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Evaluating a Sodium Dispersion Reagent for the Bouveault–Blanc Reduction of Esters

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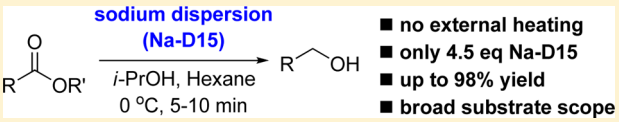
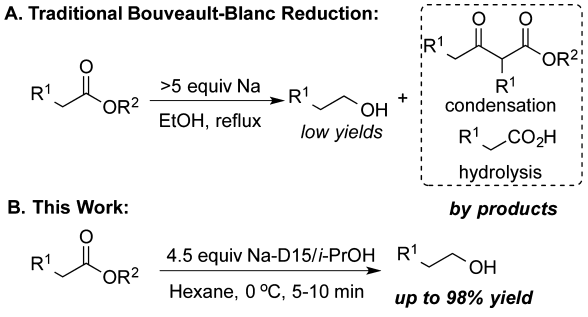
Supporting Information

ABSTRACT: A new sodium dispersion reagent has been evaluated for the reduction of esters. Na-D15, a sodium dispersion with sodium particle size of 5–15 μm, is a nonpyrophoric reagent that can be handled in air. In this study, a broad range of aliphatic ester substrates were reduced to primary alcohols by Na-D15/*i*-PrOH with good yields. The method compares favorably with modern metal hydride reductions and is much safer and efficient than the traditional Bouveault–Blanc reduction.



The dissolving metal reduction of esters has found widespread use in synthesis for access to important alcohols.[1] Compared with metal hydride reduction, this method does not suffer from the formation of toxic metal residues and has higher atom economy.[2] The process was first achieved by Bouveault and Blanc using sodium lump and absolute ethanol (Scheme 1A).[3] Since the reaction takes place on the metal surface, it is crucial that the metal is finely dispersed.[1a,b] To form the dispersion in situ, external heating is required to melt the alkali metal, and high-speed stirring is also important. To facilitate this process, the sodium lump is normally precut into small pieces.[4] These procedures can result in reproducibility problems and give rise to safety issues (e.g., excess foaming and fire).[4] Furthermore, the high temperature accelerates competitive base-promoted Claisen condensation and ester hydrolysis (Scheme 1A).[1a] Reactions at lower temperature can be achieved by using the EtOH/NH_3 solvent system instead of EtOH[1a] or using NaK instead of the pure metal.[5] These alternative protocols, however, are not general. Herein, we present the use of a pre-prepared, nonpyrophoric, and high surface area sodium dispersion, Na-D15, in place of sodium lump for the Bouveault–Blanc reduction. To our knowledge, no systematic study of the application of a pre-prepared sodium dispersion for the electron transfer reductions of esters has been reported.

Scheme 1. Na-D15/*i*-PrOH-Promoted Electron Transfer Reductions of Esters



The sodium dispersion Na-D15 (Scheme 1B) is prepared by a robust, reliable, and scalable sodium dispersion technology.[6] It is a free-flowing suspension that has an optimized particle size (5–15 μm). Na-D15 is transferable by syringe or pipette and can easily be handled in the open atmosphere, thus its use offers key advantages over that of alternative sodium dispersions. The feasibility of using Na-D15 as a base in large-scale industry synthesis has already been demonstrated.

The initial trial of the ester reduction using Na-D15 was carried out under the same reaction conditions as those employed for the classic Bouveault–Blanc reduction; however, the reaction was carried out at 0 °C rather than at reflux.[4d] When 5.0 equiv of Na-D15 was used in EtOH, only 10% of the desired alcohol product **2a** was detected (entry 1, Table 1) with 90% of the ester recovered. The low yield was due to the competitive oxidation of sodium by EtOH. We found that the yield could be increased to 80% by using 10 equiv of Na-D15 (entry 2, Table 1). Replacing EtOH with MeOH resulted in a lower yield (entry 3, Table 1).

