Synthesis of Optically Active α-Hydroxy Carbonyl Compounds by the Catalytic, Enantioselective Oxidation of Silyl Enol Ethers and Ketene Acetals with (Salen)manganese(III) Complexes

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Abstract: A set of silyl enol ethers and ketene acetals **1a**−**h** with α- and/or *β*-phenyl as well as alkyl substituents of different steric bulk has been submitted to the enantioselective catalytic oxidation by chiral (salen)Mn^{III} complexes **3**. Highest conversions and best enantioselectivities have been obtained with bleach rather than iodosobenzene as oxygen source for the active oxo−metal species. With regard to substrate structure, ee values up to 89% have been achieved for enol ethers with short and unbranched alkyl substituents at the siloxy position. While *β*-phenyl groups are beneficial for enantiofacial control, phenyl substituents α to the siloxy functionality result in lower ee values, while the diphenyl-substituted derivative **1d** displays the lowest stereoselectivity. The fact that *β*- versus α-phenyl substituents exhibit not only differences in the magnitude but also in the sense (opposite absolute product configuration) of the stereoselectivity may be utilized as a valuable mechanistic probe to assess steric and electronic effects in the substrate and the catalyst as a function of the type and pattern of substitution. Our results display that steric interactions between the substrate and the oxo−metal complex are mainly responsible for the observed stereochemical preferences. Indeed, significantly increased enantioselectivities are achieved even for the remote siloxy group when bulkier derivatives are employed. In contrast, primarily electronic effects operate in the (salen)Mn^{III} catalyst **3** since electron-donating groups in the 5,5′ positions of the salicylaldehyde ligand afford higher ee values in this catalytic oxidation. The skewed side-on approach (trajectory *b*) of the substrate onto the oxo−metal catalyst is favored, the metallaoxetane mechanism adequately accounts for the observed enantioselectivities. Herewith a synthetically valuable method for the preparation of optically active α-hydroxy carbonyl products **2** has been made available through the catalytic, enantioselective oxidation of the silyl enol ethers **1** by (salen)Mn^{III} complexes.

Introduction

The optically active α-hydroxy ester and α-hydroxy ketone functionalities are widespread in natural products and have during the last years been frequently used as convenient building blocks in organic synthesis.[1] For example, the enantiopure α-hydroxy ketone **2a** is an intermediate product of the "Knoll process", the major industrial route to the sympathomimetica ephedrine and pseudoephedrine with an adrenalin-like activity.[2]

Unquestionably, efficient methods for the construction of enantiomerically pure or at least enriched α-hydroxy carbonyl compounds are in demand.[3] For their preparation, the methodology of electrophilic hydroxylation of enolates, in which the optically active organic or organometallic auxiliary is covalently bound to the enol unit, has mainly been employed.[4,5] Alternatively, prochiral enolates have been directly oxidized by optically active oxidants, e.g., oxaziridines.[3,6] Highly enantioselective catalytic methods are known such as the oxidation of enol ethers by the osmium-catalyzed asymmetric dihydroxylation,[7] the kinetic resolution of α-hydroperoxy esters with horseradish peroxidase[8] and that of α-hydroxy esters and ketones with lipases.[9]

A recent major advance in catalytic enantioselective oxidations has been the epoxidation of prochiral, unfunctionalyzed olefins.[10] For this purpose (salen)Mn^{III} complexes, which are accessible from readily available precursors,[11] have been

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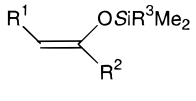
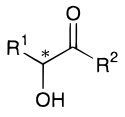
developed as highly enantioselective catalysts not only for the epoxidation of aryl-conjugated, cis-disubstituted olefins, but also for the epoxidation of tri- and tetrasubstituted derivatives.[12] An increase of the enantioselectivities for these substrates has been achieved by modulating steric[10] and electronic properties[13] of the catalyst through varying the substitution pattern at the salicylidene moiety and the chiral diamine part.

In this context, recently we have reported in a preliminary contribution that also silyl enol ethers are good prochiral substrates for such oxidations to afford optically active α-hydroxy carbonyl compounds.[14] Similarly, the enantioselective oxidation of alkyl and acetyl enol ethers with (salen)Mn^{III} complexes to α-hydroxy acetals has been conducted.[15] Previously an optically active pyrrolidine-based (salen)Mn^{III} complex was employed as catalyst for the enantioselective oxidation of silyl enol ethers with iodosobenzene (ee 14−62%).[16]

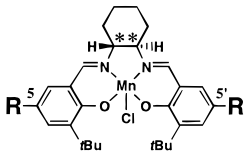
For the present study, the silyl enol ethers **1** and the (salen)-Mn^{III} complexes **3** were chosen to assess the structural and electronic factors that influence the enantioselectivity of this metal-catalyzed oxidation, in the hope to increase its stereocontrol by proper tuning of the substrate and catalyst. The ideal



1a-h



2a-h



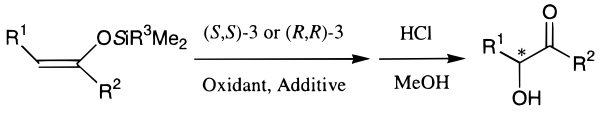
3a-c

1, **2**	R^1	R^2	R^3
a	Ph	Me	Me
a'	Ph	Me	*t*Bu
b	Ph	Et	Me
c	Ph	*t*Bu	Me
d	Ph	Ph	Me
e	Me	Ph	Me
e'	Me	Ph	*t*Bu
f	Et	Ph	Me
g	Ph	OMe	Me
g'	Ph	OMe	*t*Bu
h	Ph	SEt	Me

	3a	**3b**	**3c**
R	*t*Bu	MeO	iPr$_3$SiO

substrate[17] would be the cis-disubstituted silyl enol ether derived from phenyl acetaldehyde (R^1 = Ph and R^2 = H), but the resulting α-hydroxy aldehyde is too labile for handling.[18] Therefore, it was necessary to place an alkyl or a phenyl group in the α position to the siloxy group as third substituent, which would afford the more persistent α-hydroxy ketones **2** as

Scheme 1. Asymmetric Oxidation of the Silyl Enol Ethers and Silyl Ketene Acetals **1** by (salen)Mn(III) Catalysts **3**



1a-h **2a-h**

products. It was expected that the direction of the enantiofacial attack should decisively depend on the steric nature of this third substituent.

