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

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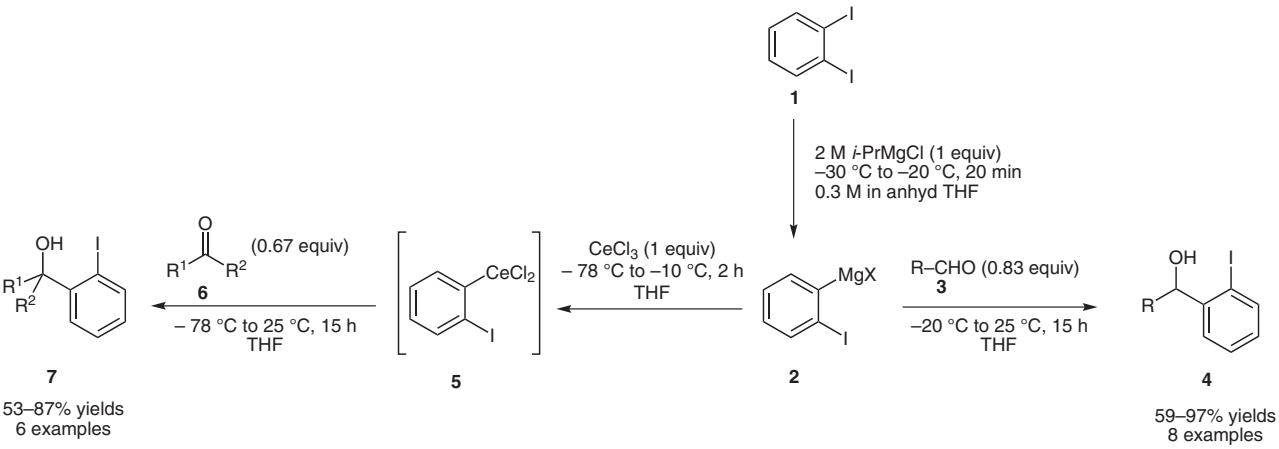
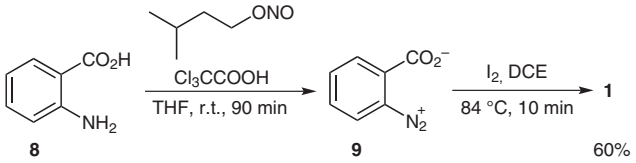
Abstract: A wide range of both secondary and tertiary *ortho*-iodobenzyl alcohols was synthesized via addition of *ortho*-iodophenyl Grignard reagents to aldehydes and ketones. Significant improvements in terms of yields were observed with ketones upon addition of $CeCl_3$. The potential application 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



Scheme 1

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 reactions[1] 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 isoamyl 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

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of **2** with carbonyl compounds would directly afford the desired *ortho*-iodobenzyl alcohols, we set out to inspect the reactivity of **2** with various electrophiles.

Although the use of 2-iodophenylmagnesium species **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 **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 °C and the resulting mixture was gradually warmed to –20 °C over a period of 20 minutes, species **2** was quantitatively formed. Thus, GC-MS analysis of hydrolyzed samples of such mixtures showed the presence of iodobenzene exclusively (Figure 1).

