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Ruthenium-Mediated Oxidation under Buffered Conditions: A Simple and Useful Protocol for the Synthesis of Norbornyl α-Diketones with Acid Sensitive Functionalities

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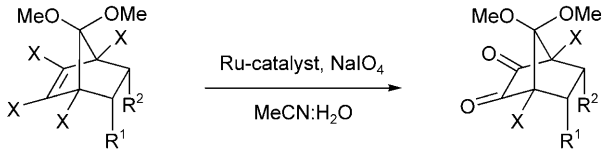
Abstract: The supported ruthenium-catalyzed oxidation of the 1,2-dihaloalkene moiety in tetrahalonorbornyl derivatives possessing acid labile functionalities to afford the corresponding α-diketones is demonstrated. The protocol was successfully applied in the synthesis of a cyclopenta-annulated δ-lactone derived from D-mannitol.

Keywords: Diels–Alder reaction; α-diketones; δ-lactones; oxidation; ruthenium; supported catalysts

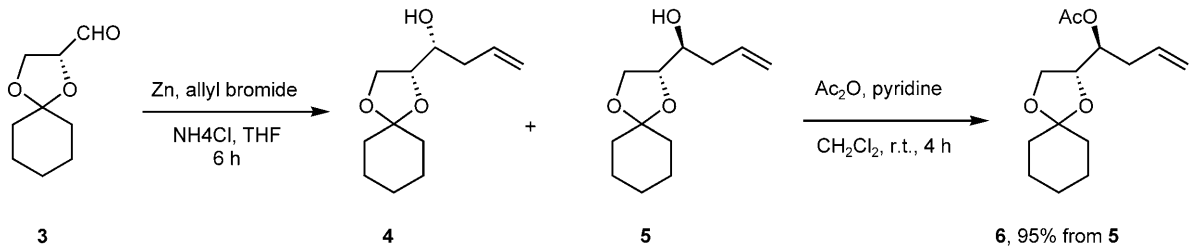


Scheme 1. Ruthenium-catalyzed oxidation of the tetrahalonorbornyl derivatives.[5,6]

Transition metal-catalyzed reactions remained the organic chemist's forte for a long time and have been incessantly used for several important organic transformations ever since the advent of their use as catalysts.[1] Ruthenium is unique among the transition metals because of the broad range of oxidation states feasible (−2 to +8). This uniqueness of ruthenium, coupled with its presence in the centre of the periodic table offers desirable properties that are favourable for catalysis.[2] Ru-mediated oxidations are resourceful and have wide ranging applications along with the various other uses of Ru-based catalysis. RuO_4, a very powerful oxidizing agent was the first Ru species that was found to be useful in organic synthesis.[3] Although RuO_4 was used in stoichiometric amounts in the beginning, gradually several methods were developed to use catalytic amounts of $RuCl_3$ or RuO_2 as readily available catalyst precursor along with a co-oxidant of choice.[4]

In the recent past, we have demonstrated the conversion of tetrahalonorbornyl derivatives (**1**) to the corresponding norbornyl α-diketones (**2**) by employing catalytic $RuCl_3 \cdot 3H_2O$ along with the co-oxidant $NaIO_4$ in a solvent mixture of acetonitrile and water (Scheme 1).[5] Subsequently, with the intent to make the catalyst handling easier, and to come up with a benign and economical protocol, we developed a supported catalyst, Ru-LDH (layered double hydroxide).[6] The improved catalyst also gave us the advantage of reusing the ruthenium catalyst without any problem. The α-diketones obtained were efficiently and extensively used by our group for the synthesis of various natural products, intermediates and non-natural products.[7] This methodology was even used by others with equal efficacy in some applications.[8] While the α-diketones are high yielding in most of the cases, we faced problems while handling substrates that have acid-labile functionalities. Herein, we detail the extension of our recently reported protocol for the synthesis of achiral cyclopenta-annulated δ-lactones[9] to the enantiomerically pure δ-lactones, which involves the use of buffered ruthenium oxidation conditions.

