Direct and Efficient N-Heterocyclic Carbene-Catalyzed Hydroxymethylation of Aldehydes

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1 General Information

Unless otherwise specified, all reactions were carried out in flame dried reaction vessels under argon. Reaction temperatures are reported as the temperature of the bath surrounding the reaction vessel.

THF was purified by distillation over Na-benzophenone and was transferred under argon. Dry ethanol was purchased from Acros and stored under argon over 4 Å molecular sieves. Depending on the quality of the aldehydes, aldehydes were purified either by distillation or washing with NaHCO₃ after dissolving in ether, prior to use. Paraformaldeyhde was dried under vacuum over P_2O_5 and stored under argon atmosphere.

Analytical thin layer chromatography was performed on Polygram SIL G/UV254 plates. Visualization was accomplished with short wave UV light or KMnO₄ staining solutions followed by heating. Flash chromatography was performed on Merck silica gel (40-63 mesh) by standard techniques or using a Büchi Sepacore Flash Chromatography or a Biotage Isolera Flash Purification System eluting with solvents as indicated.

All new compounds were fully characterized. NMR-spectra were recorded on a Bruker ARX-300, AV-300, AV-400 MHz or on a Varian Associated, Varian 600 unity plus. Chemical shifts (δ) are quoted in ppm downfield of tetramethylsilane. Coupling constants (*J*) are quoted in Hz.

Infrared spectra were recorded on a Varian Associated FT-IR 3100 Excalibur with ATR unit. The wave numbers (\tilde{v}) of recorded IR-signals are quoted in cm⁻¹. ESI mass spectra were recorded on a Bruker Daltonics MicroTof.

GC/MS Spectra were recorded on an Agilent Technologies 7890A GC-system with Agilent 5975C VL MSD or 5975 inert Mass Selective Detector (EI) and a HP-5MS column (0.25 mm x 30 m, Film: 0.25 μ m). The method used start with the injection temperature T₀; after holding this temperature for 3 min, the column is heated to temperature T₁ (ramp) and this temperature is held for an additional time t:

Method **50_20**: T₀ = 50 °C, T₁ = 280 °C, ramp = 20 °C/min, t = 3 min.

High Performance Liquid Chromatography (HPLC-MS) was performed on an Agilent Technologies (6110 Quadrupole LC/MS) using a methanol/ H_2O mixture with 0.025% acetic acid as mobile phase and an Aligent Eclipse XDB column (3.0 x 150 mm, Film: 5 µm).

2 Optimization Study

All optimization reactions were run on a 0.25 mmol scale. The given yields were determined by ${}^{1}H$ NMR spectroscopy of crude products in CDCl₃ using mesitylene as internal standard.

2.1 Catalyst Loading, Catalyst-Base Ratio

	10 mol% 6 20 mol% N(ⁱ Pr) ₂ Et <u>1 eq. (CH₂O)_n THF (0.25 M) 60 °C, 6 h</u>		ОН
entry	variation	time	yield [%]
1	10 mol% 6, 10 mol% N(ⁱ Pr) ₂ Et	24 h	69
2	10 mol% 6 , 10 mol% N(ⁱ Pr)₂Et	12 h	27
3	no variation	6 h	73
4	5 mol% 6 , 10 mol% N(ⁱ Pr) ₂ Et	6 h	62
5	1 mol% 6 , 2 mol% N(ⁱ Pr) ₂ Et	6 h	26

Table 1.

2.2 Equivalents of $(CH_2O)_{n}$, Time

	10 mol% 6 20 mol% N(ⁱ Pr) ₂ Et <u>3 eq. (CH₂O)_n H THF (0.25 M) 60 °C, 6 h</u>	-	ОН
entry	equivalents (CH ₂ O) _n	time	yield [%]
1	1	6 h	73
2	1	48 h	74
3	1.5	6 h	71
4	1.5	24 h	87
5	3	6 h	quant.
6	3	24 h	quant.
7	5	6 h	90
8	5	24 h	96

Та	bl	е	2.

3 General Procedure for the N-Heterocyclic Carbene-Catalyzed Hydroxymethylation of Aldehydes



In an oven-dried Schlenk-flask sealed with a rubber septum and equipped with a magnetic stir bar, 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.

4 Substrates

The products shown in entry 1^1 , 2^2 , 3^3 , 5^4 , 6^2 , 7^5 , 8^6 , 9^4 , 11^1 , 13^1 , 14^7 in **Table 2** of the article were already reported and characterized. The analytical data obtained for these compounds was in agreement with the literature.

