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DMF Dimethyl Acetal as Carbon Source for α-Methylation of Ketones: A Hydrogenation–Hydrogenolysis Strategy of Enaminones

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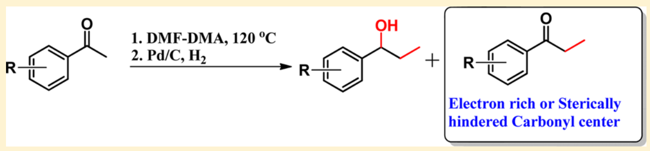
Supporting Information

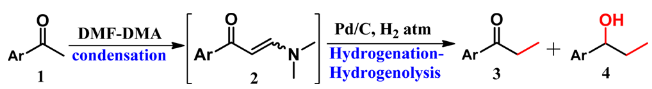
ABSTRACT: A novel heterogeneous catalytic hydrogenation–hydrogenolysis strategy has been developed for the α-methylation of ketones via enaminones using DMF dimethyl acetal as carbon source. This strategy provides a very convenient route to α-methylated ketones using a variety of ketones without any base or oxidant.



Methyl functionalization of a carbon center using a readily available catalyst and carbon source is a challenging task for chemists. Methylation is not only associated with biological processes but also has significant value in synthetic chemistry for fine chemical synthesis and functionalization of biologically active molecules.[1] α-Methylation of ketones is one of the most important and frequently used methods in organic synthesis.[2] Alkylation of enolate is the classical method for this reaction, where the carbonyl compounds are intended to be an enolate nucleophile to attack an electrophilic alkylating agent.[3] Most commonly, strong bases are used to ensure all the starting carbonyl converts into its corresponding enolate anion to avoid self-condensation of carbonyl compounds. Furthermore, low temperature (about −78 °C) is required for some reactive enolate species to survive. To improve this reaction, several methods have been developed such as the use of KH–BEt_3 with MeI,[4] Et_3GeNa–YCl_3 with MeI,[5] $PhSeCH_2Li$–*m*-CPBA,[6] CH_2N_2–$BF_3{\cdot}Et_2O$,[7] HCHO–basic zeolites,[8] CH_4–MgO,[9] and N_2CHCO_2Et–LDA–$Rh_2(OAc)_4$.[10] However, these methods use toxic or explosive reagents[4−7,10] and require harsh reaction conditions.[8−10] Recently, a few new catalytic methods have been developed using sustainable feedstock for the methyl source. Xiao and co-workers reported Rh-catalyzed α-methylation of ketones using DMF as carbon source; where strong oxidant persulfate was used to form an iminium intermediate of DMF for the enolate attack.[11] Additionally Rh- and Ir-catalyzed α-methylation of ketones using methanol as methyl source have been reported independently by the Donohoe[12] and Obora[13] groups. However, in both cases, strong bases are required and double methylation occurs. In this context, there is a strong desire for the development of new synthetic strategy for the α-methylation of ketone using readily available reagent and catalyst without any base or oxidant.

Recently, we have developed a Pd–graphene composite material as catalyst for C–C bond formation and reduction of C–C double bonds. While screening the reaction conditions, we were surprised to find that hydrogenation of enaminone derived from acetophenone and dimethylformamide–dimethyl acetal (DMF–DMA) produced phenylpropanol. This finding prompted us to explore the possibility of developing a novel synthetic strategy for the α-methylation of carbonyl compounds. On the other hand, enaminones are versatile synthetic intermediates for the synthesis of various heterocycles[14] and other valuable products.[15] To the best of our knowledge, however, this intermediate has not been used for the α-methylation of ketone. Herein, we report a novel synthetic strategy for α-methylation of ketones. Our synthetic strategy consists of condensation of ketones with DMF–DMA followed by hydrogenation–hydrogenolysis of enaminones. The novel hydrogenation–hydrogenolysis step was catalyzed by Pd/C under H_2 atmosphere (Scheme 1).

Scheme 1. α-Methylation of Ketones via Enaminones



Initially, acetophenone **1a** was chosen as the model substrate for the α-methylation via enaminone **2a** with various heterogeneous catalysts, and extensive investigations were carried out to optimize the reaction conditions (Table 1). The synthesis of enaminones from ketones and DMF–DMA is well precedente, and this intermediate was used for hydrogenation–hydrogenolysis reaction without chromatographic purification.[16] As a starting point, hydrogenation experiments were performed using 10 mol % of Pd/C in the presence of H_2 (balloon) for 12 h at rt, giving the phenylpropanol **4a**. Under the same reaction conditions, other heterogeneous catalysts such as Pd/$CaCO_3$, Pd/Al_2O_3, Pd/SiO_2, and Ru/C gave a moderate yield of **4a** along with **3a**. As a control experiment, the reaction was performed in the absence of catalyst, and no product was observed. The catalyst Pd/C was considered and particularly chosen in this strategy for the α-methylation of ketones as it is commercially available and inexpensive. With the optimized reaction conditions in hand, we examined the scope of the reaction in order to establish the generality of our

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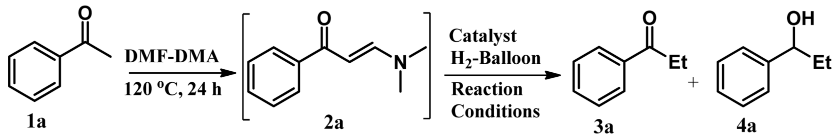
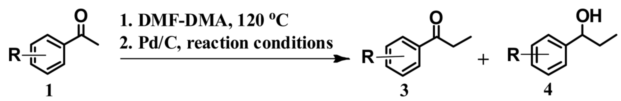
Table 1. Optimization of Conditions for the α-Methylation of Ketone 1a[a]

