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Diastereoselective Oxidation of Lithium and Chlorotitanocene Enolates Derived from Camphor

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Abstract: The diastereoselective oxidation of the camphor lithium enolate **2** and the corresponding chlorotitanocene enolate **4** by various electrophilic oxidants has been examined. The diastereoselectivity of the oxygen transfer depends on the metal fragment coordinated to the enolate. Thus, the chlorotitanocene enolate **4** leads to a much higher diastereomeric excess (de 88 to > 90%) than the corresponding lithium enolate **2** (de 12 to 60 %), with the formation of *exo*-3-hydroxycamphor (**5**) as the main isomer. Copyright © 1996 Elsevier Science Ltd

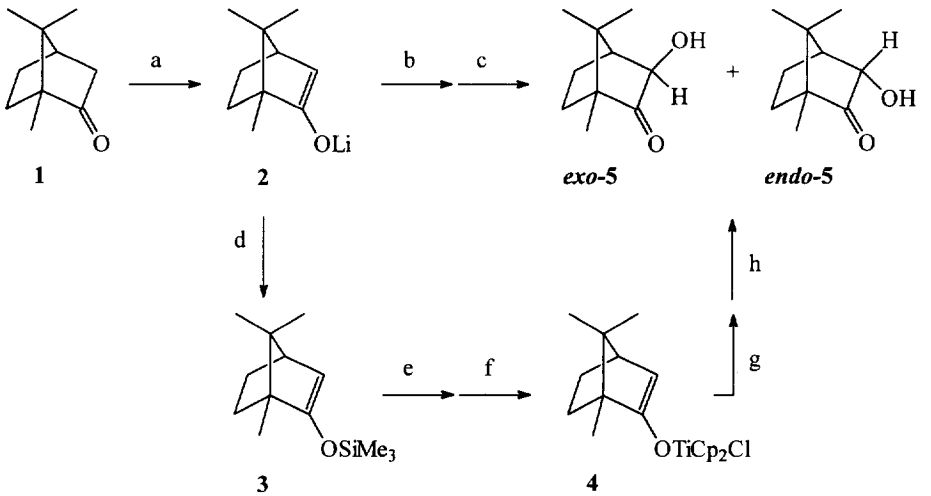
Introduction

α-Hydroxy carbonyl compounds represent important building blocks in the synthesis of complex natural products and are featured in many biologically active materials.[1] Consequently, a variety of methods for the preparation of this structural unit have been developed. A convenient and direct approach is the oxidation of enolates by using aprotic, electrophilic oxidants.[2-6] In this context, recently it was shown that the diastereoselectivity of the oxidation of chiral metal enolates is highly dependent on the metal fragment.[4] Thus, the increase of the diastereomeric excess in the order Ti > Si > Na, Li was related to the steric demand of the metal fragment ligated to the enolate. Moreover, the sterically less favoured diastereomer was mainly observed, e.g. *exo*-3-hydroxycamphor (**5**).

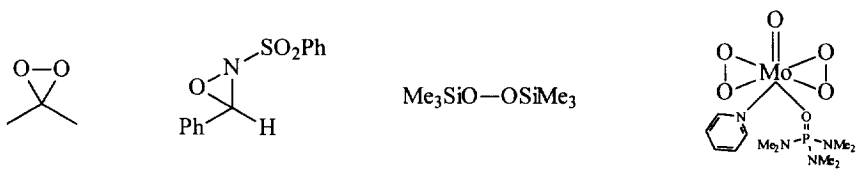
To assess the factors responsible for such a diasteroeselectivity trend in the oxidation of the lithium **2** and the chlorotitanocene **4** enolates of camphor, we decided to employ different electrophilic oxidants. Thus, dimethyldioxirane[7] (DMD), racemic 3-phenyl-2-phenylsulfonyloxaziridine[8] (PPO), bis(trimethylsilyl) peroxide[9] (BTSP), and the molybdenum peroxide reagent MoO_5·pyridine·HMPA[10] (MoOPH) were used as oxgen transfer agents. Of particular interest was to examine whether the stereoselectivity of the α hydroxylation is subject only to steric effects or whether also the electronic properties of the metal fragment and the nature of the oxidant play a significant role.

