A Concise Synthesis of ortho-Iodobenzyl Alcohols via Addition of ortho-Iodophenyl Grignard Reagent to Aldehydes and Ketones

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Abstract: A wide range of both secondary and tertiary ortho-iodobenzyl alcohols was synthesized via addition of ortho-iodophenyl Grignard reagents to aldehydes and ketones. Significant improvements in terms of yields were observed with ketones upon addition of CeCl₃. The potential application of the target compounds as precursors for novel electrophilic trifluoromethylating reagents based on hypervalent iodine derivatives was demonstrated.

Key words: addition reactions, Grignard reactions, organometallic reagents, benzyl alcohols, hypervalent iodine compounds

Aryl iodides frequently appear in chemical synthesis as target compounds or remarkably versatile intermediates. Especially the latter role places these compounds in the unique position to be transformed into a plethora of important products, usually by transition-metal-catalyzed coupling reactions¹ or via the corresponding organolithium or organomagnesium species.² Due to our interest in the chemistry of hypervalent iodine compounds,³ we needed a concise and efficient access to ortho-iodobenzyl alcohol derivatives. Though a broad palette of established protocols installing the iodine atom at the aromatic system is available,⁴ only a few of them are concerned with the iodination at the ortho-position.⁵ We felt intrigued by an alternative approach, which would rely upon modification of an aromatic system in the position ortho to iodine and considered 1,2-diiodobenzene (1) as a potential ortho-iodophenyl surrogate. Although one may argue that 1 is a rather expensive reagent, it can be purchased from bulk suppliers at a significantly lower price or promptly synthesized from cheap and readily available starting materials. Thus, anthranilic acid (8) undergoes diazotation upon treatment with isomyl nitrite in the presence of trichloroacetic acid.⁶ The resulting benzenediazonium-2-carboxylate (9) then forms benzyne, which is rapidly intercepted by iodine to afford 1 in satisfactory yield of 60% (Scheme 2).

Scheme 2  Facile synthesis of 1,2-diiodobenzene (1)

Selective replacement of one iodine atom in 1,2-diiodobenzene by transition-metal-catalyzed cross-coupling has already been described,⁷ also the formation of the corresponding 2-iodophenylmagnesium species 2, however, without systematic study of its reactivity.⁸ As the reaction
of \( \text{2} \) with carbonyl compounds would directly afford the desired ortho-iodobenzyl alcohols, we set out to inspect the reactivity of \( \text{2} \) with various electrophiles.

Although the use of 2-iodophenylmagnesium species \( \text{2} \) is described in the literature,\(^9\) its detailed and reproducible preparation is not. We thus primarily focused our attention on establishing conditions under which \( \text{2} \) is formed in an efficient and reliable manner. Extensive experimentation revealed that when 2 mmol of a 0.3 M solution of diiodobenzene (1) in anhydrous THF was treated with 1 mL of a 2 M solution of isopropylmagnesium chloride at \(-30\,^\circ\text{C}\) and the resulting mixture was gradually warmed to \(-20\,^\circ\text{C}\) over a period of 20 minutes, species \( \text{2} \) was quantitatively formed. Thus, GC-MS analysis of hydrolyzed samples of such mixtures showed the presence of iodobenzene exclusively (Figure 1).

We then proceeded to study the reactivity of \( \text{2} \) with various electrophiles (Scheme 1). A broad palette of both electron-rich and electron-poor aromatic and aliphatic aldehydes were tested and the reaction proved efficient yielding the anticipated ortho-iodobenzyl alcohols bearing a variety of functional groups (Table 1).

