JOC The Journal of Organic Chemistry

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Solvent-Free Methallylboration of Ketones Accelerated by *tert*-Alcohols

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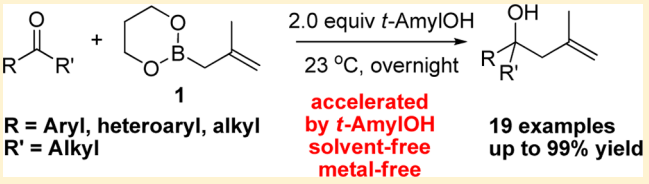
Supporting Information

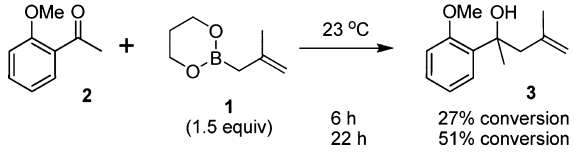
ABSTRACT: A solvent- and metal-free process has been developed for the direct methallylboration of ketones employing the stable *B*-methallylborinane **1**, which was accelerated by tertiary alcohols. In the presence of 2.0 equiv of readily available tertiary alcohols such as *tert*-amyl alcohol, the methallylation products were prepared at room temperature in excellent yields. The salient features of the described process include simple operation, high efficiency, and mild reaction conditions.



Over the past two decades, numerous efforts have been directed toward the synthesis of tertiary homoallylic alcohols via the allylation of ketones.[1] In particular, allyl organoboron reagents have been extensively employed for this process, but typically, a metal catalyst is required to affect the allylboration (In,[2−4] Cu,[5] Ir,[6] Zn,[7] Ni[8]). Alternatively, the direct metal-free allylboration of ketones represents the most simple, convenient, and economical method for the synthesis of tertiary homoallylic alcohols.[9] However, to date, this type of reaction manifold has not been well explored.[10] Ketones bearing a coordinating functional group that can serve as an activating group, such as a hydroxyl group, have been reported to react efficiently in the metal-free allylboration.[11] However, simple ketones such as acetophenone give poor reaction rates.[12] Furthermore, these reactions utilize allyldiisopropoxyborate which is a hydrolytically unstable reagent and, therefore, can be difficult to handle. The sensitivity of this reagent toward hydrolysis has prevented its further application especially on industrial scale. To circumvent this issue, more stable allylboron reagents such as allyltrifluoroborates[13,14] and allyl dioxazaborolidines[15] have been employed, but strong Brønsted acids such as TsOH and CF_3CO_2H were essential to affect the desired transformation. Diminished efficiency was observed when weaker acids such as PhOH were applied using these reagents. Considering the importance of the allylation of ketones, it is highly desirable to further investigate the direct metal-free allylboration of ketones. As a part of our continuous research program directed at the methallylation of ketones,[16] herein, we report our research progress regarding the development of a mild solvent- and metal-free process for the methallylboration of ketones, which we have found is accelerated by tertiary alcohols.[17]

To develop a practical method for the direct metal-free methallylation of ketones, *B*-2-(2-methylallyl)-1,3,2-dioxaborinane (**1**) was chosen as a methallyl-transfer reagent for further investigation because of its excellent stability. Methallylboron reagent **1** is a colorless liquid that is easily synthesized, purified, and stored in the freezer for months without decomposition.[18] Our work commenced with the methallylation of 2-methoxyacetophenone (**2**) by simply mixing with **1** under nitrogen under neat conditions. In the presence of 1.5 equiv of **1**, the methallylboration is sluggish at 23 °C and gave 27% and 51% conversion after 6 and 22 h, respectively (Scheme 1).

Scheme 1. Methallylation of 2-Methoxyacetophenone 2 and 1



On the basis of the systematic studies from Brown and coworkers on the allylboration of aldehydes,[19] we envisioned that the reaction rate could be modulated by changing the availability of the lone pairs of electrons on the oxygen atom attached to boron to donate to the vacant p-orbital on boron (n→p). Because allylborations proceed through a closed chairlike transition state,[20] organoboron reagents with diminished n→p donation are more reactive in the allylboration due to the enhanced Lewis acidity at the boron atom. Furthermore, we hypothesized that a hydrogen-bonding interaction between an appropriate donor and the oxygen atom of the organoboron reagent could have the same effect. Therefore, we explored the use of a suitable alcohol additive that could enable the direct methallylboration to occur in a mild, effective, and practical manner. To this end, a variety of alcohols were investigated for the methallylboration of 2′-acetonaphthone **4**.

Received: March 28, 2013
Published: May 1, 2013

dx.doi.org/10.1021/jo4006574 | J. Org. Chem. 2013, 78, 5775−5781

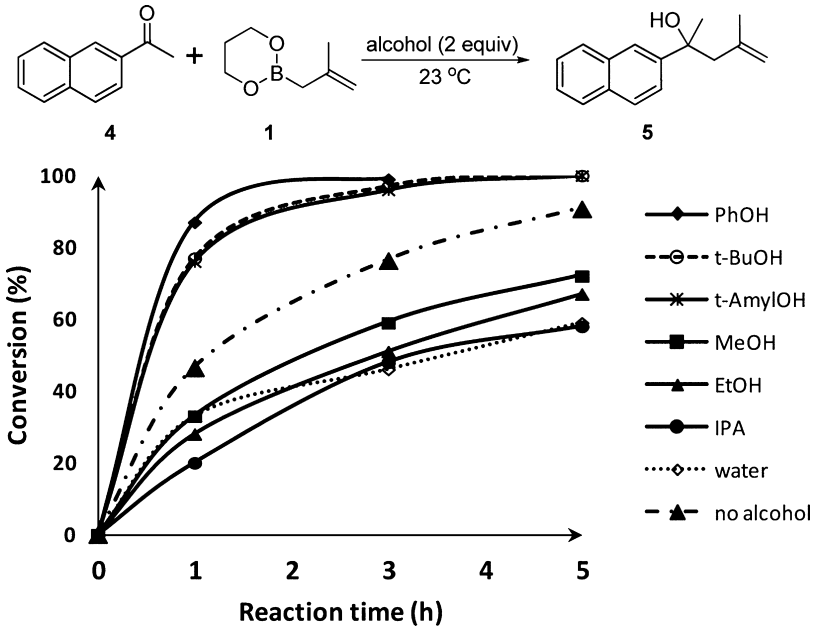


Figure 1. Alcohol effect on the methallylation of 2′-acetonaphthone **4**. All reactions were run at 23 °C with **4** (1 mmol), 1.5 equiv of **1**, and 2 equiv of alcohols or water under nitrogen.

