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Alkoxide-Catalyzed Reduction of Ketones with Pinacolborane

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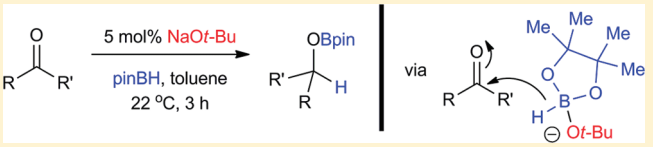
Supporting Information

ABSTRACT: The reduction of ketones with pinacolborane (4,4,5,5-tetramethyl-1,3,2-dioxaborolane) is catalyzed by 5 mol % NaO*t*-Bu at ambient temperature. The reaction is high yielding and general, providing complete conversion of aryl and dialkyl ketones. Although spectroscopic studies of the active hydride source in benzene-d_6 were complicated due to poor solubility, the data are consistent with the active hydride source being the trialkoxyborohydride, which is believed to be present in low concentration under the reaction conditions. Performing analogous studies in tetrahydrofuran resulted in a complex equilibrium between several different boron-containing species in which the trialkoxyborohydride compound was the major species.

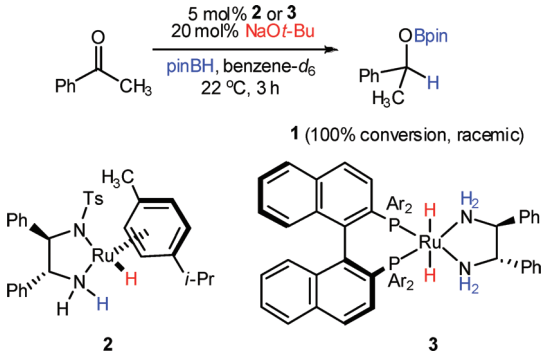


The versatility of the carbon−boron bond in target-directed synthesis[1−3] has led to numerous valuable methods to incorporate boron substituents into organic substrates.[4−14] The hydroboration of double and triple bonds, for example, has served as a long-standing method to synthesize alkyl- and vinylboronate esters.[4−6] Over the past several decades, metal catalysts have been used in hydroboration reactions to increase the substrate scope, enhance reaction rates, and alter the regio- and chemoselectivity.

The advent of metal−ligand bifunctional catalysts in the hydrogenation of polarized double bonds has led to highly efficient and stereoselective catalysts.[15−19] Our interest in developing metal−ligand bifunctional borylation catalysts[20,21] led us to explore the effectiveness of boranes as surrogates for hydrogen gas (or a hydrogen source) in Noyori's asymmetric hydrogenation and transfer hydrogenation reactions. In the process of studying these transformations, we found that the reduction of ketones with pinacolborane was mediated by a catalytic amount of sodium *tert*-butoxide. This transformation represents an important metal-free reaction that should be considered when designing and studying base-mediated catalytic hydroboration reactions. The prevalence of base additives in metal-catalyzed borylation reactions[8,22−24] prompted a detailed investigation into the nature of the active hydride source. We herein report a brief survey of the reaction scope and a spectroscopic study of the alkoxide-mediated reduction of ketones with pinacolborane.

The hydrogenation of ketones using Noyori's hydrogenation and transfer hydrogenation catalysts provides secondary alcohols in high enantioselectivity.[15−18] There are, however, some classes of substrates that result in moderate to low selectivity. Replacing the acidic hydrogen of these catalysts with the sterically more demanding Lewis acid Bpin (4,4,5,5-tetramethyl-1,3,2-dioxoborolane) was expected to enhance the stereoselectivity. Initial experiments were conducted with 5 mol % Noyori precatalysts **2** and **3** and 20 mol % NaO*t*-Bu, a required additive to generate the catalytically active 16-electron complexes[25] (Scheme 1). Under these conditions, the reduction of acetophenone with pinacolborane reached full conversion at 22 °C in 3 h. Trialkoxyborane product **1** was hydrolyzed on silica gel to provide 2-phenylethanol and analyzed by gas chromatography (chiral support column), which showed that the alcohols were racemic in both cases.

