Direct, Metal-Free Synthesis of Benzyl Alcohols and Deuterated Benzyl Alcohols from *p*-Toluenesulfonylhydrazones Using Water as Solvent

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Abstract: A novel library of diverse alcohols was synthesized by metal-free couplings of diazoalkanes derived from *p*-toluenesulfonylhydrazones to water under reflux and microwave conditions, in high yields. In addition, this protocol was successfully applied in the synthesis of deuterium-labeled alcohols using deuterium oxide.

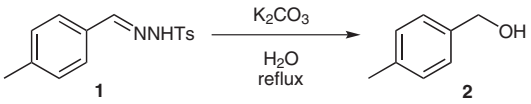
Key words: alcohols, deuterated alcohols, *p*-toluenesulfonylhydrazones, coupling

p-Toluenesulfonylhydrazones are interesting compounds which have been used in many chemical transformations. In particular, the generation of carbene/carbenoid intermediates derived from *p*-toluenesulfonylhydrazones has become an attractive method for coupling and C–C bond formation in the last years. Recent work by Aggarwal,[1] Barluenga and Valdés,[2] Cheung,[3] Yu,[4] and Hamze,[5] and their co-workers, and also our group[6] has demonstrated that *p*-toluenesulfonylhydrazones might be an effective source of diazoalkanes which represent the most important carbenoid precursors in metal-catalyzed processes. Moreover, a current trend in this area is the use of metal-free conditions that provides a novel kind of C–C bond coupling,[7] as well as novel methods for the synthesis of ethers[8] and sulfides.[9]

In connection with other studies, we required some non-commercially available alcohols which we decided to prepare from the corresponding carbonyl compounds using a reductive carbene coupling approach. Although this approach is already known under classic photolytic conditions,[10] it has been considered only for mechanistic studies because the reactions afford low yields and many rearrangement side products. This fact inspired us to reinvestigate this process in order to find an efficient methodology for this transformation. Herein, a summary of our successful endeavors in this area is described.

In a model study, 4-methylbenzaldehyde *p*-toluenesulfonylhydrazone (**1**) was reacted with an excess of potassium carbonate (3.5 equiv), and the resulting potassium salt was treated with water at reflux temperature for different times. The results are summarized in Table 1 and show that after 24 hours alcohol **2** was obtained as the only reaction product in 85% yield.

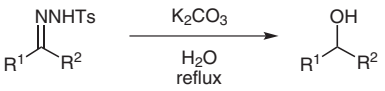
Table 1 Effect of Time on Alcohol Formation



Entry	Time (h)	Yield (%) of **2**
1	2	35
2	4	50
3	8	65
4	12	72
5	24	85
6	48	83

In order to explore the reaction scope, several tosylhydrazones were reacted under similar conditions; the results are presented in Table 2. In all cases, the corresponding alcohols were obtained in moderate to good yield. More

Table 2 Alcohols Prepared under Reflux Conditions



Entry	R^1	R^2	Yield (%)
1	H	4-MeC_6H_4	85
2	H	Ph	45
3	H	4-ClC_6H_4	40
4	H	3-ClC_6H_4	66
5	H	4-$Me_2NC_6H_4$	63
6	Me	Ph	60
7	Me	4-$MeOC_6H_4$	62
8	H	2,6-$Cl_2C_6H_3$	62

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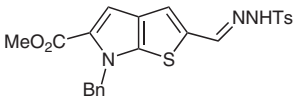
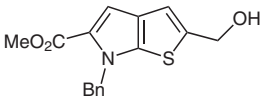
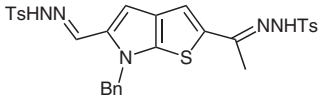
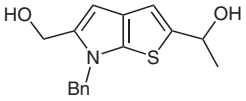
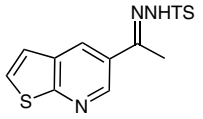
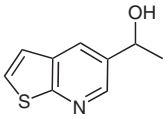
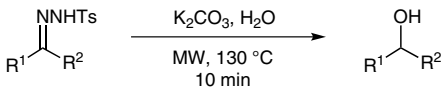
Table 3 More Complex Alcohols Prepared under Reflux Conditions

Entry	Tosylhydrazone	Alcohol	Yield (%)
1			59
2			45
3			56

complex tosylhydrazones also gave alcohols (Table 3); only the starting material was recovered in some cases.

