$CaCl_2$- or $MgCl_2$-Catalyzed Allylic Oxidations of Ionone-like Dienes

Min Yang,[a,c] Qian-Rong Peng,[b] Jing-Bo Lan,[a] Guang-Fu Song,[c] Ru-Gang Xie*[a]

[a] Department of Chemistry, Sichuan University, Chengdu, 610064, P. R. of China
Fax +86(28)85411684; E-mail: orgxie@scu.edu.cn; E-mail: schemorg@mail.sc.cninfo.net

[b] Technology Center, Guizhou Huang Guo Shu Tobacco Group, Guiyang, 550003, P. R. of China

[c] Department of Chemistry Technology, Guizhou University, Guiyang, 550003, P. R. of China

Received 16 April 2006

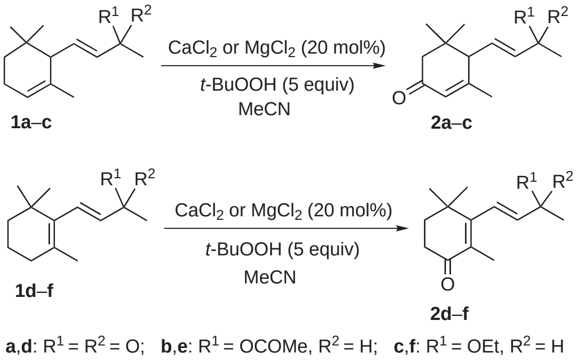
Abstract: The allylic oxidation of ionone-like dienes catalyzed by $CaCl_2$ or $MgCl_2$ with TBHP is presented. The method provides a facile method to synthesize dienones derived from ionone-like dienes in good to moderate yields. A plausible mechanism for the oxidation is proposed.

Key words: allylic oxidation, ionone-like dienes, calcium chloride, magnesium chloride, *tert*-butyl hydroperoxide

The allylic oxidation of alkenes to carbonyl compounds is a useful transformation in organic synthesis. It is undergoing continual refinement with the aim to develop more environmentally friendly, efficient, and selective processes. Some new strategies have been reported for such a transformation, such as the protocols using *tert*-butyl hydroperoxide (TBHP) catalyzed by transition metal ion centers (Cr, Ru, Cu, Co, Pd),[1] iodoxybenzene catalyzed by fluorous seleninic acid,[2] or TBHP catalyzed by dirhodium(II) caprolactamate.[3]

Ionones and their derivatives are important synthetic building blocks in the synthesis of many biologically active compounds.[4] The introduction of a carbonyl group at their allylic C–H bond can result not only in more complex molecules, but also yield more important intermediates for further transformations.[5] However, the direct synthesis of dienones through the allylic oxidation of ionones and their derivatives required either a stoichiometric amount of chromium reagents or a catalytic amount of chromium trioxide with TBHP.[5] Although the latter protocol avoided the use of stoichiometric reagents, the hazard arising from chromium trioxide remains an environmental problem. Therefore, it is highly desirable to develop practical, efficient, and safer reactions for the allylic oxidation of ionones and their derivatives.

It is well known that the most effective catalysts for oxidation are transition-metal ions that readily undergo one or more electron redox processes, for example Fe^{2+}/Fe^{3+}, Cu^{+}/Cu^{2+}, Co^{2+}/Co^{3+}, Mn^{2+}/Mn^{3+}, Cr^{3+}/Cr^{6+}, V^{4+}/V^{5+}, Rh^{4+}/Rh^{5+}.[6] To date only a few reports were presented on the use of Ca^{2+} as a catalyst in oxidation reactions, such as the oxidation of alcohols and the functionalization of saturated hydrocarbons with CO to carboxylic acids and esters.[7] It is interesting to note that in nature alkali-earth-metal ions, such as Ca^{2+} and Mg^{2+}, can act as Lewis acid catalysts.[8] Hence, we reasoned that such metal ions could catalyze the allylic oxidation through Lewis acid catalysis. As part of our continuing interests in exploring novel uses of simple metal catalysts,[9] herein we reported that Ca^{2+} and Mg^{2+} ions exhibited good catalytic activity in the allylic oxidation of α-ionone-like dienes.