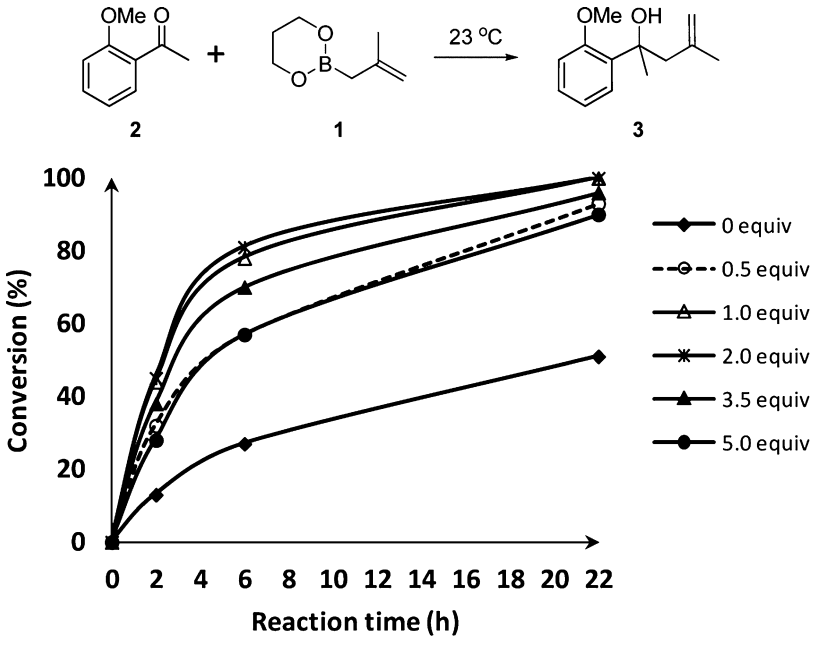


Figure 2. Effect of amount of *tert*-amylOH on the methallylation of 2-methoxyacetophenone **2**. All reactions were run with 1.5 equiv of **1** and variable amounts of *tert*-amylOH at 23 °C under nitrogen.

Our results clearly indicated that the addition of different alcohols resulted in variable reaction rates (Figure 1). The use of primary or secondary alcohols gave reduced reaction rate. ^{11}B NMR studies indicated that borinane **1** did not undergo protodeboronation immediately in the presence of MeOH, but different borate species were observed. We speculated that primary and secondary alcohols (i.e., MeOH, EtOH, 2-PrOH) could undergo ligand exchange with the cyclic alcohol of reagent **1** and form an inactive borate complex. Without addition of any alcohol, the reaction gave 90% conversion after 5 h. In comparison, in the presence of 2.0 equiv of bulky tertiary alcohols (i.e., as *t*-BuOH or *tert*-amylOH), all reactions became faster and full conversions were achieved after 5 h. Additionally, the use of 2.0 equiv of phenol as an additive gave complete conversion in only 4 h. However, in the presence of 2.0 equiv of water, the reaction was again slow. Based on the above results, we chose to further investigate the use of *tert*-amylOH in the methallylation reaction due to the convenience of this reagent relative to *t*-BuOH.[21]

To further illustrate the effect of *tert*-amylOH on the methallylboration of ketones, we investigated the reaction rate with sterically hindered 2-methoxyacetophenone **2** in the presence of variable amounts of *tert*-amylOH (Figure 2). Without *tert*-amylOH, the reaction was slow and gave only 51% conversion after 22 h at 23 °C as mentioned before. Clearly, the addition of *tert*-amyl alcohol led to faster reaction, and our

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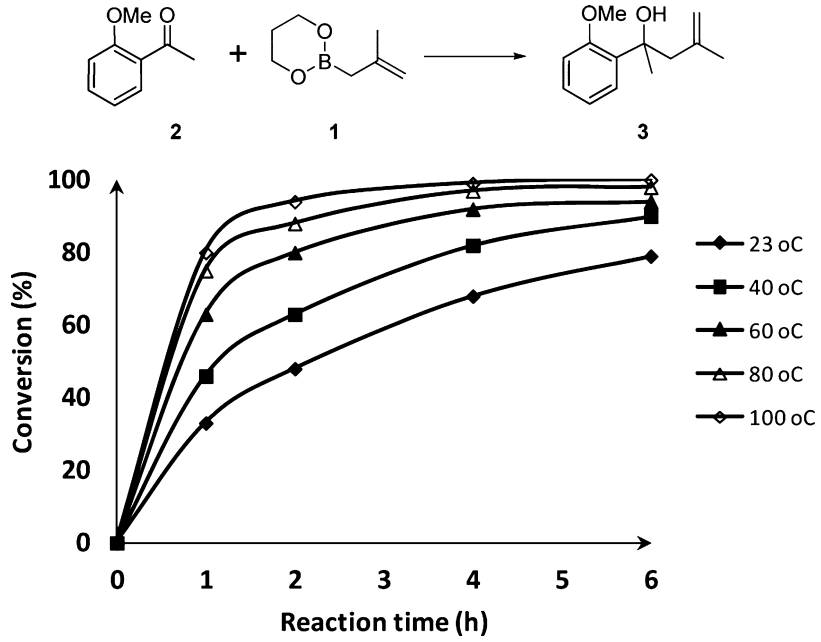


Figure 3. Effect of reaction temperature on the methallylation of 2-methoxyacetophenone **2**. All of the reactions were run with 1.5 equiv of **1** and 2.0 equiv of *tert*-amylOH under nitrogen.

studies showed that the optimal amount of *tert*-amylOH was 1.0−3.5 equiv relative to **2**. The addition of a large excess of *tert*-amylOH (5.0 equiv) was observed to retard the reaction rate, and only 90% conversion was obtained after 22 h.

