Organocatalysis by bimacrocyclic NHCs: unexpected formation of a cyclic hemiacetal instead of a γ-butyrolactone†‡

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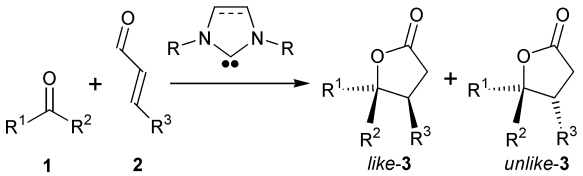
Two bimacrocyclic imidazolinium salts of different size, precursors to respective NHCs (N-heterocyclic carbenes), were tested as precatalysts in the reaction of aromatic aldehydes or ketones with enals. The expected lactones were produced in most cases, but in the reaction of methyl 4-formylbenzoate with cinnamaldehyde, the larger bimacrocycle led to the formation of a cyclic hemiacetal, while the smaller bimacrocycle gave the anticipated lactone.

Introduction

The ability of thiamine to act as a nucleophilic catalyst after deprotonation was recognized in 1958 by Breslow.[1] He established the mechanism for the acyloin condensation catalyzed by thiamine, based on the umpolung of a carbonyl carbon atom by the deprotonated thiazolium salt, in a fashion analogous to catalysis by cyanide ions.[2] The scope of this reaction was expanded by Stetter in 1976, who reacted aldehydes with Michael acceptors in the presence of either cyanide or thiazolium salts and base (Stetter reaction).[3]

Deprotonated azolium salts have received great attention since the isolation of a stable crystalline carbene (derived from an imidazolium salt) by Arduengo in 1991,[4] and the term N-heterocyclic carbenes (NHCs) has been coined for these species, which were called zwitterions by Breslow. NHCs are nowadays frequently used in organocatalysis[5] and they have also found numerous applications as beneficial ligands in organometallic chemistry.[6] A number of chiral thiazolium and triazolium salts have been synthesized and successfully applied in asymmetric acyloin condensations and Stetter reactions.[7]

Interestingly, neither acyloin nor Stetter products, but instead γ-butyrolactones **3** are formed if the imidazolium salt **4** is used as precatalyst in the reaction of aldehydes **1** (R^1 = H) with α,β-unsaturated aldehydes **2** (Scheme 1). Also ketones **1** may be used in the reaction, and the favored formation of *like*-**3** was observed in all cases.[8] A reasonable mechanism was proposed for the reaction, involving the vinylogous umpolung of the β carbon atom of the enal **2** caused by nucleophilic attack of the NHC on its carbonyl carbon atom.[8] The proposed catalytic cycle was supported by the observation of postulated intermediates by ESI mass spectrometry.[9] It was reported that some other imidazolium salts with different N-substituents are less reactive and selective than **4**,[8b] while the use of some thiazolium-derived NHC catalysts has recently been found to result in the predominant formation of *unlike*-**3**.[10] Imidazolinium salts have not yet been tested in this reaction.



this publication:

1a: $R^1 = CF_3$, $R^2 = C_6H_5$
1b: R^1 = H, R^2 = 4-Cl-C_6H_4
1c: R^1 = H, R^2 = 4-MeOOC-C_6H_4
2a: $R^3 = C_6H_5$
2b: R^3 = 4-MeO-C_6H_4

3a: $R^1 = CF_3$, $R^2 = C_6H_5$, $R^3 = C_6H_5$
3b: $R^1 = CF_3$, $R^2 = C_6H_5$, R^3 = 4-MeO-C_6H_4
3c: R^1 = H, R^2 = 4-Cl-C_6H_4, $R^3 = C_6H_5$
3d: R^1 = H, R^2 = 4-MeOOC-C_6H_4, $R^3 = C_6H_5$

Scheme 1 NHC-catalyzed formation of lactones **3**.

