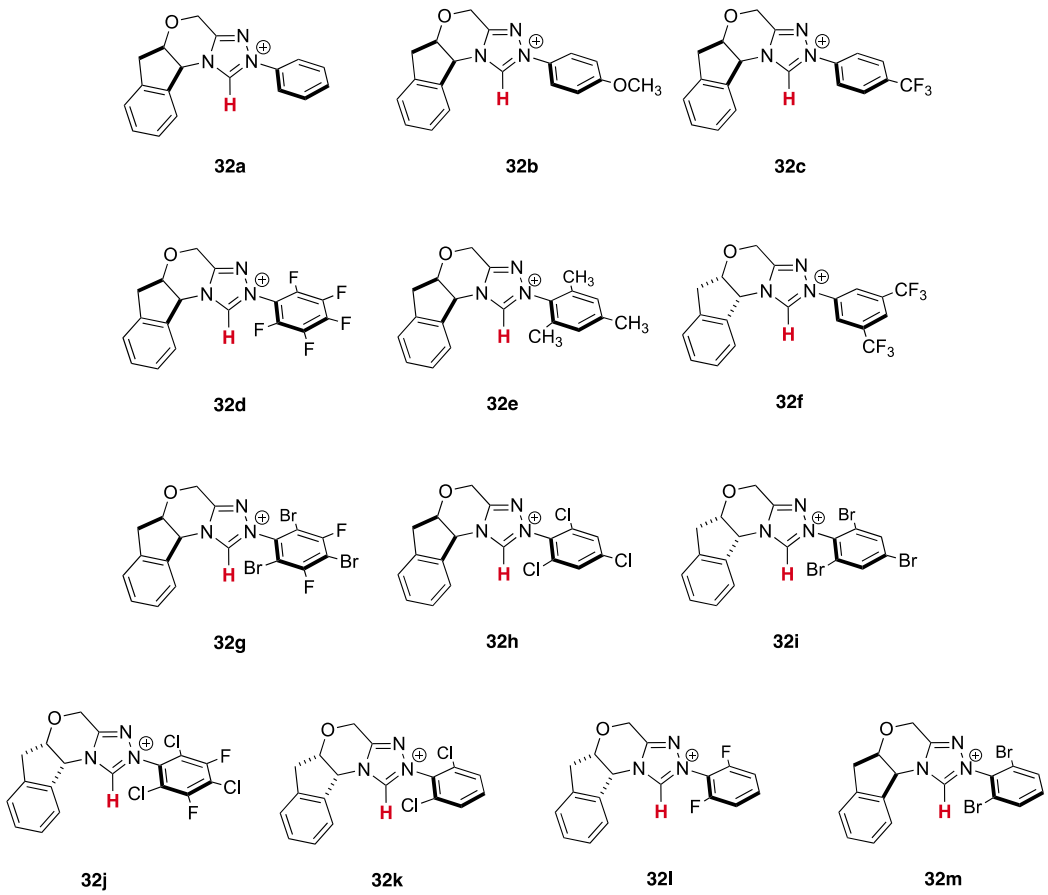
Why the more acidic precatalysts favor the *Z* enol is not clear, though we noted in our publication that the calculated transition states do show that the *Z* enol has an O-aryl interaction that would be more stable for aryl rings with electron withdrawing substituents (more acidic triazolium precatalysts; see **31c TSb** versus **31d TSb**, Scheme 16). A reviewer of this current manuscript also noted that the precursor to the *E* enol could have pi-stacking between the catalyst aryl ring and the olefin; such an interaction would be favored for electron-poor aryl groups. The reviewer suggested that perhaps this interaction must be overcome to realize the *E* enol, and therefore for acidic catalysts, the *Z* enol is favored.



Scheme 16. Calculated transition structures for formation of *Z* Breslow enol.

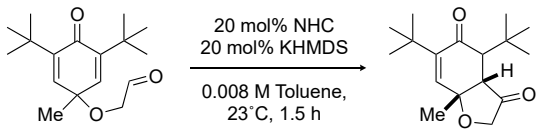
NHC acidity and enantioselectivity.