It is important to note that some of these compounds could not be prepared by ortho-directing lithiation followed by quenching with iodine because of the incompatibility of some substituents with the reaction conditions of the lithiation process (e.g., substrates \( \text{3d} \) and \( \text{3g} \)). Also the two methoxy groups in \( \text{3b} \) would direct the metalation to occur ortho to a methoxy group,\(^10\) thus rendering our desired product \( \text{4b} \) inaccessible. Interestingly, when 3-acetoxybenzaldehyde (\( \text{3h} \)) was exposed to \( \text{2} \), the reaction took place exclusively at the aldehyde functionality leaving the ketone moiety intact. The lower yield might be explained by the formation of by-products resulting from aldol condensation.

We subsequently sought to expand our protocol to other electrophiles. Preliminary results showed that ketones reacted only sluggishly and in the case of sterically hindered ones, the addition of \( \text{2} \) did not occur at all (Table 2). We considered the use of more nucleophilic analogues of \( \text{2} \) and were delighted to witness that the use of corresponding organocerium species \( \text{5} \), prepared by the transmetalation of \( \text{2} \) with anhydrous \( \text{CeCl}_3 \),\(^{11}\) led to significantly increased yields of the desired 2-iodobenzyl alcohols (Scheme 1, Table 2).

It is noteworthy that with some substrates \( \text{5} \) was prone to react even if \( \text{2} \) proved completely unreactive (ketone \( \text{6b} \)). A broad palette of various \( \alpha,\alpha \)-disubstituted ortho-iodobenzyl alcohols thus became accessible. To underline the synthetic utility of our strategy, note that the 2-iodobenzyl alcohol \( \text{7g} \) can also be synthesized from expensive, commercially available hexafluorocumyl alcohol via ortho-lithiation followed by the reaction with iodine in only 65% yield, whereby the purification of the product is rather troublesome.\(^{5b}\) In our hands, \( \text{7g} \) was formed in 80% yield with two equivalents of hexafluoroacetone (\( \text{6g} \)), but

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**Table 1** Reactivity of \( \text{2} \) with Various Aldehydes

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{3a} )</td>
<td>( \text{4a} )</td>
<td>89</td>
</tr>
<tr>
<td>( \text{3b} )</td>
<td>( \text{4b} )</td>
<td>79</td>
</tr>
<tr>
<td>( \text{3c} )</td>
<td>( \text{4c} )</td>
<td>94</td>
</tr>
<tr>
<td>( \text{3d} )</td>
<td>( \text{4d} )</td>
<td>97</td>
</tr>
<tr>
<td>( \text{3e} )</td>
<td>( \text{4e} )</td>
<td>94</td>
</tr>
<tr>
<td>( \text{3f} )</td>
<td>( \text{4f} )</td>
<td>78</td>
</tr>
<tr>
<td>( \text{3g} )</td>
<td>( \text{4g} )</td>
<td>59</td>
</tr>
<tr>
<td>( \text{3h} )</td>
<td>( \text{4h} )</td>
<td>71</td>
</tr>
</tbody>
</table>
the yield could be increased to 96% upon bubbling 6g through the reaction mixture. Unfortunately, in the case of camphor (6f) the reaction failed completely in both cases. We suspect that the steric hindrance around the carbonyl functionality in camphor is too important for the rather bulky 2-iodophenyl organometallic species 2 or 5.

Further attempts to react 2 or 5 with other electrophiles proved less fruitful as esters were left intact and nitriles or imines gave complex reaction mixtures of a negligible synthetic value. Only acetic anhydride readily reacted with 5 to afford the anticipated 1-(2-iodophenyl)ethanone (7h) in 82% yield.

To demonstrate the synthetic potential of the target compounds, we chose the bistrifluoromethylated 2-iodobenzyl alcohol 7g and submitted it to oxidative cyclization with t-BuOCl (Scheme 3). Thus, the resulting 1-chlorobenziodoxole 10 was obtained in 90% yield over two steps, this being a significant improvement compared to previous efforts. Intermediate 10 was then treated with potassium acetate to smoothly afford the acetate 11. Subsequent substitution of the acetoxy group by the action of Ruppert’s reagent (TMSCF3) in the presence of cesium fluoride furnished the I–CF3 3-iodane 12. The entire synthesis starting from diodobenzene proved highly efficient as 12 was obtained in only 4 steps with an overall yield of 53%, while the original preparation afforded 31% from hexafluorocumyl alcohol.

