CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201204428

Mechanistic Insight into the Staudinger Reaction Catalyzed by N-Heterocyclic Carbenes

Morgan Hans,[a] Johan Wouters,[b] Albert Demonceau,[a] and Lionel Delaude*[a]

Abstract: Four zwitterions were prepared by treating 1,3-dimesitylimidazolin-2-ylidene (SIMes) or 1,3-dimesitylimidazol-2-ylidene (IMes) with either *N*-tosyl benzaldimine or diphenylketene. They were isolated in high yields and characterized by IR and NMR spectroscopy. The molecular structures of three of them were determined by using X-ray crystallography and their thermal stability was monitored by using thermogravimetric analysis. The imidazol(in)ium-2-amides were rather labile white solids that did not show any tendency to tautomerize into the corresponding 1,2,2-triaminoethene derivatives. They displayed a mediocre catalytic activity in the Staudinger reaction of *N*-tosyl benzaldimine with diphenylketene. In contrast, the imidazol(in)ium-2-enolates were orange-red crystalline materials that remained stable over extended periods of time. Despite their greater stability, these zwitterions turned out to be efficient promoters for the model cycloaddition under scrutiny. As a matter of fact, their catalytic activity matched those recorded with the free carbenes. Altogether, these results provide strong experimental insight into the mechanism of the Staudinger reaction catalyzed by N-heterocyclic carbenes. They also highlight the superior catalytic activity of the imidazole-based carbene IMes compared with its saturated analogue SIMes in the reaction under consideration.

Keywords: carbenes · lactams · organocatalysis · reaction mechanisms · zwitterions

Introduction

Over the past two decades, stable N-heterocyclic carbenes (NHCs) have become ubiquitous ligands in organometallic chemistry and in homogeneous catalysis.[1] They have also emerged as powerful nucleophilic organocatalysts for polymer chemistry[2] and organic synthesis.[3] Initial research in this field focused on their ability to invert the polarity of a carbonyl group, thereby allowing the formation of acyl anions from aldehydes through an "umpolung" process.[4] Historically, the benzoin condensation and the Stetter reaction were the first chemical transformations that took advantage of this mode of activation,[5] but recent years have seen the development of an impressive range of enantioselective enolate and homoenolate coupling reactions based on chiral NHCs.[6] Stable carbenes or their immediate precursors were also successfully used to catalyze Michael addition, oxidation, or transesterification reactions, to name just a few.[7]

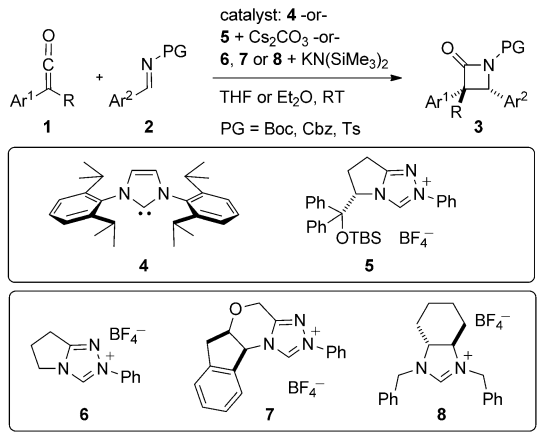
First reported by Staudinger in 1907,[8] the [2+2] cycloaddition of ketenes with imines to give β-lactams is a versatile and efficient synthetic route to access an important class of nitrogen heterocycles with outstanding biological and pharmaceutical activities.[9] Although this reaction was discovered more than a century ago and has been extensively studied ever since,[10] intimate details of its mechanism are still heavily debated, especially those concerning the regio- and the stereoselectivity of the transformation.[11]

In 2008, the groups of Ye[12] and Smith[13] reported almost simultaneously the asymmetric synthesis of β-lactams by using chiral NHC catalysts generated in situ by deprotonation of imidazol(in)ium or triazolium salts (Scheme 1). Ye et al. first carried out preliminary tests using the achiral 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene carbene **4** before employing the (*R*)-pyroglutamic acid-derived precatalyst **5** to perform the cycloaddition of unsymmetrical alkylarylketenes **1** and N-protected aldimines **2** with excellent enantio- and diastereoselectivities.[12] Smith and co-workers devised a similar strategy starting from diphenylketene or isobutylphenylketene and *N*-tosyl aldimines, with either triazolium **7** or imidazolinium salt **8** being the optimal precatalysts for obtaining β-lactams **3** in high enantiomeric excesses.[13] More recently, Feroci and Inesi et al. reported an electrochemical process for the Staudinger reaction of an acyl chloride **9** and a non-electrophilic *N*-aryl aldimine **10** in 1-butyl-3-methylimidazolium tetrafluoroborate (BMIM-BF_4).[14] The ionic liquid acted both as a solvent and a cata-

[a] M. Hans, Prof. A. Demonceau, Prof. L. Delaude
Laboratory of Organometallic Chemistry
and Homogeneous Catalysis
Institut de chimie (B6a), Université de Liège
Sart-Tilman par 4000 Liège (Belgium)
Fax: (+32) 4-366-3497
E-mail: l.delaude@ulg.ac.be

[b] Prof. J. Wouters
Department of Chemistry
Facultés Universitaires N.-D. de la Paix,
61 Rue de Bruxelles, 5000 Namur (Belgium)

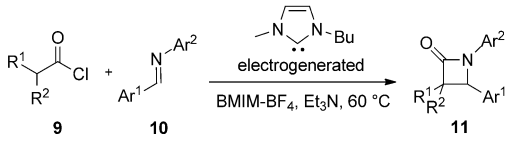
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201204428.



Scheme 1. NHC-based catalytic systems investigated by the groups of Ye (top frame) and Smith (bottom frame) for the synthesis of β-lactams. Protecting group (PG) = *tert*-butoxycarbonyl (Boc), carbobenzyloxy (Cbz), tosyl (Ts).

lyst precursor to afford the electrogenerated NHC active species that catalyzed the formation of racemic, predominantly *trans* β-lactams **11** (Scheme 2).

Two possible mechanisms were proposed to account for the catalytic activity of NHCs in Staudinger reactions



Scheme 2. Synthesis of β-lactams using an electrogenerated NHC in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate (BMIM-BF_4).