The silyl ketene acetals **1g**−**h** were chosen to probe the electronic effect of a methoxy or a thioethyl group on the enantioselectivity compared to an alkyl or aryl R^2 group. To test the influence of the steric nature of the siloxy protecting group on the enantioselectivity, besides the trimethylsilyl derivatives TMS-**1**, also the sterically more demanding *tert*-butyldimethylsilyl-substituted TBDMS-**1′** substrates were selected for this catalytic oxidation. The electronically modified salen complexes **3b**,**c** with electron-donating substituents in the 5,5′ positions should provide valuable mechanistic information on the electronic role that the manganese catalyst **3** plays in this enantioselective catalytic oxyfunctionalizaion.

We present herewith the full details of the (salen)Mn-catalyzed oxidation of phenyl-substituted silyl enol ethers and ketene acetals **1** to the respective optically active α-hydroxy carbonyl products **2**. Our results demonstrate that the substitution pattern in the substrates **1** significantly influences the enantioselectivity and the absolute configuration of the products **2** in this novel metal-catalyzed α-hydroxylation. However, through electronic tuning of the (salen)Mn^{III} catalyst **3** only moderately enhanced stereocontrol may be achieved.

Results

Syntheses. The synthesis of the (salen)Mn^{III} complexes **3b**,**c** was conducted according to reported procedures.[11,19]

The silyl enol ethers and ketene acetals **1a**−**h** were prepared by following literature methods, in which the corresponding ketone or ester was deprotonated with LDA, NaH, or NaN-$(SiMe_3)_2$. The reaction conditions were optimized to get mainly enolates which on treatment with chlorosilane afforded the *Z*-configured silyl enol ethers **1**. The *E*/*Z* ratios were determined by analysis of the characteristic olefinic proton resonances in the ^{1}H NMR spectra of the silylated products.[20] Racemic samples of α-hydroxy ketones **2a**−**f** were obtained by dimethyldioxirane oxidation of the corresponding silyl enol ether **1a**−**f**.[21]

Enantioselectivity Studies. The catalytic oxidations were carried out at 0 °C with NaOCl (7.5 equiv) in a phosphate buffer (pH 11.3) or PhIO (1.5 equiv) as oxygen atom source, with 30 mol % 4-phenylpyridine *N*-oxide (PPNO) as additive and 7 mol % of the appropriate (salen)Mn complex **3** as catalyst.[10,19] The optically active α-hydroxy carbonyl compounds were released from the resulting α-siloxy/α-hydroxy product mixture by treatment with acidified (HCl) or pure methanol (Scheme 1).[21] In general, the substrate conversion was very fast and usually

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Table 1. Enantioselective Oxidation of Silyl Enol Ethers **1a**−**f** and Silyl Ketene Acetals **1g**,**g′**,**h** by the (*S*,*S*)-(salen)Mn^{III} Catalyst **3a** with NaOCl[a]

entry	substrate	conv[b,c,d] (%)	ee (%)[d,e] **2**	config[f] **2**
1	**1a**	91 (81)	79 (56)	*S* (+)
2	**1a′**	59	86	*S* (+)
3	**1b**	82 (88)	87 (60)	*S* (+)
4	**1c**	96	35	*S* (+)
5	**1d**	88	12	*R* (−)
6	**1e**	95	42	*R* (+)
7	**1e′**	95	81	*R* (+)
8	**1f**	84	60	*R* (+)
9	**1g**[g]	64	22	*S* (+)
10	**1g′**	70	57	*S* (+)
11	**1h**[h]	-- (35)	--[i] (18)	*S* (+)

[a] 7 mol % catalyst (*S*,*S*)-**3a**, 7.5 equiv of NaOCl as 0.5 M solution in phosphate buffer (pH 11.3), 0.3 equiv of PPNO (4-phenylpyridine *N*-oxide), in CH_2Cl_2. [b] Determined by HPLC analysis (RP-18, 64:34:2 MeOH/H_2O/CH_3CN, flow rate 1.0 mL/min or Chiralcel OD, 9:1 *n*-hexane/2-propanol, flow rate 0.6 mL/min). [c] Yield of isolated product was 60−98% relative to the conversion of **1** to α-hydroxy carbonyl products **2**. [d] Values in parentheses are for PhIO (1.5 equiv). [e] Determined by HPLC analysis (Chiralcel OD, 9:1 *n*-hexane/2-propanol, flow rate 0.6 mL/min), error limits ∼<5% of the stated values. [f] Configurations assigned according to literature (refs 20 and 22−25), for **2c** in analogy to the elution order of the enantiomers **2a** and **2b**. [g] 70:30 *E*/*Z*. [h] ∼50:50 *E*/*Z*. [i] Neither product nor starting material could be reisolated.

high. The results of the oxidations with the standard catalyst (*S*,*S*)-**3a** are summarized in Table 1.

