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Asymmetric organocatalytic SOMO reactions of enol silanes and silyl ketene (thio)acetals

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Organocatalytic SOMO reactions can provide access to variously α-functionalized carbonyl compounds. Chiral imidazolidinones catalysed organo-SOMO reactions of aldehydes and ketones with cyclic and acyclic enol silanes. The resulting chiral dicarbonyl compounds were obtained in yields up to 80% and enantiomeric purities up to 90% ee. Under SOMO conditions, silyl ketene acetals did not afford the desired products. However, silyl ketene thioacetal can be employed, and the corresponding product was isolated with useful enantiomeric purity of 82% ee.

Introduction

Asymmetric organocatalysis is efficient way for synthesis of a great variety of chiral compounds. Enamine formation is one of the major activation strategies in organocatalysis.[1] It activates α-position in carbonyl compounds towards addition of a range of electrophiles. However, single-electron oxidation of an enamine lead to the formation of transient cation-radical species with singly occupied molecular orbital (SOMO). This cation-radical species can react with a variety of radical acceptors, thus constituting a complementary strategy for aldehyde or ketone α-functionalization.[2] The concept of SOMO activation was discovered by MacMillan, who showed that SOMO activation is useful synthetic method for α-functionalization of carbonyl compounds, mainly aldehydes.[3] For enantioselective SOMO reactions, MacMillan´s imidazolidinones were the best catalysts.[4] The typical oxidant is cerium-ammonium nitrate (CAN), but other oxidation reagents, based on copper, such as $Cu(OTf)_2$, $Cu(TFA)_2$, $CuCl_2$,[5] or iron $[Fe(phen)_3](PF_6)_3$, or $FeCl_3$ work well too in some cases.[6] Enamines can even be oxidized photocatalytically.[7] Use of these mild oxidizing reagents ensures wide functional group tolerance. However, oxidative conditions are also one of the limitations of the methodology, because of undesired oxidation of nucleophilic components of the reactions. Direct and enantioselective allylic alkylation of various aldehydes[3] and cyclic ketones[8] with allyl silanes afforded α-substituted carbonyl compounds, which can be employed in a variety of ways in the synthesis. This activation concept enabled enantioselective construction of five-, six- and seven-membered carbocycles and heterocycles.[9] Asymmetric α-enolation of SOMO-activated aldehydes allowed synthesis of enantioenriched γ-ketoaldehydes from simple aldehydes and enol silanes.[10] Organocatalytic SOMO vinylation of aldehydes using vinyl trifluoroborate salts led to products with formyl- and vinyl-moiety on the stereogenic centre.[11] Aldehydes with appending C=C double bond underwent organo-SOMO-catalysed cyclization.[6c]

Introduction of an aryl group into α-position of aldehydes is useful in the synthesis of many medicinal agents. Enantioselective α-heteroarylation of aldehydes with *N*-Boc-pyrrole under SOMO activation conditions played a key role in the synthesis of tashiromin.[12] Aldehydes, lactones and acyl oxazolidones were arylated in the α-position with diaryliodonium salts and a combination of copper and organic catalysts. This methodology has been applied in the synthesis of (*S*)-ketoprofen, nonsteroidal anti-inflammatory medicine.[13] Intramolecular α-arylation of aldehydes via organo-SOMO catalysis served for the construction of chiral tetrahydronaphthalene derivatives.[14]

Radical-mediated (4 + 2) coupling of aromatic aldehydes with styrenes and dienes through asymmetric SOMO-catalysis provided cyclic products with high chemical efficiency, regioselectivity, and stereoselectivity.[6a] Similarly, (3 + 2)

cycloaddition provided stereochemically complex pyrrolidines.[6b]

Carbo-oxidation of styrenes via organo-SOMO catalysis provided γ-nitrate-α-alkyl aldehydes, which were useful building blocks for the synthesis of enantioenriched butyrolactones, pyrrolidines, and α-formyl homobenzylation adducts.[15] Enantioselective oxidative nitroalkylation of aldehydes with various silyl nitronates was an efficient method for the synthesis of β-nitroaldehydes.[16] Another application was enantioselective α-benzylation of aldehydes with electron-deficient aryl and heteroaryl bromides using photoredox-organocatalysis.[17]

We have recently explored use of organometallic reagents such as organoindiums and copper-acetylide in organo-SOMO reaction.[18]

Heterofunctionalization in the α-position of carbonyl compounds are also possible via organo-SOMO catalysis.[5a, 19]

In this context, we decided to explore broadening of the scope for organo-SOMO catalysis. This paper describes evaluation of SOMO catalysis in α-enolation of aldehydes with cyclic enol silanes, silyl ketene acetals and silyl ketene thioacetals, and α-enolation of cyclic ketones.