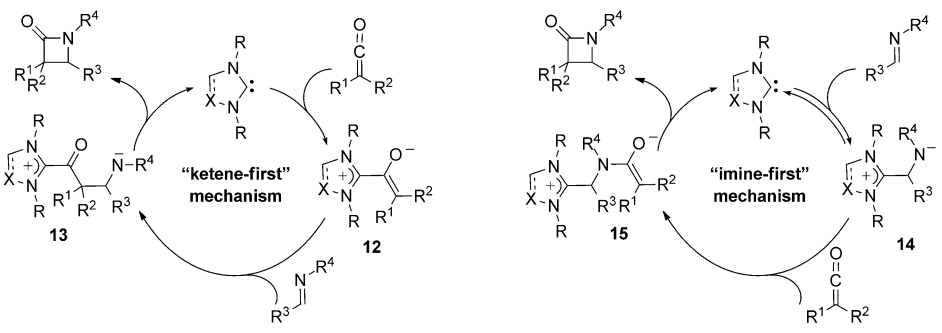
(Scheme 3).[12,15] In the "ketene-first" approach, the nucleophilic carbene initially attacks the ketene to generate a zwitterionic azolium enolate **12**, which further reacts with the imine in a Mannich-like reaction to form intermediate **13**, whose cyclization affords the final product and closes the catalytic cycle. Alternatively, in the "imine-first" mechanism the two reactants are added in reverse order: the imine is first activated by the catalyst, leading to the formation of azolium amide **14**. This intermediate zwitterion then attacks the ketene to form enolate **15**, whose cyclization releases the final product and regenerates the catalyst.

Experiments carried out by Smith et al. showed that the addition of diphenylketene to a catalyst generated in situ from triazolium salt **6** and potassium bis(trimethylsilyl)-amide, followed by *N*-tosyl benzaldimine led to the corresponding β-lactam in high yield, whereas the reverse addition order did not result in any conversion even after 5 days, thereby supporting the "ketene-first" mechanism.[13] However, when Ye and co-workers used 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene **4** as a catalyst, they were able to isolate a zwitterion of type **14** rather than **12**, which further reacted with phenylethylketene to give a β-lactam.[12] In line with earlier NMR studies from He and Bode,[16] the Chinese team noted that the formation of betaine **14** was reversible[17] and that the cyclization of intermediate **15** was disfavored according to Baldwin's rules.[18] Nevertheless, their experimental data did not rule out entirely the possibility of an "imine-first" mechanism. Theoretical calculations performed by Liu et al., on the other hand, strongly suggested that the NHC-catalyzed Staudinger reaction proceeded exclusively through the "ketene-first" pathway and helped understand the stereoselectivities observed for some of the experimental systems investigated previously.[19]

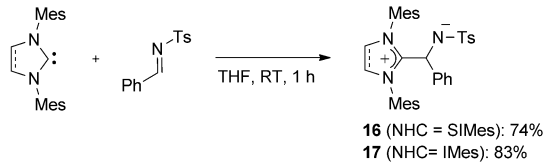
In light of our sustained interest for the betaines of NHCs,[20] we decided to thoroughly investigate the intermediacy of NHC•imine or NHC•ketene zwitterions in the Staudinger reaction. We reasoned that isolating and fully characterizing both types of adducts would provide valuable information about their physico-chemical properties and ease their differentiation in mechanistic studies. In this contribution, we disclose the synthesis of four representative imidazol(in)ium amide or enolate inner salts and we probe their catalytic activity in the [2+2] cycloaddition of diphenylketene and *N*-tosyl benzaldimine.

Results and Discussion

Synthesis of NHC•imine zwitterions: In a first series of experiments, *N*-tosyl benzaldimine was treated with two of the most common NHCs investigated so far, namely 1,3-dimesitylimidazolin-2-ylidene (nicknamed SIMes) and its imidazole-based cousin IMes (Scheme 4). These two carbenes were generated in situ by deprotonation of the corresponding imidazol(in)ium salts with potassium bis(trimethylsilyl)-amide in THF. After filtration of the inorganic byproducts, a solution of the protected aldimine in THF was added and white precipitates appeared within a few minutes. After 1 h,



Scheme 3. Possible mechanisms for the Staudinger reaction catalyzed by N-heterocyclic carbenes.



Scheme 4. Synthesis of imidazol(in)ium-2-amides **16** and **17**.

they were filtered, rinsed with diethyl ether, and dried under high vacuum to afford imidazol(in)ium-2-amides **16** and **17** isolated in 74 and 83% yields, respectively. Although both zwitterions were better kept under an inert atmosphere, compound **17** showed a higher resistance to air and moisture than **16** in the solid state. Moreover, solutions of **17** in CD_2Cl_2 remained stable overnight, whereas a rapid decomposition occurred in the case of betaine **16**. In some instances, the latter salt precipitated as a THF solvate. When this happened, heating under vacuum and washing with diethyl ether allowed to release the solvent and to obtain the pure NHC·imine compound.

^{1}H NMR analysis confirmed the formation of 1:1 stoichiometric adducts between the two nucleophilic carbenes and the *N*-tosyl imine. The characteristic highly deshielded formamidinium and aldimine protons of the starting materials located between $\delta = 8.5$ and 10 ppm were missing. They were replaced by a diagnostic singlet at about $\delta = 5.5$ ppm assigned to the Ph–CH–NTs methine unit linked to the azolium moiety. This signal was clearly separated from the various other aromatic and aliphatic resonances due to the tosyl, phenyl, and mesityl groups. It is noteworthy that the *ortho*-methyl substituents on the mesityl rings resonated as two singlets integrated for 6H each and that the ethylene backbone of the central heterocycle in **16** appeared as a second-order multiplet. These observations reveal a lack of symmetry and the absence of free rotation on the NMR timescale for the three exocyclic substituents connected to the central imidazol(in)ium core.

Crystals of 1,3-dimesitylimidazolinium-*N*-benzyl-*N*-tosylamide **16** suitable for X-ray diffraction analysis were obtained by slow diffusion of *n*-pentane into a dichloromethane solution kept at −18 °C. Examination of their molecular structure showed that the tosyl and phenyl groups were almost perpendicular (torsion angle 87.9(3)°), whereas they are assumed to be *trans* to each other in the starting imine (Figure 1). Within the heterocyclic ring, the C1–N1 and C1–N2 distances were almost identical and close to 1.32 Å. This indicates a significant C=N double bond character, which can be easily rationalized by assuming equal contributions of the $^+$N1–C2=N2 and N1=C1–N2$^+$ canonical forms, as previously observed in the betaines formed between SIMes and either CO_2,[21] COS,[22] or CS_2.[23] Contrastingly, the C6–N3 distance of 1.448(5) Å is much closer to a typical single C–N bond (1.47 Å) than to a C=N double bond (1.34 Å),[24] in line with the transformation of the aldimine starting material into a non-delocalized amide anion. For obvious steric reasons, this C–N bond is twisted relative to the imidazolinium plane and forms a N1–C1–C6–N3 dihedral angle of 110.6(3)°.