In conclusion, we have presented a concise approach towards a wide range of ortho-iodobenzyl alcohols by an addition of organomagnesium 2 or organocerium species 5 to aldehydes and ketones, respectively. The methodology was applied to a broad spectrum of substrates affording synthetically useful products, the preparation of which could be troublesome or impossible by other methods. In line with our research activities, one of the tertiary ortho-iodobenzyl alcohols 7g was used in the synthesis of the known hypervalent trifluoromethyl iodine compound 12 in a significantly improved yield compared to that previously reported.

All manipulations were performed under argon using standard Schlenk techniques, unless otherwise stated. 1H, 19F, and 13C NMR spectra were recorded on Bruker Avance spectrometers AC 200, DPX 250, and DPX 300. 1H positive chemical shifts in ppm are downfield from TMS. 19F NMR spectra were referenced to external CFCl3. Mass spectra were measured by the MS service of the Laboratorium für Organische Chemie (ETH Zürich). IR spectra were recorded on PerkinElmer Spectrum BX spectrometer.

**Table 2** Comparison of the Reactivity of 2 or 5 with Various Ketones

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%) with 2</th>
<th>Yield (%) with 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>7a</td>
<td>&lt;10</td>
<td>53</td>
</tr>
<tr>
<td>6b</td>
<td>7b</td>
<td>–a</td>
<td>87</td>
</tr>
<tr>
<td>6c</td>
<td>7c</td>
<td>22</td>
<td>66</td>
</tr>
<tr>
<td>6d</td>
<td>7d</td>
<td>64</td>
<td>72</td>
</tr>
<tr>
<td>6e</td>
<td>7e</td>
<td>44</td>
<td>53</td>
</tr>
<tr>
<td>6f</td>
<td>7f</td>
<td>–a</td>
<td>–a</td>
</tr>
<tr>
<td>6g</td>
<td>7g</td>
<td>80b (96)c</td>
<td>–</td>
</tr>
<tr>
<td>6h</td>
<td>7h</td>
<td>33</td>
<td>82</td>
</tr>
</tbody>
</table>

* No product detected.
* 2 equiv of hexafluoroacetone were used.
* Hexafluoroacetone was introduced directly into the reaction mixture in large excess.

**Scheme 3** Synthesis of electrophilic trifluoromethylating reagent 12

In conclusion, we have presented a concise approach towards a wide range of ortho-iodobenzyl alcohols by an addition of organomagnesium 2 or organocerium species 5 to aldehydes and ketones, respectively. The methodology was applied to a broad spectrum of substrates affording synthetically useful products, the preparation of which could be troublesome or impossible by other methods. In line with our research activities, one of the tertiary ortho-iodobenzyl alcohols 7g was used in the synthesis of the known hypervalent trifluoromethyl iodine compound 12 in a significantly improved yield compared to that previously reported.
necessary security measures should be taken and the compound should be constantly kept wet with solvent. It was filtered on a plastic funnel equipped with a glass frit and washed with THF (3 × 50 mL) and subsequently with 1,2-dichloroethane (3 × 50 mL). The precipitate was then transferred with the aid of a plastic spoon and 1,2-dichloroethane (50 mL) to a beaker. The resultant slurry was then carefully (!) added via pipette to a gently boiling solution of I\(_2\) (18.5 g, 72.8 mmol, 2 equiv) in 1,2-dichloroethane (175 mL). The resulting solution was then refluxed for 2 h until the frothing ceased. It was cooled down to r.t.,aq sat. Na\(_2\)SO\(_4\) (100 mL) was added, and the mixture was stirred for 15 min. The aqueous phase was then extracted with CH\(_2\)Cl\(_2\) (3 × 100 mL). The combined organic layers were dried (MgSO\(_4\)) and concentrated. Flash chromatography (silica gel, hexane) and distillation yielded 1,2-diiodobenzene as a colorless oil (71 g, 60%; bp 64–65 °C/0.05 mbar).

