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# Titanium *cis*-1,2-Diaminocyclohexane (*cis*-DACH) Salalen Catalysts of Outstanding Activity and Enantioselectivity for the Asymmetric Epoxidation of Non-Conjugated Terminal Olefins with $H_2O_2$**

Markus Lansing,[a] Hauke Engler,[a] Tobias M. Leuther,[a] Jörg-M. Neudörfl,[a,b] and Albrecht Berkessel*[a]

**Abstract:** *We report a new and readily accessible class of titanium salalen complexes derived from cis-1,2-diaminocyclohexane (cis-DACH) and fluorinated salicylic aldehyde derivatives. With aqueous hydrogen peroxide as oxidant, these complexes effect the epoxidation of terminal, non-conjugated olefins in high yield and high enantioselectivity. We furthermore discovered that addition of certain acidic or basic co-catalysts significantly accelerates the epoxidation. For example, in the presence of 1 mol% Ti-catalyst and 1 mol% pentafluorobenzoic acid, 1-octene epoxidation (95 % ee) is completed at RT within 8 h. The catalytic process is compatible with many functional groups (e.g. ethers, esters, halides, nitriles, nitro groups), while free hydroxyl groups appear to slow down the reaction to some extent. Catalyst recycling is possible.*

In 2005, Katsuki *et al.* introduced titanium salalen complexes as novel and highly enantioselective catalysts for the asymmetric epoxidation of a variety of non-functionalized olefins (both conjugated and non-conjugated), using hydrogen peroxide as the oxidant.[1] Salalen ligands are mono-reduced salens, carrying one imine and one amine functionality. For example, the catalyst *trans*-**1** (Figure 1) which is based on *trans*-1,2-diaminocyclohexane (*trans*-DACH) was reported to effect the epoxidation of 1,2-dihydronaphthalene with quantitative yield and over 99% *ee*. Even more remarkably, the epoxidation of 1-octene and vinyl cyclohexane were reported to proceed with 85% yield / 82% *ee*, and 72% yield / 95% *ee*, respectively. 1-Octene in particular is a terminal olefin notoriously difficult to epoxidize asymmetrically - in 2005/2007, the epoxide yields/enantioselectivities achieved by Katsuki et al. were the highest ever reported.[1]

Our own work in this area has focused on (i) the simplification of the salalen ligand structure, and at the same time (ii) on increasing catalyst stability and performance.[2] In 2013, we reported that the switching from *trans*-DACH to *cis*-DACH as building block largely increases the catalyst's stability against oxidative degradation under the reaction conditions.[3,4] We observed that ligands as simple as *cis*-**2a** and *cis*-**2b** (Figure 1), at loadings as low as 1 mol%, are able to effect e.g. 1-octene epoxidation with 82% yield and 95% *ee*.[4] The combination of the *cis*-DACH substructure with the axially chiral binaphthyl motif led to a new (stereo)isomeric salalen ligands, the screening of which resulted in the identification of the examples *cis*-**3a**,**b** shown (Figure 1).[5] The Ti-complexes derived from *cis*-**3a**,**b** effect the asymmetric epoxidation of 1-octene, too, and again with high yields and enantioselectivities, at low catalyst loadings.[5]

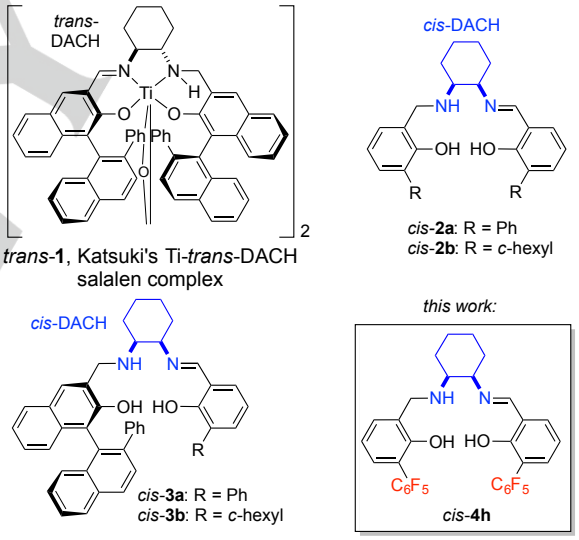


**Figure 1.** Katsuki's *trans*-DACH Ti-salalen complex *trans*-**1**, and our *cis*-DACH derived salalen ligands *cis*-**2a**,**b**, *cis*-**3a**,**b**, and *cis*-**4j**.[1,4,5]

