Third International Electronic Conference on Synthetic Organic Chemistry (ECSOC-3), www.mdpi.org/ecsoc-3.htm, September 1-30, 1999

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Stereoselective a-Oxyfunctionalisation of Benzo(hetera)cyclanones by Dimethyldioxirane

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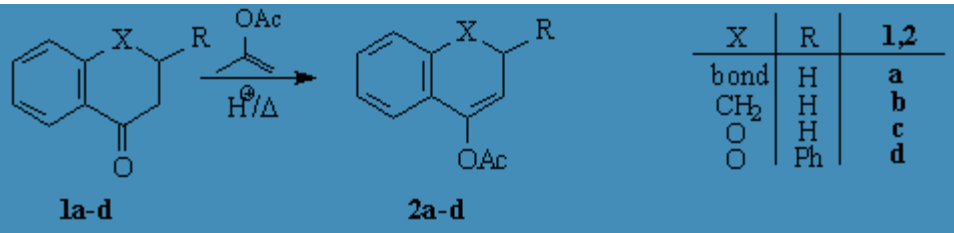
Received: 1 August 1999 / Uploaded: 16 August 1999

a-Hydroxy ketones including their cyclic derivatives are important synthetic building blocks. Chiral, non-racemic a-hydroxy ketones (and esters) are widespread in natural products. Therefore, there is a high demand to develop efficient methods for the construction of their enantiopure or at least enantiomerically enriched representatives and a number of procedures have been published in the last decades [1,2]. Our interest in the synthesis of a-hydroxy benzo(hetera)cyclanones, particularly 3-hydroxychromanones, prompted us to investigate the synthetic utility of the recently developed electrophilic chiral oxidizing system, namely dimethyldioxirane (DMD)/Jacobsen's catalyst [3] in the oxyfunctionalization of enol derivatives. Enol acetates were choosen as prochiral substrates because their higher stability as compared to silyl enol ethers and their high reactivity toward DMD [4].

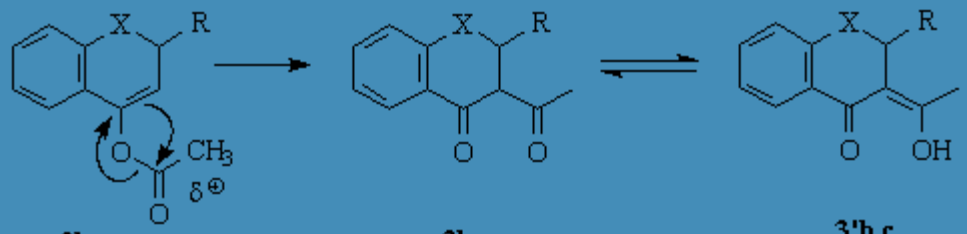
Enol acetates **2a-d** were prepared from the corresponding ketones **1a-d** by the well-known acid-catalyzed method [5] in moderate-to-good yields (48-65%).

In the case of tetralone (**1b**) and 4-chromanone (**1c**), small amount (4-8%) of a-acetylcyclanones **3b,c** have also been isolated. The formation of these by-products may be explained by more stable 1,3-diketones **3b,c** during the prolonged heating (Scheme 1) .



