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Graphical Abstract

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Microwave-assisted synthesis of hydroxymethyl ketones using azolium-2-carboxylate zwitterions as catalyst precursors

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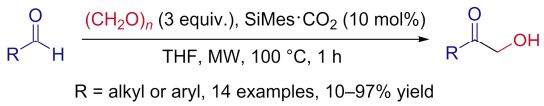

R = alkyl or aryl, 14 examples, 10–97% yield

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This paper is dedicated to the memory of Ronald Breslow (1931–2017) by one of the authors (L.D.)

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ABSTRACT

Following an initial screening of six common imidazolium, imidazolinium, and dithiolium salts in the presence of a base, 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IDip) and 1,3-dimesitylimidazolin-2-ylidene (SIMes) were identified as promising organocatalysts for the microwave-assisted synthesis of hydroxymethyl ketones from aldehydes and paraformaldehyde. The azolium-2-carboxylate zwitterions IDip·CO_2 and SIMes·CO_2 were then tested as single-component N-heterocyclic carbene (NHC) precursors in the hydroxymethylation of heptanal and benzaldehyde. The latter adduct was an efficient precatalyst for the two reactions. It was successfully applied to a broad range of aliphatic and aromatic substrates (14 examples, 10–97% yields).

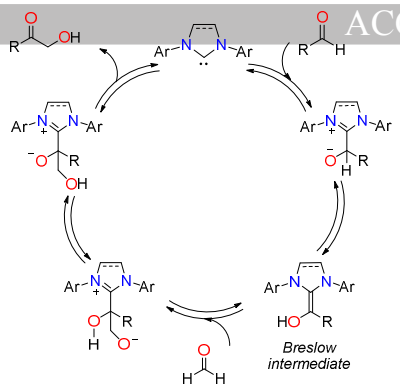
1. Introduction

The α-hydroxymethyl ketone motif (also called acyloin) is present in various important biologically active compounds, such as antidepressant drugs, HIV-protease inhibitors,[1] selective inhibitors of amyloid-β protein production, agents for the treatment of Alzheimer's disease,[2] antitumor,[3,4] antibiotic,[5,6] and antifungal[7] agents. Moreover, the CO–CH_2OH unit is easily converted into many other functional groups, which contribute to further expand its synthetic potential. Hence, chemical or enzymatic pathways leading to hydroxymethyl ketones have found many applications in organic synthesis and pharmaceutical chemistry.[2] Currently, the most common strategies to access these compounds involve oxidation,[8–14] reduction,[15,16] or hydrolysis[17,18] of more complex substrates. Obviously, a simple and efficient catalytic method that would allow the direct hydroxymethylation of aldehydes via C–C bond formation would provide a highly valuable alternative to these stoichiometric functional group interconversions in terms of atom economy and sustainability.[19]

Over the past 25 years, N-heterocyclic carbenes (NHCs) have emerged as powerful tools for organometallic chemistry and organic synthesis.[20] At first, they served as ancillary ligands for a wide range of transition metal complexes that found numerous applications in homogeneous catalysis,[21,22] with the best example probably being Grubbs' and Hoveyda-Grubbs' second-generation olefin metathesis catalysts.[23,24] In the past decade, their use as stand-alone organocatalysts for various reactions has also undergone significant developments.[25] The majority of these processes are initiated by a nucleophilic attack of the carbene onto carbonyl groups. According to the mechanism originally postulated by Breslow for the condensation of aldehydes,[26,27] the result is a polarity reversal ("umpolung") of these substrates and their conversion into self-condensation products with the formation of a new C–C bond.[28,29]

The NHC-catalyzed hydroxymethylation of several classes of aldehydes with paraformaldehyde was first reported by Kuhl and Glorius in 2011.[30] A plausible catalytic cycle for this transformation involves the nucleophilic attack of the carbene onto the substrate (Scheme 1, step 1), followed by a proton transfer to afford a Breslow intermediate (step 2), and its addition onto formaldehyde (step 3). Another proton transfer and the release of the final product regenerate the catalyst (steps 4 and 5). Experimental protocols devised so far usually require heating for extended periods of time (at least 24 h).[30,31]

In a recent report, we showed that microwave irradiation promoted the fast and efficient conversion of aldehydes and paraformaldehyde into α-hydroxymethyl ketones using NHC organocatalysts derived from thiazolium salts under environmentally friendly conditions.[32] These results prompted us to further investigate the influence of other types of NHC precursors on the catalytic system. Herein, we disclose the results of these endeavors.