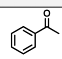
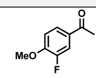
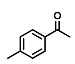
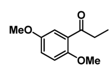
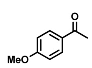
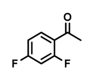
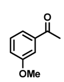
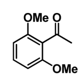
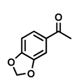
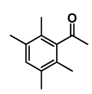
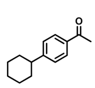
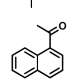
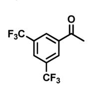
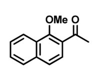
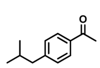
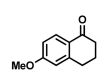
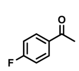
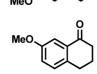
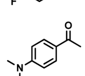
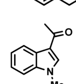


entry	catalyst (10 mol %)	reaction conditions	yield[b] (%) 3a	4a
1	Pd/C	EtOH, rt, 12 h	traces	79
2	Pd/C	EtOH, 50 °C, 6 h	traces	77
3	$Pd/CaCO_3$	EtOH, rt, 12 h	12	30
4	Pd/Al_2O_3	EtOH, rt, 12 h	18	35
5	Pd-rGO	EtOH, rt, 12 h	traces	72
6	Rh/C	EtOH, rt, 12 h	10	49
7	no catalyst	EtOH, 50 °C, 24 h	nd	nd

[a]Reaction conditions: acetophenone (1 mmol), DMF−DMA (~20 mmol), 120 °C, 24 h in an open flask, workup and added ethanol (7 mL), Pd/C (10 mol %), H_2 (balloon), rt. [b]All yields are isolated yields. nd = not detected. rGO: reduced graphene oxide.

Table 2. Scope of the α-Methylation of Ketones[a]



entry	ketone 1(a-j)	Reaction conditions	yield (%)[b] 3(a-j)	4(a-j)	entry	ketone 1(k-t)	reaction conditions	yield (%)[b] 3(k-t)	4(k-t)
1		H_2(BP), RT, 12h	trace	79	11		H_2(2.5 bar), RT, 6h	20	50
2		H_2(BP), RT, 12h	trace	69	12		H_2(BP), RT, 18h	81	nd
							H_2(2.5 bar), RT, 7h	83	nd
3		H_2(BP), RT, 12h	18	55	13		H_2(BP), RT, 12h	65	trace
4		H_2(BP), RT, 12h	trace	71	14		H_2(BP), RT, 12h	80	nd
5		H_2(BP), RT, 12h	trace	67	15		H_2(BP), RT, 12h	71	nd
6		H_2(BP), RT, 18h	12	23	16		H_2(2.5 bar), RT, 6h	48	22
7		H_2(BP), RT, 12h	nd	77	17		H_2(2.5 bar), RT, 6h	77	nd
8		H_2(BP), RT, 18h	21	44	18		H_2(BP), RT, 8h	71	trace
9		H_2(BP), RT, 12h	trace	75	19		H_2(BP), RT, 10h	67	trace
10		H_2(BP), RT, 12h	trace	82	20		H_2(BP), RT, 10h	73	trace

[a]Reaction conditions: ketone (1 mmol), DMF−DMA (~15−20 mmol), 120 °C, 24 h in an open flask, workup; ethanol (7 mL), Pd/C (10 mol %), H_2 (BP = balloon pressure or 2.5 bar pressure), rt. [b]All yields are isolated yields.

strategy. Various ketones **1a−t** were α-methylated via enaminones **2a−t**, and the results are summarized in Table 2.

(*E*/*Z*)-Aryl and (*E*/*Z*)-heteroaryl 3-(dimethylamino)-3-prop-2-enone (enaminones); are efficiently prepared by the condensation of respective aryl and heteroaryl methyl ketones with excess of DMF−DMA at 120 °C. In most of the cases, enaminones were isolated for this strategy after a simple workup without chromatographic purification. Aryl and heteroaryl methyl ketones having neutral, electron-donating, and electron-withdrawing groups were smoothly converted to

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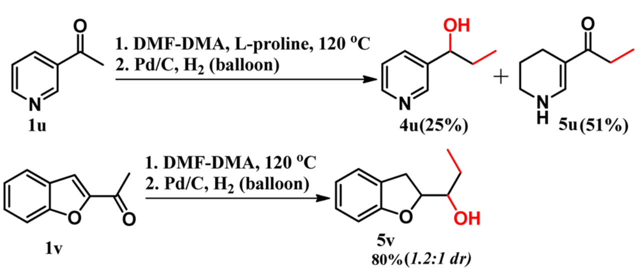
the corresponding α-methylated products **3** and **4** in 35−82% yields. The results show that the electronic effect of substituents as well as *ortho*-, *meta*-, and *para*-substitution at the aryl ring play an important role in this reaction. Specifically, aryl methyl ketones having electron-withdrawing groups (F- and CF_3-) at *meta*- and *para*-substitution sites gave phenylpropanol products **4** in high yield (Table 2, entries 7 and 9).

