Organocatalysis

DOI: 10.1002/anie.200603380

# N-Heterocyclic Carbenes as Organocatalysts

*Nicolas Marion, Silvia Díez-González,* and Steven P. Nolan**

**Keywords:**
asymmetric catalysis · C–C coupling · homogeneous catalysis · N-heterocyclic carbenes · organocatalysis

*Organocatalyzed reactions represent an attractive alternative to metal-catalyzed processes notably because of their lower cost and benign environmental impact in comparison to organometallic catalysis. In this context, N-heterocyclic carbenes (NHCs) have been studied for their ability to promote primarily the benzoin condensation. Lately, dramatic progress in understanding their intrinsic properties and in their synthesis have made them available to organic chemists. This has resulted in a tremendous increase of their scope and in a true explosion of the number of papers reporting NHC-catalyzed reactions. Here, we highlight the ever-increasing number of reactions that can be promoted by N-heterocyclic carbenes.*

## Introduction

N-heterocyclic carbenes (NHCs) are by far the most studied members of the family of nucleophilic carbenes.[1,2] They are generally known as excellent ligands for metal-based catalysis, but there is also increasing interest in the role of nucleophilic carbenes as organocatalysts. Metal-free catalyzed processes are interesting alternatives to classical organic transformations since they are often more economical and environmentally friendly. In this article, we give a comprehensive overview of the numerous applications of imidazolylidene, imidazolinylidene, triazolylidene, and thiazolylidene in organocatalysis (Figure 1).

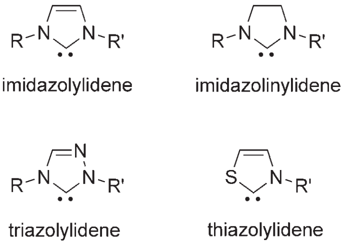


**Figure 1.** General structures of nucleophilic carbenes.

## 1. Condensation Reactions

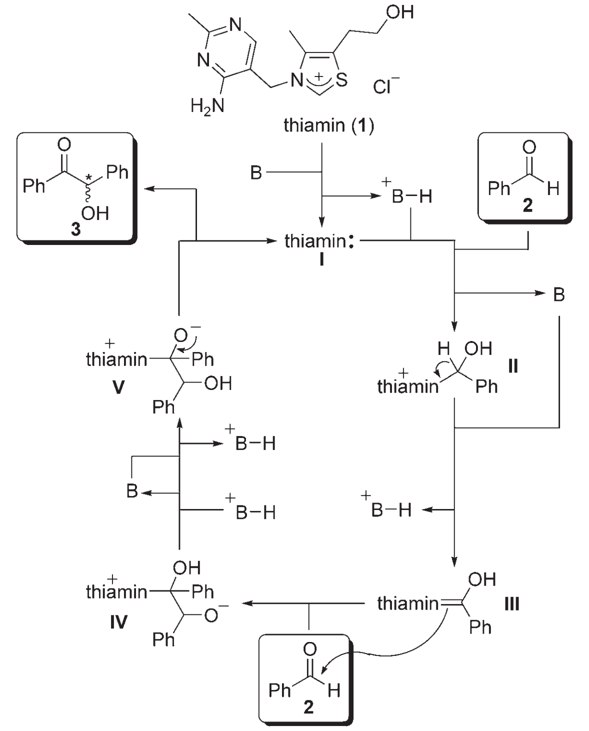
The benzoin condensation catalyzed by azolium salts has been widely studied. Catalytic, synthetic, and mechanistic aspects of this reaction have been examined.[3] Numerous reactions that can also be considered condensations can be catalyzed by N-heterocyclic carbenes (NHCs). Because of their relevance to C–C bond formation and because of the ubiquity—and wide diversity—of carbonyl compounds, these reactions have attracted much attention. Furthermore, the creation of a stereogenic center during the course of the reaction has further challenged the design of asymmetric catalysts. Some excellent reviews, mainly focused on the benzoin condensation, have already appeared in the literature;[3,4] therefore, we will review here only the latest advances.

### 1.1. Benzoin Condensation

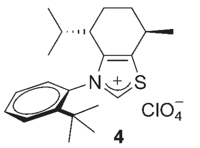
The benzoin condensation reaction has attracted much attention for several decades notably because of its use in C–C bond formation. It was shown early on by Ugai et al. that naturally occurring thiamin (**1**) catalyzes the self-condensation of benzaldehyde (**2**) to produce benzoin (**3**) (Scheme 1).[5,6] While several mechanistic proposals were still being debated,[7] Breslow[8] proposed in his 1958 groundbreaking paper that the C2 conjugate base of the thiazolium ring in thiamin (**I**) acts as a nucleophile and activates the carbonyl for subsequent condensation, leading to **IV**. Base-promoted isomerization then affords **V**, which produces **3** and regenerates catalyst **I**.[8,9] In addition to the formation of a new C–C bond, the benzoin condensation features the creation of a stereogenic center in **3**. It then naturally, as early as 1966, became a benchmark reaction to evaluate the potential of chiral heterazolium salts. A wide variety of

---

[*] N. Marion, Dr. S. Díez-González, Prof. Dr. S. P. Nolan
Institute of Chemical Research of Catalonia (ICIQ)
Av. Països Catalans, 16, 43007 Tarragona (Spain)
Fax: (+34) 977-920-224
E-mail: sdiez@iciq.es
snolan@iciq.es



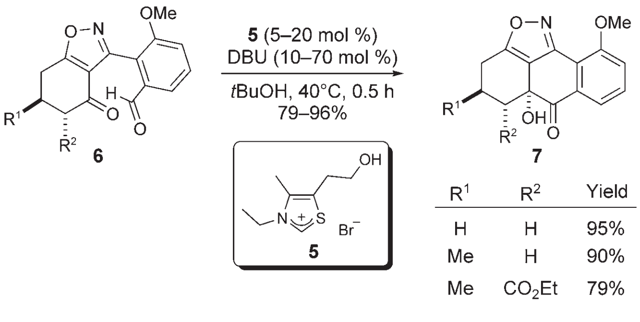
*Scheme 1.* Breslow mechanism for the benzoin condensation catalyzed by **1**.



**4**

thiazolium, imidazolium, and triazolium salts presenting great structural diversity have been developed over the years, and this has resulted in constant improvements in yield and selectivity.[3] Going beyond the usual focus on central chirality, Bach et al. recently demonstrated that axially chiral *N*-arylthiazoliums such as **4** catalyze the benzoin condensation and the Stetter reaction.[10] Even though the yields and *ee* values are low (up to 40–50% *ee*) compared to those of other systems, it was shown that axial chirality is a viable approach in this reaction.

Surprisingly, while numerous catalytic systems have been developed in the last fifty years for intermolecular acyloin condensation, the first intramolecular version appeared only in 2003. Suzuki and co-workers disclosed the facile synthesis of functionalized preanthraquinones **7** catalyzed by thiazolium bromide **5** in the presence of DBU (1,8-diazabicyclo-[5.4.0]undec-7-ene) (Scheme 2).[11] Noteworthy, the viability of ketones as benzoin-type condensation partners opened new fields of investigation for stereoselective reactions. Subsequently, the groups led by Enders and Suzuki independently reported asymmetric intramolecular cross-benzoin reactions[12] in which they achieved good to high yields and enantioselecitivities of α-hydroxyketones **8**. Representative examples are shown in Scheme 3. It is worth noting that once again the triazolium scaffold proved superior to the thiazolium framework for asymmetric induction.



| $R^1$ | $R^2$ | Yield |
|---|---|---|
| H | H | 95% |
| Me | H | 90% |
| Me | $CO_2Et$ | 79% |

*Scheme 2.* Intramolecular cross-benzoin condensation of ketones and aldehydes.

*Nicolas Marion received his BSc in chemistry and his MSc in organic chemistry from the Université Pierre et Marie Curie in Paris, where he worked under the supervision of Prof. Max Malacria. In 2004 he joined the research group of Prof. Steven P. Nolan at the University of New Orleans and followed him to the ICIQ in Tarragona, where he is currently completing his PhD on the use of NHC in homogeneous catalysis.*

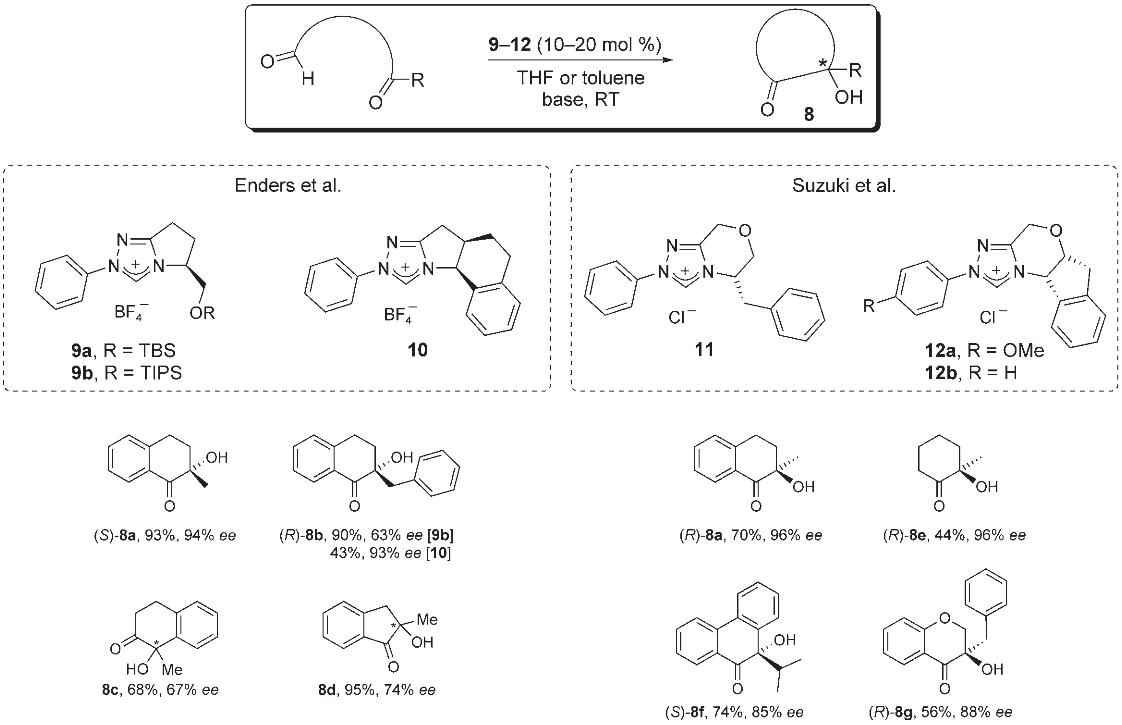
*Silvia Díez-González received her MSc in organic chemistry from the Universidad del País Vasco (Spain) and the Université de Paris Sud-Orsay (France), where she then completed her PhD on organosilicon chemistry. In 2004 she obtained a postdoctoral position in the research group of Prof. Steven P. Nolan at the University of New Orleans and followed him to the ICIQ in Tarragona, where she took a position of group coordinator.*