Given the fast side reaction between Na-D15 and the protic solvent and the poor miscibility of the suspending agent in Na-D15 in alcohols, the application of other aprotic solvents was explored. When hexane was used as the solvent, an excellent 93% yield was obtained (entry 4, Table 1). EtOH could be replaced by other proton sources, and *i*-PrOH was found to be the most effective alcohol whose use led to a quantitative yield of **2a** (entry 8, Table 1). When approximately quantitative[7] Na-D15 was used, an excellent 94% yield of **2a** was also obtained (entry 10, Table 1). No competitive Claisen condensation and/or ester hydrolysis was observed under these conditions. When H_2O was used instead of an alcohol, intermolecular acyloin

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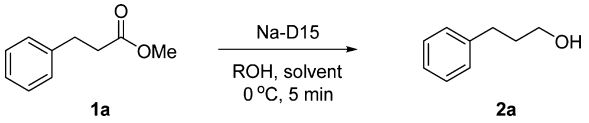
Table 1. Optimization of the Ester Reductions Using Na-D15[a]



1a 2a

entry	solvent	ROH	ROH (equiv)	Na-D15 (equiv)	yield of **2a** (%)
1	EtOH	EtOH	51[b]	5.0	10
2	EtOH	EtOH	51[b]	10	80
3	MeOH	MeOH	74[b]	10	66
4	hexane	EtOH	10	10	93
5	hexane	EtOH	10	8	90
6	hexane	EtOH	10	6	86
7	hexane	MeOH	10	10	71
8	hexane	*i*-PrOH	10	10	>99
9	hexane	*i*-PrOH	6.0	6.0	>99
10	hexane	*i*-PrOH	4.5	4.5	94
11	THF	*i*-PrOH	4.5	4.5	86
12	Et_2O	*i*-PrOH	4.5	4.5	93
13	toluene	*i*-PrOH	4.5	4.5	90
14	hexane	*t*-BuOH	4.5	4.5	87

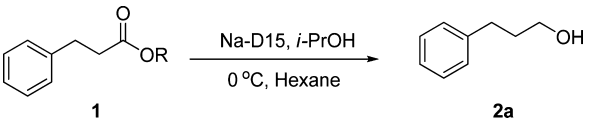
[a]Yield determined by ^{1}H NMR spectroscopy using CH_3NO_2 as an internal standard. [b]ROH was used as the solvent.

condensation gave rise to the major product, most likely due to the poor miscibility of H_2O in hexane.[1b] Different solvents were then screened: hexane, which is seldom used for Bouveault–Blanc reductions, is superior to arene solvents[8] (e.g., toluene), and Lewis basic solvents (e.g., THF and Et_2O), which are commonly used in dissolving metal reductions (entries 10–13, Table 1).

Following the optimization studies, the influence of the ester group was investigated using a range of esters derived from hydrocinnamic acid. Methyl, ethyl, isopropyl, *n*-butyl, phenyl, and 2-methoxyethyl esters were all reduced in high yield (Table 2). More hindered ester **1c** was reduced in a slightly lower yield (entry 3, Table 2). Similarly, allyl and benzyl esters were also reduced to the corresponding alcohols in high yields (entries 5 and 6, Table 2).

The scope of this reduction was then investigated using a range of aliphatic ester and lactone substrates. The results demonstrate that a broad range of esters readily participate in the reaction (Scheme 2). Primary, secondary, and tertiary alkyl esters were all reduced to the corresponding primary alcohols

Table 2. Reduction of Hydrocinnamic Esters with Na-D15[a]

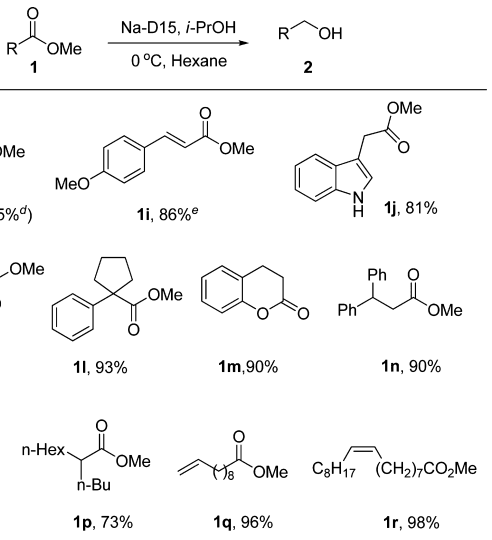


1 2a

entry	ester	R	product	yield of **2a** (%)[b]
1	**1a**	Me	**2a**	94
2	**1b**	Et	**2a**	97
3	**1c**	*i*-Pr	**2a**	88
4	**1d**	*n*-Bu	**2a**	93
5	**1e**	allyl	**2a**	80
6	**1f**	Bn	**2a**	88
7	**1g**	Ph	**2a**	97
8	**1h**	$(CH_2)_2OMe$	**2a**	98

[a]Conditions: Na-D15 (4.5 equiv), *i*-PrOH (4.5 equiv), hexane, 0 °C, 5–10 min. [b]Isolated yields.

