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A Practical and Versatile Access to Dihydrosalen (Salalen) Ligands: Highly Enantioselective Titanium *In Situ* Catalysts for Asymmetric Epoxidation with Aqueous Hydrogen Peroxide

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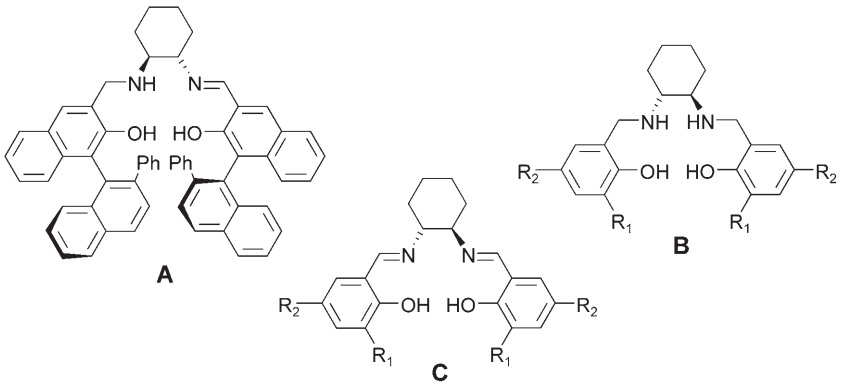
Abstract: A modular synthesis for chiral and non-symmetrical salalen ligands (i.e., mono-reduced salens), carrying an imine and an amine functionality has been developed. The ligands can be assembled *in situ* by Schiff base formation of an *N*-(2-hydroxybenzyl)diamine with a salicylic aldehyde, thus allowing rapid and easy variation/optimization of the ligand structure. Aiming at optimal activity and enantioselectivity in the titanium-catalyzed asymmetric epoxidation of non-functionalized olefins, a positional scanning of the two ligand halves was carried out. High epoxide yields were achieved, and up to 98% *ee*. The composition of the titanium complex catalysts was determined by high resolution mass spectrometry and X-ray crystallography for one selected example.

Keywords: asymmetric catalysis; epoxidation; *in situ* catalysts; salalen ligands; titanium