We haverecently reported the synthesis of bimacrocyclic imidazolinium salts as precursors to respective NHC catalysts, aiming to govern the selectivity in reactions catalyzed by these NHCs.[11] We have therefore tested the bimacrocyclic salts **6a** and **6b** in the formation of γ-butyrolactones **3** and compared them to the precatalyst **4** which was used in the literature. In order to study the influence of the nature of the heterocycle, the respective saturated imidazolinium salt[12] **5** was also tested in the reaction (see Fig. 1).

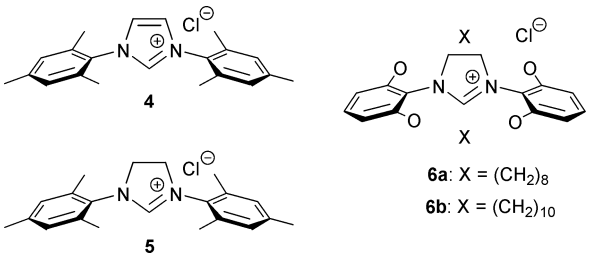


Fig. 1 NHC-precatalysts tested in the formation of lactones **3**.

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† Electronic supplementary information (ESI) available: NMR spectra of compounds **7**, **8** and **9**. CCDC reference number 680462. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b815828b

‡ Concave Reagents, Part 57. For preceding publication (Part 56), see O. Winkelmann, C. Näther and U. Lüning, *J. Organomet. Chem.*, 2008, **693**, 2784.

Table 1 Catalytic activity of the NHC-precursors **4–6** in the formation of γ-butyrolactones **3**[a]

	Product yield (%)[b] (*like*:*unlike*)[c]			
Precatalyst	**3a**	**3b**	**3c**	**3d**
4 (10 mol%)	92 (67:33)	94 (68:32)	39 (82:18)[d]	52 (82:18)
4 (10 mol%)[e]	92 (65:35)[e]	—	—	—
5 (10 mol%)	93 (54:46)	95 (54:46)	8 (73:27)[d]	2 (74:26)
5 (25 mol%)[e]	—	—	—	39 (73:27)[e]
6a (10 mol%)	38 (46:54)	—	—	—
6a ((25 mol%)	86 (47:53)	72 (45:55)	4 (34:66)[d]	41 (52:48)[e]
6b (10 mol%)	39 (48:52)	—	—	—
6b (25 mol%)	80 (48:52)	68 (46:54)	2 (33:67)[d]	3 (50:50)[e]
6b (25 mol%)[e]	88 (48:52)[e]	—	4 (36:64)[e]	—

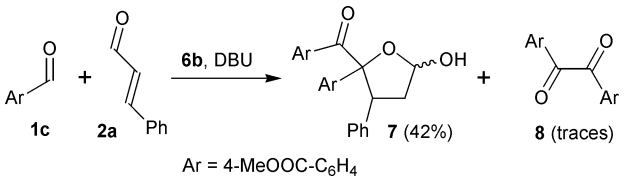
[a] Conditions: 0.5 mmol enal **2**, 1 mmol α,α,α-trifluoroacetophenone (**1a**) or benzaldehyde **1b**/**1c**, azolium salt **4–6** (50 or 125 μmol), DBU (1 equiv. based on azolium salt), 16 h in 2 mL of THF at room temperature. [b] Determined by GC using *n*-hexadecane as the internal standard, average of two experiments. [c] Diastereomeric ratio determined by GC, average of two experiments. [d] 0.5 mmol enal **2a**, 0.5 mmol substituted benzaldehyde **1b**. [e] 16 h at 40 °C.

