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α-Chymotrypsin-Induced Acetalization of Aldehydes and Ketones with Alcohols

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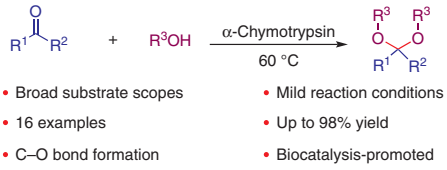

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Abstract This is the first report of a simple and general method for acetalization of aldehydes via an α-chymotrypsin-induced reaction under mild conditions. A broad range of aromatic and heteroaromatic aldehydes have been acetalized under neutral conditions in good yields using a catalytic amount of chymotrypsin.

Key words α-chymotrypsin, acetalization, biocatalysis, green chemistry

The carbonyl group is one of the most important functional groups in contemporary organic synthesis.[1,2] The diverse reactivity of the carbonyl group allows for its facile transformation into various other functional groups, including imines, alcohols, and olefins. Protection of carbonyl compounds like aldehydes and ketones via acetal or ketal formation has been a common and powerful tool in multistep synthesis.[3] In addition, the acetal functional group can also be used as a reaction intermediate.[4] The traditional way to synthesize acetal or ketal compounds is the use of acids, metals, or ionic solvents,[5] for example, CF_3CO_2Na,[6] $CuBF_4$,[7] $Rh_2(CO)_4Cl_2$,[8] Rh,[9] and Pd(II).[10] Recently, research efforts have been devoted to developing synthetic strategies involving metal-organic frameworks,[11] electrochemistry,[12] and photocatalysis.[13] However, these procedures have limited scope for acetals, like extended reaction times, or can cause potential metal and chemical pollution.

Biocatalysis offers an alternative approach to functional compounds with high efficiency and is environmentally friendly. As a biodegradable green biocatalyst in organic synthesis, enzymes have many fascinating features, such as excellent regio-, chemo-, and stereoselectivity, high catalytic efficiency, mild reaction conditions, fewer by-products, and fewer synthetic steps, compared to conventional chemical catalysis.[14] Additionally, it is the advantages of these enzymes that are frequently reported in organic reactions catalyzed by enzymes.[15–20] Due to the aforementioned properties possessed by enzymes, researchers are currently focusing on the combination of enzymes and conventional catalysts to develop organic reactions that cannot be achieved by a single catalyst, such as photoenzymatic ones.[21–23] As a well-studied hydrolase, α-chymotrypsin has been demonstrated that it can keep its activity in organic solvents.[24] Herein, we report a general and direct acetalization method for aldehydes with alcohols using a biocatalytic process under neutral conditions.

A model reaction was investigated using readily available and reasonably priced 4-nitrobenzaldehyde (**1a**) and methanol (**2a**) by varying enzyme sources, the amount of enzyme, and temperatures to obtain the optimum reaction conditions, the results of which are summarized in Table 1. Initially, the reaction was performed using excess methanol as a solvent without any catalyst at 60 °C (Table 1, entry 1). However, these reaction conditions were ineffective. Different enzyme sources were chosen when the reaction was performed under specific conditions for 28 hours. When other enzymes were selected as catalysts, such as amano lipase A from *Aspergillus niger*, pepsin from porcine gastric mucosa, lipase from porcine pancreas, amano lipase M from *Mucor javanicus*, and papain from papayalatex, no products were obtained (entries 2–6). Nevertheless, bovine trypsin showed low activity toward this reaction (entry 7). Surprisingly, α-chymotrypsin possessed excellent catalytic activity (entry 8).

These results indicate the necessity of a catalyst for this reaction. Furthermore, the effect of the amount of α-chymotrypsin was also investigated. In this study, we performed numerous experiments with the catalyst amount varying in the range from 0 to 16000 U under similar conditions (Table 1, entry 1, entries 8–12). When the amount of

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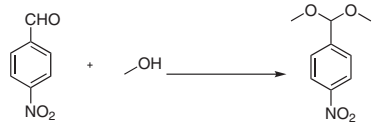
Table 1 Optimization of the Reaction Conditions[a]