The oxidation of the silyl enol ether **1a** with catalyst **3a** and NaOCl proceeded to 88% conversion (HPLC analysis) in less than 1 h, but the conversion could not be increased significantly (91%, 24 h) by allowing longer reaction times (Table 1, entry 1). The reason is that under the aqueous reaction conditions, the hydrolysis of the silyl enol ethers and ketene acetals competes with the catalytic oxidation to afford the nonhydroxylated ketone or ester, the starting materials for the silylated substrates **1**. To achieve the highest possible conversion and to facilitate the separation of the decomposed catalyst, the reaction time was extended in most cases up to 24 h. Fortunately, control experiments established that under these reaction conditions the optically active α-hydroxy products **2** were not racemized.

Experiments with PhIO as oxygen atom source to perform catalytic oxidations under water-free conditions to avoid the competing hydrolysis of the silyl enol ethers showed that conversions could also not be raised significantly. In fact, the conversion even dropped under these conditions, but worse, the observed enantiomeric excess was on the average ∼25% lower than for NaOCl in aqueous media (Table 1, entries 1 and 3). This could be due to the fact that with PhIO also oxo Mn^{IV} species besides oxo Mn^{V} are generated. Both species were detected and isolated in the oxidation of manganese porphyrin complexes with iodosobenzene and the oxo Mn^{IV} species is known to decrease the diastereoselectivity in the epoxidation of *cis*-β-methylstyrene.[26] This feature could also be responsible for the decrease of the enantioselectivity in the here described oxidations with iodosobenzene.

In the set of chosen *Z*-configured trimethylsilyl enol ethers **1a**−**f**, the best enantioselectivities in the oxidation with catalyst (*S*,*S*)-**3a** and bleach were obtained for the silyl enol ethers **1a**,**b**, which bear one phenyl group in the β position to the siloxy group (R^1 = Ph) and a less sterically demanding alkyl group (R^2 = Me, Et; **1a**,**b**) in the α position to the siloxy group (Table 1, entries 1,3). The ethyl-substituted derivative **1b** resulted in an enantiomeric excess of 87%, which is a slightly better value than for the methyl-substituted substrate **1a** (ee 79%).

An increase of the steric demand of the R^2 substituent by using the bulky *tert*-butyl group (**1c**) led to a drastic decrease of the enantioselectivity (Table 1, entry 4). With the diphenyl-substituted substrate **1d** (R^1 = R^2 = Ph) the catalytic oxidation gave the benzoin (**2d**) with the lowest (12%) ee value in Table 1 (entry 5). Contrary to the *S* configuration for α-hydroxy ketones **2a**−**c** with the catalyst (*S*,*S*)-**3a**, the *R* configuration prevails in the case of the product **2d**.

The substrates **1e**,**f** with R^1 an alkyl and R^2 a phenyl group, afforded α-hydroxy ketones **2e**,**f** in enantiomeric excess up to 60% for the *R* enantiomer (Table 1, entries 6,8). Comparison of the absolute configurations of the products **2e**,**f** with the already discussed ones **2a**−**d**, reveals that the β-phenylated (R^1 = Ph) substrates **1a**−**c** afford the (*S*)-configured α-hydroxy ketones **2a**−**c** as the major enantiomer (Table 1, entries 1, 3, and 4). In contrast, the α-phenylated (R^2 = Ph) substrates **1d**−**f** preferentially lead to the *R* enantiomer of the α-hydroxy ketones **2d**−**f** (Table 1, entries 5, 6, and 8).

Catalytic oxidation of silyl enol ethers **1a′**,**e′**, which are functionalized with the bulkier TBDMS instead of the TMS group, was performed to compare the influence on the enantioselectivity of the steric bulk of the siloxy group. For the TBDMS-substituted substrate **1e′** an increase of the ee values to 81% was observed (Table 1, entry 7), compared to only 42% for the TMS-substituted substrate **1e** (Table 1, entry 6). The same trend was obtained in the oxidation of the substrates **1a′** versus **1a**, but the increase was smaller yet still significant (Table 1, entries 1 and 2). The absolute configurations of the products **2a**,**e** were the same for the TMS and the TBDMS groups.

The use of silyl ketene acetals **1g**,**g′**,**h** as substrates for the catalytic oxidation with Mn^{III} complex (*S*,*S*)-**3a** showed that the *S* configuration predominates in the resulting α-hydroxy esters **2g**,**h** (Table 1, entries 9−11), the same as for the silyl enol ethers **1a**−**c** (Table 1, entries 1−4). The change of the substituent R^2 from Me (**1a**) to MeO (**1g**) or EtS (**1h**) had no influence on the absolute configuration of the α-hydroxylated products **2**, but on the enantioselectivity of the reaction. The ee values for **1g**,**h** were only ∼20%, but the starting materials consisted of *Z*/*E* diastereomeric mixtures of **1g**,**h** (Table 1, entries 9 and 11). Indeed, the diastereomerically pure silyl ketene acetal **z**-1g′ yielded a higher ee value of 57% (Table 1, entry 10). For the hydrolytically labile phenylketene (*S*)-ethyl *O*-trimethylsilyl acetal **1h**, only with PhIO oxidation to the α-hydroxy thioester **2h** was observed. With aqueous bleach merely decomposition products were detected (Table 1, entry 11).

