Cadmium-Mediated Carbonyl Benzylation in Tap Water

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Abstract: Zn/CdCl2 has been developed as a mediator in the benzylation of various aldehydes in tap water affording the corresponding alcohols in moderate to good yields. The addition of a catalytic amount of InCl3 increases the yield of benzylation product significantly. It can selectively mediate the benzylation of aldehydes in the presence of ketones. A mechanism involving the formation of a cation π-complex is proposed based on the experimental facts.

Key words: cadmium, tap water, Barbier-type reaction, organometallics, benzylation

Benzylation of carbonyl compounds by benzyl halides, mediated by metals, to produce 1,2-dialy alcohol is one of the most useful processes in organic synthesis because of the great potential for 1,2-dialy alcohol to be converted to important building blocks in natural product synthesis. Usually, this type of reaction is performed in anhydrous organic solvent. Since the 1980s, the importance of organic reactions carried out in aqueous media has been gradually recognized not only because the tedious protection-deprotection processes can be simplified for certain functional groups containing acidic hydrogen atoms, but also because there is a growing public interest in green chemistry. Among the range of organic reactions carried out in aqueous media, Barbier-type reactions have been extensively studied. So far many metals, such as indium, zinc, and tin, have been reported to be effective in mediating the alkylation of carbonyl compounds to the corresponding homoallylic alcohols in aqueous media. In addition to allyl halides, cinnamyl5 and propargyl halides,7 α-bromo ketones7 and ester8 have been successfully coupled with carbonyl compounds. Surprisingly, benzylation of carbonyl compounds in aqueous media has not been the topic of much interest. More recently, a cadmium salt has been developed to help promote carbonyl alkylation9 and carbonyl benzylation.10 Described below is the study of carbonyl benzylation mediated by Zn/CdCl2 in water (Scheme 1).

In our initial attempts to carry out the benzylation of benzaldehyde in the presence of zinc powder in distilled water, the desired product, 1,2-diphenylethanol was not observed at all (Table 1, entry 1). In fact the products were biphenyl ethane (the major product) along with toluene, benzyl alcohol and a small amount of 1,2-diphenylethene-1,2-diol. When a catalytic amount of CdCl212 was added to this reaction system, biphenyl ethane and toluene were still the major products, however, careful examination of the crude extract of the reaction mixture revealed the presence of the desired product, but in only 5% yield (Table 1, entry 2). This result indicated that CdCl2 could promote the benzylation reaction. In order to improve the yield of benzylation product, the amount of CdCl2 was increased and it was found that the dosage of CdCl2 affected the yield. When the amount of CdCl2 was increased from 0.5 to 1 equivalent the yield of benzylation product was enhanced from 56% to 65% (Table 1, entries 7 and 8). Nevertheless, no benzylation product was observed when either only CdCl2 (Table 1, entry 3) or regular cadmium powder was employed in the reaction (Table 1, entry 4). Therefore it was reasoned that zinc and CdCl2 cooperated to promote the benzylation reaction. Subsequently, different metals and Lewis acid were employed instead of zinc and cadmium chloride, to increase the yield and to gain a better understanding of the mechanism. As shown in Table 1 (entries 5, 6, 10–12), among all of the bimetal systems tested, Zn/CdCl2 is the most effective system for the carbonyl benzylation reaction. Interestingly, when 0.1 mmol of InCl3 was added to this system, the yield of benzylation product was increased significantly, although Zn/InCl3 alone did not mediate the reaction with benzaldehyde (Table 1, entries 12–14). Additionally, BiCl3 and SnCl4 were also tested as the third component in the system, however, the yield of benzylation product decreased even further (Table 1, entries 15, 16).

Subsequently, a variety of aldehydes were tested in Zn/CdCl2 and Zn/CdCl2/InCl3 systems and the results are summarized in Table 2. All of the compounds in this table were characterized by IR, MS, 1H NMR, and 13C NMR spectroscopy.

All of these reactions were carried out in water, without the help of either buffer solution or organic co-solvent. The yield of desired product was not affected regardless...
The nature of the benzyl halide affected the outcome of the reaction; benzyl chloride is more efficient than benzyl bromide, probably due to the higher activity of benzyl bromide. In fact, a higher yield of biphenyl ethane, resulting from the self-coupling, was observed when benzyl bromide was used as the reactant. However, addition of InCl₃, which serves as a Lewis acid, can catalyze the reactions and improve the yield of benzylation product significantly.