Results and discussion

Chiral imidazolidinones **C1**–**C5** (Figure 1) and their salts were used as the catalysts in this study.

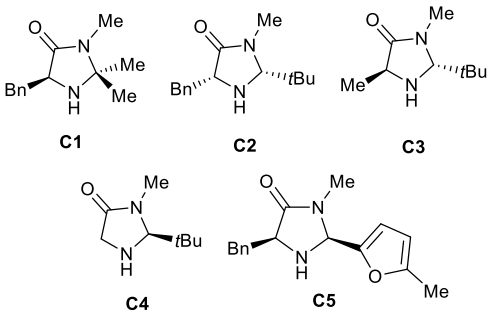
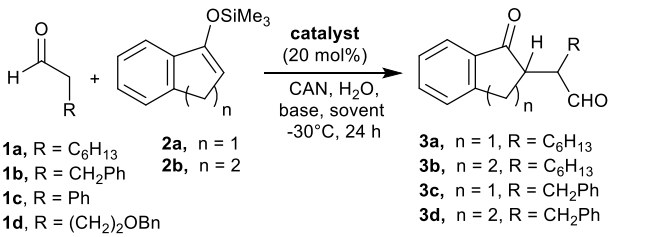


Figure 1

We started our investigation with α-enolation of aldehydes with cyclic enol silanes. Four structurally diverse aldehydes 1a-d were submitted to the reaction with enol silanes generated from cyclic ketones 2. Reaction conditions were probed in the reaction of octanal (1a) with enol silanes 2. Interestingly, the best solvent was acetone. The reaction did not proceed in other potentially suitable organic solvents like DME, THF or MeCN (Table 1). The reactions worked best at lower temperatures, with temperature -30°C as optimal with respect to acceptable reaction speed and limited proportion of side reactions observed. Sterically hindered bases, such as lutidine and 2,6-di-tert-butylpyridine (DTBP) were effective. Lutidine, however, seem less suitable because it gives more side reactions. Cerium-ammonium nitrate (CAN) was the best oxidant. The reaction of octanal (1a) with enol silane 2a afforded the product 3a in only low yields (13-26%). The reaction proceeded highly diastereoselectively (d.r. 100:0); virtually no minor diastereomer could be detected in the reaction mixture. Evaluation of solvent and base influences is summarized in Table 1.



Scheme 1

Table 1. Influence of base and solvent on the reaction of aldehydes **1** with cyclic enol silanes **2**.[a]

Entry	Starting materials	Base	Catalyst	Solvent	Yield	ee[b]
1	**1a**, **2a**	lutidine	**C1**.HCl	Me_2CO	11	9
2	**1a**, **2a**	DTBP	**C1**.HCl	Me_2CO	18	8
6	**1a**, **2b**	lutidine	**C1**.HCl	Me_2CO	26	11
7	**1a**, **2b**	DTBP	**C1**.HCl	Me_2CO	38	14
8	**1a**, **2b**	DTBP	**C1**.HCl	MeOH	0	-
9	**1a**, **2b**	DTBP	**C1**.HCl	THF	0	-
10	**1a**, **2b**	DTBP	**C1**.HCl	MeCN	0	-
11	**1a**, **2b**	lutidine	**C1**.HCl	DME	traces	-
12	**1b**, **2b**	DTBP	**C1**.HCl	Me_2CO	70	90

[a] Reaction conditions: catalyst (0.05 mmol), aldehyde (0.25 mmol), enolsilane (0.5 mmol), water (0.5 mmol, 8 μL), CAN (0.5 mmol, 274 mg), base (0.5 mmol), solvent (0.82 mL) -30°C, 24 h; [b] determined by enantioselective HPLC

On the other hand, tested catalysts imparted only low enantioselectivities. As highlighted in Table 2, the reaction of octanal (**1a**) with enol silane **2a** using imidazolidinone catalysts **C1 - C3** afforded the product **3a** with enantiomeric purity up to 22% ee (Table 2, entries 1–3). The reaction of octanal (**1a**) with enol silane **2a** with catalyst **C5** did not proceed (Table 2, entry 4). 3-Phenylpropanal (**1b**) did not react with enol silane **2a** using **C2**.TFA as a catalyst and only starting compounds were detected in the reaction mixture after the reaction (Table 2, entry 5).