The results on the asymmetric oxidations with the modified catalysts (*R*,*R*)-**3b**,**c**, which possess electron-donating substituents at the 5,5′ positions, are given in Table 2 and compared to those with catalyst (*R*,*R*)-**3a**. Conversions to the hydroxylated products **2** were for most oxidations with catalysts (*R*,*R*)-**3b**,**c** (Table 2) as high as for the catalyst (*S*,*S*)-**3a** (Table 1). The conversions were usually in the range of 80−100% with insignificant differences between the catalysts **3a**−**c**, but the enantioselectivities differed significantly. For silyl enol ether **1a** an increase in enantiomeric excess from 79% for catalyst

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Table 2. Influence of 5,5′ Substitution in the (*R*,*R*)-(salen)Mn^{III} Catalysts **3a**−**c** on the Enantioselectivity in the Oxidation of Silyl Enol Ethers and Silyl Ketene Acetals **1**[a]

		(*R*,*R*)-**3a**		(*R*,*R*)-**3b**		(*R*,*R*)-**3c**		
entry	substrate	conv[b,c] (%)	ee (%)[d] **2**	conv[b,c] (%)	ee (%)[d] **2**	conv[b,c] (%)	ee (%)[d] **2**	configuration of **2**[e]
1	**1a**	91	79	99	89	98	87	*R* (−)
2	**1b**	82	86	72	87	92	83	*R* (−)
3	**1c**	95	34	49	37	95	51	*R* (−)
4	**1d**	98	11	98	28	99	18	*S* (+)
5	**1e**	95	42	88	74	85	74	*S* (−)
6	**1e′**	95	81	99	84	99	81	*S* (−)
7	**1f**	83	60	88	75	91	77	*S* (−)
8	**1g′**	70	53	85	68	70	53	*R* (−)

[a] 7.5 equiv of NaOCl as 0.5 M solution in phosphate buffer (pH 11.3), 0.3 equiv of PPNO (4-phenylpyridine *N*-oxide), in CH_2Cl_2. [b] Determined by HPLC analysis (RP-18, 64:34:2 MeOH/H_2O/CH_3CN, flow rate 1.0 mL/min or Chiralcel OD, 9:1 *n*-hexane/2-propanol, flow rate 0.6 mL/min). [c] Yield of isolated product was 60−98% relative to conversion of **1** to α-hydroxycarbonyl products **2**. [d] Determined by HPLC analysis (Chiralcel OD, 9:1 *n*-hexane/2-propanol, flow rate 0.6 mL/min), error limits ∼<5% of the stated values. [e] Oxidation with (*R*,*R*)-**3**, configurations assigned according to literature (refs 20 and 22−25), for **2c** in analogy to the elution order of the enantiomers of **2a** and **2b**.

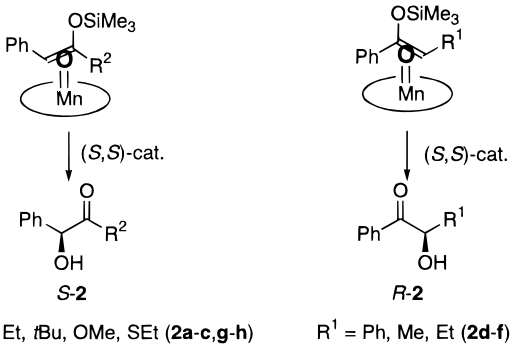

Figure 1. Absolute product configurations in the oxy functionalizations of the silyl enol ethers and ketene acetals **1a**−**h** with catalyst (*S*,*S*)-**3a**.

(*S*,*S*)- or (*R*,*R*)-**3a** to 89% for the 5,5′-MeO-substituted derivative (*R*,*R*)-**3b** was observed (Table 2, entry 1). For this substrate, the TIPSO-substituted catalyst (*R*,*R*)-**3c** afforded an ee value of 87%, and constitutes no improvement over catalyst **3b** (Table 2, entry 1). In general, the differences for the catalysts **3a**−**c** are not substantial (∼15% increase in the ee values) but significant for most substrates in Table 2. An exception is the silyl enol ether of the propiophenone **1e**, for which the ee value increased by 32% (Table 2, entry 5) for the catalysts **3b**,**c** (74% ee) in comparison to catalyst **3a** (42% ee).

In most cases the catalyst (*R*,*R*)-**3b** with the sterically less bulky but electron-rich methoxy substituent afforded the best enantioselectivities in the oxidation of silyl enol ethers **1a**,**b**,**d**−**e′** and ketene acetal **1g′** (Table 2, entries 1, 2, 4−6, and 8). The ee values for catalyst **3c** with the electron-donating and more bulky TIPSO group are similar to those for catalyst **3b** (Table 2, entries 1, 5, and 7) or fall between the values for the catalysts **3a**,**b** (Table 2, entries 2, 4, 6, and 8). Only for substrate **1c** was the TIPSO-substituted catalyst (*R*,*R*)-**3c** (51% ee) the most effective (Table 2, entry 3).

