Asymmetric Catalysis in Liquid Confinement: Probing the Performance of Novel Chiral Rhodium Diene Complexes in Microemulsions and Conventional Solvents

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Abstract: The role of liquid confinement on the asymmetric Rh catalysis was studied using the 1,2-addition of phenylboroxine **2** to *N*-tosylimine **1** in the presence of $[RhCl(C_2H_4)_2]_2$ and chiral diene ligands as benchmark reaction. To get access to Rh complexes of different polarity, enantiomerically pure C_2-symmetric *p*-substituted 3,6-diphenylbicyclo[3.3.0]octadienes **4** and diastereomerically enriched unsymmetric norbornadienes **5** and **6** carrying either the Evans or the SuperQuat auxiliary were synthesized. A microemulsion containing the equal amounts of H_2O/KOH and toluene/reactants was formulated using the hydrophilic sugar surfactant *n*-octyl β-D-glucopyranoside (C_8G_1) to mediate the miscibility between the nonpolar reactants and KOH, needed to activate the Rh diene complex. Prominent features of this organized reaction medium are its temperature insensitivity as well as the presence of water and toluene-rich compartments with a domain size of 55 Å confirmed by SAXS. While bicyclooctadiene ligands **4a**,**b**,**e** performed equally well under homogeneous and microemulsion conditions, ligands **4c**,**d** gave a different chemoselectivity. For norbornadienes **5**, **6**, however, microemulsions markedly improved conversion and enantioselectivity as well as reaction rate, as was confirmed by kinetic studies using ligand **5b**.

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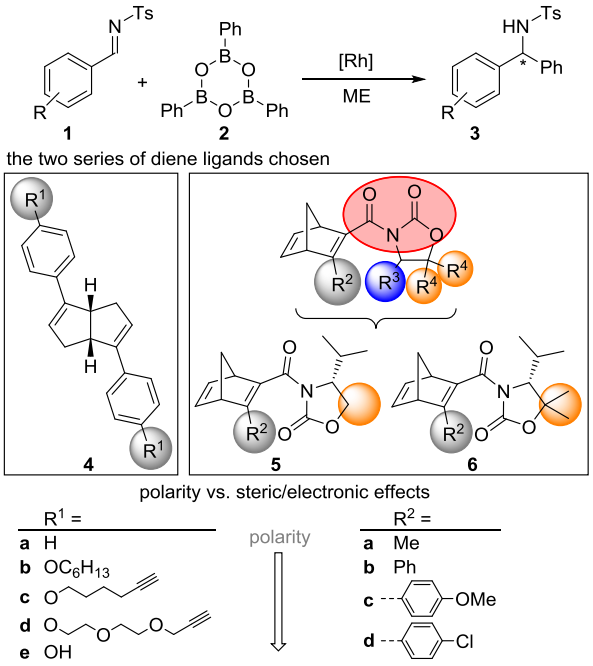
Introduction

Microemulsions are thermodynamically stable and macroscopically homogeneous mixtures of at least two immiscible and an amphiphilic component. Contrary to regular solutions, microemulsions are composed of nanometer-scaled water and oil-domains separated by a surfactant monolayer. Adjusting the properties of the amphiphilic film by e.g. temperature, pressure, co-surfactant/surfactant ratio or electrolyte concentration a variety of nanostructures are accessible ranging from spherical over cylindrical droplets to network-like and bicontinuous structures.[1,2] Due to their ability to overcome the reactants incompatibility faced in organic synthesis and the enormous internal interfacial area,[3] they were widely used in organic syntheses instead of conventional solvents to mediate the miscibility between polar and nonpolar reactants. Thus increased reaction rates and enhanced yields compared to two-phase systems were achieved.[4]

Over the last decade homogeneous metal catalysis has strongly benefited from microemulsions due to improved solubility of reactants and mass transport as compared to conventional solvents or biphasic reaction media.[5] Most work has focused on industrially relevant transition metal-catalyzed reactions in microemulsions,[6] such as Rh-catalyzed hydrogenations and hydroformylations,[7–10] Rh- and Pd-catalyzed disproportionation of dihydroarenes,[11] Rh-catalyzed cyclotrimerizations of alkynes,[12] photocatalytic water splitting with Ir and Rh complexes[13] as well as biocatalytic reactions.[14,15] Besides the use of various enzymes[11,12] surprisingly little work has been carried out on homogeneous asymmetric catalysis in microemulsions. Among the few examples are a vitamin B_{12}-catalyzed epoxide isomerization towards an allylic alcohol reported by Rusling.[16] Both the product ratio and the enantioselectivity were found to depend on the type of microemulsion and surfactant. On the other hand, Lipshutz demonstrated in the asymmetric Au-catalyzed lactonization of allenic acids in microemulsions the role of the chiral phosphane ligand on the *ee* values.[17]

Asymmetric catalysis with chiral Rh diene complexes has experienced much progress over the last two decades[18] since Hayashi's,[19] Carreira's[20] and Grützmacher's[21] ground-braking discoveries. Since then a broad range of chiral diene ligands has been developed, most prominently bicyclic dienes,[22,23] but also acyclic[24,25] and planar chiral dienes.[26] Rh- and Ir-complexes carrying chiral diene ligands turned out to be particularly successful for asymmetric C–C, C–O and C–N bond formations,[27–29,30] but also cycloadditions,[31,32] reductions[33] and other more complex transformations[34] have been realized. Mechanistic insight was obtained by several theoretical studies.[23a,35] While asymmetric catalytic reactions in micellar systems were successfully performed,[36] asymmetric catalysis with Rh diene complexes in bicontinuous microemulsions have not been reported so far. Therefore, we probed for the first time the influence of microemulsions as organized reaction media for the Rh-catalyzed asymmetric arylation of *N*-tosylimines **1** with the organoboron reagent **2** to the corresponding secondary amines **3** as benchmark reaction. Moreover, this benchmark system contains multi-components as e.g. aqueous/organic solvent mixtures, bases and/or salts, which often requires tedious reaction optimization due to sluggish reaction rates and poor yields.[23a,25,37] Thus, we anticipated that particularly bicontinuously structured microemulsions should overcome limitations of conventional solvents caused by mass transport due to the simultaneous existence of polar and nonpolar nano-domains controlling the catalyst–substrate interactions. In addition, the location of reactant, base as well as catalyst and ligands within either the polar or nonpolar nano-domains or the surfactant film of the microemulsion will have a strong influence on the catalytic reaction. In order to get access to Rh complexes of different polarity, we synthesized two series of novel chiral diene ligands **4**–**6** being suitable for this purpose. Ligands **4** were chosen because the *concave* diarylbicyclo[3.3.0]octadiene core creates a symmetric relatively nonpolar ligand sphere around the Rh center, which can be manipulated by attachment of substituents at the 4-position of

the phenyl rings. On the other hand, the unsymmetric norbornadiene ligands **5** and **6** with the attached oxazolidinone unit not only generate a less symmetric and much more polar environment around Rh, but in addition, the oxazolidinone unit might coordinate the Rh (Scheme 1).[38] In the current report we compare the Rh catalysis in microemulsions with the one in conventional reaction media (toluene and dioxane).