Scheme 2. Reduction of Esters with Na-D15[a,b]

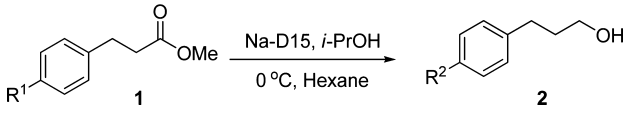


[a]Conditions: **1** (0.50 mmol, 1.0 equiv), Na-D15 (4.5 equiv), *i*-PrOH (4.5 equiv), hexane, 0 °C, 5–10 min. [b]Isolated yields. [c]Conditions: **1** (5.0 mmol). [d]Conditions: **1** (25.0 mmol). [e]Conditions: Na-D15 (6.5 equiv), *i*-PrOH (6.5 equiv); 3-(4-methoxyphenyl)propan-1-ol formed as the product.

in excellent yields. Minimal impact on the yield was observed with sterically hindered substituents (**1l** and **1o**, Scheme 2). A substrate with an acidic proton was also tolerated very well (**1n**, Scheme 2). The substrates bearing both internal and terminal olefins (**1q** and **1r**, Scheme 2) were reduced smoothly to the corresponding alcohols. The α,β-unsaturated ester underwent full reduction with Na-D15/*i*-PrOH to give the saturated alcohol (**1i**, Scheme 2). Furthermore, this protocol tolerates the heterocyclic ring in ester **1j** and is able to reduce lactone **1m** to the corresponding diol. Importantly, no significant change in yields has been observed upon scale up of this reaction from 0.50 to 25 mmol (**1a**, Scheme 2).

Table 3 shows further examples of functional group tolerance. Functional groups such as −F, −OMe, −SMe, and $-NH_2$ (entries 1 and 3–5, Table 3) are tolerated well. It is

Table 3. Functional Group Tolerance in the Reduction of Esters with Na-D15[a,b]



1 2

entry	1	R^1	2	R^2	yield of **2a** (%)
1	**1s**	F	**2s**	F	90
2[c]	**1t**	Cl	**2a**	H	81
3	**1u**	OMe	**2u**	OMe	90
4	**1v**	SMe	**2v**	SMe	78
5	**1w**	NH_2	**2w**	NH_2	73

[a]Conditions: **1** (0.50 mmol, 1.0 equiv), Na-D15 (4.5 equiv), *i*-PrOH (4.5 equiv), hexane, 0 °C, 5–10 min. [b]Isolated yields. [c]Conditions: Na-D15 (6.5 equiv), *i*-PrOH (6.5 equiv); 3-phenylpropan-1-ol formed as the product.

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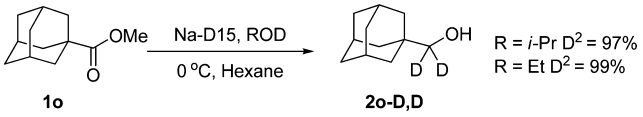
noteworthy that aryl fluorides are not tolerated in the improved Bouveault−Blanc reduction using Na-SG(I) (stage I sodium in silica gel).[1d] Na-SG(I) is a stabilized sodium metal, which eliminates the dangers of handling neat sodium while retaining its reactivity. However, chloride on an aromatic ring was fully reduced when 6.5 equiv of Na-D15 was used (entry 2, Table 3).

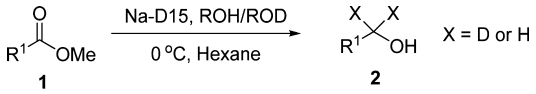
Next, the reduction of esters using deuterated alcohols was conducted (Scheme 3). The formation of **2**-D,D compounds

Scheme 3. Deuterium Incorporation



suggests that anions are generated and protonated by the alcohol during a series of single electron transfers. The kinetic isotope effect was determined as shown in Table 4. The results

Table 4. Determination of Primary Kinetic Isotope Effect



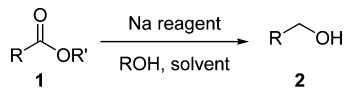
entry	ester	ROH/ROD	k_H/k_D
1	**1a**	*i*-PrOH/*i*-PrOD	1.1
2	**1a**	EtOH/EtOD	1.4
3	**1o**	*i*-PrOH/*i*-PrOD	1.0
4	**1o**	EtOH/EtOD	1.3

suggest that, when EtOH and *i*-PrOH were used as the proton donor, the proton transfer is not involved in the rate-determining step for the reduction of simple and sterically demanding esters.[1m,n,9]

Finally, the performance of Na-D15 was compared with that of Na-SG(I):[1d,10] similar yields were obtained using Na-SG(I) for the reduction of **1b** and **1o**; however, 15 equiv of Na-SG(I) was required to achieve full conversion (entries 5 and 6, Table 5).