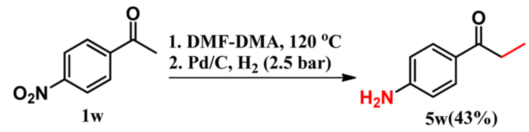
Notably, substrates with a strong electron-donating group substituted at the *para*-position of the aryl ring afforded phenylpropanol **4** in only moderate yields along with the α-methylated keto product **3** (Table 2, entries 3, 6, and 8). However, an electron-donating group at the *meta*-position gave a good yield of alcohol **4** along with a trace of α-methylated keto product **3** (Table 2, entry 4). Surprisingly, the ortho-substituted aryl methyl ketones, regardless of their electronic nature as electron-donating or electron-withdrawing, exclusively gave the α-methylated keto products **3**, which might be due to the steric effect (Table 2, entries 12−15). *N*,*N*-Dimethylacetophenone **1j** exceptionally gave the corresponding phenylpropanol **4j** in high yield, which could be used as a raw material for the synthesis of the potent histone deacetylase inhibitor (±)-trichostatin A.[17] The cyclic ketones were also investigated, and the α-methylated keto products were obtained in good yields (Table 2, entries 18 and 19). The yield of α-methylated keto products **3r** and **3s** also might be caused by the steric effect of fused rings. Having succeeded in the α-methylation of aryl methyl ketones, we extended this strategy for the methylation of heteroaryl methyl ketones. Accordingly, *N*-protected indole derivative 1-(1-methyl-1*H*-indol-3-yl)-ethanone **1t** was condensed with DMF−DMA followed by hydrogenation−hydrogenolysis over Pd/C under H_2 (balloon). The α-methylated keto product 1-(1-methyl-1*H*-indol-3-yl)-propan-1-one **3t** was obtained with 73% yield as the only isolable product. Additionally, the α-methylation of 3-acetylpyridine was attempted using the same reaction strategy; interestingly, 1-(pyridin-3-yl)propan-1-ol **4u** along with another reduced product 1-(1,4,5,6-tetrahydropyridin-3-yl)propan-1-one **5u** were obtained with 25% and 51% yield, respectively. This result encouraged us to further explore our strategy; in this regard, 2-acetylbenzofuran **1v** was considered and transformed into the corresponding enaminone followed by hydrogenation over Pd/C. Interestingly, an α-methylated over-reduced product **5v** was obtained in 80% yield as mixture of diastereomers in 1.2:1 ratio (Scheme 2).

Scheme 2. α-Methylation of Heteroaryl Methyl Ketone



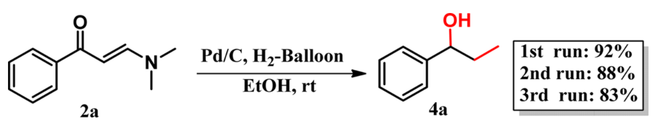
We planned to employ our synthetic method to prepare 4-aminopropiophenone (PAPP)[18] **5w**, which is a biologically important molecule and a raw material for the synthesis of pharmaceutically important compounds.[19] The desired compound **5w** was derived from 4-nitroacetophenone via enaminone followed by our synthetic strategy, and the PAPP was obtained with 43% overall yield (Scheme 3).

Scheme 3. . Synthesis of 4-Aminopropiophenone



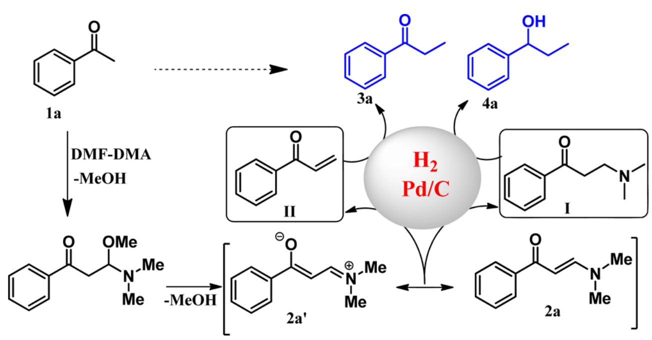
With a view toward economic and environmental concerns, the recyclability of the catalyst was explored. In this regard, the purified (*E*)-3-(dimethylamino)-1-phenylprop-2-en-1-one **2a** was chosen and hydrogenated under H_2 (balloon). Upon completion of the reaction, the catalyst was filtered and washed with ethanol and reused at least three times. Although the catalytic activity gradually diminished (yield of **4a**: first reuse 92%, second reuse 88%, third reuse 81%), the yield was still 80% even after the third reuse (Scheme 4).

Scheme 4. Recyclability of Catalyst



A plausible reaction mechanism for the α-methylation of ketone is proposed in Scheme 5. Ketone **1a** undergoes

Scheme 5. Plausible Reaction Mechanism



condensation with DMF−DMA to afford enaminone **2a**, which undergoes hydrogenation followed by hydrogenolysis of intermediate **I** (Scheme 6). To elucidate the mechanism, the intermediate **I**[20] was independently synthesized from acetophenone **1a** and treated with Pd/C under hydrogen atmosphere at room temperature overnight. The expected phenylpropanol **4a** was obtained in 88% yield, whereas the keto product **3a** was not observed in this experiment. These results suggested that 3-(dimethylamino)propiophenone **I** is the key intermediate for phenylpropanol **4a**. The formation of keto product **3a** is not clear at present. However, it is proposed that it proceeds via intermediate **II** as shown in Scheme 5.[21]

In summary, we have developed a novel one-pot hydrogenation−hydrogenolysis strategy for the α-methylation of ketones via enaminones. This method offers significant advantages such as commercially available reagents and catalyst, an operationally simple procedure, high conversion, and use of recyclable catalysts. The present reaction will serve as an

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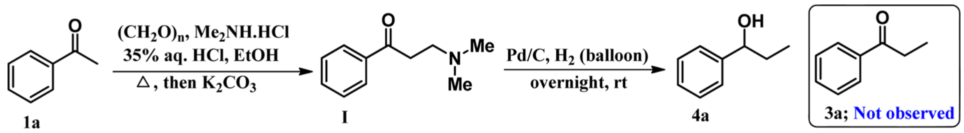
Scheme 6. Independent Experiment for Mechanism



alternative strategy for the α-methylation of ketones without any base or oxidant.

