Research Article

Cyclopentadienyl Ruthenium(II) Complex-Mediated Oxidation of Benzylic and Allylic Alcohols to Corresponding Aldehydes

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Received 2 May 2019; Revised 9 July 2019; Accepted 17 July 2019; Published 18 August 2019

Academic Editor: Guillaume Berionni

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This work reports an efficient method for the oxidation reaction of aliphatic, aromatic allylic, and benzylic alcohols into aldehydes catalyzed by the cyclopentadienyl ruthenium(II) complex (RuCpCl(PPh3)2) with bubbled O2. Through further optimizing controlled studies, the tendency order of oxidation reactivity was determined as follows: benzylic alcohols > aromatic allylic alcohols >> aliphatic alcohols. In addition, this method has several advantages, including a small amount of catalyst (0.5 mol%) and selective application of high discrimination activity of aliphatic, aromatic allylic, and benzylic alcohols.

1. Introduction

Oxidation reactions are very useful functional transformations in organic synthesis [1, 2]. Many of the metal-based oxidizing reagents have been developed to achieve the efficient oxidation of alcohols such as PI Au [3], ARP-Pt [4], Ru/Al2O3 [5, 6], Pd/HAP [7, 8], Au-Pd/TiO2 [9], and HB Ru [10]. However, these catalysts are generally difficult to obtain because of their expensive cost and harsh production. In addition, other oxidation methods for alcohols using the readily available carbon-supported metal catalysts [11–14] including many famous Pd/C [15–17], Pt/C [18–23], or Au/C [24–30] catalysts [31, 32] were also enthusiastically investigated. Unfortunately, these catalysts needed addition of adjunction metals such as Co or Cd, or presence of oxygen or air under higher pressure and/or temperature, and/or stronger basic conditions to obtain the desired products. Furthermore, the rare earth elements have occupied an especially important place in the past two decades because of their high reactivity in various catalytic processes [33–39]. One of these rare elements is ruthenium. Some species of ruthenium have been widely developed and used as efficient catalysts for oxidation reactions [40, 41].

Among a variety of catalysts reported in the literature for the redox process of carbonyl compounds [42], the use of ruthenium complexes has garnished significant attention. For example, several ruthenium complexes have been employed as catalysts for the hydrogenation of carbonyl compounds,
Table 1: Study of oxidation conditions of benzyl alcohol 1a with RuCpCl(PPh₃)₂.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Solvent</th>
<th>Reaction condition</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>CH₂Cl₂</td>
<td>Reflux for 24 h</td>
<td>2a</td>
<td>Trace</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>CH₂Cl₂</td>
<td>Reflux for 48 h</td>
<td>2a</td>
<td>&lt;10</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>Benzene</td>
<td>Reflux for 24 h</td>
<td>2a</td>
<td>Trace</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>Benzene</td>
<td>Reflux for 48 h</td>
<td>2a</td>
<td>&lt;6</td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td>Acetone</td>
<td>Reflux for 24 h</td>
<td>2a</td>
<td>Nondetectable</td>
</tr>
<tr>
<td>6</td>
<td>1a</td>
<td>Acetone</td>
<td>Reflux for 48 h</td>
<td>2a</td>
<td>54</td>
</tr>
<tr>
<td>7</td>
<td>1a</td>
<td>THF</td>
<td>Reflux for 24 h</td>
<td>2a</td>
<td>Nondetectable</td>
</tr>
<tr>
<td>8</td>
<td>1a</td>
<td>THF</td>
<td>Reflux for 48 h</td>
<td>2a</td>
<td>71</td>
</tr>
</tbody>
</table>

Table 1 provides information about the study of oxidation conditions of benzyl alcohol 1a with RuCpCl(PPh₃)₂.