Moreover, we also investigated the temperature effect on the methallylboration of ketones. Not surprisingly, a higher temperature gave a faster reaction (Figure 3). In all cases, full conversion with **2** was observed with 1.5 equiv of **1** after overnight. The reaction time was shortened to 6 h at 80 °C, and the product **3** was isolated in 96% isolated yield. At 40 °C, the reaction was complete after 16 h and gave the product **3** in 95% isolated yield. In comparison, the reaction at 40 °C without *tert*-amylOH gave the product **3** with 76% isolated yield after 16 h. While increased reaction temperature allows for a reduction in reaction time for the methallylboration and can be used for simple ketones, we wanted a methallylboration procedure that would be compatible with more elaborate, highly functionalized ketones that could be sensitive to high reaction temperatures; therefore, we decided to further investigate this process under ambient conditions (23 °C).

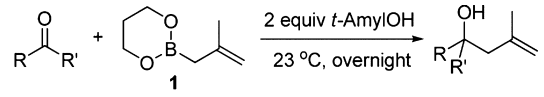
The scope of the current method for the methallylation of ketones was next investigated employing a variety of ketones including aliphatic ketones, aromatic ketones, and heteroaromatic ketones with diverse functional groups (Table 1). All of the reactions were run overnight at 23 °C in the presence of 2.0 equiv of *tert*-amylOH. In all cases, the crude methallylation products were purified by passing through a short silica gel column without tedious workup. Typically, good to excellent yields were obtained. When methyl ketones **2**, **4**, **6**, and **8** (Table 1, entries 1−4) were used, the corresponding products **3**, **5**, **7**, and **9** were isolated in greater than 90% yield. The reaction tolerated bromo and cyano functional groups at the α-position of the ketones (entries 5 and 6, respectively) affording the desired methallylation products in quantitative yields. No elimination was observed when β-chloro ketone **14** was applied (Table 1, entry 7). The corresponding product **15** was isolated in 89% yield. In the presence of *tert*-amylOH, even less reactive alkyl ketones **16** and **18** reacted smoothly with borinane **1** (Table1, entries 8 and 9). Current reaction conditions also tolerated a variety of acid-sensitive function groups such as acetal, THP, and Boc (Table 1, entries 9, 11, and 12, respectively). It is well-known that function groups such as phenyl acetate are not compatible with organometallic reagents such as Grignard reagents. Under our conditions, the product **21** with an acetate moiety was isolated in 94% yield (Table 1, entry 10). Excellent yields were observed when heteroaryl ketones such as **26** and **28** were used (Table 1, entries 13 and 14). When β-keto acid **30** was applied, the corresponding product **31** was isolated in 89% yield after overnight in the absence of *tert*-amylOH, which indicated that the acid functional group could promote the methallylation (Table 1, entry 15). In the case of β-hydroxy ketone **32**, the reaction proceeded smoothly to give the product **33** in 85% yield (Table 1, entry 16).[22] As discussed before, the methallylation reaction was accelerated by phenol. When cyclic alkyl ketone **38** containing a phenol function group was used, the allylboration gave the product **39** in 82% yield without the addition of *tert*-amylOH (Table 1, entry 19). When the phenol was protected as an acetate, no reaction was observed without *tert*-amylOH (Table 1, entry 20).

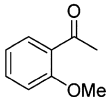
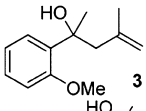
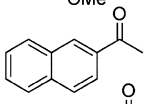
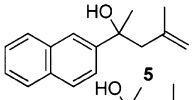
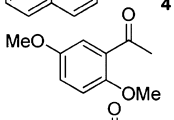
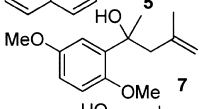
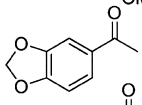
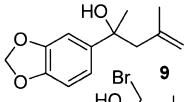
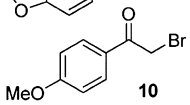
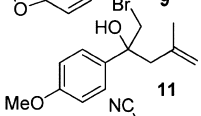
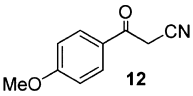
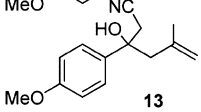
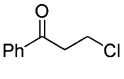
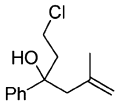
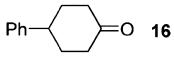
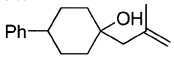
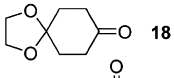
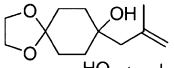
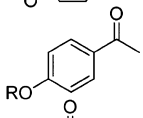
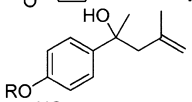
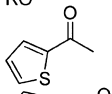
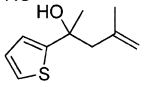
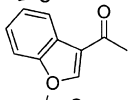
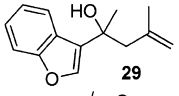
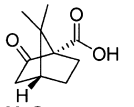
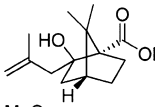
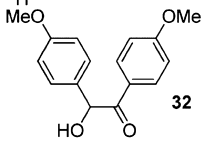
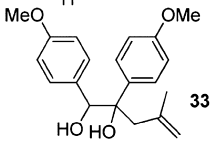
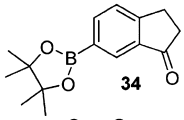
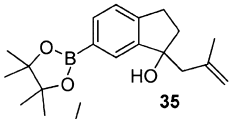
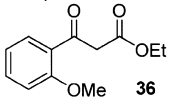
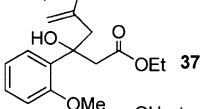
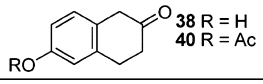
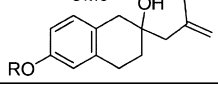
To further demonstrate the synthetic utility of the current method, the methallylation of ketone **32** has been performed on 10 g scale. After the reaction went to completion at 30 °C overnight, the product **33** was precipitated from the reaction mixture by the addition of water and isolated directly by filtration as a white solid in 80% yield.

