Asymmetric Catalysis

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Asymmetric Hydroalkoxylation of Non-Activated Alkenes: Titanium-Catalyzed Cycloisomerization of Allylphenols at High Temperatures**

*Johannes Schlüter, Max Blazejak, Florian Boeck, and Lukas Hintermann**

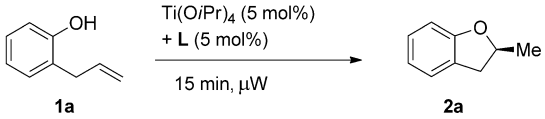
Dedicated to Professor Keisuke Suzuki on the occasion of his 60th birthday

Abstract: *The asymmetric catalytic addition of alcohols (phenols) to non-activated alkenes has been realized through the cycloisomerization of 2-allylphenols to 2-methyl-2,3-dihydrobenzofurans (2-methylcoumarans). The reaction was catalyzed by a chiral titanium–carboxylate complex at uncommonly high temperatures for asymmetric catalytic reactions. The catalyst was generated by mixing titanium isopropoxide, the chiral ligand (aS)-1-(2-methoxy-1-naphthyl)-2-naphthoic acid or its derivatives, and a co-catalytic amount of water in a ratio of 1:1:1 (5 mol% each). This homogeneous thermal catalysis (HOT-CAT) gave various (S)-2-methylcoumarans with yields of up to 90% and in up to 85% ee at 240°C, and in 87% ee at 220°C.*

Hydroalkoxylation is defined as the addition of alcohols (or phenols) to alkenes in order to produce ethers.[1–3] For non-activated alkenes, this synthetically important hydrofunctionalization[2] is catalyzed by strong mineral acids, with limited prospect for stereoselective catalysis. Contrary to the related hydroamination of alkenes, for which several metal-catalyzed asymmetric versions have been reported,[4] asymmetric hydroalkoxylations of non-activated alkenes, as opposed to activated allenes,[5] are hardly known. Hydroalkoxylations that are catalyzed by strong Lewis acids and lead to Markovnikov selectivity have been described,[1b,6] but they suffer from competing hidden catalysis by Brønsted acids,[7] and asymmetric versions are still unknown.[1b] Hartwig has reported singular examples of Ir^{I}-catalyzed hydroalkoxylations with moderate induction.[8] Alternative approaches to catalytic, stereo- or regioselective hydroalkoxylations rely on photocatalysis[9] or oxidation–reduction processes.[10,11] We now report the redox-neutral, asymmetric hydroalkoxylation of a non-activated alkene that is catalyzed by a chiral titanium–carboxylate complex under thermally forcing conditions (220–240°C).

The cyclization of 2-allylphenols (**1**) to 2-methylcoumarans (2-metyl-2,3-dihydrobenzofurans; **2**) served as the test reaction to screen for hydroalkoxylation catalysts (see Table 1). We have shown that aluminum isopropoxide is a catalyst that gives high yields of **2** in short reaction times at 250°C (microwave heating; 10 bar).[12] The basic alkoxide ligands in this system render competing hidden catalysis by Brønsted acids[7] unlikely. We chose this process as a platform to search for an asymmetric catalytic hydroalkoxylation reaction by combining aluminum isopropoxide with chiral steering ligands such as those shown in Figure 1.

Table 1: Screening for asymmetric hydroalkoxylation with titanium catalysts.[a]



1a **2a**

Entry	Ligand	Solvent	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	-	PhCl	250	–	–
2	**L2**	PhCl	250	–	–
3	**L2**	PhMe	250	10	0
4	**L1**	PhCl	250	16	13
5	**L1**	PhMe	250	62	64
6	**L1**	PhMe	180	–	–
7	**L1**	PhMe	200	4	68
8	**L1**	PhMe	240	32	70
9	**L1**	PhMe	280	67	48

[a] Reaction conditions: **1a** (1.1 mmol); $Ti(OiPr)_4$ (5 mol%), **L*n*** (5 mol%); PhMe (3 mL). [b] Determined by quantitative ^{1}H NMR (qNMR) analysis using an internal standard. [c] Determined by HPLC on a chiral stationary phase.