Mechanistic Discussion

The results presented above demonstrate that the choice of the enol-ether substrates **1a**−**h** has been instructive in exploring the stereocontrol in the (salen)Mn-catalyzed oxidation of trisubstituted olefins. Thus, the degree of enantioselectivity and the absolute product configuration in the manganese-assisted oxyfunctionalizations of the silyl enol ethers and ketene acetals **1a**−**h** to the corresponding α-hydroxy carbonyl compounds (Figure 1) are controlled by the substitution pattern of the substrates **1** and the arene substituents of the (salen)Mn catalysts **3**. The trends in these structural factors shall now be analyzed in terms of the mechanistic models proposed to rationalize the high enantioselectivities observed in the epoxidation of cis-di- and trisubstituted olefins with (salen)Mn catalysts **3**. These models shall be applied to the silyl enol ethers **1** in terms of the orientation of the incoming olefin (its plane and that of the salen ligand perpendicular) in a side-on approach onto the metal oxo ligand along the direction of the chiral diamine bridge from the back (trajectory *a*, Figure 2)[17,19b−c] and the skewed side-on attack along the metal C=N ligand of the diamine bridge (trajectory *b*, Figure 2).[27] The top-on approach (the olefin and salen-ligand planes parallel) has been proposed only for tetrasubstituted olefins because of steric reasons[12c] and should not be relevant for the trisubstituted olefins employed herein.[12a,b] Along the trajectories *a* and *b* we shall explicitely consider the likely transition states for the oxygen transfer from the oxo-metal complex to the olefin to form the possible radical[19] or metallaoxetane intermediates.[28]

Substrate Structure. The silyl enol ethers **1a**−**c** and ketene acetals **1g**,**h** attack the oxo-metal complex of the catalyst (*S*,*S*)-**3a** to result the *S*-configured, α-hydroxylated products **2a-c**,**g**,**h**, (Table 1, entries 1−4, and 9−11), as it is shown in Figure 2A for the substrate **1a** as an illustrative example. In the side-on approach along the trajectory *a* (Jacobsen's model),[17,19b−c] the two possible enantiofacial orientations of the enol ether are specified, of which the *gray* structure would lead to the *R*- and the *black* one to the *S*-configured products. Both arrangements are equally favored, since the steric interactions between the methyl group of the substrate and the axial hydrogens of the cyclohexanediamine unit of the catalyst should be similar. Therefore, a very low enantioselectivity is to be expected for this approach. The facts are, however, as mentioned above, that for the substrates **1a-c**,**g**,**h** preferential formation of the *S* enantiomers for the oxidation products was observed (ee up to 87%). In contrast, both possible enantiofacial orientations of the enol ether **1a** in a skewed side-on approach along the trajectory *b* (Katsuki's model)[12b,27] are sterically differentiable. To avoid the repulsive steric and electronic ($\pi-\pi$ interaction between the arene rings of salen ligand and substrate[12b,27]) interactions, the phenyl group of the substrate should be as far as possible away from the salicyl moiety.[10c,12b,27] Therefore, the enantiofacial approach which leads to the *S*-configured α-hydroxylated products should be favored, in accord with our experimental data.

(27) (a) Hosoya, N.; Hatayama, A.; Yanai, K.; Fujii, H.; Irie, R.; Katsuki, T. *Synlett* **1993**, 641-645. (b) Hamada, T.; Irie, R.; Katsuki, T. *Synlett* **1994**, 479−481.

(28) (a) Norrby, P.-O.; Linde, C.; Åkermark, B. *J. Am. Chem. Soc.* **1995**, *117*, 11035−11036. (b) Linde, C.; Arnold, M.; Norrby, P.-O.; Åkermark, B. *Angew. Chem., Int. Ed. Engl.* **1997**, 36, 1723−1725. (c) Hamada, T.; Fukuda, T.; Imanishi, H.; Katsuki, T. *Tetrahedron* **1996**, *52*, 515−530.