In summary, a new sodium dispersion has been evaluated for the reduction of aliphatic esters to primary alcohols in *i*-PrOH/hexane. Only 4.5 equiv of the reagent was required in this method. A broad range of aliphatic esters was reduced in high yields under mild conditions without external heating. The

Table 5. Comparison of Na-D15 and Na-SG(I)



entry	1	Na reagent (equiv)	ROH (equiv)	solvent	yield of **2** (%)
1[a]	**1b**	Na-D15 (4.5)	*i*-PrOH (4.5)	hexane	97
2[a]	**1o**	Na-D15 (4.5)	*i*-PrOH (4.5)	hexane	99
3[a,b]	**1b**	Na-SG(I) (4.5)	MeOH (26.5)	THF	36
4[a,b]	**1o**	Na-SG(I) (4.5)	MeOH (26.5)	THF	21
5[c]	**1b**	Na-SG(I) (15)	MeOH (26.5)	THF	99
6[c]	**1o**	Na-SG(I) (15)	MeOH (26.5)	THF	97

[a]Yield determined by ^{1}H NMR spectroscopy using CH_3NO_2 as an internal standard. [b]Conditions: **1** (0.5 mmol, 1 equiv), Na-SG(I) (35 wt %, 4.5 equiv), MeOH (26.5 equiv, added dropwise over 5 min at 0 °C), 0 °C to rt, 35 min. [c]Results reported in ref 1d.

base-promoted side reactions observed in traditional Bouveault−Blanc reductions were suppressed by using Na-D15, and higher yields were obtained. The chemoselectivity of Na-D15 has been demonstrated to be comparable with metal hydrides. Given that Na-D15 is easy to handle and stable, this protocol provides an attractive alternative to the use of pyrophoric metal hydrides for ester reduction.

EXPERIMENTAL SECTION

Glassware was dried in an oven overnight before use. Thin layer chromatography was carried out on SIL G/UV254 silica−aluminum plates, and plates were visualized using ultraviolet light (254 nm) and $KMnO_4$ solution. For flash column chromatography, 35−70 μm silica gel 60 was used. NMR data were collected at either 400 or 500 MHz. All samples were analyzed in $CDCl_3$ unless otherwise stated. Reference values for residual solvent were taken as δ = 7.27 ($CDCl_3$) for ^{1}H NMR; δ = 77.1 ($CDCl_3$) for ^{13}C NMR. Multiplicities for coupled signals were designated using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, br = broad signal and are given in hertz.

All compounds used in this study have been described in the literature[1] or are commercially available. All solvents and reagents were used as supplied. Esters were purchased from commercial suppliers or prepared by standard methods.[1d,m]

General Procedure for the Reduction of Esters with Na-D15. To a solution of ester (0.500 mmol) in anhydrous hexane (2.5 mL) was added anhydrous *i*-PrOH (2.25 mmol, 172 μL), followed by Na-D15 (27.7 wt %, 2.25 mmol, 209 μL) under N_2 at 0 °C, and the resulting solution was stirred vigorously. After 5 min at 0 °C, the temperature was increased to rt. After the specified time (typically 0−10 min), the reaction was quenched by an aqueous solution of HCl (1.0 mL, 3.0 M) and the reaction mixture was diluted with Et_2O (10 mL) and brine (20 mL). The aqueous layer was extracted with Et_2O (2 × 10 mL), and the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica, 0−30% EtOAc/hexane).

3-Phenylpropan-1-ol ***2a***[1m] *(entry 1, Table 2).* According to the general procedure, the reaction of methyl 3-phenylpropanoate (0.50 mmol), *i*-PrOH (2.25 mmol), and Na-D15 (2.25 mmol) for 5 min at 0 °C, after chromatography (hexanes, 30% EtOAc/hexane), afforded **2a** (64.0 mg) in 94% yield as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.29 (m, 2H), 7.25−7.19 (m, 3H), 3.69 (t, J = 6.3, 2H), 2.73 (t, J = 7.8, 2H), 1.96−1.88 (m, 2H), 1.76 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.9, 128.5, 128.4, 125.9, 62.3, 34.2, 32.1.