The success of this process motivated us to explore alternative energy sources. Previous reports have shown that microwave (MW) irradiation facilitates chemical processes.[8] In our case, the use of microwave irradiation as an energy source resulted in increased reaction yields. Experiments demonstrated that the process is improved through the use of microwave irradiation, showing shorter reaction times and almost quantitative yields (Table 4). Furthermore, rearrangements or other undesired products were not observed. At present, the use of microwave irradiation in carbene insertions on O–H bonds has only been used to prepare ethers; this is the first report of the synthesis of alcohols through a similar approach.

Table 4 Alcohols Prepared under Microwave Conditions

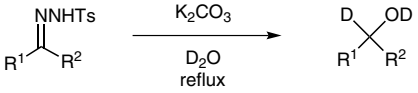


Entry	R^1	R^2	Yield (%)
1	H	4-MeC_6H_4	99
2	H	Ph	94
3	H	4-ClC_6H_4	95
4	H	3-ClC_6H_4	92
5	H	4-$Me_2NC_6H_4$	89
6	Me	Ph	95
7	Me	4-$MeOC_6H_4$	99
8	H	2-$MeOC_6H_4$	99
9	H	4-FC_6H_4	80
10	H	4-BrC_6H_4	89
11	H	2-BrC_6H_4	89
12	Me	4-Tol	97
13	Me	4-ClC_6H_4	99

These elements suggest that tosylhydrazone couplings to water could be a useful method for synthesizing alcohols which minimizes the use of reducing agents. In addition, this method is performed in water as solvent, avoiding the use of additional organic solvents or special reaction conditions.

One of the additional advantages that we found with this methodology is its application in the synthesis of deuterium-labeled alcohols from *p*-toluenesulfonylhydrazones and deuterium oxide instead of water. For this purpose, we carried out a series of preliminary experiments with deuterium oxide under reflux temperature conditions. The results (Table 5) indicated that the yields are similar to those obtained using water as solvent.

Table 5 Deuterium-Labeled Alcohols Prepared under Reflux Conditions

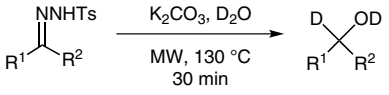


Entry	R^1	R^2	Yield (%)
1	H	Ph	82
2	H	4-MeC_6H_4	90
3	H	4-$Me_2NC_6H_4$	55
4	H	4-ClC_6H_4	65
5	H	2,6-$Cl_2C_6H_3$	60
6	Me	Ph	70

In addition, we carried out insertion reactions of *p*-toluenesulfonylhydrazones with deuterium oxide under microwave irradiation conditions, to obtain the corresponding deuterium-labeled alcohols (Table 6). The noteworthy fact in this case is that the process occurred in higher yields than under conventional heating conditions. To the best of our knowledge, this is the first example of a selective deuterium labeling on the oxygen atom and the C-1 atom in an alcohol in one step, which also displays a novel metal-free method to prepare the labeled alcohols,

in contrast to the traditional metal-catalyzed[11] and metal deuteride[12] protocols.

Table 6 Deuterium-Labeled Alcohols Prepared under Microwave Conditions



Entry	R^1	R^2	Yield (%)
1	H	Ph	98
2	H	4-MeC_6H_4	97
3	H	4-$Me_2NC_6H_4$	75
4	H	4-ClC_6H_4	96
5	H	2,6-$Cl_2C_6H_3$	93
6	Me	Ph	97

In summary, *p*-toluenesulfonylhydrazones are easily converted into alcohols through a process that combines the use of water as a green solvent and microwave irradiation as an alternative energy source. Thus, this reaction represents an alternative methodology for the synthesis of benzyl alcohols from aldehydes and ketones which complements the conventional reduction procedures based on active metal or metal hydride reagents. In addition, this method was successfully extended to the synthesis of deuterium-labeled alcohols from *p*-toluenesulfonylhydrazones and deuterium oxide. This route to alcohols is efficient and the simplicity of the method should ensure a widespread application.