X	R	1,2
bond	H	a
CH_2	H	b
O	H	c
O	Ph	d

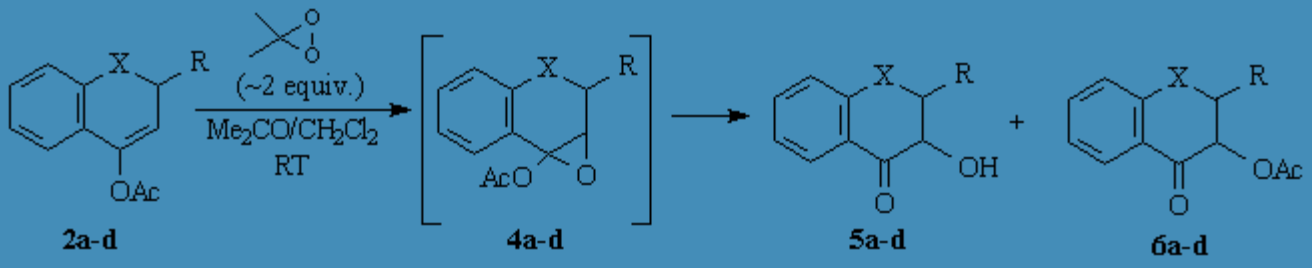
1a-d **2a-d**



2b,c **3b,c** **3'b,c**

Scheme 1

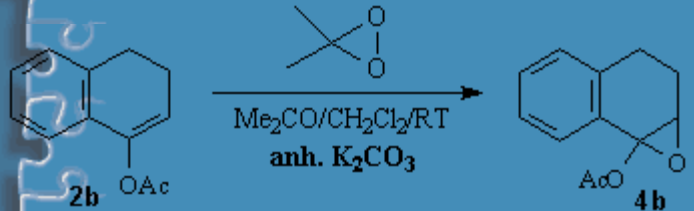
When enol acetates **2a,b** were reacted with DMD under the standard conditions, only a-hydroxy ketones **5a,b** and a-acetoxy ketones **6a,b** have been isolated, traces of the intermediate epoxides **4a,b** could only be detected by TLC. When the reaction was conducted in the presence of anhydrous K_2CO_3 as additive to eliminate of any water and trace of acids, we were able to obtain epoxide **4b** in pure, crystalline form but analogous reaction of **2a** afforded only a mixture of **4a,5a** and **6a**. Oxidation of heterocyclic enol acetates **2c,d** proceeded smoothly and furnished only the corresponding a-ketols **5c,d** and acetate **6c,d** without any detectable amount of epoxides **4c,d** (Scheme 2). We can conclude that the stability of epoxides **4** highly depends on the structure of the substrate. Some selected results of oxidation experiments are shown in Table 1.



2a-d **4a-d** **5a-d** **6a-d**

X	R	2,4,5,6
bond	H	a
CH_2	H	b
O	H	c
O	Ph	d

Scheme 2



2b **4b**

Table 1. Oxidation of enol acetates **2** by DMD

Substrate	Additive	T (^oC)	NMR product ratio	Isolated yields (%) **4**	Isolated yields %) **5**	Isolated yields (%) **6**
2a	none	RT	-	0	31	49
2a	anh. K_2CO_3	-20	**4a:5a:6a**=75:2:23	-	-	-
2b	none	RT	**5b:6b**=35:65	0	29	63
2b	10 % H_2O	RT	**5b:6b**=46:54	0	24	22
2b	anh. K_2CO_3	-20	-	84	traces	traces
2c	anh. K_2CO_3	-20	**5c:6c**=43:57	0	15	34
2d	anh. K_2CO_3	-20	-	0	34[a,c]	17[b,c]

a pure 2,3-*trans* diastereomer

b mixture of diastereomers; 2,3-*cis*/2,3-*trans*=63:37 (^{1}H NMR)

c 3% flavone has also been isolated

Availability of the moderately stable, crystalline epoxide 4**b** allowed us to investigate the ring-opening process of a-acetoxy epoxides. The slow reaction in the absence of acids even at elevated temperature (Table 2, Entries 1, 2) clearly indicate that acetates **6a-d** do not form in the well-documented thermal rearrangement [2g, 6] but in a different, probably acid-catalysed pathway. 2-Acetoxytetralone (**6b**) proved to be stable under the rearrangement conditions, this control experiment unequivocally indicates that **5b** and **6b** form in two distinct way. Appropriate conditions were also found to transform epoxide 4**b** into a-ketol **5b** as a major or exclusive product (Table 2, Entries 4,5) (Scheme 3). **Scheme 3**