3-Phenylpropan-1-ol ***2a***[1m] *(entry 2, Table 2).* According to the general procedure, the reaction of ethyl 3-phenylpropanoate (0.50 mmol), *i*-PrOH (2.25 mmol), and Na-D15 (2.25 mmol) for 5 min at 0 °C afforded **2a** (66.1 mg) in 97% yield. Spectroscopic properties matched those previously described.

3-Phenylpropan-1-ol ***2a***[1m] *(entry 3, Table 2).* According to the general procedure, the reaction of isopropyl 3-phenylpropanoate (0.50 mmol), *i*-PrOH (2.25 mmol), and Na-D15 (2.25 mmol) for 5 min at 0 °C and 10 min at rt afforded **2a** (60.1 mg) in 88% yield. Spectroscopic properties matched those previously described.

3-Phenylpropan-1-ol ***2a***[1m] *(entry 4, Table 2).* According to the general procedure, the reaction of butyl 3-phenylpropanoate (0.50 mmol), *i*-PrOH (2.25 mmol), and Na-D15 (2.25 mmol) for 5 min at 0 °C afforded **2a** (63.3 mg) in 93% yield. Spectroscopic properties matched those previously described.

3-Phenylpropan-1-ol ***2a***[1m] *(entry 5, Table 2).* According to the general procedure, the reaction of allyl 3-phenylpropanoate (0.50 mmol), *i*-PrOH (2.25 mmol), and Na-D15 (2.25 mmol) for 5 min at 0 °C afforded **2a** (54.5 mg) in 80% yield. Spectroscopic properties matched those previously described.

3-Phenylpropan-1-ol ***2a***[1m] *(entry 6, Table 2).* According to the general procedure, the reaction of benzyl 3-phenylpropanoate (0.50 mmol), *i*-PrOH (2.25 mmol), and Na-D15 (2.25 mmol) for 5 min at 0 °C afforded **2a** (60.2 mg) in 88% yield. Spectroscopic properties matched those previously described.

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3-Phenylpropan-1-ol ***2a***[1m] *(entry 7, Table 2).* According to the general procedure, the reaction of phenyl 3-phenylpropanoate (0.50 mmol), *i*-PrOH (2.25 mmol), and Na-D15 (2.25 mmol) for 5 min at 0 °C afforded **2a** (66.2 mg) in 97% yield. Spectroscopic properties matched those previously described.

3-Phenylpropan-1-ol ***2a***[1m] *(entry 8, Table 2).* According to the general procedure, the reaction of 2-methoxyethyl 3-phenylpropanoate (0.50 mmol), *i*-PrOH (2.25 mmol), and Na-D15 (2.25 mmol) for 5 min at 0 °C afforded **2a** (66.9 mg) in 98% yield. Spectroscopic properties matched those previously described.

3-Phenylpropan-1-ol ***2a***[1m] *(25 mmol scale reaction, Scheme 2).*[11] Na-D15 (112.5 mmol) was transferred to a 250 mL round-bottom flask under N_2. Hexane (110 mL) was added, and the suspension was cooled to 0 °C. A solution of methyl 3-phenylpropanoate (25.0 mmol) and *i*-PrOH (112.5 mmol) in hexane (15 mL) was then transferred into the flask in one portion. The reaction mixture was stirred at 0 °C for 5 min, and the temperature was increased to rt. After 5 min, the reaction was quenched by an aqueous solution of HCl (50 mL, 3.0 M). The reaction mixture was diluted with Et_2O (100 mL) and brine (100 mL), and the aqueous layer was extracted with Et_2O (3 × 100 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica, 30% EtOAc/hexane), affording **2a** (3.23 g) in 95% yield as a colorless oil. Spectroscopic properties matched those previously described

3-(4-Methoxyphenyl)propan-1-ol ***2i***[1m] *(Scheme 2).* According to the general procedure, the reaction of (*E*)-methyl 3-(4-methoxyphenyl)acrylate (0.50 mmol), *i*-PrOH (3.25 mmol), and Na-D15 (3.25 mmol) for 5 min at 0 °C and 5 min at rt, after chromatography (hexanes, 30% EtOAc/hexane), afforded **2i** (71.6 mg) in 86% yield as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15−7.11 (m, 2H), 6.87−6.82 (m, 2H), 3.80 (s, 3H), 3.68 (t, *J* = 6.3, 2H), 2.66 (t, *J* = 7.6, 2H), 1.91−1.84 (m, 2H), 1.56 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.8, 133.9, 129.4, 113.9, 62.3, 55.3, 34.5, 31.2.