When octanal (**1a**) reacted with (3,4-dihydronaphthalen-1-yloxy)trimethylsilane (**2b**), the corresponding product **3b** was isolated in 38 % with catalyst **C1**.HCl. Other catalysts **C2 - C4** afforded the product **3b** in yields ranging from 15 - 26 % yield (Table 2, entries 7-9). These catalysts were not very enantioselective, with the exception of catalyst **C3**. The catalyst **C3**.HCl afforded the product **3b** with promising enantiomeric ratio of 64% ee. Unfortunately, the reaction time had only marginal effect of the yield of the product as prolonging the reaction time from 24 to 48 h resulted in only slight improvement of the yield to 20 % (Table 2, entry 10). In contrast to reactions of enol silane **2a**, enol silane **2b**, derived from 1-tetralone, reacted with 3-phenylpropanal (**1b**) more smoothly. Furthermore, the reaction was also more enantioselective. Using catalyst **C1**.HCl, the corresponding product **3d** was isolated in 70 % yield with high enantiomeric purity of 90% ee. From this experiment, an aldol product was also isolated in 20 % yield. The

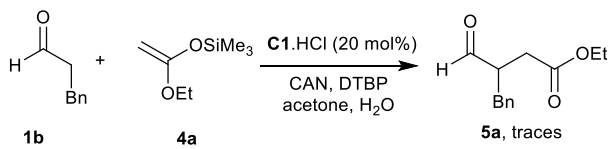
catalyst **C3**.HCl afforded the product **3d** in similar yield (63 %), but with somewhat lower enantiomeric purity (ee 58%). Experiment on a larger scale (1 mmol of aldehyde **1b**) enabled more convenient isolation and thus 68 % of the product **3d** was obtained with the same enantiomeric ratio (ee 60%). The product of the aldol reaction was isolated in both cases too (Table 2, entries 12–13). When catalyst **C5** was used in the reaction of aldehyde **1b** with enol silane **2b**, the product **3d** was isolated in 66 % yield. This catalyst, however, was much less enantioselective (ee. 28%) (Table 2, entry 14). The reactions of 2-phenylacetaldehyde (**1c**) and 4-(benzyloxy)butanal (**1d**) did not afford expected products with enol silane **2b** (Table 2, entries 15,16).

Table 2. SOMO reactions of aldehydes with cyclic enol silanes.[a]

Entry	Aldehyde	Enolsilane	Catalyst	Yield	ee[b]
1	**1a**	**2a**	**C1**.HCl	18	8
2	**1a**	**2a**	**C2**.TFA	26	22
3	**1a**	**2a**	**C3**.HCl	13	14
4	**1a**	**2a**	**C5**	0	-
5	**1b**	**2a**	**C2**.TFA	0	-
6	**1a**	**2b**	**C1**.HCl	38	14
7	**1a**	**2b**	**C2**.TFA	26	20
8	**1a**	**2b**	**C3**.HCl	15	64
9	**1a**	**2b**	**C4**.TFA	17	12
10	**1a**	**2b**	**C3**.HCl	20[c]	60
11	**1b**	**2b**	**C1**.HCl	70[d]	90
12	**1b**	**2b**	**C3**.HCl	63[d,e]	58
13	**1b**	**2b**	**C3**.HCl	68[d,e]	60
14	**1b**	**2b**	**C5**	66[d,e]	28
15	**1c**	**2b**	**C1**.HCl	0	-
16	**1d**	**2b**	**C1**.HCl	0	-

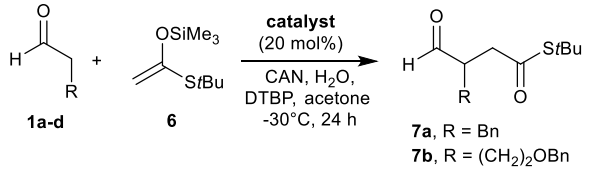
[a] Reaction conditions: catalyst (0.05 mmol), aldehyde (0.25 mmol), enolsilane (0.5 mmol), water (0.5 mmol, 8 µL), CAN (0.5 mmol, 274 mg), 2,6-di-*tert*-butyl pyridine (0.5 mmol, 113 µL), acetone (0.82 mL) -30°C, 24 h; [b] determined by enantioselective HPLC; [c] reaction time 48 h; [d] product of the aldol reaction was isolated in 17–22 % yield; [e] Reaction was performed with 1 mmol of aldehyde.

An interesting extension to the use of enol silanes in organo-SOMO reactions would be an application of the corresponding enol silanes derived from esters or thioesters of carboxylic acids. Therefore, we continued our study with attempts on organo-SOMO reaction of aldehydes with silyl ketene acetals. We have tested three different silyl ketene acetals **4**, derived from acetic and phenylacetic acids, with aldehydes **1b-d**. However, no useful quantity of the corresponding product **5** could have been isolated under a range of experimental conditions. Only the reaction of aldehyde **1b** with silyl ketene acetal **4a** afforded just traces of the corresponding compound **5** (Scheme 2).



Scheme 2

Interestingly, more useful results were obtained in the organo-SOMO reaction of aldehydes **1** with the corresponding silyl ketene thioacetal **6** (Scheme 3). Aldehydes **1a** and **1c** did not afford the desired products. The aldehyde **1d** reacted, but the product **7b** was unstable. Preparatively useful results were only obtained with 3-phenylpropanal **1b**.