Scheme 1. Metal-Catalyzed Reduction of Acetophenone



The complete lack of stereoselectivity in these transformations was puzzling on the basis of the high stereoselectivity induced by the parent hydrogenation reactions.[15−18] A control experiment was conducted to determine the active species of the catalytic addition of pinacolborane. The reduction was repeated in the absence of precatalyst **2** or **3**, which also provided reduction of acetophenone in 3 h at 22 °C (eq 1), demonstrating that the alkoxide could catalytically activate pinacolborane toward addition to acetophenone. We initiated a study of this transformation to provide insight into the role

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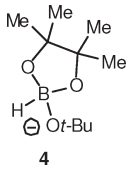

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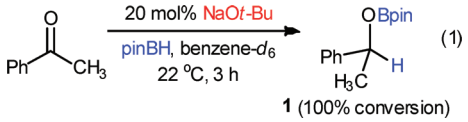
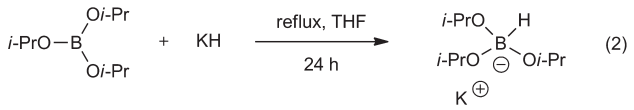
Figure 1. Proposed active reducing agent.

of base additives in transition metal-catalyzed borylation reactions.[8,22−24]

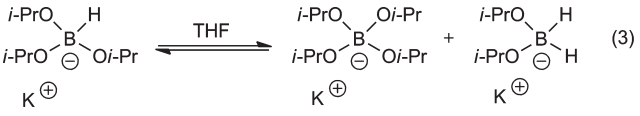


In the early 1980s, Brown described the reactivity of alkali metal hydrides (LiH, NaH, KH) toward trialkoxyboranes, demonstrating that an equivalent of the metal hydride could be added to trialkoxyboranes to provide trialkoxyborohydrides cleanly (eq 2).[26,27] Potassium hydride was shown to provide complete conversion to products in the shortest reaction times. The resulting trialkoxyborohydrides were also shown to reduce ketones rapidly.[27] On the basis of this precedent, we postulated that the active hydride source was trialkoxyborohydride **4**, derived from addition of NaO*t*-Bu to pinacolborane (Figure 1).



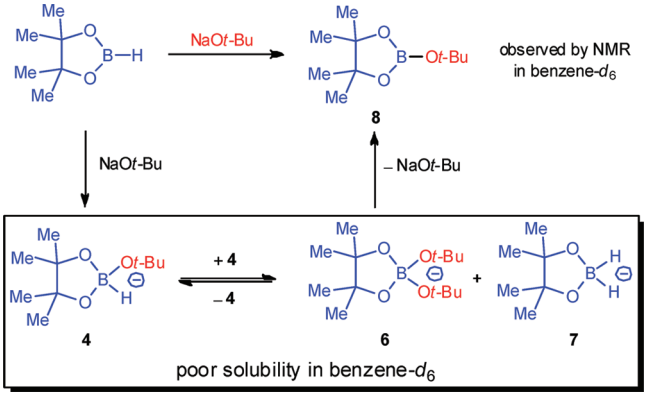
To examine the nature of the catalytically active borohydride, a stoichiometric equivalent of NaO*t*-Bu was added to pinacolborane in benzene-d_6 and examined by NMR spectroscopy. In the ^{1}H NMR spectrum, the *tert*-butyl hydrogens of NaO*t*-Bu (1.30 ppm) and the tetramethyl hydrogens of the pinacol group (0.99 ppm) were completely replaced by new resonances at 1.38 and 1.06 ppm, respectively. In the ^{11}B{^{1}H} NMR spectrum, the resonance for pinacolborane (28.5 ppm) shifted to 22.2 ppm.[28] Although it was apparent that a reaction between NaO*t*-Bu and pinacolborane had occurred, the ^{11}B NMR chemical shift was not consistent with the trialkoxyborohydrides reported by Brown (^{11}B NMR: δ 0−7 ppm).[27]

