Palladium-Catalyzed Oxidation of Primary and Secondary Allylic and Benzylic Alcohols

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An efficient procedure for the oxidation of primary and secondary allylic and benzylic alcohols to aldehydes and ketones, respectively, has been achieved using catalytic Pd(OAc)$_2$ in dimethyl sulfoxide (DMSO) with oxygen gas as the sole reoxidant of the palladium. Secondary substrates show increased reaction rates and improved yields with the addition of 2 equiv of NaHCO$_3$. The reactions are free of acetal/ketal and ester byproducts.

Introduction

The palladium-catalyzed oxidation of alcohols was perhaps first described by Berzelius in 1828, when he reported the reduction of most of the palladium from a wet ethanolic solution of K$_2$PdCl$_4$.[1] Recent efforts to make this oxidation synthetically useful have focused on the need to make the process catalytic in palladium, thereby requiring a means of oxidizing the reduced palladium back to the active state. Efforts toward the development of catalytic procedures have concentrated on the use of reoxidants such as metal salts,[2] peroxides,[3] and organic halides[4] or have used the allylic carbonate derivative of the alcohol to be oxidized.[5] The ideal reagent for this purpose is molecular oxygen, which is readily available, inexpensive, and nontoxic and should produce water as the sole byproduct.

Procedures for the palladium-catalyzed oxidation of alcohols using O$_2$ as the reoxidant have been developed, but have been limited as to the type of substrate which can be oxidized or the need for coreagents in order to obtain reasonable yields of the desired carbonyl products.[6] The use of O$_2$ as the sole reoxidant of palladium in the oxidation of alcohols was first reported by Schwartz in 1977.[6a] A catalytic system consisting of 1 mol % PdCl$_2$ and 0.5 equiv of NaOAc in ethylene carbonate at 38 °C with an O$_2$ atmosphere led to the efficient oxidation of saturated primary and secondary alcohols. An attempt to oxidize an olefinic alcohol failed. This was reported to be due to poisoning of the catalyst caused by strong complexation of palladium by the olefin.

In 1994, Echavarren reported that the oxidation of allylic alcohols using a catalyst system consisting of 10 mol % Pd(PPh$_3$)$_4$ in toluene in the presence or absence of both NH$_4$PF$_6$ and K$_2$CO$_3$ at 100 °C under an O$_2$ atmosphere gave moderate to good yields of the corresponding α,β-unsaturated carbonyl compounds.[6b] This system was only applied to allylic substrates. Variations of this procedure were shown to produce diallyl ethers as major byproducts.

Catalytic oxidations of alcohols using O$_2$ as the ultimate stoichiometric oxidant have not been limited to palladium chemistry. Many procedures using a variety of metals and co-oxidants have been reported. Oxygen gas has been used as the sole reoxidant in combination with Ru,[7] Co,[8] Cu,[9] Pt,[10] and Rh[11] catalysts, and procedures using Cu,[12] Ru,[13] Zr,[14] and Co[15] catalysts plus additional co-oxidants in combination with oxygen gas have been reported.

There has also been one report of a stoichiometric procedure for the selective oxidation of allylic alcohols in the presence of other hydroxyl groups.[16] Several

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Table 1. Optimization of the Palladium-Catalyzed Oxidation of *sec*-Phenethyl Alcohol (eq 1)[a]

