

In situ Aerobic Alcohol Oxidation-Wittig Reactions

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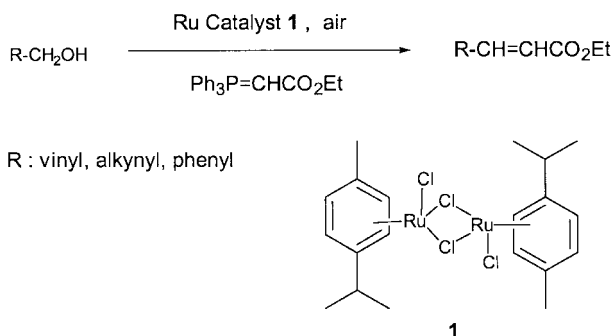
Recently, the *in situ* oxidation-Wittig reactions have been reported by several groups using stabilized Wittig reagent,¹ Barrett's group used the Dess-Martin periodinane as an oxidant,² Matsuda's group barium permanganate,³ and Taylor's group manganese dioxide.⁴ The *in situ* reaction of aldehydes formed from the corresponding primary alcohols is counted to be experimentally convenient, especially in the case of the formation of reactive or unstable aldehyde intermediates. From the reaction of chiral γ -amino alcohols, the corresponding unsaturated esters could be synthesized without loss of stereochemical integrity.⁵

However, all the procedures referred above have used the stoichiometric or excess amounts of oxidant. Moreover the oxidants contain some defects in that barium permanganate is toxic, the hazardous preparation of the Dess-Martin oxidant requires attentive handling, and even the excess amounts of manganese dioxide should be activated before use. Therefore we hoped to develop a catalytic *in situ* oxidation-Wittig reaction under air. There is no doubt that catalytic and

aerobic processes would be economical.⁶ Recently, [(η^6 -*p*-cymene)RuCl₂]₂ has been found to be a practical catalyst for the aerobic oxidation of allylic alcohols with additive Cs₂CO₃,⁷ and we want to apply the reaction condition for the homologation of α,β -unsaturated alcohols. The commercially available ruthenium reagent is commonly used without any further treatment.

Initial studies concentrated on the comparison of the reaction under different atmospheric environments and finding optimum condition (Table 1). As shown in entry 1, the reaction was tried first under N₂ to confirm whether the by-product of Wittig reaction, triphenylphosphine oxide might act as an oxidant. Only 6% yield under the condition indicated that completion of the reaction should require at least stoichiometric amounts of oxygen as oxidant. Under O₂ condition, the reaction proceeded faster, however, the atmospheric pressure of air also afforded comparable yield with longer reaction time, and the moderate temperature 55° was enough to carry out the reaction with the aid of one equivalent of additive Cs₂CO₃.⁸ The additive also helped to remove the remaining Ru-catalyst in the course of work-up, dissolving the complex into the aqueous phase. From the preliminary study, we found that it would be proper to use 4 mol% of the ruthenium catalyst, 1.1 equivalents of Ph₃P = CHCO₂Et, and one equivalent of Cs₂CO₃ in toluene under air.

This homologation sequence was applied to several synthetically useful examples (Table 2). The reaction of cinnamyl alcohol **2** provided the desired product in 71% yield (E/Z = 20). And **9** was also obtained in good yield.