The probable insolubility of **4** in benzene-d_6 led to a re-examination of this reaction in THF, which also allowed closer comparison to the borohydrides reported by Brown in his studies. In THF-d_8, a complex ^{1}H NMR spectrum resulted. Characteristic peaks for the pinacol and *tert*-butyl hydrogens were not readily identified, but a resonance representing a boron-bound hydride was present at −0.09 ppm (split into four equally sized singlets, J_{BH} = 81.5 Hz). The complex nature of the spectrum and the presence of boron-bound hydrides are consistent with a dynamic equilibrium between several complexes, including the disproportionation reaction reported by Brown for trialkoxyborohydrides (eq 3).[27]



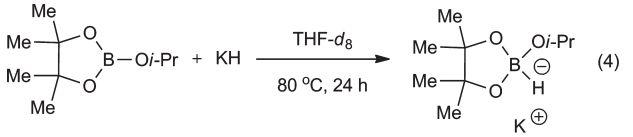
A ^{11}B {^{1}H} NMR spectrum of the reaction between NaO*t*-Bu and pinacolborane in THF-d_8 was obtained to clarify the identity of the mixture and the boron-bound hydride complexes. Five

Scheme 2. Explanation of Observed Spectroscopic Data



resonances were observed (δ 23.1, 10.2, 6.2, −13.1, −41.2 ppm). The resonance at 6.2 ppm is significantly larger than the remaining four peaks and was tentatively assigned as complex **4** on the basis of the chemical shifts reported by Brown for trialkoxyborohydrides (vide supra).[27]

A ^{1}H-coupled ^{11}B NMR spectrum was then obtained, revealing singlets for the three upfield resonances, a broad doublet at δ −13.1 ppm (J = 77.1 Hz),[29] and a quintet at δ −41.2 ppm (J = 81.0 Hz). The quintet was identified as $NaBH_4$ by comparison to an authentic sample.[30] Although the major peak (δ 6.2 ppm) is not a doublet, several of the trialkoxyborohydrides reported by Brown were reported as broad singlets (for example, potassium tricyclopentoxyborohydride).[27] For comparison, trialkoxyborohydride **5** was synthesized by the addition of KH to pinBO*i*-Pr (2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane) by heating to 80 °C for 24 h in THF-d_8 (eq 4). The resulting product was analyzed by ^{1}H-coupled ^{11}B NMR spectroscopy, revealing one major singlet at δ 7.6 ppm. On the basis of these results, we have assigned the resonance at δ 6.2 ppm as complex **4**.



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On the basis of the spectroscopic data reported above, the catalytic reaction conditions (in benzene-d_6) are believed to involve low concentrations of trialkoxyborohydride **4**, which is in equilibrium with the associated disproportionation products **6** and **7** (Scheme 2). Sodium trialkoxyborohydride and sodium borohydride may also be present in low concentrations[31] by analogy to the spectroscopic studies in THF-d_8. In benzene-d_6, all of the tetra-substituted borate salts have poor solubility, which leaves trialkoxyborane as the only observable product by NMR spectroscopy. On the basis of the rapid exchange between all the borohydride derivatives, it is possible that any of these complexes serve as the active hydride source.

A proposed catalytic cycle is shown (Scheme 3), which assumes that **4** is the active hydride source in order to simplify the mechanistic picture. An initial activation of pinacolborane by NaO*t*-Bu is followed by hydride addition to acetophenone to generate sodium α-phenylethylalkoxide, the catalytically relevant alkoxide base. The α-phenylethylalkoxide could then activate a second equivalent of pinacolborane to generate **4′**. Hydride **4′** can then form reduced product **1** upon addition to acetophenone.