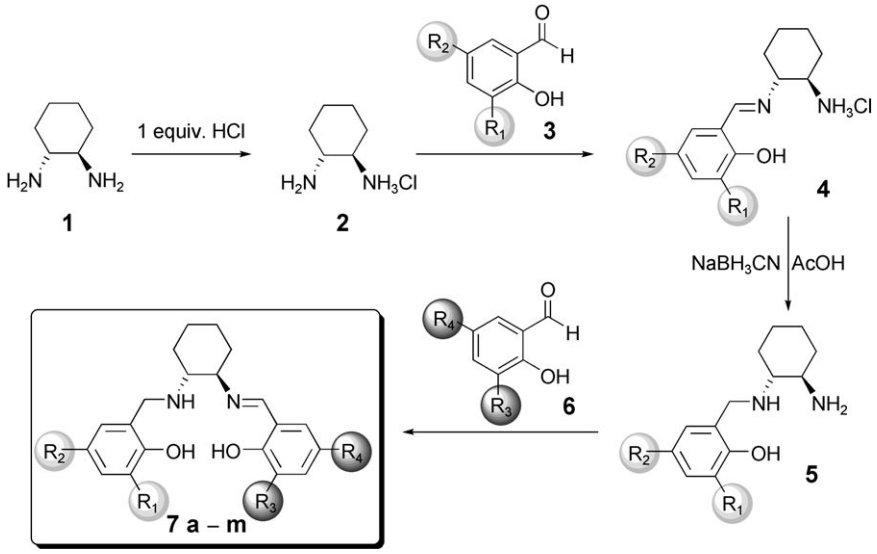
Introduction

Optically active epoxides are versatile intermediates that can be converted into a wide variety of enantiomerically pure products. Various methods have been developed for the preparation of enantiomerically enriched epoxides, with asymmetric epoxidation (AE) of olefins being the most direct approach.[1] Established methods include the Ti-catalyzed AE of allylic alcohols,[2] the transition metal-catalyzed epoxidation of non-functionalized olefins,[3] chiral ketone-catalyzed epoxidation[4] and the nucleophilic epoxidation of electron-deficient olefins.[5] In terms of convenience and atom efficiency, aqueous hydrogen peroxide is the oxidant of choice, as it is cheap, safe, easy to handle, and produces water as the sole by-product.[6] Significant effort has been devoted to the development of AE methods using hydrogen peroxide as the oxidant.[4,7] In this context, Shi et al. combined carbohydrate-derived organocatalysts with acetonitrile as H_2O_2 activator.[8] Beller et al. and Strukul et al. employed chiral ruthenium and platinum catalysts for the AE, including terminal olefins as substrates.[9] In contrast, the recent work by Katsuki et al. is based on titanium in combination either with a semi-reduced salen-type ligand (a so-called salalen, **A**, Scheme 1), or a fully reduced salen (salan, **B**, Scheme 1). Salan ligands were prepared by borohydride (full) reduction of ordinary salens, and their titanium complexes can be conveniently synthesized *in situ* by addition of Ti(O-*i*-Pr)$_4$. High enantioselectivity was achieved for a number of conjugated olefins, and even for non-conjugated terminal olefins such as 1-octene.[10]

Ti-salalen complexes of ligands such as **A** were accessed by Katsuki et al. *via* Meerwein–Ponndorf–Verley reduction of the fully assembled salen complexes, such as those derived from **C** (Scheme 1). Based on our earlier work on Mn- and Ni-salalen complexes,[11] we reasoned that a more convenient and versatile method for the preparation of salalen ligands (and complexes) may consist in the procedure shown in Scheme 2. The salan ligands **B** are, by nature of their synthesis from salens, "symmetrical" ($R_1 = R_3$, $R_2 = R_4$). Salalen ligands such as **7** can either be prepared in a "symmetrical" fashion using the same salicylic aldehyde twice (**3** = **6**, Scheme 2), or in an "non-symmetrical" fashion, using two different salicylic aldehydes **3** and **6**. The purpose of our study was (i) to prove the versatility of our novel synthesis of salalen ligands **7** (Scheme 2), and (ii) to exploit this versatility for the optimization of simple salalen ligands **7** in the Ti-catalyzed AE with H_2O_2. We focussed the latter part of our study on non-functional-



Scheme 1. Reduction stages of salens **C**: half-reduced (salalen **A**), fully reduced (salan **B**), non-reduced (salen **C**).



Scheme 2. Synthesis of DACH-salalen ligands **7a–m**.

ized olefins (such as 1,2-dihydronaphthalene) as they pose a major challenge in AE, and to assure direct comparability with the work of Katsuki et al.

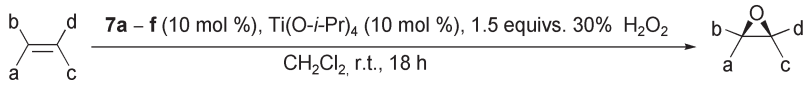
Results and Discussion

First, the diamine component (e.g., *trans*-1,2-diaminocyclohexane, DACH; **1**), in the form of its anhydrous monohydrochloride **2**,[12] is condensed with one equivalent of a salicylic aldehyde **3**, and the resulting imine **4** is reduced to the monoalkylated diamine **5** (Scheme 2). For the reduction step, sodium cyanoborohydride in pure acetic acid proved best. With the amine component **5** in hand, condensation with one equivalent of a second salicylic aldehyde **6** affords the salalen ligand **7**. Our synthetic method thus allows facile access to a variety of both "symmetrical" and "non-symmetrical" salalen ligands **7**, with easily tunable steric and electronic properties.

With the above synthetic route in hand, we proceeded to a positional scanning of the "left" (i.e., substituents R_1 and R_2) and "right" (i.e., substituents R_3 and R_4) halves of the salalen ligand. The novel and non-symmetrical salalen ligands **7a–m** were prepared and examined for their activity and asymmetric induction in the epoxidation of several olefins with aqueous hydrogen peroxide. The Ti complexes were generated *in situ* from the salalen ligands **7** and Ti(O-*i*-Pr)$_4$. In the absence of either the salalen ligands **7** or Ti(O-*i*-Pr)$_4$, no epoxidation took place. As also observed by Katsuki et al., the corresponding non-reduced salens were catalytically ineffective.[10]

We first investigated the effect of the "left" half of the ligands **7** by varying the salicylic aldehyde **3**. The condensation of the resulting amines **5** with unsubstituted salicylic aldehyde ($R_3 = R_4 = H$) afforded the

Table 1. Positional scanning of the "left" half of the salalen ligands **7**: variation of the salicylic aldehyde **3**.