2. Results and Discussion

Benzyl alcohol 1a is an important precursor for organic synthesis and a useful solvent because of its polarity, low toxicity, mildly pleasant aromatic odor, and low vapor pressure [52-54]. The chemoselective oxidation property of compound 1a was also very useful in functional transformations for the preparation of aldehydes [55, 56] and their dicarboxylic analogues [57, 58]. For these reasons, we carried out a plausible oxidation of benzyl alcohol 1a. We preliminarily investigated a versatile oxidation method for compound 1a with 0.5 mol% amount of the cyclopentadienyl ruthenium(II) complex (RuClC(PPh₃)₂) catalyst with bubbled O₂ in CH₂Cl₂ solution at reflux for 24 h. However, only trace amounts of benzaldehyde 2a were achieved (entry 1 in Table 1). We then increased the reaction time to 48 h, which resulted in the desired oxidation product 2a, but at a low yield (<10%; entry 2 in Table 1). To identify the optimal reaction conditions, we attempted to screen the ACS grade of solvents (i.e., benzene, acetonitrile, and THF) and the reaction time at room temperature or reflux. Based on the experimental results in Table 1, we observed that the ideal conditions for this reaction were to use THF as the reaction solvent and to reflux for 48 h. The corresponding oxidation product 2a can be afforded in 71% isolated yield (entry 8 in Table 1). Consequently, optimization of the amount of the catalyst from 0.5, 1.0, 2.0, to 5.0 mol% was performed. However, this did not lead to any further improvement. The structure of product 2a was completely characterized by spectroscopic methods and consistent with an Aldrich-authentic sample. Following the results in Table 1, we found that RuCpCl(PPh₃)₂ possessed the oxidation reactivity necessary for transferring benzyl alcohols to the corresponding aldehydes.

In order to explore the substrate scope of the new oxidation reaction, we first examined the reactions of substituted benzyl alcohols 1b-f containing either electron-donating or electron-withdrawing groups 1b-d and substituted benzyl alcohols 1e-f. Fortunately, most of the substituted benzyl alcohols 1b-f were successfully converted to the corresponding aldehyde products 2b-f in moderate yields (>68%; Table 2). On the contrary, benzyl alcohols with para-Me (1b) and para-OMe (1c) electron-donating groups were oxidized to give the corresponding aldehyde products 2b-c in 73% and 80% yields, respectively (entries 1 and 2 in Table 2). In addition, the conversion of para-CN-benzyl alcohol 1d to aldehyde 2d in 68% yield seemed to have lower reactivity compared to benzyl alcohols with electron-donating groups 1b-c (entries 1 and 2 in Table 2). For disubstituted benzyl alcohols 1e and 1f, the most effective results were achieved in 82% and 86% yields, respectively, demonstrating a strong and significant electron-assisted effect (entries 4 and 5 in Table 2). Following the above study, it was found the cyclopentadienyl ruthenium(II) complex (RuClC(PPh₃)₂) possessed significant oxidizing activity for discrimination of benzyl alcohols.

To further expand our study, we investigated allyllic systems such as (E)-3-arylprop-2-en-1-ols (1g) and cyclohex-2-enol (1h). The RuClC(PPh₃)₂ catalyst (0.5 mol%) successfully reacted towards (E)-3-arylprop-2-en-1-ols (1g)
<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohols 1b–k</th>
<th>Reaction time (h)</th>
<th>Yields of products 2b–k</th>
<th>Yields (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1b</td>
<td>~48 h</td>
<td>2b</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>1c</td>
<td>~48 h</td>
<td>2c</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>1d</td>
<td>~48 h</td>
<td>2d</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>1e</td>
<td>~48 h</td>
<td>2e</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>1f</td>
<td>~48 h</td>
<td>2f</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>1g</td>
<td>~48 h</td>
<td>2g</td>
<td>68</td>
</tr>
<tr>
<td>7</td>
<td>1h</td>
<td>~48 h</td>
<td>2h</td>
<td>69</td>
</tr>
<tr>
<td>8</td>
<td>1i</td>
<td>~48 h</td>
<td>2i</td>
<td>17&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>1j</td>
<td>~48 h</td>
<td>2j</td>
<td>35</td>
</tr>
<tr>
<td>10</td>
<td>1k</td>
<td>~48 h</td>
<td>2k</td>
<td>—</td>
</tr>
</tbody>
</table>

<sup>a</sup>The starting material was recovered.
and cyclohex-2-enol (1h) in the presence of THF at reflux for ~48 h to give the desired oxidation products 2g and 2h in 68% and 69% yields, respectively (entries 6 and 7 in Table 2). The yielding results of the allylic system 1g–h were noticeably lower than the conversion of benzylic alcohols 1e–f.