Results

The lithium enolate **2** was generated by deprotonation of camphor (**1**) with lithium diisopropylamide [Scheme 1, step (a)], which was subsequently oxidized by DMD (as acetone solution), PPO, BTSP and MoOPH [Scheme 1, steps (b) and (c)]. After aqueous workup, 3-hydroxycamphor (**5**) was obtained. The oxidation by DMD, PPO



(a) LDA (1.1 equiv), THF, -78 °C, 45 min; (b) DMD, PPO, BTSP or MoOPH (1.3-2.0 equiv), -20 °C; (c) NH_4F, H_2O, 20 °C; (d) Me_3SiCl (1.2 equiv), -78 to 20 °C, 75 min; (e) MeLi (1.1 equiv), THF, 0 to 20 °C; (f) Cp_2TiCl_2 (1.2 equiv), THF, -50 to -20 °C, 12-13 h; (g) DMD, PPO, BTSP or MoOPH; (h) NH_4F, H_2O, 20 °C, 2-3 h for DMD, PPO, BTSP and Na_2SO_3, NH_4F, H_2O, 20°C, 2-3 h for MoOPH.



DMD **PPO** **BTSP** **MoOPH**

Scheme 1

and BTSP (Table 1, entries 1-3) led to *exo*-3-hydroxycamphor (**5**) as the main diastereomer in moderate diasteromeric excess for DMD (de 52%) and BTSP (de 58%), but low diastereoselectivity for PPO (de 12%). In a preparative run, the DMD oxidation of the titanium enolate **4** afforded the *exo*-3-hydroxycamphor (**5**) in 79% yield (isolated pure material) and with the same diastereoselectivity (entry 6).

Table 1. Oxidation of the Camphor Lithium **2** and Chlorotitanocene **4** Enolates to 3-Hydroxycamphor (**5**)

entry	metal	oxidant	(equiv)	temp [°C]	time [h]	convn[a] [%]	yield[a,b] [%]	de[a] [%] (main isomer)
1	Li	DMD[c]	(1.64)	-78	0.03	> 95	> 95	52 (*exo*-**5**)
2	Li	PPO	(2.00)	-78	0.42	> 95	> 95	12 (*exo*-**5**)
3	Li	BTSP	(1.26)	20	12	63[d]	> 95	58 (*exo*-**5**)
4	Li	MoOPH	(1.56)	-20	0.25	76	> 95	60 (*endo*-**5**)
5	$TiCp_2Cl$	DMD[c]	(1.60)	-78	0.03	84[e]	93	88 (*exo*-**5**)
6	$TiCp_2Cl$	DMD[c]	(2.00)	-78	0.03	> 80[f]	79[g]	88 (*exo*-**5**)
7	$TiCp_2Cl$	PPO	(2.00)	20[h]	4	28[d]	42	> 90[i] (*exo*-**5**)
8	$TiCp_2Cl$	BTSP	(4.00)	20	48	< 5[j]	< 5[j]	< 5[j] (*exo*-**5**)
9	$TiCp_2Cl$	MoOPH	(2.50)	20	1	9	90	> 90 (*exo*-**5**)

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture; error ± 3% of the stated values; [b] yields are based on converted starting material if not stated differently; [c] DMD was used as ca. 0.06-0.09 *M* acetone solution; [d] camphorquinone was identified as additional product; [e] *exo*- and *endo*-3-chlorocamphor was identified as additonal products; [f] conversion could not be determined exactly because of overlapping signals; only traces of *exo*- and *endo*-3-chlorocamphor were detected; [g] yield of isolated material after column chromatography; [h] the oxidant was added at -50 °C and the reaction run at the stated temperature; [i] no *endo*-**5** was detected in the ^{1}H NMR spectrum of the crude reaction mixture; [j] only traces of *exo*-**5** were detected in the ^{1}H NMR spectrum of the crude reaction mixture.