Clearly, the preparation of ligands such as *cis*-**3a**,**b** requires significantly more steps than that of *cis*-**2a** or *cis*-**2b**.[6] It was therefore our aim to achieve catalyst performance as good as, or preferably even better than those provided by ligands *cis*-**3a**,**b** with simpler ligand architectures. An equally important issue to be addressed was the still relatively long reaction time, typically in the order of 30-100 h.[4,5] Given the overall beneficial effect of the *cis*-DACH backbone, we decided to retain this structural element and to focus our study on the further modification of the salicylic aldehyde moieties. As one example from the Ti-salan area pointed to the positive influence of $CF_3$-substitution, we decided to investigate the effect of methylation and in particular fluorination in a more general sense.[7] In this article, we disclose the identification and outstanding performance of the simple

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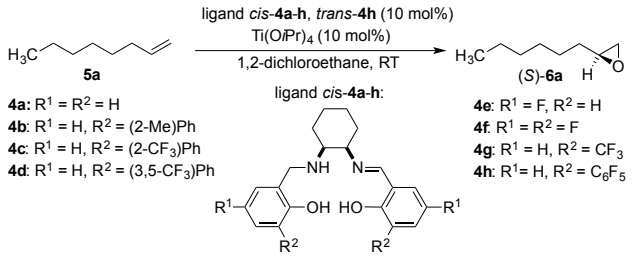
Supporting information for this article is given via a link at the end of the document.

bis(pentafluorophenyl) salalen ligand *cis*-**4h** (Figure 1) which more than fulfilled both of the above mentioned expectations, and defines a new level of performance for the catalytic asymmetric epoxidation of terminal olefins with hydrogen peroxide.

**Table 1.** Evaluation of the modified *cis*-DACH salalen ligands *cis*-**4a**-**h** in the catalytic asymmetric epoxidation of 1-octene (**5a**).[a]




| Entry[a] | Ligand | Time [h] | Conv. [**5a**] (%)[b] | Yield [(*S*)-**6a**] (%)[b] | *ee* [(*S*)-**6a**] (%)[b] |
|---|---|---|---|---|---|
| 1 | *cis*-**4a** | 48 | 51 | 47 | 82 |
| 2 | *cis*-**4b** | 48 | 77 | 75 | 85 |
| 3 | *cis*-**4c** | 48 | 64 | 62 | 89 |
| 4 | *cis*-**4d** | 82 | 28 | 28 | 93 |
| 5 | *cis*-**4e** | 40 | 46 | 44 | 84 |
| 6 | *cis*-**4f** | 48 | 66 | 63 | 83 |
| 7 | *cis*-**4g** | 42 | 35 | 9 | 67 |
| 8 | *cis*-**4h** | **45** | **quant** | **quant.** | **94** |
| 9 | *cis*-**4h** | 18 | 90 | 89 | 94 |
| 10 | *trans*-**4h** | 18 | 74 | 74 | 84[c] |

[a] All reactions were performed at a molar ratio of substrate/ligand/Ti(O*i*Pr)$_4$/30% aq. $H_2O_2$ of 1:0.1:0.1:1.5, [substrate] = 0.2 mol $L^{-1}$; [b] determined by GC on chiral stationary phase (see Supporting Information for analytical details). [c]: The (*R*)-enantiomer of the epoxide was formed predominantly.

Table 1 summarizes the results achieved with our set of modified *cis*-DACH salalen ligands, using 1-octene (**5a**) as the test substrate. Ligand *cis*-**4a**, derived from unsubstituted salicylic aldehyde, represents the "reference point" of this study. *Ortho*-tolyl substituents (*cis*-**4b**, entry 2) improved both the catalyst activity and enantioselectivity. With ligands *cis*-**4c**-**h**, we intended to survey the effects of fluorination on catalyst performance and selectivity. In the ligand *cis*-**4c**, the *ortho*-tolyl substituent present in *cis*-**4b** is modified to its fluorinated analog *ortho*-(trifluoromethyl)phenyl.[9] The comparison of entries 2 and 3 of Table 1 reveals that fluorination at this position results in somewhat lower activity, but higher enantioselectivity. Introduction of a second trifluoromethyl group in ligand *cis*-**4d** [$R^2$ = 3,5-bis(trifluoromethyl)phenyl] increases the enantioselectivity further, but once again, the catalyst activity is reduced (entry 4).[9] Fluorination of the parent ligand *cis*-**4a** *para* to the phenolic hydroxyl groups leads to *cis*-**4e** (entry 5). The effect of this modification on catalytic activity and enantioselectivity is negligible (compare entries 1 and 5 of Table 1). Additional *ortho* fluorination (*cis*-**4f**, entry 6) resulted in a minor increase of activity and did not affect enantioselectivity. Introduction of a $CF_3$-group *ortho* to the phenolic hydroxy functions again proved deleterious to catalyst activity (*cis*-**4g**, entry 7). Up to this point, *ortho*-tolyl (*cis*-**4b**) and *ortho*-$CF_3$-phenyl (*cis*-**4c**) substitution proved optimal. Note that similar observations had been made by Katsuki *et al*. for salan-ligands.[8]

