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Practical Oppenauer (OPP) Oxidation of Alcohols with a Modified Aluminum Catalyst

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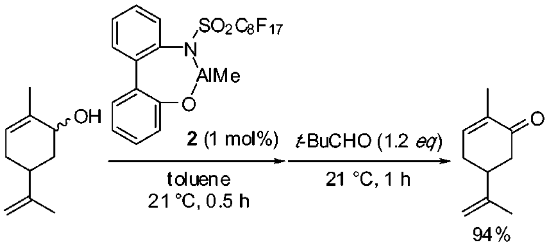
ABSTRACT



Modified aluminum catalyst 2 was found to be highly effective for Oppenauer (OPP) oxidation of alcohols under mild conditions. For example, oxidation of carveol in toluene with *t*-BuCHO (1.2 equiv) as a hydride acceptor in the presence of 2 (1 mol %) proceeded smoothly at 21 °C to give carvone in 94% yield after 1 h. A practical aspect of this system was highlighted by the facile OPP oxidation of terpenoids and steroids with 1.2–3.0 equiv of acetone and 2 (3–5 mol %).

The oxidation of alcohols into the corresponding carbonyl compounds is undoubtedly one of the indispensable transformations in organic synthesis, and numerous studies have been made aiming for the development of a more efficient and milder oxidation method.[1] Although stoichiometric oxidizing agents[2] such as hypochlorite,[3] chromium reagents[4] (PCC[4c] and PDC[4d]), active manganese oxides,[5] permanganate,[6] Dess−Martin periodinane,[7] *o*-iodoxybenzoic acid (IBX),[8] and activated DMSO in Swern oxidation[9] have been routinely used in laboratories, these are often toxic and hazardous and need halogenated solvents to attain sufficient reactivity, eventually generating noxious wastes. On the other

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[2] For recent examples of new oxidation methods, see: (a) Mukaiyama, T.; Matsuo, J.; Yanagisawa, M. *Chem. Lett.* **2000**, 1072. (b) Matsuo, J.; Kitagawa, H.; Iida, D.; Mukaiyama, T. *Chem. Lett.* **2001**, 150. (c) De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 3041. (d) Matano, Y.; Nomura, H. *J. Am. Chem. Soc.* **2001**, *123*, 6443.

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[5] Highet, R. J.; Wildman, W. C. *J. Am. Chem. Soc.* **1955**, *77*, 4399.

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[7] (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (c) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899. (d) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.

[8] (a) Frigerio, M.; Santagostino, M. *Tetrahedoron Lett.* **1994**, *35*, 8019. (b) Mulbaier, M.; Giannis, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4393. (c) Sorg, G.; Mengel, A.; Jung, G.; Rademann, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4395. (d) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245.

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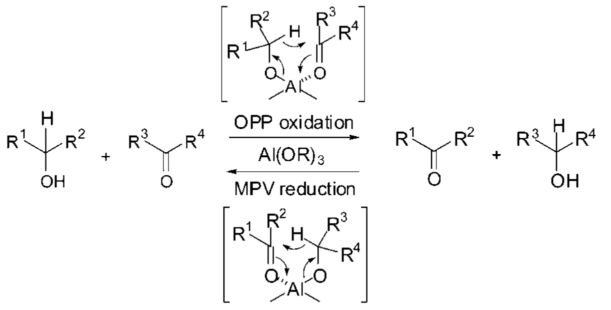
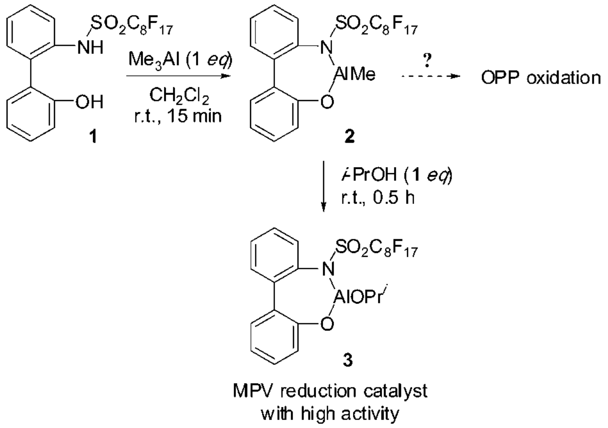
hand, many useful catalytic oxidation methods have been elaborated,[10−17] among which aerobic oxidation procedures with transition metal catalysts have an advantage from economic and environmental viewpoints.[12−17] However, these systems require relatively expensive metal catalysts, a large quantity of additives, and a higher reaction temperature to obtain satisfactory results.