To obtain the chiral δ-lactone, we wanted to use homoallyl alcohol **5** as the dienophile because of our interest in using D-mannitol-derived products for the synthesis of enantiomerically pure tetrahalonorbornyl derivatives.[7a] Treatment of the D-mannitol-derived *R*-2,3-*O*-cyclohexylideneglyceraldehyde **3** with allylzinc bromide as per the known protocol afforded a 3:1 diastereomeric mixture of the chromatographically separable homoallyl alcohols **4** and **5** in 75% yield (Scheme 2).[10] With our previous experience, wherein the Diels–Alder reaction of 1,2,3,4-tetrachloro-5,5-di-



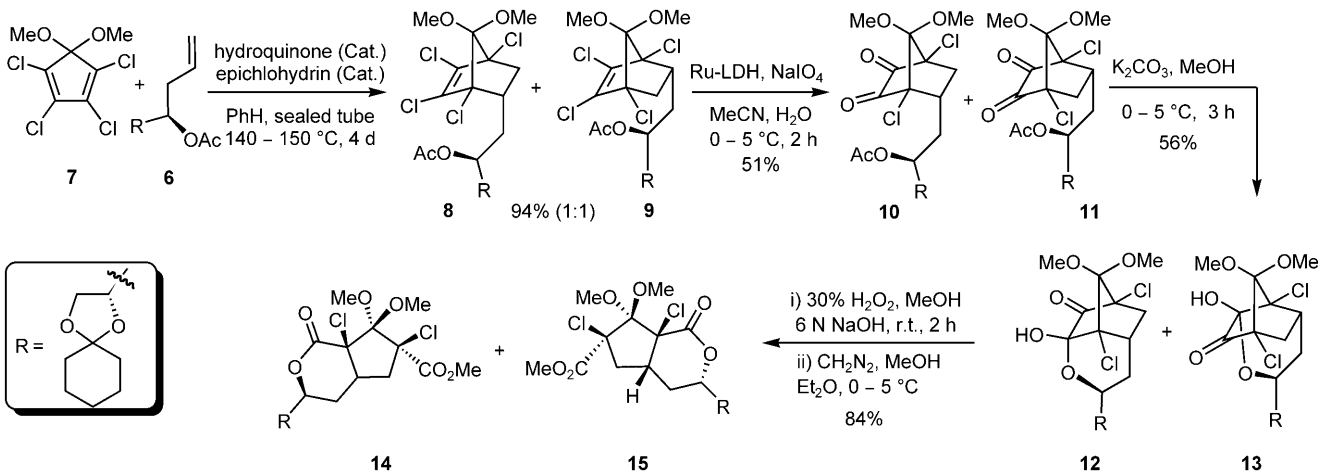
Scheme 2. Synthesis of the dienophile **6**.

methoxycyclopenta-1,3-diene (**7**) and homoallyl alcohols led to complications,[9] we decided to protect the alcohol group of the homoallyl alcohol **5** as the acetate **6** before subjecting it to the Diels–Alder reaction.

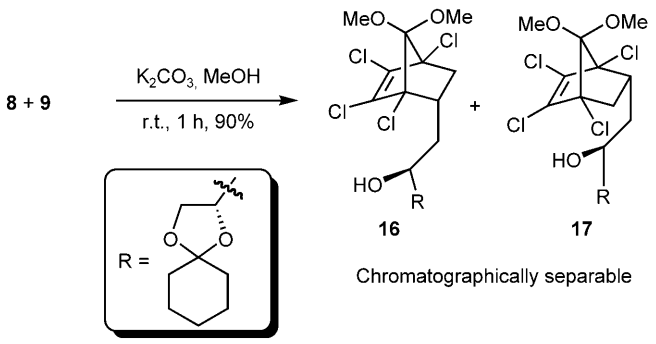
The Diels–Alder reaction was carried out by heating the diene **7** and dienophile **6** in benzene with catalytic amounts of epichlorohydrin (acid scavenger) and hydroquinone (free radical scavenger) in a sealed tube at 140–150 °C over 4 days affording the tetrachloronorbornyl adducts **8** and **9** in excellent yield. The products, after column chromatography, were analyzed by ^{1}H and ^{13}C NMR to determine the structure and diastereomeric ratio. From the NMR spectra, it was clear that two diastereomers were formed and their ratio was obtained from the ^{1}H NMR integration of the acetate group's methyl protons of the diastereomers **8** and **9**. The diastereomers were chromatographically inseparable. So, based on our previous experience with the synthesis of achiral δ-lactones,[9] we decided to continue with our synthetic plan with the mixture of diastereomers **8**, **9** and expected that we would be able to separate them at a later stage.