1a **2a** **3a**

Entry	Catalyst (U)	Temp (°C)	Time (h)	Added H_2O (μL)	Yield (%)[b]
1	blank	60	28	0	no reaction
2[c]	amano lipase A from *Aspergillus niger* (300000 U/g)	60	28	0	no reaction
3[c]	pepsin from porcine gastric mucosa (601 U/mg)	60	28	0	no reaction
4[c]	lipase from porcine pancreas (30-90 U/mg)	60	28	0	no reaction
5[c]	amano lipase M from *Mucor javanicus* (> =10000 U/g)	60	28	0	no reaction
6[c]	papain from papayalatex (1.5–10 U/mg)	60	28	0	no reaction
7[c]	bovine trypsin (> =2500 U/mg)	60	28	0	20
8[c]	α-chymotrypsin (800 U/mg)	60	28	0	88
9	α-chymotrypsin (1600 U)	60	28	0	78
10	α-chymotrypsin (4000 U)	60	28	0	88
11	α-chymotrypsin (8000 U)	60	28	0	89
12	α-chymotrypsin (16000 U)	60	28	0	90
13	α-chymotrypsin (4000 U)	25	28	0	28
14	α-chymotrypsin (4000 U)	40	28	0	45
15	α-chymotrypsin (4000 U)	50	28	0	56
16	α-chymotrypsin (4000 U)	70	28	0	70
17	α-chymotrypsin (4000 U)	60	28	20	83
18	α-chymotrypsin (4000 U)	60	28	50	74
19	α-chymotrypsin (4000 U)	60	28	100	61
20	α-chymotrypsin (4000 U)	60	28	200	48
21	α-chymotrypsin (4000 U)	60	12	0	60
22	α-chymotrypsin (4000 U)	60	24	0	77
23	α-chymotrypsin (4000 U)	60	28	0	88
24	α-chymotrypsin (4000 U)	60	30	0	93
25	α-chymotrypsin (4000 U)	60	36	0	93
26	α-chymotrypsin (4000 U)	60	48	0	93

[a] Reaction conditions: **1a** (0.2 mmol), 2 mL of **2a** for a specific time.
[b] Yields refer to isolated products.
[c] Enzyme (15 mg).

catalyst was 4000 U, the yield of the reaction was 88% (entry 10). An increase in the amount of catalyst resulted in the yield remaining nearly constant (entries 11, 12). Therefore, 4000 U was selected as the optimal amount for the reaction. Thereafter, the model reaction was screened using α-chymotrypsin as the catalyst and excess methanol as the solvent at different temperatures (entry 10, entries 13–16). Product **3a** was obtained in excellent yield at 60 °C. α-chymotrypsin showed low activity toward this reaction when the temperature was too high or too low. When the temperature was too low, the enzyme could not fully exert its catalytic activity. When the temperature was too high, the enzyme became deactivated. The aforementioned results indicate that the optimal temperature was 60 °C for this reaction.

Water content strongly affects the catalytic behavior of an enzyme in non-aqueous media. Thus, the effect of water content on the reaction yield was investigated. The yield was found to decrease with increasing water content. Since the formation and hydrolysis of acetal are in equilibrium, addition of water inhibits the progress of the reaction. Finally, the duration of the reaction between 4-nitrobenz-

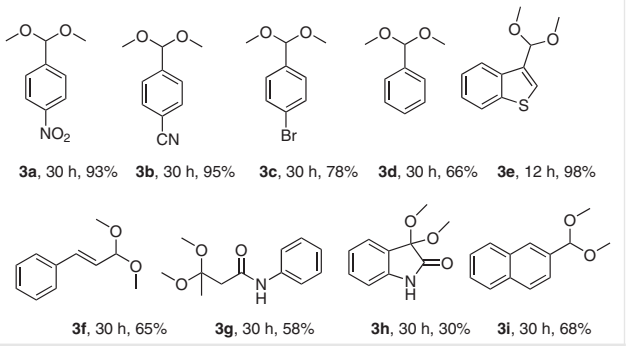


Figure 1 The range of aldehydes and ketones

aldehyde and methanol catalyzed by α-chymotrypsin was investigated. Under the optimal conditions, the yield of the product was 93% after 30 hours (Table 1, entry 24). As the reaction time was prolonged, there was no significant increase in yield; thus, 30 hours was selected as the optimal reaction time. In summary, the optimal conditions were as follows: 0.2 mmol of aldehyde was reacted with excess methanol, catalyzed by 4000 U of α-chymotrypsin at 60 °C for 30 hours.

The substrate scope was further investigated as shown in Figures 1 and 2. Aromatic aldehydes containing electron-donating and electron-withdrawing substituents were studied; the reaction worked well with electron-withdrawing substituents (Figure 1, 3a–d). For electron-donating substituents, the pure products could not be obtained because the formation and hydrolysis of acetal are in equilibrium and the product decomposed into raw materials during post-treatment. Moreover, benzothiophene-3-carbaldehyde and cinnamaldehyde were chosen to investigate the reaction scope of heterocyclic and aliphatic aldehydes. Both substrates produced the target products in high yields (Figure 1, 3e, 3f). Furthermore, carbonyl-containing substrates, such as acetoacetanilide and isatin were acetalized in moderate yields (Figure 1, 3g, 3h). Finally, 2-naphthaldehyde was selected to investigate whether the reaction was also applicable to naphthalene rings; the 68% yield suggested successful reaction (Figure 1, 3i).