*Steven P. Nolan received his BSc in chemistry from the University of West Florida and his PhD from the University of Miami, where he worked under the supervision of Prof. Carl D. Hoff. After a postdoctoral stay with Prof. Tobin J. Marks at Northwestern University, he joined the Department of Chemistry of the University of New Orleans in 1990. He is now Group Leader and ICREA Fellow at the ICIQ in Tarragona (Spain). His research interests include organometallic chemistry and homogeneous catalysis.*

Finally, it should also be mentioned that the benzoin condensation can be promoted by a large palette of NHCs ranging from chiral rotaxane[13] to extremely simple and commercially available organic ionic liquids such as [bmim]Br (butylmethylimidazolium bromide) and [emim]Br (ethylmethylimidazolium bromide).[14]

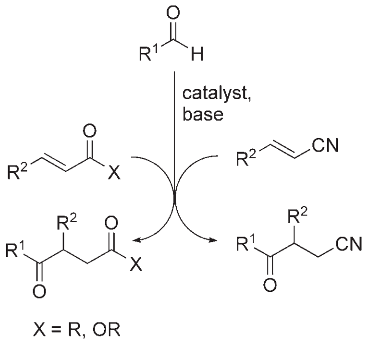
### *1.2. The Stetter Reaction*

The benzoin condensation was extended to Michael acceptors in the early 1970s,[15] and this is now a versatile



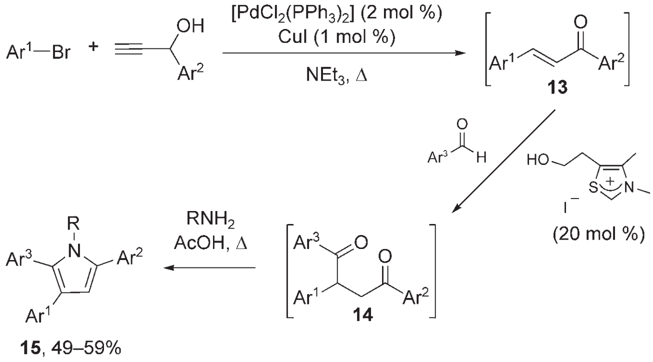
**Scheme 3.** Asymmetric intramolecular cross-benzoin condensation of ketones and aldehydes. TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.

method for the preparation of 1,4-diketones mostly, but also of 4-ketoesters and 4-ketonitriles (Scheme 4).[16] Commonly known as the Stetter reaction, this process was first reported to be catalyzed by cyanide, although azolium salts[17] are more efficient with aliphatic aldehydes.



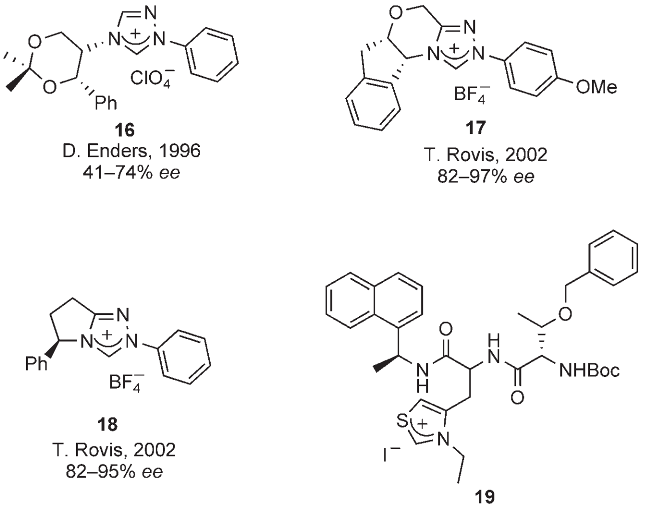
**Scheme 4.** The Stetter reaction.

The importance of the Stetter reaction products as valuable precursors in the synthesis of cyclopentanone derivatives[18] and heterocycles[19] explains its now very common use in total synthesis,[20] in solid-phase organic synthesis,[21] and in the preparation of extended heterocyclic systems.[22] Interestingly, one-pot multicomponent reactions have also been developed, allowing for straightforward preparation of highly substituted products from simple starting materials. The four-component synthesis of pyrrole derivatives reported by Müller and co-workers is an elegant example.[23] Chalcones **13**, formed from electron-poor aryl halides and aryl propargyl alcohols in a coupling/isomerization sequence,[24] can be transformed in a one-pot sequence first to the corresponding 1,4-diketones **14** and then to pyrrole derivatives **15** (Scheme 5).[25]



**Scheme 5.** One-pot four-component synthesis of pyrrole derivatives.

The intramolecular version of the Stetter reaction[26] was first rendered asymmetric by Enders et al.[3,27,28] Chiral triazolium salt **16** catalyzed the formation of 1,4-ketoesters in good yield and moderate selectivity (Figure 2). Better asymmetric induction was later achieved by Rovis et al. with triazolium salts **17** and **18** in which the chiral group is fused to a second ring.[29] These compounds have notably catalyzed the cyclization of aliphatic aldehydes and the formation of quaternary stereocenters.[30] Thiazolium-containing peptides **19** have also been used in this reaction, although only with moderate enantioselectivity.[31]



**16**
D. Enders, 1996
41–74% *ee*

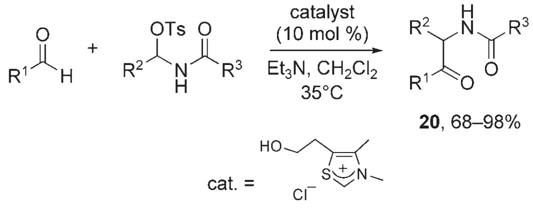
**17**
T. Rovis, 2002
82–97% *ee*

**18**
T. Rovis, 2002
82–95% *ee*

**19**
S. J. Miller, 2005
64–76% *ee*

***Figure 2.*** Selected catalysts for the asymmetric Stetter reaction.

The scope of the Stetter reaction was further expanded by the use of in situ generated acylimines as acceptors.[32] The cross-condensation of a variety of aldehydes and arylsulfonyl amides efficiently yielded the corresponding α-amido ketones **20**, even starting from α,β-unsaturated aldehydes that did not undergo homocondensation [Eq. (1)].

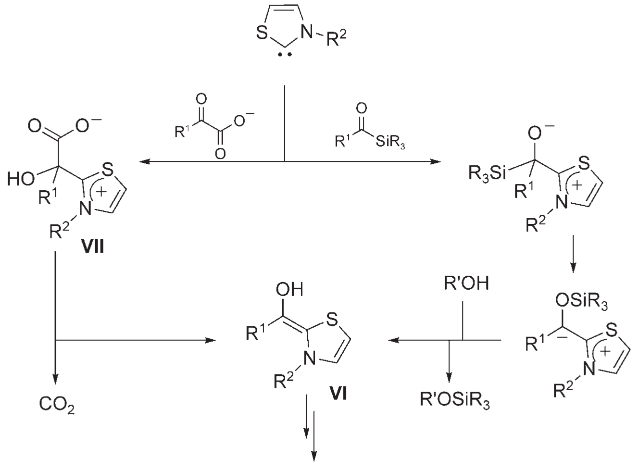


**20**, 68–98%

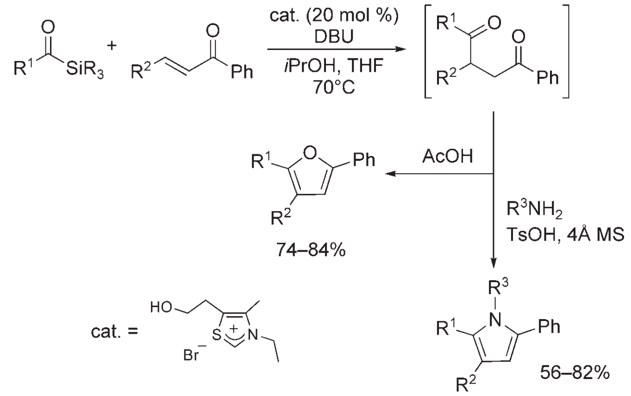
(1)

On the other hand, the formation of self-condensation or benzoin by-products from highly reactive aldehydes can be prevented by employing other carbonyl anion precursors such as α-keto carboxylates or acylsilanes. First reported with unsaturated ketones and esters,[33] the sila-Stetter reaction can also be applied to *N*-diarylphosphinoylimines to directly prepare the corresponding α-amino ketones.[34] In these transformations, after the initial attack of the carbene to the carbonyl function, a 1,2-silyl migration (Brook rearrangement[35]) is proposed to lead to the formation of the acyl anion equivalent. Desilylation of this intermediate by an alcohol would then afford the conventional umpoled species **VI** (Scheme 6). From keto carboxylates,[36] decarboxylation of the initial adduct **VII** would produce the same intermediate.

This methodology has also been applied successfully to the preparation of highly substituted heterocycles. Notably, 1,4-diketones have been transformed in situ to their corresponding pyrroles[37] under standard conditions or to furans[38] upon addition of acid (Scheme 7).