Having obtained the Diels–Alder adducts **8** and **9**, we wanted to convert them to α-diketones *en route* to the δ-lactones. Treatment of the tetrachloronorbornyl derivatives **8** and **9** with 1 mol% Ru-LDH and 1.6 equivalents of $NaIO_4$ in acetonitrile-water mixture (6:1),[6] furnished a mixture of inseparable α-diketones **10** and **11** in 51% yield (Scheme 3). Unlike the synthesis of achiral δ-lactones reported previously, where the acetate group deprotection was carried out with HCl or K_2CO_3, the presence of the acid-sensitive cyclohexylidene moiety makes it not possible to use HCl. Treating the mixture of α-diketones **10** and **11** with K_2CO_3 furnished the α-keto hemiketals **12** and **13** in 56% combined yield (Scheme 3). This inseparable diastereomeric mixture of α-keto hemiketals was analyzed by ^{1}H and ^{13}C NMR and carried forward for the next step. For the cleavage of α-keto hemiketals to δ-lactones, we applied the same protocol that was previously used by us for the synthesis of γ,δ-lactone fused cyclopentanoids.[7i,9] The mixture of α-keto hemiketals **12** and **13** was treated with alkaline H_2O_2 followed by esterification with diazomethane to give a diastereomeric mixture of δ-lactone fused cyclopentanoids **14** and **15**. Contrary to our expectations based on the previous results,[9] these δ-lactones **14** and **15** were chromatographically inseparable.

In the above-described synthesis (Scheme 3), there are three problems: a) the separation of diastereomeric δ-lactones **14** and **15**, b) lower yields of the α-diketones **10** and **11** from the corresponding tetra-



Scheme 3.



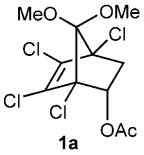
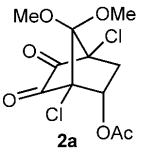
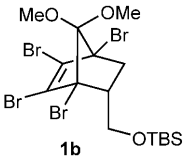
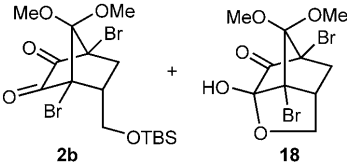
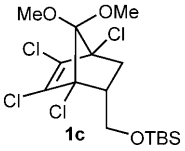
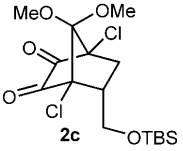
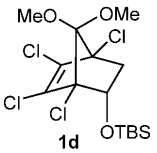
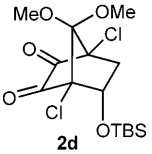
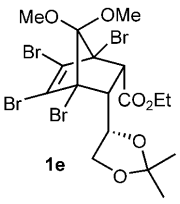
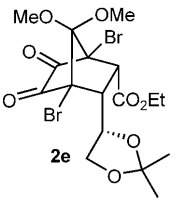
Scheme 4.

chloronorbornyl derivatives **8** and **9**, and c) lower yields of the α-keto hemiketals **12** and **13**.

To begin with, we wanted to check for the separation of the diastereomeric Diels–Alder adducts, by changing the alcohol protection group of the dienophile. Protecting the homoallyl alcohol **5** as the silyl ether followed by Diels–Alder reaction with **7** failed to help the diastereomeric separation. At this juncture, we wanted to check if the diastereomers could be separated by acetate deprotection of the tetrachloronorbornyl derivatives **8** and **9**. To our delight, the diastereomeric alcohols **16** and **17** obtained by the K_2CO_3-mediated acetate deprotection of a mixture of **8** and **9** were separable on silica gel column chromatography (Scheme 4). While the structures of alcohols **16** and **17** were confirmed from the ^1H and ^{13}C NMR data, it was not possible to assign the configurations with certainty from the NMR spectra alone. So, we decided to carry out single crystal X-ray analysis at a later stage to ascertain the configuration.