Results and discussion

The results obtained with the different precatalysts are summarized in Table 1. Using 10 mol% of the NHC-precursors **4** or **5** and DBU as the base, high yields of the products **3a** and **3b** were obtained in the reaction of α,α,α-trifluoroacetophenone (**1a**) with cinnamaldehyde (**2a**) or 4-methoxy-cinnamaldehyde (**2b**) at room temperature. Higher loadings (25 mol%) of the precatalysts **6** were needed to obtain comparable yields of the products **3a** and **3b**, while the yields could not be raised significantly at elevated temperature (40 °C). Even with 25 mol% of **6**, incomplete conversion of the enal **2b** was observed in the formation of **3b** after 16 h. The favored formation of *like*-**3a** and *like*-**3b** was observed with precatalyst **4** as reported by Glorius and Burstein.[8a] Interestingly the diastereoselectivity dropped with the use of the analogous saturated NHC-precursor **5**, showing clearly that the selectivity of the reaction is affected by the nature of the NHC (imidazol-2-ylidene vs. imidazolidin-2-ylidene). The bimacrocycles **6** were found to be similarly little selective as **5**. While still a small excess of *like*-**3a** and *like*-**3b** was produced with **5**, a slight but definite preference for *unlike*-**3a** and *unlike*-**3b** was observed with both bimacrocycles **6a** and **6b**. The diastereoselectivities remained unchanged at 40 °C.

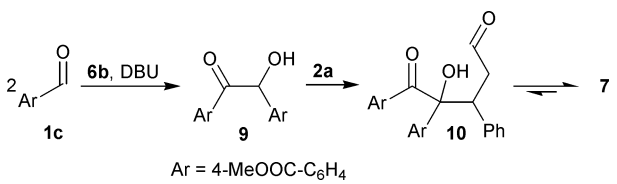
In the reaction of cinnamaldehyde (**2a**) with 4-substituted benzaldehydes **1b** and **1c** (products **3c**, **3d**), a decrease in yield compared to products **3a** and **3b** was observed with all NHC precursors, and the saturated precatalysts **5** and **6** were found to be inferior to **4**. Although the best results were obtained with the imidazolium salt **4**, the yields reported in the literature (54% for **3c**, 70% for **3d**) exceed our findings. The reported high diastereoselectivities were reproduced for both products. In the case of product **3c**, the poor yields are caused by incomplete conversion and by the formation of numerous unidentified by-products. Incomplete conversion also prevented the formation of high yields of **3d**. Interestingly, reasonable amounts of **3d** could be obtained using 25 mol% of **5** or **6a** at 40 °C, while **6b** produced only traces of the expected product under the same conditions. Regarding the *like*/*unlike*-selectivity, a decrease was again observed going from **4** (unsaturated) to **5** (saturated), but less expressed than for the products **3a** and **3b**. With the bimacrocyclic precatalysts **6**, the selectivity was reversed for product **3c**, while equal amounts of *like*- and *unlike*-**3d** were produced.

The poor yield of **3d** obtained with the NHC precursor **6b** could be attributed to the formation of an additional product: hemiacetal **7** (see Scheme 2). It results from the connection of two aldehydes **1c** with one enal **2a** and was isolated in 42% yield from the reaction mixture. Also, a small amount of benzil **8** was obtained. By GC analysis alone, the new product **7** can be overlooked. It decomposes under GC conditions and cinnamaldehyde (**2a**), benzil **8** and benzoin **9** are detected. Small amounts of these decomposition products are observed with all precatalysts in the reaction of **1c** and **2a**, but they are found as the most prominent peaks with **6b**.



Scheme 2

An equilibrium between both anomeric forms (ratio 10:1) of **7** is observed in $CDCl_3$ at room temperature, with the hydroxyl and phenyl group being oriented *trans* in the major anomer, as can be deduced from the NOESY spectrum. The relative stereochemistry at the quaternary carbon atom could not be assigned undoubtedly. A molecule related to **7** has been reported to be produced from cinnamaldehyde (**2a**), acetaldehyde and fermenting baker's yeast,[13] and the reported NMR assignments support our structure elucidation (also regarding the anomers). In analogy to the mechanistic explanation of the enzymatic reaction, the isolation of **7** implies the formation of benzoin **9**, whose anion reacts with the Michael-acceptor **2a**.[14,15] The resulting hydroxyaldehyde **10** undergoes ring closure to hemiacetal **7**, as the NMR spectra prove (see Scheme 3). The additionally isolated benzil **8** seems to result from the oxidation of benzoin **9** during work-up.[16]