In summary, a facile and efficient solvent- and metal-free process has been developed for the direct methallylboration of ketones, which was accelerated by tertiary alcohols such as *tert*-amyl alcohol. Under our optimized reaction conditions, a wide array of ketones with acid- or base-sensitive functional groups such as THP, Boc and OAc underwent direct methallylboration smoothly. The methallylation products were easily isolated in high yields without tedious workup. The salient features of this process include simple operation, high efficiency, and mild reaction conditions, which should make it appealing for practical applications especially when strong acids and bases

dx.doi.org/10.1021/jo4006574 | *J. Org. Chem.* 2013, 78, 5775−5781

Table 1. Methallylation of Ketones with Borinane 1[a]



entry	ketone	product	yield[b]
1	 **2**	 **3**	93%
2	 **4**	 **5**	95%
3	 **6**	 **7**	90%
4	 **8**	 **9**	96%
5	 **10**	 **11**	99%
6	 **12**	 **13**	99%
7	 **14**	 **15**	89%
8	 **16**	 **17**	90%
9	 **18**	 **19**	90%
10 11 12	 **20** R = Ac **22** R = THP **24** R = Boc	 **21** **23** **25**	94% 91% 98%
13	 **26**	 **27**	92%
14	 **28**	 **29**	98%
15[c]	 **30**	 **31**	89%
16	 **32**	 **33**	85%
17	 **34**	 **35**	84%
18	 **36**	 **37**	93%
19[c] 20[c]	 **38** R = H **40** R = Ac	 **39** **41**	82% 0 %

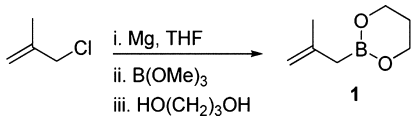
[a]All of the reactions were run with ketones (1 mmol), 1.5 equiv of **1**, and 2.0 equiv of *tert*-amylOH at 23 °C unless noted elsewhere. [b]Isolated yields after chromatography on silica gel. [c]No *tert*-amylOH was added.

have to be avoided to achieve highly selective methallylation reactions.

EXPERIMENTAL SECTION

General Methods. All reactions were run in an oven-dried flask under nitrogen. Unless otherwise noted, reagents were commercially available and were used without purification. HPLC conditions for reaction monitoring and quantitation: column Halo C8, 4.6 × 150 mm, 2.7 μm particle size, column temperature at 25 °C, mobile phase A (0.2% H_3PO_4 in water), mobile phase B (acetonitrile), flow rate 1.2 mL min^{-1}, gradient program 30% B to 70% B in 6 min, to 85% B in 1 min, to 98% B in 0.5 min, hold at 98% B for 4.5 min, λ = 220 nm, flow rate 1.0 mL min^{-1}. The samples for HPLC were diluted with MeOH. Chemical shifts are reported in δ (ppm) relative to TMS in $CDCl_3$ as internal standard (^{1}H NMR) or the residual $CHCl_3$ signal (^{13}C NMR).

Synthesis of B-2-(2-Methylallyl)-1,3,2-dioxaborinane 1.



To a dry three-necked flask were charged Mg turnings (12.0 g, 497 mmol) under argon. THF (350.0 mL) was added followed by addition of 1.2 M DIBAL-H in heptane (8.28 mL, 0.03 equiv). The solution was allowed to sit for 1 h and became gray. 3-Chloro-2-methylprop-1-ene (30 g, 331.3 mmol) was added to the flask while the temperature was maintained between 20 and 25 °C. After the complete addition, the mixture was stirred for 2 h at that temperature. The solution was titrated with bipyridine as indicator. The concentration is about 0.62 M.

To a dry flask were charged the Grignard reagent (248 mmol, 400 mL) prepared above and MTBE (200 mL). After the mixture was cooled to −60 °C (dry ice bath), trimethyl boronate (25.8 g, 248 mmol, 1.0 equiv) was added while the internal temperature was maintained below −60 °C. The resulting solution was stirred at −50 to −60 °C for 30 min and then slowly warmed to 0 °C over 30 min. AcCl (17.5 g, 223.2 mmol, 0.900 equiv) was charged while the temperature was controlled below 5 °C. After that, the reaction mixture was allowed to warm to room temperature and then propane-1,3-diol (17.0 g, 223 mmol, 0.900 equiv) was charged into the flask in one portion. The resulting reaction mixture was stirred at 23 °C overnight. 1,4-Dioxane (32.78 g, 372 mmol, 1.50 equiv) was added to the mixture. After 2 h, the solid was filtered off through a Celite pad, which was washed with MTBE (200 mL). The residue on removal of the solvent was diluted with hexane (100 mL). The solid was removed by filtration. The filtrate was concentrated and purified by passing a short silica gel column with 10% MTBE in hexane as elute or by distillation under vacuum to give the product **1** as a colorless liquid (34.8 g, 75%): ^{1}H NMR (400 MHz, $CDCl_3$), δ 4.64 (d, 1H, J = 0.84 Hz), 4.58 (d, 1H, J = 0.84 Hz), 4.0−3.98 (m, 4H), 1.97−1.91 (m, 2H), 1.75 (bs, 3H), 1.63 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 109.3, 61.8, 50.2, 27.3, 24.4; HRMS (TOF-MS, electrospray negative ionization) m/z calcd for $C_{15}H_{10}BO_4^-$ $[C_4H_9BO_2 + HCO_2]^-$ 145.06776, found 145.0676.

General Procedure for Methallylation of Ketones. To a dry flask were charged ketone (1.0 mmol), **1** (1.5 equiv), and *tert*-amylOH (2.0 equiv) under nitrogen. The resulting mixture was stirred under nitrogen at room temperature for overnight. Purification of the reaction mixture by column chromatography on silica gel gave analytically pure product.