Another important piece of information derived from the crystal structure of compound **16** is that the C1–C6 bond length of 1.518(5) Å corresponds to a C–C single bond.[24] This result nicely corroborates ^{1}H and ^{13}C NMR analyses that showed the presence of a strongly deshielded aliphatic CH group within the structures of adducts **16** and **17** (Scheme 5). Altogether, these data support the formulation of both products as imidazol(in)ium-2-amide zwitterions in the solid state and in solution. This observation is not trivial, because when Berkessel and co-workers added benzaldehyde to SIMes, the sole product that they unambiguously identified by using NMR spectroscopy was the neutral 2,2-diamino enol **18** and not the tautomeric imidazolinium-2-

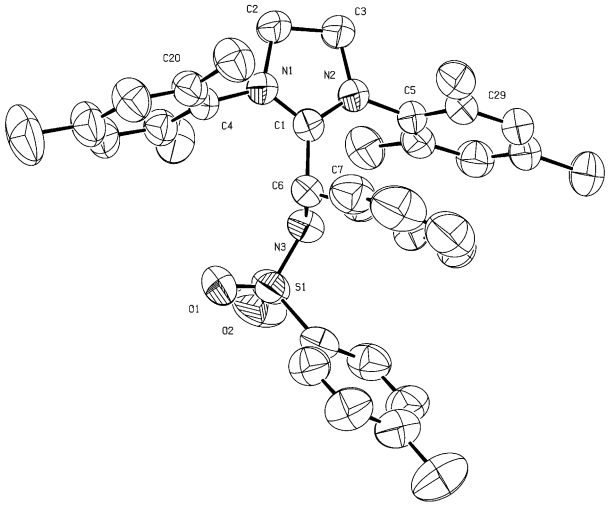
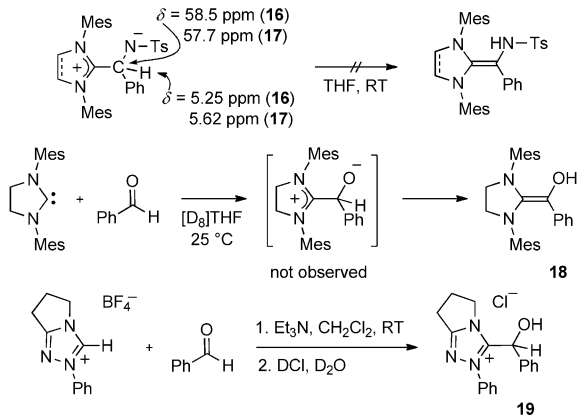


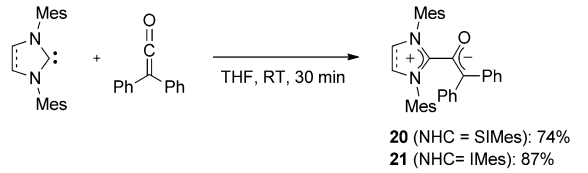
Figure 1. ORTEP diagram of imidazolinium-2-amide **16** with thermal ellipsoids drawn at 50% probability. Co-crystallized CH_2Cl_2 and H atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: C1–N1 1.324(4), C1–N2 1.322(2), C1–C6 1.518(5), C6–N3 1.448(5); N1-C1-N2 110.4(3), C1-N1-C4-C20 103.7(4), C1-N2-C5-C29 −98.8(4), N1-C1-C6-N3 110.6(3).



Scheme 5. Possible tautomers formed upon addition of aldehydes or aldimines to NHCs.

alkoxy zwitterion.[25] This difference of reactivity can be explained by a better stabilization of the negative charge by the tosylamide anion compared with an alkoxy species. On the other hand, Smith et al. recently disclosed that the addition of a range of 4-substituted benzaldehydes to an in situ-generated triazolylidene carbene afforded the corresponding 3-(hydroxybenzyl)azolium products.[26] Although the yields were very low, crystallization from DCl/D_2O allowed them to unambiguously determine the structure of chloride salt **19** and its *p*-methylbenzyl or *p*-fluorobenzyl analogues by using X-ray diffraction analysis. This difference of behavior is probably linked to the much greater acidity of triazolium salts[27] compared with their imidazol(in)ium counterparts,[28] but further investigations are needed to clarify this point.

Synthesis of NHC·ketene zwitterions: In a second series of experiments, we have prepared two representative NHC·ketene betaines by treating diphenylketene with either SIMes or IMes in 1:1 molar proportions (Scheme 6). Once again, the free carbenes were generated in situ by deprotonating imidazol(in)ium salt precursors with potassium bis(trimethylsilyl)amide in THF under an inert atmosphere. Due to its strong tendency to polymerize, the ketene was also synthesized immediately prior to use following a well-established procedure.[29] Thus, diphenylacetyl chloride was treated with triethylamine in THF. The resulting bright-yellow suspension was stirred for 30 min at room temperature. It was then filtered through Celite and added to the pale-yellow carbene solution. An intense red color appeared within a few minutes, indicative of the formation of imidazol(in)ium-2-ethenolate zwitterions. After work up, compounds **20** and **21** were isolated as bright-orange microcrystalline powders in high yields. They were stable enough to be brought back to air. The imidazolium inner salt **21** could be kept for more than a year in a closed vial at room temperature without any degradation, whereas its imidazolinium counterpart **20** had a much shorter shelf-life under the same conditions. To the best of our knowledge, the only report on the synthesis of NHC·ketene zwitterions prior to this work dates back to 1970 when Regitz et al. succinctly described the cleavage of two enetetramines with diphenylketene to afford the corresponding betaines.[30]



20 (NHC = SIMes): 74%
21 (NHC= IMes): 87%

Scheme 6. Synthesis of imidazol(in)ium-2-enolates **20** and **21**.

Various analytical techniques confirmed the identity and the purity of zwitterions **20** and **21**. On ^1H NMR spectroscopy, the disappearance of the strongly deshielded imidazol(in)ium proton located at $\delta = 9.5$ ppm for SIMes·HCl or $\delta = 8.8$ ppm for IMes·HBF_4 and the appearance of new aromatic signals, which integrated for 10 hydrogen atoms, supported the formation of a 1:1 adduct between an NHC and diphenylketene. As observed for compounds **16** and **17**, the *ortho*-methyl substituents on the mesityl groups resonated as two singlets integrated for 6H each in products **20** and **21**. Likewise, the four imidazoline protons of SIMes or the two imidazole protons of IMes located at about $\delta = 4$ or 7 ppm, respectively, became non-equivalent and gave rise to a second-order multiplet in **20** or a doublet in **21**. These data indicate a loss of symmetry within the imidazol(in)ium moiety when it is associated to the ethenolate fragment.