We also studied the acidity of chiral triazolium precatalysts **32**, both experimentally and computationally (Scheme 17). As with series **31**, the computational and experimental results correlate, and more electron withdrawing groups result in greater acidity. The major exception is **32a** versus **32m**; although **32m** has two bromide groups on the phenyl ring, it is not more acidic than **32a**. However, as discussed for the achiral series **31**, calculations show that the diortho positioning of the bromides forces the phenyl ring out of planarity with the azolium ring, such that the influence of the electron withdrawing substituents is less.



Scheme 17. Chiral precatalysts examined by Lee, Rovis and coworkers.

With series **31**, the effect of acidity on diastereoselectivity was probed; with these species, we can test the effect of acidity on enantioselectivity. The NHC-catalyzed asymmetric intramolecular Stetter reaction of **33** to yield **34** (Scheme 18) was studied. For this reaction, we see a correlation with acidity as well, where less acidic triazolium precatalysts **32** yield improved enantioselectivity (note in plot below, "*ent*" just indicates that the enantiomer of the precatalyst shown in series **32** was used). We postulate that the provenance for this effect may be related to hydrogen bonding that decreases the *ee;* less acidic triazoliums are less effective at hydrogen bonding and therefore increase the *ee.* One reviewer of this current manuscript also noted the possibility of a diortho substituent effect enhancing stereoselectivity; generally we do find that these types of plots improve when catalysts with diortho substituents are plotted separately from those without (as discussed in the original paper). The plot in Scheme 19 definitely shows an increase in *ee* with increasing acidity, even for those precatalysts that lack diortho substitution, but of course we cannot discount the additional role that that substitution may play in increasing enantioselectivity. The goal in the original paper was to show that a correlation does appear to exist between *ee* and acidity; the exact provenance of that correlation remains, for now, unknown.

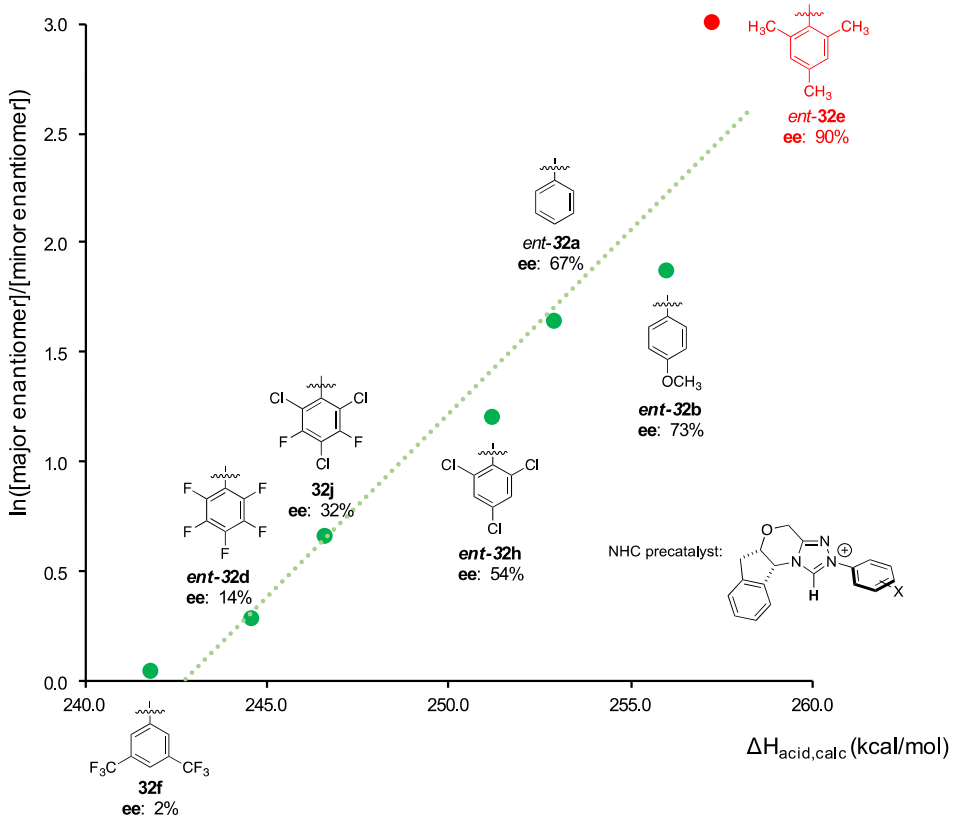


33 **34**

Scheme 18. Enantioselective Stetter reaction.