Scheme 3

The reaction of 3-phenylpropanal (**1b**) with silyl ketene thioacetal **6** provided the product **7a** in up to 43% yield (Table 3, entry 3). The most enantioselective catalyst was imidazolidinone **C3**, which afforded the product **7a** with enantiomeric purity of 82% ee. The results of SOMO reaction of aldehydes with silyl ketene thioacetals are gathered in Table 3.

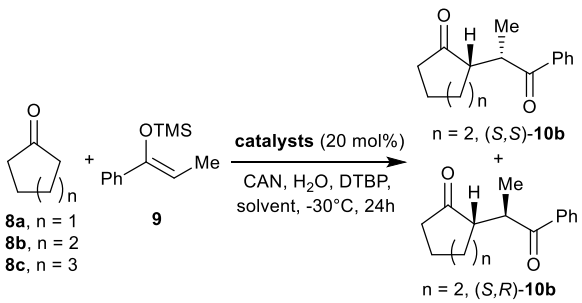
Table 3. SOMO reaction of aldehydes with silyl ketene thioacetals.[a]

Entry	Aldehyde	Catalyst	Solvent	Yield (%)	ee[b]
1	**1a**	**C1**.HCl	Me_2CO	0	-
2	**1b**	**C1**.HCl	Me_2CO	36	70
3	**1b**	**C3**.HCl	Me_2CO	43	82
4	**1b**	**C1**.HCl	THF	18	n.d.
5	**1b**	**C1**.HCl	DME	0	-
6	**1b**	**C4**.TFA	Me_2CO	40	62
7	**1c**	**C1**.HCl	Me_2CO	0	-
8	**1d**	**C1**.HCl	Me_2CO	6[c]	-

[a] Reaction conditions: catalyst (0.05 mmol), aldehyde (0.25 mmol), enolsilane (0.5 mmol), water (0.5 mmol, 8 µL), CAN (0.5 mmol, 274 mg), 2,6-di-*tert*-butyl pyridine (0.5 mmol, 113 µL), acetone (0.82 mL) -30°C, 24 h; [b] determined by enantioselective HPLC; [c] product decomposes.

There has been only one example of α-enolation of ketones using SOMO catalysis. Therefore, we continued our research with reaction of cycloalkanones **8** with enol silane **9**. In contrast to previous reactions with cyclic enol silane, reactions of cyclohexanone (**8b**) with enol silane **9** also proceeded in DME at -30 °C for 24 h with CAN as an oxidant and DTBP as a base. As revealed in Table 4, diastereomeric ratio of the products (*S,S*)-**10a** and (*S,R*)-**10b** was in the range 67:37 – 55:45. Each of these diastereomers can be separated by flash chromatography. Somewhat counterintuitively, the best solvent was again acetone. In this solvent and using catalyst **C1**, the product **10b** was isolated in combined 80% yield (Table 4, entry 2). Less product **10b** was isolated from the experiment in DME (Table 4, entry 3). Interestingly, the reaction of cyclohexanone (**8b**) with enol silane **9** catalysed by the catalyst **C3**.HCl in acetone gave only product of the aldol reaction, whereas the reaction in DME with **C3**.HCl provided 60 % of **10a** (Table 4, entries 6 and 7). Using catalyst **C4**.TFA no products were observed neither in acetone nor in DME. Surprisingly, neither cyclopentanone (**8a**) nor

cycloheptanone (**8c**) did not afford the desired product in the organo-SOMO reaction with enol silane **9** (Table 4, entries 1 and 8).



Scheme 4

Table 4. SOMO reactions of cycloalkanones (**8**) with enol silane **9**[a]

Entry	Ketone	Catalyst	Solvent	Yield of 10b[b]	d.r.[c]	ee[d]
1	**8a**	**C1**.HCl	Me_2CO	0	-	-
2	**8b**	**C1**.HCl	Me_2CO	50/30	63 : 37	0/2
3	**8b**	**C1**.HCl	DME	41/20	67 : 33	4/0
4	**8b**	**C2**.TFA	Me_2CO	38/21	64 : 36	2/2
5	**8b**	**C2**.TFA	DME	30/25	55 : 45	n.d.
6	**8b**	**C3**.HCl	Me_2CO	0/0[e]	-	-
7	**8b**	**C3**.HCl	DME	36/24	60 : 40	0/0
8	**8c**	**C1**.HCl	Me_2CO	0	-	

[a] Catalyst (20 mol%) cycloalkanone (0.25 mmol), trimethyl(1-phenylprop-1-enyloxy)silane (0.5 mmol, 100 µL), water (0.5 mmol, 8 µL), CAN (0.5 mmol, 274 mg), and 2,6-di-*tert*-butyl pyridine (0.5 mmol, 113 µL), acetone (0.82 mL), -30°C, 24 h; [b] (*S,S*)-**10b**/(*S,R*)-**10b**; [c] determined by ^{1}H NMR of the crude reaction mixture; [d] determined by enantioselective HPLC, (*S**,*S**)-**10b**/(*S**,*R**)-**10b**; [e] Only product of the aldol reaction was detected in the reaction mixture.