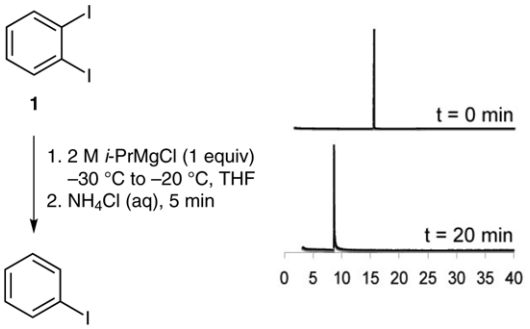


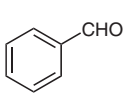
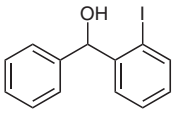
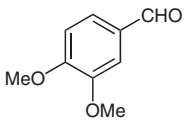
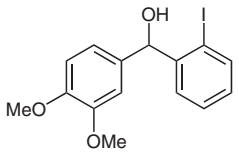
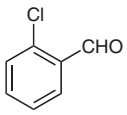
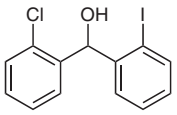
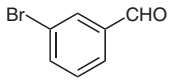
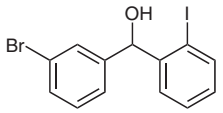
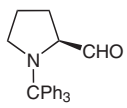
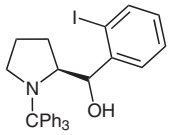
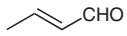
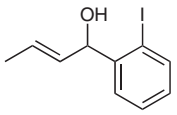
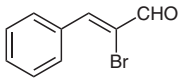
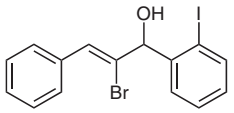
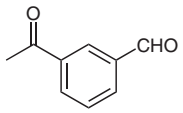
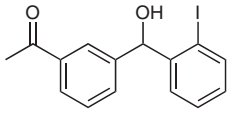
Figure 1 Formation of 2-iodophenylmagnesium halide and GC traces of the hydrolyzed reaction mixture

We then proceeded to study the reactivity of **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 **3d** and **3g**). Also the two methoxy groups in 3,4-dimethoxybenzaldehyde (**3b**) would direct the metalation to occur *ortho* to a methoxy group,[10] thus rendering our desired product **4b** inaccessible. Interestingly, when 3-acetoxybenzaldehyde (**3h**) was exposed to **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.

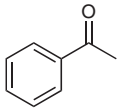
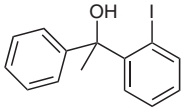
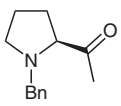
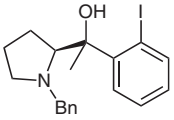
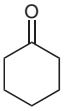
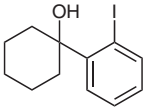
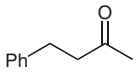
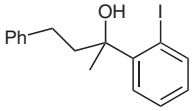
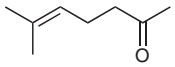
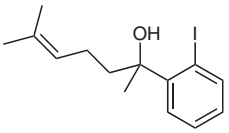
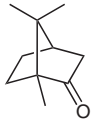
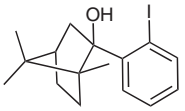
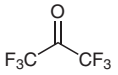
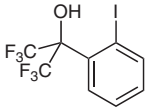
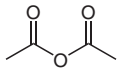
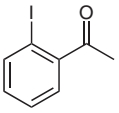
We subsequently sought to expand our protocol to other electrophiles. Preliminary results showed that ketones reacted only sluggishly and in the case of sterically hindered ones, the addition of **2** did not occur at all (Table 2). We considered the use of more nucleophilic analogues of **2** and were delighted to witness that the use of corresponding organocerium species **5**, prepared by the transmetalation of **2** with anhydrous $CeCl_3$,[11] led to significantly increased yields of the desired 2-iodobenzyl alcohols (Scheme 1, Table 2).

Table 1 Reactivity of **2** with Various Aldehydes

Substrate	Product	Yield (%)
 **3a**	 **4a**	89
 **3b**	 **4b**	79
 **3c**	 **4c**	94
 **3d**	 **4d**	97
 **3e**	 **4e**	94
 **3f**	 **4f**	78
 **3g**	 **4g**	59
 **3h**	 **4h**	71

It is noteworthy that with some substrates **5** was prone to react even if **2** proved completely unreactive (ketone **6b**). A broad palette of various α,α-disubstituted *ortho*-iodobenzyl alcohols thus became accessible. To underline the synthetic utility of our strategy, note that the 2-iodobenzyl alcohol **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, **7g** was formed in 80% yield with two equivalents of hexafluoroacetone (**6g**), but