2-(2-Methoxyphenyl)-4-methylpent-4-en-2-ol **3**. The general procedure above was followed using 1-(2-methoxyphenyl)ethanone **2** (150.2 mg, 1.0 mmol), **1** (1.5 mmol, 1.5 equiv), and *tert*-amyl alcohol (176.3 mg, 2.0 mmol). After being allowed to sit overnight, the reaction mixture was purified by column chromatography on silica gel (eluting with 5% EtOAc/hexanes) to afford the product **3** as a liquid (191.8 mg, 93%): ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.37 (dd, 1H, J = 1.7, 7.7 Hz), 7.23 (m, 1H), 3.94−6.88 (m, 2H), 4.81 (bs, 1H), 4.67 (bs, 1H), 3.89 (s, 3H), 3.68 (s, 1H), 2.88 (d, 1H, J = 13.1 Hz), 2.54 (d, 1H, J = 9.9 Hz), 1.60 (s, 3H),

dx.doi.org/10.1021/jo4006574 | J. Org. Chem. 2013, 78, 5775−5781

1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 143.2, 135.1, 128.2, 126.7, 120.8, 114.9, 111.1, 73.8, 55.2, 49.7, 27.3, 23.9; HRMS (ES pos) m/z calcd for $C_{13}H_{17}O^+$ ($M - H_2O + H^+$) 189.1274, found 189.1265.

4-Methyl-2-(naphthalen-2-yl)pent-4-en-2-ol **5**.[23] The general procedure above was followed, using 1-(naphthalen-2-yl)ethanone **4** (170.2 mg, 1.0 mmol), **1** (1.5 mmol, 1.5 equiv), and *tert*-amyl alcohol (176.3 mg, 2.0 mmol). After being allowed to sit overnight, the reaction mixture was purified by column chromatography on silica gel (eluting with 5% EtOAc/hexanes) to afford the product **5** as a solid (215.0 mg, 95%): mp 46−47 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.93 (s, 1H), 7.81 (t, 3H, J = 8.7 Hz), 7.53 (d, 1H, J = 8.8 Hz), 7.42−7.48 (m, 2H), 4.89 (s, 1H), 4.77 (s, 1H), 2.76 (d, 1H, J = 13.0 Hz), 2.60 (d, 1H, J = 13.2 Hz), 2.48 (s, 1H), 1.63 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 142.5, 133.2, 132.2, 128.2, 127.7, 127.5, 126.0, 125.6, 123.8, 123.0, 115.8, 73.4, 51.8, 30.8, 24.3; HRMS (ES pos) m/z calcd for $C_{16}H_{17}^+$ ($M - H_2O + H^+$) 209.1325, found 209.1318.

2-(2,5-Dimethoxyphenyl)-4-methylpent-4-en-2-ol **7**. The general procedure above was followed using 1-(2,5-dimethoxyphenyl)-ethanone **6** (18.2 mg, 1.0 mmol), **1** (1.5 mmol, 1.5 equiv), and *tert*-amyl alcohol (176.3 mg, 2.0 mmol). After being allowed to sit overnight, the reaction mixture was purified by column chromatography on silica gel (eluting with 5% EtOAc/hexanes) to afford the product **7** as a solid (198.2 mg, 90%): mp 45−46 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ 6.99 (d, 1H, J = 3.1 Hz), 6.81 (d, 1H, J = 8.8 Hz), 6.75−6.72 (m, 1H), 4.82 (bs, 1H), 4.68 (bs, 1H), 3.85 (s, 3H), 3.77 (s, 3H), 3.66 (s, 1H), 2.90 (d, 1H, J = 13.1 Hz), 2.52 (d, 1H, J = 13.2 Hz), 1.58 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 150.9, 143.2, 136.5, 114.9, 113.7, 111.9, 111.6, 73.7, 55.7, 49.6, 27.4, 23.9; HRMS (ES pos) m/z calcd for $C_{14}H_{19}O_2^+$ ($M - H_2O + H^+$) 219.1380, found 219.1368.

2-(Benzo[d][1,3]dioxol-5-yl)-4-methylpent-4-en-2-ol **9**. The general procedure above was followed using 1-(benzo[d][1,3]dioxol-5-yl)-ethanone **8** (164.2 mg, 1.0 mmol), **1** (1.5 mmol, 1.5 equiv), and *tert*-amyl alcohol (176.3 mg, 2.0 mmol). After being allowed to sit overnight, the reaction mixture was purified by column chromatography on silica gel (eluting with 5% EtOAc/hexanes) to afford the product **9** as a liquid (211.4 mg, 96%): ^{1}H NMR (400 MHz, $CDCl_3$), δ 6.95 (s, 1H), 6.90 (dd, 2H, J = 1.4, 7.9 Hz), 6.75 (d, 1H, J = 8.1 Hz), 5.94 (s, 2H), 4.90 (s, 1H), 4.73 (s, 1H), 2.59 (d, 1H, J = 13.3 Hz), 2.47 (d, 1H, J = 13.4 Hz), 2.29 (s, 1H), 1.52 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 146.0, 142.5, 142.3, 117.9, 115.7, 107.7, 106.0, 100.9, 73.1, 52.1, 30.8, 24.2; HRMS (ES pos) m/z calcd for $C_{13}H_{15}O_2^+$ ($M - H_2O + H^+$) 203.1067, found 203.1056.

1-Bromo-2-(4-methoxyphenyl)-4-methylpent-4-en-2-ol **11**. The general procedure above was followed using 2-bromo-1-(4-methoxyphenyl)ethanone **10** (229.1 mg, 1.0 mmol), **1** (1.5 mmol, 1.5 equiv), and *tert*-amyl alcohol (176.3 mg, 2.0 mmol). After being allowed to sit overnight, the reaction mixture was purified by column chromatography on silica gel (eluting with 5% EtOAc/hexanes) to afford the product **11** as a liquid (282.3 mg, 99%): ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.36−7.26 (m, 2H), 6.90−6.87 (m, 2H), 4.86 (bs, 1H), 4.71 (bs, 1H), 3.81 (s, 3H), 3.76 (s, 2H), 2.74 (d, 1H, J = 13.6 Hz), 2.65 (d, 1H, J = 13.8 Hz), 2.63 (s, 1H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 141.5, 135.2, 126.7, 116.1, 113.6, 74.3, 55.2, 48.2, 45.3, 24.1; HRMS (ES pos) m/z calcd for $(C_{13}H_{16}BrO)^+$ ($M - H_2O + H^+$) 267.0379, found 267.0380.