After solving the problem of the diastereomeric separation, the next issue was the lower yield of α-diketone formation from the Ru-catalyzed oxidation of the mixture of tetrachloronorbornyl derivatives **8** and **9**. The Ru-catalyzed norbornyl α-diketone formation reactions usually are very high yielding.[5,6] Lower

Table 1. Ru-LDH oxidations of tetrahalonorbornyls (substrates **1a**–**1d** are racemic).[a]

Entry	Tetrahalonorbornyl	Time	Product	Yield [%][b]
1	 **1a**	1 h	 **2a**	96
2	 **1b**	2 h	 **2b** **18**	85[c]
3	**1b**	3 h	**2b**	93
4	 **1c**	3 h	 **2c**	94
5	 **1d**	2 h	 **2d**	84
6	 **1e**	8 h	 **2e**	91

[a] *Reaction conditions*: 0.5 mmol tetrahalonorbornyl, 1.6 mmol $NaIO_4$, 1 mol% Ru-LDH relative to tetrahalonorbornyl, 1.5 mmol $NaHCO_3$ in MeCN:H_2O (7 mL, 6:1).
[b] Isolated yields.
[c] $NaHCO_3$ was not used.

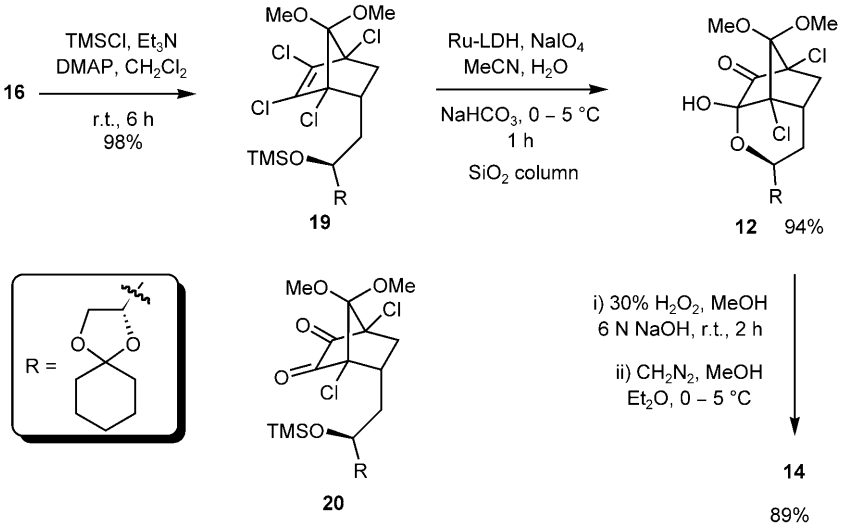
yields in this particular case (Scheme 3) can be attributed to the acid-labile cyclohexylidene groups. We have observed in the past that the reaction mixtures during the Ru-catalyzed oxidations of tetrahalonorbornyl derivatives tend to become acidic, resulting in lower yields of the diketones when the substrates contained acid-sensitive groups.

With the intent of developing suitable reaction conditions for the Ru-LDH oxidation of acid-labile tetrahalonorbornyl derivatives to their corresponding α-diketones, we wanted to check the applicability of Plietker's protocol,[11] i.e., the use of $NaHCO_3$ as buffer during Ru-catalyzed ketohydroxylation, for our reactions. To check if the addition of $NaHCO_3$ affects the formation of α-diketones, a sample reaction was carried out with the tetrachloronorbornyl derivative **1a**. Treatment of **1a** with 1 mol% Ru-LDH, 1.6 equivalents of $NaIO_4$, and 3 equivalents of $NaHCO_3$ in acetonitrile-water (6:1), furnished the α-diketone **1b** in 96% yield (entry 1, Table 1). Having confirmed that the addition of $NaHCO_3$ has no impact on the formation of α-diketone, these conditions were applied to a few other tetrahalonorbornyl derivatives possessing acid-labile functionalities (Table 1).