4.1 4-(2-Hydroxyacetyl)-benzoic acid methylester (entry 4)



¹H NMR (300 MHz, CDCI₃): δ/ppm: 8.14-8.18 (m, 2H, CH_{arom}), 7.86-8.00 (m, 2H, CH_{arom}), 4.91 (s, 2H, CH₂), 3.96 (s, 3H, OCH₃);
¹³C NMR (100 MHz, d⁶-DMSO): δ/ppm: 199.1, 165.6, 138.1, 133.4, 129.5, 128.0, 65.7, 52.5; R_f (PE/EtOAc 8:2): 0.17; HR-MS: m/z

¹ T. Matsumoto, M. Ohishi, S. Inoue, *J. Org. Chem.* **1985**, *50*, 603.

² T. Tsujigami, T. Sugai, H. Ohta, *Tetrahedron: Asymmetry* **2001**, *12*, 2543.

³ Y.-Y. Xie, Z.-C- Chen, Synthetic Commun. **2002**, 32, 1875; C. Paizs, M. Toşa, C. Majdik, V. Bódai, L. Novák, F.-D. Irimie, L. Poppe, J. Chem. Soc. Perkin Trans. 1, **2002**, 2400.

⁴ N. Yoshikawa, T. Suzuki, M. Shibasaki, *J. Org. Chem.* **2002**, *67*, 2556.

⁵ Patent: R. A. Borman, R. A. Coleman, K. L. Clark, A. W. Oxford, G. Hynd, J. A. Archer, A. Aley, N. V. Harris, EP 1648876.

⁶ Z.-L. Wei, Z.-Y- Li, G.-Q. Lin, *Tetrahedron*, **1998**, *54*, 13059.

⁷ D. R. Coghlan, D. P. G. Hamon, R. A. Massy-Westropp, D. Slobedman, *Tetrahedron Asymmetry* **1990**, *1*, 299.

 $[M+Na]^+$: calculated for $[C_{10}H_{10}O_4Na]^+$: 217.0471, experimental: 217.0476; **LC-MS**: 14.46 min.; **IR (ATR):** 3600-3200, 1719, 1682, 1435, 1416, 1279, 1228, 1098, 982, 954, 766.

4.2 2-Hydroxy-1-(2-(prop-2-ynyloxy)phenyl)ethanone (entry 10)⁸

¹H NMR (400 MHz, CDCl₃): δ /ppm: 8.07-8.05 (m, 1H, CH_{arom}), 7.56 (ddd, OH J = 8.4 Hz, J = 7.3 Hz, J = 1.8 Hz, 1H, CH_{arom}), 7.15-7.07 (m, 2H, 4-H, CH_{arom}), 4.83 (d, J = 2.4 Hz, 2H, OCH₂), 4.81 (s, 2H, CH₂OH), 3.71 (brs, 1H, OH), 2.58 (t, J = 2.4 Hz, 1H, CH); ¹³C NMR (100 MHz, CDCl₃): δ /ppm:

199.1, 158.1, 135.26, 131.32, 123.8, 122.00, 113.12, 77.4; 76.8, 70.2, 56.4; \mathbf{R}_{f} (Tol/MTBE 95:5): 0.19; **HR-MS (ESI):** m/z [M+Na]⁺: calculated for [C₁₁H₁₀O₃Na]⁺: 213.0522, experimental: 213.0527; **LC-MS**: 20.71 min; **IR (ATR):** 3453, 3249, 3080, 3000-2900, 2114, 1650, 1597, 1484, 1453, 1294, 1268, 1215, 1170, 1117, 1084, 1006, 975, 924, 752, 728, 672.