Scheme 1. Plausible mechanism for the hydroxymethylation of aldehydes using NHCs as catalysts.

2. Results and discussion

To begin our study, several common imidazolium (**1**–**3**), imidazolinium (**4**, **5**), or dithiolium salts (**6**) were screened in the catalytic hydroxymethylation of aliphatic and aromatic aldehydes with paraformaldehyde. The most efficient catalyst precursor identified thus far, namely, thiazolium perchlorate **7** served as a benchmark for these experiments (Chart 1). All these acidic salts were deprotonated with a base to release the corresponding free carbenes *in situ*. The reactions were carried out by using the microwave-assisted procedure previously optimized in our laboratory.[32] Thus, one equivalent of an aldehyde was reacted with three equivalents of paraformaldehyde in the presence of an NHC precursor (10 mol%) and diisopropylethylamine (20 mol%) in dry tetrahydrofuran for 1 h at 100 °C (Table 1).

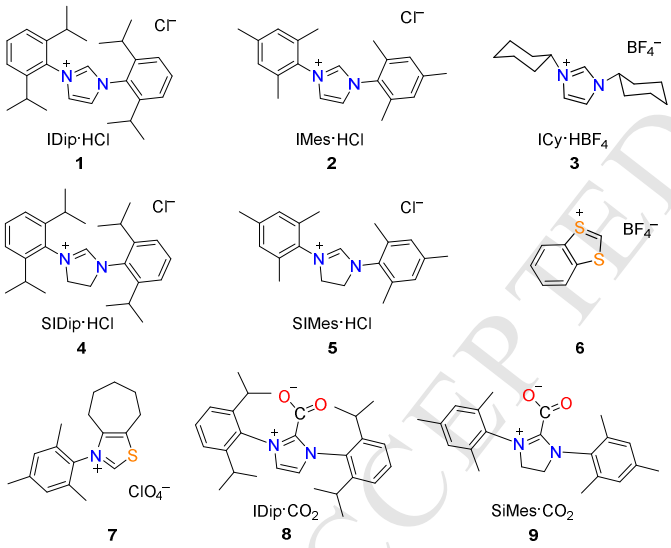
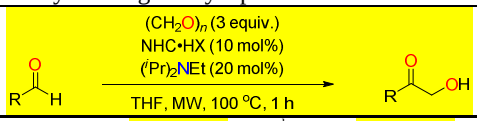


Chart 1. NHC precursors used in this study.

Heptanal and benzaldehyde were chosen as representative aliphatic and aromatic aldehydes and the experimental results are listed in Table 1. Within the series of dinitrogen and disulfur heterocycles under investigation (**1**–**6**), 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (**1**) afforded the highest yields of both target compounds. This bulky imidazolium salt that we shall designate IDip·HCl also outperformed the mixed nitrogen/sulfur-based thiazolium precatalyst **7** in the hydroxymethylation of benzaldehyde, but not in the case of heptanal. With the aromatic substrate, conversion reached 65% after 1 h and 2-hydroxyacetophenone was isolated in 52% yield after purification by flash column chromatography. It is noteworthy that the second best catalyst precursor of our set was the ubiquitous mesityl-substituted imidazolinium salt nicknamed SIMes·HCl (**5**).