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

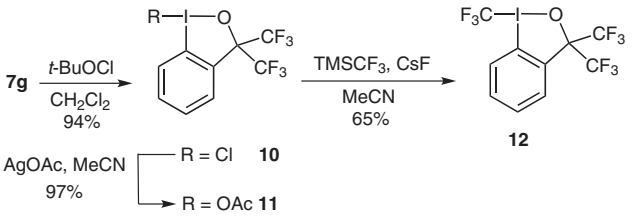
Substrate	Product	Yield (%) with **2**	Yield (%) with **5**
 **6a**	 **7a**	<10	53
 **6b**	 **7b**	–[a]	87
 **6c**	 **7c**	22	66
 **6d**	 **7d**	64	72
 **6e**	 **7e**	44	53
 **6f**	 **7f**	–[a]	–[a]
 **6g**	 **7g**	80[b] (96)[c]	–
 **6h**	 **7h**	33	82

[a] No product detected.
[b] 2 equiv of hexafluoroacetone were used.
[c] Hexafluoroacetone was introduced directly into the reaction mixture in large excess.

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.[3a,12] 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 ($TMSCF_3$) in the presence of cesium fluoride furnished the I–CF_3 λ^3-iodane **12**. The entire synthesis starting from diiodobenzene 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.



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.

All manipulations were performed under argon using standard Schlenk techniques, unless otherwise stated. ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded on Bruker Avance spectrometers AC 200, DPX 250, and DPX 300. ^{1}H positive chemical shifts in ppm are downfield from TMS. ^{19}F NMR spectra were referenced to external $CFCl_3$. 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.

Diiodobenzene (1)

Anthranilic acid (**8**; 5 g, 36.4 mmol) and trichloroacetic acid (45 mg, 0.28 mmol, 0.7 mol%) were dissolved in THF (35 mL) in a beaker and the solution was cooled down to 0 °C. Isoamyl nitrite (8.1 mL, 59.8 mmol, 1.64 equiv) was added dropwise and the resulting mixture was maintained at 18–25 °C and magnetically stirred for 2 h. A pale brown precipitate was formed. Benzenediazonium carboxylate is reported to detonate violently upon scratching or heating.[6] All

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. $Na_2S_2O_3$ (100 mL) was added, and the mixture was stirred for 15 min. The aqueous phase was then extracted with CH_2Cl_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 (7.1 g, 60%); bp 64–65 °C/0.059 mbar.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.05 (ddd, ^3J = 6 Hz, ^4J = 3.6 Hz, ^5J = 0.6 Hz), 7.90 (ddd, ^3J = 6 Hz, ^4J = 3.6 Hz, ^5J = 0.6 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 108.0 (CI), 129.2, 139.5.

Addition of *ortho*-Iodophenylmagnesium 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, 1 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. A solution of aldehyde **3** (1.67 mmol) in THF (2 mL) was added at –20 °C and the mixture was allowed to warm up to r.t. overnight. After dilution with Et_2O (10 mL), the mixture was hydrolyzed in an ice bath with aq sat. NH_4Cl (10 mL), the layers were separated, and the aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to dryness in vacuo. The crude product obtained was purified by flash chromatography (silica gel, hexane–EtOAc).

Addition of *ortho*-Iodophenylcerium Species 5 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 organocerium 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_2O (10 mL), the mixture was hydrolyzed in an ice bath with aq sat. NH_4Cl (10 mL), the layers were separated, and the aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic layers were dried (Na_2SO_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 μL, 0.98 mmol), **4a** was synthesized according to GP1. Column chromatography (hexane–EtOAc, 4:1) gave a colorless oil (270 mg, $C_{13}H_{11}IO$, M = 310.13 g/mol, 89%).

IR (neat): 3326, 3059, 3027, 2897, 1584, 1562, 1493, 1451, 1434, 1308, 1266, 1232, 1181, 1114, 1077, 1021, 1005, 948, 915, 850, 820, 744, 718, 695, 670, 640 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.73 (s, 1 H, OH), 6.07 (s, 1 H, C*H*OH), 7.01 (dt, ^3J = 7.5 Hz, J = 1.5 Hz, 1 H, ArH), 7.28–7.45 (m, 6 H, ArH), 7.55 (dd, J = 7.8, 1.8 Hz, 1 H, ArH), 7.87 (dd, J = 0.9, 7.8 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 79.0 (COH), 98.8 (CI), 127.3, 127.8, 128.4, 128.5, 128.6, 129.5, 139.6, 142.2, 145.4.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{13}H_{11}IO$: 309.9855 (100.0%), 310.9888 (14.1%); found: 309.9850 (100.0%), 310.9887 (13.9%).