Configuration of products can be rationalized by models of transition states (Figure 2). These models are based on MacMillan´s proposals in similar reactions.[10] For the reaction of aldehyde **1b** with enol silane **2b**, the catalyst **C1** shields *Re*-face of the cation-radical and thus direct the attack of the enol silane from *Si*-face. High diastereoselectivity of the reaction is likely dictated by considerably smaller steric repulsions in the *antiperiplanar* arrangement of silyl enol ether and iminium kation radical in comparison to *synclinal* arrangement of the reagents. On the hand, in the reaction of aldehyde **1b** with silyl ketene thioacetal **6**, catalyst **C3** was the most efficient. The *tert*-butyl group shields *Si*-face of the cation-radical and thus the attack proceeds from less hindered *Re*-face. Presumably, larger *tert*-butyl group dominates closer, but smaller methyl group. This leads to product (*S*)-**7a**. This notion is also supported by the fact that utilization of catalyst **C1** in the reaction of aldehyde **1b** with thioacetal **6** afforded the product **7a** with opposite configuration (based on retention times from enantioselective HPLC).

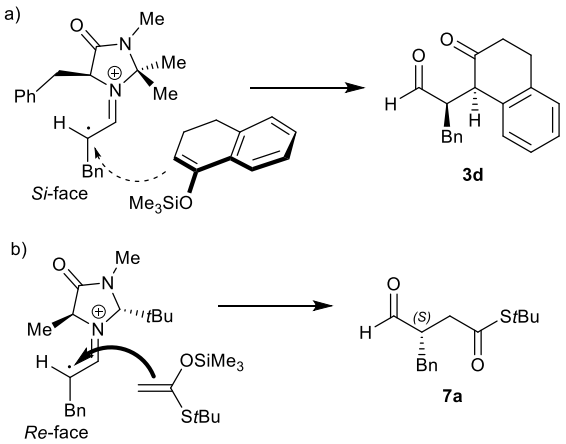


Figure 2

The relative configuration of compound **3d** was determined to be *syn* by NOESY NMR experiments (for details see supporting information).

Absolute configuration of the compound **7a** was determined by comparison of its electronic circular dichroism (ECD) spectra with those calculated. ECD spectra were calculated by TDDFT using two functionals B3LYP and M06 and both afforded similar spectra. The calculated spectra for (*S*)-**7a** matched well experimentally measured spectrum of this compound (Figure 3).

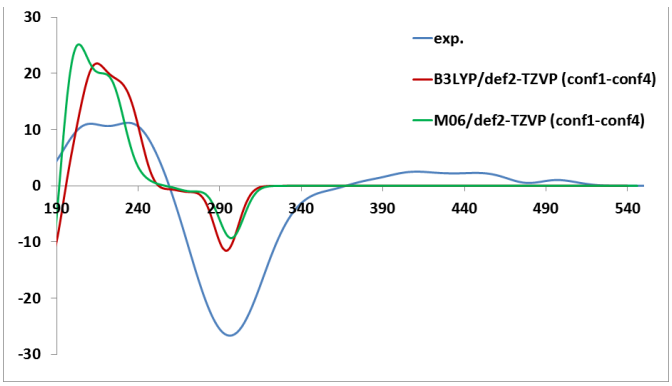
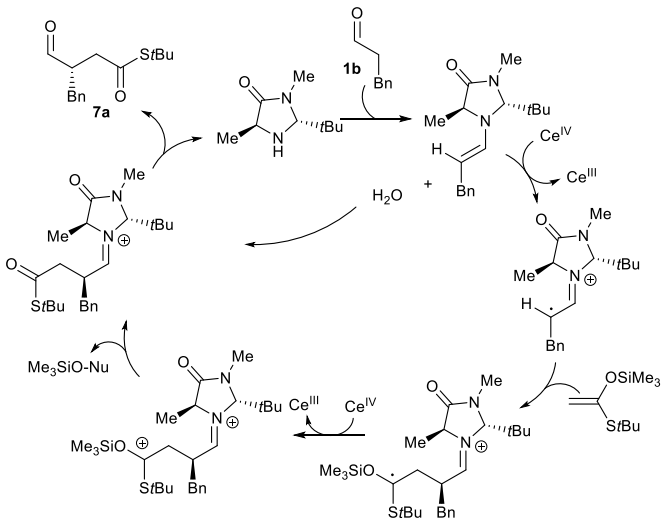


Figure 3. Comparison of calculated and experimentally determined ECD spectra of compound (*S*)-**7a** (Δε (M^{-1}, cm^{-1}) /λ (nm)).

