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Asymmetric oxidation of silyl enol ethers using chiral dioxiranes derived from α-fluoro cyclohexanones

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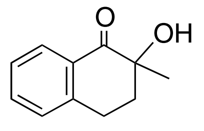
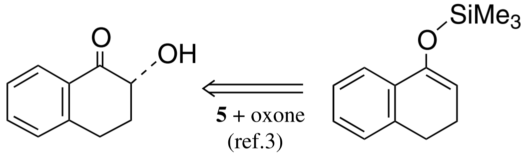
Abstract—Asymmetric oxidation of silyl enolethers derived from tetralone, 2-methyl-tetralone, propiophenone and deoxybenzoin using chiral dioxiranes generated in situ from oxone and new chiral α-fluorinated cyclohexanones or fructose-derived ketone have been studied. It was observed that tetrasubstituted silyl enolethers are poor substrates, that substitution at C8 of the fluoro-ketones has a significant effect on the enantioselectivities obtained and that the fructose-derived-ketone provides higher enantioselectivities. The absolute configuration of the major hydroxy ketones obtained can be rationalized using a spiro model proposed for epoxidation of olefins.

1. Introduction

During work on the synthesis of unnatural amino acids[1] we became interested in the synthesis of enantiopure or enantioenriched 2-hydroxy-2-methyl-1-tetralone **1**.[2] Because 2-hydroxy-1-tetralone **2** had already been obtained by Shi[3] in reasonable yield (70%) and 83% ee by oxidation of silyl enolether **3** with the chiral dioxirane (0.3 equiv.) derived from ketone **5**, we envisaged to oxidize the silyl enolether of 2-methyl-1-tetralone (**4**) with chiral dioxiranes derived from α-fluoro cyclohexanones **6**–**9**, which had already proved to be efficient for epoxidation of *trans* olefins.[4,5]

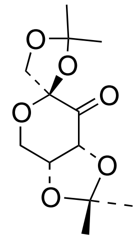


1 (*R* and/or *S*)

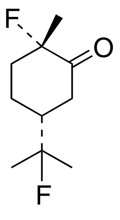


2: 70% yield
83% ee

3



5 (Shi)



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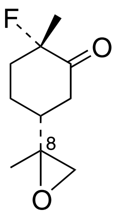

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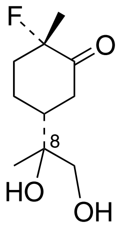

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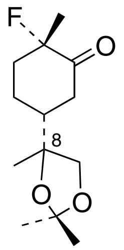

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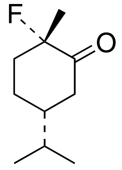

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Keywords: fluoro cyclohexanone; dioxiranes; asymmetric oxidation; α-hydroxyketone.

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Moreover, some discrepancies having appeared between Shi's and Adam's results[3,6] concerning the necessary amount of chiral ketone **5** and values of yields and ee% during oxidation of the silyl enolether **11t**, this enol has been re-examined as well as enol **3**.

We therefore present here the use of ketones **7**–**9** for oxidation of silyl enolethers **3t**, **10t** and **11t**, the use of ketones **6** for oxidation of silyl enolethers **3**, **3t**, **4**, **4t** and **10t** and the use of Shi's ketone **5** for oxidation of silyl enol ethers **3**, **4** and **10t** (for comparison with literature's results).

2. Results

The ketones have been synthesized from commercially available (+)-dihydrocarvone;[5] they were obtained as 1/1 diastereomeric mixture (creation of a new chiral carbon C8) and used without separation because we had already shown during asymmetric epoxidation of olefins that the configuration at C8 has no effect on the enantioselectivity.[5]

The silyl enol ethers have been prepared in quantitative yields after modification of the literature work-up.[7,8]

Oxidation[9] of *t*-butyldimethylsilyl enolethers **3t**, **4t**, **10t** and **11t** provided the silyl-protected hydroxy-ketones which were then hydrolyzed using HCl 5%/MeOH into the desired hydroxy-ketones **1**, **2**, **12** and **13** while oxidation of trimethylsilyl enol ethers **3** and **4** provided directly the desired hydroxyketone **1**.