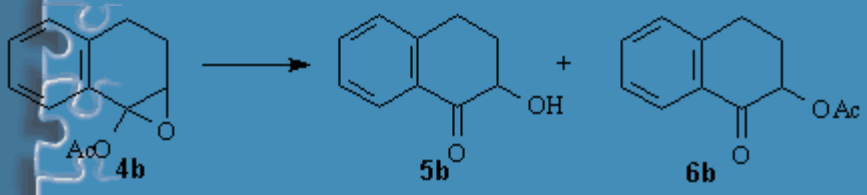
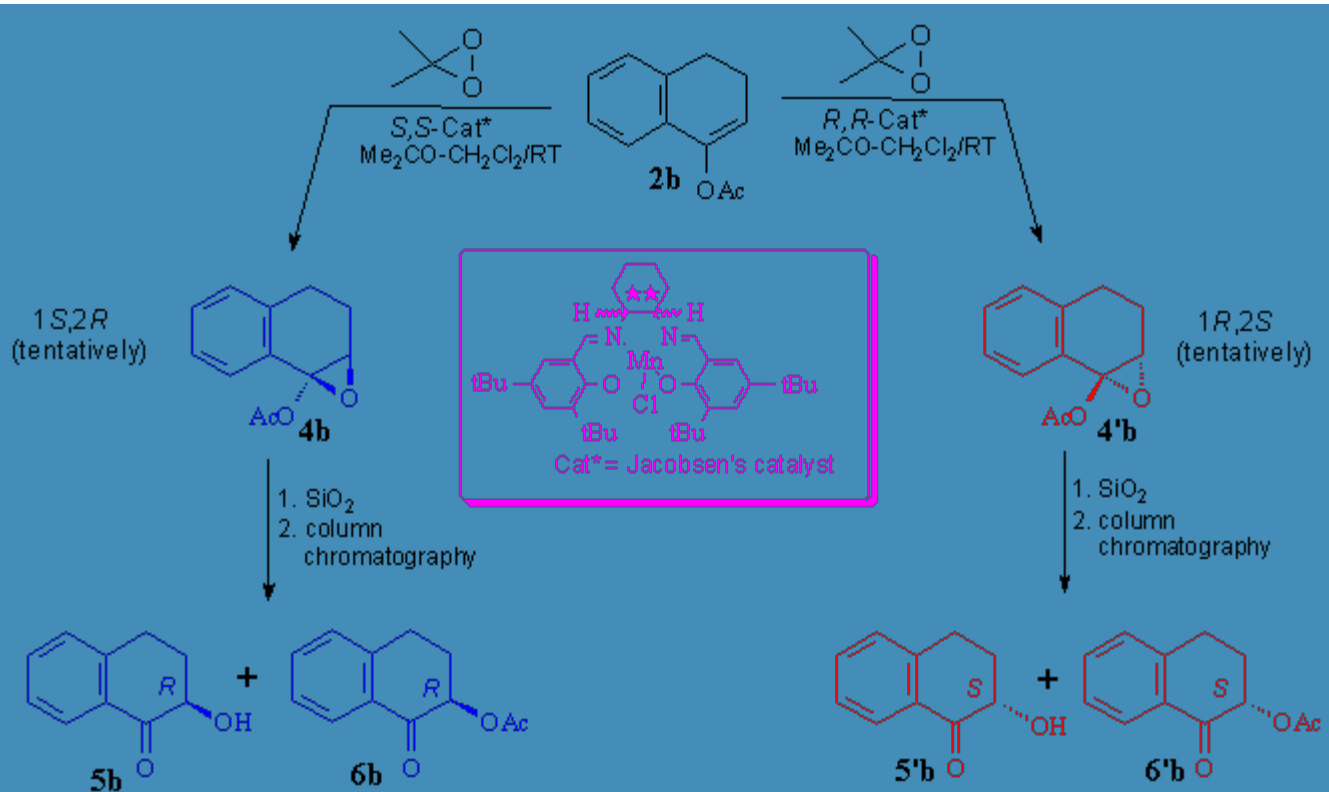


Table 2. Ring-opening of 1-acetoxy-1,2-epoxytetralin (**4b**)