Scheme 1 The allylic oxidation of ionone-like dienes

Using α-ionone (1 mmol) as the substrate and TBHP (5 equiv) as the oxidant in acetonitrile at 60 °C, we initially examined the catalytic effects of several simple calcium or magnesium salts. Among them, both $CaCl_2$ and $MgCl_2\cdot 6H_2O$ gave good product yields (66% and 65%, respectively for **2a**). Compound **2a** was also obtained in 45% yield with $MgSO_4$. However, only trace amounts of **2a** were found when $CaSO_4$, $Ca(OAc)_2\cdot H_2O$, $CaCO_3$, $CaHPO_4\cdot 2H_2O$, $Mg(OAc)_2\cdot 4H_2O$, and $(MgCO_3)_4\cdot Mg(OH)_2\cdot 5H_2O$ were employed. In the presence of $Ca(NO_3)_2\cdot 4H_2O$ as well as $Mg(ClO_4)_2\cdot 6H_2O$, the allylic oxidation did not proceed and **1a** could be recovered.

We then investigated the effect of the amount of $CaCl_2$ or $MgCl_2\cdot 6H_2O$ had on the allylic oxidation. As shown in Table 1, only trace amounts of the desired product were observed in the absence of $CaCl_2$ or $MgCl_2\cdot 6H_2O$. The yields were poor, when less than 20 mol% of $CaCl_2$ or $MgCl_2\cdot 6H_2O$ were used. However, good yields were obtained (65–67%) with 20–30 mol% of the catalyst (Table 1, entries 4, 5, 8, and 9). In addition, the yields of **2a** could not increase further when using more than 30 mol% catalyst.

SYNLETT 2006, No. 16, pp 2617–2620
Advanced online publication: 22.09.2006
DOI: 10.1055/s-2006-951476; Art ID: W08206ST

Table 1 Effect of Catalyst Loading[a]

Entry	Catalyst	Loading (mol %)	Conversion (%)[b]	Yield (%)[c]
1	–	0	17	trace
2	$CaCl_2$	5	71	39
3	$CaCl_2$	10	82	50
4	$CaCl_2$	20	95	66
5	$CaCl_2$	30	97	67
6	$MgCl_2\cdot 6H_2O$	5	40	17
7	$MgCl_2\cdot 6H_2O$	10	84	50
8	$MgCl_2\cdot 6H_2O$	20	95	65
9	$MgCl_2\cdot 6H_2O$	30	95	66

[a] Conditions: α-ionone (1 mmol), TBHP (5 equiv), MeCN (6 mL), 60 °C, 4 h.
[b] Conversions of **1a**.
[c] Isolated yields of **2a**.

It was noted that the amount of TBHP used not only affected the outcome of oxidation reactions, but also created experimental hazards.[1d] We noted that a large amount of TBHP (5–30 equiv) had been used in previous reports.[1] Hence, we investigated the amount of TBHP required in the oxidation reactions (Table 2). As shown in Table 2, when the amount of TBHP reached three and five equivalents, the desired product could be obtained in good yields (64–66%; Table 2, entries 3, 4, 7, and 8). Further addition of TBHP did not improve the product yield. It was thus established that this catalytic system required a lower amount of TBHP (3–5 equiv) than those required in previous reports.[1a–h]

Table 2 Effect of the Amount of Oxidant[a]

Entry	Catalyst	TBHP (equiv)	Conversion (%)[b]	Yield (%)[c]
1	$CaCl_2$	1	53	36
2	$CaCl_2$	2	75	50
3	$CaCl_2$	3	94	64
4	$CaCl_2$	5	95	66
5	$MgCl_2\cdot 6H_2O$	1	62	34
6	$MgCl_2\cdot 6H_2O$	2	78	50
7	$MgCl_2\cdot 6H_2O$	3	91	65
8	$MgCl_2\cdot 6H_2O$	5	95	65

[a] Conditions: α-ionone (1 mmol), $CaCl_2$ or $MgCl_2\cdot 6H_2O$ (20 mol%), MeCN (6 mL), 60 °C, 4 h.
[b] Conversions of **1a**.
[c] Isolated yields of **2a**.