(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, $C_{15}H_{15}IO_3$, M = 370.18 g/mol, 79%).

IR (neat): 3476, 3000, 2932, 2833, 1592, 1561, 1512, 1460, 1436, 1416, 1254, 1232, 1185, 1024, 1006, 912, 858, 806, 781, 742, 670, 635 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.98 (d, ^3J = 3.0 Hz, 1 H, OH), 3.81, 3.82 (2 s, 2 × 3 H, 2 × OCH_3), 5.94 (d, ^3J = 2.7 Hz, 1 H, C*H*OH), 6.78 (d, ^3J = 8.4 Hz, ArH), 6.86 (dd, ^4J = 1.8 Hz, ^3J = 8.4 Hz, ArH), 6.96 (m, 2 H, ArH), 7.35 (t, ^3J = 7.2 Hz, 1 H, ArH), 7.53 (dd, ^4J = 1.5 Hz, ^3J = 7.8 Hz, 1 H, ArH), 7.81 (d, ^3J = 7.8 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.9 (2 × OCH_3), 78.7 (CHOH), 98.6 (CI), 110.7, 110.9, 119.6, 128.1, 128.5, 129.3, 134.9, 139.5, 145.6, 148.5, 148.9.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{15}H_{15}IO_3$: 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, $C_{13}H_{10}ClIO$, M = 344.57 g/mol, 94%).

IR (neat): 3268, 3060, 2904, 1592, 1574, 1563, 1460, 1435, 1332, 1304, 1269, 1229, 1199, 1181, 1159, 1128, 1111, 1052, 1026, 1005, 942, 908, 867, 852, 815, 730, 688, 665, 637 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.98 (br s, 1 H, OH), 6.29 (s, 1 H, C*H*OH), 7.02 (m, 1 H, ArH), 7.25–7.35 (m, 6 H, ArH), 7.88 (d, ^3J = 7.9 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 76.4 (CHOH), 99.7 (CI), 127.0 (CCl), 128.4, 128.46, 128.51, 129.1, 129.6, 129.7, 133.8, 139.5, 139.7, 143.8.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{13}H_{10}ClIO$: 343.9465 (100.0%), 345.9435 (32.0%), 344.9498 (14.1%), 346.9469 (4.5%); found: 343.9459 (100.0%), 345.9434 (34.0%), 344.9485 (16.3%), 346.9465 (5.4%).

(3-Bromophenyl)(2-iodophenyl)methanol (4d)

Starting from **3d** (64 μL, 0.54 mmol), **4d** was synthesized according to GP1. Column chromatography (hexane–EtOAc, 7:1) gave a colorless oil (203 mg, $C_{13}H_{10}BrIO$, M = 389.03 g/mol, 97%).

IR (neat): 3323, 3059, 1592, 1567, 1462, 1431, 1180, 1115, 1071, 1030, 1008, 885, 778, 755, 725, 699, 668 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.01 (s, 1 H, OH), 6.00 (s, 1 H, C*H*OH), 7.01 (m, 1 H, ArH), 7.20 (t, ^3J = 7.8 Hz, 1 H, ArH), 7.30–7.43 (m, 4 H, ArH), 7.59 (s, 1 H, ArH), 7.85 (d, ^3J = 7.8 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 78.3 (CHOH), 98.7 (CI), 122.7 (CBr), 125.9, 128.4, 128.8, 129.8, 130.1, 130.2, 130.9, 139.7, 144.5, 144.8.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{13}H_{10}BrIO$: 387.8960 (100.0%), 389.8939 (97.3%), 388.8993 (14.1%), 390.8973 (13.7%); found:

387.8957 (100.0%), 389.8943 (99.1%), 388.8965 (19.5%), 390.8967 (15.2%).

(2-Iodophenyl)(1-tritylpyrrolidin-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, $C_{30}H_{28}INO$, M = 545.45 g/mol, 94%); mp 103 °C.