The reaction conditions were so mild as to not affect groups such as chloro (Table 2, entries 5, 8), methoxy (Table 2, entries 7, 9), or methyl (Table 2, entry 6) on the aromatic ring. Especially, substrates containing hydroxyl group were successfully employed in this reaction without protection (Table 2, entries 10, 11), yielding the corresponding diaryl alcohol.

In the Zn/CdCl₂/InCl₃ system, all the aromatic aldehydes were benzylation effectively to afford the desired product in high yields (Table 2, entries 1–11). The conjugated aliphatic aldehyde also underwent benzylation in good yield (Table 2, entry 12). However, the reaction of aliphatic aldehydes afforded only the corresponding products in poor yields (Table 2, entries 13 and 14). Disappointingly, ketones could not be benzylation under these conditions (Table 2, entries 15–17) since they are less reactive than aldehydes.

The different reactivity of aldehydes and ketones led us to exploit the chemoselectivity of this benzylation reaction in water. When using this tri-metal system, the benzylation of 4-acetylbenzaldehyde (1r) afforded exclusively the product (3r) in 94% yield, the ketone moiety is unaffected (Equation 1). These results indicated that Zn/CdCl₂/InCl₃ could selectively mediate the benzylation of an aldehyde in the presence of a ketone.

Equation 1

Additionally, the diastereoselectivity of both Zn/CdCl₂ and Zn/CdCl₂/InCl₃ mediated benzylation was studied using 2-chlorophenylethane (Table 3). In all the cases, InCl₃ cannot affect the diastereoselectivity of benzylation product although it can improve the reaction yield significantly. Interestingly, the syn-product is favored by ortho-substituted benzaldehyde regardless whether the substituting group is electron-donating (entry 5) or electron-withdrawing (entry 3). On the other hand, the anti-product is slightly favored by para-substituted benzaldehydes regardless of whether the substituting group is electron-donating (entry 4) or electron-withdrawing (entry 2).

Considering the toxicity of the cadmium compound, the potential to recycle the reagent system was studied. In order to recover CdCl₂ and InCl₃, the reaction mixture was extracted with ethyl acetate and the organic layer was washed with water thrice; the aqueous layers were combined and concentrated. ICP-MS determination of the amount of cadmium in the organic layer showed that more than 99.99% cadmium was in the aqueous phase. The reactivity of recovered CdCl₂ and InCl₃ was investigated. To recovered CdCl₂ and InCl₃ were added bezaldehyde (1.0 mmol), benzyl chloride (2.0 mmol), and zinc powder (2.0 mmol). Then the reaction mixture was allowed to stir at room temperature for 3 hours; the reaction mixture was treated in the same manner as mentioned above and the reaction yield was determined by 1H NMR and ICP-AES. As indicated in Table 4 below, recovered CdCl₂ and InCl₃ with added Zn can effectively mediate the benzylation reaction even after it is recycled several times. Thus the tox-

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**Table 1** Benzylation of the Benzaldehyde under the Various Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Conditions</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>Zn powder</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>Zn/CdCl₂</td>
<td>12</td>
<td>5</td>
</tr>
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<tr>
<td>4</td>
<td>Br</td>
<td>CdCl₂</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Br</td>
<td>Mg/CdCl₂</td>
<td>24</td>
<td>f</td>
</tr>
<tr>
<td>6</td>
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<td>56</td>
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<tr>
<td>8</td>
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<td>3</td>
<td>65</td>
</tr>
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<td>9</td>
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<td>84</td>
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<tr>
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<td>3</td>
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</tr>
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<td>Zn/InCl₃</td>
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<td>0</td>
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<tr>
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<td>80</td>
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<tr>
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<td>16</td>
<td>Cl</td>
<td>Zn/CdCl₂/SnCl₂</td>
<td>3</td>
<td>72</td>
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</tbody>
</table>

**a** Zn powder (2 equiv) and Lewis acid (1 equiv) unless otherwise noted.

**b** Isolated yield.

**c** CdCl₂ (0.1 equiv; based on benzaldehyde).

**d** CdCl₂ (0.5 equiv; based on benzaldehyde).

**e** InCl₃, BiCl₃, and SnCl₂ (0.1 equiv; based on benzaldehyde).

**f** Determined by GC-MS.

**g** Pinacol coupling product was observed by analysis of GC-MS.
ic reagent in this system is not only completely recovered but also efficiently reused.