The enantiomeric purities of the hydroxy-ketones were determined by chiral chromatography[10] and the absolute configuration through correlation of the signs of the optical rotation with known compounds.[11–13]

The results are gathered in Table 1.

All fluoro ketones gave good to quantitative overall yields in the desired α-hydroxy ketones **1**, **2**, **12** and **13** (Scheme 1 and Table 1). No lactones coming from Baeyer–Villiger oxidation have been detected and the ketones can be recovered through chromatography after reaction although sometimes in low yield because of the small amounts used.

The *t*-butyl silyl enol ether **3t** derived from 1-tetralone, which is a *trans* silyl enol ether, led to a lower enantioselectivity than **10t** and **11t** which are *cis* silyl enolethers (40–52% ee instead of 56–68% and 54–74% ee) (Table 1). When the less hindered $SiMe_3$ group is used, a lower enantioselectivity was obtained (Table 1) lines 1/5 (67/33 versus 75/25) and lines 7/8 (53/47 versus 58/42). This has already been observed by Adam et al. in the case of the silyl enol ethers derived from phenylethylketone[6] (54% ee with $SiMe_3$ versus 82% ee with $SiMe_2tBu$).

Among the new ketones **6**–**9**, ketone **9** provided the highest levels of enantioselectivity upon oxidation of **3t**, **10t** and **11t** (Table 1, lines 4, 13, 17).

Table 1. Oxidation of silyl enol ethers **3t**, **3**, **4t**, **4**, **10t** and **11t** using 0.3 equiv. of ketone[9]

Silyl enol ether	Ketone	Yield (%)[a]	er (%)[b] conf.	Absol. (%)	ee (%)	Product
3t	**6**	90	75/25	*S* (−)	50	**2**
3t	**7**	90	70/30	*S* (−)	40	**2**
3t	**8**	90	74/26	*S* (−)	48	**2**
3t	**9**	95	76/24	*S* (−)	52	**2**
3	**6**	74	67/33	*S* (−)	34	**2**
3	**5**	65	87/13	*R* (+)	74[c]	**2**
4t	**6**	78	58/42[d]	*S* (−)	16	**1**
4	**6**	90	53/47[d]	*S* (−)	6	**1**
4	**5**	62	53/47[d]	*S* (−)	6	**1**
10t	**6**	90	81/19	*S* (−)	62	**12**
10t	**7**	90	78/22	*S* (−)	56	**12**
10t	**8**	67	80/20	*S* (−)	60	**12**
10t	**9**	95	84/16	*S* (−)	68	**12**
10t	**5**	73	91/09	*R* (+)	82[e]	**12**
11t	**7**	71	77/23	*S* (+)	54	**13**[f]
11t	**8**	83	85/15	*S* (+)	70	**13**
11t	**9**	90	87/13	*S* (+)	74	**13**

[a] Overall yield of the two steps (Scheme 1).