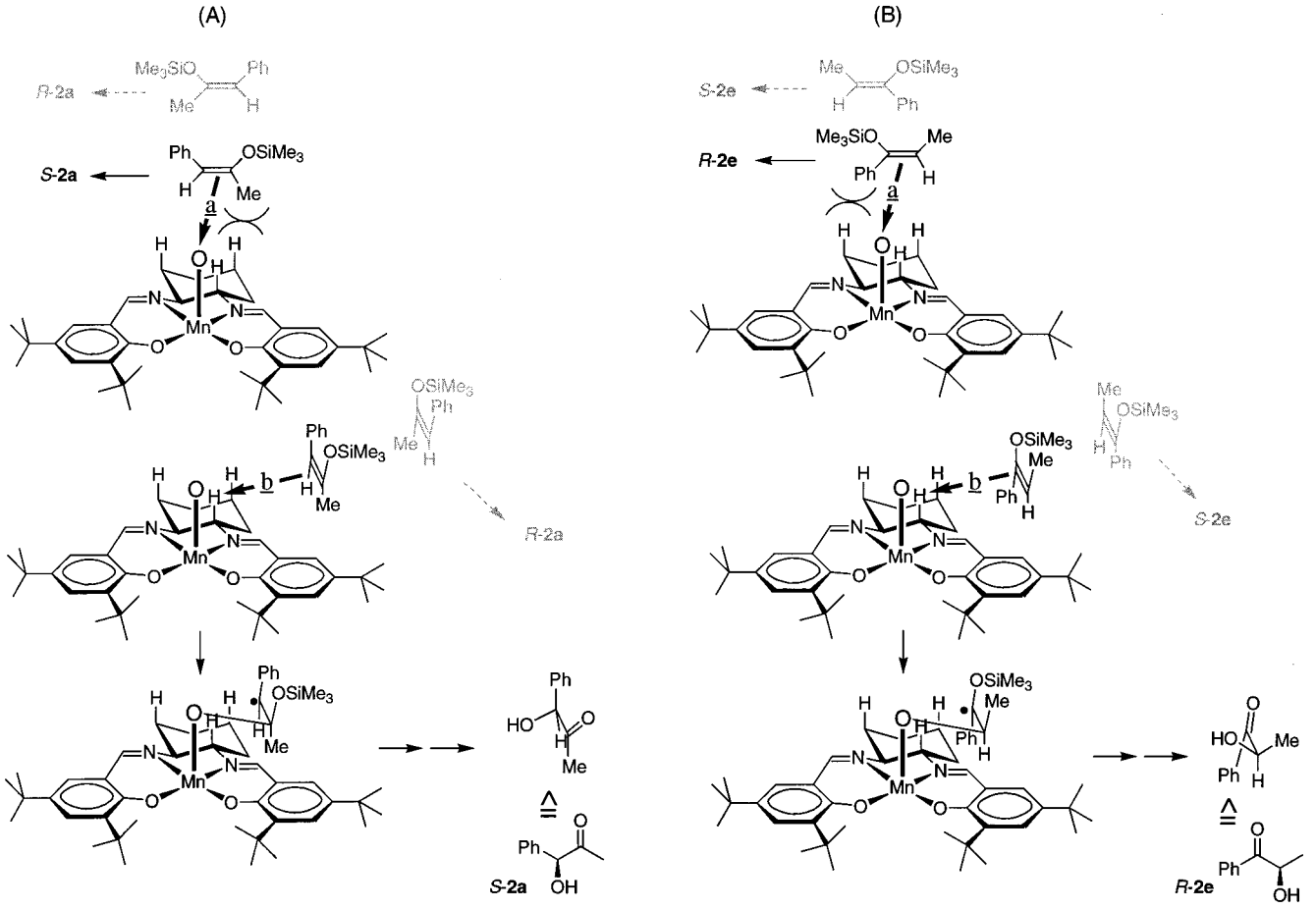

Figure 2. Trajectories *a* and *b* and the radical mechanism for the oxidation of the silyl enol ethers **1a** (A) and **1e** (B) by the oxo−metal complex of catalyst (*S*,*S*)-**3a**.

Since in the side-on approach along the trajectory *b* the substituent R^2 of the enol ethers **1a-b**,**g**,**g′**,**h** is directed toward the salicyl moiety of the catalyst, an increase of the steric demand for the R^2 substituent (*t*Bu in substrate **1c**) results in major steric interactions and leads to a much lower enantioselectivity (Table 1, entry 4). When the R^2 alkyl group is replaced by a methoxy or thioethyl substituent (Table 1, entries 9−11), a lower enantioselectivity is also observed.

Contrary to the substrates **1a-c**,**g**,**g′**,**h** with a phenyl group in the β position (R^1 = Ph) to the siloxy group (Table 1, entries 1−4 and 9−11), substrates **2e**−**f** with an α-phenyl substituent (R^2 = Ph) display the opposite enantiofacial selectivity in the resulting α-hydroxy ketones (*R*)-**2e**,**f** (Table 1, entries 6−8). Again, this enantioselectivity cannot be rationalized in terms of the trajectory *a*[12a,19b,c] because similar steric interactions apply for both possible enantiofacial approaches, as illustrated for substrate **1e** as model case (Figure 2B). The stereochemical course in this oxidation follows again the expectations of the skewed side-on approach for the enolate **1e** along trajectory *b*. The enantiofacial approach to result in the *S*-configured product (*gray* structure in Figure 2B) will be less favored because of steric interactions of the phenyl substituent at the R^1 position of the substrate **1e** with the *t*Bu group of the salicyl moiety, as well as repulsive steric and electronic interactions with the aryl ring of the salicyl ligand.[10c,12b,27] As observed, the *R*-configured enantiomer (*black* structure in Figure 2B) prevails in the oxyfunctionalization of the silyl enol ether **1e** with the catalyst (*S*,*S*)-**3a**.

For the diphenyl-substituted silyl enol ether **1d**, which cannot avoid having one phenyl group near the salicylaldehyde ligand of the catalyst during the oxygen transfer along the trajectory *b*, the enantioselectivity is substantially lower than for the silyl enol ethers **1e**,**f** with an aliphatic R^1 group (Table 1, entries 5−8). These results once more demonstrate that the skewed side-on approach along the trajectory *b*[10c,12b,27] is the more favored pathway than the trajectory *a* in these oxidations.

With the preferred substrate approach (skewed side-on trajectory *b*) and the favored orientation (*black* structures) defined in Figure 2, it is now instructive to diagnose the possible transition states for the oxygen transfer. Once the enol-ether substrate has penetrated far enough into the salen complex to be sufficiently proximate to the oxo−metal functionality for bonding with the oxenoid oxygen atom, two mechanistic alternatives apply for the oxygen transfer. There are the currently much debated homolytic pathway proposed by Jacobsen[10a,b,19] to afford a radical intermediate and the concerted route propagated by Katsuki[10c,15,28c] and Norrby−Åkermark[28a,b] to form the metallaoxetane cycloadduct.

We shall scrutinize first the Jacobsen proposal to assess how well it rationalizes the observed enantioselectivities in Table 1. The preferred radical intermediate for the enol ether **1a** with R^1 a phenyl substituent (Figure 2A) should be the one with the unpaired spin at the benzyl site in view of the more effective phenyl conjugation. Subsequently the radical intermediate collapses to an intermediary epoxide and the latter transposes to the observed α-hydroxy ketone (*S*)-**2a**.