***Scheme 6.*** Generation of acyl anion equivalents.

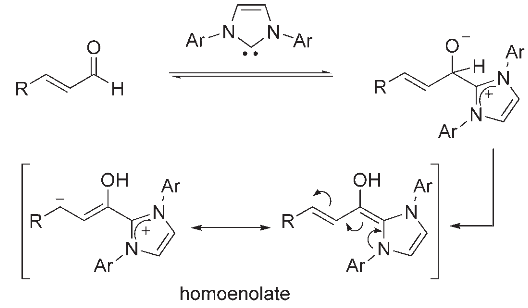


***Scheme 7.*** One-pot synthesis of heterocycles. TsOH = toluenesulfonic acid.

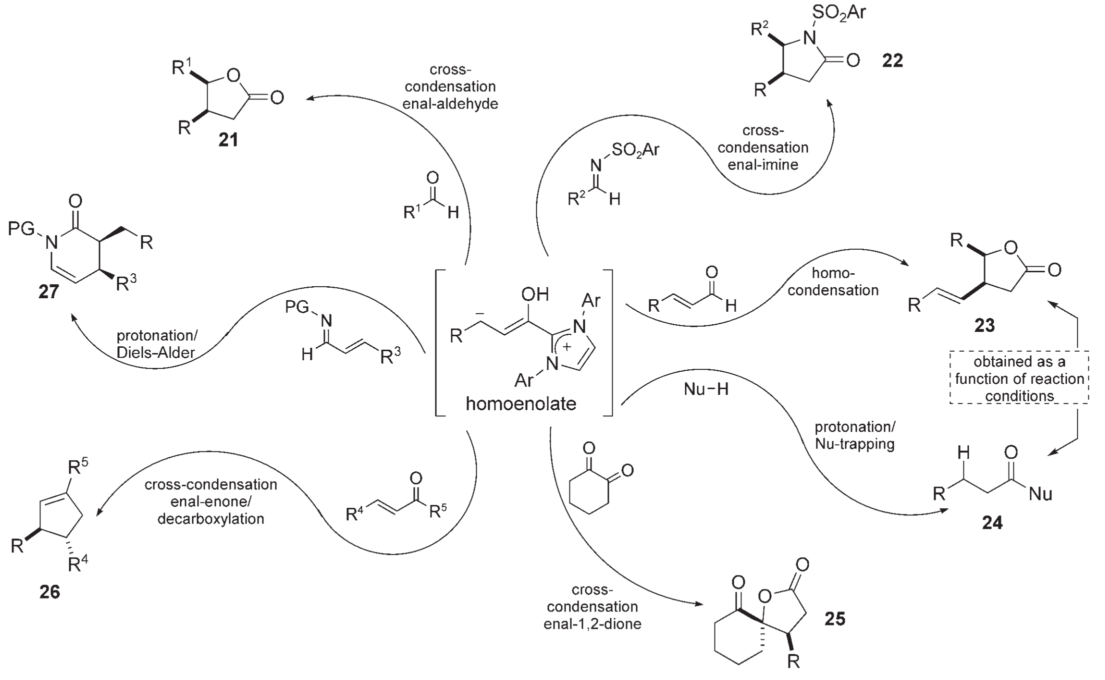
### *1.3. Generation of Homoenolates*

A novel aspect of NHC-catalyzed reactions is their use to generate homoenolates from α,β-unsaturated aldehydes (Scheme 8) leading to unprecedented reaction outcomes (Scheme 9).[39]

The research groups led by Glorius[40] and Bode[41] reported independently the formation of γ-butyrolactones **21** from conjugated enals and aromatic aldehydes (Scheme 9). Both groups highlighted the necessity for carefully adjusting the steric bulk of the NHC. Thiazolium



***Scheme 8.*** NHC-promoted generation of homoenolates.



***Scheme 9.*** Applications of NHC-generated homoenolates. PG = protecting group.

precursors, in which only one side of the ring is substituted, provided only trace amounts of benzoin condensation while imidazolium salts, properly sterically encumbered, resulted in selective formation of the desired lactones. IMes, flanked with mesityl groups, was found to be an excellent catalyst, unlike ICy (unreactive) and IPr (unselective), and produced *cis* lactones in high yields and selectivity (Figure 3). Glorius and co-workers, who lately expanded the scope of this transformation,[42] have shown the feasibility of an enantioselective version of this reaction using **28** but reached only 25 % *ee*.

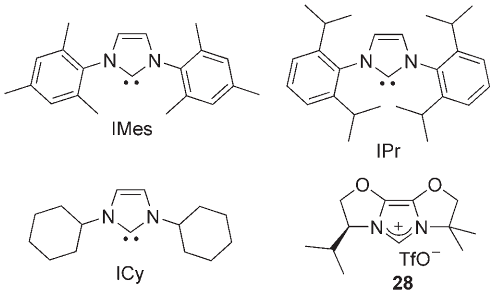


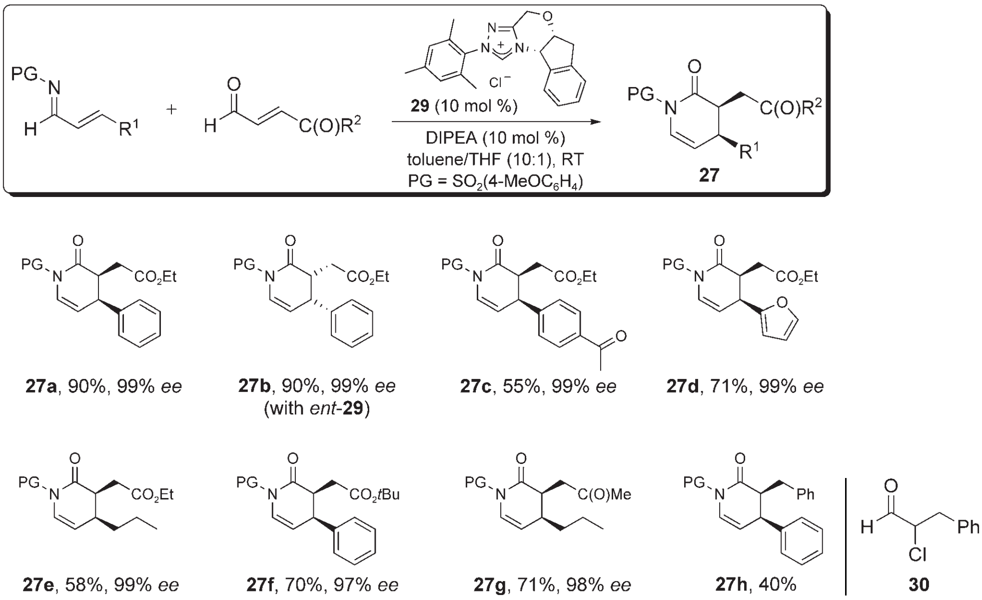
***Figure 3.*** Imidazolium-derived catalysts.

Subsequent to this first report, Bode et al. reported the use of a different electrophile to trap the homoenolate. Following the same reaction pathway, *N*-sulfonylimines readily react with the homoenolate–NHC adduct to produce, after expulsion of the carbene moiety, *cis* γ-lactams **22** (Scheme 9).[43] The authors eventually showed the critical choice of the protecting group on the imine. *N*-alkyl and *N*-aryl imines were found unreactive, while *N*-phosphinoyl imine reacted stoichiometrically with the organocatalyst.

Interestingly, the homoenolate can be trapped by a proton, leading to the formation of an activated carboxylate that further reacts with a nucleophile to produce compounds of type **24**. Scheidt and Chan reported that alcohols could be used in this context (Scheme 9).[44] Bode and Sohn later observed that the choice of the base was critical in this type of reactions.[45] It was notably shown that diisopropylethylamine (DIPEA) led to saturated esters **24** while KO*t*Bu afforded γ-butyrolactones **23**.

In 2006, Bode and co-workers extended the use of NHC-generated homoenolates to the Diels–Alder reaction.[46] In their mechanistic proposal, the homoenolate undergoes a proton transfer to generate a triazolium enolate, which further serves as dienophile in an azadiene Diels–Alder reaction with α,β-unsaturated imines. The optimization studies for this synthesis of dihydropyridinones proved critical, since the two reactants are very similar. While homoenolates formed from imidazoliums were reluctant to protonate, triazolium salts were found more efficient but with a tendency to react primarily with the enimine instead of the enal. Extensive optimization showed that a more activated enal, bearing an ester function *trans* to the aldehyde, in conjugation with a bulky triazolium was mandatory to avoid formation of γ-lactams **22** (Scheme 9) and produces in high yields the desired dihydropyridinones **27** (Scheme 10). It is noteworthy that the authors, concomitant with their findings, rapidly developed an asymmetric version of the reaction that proved extremely efficient (99 % *ee* for most of the substrates). Interestingly, α-chloroaldehyde **30** could participate as well in the Diels–Alder reaction, owing to its propensity to undergo enolate formation in the presence of NHC,[47] and led to compound **27h**.

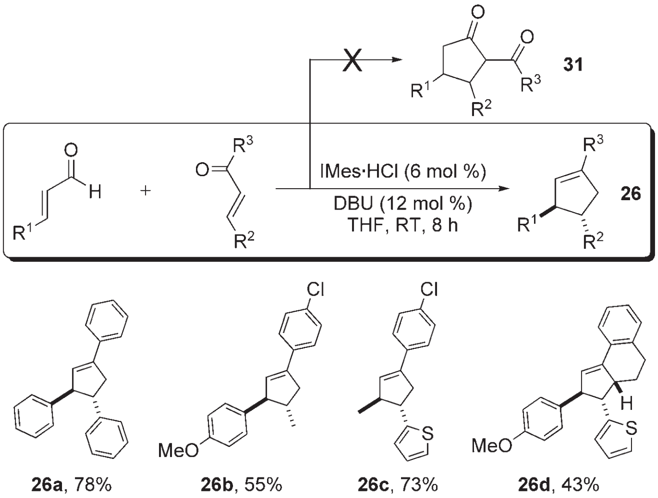
Very recently, two contributions have widened the scope of NHC-generated homoenolates. Glorius et al. had previ-



**Scheme 10.** NHC-catalyzed azadiene Diels–Alder reactions.

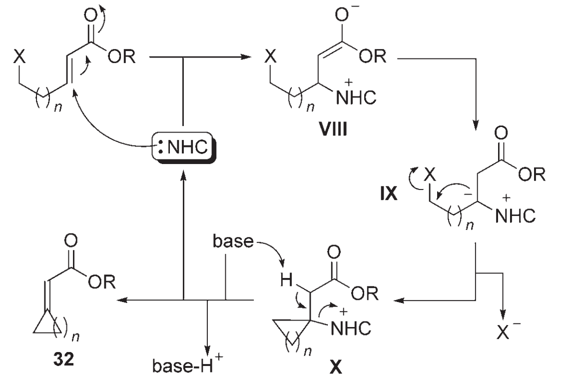
ously described that ketones failed to participate in the cyclization process leading to lactones, with the exception of α,α,α-trifluoroacetophenone.[40] Nair et al. then envisaged the possible participation of an activated carbonyl such as a vicinal dione and showed that imidazole carbenes catalyze the spiro-annulation of 1,2-cyclohexanedione with a wide array of cinnamaldehydes.[48] Although the reaction is limited to 1,2-cyclohexanedione and substituted cinnamaldehydes, this is one of the few[49] straightforward routes to spiro γ-butyrolactone **25** (Scheme 9).