IR (neat): = 2970, 1596, 1488, 1446, 1203, 1083, 1032, 1008, 937, 904, 850, 743, 661, 632, 610 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.02 (m, 1 H, NCH_2CH_2), 0.70 (m, 1 H, NCH_2CH_2), 1.21–1.33 (m, 2 H, $NCHCH_2$), 3.12 (m, 1 H, NCH_2), 3.24 (m, 1 H, NCH_2), 4.20 (br s, 1 H, OH), 4.27 (m, 1 H, NCH), 5.12 (d, ^3J = 3.6 Hz, 1 H, CHOH), 6.91 (m, 1 H, ArH), 7.19–7.34 (m, 10 H, ArH), 7.54–7.69 (m, 8 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.6 (NCH_2CH_2), 26.8 ($NCHCH_2$), 53.6 (NCH_2), 61.4 (NCH), 76.5 (CPh_3), 78.4 (CHOH), 95.7 (CI), 126.4, 127.5, 127.65, 127.74, 128.2, 128.6, 129.9, 139.0, 144.2 (ArC).

(*E*)-1-(2-Iodophenyl)but-2-en-1-ol (4f)
Starting from **3f** (59 μL, 0.71 mmol), **4f** was synthesized according to GP1. Column chromatography (hexane–EtOAc, 7:1) gave a pale yellow oil (153 mg, $C_{10}H_{11}IO$, M = 274.10 g/mol, 78%).

IR (neat): 3316, 3056, 2912, 2359, 2339, 1668, 1583, 1561, 1461, 1434, 1376, 1308, 1193, 1104, 1074, 1003, 962, 926, 838, 752, 720, 663 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.73 (ddd, *J* = 0.9, 1.4, 6.5 Hz, 3 H, CH_3), 2.55 (br s, 1 H, OH), 5.37 (d, *J* = 5.9 Hz, 1 H, CHOH), 5.61 (qdd, *J* = 1.5, 6.4, 15.3 Hz, 1 H, CH_3CH), 5.85 (m, 1 H, CH_3CHCH), 6.98 (td, *J* = 1.7, 7.7 Hz, 1 H, ArH), 7.38 (td, *J* = 0.9, 7.7 Hz, 1 H, ArH), 7.52 (dd, *J* = 1.7, 7.8 Hz, 1 H, ArH), 7.83 (dd, *J* = 1.1, 7.9 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.9 (CH_3), 77.8 (CHOH), 98.2 (CI), 127.6, 128.4, 128.6, 129.2, 131.8, 139.4, 145.1.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{10}H_{11}IO$: 273.9855 (100.0%), 274.9888 (10.8%); found: 273.9842 (100.0%), 274.9875 (13.4%).

(*Z*)-2-Bromo-1-(2-iodophenyl)-3-phenylprop-2-en-1-ol (4g)
Starting from **3g** (100 mg, 0.47 mmol), **4g** was synthesized according to GP1. Column chromatography (hexane–EtOAc, 7:1) gave a pale brown oil (116 mg, $C_{15}H_{12}BrIO$, M = 415.06 g/mol, 59%).

IR (neat): 3346, 3054, 3024, 2919, 1688, 1637, 1598, 1584, 1564, 1490, 1462, 1445, 1434, 1260, 1189, 1116, 1064, 1029, 948, 907, 861, 809, 750, 726, 657, 620 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.79 (br s, 1 H, OH), 5.72 (s, 1 H, CHOH), 7.08 (dt, *J* = 1.5, 7.5 Hz, 1 H, ArH), 7.34–7.47 (m, 5 H, ArH), 7.64–7.69 (m, 3 H, ArH), 7.90 (dd, *J* = 1.2, 7.8 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 82.2 (CHOH), 99.4 (CI), 126.7, 128.2, 128.3, 128.5, 128.6, 129.1, 130.1, 130.4, 135.1, 139.7, 142.1.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{12}BrIO$: 413.9116 (100.0%), 415.9096 (97.3%), 414.9150 (16.2%), 416.9129 (15.8%), 415.9183 (1.2%), 417.9163 (1.2%); found: 413.9112 (100.0%), 415.9093 (96.7%), 414.9146 (18.1%), 416.9131 (16.4%).