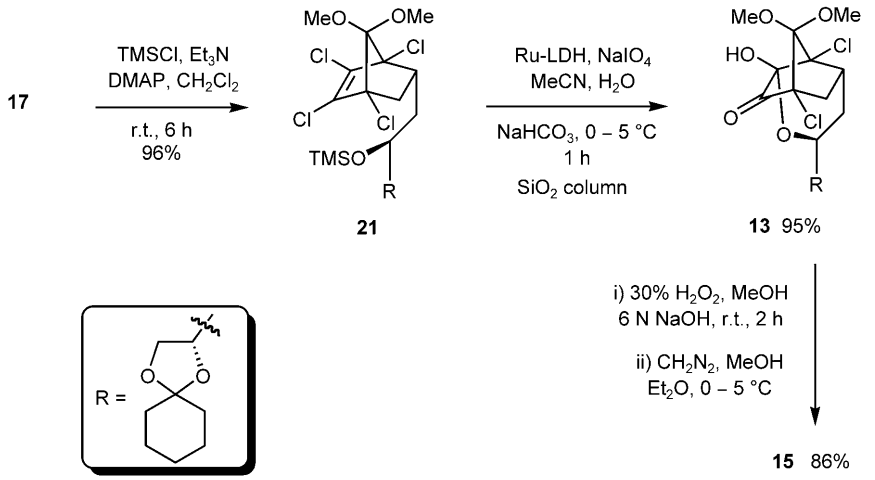
To show the difference between having and not having added $NaHCO_3$ in the reaction mixture, the ruthenium mediated oxidation of **1b** was carried out without adding $NaHCO_3$ (entry 2). The reaction resulted in the formation of α-diketone **2b** and the hemiketal **18**. When the same reaction was carried out with the addition of $NaHCO_3$, only the α-diketone **2b** was obtained (entry 3). Similarly, the silyl-protected tetrahalonorbornyl derivatives **1c**, **1d**, and **1e** were converted to their corresponding α-diketones **2c, 2d** and **2e**, respectively (entries 4, 5 and 6), in excellent yields. The enantiomerically pure α-diketone **2e** was of particular interest because of its potential applications. Work is in progress to exploit the rich functionalization that the α-diketone **2e** is endowed with.

To proceed further towards the δ-lactone fused cyclopentanoids, it was necessary to protect the alcohol in **16** with a protecting group that can be easily removed after the formation of the α-diketone. Attempted protection of the hydroxy group in **16** as the TBS ether was not possible under various conditions. This could be because TBSCl is bulky and the secondary alcohol is sterically not accessible. However, the alcohol was protected as the TMS ether **19**. Oxidation of the TMS ether **19** was carried out under the Ru-catalyzed buffered conditions as detailed in Table 1, expecting the diketone **20**. Interestingly, oxidation of the TMS ether **19** resulted in the formation of hemiketal **12**. Working up the reaction mixture after the Ru-catalyzed oxidation, we have obtained the diketone **20** (evident from the characteristic bright yellow colour of all the norbornyl α-diketones), but when purified through silica gel column the labile TMS group was knocked out resulting in the hemiketal **12** (Scheme 5). This was gratifying because this solved both the problems i.e., lower yields during α-diketone and hemiketal formations. The presence of the hemiketal was proved from the presence of three signals for ketal carbons at 110.5, 103.0, and 95.8 ppm in the ^{13}C NMR spectrum of **12.** The α-keto hemiketal **12** was treated with alkaline H_2O_2 followed by esterification with diazomethane to give the δ-lactone fused cyclopentanoid **14** which was characterized by ^{1}H and ^{13}C NMR spectroscopy. Presently, efforts to check the use of δ-lactone **14** as a precursor for conformationally constrained analogues of diacylglycerol (DAG) are in progress.

Furthermore, the second diastereomeric alcohol **17** was converted to the hemiketal **13** through Ru-catalyzed oxidation of the TMS ether **21** (Scheme 6). This



Scheme 5. Synthesis of the δ-lactone **14**.