Subsequently, Nair and co-workers reported the use of activated α,β-unsaturated ketones.[50] Their first intention was to involve an activated C=C bond present in the homoenolate acceptor to ultimately produce highly substituted acylcyclopentanones **31** (Scheme 11). Amazingly, in lieu of the expected ketones they observed the formation of trisubstituted cyclopentenes **26**. To rationalize this result, they proposed a catalytic cycle involving the formation of an NHC-stabilized enolate followed by β lactonization and decarboxylation. The higher complexity possible with this synthetic method was highlighted by the reaction of thienylidene tetralone, which produced cyclopentene **26d** which has the double bond adjacent to the point of ring fusion. The latter example bodes well for the future of NHC-catalyzed reactions in total syntheses of biologically active compounds.[51]

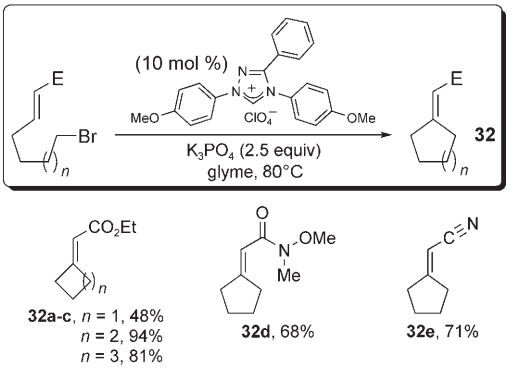


**Scheme 11.** NHC-catalyzed synthesis of cyclopentenes from enals and enones.

In addition to α,β-unsaturated aldehydes, Fu et al. recently reported that α,β-unsaturated esters could be suitable precursors for the generation of homoenolates.[52] In this case, the mechanism for the umpolung of the β carbon of the esters was proposed to proceed through addition of the carbene at the position β to the unsaturated ester (Scheme 12, **VIII**). Base-catalyzed tautomerization, which is supported by deuterium-scrambling experiments, would result in a formal negative charge at the β position, affording the umpoled intermediate **IX**. Intramolecular ring-closing followed by base-promoted β elimination would then produce cyclized α,β-unsaturated esters **32** and regenerate the NHC. The scope of the reaction, which is efficient with chloride, bromide, or tosylate as leaving group, is shown in Scheme 13. During optimization studies, the authors observed that the reaction could be performed with triazolium salts but not with their imidazolium or thiazolium counterparts. It is noteworthy that the use of phosphines proved inefficient, in sharp contrast to their ability to catalyze the intramolecular alkylation of unsaturated ketones (although at the α position).[53]



**Scheme 12.** Proposed mechanism for the NHC-catalyzed intramolecular β alkylation of α,β-unsaturated esters.

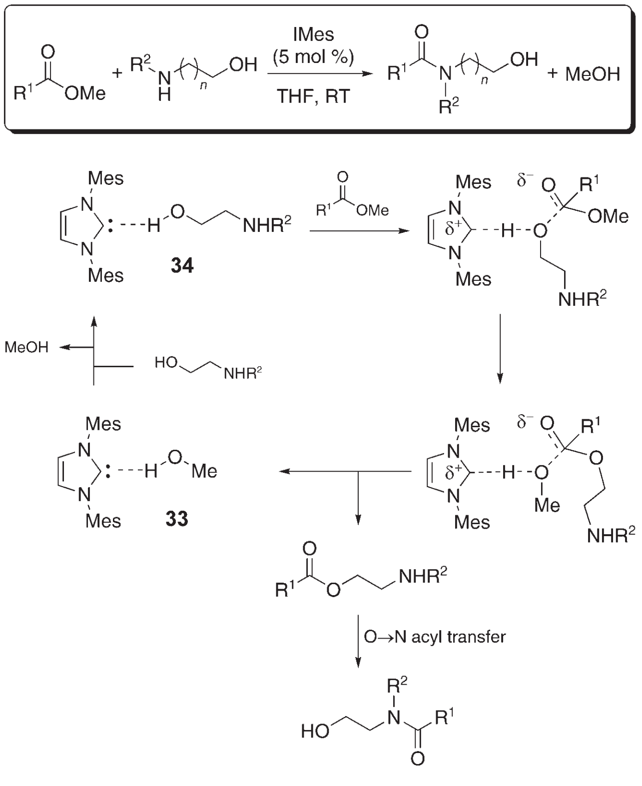


***Scheme 13.*** NHC-catalyzed intramolecular β alkylation of Michael acceptors. E = electron-withdrawing group.

## 2. Transesterification and Acylation Reactions

In 2002, the research groups led by Nolan[54] and Hedrick[55] simultaneously reported efficient protocols for NHC-catalyzed transesterification reactions.[56] Functional-group tolerance, selectivity, and low catalyst loading are the advantages of this approach.[57] Soon, the scope of the reaction was extended to secondary alcohols[58] and phosphorus esters.[59] It is noteworthy that the high efficiency of NHCs as transesterification catalysts, along with their relative nontoxicity, led to their use in the polymerization of cyclic ester monomers (see Section 3.1 for further discussion).

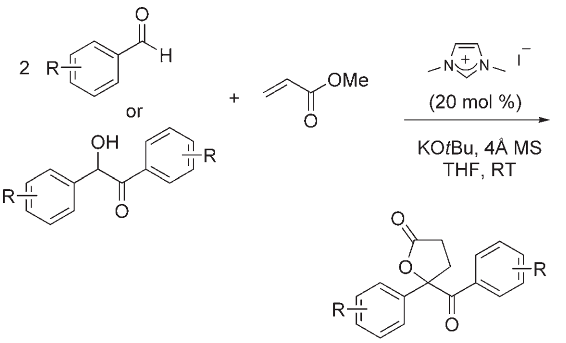
A related transformation, the amidation of unactivated esters by amino alcohols, has been reported to proceed smoothly in the presence of free IMes (Scheme 14).[60]



***Scheme 14.*** Amidation of esters with amino alcohols.

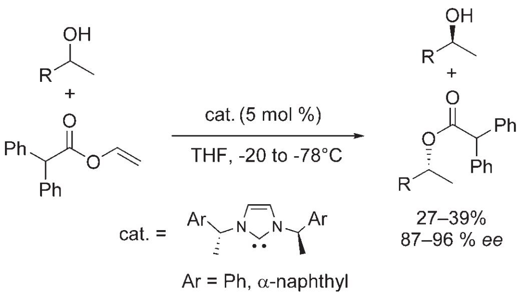
Interestingly, in preliminary mechanistic investigations the authors isolated and characterized for the first time hydrogen-bonded carbene–alcohol complexes **33** and **34**. After the initial transesterification, a rapid O→N acyl-transfer reaction would lead to the expected amide. This novel mode of catalysis, also supported by theoretical calculations,[61] opens new possibilities for NHCs in organocatalysis.

NHCs also promoted the reaction of benzoins or benzaldehydes with acrylates to yield γ-butyrolactones.[62] In this tandem reaction, it remains unclear whether the reaction product arises from a transesterification followed by a Michael addition or from a tandem Michael addition/lactonization [Eq. (2)].



(2)

Suzuki and co-workers extended these methods to the kinetic resolution of racemic alcohols using chiral NHCs, albeit with low selectivities.[63] Maruoka et al. later showed, with similar ligands, that the use of hindered acylating agents is crucial to reach good selectivity [Eq. (3)].[64]



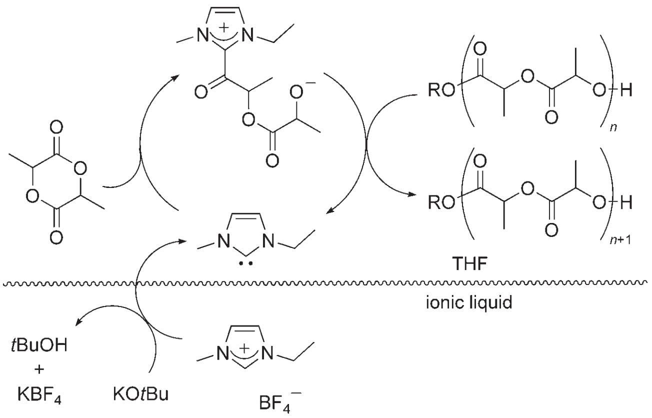
(3)

## 3. Ring-Opening Reactions

### 3.1. Ring-Opening Polymerization

Ring-opening polymerization (ROP) of cyclic esters is a particularly convenient method for the synthesis of polyesters. These versatile polymers are widely used as fibers, plastics, and coatings and, more recently, as biodegradable surgical sutures and in compounding medicines for the controlled release of drugs.[65] Their applications as biomaterials raised concerns about the removal of contaminant metal bound to the chain end.

Metal-free approaches to polyesters based on tertiary amines or phosphines[66] were followed by the use of N-heterocyclic carbenes as catalysts for the polymerization of lactides and lactones.[67] In the presence of an alcohol as initiator and an NHC as catalyst, copolymers, macromonomers, and functional oligomers were obtained as narrowly dispersed products.[68] Whereas steric hindrance lowered the carbene activity towards ROP, it was mandatory in order to attain stereoselective polymerizations.[69] In addition, ionic liquids can act as phase-segregated precatalysts allowing for fast and repetitive polymerizations (Scheme 15). The authors proposed an NHC activation of the monomer similar to the benzoin condensation, followed by addition of an alcohol to form a ring-opened adduct from which polymerization continues, releasing the carbene. However, a "catalytic anionic" reaction[70] cannot be completely ruled out as a possible propagation route.