This relationship allowed us to actually improve upon the reaction; the best *ee* for this reaction had been 73%, for **32b**. Our studies show that a lower gas phase acidity should correlate to improved *ee*; accordingly we examined precatalyst **32e**, which increased the *ee* to 90% (Scheme 19).

Thus, not only did we establish a relationship between gas phase acidity and stereoselectivity, but we also, based on that result, designed an improved catalyst for an enantioselective Stetter reaction.

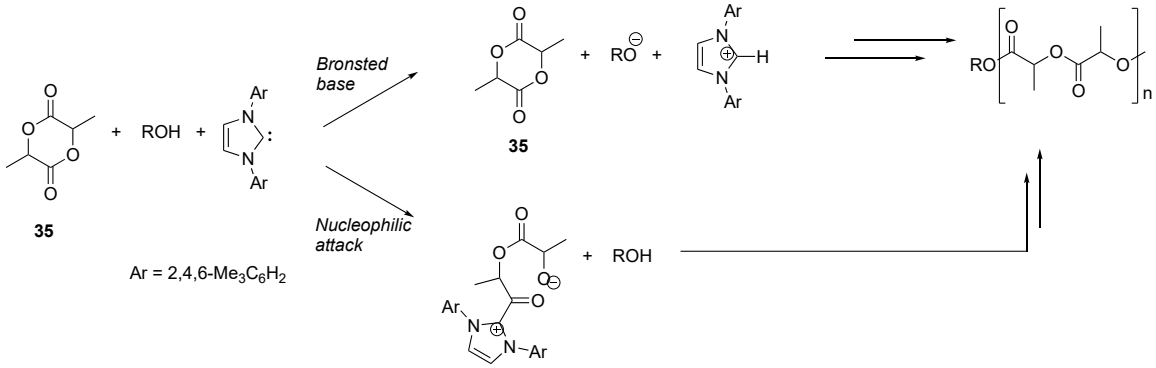


Scheme 19. Enantioselectivity versus gas phase acidity.

NHCs and Brønsted basicity.

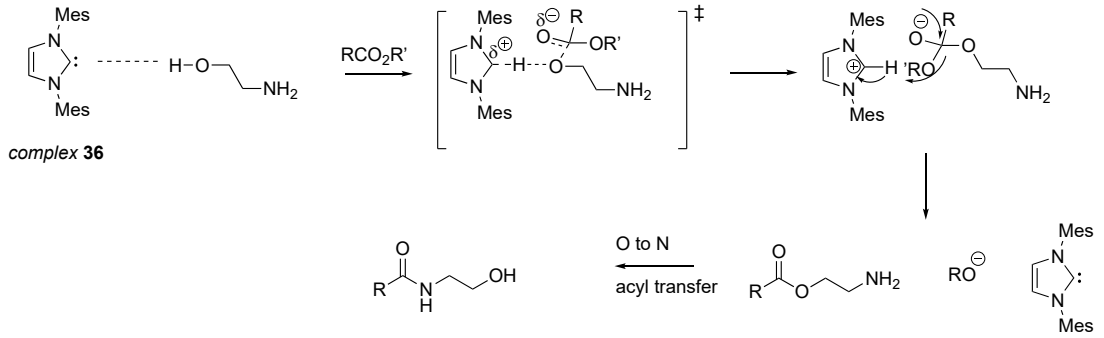
NHCs have also increasingly been used as Brønsted base catalysts. Naturally NHC basicity plays a role in any mechanisms where an NHC is a Brønsted base catalyst. Lupton and coworkers have published a fine overview of reactions catalyzed by NHCs as Brønsted base catalysts.[36] Herein we do not intend to cover every example of NHCs as Brønsted base catalysts, but highlight those studies which specifically probe Brønsted catalysis and NHC basicity.