Oppenauer (OPP) oxidation,[18−20] the reverse process of the Meerwein−Ponndorf−Verley (MPV) reduction (Scheme 1),[19b,21] is a classical yet useful method and is widely employed for the synthesis of steroids and terpenoids. Despite its operational simplicity with inexpensive and nontoxic reagents such as $Al(OBu^t)_3$ and $Al(OPr^i)_3$ as well as eminent functional group compatibility, the full synthetic potential of this oxidation has yet to be realized mainly because of the low reactivity of the metal alkoxides. Actually, use of 1 equiv of reagent or more with a large excess of hydride acceptor under relatively drastic conditions is a usual recipe but causes undesirable side reactions, i.e., dehydration of alcohols and aldol condensations. Although some beautiful modifications of OPP oxidation have been introduced, there is still room for improvement in terms of catalytic efficiency and substrate generality.[22−26] Further, only a few examples of aluminum-based OPP catalyst have appeared in the literature.[27] Recently, we disclosed new aluminum alkoxide **3** as a highly effective MPV reduction catalyst,[28] and this discovery prompted us to pursue the application of the organoaluminum precatalyst **2** to OPP oxidation (Scheme 2). In this letter, we wish to report preliminary results of this study, providing a practical catalytic OPP oxidation procedure.

Scheme 1. Opp Oxidation and MPV Reduction

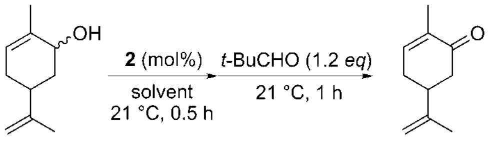


Scheme 2. Application of Catalyst **2** to OPP Oxidation



First, we examined the reactivity of aluminum catalyst **2**, prepared in situ by mixing Me_3Al and ligand **1** in CH_2Cl_2,[28] in the OPP oxidation of carveol as a representative substrate with 1.2 equiv of *t*-BuCHO as a hydride acceptor at 21 °C for 1 h (Table 1).[29] The reaction proceeded smoothly with 5 mol % of **2** to afford carvone in 90% isolated yield (entry 1). Notably, the loading of **2** can be reduced to 1 mol % without losing the catalytic activity (entry 2).[30] Needless to

Table 1. Catalytic OPP Oxidation of Carveol[a] with **2** in Various Solvents[b]



entry	**2** (mol %)	solvent	% yield[c]
1	5	CH_2Cl_2	90
2	1		94
3	1	toluene	94
4	1	cyclohexane	92
5	1	THF	80[d]
6	1	AcOEt	83[d]

[a] Cis/trans = 42:58. [b] Unless otherwise specified, the oxidation of carveol was conducted with **2** as a catalyst (prepared in each solvent) and *t*-BuCHO (1.2 equiv) as a hydride acceptor in various solvents (1 M substrate concentration) at 21 °C for 1 h, and the reaction solution was directly subjected to purification by column chromatography on silica gel without aqueous workup. [c] Isolated yield. [d] Stirred for 5 h.

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(10) For recent heterogeneous catalysts, see: (a) Nishimura, T.; Kakiuchi, N.; Inoue, M.; Uemura, S. *Chem. Commun.* **2000**, 1245. (b) Dijksman, A.; Arends, I. W. C. E.; Sheldon, R. A. *Synlett* **2001**, 102. (c) Choudary, B. M.; Kantam, M. L.; Rahman, A.; Reddy, C. V.; Rao, K. K. *Angew. Chem., Int. Ed.* **2001**, *40*, 763. (d) Itoh, A.; Kodama, T.; Inagaki, S.; Masaki, Y. *Org. Lett.* **2001**, *3*, 2653. (e) Son, Y.-C.; Makwana, V. D.; Howell, A. R.; Suib, S. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 4280.

(11) For unaerobic catalytic oxidations, see: (a) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639. (b) Mukaiyama, T.; Matsuo, J.; Iida, D.; Kitagawa, H. *Chem. Lett.* **2001**, 846. (c) Hashimoto, K.; Kitaichi, Y.; Tanaka, H.; Ikeno, T.; Yamada, T. *Chem. Lett.* **2001**, 922.