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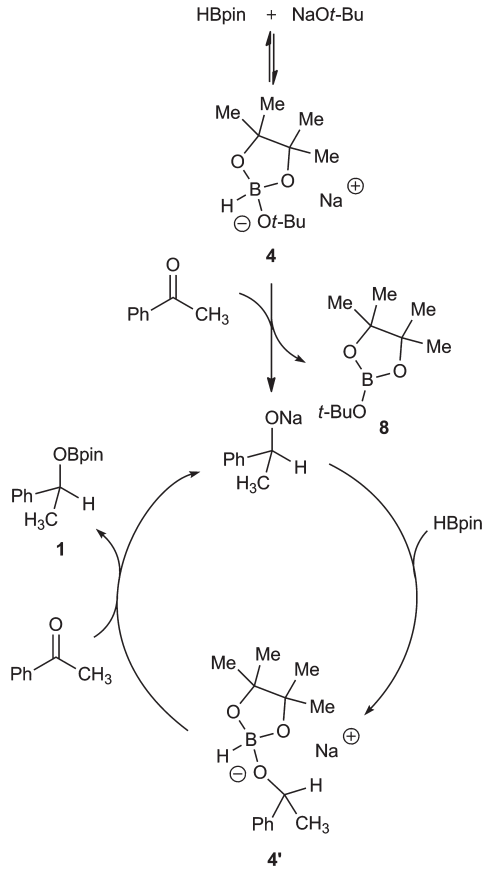
Scheme 3. Proposed Catalytic Cycle for Alkoxide-Mediated Reduction of Ketones



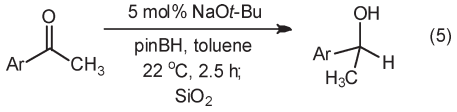
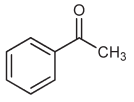
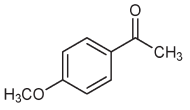
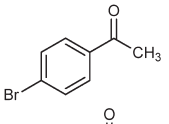
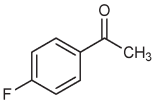
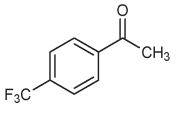


Table 1. Alkoxide-Catalyzed Reduction of Acetophenone Derivatives (eq 5)

Entry	Ketone	Yield (%)
1		93
2		95
3		97
4		94
5		93

A brief study of the reaction scope was carried out to gain more insight into this transition metal-free reduction. Several acetophenone derivatives were subjected to the reaction conditions (1.1 equivalents of H−Bpin, 5 mol % NaO*t*-Bu, toluene, 22 °C, 2.5 h). The resulting reduction products were purified by silica gel chromatography, resulting in hydrolysis of the O−B bond. The corresponding secondary alcohols were isolated in >90% yield (Table 1, eq 5).

The reduction of dialkyl ketones was achieved under conditions identical to the acetophenone derivatives, providing high yields of the corresponding secondary alcohol (Table 2, eq 6). The reduction of 2-methylcyclohexanone was explored to determine the inherent selectivity imparted during the reduction; 2-methylcyclohexanol was formed in a 1.3:1 ratio of *trans*−*cis* diastereomers. This selectivity is comparable to the selectivities reported by Brown for the reduction of 2-methylcyclohexanone with sterically hindered potassium trialkoxyborohydrides[27] and for addition of $NaBH_4$.[32]

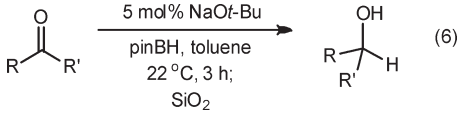
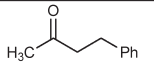
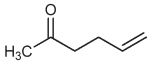
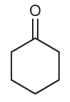
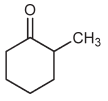


Table 2. Alkoxide-Catalyzed Reduction of Dialkyl Ketones (eq 6)

Entry	Ketone	Yield (%)
1		98
2		66
3		64
4		86% (1.3:1 *trans*:*cis*)

In summary, alkoxide-mediated reduction of ketones with pinacolborane is a potential competing reaction in metal-catalyzed borylation reactions. A catalytic amount of sodium *tert*-butoxide mediates the reduction of ketones by hydride addition to the carbonyl. The active hydride source could not be isolated, but spectroscopic data and literature precedent support an equilibrium between sodium trialkoxyborohydride and sodium borohydride, as well as the di- and trihydride complexes. A range of ketones were subjected to the reaction conditions, providing the corresponding alcohols in high yields demonstrating the potential of this transformation as an operationally simple reduction of carbonyls.