Scheme 3

The new product **7** was only found starting from aldehyde **1c** and only when using precatalyst **6b**. **1c** carries an electron-withdrawing group in the *p*-position of the phenyl ring which makes the aldehyde function more electrophilic. Instead of an addition of the NHC to the carbonyl group of enal **2a**, which leads to the formation of lactone **3d**, the NHC reacts with aldehyde **1c**. The following benzoin reaction with **1c** is also faster than the competing Stetter reaction with **2a** due to the electron withdrawing effect of the ester group of **1c**, and thus allows the formation of hemiacetal **7**.

Remarkably, reasonable amounts of the hemiacetal **7** were only found with precatalyst **6b** in contrast to the NHC-precursors **4**, **5** and **6a**. How does the NHC derived from **6b** differ from the other NHCs that were tested in the reaction? There are four differences to be discussed: (i) **6b** yields an NHC which contains a saturated heterocycle, (ii) the NHCs derived from **6** are more electron-rich than the other NHCs,[17] (iii) **6b** is a bimacrocyclic compound, and (iv) the bimacrocycle in **6b** is larger than that in **6a**. Although the formation of either lactone **3d** or benzoin **9** is catalyzed by the respective NHC, the geometrical properties of the precatalysts may reflect those of the NHCs.[18] Both imidazolinium salts **6** have been crystallized and X-ray analyses have been carried out. Fig. 2 shows the structure of the larger bimacrocycle **6b**; Fig. 3 compares it to the structure of **6a** which has already been published.[11a]

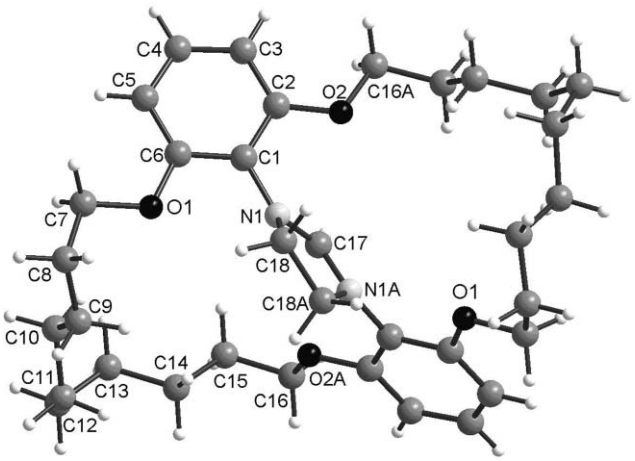


Fig. 2 Crystal structure of imidazolinium chloride **6b**.[19] The chloride anion and two molecules of chloroform are omitted for clarity. Selected bond lengths [Å] and bond angles [°]: N1-C17 1.315(3), N1-C18 1.483(4), N1-C1 1.429(4), C18-C18A 1.508(8); N1-C17-N1A 113.1(4), C17-N1-C18 109.4(3), N1-C18-C18A 102.6(2); C17-N1-C1-C6 132.5(3), C17-N1-C1-C2 –48.8(4).

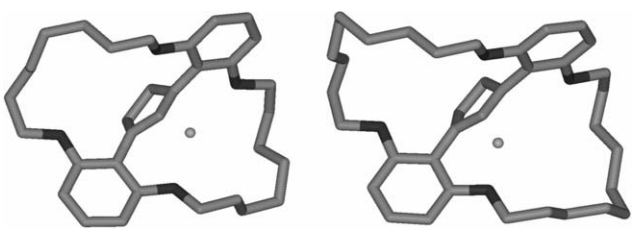


Fig. 3 Comparison of the crystal structures of **6a** (left) and **6b** (right). Hydrogen atoms and solvent molecules are omitted for clarity.