Table 1. Microwave-assisted hydroxymethylation of heptanal and benzaldehyde using catalyst precursors **1**–**7**



NHC precursor	Conversion[a]/yield[b] of 1-hydroxy-2-octanone (%)	Conversion[a]/yield[b] of 2-hydroxyacetophenone (%)
1	17[a]	65[a] (52)[b]
2	7[b]	7[b]
3	0[a]	0[a]
4	7[b]	10[b]
5	15[b]	29[a] (14)[b,c]
6	0[a]	0[a]
7	58[b]	45[b]

[a] Conversion determined by NMR based on the relative integration of the two protons next to the hydroxyl group of the product and the aldehyde proton of the reactant.

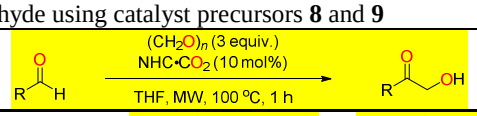
[b] Isolated yield after flash column chromatography.

[c] Reaction performed in a round bottom flask with a reflux condenser under argon using a thermostated oil bath at 70 °C for 24 h.

Next, we decided to probe the catalytic activity of azolium-2-carboxylate zwitterions **8** and **9** (Chart 1). These betaines are the inner salt analogues of IDip·HCl (**1**) and SIMes·HCl (**5**). They behave as convenient surrogates for air- and moisture-sensitive carbenes.[33] Indeed, several research groups have already taken advantage of these labile adducts for the stoichiometric preparation of transition metal complexes bearing NHC ligands with concomitant release of carbon dioxide.[34–37] In organocatalysis, their use as NHC precursors is still underdeveloped with only a few applications in organic synthesis[38–40] and polymer chemistry.[41,42] It should be pointed out, however, that a thiazolium-2-carboxylate zwitterion was found to induce the self-condensation of aliphatic and aromatic aldehydes already in 1985.[43]

To our great satisfaction, IDip·CO_2 (**8**) and SIMes·CO_2 (**9**) were efficient catalyst precursors for the hydroxymethylation of the two model aliphatic and aromatic aldehydes (Table 2). The latter betaine performed particularly well in the synthesis of 1-hydroxy-2-octanone from heptanal and paraformaldehyde. In most cases, recourse to the azolium-2-carboxylate inner salts led to higher yields than the combination of IDip·HCl (**1**) or SIMes·HCl (**5**) and diisopropylethylamine. The zwitterions also compared favorably with thiazolium salt **7** whose synthesis is less straightforward.

Table 2. Microwave-assisted hydroxymethylation of heptanal and benzaldehyde using catalyst precursors **8** and **9**



NHC precursor	Yield of 1-hydroxy-2-octanone (%)[a]	Yield of 2-hydroxy-acetophenone (%)[a]
8	21	29
9	76 (9)[b]	44 (0)[b]

[a] Isolated yield after flash column chromatography.

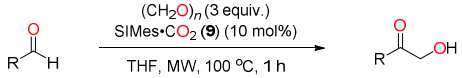
[b] Reaction performed in a round bottom flask with a reflux condenser under argon using a thermostated oil bath at 70 °C for 24 h.

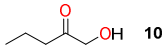
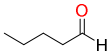
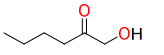
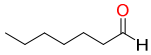
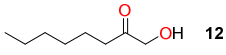
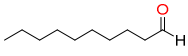
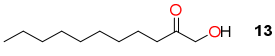
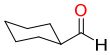
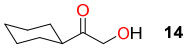
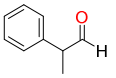
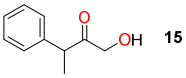
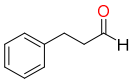
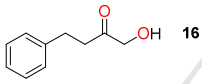
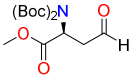
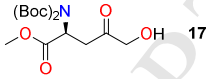
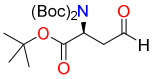
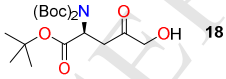
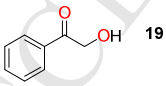
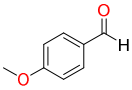
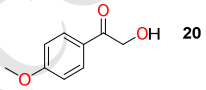
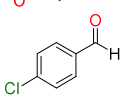
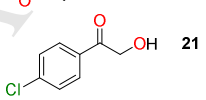
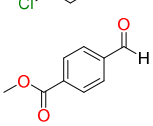
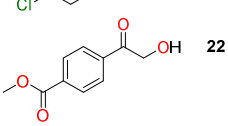
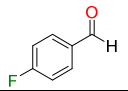
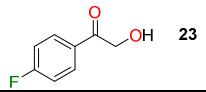
Control experiments carried out under reflux conditions in an oil bath at 70 °C revealed that the NHC·CO_2 precatalysts were