To evaluate the substrate scope and limitation, this study has been extended to a variety of aliphatic or alicyclic alcohols such as 3-arylpropan-1-ols (1i), heptan-1-ol (1j), and 2-isopropyl-5-methylcyclohexanol (1k). In general, a longer reaction time (~60 h) was required compared to benzylic and allylic alcohols 1a–h for oxidation reaction (entries 8–10 in Table 2). Under the same condition, aliphatic or alicyclic alcohols 1i–k presented poor oxidizing reactivity, resulting in trace to 35% yields. For compound 1k, no trace of the oxidation product was detected in the 1H NMR spectrum of the crude reaction mixture (entry 10 in Table 2). Following the above study, it was found the cyclopentadienyl ruthenium(II) complex (RuCpCl(PPh3)2) possessed significant oxidizing activity for discrimination of aromatic allylic and benzylic alcohols. In addition, the oxidation reaction of benzylic alcohol 1a with the RuCpCl(PPh3)2 catalyst (0.5 mol%) was found to produce better isolated yields compared to both allylic alcohol 1g and aliphatic alcohol 1i.

4-(Hydroxymethyl)benzenepropanol 3 was synthesized by the reported method as the important bifunctional substrate for the chemoreactivity oxidation study [59]. We initially carried out a careful study of possible oxidations of compound 3 with 1.25 mol% amount of the cyclopentadienyl ruthenium(II) complex (RuCpCl(PPh3)2) catalyst with bubbled O2 in CH2Cl2 solution at reflux for 48 h. The versatile oxidation was monitored by TLC and sampled for 1H NMR characteristic identification (see Figure 1). When the reaction was performed for 4 h, the crude solution was sampled, worked up, and eluted from the column. Most of starting material 3 was recovered, and the corresponding mixture products 4-(3-hydroxypropyl)benzaldehyde 4 and the small amount of 4-(3-oxopropyl)benzaldehyde 5 were given out in 21% and <5% yields, respectively (see Scheme 1 and Figure 1). When the reaction time was prolonged from 4 h to

![Figure 1: 1H NMR characteristic identification of compounds 3 (□), 4 (○), and 5 (△).](image-url)

**Scheme 1:** Chemoreactivity oxidation results of 4-(hydroxymethyl)benzenepropanol 3.
24 h or 48 h under the same condition, we observed that the expected oxidation product 4 was significantly promoted from 21% to 48% or 54% yields, respectively [60]. Comparatively, only a small amount of oxidation product 4-(3-oxopropyl)benzaldehyde 5 was achieved (~5% to 12% and 15%; Scheme 1) [60]. Based on the above experimental results, we proved again that the benzylic alcohol possessed more efficient oxidative reactivity than the aliphatic alcohol.

3. Conclusions

We have successfully developed the oxidation reaction for aliphatic, aromatic allylic, and benzylic alcohols with 0.5 mol% of the cyclopentadienyl ruthenium(II) complex (Ru$_7$C$_8$(P$_3$H$_9$)$_3$P.$\delta$.). Based on the further controlled studies, the reactive tendency was determined as follows: benzylic alcohols > aromatic allylic alcohols >> aliphatic alcohols. On the contrary, mono- and disubstituted benzylic alcohols with electron-donating groups can provide the best oxidation results. In addition, this new method has several advantages including a small amount of catalyst (0.5 mol%) and high discrimination activity of aliphatic, aromatic allylic, and benzylic alcohols.