To gain a greater insight into the mechanism of the present reaction, several experiments were performed:

(1) GC–MS analysis revealed that biphenyl ethane and toluene, the byproducts of the carbonyl benzylation, resulted only when 1 equivalent of zinc powder and benzyl bromide were stirred in water. Similar results were obtained when 1 mole equivalent of zinc powder, benzaldehyde, and benzyl bromide were subjected to the same process. However, addition of 1.0 equivalent of CdCl₂ furnished the benzylation product with a concomitant decrease in byproduct (biphenyl ethane and toluene) formation. These results showed that zinc not only reacts with benzyl halide to give biphenyl ethane and toluene but that addition of CdCl₂ could significantly change this process from the self-coupling of benzyl halide to carbonyl benzylation.

(2) Compared with benzyl bromide, benzyl chloride cannot react with zinc in water, thus indicating that when carbonyl compounds were involved, these two benzyl halides proceeded by a different path.

(3) As mentioned in Table 1, no product was observed when either CdCl₂ or zinc was employed alone. The corresponding product was not formed either when Zn was replaced by other metals or when CdCl₂ was substituted for other Lewis acids. Therefore, both Zn and CdCl₂ are essential to the carbonyl benzylation.

In order to explain these experimental facts, a hypothesis is proposed in Scheme 2. In the absence of CdCl₂, zinc can react with both benzyl halide and aldehyde. It is known that aqueous media can serve as solvents for the generation of allylic zinc halides and their addition to aldehydes and ketones. In the same manner, benzylzinc bromide is generated on the surface of zinc. This intermediate is in equilibrium with the charge-separated form and the radi-
The addition of CdCl₂ changes the reaction path promoting carbonyl benzylation path 3, possibly due to the formation of a cation-π-complex from Cd²⁺ and benzyl halide. At the same time, the metal ion In³⁺ serves as a Lewis acid and activates the carbonyl group. All of these factors mentioned above allow the reaction to proceed through path 3 (carbonyl benzylation) to afford 1,2-diphenyl-ethanol in a high yield.

Based on these experimental facts, a possible mechanism is proposed in Scheme 3. Initially, Zn inserts into the C–X bond to generate benzylzinc halide, simultaneously, Cd²⁺ is reduced by zinc and the resulting Cd⁰ loses an electron to give an oxidant, a singly-charged cadmium (Cd⁺). Secondly, benzylzinc halide coordinates with Cd⁺ to form Cd⁺–π-benzyl halide (II; Scheme 3). Then, this complex (II) adds to the activated carbonyl compounds and gives the benzylation products.

As for benzyl chloride, as shown above, no chemical change was observed when it was left in water with zinc for prolonged periods. However, carbonyl benzylation were complete within 3 hours (either benzyl chloride or bromide) upon addition of cadmium. Therefore it is possible that Cd⁺ coordinates with benzyl halide to form Cd⁺–π-benzyl halide (I; Scheme 4). Then, Zn inserts into the C–X bond to generate complex (II), which adds to the activated carbonyl compounds and gives the benzylation products.

In conclusion, Zn/CdCl₂ was applied to carbonyl benzylation, affording the corresponding products in good yields. InCl₃ promotes carbonyl benzylation and increases
the reaction yield significantly. Good diastereoselectivity also can be achieved, once the positions of the groups on the aromatic ring are chosen appropriately. Also, good chemoselectivity can be obtained in this system. The reaction mechanism was proposed on the basis of the experimental results.

Zn powder, Cd powder, CdCl₂, BiCl₃, SnCl₂, InCl₃, BnBr, and BnCl were purchased from Shanghai Chemical Industry Co., Ltd. and other chemicals were purchased from Aldrich Chemical Industry Co., Ltd. All the chemicals were not purified before being used. IR spectra were recorded on a Perkin-Elmer, 2000 FTIR. MS were recorded on a Bruker DMX500. ¹H NMR spectra were obtained on a HP 5890 (II)/HP5972. ¹H NMR spectra were recorded on a Bruker DMX500.

Carbonyl Benzylation; General Procedure

To a mixture of benzaldehyde (1.0 mmol) and BnCl (2.0 mmol) in H₂O (5 mL), Zn powder (2.0 mmol), CdCl₂ (1.0 mmol), and InCl₃ (0.1 mmol) were added. The mixture was stirred at room r.t. for the time period shown in Table 2. Then the mixture was extracted with EtOAc (3 × 10 mL) and dried over anhyd MgSO₄. The organic solvent was removed under reduced pressure. The residue was purified by column chromatography (EtOAc–petroleum ether, 1:6) to afford analytically pure product. IR, NMR and MS spectral data of benzylation products are followed:

1-(1-Naphthyl)-2-phenylethanol (3e)

FT-IR (KBr): 3420, 1602, 1492, 1046 cm⁻¹.