While experiments with aluminum-based catalysts were not successful, combinations of $Ti(OiPr)_4$, which itself is not catalytically active (Table 1, entry 1), with some ligands were

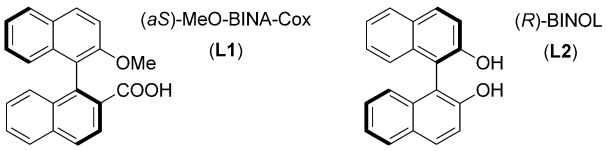


Figure 1. Chiral, chelating oxygen donor ligands used in this study.

productive. Catalysts with BINOL (**L2**) showed low activity and did not result in stereoselectivity (entries 2 and 3), but the chiral carboxylic acid MeO-BINA-Cox[13] (**L1**; Figure 1) led to the in situ formation of a catalyst that produced 2-methylcoumaran (**2a**) with distinct enantiomeric excess at 250°C (Table 1, entries 4 and 5).

[*] M. Sc. J. Schlüter, M. Sc. M. Blazejak, Dr. F. Boeck, Prof. Dr. L. Hintermann
Department Chemie, Technische Universität München
Lichtenbergstr. 4, 85748 Garching bei München (Germany)
E-mail: lukas.hintermann@tum.de

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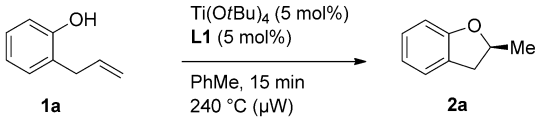
The influence of the solvent (entries 4,5), the reaction temperature (entries 5–9),[14] and other factors, including the ligand/metal ratio and the concentration, were elucidated with (*aS*)-**L1** as the steering ligand at reaction times of 15 min.[15,16] The product was not formed in catalytic reactions performed below 200 °C (entry 6). The remarkable enantioselectivity of 70 % *ee* that was obtained at 240 °C (entry 8) provides an example for asymmetric catalysis at uncommonly high temperatures (HOT-CAT).[17,18] Curiously, the repetition of experiments from Table 1 over time gave variable results (e.g. 8–32 % yield for entry 8). The cause of these variations was the presence of trace amounts of water in either the starting material **1a** or the solvent. Catalytic reactions performed with dried substrate and solvent gave a low yield (Table 2, entry 1), whereas reactions with co-catalytic amounts of water showed the highest catalytic activity and selectivity (entries 2 and 3), which again eroded upon addition of additional water (entries 4 and 5).

Table 2: Influence of water on the asymmetric catalytic hydroalkoxylation.[a]



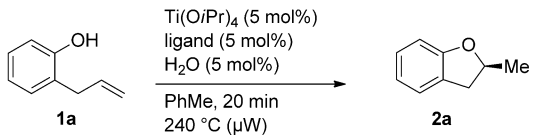
1a **2a**

Entry	H_2O [ppm][b]	H_2O [mol %][c]	Yield [%][d]	*ee* [%]
1	10	0.1	19	60
2	330	5.1	55	70
3	500	7.8	59	60
4	1000	15.4	32	48
5	2050	31.3	10	7

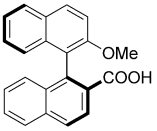
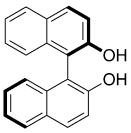
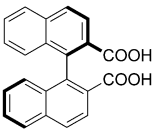
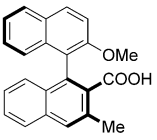
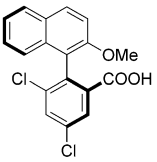
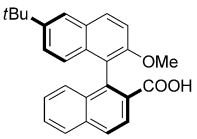
[a] Reaction conditions: **1a** (1.1 mmol); PhMe (3 mL). [b] Sum of added water and water content of the solvent (10 ppm). [c] Relative to **1a**. [d] Determined by qNMR analysis using an internal standard.

The results imply that the in situ generation of the catalyst requires a single equivalent of water per titanium atom. Catalytic reactions were henceforth carried out with dry reactants and solvents,[19] but with added water as the co-catalyst.[20] To this effect, $Ti(OR)_4$ (5 mol %), MeO-BINA-Cox (5 mol %), and water (5 mol %) were preheated in toluene at 60 °C for 10 min. After the addition of the substrate, the reaction mixture was heated to 240 °C for 20–50 min. Both $Ti(OiPr)_4$ and $Ti(OtBu)_4$ gave similar results,[15] but the heavier Group 4 metal alkoxides ($Zr(OtBu)_4$: 21 % yield, 12 % *ee*; $Hf(OtBu)_4$: 25 % yield, 34 % *ee*) gave less active and selective catalysts. The standard reaction with (*aS*)-MeO-BINA-Cox (**L1**; Table 3, entry 1a) was not affected to a great extent by the presence of 2,6-di-*tert*-butylpyridine (entries 1b and c), excluding the interference of a strong Brønsted acid in this catalysis. In the absence of a metal precursor, carboxylic acid **L1** did not show catalytic activity.[15] Catalysis with (a*R*)-BINOL gave the racemic product in a low yield (Table 3, entry 2). Dicarboxylic acid **L3** displayed low activity, but a distinct stereoselective induction (entry 3). Derivatives of **L1** were more successful: the methylated **L4**[21] showed higher activity with lower enantioselectivity (entry 4).