3-Hydroxy-3-(4-methoxyphenyl)-5-methylhex-5-enenitrile **13**. The general procedure above was followed, using 3-(4-methoxyphenyl)-3-oxopropanenitrile **12** (175.2 mg, 1.0 mmol), **1** (1.5 mmol, 1.5 equiv), and *tert*-amyl alcohol (176.3 mg, 2.0 mmol). After being allowed to sit overnight, the reaction mixture was purified by column chromatography on silica gel (eluting with 5% EtOAc/hexanes) to afford the product **13** as a liquid (229.0 mg, 99%): ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.38−7.36 (m, 2H), 6.91−6.89 (m, 2H), 4.97 (bs, 1H), 4.83 (bs, 1H), 3.81 (s, 3H), 2.83 (s, 2H), 2.78 (d, 1H, J = 13.5 Hz), 2.71 (d, 1H, J = 13.5 Hz), 2.68 (s, 1H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 141.0, 135.4, 126.2, 117.3, 117.2, 113.9, 72.9, 55.3, 49.2, 32.9, 24.0; HRMS (ES pos) m/z calcd for $C_{14}H_{21}N_2O_2^+$ ($M + NH_4^+$) 249.1598, found 249.1588.

1-Chloro-5-methyl-3-phenylhex-5-en-3-ol **15**. The general procedure above was followed using 3-chloro-1-phenylpropan-1-one **14** (168.6 mg, 1.0 mmol), **1** (1.5 mmol, 1.5 equiv), and *tert*-amyl alcohol (176.3 mg, 2.0 mmol). After being allowed to sit overnight, the reaction mixture was purified by column chromatography on silica gel (eluting with 5% EtOAc/hexanes) to afford the product **15** as a liquid (200.0 mg, 89%): ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.30−7.40 (m, 4H), 7.21−7.26 (m, 1H), 4.92 (s, 1H), 4.77 (s, 1H), 3.53−3.60 (m, 1H), 3.10−3.17 (m, 1H), 2.67 (d, 1H, J = 13.7 Hz), 2.54 (d, 1H, J = 13.7 Hz), 2.52 (s, 1H), 2.24−2.40 (m, 2H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 141.7, 128.3, 126.9, 125.1, 116.5, 74.5, 51.5, 46.4, 40.2, 24.3; HRMS (ES pos) m/z calcd for $C_{13}H_{21}ClNO^+$ ($M + NH_4^+$) 242.1306, found 242.1297.

1-(2-Methylallyl)-4-phenylcyclohexanol **17**. The general procedure above was followed using 4-phenylcyclohexanone **16** (174.2 mg, 1.0 mmol), **1** (1.5 mmol, 1.5 equiv), and *tert*-amyl alcohol (176.3 mg, 2.0 mmol). After being allowed to sit overnight, the reaction mixture was purified by column chromatography on silica gel (eluting with 5% EtOAc/hexanes) to afford the product **17** as a liquid (207.3 mg, 90%): ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.31−7.16 (m, 5H), 4.96 (bs, 1H), 4.79 (bs, 1H), 2.50−2.44 (m, 1H), 2.22 (bs, 2H), 1.92−1.71 (m, 8H), 1.58−1.50 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 142.4, 128.3, 126.9, 126.0, 114.9, 70.0, 51.7, 44.0, 37.8, 29.4, 25.5; HRMS (ES pos) m/z calcd for $C_{16}H_{26}NO^+$ ($M + NH_4^+$) 248.2009, found 248.2006.

8-(2-Methylallyl)-1,4-dioxaspiro[4.5]decan-8-ol **19**. The general procedure above was followed using 1,4-dioxaspiro[4.5]decan-8-one **18** (156.2 mg, 1.0 mmol), **1** (1.5 mmol, 1.5 equiv), and *tert*-amyl alcohol (176.3 mg, 2.0 mmol). After being allowed to sit overnight, the reaction mixture was purified by column chromatography on silica gel (eluting with 5% EtOAc/hexanes) to afford the product **19** as a liquid (191.2 mg, 90%): ^{1}H NMR (400 MHz, $CDCl_3$), δ 4.94 (bs, 1H), 4.77 (bs, 1H), 3.98−3.91 (m, 4H), 2.21 (bs, 2H), 1.95−1.90 (m, 2H), 1.84 (s, 3H), 1.72−1.56 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 115.0, 108.8, 70.0, 64.3, 64.2, 49.9, 35.2, 30.6, 25.3; HRMS (ES pos) m/z calcd for $C_{12}H_{19}O_2^+$ ($M - H_2O + H^+$) 195.1380, found 195.1375.

4-(2-Hydroxy-4-methylpent-4-en-2-yl)phenyl acetate **21**. The general procedure above was followed using 4-acetylphenyl acetate **20** (178.2 mg, 1.0 mmol), **1** (1.5 mmol, 1.5 equiv), and *tert*-amyl alcohol (176.3 mg, 2.0 mmol). After being allowed to sit overnight, the reaction mixture was purified by column chromatography on silica gel (eluting with 5% EtOAc/hexanes) to afford the product **21** as a liquid (220.2 mg, 94%): ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.45 (dd, 2H, J = 4.0, 8.0 Hz), 7.04 (dd, 2H, J = 4.0, 8.0 Hz), 4.91 (s, 1H), 4.75 (s, 1H), 2.62 (d, 1H, J = 13.4 Hz), 2.51 (d, 1H, J = 13.4 Hz), 2.30 (s, 3H), 1.56 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 149.3, 145.6, 142.4, 126.0, 121.0, 115.8, 73.1, 52.0, 30.6, 24.3, 21.2; HRMS (ES pos) m/z calcd for $C_{14}H_{22}NO_3^+$ ($M + NH_4^+$) 252.1594, found 252.1585.