In contrast to DMD, PPO and BTSP, for MoOPH (entry 4) the *endo* diastereomer was mainly formed (de 60%), in accordance with Vedejs[6,10] results. For the oxidation of the lithium enolate **2** by DMD (entry 1), the same diastereoselectivity has already been described.[5] In the case of PPO, contrary to our results, an *endo* selectivity has been reported, but no de values were given[3], when the lithium enolate **2** was prepared by deprotonation with lithium hexamethyldisilazene.

As the results in Table 1 reveal, a substantial difference in the reactivity of the oxidants was observed. For example, whereas the DMD oxidation of the lithium enolate **2** (conducted contrary to literature procedure[5] by addition of the DMD solution to the enolate) led to complete conversion to the acyloin **5** within 2 min at -78 °C (entry 1), for BTSP the conversion was only 63% even after 12 h at room temperature (entry 3). Furthermore, also the overoxidation product camphorquinone was observed.

The camphor chlorotitanocene enolate **4** was synthesized by the transmetalation reaction of the corresponding lithium enolate **2** with Cp_2TiCl_2. When the lithium enolate **2** was generated by deprotonation of camphor (**1**) with lithium diisopropylamide, the liberated diisopropylamine was also oxidized in the course of the oxidation of the chlorotitanocene enolate **4** with DMD and PPO; consequently, the yield of

α-hydroxyketone **5** dropped (oxidations of the enolate **4** with MoOPH were not conducted in the presence of amine). Therefore, the lithium enolate **2** was prepared under amine-free conditions by desilylation of the trimethylsilyl enol ether **3** with methyllithium [Scheme 1, steps (d) and (e)]. Subsequent reaction of the enolate **2** with Cp_2TiCl_2 afforded the titanium enolate **4** [Scheme 1, step (f)], which was then oxidized by DMD, PPO, BTSP and MoOPH [Scheme 1, step (g)]. The oxidation of the titanium enolate **4** (entries 5-8) gave much higher diastereoselectivities (de 88 to > 90%) than the lithium enolate **2** (entries 1-4), irrespective of the oxidant. Of note is the preferential *exo* diastereoselectivity in all cases. This means that for the MoOPH oxidation a reversed stereoselectivity is observed in the oxygen transfer when switching from the lithium **2** (entry 4) to the titanium enolate **4** (entry 9). Moreover, with increasing size of the oxidant, the diastereomeric excess is raised. While the reaction of the titanium enolate **4** with DMD (entry 5) also led to small amounts of the *endo*-**5**, the *exo*-**5** diastereomer was exclusively obtained with PPO, BTSP and MoOPH (entries 6-8). As a parallel trend, a decrease of the reactivity of the oxidants was observed as reflected by the reaction conditions in Table 1. Whereas the titanium enolate **4** was oxidized in 84% within 2 min at -78 °C by DMD (entry 5), the reaction temperature had to be raised to room temperature for the oxidation by PPO (entry 7). Even after 4 h, only 28% conversion was obtained with a high portion of the overoxidation product, namely camphorquinone. The MoOPH oxidant (entry 9) also required high reaction temperatures (20 °C) and only a low conversion of 9% was achieved. Again, BTSP (entry 8) was quite unreactive and led even after 48 h at room temperature only to traces of the *exo*-**5** product.

A temperature dependence was observed for the oxidation of the titanium enolate **4** with DMD in acetone. By gradually raising the temperature from -78 to ca. 20 °C (room temperature), a drastic decrease in the acyloin product **5** was found, with substantial formation of the acetone aldol product. At the elevated temperature, the titanium enolate **4** deprotonates acetone to inititate the aldol addition. Therefore, for best results, the reaction temperature has to be kept as low as possible, preferably at -78 °C.