		Substituents				8		9		10	
Entry	Ligand no.	R_1	R_2	R_3	R_4	Yield[a] [%]	*ee*[b] [%]	Yield[c] [%]	*ee*[b] [%]	Yield[c] [%]	*ee*[b] [%]
1	**7a**	F	F	H	H	0	-	0	-	0	-
2	**7b**	Cl	Cl	H	H	69	91	23	75	4	66
3	**7c**	I	I	H	H	6	36	1	-	traces	-
4	**7d**	OMe	H	H	H	25	93	2	75	traces	-
5	**7e**	*t*-Bu	*t*-Bu	H	H	45	96	4	74	2	47
6	**7f**	Ph	H	H	H	76	98	24	77	5	73

[a] Determined by HPLC analysis.
[b] See Supporting Information for details of *ee* analysis.
[c] Determined by GC analysis.

salalen ligands **7a–f**. As test substrates, we chose 1,2-dihydronaphthalene (**8**), styrene (**9**) and non-conjugated vinylcyclohexane (VCH, **10**). The results are summarized in Table 1.

The first ligand examined (**7a**) was based on 3,5-difluorosalicylic aldehyde, and did not show significant catalytic activity (entry 1). Good yields and high enantioselectivities were obtained with chloro substituents in the positions R_1 and R_2 (ligand **7b**, entry 2). The diiodide **7c** showed lower activity and selectivity (entry 3). Changing to an electron-donating methoxy substituent in the 3-position (**7d**) led to diminished yields (entry 4). We furthermore synthesized the 3,5-di-*tert.*-butylated salalen **7e** and obtained moderate yield and excellent enantiomeric excess in the epoxidation of 1,2-dihydronaphthalene (**8**). Unfortunately, the yields for styrene (**9**) and VCH (**10**) were comparatively low (entry 5). The best activity and enantioselectivity for all three substrates **8–10** was achieved with the 3-phenyl-substituted DACH-salalen **7f** (entry 6). The amines **5** (Scheme 1), when employed as tridentate ligands with Ti(O-*i*-Pr)$_4$, did not afford active epoxidation catalysts.

After identification of 3-phenyl-substitution as most effective for the "left" half of the ligands **7a–f**, we turned to the scanning of the "right" half of the salalen ligands **7**. While keeping R_1 = Ph and R_2 = H of the amine **5** constant (Scheme 1), the substituents R_3 and R_4 were varied. Thus, a second set of salalen ligands **7g–m** was prepared by varying the salicylic aldehyde **6** in our synthetic route (Scheme 1). The results are summarized in Table 2.

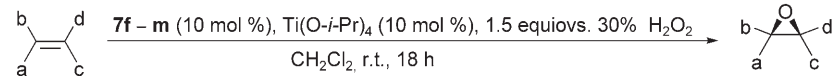
For comparison, entry 1 reiterates the results obtained with ligand **7f**, with no substituents on the "right" side, that is, $R_3 = R_4 = H$. Again, introduction of fluoro substituents led to inactivity (ligand **7g**, $R_3 = R_4 = F$; entry 2). Iodo- and in particular chloro-substituents in the positions R_3 and R_4 led to good yields and high enantioselectivities in the epoxidation of 1,2-dihydronaphthalene (**8**) (Table 2, entries 3 and 4). Changing to electron-withdrawing nitro groups led to diminished activity (ligand **7j**, entry 5), albeit at high *ee*. Similarly, methoxy substitution (R_3 = OMe, R_4 = H) gave moderate yields (ligand **7k**; entry 6), but high enantioselectivity. Changing to sterically demanding *tert*-butyl groups in positions R_3 and R_4 proved detrimental for the catalyst activity (entry 7). Apparently, the catalytic system is highly sensitive to steric congestion around the R_3 position. By far the best results were obtained with a phenyl substituent in position R_3 (entry 8).

All results reported so far were obtained by *in situ* formation of the Ti catalyst from a pre-formed ligand (**7a–m**) and Ti(O-*i*-Pr)$_4$. Please note, however, that the synthesis of the ligand itself can be performed *in situ* as well. In other words, by just mixing an amine **5** (Scheme 1) with a salicylic aldehyde **6** and subsequently adding Ti(O-*i*-Pr)$_4$, the catalytically active Ti complex is formed. The preparation of structurally diverse Ti-salalen catalysts is thus reduced to the simple combination of stock solutions of the amines **5**, the salicylic aldehydes **6** and of Ti(O-*i*-Pr)$_4$. The efficiency of this "*total in situ*" approach is demonstrated by entry 8 of Table 2 (values in parentheses): in fact, the "*total in situ*" catalyst even showed enhanced enantioselectivity.