The ^{13}C NMR spectrum of betaine **20** featured a strongly deshielded signal for the central carbon atom of the ethenolate group ($\delta = 171.4$ ppm), down from $\delta = 196.9$ ppm in free diphenylketene (Table 1). This signal was further lowered to $\delta = 153.9$ ppm in the imidazolium inner salt **21**, in line with the greater donor ability of IMes versus SIMes.[31] Conversely, in both adducts, the remote carbon atom of the ethenolate functional group resonated at about $\delta = 112$ ppm, whereas the original signal was found at $\delta = 57.9$ ppm in free diphenylketene. We tentatively assign this downfield shift to a greater delocalization of the $C^1{=}C^2$ electron density as it participates to the stabilization of the negative charge in the zwitterions.

Table 1. Evolution of ^{13}C NMR chemical shifts upon reaction of diphenylketene with SIMes or IMes.

Compound	δ C^1 [ppm]	δ C^2 [ppm]
$Ph_2C^2{=}C^1{=}O$	196.9[a]	57.9[a]
SIMes·$Ph_2C^2{=}C^1{=}O$ (**20**)	171.4[b]	111.9[b]
IMes·$Ph_2C^2{=}C^1{=}O$ (**21**)	153.9[b]	112.6[b]

[a] In $CDCl_3$ at 298 K. [b] In CD_2Cl_2 at 298 K.

Crystals suitable for X-ray diffraction analysis were easily obtained by dissolving compounds **20** and **21** in acetonitrile, followed by slow evaporation of the saturated solutions in an open vessel at room temperature. Both zwitterions crystallized in the same monoclinic *Cc* space group and displayed similar features. Only the molecular structure of imidazolinium derivative **20** is depicted in Figure 2 and briefly discussed here (see the Supporting Information for more details about imidazolium inner salt **21**).

Apart from different tilt angles for the mesityl groups, there was no significant deviation of geometry within the imidazolinium moiety of enolate **20** compared to the amide **16** (cf., Figure 1, see also the Supporting Information, Figure S3). For both types of adducts, the C1–C6 distances between the anionic and cationic fragments were the same (1.517(3) Å in **20**, 1.518(5) Å in **16**) and corresponded to a C–C single bond.[24] These values sharply contrast with the lengths measured for the C6–C7 (1.386(3) Å) and C6–O1 (1.266(2) Å) bonds in compound **20**, which matched those recorded for typical C=C and C=O double bonds.[24] These data indicate that the negative charge of the zwitterion is

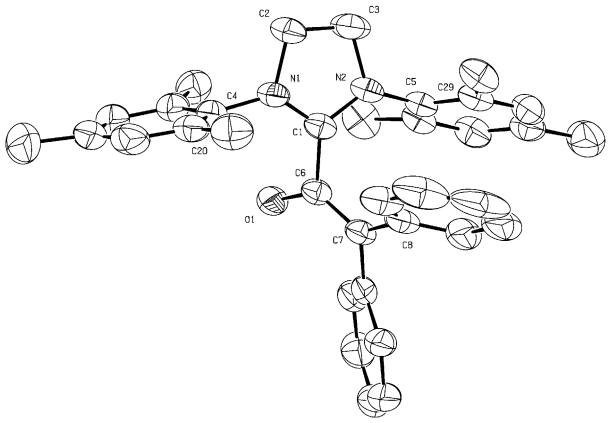


Figure 2. ORTEP diagram of imidazolinium-2-enolate **20** with thermal ellipsoids drawn at 50% probability. H atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: C1–N1 1.333(3), C1–N2 1.344(2), C1–C6 1.517(3), C6–O1 1.266(2); N1-C1-N2 110.2(2), C1-N1-C4-C20 99.3(3), C1-N2-C5-C29 −122.2(2), N1-C1-C6-O1 48.5(3).

delocalized over the C7−C6−O1 motif, in the same way as its positive charge is distributed over the N1−C1−N2 subunit.

Thermogravimetric analyses: To complete their characterization and to probe their thermal stability, we have carried out thermogravimetric analyses (TGA) of the four zwitterions under investigation. Changing the nature of the anionic or cationic moiety led to markedly different decomposition profiles (Figure 3). As expected, the two NHC·imine adducts **16** and **17** were significantly less stable than the NHC·ketene betaines **20** and **21**. More surprisingly, replacing IMes with SIMes also dramatically reduced the thermal stability of zwitterions **16** and **20** versus **17** and **21**. This is a rather unprecedented observation, as the presence or the absence of a backbone C=C double bond in all the NHC·CO_2,[32] NHC·COS,[22] and NHC·CS_2 zwitterions[23] analyzed so far by TGA altered only slightly the onset of their thermolysis.

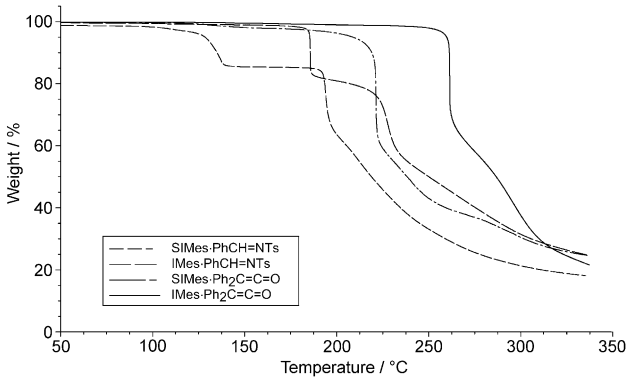
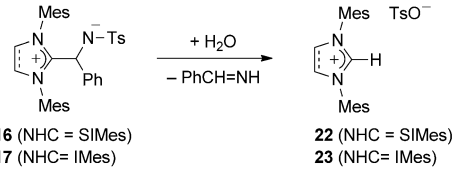


Figure 3. TGA curves of the four zwitterions under investigation.