4.3 1-Hydroxy-1H-2-benzopyran-4(3H)-one (entry 12)

¹H NMR (300 MHz, DMSO): δ /ppm: 7.88-7.84 (m, 1H, 5-H), 7.72 (td, J = 7.5 Hz, J = 1.4 Hz, 1H, 7-H), 7.58-7.51 (m, 1H, 6-H), 7.49 (ddt, J = 7.6 Hz, J = 1.2 Hz, J = 0.6 Hz, 1H, 8-H), 7.34 (d, J = 6.3 Hz, 1H, OH), ^{8a} 1⁰2

 $^{\circ}$ $^{\circ}$ $^{\circ}$ 6.03 (d, *J* = 6.3 Hz, 1H, 1-H), 4.62 (d, *J* = 17.3 Hz, 1H, 3-H), 4.29 (d, *J* = 17.3 Hz, 1H, 3-H); ¹³C NMR (101 MHz, DMSO): δ/ppm: 194.4 (C4), 143.0 (C8a), 134.6 (C7), 128.9 (C6), 128.4 (C4a), 126.0 (C8), 125.0 (C5), 91.1 (C1), 66.3 (C3); **R**_f (PE/EtOAc 8:2): 0.19; **t**_R (50_20): 10.90 min; MS (GC-MS): m/z (%): 164 (3), 146 (5), 135 (9), 134 (80), 133 (10), 118 (5), 106 (19), 105 (100), 104 (5), 91 (6), 90 (5), 89 (6), 78 (10), 77 (38), 76 (9), 74 (5), 63 (6), 51 (15), 50 (10); HR-MS (ESI): m/z [M+Na]⁺: calculated for [C₉H₈O₃Na]⁺: 187.0366, experimental: 140.0389, m/z [M+Na+MeOH]⁺: calculated for [C₁₀H₁₂O₄Na]⁺: 219.0628, experimental: 219.0633; IR (ATR): 3500-3100, 1676, 1601, 1418, 1308, 1281, 1244, 1206, 1101, 1054, 1025, 988, 947, 865, 742; EA (%): calculated for C₉H₈O₃: C 65.85, H 4.91, found: C 65.73, H 4.92.

⁸ The 2-(Prop-2-ynyloxy)benzaldehyde was prepared following a reported procedure: F. Birbaum, A. Neels, C. G. Bochet, *Org. Lett.* **2008**, *10*, 3175.

5 Synthesis of 1-phenyl-2-hydroxyethanon (7) on a 10 mmol scale

According to the general procedure, thiazolium salt **6** (372 mg, 1 mmol, 0.1 eq.), paraformaldehyde (900 mg, 30.0 mmol, 3.0 eq.), benzaldehyde (1.0 mL, 10 mmol, 1.0 eq.) and N(ⁱPr)₂Et (0.33 mL, 2.0 mmol, 0.2 eq.) were solved in dry THF (40 mL). The resulting mixture was heated to 60 °C for 6 h. The solvent was evaporated and the crude product pre-adsorbed on Celite. Flash Chromatography on silica gel (200 g, PE/EtOAc 95:5 \rightarrow 1:1) afforded 958 mg (7.0 mmol, 70%) of 1-phenyl-2-hydroxyethanone (**7**). Additionally, 38 mg (0.2 mmol, 4%⁹) benzoin (**8**) was isolated. The obtained analytical data of the latter was in agreement with the analytical data of the commercially available compound.¹⁰

6 Isolation of 9 as Di(triethylsilyloxy)acetone

In a flame-dried screw-capped test tube equipped with a magnetic stir bar, thiazolium salt **6** (37 mg, 0.1 mmol, 0.1 eq.), and paraformaldehyde (90 mg, 3.0 mmol, 3.0 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 for 90 min. After cooling to room temperature imidazole (170 mg, 2.5 mmol, 2.5 eq.) was added followed by drop-wise addition of freshly distilled triethylsilyl chloride (0.4 mL, 2.5 mmol, 2.5 eq.) at 0 °C. The reaction mixture was stirred at room temperature for 2 h and filtered through silica to remove imidazolium chloride. Evaporation of the solvent afforded the crude product which was pre-adsorbed on Celite. Flash Chromatography on silica gel (15 g, PE/EtOAc 95:5; 30 g, PE/DCM 8:2 \rightarrow DCM) gave the pure as a colourless liquid (88 mg, 0.28 mmol, 28%).

¹H NMR (400 MHz, CDCl₃): $\overline{0}$ /ppm: 4.42 (s, 4H, CH₂), 0.96 (t, J = 8.0 Hz, 18H, CH₃), 0.63 (q, J = 8.0 Hz, 12H, CH₂); ¹³C NMR (100 MHz, CDCl₃) $\overline{0}$ /ppm: 208.9 (CO), 67.7 (CH₂), 6.8 (CH₃), 4.4

(CH₂); **R**_f (PE/EtOAc 95:5): 0.46; **t**_R **(50_20):** 12.67 min.; **MS (GC-MS):** m/z (%): 289 (17), 259 (19), 157 (19), 129 (15), 118 (10), 117 (100), 115 (50), 103 (16), 101 (7), 88 (8), 87 (42), 75 (19), 59 (27), 47 (8), 45 (10); **HR-MS (ESI):** m/z [M+Na]⁺: calculated for $[C_{15}H_{24}O_3Si_2Na]^+$: 341.1939, experimental: 341.1951; **IR (ATR):** 2955, 2912, 2878, 1743, 1458, 1415, 1241, 1185, 1136, 1097, 1005, 778, 726.