**Scheme 15.** Biphasic NHC-catalyzed polymerization.

To avoid the presence of a strong base in the reaction mixture, active carbene catalysts can be thermally generated from silver complexes[71] or neutral haloalkane adducts[72] instead of from NHC salts. When these adducts are derived from alcohols, they play a dual role: catalyst and initiator (Figure 4).[73] While imidazolidines can deliver carbene at room temperature, alkoxytriazolines dissociate at 90 °C. The reversibility of this process has been exploited for an on-demand living polymerization of lactide: an active or dormant form of the catalyst can be formed depending on the reaction temperature.[74]

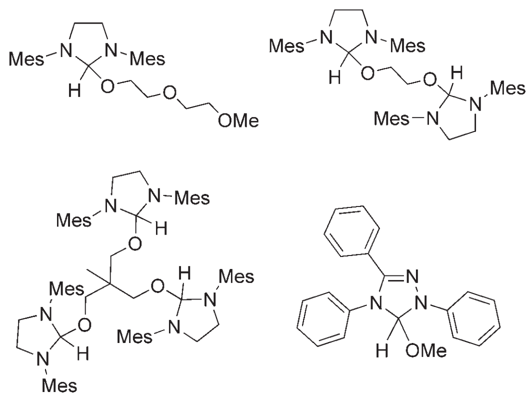
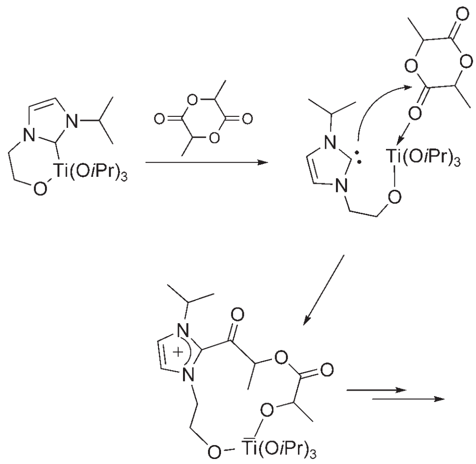


**Figure 4.** Adducts for ROP. Mes = mesityl.

Additionally, titanium and yttrium alkoxy-NHC complexes have been reported to act as bifunctional catalysts that use both Lewis acid and base functionalities to initiate ROP.[75] As shown in Scheme 16, an initiating nucleophilic attack on the metal-coordinated monomer by the labilized carbene would be followed by coordination insertion polymerization of the rest of the lactide monomer. In an earlier report on zinc-catalyzed polymerization, the catalytic contribution of a small amount of free carbene had already been suggested.[76]

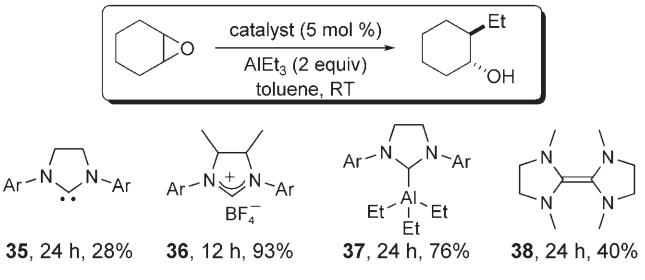


**Scheme 16.** Titanium(IV)-catalyzed polymerization.

### 3.2. Ring-Opening Reactions of Three-Membered Rings

In contrast to other electrophiles, particularly aldehydes, epoxides and aziridines have been scarcely examined in NHC-catalyzed transformations. In 2001, an early report from Nguyen et al. mentioned NHCs as promoters for the ring-opening alkylation of *meso* epoxides by trialkylaluminium complexes.[77] Interestingly, but confusingly, the authors reported that NHC **35**, imidazolium salts **36**, a well-defined NHC trialkylaluminium complex **37**, and Wanzlick-type olefins **38** catalyzed the transformation shown in Scheme 17. The role of the NHC, or of its analogues, remains unclear.

In 2006, Wu and co-workers established that NHCs are efficient catalysts for the ring-opening of aziridines by silylated nucleophiles.[78] TMS–$N_3$, TMS–I, and TMS–Cl



**35**, 24 h, 28% **36**, 12 h, 93% **37**, 24 h, 76% **38**, 24 h, 40%

**Scheme 17.** NHC-catalyzed ring opening of *meso* epoxides.

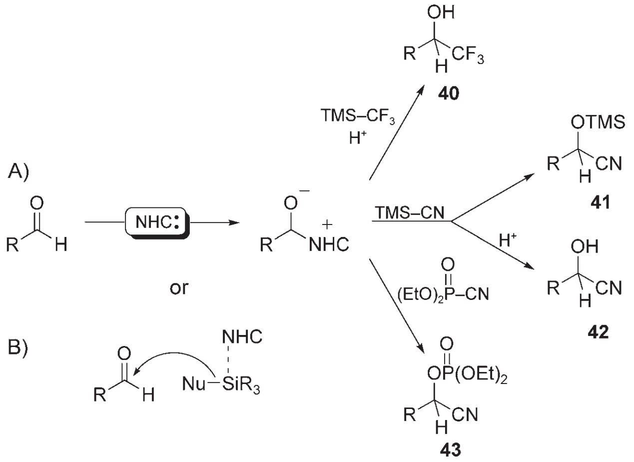
(TMS = trimethylsilyl) in the presence of IMes afforded *anti* α-chloro- and α-iodoamines in high yields. To rationalize their results, the authors proposed the formation of a pentavalent silicon species, [(IMes)SiMe$_3$X], allowing for a more facile departure of the nucleophilic X$^-$. Unfortunately, no catalytic cycle was proposed, and the regeneration of the free NHC was not mentioned.

Very recently, an unexpected reaction of aziridines and aldehydes in the presence of a carbene organocatalyst and air was reported.[79] In their attempts to produce β-aminoketone, Chen and co-workers observed the formation of **39**, the product of the formal ring-opening of the aziridine by the carboxylate of the oxidized aldehydes (Scheme 18). It was noticed that when performed under anaerobic conditions, the reaction led mainly to the benzoin condensation product. A plausible catalytic cycle proposed by Chen and co-workers is depicted in Scheme 18. After a rather classical pathway leading to **XII**, they envisaged the formation of enol ether **XIII** which would react with molecular oxygen. Then, a bimolecular process between **XIII** and **XIV** would afford alkoxide **XV** followed by formation of the carbonyl bond and release of free IMes.

The scope of the reaction was investigated, and it proved highly tolerant to a wide range of chemical functionalities. Furthermore, when monosubstituted aziridines were used, the ring-opening occurred regioselectively at the less hindered carbon.

## 4. 1,2-Addition Reactions

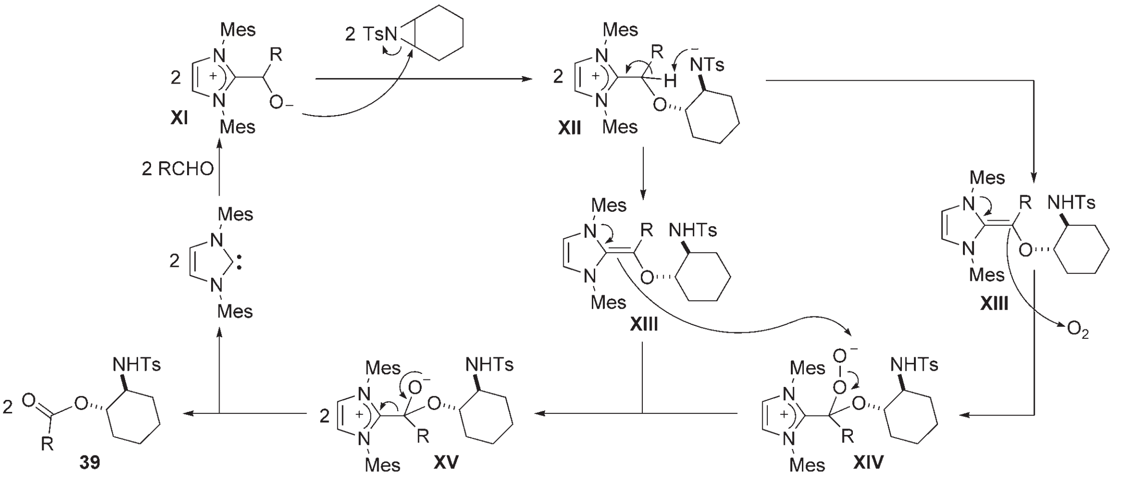
The addition of a nucleophilic carbene to an aldehyde leads to the formation of an oxo anion, which is the precursor of the azolium enol widely used in catalysis as a nucleophile for C–C bond formation (as seen above). Under proper reaction conditions one can envisage trapping this alkoxide with an electrophile and further functionalizing the azolium–ether adduct with a nucleophile (Scheme 19).



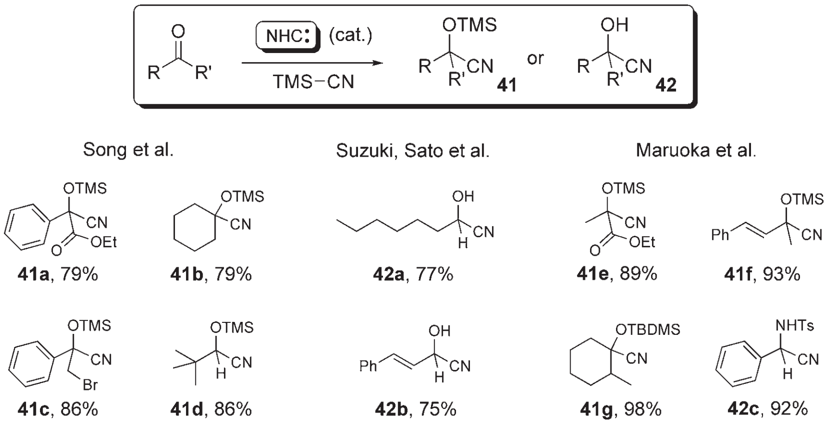
*Scheme 19.* NHC-catalyzed 1,2-addition reactions and proposed activated intermediates.

Along these lines, Song and co-workers reported the NHC-catalyzed trifluoromethylation of carbonyl compounds.[80] In their study, alcohols **40** were obtained in high yields after hydrolysis upon workup. This transformation was compatible with a wide range of functional groups and could be applied to enolizable aldehydes and to ketones in good yields. The same group then reported the closely related cyanosilylation of carbonyl compounds leading to **41** with as low as 0.01 mol% of catalyst (Scheme 20).[81] As in reports on cyanosilylation catalyzed by amine *N*-oxides,[82] it was proposed that the NHC activates TMS–CN by forming a pentavalent silicon center, therefore enhancing the nucleophilicity of the cyanide anion for addition onto the carbonyl group (Scheme 19, path B).