4. Experimental Section

All reagents were used as obtained commercially. All reactions were carried out under argon or nitrogen atmosphere and monitored by TLC. Flash column chromatography was carried out on silica gel (230–400 mesh). An analytical thin-layer chromatography (TLC) was performed using precoated plates (silica gel 60 F-254) purchased from Merck Inc. Flash column chromatography purification was carried out by gradient elution using n-hexane in ethyl acetate (EtOAc) unless otherwise stated. Infrared (IR) spectra were measured with a Bomem Michelson Series FT-IR spectrometer. Wavenumbers reported are referenced to the polystyrene absorption at 1601 cm$^{-1}$. Absorption intensities are recorded by the following abbreviations: s, strong; m, medium; and w, weak. All proton and carbon-13 NMR spectra were obtained by Bruker instruments (400 MHz and 100 MHz, respectively). Proton and carbon-13 NMR spectra were acquired using deuterochloroform (CDCl$_3$) solvent. Multiplicities are recorded by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and J, coupling constant (Hz). ESI-MS analyses were performed on an Applied Biosystems API 300 mass spectrometer. High-resolution mass spectra were obtained from a JEOL JMS-HX110 mass spectrometer.

4.1. Standard Procedure for the Oxidation of Aliphatic, Aromatic Allylic, and Benzylic Alcohols 1a–j to Corresponding Aldehydes 2a–j with Cyclopentadienyl Ruthenium(II) Complex. Aliphatic, aromatic allylic, or benzylic alcohols (1a–j, ∼1.0 mmol, 1.0 equiv) and Ru$_7$C$_8$(P$_3$H$_9$)$_3$P.$\delta$. (∼0.5 mol %) with bubbled O$_2$ were stirred in anhydrous THF (2.0 mL) and heated at reflux for 24–48 h under the argon atmospheric pressure. When the oxidation reaction was completed, the solution was filtered through Celite, and the Celite bed was washed with hot THF. The filtrate was concentrated to remove THF under reduced pressure. The residue was added (CH$_2$Cl$_2$, 15 mL), washed with saturated aqueous NaHCO$_3$ (15 mL), and extracted with CH$_2$Cl$_2$ (10 mL × 2). The combined organic layers were washed with brine (15 mL), dried over MgSO$_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (n-hexane/EtOAc = 4/1) on silica gel to give the corresponding aldehyde products 2a–j in 17–86% yields. The physical properties and spectroscopic characteristics of the isolated aliphatic, aromatic allylic, and benzylic alcohols, including 2a–j, were consistent with those of the authentic sample [61].

Benzaldehyde (2a) [61]: light yellow liquid; $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.48–7.52 (m, 2H, ArH), 7.58–7.63 (m, 1H, ArH), 7.84–7.87 (m, 2H, ArH), and 9.99 (s, 1H, CHO); $^1$C NMR (CDCl$_3$, 100 MHz): δ 117.69 (2 × CH), 129.69 (2 × CH), 134.41, 136.34, and 192.37; IR (KBr): 3043, 2945, 1672, 1601, 1577, 1512, 1315, 1260, 1158, and 189.98; MS (EI): 136 (72), 135 (100), 92 (14), 77 (21), 55 (12), and 50 (13).

4-Tolualdehyde (2b) [61]: colorless liquid; $^1$H NMR (CDCl$_3$, 400 MHz): δ 2.42 (s, 3H, Me), 7.31 (d, J = 7.9 Hz, 2H, ArH), 7.75 (dd, J = 6.6 and 1.6 Hz, 2H, ArH), and 9.94 (s, 1H, CHO); $^1$C NMR (CDCl$_3$, 100 MHz): δ 21.85, 129.68 (2 × CH), 129.83 (2 × CH), 134.16, 145.54, and 192.01; IR (KBr): 3043, 2945, 1672, 1574, 1282, 959, 947, 838, and 752 cm$^{-1}$; MS (EI): 120 (34), 119 (100), 92 (11), 91 (97), and 65 (18).