The starting materials were purchased from Aldrich Chemical Co. and were used without further purification. *p*-Toluenesulfonylhydrazones were prepared according to the literature.[1–3] Solvents were distilled before use. Water was deionized using Millipore System Direct-Q equipment. Silica gel (230–400 mesh) was purchased from Merck. Silica plates of 0.20-mm thickness were used for thin-layer chromatography. Melting points were determined with a Fischer-Johns Scientific melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded using a Bruker Avance 300-MHz or a Varian 500-MHz instrument. The chemical shifts (δ) are given in ppm relative to TMS as internal standard (0.00). For analytical purposes, the mass spectra were recorded on a Shimadzu GCMS-QP2010 Plus or a JEOL JMS-5X 10217 spectrometer in the EI mode (70 eV, 200 °C) via direct inlet probe [only the molecular parent ions (*m*/*z*)]. IR spectra were recorded on a Nicolet Magna 55-X FT instrument. The microwave-assisted reactions were performed using an Anton-Paar Synthos 300 focused microwave unit (constant factor of the microwave 1.214). The temperature was monitored with an IR temperature sensor. In all experiments, the microwave temperature was held constant. Reactions were carried out in 5-mL glass vessels, which were sealed with a cap septum. The specific reaction time corresponds to the total irradiation time.

Synthesis of Alcohols under Conventional Heating Conditions; General Procedure

The appropriate tosylhydrazone (0.3 mmol) was added to a stirred soln of K_2CO_3 (145.1 mg, 1.05 mmol, 3.5 equiv) in H_2O (10 mL). The resulting mixture was heated at reflux temperature for 24 h. The reaction mixture was cooled to r.t. and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The organic phases were combined, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the final product was purified by silica gel column chromatography (hexane–EtOAc, 95:5).

Synthesis of Alcohols under Microwave Irradiation Conditions; General Procedure

A 5-mL microwave vial was charged with K_2CO_3 (241.5 mg, 1.75 mmol, 3.5 equiv), the corresponding tosylhydrazone (0.5 mmol), H_2O (5 mL) and a cylindrical magnetic stirring bar. The vessel was sealed with a septum, placed into the microwave cavity of an Anton-Paar microwave unit and irradiated to heat the reaction mixture at 130 °C. The total heating time was 10 min at 130 °C. When the reaction was completed, the vial was cooled to r.t. The vial was then opened and the contents were poured into a separating funnel. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the final product was purified by silica gel column chromatography (hexane–EtOAc, 95:5).

***p*-Tolylmethanol (Tables 2 and 4, Entry 1)**

Yields: 31 mg (85%, from 0.3 mmol of tosylhydrazone under reflux conditions) and 60 mg (99%, from 0.5 mmol of tosylhydrazone under microwave conditions); white solid; mp 61 °C.

IR (ATR): 3267, 3049, 1618 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.26 (s, 3 H), 4.54 (s, 2 H), 7.08 (d, *J* = 7.5 Hz, 2 H), 7.16 (d, *J* = 7.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.30 (CH_3), 65.36 (CH_2), 127.27 (2 × CH), 129.38 (2 × CH), 137.51 (C), 138.07 (C).

HRMS (EI): *m*/*z* calcd for $C_8H_{10}O$: 122.0732; found: 122.0735.

Phenylmethanol (Tables 2 and 4, Entry 2)

Yields: 14.6 mg (45%, from 0.3 mmol of tosylhydrazone under reflux conditions) and 50.7 mg (94%, from 0.5 mmol of tosylhydrazone under microwave conditions); colorless oil.

IR (ATR): 3326, 3088, 1611 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.60 (s, 2 H), 7.22 (m, 3 H), 7.29 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 65.49 (CH_2), 127.15 (2 × CH), 127.81 (2 × CH), 128.72 (CH), 141.02 (C).

HRMS (EI): *m*/*z* calcd for C_7H_8O: 108.0575; found: 108.0579.

(4-Chlorophenyl)methanol (Tables 2 and 4, Entry 3)

Yields: 17 mg (40%, from 0.3 mmol of tosylhydrazone under reflux conditions) and 67.5 mg (95%, from 0.5 mmol of tosylhydrazone under microwave conditions); white solid; mp 72 °C.