Imidazolinium-2-amide **16** began to lose weight at about 100°C to afford a stable pale-yellow solid that resisted further degradation until about 180°C. ^{1}H and ^{13}C NMR analysis of this product revealed that it was most likely 1,3-dimesitylimidazolinium tosylate **22** formed upon elimination of benzaldimine (Scheme 7). Imidazolium-2-amide **17** displayed a similar behavior, although its TGA curve was shifted to higher temperatures. Thus, a first transition corresponding to an 18.4% weight loss occurred at 185°C and the residue was tentatively identified as 1,3-dimesitylimidazolium tosylate **23**. Further thermolysis of this salt took place around 225°C and left only a black tar. Additional experimental evidence supporting the formation of salt **23** came from failed attempts to slowly recrystallize compound **17** for X-ray diffraction analysis. Instead, the molecular structure of imidazolium tosylate **23** was obtained (see the Supporting Information for crystallographic details and an ORTEP plot).



16 (NHC = SIMes)
17 (NHC= IMes)

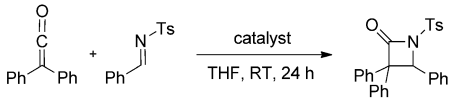
22 (NHC = SIMes)
23 (NHC= IMes)

Scheme 7. Possible degradation of imidazol(in)ium-2-amides **16** and **17**.

In sharp contrast with imidazol(in)ium-2-amides **16** and **17**, which led to bimodal TGA curves, the thermolysis of ethenolates inner salts **20** and **21** did not afford any stable intermediate. The imidazolinium betaine **20** underwent a steep transition at about 220°C, which took place at around 260°C for its imidazolium counterpart **21**. In both cases, this event corresponded to approximately 40% weight loss and was assigned to the release of diphenylketene. It was followed by a non-distinct part of the TGA curve that is typical of the progressive break up of free NHCs at high temperature.

Catalytic tests: To assess the role of NHC·imine and NHC·ketene zwitterions in the Staudinger reaction, we have carried out the [2+2] cycloaddition of diphenylketene and *N*-tosyl benzaldimine by using various catalytic systems (Table 2). In a first set of experiments, an imidazol(in)ium salt (SIMes·HCl or IMes·HBF_4) was deprotonated with cesium carbonate (0.25 mmol each) in THF, whereas diphenylacetyl chloride was dehydrochlorinated with triethylamine (3.25 mmol each) in the same solvent. After 20 min, triethylammonium chloride was filtered off and the solution of diphenylketene was added to the suspension of free carbene, followed by a solution of *N*-tosyl benzaldimine (2.5 mmol) in THF. The reaction mixture was stirred for 24 h at room temperature before work up and ^{1}H NMR analysis. Under these conditions, the SIMes and IMes car-

Table 2. Influence of the NHC catalyst on the Staudinger reaction of diphenylketene and *N*-tosyl benzaldimine.



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Entry	Catalyst [(mol%)]	Yield[a] [%]
1	SIMes·HCl + Cs_2CO_3 (10)	47
2	IMes·HBF_4 + Cs_2CO_3 (10)	71
3	SIMes·PhCH=NTs (**16**) (10)	10
4	IMes·PhCH=NTs (**17**) (10)	57
5	SIMes·Ph_2C=C=O (**20**) (10)	47
6	IMes·Ph_2C=C=O (**21**) (10)	71 (65)[b]
7	IMes·Ph_2C=C=O (**21**) (5)	56
8	IMes·Ph_2C=C=O (**21**) (2.5)	48

[a] Determined by comparing the integrals of the PhC*H*NTs proton in β-lactam **24** ($\delta = 5.80$ ppm) and in the aldimine starting material ($\delta = 9.02$ ppm). [b] Yield of the isolated product after chromatographic purification.

benes afforded β-lactam **24** in 47 and 71% yields, respectively (Table 2, entries 1 and 2).

Next, we turned our attention to the NHC·imine adducts **16** and **17**. To take into account the incorporation of one of the reagents in the catalyst precursor and to maintain the same molar ratios between the various reaction partners, the amount of *N*-tosyl benzaldimine added was reduced to 2.25 mmol. As observed when using a combination of base and imidazol(in)ium salt, the reaction mixtures containing zwitterions **16** and **17** were initially yellow and became progressively orange-red within the time course of the transformation, in line with the in situ-formation of enolate **20** or **21**. Yields recorded after 24 h with the tosylamide inner salts were significantly lower than those obtained with the free NHCs and confirmed the superior catalytic activity of IMes versus SIMes in the formation of β-lactam **24** (Table 2, entries 3 and 4).

When NHC·ketene zwitterions **20** and **21** were employed to promote the model cycloaddition under scrutiny, the amount of diphenylketene was reduced to ensure that the stoichiometry initially defined was preserved. The orange color of the enolate inner salts was visible at the onset of the reactions and gradually evolved into red and then brown hues over time. Strikingly, the yields of product **24** obtained with adducts **20** and **21** matched exactly those recorded with the free carbenes generated in situ (Table 2, entries 5 and 6). Thus, the desired β-lactam was formed in 71% yield after 24 h by using 10 mol% of compound **21** as a catalyst. Purification of the crude product by column chromatography afforded pure (±)-3,3,4-triphenyl-1-tosylazetidin-2-one (**24**) isolated as a white powder in 65% yield. When the catalyst loading was decreased to 5 or 2.5 mol%, the yields dropped down to 56 and 48%, respectively (Table 2, entries 7 and 8).

Conclusion and Perspectives

In this study, two representative NHCs were treated with *N*-tosyl benzaldimine or diphenylketene to afford four new zwitterionic products. These were isolated in high yields and fully characterized by various analytical techniques. Their thermal stabilities were monitored by TGA and the molecular structures of three of them were determined by X-ray crystallography. The imidazol(in)ium-2-amides **16** and **17** were rather labile white solids that did not show any tendency to tautomerize into the corresponding 1,2,2-triaminoethene derivatives. They displayed a mediocre catalytic activity in the Staudinger reaction of *N*-tosyl benzaldimine with diphenylketene. Contrastingly, the imidazol(in)ium-2-enolates **20** and **21** were orange-red crystalline materials that remained stable over extended periods of time, probably due to the better delocalization of their negative charge compared with the amide inner salts. Despite their greater stability, these zwitterions turned out to be efficient promoters for the model cycloaddition under scrutiny. As a matter of fact, their catalytic activity matched exactly those recorded with free carbenes. Altogether, these results provide strong experimental support in favor of the "ketene-first" mechanism postulated by Ye et al. for NHC-promoted Staudinger reactions.[12,15] They also highlight the superior catalytic activity of the imidazole-based carbene IMes compared with its saturated analogue SIMes in the reaction under consideration.