 $[\]frac{9}{10}$ The yield is referred to benzaldehyde and not to the maximum amount of benzoin.

¹⁰ Benzoin was purchased from Sigma-Aldrich.

7 Control Experiment: Two-step Synthesis of 1-Phenyl-1,2ethanediol



In a flame-dried screw-capped test tube equipped with a magnetic stir bar, 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. After 6 h the reaction mixture was cooled to room temperature, THF was removed under reduced pressure and the obtained crude product was further dried under high vacuum over night. The residue was dissolved in dry ethanol (8 mL) and cooled to -15 °C before adding NaBH₄ (76 mg, 2.0 mmol, 2.0 eq.) in one portion. The reaction mixture was allowed to warm to room temperature for 4 h. Excess of NaBH₄ was quenched by slow addition of HCl (1M). The aqueous phase was separated and extracted with diethyl ether (6 x 30 mL). The combined organic layers were washed with brine, dried over MgSO₄ and the solvent was evaporated under reduced pressure. The obtained crude product was pre-adsorbed with Celite before purified by flash chromatography on silica (25 g, DCM:MeOH 98:2→90:10) giving the pure product as a white solid (109 mg, 0.79 mmol, 79%). The analytical data was in agreement with the literature.¹¹

8 Mechanistic Investigation

8.1 Benzoin as Substrate in the Hydroxymethylation Reaction



In a flame-dried screw-capped test tube equipped with a magnetic stir bar thiazoliumsalt **6** (9 mg, 0.025 mmol, 0.1 eq.), paraformaldehyde (22.5 mg, 0.75 mmol,

¹¹ R. Kadyrov, R. M. Koenigs, C. Brinkmann, D. Voigtlaender, M. Rueping, *Angew. Chem. Int. Ed.* **2009**, *48*, 7556.

3.0 eq.) and benzoin (26.5 mg, 0.125 mmol, 0.5 eq.) were dissolved in dry THF (1 mL). $N({}^{i}Pr)_{2}Et$ (8.3 µL, 0.05 mmol, 0.2 eq.) was added and the resulting mixture was heated to 60 °C. After 24 h, the mixture was filtered through a pasteur pipette packed with silica. The solvent was evaporated and the residue dissolved in CDCl₃. The yield was determined by ¹H NMR spectroscopy with mesitylene (35 µL, 0.25 mmol, 1.0 eq.) as internal standard.

¹H NMR spectrum in CDCl₃ and mesitylene as standard:



8.2 Test for Reversible Product Formation



In a flame-dried screw-capped test tube equipped with a magnetic stir bar thiazolium salt **6** (9 mg, 0.025 mmol, 0.1 eq.) and the respective α -hydroxyketone (0.25 mmol, 1.0 eq.) were dissolved in dry THF (1 mL). N(ⁱPr)₂Et (8.3 µL, 0.05 mmol, 0.2 eq.) was added and the resulting mixture was heated to 60 °C. After 24 h the mixture was filtered through a pasteur pipette filled with silica. The solvent was evaporated and the residue dissolved in CDCl₃ adding mesitylene (35 µL, 0.25 mmol, 1 eq.) as internal standard.

1: No decomposition of the starting material was observed. **7** was completely recovered as per the ¹H NMR spectrum.

2: Only 54% of **7b** was recovered as per the ¹H NMR spectrum.