almost inactive at this temperature (Table 2), whereas the NHC·HCl salts mixed with $^{i}Pr_2NEt$ led to significant conversions under similar conditions (*cf.* Table 1). This discrepancy might be correlated with thermogravimetric analysis data, which showed that IDip·CO_2 (**8**) did not lose weight below *ca.* 120 °C in the solid state, while SIMes·CO_2 (**9**) resisted degradation up to *ca.* 160 °C.[34] Thus, performing the reaction in a pressure vial at 100 °C under microwave irradiation was not only very convenient from a practical point of view, it was also a requisite to induce a thermal decarboxylation of the zwitterionic adducts.

Having identified 1,3-dimesitylimidazolinium-2-carboxylate (**9**) as a valuable, single-component catalyst precursor for the hydroxymethylation of heptanal and benzaldehyde, we decided to probe the scope of the reaction by testing additional aliphatic and aromatic substrates. These reactants and the hydroxymethyl ketones obtained are depicted in Table 3, along with the yields recorded after purification of the products by flash column chromatography.

Table 3. Microwave-assisted hydroxymethylation of various aliphatic and aromatic aldehydes catalyzed by SIMes·CO_2 (**9**)



Entry	Reactant	Product	Yield (%)[a]
1		 **10**	15
2		 **11**	37
3		 **12**	77
4		 **13**	97
5		 **14**	52
6		 **15**	25
7		 **16**	49
8		 **17**	20
9		 **18**	26
10		 **19**	44
11		 **20**	<10
12		 **21**	94
13		 **22**	96
14		 **23**	53

[a] Isolated yield after flash column chromatography.

First, we repeated the synthesis of 1-hydroxy-2-octanone (**12**), which was isolated in 77% yield after 1 h of reaction under microwave irradiation at 100 °C (Table 3, entry 3). An almost quantitative yield of 1-hydroxy-2-undecanone (**13**) was obtained starting from decanal (entry 4), whereas butanal and pentanal afforded the C_5 and C_6 linear hydroxymethyl ketones **10** and **11** in 15 and 37% yield, respectively (entries 1 and 2). The progressive drop in yield observed when the alkyl chain was shortened is probably due to the greater volatility of the reactants and products, thereby leading to significant loss of materials during experimental set-up and work-up. Additional syntheses performed with various branched aldehydes afforded products **14**–**18** in moderate to satisfactory yields (entries 5–9). With these bulkier substrates, it can be assumed that the activation of the carbonyl group by nucleophilic attack of the NHC catalyst is sterically hindered. It should be emphasized that only a few successful hydroxymethylation reactions of aliphatic aldehydes were reported in the literature so far.[30,32] Moreover, to the best of our knowledge, compound **18** had never been synthesized before. Hence, despite the modest yields obtained in some cases, the present study represents a significant advance in the field.

