# Iridium-Catalyzed Oxidative Dimerization of Primary Alcohols to Esters Using 2-Butanone as an Oxidant

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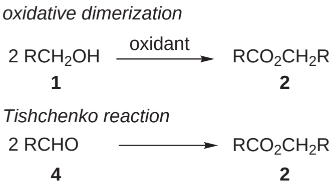
**Abstract:** Oxidative dimerization of primary alcohols with 2-butanone in the presence of an amino alcohol-based Ir bifunctional catalyst was accomplished for the first time. The reaction proceeds with 1–2 mol% of the catalyst and 0.3 mol equivalents of $K_2CO_3$ in 2-butanone at room temperature to give the corresponding dimeric esters in 30–93% yield.

**Key words:** alcohols, esters, hydrogen transfer, iridium catalyst, oxidative dimerization

For the synthesis of dimeric esters, oxidative dimerization[1] of primary alcohols is an important method as well as the Tishchenko reaction[2] of aldehydes (Scheme 1).

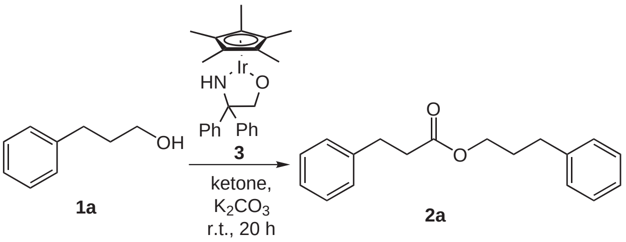


**Scheme 1**

To date, various reaction systems have been developed, which include stoichiometric oxidation using $Na_2Cr_2O_7$,[3] $Br_2$–HMPT,[4] $Ca(OCl)_2$,[5] NaOCl,[5] $NaBrO_2$,[6] $NaBrO_3$–$NaHSO_3$,[7] PCC–$Al_2O_3$,[8] and so on. Recently, Bobbitt et al. reported oxidative dimerization of polyfunctional primary alcohols using oxoammonium salts.[9] Kita et al. have developed an oxidative methyl esterification of primary alcohols using a hypervalent iodine reagent.[10] Several catalytic methods have been developed using, for example, $Pd(OAc)_2$–$CCl_4$,[11] $Ru_3(CO)_{12}$–tolane,[12] $RuH_2(PPh_3)_4$ (180 °C),[13] $Pd(OAc)_2$–PhBr,[14] BTMA–Mo (benzyltrimethylammonium tetrabromooxomolybdate)–*t*-BuOOH,[15] $MoO_3$–$Sb_2O_4$ (300 °C, dehydrogenation).[16] However, these catalytic reactions require heating. Moreover, except for the Shvo[12] and Murahashi[13] methods, benzyl alcohols are usually difficult substrates for oxidative dimerization by catalytic or stoichiometric methods, and the major products are not the dimeric esters, but benzaldehydes.[4,5,7,8,11,14] Thus, an efficient oxidative dimerization with broad generality has not yet been developed. Recently, we have developed an Ir aminoalkoxide complex, which catalyzes the oxidative lactonization of diols and Oppenauer oxidation of primary alcohols.[17,18] In this paper, we present the Ir complex-catalyzed oxidative dimerization of various primary alcohols at room temperature. This reaction is also the first example for the use of ketone as a cooxidant.[19]

When a mixture of 3-phenylpropanol (**1a**) in 2-butanone (2.7 equiv) containing the Ir complex **3**[17a] and $K_2CO_3$ (2-butanone:**1a**:**3**:$K_2CO_3$ = 270:100:2:30) was stirred at room temperature for 20 hours, 3-phenyl-1-propyl 3-phenylpropanoate (**2a**) was obtained in 89% yield (Table 1, entry 4). The reaction proceeded similarly in acetone, 3-pentanone (entries 5, 6). To obtain the dimeric ester in high yield, the uses of $K_2CO_3$ and high-concentration conditions are crucial. Without the base, the reaction in 2-butanone proceeded in only 30% yield after 20 hours (entry 1). However, the yield increased to 76% in the presence of just 5 mol% of $K_2CO_3$ (entry 2).[20] The reaction using 0.3 M 2-butanone solution (37 equiv) was slower and gave only 9% yield (entry 3).

**Table 1** Oxidative Dimerization of **1a**[a]



| Entry | Ketone | $K_2CO_3$ (equiv) | Conversion (%) | Yield of **2a** (%) |
|---|---|---|---|---|
| 1 | 2-Butanone | None | 33 | 30 |
| 2 | 2-Butanone | 0.05 | 78 | 76 |
| 3[b] | 2-Butanone | 0.3 | 81 | 9 |
| 4 | 2-Butanone | 0.3 | 92 | 89 |
| 5 | Acetone | 0.3 | 86 | 82 |
| 6 | 3-Pentanone | 0.3 | 87 | 85 |

[a] Unless otherwise stated, the reaction was carried out using **1a** (1.0 mmol), ketone (2.7 mmol), **3** (0.02 mmol, 2 mol%), and $K_2CO_3$ (0–0.3 mmol**)** at r.t. for 20 h.
[b] 37 Equiv of 2-butanone were used.