Scheme 1

Table 1. *In situ* aerobic oxidation-Wittig reaction conditions^a

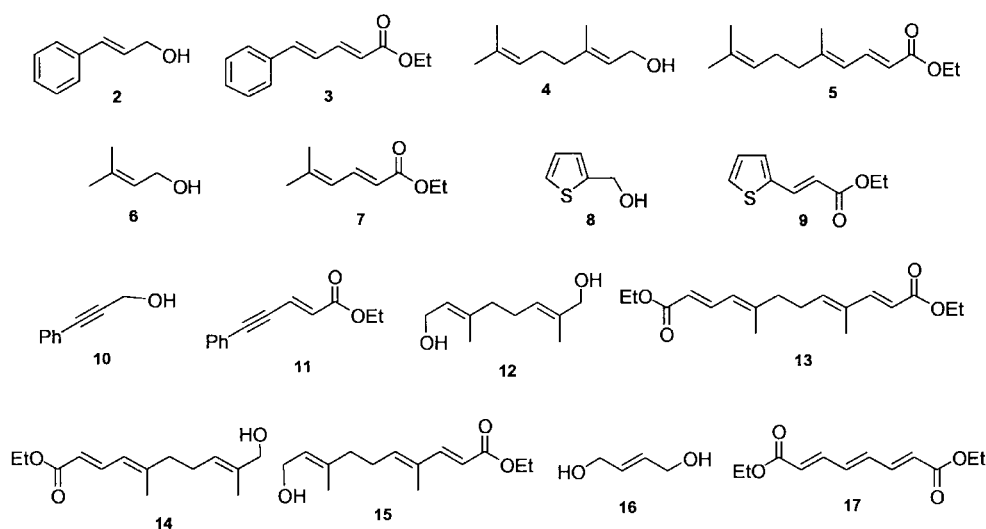
| Entry | Additive | Solvent | Conditions | Yield (%) | E/Z |
|-------|---------------------------------|---------|----------------------------|-----------|------|
| 1 | Cs ₂ CO ₃ | toluene | 40 °C, 24h, N ₂ | 6% | 24/1 |
| 2 | Cs ₂ CO ₃ | toluene | 40 °C, 24h, air | 42% | 24/1 |
| 3 | Cs ₂ CO ₃ | toluene | 55 °C, 12h, O ₂ | 75% | 24/1 |
| 4 | Cs ₂ CO ₃ | toluene | 55 °C, 24h, air | 72% | 24/1 |

^aThe mixture of benzyl alcohol, the stabilized Wittig reagent, Ph₃P = CHCO₂Et (1.2 equiv.), Cs₂CO₃ (1 equiv.), and the Ru-catalyst (4 mol%) in toluene was heat for the specified time.

Table 2. *In situ* aerobic oxidation-Wittig reaction condition^a

| Substrate | Product | Conditions | Yield (%) ^b | E/Z |
|-----------|-----------------|------------------|--|------------------|
| 2 | 3 | 55 °C, 25h, air | 71% | 20/1 |
| 4 | 5 | 55 °C, 24h, air | 23% | 3/1 |
| 4 | 5 | 100 °C, 26h, air | 47% | 3/1 |
| 6 | 7 | 55 °C, 24h, air | 43% | 4/1 |
| 8 | 9 | 55 °C, 23h, air | 83% | 50/1 |
| 10 | 11 | 55 °C, 24h, air | 28% | 9/1 |
| 12 | 13,14,15 | 65 °C, 24h, air | 9% (15) 45% (16,17) ^c | |
| 16 | 17 | 55 °C, 24h, air | 6% | 2/1 ^d |

^aToluene was used as a solvent, and Cs₂CO₃ (1 eq.) was added as an additive. ^bYields were determined after separation. ^c45% is the combined yield of **16** and **17** (formed in ca. 1 : 1 ratio). ^dThe ratio is that of E,E/E,Z,E,E.



However, some limitations of this reaction have been also found. Low yield, 28%, was detected in the reaction of **4** at 55 °C, but the yield was raised at 100 °C. Compound **12** afforded tetraene diester **13** in only 9% yield and *ca.* 1 : 1 mixture of **14** and **15** in 45% yield. Prolonged heating of the mixture even at higher temperature did not change much the yields of each compounds, **13**, **14**, and **15**. Similarly, the triene diester **17** was obtained in 6% yield. It seems that the diester precursors poison the catalyst through complexation.

In conclusion, the *in situ* aerobic alcohol oxidation-Wittig reaction using a ruthenium catalyst has been applied to α,β -unsaturated alcohols to obtain the corresponding esters for the first time. This process is expected to be explored usefully in organic syntheses.

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- Representative procedure: A mixture of benzyl alcohol (104 mg, 0.91 mmol), Cs₂CO₃ (300 mg, 0.91 mmol), ethoxycarbonylmethylenetriphenylphosphorane (368 mg, 1.0 mmol), and dichloro(*p*-cymene)ruthenium (II) dimer (22 mg, 0.036 mmol) in toluene (4 mL) was heated at 55 °C under air for 26 hr. The mixture was diluted with 10 mL of ethylacetate and the organic layer was washed with water twice and brine once. After dry over anhydrous magnesium sulfate and concentration, the crude product was purified by column chromatography to afford 116 mg of ester in 72% yield.