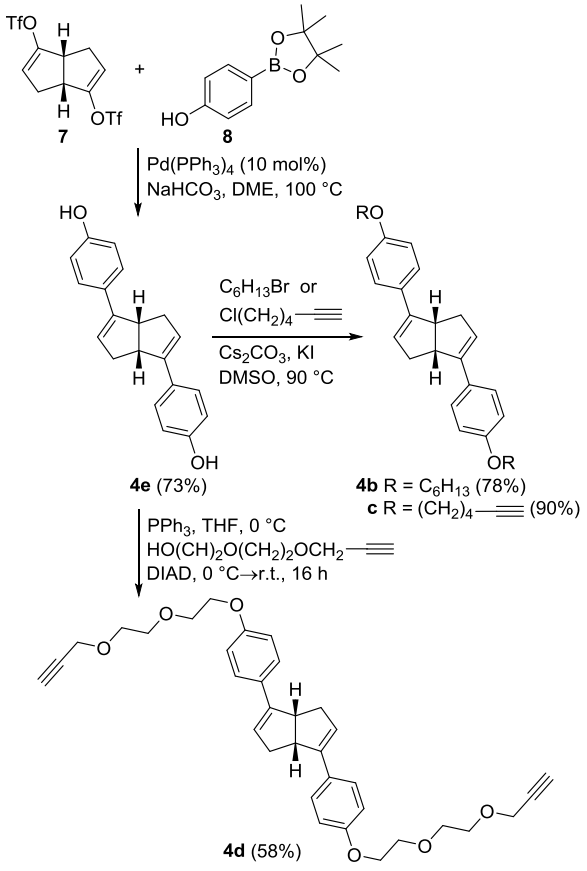


Scheme 1. Envisioned Rh-catalyzed asymmetric 1,2-additions in the presence of novel chiral bicyclo[3.3.0]octadiene and norbornadiene based ligands **4**–**6**.

Results and Discussion

Synthesis of diene ligands: The synthesis of chiral bicyclo[3.3.0]octa-1,4-dienes **4**, which were based on the known tetrahydropentalene ligand **4a**,[23b,37d] commenced with Suzuki coupling between the borolane **8**[39] and bisenoltriflate **7**[23b] with 10 mol% of $Pd(PPh_3)_4$ and aqueous $NaHCO_3$ in DME at 100°C to yield enantiomerically pure dihydroxy ligand **4e** in 73% (>99% *ee*, based on the enantiomeric purity of used (3a*R*,6a*R*)-**4a**[23b,37d] determined by GC on chiral stationary phase. For details see Supporting Information) (Scheme 2). Williamson etherification

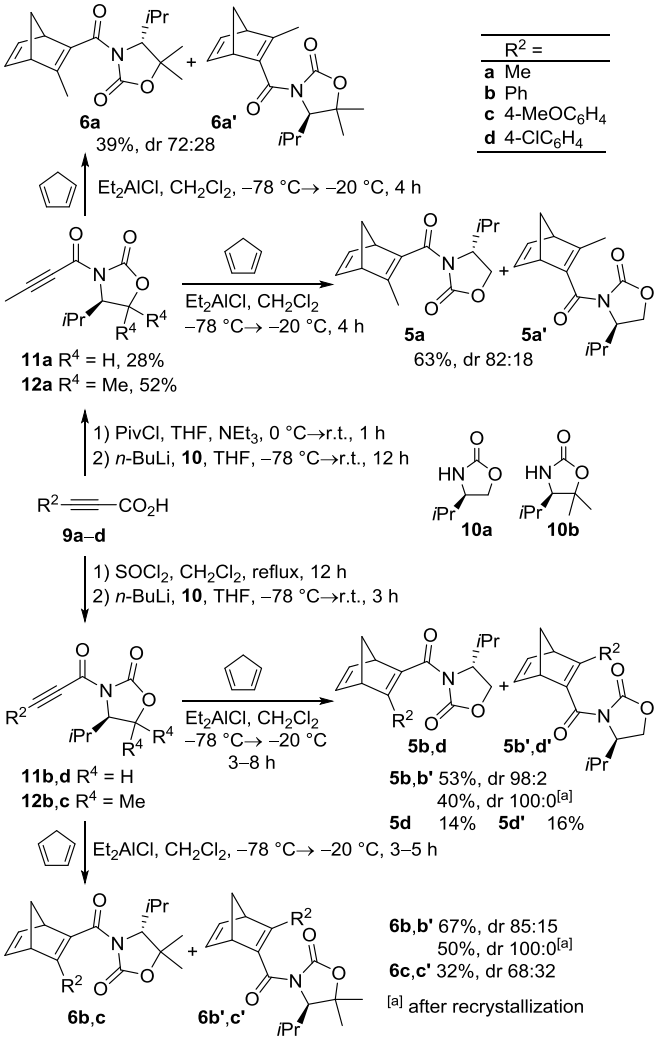
of **4e** with hexylbromide or 6-chloro-1-hexyne in the presence of Cs_2CO_3 and KI in DMSO at 90°C gave enantiomerically pure ethers **4b** and **4c** in 78% and 90% yield, respectively. Under Mitsunobu conditions **4e** reacted with 2-[2-(prop-2-ynyloxy)ethoxy]ethanol in the presence of PPh_3 and diisopropyl azodicarboxylate (DIAD) to enantiomerically pure alkynyl-terminated ligand **4d** in 58% yield (Scheme 2).



Scheme 2. Synthesis of novel chiral bicyclo[3.3.0.]octadiene ligands **4**. For details see Supporting Information.

The synthesis of chiral unsymmetrically substituted norbornadienes **5** and **6** carrying either the D-valine-derived Evans oxazolidinone[40] or the corresponding sterically more demanding SuperQuat auxiliary[41] is shown in Scheme 3. Methyl-substituted acyloxazolidinones **11a**, **12a** were obtained in 28% and 52% yield, respectively, by reaction of tetrolic acid **9a**[42] with pivaloyl

chloride and Et_3N in THF at 0°C,[43] followed by addition of the lithiated oxazolidinone **10a**,**b** to the *in situ* formed mixed anhydride. The aryl-substituted precursors **11b**,**d** and **12b**,**c** were obtained by treatment of the respective **9**[42] with thionyl chloride under reflux[44] and subsequent reaction with the lithiated oxazolidinones **10a**,**b** in THF at –78°C.[45] After warming to room temperature, acyloxazolidinones **11b**,**d** and **12b**,**c** were isolated in 40–81%.



Scheme 3. Synthesis of chiral norbornadiene oxazolidinone ligands **5** and **6** applying literature procedures.[40,43–46] For details see Supporting Information.