Our next approach focused on the fluorination of the *ortho*-phenyl substituents in ligand *cis*-**2a** ("R" in Figure 1), and the bis-pentafluorophenyl variant of *cis*-**2a** is represented by the ligand *cis*-**4h** (Table 1, entries 8,9). We were delighted so see that both, the catalytic activity and the enantioselectivity of this readily available ligand by far exceed that of all other salalen ligands reported: after only 45 h reaction time, (*S*)-1-octene epoxide [(*S*)-**6a**] was formed in quantitative yield, and with 94% *ee* (Table 1, entry 8). In fact, 90% conversion of 1-octene (**5a**) was achieved already after 18 h reaction time (Table 1, entry 9). For comparison, the *trans*-DACH derived ligand *trans*-**4h** was prepared and tested as well. The results shown for *trans*-**4h** in entry 10 of Table 1 prove the superiority of *cis*-DACH ligand *cis*-**4h**.

The X-ray crystal structures of the dimeric Ti μ-dioxo and μ-oxo-μ-peroxo complexes derived from ligand *cis*-**4h** are shown in Figure 2.[9] As is the case for other salalens, *anti*-configurated dimeric Ti complexes are found in the crystal, with the ligand *cis*-**4h** coordinating the Ti-ion in *cis*-β mode.[4,5]

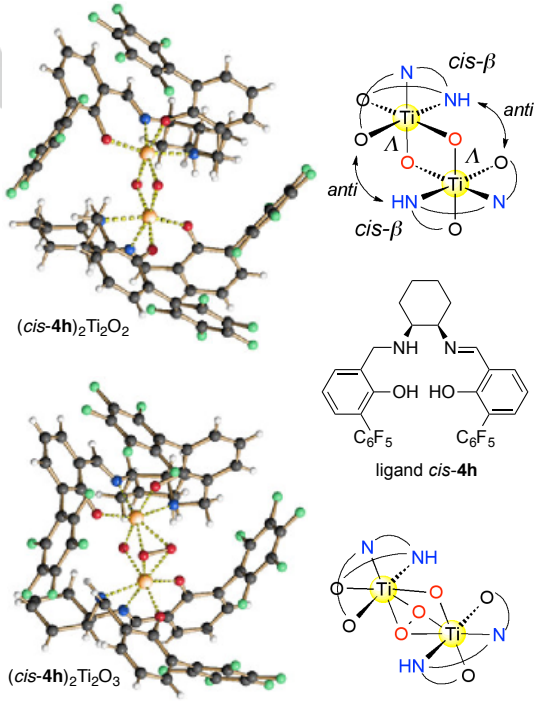
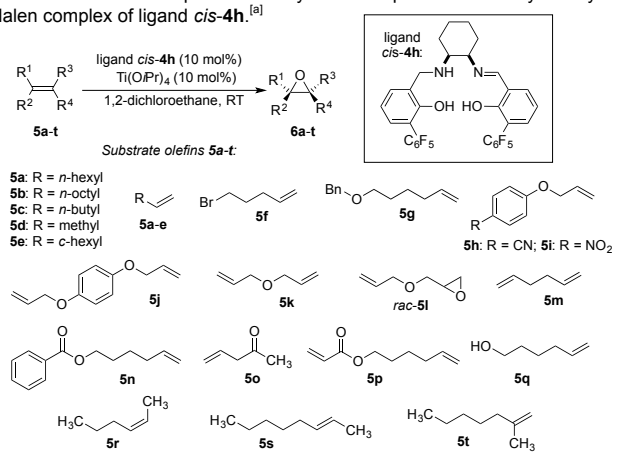



**Figure 2.** X-ray crystal structures of the bis-μ-oxo- (top) the μ-oxo-μ-peroxo-titanium complexes (bottom) derived from the *cis*-salalen ligand *cis*-**4h**.