¹H NMR (CDCl₃): δ = 1.95–2.12 (br, 1 H), 2.95 (d, 2 H, J = 5.52 Hz), 5.81 (t, 1 H, J = 5.52 Hz), 7.13–7.30 (m, 9 H).

¹C NMR (CDCl₃): δ = 42.68, 77.49, 110.37, 126.80, 128.28, 128.61, 129.57, 137.58, 142.07, 155.94.

GC-MS: m/z = 232.5.

1-(4-Methylphenyl)-2-phenylethanol (3f)

GC-MS: m/z = 212.

1-(4-Chlorophenyl)-2-phenylethanol (3g)

GC-MS: m/z = 228.

1-(2-Furanyl)-2-phenylethanol (3d)


1-(1-Naphthyl)-2-phenylethanol (3e)

1H NMR (CDCl₃): δ = 1.85–2.00 (br, 1 H), 3.14 (d, 2 H, J = 4.95 Hz), 4.87 (t, 1 H, J = 4.95 Hz), 7.17–7.34 (m, 10 H).

¹C NMR (CDCl₃): δ = 46.37, 75.60, 126.22, 126.92, 127.92, 128.82, 128.88, 129.84, 130.00, 138.36.

GC-MS: m/z = 198.

1-Piperonyl-2-phenylethanol (3b)

1H NMR (CDCl₃): δ = 2.05–2.15 (br, 1 H), 2.94 (d, 2 H, J = 6.07 Hz), 4.75 (t, 1 H, J = 6.07 Hz), 5.90 (s, 2 H), 6.73 (m, 2 H), 6.86 (s, 1 H), 7.14–7.16 (m, 2 H), 7.21–7.22 (m, 1 H), 7.25–7.27 (m, 2 H).

¹C NMR (CDCl₃): δ = 46.19, 75.98, 101.13, 106.64, 108.17, 119.51, 126.74, 128.63, 129.64, 138.18, 147.07, 147.86.

HRMS-GC: m/z calcd for C₁₄H₁₆O₃, 242.0943; found, 242.0942.

1-(2-Furanylnyl)-2-phenylethanol (3d)

1H NMR (CDCl₃): δ = 1.85–2.00 (br, 1 H), 3.14 (d, 2 H, J = 4.95 Hz), 4.87 (t, 1 H, J = 4.95 Hz), 7.17–7.34 (m, 10 H).

¹C NMR (CDCl₃): δ = 46.37, 75.60, 126.22, 126.92, 127.92, 128.82, 128.88, 129.84, 130.00, 138.36.

GC-MS: m/z = 198.

1-(2-Methoxyphenyl)-2-phenylethanol (3i)

FT-IR (KBr): 3417, 1612, 1513, 1033 cm⁻¹.

¹H NMR (CDCl₃): δ = 2.45–2.55 (br, 1 H), 2.99–3.03 (m, 1 H), 3.18–3.21 (m, 1 H), 3.89 (s, 3 H), 5.20 (t, 1 H, J = 6.64 Hz), 6.45–7.38 (m, 9 H).
1H NMR (CDCl₃): δ = 2.74 (t, J = 6.92 Hz), 2.88–2.90 (m, 1 H), 7.13–7.15 (m, 5 H).
13C NMR (CDCl₃): δ = 138.37, 55.44, 110.54, 120.86, 126.45, 126.92, 128.43, 128.46, 129.65, 132.02, 139.08, 156.41.

GC-MS: m/z = 228.

1-2-Hydroxy-5-methoxyphenyl)-2-phenylethanol (3k)
FT-IR (KBr): 3388, 3026, 2921, 1601, 1497, 1071 cm⁻¹.
1H NMR (CDCl₃): δ = 1.90–2.12 (br, 1 H), 2.63–2.99 (m, 2 H), 4.49–4.52 (m, 1 H), 6.22–6.60 (m, 1 H), 6.55–6.60 (d, J = 15.88 Hz), 7.23–7.36 (m, 10 H).
13C NMR (CDCl₃): δ = 44.34, 73.62, 126.65, 126.78, 127.81, 128.70, 128.73, 129.75, 130.54, 131.64, 136.87, 137.84.

HRMS-GC: m/z calcd for C₁₅H₁₇O₂, 244.1201; found, 244.1193.