1-{3-[Hydroxy-(2-iodophenyl)methyl]phenyl}ethanone (4h)
Starting from **3h** (186 mg, 1.25 mmol), **4h** was synthesized according to GP1. Column chromatography (hexane–EtOAc, 8:2) gave a colorless foam (312 mg, $C_{15}H_{13}IO_2$, M = 352.17 g/mol, 71%).

IR (neat): 3396, 3060, 2973, 2870, 1671, 1599, 1583, 1562, 1460, 1433, 1357, 1269, 1167, 1114, 1035, 977, 955, 916, 826, 792, 761, 735, 692, 670, 645 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.45 (s, 3 H, CH_3), 3.71 (br s, 1 H, OH), 5.99 (s, 1 H, CHOH), 6.89 (t, ^3J = 7.8 Hz, 1 H, ArH), 7.24–7.33 (m, 2 H, ArH), 7.41–7.49 (m, 2 H, ArH), 7.73 (d, ^3J = 7.8 Hz, 1 H, ArH), 7.96 (s, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.5 (CH_3), 78.2 (CHOH), 98.5 (CI), 127.0, 127.4, 128.2, 128.50, 128.54, 129.4, 131.8 (ArC), 136.9 (*C*C=O), 139.4 (*C*HCI), 142.8 (ArC), 145.0 (*C*CI).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{13}IO_2$: 351.9960 (100.0%), 352.9994 (16.2%); found: 351.9953 (100.0%), 352.9985 (16.6%).

1-(2-Iodophenyl)-1-phenylethanol (7a)[13]
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, $C_{14}H_{13}IO$, M = 324.16 g/mol, 53%).

IR (neat): 3518, 3056, 2978, 1672, 1581, 1493, 1446, 1427, 1371, 1325, 1271, 1224, 1126, 1069, 1028, 1007, 908, 756, 725, 699, 648 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.03 (s, 3 H, CH_3), 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).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.7 (CH_3), 78.1 (COH), 96.5 (CI), 126.5, 127.1, 128.0, 128.2, 128.3, 129.2, 142.6, 147.1, 147.5 (ArC).

1-(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, $C_{19}H_{22}INO$, 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, $CDCl_3$): δ = 1.78 (m, 2 H, NCH_2CH_2), 1.87 (s, 3 H, CH_3), 2.14 (m, 2 H, $NCHCH_2$), 2.48 (m, 1 H, NCH_2), 2.94 (m, 1 H, NCH_2), 3.17 (s, 2 H, $PhCH_2$), 4.31 (t, ^3J = 7.5 Hz, 1 H, NCH), 5.10 (br s, 1 H, OH), 6.89 (dd, ^3J = 7.5 Hz, ^4J = 1.5 Hz, 1 H, ArH), 7.11 (d, ^3J = 6.6 Hz, 2 H, C_6H_5), 7.22–7.32 (m, 3 H, C_6H_5), 7.41 (dd, ^3J = 7.8 Hz, ^4J = 1.5 Hz, 1 H, ArH), 8.00 (dd, ^3J = 7.8 Hz, ^4J = 1.5 Hz, 1 H, ArH), 8.18 (dd, ^3J = 7.8 Hz, ^4J = 1.5 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.2 (NCH_2CH_2), 24.7 (CH_3), 27.2 ($NCHCH_2$), 54.6 ($PhCH_2$), 59.9 (NCH_2), 67.4 (CCH_3), 73.4 (NCH), 93.9 (CI), 126.6, 127.89, 127.92, 128.0, 128.26, 128.33, 139.4, 142.3, 150.1 (ArC).

HRMS (EI): *m*/*z* $[M - CH_3]^+$ calcd for $C_{19}H_{22}INO$: 392.0511 (100.0%), 393.0545 (19.5%); found: 392.0508 (100.0%), 393.0540 (24.6%).