■ EXPERIMENTAL SECTION

General Information. All chemicals were used as received without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature on a 300 or 500 MHz NMR spectrometer (75 or 125 MHz for ^{13}C). NMR chemical shifts are reported on the δ scale (ppm) downfield from tetramethylsilane (δ = 0.0 ppm) using the residual solvent signal at δ = 7.26 ppm (^{1}H) or δ = 77 ppm (^{13}C) as internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad). IR spectra were recorded on a spectrophotometer using $CHCl_3$. Hydrogenation under pressure (2.5 bar) was carried out in hydrogenation apparatus. Column chromatography was performed with silica gel 60 (100−200 mesh).

Experimental Procedure for the Synthesis of Enaminones 2a−w (2a as an Example). Acetophenone **1a** (1 mmol) and DMF−DMA (20 mmol) was stirred at 120 °C (oil bath) in an open flask. After disappearance of the reactant (monitored by TLC), water was added to the mixture (50 mL), and the mixture was extracted with EtOAc (3 × 30 mL). The extract was dried over anhydrous Na_2SO_4 and concentrated. The crude residue was used for the one-pot hydrogenation−hydrogenolysis reaction without chromatographic purification [L-proline (5 mol %) was added during the synthesis of **2p**, **2q**, **2t**, and **2v**].[16]

Experimental Procedure for the Hydrogenation−Hydrogenolysis of Enaminones (4a as an Example). Crude enaminone **2a** as obtained from the previous step was dissolved in ethanol (20 mL). 10% Pd/C (106 mg, 10 mol % of **1a**) was added, and the heterogeneous mixture was vigorously stirred at room temperature under atmospheric hydrogen pressure (balloon) for 12 h. The reaction mixture was filtered (using a Buchner funnel with sintered disk) and washed with ethanol (2 × 10 mL). The filtrate and washings were combined and concentrated under reduced pressure. After the evaporation, the residue was purified by column chromatography on silica gel (ethyl acetate/hexanes, 1:10) to afford the product **4a**. (For crude substrates **2k,l,p,q,w**, 2.5 bar hydrogen pressure was used instead of hydrogen balloon in a *hydrogenation apparatus.*)

*1-Phenylpropan-1-ol (**4a**).*[22−24] Flash column chromatography on silica gel (ethyl acetate/hexanes 1:10) gave **4a** (107 mg, 79% yield) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18−7.45 (m, 5H), 4.59 (t, *J* = 6.6 Hz, 1H), 1.9 (br s, 1H), 1.66−1.90 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6, 128.4, 127.5, 126.0, 75.9, 31.8, 10.2; IR ($CHCl_3$) 3368, 2964, 2932, 2876, 1453, 974 cm^{-1}.

*1-p-Tolylpropan-1-ol (**4b**).*[23,24] Flash column chromatography on silica gel (ethyl acetate/hexanes 1:10) gave **4b** (104 mg, 69% yield) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, *J* = 7.9 Hz, 2H), 7.14 (d, *J* = 7.8 Hz, 2H), 4.54 (t, *J* = 6.6 Hz, 1H), 2.34 (s, 3H), 1.99 (br s, 1H), 1.61−1.9 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.6, 137.1, 129.1, 125.9, 75.9, 31.8, 21.1, 10.2; IR ($CHCl_3$) 3367, 2962, 2927, 2875, 1456, 1098, 1040, 1014, 874 cm^{-1}.

*1-(4-Methoxyphenyl)propan-1-one (**3c**).*[11] Flash column chromatography on silica gel (ethyl acetate/hexanes 1:12) gave **3c** (30 mg, 18% yield) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H), 2.96 (q, *J* = 7.2 Hz, 2H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.5, 163.3, 130.2, 130.0, 113.6, 55.4, 31.4, 8.4; IR ($CHCl_3$) 2974, 2936, 1679, 1601, 1257, 1227, 1170 cm^{-1}.

*1-(4-Methoxyphenyl)propan-1-ol (**4c**).*[23,25] Flash column chromatography on silica gel (ethyl acetate/hexanes 1:12) gave **4c** (91 mg, 55% yield) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.5 Hz, 2H), 6.79 (d, *J* = 8.5 Hz, 2H), 4.44 (t, *J* = 6.7 Hz, 1H), 3.71 (s, 3H), 1.99 (br s, 1H), 1.53−1.81 (m, 2H), 0.81 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 136.8, 127.2, 113.6, 75.6, 55.3, 31.7, 10.2; IR ($CHCl_3$) 3391, 2962, 2933, 2876, 1612, 1513, 1248, 1175, 1038 cm^{-1}.