Discussion

Except for the reaction of the lithium enolate **2** with MoOPH (entry 4), all oxidants and both enolates **2** and **4** resulted preferentially in the sterically disfavoured *exo*-3-hydroxycamphor (**5**) diastereomer (entries 1-3 and 5-8). For the titanium enolate **4** consistently very high diastereomeric excesses were achieved compared to the lithium enolate **2**, except with the ineffective oxidant BTSP (entry 8). Steric and stereoelectronic reasons seem to be responsible for this stereochemical pereference. The steric hindrance exercised by the *gem*-dimethyl-substituted bridge of the camphor enolate is expected to oblige the oxidant to attack preferentially from the *endo* side of the enolate double bond; thus, the *endo* isomer would be favoured. However, on account of stereoelectronic control, an electrophilic oxidant can in principle approach the enolate from the *exo* side. Such a stereoelectronic effect has been postulated for the reactions of electrophiles with enolates[11, 12] in analogy to the

Bürgi-Dunitz trajectory for the attack of nucleophiles on carbonyl substrates.[13] In the Bürgi-Dunitz trajectory[13] the preferred attack of the nucleophile on the carbonyl group requires a Nu-C-O angle of 105 ± 5°, as dictate by repulsive interactions between the frontier orbitals of the nucleophile and the carbonyl group. Similarly, the repulsion between the LUMO of the electrophile and the HOMO of the enolate oxygen is expected to promote a nonperpendicular orientation of the approaching reaction partners. Therefore, an electrophilic oxidant should preferentially attack the β-carbon atom of the enolate double bond at an angle > 90° (Figure 1). In this way the

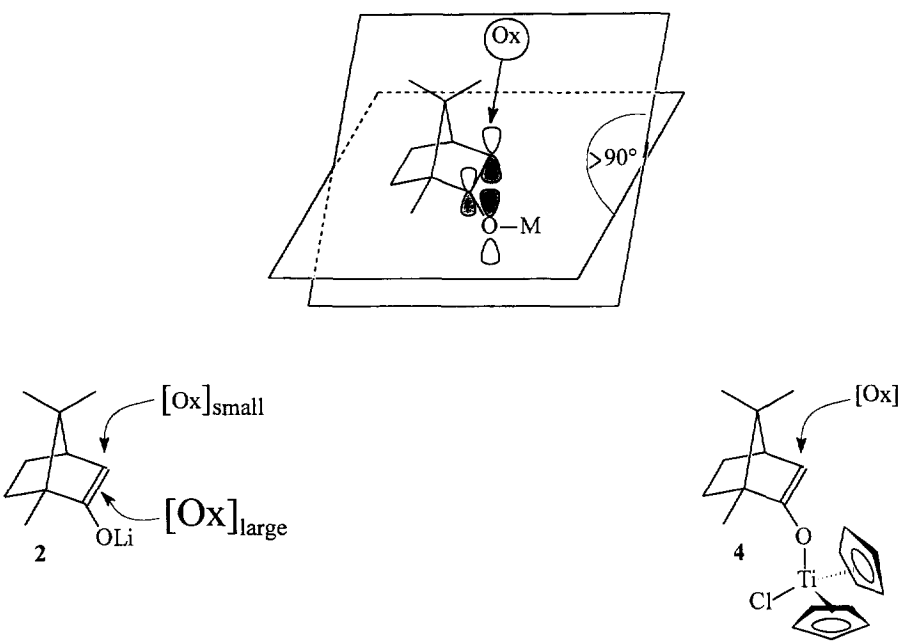


Figure 1. Preferred attack of electrophilic oxidants on camphor enolates.

steric interaction between the methyl substituent of the *gem*-substituted methylene bridge and the oxidant is reduced and, thus, an *exo* attack feasible. Yet, with growing size of the oxidant, the steric repulsion with the geminal methyl group can encumber the *exo* attack. Consequently, in the series DMD, PPO and MoOPH such *exo* attack on the lithium enolate **2** becomes less favoured and finally for the rather bulky MoOPH, the oxygen transfer is preferred from the *endo* side (Figure 1). Moreover, recent calculations suggest coordination of oxaziridines[14] to the lithium cation of enolates and complexation is also postulated for the oxidation of nucleophiles by MoOPH.[15] Such additional coordination of the oxidant to the lithium enolate **2** would also favour oxygen transfer from the *endo* side.