4-Methoxybenzaldehyde (2c) [61]: light yellow liquid; $^1$H NMR (CDCl$_3$, 400 MHz): δ 3.79 (s, 3H, OMe), 6.90–6.93 (m, 2H, ArH), 7.73–7.76 (m, 2H, ArH), and 9.79 (s, 1H, CHO); $^1$C NMR (CDCl$_3$, 100 MHz): δ 54.74, 113.61 (2 × CH), 129.24, 131.16 (2 × CH), 163.89, and 189.98; IR (KBr): 3520, 3356, 2969, 2839, 2741, 1682, 1601, 1577, 1512, 1315, 1260, 1158, and 1026 cm$^{-1}$; MS (EI): 136 (72), 135 (100), 92 (14), 77.0 (24), and 65 (10).

4-Cyanobenzaldehyde (2d) [61]: white crystal, m.p. 99–102°C; $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.83 (d, J = 8.2 Hz, 2H, ArH), 7.98 (d, J = 8.2 Hz, 2H, ArH), and 10.07 (s, 1H, CHO); $^1$C NMR (CDCl$_3$, 100 MHz): δ 117.57, 117.74, 129.90 (2 × CH), 132.92 (2 × CH), 138.74, and 190.70; IR (KBr): 2850, 2231, 1707, 1608, 1517, 1387, 1295, 1203, 1123, 1172, 832, 737, and 546 cm$^{-1}$; MS (EI): 131 (84), 130 (100), 105 (28), 103 (23), 102.0 (57), 91 (12), 77 (16), 76 (18), 75 (12), and 51 (12).

3,4-Dimethoxybenzaldehyde (2e) [61]: light yellow liquid; $^1$H NMR (CDCl$_3$, 400 MHz): δ 3.93 (s, 3H, OMe), 3.96 (s, 3H, OMe), 6.98 (d, J = 8.2 Hz, 1H, ArH), 7.40 (d, J = 7.6 Hz, 1H, ArH), 7.45 (dd, J = 8.2 and 1.9 Hz, 1H, ArH), and 9.84 (s, 1H, CHO); $^1$C NMR (CDCl$_3$, 100 MHz): δ 55.60, 55.80, 108.63, 110.11, 126.42, 129.79, 149.26, 154.13, and 190.47; IR (KBr): 2938, 2840, 1683, 1588, 1513, 1462, 1421, 1268, 1243,

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1135, 1021, 811, and 731 cm$^{-1}$; MS (EI): 167 (18), 166 (100), 165 (71), 159 (22), 95 (33), 91.0 (40), 79 (14), 77 (22), 73 (26), and 60 (15).

4-Benzylxoy-3-methoxybenzaldehyde (2f) [61]: orange liquid; $^{1}H$ NMR (CDCl$_3$, 400 MHz): $\delta$ 3.89 (s, 3H, OMe), 5.19 (s, 2H, OCH$_2$), 6.95 (d, $J$ = 8.2 Hz, 1H, ArH), 7.30 (d, $J$ = 7.3 Hz, 1H, ArH), 7.33–7.37 (m, 3H, ArH), 7.39–7.42 (m, 3H, ArH), and 9.79 (s, 1H, CHO); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 55.85, 70.67, 109.22, 112.24, 126.39, 127.08 (2 × CH), 128.05, 128.56 (2 × CH), 130.14, 135.87, 149.90, 153-44, and 190.72; IR (KBr): 2938, 2833, 2731, 1683, 1588, 1509, 1462, 1424, 1264, 1237, 1135, 1026, and 734 cm$^{-1}$; MS (EI): 242 (49), 92 (43), 91 (100), and 65 (41).