1-(2-Iodophenyl)cyclohexanol (7c)
Starting from **6c** (0.2 mL, 1.92 mmol), **7c** was synthesized according to GP2. Column chromatography (hexane–EtOAc, 50:1) gave a white powder (384 mg, $C_{12}H_{15}IO$, M = 302.15 g/mol, 66%).

IR (neat): 3348, 3054, 2927, 2857, 1557, 1451, 1428, 1396, 1354, 1320, 1281, 1264, 1190, 1150, 1138, 1063, 1032, 1013, 1000, 968, 946, 906, 899, 861, 844, 716, 657, 624 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.28–1.42 (m, 1 H, CH), 1.69–1.91 (m, 5 H, CH), 2.02–2.21 (m, 4 H, CH), 2.32 (s, 1 H, OH), 6.92 (t, *J* = 7.4 Hz, 1 H, ArH), 7.35 (t, *J* = 7.8 Hz, 1 H, ArH), 7.62 (t, *J* = 7.9 Hz, 1 H, ArH), 7.99 (t, *J* = 7.9 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.0, 25.3, 36.0, 74.0 (COH), 93.5 (CI), 127.0, 128.2, 128.6, 143.0, 148.4 (ArC).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{15}IO$: 302.0168 (100.0%), 303.0201 (13.0%); found: 302.0162 (100.0%), 303.0198 (15.3%).

2-(2-Iodophenyl)-4-phenylbutan-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 yellowish oil (170 mg, $C_{16}H_{17}IO$, M = 352.21 g/mol, 72%).

IR (neat): 3460, 3024, 2927, 1602, 1557, 1496, 1454, 1427, 1372, 1263, 1122, 1063, 1004, 882, 757, 725, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.83 (s, 3 H, CH_3), 2.24 (m, 1 H, CH), 2.36 (br s, 1 H, OH), 2.48 (m, 1 H, CH), 2.60 (m, 1 H, CH), 2.84 (m, 1 H, CH), 6.96 (t, ^3J = 7.5 Hz, 1 H, ArH), 7.22–7.35 (m, 5 H, ArH), 7.41 (t, J = 7.4 Hz, 1 H, ArH), 7.79 (d, ^3J = 7.8 Hz, 1 H, ArH), 8.04 (d, ^3J = 7.8 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.5 (CH_3), 30.8 (CH_2Ph), 42.7 (CH_2), 75.8 (COH), 93.1 (CI), 125.8, 127.8, 128.2, 128.4, 128.5, 128.7, 142.2, 142.8, 147.6 (ArC).

HRMS (EI): m/z $[M]^+$ calcd for $C_{16}H_{17}IO$: 352.0324 (100.0%); found: 352.0316 (100.0%).

2-(2-Iodophenyl)-6-methylhept-5-en-2-ol (7e)

Starting from **6e** (63 mg, 0.50 mmol), **7e** was synthesized according to GP2. Column chromatography (hexane–EtOAc, 9:1) gave a colorless oil (88 mg, $C_{14}H_{19}IO$, M = 330.20 g/mol, 53%).

IR (neat): 3448, 2967, 2923, 1558, 1454, 1428, 1264, 1122, 1074, 1046, 1003, 884, 828, 757, 722 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 3 H, CH_3), 1.64 (s, 3 H, CH_3), 1.69 (s, 3 H, CH_3), 1.87–1.92 (m, 4 H, CH_2), 5.09 (br s, 1 H, OH), 6.86 (dd, ^3J = 7.2 Hz, 1 H, ArH), 7.31 (dd, ^3J = 7.2 Hz, 1 H, ArH), 7.67 (d, ^3J = 7.2 Hz, 1 H, ArH), 7.94 (d, ^3J = 7.2 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.7 (CH_3), 23.0 (CH_3), 25.7 (CH_3), 28.2 (CH_2), 40.4 (CH_2), 76.0 (COH), 93.0 (CI), 123.9 (*C*H=C), 127.7, 127.9, 128.4 (ArC), 132.4 (*C*=CH), 142.6, 147.9 (ArC).

HRMS (EI): m/z $[M + Ag]^+$ calcd for $C_{14}H_{19}IO$: 436.9532 (100.0%), 437.9565 (15.1%); found: 436.9528 (100.0%), 437.9562 (14.5%).