On first glance, the structures of both bimacrocycles **6a** and **6b** seem quite similar. The phenyl substituents are substantially twisted out of a coplanarity with the heterocycle, and the conrotatory fashion of this twist leads to a C_2-symmetric structure. However, a look at the interplanar angles between the imidazolinium ring and the adjacent aryl rings (derived from the torsion angles C17-N1-C1-C2, C17-N1-C1-C6) reveals that the phenyl substituents twist more out of a coplanar geometry in **6a** (the interplanar angle is 54°) than they do in the larger cycle **6b** (48°).

In the non-C_2-symmetric carbene derived from **4**, the mesityl substituents are oriented almost perpendicular to the heterocycle, with interplanar angles of 80° and 71°.[20] In this respect, **6a** can probably behave more similar to the non-macrocyclic analogues **4** and **5**, and thus **6b** has a special combination of properties allowing to form the new product **7**.

Conclusions

Our observations indicate that the NHC derived from **6b** is not too sterically encumbered to allow the formation of benzoin **9**, and this reaction might be favored over lactone formation and Stetter reaction due to the electron-poor benzaldehyde **1c**. However, it is still unclear why only NHC-precursor **6b** led to the formation of the new product, hemiacetal **7**, and this new reaction pathway requires further investigation.

Experimental

The azolium chlorides **4**,[18] **5**[18] and **6**[11a] were synthesized according to literature procedures. Pure samples of the lactones **3** for GC-calibration were obtained with precatalyst **4** after column chromatography, matching the spectroscopic data given in the literature.[21] All aldehydes and ketones were purified by either destillation (**2a**) or column chromatography on silica gel (**1b**, **1c**, **2b**) before use. Dry THF was obtained by heating at reflux with lithium aluminium hydride. ^{1}H and ^{13}C NMR spectra were recorded with Bruker ARX 300, DRX 500 or AV 600 instruments at room temperature and are referenced to tetramethylsilane. IR spectra were recorded with a Perkin-Elmer Paragon 1000, equipped with an ATR unit. Mass spectra were recorded with a Finnigan MAT 8200 or MAT 8230. Elemental analyses were carried out with a EuroEA 3000 Elemental Analyzer from Euro Vector. GC analyses were performed on an Agilent 6890 N gas chromatograph.

General procedure for the synthesis of γ-butyrolactones 3

A flask was charged with the respective catalyst (0.05 or 0.13 mmol), the flask was flushed with nitrogen and sealed with a rubber septum. *Via* syringe, a solution of the enal **2** (0.50 mmol) and the electrophilic aldehyde or ketone **1** (1.0 mmol) in dry THF (2 mL) was added and the mixture was stirred for 5 min. DBU (1 equiv. based on catalyst) was added *via* microliter-syringe, and the mixture was stirred at room temperature. After 16 h, the mixture was passed through a short pad of silica gel and the silica gel was rinsed with ethyl acetate (20 mL). To this solution was added *n*-hexadecane as the internal standard and the mixture was analyzed by GC; conditions: split ratio 11:1, injector temp. 250 °C, detector temp. 300 °C; column: HP-5/30 m; temperature: 100 °C for 2 min, 15 °C/min until 300 °C, 10 min 300 °C.

5-Hydroxy-2-[4-(methoxycarbonyl)-phenyl]-2-[4-(methoxycarbonyl)-phenylcarbonyl]-3-phenyl-tetrahydrofuran (7)

Following the general procedure, cinnamaldehyde (**2a**, 66 mg, 0.50 mmol) and methyl 4-formylbenzoate (**1c**, 164 mg, 1.00 mmol) were reacted with imidazolinium chloride **6b** (75 mg, 0.13 mmol) and DBU (20 μL, 0.13 mmol). After GC analysis, the solvent was evaporated *in vacuo* and the crude product was purified by column