EXPERIMENTAL SECTION

General Experimental Information. All materials were manipulated under a positive pressure of dry nitrogen. Stoichiometric reactions for spectroscopic studies of the active hydride source were handled under dry nitrogen in an inert atmosphere glovebox. NMR spectra were collected at 500 MHz for ^{1}H NMR, 125 MHz for ^{13}C NMR, and 160 MHz for ^{11}B NMR. ^{1}H NMR spectra are referenced to chloroform-*d* at 7.24 ppm or benzene-d_6 at 7.16 ppm. The ^{1}H NMR data are reported as follows: chemical shift in ppm, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; sep, septet; m, multiplet), coupling

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constants (Hz), and integration. ^{13}C NMR spectra are referenced to chloroform-*d* at 77.23 ppm or benzene-d_6 at 128.39 ppm. ^{11}B NMR spectra were referenced to an external $BF_3 \cdot Et_2O$ sample in benzene-d_6 (0.0 ppm). Benzene-d_6 was purchased from a chemical supplier and was dried and distilled from CaH_2; degassed using three freeze, pump, thaw cycles; and stored in an inert atmosphere glovebox. Toluene was dried in a solvent purification system by passing through an activated alumina column and an oxygen scavenging column under nitrogen. Sodium *tert*-butoxide, pinacolborane, tetrahydrofuran-d_8, and chloroform-*d* were purchased and used as received. Ketones were typically distilled from CaH_2 and stored under nitrogen prior to use. Potassium hydride was washed with hexanes (× 3), dried in vacuo, and stored in an inert atmosphere glovebox.

Addition of NaO*t*-Bu to Pinacolborane. *In Benzene-d_6.* To a resealable NMR tube was added sodium *tert*-butoxide (0.024 g, 0.250 mmol), benzene-d_6 (0.50 mL), and pinacolborane (0.036 mL, 0.250 mmol). After 0.5 h, the resulting reaction mixture was examined by NMR spectroscopy. ^{1}H NMR (500 MHz, benzene-d_6): δ 1.38 (s, 9H), 1.06 (s, 12H); ^{13}C NMR (125 MHz, benzene-d_6): δ 81.4, 73.1, 29.9, 24.2; ^{11}B {^{1}H} NMR (160 MHz, benzene-d_6): δ 22.2.

In Tetrahydrofuran-d_8. To a resealable NMR tube was added sodium *tert*-butoxide (0.024 g, 0.250 mmol), tetrahydrofuran-d_8 (0.50 mL), and pinacolborane (0.036 mL, 0.250 mmol). After 0.5 h, the resulting reaction mixture was examined by NMR spectroscopy. ^{1}H NMR (500 MHz, THF-d_8) complex mixture; ^{11}B NMR (160 MHz, THF-d_8): δ 23.1, 10.2, 6.2, −13.1 (d, J = 77.1 Hz), −41.2 (qn, J = 81.0 Hz).

Addition of KH to 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. To a resealable NMR tube was added potassium hydride (0.008 g, 0.199 mmol), tetrahydrofuran-d_8 (0.50 mL), and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.020 mL, 0.098 mmol). After 24 h at 80 °C, the reaction mixture was analyzed by NMR spectroscopy. ^{1}H NMR (500 MHz, THF-d_8) complex mixture; ^{11}B NMR (160 MHz, THF-d_8): δ 7.6, ∼6.8, ∼22 (br).