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(13) Cu catalysts: (a) Marko, I. E.; Giles, P. R.; Tsukazaki, M.; Brown, S. M.; Urch, C. J. *Science* **1996**, *274*, 2044. (b) Marko, I. E.; Gautier, A.; Mutonkole, J.-L.; Dumeunier, R.; Ates, A.; Urch, C. J.; Brown, S. M. *J. Organomet. Chem.* **2001**, *624*, 344.

(14) Ru catalysts: (a) Marko, I. E.; Giles, P. R.; Tsukazaki, M.; Chelle-Regnaut, I.; Urch, C. J.; Brown, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 12661. (b) Dijksman, A.; Marino-Gonzalez, A.; Mairata i Payeras, A.; Arends, I. W. C. E.; Sheldon, R. A. *J. Am. Chem. Soc.* **2001**, *123*, 6826.

(15) Mo catalyst: Lorber, C. Y.; Smidt, S. P.; Osborn, J. A. *Eur. J. Inorg. Chem.* **2000**, 655.

(16) V catalyst: Maeda, Y.; Kakiuchi, N.; Matsumura, S.; Nishimura, T.; Uemura, S. *Tetrahedron Lett.* **2001**, *42*, 8877.

(17) Co catalyst: Iwahama, T.; Yoshino, Y.; Keitoku, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2000**, *65*, 6502.

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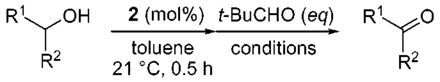
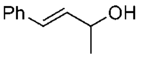
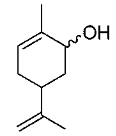
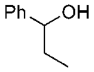
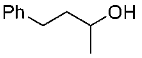
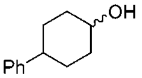
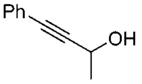
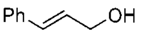
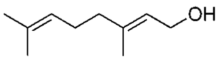
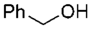
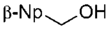
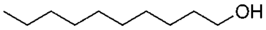
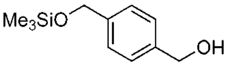
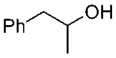
Table 2. Catalytic OPP Oxidation of Various Alcohols with **2**[a,b]



Entry	alcohol	**2** (mol%)	*t*-BuCHO (equiv)	conditions (°C , h)	% yield [c]
1		1	1.2	21, 1	94
2 [d]		1 (Me_3Al)	1.2	21, 18	27
3 [e]		1	1.2	21, 1	94
4		2	1.2	21, 1	87
5		2	1.2	21, 5	93
6 [f,g]		2	1.2	21, 3	84
7 [g,h]		2	3	21, 1	90
8		3	3	21, 5	80
9		2	1.2	21, 5	88
10		3	3	21, 0.5	85 (97 : 3) [i]
11		3	3	0, 0.25; 21, 0.4	86 (>99 : 1) [i]
12		2	3	21, 1	82
13		2	3	21, 1	93
14		2	1.2	21, 3	— [j]
15		5	3	21, 1	98
16		2	1.2	21, 3	85

[a] Unless otherwise noted, the oxidation was carried out by the successive treatment of substrate with **2** (1−3 mol %) for 0.5 h and *t*-BuCHO (1.2−3 equiv) in toluene (1 M substrate concentration) at 21 °C under the indicated conditions. [b] Reaction solution was directly subjected to purification by column chromatography on silica gel without aqueous workup. [c] Isolated yield. [d] Reaction was performed with 1 mol % Me_3Al as a catalyst. [e] Cis/trans = 42:58. [f] Cis/trans = 11:89. [g] Substrate concentration = 0.5 M. [h] Cis/trans = 18:82. [i] *E*/*Z* ratio of the product. [j] Although the starting alcohol was consumed, homo- and cross-Tishchenko reaction products were obtained as byproducts (decyl decanoate, 34%; neopentyl decanoate, 6%) together with the desired decanal (3%).

say, however, use of CH_2Cl_2 as a solvent is not recommended, and thus we investigated the applicability of other solvents in this reaction. Fascinatingly, comparable reactivity was attained in toluene and cyclohexane with 1 mol % of **2** (entries 3 and 4). It was of interest that the reaction proceeded even in THF and AcOEt to furnish carvone in good yields after stirring for 5 h (entries 5 and 6). On the basis of the results, we selected toluene as the most suitable solvent.[31]