IR (ATR): 3270, 3259, 2955, 1592 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.64 (s, 2 H), 7.27 (d, *J* = 8 Hz, 2 H), 7.31 (d, *J* = 8 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 64.64 (CH_2), 128.48 (2 × CH), 128.85 (2 × CH), 133.49 (C), 139.54 (C).

HRMS (EI): *m*/*z* calcd for C_7H_7ClO: 142.0185; found: 142.0187.

(3-Chlorophenyl)methanol (Tables 2 and 4, Entry 4)

Yields: 28.1 mg (66%, from 0.3 mmol of tosylhydrazone under reflux conditions) and 65.3 mg (92%, from 0.5 mmol of tosylhydrazone under microwave conditions); colorless oil.

IR (ATR): 3321, 3067 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.59 (s, 2 H), 7.15 (m, 1 H), 7.19 (m, 1 H), 7.21 (m, 1 H), 7.42 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 64.67 (CH_2), 125.01 (CH), 127.12 (CH), 127.86 (CH), 129.98 (CH), 134.60 (C), 143.02 (C).

HRMS (EI): *m*/*z* calcd for C_7H_7ClO: 142.0185; found: 142.0188.

[4-(Dimethylamino)phenyl]methanol (Tables 2 and 4, Entry 5)
Yields: 28.5 mg (63%, from 0.3 mmol of tosylhydrazone under reflux conditions) and 67.2 mg (89%, from 0.5 mmol of tosylhydrazone under microwave conditions); colorless oil.

IR (ATR): 3239, 3093, 1614 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.90 (s, 3 H), 2.98 (s, 3 H), 4.48 (s, 2 H), 7.16 (d, *J* = 8.9 Hz, 2 H), 7.31 (d, *J* = 8.9 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 40.43 (CH_3), 40.87 (CH_3), 53.90 (CH_2), 111.76 (C), 128.82 (2 × CH), 134.43 (2 × CH), 152.26 (C).

HRMS (EI): *m*/*z* calcd for $C_9H_{13}NO$: 151.0997; found: 151.0999.

1-Phenylethanol (Tables 2 and 4, Entry 6)
Yields: 21.9 mg (60%, from 0.3 mmol of tosylhydrazone under reflux conditions) and 57.9 mg (95%, from 0.5 mmol of tosylhydrazone under microwave conditions); colorless oil.

IR (ATR): 3364, 3086, 2973, 1601 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.39 (d, *J* = 4 Hz, 3 H), 4.59 (m, 1 H), 7.15–7.19 (m, 3 H), 7.42 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.81 (CH_3), 65.40 (CH), 127.19 (2 × CH), 127.79 (CH), 128.73 (2 × CH), 141.30 (C).

HRMS (EI): *m*/*z* calcd for $C_8H_{10}O$: 122.0732; found: 122.0735.

1-(4-Methoxyphenyl)ethanol (Tables 2 and 4, Entry 7)
Yields: 28.3 mg (62%, from 0.3 mmol of tosylhydrazone under reflux conditions) and 75.3 mg (99%, from 0.5 mmol of tosylhydrazone under microwave conditions); colorless oil.

IR (ATR): 3385, 3066, 1601 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 5 Hz, 3 H), 3.70 (s, 3 H), 4.75 (m, 1 H), 6.78 (d, *J* = 8.6 Hz, 2 H), 7.20 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.18 (CH_3), 55.43 (CH_3), 70.09 (CH), 113.97 (2 × CH), 126.81 (2 × CH), 138.18 (C), 159.10 (C).

HRMS (EI): *m*/*z* calcd for $C_9H_{12}O_2$: 152.0837; found: 152.0839.

(2,6-Dichlorophenyl)methanol (Table 2, Entry 8)
Yield: 32.7 mg (62%); white solid; mp 98 °C.

IR (ATR): 3321, 3067 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.97 (s, 2 H), 7.32 (m, 1 H), 7.35 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 60.47 (CH_2), 128.73 (2 × CH), 128.84 (CH), 136.22 (2 × C), 142.28 (C).

HRMS (EI): *m*/*z* calcd for $C_7H_6Cl_2O$: 175.9796; found: 175.9799.