2-(1H-Indol-3-yl)ethanol ***2j***[1m] *(Scheme 2).* According to the general procedure, the reaction of methyl 2-(1*H*-indol-3-yl)acetate (0.50 mmol), *i*-PrOH (4.50 mmol), and Na-D15 (2.25 mmol) for 5 min at 0 °C and 30 min at rt, after preparative TLC (20% EtOAc/hexane), afforded **2j** (65.3 mg) in 81% yield as a brown oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (br, 1H), 7.66−7.63 (m, 1H), 7.41−7.38 (m, 1H), 7.25−7.21 (m, 1H), 7.17−7.13 (m, 1H), 7.11−7.09 (m, 1H), 3.93 (t, *J* = 6.3, 2H), 3.06 (m, 2H), 1.59 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.5, 127.5, 122.6, 122.3, 119.6, 118.9, 112.4, 111.3, 62.7, 28.8.

2-(4-Isobutylphenyl)propan-1-ol ***2k***[1m] *(Scheme 2).* According to the general procedure, the reaction of methyl 2-(4-isobutylphenyl)-propanoate (0.50 mmol), *i*-PrOH (2.25 mmol), and Na-D15 (2.25 mmol) for 5 min at 0 °C and 10 min at rt, after chromatography (hexanes, 20% EtOAc/hexane), afforded **2k** (91.6 mg) in 95% yield as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17−7.10 (m, 4H), 3.69 (d, *J* = 6.9, 2H), 2.98−2.90 (m, 1H), 2.46 (d, *J* = 7.3, 2H), 1.92−1.81 (m, 1H), 1.48 (br, 1H), 1.28 (d, *J* = 6.9, 3H), 0.92 (d, *J* = 6.6, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.8, 140.1, 129.4, 127.2, 68.8, 45.1, 42.1, 30.3, 22.5, 17.7.

(1-Phenylcyclopentyl)methanol ***2l***[1d] *(Scheme 2).* According to the general procedure, the reaction of methyl 1-phenylcyclopentane-carboxylate (0.50 mmol), *i*-PrOH (2.25 mmol), and Na-D15 (2.25 mmol) for 5 min at 0 °C and 30 min at rt, after chromatography (hexanes, 20% EtOAc/hexane), afforded **2l** (82.0 mg) in 93% yield as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.32 (m, 4H), 7.25−7.21 (m, 1H), 3.54 (s, 2H), 2.08−2.00 (m, 2H), 1.94−1.86 (m, 2H), 1.80−1.68 (m, 4H), 1.30 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.9, 128.4, 127.4, 126.3, 70.4, 53.4, 34.4, 23.9.

2-(3-Hydroxypropyl)phenol ***2m***[1m] *(Scheme 2).* According to the general procedure, the reaction of chroman-2-one (0.50 mmol), *i*-PrOH (4.50 mmol), and Na-D15 (2.25 mmol) for 30 min at rt, after chromatography (hexanes, 30% EtOAc/hexane), afforded **2m** (68.5 mg) in 90% yield as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14−7.09 (m, 2H), 6.91−6.83 (m, 2H), 4.46 (br, 2H), 3.65 (t, *J* = 5.8, 2H), 2.79 (t, *J* = 6.8, 2H), 1.94−1.85 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 130.7, 127.6, 127.3, 120.9, 116.1, 60.9, 32.3, 25.3.

3,3-Diphenylpropan-1-ol ***2n***[12] *(Scheme 2).* According to the general procedure, the reaction of methyl 3,3-diphenylpropanoate (0.50 mmol), *i*-PrOH (2.25 mmol), and Na-D15 (2.25 mmol) for 5 min at 0 °C and 10 min at rt, after chromatography (hexanes, 30% EtOAc/hexane), afforded **2n** (96.0 mg) in 90% yield as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.27 (m, 8H), 7.23−7.18 (m, 2H), 4.17 (t, *J* = 7.9, 1H), 3.64 (t, *J* = 6.4, 2H), 2.39−2.32 (m, 2H), 1.40 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 128.6, 127.9, 126.4, 61.2, 47.5, 38.1.