For the enol ether **1e** with R^2 a phenyl group (Figure 2B), the site of preferred homolytic attack in the Jacobsen mechanism is clear-cut, namely the oxenoid oxygen atom is fixed at the methyl-bearing terminal. For the resulting intermediary radical

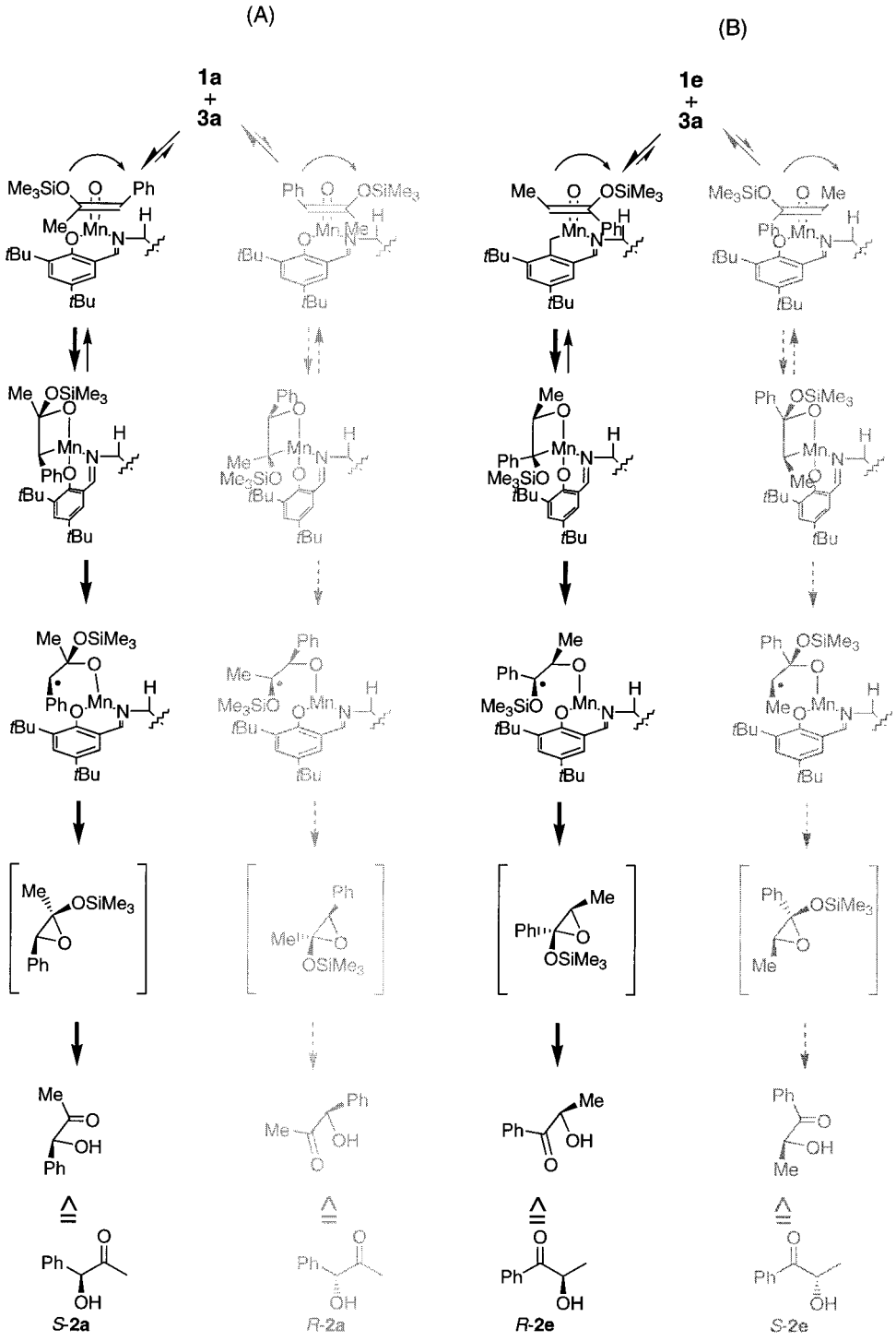

Figure 3. Metallaoxetane mechanism for the oxidation of the silyl enol ethers **1a** (A) and **1e** (B) by the oxo complex of catalyst (*S,S*)-**3a**.

the unpaired spin is localized at the R^2 site, which is stabilized by phenyl as well as silyloxy conjugation. Subsequent collapse to the epoxide and transposition of the latter affords the α-hydroxy ketone (*R*)-**2e**, again as observed (Table 1).

A relevant feature of the Jacobsen stepwise mechanism, in fact, the prevalent incentive to propose radical intermediates, is the loss of epoxide diastereoselectivity for phenyl-substituted *cis*-olefins due to rotation about the C−C bond before collapse to the epoxide product. Our enol−ether substrates, unfortunately, do not provide any information on this point because the stereocenter at the silyloxy-substituted site is lost due to ketone formation in the final α-hydroxycarbonyl product. To attribute the lower (up to 80%) enantioselectivity for the enol ether **1a** compared to cis-disubstituted alkenes (up to 98%[10]) to C−C bond rotation in the radical intermediate does not apply. If this were so, for the enol ether **1e** higher (>95%) ee values would have to be expected because the final chirality center is permanently fixed through C−O bond formation in the radical intermediate (Figure 2B).