The high *exo* diastereoselectivity in the oxidation of the chlorotitanocene enolate **4** appears to be mainly controlled by the steric demand of the titanium fragment as recently proposed.[4] Due to steric interactions with

the *gem*-substituted dimethyl bridge, the bulky chlorotitanocene moiety is preferentially placed at the *endo* side of the double bond. In this way this side of the enolate plane is shielded toward attack of the oxidant and oxygen transfer occurs from the *exo* side (Figure 1). This is substantiated by the fact that on increase of the steric demand of the oxidant, the amount of *endo* diastereomer **5** is not raised for the titanium enolate **4** as is observed for the lithium enolate **2**; consequently for the former, exclusively the oxidation product *exo*-**5** is obtained. However, the growing steric interaction with the dimethyl-substituted bridge when changing from DMD to the larger PPO and MoOPH causes a drastic decrease in the rate of oxygen transfer because oxygen transfer from the *endo* side is prohibited by the bulky titanium fragment. Since attack at the double bond is hindered for the *exo* as well as for the *endo* side, a low reactivity is registered. Furthermore, coordination of the oxidant to the titanium center seems to be unlikely because of the electronic and steric saturation by the cyclopentadienyl ligands and the camphor. Therefore, electronic effects should not play a significant role and the diastereoselectivity in the oxygen transfer should not be influenced.

In summary, the diastereoselectivity in the oxidation of the lithium enolate **2** depends mainly on the steric demand of the oxidant such that for the large MoOPH *endo* rather than the usual *exo* attack is observed. In the case of the chlorotitanocene enolate **4,** the high preference of the *exo* product for all oxidants is mainly enforced by the large steric demand of the titanium fragment ligated to the enolate. The increasing size of the oxidant enhances the diastereoselectivity, but also significantly decreases its reactivity.

Experimental

General. All glassware was dried under vacuum (ca. 150 °C/0.1Torr) and all reactions were run under an argon gas atmosphere. THF was distilled under an argon gas atmosphere from potassium/benzophenone. The silyl enol ether **3**,[16] Cp_2TiCl_2,[17] 3-phenyl-2-phenylsulfonyloxaziridine (PPO)[8], MoO_5·pyridine·HMPA (MoOPH)[10] and dimethyldioxirane (DMD) (as acetone solution)[7] were synthesized according to literature. DMD was dried twice for two days each time over fresh molecular sieves (4 Å) at -20 °C. LDA was prepared and titrated according to the literature procedure[10]. The conversion and diastereomeric excess (de) were in all cases determined by ^{1}H NMR spectroscopy directly of the crude product mixture by analysis of the α proton of camphor (**1**) [d 2.35 (ddd)] and the α-hydroxy protons *exo* 3-H [δ 3.74 (s)] and *endo* 3-H [δ 4.20 (d)] of the two 3-hydroxycamphor isomers.

General Procedure of the Oxidation of the Lithium Enolate **2** *by DMD and PPO.* A solution of D-camphor (76.0 mg, 0.500 mmol) in THF (2 mL) was added dropwise under an argon gas atmosphere to a -78 °C cooled LDA solution in THF (1.1 equiv.). After stirring for 45 min, to the reaction mixture was rapidly added a -78 °C cold dimethyldioxirane solution (10.0 mL, 0.082 mmol) or a solution of 3-phenyl-2-phenylsulfonyloxaziridine (261 mg, 1.00 mmol) in THF (5 mL). After 2 min for DMD and 25 min for PPO, the reaction mixture was hydrolyzed by the addition of an aqueous, saturated NH_4F solution (1.5 mL) and stirred

for 1 h at room temperature (ca. 20 °C). The reaction mixture was filtered over Celite and the filtrate was concentrated under vacuum (20 °C/20 Torr) to about 2 mL. The residue was taken up into Et_2O (10 mL) and the organic layer dried over $MgSO_4$. After removal of the drying agent, the solvent was evaporated under vacuum (20 °C/20 Torr) and the conversion and diasteromeric excess were determined as described above.