The effect of reaction temperature on the efficacy of the oxidation was also examined. When the $CaCl_2$-promoted allylic oxidation of α-ionone **1a** in acetonitrile was conducted at 20 °C, 40 °C, and 50 °C, 3-oxo-α-ionone **2a** was obtained in 20%, 31%, and 45% yields, respectively. Good yields (66% and 67%) were obtained when the reaction was run at 60 °C and 70 °C. However, at 80 °C a slight decrease in the yield of **2a** (64%) was observed. Similar results were obtained when $MgCl_2\cdot 6H_2O$ was employed. Thus, the optimum reaction temperature was determined to be 60–70 °C.

We also investigated the effect of other solvents on the allylic oxidations at 60 °C or under reflux. It was found that with 20 mol% of $CaCl_2$ or $MgCl_2\cdot 6H_2O$, good yields (65% and 63%, respectively) of **2a** were obtained in acetone and moderate yields (54% and 58%, respectively) of **2a** were afforded in dichloromethane. Using chloroform, hexane, benzene, toluene, tetrahydrofuran, diethyl ether, and ethyl acetate as solvent, the allylic oxidation of α-ionone **1a** could also produce 3-oxo-α-ionone **2a** but in poor yields. Moreover, we also found that under solvent-free conditions 33% and 24% yields of **2a** were afforded, respectively, when 20 mol% of $CaCl_2$ and $MgCl_2\cdot 6H_2O$ were employed.

Utilizing optimized conditions, 20–30 mol% of $CaCl_2$ or $MgCl_2\cdot 6H_2O$, 3–5 equivalents of 70% aqueous TBHP in acetonitrile at 60 °C, we examined the oxidation of other ionone-like dienes including α/β-ionone (**1a** and **1d**), α/β-ionyl acetates (**1b** and **1e**), and α/β-ionyl ether (**1c** and **1f**) (Table 3). α-Ionone and its acetate as well as ether derivatives could be oxidized to the corresponding dienones in better yields than that of β-ionone and its derivatives. This was probably due to the increased steric hindrance of the allylic methyl of β-ionone and its derivatives. It is also noteworthy that the oxidation of β-ionyl acetate and α/β-ionyl ether had to be conducted in a shorter reaction time because prolonging the reaction time resulted in the oxidative cleavage of the ester and ether bond to produce the corresponding 4-oxo-β-ionone **2b** or 3-oxo-α-ionone **2a**.

Mechanistically, the evolution of oxygen was confirmed by passing the evolved gas through aqueous potassium pyrogallate and is consistent with the formation of *tert*-butyl peroxy radical *t*-BuOO·. Furthermore, the UV-visible spectrum of the catalyst upon addition of TBHP revealed a low-energy absorption at 269 nm, probably due to the coordination of Ca^{2+} or Mg^{2+} to the oxygen atom of TBHP. The resulting mixture was investigated by GCMS after the reaction proceeded for 1 h, 2 h, and 3 h; in all cases the existence of α-ionone-*tert*-butyl peroxyether **7** was confirmed. Based on the above observations, we speculated a radical mechanism catalyzed by the Lewis acid accounted for the reaction (Scheme 2). Hence, Ca^{2+} or Mg^{2+} was coordinated to the oxygen atom of TBHP and promoted the homolysis of the O–O bond to produce radicals HO· and *t*-BuO·. The *t*-BuO· then reacted with TBHP to yield *tert*-butyl peroxy radical *t*-BuOO· (**3**), which could then abstract a hydrogen atom from compound **1a** to yield an allylic radical **6**. At the same time, HO· carried by