The [4+2] cycloaddition of the propargyl acyloxazolidinones **11** and **12** with cyclopentadiene was carried out in the presence of 1.6 equiv. of Et_2AlCl in CH_2Cl_2 at –78°C and slow warming to –20°C (Scheme 3).[40,46] Other investigated methods, however, failed (see Supporting Informa-

tion). In all cases, norbornadiene ligands **5** and **6** were obtained as diastereomeric mixtures **5**, **5'** and **6**, **6'** consisting of the enantiomerically pure diastereomers (based on the use of enantiomerically pure auxiliaries **10a**,**b**) (Scheme 3). Dienes **5b**, **5d**, **5d'** and **6b** were isolated as single diastereomers in enantiomerically pure form by recrystallization (Scheme 3).

Single crystal structure determination was possible for bicyclo[3.3.0]octa-1,4-diene **4d** as well as norbornadienes **5b**, **5d'** and **6b** (Figures S5, S6).[47] Fortunately, X-ray crystal structure data could also be obtained for two Rh complexes (Figure 1, Table S3).[47]

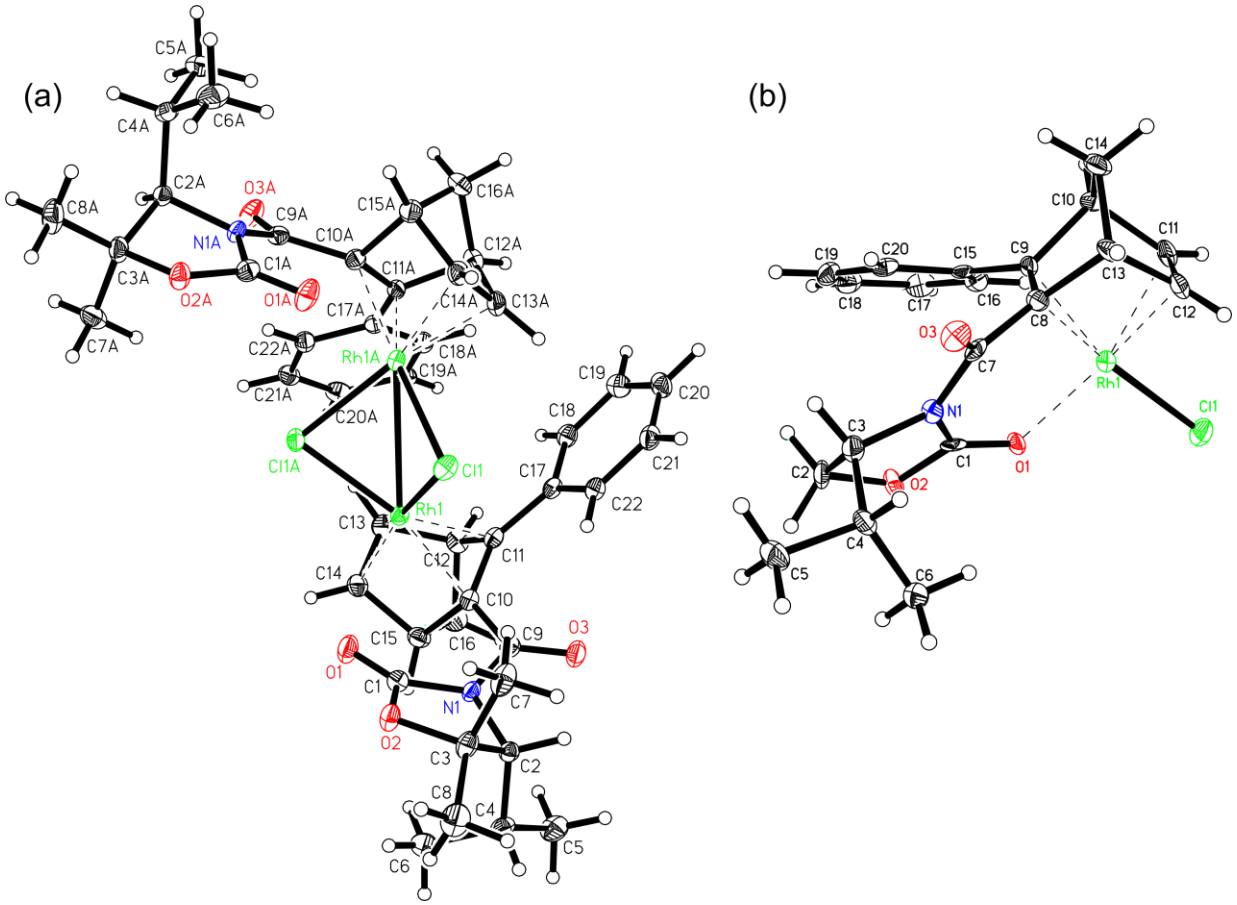


Figure 1. Structure of complexes $[RhCl(\mathbf{6b})]_2$ (a) and [RhCl(**5b**)] (b) in the solid state. The absolute configuration was determined by anomalous dispersion with relevant Flack parameters x = –0.031(6) and 0.01(3), respectively. For getting better overall standard deviations of the geometric parameters of the $[RhCl(\mathbf{6b})]_2$ X-ray structure, a severely disordered Et_2O solvate molecule was removed with SQUEEZE as implemented in PLATON.[48] The Rh1···O1 and Rh1–Cl1 distances in [RhCl(**5b**)] are shorter than in $[RhCl(\mathbf{6b})]_2$ and interactions of C8=C9, C11=C12 to Rh elongate the double bonds.

While the SuperQuat auxiliary-derived ligand **6b** formed a binuclear μ-chloro-bridged Rh complex [RhCl(**6b**)]$_2$ (Figure 1a) with bond lengths and angles, which are in good agreement with literature data,[23a] the corresponding Evans auxiliary-derived ligand **5b** formed a mononuclear complex [RhCl(**5b**)] (Figure 1b), where the carbonyl group of the oxazolidinone unit coordinates the Rh center, resulting in an elongation of the C1=O1 double bond to 1.227(4) Å (see Supporting Information).