Having identified imidazolium-2-enolate **21** as a stable, crystalline key intermediate in the synthesis of racemic β-lactam **24**, we are now focusing our research efforts on the synthesis and characterization of additional NHC·ketene zwitterions derived from either chiral azolium salts or unsymmetrical ketenes. We anticipate that determining the molecular structures of these adducts will help us gain further valuable insight into the regio- and stereoselectivity of NHC-mediated Staudinger reactions and of related enantioselective cycloaddition processes.

Experimental Section

General information: Unless otherwise specified, all the syntheses were carried out under a dry argon atmosphere by using standard Schlenk techniques. Solvents purchased from Labotec were distilled from appropriate drying agents and deoxygenated prior to use. Anhydrous triethylamine purchased from Aldrich was deoxygenated prior to use. Cesium carbonate was kept in an oven at 80°C. Silica gel 60 (60 Å pore size, 0.063–0.2 mm particle size) supplied by Biosolve was used for column chromatography. Petroleum ether refers to the fraction of b.p. 40–60°C. Diphenylacetyl chloride,[29] *N*-benzylidene-4-methylbenzenesulfonamide,[13] *N*,*N*′-dimesitylethylenediimine,[33] and 1,3-dimesitylimidazolinium chloride (SIMes·HCl)[33] were prepared according to literature methods. All the other chemicals were obtained from Aldrich and used without any further purification. Melting points were recorded with an Electrothermal apparatus and are not corrected. ^{1}H and ^{13}C NMR spectra were recorded at 298 K with a Bruker DRX 400 spectrometer operating at 400.13 and 100.62 MHz, respectively. Chemical shifts are listed in parts per million downfield from TMS and are referenced to solvent peaks or TMS. Infrared spectra were recorded with a PerkinElmer Spectrum One

FT-IR spectrometer. Thermogravimetric analyses were performed under nitrogen with a TA Q500 instrument by using a dynamic heating ramp. Elemental analyses were carried out in the Laboratory of Pharmaceutical Chemistry at the University of Liège.

Synthesis of NHC·imine zwitterions: An oven-dried 100 mL round-bottomed flask equipped with a magnetic stirring bar and capped with a three-way stopcock was charged with an imidazol(in)ium salt (5 mmol) and dry THF (15 mL). A 0.5 M solution of potassium bis(trimethylsilyl)-amide (1.20 g, 6 mmol) in dry THF (12 mL) was added with a cannula. The resulting yellow suspension was stirred for 30 min at room temperature. It was allowed to settle and the supernatant solution was filtered through Celite under an inert atmosphere into a two-necked 250 mL round-bottomed flask equipped with a magnetic stirring bar and capped with a three-way stopcock. The filter cake was rinsed with dry THF (2× 5 mL). Next, a solution of *N*-benzylidene-4-methylbenzenesulfonamide (1.2966 g, 5 mmol) in dry THF (10 mL) was added with a cannula. A white precipitate appeared within a few minutes. After 1 h, the suspension was brought back to air and filtered through a Büchner funnel. The precipitate was washed with diethyl ether (3×10 mL) and dried under high vacuum.

1,3-Bis(2,4,6-trimethylphenyl)imidazolinium-*N*-benzyl-*N*-tosylamide (SIMes·PhCH=NTs, 16): White powder (2.08 g, 74% yield). M.p.: 146.2–146.4 °C; ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.06–7.04 (m, 4H, CH_{ar}), 6.95 (t, $^3J_{H\text{-}H}$ = 6.9 Hz, 1H, CH_{ar}), 6.79 (s, 2H, CH_{ar}), 6.76–6.70 (m, 4H, CH_{ar}), 6.51 (d, $^3J_{H\text{-}H}$ = 6.5 Hz, 2H, CH_{ar}), 5.25 (s, 1H, CH), 4.12–3.89 (m, 4H, CH_2), 2.54 (s, 6H, Mes-CH_3), 2.35 (s, 6H, Mes-CH_3), 2.16 (s, 3H, Ts-CH_3), 1.89 ppm (s, 6H, Mes-CH_3); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 170.0 (C_2), 147.1 (C_{ar}), 140.4 (C_{ar}), 138.1 (C_{ar}), 137.5 (C_{ar}), 137.1 (C_{ar}), 136.9 (C_{ar}), 131.6 (C_{ar}), 130.0 (CH_{ar}), 130.0 (CH_{ar}), 129.3 (CH_{ar}), 128.1 (CH_{ar}), 127.6 (CH_{ar}), 127.4 (CH_{ar}), 125.9 (CH_{ar}), 58.5 (CH), 50.5 (CH_2), 21.4 (Mes-CH_3), 21.3 (Ts-CH_3), 19.0 (Mes-CH_3), 17.9 ppm (Mes-CH_3); IR (KBr): $\tilde{\nu}$ = 3167 (w), 3158 (w), 2922 (m), 2860 (w), 1612 (s), 1568 (s), 1523 (w), 1492 (m), 1381(w), 1313 (w), 1281 (s),1238 (s), 1208 (w), 1184 (w), 1150 (s), 1118 (s), 1067 (m), 906 cm^{-1} (s); elemental analysis calcd (%) for $C_{35}H_{39}N_3O_2S$ (565.77): C 74.3, H 7.0, N 7.4, S 5.7; found: C 74.0, H 6.8, N 7.2, S 5.6. Note: For some batches, NMR analysis of the product indicated that a solvate with approximately 0.9 equiv of THF had formed. When this happened, heating under vacuum and washing with diethyl ether allowed to release the solvent and to obtain pure compound **16**.