entry	catalyst	equiv of base	temp (°C)	time (h)	solvent	yield (%)
1	5% $Pd(OAc)_2$	2 Na_2CO_3	80	72	DMSO	70
2	5% $Pd(OAc)_2$	2 Na_2CO_3	80	72	$DMSO/H_2O$[b]	23
3	5% $Pd(OAc)_2$	2 Na_2CO_3	80	72	CH_3CN	7
4	5% $Pd(OAc)_2$	2 $NaHCO_3$	80	72	DMSO	80
5	5% $Pd(OAc)_2$	2 NaOAc	80	72	DMSO	24
6	5% $PdCl_2$	2 Na_2CO_3	80	72	DMSO	19
7	5% $PdCl_2$	2 $NaHCO_3$	80	72	DMSO	40
8	5% $PdCl_2$	2 NaOAc	80	72	DMSO	29
9	5% $Pd(O_2CCF_3)_2$	2 Na_2CO_3	80	72	DMSO	59
10	5% $Pd(O_2CCF_3)_2$	2 $NaHCO_3$	80	72	DMSO	54
11	5% $Pd(O_2CCF_3)_2$	2 NaOAc	80	72	DMSO	33
12	5% $Pd(dba)_2$	2 Na_2CO_3	80	72	DMSO	17
13	5% $Pd(dba)_2$	2 $NaHCO_3$	80	72	DMSO	15
14	5% $Pd(dba)_2$	2 NaOAc	80	72	DMSO	21
15	5% $Pd(OAc)_2$	2 $NaHCO_3$	60	72	DMSO	56
16	5% $Pd(OAc)_2$	2 $KHCO_3$	60	72	DMSO	37
17	5% $Pd(OAc)_2$	2 Na_2CO_3	60	72	DMSO	43
18	5% $Pd(OAc)_2$	2 K_2CO_3	60	72	DMSO	37
19	5% $Pd(OAc)_2$	2 $LiOAc·2H_2O$	80	72	DMSO	48
20	5% $Pd(OAc)_2$	2 KOAc	80	72	DMSO	24
21	5% $Pd(OAc)_2$	2 CsOAc	80	72	DMSO	24
22	5% $Pd(OAc)_2$	2 $KHCO_3$	80	72	DMSO	64
23	5% $Pd(OAc)_2$	2 Li_2CO_3	80	72	DMSO	57
24	5% $Pd(OAc)_2$	2 K_2CO_3	80	72	DMSO	66
25	5% $Pd(OAc)_2$	2 Et_3N	80	72	DMSO	14
26	5% $Pd(OAc)_2$	2 $NaHCO_3$	80	48	DMSO	65
27	5% $Pd(OAc)_2$	2 $KHCO_3$	80	48	DMSO	69
28	5% $Pd(OAc)_2$	2 Na_2CO_3	80	48	DMSO	74
29	5% $Pd(OAc)_2$	2 K_2CO_3	80	48	DMSO	67
30	5% $Pd(OAc)_2$	2 $NaHCO_3$	80	24	DMSO	91
31	5% $Pd(OAc)_2$	2 $KHCO_3$	80	24	DMSO	74
32	5% $Pd(OAc)_2$	2 Na_2CO_3	80	24	DMSO	50
33	5% $Pd(OAc)_2$	2 K_2CO_3	80	24	DMSO	66
34	5% $Pd(OAc)_2$	2 K_2CO_3	80	12	DMSO	77
35	5% $Pd(OAc)_2$		80	24	DMSO	30
36	5% $Pd(OAc)_2$	0.1 $NaHCO_3$	80	24	DMSO	44
37	5% $Pd(OAc)_2$	0.5 $HaHCO_3$	80	24	DMSO	65
38	5% $Pd(OAc)_2$	1 $NaHCO_3$	80	24	DMSO	83
39	5% $Pd(OAc)_2$	2 $NaHCO_3$	80	24	0.5 mL of DMSO	61
40	5% $Pd(OAc)_2$	2 $NaHCO_3$	80	24	0.1 mL of DMSO	62

[a] All reactions were conducted using 1 mmol of substrate in 1 mL of solvent unless otherwise stated. [b] 9:1 mixture of $DMSO/H_2O$.

unsaturated di- and trihydroxylated substrates were treated with 1 equiv of $Pd(OAc)_2$ or $PdCl_2$ and 1.2 equiv of NaOAc at room temperature in dimethylformamide (DMF) containing 1% of water to achieve oxidations with high selectivity and yield.

The goal of our work was to develop a simple general procedure for the palladium-catalyzed oxidation of allylic and benzylic alcohols, since a satisfactory procedure for the palladium-catalyzed oxidation of saturated primary and secondary alcohols, using oxygen gas as the sole reoxidant of the palladium, had been put forth by Schwartz.[6a] Previous work in this research group[17] and others[18] has suggested that a catalyst consisting of 5 mol % $Pd(OAc)_2$ in DMSO with an O_2 atmosphere leads to high turnovers of the palladium(II) catalyst. This same catalyst system has indeed proven to be effective for the oxidation of allylic and benzylic alcohols as herein described.

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Results and Discussion

Our investigation began with an effort to optimize reaction conditions for the oxidation of alcohols using catalytic palladium and O_2 gas as the stoichiometric reoxidant. *sec*-Phenethyl alcohol was chosen as a model substrate for the optimization process (eq 1, Table 1).
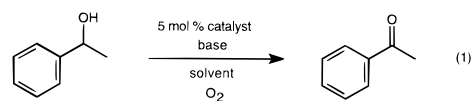
The reaction yields were determined by gas chromatographic analysis using an internal standard unless otherwise stated. Randomly selected reactions were isolated to compare the isolated yields to those determined by gas chromatography. In each case, the isolated yield was within 4% of the value determined by gas chromatography.