Formulation and optimization of the microemulsions: Often micellar systems are used as reaction media for catalytic reactions.[36a,d] However, for the studied Rh-catalyzed asymmetric 1,2-addition we extended the micellar system by a hydrophobic component, using a thermodynamically stable microemulsion as a reaction medium. Thus, a perfect solvent environment is provided for all reaction partners. The aqueous domains of the microemulsion are a good solvent for KOH, needed to activate catalyst/ligand system; the hydrophobic reactants *N*-tosylimine **1** and triphenylboroxine **2** feel fine in the toluene domains, while the catalyst/ligand system, possessing both polar and non-polar parts, can reside in/at the amphiphilic surfactant film. Assuming that the bicontinuous structure allows for the easiest access of the catalyst/ligand system with respect to both KOH and the reactants, we aimed for a microemulsion containing equal amounts of water and oil (α = 0.50). Furthermore, due to the fact that the solubility of the reactants **1** and **2** in toluene is limited at low temperatures, a reaction temperature of T = 60.0°C was envisaged. Thus, the bicontinuous microemulsion containing water/KOH, toluene/reactants **1** and **2** as well as the surfactant and catalyst/ligand system should be stable around T = 60.0°C. In order to formulate such a microemulsion, we studied the phase behaviour of the described system H_2O–cyclohexane–non-ionic surfactant[49] as starting system. To avoid the formation of liquid crystalline phases on one hand and to decrease the temperature-sensitivity of the system on the

other hand, the pentaethylene glycol monohexyl ether (C_6E_5) surfactant with a shorter chain was used instead of octaethylene glycol monodecyl ether ($C_{10}E_8$). The phase behaviour of the H_2O–cyclohexane–C_6E_5 microemulsion systems was investigated as a function of temperature and surfactant mass fraction, i.e. recording $T(\gamma)$-sections through the phase prism at a constant mass fraction $\alpha = 0.50$ of oil in the mixture of water and oil.[1]

As shown in Figure 2, the phase boundaries show the typical behaviour of microemulsion systems (at $\alpha = 0.50$) stabilized by a non-ionic surfactant.

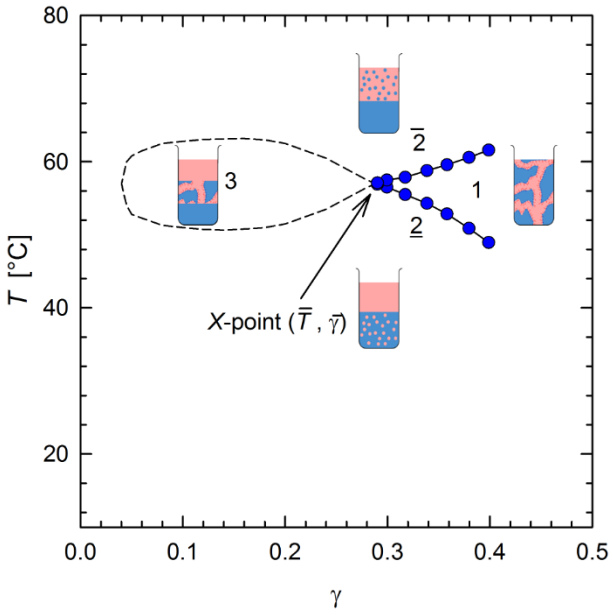


Figure 2. $T(\gamma)$-section of the systems H_2O–cyclohexane–C_6E_5 (●) at $\alpha = 0.50$ (starting system). Schematic test tubes visualize the state of the sample at different temperatures and surfactant mass fractions γ. $\underline{2}$: coexistence of an oil-in-water microemulsion with an oil-excess phase; $\overline{2}$: co-existence of water-in-oil microemulsion with a water-excess phase; 1: one phase microemulsion; 3: coexistence of microemulsion phase with water- and oil-excess phase.

At low temperatures, an oil-in-water microemulsion coexists with an oil-excess phase (denoted as $\underline{2}$), while at high temperatures a water-in-oil microemulsion coexists with a water-excess phase (denoted as $\overline{2}$). At temperatures in between, three phases, i.e. a microemulsion phase which coexists with a water- and an oil-excess phase (denoted as 3), or a one phase microemulsion can

be observed. The pivotal point of these phase diagrams is the so-called *X*-point, which defines the minimum surfactant mass fraction $\overline{\gamma}$ that is needed to solubilize equal amounts of water and oil into each other at the phase inversion temperature $\overline{T}$ (PIT). Note that the envisaged bicontinuous structure is formed near the PIT at $\gamma \geq \overline{\gamma}$. The *X*-point of H_2O–cyclohexane–C_6E_5 system (at α = 0.50) is located at $\overline{T}$ = 57.0±0.5°C and $\overline{\gamma}$ = 0.285±0.005.

Based on this microemulsion, cyclohexane was replaced with toluene causing a shift of the phase boundaries to lower temperatures. Therefore, the surfactant C_6E_5 was partly replaced with the hydrophilic sugar surfactant C_8G_1 (*n*-octyl β-D-glucopyranoside) to compensate the shift to lower temperatures. These optimization steps are shown and discussed extensively in SI (Figures S1, S2). The phase behaviour of the obtained H_2O–toluene–C_6E_5/C_8G_1 system (α = 0.50, δ = 0.70, mass fraction of C_8G_1 in the surfactant mixture) is shown in Figure 3, △. As can be seen, the *X*-point of this system is located at $\overline{T}$ = 55.8±0.5°C and $\overline{\gamma}$ = 0.245±0.005.

Before this toluene-microemulsion could be used as reaction medium, the influence of KOH, catalyst and ligands as well as reactants on the phase behaviour had to be examined. The influence of KOH and the Rh-catalyst with the two different ligands **4a** and **5b** on the phase boundaries of the H_2O–toluene–C_6E_5/C_8G_1 system (α = 0.50, δ = 0.70) is shown in Figure 3a. It is apparent that a low KOH concentration (**x**) (ε = 0.0033) (the parameter ε is the mass fraction of KOH in the H_2O/KOH mixture), the combination of Rh-catalyst and ligand **4a** (□) as well as Rh-catalyst and ligand **5b** (●) had no effect on the phase behaviour of the system.

The effect of the reactant *N*-tosylimine **1** on the phase behavior of the formulated toluene microemulsion is shown in Figure 3b (□). *N*-tosylimine **1** shifted the phase boundaries to lower temperatures by approximately 15 K, which might be a consequence of its larger polarity compared to toluene.[50] In the same manner as for *N*-tosylimine **1**, the influence of triphenylboroxine **2** on the phase behaviour of the microemulsion was studied.