The earliest work showing the utility of NHCs as Brønsted base catalysts, for transesterification, was first reported by Hedrick and Nolan, independently, in 2002.[42-44] Hedrick and coworkers examined the NHC-catalyzed living ring-opening polymerization of lactides and lactones.[42] Reaction of lactide **35** with an alcohol and a diaryl imidazolylidene (Ar = 2,4,6-$Me_3C_6H_2$) resulted in polymers of predictable molecular weight (Scheme 20). Both a Brønsted base and a nucleophilic mechanism were considered. Because the NHC has a pK_a of 24, while the alcohol pK_a value is 29, the authors leaned toward the nucleophilic mechanism.



Scheme 20. Brønsted versus nucleophilic mechanism.

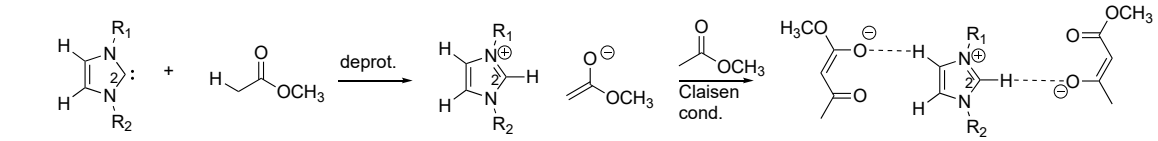
Later work by Movassaghi and Schmidt on NHC-catalyzed conversion of esters into amides lent support for a Brønsted base catalysis mechanism (Scheme 21).[45] These authors were able to characterize, via X-ray crystallography, a stable carbene-alcohol complex (of the form shown in **36**, except with methanol). This led them to propose the mechanism shown in Scheme 21, with the NHC as a Brønsted base catalyst.



Scheme 21. NHC-catalyzed conversion of esters to amides.

Hu and coworkers provided computational support for a Brønsted base-type role for the NHCs in such reactions, finding that a mechanism through a hydrogen-bonded carbene-alcohol complex is calculated to be the most energetically favorable pathway. The NHC therefore is predicted not to deprotonate the alcohol, but to facilitate proton transfer from the incoming to the outgoing alcohol, without ionic intermediates.[46]

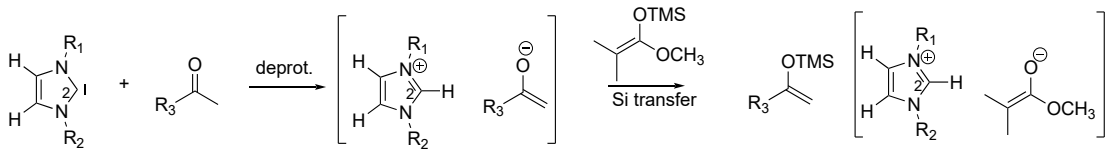
Important early and continued work by Nolan and coworkers have delved deeply into the role of NHCs as catalysts for transesterification.[44,47,48] Imidazolylidene **37**, with 1-adamantyl substitution, was found to be an effective catalyst; for transesterification with alcohols and esters, quantitative conversion at room temperature is observed. In the reaction of **37** with methyl acetate, Nolan and coworkers were able to obtain a single crystal X-ray diffraction structure of complex **38** (Scheme 22). The proton on the NHC carbon 2 was confirmed also by ^{1}HNMR. The authors noted that in addition to the hydrogen bond to the C2-H, there is also an unusual hydrogen bond at the C5 position, with the carbonyl oxygen from the Claisen carbanion of a neighboring adduct interacting with the C5-H. The existence of such a structure led the authors to propose a mechanism where the NHC abstracts a proton from methyl acetate. The authors noted that such a mechanism is feasible due to the basicity of the carbene.[48]



Scheme 22. NHC proton abstraction in transesterification.

The strong basicity of NHCs was also invoked in a silyl transfer reaction reported by Song and coworkers (Scheme 23).[49] The diadamantyl imidazolylidene **37** effects deprotonation of a series of ketones, allowing conversion into the corresponding silyl enol ethers. No specific studies were conducted to prove a

Brønsted base role for the NHC, but the authors note that the pK_a of imidazolylidene with *N-tert*-butyl substituents is 20 in THF and 22.7 in DMSO, which should be strong enough to deprotonate the reactant ketone to form the corresponding enolate. Subsequent silyl transfer from a trialkylsilyl ketene acetal yields an ester enolate, which, with a pK_a of roughly 25, should be able to deprotonate the imidazolium to regenerate the free carbene.