The scope and limitations of this optimized catalytic OPP oxidation with **2** were explored with various alcohols, and the results are summarized in Table 2. *Secondary* aliphatic alcohols as well as *secondary* allylic and benzylic alcohols were smoothly oxidized into the corresponding ketones in good to excellent yields in the presence of 1−2 mol % of **2** (entries 1 and 3−6), and the yield could be improved by increasing the amount of *t*-BuCHO (entry 7). The use of Me_3Al itself as a catalyst, however, gave a poor result even after 18 h of stirring (entry 2), indicating the significant rate-acceleration effect of ligand **1** as previously observed in MPV reduction.[28] *Secondary* propargylic alcohol was also efficiently converted to the corresponding ketone with 3 mol

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(19) Reviews: (a) Djerassi, C. *Org. React.* **1951**, *6*, 207. (b) de Graauw, C. F.; Peters, J. A.; van Bekkum, H.; Huskens, J. *Synthesis* **1994**, 1007.

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(21) (a) Meerwein, H.; Schmidt, R. *Liebigs Ann. Chem.* **1925**, *444*, 221. (b) Verley, A. *Bull. Soc. Chim. Fr.* **1925**, *37*, 537. (c) Ponndorf, W. *Angew. Chem.* **1926**, *39*, 138. (d) Wilds, A. L. *Org. React.* **1944**, *2*, 178.

(22) For the use of borinic acid as an OPP catalyst, see: Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1997**, *62*, 5664.

(23) Zirconium alkoxide: Krohn, K.; Knauer, B.; Kupke, J.; Seebach, D.; Beck, A. K.; Hayakawa, M. *Synthesis* **1996**, 1341.

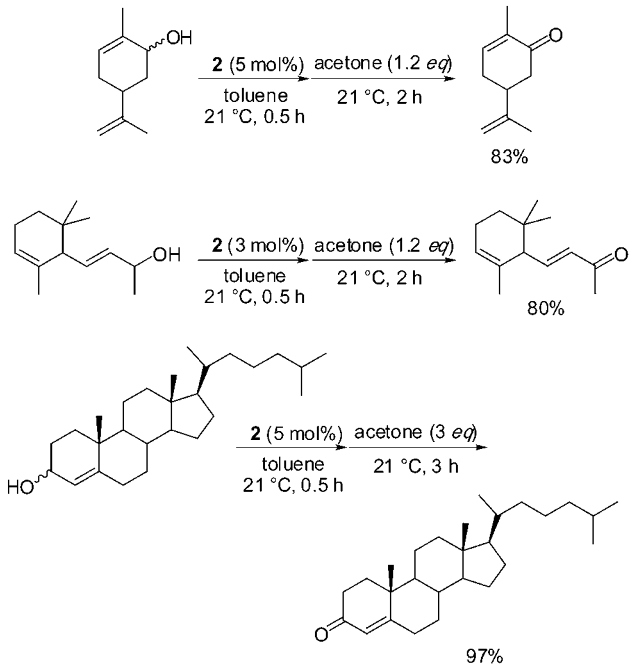
(24) Zirconocene complexes: (a) Ishii, Y.; Nakano, T.; Inada, A.; Kishigami, Y.; Sakurai, K.; Ogawa, M. *J. Org. Chem.* **1986**, *51*, 240. (b) Nakano, T.; Terada, T.; Ishii, Y.; Ogawa, M. *Synthesis* **1986**, 774. (c) Nakano, T.; Ishii, Y.; Ogawa, M. *J. Org. Chem.* **1987**, *52*, 4855.

% of **2** (entry 8). Moreover, the present method was found to be applicable to the oxidation of *primary* allylic and benzylic alcohols in a successful manner (entries 9−13). In the case of geraniol, *E*/*Z* isomerization was completely suppressed by starting the reaction at 0 °C (entries 10 and 11). Unfortunately, the reaction of simple *primary* aliphatic alcohols suffered from the Tishchenko reaction[32] of the desired aldehydes, furnishing the corresponding dimer together with the products of mixed Tishchenko reaction with *t*-BuCHO (entry 14). An additional characteristic feature of this oxidation protocol was demonstrated in the reactions involving both acid- and base-labile compounds. For example, exposure of monotrimethylsilyl ether of 1,4-benzenedimethanol to this OPP oxidation condition resulted in almost quantitative formation of the corresponding monoaldehyde without Si−O bond cleavage, and none of the undesired terephthalaldehyde was obtained (entry 15).[2a] On the other hand, the alcohol bearing a *β*-aryl substituent such as 3-phenyl-2-propanol underwent smooth oxidation to give enolizable benzyl methyl ketone in good yield (entry 16).[2b]