With the highly active and selective ligand *cis*-**4h** in hand, we set out to gather information on its substrate scope, and the results of our study are summarized in Table 2. As shown in entries 1-5, non-functionalized terminal olefins are excellent substrates, and even propene (**5d**) is epoxidized with 92% *ee*. The values obtained for 5-bromopentene (**5f**, entry 6) show that halide substitution is well tolerated, as is the ether functionality

**Table 2.** Substrate scope of the asymmetric epoxidation catalyzed by Ti-salalen complex of ligand *cis*-**4h**.[a]




| Entry[a] | Olefin | Reaction time [h] | Conv. (%)[b] | Epoxide yield (%)[b] | Epoxide ee (%)[b] |
|---|---|---|---|---|---|
| 1 | **5a** | 45 | quant. | quant. | 94 |
| 2 | **5b** | 45 | quant. | quant. | 96 |
| 3 | **5c** | 45 | quant. | 62[c] | 94 |
| 4 | **5d** | 45 | n.d. | 56[d] | 92[d] |
| 5 | **5e** | 45 | quant. | quant. | 94 |
| 6 | **5f** | 40 | quant. | quant. | 95 |
| 7 | **5g** | 45 | 93 | 63 | 95 |
| 8 | **5h** | 45 | 80 | 75 | 96 |
| 9 | **5i** | 45 | 90 | 87 | 96 |
| 10 | **5j** | 40 | 89 | 34/34[e] | 88/>99 (dr 9:1)[e,f,g] |
| 11 | **5k** | 45 | 64 | 51/14[e] | 87/>99 (dr 7:1)[e,f] |
| 12 | *rac*-**5l** | 45 | 49 | 40 | 95 (dr 1.1:1)[f] |
| 13 | **5m** | 45 | quant. | 69 | >99 (dr 18:1)[f,g] |
| 14 | **5n** | 45 | quant. | 97 | 93 |
| 15 | **5o** | 100 | n.d | trace | n.d. |
| 16 | **5p** | 42 | 65 | 40 | 92[h] |
| 17 | **5q** | 45 | 58 | 34 | 93 |
| 18 | **5r** | 45 | quant. | 93 | 84 |
| 19 | **5s** | 40 | 94 | 85 | 4 |
| 20 | **5t** | 45 | n.d. | trace | 15 |

[a] All reactions were performed at a molar ratio of substrate/ligand/Ti(O*i*Pr)$_4$/30% aq. $H_2O_2$ of 1:0.1:0.1:1.5, unless noted otherwise, [substrate] = 0.2 mol L$^{-1}$; [b] determined by GC or HPLC on chiral stationary phase (see Supporting Information for analytical details); [c] losses of material due to the high volatility of substrate olefin **5c** and product epoxide **6c**; [d] reaction was run with a ligand/Ti(O*i*Pr)$_4$/30% aq. $H_2O_2$ ratio of 1:1:15 at 0 °C under a propene atmosphere; yield based on $H_2O_2$; [e] values refer to mono- and diepoxide product; [f] dr: *RR*/*SS* : *RS*; [g] reaction was performed with a substrate/ligand/Ti(O*i*Pr)$_4$/30% aq. $H_2O_2$ ratio of 1:0.1:0.1:3.0; [h] epoxidation exclusively at the non-conjugated C=C double bond.