Table 3 Allylic Oxidation of Six Substrates[a,10]

Entry	Substrate	Catalyst	Time (h)	Product	Yield (%)[b]
1	**1a**	$CaCl_2$	4	**2a**	66
2	**1b**	$CaCl_2$	5	**2b**	65
3	**1c**	$CaCl_2$	2	**2c**	55[c]
4	**1d**	$CaCl_2$	5	**2d**	58
5	**1e**	$CaCl_2$	1.5	**2e**	52[c]
6	**1f**	$CaCl_2$	1	**2f**	45[c]
7	**1a**	$MgCl_2\cdot 6H_2O$	4	**2a**	65
8	**1b**	$MgCl_2\cdot 6H_2O$	5	**2b**	63
9	**1c**	$MgCl_2\cdot 6H_2O$	2	**2c**	54[c]
10	**1d**	$MgCl_2\cdot 6H_2O$	5	**2d**	60
11	**1e**	$MgCl_2\cdot 6H_2O$	1.5	**2e**	53[c]
12	**1f**	$MgCl_2\cdot 6H_2O$	1	**2f**	42[c]

[a] Conditions: substrate (1 mmol), $CaCl_2$ or $MgCl_2\cdot 6H_2O$ (20 mol%), TBHP (5 equiv), MeCN (6 mL), 60 °C.
[b] Isolated yields.
[c] TBHP (3 equiv).

complex **4** reacted with TBHP to produce water and complex **5**. The complex transferred *t*-BuOO· to the allylic radical **6** to form *tert*-butyl peroxyether **7** and regenerate the catalyst (Ca^{2+} or Mg^{2+}). Finally, rapid decomposition of **7** yielded oxidation product enone **2a**.

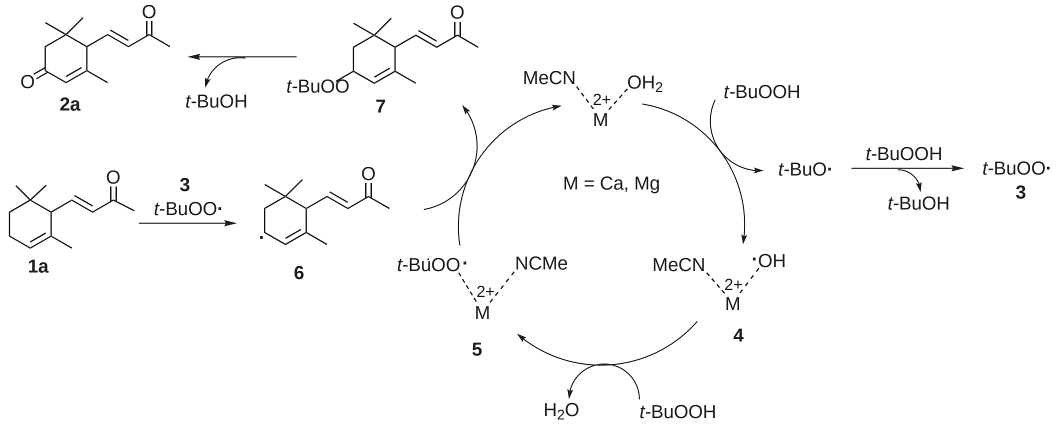
In summary, we have developed a novel catalytic allylic oxidation of ionone-like dienes based on $CaCl_2$ or $MgCl_2$, which offers an efficient and facile way to synthesize dienones in moderate to good yields. The use of the alkali-earth-metal catalyst, which is inexpensive and non-toxic, could open a new area in allylic oxidation reactions. Efforts are currently underway in our laboratories to elucidate the details of the reaction mechanism.

Acknowledgment

We thank the Science Research Program of Guizhou Huang Guo Shu Tobacco Group for financial support.