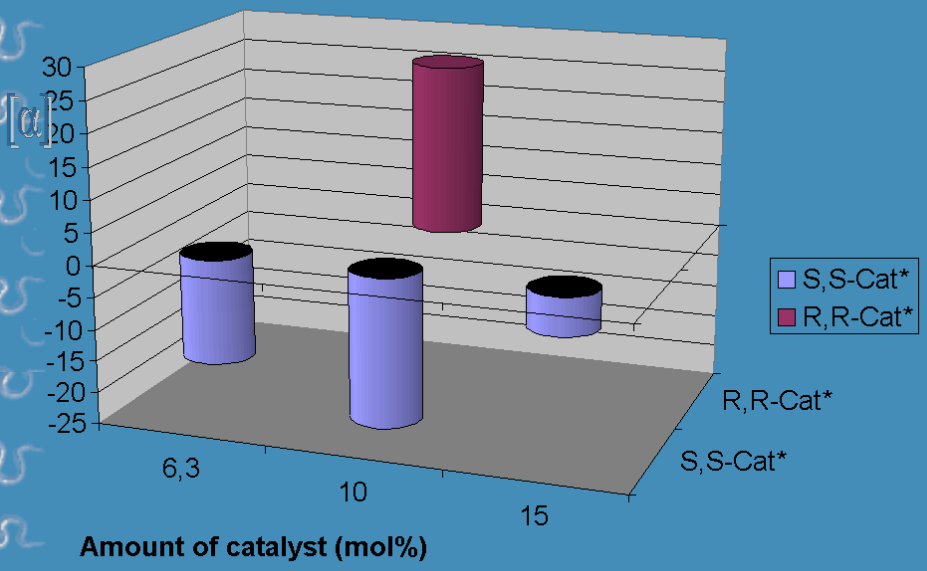
Entry	Conditions	Conversion (%)	NMR product ratio (**5b:6b**)	Isolated yields (%) **5b**	Isolated yields (%) **6b**
1	abs. PhH/RT/2d	no reaction	no reaction	no reaction	no reaction
2	abs. PhH/RT/2d	13	58:42	-	-
3	SiO_2/CH_2Cl_2/RT 2d	100	48:52	39	47
4	TFA (1 equiv.) MeOH/RT/1h	100	91:9	85	9
5	K_2CO_3/MeOH /N_2/RT/20 min	100	100:0	86	0

Oxidation of enol acetate **2b** by DMD in the presence of *R,R*- or *S,S*- Jacobsen's salen catalyst afforded optically active intermediate epoxides **4b** wich were transformed by SiO_2 (Kieselgel) treatment into the corresponding chiral, non-racemic 2-hydroxy- (**5b**) and 2-acetoxytetralone (**6b**) (Scheme 4).



Scheme 4

Absolute configurations of the products were determined by comparison of the sign of the measured specific rotation with literature values [2a,d]. The effect of the catalyst loading on the optical purity of the intermediate epoxide **4b** (Figure 1) and ring-opened products **5b, 6b** (Figure 2) as well as the effect of used co-ligands (axial ligands) on the optical purity of products **4b, 5b** and **6b** (Figure 3) and on the e.e. values [7] of products **5b, 6b** (Figure 4) were also studied. Best enantioselectivities were achieved by using 10 mol% Jacobsen's catalyst in the presence of 40 mol% imidazole or 4-phenylpyridine-N-oxide (PPNO) as co-ligand. **Figure 1**