*1-(3-Methoxyphenyl)propan-1-ol (**4d**).*[24] Flash column chromatography on silica gel (ethyl acetate/hexanes 1:10) gave **4d** (118 mg, 71% yield) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (t, *J* = 8 Hz, 1H), 6.92 (s, 1H), 6.90 (s, 1H), 6.81 (d, *J* = 8.4 Hz, 3H), 4.56 (t, *J* = 6.5 Hz, 1H), 3.80 (s, 3H), 1.86 (br s, 1H), 1.68−1.84 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 146.5, 129.3, 118.4, 118.0, 112.8, 111.5, 75.7, 55.1, 31.8, 10.1; IR ($CHCl_3$) 3392, 2964, 2935, 1602, 1586, 1487, 1455, 1261, 1042 cm^{-1}.

*1-(Benzo[d][1,3]dioxol-5-yl)propan-1-ol (**4e**).*[23,25] Flash column chromatography on silica gel (ethyl acetate/hexanes 1:10) gave **4e** (121 mg, 67% yield) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (s, 1H), 6.75 (s, 2H), 5.92 (s, 2H), 4.47 (t, *J* = 6.6 Hz, 1H), 2.08 (br s, 1H), 1.58−1.86 (m, 2H), 0.87 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7, 146.8, 138.7, 119.4, 107.9, 106.4, 100.9, 75.8, 31.8, 10.2; IR ($CHCl_3$) 3379, 2965, 2932, 2877, 1504, 1487, 1441, 1248, 1040, 931, 811 cm^{-1}.

*1-(4-Cyclohexylphenyl)propan-1-one (**3f**).*[26] Flash column chromatography on silica gel (ethyl acetate/hexanes 1:10) gave **3f** (26 mg, 12% yield) as a gummy liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 2.98 (q, *J* = 7.2 Hz, 2H), 2.56 (br s, 1H), 1.34−1.95 (m, 10H), 1.21 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.6, 153.5, 134.8, 128.2, 127.0, 44.6, 34.1, 31.6, 26.7, 26.0, 8.3; IR ($CHCl_3$) 2926, 2852, 1685, 1606, 1222 cm^{-1}.

*1-(4-Cyclohexylphenyl)propan-1-ol (**4f**).* Flash column chromatography on silica gel (ethyl acetate/hexanes 1:10) gave **4f** (50 mg, 23% yield) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 4.51 (t, *J* = 6.5 Hz, 1H), 2.48 (br s, 1H), 1.98 (br s, 1H), 1.66−1.92 (m, 7H), 128−1.51 (m, 5H), 0.89 (t, *J* = 7.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.3, 142.1, 126.8, 126.0, 75.8, 44.3, 34.5, 31.9, 26.9, 26.2, 10.3; IR ($CHCl_3$) 3367, 2925, 2851, 1448, 826 cm^{-1}; MS (EI) *m/z* 218.1 (M)$^+$. Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.47; H, 10.22.

*1-[3,5-Bis(trifluoromethyl)phenyl]propan-1-ol (**4g**).*[25] Flash column chromatography on silica gel (ethyl acetate/hexanes 1:10) gave **4g** (209 mg, 77% yield) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 2H), 7.78 (s, 1H), 4.76 (t, *J* = 6.4 Hz, 1H), 2.00 (br s, 1H), 1.73−1.86 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 131.6 (q, *J* = 33.3 Hz), 126.1 (q, *J* = 2.8 Hz), 123.4 (q, *J* = 272.6 Hz), 121.3 (q, *J* = 3.7 Hz), 74.6, 32.2, 9.7; IR ($CHCl_3$) 3199, 2979, 1463, 1383, 1291, 1116 cm^{-1}.

*1-(4-Isobutylphenyl)propan-1-one (**3h**).* Flash column chromatography on silica gel (ethyl acetate/hexanes 1:15) gave **3h** (40 mg, 21% yield) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 8 Hz, 2H), 2.97 (q, *J* = 7.3 Hz, 2H), 2.52 (d, *J* = 7.2 Hz, 2H), 1.68−1.99 (m, 1H), 1.21 (t, *J* = 7.3 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.5, 147.3, 134.7, 129.3, 127.9, 45.4, 31.6, 30.1, 22.3, 8.3; IR ($CHCl_3$) 2957, 2934, 2870, 1686, 1608, 1465, 1415, 1225, 1182, 953 cm^{-1}; MS (EI) *m/z* 190.1 (M)$^+$. Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.17; H, 9.60.

*1-(4-Isobutylphenyl)propan-1-ol (**4h**).* Flash column chromatography on silica gel (ethyl acetate/hexanes 1:15) gave **4h** (85 mg, 44% yield) as a liquid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 8.1 Hz, 2H), 4.48 (t, *J* = 6.6 Hz, 1H), 2.39 (d, *J* = 7.2 Hz, 2H), 1.58−1.95 (m, 4H), 0.54−1.11 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.7, 140.9, 129.0, 125.6, 75.8, 45.0, 31.7, 30.1, 22.3, 10.1; IR ($CHCl_3$) 3393, 2957, 1464, 1383, 846, 893 cm^{-1}; MS (EI) *m*/

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J. Org. Chem. 2015, 80, 4722−4728

z 192.1 (M)$^+$. Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.11; H, 10.53.