The Jacobsen homolytic pathway, provided a skewed side-on approach (trajectory *b*) of the substrate applies, explains quite adequately the observed enantioselectivities for the trimethylsilyl derivatives **1e,g**; however, it is difficult to understand in terms of radical intermediates why for the *tert*-butyldimethylsilyl derivatives **1e′**,**g′** the enantioselectivities are dramatically increased by such remote groups. This feature had so far not

been examined for trisubstituted olefins, since most employed substrates contained the double bond to be oxidized in a ring system (usually decreased ee values were obtained for larger cycloalkenes) or were phenyl-substituted ethylenes without variation of the steric bulk of the remote substituents.[10,12,15,16]

Let us now analyze the observed enantioselectivities in terms of the alternative Katsuki metallaoxetane mechanism. The key feature here is that the metallaoxetane is enantioselectively formed and subsequently diastereoselectively dissociated into the epoxide product, with or without the intervention of radicals. This more complex mechanism is illustrated in detail for the enol ethers **1a** (Figure 3A) and **1e** (Figure 3B) as model substrates, viewed along the skewed side-on trajectory *b*, in which energy-favored structures are coded in *black*, the others in *gray*. In this [2 + 2] cycloaddition the olefinic substrate approaches the oxo−metal bond crosswise and once the two partners are close enough for bonding, the substrate may either rotate clockwise or counterclockwise to afford the metallaoxetane intermediate; the rotation with the lower steric interactions is selected. Thus, for the enol ether **1a** (Figure 3A) the clockwise rotation applies because it is sterically less encumbered since the bulky siloxy group avoids bumping into the arene framework of the salen complex. Subsequently the metallaoxetane opens up fast to the benzylic radical intermediate, which then collapses by way of the epoxide to the *S*-configured, α-hydroxylated ketone (*S*)-**2a**. Alternatively, the intermediary epoxide may be generated directly from the metallaoxetane adduct.[28b] [Note that the radical intermediates in the Jacobsen (Figure 2A) and the Katsuki (Figure 3A) mechanisms are identical! Moreover, since the stereochemical information at the silyloxy-substituted site is lost in this oxidation process, it is not possible to assess whether rotation about the C−C bond in the radical intermediate takes place prior to epoxide ring closure.]

The favored route in the metallaoxetane model for the enol ether **1e** is displayed by the *black* structures in Figure 3B. Again steric and electronic interactions of the phenyl group with the salicylidene moiety are minimized by clockwise rotation in the crosswise [2 + 2] encounter complex to produce the metallaoxetane. The latter opens up fast to the stabilized radical, whose collapse to the epoxide and rearrangement leads to the observed α-hydroxy ketone (*R*)-**2e**. [Note that rotation about the C−C bond in the radical would have no consequence on the enantioselectivity since the chirality center is permanently fixed to the oxenoid oxygen atom (Figure 3B)!]

How does the metallaoxetane mechanism cope with the fact that remote bulky silyl substituents enhance drastically the enantioselectivity (compare the trimethylsilyl derivatives **1e**,**g** with the *tert*-butyldimethylsilyl ones **1e′**,**g′** in Table 1). A buttressing effect in the highly substituted C−Mn bond of the strained four-membered ring of the metallacycle appears to be responsible, which promotes its faster ring opening to the radical intermediate. Thus, metallaoxetane formation becomes less reversible and the formation of the metallaoxetane from the disfavored orientation (*gray* structure) will be supressed; as the result the overall oxidation proceeds more enantioselectively. Since the radical mechanism (Figure 2) does not explain the enhanced enantioselectivity caused by remote bulky silyl groups in the enol-ether substrates, the present set of stereochemical data (Table 1) are more adequately accommodated by the metallaoxetane model.

Catalyst Structure. The best enantioselectivities for the substrates **1** pertain to the 5,5′-dimethoxy-substituted (salen)-Mn^{III} catalyst **3b** (Table 2), but the improvement is relatively small (at best ∼15% in the ee values). These substituent effects of the catalysts **3** on the enantioselectivity in the oxidation of the silyl enol ethers and ketene acetals may be explained primarily in terms of the electronic influence on the reactivity of the active oxo−metal species rather than steric interactions. The electron-donating substituents in the catalysts **3b**,**c** decrease the reactivity of the oxo species and the oxidation of the silyl enol ethers with these less reactive oxo species involves a more product-like transition state with more specific nonbonded interactions and, consequently, enhanced enantioselectivities.[13] That merely steric effects between the approaching substrate and the catalyst are not the decisive factor becomes evident from the comparison of the 5,5′-di-*tert*-butyl- (**3a**) and the 5,5′-dimethoxy-substituted (**3b**) catalysts. Although the latter possesses the less sterically demanding substituents, it controls the higher enantioselectivity, presumably through electronic effects. This conclusion is further substantiated by the fact that sterically shielding features of the triisopropylsiloxy group in the catalyst **3c** do not raise the enantioselectivity compared to the methoxy derivative **3b**.

In summary, the stereocontrol in the catalytic, enantioselective α hydroxylation presented here is imposed by the substitution pattern and steric bulk of the enol ether substrates **1** and the electronic nature of the 5,5′ substituents in the salen ligand of the manganese catalyst **3**. Besides the direct access to synthetically valuable, optically active α-hydroxy carbonyl products **2**, the silyl enol ethers **1** comprise mechanistically informative substrates to probe steric and electronic effects in the catalytic, enantioselective oxidation by (salen)Mn^{III} complexes. The favored attack of the olefinic substrate on the oxo−metal complex has been identified as the skewed side-on trajectory *b* (Figure 2). Of the two currently debated mechanisms for the oxygen transfer, namely the radical versus the metallaoxetane models, the latter accounts more adequately for the observed enantioselectivity.

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Supporting Information Available: Synthetic details and characteristic spectral data of the (salen)Mn(III) complexes **3b**,**c**, the silyl enol ethers and silyl ketene acetals **1a**−**h**, the racemic α-hydroxy ketones and esters **2a**-**h**, the general catalytic oxidation procedure, analytical protocols for measuring of the enantiomeric excess and results of frontier orbital calculations of substrates **1** (23 pages). See any current masthead page for ordering and Internet access instructions.

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