A set of initial conditions was selected consisting of 1 mmol of substrate alcohol, 5 mol % $Pd(OAc)_2$, and 2 equiv of Na_2CO_3 in 1 mL of solvent under an atmosphere of oxygen with stirring at 80 °C for 72 h. The first variable examined was the solvent (Table 1, entries 1−3). Previous work by this group[17] and others[18] suggested that DMSO is likely to be the solvent of choice for such palladium(II)-catalyzed transformations using O_2 as the reoxidant. Nevertheless, other solvents that displayed moderate results in other Pd(II)-catalyzed transforma-

tions were examined. The use of DMSO as the solvent led to complete conversion of the starting alcohol and afforded the desired ketone in 70% yield. Acetonitrile or a 9:1 mixture of DMSO/H$_2$O showed greatly diminished reactivity and yields under the selected reaction conditions. As expected, DMSO appears to be the most effective solvent for oxidation of the chosen substrate under the selected reaction conditions.

The next task was to find the best catalyst for the transformation. A series of four catalysts was examined with three commonly employed inorganic bases (entries 1 and 4−14). Three bases were examined to prevent a catalyst from being excluded because it did not perform well with a particular base. A survey of the results show Pd(OAc)$_2$ to be the most effective catalyst for the reaction under the various conditions examined. The other palladium(II) salts examined, PdCl$_2$ and Pd(O$_2$CCF$_3$)$_2$, gave moderate results, while the palladium(0) complex, Pd-(dba)$_2$, gave poor results.

The reaction temperature was the next variable examined (compare entries 1, 4, 22 and 24 with 15−18). The best reactions from those presented above were complete within the allowed 3 day reaction time. The temperature of a series of reactions was reduced from 80 to 60 °C to see if the higher temperature is indeed necessary to achieve complete reaction in the allotted time. Again, a series of commonly used inorganic bases was employed, including a couple not examined earlier. The results indicate that the higher temperature is necessary to achieve complete conversion of starting material and the highest yields of product. None of the reactions at 60 °C had reached completion in the 72 h reaction period.

Having established what appeared to be the optimal solvent, catalyst, and temperature, attention was turned toward the base. A series of inorganic bases and one organic base, triethylamine, were examined (entries 1, 4, 5, and 19−25). From these data, NaHCO$_3$, KHCO$_3$, Na$_2$CO$_3$, and K$_2$CO$_3$ were observed to afford the highest yields. The results from these four bases were similar enough that one could not select a single best base under the reaction conditions examined.

The four bases observed above were each used in a series of experiments designed to examine the reaction time (entries 1, 4, 22, 24, and 26−34). Up to this point, the reactions were allowed to stir at 80 °C for 72 h regardless of how long the reaction may have taken to reach completion. All of the optimal experiments chosen showed complete conversion of starting material, but the optimal reaction time had not been determined. Preliminary data indicated that the product is not completely stable under the reaction conditions. In several instances, the product yields were observed to decrease over time. This is most likely due to base-induced condensation reactions of the product, although no products of this type have actually been isolated. With shorter reaction times, differences in the reactivity and yields of the different bases might also be established. The highest yield (91%) in fact was obtained using NaHCO$_3$ and only a 24 h reaction time (entry 30).

The stoichiometry of the base was examined using a variety of concentrations of NaHCO$_3$, from none to 2 molar equiv (entries 4 and 35−38). The yields of the desired product increased as the amount of NaHCO$_3$ increased. Above 2 equiv, the reaction mixture became

clearly heterogeneous and magnetic stirring was impeded.

Finally, the concentration of the reaction was examined (entries 4, 39, and 40). All previous reactions had employed 1 mL of solvent for 1 mmol of substrate. Reducing the amount of solvent would be desirable to limit the amount of waste generation from this procedure, especially if the oxidation were performed on a larger scale. Reducing the amount of solvent made the reactions clearly heterogeneous, and magnetic stirring was impeded. The yields for the reactions run at higher concentrations were diminished compared to those at the standard concentration.