The SOMO reactions of aldehydes and ketones with enols silanes and silyl ketene thioacetals most likely proceed via SOMO mechanism postulated by Flowers and co-workers.[20] Based on this proposal, we have suggested following tentative mechanisms for reaction of silyl ketene thioacetals (Scheme 5).



Scheme 5

Conclusions

In summary, this paper has provided a study of possibilities and limitations of new examples organo-SOMO catalysed reactions. Aldehydes reacted with cyclic enolsilanes and the corresponding product was obtained in up to 70 %, as a single diastereomer and enantiomeric purity up to 90% ee. Organo-SOMO reactions of silyl ketene acetals failed to provide the desired products with aldehydes. On the other hand, silyl ketene thioacetal was a useful partner in ths type of transformation. The corresponding product was formed in enantiomeric purity of 82% ee. From among several cyclic ketones, which were subjected to the organo-SOMO reaction with a silyl enol ether, only cyclohexanone provided the desired product in good yield. It was isolated as two diastereomer with d.r. up to 67:33 and virtually racemic.

Experimental section

General

All reactions were carried out in an inert atmosphere of Ar. Solvents were dried and purified by standard methods before use. NMR spectra were recorded on Varian Mercury plus instrument (300 and 600 MHz for ^{1}H; 75 and 150 MHz for ^{13}C). Chemical shifts (δ) are given in ppm relative to tetramethylsilane. Flash chromatography was performed on Merck silica gel 60. Thin-layer chromatography was performed on Merck TLC-plates silica gel 60, F-254. Enantiomeric excesses were determined by HPLC on Chiralcel OD-H, Chiralpak AD-H or Chiralpak AS-H (Daicel Chemical Industries) column using hexane/*i*PrOH as a mobile phase and detection with UV-detector at 254 nm.

Starting materials, which were not commercially available, were synthesized according to the literature procedures; (1*H*-inden-3-yloxy)trimethylsilane (**3a**),[21] (3,4-dihydro-1-naphthalenyloxy)(trimethyl)silane (**3b**),[22] trimethyl(1-phenylprop-1-enyloxy)silane (**9**),[23] (1-(*tert*-butylthio)vinyloxy)trimethylsilane (6).[24]

General procedure for enantioselective α-enolation with cyclic silyl(enol)ethers

A solution of the catalyst (20 mol%) in acetone (0.0625 M 0.82mL) was prepared in a vial equipped with a magnetic stir bar at -78 °C under argon atmosphere. In this order, aldehyde (0.25 mmol), enolsilane (0.5 mmol), water (0.5 mmol, 8 µL), CAN (0.5 mmol, 274.1mg), and 2,6-di-*tert*-butyl pyridine (0.5 mmol, 113 µL) were added to this mixture. After purging the solution with argon for 1 min, this mixture was warmed to -30 °C and stirred at constant temperature for 24 h. The cold reaction mixture was poured into Et_2O (20 mL) and filtered through SiO_2, washed with ether diethyl ether (20 mL) and concentrated *in vacuo*. The resulting residue was purified by column chromatography (SiO_2, hexane-EtOAc, 9:1) to provide the title compound.

General procedure for α-enolation of cyclohexanone

A solution of the catalyst (20 mol%) in acetone (0.0625 M, 0.82 mL) was prepared in a vial equipped with a magnetic stir bar at -78°C under argon atmosphere. In this order, cyclohexanone (0.25 mmol, 26 µL), trimethyl(1-phenylprop-1-enyloxy)silane (0.5 mmol, 100 µL), water (0.5 mmol, 8 µL), CAN (0.5 mmol, 274 mg), and 2,6-di-*tert*-butyl pyridine (0.5 mmol, 113 µL) are added to this mixture. After purging the solution with argon for 1 min, this mixture was warmed to -30 °C and stirred at constant temperature for 24 h. The cold reaction was poured into diethyl ether (20 mL) and filtered through SiO_2, washed with diethyl ether (20 mL) and concentrated *in vacuo*. The resulting residue was purified by column chromatography (SiO_2, hexane-EtOAc, 9:1) to provide the title compound.