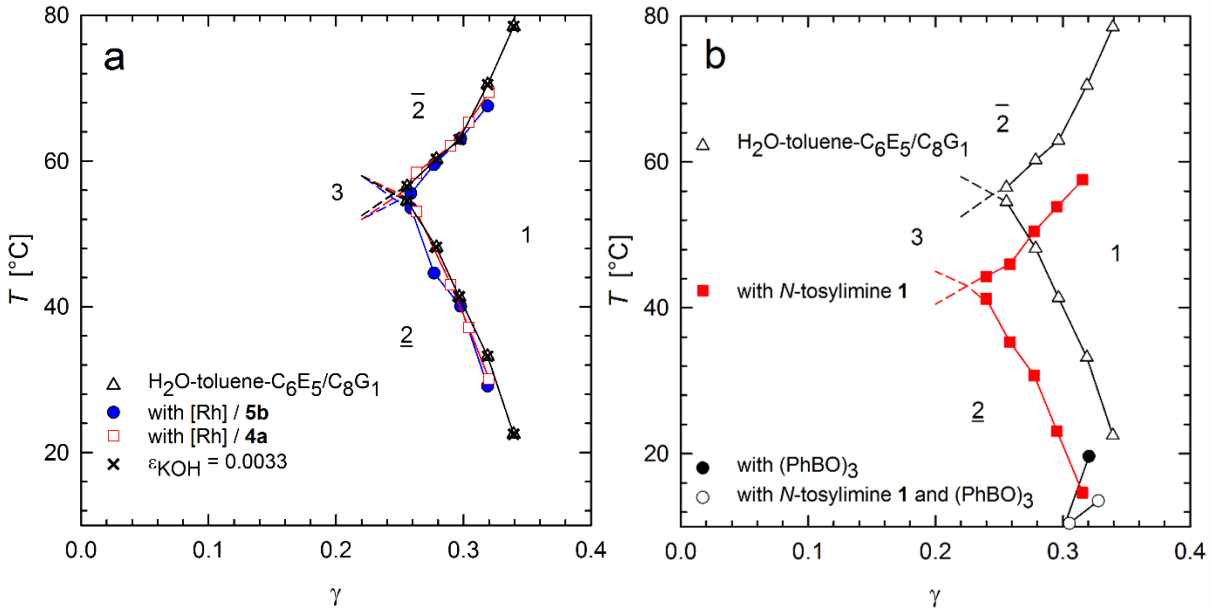


Figure 3. Influence of (a) KOH (ε = 0.0033), Rh-catalyst and ligands and (b) the reactants on the *T*(γ)-section of the base system H_2O–toluene–C_6E_5/C_8G_1 (δ = 0.70) (△) at α = 0.50 (a) and α = 0.52 (b). Due to the small concentrations, KOH (×), the Rh-catalyst with ligand **4a** (□) and ligand **5b** (●) had almost no influence on the phase boundaries of the base system. (b) Contrary reactants *N*-tosylimine **1** (7.1 wt%) (■) and triphenylboroxine **2** (8.8 % wt%) (●) in toluene at γ = 0.32 and α = 0.52 strongly shifted the phase boundaries to lower temperature as well as the mixture of **1**/**2** (7.1 wt%/8.8 wt% in toluene at γ = 0.32 and α = 0.54) (○).

As shown in Figure 3b (●), using a mixture of **2** and toluene instead of toluene the phase boundaries were shifted strongly to lower temperatures. Thus, only the upper $1 \rightarrow \bar{2}$ phase boundary could be detected. This strong effect of triphenylboroxine **2** on the phase behaviour might be related to the presumable formation of hydrolysis products as e.g. boronic acid, which would rather act as hydrophobic co-surfactants changing the curvature of the amphiphilic film and thus the phase behaviour of the microemulsion system. In order to prove this hypothesis, we measured the interfacial tension between water and toluene as a function of the triphenylboroxine concentration in toluene at *T* = 25°C using the pendant drop method. The interfacial tension was found to decrease from 36 mNm^{-1} (value from[51]) to 12 mNm^{-1} with increasing triphenyl-boroxine concentration to 2.0 wt%, which strongly indicates the formation of amphiphilic

hydrolysis products as e.g. boronic acid. The observed trends are more detailed discussed in SI (Figure S4).

For the Rh-catalyzed asymmetric 1,2-addition a toluene microemulsion has to be formulated containing both reactants. Therefore, also the influence of the *N*-tosylimine **1**/triphenylboroxine **2** mixture (7.1 wt%/8.8 wt% in toluene at $\gamma = 0.32$) on the phase behaviour of the microemulsion was studied (Figure 3b, ○). The mixture of **1** and **2** shifted the phase boundaries to even lower temperatures as expected from the trends found for the microemulsions containing only one reactant.

Aiming for a bicontinuously structured microemulsion at $T \approx 60°C$ which contains KOH, Rh-catalyst and ligands as well as the two reactants the phase boundaries had to be shifted strongly to higher temperatures. Interestingly, replacing the remaining C_6E_5 surfactant with C_8G_1, the shift of the phase boundaries to lower temperatures caused by **2** and **1** could be compensated. Figure 4 shows the phase behaviour of the reaction microemulsion H_2O/KOH–toluene/*N*-tosylimine **1**/triphenylboroxine **2**–C_8G_1 with $\alpha = 0.54$, $\varepsilon_{KOH} = 0.0033$, **1** (7.1 wt%) and **2** (8.8 wt%). The steepness of the phase boundaries is a consequence of the weak temperature dependence of the amphiphilic film curvature. With increasing temperature, the hydration of the hydroxyl groups decreases, while the toluene and reactants molecules have a stronger tendency to penetrate the alkyl chains of the amphiphilic film. As both hydration and penetration are only weakly temperature dependent, the reaction microemulsion might also be less sensitive to composition changes generated by the Rh-catalyzed asymmetric 1,2-addition. The *X*-point of the reaction microemulsion is located at $\overline{T} = 48.4 \pm 0.5°C$ and $\overline{\gamma} = 0.19 \pm 0.005$.

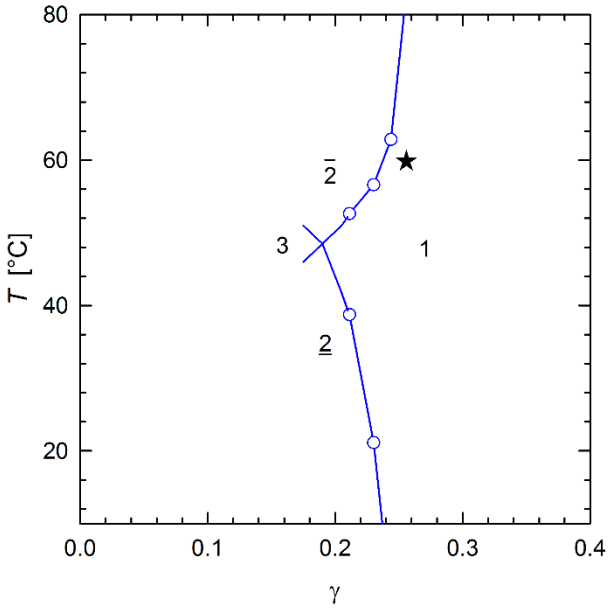


Figure 4. $T(\gamma)$-section of the system H_2O/KOH–toluene/*N*-tosylimine **1**/triphenylboroxine **2**–C_8G_1 at $\alpha = 0.54$, $\varepsilon_{KOH} = 0.0033$, **1** (7.1 wt%) and **2** (8.8 wt%) in toluene at $\gamma = 0.30$. Due to the weak temperature dependence of the C_8G_1 surfactant, a wide one-phase regime can be observed. The Rh-catalyzed asymmetric 1,2-addition at $\gamma = 0.26$ and a temperature of $T = 60°C$ is indicated by the star.