1 ő 11 10 mol% 6 20 mol% N(ⁱPr)₂Et THF 60 °C, 24 h 7 11 7 ő remained ÓН unreacted 8b Ö 11:8b 6:5 2 OН 10 mol% 6 12 **7b** 41% Ô 20 mol% N(ⁱPr)₂Et THF 60 °C, 24 h 7b 12 Ô ÓΗ ÓН 13 ö 8

8.3 Stability of 7 and 7b in Presence of Another Electrophile

In a flame-dried screw-capped test tube equipped with a magnetic stir bar thiazolium salt **6** (9 mg, 0.025 mmol, 0.1 eq.), the respective α -hydroxyketone (0.125 mmol, 0.5 eq.) and the respective aldehyde (0.125 mmol, 0.5 eq.) were dissolved in dry THF (1 mL). N(ⁱPr)₂Et (8.3 µL, 0.05 mmol, 0.2 eq.) was added and the resulting mixture was heated to 60 °C. After 24 h the mixture was filtered through a pasteur pipette filled with silica. The solvent was evaporated and the residue dissolved in CDCl₃ adding mesitylene (35 µL, 0.25 mmol, 1.0 eq.) as internal standard.

1-phenyl-2-hydroxyethanone 7 did not react under the present reaction conditions.
4-formyl-benzoic acid methyl ester 11 was converted to the homo-benzoin product 8b in 56% yield. Its presence was additionally confirmed by HR-MS (ESI) spectrometry.
8b: HR-MS (ESI): m/z [M+Na]⁺: calculated for [C₁₈H₁₆O₆Na]⁺: 351.0845, experimental:

351.0826.

2: 41% of 4-(2-hydroxyacetyl)-benzoic acid methyl ester 7b was recovered in ¹H NMR spectrum of the crude product after 24 h. The amount of benzoin products 13 and 8 could not be determined by ¹H NMR spectroscopy. Their formation was confirmed by HR-MS spectrometry.

13: HR-MS (ESI): m/z [M+Na]⁺: calculated for $[C_{16}H_{14}O_4Na]^+$: 293.0784, experimental: 293.0780.

HR-MS (ESI): m/z [M+Na]⁺: calculated for $[C_{14}H_{12}O_2Na]^+$: 235.0730, experimental: 8: 235.0727.



¹H NMR of experiment **1**:

8.4 Competition Experiments



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

Table 3.

In a flame-dried screw-capped test tube equipped with a magnetic stir bar thiazolium salt **6** (9 mg, 0.025 mmol, 0.1 eq.), paraformaldehyde (22.5 mg, 0.75 mmol, 3.0 eq.), *p*-anisaldehyde (15 μ L, 0.125 mmol, 0.5 eq.) and 4-formyl-benzoic acid methyl ester (20.5 mg, 0.125 mmol, 0.5 eq.) were dissolved in dry THF (1 mL). N(ⁱPr)₂Et (8.3 μ L, 0.05 mmol, 0.2 eq.) was added and the resulting mixture was heated to 60 °C. After the respective time noted in the table 3, the mixture was filtered through a pasteur pipette filled with silica. The solvent was evaporated and the residue dissolved in CDCl₃. The yield was determined by ¹H NMR spectroscopy with mesitylen (35 μ L, 0.25 mmol, 1.0 eq.) as internal standard.

Selected ¹H NMR spectra of the competition experiment:

Section of the ¹H NMR spectrum after 15 min:



Section of the ¹H NMR spectrum after 30 min:



Section of the ¹H NMR spectrum after 60 min:



9 Spectra

9.1 1-Phenyl-2-hydroxyethanone (entry 1)



9.2 1-(4-Chlorophenyl)-2-hydroxyethanone (entry 2)



9.3 1-(4-Bromophenyl)-2-hydroxyethanone (entry 3)



110 100 f1 (ppm)

9.4 4-(2-Hydroxyacetyl)-benzoic acid methyl ester (entry 4)



9.5 1-(4-Methylphenyl)-2-hydroxyethanone (entry 5)



9.6 1-(4-Methoxyphenyl)-2-hydroxyethanone (entry 6)



9.7 1- (3-Bromophenyl)-2-hydroxyethanone (entry 7)





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9.8 1-(2-Chlorophenyl)-2-hydroxyethanone (entry 8)



9.9 1-(2-Methylphenyl)-2-hydroxyethanone (entry 9)



9.10 2-Hydroxy-1-[2-(prop-2-ynyloxy)phenyl] ethanone (entry 10)



9.11 2-Hydroxy-1-(2-furyl)ethanone (entry 11)



9.12 1-Hydroxy-1H-2-benzopyran-4(3H)-one (entry 12)



110 100 f1 (ppm)





The yield for entry 13 (Table 2) was determined by ¹H NMR, since the product isolation proved difficult.

9.14 1-Hydroxy-3-methyl-3-phenylpropan-2-one (entry 14)







9.16 1-Phenyl-1,2-ethanediol