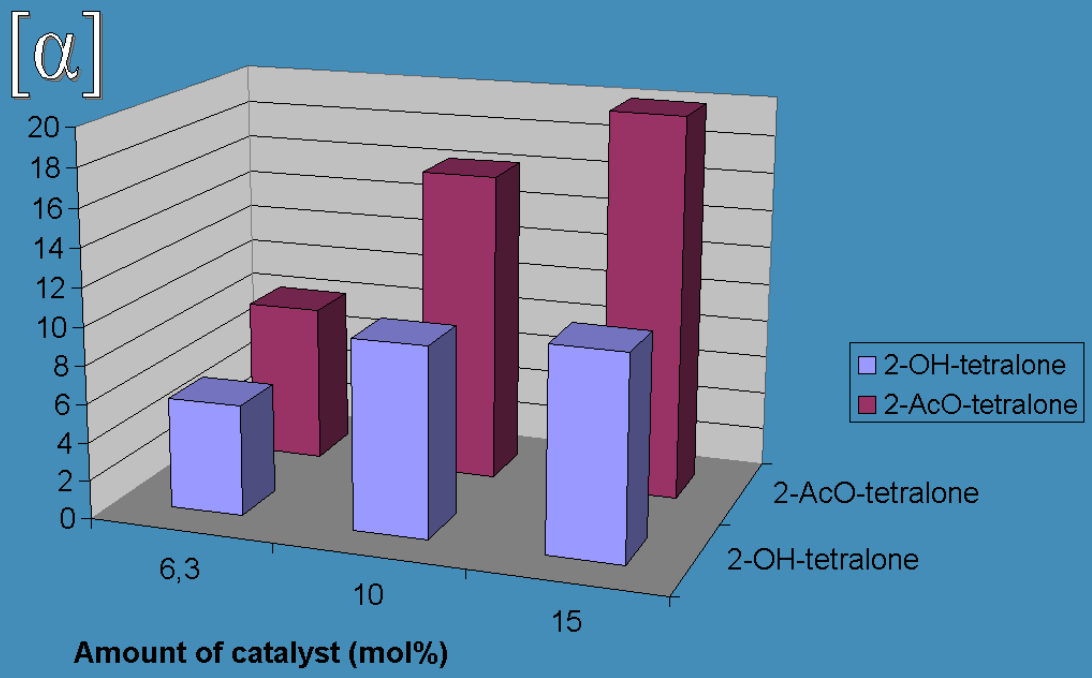


Figure 2

Figure 3

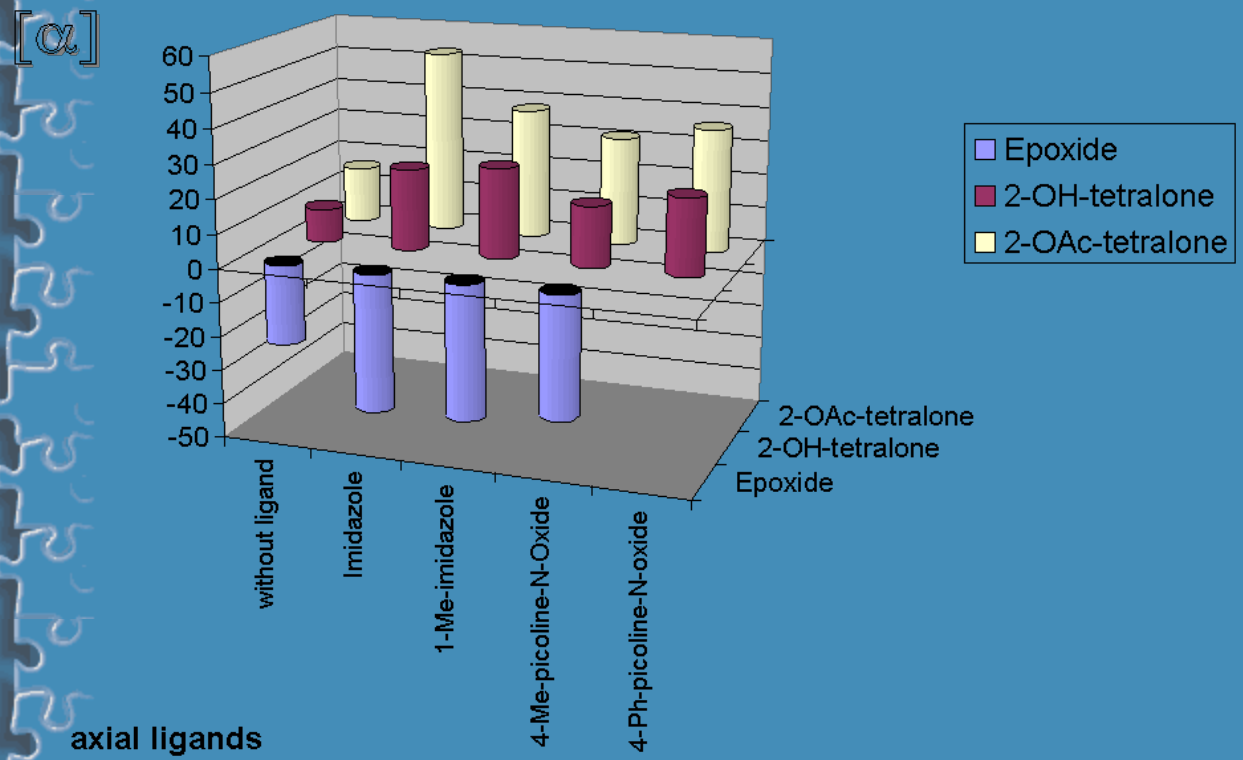
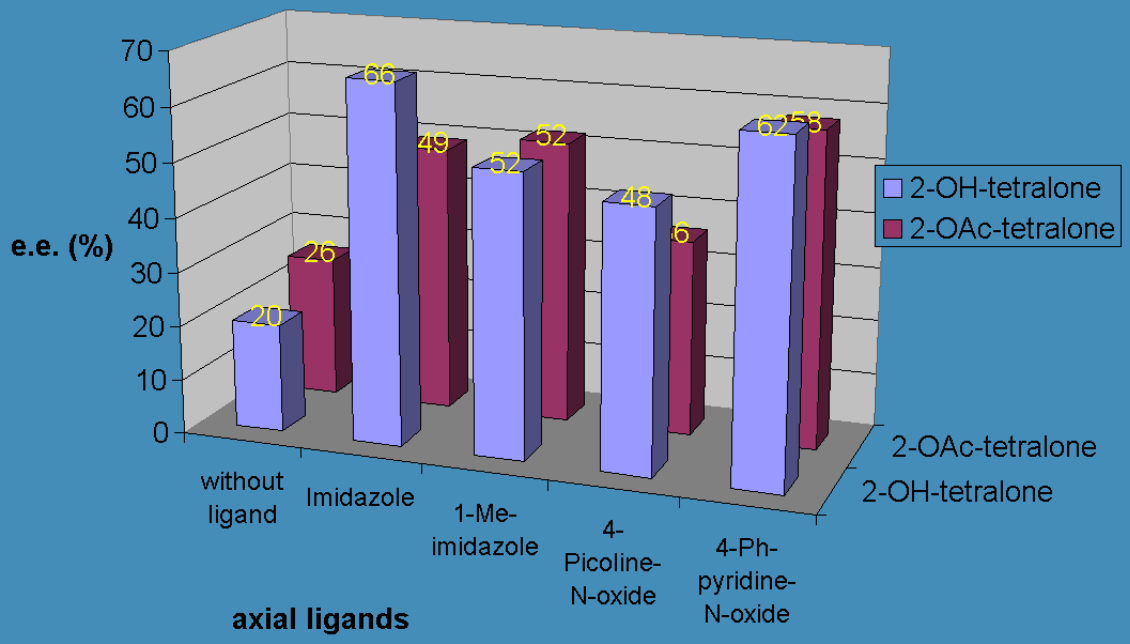


Figure 4



In summary, enol acetates of benzo(hetera)cyclanones are synthetically useful substrates for dioxirane oxidation. The use of Jacobsen's catalyst as chiral oxidant in the presence of DMD as oxygen donor allows enantioselective a-oxyfunctionalisation. Enhancement of enantioselectivity (up to 60-70% e.e.) could be achieved by using various co-ligands.

Acknowledgements: Financial support of National Fund of Science and Research (OTKA # T22290) is highly appreciated. References

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[7] Determined by HPLC (chiral column Chiralcel OB, hexane-iPrOH=9:1).