4-Methyl-2-(4-(tetrahydro-2H-pyran-2-yloxy)phenyl)pent-4-en-2-ol **23**. The general procedure above was followed using 1-(4-(tetrahydro-2*H*-pyran-2-yloxy)phenyl)ethanone **22** (220.3 mg, 1.0 mmol), **1** (1.5 mmol, 1.5 equiv) and *tert*-amyl alcohol (176.3 mg, 2.0 mmol). After being allowed to sit overnight, the reaction mixture was purified by column chromatography on silica gel (eluting with 5% EtOAc/hexanes) to afford the product **23** as a solid (251.5 mg, 91%): mp 38−39 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.34 (dd, 2H, J = 4.0, 8.0 Hz), 7.00 (dd, 2H, J = 4.0, 8.0 Hz), 5.39 (s, 1H), 4.89 (s, 1H), 4.74 (s, 1H), 3.92 (m, 1H), 3.62 (m, 1H), 2.54 (dd, 2H, J = 1.2, 16 Hz), 2.25 (s, 1H), 2.0 (m, 1H), 1.87−1.84 (m, 2H), 1.68−1.63 (m, 3H), 1.54 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 142.7, 141.1, 125.9, 115.9, 115.5, 96.5, 73.0, 62.1, 52.1, 30.6, 25.2, 24.3, 18.9; HRMS (ES pos) m/z calcd for $C_{19}H_{31}N_2O_3^+$ ($M + CH_3CN + NH_4^+$) 335.2329, found 335.2315.

tert-Butyl 4-(2-Hydroxy-4-methylpent-4-en-2-yl)phenyl Carbonate **25**. The general procedure above was followed using 4-acetylphenyl *tert*-butyl carbonate **24** (236.3 mg, 1.0 mmol), **1** (1.5 mmol, 1.5 equiv), and *tert*-amyl alcohol (176.3 mg, 2.0 mmol). After being allowed to sit overnight, the reaction mixture was purified by column chromatography on silica gel (eluting with 5% EtOAc/hexanes) to afford the product **25** as a solid (286.5 mg, 98%): mp 62−64 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.44 (d, 2H, J = 8.9 Hz), 7.12

dx.doi.org/10.1021/jo4006574 | J. Org. Chem. 2013, 78, 5775−5781

(d, 2H, J = 8.6 Hz), 4.90 (s, 1H), 4.74 (s, 1H), 2.62 (d, 1H, J = 13.4 Hz), 2.51 (d, 1H, J = 13.4 Hz), 2.30 (s, 2H), 1.55 (bs, 12H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 149.7, 145.5, 142.4, 125.9, 120.7, 115.8, 83.4, 73.0, 51.9, 30.7, 27.7, 24.3. HRMS (ES pos) m/z calcd for $C_{17}H_{28}NO_4^+$ ($M + NH_4^+$) 310.2013, found 310.2010.

4-Methyl-2-(thiophene-2-yl)pent-4-en-2-ol ***27***.[24] The general procedure above was followed using 1-(thiophen-2-yl)ethanone **26** (126.2 mg, 1.0 mmol), **1** (1.5 mmol, 1.5 equiv), and *tert*-amyl alcohol (176.3 mg, 2.0 mmol). After being allowed to sit overnight, the reaction mixture was purified by column chromatography on silica gel (eluting with 5% EtOAc/hexanes) to afford the product **27** as a waxy solid (167.7 mg, 92%): ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.27 (m, 1H), 7.14 (m, 1H), 7.04 (m, 1H), 4.91 (s, 1H), 4.75 (s, 1H), 2.59 (d, 1H, J = 13.3 Hz), 2.50 (dd, 1H, J = 0.8, 13.2 Hz), 1.56 (bs, 12H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 142.5, 125.8, 119.3, 115.6, 72.4, 51.8, 30.2, 24.0; HRMS (ES pos) m/z calcd for $C_{10}H_{13}S^+$ ($M - H_2O + NH_4^+$) 165.0732, found 165.0726.

2-(Benzofuran-3-yl)-4-methylpent-4-en-2-ol ***29***. The general procedure above was followed using 1-(benzofuran-3-yl)ethanone **28** (160.2 mg, 1.0 mmol), **1** (1.5 mmol, 1.5 equiv), and *tert*-amyl alcohol (176.3 mg, 2.0 mmol). After being allowed to sit overnight, the reaction mixture was purified by column chromatography on silica gel (eluting with 5% EtOAc/hexanes) to afford the product **29** as a solid (212.0 mg, 98%): mp 37−38 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.51−7.44 (m, 2H), 7.26−7.18 (m, 2H), 6.60 (s, 1H), 4.92 ((m, 1H), 4.91 (s, 1H), 4.75 (s, 1H), 2.81 (d, 1H, J = 13.2 Hz), 2.57 (dd, 1H, J = 0.72, 13.2 Hz), 1.56 (bs, 12H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 142.5, 125.8, 119.3, 115.6, 72.4, 51.8, 30.2, 24.0; HRMS (ES pos) m/z calcd for $C_{14}H_{15}O^+$ ($M - H_2O + H^+$) 199.1117, found 199.1123.

(1S,2S,4R)-2-Hydroxy-7,7-dimethyl-2-(2-methylallyl)bicyclo-[2.2.1]heptane-1-carboxylic Acid ***31***. To a dry vial was charged (*1S,4R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-carboxylic acid **30** (182.2 mg, 1.0 mmol) and **1** (1.5 mmol, 1.5 equiv) under nitrogen. After being allowed to sit overnight, the reaction mixture was purified by column chromatography on silica gel (eluting with 5% EtOAc/hexanes) to afford the product **31** as a solid (212.1 mg, 89%): mp 132−134 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ 5.09 (s, 1H), 4.90 (s, 1H), 2.58−2.20 (m, 4H), 1.94−1.85 (m, 5H), 1.75−1.68 (m, 2H), 1.34 (s, 3H), 1.16−1.11 (m, 1H), 1.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 1757, 142.1. 117.8, 79.9, 62.6, 52.9, 47.9, 47.7, 46.6, 27.0, 26.7, 24.2, 22.0, 21.6; HRMS (ES pos) m/z calcd for $C_{14}H_{23}O_3^+$ ($M + H^+$) 239.1642, found 239.1638.