1-(4-Fluorophenyl)propan-1-ol (4i)..[23,24] Flash column chromatography on silica gel (ethyl acetate/hexanes 1:10) gave **4i** (116 mg, 75% yield) as a liquid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21–7.26 (m, 2H), 6.96 (t, J = 8.6 Hz, 2H), 4.52 (t, J = 6.6 Hz, 1H) 1.57–1.80 (m, 3H), 0.82 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1 (d, J = 245.1 Hz), 140.3 (d, J = 3.2 Hz), 127.6 (d, J = 8.0 Hz), 115.2 (d, J = 21.3 Hz), 75.4, 32.0, 10.1; IR ($CHCl_3$) 3367, 2963, 2930, 1605, 1509, 1222, 1015, 834 cm^{-1}.

1-[4-(Dimethylamino)phenyl]propan-1-ol (4j).[17] Flash column chromatography on neutral alumina (ethyl acetate/hexanes 1:12) gave **4j** (147 mg, 82% yield as a gummy liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, J = 8.5 Hz, 2H), 6.70 (d, J = 8.5 Hz, 2H), 4.45 (t, J = 6.7 Hz, 1H), 2.92 (s, 6H), 2.14 (br s, 1H), 1.61–1.90 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.2, 132.8, 127.0, 112.67, 75.7, 40.7, 31.6, 10.4.

1-(3-Fluoro-4-methoxyphenyl)propan-1-one (3k).[27] Flash column chromatography on silica gel (ethyl acetate/hexanes 1:10) gave **3k** (36 mg, 20% yield) as a white solid: mp 76–80 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60–7.70 (m, 2H), 6.92 (t, J = 8.4 Hz, 1H), 3.87 (s, 3H), 2.86 (q, J = 7.3 Hz, 2H), 1.14 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5, 151.9 (d, J = 247 Hz), 151.6 (d, J = 10.9 Hz), 130.2 (d, J = 4.7 Hz), 125.1 (d, J = 3.2 Hz), 115.6 (d, J = 18.9 Hz), 112.2, 56.1, 31.8, 8.2; IR ($CHCl_3$) 2978, 1673, 1614, 1580, 1516, 1432, 1285, 1140, 1017, 801 cm^{-1}.

1-(3-Fluoro-4-methoxyphenyl)propan-1-ol (4k). Flash column chromatography on silica gel (ethyl acetate/hexanes 1:10) gave **4k** (92 mg, 50% yield) as a liquid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (dd, J_1 = 2 Hz, J_2 = 12.2 Hz, 1H), 6.95 (d, J = 8.3 Hz, 1H), 6.84 (t, J = 8.5 Hz, 1H), 4.45 (t, J = 6.6 Hz, 1H) 3.81 (s, 3H), 1.85 (br s, 1H), 1.56–1.77 (m, 2H), 0.82 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.2 (d, J = 245 Hz), 146.7 (d, J = 10.8 Hz), 137.6 (d, J = 5.3 Hz), 121.6 (d, J = 3.4 Hz), 113.6 (d, J = 18.5 Hz), 113.0, 74.9, 56.2, 31.6, 9.9; IR ($CHCl_3$) 3391, 2965, 2935, 1518, 1275, 1127, 1027 cm^{-1}; MS (EI) m/z 184 (M)$^+$. Anal. Calcd for $C_{10}H_{13}FO_2$: C, 65.20; H, 7.11. Found: C, 65.27; H, 7.13.

1-(2,5-Dimethoxyphenyl)propan-1-one (3l).[28] Flash column chromatography on silica gel (ethyl acetate/hexanes 1:10) gave **3l** (161 mg, 83% yield) as a gummy liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 2.8 Hz, 1H), 7.01 (dd, J_1 = 2.8 Hz, J_2 = 8.9 Hz, 1H), 6.90 (d, J = 8.9 Hz, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 2.99 (q, J = 7.2 Hz, 2H), 1.16 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 153.4, 153.0, 128.7, 119.6, 113.9, 113.1, 56.0, 55.8, 36.9, 8.4; IR ($CHCl_3$) 2973, 2939, 2836, 1675, 1496, 1464, 1412, 1278, 1223, 1168, 1049, 1023, 814 cm^{-1}.

1-(2,4-Difluorophenyl)propan-1-one (3m). Flash column chromatography on silica gel (ethyl acetate/hexanes 1:10) gave **3m** (110 mg, 65% yield) as a liquid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87–8.03 (m, 1H), 6.92–6.98 (m, 1H), 6.83–6.89 (m, 1H) 2.97 (q, J = 7.2 Hz, 2H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.4 (d, J = 4.7 Hz), 165.5 (dd, J_1 = 12.2 Hz, J_2 = 256 Hz), 162.6 (dd, J_1 = 12.5 Hz, J_2 = 257 Hz), 132.5 (dd, J_1 = 4.4 Hz, J_2 = 10.6 Hz), 122.0 (dd, J_1 = 4 Hz, J_2 = 14 Hz), 111.9 (dd, J_1 = 3.3 Hz, J_2 = 21.3 Hz), 104.6 (dd, J_1 = 25 Hz, J_2 = 27 Hz), 36.6 (d, J = 7.6 Hz), 7.8 (d, J = 2.2 Hz); IR ($CHCl_3$) 2982, 2941, 1691, 1428, 1236, 973 cm^{-1}; MS (EI) m/z 170 (M)$^+$. Anal. Calcd for $C_9H_8F_2O$: C, 63.53; H, 4.74. Found: C, 63.39; H, 4.79.