of the substrates **5g** to **5l** (entries 7-12). The allyl diethers **5j** and **5k** (entries 10,11) afforded lower yields, moderate diastereoselectivities (*RR*/*SS* : *RS* = 7-9:1), but high enantiopurity (up to >99% *ee*) of the main di-epoxide product, due to double stereodifferentiation. When the racemic mono-epoxide of diallyl ether (*rac*-**5l**, entry 12) was used as the substrate, the homochiral diepoxide and the *meso*-product were formed in almost equal amounts (1.1:1), confirming that the catalyst overrides the substrate control. Again, the homochiral di-epoxide was formed in high enantiopurity (95% *ee*). The 1,ω-diolefin 1,5-hexadiene (**5m**, entry 13) behaves as an excellent substrate in the sense that it is converted to its di-epoxide in good yield and high diastereoselectivity (18:1), affording the main di-epoxide product in virtually enantiopure form. As exemplified by the benzoate **5n** (entry 14), the ester functionality is well tolerated. In contrast, electron-withdrawing groups such as neighboring carbonyl functions (as in the case of the allyl ketone **5o**, or the acrylate **5p** entries 15,16) prevent the epoxidation of the C=C double bond. In the 5-hexenyl acrylate (**5p**), there is a clear discrimination of the substrate's two C-C double bonds, with the terminal, non-conjugated one being epoxidized with the "usual" high enantioselectivity, while the acrylate moiety remains untouched (entry 16). As observed before with other salalen ligands,[4,5] the presence of alcohol OH in the substrate appears to somewhat slow down the epoxidation, but the very high enantioselectivity is retained [*e.g.* 5-hexenol (**5q**), entry 17]. Finally, the substrates **5r-t** give an impression of the catalysts action upon the three possible forms of disubstituted olefins: for the internal *cis*-olefin **5r**, a high epoxide yield at somewhat reduced *ee* (84%, entry 18) resulted. Similar yields, but almost no enantioselectivity are typical for *trans*-olefins such as *trans*-2-octene (**5s**, entry 19). Extremely slow conversion and low *ee* was the result for the 2,2-disubstituted substrate olefin **5t** (entry 20).

In the course of our reaction optimization, we observed that the addition of carboxylic acids as co-catalysts results in a quite remarkable acceleration. From a broader screening of acid and bases as co-catalysts (see Supporting Information), pentafluorobenzoic acid, tetra-*n*-butylammonium hydrogensulfate (TBAHS) and 2,6-di-*tert*-butylpyridine emerged as the most beneficial additives. Figure 3 displays the time courses of 1-octene (**5a**) epoxidation, in the presence and absence of these three additives. Overall, addition of the co-catalysts results in a shortening of the reaction time for full olefin conversion from ca. 45 h to ca.

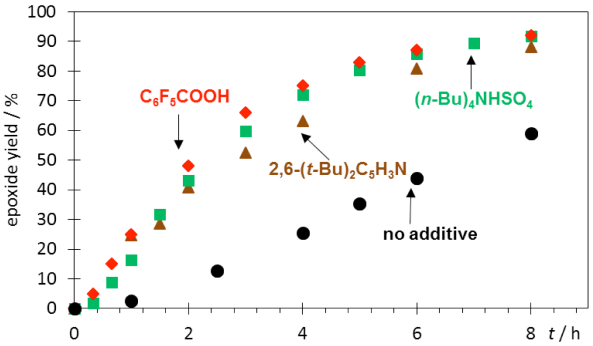
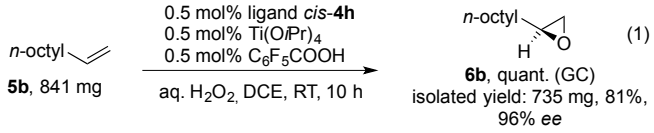



**Figure 3.** Effect of the additives pentafluorobenzoic acid, tetra-*n*-butylammonium hydrogensulfate (TBAHS), and 2,6-di-*tert*-butylpyridine on the time course of 1-octene (**5a**) epoxidation; 10 mol% of additive were used, all other reaction conditions as in Tables 1,2.

8 h. At the same time, both the yield and the enantiomeric purity of the product epoxide [(*S*)-**6a**] remained unchanged. We furthermore observed that the epoxidation proceeds faster at higher substrate concentrations, which in turn allowed for lowering of the catalyst loading. When the olefin concentration is raised to ca. 6 mol $L^{-1}$, and using TBAHS as co-catalyst, the epoxidation of 1-octene (**5a**) reaches completion within 8 h in the presence of 1 mol% catalyst/additive, while the epoxide is formed in unaltered enantiopurity (95% *ee*). As shown exemplarily in eq. 1, 1-decene (**5b**) is fully converted to its epoxide (96% *ee*) within 10 h, with as little as 0.5 mol% catalyst/pentafluorobenzoic acid as additive. Under these conditions, the catalyst can even be recovered and recycled by simple removal of all volatiles *in vacuo* (see Supporting Information for experimental details).