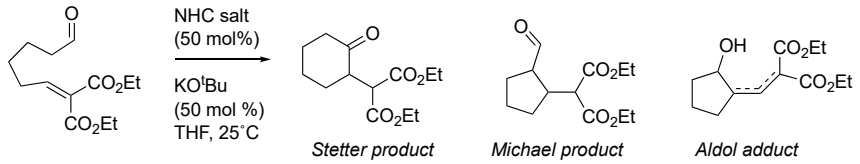


37
$R_1 = R_2$ = 1-adamantyl

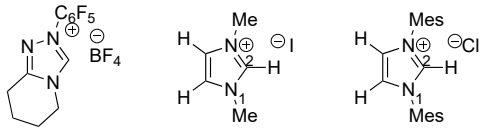
Scheme 23. NHC-catalyzed silyl transfer.

In 2011, Hong and coworkers explored the use of NHCs to effect intramolecular Michael reactions of aliphatic aldehyde enolates.[50] The authors noted that examples of the reaction of aldehyde enolates with α,β unsaturated compounds are limited, due to the high reactivity of the formyl group under the acidic or basic conditions normally used to directly generate aldehyde enolates.

For the reaction shown in Scheme 24, these authors found that if protonated NHC **39** was used, only the Stetter product was observed. If protonated NHC **13** was the catalyst, only the Michael adduct was observed. If protonated imidazolium with aryl groups were used, such as **40**, an Aldol adduct was the major product. The authors concluded that the reactivity differences were attributable to the basicity of the carbene catalyst; the imidazolium **13** is more basic than both the imidazolium **40** and the triazolium **39**, which appears to favor the Michael pathway (Scheme 25). The authors also note that while the imidazolylidene derived from **13** is the most basic of the NHCs studied, and therefore is the best catalyst for the Michael adduct formation, it is still a mild Brønsted base as compared to bases commonly used for this type of transformation; these milder conditions are a promising synthetic strategy.



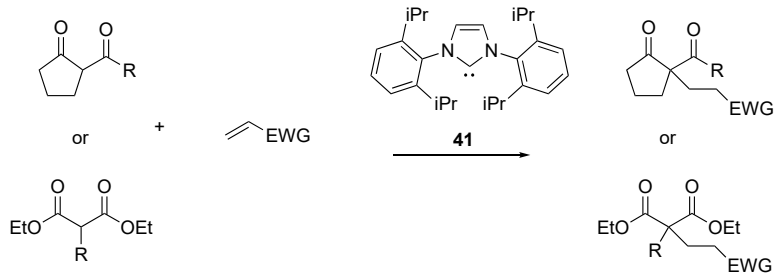
Scheme 24. Competing NHC-catalyzed pathways.



39 **13** **40**

Scheme 25. NHCs with different basicities.

Michael additions catalyzed by NHCs as Brønsted base catalysts have been studied by various groups over the years; highlights where NHC basicity are specifically studied follow. Early work by Coquerel and Rodriguez explored a Michael addition spirocyclization; the authors speculated that the NHC was acting as a Brønsted base.[51] Subsequent work with various 1,3 dicarbonyl compounds (Scheme 26), showed that NHC **41** is the most effective catalyst.[52] Other bases, with and without nucleophilic additives, were ineffective catalysts; the authors suggest that the NHC is acting as both a Bronsted base (activating the nucleophile as Nolan suggests, see Scheme 22), as well as possibly a Lewis acid, with the C2 activating the electrophile. Coquerel and Rodriguez later extended this work to include hetero Michael additions as well, with RSH and $R_2P(OH)$ species as nucleophiles.[53]



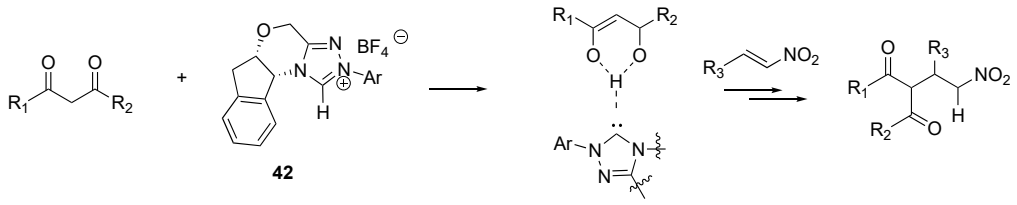
Scheme 26. Coquerel and Rodriguez's studies of NHC-catalyzed Michael additions.