In order to determine the size of the water and toluene/reactant domains inside the one-phase microemulsion, SAXS experiments were performed at $\gamma = 0.26$ and $T = 60°C$. Figure 5 displays the scattering data plotting the scattering intensity as a function of the scattering vector q in a double-log plot. The scattering curves exhibit the typical shape found for bicontinuous micro-emulsions:[52] Starting from low q-values, the scattering intensity slightly increases, runs through a maximum at middle q-values before the intensity decreases with q^{-3} rather than q^{-4}. Note that this finding can be explained by the combination of film and bulk contrast contributions.

By using the *Teubner-Strey* model[52] a correlation length of $\xi_{TS} = 3.3\pm0.2$ nm and a size of $d_{TS}/2 = 5.5\pm0.2$ nm was obtained for the water and toluene/reactant domains. Considering that the concentration of the catalyst/ligand complex with respect to reactant **1** is 2.5 mol%, on average every second toluene domain contains a catalyst/ligand complex.

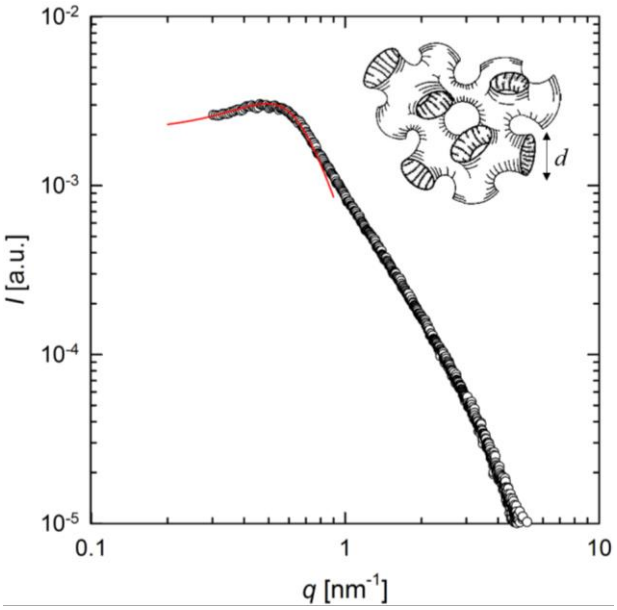
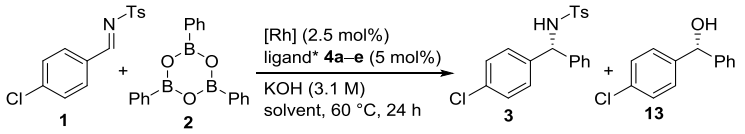


Figure 5. SAXS scattering curve (black) of the one-phase microemulsion of H_2O/KOH–toluene/*N*-tosylimine **1**/triphenylboroxine **2**–C_8G_1 system at $\gamma = 0.26$, $\alpha = 0.54$, $\varepsilon_{KOH} = 0.0033$, **1** (7.1 wt%) and **2** (8.8 wt%) in toluene at $\gamma = 0.30$ and $T = 60.0$°C. The red solid line is the fit of the scattering peak by the *Teubner-Strey* model.[52]

When the Rh-catalyzed asymmetric 1,2-addition was conducted in the H_2O/KOH–toluene/*N*-tosylimine **1**/triphenylboroxine **2**–C_8G_1 microemulsion at $T = 60$°C, we observed that the reaction medium changed from the one phase to the $\underline{2}$ phase state, where an oil-in-water microemulsion coexists with an oil-excess phase. In order to explore this observation, we studied the influence of the changing reactant/product ratio on the phase behaviour of the toluene microemulsion. As can be seen in Figure S3, replacing the two reactants **1** and **2** with the product, i.e. the corresponding secondary amine **3**, the lower $\underline{2} \rightarrow 1$ phase boundary indeed shifted to higher temperature. This effect can most probably related to both the increasing amount of amine **3**, which is more hydrophobic than *N*-tosylimine **1** and the decreasing amount of triphenylboroxine **2** corresponding to a decreasing amount of its amphiphilic hydrolysis products which act as hydrophobic co-surfactants.

Rh-catalyzed asymmetric 1,2-additions: The application of chiral bicyclo[3.3.0]octadienes **4** as ligands in Rh-catalyzed asymmetric 1,2-additions of triphenylboroxine **2** to (4-chlorophenyl)-*N*-tosylimine (**1**) was studied under homogeneous conditions and in microemulsions (Table 1). As benchmark catalysts $[Rh(COD)OH]_2$ and the *in situ* formed catalyst from $[Rh(C_2H_4)_2Cl]_2$ and known (3a*R*,6a*R*)-diphenyldiene **4a** were used.

Table 1. Comparison of 1,2-additions of boroxine **2** to *N*-tosylimine **1** in solution and microemulsion (ME) catalyzed by a complex of Rh/ligand **4**. The progress of the reactions was monitored by ^{1}H-NMR spectroscopy.



Entry	Ligand	Solvent	NMR yield [%][a]			Yield [%][b]		*ee* [%]	
			1	**3**	**13**	**3**	**13**	**3**	**13**
1	COD	dioxane	36	59	–	58	–	0	–
2	**4a**	dioxane	–	>99	–	>99	–	>99	–
3	**4a**	toluene	–	90	10	82	9	99	10
4	**4b**	dioxane	–	96	4	85	–	97	–
5	**4c**	dioxane	1	61	28[c]	56	21	93	2
6	**4d**	dioxane	33	55	2[c]	50	30	91	8
7	**4e**	dioxane	–	98	2	97	–	97	–
8	**4a**	ME[d]	2	96	2	93	–	>99	–
9	**4b**	ME[d]	2	87	11	82	–	95	–
10	**4c**	ME[d]	5	15	78	15	74	93	5
11	**4d**	ME[d]	1	35	64	32	60	86	5
12	**4e**	ME[d]	1	95	4	95	–	97	–

[a] Mesitylene was used as the internal standard.[53] [b] Isolated yields. [c] Aldehyde **14** was detected by ^{1}H-NMR in 3% and 4% (entries 5, 6). [d] ME: 0.60 g C_8G_1, 0.89 mL toluene and 0.77 mL H_2O at $\gamma = 0.26$ and $\alpha = 0.54$.