1,1,1,3,3,3-Hexafluoro-2-(2-iodophenyl)propan-2-ol (7g)

A modified GP1 was applied: In a Schlenk flask, 1,2-diiodobenzene (2.6 g, 7.9 mmol) was dissolved in anhyd THF (26 mL) under argon. After cooling to –30 °C, isopropylmagnesium chloride (2.0 M solution in THF, 4 mL) was added dropwise and the resulting orange colored mixture was warmed to –20 °C over a period of 20 min and subsequently cooled down to –78 °C. A solution of hexafluoroacetone (2 mL, 15.9 mmol, 2 equiv) in THF (10 mL) was added via cannula and the mixture was allowed to warm up to r.t. overnight. After dilution with Et_2O (30 mL), the mixture was hydrolyzed in an ice bath with aq sat. NH_4Cl (30 mL), the layers were separated, and the aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to dryness in vacuo. The pure product was obtained after purification by flash chromatography (silica gel, pentane–Et_2O, 50:1, then 3:1) as a colorless oil (2.3 g, $C_9H_5F_6IO$, M = 370.03 g/mol, 80%).

IR (neat): 3456, 3382, 1587, 1566, 1472, 1437, 1423, 1171, 1102, 1054, 1012, 963, 947, 921, 868, 757, 727, 698, 678, 638, 630 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.55 (br s, 1 H, OH), 7.12 (dt, J = 1.5, 8.1 Hz, 1 H, ArH), 7.44 (dt, J = 1.2, 8.4 Hz, 1 H, ArH), 7.65 (d, J = 8.2 Hz, 1 H, ArH), 8.15 (dd, J = 1.2, 8.0 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 78.8 (q, J = 29.9 Hz, COH), 90.5 (CI), 122.6 (q, J = 290.1 Hz, CF_3), 128.0, 129.7, 130.0, 131.4, 144.7 (ArC).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –73.4.

HRMS (EI): m/z $[M]^+$ calcd for $C_9H_5F_6IO$: 369.9289 (100.0%), 370.9323 (9.7%); found: 369.9286 (100.0%), 370.9335 (9.6%).

1-(2-Iodophenyl)ethanone (7h)

Starting from **6h** (51 mg, 0.50 mmol), **7h** was synthesized according to GP2. Column chromatography (hexane–EtOAc, 9:1) gave a yellow liquid (101 mg, C_8H_7IO, M = 246.05 g/mol, 82%).

IR (neat): 2919, 2359, 1580, 1560, 1460, 1422, 1354, 1280, 1241, 1165, 1088, 1035, 1014, 958, 756, 719, 642, 631 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.59 (s, 3 H, CH_3), 7.09 (dd, ^3J = 7.5 Hz, 1 H, ArH), 7.36–7.46 (m, 2 H, ArH), 7.91 (d, ^3J = 7.5 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.5 (CH_3), 90.9 (CI), 128.0, 128.3, 131.8, 140.9, 144.1 (ArC), 201.8 (C=O).

HRMS (EI): m/z $[M]^+$ calcd for C_8H_7IO: 245.9542 (100.0%), 246.9575 (8.7%); found: 245.9539 (100.0%), 246.9601 (9.2%).

1-Chloro-1,3-dihydro-3,3-bis(trifluoromethyl)-1,2-benziodoxole (10)[5b]

To a solution of **7g** (5.92 g, 15.99 mmol) in CCl_4 (6 mL) was added freshly prepared *tert*-butyl hypochlorite[14] (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, $C_9H_4ClF_6IO$, M = 404.48 g/mol, 94%).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.72 (m, 2 H, ArH), 7.82 (m, 1 H, ArH), 8.07 (d, ^3J = 8.4 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 85.2 (CCF_3), 113.4 (CI), 122.9 (q, $^1J_{C,F}$ = 289.5 Hz, CF_3), 128.5, 129.7, 131.6, 132.1, 133.8 (ArC).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –75.7 (s, CF_3).

HRMS (EI): m/z $[M - CF_3]^+$ calcd for $C_9H_4ClF_6IO$: 334.8947; found: 334.8938.

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