1,3-Bis(2,4,6-trimethylphenyl)imidazolium-*N*-benzyl-*N*-tosylamide (IMes·PhCH=NTs, 17): After 1 h, no precipitate had formed in the reaction mixture. The solvent was removed under high vacuum and the pale-yellow oily residue was brought back to air. Crystallization was induced by trituration with diethyl ether (10 mL). The precipitate was filtered through a Büchner funnel, washed with diethyl ether (3×10 mL), and dried under high vacuum to afford the title compound as a white powder (2.35 g, 83% yield). M.p.: 147–148 °C. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.12–7.07 (m, 6H, CH_{ar}), 6.95 (t, $^3J_{H\text{-}H}$ = 6.9 Hz, 1H, CH_{ar}), 6.87 (s, 2H, CH_{ar}), 6.81–6.72 (m, 4H, CH_{ar}), 6.60 (d, $^3J_{H\text{-}H}$ = 6.6 Hz, 2H, CH_{ar}), 5.62 (s, 1H, CH), 2.40 (s, 6H, Mes-CH_3), 2.32 (s, 6H, Mes-CH_3), 2.16 (s, 3H, Ts-CH_3), 1.68 ppm (s, 6H, Mes-CH_3); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 151.2 (C_2), 146.9 (C_{ar}), 141.4 (C_{ar}), 138.8 (C_{ar}), 138.5 (C_{ar}), 136.5 (C_{ar}), 136.3 (C_{ar}), 131.7 (C_{ar}), 129.8 (CH_{ar}), 129.7 (CH_{ar}), 128.9 (CH_{ar}), 128.1 (CH_{ar}), 127.5 (CH_{ar}), 127.4 (CH_{ar}), 126.0 (CH_{ar}), 123.2 (CH_{ar}), 57.7 (CH), 21.5 (Mes-CH_3), 21.3 (Ts-CH_3), 18.8 (Mes-CH_3), 17.7 ppm (Mes-CH_3); IR (KBr): $\tilde{\nu}$ = 3137 (w), 3084(m), 3025 (m), 2965 (w), 2920 (m), 2861 (w), 1608 (w), 1562 (w), 1495 (s), 1451 (m), 1383 (w), 1330 (w), 1289 (w), 1233 (s), 1160 (s), 1149 (s), 1117 (s), 1080 (s), 1066 (s), 1035 (m), 967 (w), 905 cm^{-1} (s); elemental analysis calcd (%) for $C_{35}H_{37}N_3O_2S$ (563.75): C 74.6, H 6.6, N 7.5, S 5.7; found: C 74.3, H 6.5, N 7.3, S 5.6.

Synthesis of NHC·ketene zwitterions: An oven-dried 100 mL round-bottomed flask equipped with a magnetic stirring bar and capped with a three-way stopcock was charged with an imidazol(in)ium salt (5 mmol) and dry THF (50 mL). A 0.5 M solution of potassium bis(trimethylsilyl)-amide (1.20 g, 6 mmol) in dry THF (12 mL) was then added with a cannula. The resulting yellow suspension was stirred for 30 min at room temperature. It was allowed to settle and the supernatant solution was filtered through Celite under an inert atmosphere into an oven-dried two-necked 250 mL round-bottomed flask equipped with a magnetic stirring bar and capped with a three-way stopcock. The filter cake was rinsed with dry THF (2×5 mL). An oven-dried 50 mL round-bottomed flask equipped with a magnetic stirring bar and capped with a three-way stopcock was charged with diphenylacetyl chloride (5 mmol, 1.1535 g) and dry THF (20 mL). Triethylamine (5 mmol, 0.7 mL) was added with a syringe. The resulting yellow suspension was stirred for 30 min at room temperature. It was filtered through Celite under an inert atmosphere into the two-necked 250 mL round-bottomed flask containing the carbene solution. The filter cake was rinsed with dry THF (2×5 mL). The reaction mixture turned red within a few minutes. After 30 min, the solvent was removed under high vacuum and the resulting viscous oil was brought back to air. It was dissolved in dichloromethane (20 mL) and precipitated by slowly adding petroleum ether (50 mL) under vigorous stirring. The solid product was filtered through a Büchner funnel, washed with petroleum ether (3×10 mL) and dried under high vacuum.

1,3-Bis(2,4,6-trimethylphenyl)imidazolinium-2,2-diphenylethenolate (SIMes·Ph_2C=C=O, 20): Orange powder (1.86 g, 74% yield). ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.19–7.11 (m, 5H, CH_{ar}), 6.95–6.92 (m, 4H, CH_{ar}), 6.80 (s, 2H, CH_{ar}), 6.75 (t, $^3J_{H\text{-}H}$ = 6.7 Hz, 1H, CH_{ar}), 6.60 (d, $^3J_{H\text{-}H}$ = 6.6 Hz, 2H, CH_{ar}), 4.15–3.97 (m, 4H, CH_2), 2.70 (s, 6H, CH_3), 2.26 (s, 6H, CH_3), 1.90 ppm (s, 6H, CH_3); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 171.4 (CO), 150.0 (C_2), 144.7 (C_{ar}), 142.8 (C_{ar}), 139.3 (C_{ar}), 138.2 (C_{ar}), 135.7 (C_{ar}), 133.3 (CH_{ar}), 133.0 (C_{ar}), 129.9 (CH_{ar}), 129.6 (CH_{ar}), 128.7 (CH_{ar}), 128.4 (CH_{ar}), 127.2 (CH_{ar}), 125.8 (CH_{ar}), 122.7 (CH_{ar}), 111.9 (($Ph)_2$C), 50.5 (CH_2), 21.2 (CH_3), 19.5 (CH_3), 18.4 ppm (CH_3); IR (KBr): $\tilde{\nu}$ = 3045 (w), 2919 (m), 2167 (m), 1598 (m), 1513 (s), 1486 (m), 1436 (m), 1371 (w), 1345 (m), 1324 (w), 1305 (w), 1279 (s), 1209 (w), 1171 (w), 1142 (w), 1071 (w), 1030 (m), 991 (w), 933 cm^{-1} (w); elemental analysis calcd (%) for $C_{35}H_{36}N_2O$ (500.67): C 84.0, H 7.3, N 5.6; found C 83.8, H 7.0, N 5.6.

1,3-Bis(2,4,6-trimethylphenyl)imidazolium-2,2-diphenylethenolate (IMes·Ph_2C=C=O, 21): Orange powder (2.18 g, 87% yield). ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.30 (d, $^3J_{H\text{-}H}$ = 7.3 Hz, 2H, CH_{ar}), 7.10–6.94 (m, 9H, CH_{ar}), 6.90 (s, 2H, CH_{ar}), 6.76 (t, $^3J_{H\text{-}H}$ = 6.8 Hz, 1H), 6.55 (d, $^3J_{H\text{-}H}$ = 6.5 Hz, 2 H CH_{ar}), 2.48 (s, 6H, CH_3), 2.34 (s, 6H, CH_3), 1.76 ppm (s, 6H, CH_3); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 153.9 (CO), 149.9 (C_2), 145.0 (C_{ar}), 143.2 (C_{ar}), 140.2 (C_{ar}), 137.6 (C_{ar}), 134.8 (C_{ar}), 133.6 (CH_{ar}), 133.0 (C_{ar}), 129.7 (CH_{ar}), 129.6 (CH_{ar}), 128.4 (CH_{ar}), 128.3 (CH_{ar}), 127.2 (CH_{ar}), 125.6 (CH_{ar}), 122.5 (CH_{ar}), 122.4 (CH_{ar}), 112.6 (($Ph)_2$C), 21.3 (CH_3), 19.2 (CH_3), 18.5 ppm (CH_3); IR (KBr): $\tilde{\nu}$ = 3159 (w), 3042 (w), 2919 (w), 1584 (m), 1528 (s), 1486 (s), 1444 (m), 1400 (m), 1325 (m), 1305 (m), 1227 (m), 1164 (w), 1030 (w), 938 cm^{-1} (w); elemental analysis calcd (%) for $C_{35}H_{34}N_2O$ (498.66): C 84.3, H 6.9, N 5.6; found: C 84.6, H 6.8, N 5.7.