1,4-Diphenylbut-3-en-2-ol (3l)
FT-IR (KBr): 3388, 3026, 2921, 1601, 1497, 1071 cm⁻¹.
1H NMR (CDCl₃): δ = 2.74 (t, J = 6.92 Hz), 2.88–2.90 (m, 1 H), 7.13–7.15 (m, 5 H).
13C NMR (CDCl₃): δ = 138.37, 55.44, 110.54, 120.86, 126.45, 126.92, 128.43, 128.46, 129.65, 132.02, 139.08, 156.41.

HRMS-GC (EI): m/z calcd for C₁₅H₁₇O₂, 244.1201; found, 244.1193.

2-Phenylethanol (3m)
FT-IR (KBr): 3383, 5174, 1495, 1080 cm⁻¹.
1H NMR (CDCl₃): δ = 0.90 (t, J = 6.64 Hz), 1.27–1.30 (m, 6 H), 1.52–1.54 (m, 4 H), 2.62–2.69 (m, 1 H), 2.70–2.81 (br, 1 H), 2.82–2.87 (m, 1 H), 3.78–3.86 (m, 1 H), 7.21–7.35 (m, 5 H).
13C NMR (CDCl₃): δ = 14.31, 22.83, 25.94, 29.53, 32.05, 37.05, 44.26, 72.92, 126.64, 128.76, 129.86, 138.86.

HRMS-GC (EI): m/z calcd for C₇H₁₀O, 206.1671; found, 206.1671.

1-4-(Acetylated)-2-phenylethanol (3o)
FT-IR (KBr): 3459, 2923, 1666, 1003, 1045 cm⁻¹.
1H NMR (CDCl₃): δ = 2.21–2.38 (br, 1 H), 2.56 (s, 3 H), 2.99 (d, 2 H, J = 6.61 Hz), 4.93 (t, 1 H, J = 6.61 Hz), 7.14–7.17 (m, 2 H), 7.22–7.31 (m, 3 H), 7.40 (d, 2 H, J = 8.33 Hz), 7.89 (d, 2 H, J = 8.33 Hz).
13C NMR (CDCl₃): δ = 26.67, 46.08, 74.86, 126.14, 126.87, 128.56, 128.65, 129.61, 136.43, 137.48, 149.27, 198.00.

HRMS-GC (CI): m/z calcd for C₁₅H₁₀O₂ (M + H), 241.1229; found, 241.1244.
1H NMR (CDCl3): δ = 1.23 (anti) and 1.40 (syn) (d, J = 7.10 Hz, 3 H), 2.50–2.68 (br, 1 H), 3.20–3.33 (anti) and 3.31–3.36 (syn) (m, 1 H), 3.84 (syn) and 3.87 (anti) (2H), 5.04 (syn) and 5.13 (anti) (d, J = 5.86, 8.20 Hz, 1 H), 6.88–7.41 (m, 9 H).

13C NMR (CDCl3): δ = 12.79, 127.95, 127.98, 128.06, 128.12, 128.25, 128.8, 128.41, 128.46, 130.89, 130.90, 144.40, 144.62, 156.26, 156.96.

HRMS-GC: m/z calc for C14H16O2, 242.0931; found, 242.0932.

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References


(9) (a) To the best of our knowledge there was one reported example of carbonyl benzylzation when we began this research. In this study the buffer solution and in some cases organic co-solvents were used, see: Bieler, L. W.; Storch, E. C.; Malvestiti, I.; Silva, M. F. Tetrahedron Lett. 1998, 39, 9393. (b) Recently Guo et al. have report that magnesium can mediate carbonyl benzylzation in aqueous media see: Deng, W.; Tan, X.-H.; Liu, L.; Guo, Q.-X. Chin. J. Chem. 2004, 22, 747.


(18) CdH4Cd+ had been observed, see: John, H. E.; Ian, G. D.; Reetz, M. T.; Wenderoth, B. Tetrahedron Lett. 1997, 38, 9373.


(20) It is easier for Cd than Zn to lose an electron. It is therefore not hard for a cadmium cluster to lose an electron to oxidants in water. Of course this does not mean the standard reduction potential of Cd2+/Cd is more negative than that of Zn2+/Zn. There are many reports on Cd2+. for example: Liao, M.-S.; Cadmium salt was reported as a Lewis acid for carbonyl allylation, see: (a) Sain, B.; Prajapati, D.; Sandhu, J. S. Tetrahedron Lett. 1992, 33, 4795. (b) Kobayashi, S.; Aoyama, N.; Manabe, K. Synlett 2002, 483.