General Procedure for the Reduction of Ketones. *1-Phenylethanol.*[33] To a 50 mL round-bottom flask equipped with a stir bar was added NaO*t*-Bu (0.0115 g, 0.120 mmol), toluene (23 mL), acetophenone (0.300 mL, 2.57 mmol), and pinacolborane (0.410 mL, 2.85 mmol). After 2.5 h of stirring under nitrogen gas, the volatiles were removed in vacuo. The crude reaction mixture was purified by flash column chromatography (20:80 ethyl acetate−hexanes) to provide 1-phenylethanol as a colorless oil (0.291 g, 93%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (d, J = 7.3 Hz, 2 H), 7.25 (t, J = 5.8 Hz, 2 H), 4.87 (q, J = 6.4 Hz, 1 H), 1.95 (d, J = 6.6 Hz, 1 H), 1.48 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.0, 128.7, 127.7, 125.6, 70.6, 25.4; IR (neat) 3343 (br), 2972, 1492, 1449, 1203, 1097, 1075, 1028, 1009, 897, 758, 697 cm^{-1}.

1-(4-Fluorophenyl)ethanol.[33] The general procedure was followed with 4-fluoroacetophenone (0.310 mL, 2.57 mmol). Purification by flash column chromatography (20:80 ethyl acetate−hexanes) provided 1-(4-fluorophenyl)ethanol as a colorless oil (0.337 g, 94%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32 (m, 2 H), 7.01 (m, 2 H), 4.89 (q, J = 3.4 Hz, 1 H), 1.79 (d, J = 3.4 Hz, 1H), 1.46 (d, J = 6.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.3, 141.7 (d, J = 2.8 Hz), 127.2 (d, J = 7.7 Hz), 115.4 (d, J = 21.1 Hz), 70.0, 25.5; IR (neat) 3331 (br), 2973, 1603, 1508, 1220, 1106, 1082, 1008, 897, 832 cm^{-1}.

1-(4-Methoxyphenyl)ethanol.[33] The general procedure was followed with 4-methoxyacetophenone (0.386 g, 2.57 mmol). Purification by flash column chromatography (35:65 ethyl acetate−hexanes) provided 1-(4-methoxyphenyl)ethanol as a colorless oil (0.370 g, 95%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27 (d, J = 8.8 Hz, 2 H), 6.87 (d, J = 8.3 Hz, 2 H), 4.81 (q, J = 6.3 Hz, 1 H), 3.78 (s, 3 H), 1.78 (br s, 1 H), 1.47 (d, J = 6.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.0, 138.2, 126.9, 114.0, 70.2, 55.5, 25.2; IR (neat) 3350 (br), 2969, 1611, 1510, 1241, 1204, 1174, 1115, 1086, 1033, 1004, 829, 807 cm^{-1}.

1-(4-Trifluoromethylphenyl)ethanol.[34] The general procedure was followed with 4-trifluoromethylacetophenone (0.483 g, 2.57 mmol). Purification by flash column chromatography (50:50 ethyl acetate−hexanes) provided 1-(4-trifluoromethylphenyl)ethanol as a colorless oil (0.451 g, 93%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.58 (d, J = 8.3 Hz, 2 H), 7.48 (d, J = 7.8 Hz, 2 H), 4.96 (q, J = 6.3 Hz, 1 H), 1.92 (br s, 1 H), 1.48 (d, J = 6.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.9, 125.7, 125.6, 125.4 (q, J = 3.8 Hz), 110.2, 70.0, 25.6; IR (neat) 3336 (br), 2977, 1621, 1414, 1322, 1205, 1162, 1114, 1088, 1066, 1015, 898, 839, 737 cm^{-1}.

1-(4-Bromophenyl)ethanol.[35] The general procedure was followed with 4-bromoacetophenone (0.511 g, 2.57 mmol). Purification by flash column chromatography (20:80 ethyl acetate−hexanes) provided 1-(4-bromophenyl)ethanol as a colorless oil (0.503 g, 97%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.47 (d, J = 8.3 Hz, 2 H), 7.26 (d, J = 7.8 Hz, 2 H), 4.88 (q, J = 6.4 Hz, 1 H), 1.82 (br s, 1 H), 1.48 (d, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.8, 131.7, 127.3, 121.3, 70.0, 25.5; IR (neat) 3319 (br), 2972, 1592, 1488, 1447, 1401, 1111, 1069, 1008, 896, 820, 770, 715 cm^{-1}.