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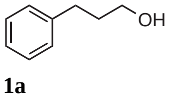
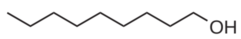
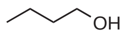
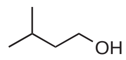
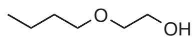
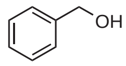
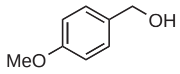
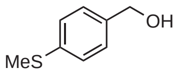
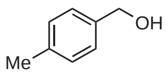
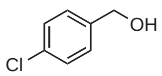
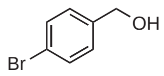
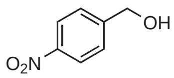
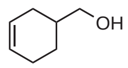
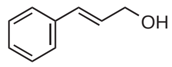
**Table 2** Oxidative Dimerization of Primary Alcohols Catalyzed by an Ir Catalyst **3**[a]

| Entry | Alcohol | Time (h) | Conversion (%) | Yield (%)[b] |
|---|---|---|---|---|
| 1 |  **1a** | 20 | 92 | 89 (97) |
| 2 |  **1b** | 40 | 93 | 86 (92) |
| 3 |  **1c** | 48 | 87 | 83 (95)[c] |
| 4 |  **1d** | 48 | 76 | 72 (95)[c] |
| 5 |  **1e** | 48 | 81 | 73 (90)[d] |
| 6 |  **1f** | 25 | 95 | 93 (98) |
| 7 | | 45 | 86 | 81 (94)[e] |
| 8 |  **1g** | 26 | 92 | 89 (97) |
| 9 |  **1h** | 26 | 93 | 87 (94) |
| 10 |  **1i** | 25 | 93 | 86 (92) |
| 11 |  **1j** | 25 | 97 | 91 (94) |
| 12 |  **1k** | 24 | 95 | 91 (96) |
| 13 |  **1l** | 48 | 84 | 80 (95) |
| 14 |  **1m** | 96 | 76 | 67 (88)[d] |
| 15 |  **1n** | 17 | 98 | 30 (31) |

[a] Unless otherwise stated, the reaction was carried out using **1** (1.0 mmol), 2-butanone (2.7 mmol), **3** (0.02 mmol, 2 mol%), and $K_2CO_3$ (0.3 mmol) at r.t.

[b] Yield in parentheses are based on the consumed alcohols.

[c] Yields of esters and recovered alcohol were determined by GC.

[d] Yields of recovered alcohol were determined by GC.

[e] With 1 g of **1f** and 1 mol% of catalyst.

Having succeeded in optimizing the reaction conditions, we next investigated the catalytic oxidative dimerization of other substrates. As shown in Table 2,[21,22] both aliphatic and benzylic alcohols could be converted to the corresponding dimeric esters in high yields. The esters **2c**,**d**, which are used as perfume materials (apple flavor), were obtained in 83% and 72% yields, respectively. The reaction of alcohol containing a β-oxygen proceeded in 73% yield. Benzyl alcohol afforded benzyl benzoate in 93% yield (entry 6). A gram-scale reaction can be performed in the presence of even 1 mol% catalyst (entry 7). The reaction proceeds smoothly even in the case of benzyl alcohols with an electron-donating group (entries 8–10). To our knowledge, this represents the first successful oxidative dimerization of benzylic alcohols with an electron-donating group. Moreover, the oxidation of benzyl alcohol with a substituent such as sulfide, which is susceptible to oxidation, proceeded without any difficulty (entry 9). Benzyl alcohols with an electron-withdrawing group were also good substrates (entries 11–13). The reaction of the unsaturated alcohol **1m** gave **2m** in 67% yield, albeit with a longer reaction time. However, the reaction of cinnamyl alcohol **1n** gave **2n** in only 30% yield, along with a mixture of partially or fully saturated products.[23]

A probable mechanism for the Ir-catalyzed oxidative dimerization is shown in Scheme 2. At first, the Ir complex **3** oxidizes primary alcohol **1** to give the corresponding aldehyde **5**, which reacts with another alcohol **1** to give hemiacetal **6**. Then, the second oxidation of the hemiacetal **6** affords the dimeric esters **2**. The role of 2-butanone as a co-oxidant is confirmed by the observation of 2-butanol in $^1$H NMR after the reaction.

In conclusion, we have developed a highly efficient catalytic oxidative dimerization of various primary alcohols with high yield. This simple and economical process should be useful for contemporary organic synthesis. Further details and an extension of this work will be reported in due course.