1-(2,6-Dimethoxyphenyl)propan-1-one (3n).[29] Flash column chromatography on silica gel (ethyl acetate/hexanes 1:10) gave **3n** (155 mg, 80% yield) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (t, J = 8.4 Hz, 1H), 6.47 (d, J = 8.4 Hz, 2H), 3.70 (s, 6H), 2.68 (q, J = 7.2 Hz, 2H), 1.07 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.9, 156.5, 130.3, 120.4, 103.8, 55.8, 37.8, 7.5; IR ($CHCl_3$) 2988, 2943, 1702, 1595, 1474, 1260, 1113 cm^{-1}.

1-(2,3,5,6-Tetramethylphenyl)propan-1-one (3o).[30] Flash column chromatography on silica gel (ethyl acetate/hexanes 1:10) gave **3o** (135 mg, 71% yield) as a gummy liquid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 (s, 1H), 2.62 (q, J = 7.2 Hz, 2H), 2.13 (s, 6H), 1.97 (s, 6H), 1.13 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.5, 142.8, 134.2, 131.3, 127.8, 38.4, 19.3, 15.8, 7.4; IR ($CHCl_3$) 2970, 2938, 1699, 1467, 1447, 1408, 1260, 1022, 1003 cm^{-1}.

1-(Naphthalen-1-yl)propan-1-one (3p).[31] Flash column chromatography on silica gel (ethyl acetate/hexanes 1:10) gave **3n** (88 mg, 48% yield) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 7.86 (t, J = 8 Hz, 2H), 7.42–7.63 (m, 3H), 3.08 (q, J = 7.3 Hz, 2H), 1.28 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.3, 136.2, 133.9, 132.3, 130.2, 128.4, 127.8, 127.2, 126.4, 125.8, 124.4, 35.4, 8.7; IR ($CHCl_3$) 3049, 2977, 2937, 1682, 1508, 1230, 1110, 932, 796 cm^{-1}.

1-(Naphthalen-1-yl)propan-1-ol (4p).[23,25] Flash column chromatography on silica gel (ethyl acetate/hexanes 1:10) gave **4n** (41 mg, 22% yield) as a liquid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, J = 7.5 Hz, 1H), 7.83 (dd, J_1 = 2.5 Hz, J_2 = 6.8 Hz, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.56 (d, J = 7.1 Hz, 1H), 7.37–7.50 (m, 3H), 5.27–5.33 (m, 1H), 2.2 (br s, 1H), 1.78–2.02 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.2, 133.7, 130.4, 128.8, 127.7, 125.8, 125.4, 125.3, 123.2, 122.8, 72.4, 31.0, 10.4; IR ($CHCl_3$) 3369, 2964, 2931, 1510. 1460, 968, 798, 770 cm^{-1}.

1-(1-Methoxynaphthalen-2-yl)propan-1-one (3q). Flash column chromatography on silica gel (ethyl acetate/hexanes 1:10) gave **3o** (165 mg, 77% yield) as a gummy liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (br s, 1H), 7.85 (br s, 1H), 7.52–7.67 (m, 4H), 3.98 (s, 3H), 3.13 (q, J = 7.2 Hz, 2H), 1.24 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.8, 156.6, 136.6, 128.1, 128.0, 126.6, 125.5, 124.2, 123.3, 63.8, 36.3, 8.6; IR ($CHCl_3$) 3468, 3059, 2976, 2937, 1677, 1370, 1206, 1102, 1078, 988 cm^{-1}; MS (EI) m/z 214 (M)$^+$. Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.55; H, 6.66.

6-Methoxy-2-methyl-3,4-dihydronaphthalen-1(2H)-one (3r).[32] Flash column chromatography on silica gel (ethyl acetate/hexanes 1:10) gave **3p** (135 mg, 71% yield) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 8.7 Hz, 1H), 6.82 (dd, J_1 = 1.8 Hz, J_2 = 8.7 Hz, 1H), 6.68 (s, 1H), 3.85 (s, 3H), 2.86–3.08 (m, 2H), 2.46–2.62 (m, 1H), 2.11–2.24 (m, 1H), 1.76–1.96 (m, 1H), 1.26 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.6, 163.3, 146.6, 129.7, 126.0, 113.0, 112.4, 55.4, 42.2, 31.4, 29.2, 15.5; IR ($CHCl_3$) 2962, 2932, 2859, 2839, 1675, 1599, 1494, 1458, 1358, 1252, 1134, 1032, 970 cm^{-1}.

7-Methoxy-2-methyl-3,4-dihydronaphthalen-1(2H)-one (3s).[32] Flash column chromatography on silica gel (ethyl acetate/hexanes 1:10) gave **3q** (127 mg, 67% yield) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.05 (d, J = 8.4 Hz, 1H), 6.94 (dd, J_1 = 2.2 Hz, J_2 = 8.4 Hz, 1H), 3.73 (s, 3H), 2.16–2.94 (m, 2H), 2.39–2.54 (m, 1H), 2.02–2.15 (m, 1H), 1.67–1.84 (m, 1H), 1.17 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.6, 171.1, 158.3, 136.7, 133.1, 129.9, 121.3, 109.4, 55.4, 42.4, 31.5, 27.9, 15.4; IR ($CHCl_3$) 2961, 2931, 1683, 1609, 1496, 1271, 1246 cm^{-1}.