The final optimized reaction conditions for the palladium(II)-catalyzed oxidation of 1 mmol of *sec*-phenethyl alcohol were determined to be 5 mol % Pd(OAc)$_2$ and 2 equiv of NaHCO$_3$ in 1 mL of DMSO for 24 h at 80 °C under an atmosphere of O$_2$ (procedure A). The goal was now to apply the optimized conditions to a variety of primary and secondary allylic and benzylic alcohols (Table 2).
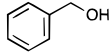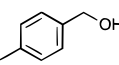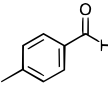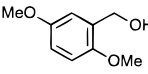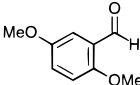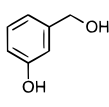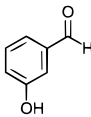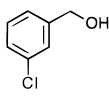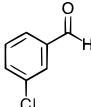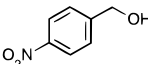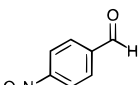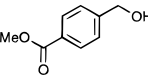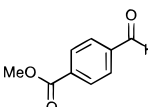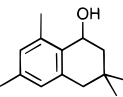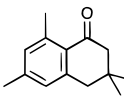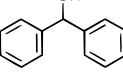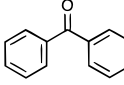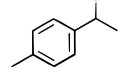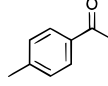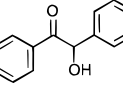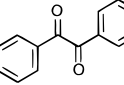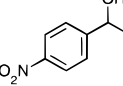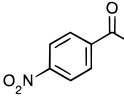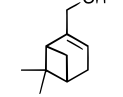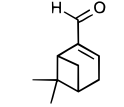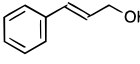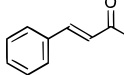
Application of the optimized reaction conditions to benzyl alcohol lead to a bad mixture of products, although the desired benzaldehyde was the major component of the mixture. Upon removal of the base from the reaction, benzaldehyde was obtained cleanly in a 90% yield as determined by gas chromatography. This problem of the optimized conditions leading to significant byproduct formation was prevalent with most primary alcohol substrates; so this base-free procedure was adopted as an alternative procedure (procedure B). Procedure A works well for secondary allylic and benzylic substrates. The base present in procedure A tends to promote the generation of side products when primary allylic and benzylic substrates are used; therefore, procedure B was developed. Procedure B also works on most secondary allylic and benzylic alcohols, but the rates of reaction are generally significantly slower in the absence of the base.

In general, the reactions of primary benzylic alcohols were very clean using procedure B (entries 1−7). An interesting electronic effect seems to exist for these benzylic systems. Comparing benzyl alcohol (entry 1) to the benzylic alcohols with electron-releasing substituents (entries 2 and 3), we found that the reaction times for the electron-rich arenes were significantly shorter. The oxidation of *m*-hydroxybenzyl alcohol required a longer reaction time (entry 4), which might be attributed to coo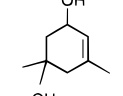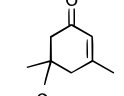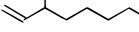rdination of the phenoxide to the palladium catalyst, thereby decreasing the rate of reaction. Primary benzylic systems with electron-withdrawing groups (entries 5−7) also required longer reaction times and gave lower yields. Most of the reactions of these substrates did not go to completion. In the case of *p*-nitrobenzyl alcohol (entry 6), a significant amount of the product *p*-nitrobenzaldehyde (>20%) was converted to nitrobenzene, presumably by palladium-catalyzed decarbonylation.[19] Increasing the temperature and/or adding base to these reactions did not improve the yields.

Secondary benzylic substrates generally gave very clean, high-yielding reactions (entries 8−12). The addition of base served to increase the rate of reaction without leading to significant amounts of side-products. In some cases, the rate enhancement was substantial. For ex-