In a final series of experiments, we investigated the reactivity of various *para*-substituted benzaldehydes with paraformaldehyde in the presence of SIMes·CO_2 (**9**) in a microwave reactor at 100 °C. As already evidenced using thiazolium salt **7** as a catalyst precursor,[30,32] electron-withdrawing groups led to higher yields of 2-hydroxyacetophenones than electron-donating ones. Indeed, almost quantitative yields of products **21** and **22** bearing *para*-chloro and *para*-methoxycarbonyl substituents, respectively, were attained within 1 h (Table 3, entries 12 and 13), whereas unsubstituted benzaldehyde led to a 44% yield under the same conditions (entry 10). The activating effect of a fluorine atom in *para*-position was less pronounced and derivative **23** was isolated in 53% yield (entry 14). Conversely, the introduction of a *para*-methoxy group significantly decreased the yield of product **20** that stagnated below 10% (entry 11). Last but not least, we were pleased to note that SIMes·CO_2 (**9**) afforded higher yields of aromatic hydroxymethyl ketones **21** and **22** than thiazolium salt **7** and diisopropylethylamine whether these catalyst precursors were heated at 60 °C for 24 h in a Schlenk flask or at 100 °C for 1 h in a microwave reactor.[30,32]

3. Conclusion

The catalytic activity of six common NHCs generated *in situ* by deprotonation of imidazolium, imidazolinium, and dithiolium salts (**1**–**6**) with a base was probed in the hydroxymethylation of two representative aliphatic and aromatic aldehydes using a microwave-assisted procedure previously optimized for thiazolium salt **7** in our laboratory. This screening allowed us to identify 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IDip) and 1,3-dimesitylimidazolin-2-ylidene (SIMes) as promising nucleophilic catalysts for the synthesis of hydroxymethyl ketones via C–C bond formation.

We then investigated the use of azolium-2-carboxylates **8** and **9** as a convenient alternative to the association of azolium chlorides and a base. Indeed, IDip·CO_2 and SIMes·CO_2 are stable zwitterionic adducts that can be easily prepared on a multigram scale and kept for extended periods of time before being handled in the air to ultimately release free carbenes without the need for a base or any other additive. To our great satisfaction, SIMes·CO_2 (**9**) proved to be an efficient catalyst precursor for the two test-reactions under consideration. It was also successfully applied to the hydroxymethylation of a broad range of aliphatic and aromatic substrates. Hence, recourse to an NHC·CO_2 betaine under microwave irradiation is a catalytic method of choice for accessing the important class of α-hydroxymethyl ketones, espe-

cially those derived from aliphatic aldehydes, which are notoriously difficult to obtain.

4. Experimental section

4.1. Materials and methods

Melting points were determined on a Büchi 530 apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ at 298 K on a Varian Mercury spectrometer using the $CHCl_3$ residual peak as an internal reference for ^1H (7.27 ppm) and the central peak of $CDCl_3$ at 77.0 ppm for ^{13}C. A CEM Discover apparatus was used for microwave irradiation. TLC plates (silica gel 60 F_{254}) and silica gel 60 (230–400 mesh) for flash column chromatography were purchased from Merck. Spots were detected with UV light and/or phosphomolybdic acid and/or ninhydrin in EtOH stain. THF was dried by standard procedures and stored over molecular sieves. Aldehydes were purified by extraction with 10% aqueous $NaHCO_3$ or distillation and employed within a day. 1,3-Benzodithiolium tetrafluoroborate (**6**) was purchased from TCI. Imidazol(in)ium salts **1**–**5**,[44] thiazolium salt **7**,[45] and imidazol(in)-ium-2-carboxylates **8** and **9**[34] were prepared according to literature. All the other solvents and chemicals were reagent grade and used without any further purification. Petroleum ether (PE) refers to the fraction of b.p. 40–60 °C. All the products gave satisfactory elemental analysis. The microwave-assisted synthesis of hydroxymethyl ketones using NHC·HX precursors **1**–**7** was carried out according to literature.[32] The two protected aldehydes that derived from L-aspartic acid were prepared according to the literature.[46,47]

*4.2. Typical procedure for the synthesis of hydroxymethyl-ketones using catalyst **9***

A solution of an aldehyde (1.0 mmol) in dry THF (0.29 mL), SIMes·CO_2 (0.1 mmol, 35 mg), and paraformaldehyde (3 mmol, 90 mg) were introduced into a 10 mL glass vial. The vial was flushed with argon and the reaction mixture was stirred and heated to 100 °C for 1 h in a microwave reactor (50 W maximum power). After cooling to room temperature, the solvent was evaporated under reduced pressure. The residue was taken up with CH_2Cl_2 (15 mL) and H_2O (15 mL). The aqueous layer was extracted twice with CH_2Cl_2 (15 mL each). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The product was purified by flash column chromatography using the eluents described below.