chromatography [silica gel, cyclohexane/ethyl acetate (3:1), R_f = 0.27]. A colorless solid was obtained (96 mg, 42%). M.p. 163 °C. ^{1}H-NMR (600 MHz, $CDCl_3$)[22]: δ (ppm) = 7.89 (m_c, 4H, Ar-H), 7.72 (d, ^3J = 8.8 Hz, 2H, Ar-H), 7.11 (m_c, 2H, Ar-H), 7.05–7.00 (m, 3H, Ar-H), 6.93 (m_c, 2H, Ar-H), 6.07 (dd, ^3J = 5.0 Hz, ^3J = 1.3 Hz, 1H, 5-H), 4.92 (dd, ^3J = 8.9 Hz, ^3J = 7.8 Hz, 1H, 3-H), 3.87 (s, 3H, COOCH_3), 3.82 (s, 3H, COOCH_3), 2.80 (br s, 1H, O*H*), 2.47 (ddd, ^2J = 13.3 Hz, ^3J = 9.0 Hz, ^3J = 5.0, 1H, 4-H_a), 2.41 (ddd,^2J = 13.3 Hz, ^3J = 7.7 Hz, ^3J = 1.5, 1H, 4-H_b). ^{13}C-NMR (150 MHz, $CDCl_3$)[23]: δ (ppm) = 198.2 (*C*O), 166.7 (*C*OOCH$_3$), 166.2 (*C*OOCH$_3$), 142.8 (Ar-C), 138.7 (Ar-C), 138.6 (Ar-C), 133.0 (Ar-C), 130.5 (Ar-CH), 129.3 (Ar-CH), 129.2 (Ar-CH), 129.1 (Ar-CH), 127.9 (Ar-CH), 126.7 (Ar-CH), 125.5 (Ar-CH), 99.2 (C-5), 94.9 (C-2), 52.3 (COO*C*H$_3$), 52.0 (COO*C*H$_3$), 49.6 (C-3), 40.3 (C-4). IR: $\tilde{\nu}$ (cm^{-1}) = 3509, 2932, 1713, 1674, 1606, 1567, 1498, 1434, 1273, 1228, 1108, 1068, 1016, 990, 956, 821, 720, 696, 588. MS (EI): *m*/*z* (%) = 429 (3) [M − OCH$_3$]$^+$, 297 (100) [M − $C_9H_7O_3$]$^+$, 163 (58) [$C_9H_7O_3$]$^+$. MS (CI): *m*/*z* (%) = 461 (22) [M + H]$^+$. Found: C, 70.35; H, 5.57. $C_{27}H_{24}O_7$ requires C, 70.42; H, 5.25

1,2-Bis-(4-methoxycarbonylphenyl)-ethane-1,2-dione (8)

From the above-described reaction was isolated **8** (R_f = 0.44) as a yellow solid (5 mg, 4%). ^{1}H-NMR (500 MHz, d_6-DMSO): δ (ppm) = 8.17 (d, ^3J = 8.6 Hz, 4H, Ar-H), 8.11 (d, ^3J = 8.6 Hz, 4H, Ar-H), 3.91 (s, 6H, COOCH_3). ^{13}C-NMR (125 MHz, d_6-DMSO): δ (ppm) = 192.9 (s, *C*O), 165.3 (s, *C*OOCH$_3$), 135.3 (Ar-C), 135.1 (Ar-C), 130.2 (Ar-CH), 129.9 (Ar-CH), 52.7 (COO*C*H$_3$). IR: $\tilde{\nu}$ (cm^{-1}) = 2925, 1717, 1663, 1569, 1500, 1281, 1188, 1102, 1012, 949, 889, 859, 820, 781, 730, 713, 674, 629, 534. MS (EI): *m*/*z* (%) = 326 (2) [M]$^+$, 163 (100) [$C_9H_7O_3$]$^+$. MS (CI): *m*/*z* (%) = 327 (100) [M + H]$^+$.