Methyl 6-Benzyl-2-(hydroxymethyl)-6*H*-thieno[2,3-*b*]pyrrole-5-carboxylate (Table 3, Entry 1)
Yield: 53.4 mg (59%); colorless oil.

IR (ATR): 3600, 3022, 2953, 1696, 1517 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.83 (s, 3 H), 4.72 (s, 2 H), 5.29 (s, 2 H), 6.55 (s, 1 H), 7.22–7.32 (m, 5 H), 7.36 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 50.4 (CH_2), 51.8 (CH_3), 57.3 (CH_2), 102.8 (CH), 125.5 (CH), 127.5 (2 × CH), 128.2 (CH), 128.4 (C), 128.8 (2 × CH), 135.2 (C), 139.8 (2 × C), 141.6 (C), 164.0 (C).

HRMS (EI): *m*/*z* calcd for $C_{16}H_{15}NO_3S$: 301.0773; found: 301.0776.

1-[6-Benzyl-5-(hydroxymethyl)-6*H*-thieno[2,3-*b*]pyrrol-2-yl]ethanol (Table 3, Entry 2)
Yield: 38.8 mg (45%); colorless oil.

IR (ATR): 3600, 3321, 3067 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.52 (d, *J* = 6.3 Hz, 3 H), 4.60 (s, 2 H), 4.95 (q, *J* = 6.3 Hz, 1 H), 5.21 (s, 2 H), 6.29 (s, 1 H), 6.81 (s, 1 H), 7.17 (m, 2 H), 7.27–7.30 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.9 (CH_3), 50.4 (CH_2), 57.6 (CH_2), 67.3 (CH), 101.9 (CH), 114.4 (CH), 127.5 (2 × CH), 127.6 (C), 128.1 (CH), 129.0 (2 × CH), 136.3 (C), 136.5 (C), 137.4 (C), 142.0 (C).

HRMS (EI): *m*/*z* calcd for $C_{16}H_{17}NO_2S$: 287.0980; found: 287.0984.

1-Thieno[2,3-*b*]pyridin-5-ylethanol (Table 3, Entry 3)
Yield: 30.1 mg (56%); colorless oil.

IR (ATR): 3321, 3067, 1597 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.54 (d, *J* = 6.3 Hz, 3 H), 5.04 (q, *J* = 6.6 Hz, 1 H), 7.19 (d, *J* = 5.7 Hz, 1 H), 7.50 (d, *J* = 6.0 Hz, 1 H), 8.07 (d, *J* = 2.1 Hz, 1 H), 8.46 (d, *J* = 2.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.7 (CH_3), 68.2 (CH), 121.6 (CH), 127.6 (CH), 128.2 (CH), 132.6 (C), 137.6 (C), 145.1 (CH), 160.6 (C).

HRMS (EI): *m*/*z* calcd for C_9H_9NOS: 179.0405; found: 179.0408.

(2-Methoxyphenyl)methanol (Table 4, Entry 8)
Yield: 68.3 mg (99%); colorless oil.

IR (ATR): 3366, 3066, 1690 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.33 (s, 3 H), 4.16 (s, 2 H), 6.33 (m, 1 H), 6.37 (m, 1 H), 6.44 (m, 1 H), 6.76 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.36 (CH_2), 62.12 (CH_3), 126.47 (CH), 128.68 (CH), 129.04 (CH), 129.60 (CH), 131.05 (C), 157.53 (C).

HRMS (EI): *m*/*z* calcd for $C_8H_{10}O_2$: 138.0681; found: 138.0684.

(4-Fluorophenyl)methanol (Table 4, Entry 9)
Yield: 50.4 mg (80%); colorless oil.

IR (ATR): 3220, 3011, 1605 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.56 (s, 2 H), 6.96 (d, *J* = 8.5 Hz, 2 H), 7.25 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 64.76 (CH_2), 115.68 (2 × CH), 128.97 (2 × CH), 136.72 (C), 164.09 (C).

HRMS (EI): *m*/*z* calcd for C_7H_7FO: 126.0481; found: 126.0485.

(4-Bromophenyl)methanol (Table 4, Entry 10)
Yield: 82.7 mg (89%); white solid; mp 82 °C.

