Direct and efficient N-heterocyclic carbene-catalyzed hydroxymethylation of aldehydes†‡

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The N-heterocyclic carbene-catalyzed coupling of several aldehydes with paraformaldehyde is reported, directly providing the corresponding valuable hydroxymethyl ketones. Results of first mechanistic experiments for this remarkably selective transformation are also provided.

The hydroxymethyl ketone moiety is an important motif of synthetic precursors and biologically active compounds.[1] Consequently, many methods for its preparation have been reported. However, most of these methods are rather simple hydrolyses[2] or oxidations[3] and do not form any new C–C bonds.

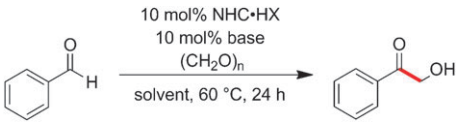
An attractive alternative strategy is based on the N-heterocyclic carbene (NHC)[4] catalyzed umpolung of aldehydes by the formation of the Breslow-intermediate and the addition of this nucleophilic species to electrophiles as found in the well-known Benzoin condensation[5,6] and related reactions.[5,7,8] In these transformations, many selectivity issues arise and the recent interest into and progress in the field of NHCs has allowed the development of new, efficient and highly selective processes. In this respect, the NHC-catalyzed addition of aldehydes to formaldehyde seems to be straightforward and an efficient route for the formation of hydroxymethyl ketones. Thus, it comes as a surprise that this strategy has only rarely been applied.[9,10] In these remarkable pioneering reports by Inoue *et al.*[9] using an NHC-organocatalyst and Demir *et al.*[10a] and Müller *et al.*[10b] employing an enzyme as the catalyst, the validity of this approach was impressively shown. However, all of these reports have significant drawbacks, including low isolated yields (ranging from 6–17% for the work of Inoue *et al.*[9]) or high dilution (<0.02 M[10a]), a large excess of formaldehyde (*e.g.* 32 eq.[10a]) or long reaction time (*e.g.* 4 days[10a]).

An improved preparative method that builds up hydroxymethyl ketones from readily available aldehydes and formaldehyde, increasing the complexity of the carbon skeleton, would be highly desirable. Herein, we report the NHC-catalyzed direct coupling of aldehydes with formaldehyde resulting in hydroxymethyl ketones in good isolated yields.

We commenced our investigation with the hydroxymethylation of benzaldehyde, employing paraformaldehyde (Table 1) as the CH_2O source. Since in many recent studies the choice of NHC has been crucial,[5] we started off by screening different classes of NHC-organocatalysts (entries 1–6). Whereas imidazolylidenes and benzimidazolylidenes failed completely (entries 1 and 2), thiazolylidenes derived from **3** and **4**[9] resulted in the formation of small amounts of product (entries 3 and 4). This could be somewhat improved by the use of the thiazolylidene derived from **5**, commonly applied in NHC-organocatalysis[5] (entry 5). Interestingly, however, the major improvement came with employing the NHC derived from **6** (entry 6), which was designed by us for dual organo-/metal-catalysis.[11] Further optimization of base and solvent proved $N(iPr)_2Et$ in THF to be the best combination (entry 8), providing the hydroxymethylated product in 74% yield (based on ^1H NMR).

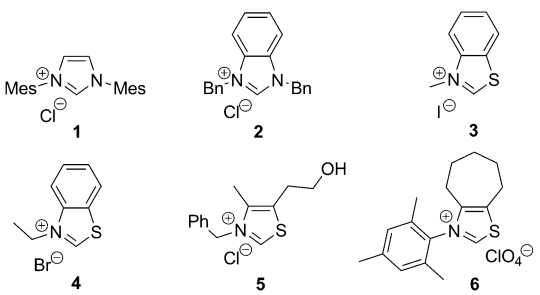
After additional optimization,[12] we investigated the scope of this potentially useful hydroxymethylation reaction, employing 3 eq. of paraformaldehyde (Table 2).[13] Several different classes

Table 1 Initial optimization study for the hydroxymethylation of benzaldehyde[a]



Entry	NHC·HX	Base	Solvent	Yield[a] (%)
1[b]	**1**	NEt_3	THF	0
2[b]	**2**	NEt_3	THF	0
3[b]	**3**	NEt_3	THF	9
4[b]	**4**	NEt_3	THF	15
5[b]	**5**	NEt_3	THF	26
6[b]	**6**	NEt_3	THF	66
7[c]	**6**	NEt_3	THF	53
8[c]	**6**	$N(iPr)_2Et$	THF	74
9[c]	**6**	DBU	THF	53
10[c]	**6**	$N(iPr)_2Et$	^{t}AmylOH	66
11[c]	**6**	$N(iPr)_2Et$	DMF	68
12[c]	**6**	$N(iPr)_2Et$	Toluene	57

[a] Yield determined by ^1H NMR (mesitylene as internal standard). [b] 2 eq. $(CH_2O)_n$, C_{PhCHO} = 0.5 mol L^{-1}. [c] 1 eq. $(CH_2O)_n$, C_{PhCHO} = 0.5 mol L^{-1}.