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Table 2. Oxidation of Primary and Secondary Allylic and Benzylic Alcohols

entry	substrate	product	procedure	time (d)	% isolated yield
1	benzyl alcohol	benzaldehyde	B	2	90[a]
2	p-methylbenzyl alcohol	p-tolualdehyde	B	1	92
3	2,5-dimethoxybenzyl alcohol	2,5-dimethoxybenzaldehyde	B	0.5	95
4	3-hydroxybenzyl alcohol	3-hydroxybenzaldehyde	B	3	66
5	3-chlorobenzyl alcohol	3-chlorobenzaldehyde	B	3	48[a]
6	4-nitrobenzyl alcohol	4-nitrobenzaldehyde	B	3	57
7	methyl 4-(hydroxymethyl)benzoate	methyl 4-formylbenzoate	B	3	59
8	tetralin alcohol	tetralone	A	7	96
9	benzhydrol	benzophenone	A	1	95
10	1-(p-tolyl)ethanol	4'-methylacetophenone	A	1	81
11	benzoin	benzil	A	1	83
12	1-(4-nitrophenyl)ethanol	p-nitroacetophenone	A	3	57
13	myrtenol	myrtenal	B	2	50[a]
14	cinnamyl alcohol	cinnamaldehyde	B	1.5	69[b]
15	2-cyclohexen-1-ol	2-cyclohexen-1-one	B	1	42[a,c]
16	isophorol	isophorone	A	2	67
17	1-octen-3-ol	1-octen-3-one	B	1	53[a]

[a] Yield determined by gas chromatography. [b] Reaction used 1 mmol of substrate in 5 mL of DMSO. [c] Phenol observed in 37% yield by gas chromatography.

ample, the oxidation of benzoin (entry 11) with base is complete in 1 day, but without base the reaction requires more than 5 days to reach completion. The electronic effect observed for the primary benzylic systems also seems to be prevalent in the case of secondary benzylic systems. *p*-Nitroacetophenone (entry 12) required a longer reaction time and gave a decreased yield when compared to more electron-rich secondary benzylic substrates.

In general, reactions of primary and secondary allylic substrates were not as clean as the benzylic systems and lead to lower yields (entries 13−17). Allylic alcohols have been shown to form diallyl ethers under conditions similar to those used for this oxidation, although none have been observed using our process.[6b] Some modifications to the general procedure were made to optimize the yields for some allylic substrates. For example, cinnamyl alcohol (entry 14) gave the best results when the reaction was diluted to 1 mmol of substrate in 5 mL of DMSO. The increased yield can possibly be attributed to the fact that we are disfavoring intermolecular processes by dilution of the reaction mixture. Using procedure A on 2-cyclohexen-1-ol led to phenol as the major product. By using procedure B with no base, the yield of 2-cyclohexen-1-one was increased to 42%, but phenol was still observed in 37% yield (entry 15).

While most reactions were run on just a 1 mmol scale, the oxidation conditions also proved successful on a larger scale. A 10 mmol reaction of 2,5-dimethoxybenzyl alcohol using procedure B provided the aldehyde in an 81% isolated yield and a 100 mmol reaction of benzhydrol using procedure A provided the corresponding ketone in an 83% isolated yield.

This catalytic process is believed to proceed via coordination of the alcohol substrate to the palladium(II) catalyst, followed by β-hydride elimination to form the carbonyl product and a palladium hydride species. The palladium hydride species then undergoes reductive elimination to form palladium(0). Molecular oxygen oxidizes the palladium(0) species back to the active state, thereby allowing the cycle to continue.

Conclusion

An efficient system for the palladium-catalyzed oxidation of primary and secondary allylic and benzylic alcohols has been developed using O_2 as the sole reoxidant of the palladium. The conditions have been applied to a wide variety of substrates producing the desired carbonyl compounds in moderate to excellent yields. The reaction has been shown to be effective on a 100 mmol scale with no change in reactivity or yield.

Experimental Section

General Procedures. All ^1H and ^{13}C NMR spectra were recorded at 400 and 100.5 MHz, respectively. Thin-layer chromatography (TLC) was performed using commercially prepared 60 mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm) or basic KMnO₄ solution [3 g of KMnO₄ + 20 g of K₂CO₃ + 5 mL of NaOH (5%) + 300 mL of H₂O]. All melting points are uncorrected.