The reaction was also compatible with ethanol, which could react with several aldehydes to form the target acetals in high yields (Figure 2, 3j, 3k, 3l). However, when propanol was used as a protecting group, the yield was reduced (Figure 2, 3m). Moreover, this reaction was not limited to methanol or ethanol as a protecting group, because ethylene glycol also delivered acetals in medium yield (Figure 2, 3n). To further assess the usefulness of our protocol, we considered the effect of space. The steric hindrance of aldehyde protection usually causes lower yields, and therefore,

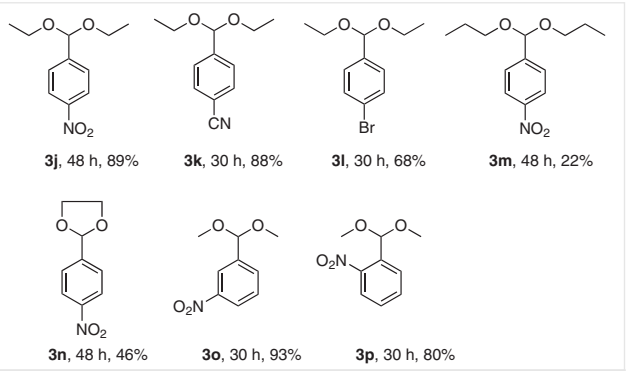
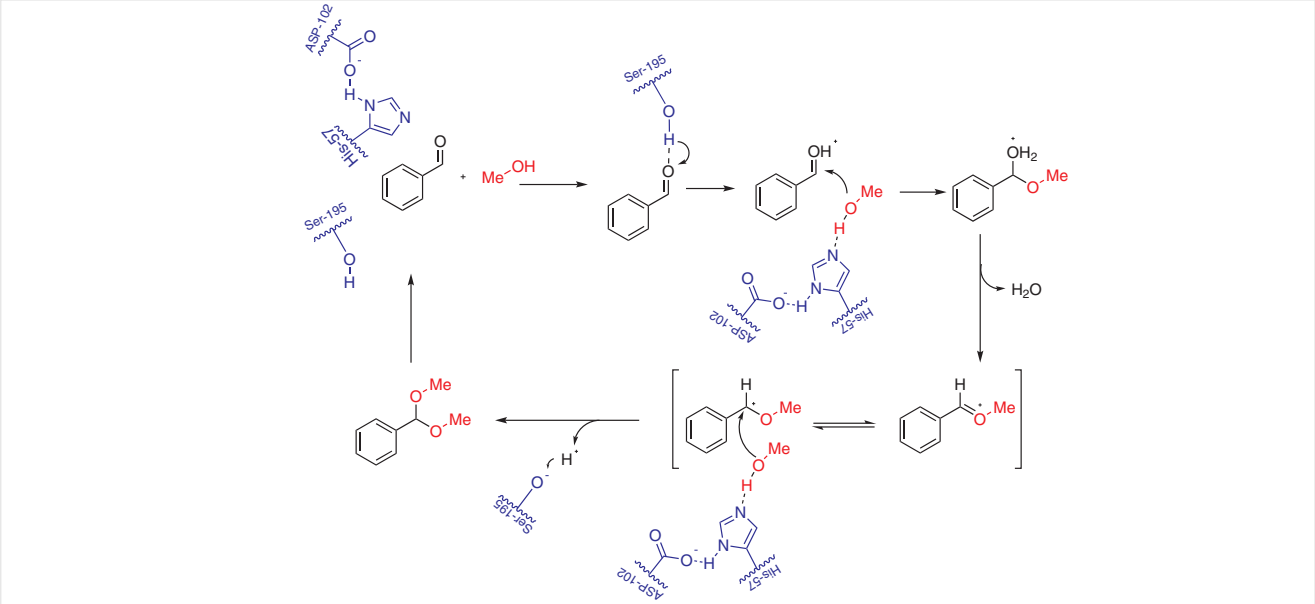


Figure 2 The range of alcohols and the effects of space



Scheme 1 Possible reaction mechanisms for acetalization

more drastic reaction conditions are required. However, *ortho*- and *meta*-substituted aldehydes could smoothly afford the target acetal products in high yield under standard conditions (Figure 2, 3o, 3p). Thus, these results revealed that the present α-chymoprotein catalyzed acetalization strategy is feasible.