IR (ATR): 3311, 3075, 1592 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.53 (s, 2 H), 7.12 (d, *J* = 8.2 Hz, 2 H), 7.37 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 64.66 (CH_2), 121.56 (C), 128.73 (2 × CH), 131.75 (2 × CH), 139.93 (C).

HRMS (EI): *m*/*z* calcd for C_7H_7BrO: 185.9680; found: 185.9682.

(2-Bromophenyl)methanol (Table 4, Entry 11)
Yield: 82.9 mg (89%); white solid; mp 78 °C.

IR (ATR): 3297, 3207, 2955, 1966 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.67 (s, 2 H), 7.39 (m, 1 H), 7.45 (m, 1 H), 7.50 (m, 1 H), 7.65 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 65.25 (CH_2), 127.33 (C), 127.84 (CH), 129.40 (CH), 130.29 (CH), 136.98 (CH), 139.90 (C).

HRMS (EI): *m*/*z* calcd for C_7H_7BrO: 185.9680; found: 185.9685.

1-*p*-Tolylethanol (Table 4, Entry 12)
Yield: 65.9 mg (97%); colorless oil.

IR (ATR): 3346, 3096, 2920 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.40 (d, *J* = 6.5 Hz, 3 H), 2.26 (s, 3 H), 4.78 (q, *J* = 6.4 Hz, 1 H), 7.08 (d, *J* = 7.6 Hz, 2 H), 7.18 (d, *J* = 7.6 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.25 (CH_3), 25.24 (CH_3), 70.39 (CH), 125.51 (2 × CH), 129.31 (2 × CH), 137.28 (C), 143.04 (C).

HRMS (EI): *m*/*z* calcd for $C_9H_{12}O$: 136.0888; found: 136.0891.

1-(4-Chlorophenyl)ethanol (Table 4, Entry 13)
Yield: 77.2 mg (99%); colorless oil.

IR (ATR): 3346, 3086, 1652 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.34 (d, *J* = 6.5 Hz, 3 H), 4.74 (q, *J* = 6.4 Hz, 1 H), 7.27 (d, *J* = 8.6 Hz, 2 H), 7.72 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.40 (CH_3), 69.83 (CH), 126.94 (2 × CH), 128.71 (2 × CH), 133.15 (C), 144.42 (C).

HRMS (EI): *m*/*z* calcd for C_8H_9ClO: 156.0342; found: 156.0348.

Synthesis of Deuterium-Labeled Alcohols under Conventional Heating Conditions; General Procedure
The appropriate tosylhydrazone (0.3 mmol) was added to a stirred soln of K_2CO_3 (145.1 mg, 1.05 mmol, 3.5 equiv) in D_2O (10 mL). The resulting mixture was heated at reflux temperature for 24 h. The reaction mixture was cooled to r.t. and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The organic phases were combined, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the final product was purified by silica gel column chromatography (hexane–EtOAc, 95:5).

Synthesis of Deuterium-Labeled Alcohols under Microwave Irradiation Conditions; General Procedure
A 5-mL microwave vial was charged with K_2CO_3 (241.5 mg, 1.75 mmol, 3.5 equiv), the corresponding tosylhydrazone (0.5 mmol), D_2O (2.5 mL) and a cylindrical magnetic stirring bar. The vessel was sealed with a septum, placed into the microwave cavity of an Anton-Paar microwave unit and irradiated to heat the reaction mixture at 130 °C. The total heating time was 30 min at 130 °C. When the reaction was completed, the vial was cooled to r.t. using a propelled air flow. The vial was then opened and the contents were poured into a separating funnel. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the final product was purified by silica gel column chromatography (hexane–EtOAc, 95:5).

Phenyl[O,1-$^2H_2$]methanol (Tables 5 and 6, Entry 1)
Yields: 27.1 mg (82%, from 0.3 mmol of tosylhydrazone under reflux conditions) and 53.9 mg (98%, from 0.5 mmol of tosylhydrazone under microwave conditions); colorless oil.

IR (ATR): 2327 cm^{-1} (O–D).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.67 (s, 1 H), 7.36 (m, 2 H), 7.37 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 64.97 (CDH), 127.30 (2 × CH), 127.95 (CH), 128.84 (2 × CH), 141.03 (C).

HRMS (EI): *m*/*z* calcd for $C_7H_6D_2O$: 110.0699; found: 110.0702.