Scheme 6. Synthesis of the α-keto hemiketal **13**.

was done in search of a compound that would give crystals suitable for single crystal X-ray analysis (Figure 1). The structure and absolute configuration of **13** is clear from its ORTEP diagram. Once the absolute configuration of **13** was clear, the configurations of all other compounds were easily established. Compound **13** was transformed to the lactone **15** in 86% yield employing alkaline H_2O_2 followed by diazomethane treatment (Scheme 6).

In conclusion, a simple protocol for the Ru-LDH-mediated reaction for the conversion of tetrahalonorbornyl derivatives bearing acid-sensitive functionalities to their corresponding α-diketones was demonstrated. This was achieved by employing $NaHCO_3$ along with $NaIO_4$. The method was applied in the synthesis of enantiomerically pure cyclopentannulated δ-lactone.

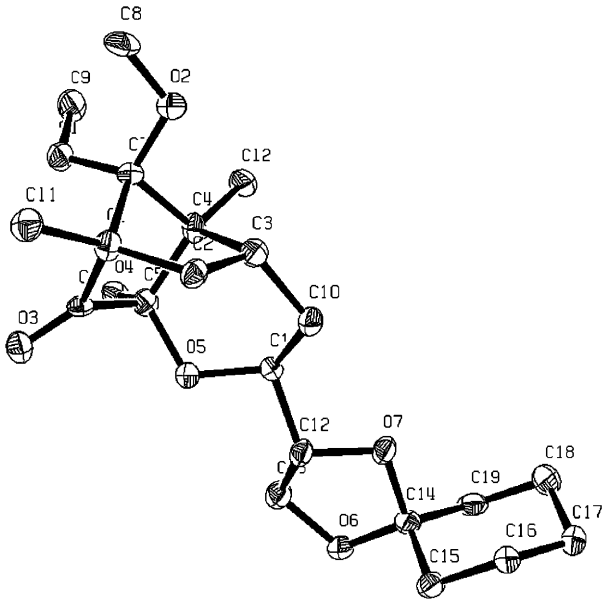


Figure 1. Structure and absolute configuration of α-keto hemiketal **13**.

Experimental Section

Procedure for Ru-Mediated Oxidation with $NaHCO_3$

To a vigorously stirred solution of the substrate (1 mmol) in MeCN (12 mL), $NaIO_4$ (1.6 mmol), Ru-LDH (50 mg), $NaHCO_3$ (3 mmol) and distilled H_2O (2 mL) were added and the mixture was allowed to stir at ambient temperature (34–37 °C) until completion of the reaction (monitored by TLC). The mixture was filtered and the residue was washed with MeCN. The filtrate (along with MeCN washings) was concentrated under reduced pressure and the crude mixture was dissolved in EtOAc, washed first with $Na_2S_2O_3$ solution (3 mL) and then with brine (3 mL). The EtOAc layer was dried (Na_2SO_4) and concentrated under vacuum to obtain the crude product which, after silica gel column chromatography (hexane and EtOAc as solvents), furnished the pure diketone.

CCDC 713443 contains the supplementary crystallographic data for this paper (α-keto hemiketal **13**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif

Supporting Information

Experimental procedures, characterization data of all the new compounds, copies of ^1H and ^{13}C NMR spectra of selected compounds are given in the Supporting Information.

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References

[1] a) J. B. Johnson, T. Rovis, *Angew. Chem.* **2008**, *120*, 852; *Angew. Chem. Int. Ed.* **2008**, ***47***, 840; b) M. T. Reetz, *Angew. Chem.* **2008**, *120*, 2592; *Angew. Chem. Int. Ed.* **2008**, *47*, 2556; c) M. Ouchi, T. Terashima, M. Sawamoto, *Acc. Chem. Res.* **2008**, *41*, 1120; d) M. Beller, C. Bolm, *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals*, Wiley-VCH, Weinheim, **2004**; e) E.-I. Negishi, L. Anastasia, *Chem. Rev.* **2003**, *103*, 1979.

[2] a) *Ruthenium in Organic Synthesis*, (Ed.: S.-I. Murahashi), Wiley-VCH, Weinheim, **2004**; b) *Ruthenium Catalysts and Fine Chemistry*, (Eds.: C. Bruneau, P. H. Dixneuf), Springer, Berlin, **2004**; c) V. Cadierno, J. Gimeno, N. Nebra, *Adv. Synth. Catal.* **2007**, *349*, 382; d) R. Drozdzak, B. Allaert, N. Ledoux, I. Dragutan, V. Dragutan, F. Verpoort, *Adv. Synth. Catal.* **2005**, *347*, 1721.