With ligand **7m** identified by positional scanning, we investigated the substrate scope of its Ti complex and further optimized the epoxidation process (Table 3).

For example, we found that the epoxidation of 1,2-dihydronaphthalene (**8**) is completed already after

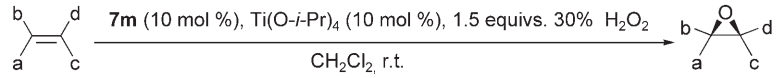
Table 2. Positional scanning of the "right" half of the salalen ligands **7**: variation of the salicylic aldehyde **6**.

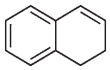
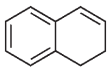
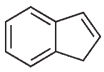
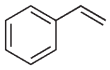
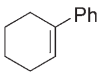
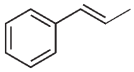
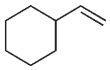
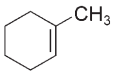
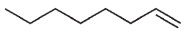


Entry	Ligand no.	Substituents				8		9		10	
		R_1	R_2	R_3	R_4	Yield[a] [%]	*ee*[b] [%]	Yield[d] [%]	*ee*[b] [%]	Yield[d] [%]	*ee*[b] [%]
1	**7f**	Ph	H	H	H	76	98	24	77	5	73
2	**7g**	Ph	H	F	F	0	-	0	-	0	-
3	**7h**	Ph	H	Cl	Cl	54	98	13	73	3	68
4	**7i**	Ph	H	I	I	26	86	3	59	traces	-
5	**7j**	Ph	H	NO_2	NO_2	12	95	2	73	2	11
6	**7k**	Ph	H	OMe	H	44	96	8	75	2	54
7	**7l**	Ph	H	*t*-Bu	*t*-Bu	traces	-	traces	-	traces	-
8	**7m**	Ph	H	Ph	H	91 (81[c])	96 (98[c])	35	78	8	81

[a] Determined by HPLC analysis.
[b] See Supporting Information for details of *ee* analysis.
[c] "*total in situ*".
[d] Determined by GC analysis.

Table 3. Asymmetric epoxidation catalyzed by **7m**.



Entry	Substrate	No.	*t* [h]	Yield[a] [%]	*ee*[b] [%]
1		**8**	18	91	96
2		**8**	3	90	95
3		**11**	18	88	97
4		**9**	18	35 (60[c])	78 (76[c])
5		**12**	18	5	77
6		**13**	18	17	30
7		**10**	18	8 (14[c])	81 (84[c])
8		**14**	18	9	49
9		**15**	18	6	60

[a] Determined by HPLC and GC analysis, respectively.
[b] See Supporting Information for details of *ee* analysis.
[c] 4.5 equivalents of H_2O_2 were used.

3 h. Work-up after this short reaction time affords yields and *ee*s comparable to those obtained after 18 h (Table 3, entries 1 and 2). Excellent yields and enantioselectivities were obtained for indene (**11**) as well (entry 3). In the case of styrene (**9**), we were able to increase the epoxide yield from 35% to 60% by

using 4.5 equivalents of aqueous hydrogen peroxide (entry 4, values in parentheses). For both 1-phenylcyclohexene (**12**) and *trans*-β-methylstyrene (**13**), the epoxide yields were relatively low (entries 5 and 6). We also tested non-conjugated olefins such as VCH (**10**), 1-methylcyclohexene (**14**) and 1-octene (**15**) (Table 3, entries 7–9). Whereas the enantioselectivity was encouraging for VCH (**10**, 84% *ee*, entry 7), the epoxide yield was unsatisfactory in all three cases. A somewhat higher yield resulted from increasing the amount of hydrogen peroxide (entry 7, values in parantheses).

The activity and selectivity of the Ti-salalen complexes are in marked contrast with the inefficiency of the corresponding titanium-salen complexes. Katsuki et al. proposed that the catalytic activity is due to hydrogen bonding of the amine NH to one of the oxygen atoms of a putative Ti-peroxo intermediate (Figure 1).[10]

In this context, it is important to note that we could indeed characterize the catalyst prepared *in situ* from the salalen ligand **7m** and Ti(O-*i*-Pr)$_4$ as a *mononuclear* species by HR-ESI-MS ($m/z = 553.197$: [Ti(salalen **7m**)·OMe]$^+$, $^-$OMe from spray solvent). To the best of our knowledge, this is the first experimental result pointing to mono-nuclearity of the Ti-salalen catalyst. Furthermore, we were able to obtain crystals suitable for X-ray analysis of the complex upon exposure to air (moisture).[13] Under these conditions, a dimeric complex was formed with two oxo bridges between the titanium nuclei (Figure 2).