References and Notes

(1) (a) Pearson, A. J.; Chen, Y. S.; Hsu, S. Y.; Ray, T. *Tetrahedron Lett.* **1984**, *25*, 1235. (b) Muzart, J. *Tetrahedron Lett.* **1987**, *28*, 4665. (c) Sakthivel, A.; Dapurkar, S. E.; Selvam, P. *Appl. Catal., A* **2003**, *246*, 283. (d) Harre, M.; Haufe, R.; Nickisch, K.; Weinig, P.; Weinmann, H.; Kinney, W. A.; Zhang, X. *Org. Process Res. Dev.* **1998**, *2*, 100. (e) Salvador, J. A. R.; Melo, M. L. S.; Neves, A. S. C. *Tetrahedron Lett.* **1997**, *38*, 119. (f) Arsenou, E. S.; Koutsourea, A. I.; Fousteris, M. A.; Nikolaropoulos, S. S. *Steroids* **2003**, *68*, 407. (g) Allal, B. A.; Firdoussi, L. E.; Allaround, S.; Karim, A.; Castanet, Y.; Mortreux, A. *J. Mol. Catal. A: Chem.* **2003**, *200*, 177. (h) Salvador, J. A. R.; Clark, J. H. *Chem. Commun.* **2001**, 33. (i) Yu, J. Q.; Corey, E. J. *Org. Lett.* **2002**, *4*, 2727. (j) Yu, J. Q.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 3232.
(2) Crich, D.; Zou, Y. *Org. Lett.* **2004**, *6*, 775.
(3) Catino, A. J.; Forslund, R. E.; Doyle, M. P. *J. Am. Chem. Soc.* **2004**, *126*, 13622.
(4) (a) Anzaldi, M.; Sottofattori, E.; Dusatti, F.; Ferro, M.; Pani, M.; Balbi, A. *Eur. J. Med. Chem.* **2000**, *35*, 797. (b) Zeng, F.; Negishi, E. I. *Org. Lett.* **2001**, *3*, 719. (c) Pommier, A.; Stepanenko, V.; Jarowicki, K.; Kocienski, P. J. *J. Org. Chem.* **2003**, *68*, 4008.
(5) (a) Aasen, A. J.; Kimland, B.; Enzell, C. R. *Acta Chem. Scand.* **1973**, *27*, 2107. (b) Aasen, A. J.; Hlubucek, J. R.; Enzell, C. R. *Acta. Chem. Scand.* **1974**, *28*, 285. (c) Davis, D. L.; Stevens, K. L.; Jurd, L. *J. Agric. Food. Chem.* **1976**, *24*, 187. (d) Kaiser, R.; Lamparsky, D. *Helv. Chim. Acta* **1978**, *61*, 2328. (e) Becher, E.; Albrecht, R.; Bernhard, K.; Leuenberger, H. G. W.; Mayer, H.; Muller, R. K.; Schuep, W.; Wagner, H. P. *Helv. Chim. Acta* **1981**, *64*, 2419. (f) Kaiser, R. US Pat. 4,963,193, **1990**. (g) Kim, B. T.; Min, Y. K.; Asami, T.; Park, N. K.; Kwon, O. Y.; Cho, K. Y.; Yoshida, S. *Tetrahedron Lett.* **1997**, *38*, 1797. (h) Young, J. J.; Jung, L. J.; Cheng, K. M. *Tetrahedron Lett.* **2000**, *41*, 3415.
(6) (a) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, **1981**. (b) *Metal-Catalyzed Selective Oxidations*. In *Peroxide Chemistry – Mechanistic and Preparative Aspects of Oxygen Transfer*; Adam, W., Ed.; Wiley: Weinheim, **2000**, 301.