Subsequently, two contributions by Suzuki, Sato et al., and Maruoka et al. independently reported the use of TMS–CN as efficient E-Nu adduct for 1,2-additions to carbonyl compounds.[83] While Maruoka et al. obtained cyanohydrin silylethers **41**, the group led by Suzuki and Sato hydrolyzed the reaction product in situ to yield unprotected cyanohydrins **42** (Scheme 20). Overall, the two catalytic systems have similar efficiency; both display a wide reaction scope, including reactions with enals and enones (**41 f** and **42 b**), which are



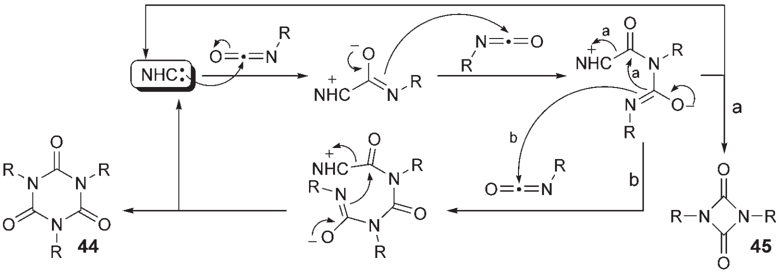
*Scheme 18.* Proposed mechanism for the formation of compounds **39**.



***Scheme 20.*** Representative scope of NHC-catalyzed cyanosilylation.

otherwise known to undergo condensation reactions. Noteworthy, Maruoka and co-workers could use hindered silyl cyanide (**41g**) and apply their methodology to α-esters (**41a** and **41e**) and imines (**42c**). On the other hand, Suzuki and Sato developed an asymmetric version of this reaction, albeit with poor selectivity (22% *ee*).

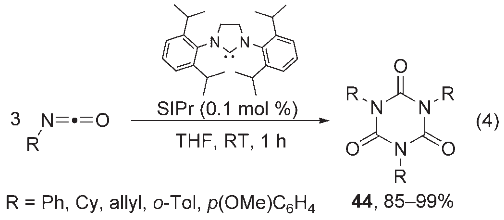
Another cyanide anion donor proved efficient under NHC catalysis. In 2006, Kondo and Aoyama reported the use of IMes for the 1,2-addition of diethyl cyanophosphonate onto aldehydes.[84] The reaction, leading to cyanohydrins phosphoryl ethers **43** (Scheme 19), typically occurred in high yields but proved incompatible with ketones.



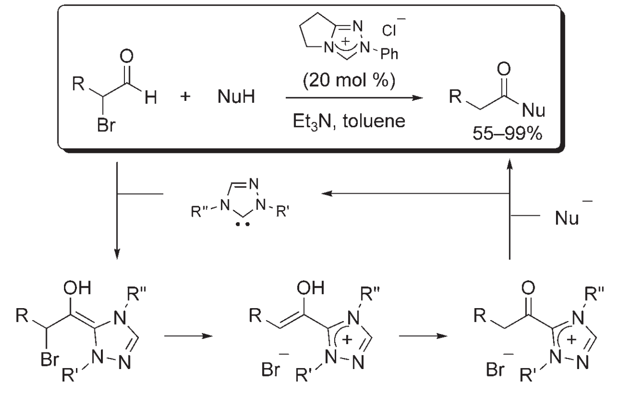
***Scheme 21.*** Proposed mechanism for the cyclodimerization and cyclotrimerization of isocyanates.

## *5. Miscellaneous Reactions*

Another type of carbonyl compound that has found application in NHC-catalyzed transformations contains the isocyanate function. Louie and co-workers reported that SIPr catalyzes the cyclotrimerization of isocyanates affording isocyanurates **44** [Eq. (4)].[85] The reaction occurred smoothly



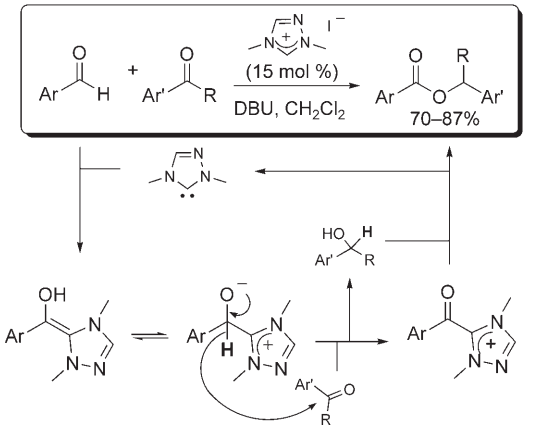
in excellent yields and was shown to be highly dependent on the nature of the NHC. Notably, in the case of cyclohexylisocyanate, IPr was inefficient and most NHCs afforded the dimer **45** as major product. Only SIPr yielded selectively the cyclotrimerized product in 95% yield. Even though the reason for such behavior is still unclear, a catalytic cycle accounting for both the formation of the dimer and of the trimer is proposed in Scheme 21.[86]



***Scheme 22.*** Internal redox reaction of α-haloaldehydes.

α-Haloaldehydes can be converted into acylating agents by an NHC-promoted internal redox reaction.[87] In this transformation, the presence of a leaving group in β position in the acyl anion equivalent is proposed to lead to an acyl azolium intermediate after tautomerization. Capture of the activated carboxylate with an appropriate nucleophile would complete the catalytic cycle (Scheme 22). Similarly, 2,2-dichloroaldehydes react with phenols in the presence of triazolinylidene carbenes to form α-chloroesters in good yield and enantioselectivity.[88] Furthermore, epoxyaldehydes[89] and formylcyclopropanes[90] can be used for the stereoselective synthesis of functionalized esters and thioesters. A somewhat related internal redox process leading to activated carboxylates has been described by Zeitler using conjugated ynals.[91] The NHC-acyl adduct was trapped by an alcohol producing α,β-unsaturated esters.

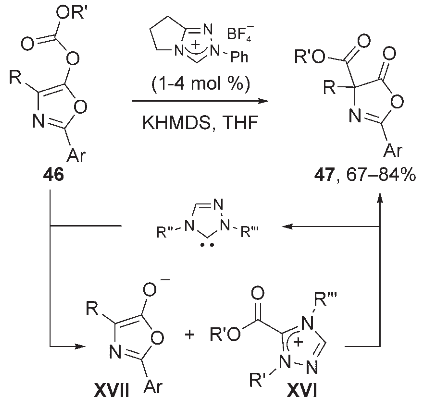
Analogous acyl azolium species have been evoked in the hydroacylation of activated ketones.[92] In this case, a hydride equivalent would be transferred to the ketone, and the resulting alcohol would undergo acylation with the acyl triazolium intermediate (Scheme 23). While this transformation proceeded smoothly at room temperature in dichloro-



*Scheme 23.* Hydroacylation of ketones.

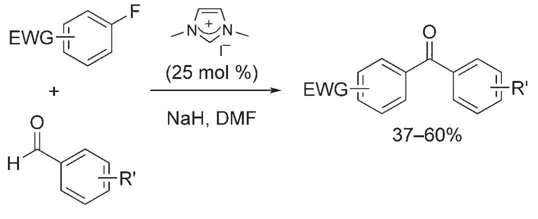
methane, the reaction could be stopped after the reduction step when a protic solvent was used.

NHCs have also been reported to promote the rearrangement of *O*-acyl carbonates **46** to their corresponding *C*-acylated isomers **47**.[93] Initial nucleophilic attack by the carbene on the carbonate would generate an acyl-transfer intermediate **XVI** as well as an enolate **XVII** (Scheme 24). Regioselective *C*-acylation of the latter would lead to the reaction product, regenerating the catalyst.



*Scheme 24.* NHC-catalyzed *O*-acyl to *C*-acyl rearrangement of carbonates. HMDS = hexamethyldisilazide.

Finally, nucleophilic benzoacylation of fluorobenzenes with electron-withdrawing groups can be achieved by the catalytic action of a carbene.[94] Even if the yields are moderate, this reaction cannot be achieved by means of a classic Friedel–Crafts reaction for example [Eq. (5); EWG = electron-withdrawing group]. Moreover, chloroarenes are inert under these reaction conditions.

 (5)

## 6. Conclusions

The use of N-heterocyclic carbenes in organocatalysis, first limited to benzoin-type reactions, has witnessed a true explosion of scope in the last few years. The ever-growing interest in NHCs leads us to believe that some of the current drawbacks (lack of other electrophiles besides aldehydes, high catalyst loading, ease of manipulation, etc.) will be solved in the very near future. Furthermore, new types of reactions (1,2-additions, opening of small rings, $O_2$ functionalization) are being developed rapidly and should point to new areas of exploration. This, in addition to enantioselective possibilities, definitely elevates the NHCs from laboratory curiosities to true, useful catalytic tools. The future is bright for applications of NHCs in organic chemistry.

*We thank the ICIQ Foundation for financial support. S.P.N. is an ICREA Research Professor. S.D.-G. thanks the Education, Research, and Universities Department of the Basque Government (Spain) for a post-doctoral fellowship. N.M. acknowledges Lilly Spain for a Student Award.*

Received: August 18, 2006
Published online: March 9, 2007

---

[1] For early references, see: a) A. Igau, H. Grutzmacher, A. Baceiredo, G. Bertrand, *J. Am. Chem. Soc.* **1988**, *110*, 6463–6466; b) A. J. Arduengo III, R. L. Harlow, M. Kline, *J. Am. Chem. Soc.* **1991**, *113*, 361–363.

[2] a) *N-Heterocyclic Carbenes in Synthesis* (Ed.: S. P. Nolan), Wiley-VCH, Weinheim, **2006**; b) *N-Heterocyclic Carbenes in Transition Metal Catalysis* (Ed.: F. Glorius), *Top. Organomet. Chem.* Vol. 28, Springer-Verlag, Berlin/Heidelberg, **2007**; c) D. Bourissou, O. Guerret, F. P. Gabbaï, G. Bertrand, *Chem. Rev.* **2000**, *100*, 39–91; d) W. A. Herrmann, *Angew. Chem.* **2002**, *114*, 1342–1363; *Angew. Chem. Int. Ed.* **2002**, *41*, 1290–1309; e) S. Díez-González, S. P. Nolan, *Coord. Chem. Rev.* **2007**, *251*, 874–883.