We were also able to crystallize the titanium complex derived from (*S*,*S*)-DACH-salalen *ent*-**7m**. As the sense of chirality at the titanium centre is controlled by the absolute configuration of the DACH backbone in the salalen ligands **7m** and *ent*-**7m**, respectively, the two complexes are mirror images.[13] For clarity, only one monomeric unit of the complexes is shown in Figure 3.

Figure 3 also illustrates the hydrogen bonding between the ligand's NH moiety and one of the oxo bridges at the titanium centre (dashed green line: 2.664 Å).

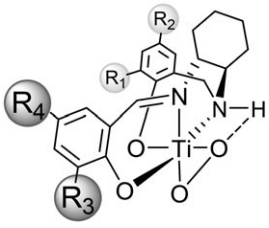


Figure 1. Putatitive peroxotitanium complex, activated by intramolecular hydrogen bonding.

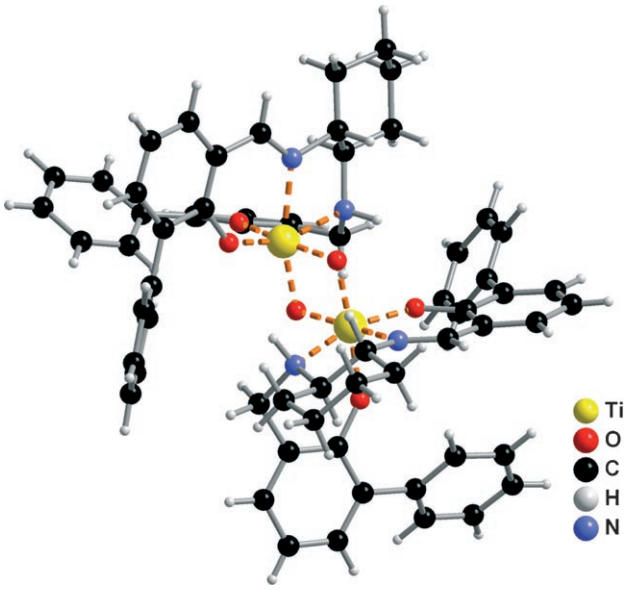


Figure 2. X-ray crystal structure of [Ti(salalen **7m**)O]$_2$.

Conclusions

In summary, we describe a versatile synthesis for the salalen ligands **7** and their application in the titanium-catalyzed AE of non-functionalized olefins with hydrogen peroxide. The catalysts can be generated *in situ* from DACH-derived salalen ligands and Ti(O-*i*-Pr)$_4$. The structure of the *in situ* generated titanium complexes was elucidated by X-ray structural analysis of one selected example. The ligands are prepared from readily accessible starting materials. By positional scanning, we identified the most active and selective ligand **7m** ($R_1 = R_3 = Ph$, $R_2 = R_4 = H$). Good to excellent enantioselectivities were achieved for several non-functionalized olefins. Future work will aim at determining the substrate scope, potential limitations by, e.g., remote oxidizable groups or strongly metal-coordinating substructures, and at further optimizing both the catalyst design and the reaction conditions.

Experimental Section

Synthesis of the Salalen Ligand 7m

Anhydrous HCl (1.31 mL, 2.61 mmol, 2 M in diethyl ether) was added to a solution of (1*R*,2*R*)-*trans*-1,2-diaminocyclohexane **1** (298 mg, 2.61 mmol) in dry diethyl ether (10 mL) over a period of 15 min. The mixture was allowed to stir at room temperature for 18 h. The precipitate was collected by vacuum filtration, washed with diethyl ether and dried under vacuum. The white solid was then dissolved in a methanol/ethanol mixture (50/50 v/v, 20 mL), and 3-phenyl-2-hydroxybenzaldehyde (466 mg, 2.35 mmol) was added in small portions. The reaction mixture was stirred overnight. After removal of the solvent, the remaining yellow solid was