***p*-Tolyl[O,1-$^2H_2$]methanol (Tables 5 and 6, Entry 2)**
Yields: 33.5 mg (90%, from 0.3 mmol of tosylhydrazone under reflux conditions) and 60.1 mg (97%, from 0.5 mmol of tosylhydrazone under microwave conditions); colorless oil.

IR (ATR): 2325 cm^{-1} (O–D).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.35 (s, 3 H), 4.62 (s, 1 H), 7.17 (d, *J* = 7.1 Hz, 2 H), 7.25 (d, *J* = 7.1 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.42 (CH_3), 65.03 (CDH), 127.42 (2 × CH), 129.51 (2 × CH), 137.69 (C), 138.07 (C).

HRMS (EI): *m*/*z* calcd for $C_8H_8D_2O$: 124.0855; found: 124.0854.

[4-(Dimethylamino)phenyl][O,1-$^2H_2$]methanol (Tables 5 and 6, Entry 3)
Yields: 25.3 mg (55%, from 0.3 mmol of tosylhydrazone under reflux conditions) and 57.4 mg (75%, from 0.5 mmol of tosylhydrazone under microwave conditions); colorless oil.

IR (ATR): 2330 cm^{-1} (O–D).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.90 (s, 6 H), 4.50 (s, 1 H), 7.18 (d, *J* = 8.9 Hz, 2 H), 7.33 (d, *J* = 8.9 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 40.43 (2 × CH_3), 53.90 (CDH), 111.76 (C), 128.82 (2 × CH), 134.43 (2 × CH), 152.26 (C).

HRMS (EI): *m*/*z* calcd for $C_9H_{11}D_2NO$: 153.1121; found: 153.1125.

(4-Chlorophenyl)[O,1-$^2H_2$]methanol (Tables 5 and 6, Entry 4)
Yields: 28.1 mg (65%, from 0.3 mmol of tosylhydrazone under reflux conditions) and 69.1 mg (96%, from 0.5 mmol of tosylhydrazone under microwave conditions); colorless oil.

IR (ATR): 2325 cm^{-1} (O–D).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.64 (s, 1 H), 7.29 (d, *J* = 8.3 Hz, 2 H), 7.32 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 64.64 (CDH), 128.48 (2 × CH), 128.85 (2 × CH), 133.49 (C), 139.54 (C).

HRMS (EI): *m*/*z* calcd for $C_7H_5D_2ClO$: 144.0309; found: 144.0310.

(2,6-Dichlorophenyl)[O,1-$^2H_2$]methanol (Tables 5 and 6, Entry 5)
Yields: 32.0 mg (60%, from 0.3 mmol of tosylhydrazone under reflux conditions) and 82.8 mg (93%, from 0.5 mmol of tosylhydrazone under microwave conditions); colorless oil.

IR (ATR): 2324 cm^{-1} (O–D).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.91 (s, 1 H), 7.32 (m, 2 H), 7.34 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 60.50 (CDH), 128.76 (2 × CH), 129.11 (CH), 131.34 (2 × C), 142.31 (C).

HRMS (EI): *m*/*z* calcd for $C_7H_4D_2Cl_2O$: 177.9919; found: 177.9921.

1-Phenyl[O,1-$^2H_2$]ethanol (Tables 5 and 6, Entry 6)
Yields: 26.0 mg (70%, from 0.3 mmol of tosylhydrazone under reflux conditions) and 60.1 mg (97%, from 0.5 mmol of tosylhydrazone under microwave conditions); colorless oil.

IR (ATR): 2325 cm^{-1} (O–D).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.51 (s, 3 H), 7.36 (m, 2 H), 7.38 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.30 (CH_3), 70.27 (CD), 125.64 (2 × CH), 127.74 (CH), 128.77 (2 × CH), 146.01 (C).

HRMS (EI): *m*/*z* calcd for $C_8H_8D_2O$: 124.0855; found: 124.0858.