(1)

In conclusion, we report a new generation of *cis*-DACH salalen ligands for the Ti-catalyzed asymmetric epoxidation of terminal olefins with hydrogen peroxide, based on the introduction of fluorine substituents adjacent to the ligands' phenolic metal binding sites. Best results were achieved with the bis(pentafluorophenyl)-substituted ligand *cis*-**4h** in the presence of e.g. pentafluorobenzoic acid or tetra-*n*-butylammonium hydrogensulfate (TBAHS) as co-catalysts. With this novel catalyst system, the highly enantioselective epoxidation of non-conjugated terminal in particular, and additionally of *cis*-1,2-disubstituted olefins can be achieved in high yields and within short reaction times. Potential applications of this epoxidation method are manifold, for example in the area of natural product synthesis[10] or pharmaceutical chemistry.[11] The mechanistic aspects of this novel and highly efficient epoxidation catalysis are currently under investigation in our laboratory, and will be reported in due course.

## Experimental Section

*Preparative Ti-salalen catalyzed asymmetric epoxidation of 1-decene (**5b**)*:
In a 5 ml vial, 20.2 mg (30.8 µmol, 0.005 equiv) of ligand *cis*-**4h**, and 8.4 mg Ti(O*i*Pr)$_4$ (30 µmol, 0.005 equiv) were dissolved in 1.5 mL of DCM and stirred under argon at RT for 1 h. The solvent was removed under reduced pressure, and the residue was dried *in vacuo* for 1 h. 1-Decene (**5b**, 841 mg, 6.01 mmol, 1.00 equiv), pentafluorobenzoic acid (6.80 mg, 32.1 mmol, 0.005 equiv) 360 µl DCE, and 0.5 mL aq. hydrogen peroxide (0.50 mL 50% w/w, 8.8 mmol, 1.47 equiv) were added, and the mixture was stirred at room temperature for 10 h. After filtering through a short pad of silica/$MnO_2$ (to deactivate excess $H_2O_2$), the phases were separated, and the aqueous phase was extracted with DCM. The combined organic phases were dried over $MgSO_4$, and the solvent was removed under reduced pressure. Purification by flash column chromatography (silica, DCM) afforded 753 mg of the epoxide **6b** (4.83 mmol, 81%, 96% *ee*) as a colorless liquid.

**Keywords:** asymmetric catalysis · epoxidation · hydrogen peroxide · titanium · *cis*-DACH

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[6] Our *cis*-DACH salalen ligands are typically prepared by the two-step route described in ref. 4, starting from enantiopure mono-*N*-alloc *cis*-DACH (ref. 3) and the corresponding salicylic aldehydes. The ease of accessibility of the latter therefore largely affects the overall practical value of the ligand synthesis.

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[9] CCDC 1451975 [(*cis*-**4c**)$_2$Ti$_2$O$_2$], CCDC 1451974 [(*cis*-**4d**)$_2$Ti$_2$O$_2$], CCDC 1451973 [(*cis*-**4h**)$_2$Ti$_2$O$_2$] and 1451976 [(*cis*-**4h**)$_2$Ti$_2$O$_3$] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.uk/data_request/cif.

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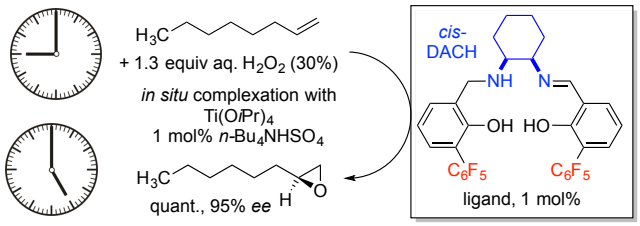
[12] The project "Sustainable Chemical Synthesis (SusChemSys)" is co-financed by the European Regional Development Fund (ERDF) and the state of North Rhine-Westphalia, Germany, under the Operational Programme "Regional Competitiveness and Employment" 2007 - 2013.

# COMMUNICATION




**Nine-to-fivers.** The titanium complex of the *cis*-DACH salalen ligand shown effects the asymmetric epoxidation of terminal, non-conjugated olefins with unprecedented efficiency and excellent selectivity. In the presence of acid/base co-catalysts, olefins such as 1-octene are epoxidized in high yield and enantioselectivity, within a few hours at room temperature, using aqueous $H_2O_2$ as terminal oxidant.

*Markus Lansing, Hauke Engler, Tobias M. Leuther, Jörg-M. Neudörfl, and Albrecht Berkessel**

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Titanium *cis*-1,2-Diaminocyclohexane (*cis*-DACH) Salalen Catalysts of Outstanding Activity and Enantioselectivity for the Asymmetric Epoxidation of Non-Conjugated Terminal Olefins with $H_2O_2$