2-(1-oxo-2,3-dihydro-1*H*-inden-2-yl)octanal (3a)

Yield: 17 mg (26%); colourless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.76 (d, *J*=6.9, 1H, CHO), 7.92 (ddd, J_1=7.8, J_2=1.3, J_3=0.6, 1H, ArH), 7.47 (ddd, J_1=7.8, J_2=7.3, J_3=1.3, 1H, ArH), 7.35 (ddd, J_1=7.8, J_2=7.3, J_3=1.2, 1H, ArH), 7.18 (ddd, J_1=7.8, J_2=1.2, J_3=0.6, 1H, ArH), 3.92 (ddd, J_1=8.1, J_2=5.2, J_3=4.1, 1H, CH), 3.18 (dd, J_1=15.8, J_2=8.1, 1H, CH_2), 3.14 (dd, J_1=15.8, J_2=4.2, 1H, CH_2), 2.80 (tdd, J_1=7.3, J_2=6.9, J_3=5.2, 1H, CH), 1.75 (td, J_1=7.5, J_2=7.3, 2H, CH_2), 1.28–1.23 (m, 8 H, 4 × CH_2), 0.87 (t, *J*=7.0, 3H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.1 (C=O), 205.1 (CHO), 150.4 (C-Ph), 136.3 (C-Ph), 134.4 (C-Ph), 127.6 (C-Ph), 126.5 (C-Ph), 126.2 (C-Ph), 57.5 (CH), 52.4 (CH), 31.8 (CH_2), 31.6 (CH_2), 29.3 (CH_2), 28.8 (CH_2), 28.3 (CH_2), 22.9(CH_2), 14.1 (CH_3).

HR-MS calc. for $C_{17}H_{23}O_2$ (MH+) 259.169, found 259.109.

HPLC (Chiralpak AD-H; *i*-PrOH-hexane 10:90, 1 mL/min; λ = 254 nm): t_R = 11.95 major, t_R = 19.14 minor.

2-(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)octanal (3b)

Yield: 26 mg (38%); colourless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.75 (d, *J*=6.9, 1H, CHO), 7.91 (ddd, J_1=7.9, J_2=1.3, J_3=0.6, 1H, ArH), 7.40 (ddd, J_1=7.5, J_2=7.3, J_3=1.2, 1H, ArH), 7.35 (ddd, J_1=7.9, J_2=7.4, J_3=1.2, 1H, ArH), 7.16 (ddd, J_1=7.5, J_2=1.2, J_3=0.6, 1H, ArH), 3.19 (ddd, J_1=10.2, J_2=5.4, J_3=2.4, 1H, CH), 2.82 (ddd, J_1=14.3, J_2=10.2, J_3=3.4, 1H, CH_2), 2.80 (ddd, J_1=14.3, J_2=3.3, J_3=2.3, 1H, CH_2), 2.78 (tdd, J_1=7.3, J_2=6.9, J_3=5.4, 1H, CH_2), 2.11 (dddd, J_1=13.6, J_2=3.4, J_3=2.4, J_4=2.3, 1H, CH_2) 1.99 (dddd, J_1=13.6, J_2=10.2, J_3=10.2, J_4=3.3, 1H, CH_2), 1.75 (td, J_1=7.5, J_2=7.3, 2H, CH_2), 1.29–1.24 (m, 8 H, 4 × CH_2), 0.87 (t, *J*=7.1, 3H, CH_3).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.9 (CHO), 202.1 (C=O), 141.7 (C-Ph), 136,9 (C-Ph), 134.2 (C-Ph), 129.1 (C-Ph), 129.0 (C-Ph), 127.2 (C-Ph), 57.6 (CH), 50.5 (CH), 31.6 (CH_2), 29.3 (CH_2), 28.8 (CH_2), 28.5 (CH_2), 28.3 (CH_2), 22.9 (CH_2), 14.0 (CH_3).
HR-MS calcd. For $C_{18}H_{25}O_2$ (MH+) 273.185, found 273.189.
HPLC (Chiralpak AD-H; *i*-PrOH-hexane 5:95, 1mL/min; λ = 254 nm): t_R = 37.88 major, t_R = 48.37 minor.