*4.2.1. 1-Hydroxy-2-pentanone (**10**)*[48]

Yellowish oil (15% yield); flash column chromatography eluent: PE/AcOEt 8/2 to 7/3 v/v; δ_H (200 MHz, $CDCl_3$) 4.24 (2H, s, C*H*$_2$OH), 3.50 (1H, s, OH), 2.33 (2H, t, *J* 8.0 Hz, CH_2), 1.72–1.59 (2H, m, CH_2), 0.85 (3H, t, *J* 8.0 Hz, CH_3); δ_C (50 MHz, $CDCl_3$) 210.7, 67.4, 31.5, 17.0, 13.6.

*4.2.2. 1-Hydroxy-2-hexanone (**11**)*[48]

Yellow oil (32% yield); flash column chromatography eluent: PE/AcOEt 8/2 to 7/3 v/v; δ_H (200 MHz, $CDCl_3$) 4.21 (2H, s, C*H*$_2$OH), 2.39 (2H, t, *J* 8.0 Hz, CH_2), 2.20–2.16 (2H, m, CH_2), 1.73–1.62 (2H, m, CH_2), 0.88 (3H, t, *J* 8.0 Hz, CH_3); δ_C (200 MHz, $CDCl_3$) 180.9, 70.2, 34.5, 25.0, 23.0, 14.4.

*4.2.3. 1-Hydroxy-2-octanone (**12**)*[49]

Yellow oil (77% yield); flash column chromatography eluent: PE/AcOEt 8/2 to 7/3 v/v; δ_H (200 MHz, $CDCl_3$) 4.22 (2H, s, C*H*$_2$OH), 3.36 (1H, s, OH), 2.38 (2H, t, *J* 8.0 Hz, CH_2), 1.60–1.40 (2H, m, CH_2), 1.40–1.10 (6H, m, CH_2), 0.85 (3H, t, *J* 8.0 Hz, CH_3); δ_C (50 MHz, $CDCl_3$) 210.2, 68.3, 38.6, 31.7, 29.1, 23.9, 22.6, 14.2; *m/z* (ESI) 145.3 ([M+H]$^+$, 52%).

*4.2.4. 1-Hydroxy-2-undecanone (**13**)*[50]

Yellowish solid (97% yield); m.p. 44–46 °C (lit. m.p. 47 °C);[50] flash column chromatography eluent: PE/AcOEt 8/2 to 7/3 v/v; δ_H (200 MHz, $CDCl_3$) 4.18 (2H, s, C*H*$_2$OH), 3.50 (1H, s, OH), 2.34 (2H, t, *J* 8.0 Hz, CH_2) 1.59–1.49 (2H, m, CH_2), 1.27–1.10 (12H, m, CH_2), 0.85 (3H, t, *J* 8.0 Hz, CH_3); δ_C (50 MHz, $CDCl_3$) 210.3, 68.3, 38.6, 32.0, 29.6, 29.5, 29.4, 29.3, 23.9, 22.8, 14.3; *m/z* (ESI) 190.2 ([M+H]$^+$, 100%).

*4.2.5. 1-Cyclohexyl-2-hydroxyethan-1-one (**14**)*[30]

Yellow oil (52% yield); flash column chromatography eluent: PE/AcOEt 8/2 to 7/3 v/v; δ_H (200 MHz, $CDCl_3$) 4.26 (2H, s, C*H*$_2$OH), 3.35 (1H, s, OH), 2.50–2.20 (1H, m, CH), 2.00–1.50 (4H, m, CH_2), 1.50–1.10 (6H, m, CH_2); δ_C (200 MHz, $CDCl_3$) 212.0, 66.4, 46.3, 28.8, 25.8, 25.4; *m/z* (ESI) 143.3 ([M+H]$^+$, 52%).