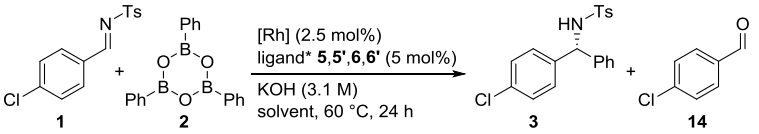
Under the conditions in Table 1 treatment of tosylimine **1** and phenylboroxine **2** with $[Rh(COD)OH]_2$ gave a mixture of unreacted imine **1** (36%) and racemic addition product **3**

(59%), while treatment in the presence of $[Rh(C_2H_4)_2Cl]_2$ and **4a** yielded enantiomerically pure product **3** in 99% with >99% *ee* at quantitative conversion (Entries 1, 2). For comparison with toluene-based microemulsions, the homogeneous catalysis was also performed in toluene[37b] instead. ^{1}H-NMR analysis of the crude product revealed a (90 : 10) mixture of product **3** and alcohol **13**, which was purified by chromatography to give **3** in 82% with high enantioselectivity (99% *ee*) and 9% of **13** (10% *ee*) (Entry 3). The addition reactions with both ligands **4b** (R = OC_6H_{13}) and **4e** (R = OH) proceeded cleanly (Entries 4, 7), whereas ligands **4c** and **4d** revealed complex crude product mixtures of unreacted **1**, addition product **3**, and byproducts **13**, **14** (see Table 2) according to ^{1}H-NMR analysis (Entries 5, 6), suggesting that the alkyne terminus interfered with the desired 1,2-addition under the used basic conditions, resulting in hydrolysis of imine **1** to aldehyde **14** and subsequent 1,2-addition to **13**. After chromatography, amine **3** was isolated in moderate yields with *ee* values of 91–93%.

In microemulsions consisting of C_8G_1 surfactant, toluene and water (see Figure 4) under otherwise same conditions the 1,2-addition with benchmark catalyst $[Rh(C_2H_4)_2Cl]_2$/**4a** gave a crude product mixture of starting material **1**, addition product **3** and alcohol **13** according to ^{1}H-NMR monitoring, from which product **3** was isolated in high yield and enantiomeric excess (93%, >99% *ee*) (Entry 8). Thus, in comparison to the homogeneous catalysis in toluene (Entry 3), both the chemoselectivity, i.e. the ratio of amine **3** vs. alcohol **13**, was shifted in favor of **3** and the isolated yield was improved. The arylation in the presence of $[Rh(C_2H_4)_2Cl]_2$ with chiral ligands **4b** and **4e**, respectively, provided results comparable to **4a** albeit with lower yields and *ee* values (Entries 9, 12). The largest difference between catalysis in conventional solvent and microemulsion, however, was observed for diene ligands **4c**, **4d** with alkynyl terminus, where a complete reversal of the chemoselectivity was detected, leading to alcohol **13** as the major product (Entries 10, 11).

We then studied the catalytic properties of chiral oxazolidinone norbornadienes **5** and **6** in both the confined system provided by the microemulsion and in conventional solution (Table 2).

Table 2. Comparison of 1,2-addition reactions in solution and microemulsion catalyzed by a complex of Rh/ligand **5** and **6**, respectively. The reaction progress was monitored by ^{1}H-NMR.



Entry	Ligand	dr	Solvent	NMR yield [%][a]			Yield [%][b]	*ee* [%]
				1	**3**	**14**	**3**	**3**
1	**5a**,**5a'**	82 : 18	dioxane	traces	91	8	61	36 (*S*)
2	**5b**,**5b'**	98 : 2	dioxane	10	89	1	69	32 (*R*)
3	**5b**,**5b'**	98 : 2	toluene	67	14	13	n.d.	n.d.
4	**5b**	100 : 0	dioxane	18	76	6	61	90 (*R*)
5	**5d**	100 : 0	dioxane	55	25	20	20	94 (*R*)
6	**5d'**	0 : 100	dioxane	15	32	53	32	56 (*S*)
7	**6a**,**6a'**	72 : 28	dioxane	11	68	20	48	74 (*R*)
8	**6b**,**6b'**	85 : 15	dioxane	17	74	9	73	94 (*R*)
9	**6b**	100 : 0	dioxane	27	55	18	55	98 (*R*)
10	**6c**,**6c'**	68 : 32	dioxane	18	60	22	61	92 (*R*)
11	**5b**,**5b'**	98 : 2	ME [c]	–	83	17	61	90 (*R*)
12	**5b**	100 : 0	ME [d]	–	93	7	84	22 (*R*)
13	**5d**	100 : 0	ME [d]	–	97	3	79	92 (*R*)
14	**5d'**	0 : 100	ME [d]	–	83	17	59	12 (R)
15	**6a**,**6a'**	72 : 28	ME [c]	–	88	12	75	70 (*R*)
16	**6b**	100 : 0	ME [c]	–	77	23	65	96 (*R*)
17	**6c**,**6c'**	68 : 32	ME [c]	–	84	16	77	90 (*R*)

[a] Mesitylene was used as the internal standard.[53] [b] Isolated yield. [c] ME: 0.60 g C_8G_1, 0.89 mL toluene, 0.77 mL H_2O at $\gamma = 0.26$ and $\alpha = 0.54$. [d] ME: 0.60 g C_8G_1, 0.81 mL toluene, 0.70 mL H_2O at $\gamma = 0.28$ and $\alpha = 0.54$.

Under the used conditions in solution in the presence of methyl Evans diene **5a,5a'** (dr 82 : 18) product **3** was isolated from a crude mixture of **3** and aldehyde **14** in 61%, but a reversed enantio-

selectivity (36% *ee* (*S*)) was observed (Entry 1). ^{1}H-NMR monitoring of the reaction using phenyl Evans diene **5b,5b'** (dr 98 : 2) as ligand in dioxane showed a (10:89:1) crude product mixture of **1** : **3** : **14**, whereas the arylation in toluene was significantly retarded resulting in a crude mixture which was dominated by starting imine **1** (67%) (Entries 2, 3). However, single diastereomer **5b** in dioxane yielded after workup amine **3** in 61% with 90% *ee* (*R*) (Entry 4). The single diastereomers **5d** and **5d'** with 4-chlorophenyl substituent, respectively, were studied in parallel experiments in dioxane (Entries 5, 6). In both cases, incomplete conversion and large amounts of aldehyde **14** were detected, providing the addition product **3** in low yields of 20% and 32%, respectively. However, ligand-controlled enantioselectivity was observed with diastereomer **5d** producing a *matched* case (94% *ee* (*R*)) (Entry 5), while diastereomer **5d'** gave the *mismatched* case (56% *ee* (*S*)) with opposite configuration of the major enantiomer of **3** (Entry 6). Incomplete conversions in conventional solution were monitored by ^{1}H-NMR for all SuperQuat dienes **6** irrespective of their diastereomeric ratios and the substituent. Amine **3** was isolated in moderate yields (48–73%) but high enantiomeric excesses of 92–98% *ee* (*R*) with exception of ligand mixture **6a**,**6a'** (74% *ee* (*R*)) (Entries 7–10).

However, the 1,2-additions of boroxine **2** to tosylimine **1** in confinement in the presence of *in situ* generated catalyst from $[Rh(C_2H_4)_2Cl]_2$ and chiral norbornadiene ligands **5** and **6**, respectively, clearly differed from those in solution. The catalysis in microemulsion went to completion with target amine **3** as the major product. No starting material **1** could be detected in the crude product but small amounts of byproduct **14** (Table 2). In microemulsion (see Figure 4) and 0.02 M KOH phenyl Evans diene **5b,5b'** (dr 98 : 2) provided amine **3** in 61% yield but significantly improved enantioselectivity (90% *ee* (*R*)) as compared to the reaction in dioxane (Entries 2, 11). In microemulsion using single diastereomer **5b** the yield of **3** was further increased to 84%, but the enantioselectivity was markedly reduced to only 22% *ee* (Entry 12).