To further improve this catalytic system as a practical oxidation method, we examined acetone as a more general and convenient hydride acceptor.[19a] Surprisingly, the oxidation of carveol with only 1.2 equiv of acetone in the presence of 5 mol % of **2** in toluene at 21 °C for 2 h gave rise to carvone in 83% yield without any aldol byproducts (Scheme 3). This observation is in sharp contrast to the common situation with the previous aluminum-based OPP oxidation system, where a 50−200-fold amount of acetone and continuous heating were required to obtain synthetically satisfactory results.[19a] As also illustrated in Scheme 3, α-ionone was readily accessible by the present procedure and a steroid such as allocholesterol was converted to the corresponding ketones in excellent yield with 3 equiv of acetone under otherwise similar conditions.

In summary, a practical and mild OPP oxidation procedure has been devised by taking advantage of the high activity of aluminum catalyst **2**. With acetone as a hydride acceptor, the present system should meet the recent economical and environmental requirements for fundamental functional group transformations. Further improvement in the OPP oxidation of aliphatic primary alcohols and application to the synthesis of natural products, including a steroid or terpenoid skeleton, are under intensive investigation in our laboratory.

Scheme 3. Catalytic OPP Oxidation of Terpenoids and Steroids with **2** Using Acetone as a Hydride Acceptor



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Supporting Information Available: Spectroscopic characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) For ruthenium- or iridium-catalyzed OPP-type oxidation, see: (a) Almeida, M. L. S.; Kocovsky, P., Backvall, J.-E. *J. Org. Chem.* **1996**, *61*, 6587. (b) Ajjou, A. N. *Tetrahedron Lett.* **2001**, *42*, 13.

(26) Lanthanide alkoxides: Namy, J. L.; Souppe, J.; Collin, J.; Kagan, H. B. *J. Org. Chem.* **1984**, *49*, 2045.

(27) For recent modifications of aluminum alkoxide, see: (a) Akamanchi, K. G.; Chaudhari, B. A. *Tetrahedron Lett.* **1997**, *38*, 6925. (b) Ooi, T.; Miura, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 2347. (c) Ooi, T.; Miura, T.; Itagaki, Y.; Ichikawa, H.; Maruoka, K. *Synthesis* **2002**, 279.

(28) Ooi, T.; Ichikawa, H.; Maruoka, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 3610.

(29) Since **2** is treated with carveol for 0.5 h before the addition of *t*-BuCHO, the in situ-derived aluminum alkoxide is the actual catalyst in the present system.[31]

(30) Although we found that the oxidation of carveol with **3** (1 mol %), prepared by simple mixing of $Al(OPr^i)_3$ [purchased from Aldrich Chemical Co., Ltd. (99.99% purity)] and **1**, under otherwise similar conditions furnished carvone in 88% yield, use of CH_2Cl_2 as a solvent was a prerequisite.[28]

(31) The following procedure is representative (entry 3, Table 2): 2-Hydroxy-2′-(perfluorooctanesulfonylamino)biphenyl (33.4 mg, 0.05 mmol) was placed in a dry, two-neck flask with a Teflon-coated stirring bar under argon, and toluene (5 mL) distilled from sodium metal was introduced. The resulting mixture was degassed, and a 0.5 M toluene solution of Me_3-Al (100 μL, 0.05 mmol) was added, followed by stirring for 15 min at 21 °C. Freshly distilled carveol (795 μL, 5.0 mmol) was introduced at the same temperature, and stirring was continued for an additional 30 min. Freshly distilled pivalaldehyde (652 μL, 6.0 mmol) was added at the same temperature, and the reaction solution was stirred for 1 h. Direct purification of this solution without aqueous workup by column chromatography on silica gel (1:18 ethyl acetate/hexane as an eluant) gave carvone (708 mg, 4.71 mmol; 94% yield). The ligand, 2-hydroxy-2′-(perfluorooctanesulfonylamino)biphenyl, can be recovered by subsequent elution with ethyl acetate.

(32) (a) Tischtschenko, W. *Chem. Zentralbl.* **1906**, *77*, I, 1309. (b) Ooi, T.; Miura, T.; Takaya, K.; Maruoka, K. *Tetrahedron Lett.* **1999**, *40*, 7695. (c) Deacon, G. B.; Gitlits, A.; Roesky, P. W.; Burgstein, M. R.; Lim, K. C.; Skelton, B. W.; White, A. H. *Chem. Eur. J.* **2001**, *7*, 127.