[3] a) C. Djerassi, R. R. Engle, *J. Am. Chem. Soc.* **1953**, *75*, 3839; b) T. K. M. Shing, V. W.-F. Tai, E. K. W. Tam, *Angew. Chem.* **1994**, *106*, 2408; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2312; c) T. K. M. Shing, E. K. W. Tam, V. W. F. Tai, I. H. F. Chung, Q. Jiang, *Chem. Eur. J.* **1996**, *2*, 50.

[4] For some recent reviews and reports on Ru-mediated oxidations, see a) T. Matsumoto, M. Ueno, N. Wang, S. Kobayashi, *Chem. Asian J.* **2008**, *3*, 196; b) S.-I. Murahashi, D. Zhang, *Chem. Soc. Rev.* **2008**, *37*, 1490; c) M. Pagliaro, S. Campestrini, R. Ciriminna, *Chem. Soc. Rev.* **2005**, *34*, 837, and references cited therein; d) M. Niggemann, A. Jelonek, N. Biber, M. Wuchrer, B. Plietker, *J. Org. Chem.* **2008**, *73*, 7028; e) B. Plietker, *Synthesis* **2005**, 2453.

[5] F. A. Khan, B. Prabhudas; J. Dash, N. Sahu, *J. Am. Chem. Soc.* **2000**, *122*, 9558.

[6] F. A. Khan, N. Sahu, *J. Catal.* **2005**, *231*, 438.

[7] For selected list of reports on the applications of norbornyl α-diketones from our group, see: a) F. A. Khan, Ch. Sudheer, *Org. Lett.* **2008**, *10*, 3029; b) F. A. Khan, B. Rout, *J. Org. Chem.* **2007**, *72*, 7011; c) F. A. Khan, B. Rout, *Tetrahedron Lett.* **2006**, *47*, 5251; d) F. A. Khan, C. N. Rao, *Tetrahedron Lett.* **2006**, *47*, 7567; e) F. A. Khan, J. Dash, Ch. Sudheer, N. Sahu, K. Parasuraman, *J. Org. Chem.* **2005**, *70*, 7565; f) F. A. Khan, J. Dash, *Eur. J. Org. Chem.* **2004**, 2692; g) F. A. Khan, J. Dash, Ch. Sudheer, *Chem. Eur. J.* **2004**, *10*, 2507; h) F. A. Khan, R. Satapathy, J. Dash, G. Savitha, *J. Org. Chem.* **2004**, *69*, 5295; i) F. A. Khan, J. Dash, N. Sahu, Ch. Sudheer, *J. Org. Chem.* **2002**, *67*, 3783; j) F. A. Khan, J. Dash, *J. Am. Chem. Soc.* **2002**, *124*, 2424; k) F. A. Khan, N. Sahu, J. Dash, B. Prabhudas, *J. Indian Inst. Sci.* **2001**, *81*, 325; l) F. A. Khan, K. Parasuraman, K. K. Sadhu, *Chem. Commun.* **2009**, DOI: 10.1039/b820479a.

[8] a) L. F. de Oliveira, V. E. U. Costa, *Tetrahedron Lett.* **2006**, *47*, 3565; b) G. Borsato, M. Crisma, O. De Lucchi, V. Lucchini, A. Zambon, *Angew. Chem.* **2005**, *117*, 7601; *Angew. Chem. Int. Ed.* **2005**, *44*, 7435; c) T.-C. Chou, K.-C. Liao, J.-J. Lin, *Org. Lett.* **2005**, *7*, 4843.

[9] F. A. Khan, K. S. Krishnakumar, Ch. Sudheer, *Synthesis* **2007**, 1054.

[10] A. Chattopadhyay, *J. Org. Chem.* **1996**, *61*, 6104.

[11] B. Plietker, *J. Org. Chem.* **2004**, *69*, 8287.