2-(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-3-phenylpropanal (3d)
Yield: 200 mg (70 %); colourless liquid.
^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.82 (t, *J*=1.4Hz, 1H, C**H**O), 8.06 (ddd, J_1=1.1Hz, J_2=7.8Hz, J_3=24.7Hz, 1H, ArH), 7.49–7.41 (m, 1H, ArH), 7.33-7.28 (m, 2H, ArH), 7.21-7.18 (m, 2H, ArH), 3.63 (td, J_1=1.9Hz, J_2=5.8Hz, 1H, CH), 3.20 (ddd, J_1=4.4Hz, J_2=13.1Hz, J_3=17.2Hz, 1H, CH), 2.99–2.95 (m, 3H, CH_2, CH) 2.79–2.77 (m, 1H, CH_2), 2.70–2.65 (m, 2H, CH_2), 2.16–2.07 (m, 2H, CH_2), 2.03–1.96 (m, 1H, CH).
^{13}C NMR (150 MHz, $CDCl_3$): δ = 201.5 (CHO), 199.9 (C=O), 144.5 (C-Ph), 140.2 (C-Ph), 133.3 (C-Ph), 132.6 (C-Ph), 128.8 (C-Ph), 128.6 (C-Ph), 128.3 (C-Ph), 127.4 (C-Ph), 126.6 (C-Ph), 126.2 (C-Ph), 47.9 (CH), 45.2 (CH), 39.2 (CH_2), 29.7 (CH_2), 28.1 (CH_2)..
HR-MS calcd. For $C_{19}H_{19}O_2$ (MH+) 279.138, found 279.157.
HPLC (Chiralpak AD-H; *i*-PrOH-hexane 10:90, 1mL/min; λ = 254 nm): t_R = 5.81 major, t_R = 10.98 minor.

S-*tert*-butyl 3-benzyl-4-oxobutanethioate (7a)
Yield: 29 mg (43%); colourless liquid.
^{1}H NMR (300 MHz, $CDCl_3$): δ = δ 9.77 (s, 1H, CHO); 7.35–7.23 (m, 3H, Ph); 7.19–7.11 (m, 2H, Ph); 3.18–3.00 (m, 2H, $PhCH_2$); 2,86 (dd, J_1 = 16.5, J_2 = 7.0 Hz, 1H, CHOCH); 2.74 (dd, J_1 = 13.6, J_2 = 7.5 Hz, 1H, $COCH_2$); 2.58 (dd, J_1 = 16.4, J_2 = 5.4 Hz, 1H, $COCH_2$); 1.44 (s, 9H, $C(CH_3)_3$).
^{13}C NMR (75 MHz, $CDCl_3$): δ 202.1 (CHO); 198.2 (CO); 137.7 (C-Ph); 129.1 (C-Ph); 128.7 (C-Ph); 126.7 (C-Ph); 49.4 (CH); 42.6 ($C(CH_3)_3$); 34.4 (CH_2); 29.8 (CH_3).
HR-MS calcd. For $C_{15}H_{20}O_2SNa$ $(M + Na)^+$ 287.10762, found 287.10803.
HPLC (Chiralpak AD-H; *i*-PrOH-hexane 10:90, 1mL/min; λ = 217 nm): t_R = 5.51 major, t_R = 8.44 minor.

(*S*)-2-((*S*)-1-oxo-1-phenylpropan-2-yl)cyclohexanone (*S,S*)-**10b** [24]
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14–7.95 (m, 2H), 7.57–7.39 (m, 1H), 7.36–7.18 (m, 2H), 3.63 (dt, *J* = 5.9, 1.9 Hz, 1H), 3.19 (ddd, *J* = 27.4, 16.0, 9.6 Hz, 1H), 2.98 (dd, *J* = 12.8, 6.7 Hz, 2H), 2.66 (dd, *J* = 8.4, 4.7 Hz, 2H), 2.21–2.05 (m, 4H), 1.25 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.7, 204.2, 137.0, 132.4, 128.4, 128.0, 55.4, 39.2, 38.8, 28.0, 25.2, 23.3, 13.1.
HPLC (Chiralpak AD-H; *i*-PrOH-hexane 5:95, 1mL/min; λ = 254 nm): t_R = 37.88 major, t_R = 48.37 minor.

(*S*)-2-((*R*)-1-oxo-1-phenylpropan-2-yl)cyclohexanone (*S,R*)-**10b** [24]
Yield: 20 mg (30 %); colourless liquid.
^{1}H NMR (300 MHz, $CDCl_3$): δ = δ 8.04 (dd, J_1 = 7.8, J_2 = 1.0 Hz, 2H), 7.47 (td, J_1 = 7.5, J_2 = 1.4 Hz, 1H), 7.31 (ddd, J_1 = 20.8, J_2 = 8.9, J_3 = 4.1 Hz, 2H), 3.60 (dt, J_1 = 6.1, J_2 = 2.0 Hz, 1H), 3.30–3.16 (m, 1H), 3.13–2.96 (m, 2H), 2.30–2.00 (m, 4H), 1.26 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.9, 204.6, 137.1, 132.4, 128.7, 128.2, 55.9, 39.5, 39.0, 28.2, 25.6, 23.6, 13.4.
HPLC (Chiralpak AD-H; *i*-PrOH-hexane 5:95, 1mL/min; λ = 254 nm): t_R = 31.73 major, t_R = 38.53 minor.

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Electronic Supplementary Information (ESI) available: pictures of ^{1}H and ^{13}C NMR spectra and HPLC chromatograms for all prepared compounds. See DOI: 10.1039/b000000x/

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