*4.2.6. 1-Hydroxy-3-phenylbutan-2-one (**15**)*[30]

Yellowish oil (25% yield); flash column chromatography eluent: PE/AcOEt 9/1 to 7/3 v/v; δ_H (200 MHz, $CDCl_3$) 7.50–7.00 (5H, m, arom), 4.20 (2H, s, C*H*$_2$OH), 3.77 (1H, q, *J* 4.0 Hz, CH), 2.88 (1H, s, OH), 1.48 (3H, d, *J* 4.0 Hz, CH_3); δ_C (50 MHz, $CDCl_3$) 210.0, 139.3, 129.1, 127.7, 127.6, 66.8, 49.1, 17.1; *m/z* (ESI) 135.0 ([M+H]$^+$, 48%).

*4.2.7. 1-Hydroxy-4-phenylbutan-2-one (**16**)*[51]

Yellow oil (49% yield); flash column chromatography eluent: PE/AcOEt 8/2 to 7/3 v/v; δ_H (200 MHz, $CDCl_3$) 7.30–7.13 (5H, m, arom), 4.16 (2H, s, C*H*$_2$OH), 2.98 (2H, t, *J* 8.0 Hz, CH_2), 2.70 (2H, t, *J* 8.0 Hz, CH_2); δ_C (200 MHz, $CDCl_3$) 209.6, 141.8, 126.3, 125.8, 125.6, 68.7, 38.0, 35.5.

*4.2.8. Methyl (S)-2-((bis-tert-butoxycarbonyl)amino)-5-hydroxy-4-oxopentanoate (**17**)*[32]

White solid (20% yield); m.p. 103–105 °C (lit. m.p. 108–110 °C);[32] $[\alpha]_D^{20}$ –69 (*c* 1.12, $CHCl_3$); flash column chromatography eluent: PE/AcOEt 8/2 to 7/3 v/v; δ_H (200 MHz, $CDCl_3$) 5.56–5.49 (1H, m, CH), 5.09 (1H, br, OH), 4.40–4.20 (2H, m, C*H*$_2$OH), 3.67 (3H, s, OCH_3), 3.47–3.34 (1H, m, C*H*H), 2.69–2.54 (1H, m, CH*H*), 1.46 (18H, s, Boc); δ_C (200 MHz, $CDCl_3$) 206.7, 170.3, 151.6, 83.7, 68.2, 54.1, 52.6, 39.3, 27.8; *m/z* (ESI) 216.3 ([M–(Boc–COOMe)]$^+$, 100%).

*4.2.9. tert-Butyl (S)-2-((bis-tert-butoxycarbonyl)-amino)-5-hydroxy-4-oxopentanoate (**18**)*

Yellow oil (57% yield); $[\alpha]_D^{20}$ –27 (*c* 1, $CHCl_3$); flash column chromatography eluent: PE/AcOEt 8/2 to 7/3 v/v; R_f (30% AcOEt/PE) 0.40; δ_H (200 MHz, $CDCl_3$) 5.50–5.45 (1H, m, CH), 4.36 (1H, d, *J* 6 Hz, C*H*HOH), 4.28 (1H, d, *J* 6 Hz, CH*H*OH), 3.46–3.33 (1H, m, C*H*H), 3.15–3.00 (1H, br, OH), 2.65–2.54 (1H, m, CH*H*), 1.49 (18H, s, Boc), 1.40 (9H, s, $C(CH_3)_3$); δ_C (200 MHz, $CDCl_3$) 206.5, 168.7, 152.1, 83.4, 82.2, 68.4, 55.0, 39.1, 29.6, 28.0; Anal. Calcd for $C_{19}H_{33}NO_8$: C, 56.56; H, 8.24; N, 3.47; found C, 56.50; H, 8.27; N, 3.50.