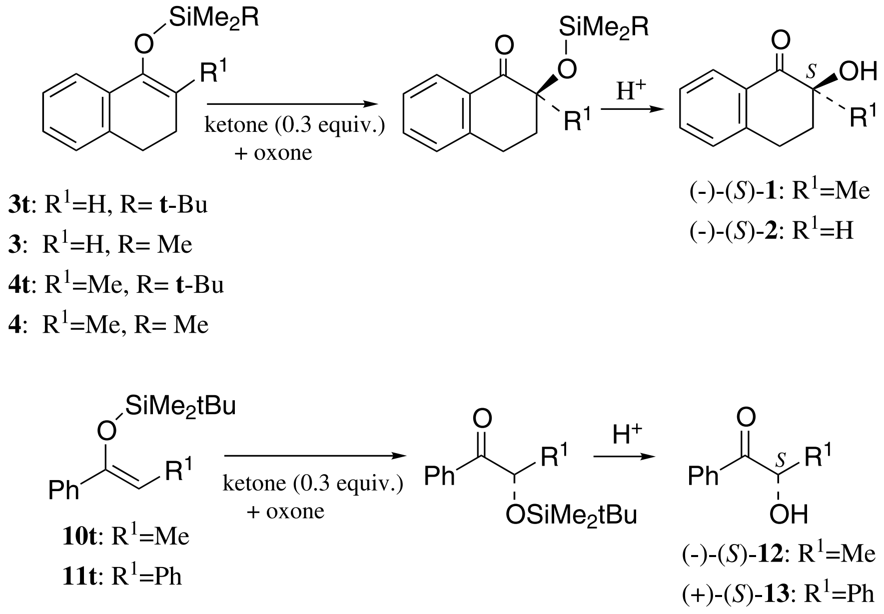
[b] Determined by GC using a Chiralcel OD column (hexane/*i*-PrOH, 9/1; 0.5 mL/min).

[c] With the same ketone **5**, 70% yield and 83% ee were announced by Shi, cf. Ref. 3.

[d] Determined by NMR using $Eu(hfc)_3$.

[e] With ketone **5**, 80% yield and 90% ee were announced by Shi[3] but Adam[6] obtained 92% yield and 82% ee by using 3 equiv. of ketone instead of 0.3 equiv.

[f] Both enantiomers are commercially available.



Scheme 1.

Ketone **5** appeared to be the most efficient with 74 and 82% ee in the cases of silyl enol ethers **3** and **11t**, respectively, compared with 34% ee from silyl enol ether **3** using ketone **6** and 68% ee from silyl enolether **11t** using ketone **9**. However, while ketone **5** provides the *R*-(+) configuration, ketone **9** provides the *S*-(−). It is also worth noting that, using ketone **5**, we reproduced better Adam's ee results (82% ee for oxidation of **10t** and not 92% as announced by Shi, cf. note e at the bottom of Table 1).

As seen in Figure 1a, the (*S*)-absolute configuration obtained for compound **1** with ketones **6**–**9** and substrates **3** (R = H, Fig. 1a) can be rationalized using the classical *spiro* model,[13] the *equatorial* ***E*-*exo*-I** approach being favored because of absence of n.n repulsions between F and O over the ***E*-*exo*-II** approach. Moreover, the low enantioselectivity obtained for compound **2** from tetrasubstituted substrate **4** (R = Me, Fig. 1a) can also be explained by the model with approaches ***E*-*exo*-I** and ***E*-*exo*-II** being equally difficult (***E*-*exo*-I** disfavored because of steric repulsions and ***E*-*exo*-II** disfavored because of n.n repulsions). Similarly the (*S*)-absolute configuration obtained for compounds **12** and **13** with ketones **6**–**9** and trisubstituted substrates **10t** and **11t** (Fig. 1b) can be rationalized by the fact that the ***E*-*exo*-II** approach is favored because of absence of n.π repulsions between F and the aryl group (compared to approach ***E*-*exo*-I**).

Because **10t** and **11t** differ only by the R group (Me or Ph), which remains in the *exo* position (Fig. 1b), it is expected that they should lead to almost identical enantioselectivities as observed.

