

## Wacker Oxidation of Alkenes Using a Fluorous Biphasic System. A Mild Preparation of Polyfunctional Ketones

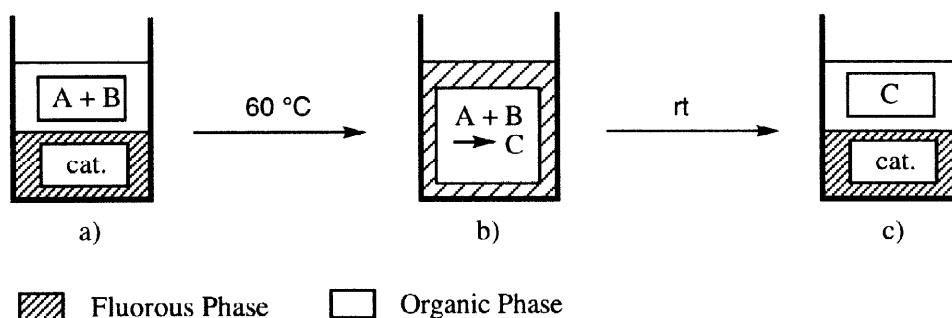
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**Abstract:** Various alkenes are oxidized to the corresponding ketones using *t*-BuOOH in the presence of a palladium(II) catalyst bearing perfluorinated ligands using a biphasic solvent system of benzene and bromoperfluorooctane. © 1998 Elsevier Science Ltd. All rights reserved.

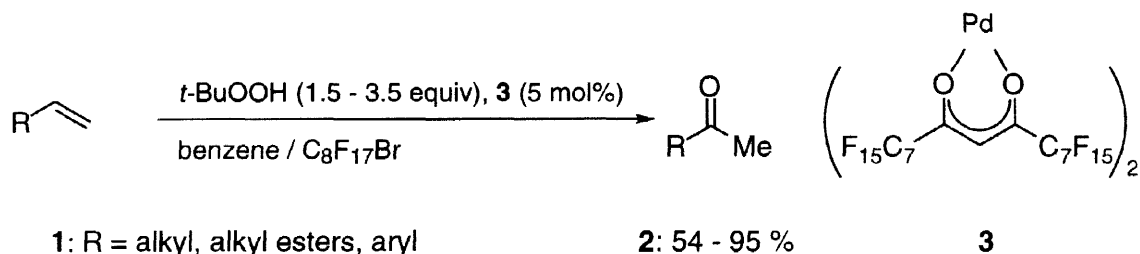
The development of highly efficient catalytic oxidation reactions is an active field of investigation. In these catalyzed reactions, it is important to be able to recover the metal catalyst and to separate it efficiently from the reaction products. Recently, we have shown that several oxidation reactions like the conversion of aldehydes to carboxylic acids, the oxidation of thioethers to sulfones or sulfoxides and the epoxidation of olefins<sup>1</sup> can be realized by using a fluorous biphasic system.<sup>2,3</sup> This biphasic solvent system popularized by the work of Horváth and Rabái<sup>2a</sup> consists of a perfluorinated solvent (*n*-C<sub>6</sub>F<sub>14</sub> or C<sub>8</sub>F<sub>17</sub>Br) containing a metal catalyst and an organic solvent (toluene or benzene) containing the starting materials (**A** and **B**). Whereas a two-phase system is formed at rt, an homogeneous solution is obtained at ca. 60 °C allowing the metal catalyzed reaction between **A** and **B** to take place. At the end of the reaction, the reaction mixture containing the product **C** is again cooled to rt, leading to two phases. The organic phase contains only the product **C** and the fluorous phase contains the catalyst which can be reused for further runs (Scheme 1).



**Scheme 1:** Fluorous biphasic system a) before b) during c) after the reaction.

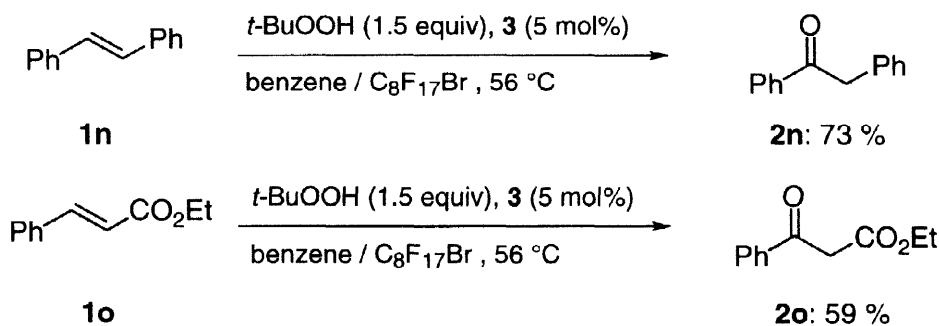
Herein, we wish to report that this methodology allows the performance of the Wacker oxidation of various polyfunctional olefins **1** under mild conditions leading to the corresponding methyl ketones of type **2** in the presence of the palladium catalyst **3** (5 mol %) in a biphasic solvent system of bromoperfluorooctane and benzene using *t*-butylhydroperoxide (1.5 - 3.5 equiv)<sup>4,5</sup> as oxidation agent (Scheme 2 and Table 1).