Oxidation of the Lithium Enolate **2** *by BTSP.* To a solution of lithium enolate **2** (1.00 mmol) in THF (2 mL), prepared as described above, the bis(trimethylsilyl) peroxide (225 mg, 1.26 mmol) was added dropwise at -78 °C. After complete addition (ca. 2 min), the cooling bath was removed and stirring was continued for 12 h at room temperature. The reaction mixture was then hydrolyzed by addition of aqueous, saturated NH_4F solution (2 mL) and stirred for 3 h. After washing the reaction mixture with aqueous, saturated NH_4Cl solution (5 mL), the aqueous layer was extracted with Et_2O (2 × 2 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated under vacuum (20 °C/20 Torr). The conversion and diastereomeric excess were determined from the crude reaction mixture as described above.

Oxidation of the Lithium Enolate **2** *by MoOPH.* To a solution of lithium enolate **2** (1.00 mmol) in THF (10 mL), prepared as described above, MoO_5·pyridine·HMPA (651 mg, 1.50 mmol) was added at once at -20 °C. The solution turned orange and then yellow. After 5 min, additional MoOPH (35.0 mg, 0.080 mmol) was added but no color change occurred. After stirring for another 10 min, an aqueous, saturated Na_2SO_3 solution (5 mL) was added to the reaction mixture to reduce excess MoOPH. The mixture was stirred for 20 min at room temperature and then washed with aqueous, saturated NaCl solution (15 mL). The aqueous layer was extracted with Et_2O (2 × 15 mL) and the combined organic layers washed with a mixture of aqueous saturated NaCl solution (10 mL) and 0.5 *N* HCl (10 mL). The aqueous extracts were again extracted with Et_2O (15 mL) and the combined organic layers dried over $MgSO_4$. After evaporation of the solvent (20 °C/20 Torr), the conversion and diastereomeric excesses were determined as described above.

Camphor Chlorotitanocene Enolate **4**. To a solution of silyl enol ether **3** (0.25 - 0.60 mmol, 1 equiv.) in THF (1 - 2 mL) was added a methyllithium solution in ether (1.1 equiv.) under an argon gas atmosphere at 0 °C. After removal of the cooling bath, the mixture was stirred for 45 min at room temperature. The reaction mixture was then cooled to -50 °C and a solution of of Cp_2TiCl_2 (1.2 equiv.) in THF (8-12 mL) was slowly added (ca. 10 min). After stirring for about 30 min, the red-brown reaction mixture was kept at -20 °C for 12-13 h to assure complete transmetalation, as monitored by ^1H NMR analysis in d_8-THF.

General Procedure of the Oxidation of the Chlorotitanocene Enolate **4**. To the chlorotitanocene enolate solution (0.25 - 0.60 mmol) in THF was added an excess of the oxidant as a solution (DMD in acetone, PPO inTHF) or neat (BTSP, MoOPH) and at a reaction temperatures stated in Table 1. After stirring for the reaction times stated in Table 1, the reaction mixture was hydrolyzed with aqueous, saturated NH_4F solution (1.5 mL)

and stirred for about 3 h at room temperature until the the color of the mixture changed from red-brown to yellow. After removal of the suspended material by filtration over Celite, the filtrate was worked up as described for the corresponding oxidation of the lithium enolate **2**.

Preparative Scale Oxidation of the Chlorotitanocene Enolate **4** *to 3-Hydroxy-1,7,7-trimethyl[2.2.1]bicycloheptan-2-one* (**5**). By following the above procedure, 503 mg (79%) of **5** was obtained as a colourless powder, mp 207-212° C (lit.[18] *exo* isomer 210-211° C), after column chromatography [silica gel, 2:1 petroleum ether (30-50° C)/diethyl ether] by starting from 848 mg (3.78 mmol) of trimethylsilyl enol ether **3**, 1.13 g (4.54 mmol) of Cp_2TiCl_2 and 103 mL (7.59 mmol) of a 0.073 *M* dimethyldioxirane solution. The *exo*:*endo* ratio was 94:6, as determined by ^{1}H NMR analysis of the crude reaction mixture as described above. The spectral data for *exo*- and *endo*-**5** match those reported[18].

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