Table 3: Ligand effects on the catalytic cyclization of **1a** to **2a**.[a]



1a **2a**

Entry	Ligand		Yield [%][b]	*ee* [%]
1a		**L1**	56	75
1b		**L1** + tBu_2Py (5 mol %)	48	75
1c		**L1** + tBu_2Py (20 mol %)	41	73
2		**L2**	10	0
3		**L3**	10	36
4		**L4**	80	57
5		**L5**	38	71
6		**L6**	93[c]	80

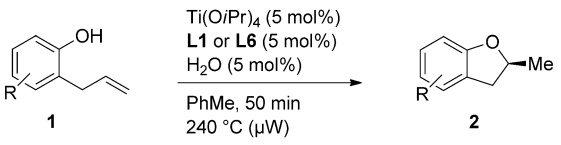
[a] Reaction conditions: **1a** (1.5 mmol); $Ti(OiPr)_4$ (5 mol %), ligand (5 mol %), H_2O (5 mol %); PhMe (3 mL). [b] Determined by qNMR analysis using an internal standard. [c] 50 min reaction time.

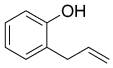
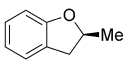
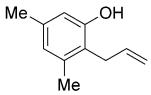
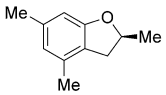
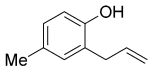
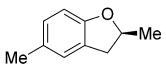
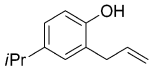
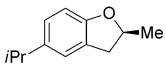
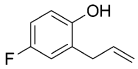
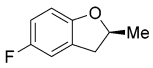
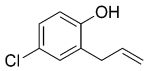
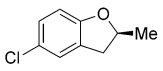
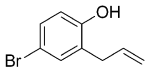
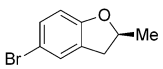
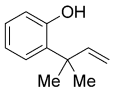
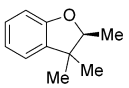
Auxiliary MNCB (**L5**)[22] displayed lower activity, but similar selectivity like **L1** (entry 5).

The screening pointed to the necessary presence of a carboxylic acid[23] and a methoxy group in the ligand. It also implied increased catalyst activity for ligands with electron-donating groups (see entry 4). Indeed, the 6′-*tert*-butylated ligand **L6** showed both higher activity and enantioselectivity (entry 6). The optimized reaction conditions, but with an extended reaction time of 50 min to increase conversion, were applied to several 2-allylphenol substrates (Table 4). Readily available **L1** served as reference ligand, while some reactions with **L6** were performed to achieve highest selectivities (Table 4).[24,25]

The yield of **2a** was significantly higher at longer reaction times, while the enantioselectivity remained unchanged (entry 1a). The invariance of product *ee* value with reaction time excludes any marked reversibility of the reaction at

Table 4: Substrate scope of catalytic hydroalkoxylation.[a]



Entry	Substrate	Product		Yield [%][b]	*ee* [%]
1a			**2a**	**L1**: 84	75
1b				**L1**: 77[c]	41[d,e]
1c				**L6**: 92	80
1d				**L6**: 82[c]	85[f]
2a			**2b**	**L1**: 88	78
2b				**L6**: 93	84
2c				**L6**: 88	87[f]
3a			**2c**	**L1**: 71	72
3b				**L6**: 79	75
3c				**L6**: 78	81[f]
4a			**2d**	**L1**: 51	61[e]
4b				**L6**: 83	77[g]
5			**2e**	**L1**: 56	72
6a			**2f**	**L1**: 90	62
6b				**L6**: 93	69
6c				**L6**: 88	73[f]
7a			**2g**	**L1**: 71	62
7b				**L6**: 86	73
8a			**2h**	**L1**: 88	67[e]
8b				**L1**: 76	71[f]

[a] Reaction conditions: **1** (1.5 mmol); Ti(O*i*Pr)$_4$ (5 mol%), **L1** or **L6** (5 mol%), H_2O (5 mol%); PhMe (3 mL); internal pressure typically 14 bar. [b] Yield of isolated product. [c] Yield determined by qNMR analysis using an internal standard. [d] At 300 °C. [e] Reaction time 20 min. [f] At 220 °C. [g] Catalyst loading: 8 mol% of each component.