*4.2.10. 2-Hydroxyacetophenone (**19**)*[52]

White solid (44% yield); m.p. 82–84 °C (lit. m.p. 84–85 °C);[52] flash column chromatography eluent: PE/AcOEt 8/2 to 7/3 v/v; δ_H (200 MHz, $CDCl_3$) 7.91 (2H, d, *J* 8.0 Hz, arom), 7.80–7.20 (3H, m, arom), 4.87 (2H, s, C*H*$_2$OH), 3.52 (1H, br, OH); δ_C (50 MHz, $CDCl_3$) 198.4, 134.3, 133.3, 128.9, 127.6, 65.4; *m/z* (ESI) 135.0 ([M–H]$^-$, 45%).

*4.2.11. 2-Hydroxy-1-(4-methoxyphenyl)ethan-1-one (**20**)*[53]

Yellow solid (6% yield); m.p. 98–100 °C (lit. m.p. 99–101 °C);[53] flash column chromatography eluent: PE/AcOEt 9/1 to 7/3 v/v; δ_H (200 MHz, $CDCl_3$) 7.89 (2H, d, *J* 8.0 Hz, arom), 6.96

(2H, d, *J* 8.0 Hz, arom), 4.81 (2H, s, CH_2OH), 3.87 (3H, s, OCH_3), 3.51 (1H, s, OH); δ_C (50 MHz, $CDCl_3$) 196.7, 164.3, 132.2, 130.0, 114.1, 64.9, 55.5.

*4.2.12. 1-(4-Chlorophenyl)-2-hydroxyethan-1-one (**21**)*[51]

Yellowish solid (94% yield); m.p. 117–119 °C (lit. m.p. 116–118 °C);[51] flash column chromatography eluent: PE/AcOEt 8/2 to 7/3 v/v; δ_H (200 MHz, $CDCl_3$) 7.86 (2H, d, *J* 6.0 Hz , arom), 7.48 (2H, d, *J* 6.0 Hz, arom), 4.84 (2H, s, CH_2OH), 3.47 (1H, br, OH); δ_C (50 MHz, $CDCl_3$) 197.9, 164.3, 132.2, 130.0, 129.7, 65.8.

*4.2.13. Methyl 4-(2-hydroxyacetyl)benzoate (**22**)*[30]

Yellowish solid (96% yield); m.p. 154–156 °C (lit. m.p. 154–156 °C);[32] flash column chromatography eluent: PE/AcOEt 9/1 to 7/3 v/v; δ_H (200 MHz, $CDCl_3$) 8.16 (2H, d, *J* 8.0 Hz, arom), 7.97 (2H, d, *J* 8.0 Hz, arom), 4.86 (2H, s, CH_2OH), 3.91 (3H, s, OCH_3), 3.16 (1H, s, OH); δ_C (50 MHz, $CDCl_3$) 214.5, 139.3, 130.4, 130.1, 127.2, 127.6, 65.8, 52.6; *m/z* (ESI) 195.1 ($[M+H]^+$, 55%).

*4.2.14. 1-(4-Fluorophenyl)-2-hydroxyethan-1-one (**23**)*[14]

White solid (53% yield); m.p. 108–110 °C (lit. m.p. 109–111 °C);[14] flash column chromatography eluent: PE/AcOEt 8/2 to 7/3 v/v; δ_H (200 MHz, $CDCl_3$) 7.93–7.86 (2H, m, arom), 7.20–7.08 (2H, m, arom) 4.79 (2H, s, CH_2OH), 3.47 (1H, br, OH); δ_C (50 MHz, $CDCl_3$) 196.8, 166.4 (d, J_{CF} 255 Hz), 130.4 (d, J_{CF} 9.5 Hz), 129.8 (d, J_{CF} 3.0 Hz), 116.2 (d, J_{CF} 22 Hz), 65.3.

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