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References

(1) (a) Fulton, J. R.; Aggarwal, V. K.; Vicente, J. *Eur. J. Org. Chem.* **2005**, 1479. (b) Aggarwal, V. K.; Alonso, E.; Bae, I.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Patel, M.; Porcelloni, M.; Richardson, J.; Stenson, R. A.; Studley, J. R.; Vasse, J. L.; Winn, C. L. *J. Am. Chem. Soc.* **2003**, *125*, 10926. (c) Aggarwal, V. K.; Fulton, J. R.; Sheldon, C. G.; Vicente, J. *J. Am. Chem. Soc.* **2003**, *125*, 6034. (d) Aggarwal, V. K.; Alonso, E.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Porcelloni, M.; Studley, J. R. *Angew. Chem. Int. Ed.* **2001**, *40*, 1430.

(2) (a) Barluenga, J.; Valdés, C. *Angew. Chem. Int. Ed.* **2011**, *50*, 7486. (b) Barluenga, J.; Quiñones, N.; Cabal, M. P.; Aznar, F.; Valdés, C. *Angew. Chem. Int. Ed.* **2011**, *50*, 2350. (c) Barluenga, J.; Tomas-Gamasa, M.; Aznar, F.; Valdés, C. *Eur. J. Org. Chem.* **2011**, 1520. (d) Barluenga, J.; Florentino, L.; Aznar, F.; Valdés, C. *Org. Lett.* **2011**, *13*, 510. (e) Barluenga, J.; Tomas-Gamasa, M.; Aznar, F.; Valdés, C. *Chem.–Eur. J.* **2010**, *16*, 12801. (f) Barluenga, J.; Tomas-Gamasa, M.; Aznar, F.; Valdés, C. *Adv. Synth. Catal.* **2010**, *352*, 3235. (g) Barluenga, J.; Escribano, M.; Moriel, P.; Aznar, F.; Valdés, C. *Chem.–Eur. J.* **2009**, *15*, 13291. (h) Barluenga, J.; Moriel, P.; Valdés, C.; Aznar, F. *Angew. Chem. Int. Ed.* **2007**, *46*, 5587.

(3) Cheung, W. H.; Zheng, S. L.; Yu, W. Y.; Zhou, G. C.; Che, C. M. *Org. Lett.* **2003**, *5*, 2535.

(4) Feng, X. W.; Wang, J.; Zhang, J.; Yang, J.; Wang, N.; Yu, X. Q. *Org. Lett.* **2010**, *12*, 4408.

(5) Hamze, A.; Treguier, B.; Brion, J. D.; Alami, M. *Org. Biomol. Chem.* **2011**, *9*, 6200.

(6) (a) Cuevas-Yañez, E.; Serrano, J. M.; Huerta, G.; Muchowski, J. M.; Cruz-Almanza, R. *Tetrahedron* **2004**, *60*, 9391. (b) García, M. A.; García-Muñoz, A.; Pena, J. A.; Trujillo-Reyes, J.; Morales-Luckie, R. A.; Avalos-Borja, M.; Vilchis-Nestor, A. R.; Sánchez-Mendieta, V.; Corona, D.; Cuevas-Yañez, E. *Lett. Org. Chem.* **2012**, *9*, 2.

(7) Barluenga, J.; Tomas-Gamasa, M.; Aznar, F.; Valdés, C. *Nat. Chem.* **2009**, *1*, 433.

(8) Barluenga, J.; Tomas-Gamasa, M.; Aznar, F.; Valdés, C. *Angew. Chem. Int. Ed.* **2010**, *49*, 4993.

(9) Ding, Q.; Cao, B.; Yuan, J.; Liua, X.; Peng, Y. *Org. Biomol. Chem.* **2011**, *9*, 748.

(10) Kirmse, W.; Zellmer, V.; Goer, B. *J. Am. Chem. Soc.* **1986**, *108*, 4912.

(11) Tse, S. K. S.; Xue, P.; Lau, C. W. S.; Sung, H. H. Y.; Williams, I. D.; Jia, G. *Chem.–Eur. J.* **2011**, *17*, 13918.

(12) (a) Chen, H.; Chan, K. K. *J. Labelled Compd. Radiopharm.* **1997**, *39*, 369. (b) Dasgupta, S. K.; Rice, D. M.; Griffin, R. G. *J. Lipid Res.* **1982**, *23*, 197. (c) Shi, B.; Jin, C. *Appl. Catal., A* **2011**, *398*, 54.