Based on our experiments and literature data,[24–33] a possible reaction mechanism is proposed for the formation of the acetal compounds, as depicted in Scheme 1. Initially, the carbonyl group is effectively activated by Ser-195 residue of the enzyme. Thereafter, the alcohol attacks the carbonyl group of aldehyde. Afterwards, intermediates are formed by dehydration. Finally, the alcohol attacks the intermediate to produce the target product.

In conclusion, herein, a convenient α-chymotrypsin-induced method for the acetalization of aldehydes and ketones with alcohols was developed. A series of acetal compounds were synthesized in good yields. The method has the advantages readily available materials and catalysts, low process cost, low toxicity, simple operation and post-treatment, and mild reaction conditions.

α-Chymotrypsin-Induced Acetalization of Aldehydes and Ketones with Alcohols; General Procedure

The respective aldehyde or ketone (0.2 mmol) and α-chymotrypsin (4000 U) were added to the corresponding alcohol (2.0 mL) and stirred at 60 °C for the specified reaction time and monitored by TLC. The excess alcohol was evaporated under reduced pressure and the residue was purified by column chromatography. The eluent used for column chromatography was EtOAc and PE in a volume ratio of 1:4; column chromatography was generally performed on silica gel (200–300 mesh).

1-(Dimethoxymethyl)-4-nitrobenzene (3a)[34]

Yellow liquid; yield: 36.6 mg (93%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 8.8 Hz, 2 H), 7.65 (d, *J* = 8.8 Hz, 2 H), 5.49 (s, 1 H), 3.35 (s, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 148.0, 145.1, 127.8, 123.4, 101.6, 52.7.

4-(Dimethoxymethyl)benzonitrile (3b)[35]

Yellow liquid; yield: 33.4 mg (95%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69–7.65 (m, 2 H), 7.58 (d, *J* = 8.1 Hz, 2 H), 5.43 (s, 1 H), 3.33 (s, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 143.2, 132.1, 127.6, 118.7, 112.3, 101.8, 52.7.

1-Bromo-4-(dimethoxymethyl)benzene (3c)[36]

Yellow liquid; yield: 35.7 mg (78%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 8.5 Hz, 2 H), 7.32 (d, *J* = 8.4 Hz, 2 H), 5.35 (s, 1 H), 3.31 (s, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 137.1, 131.3, 128.5, 122.5, 102.3, 52.6.

(Dimethoxymethyl)benzene (3d)[34]

Yellow liquid; yield: 20 mg (66%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 7.0 Hz, 2 H), 7.36 (dd, *J* = 11.4, 4.5 Hz, 2 H), 7.30 (s, 1 H), 5.38 (s, 1 H), 3.31 (s, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 138.1, 128.5, 128.2, 126.7, 103.2, 52.7.

3-(Dimethoxymethyl)benzo[*b*]thiophene (3e)[37]

Yellow liquid; yield: 40.7 mg (98%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.98 (dd, *J* = 7.3, 1.2 Hz, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.55 (s, 1 H), 7.35 (m, *J* = 16.3, 7.2, 1.2 Hz, 2 H), 5.70 (d, *J* = 0.9 Hz, 1 H), 3.33 (s, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 140.7, 137.1, 133.5, 125.6, 124.5, 124.3, 122.9, 122.7, 99.9, 52.4.

(*E*)-(3,3-Dimethoxyprop-1-en-1-yl)benzene (3f)[34]

Yellow liquid; yield: 23.1 mg (65%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 8.5 Hz, 2 H), 7.32 (t, *J* = 7.5 Hz, 2 H), 7.26 (d, *J* = 8.3 Hz, 1 H), 6.72 (d, *J* = 16.1 Hz, 1 H), 6.15 (dd, *J* = 16.2, 4.9 Hz, 1 H), 4.96 (d, *J* = 5.9 Hz, 1 H), 3.38 (s, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 136.1, 133.6, 128.6, 128.2, 126.8, 125.758, 103.0, 52.8.

3,3-Dimethoxy-*N*-phenylbutanamide (3g)[38]

White solid; yield: 26.1 mg (58%); mp 79.2–81.9 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.45 (s, 1 H), 7.50 (d, *J* = 7.6 Hz, 2 H), 7.30 (dd, *J* = 21.9, 13.5 Hz, 2 H), 7.15–7.02 (m, 1 H), 3.29 (s, 6 H), 2.74 (s, 2 H), 1.45 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.9, 138.0, 129.0, 124.1, 119.7, 100.1, 48.6, 46.0, 21.3.