Cyclohexanol.[36] The general procedure was followed with cyclohexanone (0.270 mL, 2.57 mmol). Purification by flash column chromatography (15:85 ethyl acetate−hexanes) provided cyclohexanol as a colorless oil (0.165 g, 64%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.59 (qn, J = 3.9 Hz, 1 H), 1.88 (m, 2 H), 1.71 (m, 2 H), 1.65−1.46 (m, 2 H), 1.38 (br, 1 H), 1.32−1.08 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 70.6, 35.8, 25.7, 24.3; IR (neat) 3324 (br), 2928, 2853, 1449, 1362, 1298, 1065, 1024, 967, 889, 862 cm^{-1}.

2-Methylcyclohexanol.[37,38] The general procedure was followed with 2-methylcyclohexanone (0.320 mL, 2.57 mmol). A 1.3:1 mixture of *trans*−*cis* 2-methylcyclohexanol was observed by ^{1}H NMR spectroscopy. Purification by flash column chromatography (15:85 ethyl acetate−hexanes) provided 2-methylcyclohexanol as a colorless oil (0.252 g, 86%): ***trans* isomer:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.75 (br s, 1 H), 1.92 (br, 1 H), 1.73−1.15 (m, 9 H), 0.99 (d, J = 6.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 76.7, 40.5, 35.7, 33.9, 25.9, 25.4, 18.7; ***cis* isomer:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.09 (br, 1 H), 1.92 (br, 1 H), 1.73−1.15 (m, 9 H), 0.92 (d, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 71.3, 36.0, 32.7, 29.0, 24.7, 20.8, 12.5; IR (neat) 3345 (br), 2924, 2845, 1448, 1066, 1052, 1036, 1015, 977, 928, 843 cm^{-1}.

4-Phenyl-2-butanol.[39] The general procedure was followed with benzylacetone (0.390 mL, 2.57 mmol). Purification by flash column chromatography (30:70 ethyl acetate−hexanes) provided 4-phenyl-2-butanol as a colorless oil (0.379 g, 98%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27 (t, J = 7.8 Hz, 2 H), 7.20 (m, 3 H), 3.82 (q, J = 5.9 Hz, 1 H), 2.78 (ddd, J = 16.1, 9.3, 6.8 Hz, 1 H), 2.69 (ddd, J = 16.1, 9.2, 7.3 Hz, 1H) 1.77 (m, 2 H), 1.36 (br s, 1 H), 1.22 (d, J = 5.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.3, 128.6, 126.0, 67.7, 41.1, 32.3, 23.8; IR (neat) 3339 (br), 2926, 1495, 1453, 1373, 1127, 1083, 1053, 953, 934, 904, 746, 696 cm^{-1}.

5-Hexene-2-ol.[40] The general procedure was followed with 5-hexene-2-one (0.300 mL, 2.57 mmol). Purification by flash chromatography (20:80 ethyl acetate−hexanes) provided 5-hexene-2-ol as a colorless oil (0.170 g, 66%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.81 (qn, J = 6.9 Hz, 1 H), 4.98 (m, 2 H), 3.81 (q, J = 5.3 Hz, 1 H), 2.12 (m, 2 H), 1.52 (m, 2 H), 1.47 (s, 1 H), 1.18 (d, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.7, 115.0, 67.9, 38.4, 30.4, 23.7; IR (neat) 3340, 3078, 2968, 2928, 1641, 1450, 1374, 1120, 1083, 994, 950, 934, 908, 846 cm^{-1}.

■ ASSOCIATED CONTENT

Supporting Information. Selected spectra of products and spectroscopic studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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