Other hetero Michael addition work includes that of Scheidt, who reported the oxa-Michael addition of alcohols to α,β-unsaturated carbonyl compounds.[54] Scheidt's studies, which included attempts at an enantioselective version, point to a Brønsted base mechanism as well, where the NHC deprotonates the alcohol nucleophile and forms a hydrogen-bonded NHC-alcohol complex, as first suggested by Movassaghi and Nolan in earlier work (Schemes 21, 22; *vide supra)*.[44,45,47,48,54] Aza-Michael additions catalyzed by NHCs were reported by Zhang, who also invoked formation of a hydrogen-bonded complex between the NHC and the nucleophile amine as an activation step.[55]

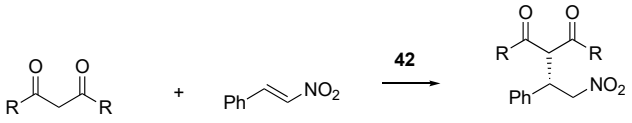
He and coworkers have examined several NHC-catalyzed Michael additions over the years as well. Their study of the sulfa-Michael reaction between thiols and enals noted that using triazolium and thiazolium NHC catalysts resulted in no

reaction, presumably due to their low Brønsted basicity; imidazolylidenes proved to be the best catalysts, including the (1,3-bis(diisopropylphenyl)-imidazole-2-ylidene) **41**.[56] Following work by Huang (*vide infra)*, these authors also found that addition of hexafluoroisopropanol (HFIP) increased product yield, presumably due to its role as a proton shuttle.[57] As with other related studies, He and coworkers propose a mechanism involving the NHC acting as a Brønsted base to attack the acidic proton of the thiol, forming a hydrogen bonded complex. He and coworkers have also studied other NHC-catalyzed Michael additions, including the vinylogous Michael addition of deconjugated butenolides with α,β-unsaturated esters and nitriles; sulfa-Michael studies with α,β-unsaturated ketones, esters, amides, sulfones and nitriles, as well as alkenyl halides as Michael acceptors; and double Michael additions between fluorenes and dienones.[58-61]

Huang and coworkers were the first to report an enantioselective Michael addition using NHCs as chiral Brønsted bases.[57] Triazolium **42** was found to be an effective catalyst for the reaction shown in Schemes 27 and 28. Interestingly, more basic NHCs such as *N,N*-dialkylimidazolylidenes were not effective catalysts. The authors postulate that the imidazolylidene NHCs are too basic and fully deprotonate the diketone, which results in the reaction stalling. They finely tuned relative pK_a values, where they ensured that the pK_a of the NHC was greater than that of the product, which would be greater than that of the dicarbonyl. Using less basic *N*,*N*-diarylimidazolium and triazolium precatalysts do work; the authors postulate that the NHC is a hydrogen bonder (Scheme 27). The authors also believe that the NHC may act as a proton shuttle promoter and further found that addition of HFIP increased both reaction rates and enantioselectivity. They postulate that HFIP is a hydrogen bond linker that stabilizes the transition state in the carbon-carbon bond-forming step.



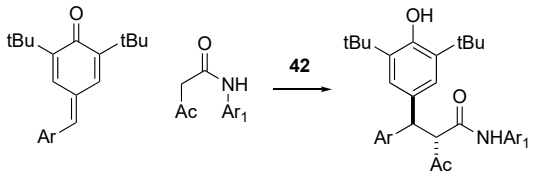
Scheme 27. Proposed mechanism for Michael addition catalyzed by chiral NHC.



Scheme 28. Enantioselectivity observed for chiral NHC-catalyzed Michael addition.