240 °C.[26] Even at 300 °C, the reaction provided a notable enantiomeric excess (entry 1b). Higher selectivity was obtained with ligand **L6** and at 220 °C (entries 1c and d). Core-alkylated 2-allylphenols were converted to 2-methylcoumarans in acceptable to high yields and enantioselectivities (entries 2–4), providing maximal values of 84% *ee* (240 °C) or 87% *ee* (220 °C) for product **2b** with ligand **L6**. Core-halogenated 2-allylphenols were also tolerated (entries 5–7). Substrate **2h** with a geminal dimethyl unit cyclized faster as a result of entropy effects (entry 8a); lowering of the reaction temperature to 220 °C also slightly increased the enantioselectivity in this case (entry 8b).

The high reaction temperature posed questions regarding the chemical and configurational stability of the catalyst. Heating of **L1** (99.7% *ee*) in toluene to 240 °C for 20 min left its *ee* value unchanged.[15] From an actual catalytic reaction (Table 3, entry 1a), **L1** could be recovered (86%) with unchanged enantiomeric excess (99.7%). The isopropyl- (**E1**; 7%) and 2-allylphenyl esters of **L1** (**E2**; 4%) were also detected in the crude reaction mixture.[15] From a catalytic reaction performed at 265 °C, reisolated **L1** (61%) had a slightly lowered *ee* value of 99.4%, whereas from catalytic reactions performed at 290 °C, none of the ligand **L1** could be recovered.

Results from preliminary studies of the in situ generated titanium catalyst by NMR spectroscopy and FAB-MS spectrometry are consistent with the in situ generation of a species of the type $[Ti_4(\mu\text{-}O)_2(OH)_4(MeO\text{-}BINA\text{-}CO_2)_4(O{i}Pr)_4]$ ($m/z = 1819.7$, $[M-OH]^+$) with two-fold symmetry. Additional studies are required to answer questions regarding the nature of the catalyst and the reaction mechanism, which might be similar to the one discussed for the reaction catalyzed by aluminum isopropoxide.[12]

In conclusion, we have described the realization of an asymmetric metal-catalyzed hydroalkoxylation of non-activated alkenes in a model system. This partial solution to a long-standing problem takes the form of a cycloisomerization of 2-allylphenols (**1**) to 2-methylcoumarans (**2**) and is catalyzed by a new chiral catalyst based on a titanium–carboxylate complex. The remarkably high temperature of the process exceeds those earlier used in asymmetric catalysis.[18] Studies of the scope and mechanism of the catalytic reaction are ongoing.

Keywords: alkenes · asymmetric catalysis · heterocycles · microwave chemistry · titanium

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Angew. Chem. **2015**, *127*, 4086–4089

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[2] a) *Hydrofunctionalization—Top. Organomet. Chem.*, *Vol. 43* (Eds.: V. P. Ananikov, M. Tanaka), Springer, Berlin, **2013**; b) J. F. Hartwig, *Nature* **2008**, *455*, 314–322; c) *Catalytic Heterofunctionalization* (Eds.: A. Togni, H. Grützmacher), Wiley-VCH, Weinheim, **2001**.

[3] Hydroalkoxylation denotes the addition of both aliphatic alcohols and phenols to alkenes, in analogy to the general term hydroamination. Phenol additions may be further specified as hydroaryloxylations.

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[5] a) E. M. Barreiro, L. A. Adrio, K. K. Hii, J. J. Brazier, *Eur. J. Org. Chem.* **2013**, 1027–1039; b) R. L. LaLonde, Z. J. Wang, M. Mba, A. D. Lackner, F. D. Toste, *Angew. Chem. Int. Ed.* **2010**, *49*, 598–601; *Angew. Chem.* **2010**, *122*, 608–611; c) G. L. Hamilton, E. J. Kang, M. Mba, F. D. Toste, *Science* **2007**, *317*, 496–499; d) Z. Zhang, R. A. Widenhoefer, *Angew. Chem. Int. Ed.* **2007**, *46*, 283–285; *Angew. Chem.* **2007**, *119*, 287–289.

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[16] Reaction times refer to hold times at the target temperature, not including the heating and cooling phase. See the Supporting Information for typical temperature and pressure progress curves.

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