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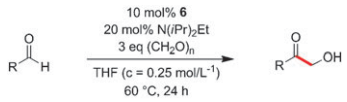
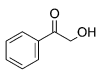
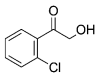
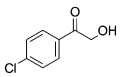
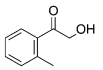
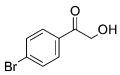
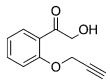
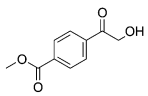
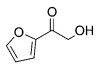
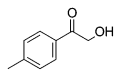
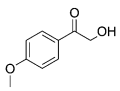
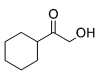
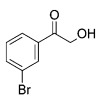
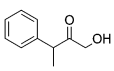
‡ Electronic supplementary information (ESI) available: Experimental procedures and characterization data. See DOI: 10.1039/c0cc02416c

Table 2 Hydroxymethylation of different classes of aldehydes: investigation of substrate scope



Entry	Product	Yield[a] (%)	Entry	Product	Yield[a] (%)
1		70[b,c]	8		77[e]
2		77[d]	9		33
3		74	10		50
4		86	11		57
5		60	12		64[f]
6		32	13		57[e]
7		85[c]	14		29

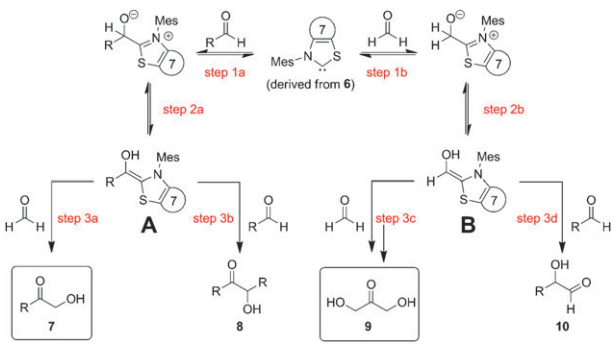
[a] Isolated yield after column chromatography. Reactions were run on a 1 mmol scale. [b] Yield determined after 6 h. [c] On a 10 mmol scale, a similar yield of 70% was obtained. [d] Yield determined after 20 h. [e] Yield determined by ^{1}H NMR; reaction on 0.25 mmol scale. [f] Yield determined after 12 h.

of aldehydes proved suitable. First, the hydroxymethylation of benzaldehyde provided 70% of the desired product, on a 1 mmol as well as on a 10 mmol scale (entry 1).§ However, generally, ^{1}H NMR analysis of the crude reaction mixture indicates a significantly higher yield. Some of the product might be lost upon column chromatography. This notion was validated by a simple control experiment: reduction of the crude reaction product with $NaBH_4$ resulted in the formation of the corresponding diol product, which could be isolated in an improved yield of 79%.[13] Several *para*-substituted benzaldehyde derivatives were smoothly hydroxymethylated in good yields, with electron-poor aldehydes leading to higher yields than electron-rich ones (entries 2–6). Although *o*-chloro benzaldehyde reacts well (entry 8), *ortho*-substitution results in reduced yields in some cases (entries 9 and 10). This kind of deterioration is often observed in NHC-catalyzed umpolung chemistry due to the increased steric shielding of the aldehyde moiety of these substrates. Several halide-containing hydroxymethyl ketones can readily be formed (entries 2, 3, 7 and 8), allowing further functionalization by standard cross-coupling methodology. The use of *o*-propargyloxy-benzaldehyde (entry 10) also represents an interesting competition experiment, since this substrate is known to undergo an NHC-catalyzed hydroacylation of the alkyne moiety.[7d] Under standard conditions, however, only the desired hydroxymethylation product was observed.

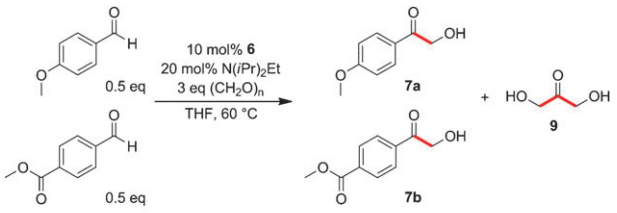
Moreover, the smooth hydroxymethylation of 2-furyl-carbaldehyde and the mono-hydroxymethylation/cyclization of benzene-1,2-dicarbaldehyde are remarkable (entries 11 and 12). The benzopyranone, formed in the latter reaction in 64% yield, is difficult to obtain with alternative methods.[14] In addition, non-aromatic aldehydes can also be hydroxymethylated (entries 13 and 14).