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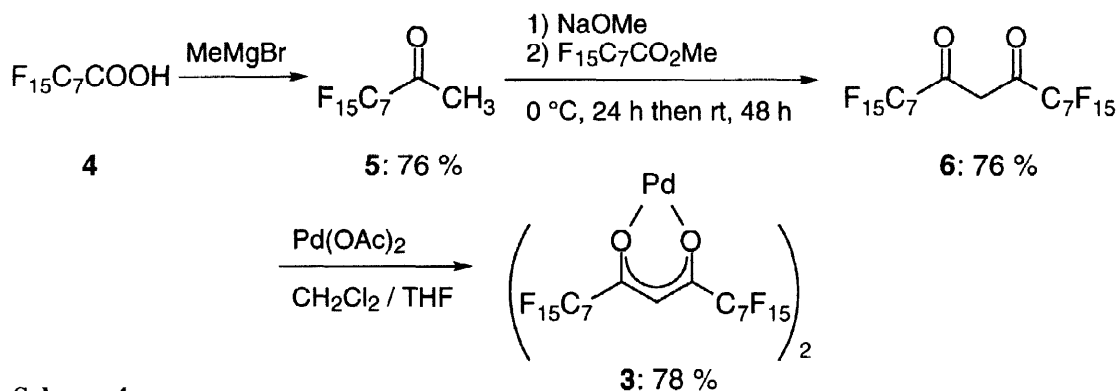
Scheme 2

The reactions are complete at 56 °C after 2-5 h in the case of the styrene derivatives **1a-h**, whereas in the case of aliphatic alkenes **1i-m**, reaction times between 8-20 h are required. With the latter class of substrates, a larger excess of *t*-BuOOH is needed (3.5 equiv). The reaction tolerates the presence of an ester function (entries 4, 10, 11 and 13 of Table 1). A Wacker oxidation is obtained not only with terminal olefins but also in the case of some activated disubstituted alkenes. Thus, stilbene (**1n**) is converted to phenyl benzyl ketone (**2n**) in 73 % yield and ethyl cinnamate (**1o**) provides the corresponding 1,3-ketoester (**2o**) in 59 % yield (Scheme 3).




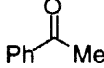
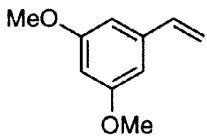
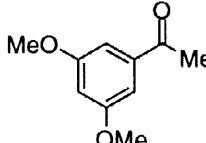
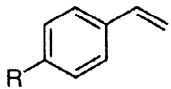
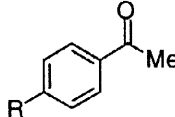
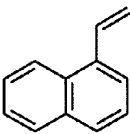
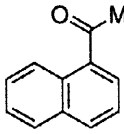
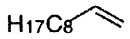
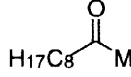
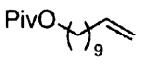
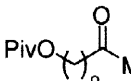

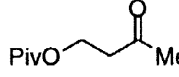
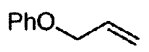
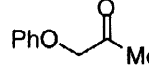
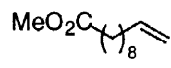
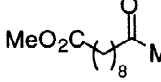
Scheme 3

The catalyst **3** was readily prepared in three steps starting from  $\text{C}_7\text{F}_{15}\text{COOH}$ .<sup>1</sup> Perfluorooctanoic acid (**4**) was treated with methylmagnesium bromide yielding the corresponding methyl ketone **5** (76 % yield). After ester condensation with methyl perfluorooctanoate the diketone **6** was obtained in 76 % yield. Its treatment with palladium(II) acetate affords the palladium bis(diketonate) complex **3** in 78 % yield (Scheme 4).<sup>6</sup>



Scheme 4

**Table 1.** Methyl ketones **2a-m** obtained by a Wacker oxidation of the alkenes **1a-m** in a biphasic system of benzene and bromoperfluorooctane using *t*-BuOOH as oxidation agent.