Cinnamaldehyde (2g) [61]: light yellow liquid; $^{1}H$ NMR (CDCl$_3$, 400 MHz): $\delta$ 7.41–7.43 (m, 3H, ArH), 7.54–7.56 (m, 2H, ArH), and 9.69 (dd, $J$ = 7.0 and 2.42 Hz, CHO); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 129.01 (2 × CH), 130.14, 135.87, 149.90, 153.44, and 190.72; IR (KBr): 3029, 2844, 1681, 1634, 1449, 1311, and 1286 cm$^{-1}$; MS (EI): 132 (38), 131 (69), 130 (36), 103 (98), 102 (63), 91 (59), 78 (41), 77 (94), 76 (40), and 51 (65).

2-Cyclohexen-1-one (2j) [61]: colorless liquid; $^{1}H$ NMR (CDCl$_3$, 400 MHz): $\delta$ 1.90–1.96 (m, 2H), 2.24–2.29 (m, 2H), 2.33 (t, $J$ = 13.48 Hz, 2H), 5.92 (d, $J$ = 10.12 Hz, 1H), and 6.89–6.94 (m, 1H); 13C NMR (CDCl$_3$, 100 MHz): $\delta$ 20.56, 22.56, 25.49, 37.92, 129.63, 150.61, and 199.40; IR (KBr) 3299, 2918, 2847, 1513, 1707, 1380, 1241, 1210, and 832 cm$^{-1}$; MS (EI): 96 (36) and 68 (100).

3-Phenylpropionaldehyde (2i) [61]: colorless liquid; $^{1}H$ NMR (CDCl$_3$, 400 MHz): $\delta$ 2.77 (td, $J$ = 7.28 and 0.87 Hz, 2H), 2.96 (t, $J$ = 7.56 Hz, 2H), 7.20 (t, $J$ = 7.38 Hz, 3H), 7.30 (t, $J$ = 7.30 Hz, 2H), and 9.81 (t, $J$ = 13.4 Hz, CHO); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 28.08, 45.18, 126.28 (2 × CH), 128.35, 128.60 (2 × CH), 140.57, and 201.46; IR (KBr): 3029, 2929, 1709, 1604, 1496, 1456, and 1298 cm$^{-1}$; MS (EI): 135 (22), 134 (100), 133 (10), 118 (12), 117 (20), 105 (27), 92 (58), 91 (96), 78 (23), and 77 (11).

Heptanal (2l) [61]: colorless liquid; $^{1}H$ NMR (CDCl$_3$, 400 MHz): $\delta$ 0.87 (t, $J$ = 6.9 Hz, 3H, Me), 1.25–1.33 (m, 6H), 1.57–1.63 (m, 2H, CH$_2$CH$_2$CHO), 2.40 (td, $J$ = 7.4 and 1.9 Hz, 2H, CH$_2$CHO), and 9.75 (t, $J$ = 1.9 Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 13.96, 22.02, 22.42, 28.80, 31.50, 43.89, and 202.94; IR (KBr): 3421, 2955, 2928, 2856, 1716, 1461, 1376, 1145, and 947 cm$^{-1}$; MS (EI): 96 (23), 86 (20), 81 (27), 72 (13), 71 (25), 70 (100), 69 (10), 68 (21), 67 (12), 60 (12), 57 (47), and 55 (59).

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Disclosure

This manuscript was also presented at National Annual Meeting of Chinese Chemical Society, National Sun Yat-sen University (Kaohsiung), Taiwan, Nov 8–9, 2018.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors’ Contributions

Ching-Yuh Chern and Ching-Chun Tseng contributed equally to this work.

Acknowledgments

The authors are grateful to the Tsusti Institute for Traditional Medicine and the Ministry of Science and Technology of the Republic of China (MOST 107-2113-M-039-006) for financial support. This work was also financially supported by Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW107-TDU-B-123004) and Chinese Medicine Research Center, China Medical University, through The Featured Areas Research Center Program within the framework of the Higher Education Sprout Project by the Ministry of Education (MOE) in Taiwan (CMRC-CHM-4).

Supplementary Materials

The supplementary materials contain experimental details, characterization data of all compounds, and copies of $^{1}H$ and $^{13}$C NMR spectra and low mass. (Supplementary Materials)

References