Addition of ortho-Idophenylmagnesium Species 2 to Aldehydes; General Procedure 1
The Grignard reagent was prepared immediately before use. In a Schlenk flask, 1,2-diiodobenzene (660 mg, 2 mmol) was dissolved in anhyd THF (6 mL) under argon. After cooling to −30 °C, isopropylmagnesium chloride (2.0 M solution in THF, 0.75 mL) was added at −20 °C over a period of 20 min. The reaction was monitored by GC-MS. Both flasks were cooled to −78 °C and the freshly prepared magnesium chloride (2.0 M solution in THF, 0.75 mL) was added anhyd THF (5 mL) under argon. After cooling to −30 °C, isopropylmagnesium chloride (2.0 M solution in THF, 0.75 mL) was added via pipette to a gently boiling solution of I\(_2\) (500 mg, 1.5 mmol) was dissolved in THF (2 mL) was added dropwise and the resulting orange colored mixture was warmed to r.t. overnight. After dilution with Et\(_2\)O (10 mL), the mixture was hydrolyzed in an ice bath with aq sat. NH\(_4\)Cl (10 mL). The combined organic layers were dried (Na\(_2\)SO\(_4\)) and evaporated to dryness in vacuo. The crude product obtained was purified by flash chromatography (silica gel, hexane–EtOAc).

Addition of ortho-Idophenylmercuric Species 3 to Ketones; General Procedure 2
Anhyd CeCl\(_3\) (370 mg, 1.5 mmol) was suspended in anhyd THF (2 mL) in a Schlenk flask and stirred for 12 h at r.t. In a second Schlenk flask, 1,2-diiodobenzene (1; 495 mg, 1.5 mmol) was dissolved in anhyd THF (5 mL) under argon. After cooling to −30 °C, isopropylmagnesium chloride (2.0 M solution in THF, 0.75 mL) was added dropwise and the resulting orange colored mixture was warmed to −20 °C over a period of 20 min. The reaction was monitored by GC-MS. Both flasks were cooled to −78 °C and the freshly prepared Grignard reagent was added slowly to the CeCl\(_3\) suspension by means of a syringe. The mixture was warmed to r.t. to ensure formation of organomercuric species by transmetalation. After cooling again to −78 °C, a solution of ketone \(6\) (1 mmol) in THF (2 mL) was added and the mixture was allowed to warm up to r.t. overnight. After dilution with Et\(_2\)O (10 mL), the mixture was hydrolyzed in an ice bath with aq sat. NH\(_4\)Cl (10 mL), the layers were separated, and the aqueous phase was extracted with Et\(_2\)O (2 × 10 mL). The combined organic layers were dried (Na\(_2\)SO\(_4\)) and evaporated to dryness in vacuo. The crude product obtained was purified by flash chromatography (silica gel, hexane–EtOAc).

(2-Iodophenyl)phenylmethanol (4a)
Starting from 3a (100 mg, 0.98 mmol), 4a was synthesized according to GP1. Column chromatography (hexane–EtOAc, 4:1) gave a colorless oil (270 mg, C\(_{13}\)H\(_{10}\)BrO, M = 310.13 g/mol, 89%).

IR (neat): 3268, 3060, 2904, 1592, 1574, 1563, 1460, 1229, 1185, 1011, 996, 868, 846, 665, 637 cm\(^{-1}\).

HRMS (EI): \([M+]^+\) calcd for C\(_{13}\)H\(_{10}\)BrO: 343.9465 (100.0%), 345.9498 (14.1%); found: 343.9478 (100.0%), 345.9500 (14.1%).