A straightforward mechanistic scenario is shown in Scheme 1. The sequence involves the nucleophilic attack of the NHC onto the aldehyde group (step 1), proton transfer giving the Breslow intermediates **A** or **B** (step 2), and finally the addition to an electrophilic aldehyde group, followed by proton transfer and elimination of the NHC catalyst (step 3). Under the optimized reaction conditions and utilizing thiazolium salt **6** as the NHC precursor, **7** and **9** are formed, with **7** being the predominant product. In addition, small amounts of **8** could be found, whereas **10** was not detectable at all.[15] Considering the high electrophilicity and steric accessibility of CH_2O, it is reasonable that the Breslow intermediates **A** and **B** preferentially attack formaldehyde, resulting in the observed product distribution.

In order to shed some light on the mechanism, the following experiments were run. First, the reversibility of the formation of benzoin **8** under hydroxymethylation conditions was demonstrated by employing **8** (R = Ph) as a substrate, resulting in the formation of 27% of the corresponding product **7**.[13] Second, on the contrary, hydroxymethylation product **7** (R = Ph) was found to be stable under reaction conditions.[13,16] Finally, a simple competition experiment was insightful (Scheme 2). Treatment of an electron-rich and an electron-poor benzaldehyde derivative in the same flask under standard conditions strikingly showed the superior reactivity of more electrophilic aldehydes, resulting in the rapid formation of hydroxymethyl ketone **7b**. **7a** and dihydroxyacetone (**9**) are formed at approximately the same rate but significantly slower than **7b**. This seems to indicate that the addition of the Breslow intermediate to formaldehyde is *not* the rate-determining step of this transformation. Finally, it should be noted that a low equilibrium concentration of free CH_2O might also play a role for the observed product distribution.



Scheme 1 Plausible mechanistic pathways.



Entry	Time/min	7a (%)[a]	7b (%)[a]	9 (%)[a]
1	15	1	55	0
2	30	6	79	4
3	45	9	85	13
4	60	11	90	12
5	90	15	91	22
6	120	18	95	21

[a] The yields are based on the respective aldehyde and were determined by ^{1}H NMR analysis of the crude reaction mixture.

Scheme 2 Competition experiment.

In conclusion, we have developed a direct NHC-catalyzed hydroxymethylation of aldehydes that tolerates several important functional groups. In addition, some light is shed on the mechanistic intricacies of this remarkably selective transformation. The rather broad scope and the attractive features of this transformation should result in ample application of this method.

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Notes and references

§ General hydroxymethylation procedure: in an oven-dried Schlenk-flask sealed with a rubber septum, thiazolium salt **6** (37 mg, 0.1 mmol, 0.1 eq.), paraformaldehyde (90 mg, 3.0 mmol, 3.0 eq.) and the aldehyde (1.0 mmol, 1.0 eq.) were suspended in dry THF (4 mL). N(*i*Pr)$_2$Et (33 μL, 0.2 mmol, 0.2 eq.) was added and the resulting mixture was heated to 60 °C. In the case of aliphatic aldehydes, the aldehyde was added after stirring the other reactants for 5 min at room temperature. After a maximum reaction time of 24 h, the solvent was evaporated and the crude product pre-adsorbed on Celite. Flash chromatography on silica gel afforded the pure product.

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12 Further screening of different amounts of catalyst, paraformaldehyde and base, showed 10 mol% of the catalyst precursor **6**, 3 eq. of the paraformaldehyde and a ratio of base (N(*i*Pr)$_2$Et) to salt **6** of 2 : 1 to be optimal.

13 See ESI‡ for further details.

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15 At this point, the intermediate formation of **10** and its conversion to the observed product **7** by keto–enol tautomerism cannot be excluded. However, whereas the acid catalyzed conversion of hydroxy phenyl acetaldehyde to hydroxymethyl phenyl ketone is reported, to the best of our knowledge the base catalyzed one is not ((*a*) F. Weygand, H. J. Bestmann, H. Ziemann and E. Klieger, *Chem. Ber.*, 1958, **91**, 1043). For literature reports on the formation of hydroxy phenyl acetaldehyde, see: (; (*b*) D. Bojer, I. Kamps, X. Tian, A. Hepp, T. Pape, R. Fröhlich and N. W. Mitzel, *Angew. Chem., Int. Ed.*, 2007, **46**, 4176; (*c*) P. Tinapp, *Chem. Ber.*, 1971, **104**, 2266).

16 However, (ir)reversibility seems to depend on the electronic nature of the R substituent: whereas **7** (R = Ph) was stable under reaction conditions, the compound **7** substituted with an electron-withdrawing ester group (R = 4-CO$_2$Me–C$_6$H$_4$) was not (ref. 13).