1-Adamantanemethanol ***2o***[1m] *(Scheme 2).* According to the general procedure, the reaction of methyl adamantane-1-carboxylate (0.50 mmol), *i*-PrOH (2.25 mmol), and Na-D15 (2.25 mmol) for 5 min at 0 °C and 15 min at rt, after chromatography (hexanes, 10% EtOAc/hexane), afforded **2o** (81.6 mg) in 98% yield as white crystals: mp 117−118 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.21 (s, 2H), 2.03−1.98 (m, 3H), 1.77−1.71 (m, 3H), 1.69−1.63 (m, 3H), 1.54−1.50 (m, 6H), 1.37 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 74.0, 39.1, 37.3, 34.6, 28.3.

2-Butyloctan-1-ol ***2p***[1n] *(Scheme 2).* According to the general procedure, the reaction of methyl 2-butyloctanoate (0.50 mmol), *i*-PrOH (2.25 mmol), and Na-D15 (2.25 mmol) for 5 min at 0 °C and 30 min at rt, after chromatography (hexanes, 10% EtOAc/hexane), afforded **2p** (68.2 mg) in 73% yield as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.55 (d, *J* = 5.4, 2H), 1.51−1.42 (m, 1H), 1.38−1.23 (m, 17H), 0.91 (t, *J* = 6.6, 3H), 0.89 (t, *J* = 7.2, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 65.8, 40.6, 32.0, 31.0, 30.7, 29.8, 29.2, 27.0, 23.2, 22.8, 14.2 × 2.

Undec-10-en-1-ol ***2q***[1n] *(Scheme 2).* According to the general procedure, the reaction of methyl undec-10-enoate (0.50 mmol), *i*-PrOH (2.25 mmol), and Na-D15 (2.25 mmol) for 5 min at 0 °C and 10 min at rt, after chromatography (hexanes, 20% EtOAc/hexane), afforded **2q** (81.9 mg) in 96% yield as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86−5.77 (m, 1H), 5.03−4.97 (m, 1H), 4.96−4.91 (m, 1H), 3.64 (t, *J* = 6.6, 2H), 2.08−2.01 (m, 2H), 1.61−1.53 (m, 2H), 1.46−1.24 (m, 13H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.3, 114.2, 63.2, 33.9, 32.9, 29.6, 29.5 × 2, 29.2, 29.0, 25.8.

(Z)-Octadec-9-en-1-ol ***2r***[1n] *(Scheme 2).* According to the general procedure, the reaction of methyl oleate (0.50 mmol), *i*-PrOH (2.25 mmol), and Na-D15 (2.25 mmol) for 5 min at 0 °C, after chromatography (hexanes, 10% EtOAc/hexane), afforded **2r** (131.7 mg) in 98% yield as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.39−5.31 (m, 2H), 3.65 (t, *J* = 6.8, 2H), 2.05−1.99 (m, 4H), 1.61−1.54 (m, 2H), 1.39−1.22 (m, 23H), 0.89 (t, *J* = 7.1, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 130.1, 129.9, 63.2, 32.9, 32.0, 29.9, 29.8, 29.6 × 2, 29.5, 29.4 × 2, 29.3, 27.3 × 2, 25.8, 22.8, 14.2.

3-(4-Fluorophenyl)propan-1-ol ***2s***[1n] *(entry 1, Table 3).* According to the general procedure, the reaction of methyl 3-(4-fluorophenyl)-propanoate (0.50 mmol), *i*-PrOH (2.25 mmol), and Na-D15 (2.25 mmol) for 5 min at 0 °C and 10 min at rt, after chromatography (hexanes, 50% EtOAc/hexane), afforded **2s** (69.6 mg) in 90% yield as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19−7.13 (m, 2H), 7.00−6.95 (m, 2H), 3.67 (t, *J* = 6.5, 2H), 2.69 (t, *J* = 7.7, 2H), 1.91−1.84 (m, 2H), 1.54 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.3 (d, *J* = 242.9), 137.4 (d, *J* = 2.7), 129.2 (d, *J* = 7.3), 115.2 (d, *J* = 21.0), 62.1, 34.4, 31.3.

3-Phenylpropan-1-ol ***2a***[1m] *(entry 2, Table 3).* According to the general procedure, the reaction of methyl 3-(4-chlorophenyl)-propanoate (0.50 mmol), *i*-PrOH (3.25 mmol), and Na-D15 (3.25 mmol) for 5 min at 0 °C and 20 min at rt, after chromatography (hexanes, 20% EtOAc/hexane), afforded **2a** (55.4 mg) in 81% yield as a colorless oil. Spectroscopic properties matched those previously described.