Huang and coworkers have expanded upon this initial work, developing an asymmetric sulfa-Michael reaction, using β-CF_3-β-aryl nitroalkene acceptors.[62] (The reaction was found to work with other simple enones as well). Hammett studies support a mechanism wherein the NHC acts as a Brønsted base catalyst by activating the acidic mercaptan nucleophile; enantioselectivity arises from a pi-pi stacking interaction between the double bond of the nitroolefin and the NHC heterocycle, whose preferred geometry is affected by sterics.[62] This work was followed by studies showing the applicability of the reaction to unsaturated ester and amide acceptors.[63] Chiral NHC catalyst **42** has also been found to catalyze aza-Michael additions between alkyl amines and β-trifluoromethyl-β-aryl-nitroolefins.[64] Since the amine nucleophiles are not particularly acidic, Huang and coworkers propose that the NHC probably activates the amine through a hydrogen-bonded complex.[64]

Recently, Guin and coworkers used chiral NHC catalyst **42** (where Ar = mesityl) to catalyze diastereoselective and enantioselective 1,6-addition reactions of 1,3 ketoamides to *p*-quinone methides (Scheme 29).[65] Reactions with *N*-alkyl amides do not proceed, leading the authors to propose that the NHC deprotonates the N-H, resulting in a chiral ion pair. The authors favor deprotonation over hydrogen-bond activation due to relative pK_a values of the ketoamide (10-12) versus the NHC (17-19). They state that for catalysis the substrate must have a lower pK_a than the NHC.

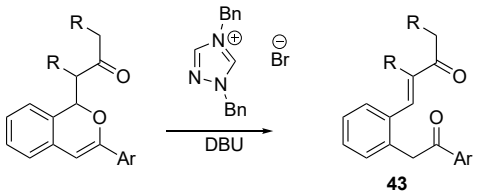


Scheme 29. Stereoselective NHC-catalyzed reactions of 1,3 ketoamides to *p*-quinone methides.

Non-chiral reactions with *p*-quinone methides were also reported by Anand and coworkers, who reported vinylogous Michael reactions of dialkylphosphites with *p*-quinone methides, leading to diarylmethyl phosphonates. As with other studies where NHCs are Brønsted base catalysts, the authors propose that the NHC abstracts an acidic proton from the dialkylphosphite.[66] These authors also found that NHCs can catalyze the addition of 2-napthols to *p*-quinone methides.[67]

One last interesting transformation in which NHCs are used as Brønsted base catalysts and in which the authors study the relationship between basicity and catalysis is the reaction of α-(isochromen-1-yl)ketones, reported by Fan and Cheng.[68] These authors found that when a triazolium precatalyst is used, the product is the isomerized β-(2-(aroylmethylene)phenyl)-α,β-unsaturated ketones

(Scheme 30). In contrast, when an imidazolium precatalyst is used, 1-aroylnapthalene derivatives are produced in high yield (Scheme 31). The authors attribute the change in reactivity to the relative basicity of the triazolylidene versus the imidazolylidene NHC catalysts. Both reactions begin by the NHC acting as a Brønsted base catalyst, deprotonating the α-proton of the ketone. However, the more basic imidazolylidene promotes the intramolecular aldol condensation of **43** to form **44.**



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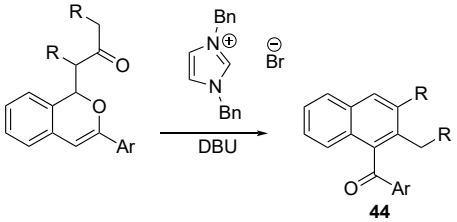
Scheme 30. Triazolylidene-catalyzed transformation of α-(isochromen-1-yl)ketones to β-(2-(aroylmethylene)phenyl)-α,β-unsaturated ketones.



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Scheme 31. Imidazolylidene-catalyzed transformation of α-(isochromen-1-yl)ketones to 1-aroylnapthalene derivatives.

As noted at the beginning of this section, other reactions using NHCs as Brønsted bases have been studied;[36] herein we have attempted to focus on examples where the basicity of the NHC was specifically addressed in the context of catalysis.

4. Conclusions and future directions.

The study of the fundamental properties of NHCs is, relative to the body of work on their catalytic utility, still limited. Herein, we show examples of studies which focus on NHC basicity and their role as catalysts. Such studies have led to deeper mechanistic understanding, as well as improved efficiency and selectivity. Continued examination of basicity as a tool for understanding NHC catalysis will be important for continued design improvement and predictive power in this field.

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