[3] Enders and Balensiefer have comprehensively reviewed (from the early work of Sheehan et al. in 1966) up to 2003, the asymmetric benzoin condensation, see: D. Enders, T. Balensiefer, *Acc. Chem. Res.* **2004**, *37*, 534–541.

[4] J. S. Johnson, *Angew. Chem.* **2004**, *116*, 1348–1350; *Angew. Chem. Int. Ed.* **2004**, *43*, 1326–1328.

[5] T. Ugai, S. Tanaka, S. Dokawa, *J. Pharm.* **1943**, *63*, 269–300.

[6] For recent leading references, see: a) N. J. Turner, *Curr. Opin. Biotechnol.* **2000**, *11*, 527–531; b) P. Dünkelmann, D. Kolter-Jung, A. Nitsche, A. S. Demir, P. Siegert, B. Lingen, M. Baumann, M. Pohl, M. Müller, *J. Am. Chem. Soc.* **2002**, *124*, 12084–12085; c) A. S. Demir, Ö. Sesenoglu, P. Dünkelmann, M. Müller, *Org. Lett.* **2003**, *5*, 2047–2050.

[7] a) K. Stern, J. Melnick, *J. Biol. Chem.* **1939**, *131*, 597–602; b) P. Karrer, *Bull. Soc. Chim. Fr.* **1947**, 149–153; c) K. Wiesner, Z. Valenta, *Experientia* **1956**, *12*, 192–193.

[8] R. Breslow, *J. Am. Chem. Soc.* **1958**, *80*, 3719–3726.

[9] For further mechanistic discussions (and debates), see: a) D. M. Lemal, R. A. Lovald, K. I. Kawano, *J. Am. Chem. Soc.* **1964**, *86*, 2518–2519; b) J. C. Sheehan, T. Hara, *J. Org. Chem.* **1974**, *39*,

1196–1199; c) Y. Yano, Y. Tamura, W. Tagaki, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 740–744; d) R. Breslow, E. Kool, *Tetrahedron Lett.* **1988**, *29*, 1635–1638; e) J. Castells, F. López-Calahorra, L. Domingo, *J. Org. Chem.* **1988**, *53*, 4433–4436; f) H. J. van der Berg, G. Challa, U. K. Pandit, *J. Mol. Catal.* **1989**, *51*, 1–12; g) F. Diederich, H. D. Lutter, *J. Am. Chem. Soc.* **1989**, *111*, 8438–8446; h) J. Castells, L. Domingo, F. López-Calahorra, *Tetrahedron Lett.* **1993**, *34*, 517–520; i) R. Breslow, R. Kim, *Tetrahedron Lett.* **1994**, *35*, 699–702; j) Y.-T. Chen, G. L. Barletta, K. Haghjoo, J. T. Cheng, F. Jordan, *J. Org. Chem.* **1994**, *59*, 7714–7722; k) F. López-Calahorra, R. Rubires, *Tetrahedron* **1995**, *51*, 9713–9728; l) R. Breslow, C. Schmuck, *Tetrahedron Lett.* **1996**, *37*, 8241–8242; m) M. J. White, F. J. Leeper, *J. Org. Chem.* **2001**, *66*, 5124–5131.

[10] J. Pesch, K. Harms, T. Bach, *Eur. J. Org. Chem.* **2004**, 2025–2035.

[11] Y. Hachisu, J. W. Bode, K. Suzuki, *J. Am. Chem. Soc.* **2003**, *125*, 8432–8433.

[12] a) D. Enders, O. Niemeier, T. Balensiefer, *Angew. Chem.* **2006**, *118*, 1491–1495; *Angew. Chem. Int. Ed.* **2006**, *45*, 1463–1467; b) H. Takikawa, Y. Hachisu, J. W. Bode, K. Suzuki, *Angew. Chem.* **2006**, *118*, 3572–3574; *Angew. Chem. Int. Ed.* **2006**, *45*, 3492–3494.

[13] Y. Tachibana, N. Kihara, T. Takata, *J. Am. Chem. Soc.* **2004**, *126*, 3438–3439.

[14] a) J. H. Davis, Jr., K. J. Forrester, *Tetrahedron Lett.* **1999**, *40*, 1621–1622; b) L.-W. Xu, Y. Gao, J.-J. Yin, L. Li, C.-G. Xia, *Tetrahedron Lett.* **2005**, *46*, 5317–5320.

[15] H. Stetter, M. Schreckenberg, *Angew. Chem.* **1973**, *85*, 89; *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 81.

[16] H. Stetter, H. Kuhlmann, *Org. React.* **1991**, *40*, 407–496.

[17] a) H. Stetter, H. Kuhlmann, *Chem. Ber.* **1976**, *109*, 2890–2896; b) H. Stetter, H. Kuhlmann, *Chem. Ber.* **1976**, *109*, 3426–3431.

[18] a) H. Stetter, *Angew. Chem.* **1976**, *88*, 695–704; *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 639–647; b) S. Raghavan, K. Anuradha, *Synlett* **2003**, 711–713.

[19] a) T. H. Jones, J. B. Franko, M. S. Blum, H. M. Fales, *Tetrahedron Lett.* **1980**, *21*, 789–792; b) T. El-Haji, J. C. Martin, G. J. Descotes, *J. Heterocycl. Chem.* **1983**, *20*, 233–235; c) H. Wynberg, J. Metsebar, *Synth. Commun.* **1984**, *14*, 1–9; d) D. M. Perrine, J. Kagan, D. B. Huang, K. Zeng, B. K. Theo, *J. Org. Chem.* **1987**, *52*, 2213–2216.

[20] Hirsutic acid C: B. M. Trost, C. D. Shuey, F. DiNinno, Jr., S. S. McElvain, *J. Am. Chem. Soc.* **1979**, *101*, 1284–1285; Roseophilin: a) P. E. Harrington, M. A. Tius, *Org. Lett.* **1999**, *1*, 649–651; b) P. E. Harrington, M. A. Tius, *J. Am. Chem. Soc.* **2001**, *123*, 8509–8514; *trans*-Sabinene hydrate: C. C. Galopin, *Tetrahedron Lett.* **2001**, *42*, 5589–5591.

[21] a) S. Raghavan, K. Anuradha, *Tetrahedron Lett.* **2002**, *43*, 5181–5183; b) N. Kobayashi, Y. Kaku, K. Higurashi, T. Yamauchi, A. Ishibashi, Y. Okamoto, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1747–1750; For supported catalysts see: c) C. S. Sell, L. A. Dorman, *J. Chem. Soc. Chem. Commun.* **1982**, 629–630; d) J. S. Yadav, K. Anuradha, B. V. Subba Reddy, B. Eeshwaraiah, *Tetrahedron Lett.* **2003**, *44*, 8959–8962; e) A. G. M. Barrett, A. C. Love, L. Tedeschi, *Org. Lett.* **2004**, *6*, 3377–3380.

[22] a) K. L. Pouwer, T. R. Vries, E. E. Havinga, E. W. Meijer, H. Wynberg, *J. Chem. Soc. Chem. Commun.* **1988**, 1432–1433; b) R. A. Jones, M. Karatza, T. N. Voro, P. U. Civcir, A. Franck, O. Ozturk, J. P. Seaman, A. P. Whitmore, D. J. Williamson, *Tetrahedron* **1996**, *52*, 8707–8724; c) R. A. Jones, P. U. Civeir, *Tetrahedron* **1997**, *53*, 11529–11540.

[23] R. U. Braun, K. Zeitler, T. J. J. Müller, *Org. Lett.* **2001**, *3*, 3297–3300.

[24] T. J. J. Müller, M. Ansorge, D. Aktah, *Angew. Chem.* **2000**, *112*, 1323–1326; *Angew. Chem. Int. Ed.* **2000**, *39*, 1253–1256.

[25] a) L. Knorr, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1635–1642; b) C. Paal, *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 367–371; c) V. Amarnath, D. C. Anthony, K. Amarnath, W. M. Valentine, L. A. Wetterau, D. G. Graham, *J. Org. Chem.* **1991**, *56*, 6924–6931.

[26] E. Ciganek, *Synthesis* **1995**, 1311–1314.

[27] D. Enders, K. Breuer, J. Runsink, J. H. Teles, *Helv. Chim. Acta* **1996**, *79*, 1899–1902.

[28] Highlight: M. Christmann, *Angew. Chem.* **2005**, *117*, 2688–2690; *Angew. Chem. Int. Ed.* **2005**, *44*, 2632–2634.

[29] a) M. S. Kerr, J. Read de Alaniz, T. Rovis, *J. Am. Chem. Soc.* **2002**, *124*, 10298–10299; b) M. S. Kerr, T. Rovis, *Synlett* **2003**, 1934–1936; c) J. Read de Alaniz, T. Rovis, *J. Am. Chem. Soc.* **2005**, *127*, 6284–6289.

[30] a) M. S. Kerr, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 8876–8877; b) N. T. Reynolds, T. Rovis, *Tetrahedron* **2005**, *61*, 6368–6378; c) Q. Liu, T. Rovis, *J. Am. Chem. Soc.* **2006**, *128*, 2552–2553; d) J. L. Moore, M. S. Kerr, T. Rovis, *Tetrahedron*, **2006**, *62*, 11477–11482.

[31] S. M. Mennen, J. T. Blank, M. B. Tran-Dubé, J. E. Imbriglio, S. J. Miller, *Chem. Commun.* **2005**, 195–197.

[32] J. A. Murry, D. E. Frantz, A. Soheili, R. Tillyer, E. J. J. Grabowski, P. J. Reider, *J. Am. Chem. Soc.* **2001**, *123*, 9696–9697; For the enantioselective version of this reaction see: S. M. Mennen, J. D. Gipson, Y. R. Kim, S. J. Miller, *J. Am. Chem. Soc.* **2005**, *127*, 1654–1655.

[33] A. E. Mattson, A. R. Bharadwaj, K. A. Scheidt, *J. Am. Chem. Soc.* **2004**, *126*, 2314–2315.

[34] A. E. Mattson, K. A. Scheidt, *Org. Lett.* **2004**, *6*, 4363–4366.

[35] A. G. Brook, *Acc. Chem. Res.* **1974**, *7*, 77–84.

[36] M. C. Myers, A. R. Bharadwaj, B. C. Milgram, K. A. Scheidt, *J. Am. Chem. Soc.* **2005**, *127*, 14675–14680.