1,2-Bis(4-methoxyphenyl)-4-methylpent-4-ene-1,2-diol ***33***. The general procedure above was followed using 2-hydroxy-1,2-bis(4-methoxyphenyl)ethanone **32** (272.3 mg, 1.0 mmol), **1** (1.5 mmol, 1.5 equiv), and *t*-amyl alcohol (176.3 mg, 2.0 mmol). After being allowed to sit overnight, the reaction mixture was purified by column chromatography on silica gel (eluting with 5% EtOAc/hexanes) to afford the product **33** as a solid (279.1 mg, 85%): mp 136−137 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.06 (d, 2H, J = 8 Hz), 6.95 (d, 2H, J = 8 Hz), 6.73−6.68 (m, 4H), 4.75−4.71 (m, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 2.90−2.69 (m, 4H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 158.3, 142.4, 134.1, 131.8, 129.0, 127.7, 116.0, 112.8, 112.7, 80.6, 55.1, 46.1, 24.4. HRMS (ES pos) m/z calcd for $C_{20}H_{26}NO_3^+$ ($M - H_2O - NH_4^+$) 328.1907, found 328.1894.

1-(2-Methylallyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-ol ***35***. The general procedure above was followed using 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1*H*-inden-1-one **34** (258.1 mg, 1.0 mmol), **1** (1.5 mmol, 1.5 equiv), and *tert*-amyl alcohol (176.3 mg, 2.0 mmol). After being allowed to sit overnight, the reaction mixture was purified by column chromatography on silica gel (eluting with 5% EtOAc/hexanes) to afford the product **35** as a liquid (264.0 mg, 84%): ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.8 (s, 1H), 7.71 (d, 1H, J = 7.5 Hz), 7.2 (d, 1H, J = 7.8 Hz), 4.92 (s, 1H), 4.80 (s, 1H), 2.96−3.06 (m, 1H), 2.77−2.86 (m, 2H), 2.34−2.45 (m, 2H), 2.02−2.12 (m, 2H), 1.75 (s, 3H), 1.34 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 146.6. 142.7, 134.9, 129.0, 124.4, 115.0, 83.7, 82.7, 48.1, 39.4, 29.8, 39.4, 29.9, 24.9, 24.8; HRMS (ES pos) m/z calcd for $C_{19}H_{26}BO_2^+$ ($M + NH_4^+$) 297.2020, found 297.2013.

Ethyl 3-Hydroxy-3-(2-methoxyphenyl)-5-methylhex-5-enoate ***37***. The general procedure above was followed, using ethyl 3-(2-methoxyphenyl)-3-oxopropanoate **36** (222.2 mg, 1.0 mmol), **1** (1.5 mmol, 1.5 equiv), and *tert*-amyl alcohol (176.3 mg, 2.0 mmol). After being allowed to sit overnight, the reaction mixture was purified by column chromatography on silica gel (eluting with 5% EtOAc/hexanes) to afford the product **37** as a liquid (258.9 mg, 93%): ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.57−7.60 (m, 1H),7.19−7.25 (m, 1H), 6.94 (t, 1H, J = 7.6 Hz), 6.84 (d, 1H, J = 8.1 Hz), 4.74 (s, 1H), 4.62 (s, 1H), 4.35 (s, 1H), 3.95 (q, 2H, J = 7.0 Hz), 3.85 (s, 3H), 3.33 (d, 1H, J = 15.1 Hz), 2.79−2.86 (m, 2H), 2.62 (d, 1H, J = 13.3 Hz), 1.56 (s, 3H), 1.03 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 155.7, 142.7, 132.6, 128.4, 127.7. 127.6, 120.5, 114.6, 110.8, 74.7, 60.3, 55.1, 47.3, 43.6, 24.1, 13.9; HRMS (ES pos) m/z calcd for $C_{18}H_{29}N_2O_4^+$ ($M + CH_3CN + NH_4^+$) 337.2122, found 337.2110.

2-(2-Methylallyl)-1,2,3,4-tetrahydronaphthalene-2,6-diol ***39***. To a dry vial were charged 6-hydroxy-3,4-dihydronaphthalen-2(1*H*)-one **38** (162.2 mg, 1.0 mmol) and **1** (1.5 mmol, 1.5 equiv) under nitrogen. After being allowed to sit overnight, the reaction mixture was purified by column chromatography on silica gel (eluting with 5% EtOAc/hexanes) to afford the product **39** as a solid (179.0 mg, 82%): mp 110−111 °C; ^{1}H NMR (400 MHz, DMSO-d_6), δ 9.0 (s, 1H), 6.78 (dd, 1H, J = 8 Hz), 6.51−6.47 (m, 2H), 4.83 (s, 1H), 4.64 (s, 1H), 4.24 (s, 1H), 2.80−2.78 (m, 1H), 2.64−2.50 (m, 3H), 1.84 (s, 3H), 1.72−1.57 (m, 2H);^{13}C NMR (100 MHz, DMSO-d_6) δ 154.8, 143.0, 136.4, 130.0, 125.6, 114.4, 113.8, 113.0, 69.7, 48.8, 40.7, 33.7, 26.1, 24.7; HRMS (ES pos) m/z calcd for $C_{14}H_{22}NO_2^+$ ($M + NH_4^+$) 236.1645, found 236.1639.

Procedure for Synthesis of 1,2-Bis(4-methoxyphenyl)-4-methylpent-4-ene-1,2-diol 33 on 10 g Scale. To a dry flask were charged 2-hydroxy-1,2-bis(4-methoxyphenyl)ethanone **32** (10.0 g, 36.7 mmol), **1** (55.1 mmol, 1.5 equiv), and *tert*-amyl alcohol (6.47 g, 73.45 mmol, 2.0 equiv) under nitrogen. The resulting solution was then allowed to stir at 35 °C overnight. After 20 mL of water was added, the resulting mixture was stirred overnight. The solid was collected and washed with water to give the analytically pure product **33** (9.7 g, 80% yield) as a white solid.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR of all new 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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dx.doi.org/10.1021/jo4006574 | *J. Org. Chem.* 2013, 78, 5775−5781