2-Hydroxy-1,2-bis-(4-methoxycarbonylphenyl)-ethanone (9)[24]

Methyl 4-formylbenzoate (**1c**, 16.4 g, 100 mmol) was heated to 50 °C with sodium cyanide (1.50 g, 30.0 mmol) in a mixture of ethanol (40 mL) and water (20 mL). After 10 min, the precipitate was collected by filtration and washed with water and ethanol. The residue was dried *in vacuo.* A colorless solid was obtained (13.5 g, 82%). ^{1}H-NMR (300 MHz, d_6-DMSO): δ (ppm) = 8.11 (d, ^3J = 8.6 Hz, 2H, Ar-H), 8.00 (d, ^3J = 8.7 Hz, 2H, Ar-H), 7.91 (d, ^3J = 8.4 Hz, 2H, Ar-H), 7.57 (d, ^3J = 8.3 Hz, 2H, Ar-H), 6.50 (br s, 1H, HCO*H*), 6.19 (s, 1H, *H*COH), 3.85 (s, 3H, COOCH_3), 3.80 (s, 3H, COOCH_3). IR: $\tilde{\nu}$ (cm^{-1}) = 3459, 2953, 1718, 1677, 1608, 1571, 1436, 1273, 1094, 982, 963, 814, 765, 719, 614, 535. MS (EI): *m*/*z* (%) = 163 (100) [$C_9H_7O_3$]$^+$. MS (CI): *m*/*z* (%) = 329 (100) [M + H]$^+$.

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17 O. Winkelmann, C. Näther and U. Lüning, *J. Organomet. Chem.*, 2008, **693**, 923. By measuring CO stretching frequencies of related NHC complexes, it was shown that the NHC derived from the smaller bimacrocycle **6a** is more electron-rich than the NHC derived from **5**. The electronic differences between **6a** and **6b** are expected to be small. The structure of **6b** (see Fig. 2 and 3 and discussion) may actually allow a better conjugation between the electron-rich bridgeheads and the heterocycle, leading to an even more electron-rich NHC compared to **6a**.
18 A. J. Arduengo III, R. Krafczyk, R. Schmutzler, H. A. Craig, J. R. Goerlich, W. J. Marshall and M. Unverzagt, *Tetrahedron*, 1999, **55**, 14523: The geometrical differences between 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride and the respective NHC are rather small, for example.
19 Suitable crystals were grown by diffusion of diethyl ether into a solution of **6b** in chloroform. Crystal data. $C_{35}H_{51}ClN_2O_4{\cdot}2CHCl_3$, M = 837.96, monoclinic, a = 26.471(3), b = 12.5614(7), c = 16.7632(14) Å, β = 128.674(9)°, U = 4351.6(6) Å^3, T = 220(2) K, space group $C2/c$ (no. 15), Z = 4, 9095 reflections measured, 3828 unique (R_{int} = 0.0469) which were used in all calculations. The final $wR(F_2)$ was 0.1870 (all data). The solvent molecules are disordered over two positions.†.
20 A. J. Arduengo III, H. V. R. Dias, R. L. Harlow and M. Kline, *J. Am. Chem. Soc.*, 1992, **114**, 5530.
21 C. Burstein, S. Tschan, X. Xie and F. Glorius, *Synthesis*, 2006, 2418.
22 Only the signals of the major anomer are listed. Most of the signals of the minor anomer are not observed due to overlap. Selected signals of the minor anomer: δ (ppm) = 5.78 (m_c, 1H, 5-H), 4.60 (dd, ^3J = 10.1 Hz, ^3J = 7.7 Hz, 3-H), 2.61 (ddd, ^2J = 13.4 Hz, ^3J = 7.7 Hz, ^3J = 5.5 Hz, 1H, 4-H_a), 2.32 (ddd, ^2J = 13.5 Hz, ^3J = 10.0 Hz, ^3J = 6.0 Hz, 1H, 4-H_b). The 10:1 ratio between the anomers was deduced from integration.
23 Only the signals of the major anomer are listed. One quaternary aromatic carbon atom was not observed, possibly due to overlap or low intensity.
24 M. Shunichi and I. Hiroo, *Jpn. Kokai Tokkyo Koho*, 1992(JP 04–364 151).