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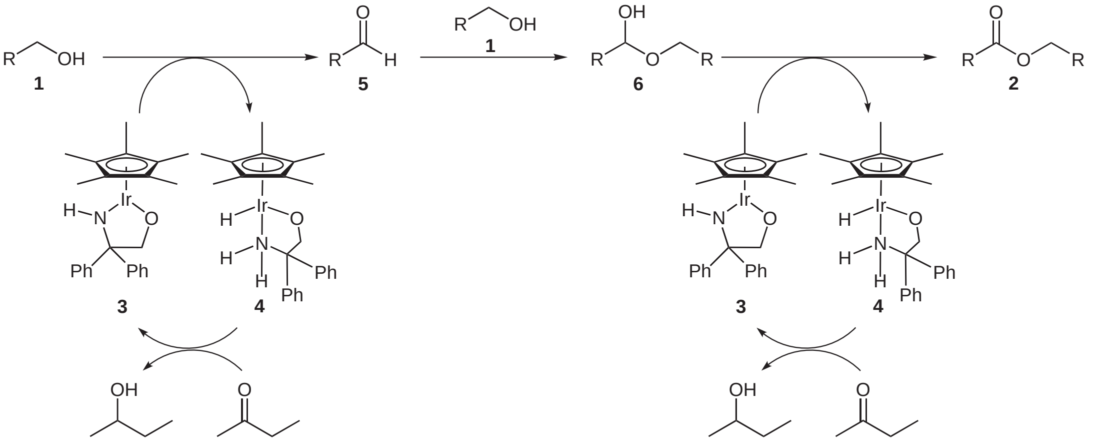

**Scheme 2**

(2) For recent examples of Tishchenko and related reactions, see: (a) Ooi, T.; Ohmatsu, K.; Sasaki, K.; Miura, T.; Maruoka, K. *Tetrahedron Lett.* **2003**, *44*, 3191. (b) Gnanadesikan, V.; Horiuchi, Y.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 7782. (c) For a recent review: Törmäkangas, O. P.; Koskinen, A. M. P. *Recent Res. Dev. Org. Chem.* **2001**, *5*, 225.

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(18) Recent examples of hydrogen transfer reaction using Cp*Ir complexes, see: (a) Mashima, K.; Abe, T.; Tani, K. *Chem. Lett.* **1998**, 1199. (b) Murata, K.; Ikariya, T.; Noyori, R. *J. Org. Chem.* **1999**, *64*, 2186. (c) Ogo, S.; Makihara, N.; Watanabe, Y. *Organometallics* **1999**, *18*, 5470. (d) Ogo, S.; Makihara, N.; Kaneko, Y.; Watanabe, Y. *Organometallics* **2001**, *20*, 4903. (e) Fujita, K.; Furukawa, S.; Yamaguchi, R. *J. Organomet. Chem.* **2002**, *649*, 289. (f) Fujita, K.; Yamamoto, K.; Yamaguchi, R. *Org. Lett.* **2002**, *4*, 2691. (g) Abura, T.; Ogo, S.; Watanabe, Y.; Fukuzumi, S. *J. Am. Chem. Soc.* **2003**, *125*, 4149. (h) Fujita, K.; Li, Z.; Ozeki, N.; Yamaguchi, R. *Tetrahedron Lett.* **2003**, *44*, 2687. (i) Fujita, K.; Kitatsuji, C.; Furukawa, S.; Yamaguchi, R. *Tetrahedron Lett.* **2004**, *45*, 3215. (j) Fujita, K.; Fujii, T.; Yamaguchi, R. *Org. Lett.* **2004**, *6*, 3525. (k) Hanasaka, F.; Fujita, K.; Yamaguchi, R. *Organometallics* **2004**, *23*, 1490.

(19) Related oxidative lactonization of diols in the presence of acetone was reported by Murahashi et al., see ref. 13a.

(20) The use of other bases, such as $Na_2CO_3$, $Cs_2CO_3$, $KHCO_3$, and KOAc resulted in lower reactivity. Although the role of the $K_2CO_3$ is not clear at present, it might increase the nucleophilicity of **1** to the corresponding aldehyde for the formation of hemiacetal. For the mechanistic study of acid- and base-catalyzed formation of the hemiacetal, see: Sorensen, P. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1987**, *109*, 4675.

(21) **General Procedure for the Oxidative Dimerization of 1.** A 10 mL test tube equipped with a magnetic stirring bar was charged with 42 mg (0.3 mmol) of $K_2CO_3$ and 1.0 mmol of alcohol under Ar. Then a solution of 11 mg (0.02 mmol, 2 mol%) of Ir complex **3** in butanone (0.24 mL, 2.7 mmol) was added to the above mixture and stirred at r.t. The mixture was passed through a short silica gel column (12 g, EtOAc) to remove the catalyst. The yields for the products of **2c** and **2d** were determined by gas chromatography using authentic samples and appropriate correction factors. The products of **2a**, **2b**, and **2d**–**m** were purified by silica gel column chromatography (hexane–EtOAc).

(22) Although TONs were not optimized at the moment, they were roughly calculated to be in range between 17 and 23 for most substrates [with single entry as high as 40 (entry 7)].

(23) The mechanism of saturation is not clear at present. Partially saturated products were observed even without $K_2CO_3$ under a high-concentration condition (4.2 M). However, such saturated products were not observed with $K_2CO_3$ under a diluted condition (0.08 M). See also ref. 17c.