Scheme 2 Mechanistic proposal for the allylic oxidation catalyzed by Lewis acid $CaCl_2$ or $MgCl_2\cdot 6H_2O$

(7) (a) Asadullah, M.; Kitamura, T.; Fujiwara, Y. *J. Catal.* **2000**, *195*, 180. (b) Suppes, G. J.; Roy, S.; Ruckman, J. *AIChE J.* **2001**, *47*, 2102.

(8) Dugas, H. *Bioorganic Chemistry: A Chemical Approach to Enzyme Action*, 3rd ed.; Springer-Verlag: New York, **1996**, 165.

(9) (a) Lan, J. B.; Chen, L.; Yu, X. Q.; You, J. S.; Xie, R. G. *Chem. Commun.* **2004**, *2*, 188. (b) Lan, J. B.; Zhang, G. L.; Yu, X. Q.; You, J. S.; Chen, L.; Yang, M.; Xie, R. G. *Synlett* **2004**, 1095. (c) Zhang, S. Y.; Lan, J. B.; Su, X. Y.; Guo, S. J.; Chen, L.; You, J. S.; Xie, R. G. *J. Chem. Res.* **2005**, *7*, 418.

(10) **Allylic Oxidation of Ionone-Like Dienes; Typical Procedure**: To a mixture of ionone-like diene **1** (1 mmol) and $CaCl_2$ or $MgCl_2{\cdot}6H_2O$ (0.2 mmol) in MeCN (6 mL) was addded aq TBHP (70%, 3–5 mmol) in one or two portions under vigorous stirring at 60 °C for 1–5 h. The resulting mixture was concentrated under reduced pressure to give a residue (0.5 mL), which was purified by column chromatography on silica gel (PE–EtOAc, 3:1) to give dienone **2** and small amounts of 5,6-β-epoxides. Alternatively, the product could be isolated by distillation under reduced pressure, particularly when the reaction was performed on >5 mmol scale. Analytical data for compounds **2a**, **2b**, **2d**, and **2e** is consistent with those previously reported.[5a,c,f]

Compound **2c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.92 (br s, 1 H), 5.46–5.49 (m, 1 H), 5.46–5.49 (m, 1 H), 3.81–3.85 (m, 1 H), 3.29–3.50 (m, 2 H), 2.50–2.53 (m, 1 H), 2.31 (d, *J* = 16.8 Hz, 1 H), 2.06 (d, *J* = 16.8 Hz, 1 H), 1.88 (d, *J* = 1.2 Hz, 3 H), 1.22 (d, *J* = 4 Hz, 3 H), 1.16 (t, *J* = 5.4 Hz, 3 H), 1.01 (s, 3 H), 0.98 (s, 3 H). ^{13}C NMR (400 MHz): δ = 198.75, 161.49, 137.07, 127.98, 125.69, 63.44, 55.46, 47.44, 35.88, 29.48, 27.27, 26.94, 23.45, 21.68, 15.22. HRMS (ESI): *m*/*z* calcd for $C_{15}H_{24}O_2$ $[M + Na]^+$: 259.1674; found: 259.1669.

Compound **2f**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.16 (d, *J* = 16.0 Hz, 1 H), 5.55 (q, *J* = 16.4 Hz, 1 H), 3.93–3.99 (m, 1 H), 3.40–3.60 (m, 2 H), 2.50 (t, *J* = 7.0 Hz, 2 H), 1.85 (t, *J* = 6.8 Hz, 2 H), 1.81 (s, 3 H), 1.31 (d, *J* = 6.8 Hz, 3 H), 1.23 (t, *J* = 7.2 Hz, 3 H), 1.16 (s, 3 H), 1.15 (s, 3 H). ^{13}C NMR (200 MHz): δ = 199.26, 160.45, 139.02, 129.92, 126.77, 63.68, 37.17, 35.33, 34.22, 27.27, 27.27, 26.50, 21.77, 15.36, 13.31. HRMS (ESI): *m*/*z* calcd for $C_{15}H_{24}O_2$ $[M + Na]^+$: 259.1674; found: 259.1674.