(3,4-Dimethoxyphenyl)(2-iodophenyl)methanol (4b)
Starting from 3b (100 mg, 0.6 mmol), 4b was synthesized according to GP1. Column chromatography (hexane–EtOAc, 3:1) gave a colorless oil (175 mg, C\(_{13}\)H\(_{10}\)BrO, M = 370.18 g/mol, 79%).

IR (neat): 3476, 3000, 2932, 2833, 1592, 1561, 1412, 1460, 1436, 1416, 1254, 1132, 1105, 1024, 1006, 952, 858, 806, 781, 742, 670, 635 cm\(^{-1}\).

HRMS (EI): \([M+]^+\) calcd for C\(_{13}\)H\(_{10}\)ClO: 370.0065 (100.0%), 371.0099 (16.2%); found: 370.0060 (100.0%), 371.0097 (16.9%).

(2-Chlorophenyl)(2-iodophenyl)methanol (4c)
Starting from 3c (80 µL, 0.71 mmol), 4c was synthesized according to GP1. Column chromatography (hexane–EtOAc, 7:1) gave a colorless oil (230 mg, C\(_{13}\)H\(_{10}\)ClO, M = 343.57 g/mol, 94%).

IR (neat): 3268, 3060, 2904, 1592, 1574, 1563, 1460, 1435, 1332, 1304, 1209, 1229, 1199, 1181, 1159, 1128, 1111, 1052, 1026, 1005, 942, 908, 867, 852, 815, 730, 688, 665, 637 cm\(^{-1}\).

HRMS (EI): \([M+]^+\) calcd for C\(_{13}\)H\(_{10}\)BrO: 387.8955 (100.0%), 389.8993 (14.1%); found: 387.8950 (100.0%), 389.8987 (13.9%).
(2-Iodophenyl)-(1-tritylpyrroloidin-2-yl)methanol (4e)
Starting from 3e (342 mg, 1 mmol), 4e was synthesized according to GP1. Column chromatography (hexane–EtOAc, 9:1) gave a white solid (513 mg, C₁₅H₁₃IO₂, M = 352.17 g/mol, 71%); mp 103 °C.
IR (neat): 2970, 1596, 1488, 1446, 1203, 1083, 1032, 908, 937, 904, 850, 743, 661, 630 cm⁻¹.
1H NMR (300 MHz, CDCl₃): δ = 0.02 (m, 1 H, NCH₂CH₂), 0.70 (m, 1 H, NCH₂CH₂), 1.21–1.33 (m, 2 H, NCH₂CH₂), 3.24 (m, 1 H, NCH), 4.20 (m, 1 H, OH), 4.27 (m, 1 H, NCH), 5.12 (d, J = 3.6 Hz, 1 H, CH₂OH), 6.91 (m, 1 H, ArH), 7.19–7.34 (m, 10 H, ArH), 7.54–7.69 (m, 8 H, ArH).
13C NMR (75 MHz, CDCl₃): δ = 126.4, 127.5, 127.65, 127.74, 128.2, 128.6, 129.9, 139.0, 144.2 (ArC).
HRMS (EI): m/z [M⁺] calcd for C₁₅H₁₃IO₂: 351.9960 (100.0%), 352.9994 (16.2%); found: 351.9953 (100.0%), 352.9985 (16.6%).

(1-I-(2-Iodophenyl)-1-phenylethanol (7a)
Starting from 6a (100 mg, 0.83 mmol), 7a was synthesized according to GP2. Column chromatography (hexane–EtOAc, 10:1) gave a colorless oil (143 mg, C₁₅H₁₃IO₂, M = 324.16 g/mol, 53%).
IR (neat): 3518, 3056, 2978, 1672, 1581, 1493, 1446, 1271, 1371, 1325, 1271, 1224, 1126, 1069, 1028, 907, 735, 692, 670, 645 cm⁻¹.
1H NMR (300 MHz, CDCl₃): δ = 2.03 (s, 3 H, CH₃), 3.34 (br s, 1 H, OH), 7.02 (dt, J = 1.6, 7.7 Hz, 1 H, ArH), 7.29–7.34 (m, 5 H, ArH), 7.48 (dt, J = 1.2, 7.5 Hz, 1 H, ArH), 7.88 (dd, J = 1.5, 7.9 Hz, 1 H, ArH), 7.94 (dd, J = 1.1, 7.8 Hz, 1 H, ArH).
13C NMR (75 MHz, CDCl₃): δ = 30.7 (CH₃), 78.1 (COH), 96.5 (Cl), 126.5, 127.1, 130.8, 128.0, 128.3, 142.6, 147.1, 147.5 (ArC).