1-(1-Methyl-1H-indol-3-yl)propan-1-one (3t).[11] Flash column chromatography on neutral alumina (ethyl acetate/hexanes 1:15) gave **3r** (137 mg, 73% yield) as brown solid: mp 69–77 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34–8.41 (m, 1H), 7.71 (s, 1H), 7.31 (s, 3H), 3.85 (s, 3H), 2.87 (q, J = 7.4 Hz, 2H), 1.25 (t, J = 1.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.4, 137.5, 135.1, 126.3, 123.2, 122.5, 122.4, 116.2, 109.6, 33.4, 32.9, 9.0; IR ($CHCl_3$) 2974, 2935, 1645, 1529, 1468, 1374, 1217, 1211, 7899 cm^{-1}; MS (EI) m/z 187 (M)$^+$.

1-(Pyridin-3-yl)propan-1-ol (4u).[23] Flash column chromatography on neutral alumina (ethyl acetate/hexanes 1:15) gave **4s** (35 mg, 25% yield) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.40 (d, J = 4.2 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.26 (dd, J_1 = 5.0 Hz, J_2 = 7.7 Hz, 1H), 4.62 (t, J = 6.5 Hz, 1H), 3.49 (br s, 1H), 1.65–1.91 (m, 2H), 10.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2, 147.6, 140.5, 133.9, 123.5, 73.1, 31.9, 9.9; IR ($CHCl_3$) 3306, 2966, 2932, 1580, 1427, 1097, 1046 cm^{-1}.

1-(1,4,5,6-Tetrahydropyridin-3-yl)propan-1-one (5u). Flash column chromatography on neutral alumina (ethyl acetate/hexanes 1:15) gave **5s** (71 mg, 51% yield) as a liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, J = 5.7 Hz, 1H), 5.35 (br s, 1H), 3.23 (s, 2H), 2.46 (q, J = 7.5 Hz, 2H), 2.34 (t, J = 6.2 Hz, 2H), 1.74–1.86 (m, 2H), 1.10 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.7, 145.6, 106.7, 40.8, 28.7, 20.6, 19.9, 10.6; IR ($CHCl_3$) 3293, 2934, 1664, 1618, 1571, 1525,

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1354, 1239, 1193 cm^{-1}; MS (EI) m/z 139.1 $(M)^+$. Anal. Calcd (%) for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.11; H, 9.45; N, 10.19.

1-(2,3-Dihydrobenzofuran-2-yl)propan-1-ol (5v). Flash column chromatography on silica gel (ethyl acetate/hexanes 1:10) gave **5t** (143 mg, 80% yield; 1.2:1 dr) as a liquid: ^1H NMR ($CDCl_3$, 500 MHz, mixture of two diastereomers) δ 7.13−7.18 (m, 1H), 7.07−7.13 (m, 1H), 6.81−6.86 (m, 1H), 6.77 (t, J = 7.9 Hz, 1H), 4.70−4.76 (m, 0.6H), 4.61−4.67 (m, 0.5H), 3.84−3.95 (m, 0.6H), 3.53−3.63 (m, 0.5H), 3.16−3.30 (m, 1H), 2.99−3.12 (m, 1H), 1.87 (br s, 1H), 1.44−1.71 (m, 2H), 1.01−1.09 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz, mixture of two diastereomers) δ 159.3, 159.0, 127.9, 127.7, 126.9, 126.6, 124.9, 124.8, 120.5, 120.4, 109.3, 109.0, 85.5, 85.4, 75.0, 73.4, 31.8, 29.2, 25.8, 25.0, 10.1, 9.9; IR ($CHCl_3$) 3428, 2964, 2933.5, 2878, 1598, 1481, 1461, 1233, 975, 750 cm^{-1}; MS (EI) m/z 179 $(M)^+$. Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.17; H, 7.98.

1-(4-Aminophenyl)propan-1-one (5w).[33] Flash column chromatography on silica gel (ethyl acetate/hexanes 1:10) gave **5u** (64 mg, 43% yield) as a brown solid: mp 141−144 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 8.7 Hz, 2H), 6.56 (d, J = 8.7 Hz, 2H), 4.12 (br s, 2H), 2.81 (q, J = 7.3 Hz, 2H), 1.11 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.3, 150.9, 130.3, 127.3, 113.6, 31.8, 8.6.

Independent Experiment for Mechanism. The intermediate 3-(dimethylamino)-1-phenylpropan-1-one (**I**) was synthesized according to the literature procedure[20] with 75% yield as oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, J = 6.8 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.7 Hz, 2H), 3.16 (t, J = 7.1 Hz, 2H), 2.76 (t, J = 7.3 Hz, 2H), 2.29 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.0, 136.8, 133.0, 128.5, 127.9, 54.2, 45.4, 36.8; IR ($CHCl_3$) 2973, 2944, 2819, 2769, 1684, 1597, 1580, 1460, 1449, 1380, 1330, 1235, 1207 cm^{-1}.

3-(Dimethylamino)-1-phenylpropan-1-one (**I**) (177 mg, 1 mmol) as obtained from the previous step was dissolved in ethanol (20 mL). 10% Pd/C (106 mg, 10 mol % of **I**) was added, and the heterogeneous mixture was vigorously stirred at room temperature under atmospheric hydrogen pressure (balloon) for 12 h. The reaction mixture was filtered (using a Buchner funnel with sintered disk) and washed with ethanol (2 × 10 mL). The filtrate and washings were combined and concentrated under reduced pressure. After the evaporation, the residue was purified by column chromatography on silica gel (ethyl acetate/hexanes, 1:10) to afford **4a** (120 mg; 88% Yield).

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and ^{13}C NMR spectra of all products). 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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