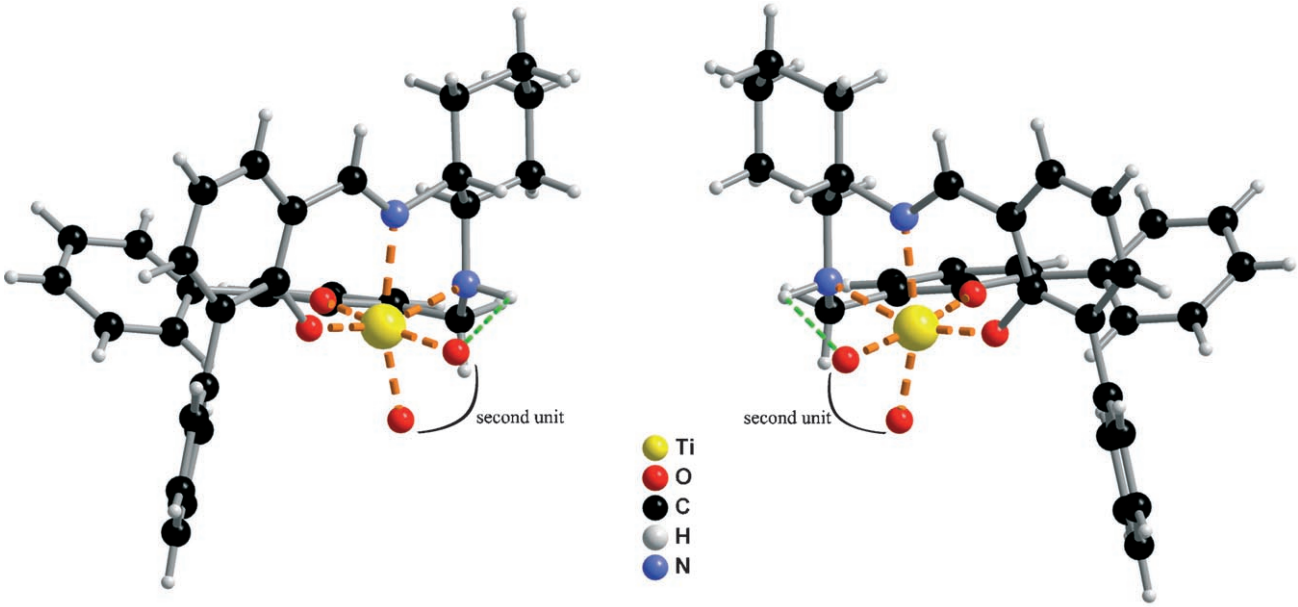


Figure 3. Mononuclear units of the [Ti(salalen **7m**)O]$_2$ and [Ti(salalen *ent*-**7m**)·O]$_2$ complexes; the dashed green lines indicate NH-oxo hydrogen bonding.

washed twice with diethyl ether and suspended in glacial acetic acid (15 mL). Sodium cyanoborohydride (126 mg, 2.00 mmol) was added in a single portion. After one hour, additional $NaBH_3CN$ (65 mg, 1.04 mmol) was added, and the solution was stirred for three hours to ensure complete reduction. 6 M aqueous KOH was added until pH 8 was reached. The resulting suspension was extracted with CH_2Cl_2, and the combined organic phases were washed with saturated aqueous $NaHCO_3$. After drying over $MgSO_4$, filtration and evaporation, the remaining oil was disssolved in a methanol/ethanol mixture (50/50 v/v, 50 mL). 3-phenyl-2-hydroxybenzaldehyde (252 mg, 1.27 mmol) was added in small portions. The mixture was stirred overnight. The solvent was removed, and the remaining yellow solid was dried under vacuum over phosphorus pentoxide at 40 °C. The product **7m** was obtained as a yellow powder; yield: 605 mg (1.27 mmol, 49 %); mp 78 °C. See Supporting Information for analytical data.

General Procedure for the Asymmetric Epoxidation of Olefins using a Catalyst Prepared in situ

To the solution of a salalen ligand **7** (10 μmol) in 500 μL of dry CH_2Cl_2, a solution of Ti(O-*i*-Pr)$_4$ (10 μmol) in 500 μL dry CH_2Cl_2, was added, and the mixture was stirred at room temperature. The substrate olefin (0.1 mmol) and 30 % aqueous hydrogen peroxide (0.15 mmol) were added, and the reaction mixture was stirred for the time specified in the Tables. An aliquot was mixed with hexane, filtered and analyzed by HPLC and GC spectroscopy, respectively. Yields were determined by comparison with the peak areas of stock solutions of the corresponding epoxides.

In a preparative experiment using 1,2-dihydronaphthalene **8** (104 mg, 0.8 mmol) as the substrate and the salalen **7m** as the ligand, 102 mg (0.7 mmol, 87 %) of the 1,2-epoxytetrahydronaphthalene (97 % *ee*) were obtained after flash chromatography on silica gel (cyclohexane:ethyl acetate, 20:1, v/v).

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