3-(4-Methoxyphenyl)propan-1-ol ***2u***[1n] *(entry 3, Table 3).* According to the general procedure, the reaction of methyl 3-(4-methoxyphenyl)propanoate (0.50 mmol), *i*-PrOH (2.25 mmol), and Na-D15 (2.25 mmol) for 5 min at 0 °C and 10 min at rt, after chromatography (hexanes, 50% EtOAc/hexane), afforded **2u** (74.9

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mg) in 90% yield as a colorless oil. Spectroscopic properties matched those previously described.

3-(4-(Methylthio)phenyl)propan-1-ol **2v**[1n] *(entry 4, Table 3).* According to the general procedure, the reaction of methyl 3-(4-(methylthio)phenyl)propanoate (0.50 mmol), *i*-PrOH (2.25 mmol), and Na-D15 (2.25 mmol) for 5 min at 0 °C and 10 min at rt, after chromatography (hexanes, 30% EtOAc/hexane), afforded **2v** (71.0 mg) in 78% yield as a light yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23−7.20 (m, 2H), 7.16−7.12 (m, 2H), 3.67 (t, J = 6.5, 2H), 2.68 (t, J = 7.8, 2H), 2.48 (s, 3H), 1.92−1.84 (m, 2H), 1.63 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.0, 135.4, 129.0, 127.3, 62.2, 34.2, 31.6, 16.4.

3-(4-Aminophenyl)propan-1-ol **2w**[1n] *(entry 5, Table 3).* According to the general procedure, the reaction of methyl 3-(4-aminophenyl)-propanoate (0.50 mmol), *i*-PrOH (2.25 mmol), and Na-D15 (2.25 mmol) for 5 min at 0 °C and 45 min at rt, after chromatography (hexanes, 50% EtOAc/hexane), afforded **2w** (55.3 mg) in 73% yield as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02−6.98 (m, 2H), 6.66−6.62 (m, 2H), 3.66 (t, J = 6.5, 2H), 2.61 (t, J = 7.6, 2H), 1.88−1.81 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3, 131.9, 129.3, 115.4, 62.4, 34.6, 31.3.

3-Phenylpropan-1-ol **2a**[1m] *(entry 3, Table 5).* According to the reported procedure,[1d] the reaction of ethyl 3-phenylpropanoate (0.50 mmol), MeOH (13.3 mmol), and stage I sodium silica gel (35 wt %, 2.25 mmol) in anhydrous THF (8.0 mL) afforded **2a** (24.7 mg) in 36% yield (^{1}H NMR vs internal standard). Spectroscopic properties matched those previously described.

1-Adamantanemethanol **2o**[1m] *(entry 4, Table 5).* According to the reported procedure,[1d] the reaction of methyl adamantane-1-carboxylate (0.50 mmol), MeOH (13.3 mmol), and stage I sodium silica gel (35 wt %, 2.25 mmol) in anhydrous THF (8.0 mL) afforded **2o** (17.5 mg) in 21% yield (^{1}H NMR vs internal standard). Spectroscopic properties matched those previously described.

Deuterium Incorporation. *(Adamantan-1-yl)methan-d$_2$-ol* ***2o-D,D.*** According to the general procedure, the reaction of methyl adamantane-1-carboxylate (0.50 mmol), *i*-PrOD (2.25 mmol), and Na-D15 (2.25 mmol) for 5 min at 0 °C afforded **2o**-D,D with 99% deuterium incorporation, yield >99% (^{1}H NMR vs internal standard): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.03−1.98 (m, 3H), 1.77−1.71 (m, 3H), 1.69−1.63 (m, 3H), 1.54−1.50 (m, 6H), 1.36 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 73.2 (m), 39.1, 37.3, 34.4, 28.3.

Determination of Primary Kinetic Isotope Effect.[1m,n] According to the general procedure, the reaction of methyl adamantane-1-carboxylate (0.17 mmol), *i*-PrOD/*i*-PrOH (1:1, 18.4 mmol), and Na-D15 (0.77 mmol) for 5 min at 0 °C and 5 min at rt afforded **2o** and **2o**-D,D. The amount of each species was determined by ^{1}H NMR. Kinetic isotope effect, k_H/k_D = 1.0.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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