Thermolysis of NHC·imine zwitterions: A platinum cell was charged with about 15 mg of an NHC·imine zwitterion and heated in a TGA instrument until the first plateau was reached. The residue was cooled to room temperature and analyzed by ^{1}H and ^{13}C NMR spectroscopy.

1,3-Bis(2,4,6-trimethylphenyl)imidazolinium *p*-toluenesulfonate (SIMes·TsOH, 22): Pale-yellow powder obtained upon heating compound **16** to 170 °C. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 10.16 (s, 1H, CH^2 Im), 6.99–6.90 (m, 8H, CH_{ar}), 4.28 (s, 4H, CH_2), 2.32 (s, 6H, *p*-CH_3 Mes), 2.29 (s, 12H, *o*-CH_3 Mes), 2.28 ppm (s, 3H, CH_3 Ts); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 162.7 (CH_2 Im), 140.8 (C_{para} Mes), 137.7 (C_{ar} Ts), 135.6 (C_{ortho} Mes), 131.1 (C_{ipso} Mes), 130.3 (CH_{meta} Mes), 128.7 (CH_{ar} Ts), 124.3 (CH_{ar} Ts), 51.8 (CH_2), 21.42 (CH_3 Ts), 21.36 (*p*-CH_3 Mes), 18.1 ppm (*o*-CH_3 Mes).

1,3-Bis(2,4,6-trimethylphenyl)imidazolium *p*-toluenesulfonate (IMes·TsOH, 23): Dark-brown oil obtained upon heating compound **17** to 195 °C. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 10.98 (s, 1H, CH^2 Im), 7.48 (s, 2H, $CH^{4,5}$ Im), 7.03 (s, 4H, *m*-CH Mes), 7.01 (d, 2H, $^3J_{H\text{-}H}$ = 7.6 Hz, CH Ts), 6.92 (d, $^3J_{H\text{-}H}$ = 7.6 Hz, 2H, CH Ts), 2.37 (s, 6H, *p*-CH_3 Mes), 2.28 (s, 3H, *p*-CH_3 Ts), 2.10 ppm (s, 12H, *o*-CH_3 Mes); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 157.3 (C_{ar} Ts), 141.7 (C_{para} Mes), 137.6 (CH^2 Im), 134.8 (C_{ortho} Mes), 131.4 (C_{ipso} Mes), 130.2 (CH_{meta} Mes), 128.7 (CH_{ar} Ts), 124.7 ($CH^{4,5}$ Im), 124.4 (CH_{ar} Ts), 21.5 (*p*-CH_3 Mes), 21.4 (CH_3 Ts), 17.8 ppm (*o*-CH_3 Mes).

Typical procedure for the Staudinger reaction: An oven-dried two-necked 50 mL round-bottomed flask equipped with a magnetic stirring bar and capped with a three-way stopcock was charged with IMes·Ph_2C=C=O (**21**) (0.1247 g, 0.25 mmol). An oven-dried 25 mL round-bottomed flask equipped with a magnetic stirring bar and capped with a three-way stopcock was charged with diphenylacetyl chloride (0.6921 g, 3 mmol) and dry THF (10 mL). Triethylamine (0.42 mL, 3 mmol) was added with a syringe. The resulting yellow suspension was stirred for 20 min at room temperature. It was filtered through Celite under an inert atmosphere into the flask containing the NHC·ketene zwitterion. The filter cake was rinsed with dry THF (2×5 mL). Next, a solution of *N*-benzylidene-4-methylbenzenesulfonamide (0.6483 g, 2.5 mmol) in dry THF (5 mL) was added with a cannula. The reaction mixture was stirred for 24 h at room temperature and the solvent was removed on a rotary evaporator. The residue was dissolved in THF (10 mL). Water (10 mL) and two drops of concentrated HCl were added. The resulting suspension was stirred for 20 min at room temperature. Water (20 mL) was added and the precipitate was filtered through a Büchner funnel. It was washed with water (2× 10 mL) and cold diethyl ether (2×10 mL). This crude product was purified by passing through a short plug of silica gel using dichloromethane as eluent. Pure (±)-3,3,4-triphenyl-1-tosylazetidin-2-one (**24**) was isolated as a white solid (0.737 g, 65% yield). ^{1}H and ^{13}C NMR data matched those reported in the literature.[13]

Acknowledgements

The authors would like to thank Mr. Guillaume Guiho and Mrs. Bernadette Norberg for their technical assistance, and the members of COST action CM0905 "Organocatalysis" for stimulating discussions.

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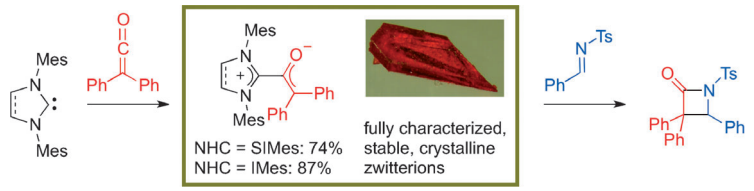
Received: December 12, 2012
Revised: April 11, 2013
Published online: ■■ ▮▮, 2013

Organocatalysis

*M. Hans, J. Wouters, A. Demonceau, L. Delaude** ..... ▮▮▮▮–▮▮▮▮

Mechanistic Insight into the Staudinger Reaction Catalyzed by N-Heterocyclic Carbenes



Catalysts caught in the act: The N-heterocyclic carbenes 1,3-dimesitylimidazolin-2-ylidene (SIMes) and 1,3-dimesitylimidazol-2-ylidene (IMes) react with *N*-tosyl benzaldimine or diphenylketene to afford the corresponding zwitterions in high yields (see scheme). The molecular structures of three of them were determined by X-ray crystallography and their thermal stability was monitored by thermogravimetric analysis. The NHC•ketene betaines were found to be key intermediates for the Staudinger reaction catalyzed by NHCs.