Reagents. All reagents were used directly as obtained commercially unless otherwise stated. KMnO₄, K₂CO₃, NaOH, NaHCO₃, benzophenone, and dimethyl sulfoxide were obtained from Fischer Scientific. CeCl₃, benzyl alcohol, benzaldehyde, *p*-methylbenzyl alcohol, *p*-tolualdehyde, 2,5-dimethoxybenzyl

alcohol, 2,5-dimethoxybenzaldehyde, 3-hydroxybenzyl alcohol, 3-hydroxybenzaldehyde, 3-chlorobenzyl alcohol, 3-chlorobenzaldehyde, 4-nitrobenzyl alcohol, 4-nitrobenzaldehyde, methyl 4-(hydroxymethyl)benzoate, methyl 4-formylbenzoate, 3,3,6,8-tetramethyltetralone, benzhydrol, methyl *p*-tolylcarbinol, 4′-methylacetophenone, benzoin, benzil, 4′-nitroacetophenone, myrtenol, myrtenal, cinnamyl alcohol, cinnamaldehyde, 2-cyclohexen-1-ol, 2-cyclohexen-1-one, isophorone, and 1-octen-3-ol were obtained from Aldrich Chemical Co. Palladium acetate was obtained from Johnson Matthey, Inc., and Kawaken Fine Chemicals Co., Ltd.

General Procedure for Alcohol Oxidation. To a mixture of substrate (1 mmol) in DMSO (1 mL) were added 5 mol % Pd(OAc)$_2$ and NaHCO$_3$ (2 equiv where indicated). The flask was equipped with a magnetic stir bar and purged with oxygen gas. A septum was placed over the opening of the flask and a balloon of oxygen gas attached to the flask through the septum by a needle. The reaction was stirred at 80 °C until the reaction had reached completion as indicated by thin-layer chromatographic analysis. The reaction mixture was cooled to room temperature and then placed directly onto a column of silica gel and eluted with an appropriate combination of hexane/ethyl acetate. The fractions containing the product were combined and concentrated in vacuo.

The products of Table 2, entries 2−4, 6−12, 14, and 16, were identified by comparing their ^{1}H and ^{13}C NMR spectra and melting points (where possible) with authentic samples. Appropriate literature references to these data follow. The yields for the products of entries 1, 5, 13, 15, and 17 were determined by gas chromatography using authentic samples and appropriate correction factors.

***p*-Methylbenzaldehyde** (entry 2). ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 21.86, 129.73, 129.84, 134.22, 145.55, 191.97. The ^{1}H NMR and IR spectral data match those found in the literature.[20]

2,5-Dimethoxybenzaldehyde (entry 3). Mp: 50−52 °C. The ^{1}H and ^{13}C NMR and IR spectral data match those found in the literature.[21]

3-Hydroxybenzaldehyde (entry 4). Mp: 103−105 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.92 (br s, 1 H), 7.16 (dt, J = 8.0, 4.0 Hz, 1 H), 7.39−7.47 (m, 3 H), 9.96 (s, 1 H). The ^{13}C NMR spectral data match those found in the literature.[22]

4-Nitrobenzaldehyde (entry 6). Mp: 106−107 °C. The ^{1}H[23] and ^{13}C[24] NMR spectral data match those found in the literature.

Methyl 4-formylbenzoate (entry 7). Mp: 61−62 °C. The ^{1}H and ^{13}C NMR and IR spectral data match those found in the literature.[25]

3,3,6,8-Tetramethyltetralone (entry 8). Mp: 58−59 °C. The ^{1}H and ^{13}C NMR spectral data match those found in the literature.[26]

Benzophenone (entry 9). Mp: 49−51 °C. The ^{1}H and ^{13}C NMR spectral data match those found in the literature.[27]

4-Methylacetophenone (entry 10). ^{13}C NMR (100.5 MHz, CDCl$_3$): δ 21.65, 26.56, 128.47, 129.27, 134.72, 143.91, 198.88. The ^{1}H NMR and IR spectral data match those found in the literature.[28]

Benzil (entry 11). Mp: 94−95 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.50 (t, J = 8.0 Hz, 4 H), 7.66 (t, J = 8.0 Hz, 2 H), 7.98 (d, J = 8.0 Hz, 4 H). The ^{13}C NMR spectral data match those found in the literature.[29]

4-Nitroacetophenone (entry 12). Mp: 79−80 °C. The ^{1}H[30] and ^{13}C[31] NMR match those found in the literature.

***trans*-Cinnamaldehyde** (entry 14). ^{13}C NMR (100.5 MHz, CDCl$_3$): δ 128.57, 128.59, 129.16, 131.34, 134.04, 152.86, 193.77. The ^{1}H NMR and IR spectral data match those found in the literature.[32]

Isophorone (entry 16). ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.04 (s, 6 H), 1.95 (d, J = 0.44 Hz, 3 H), 2.19 (s, 4 H), 5.86 (t, J = 1.28 Hz, 1 H). The ^{13}C NMR spectral data match those found in the literature.[33]

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