(1-(Benzylpyrrolidin-2-yl)-1-(2-iodophenyl)ethanol (7b)
Starting from 6b (615 mg, 3.02 mmol), 7b was synthesized according to GP2. Column chromatography (hexane–EtOAc, 9:1) gave a yellow oil (1.07 g, C₁₉H₂₂INO, M = 407.29 g/mol, 87%).
IR (neat): 2969, 2802, 1556, 1494, 1452, 1372, 1298, 1205, 1074, 1002, 757, 700 cm⁻¹.
1H NMR (300 MHz, CDCl₃): δ = 1.78 (m, 2 H, NCH₂CH₂), 1.87 (s, 3 H, CH₃), 2.14 (m, 4 H, NCH₂CH₂), 2.48 (m, 1 H, NCH), 2.94 (m, 1 H, NCH), 3.17 (s, 2 H, PhCH₂), 4.31 (t, J = 7.5 Hz, 1 H, NCH), 5.10 (br s, 1 H, OH), 6.89 (dd, J = 7.5 Hz, J = 1.5 Hz, 1 H, ArH), 7.11 (dd, J = 7.8 Hz, 2 H, CH₃), 7.22–7.32 (m, 3 H, CH₃), 7.41 (dd, J = 7.8 Hz, J = 1.5 Hz, 1 H, ArH), 8.00 (dd, J = 7.8 Hz, J = 1.5 Hz, 1 H, ArH), 8.18 (dd, J = 7.8 Hz, J = 1.5 Hz, 1 H, ArH).
13C NMR (75 MHz, CDCl₃): δ = 24.2 (NCH₂CH₂), 24.7 (CH₂), 27.2 (NCH₂CH₂), 54.6 (PhCH₂), 59.9 (NCH), 67.4 (CH₃), 73.4 (NCH), 93.9 (Cl), 126.6, 127.89, 127.92, 128.0, 128.26, 128.33, 139.4, 145.1 (ArC).
HRMS (EI): m/z [M – CH₃]⁺ calcd for C₁₉H₂₁INO: 392.0511 (100.0%), 393.0545 (19.5%); found: 392.0508 (100.0%), 393.0540 (24.6%).
2-(2-Iodophenyl)-4-phenylpentan-2-ol (7d)

Starting from 6d (0.1 mL, 0.67 mmol), 7d was synthesized according to GP2. Column chromatography (hexane–EtOAc, 10:1) gave a colorless oil (88 mg, C_{16}H_{17}IO, M = 334.8938). HRMS (EI): m/z [M + Ag]^+ calcd for C_{16}H_{17}I2O: 437.9565 (100.0%); found: 437.9562 (14.5%).

1-Chloro-1,3-dihydro-3,3-bis(trifluoromethyl)-1,2-benziodoxole (10b)

To a solution of 7g (5.92 g, 15.99 mmol) in CCl_4 (6 mL) was added freshly prepared tert-butyl hypochlorite\(^1\) (1.8 mL, 16.54 mmol) at 0 °C. The reaction mixture was maintained at 0 °C for 30 min. After warming to r.t., and filtration the title compound 10 was obtained as yellow crystals (6.06 g, C_{8}H_{7}ClF_6IO, M = 404.48 g/mol, 94%).

References


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