3,3-Dimethoxyindolin-2-one (3h)[39]

Yellow solid; yield: 11.8 mg (30%); mp 75.0–76.1 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.61 (s, 1 H), 7.40 (dd, *J* = 7.5, 1.2 Hz, 1 H), 7.30 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.08 (dt, *J* = 8.5, 4.3 Hz, 1 H), 6.90 (dd, *J* = 7.8, 0.8 Hz, 1 H), 3.58 (s, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.0, 140.5, 130.8, 125.2, 122.8, 110.9, 97.3, 50.9.

2-(Dimethoxymethyl)naphthalene (3i)[36]

Yellow liquid; yield: 26.4 mg (68%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.93 (s, 1 H), 7.88–7.77 (m, 3 H), 7.55 (d, *J* = 8.8 Hz, 1 H), 7.47 (dd, *J* = 6.2, 3.2 Hz, 2 H), 5.54 (s, 1 H), 3.36 (s, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 135.5, 133.5, 133.1, 128.4, 128.1, 127.7, 126.3, 126.2, 126.1, 124.4, 52.8.

1-(Diethoxymethyl)-4-nitrobenzene (3j)[34]

Yellow liquid; yield: 40 mg (89%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 5.1 Hz, 2 H), 7.67 (d, *J* = 8.7 Hz, 2 H), 5.58 (s, 1 H), 3.84–3.31 (m, 4 H), 1.26 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 147.9, 146.1, 127.7, 123.4, 100.1, 61.3, 15.1.

4-(Diethoxymethyl)benzonitrile (3k)[40]

Yellow liquid; yield: 35.8 mg (88%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8.4 Hz, 2 H), 7.60 (d, *J* = 8.2 Hz, 2 H), 5.53 (s, 1 H), 3.70–3.44 (m, 4 H), 1.25 (t, *J* = 7.0 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 144.3, 132.1, 127.5, 118.8, 112.1, 100.3, 61.3, 15.1.

1-Bromo-4-(diethoxymethyl)benzene (3l)[41]

Yellow liquid; yield: 34.5 mg (68%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 8.4 Hz, 2 H), 7.35 (d, *J* = 8.4 Hz, 2 H), 5.46 (s, 1 H), 3.70–3.40 (m, 4 H), 1.23 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 138.2, 131.3, 128.5, 122.3, 100.8, 61.0, 15.2.

1-(Dipropoxymethyl)-4-nitrobenzene (3m)[42]

Yellow liquid; yield: 11.1 mg (22%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 10.9 Hz, 2 H), 7.66 (d, *J* = 8.7 Hz, 2 H), 5.58 (s, 1 H), 3.47 (qt, *J* = 9.3, 6.6 Hz, 4 H), 1.73–1.52 (m, 4 H), 0.96 (t, *J* = 7.4 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 147.9, 146.2, 127.8, 123.4, 100.2, 67.3, 22.9, 10.7.

2-(4-Nitrophenyl)-1,3-dioxolane (3n)[34]

Yellow liquid; yield: 18 mg (46%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 8.7 Hz, 2 H), 7.66 (d, *J* = 8.7 Hz, 2 H), 5.90 (s, 1 H), 4.18–4.01 (m, 4 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 148.5, 145.0, 127.4, 123.6, 102.3, 65.5.

1-(Dimethoxymethyl)-3-nitrobenzene (3o)[43]

Yellow liquid; yield: 36.6 mg (93%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.34 (s, 1 H), 8.19 (dd, *J* = 8.2, 2.2 Hz, 1 H), 7.80 (d, *J* = 7.7 Hz, 1 H), 7.56 (t, *J* = 7.9 Hz, 1 H), 5.49 (s, 1 H), 3.36 (s, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 148.3, 140.4, 132.9, 129.3, 123.4, 122.0, 101.5, 52.7.

1-(Dimethoxymethyl)-2-nitrobenzene (3p)[44]

Yellow liquid; yield: 31.5 mg (80%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.81 (ddd, *J* = 13.5, 7.9, 1.1 Hz, 2 H), 7.61 (td, *J* = 7.7, 1.2 Hz, 1 H), 7.48 (td, *J* = 7.8, 1.4 Hz, 1 H), 5.93 (s, 1 H), 3.41 (s, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 149.0, 132.7, 132.5, 129.4, 128.1, 124.2, 99.5, 54.6.

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Supporting Information

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