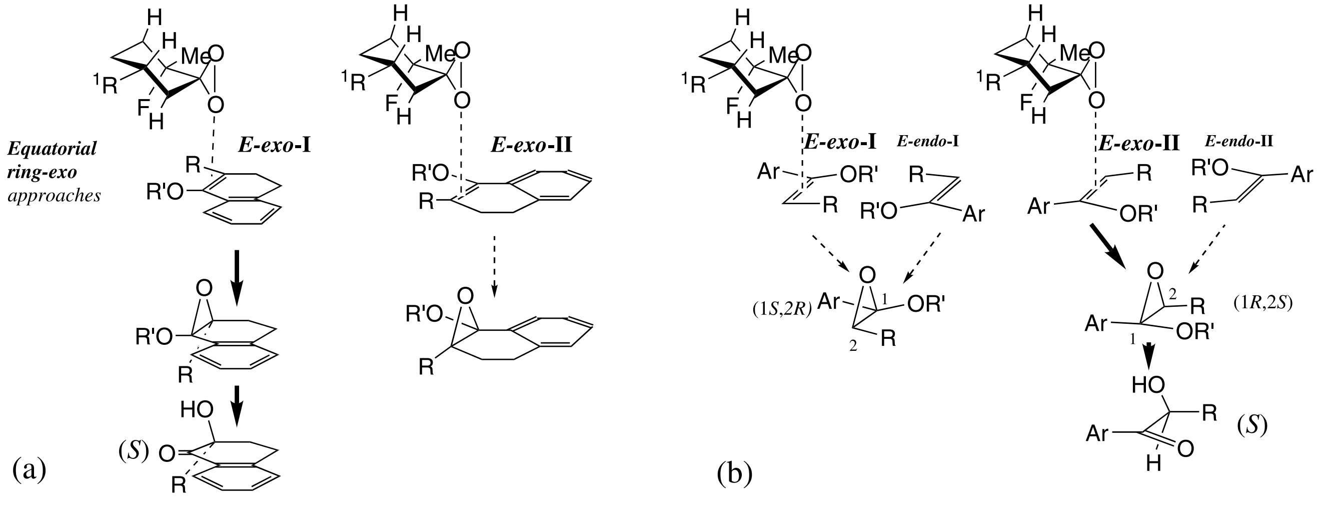


Figure 1.

The observation that the 'size' of the silyl-protecting group influence the enantioselectivity (compare lines 5 and 1 in Table 1) is consistent with the model and the ring-*exo* approaches (Fig. 1a). The $OSiR_3$ substituent, which changes 'size', is in the *endo* position, position which, being close to the chiral auxiliary, determines the enantioselectivity.

3. Conclusion

As has already been observed for the epoxidation of olefins,[5,14] the C8-substitution on the isopropyl group located at C5 has a significant influence on the enantioselectivity of oxidations of silyl enol ethers (ketone **14** having no substituent at the *iso*-Pr group provides 34% ee with silyl enol ether **10t**, while ketones **6**–**9** provide 60–68% ee) and it appears that an acetal group on the isopropyl (ketone **9**) provides higher enantioselectivities for all silyl enol ethers (52, 68, and 74% ee for **3t**, **10t** and **11t**, respectively).

Ketone **5** is the most efficient in these cases and provides the other enantiomer.

Tetrasubstituted silyl enol ethers are poor substrates and are oxidized with almost no enantioselectivity.

It is worth noting that the model (Fig. 1), involving a *spiro*-approach proposed for epoxidation of olefins holds in the case of oxidation of silyl enol ethers.

Sub-stoichiometric amounts (0.3 equiv.) of ketone have been used in all cases and these ketones, which do not undergo Baeyer–Villiger oxidation, can be recovered and reused.

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9. To a stirred mixture of silyl enolether (1 mmol) and α-fluoroketone (0.3 equiv.) were added successively (at 0°C) a 0.05 M Na_2BO_4 buffer solution (6 mL) and dimethoxyethane/CH_3CN 2:1 (18 mL) and then (within 1 h) 7 mL of aqueous solution of oxone (1.4 equiv.). During the addition of oxone, the pH was regulated (8.5–9.0) by addition of 1 M K_2CO_3 solution. The reaction mixture was quenched by addition of CH_2Cl_2 and water. The organic phase was recovered and the aqueous phase extracted with CH_2Cl_2.
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