Entry	Alkene of Type 1	Ketone of Type 2	Yield (%) <sup>a</sup>
1	 <b>1a</b>	 <b>2a</b>	95 <sup>7</sup>
2	 <b>1b</b>	 <b>2b</b>	80 <sup>7</sup>
	 <b>1c:R=i-Pr</b> <b>1d:R=OAc</b> <b>1e:R=OMe</b> <b>1f:R=Ph</b> <b>1g:R=CF<sub>3</sub></b>	 <b>2c:R=i-Pr</b> <b>2d:R=OAc</b> <b>2e:R=OMe</b> <b>2f:R=Ph</b> <b>2g:R=CF<sub>3</sub></b>	78 <sup>7</sup> 84 <sup>7</sup> 76 <sup>7</sup> 80 <sup>7</sup> 76 <sup>7</sup>
8	 <b>1h</b>	 <b>2h</b>	75 <sup>7</sup>
9	 <b>1i</b>	 <b>2i</b>	82 <sup>7</sup>
10	 <b>1j</b>	 <b>2j</b>	73 <sup>8</sup>
11	 <b>1k</b>	 <b>2k</b>	54 <sup>9a</sup>
12	 <b>1l</b>	 <b>2l</b>	58 <sup>7</sup>
13	 <b>1m</b>	 <b>2m</b>	77 <sup>9b</sup>

<sup>a</sup>Isolated yield of analytically pure products.

The catalyst can be reused several times with similar yields but progressively longer reaction times are required. Thus, in the case of the Wacker oxidation of 4-methoxystyrene (**1e**), the reaction was repeated eight times with the same catalyst leading to 4-methoxyacetophenone (**2e**) in 70 - 78 % isolated yields (Table 2).

**Table 2.** Isolated yields of **2e** obtained by the oxidation of **1e** reusing the same catalyst **3** after phase separation (see entry 5 of Table 1).

run	yield (%)	run	yield (%)
1	78	5	70
2	77	6	73
3	75	7	72
4	77	8	72

In summary, we have developped an efficient direct oxidation of alkenes to ketones using a fluorous biphasic system. This method has the advantage of easy separation of the catalyst and allows its reuse without a significant decrease of the yield.<sup>10</sup>

### Acknowledgments

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- For another oxidation in fluorous biphasic systems using *t*-BuOOH: Vincent, J.-M.; Rabion, A.; Yachandra, V. K.; Fish, R. H. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2346.
- A 25 mL-flask was charged with the diketone **6** (3.23 g, 4.0 mmol) dissolved in CH<sub>2</sub>Cl<sub>2</sub> / THF (3:1, 3 mL). After addition of palladium(II) acetate (0.45 g, 2.0 mmol, 0.5 equiv) the reaction mixture was stirred for 3 h and the orange precipitate was filtrated yielding pure palladium bis(diketonate) (**3**: 2.69 g, 78 % yield). <sup>1</sup>H-NMR (THF-*d*<sub>8</sub>, 300 MHz): δ = 6.09 (s, 2H); <sup>13</sup>C-NMR (THF-*d*<sub>8</sub>, 75 MHz): δ = 179.4 (t, *J* = 23 Hz), 120.0-108.7 (m), 92.8 (s).
- Spectroscopic data was consistent with commercially available material.
- Spectroscopic data of pure **2j**: <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): δ = 4.00 (t, *J* = 6.5 Hz, 2 H), 2.38 (t, *J* = 7.4 Hz, 2 H), 2.09 (s, 3 H), 1.55 (m, 4 H), 1.24 (m, 10 H), 1.15 (s, 9 H). <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75 MHz): δ = 209.1, 178.5, 64.3, 43.7, 38.6, 29.8, 29.2, 29.1, 28.5, 27.1, 25.9, 23.8.
- For spectroscopic data see: (a) Bach, T. *Liebigs Ann.* **1995**, 855; (b) Schulz, S.; Toft S. *Tetrahedron* **1993**, *49*, 6805.
- Typical procedure.** Preparation of 4-methoxyacetophenone (**2e**; entry 5 of Table 1). A 10 mL-Schlenk-flask was charged with 4-methoxystyrene (134 mg, 1.0 mmol), *t*-BuOOH (0.5 mL, 1.5 mmol, 1.5 equiv, 3M solution in benzene) and benzene (0.5 mL). The palladium catalyst **3** (87 mg, 0.05 mmol, 5 mol %) dissolved in C<sub>8</sub>F<sub>17</sub>Br (1.0 mL) was added. The heterogeneous reaction mixture was heated to 56 °C leading to an homogeneous solution. The reaction was complete after 3 h as indicated by GC analysis of reaction aliquots. The reaction mixture was cooled to 25 °C leading to the formation of two phases. The orange fluorous phase was separated, washed with benzene (3 times) and was ready for the use in further runs. The organic phase was diluted with ether (10 mL) and was washed with an aqueous solution of Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub> to destroy the excess of *t*-BuOOH, then with brine. After drying (MgSO<sub>4</sub>) and evaporation of the solvents, the crude oil was purified by flash chromatography (pentane:ether 9:1) yielding pure 4-methoxyacetophenone (**2e**: 114 mg, 76 % yield) as a colorless solid.