[37] A. R. Bharadwaj, K. A. Scheidt, *Org. Lett.* **2004**, *6*, 2465–2468.

[38] A. E. Mattson, A. R. Bharadwaj, A. M. Zuhl, K. A. Scheidt, *J. Org. Chem.* **2006**, *71*, 5715–5724.

[39] K. Zeitler, *Angew. Chem.* **2005**, *117*, 7674–7678; *Angew. Chem. Int. Ed.* **2005**, *44*, 7506–7510.

[40] C. Burstein, F. Glorius, *Angew. Chem.* **2004**, *116*, 6331–6334; *Angew. Chem. Int. Ed.* **2004**, *43*, 6205–6208.

[41] S. S. Sohn, E. L. Rosen, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 14370–14371.

[42] C. Burstein, S. Tschan, X. Xie, F. Glorius, *Synthesis* **2006**, 2418–2439.

[43] M. He, J. W. Bode, *Org. Lett.* **2005**, *7*, 3131–3134.

[44] A. Chan, K. A. Scheidt, *Org. Lett.* **2005**, *7*, 905–908.

[45] S. S. Sohn, J. W. Bode, *Org. Lett.* **2005**, *7*, 3873–3876.

[46] M. He, J. R. Strubble, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 8418–8420.

[47] For a discussion on the reactivity of related aldehydes in the presence of NHC, see Section 5 “Miscellaneous reactions”.

[48] V. Nair, S. Vellalath, M. Poonoth, R. Mohan, E. Suresh, *Org. Lett.* **2006**, *8*, 507–509.

[49] For representative references, see: a) A. Orduna, L. G. Zepeda, J. Tamariz, *Synthesis* **1993**, 375–377; b) I. Collins, *J. Chem. Soc. Perkin Trans. 1* **1998**, 1869–1888; c) I. Collins, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1377–1395.

[50] V. Nair, S. Vellalath, M. Poonoth, E. Suresh, *J. Am. Chem. Soc.* **2006**, *128*, 8736–8737.

[51] An interesting use of triazolium and thiazolium salts for the homocondensation of aldehydes derived from amino-acids has been reported, see: E. Dietrich, W. D. Lubell, *J. Org. Chem.* **2003**, *68*, 6988–6996.

[52] C. Fisher, S. W. Smith, D. A. Powell, G. C. Fu, *J. Am. Chem. Soc.* **2006**, *128*, 1472–1473.

[53] a) M. E. Krafft, T. F. N. Haxell, *J. Am. Chem. Soc.* **2005**, *127*, 10168–10169; b) M. E. Krafft, K. A. Seibert, T. F. N. Haxell, *Chem. Commun.* **2005**, 5772–5774.

[54] G. A. Grasa, R. M. Kissling, S. P. Nolan, *Org. Lett.* **2002**, *4*, 3583–3586.

[55] G. W. Nyce, J. A. Lamboy, E. F. Connor, R. M. Waymouth, J. L. Hedrick, *Org. Lett.* **2002**, *4*, 3587 – 3590.
[56] G. A. Grasa, R. Singh, S. P. Nolan, *Synthesis* **2004**, 971 – 985.
[57] G. A. Grasa, T. Güveli, R. Singh, S. P. Nolan, *J. Org. Chem.* **2003**, *68*, 2812 – 2818.
[58] R. Singh, R. M. Kissling, M.-A. Letellier, S. P. Nolan, *J. Org. Chem.* **2004**, *69*, 209 – 212.
[59] R. Singh, S. P. Nolan, *Chem. Commun.* **2005**, 5456 – 5458.
[60] M. Movassaghi, M. A. Schmidt, *Org. Lett.* **2005**, *7*, 2453 – 2456.
[61] C.-L. Lai, H. M. Lee, C.-H. Hu, *Tetrahedron Lett.* **2005**, *46*, 6265 – 6270.
[62] W. Ye, G. Cai, Z. Zhuang, X. Jia, H. Zhai, *Org. Lett.* **2005**, *7*, 3769 – 3771.
[63] a) Y. Suzuki, K. Yamauchi, K. Muramatsu, M. Sato, *Chem. Commun.* **2004**, 2770 – 2771; b) Y. Suzuki, K. Muramatsu, K. Yamauchi, Y. Morie, M. Sato, *Tetrahedron* **2006**, *62*, 302 – 310.
[64] T. Kano, K. Sasaki, K. Maruoka, *Org. Lett.* **2005**, *7*, 1347 – 1349.
[65] K. E. Ulrich, S. M. Cannizzaro, R. S. Langer, K. M. Shakesheff, *Chem. Rev.* **1999**, *99*, 3181 – 3198.
[66] a) F. Nederberg, E. F. Connor, M. Moller, T. Glauser, J. L. Hedrick, *Angew. Chem.* **2001**, *113*, 685 – 687; *Angew. Chem. Int. Ed.* **2001**, *40*, 2712 – 2715; b) M. Myers, E. Connor, G. Nyce, T. Glauser, A. Möck, J. L. Hedrick, *J. Polym. Sci. Part A* **2002**, *40*, 844 – 851.
[67] a) E. F. Connor, G. W. Nyce, M. Myers, A. Möck, J. L. Hedrick, *J. Am. Chem. Soc.* **2002**, *124*, 914 – 915; b) G. W. Nyce, T. Glauser, E. F. Connor, A. Möck, R. M. Waymouth, J. L. Hedrick, *J. Am. Chem. Soc.* **2003**, *125*, 3046 – 3056.
[68] Acyclic homologues of NHC have also been reported as polymerization catalyst: S. Csihony, T. T. Beaudette, A. C. Sentma, G. W. Nyce, R. M. Waymouth, J. L. Hedrick, *Adv. Synth. Catal.* **2004**, *346*, 1081 – 1086.
[69] A. P. Dove, H. Li, R. C. Pratt, B. G. G. Lohmeijer, D. A. Culkin, R. M. Waymouth, J. L. Hedrick, *Chem. Commun.* **2006**, 2881 – 2883.
[70] R. W. Alder, P. R. Allen, S. J. Williams, *J. Chem. Soc. Chem. Commun.* **1995**, 1267 – 1268.
[71] A. C. Sentman, S. Csihony, R. M. Waymouth, J. L. Hedrick, *J. Org. Chem.* **2005**, *70*, 2391 – 2393.
[72] G. W. Nyce, S. Csihony, R. M. Waymouth, J. L. Hedrick, *Chem. Eur. J.* **2004**, *10*, 4073 – 4079.
[73] S. Csihony, D. A. Culkin, A. C. Sentman, A. P. Dove, R. M. Waymouth, J. L. Hedrick, *J. Am. Chem. Soc.* **2005**, *127*, 9079 – 9084.
[74] a) O. Coulembier, A. P. Dove, R. C. Pratt, A. C. Sentman, D. A. Culkin, L. Mespouille, P. Dubois, R. M. Waymouth, J. L. Hedrick, *Angew. Chem.* **2005**, *117*, 5044 – 5048; *Angew. Chem. Int. Ed.* **2005**, *44*, 4964 – 4968; b) O. Coulembier, L. Mespouille, J. L. Hedrick, R. M. Waymouth, P. Dubois, *Macromolecules* **2006**, *39*, 4001 – 4008.
[75] D. Patel, S. T. Liddle, S. A. Mungur, M. Rodden, A. J. Blake, P. L. Arnold, *Chem. Commun.* **2006**, 1124 – 1126.
[76] T. R. Jensen, L. E. Breyfogle, M. A. Hillmyer, W. B. Tolman, *Chem. Commun.* **2004**, 2504 – 2505.
[77] H. Zhou, E. J. Campbell, S. T. Nguyen, *Org. Lett.* **2001**, *3*, 2229 – 2231.
[78] J. Wu, X. Sun, S. Ye, W. Sun, *Tetrahedron Lett.* **2006**, *47*, 4813 – 4816.
[79] Y.-K. Liu, R. Li, L. Yue, B.-J. Li, Y.-C. Chen, Y. Wu, L.-S. Ding, *Org. Lett.* **2006**, *8*, 1521 – 1524.
[80] J. J. Song, Z. Tan, J. T. Reeves, F. Gallou, N. K. Yee, C. H. Senanayake, *Org. Lett.* **2005**, *7*, 2193 – 2196.
[81] J. J. Song, F. Gallou, J. T. Reeves, Z. Tan, N. K. Yee, C. H. Senanayake, *J. Org. Chem.* **2006**, *71*, 1273 – 1276.
[82] S. S. Kim, G. Rajagopal, D. W. Kim, D. H. Song, *Synth. Commun.* **2004**, *34*, 2973 – 2980.
[83] a) Y. Suzuki, M. D. Abu Bakar, K. Muramatsu, M. Sato, *Tetrahedron* **2006**, *62*, 4227 – 4231; b) T. Kano, K. Sasaki, T. Konishi, H. Mii, K. Maruoka, *Tetrahedron Lett.* **2006**, *47*, 4615 – 4618.
[84] Y. Fukuda, Y. Maeda, K. Kondo, T. Aoyama, *Chem. Pharm. Bull.* **2006**, *54*, 397 – 398.
[85] H. A. Duong, M. J. Cross, J. Louie, *Org. Lett.* **2004**, *6*, 4679 – 4681.
[86] This catalytic cycle is proposed in consultation with Prof. Janis Louie to whom we are particularly grateful for useful discussions.
[87] N. T. Reynolds, J. Read de Alaniz, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 9518 – 9519.
[88] N. T. Reynolds, T. Rovis, *J. Am. Chem. Soc.* **2005**, *127*, 16406 – 16407.
[89] K. Y.-K. Chow, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 8126 – 8127.
[90] S. S. Sohn, J. W. Bode, *Angew. Chem.* **2006**, *118*, 6167 – 6170; *Angew. Chem. Int. Ed.* **2006**, *45*, 6021 – 6024.
[91] K. Zeitler, *Org. Lett.* **2006**, *8*, 637 – 640.
[92] A. Chan, K. A. Scheidt, *J. Am. Chem. Soc.* **2006**, *128*, 4932 – 4933.
[93] J. E. Thomson, K. Rix, A. D. Smith, *Org. Lett.* **2006**, *8*, 3785 – 3788.
[94] Y. Suzuki, T. Toyota, F. Imada, M. Sato, A. Miyashita, *Chem. Commun.* **2003**, 1314 – 1316.