The beneficial effect of the microemulsion on the Rh-catalyzed 1,2-addition was most prominently demonstrated for diastereomerically pure 4-chlorophenyl Evans diene **5d**, which strongly favored the formation of amine **3** (97% crude, 79% isolated, 92% *ee* (*R*)) with a *matched* enantioselectivity (Entry 13). The diastereomerically pure ligand **5d'** also afforded addition product **3** in much higher yield than in the conventional dioxane solution, albeit with a *mismatched* enantiocontrol (59%, 12% *ee* (*R*)) (Entry 14). As compared to the catalyses in the conventional solution dioxane, SuperQuat dienes **6a**,**6a'**, **6b** and **6c**,**6c'**, respectively, tend to increase the yield of product **3** in microemulsions, the enantioselectivities, however, retained (Entries 15–17). The more pronounced rate enhancement observed for Evans diene **5b** in microemulsion vs. dioxane (Entries 4, 12) as compared to SuperQuat diene **6b** (Entries 9, 16) might be due to different coordination modes of the Rh catalyst (Figure 1). However, based on the current results it is too early to draw further mechanistic conclusion.

Kinetic studies of Rh-catalyzed asymmetric 1,2-additions: The kinetics of the Rh-catalyzed arylation of *N*-tosylimine **1** with triphenylboroxine **2** was monitored by ^{1}H-NMR with mesitylene as internal standard. Figure 6 shows the yield obtained at T = 60°C in the different reaction media, i.e. dioxane, toluene and the microemulsion as a function of time. In agreement with previous work in the literature temperatures ≥60 °C are required to promote transmetallation.[30,35b] While in the reaction profiles shown in Figure 6a the Rh-catalyst with ligand **4a** was used, the Rh-catalyst with ligand **5b** was applied in the profiles of Figure 6b. Considering at first the profiles monitored for the Rh/ligand **4a** system, it can be seen that in dioxane (>99%) and the microemulsion (>96%) an almost complete conversion was detected at t = 4 min. However, in toluene, which shows similar kinetics, only a yield of 90 wt% was found after 4 minutes and remained constant for 24 hours. A first order kinetics with respect to *N*-tosylimine **1** was

observed in all experiments. Accordingly, the kinetic data were described by a mono-exponential fit obtained via integration of the first order rate equation

$$d[product\ \mathbf{3}]/dt = k_{\mathrm{app}}[N\text{-tosylimine }\mathbf{1}]$$

yielding the reciprocal rate constant $\tau=k_{\mathrm{app}}^{-1}$. Thereby, we estimated the systematic error with respect to time to be of the order of 20 s ($\Delta t_{\mathrm{start}}\approx$7 s: time needed to obtain a homogeneous distribution after the addition of the reactant molecules; $\Delta t_{\mathrm{end}}\approx$13 s: time needed to remove the catalyst/ligand complex by filtration to stop the reaction). The values of τ (together with the standard deviation for τ > 1 min) and the maximum yield obtained for reactions with the Rh-catalyst/ligand **4a** and ligand **5b** complexes in the different reaction media are compiled in Table 3.

Using the Rh-catalyst/ligand **4a** system, the 1,2-addition proceeded fast in all three reaction media. Although a systematic trend in the initial rate might be deducible from the first data point, we decided to estimate the value of the reciprocal rate constant τ only qualitatively due to the systematic time error of the order of 20 s and the fact that only one data point (yield after two minutes) could be recorded between the start of the reaction and complete conversion. Instead we only indicated the reciprocal rate constant to be smaller than 1 min for all three reaction media.

However, using the Rh/ligand **5b** system in the microemulsion a yield of 93% was reached after 8 minutes, whereas in dioxane a maximum yield of 76% was only detected after 128 minutes and remained constant. In toluene, only a maximum yield of 4% was observed after 24 hours. The increase of the reciprocal rate constant (Table 3), unambiguously showed that the microemulsion reaction medium provided not only an almost complete conversion, but also an almost one order of magnitude faster reaction rate than dioxane.

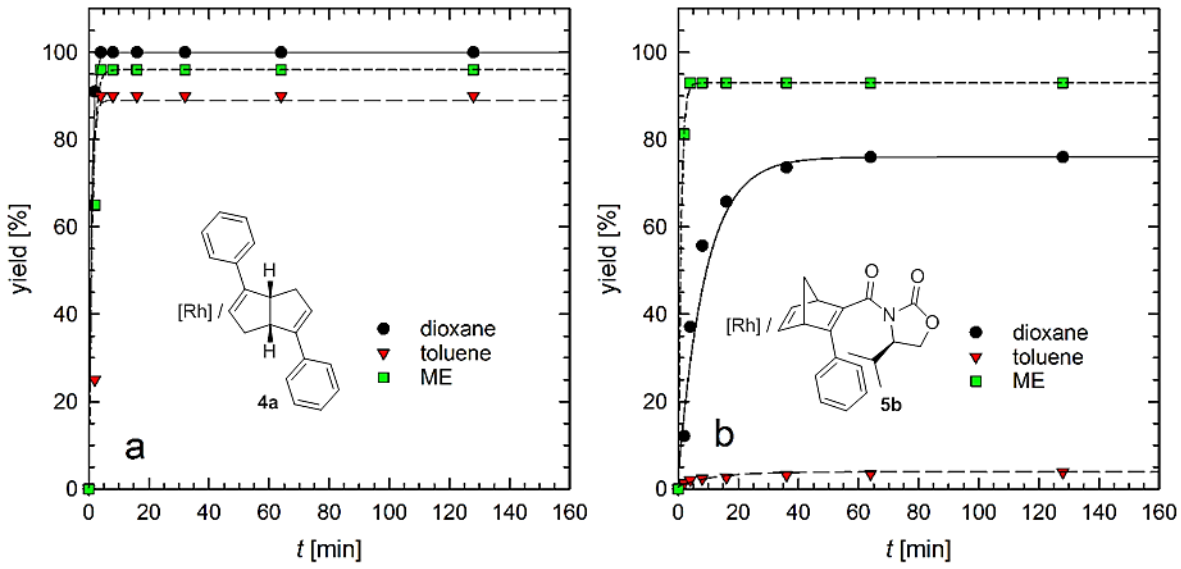


Figure 6. Yield of the rhodium-catalyzed 1,2-addition of triphenylboroxine **2** to *N*-tosylimine **1** conducted at 60°C as a function of time using different reaction media. While the kinetics obtained for the Rh/ligand **4a** system (a) proceeded so fast in all reaction media, that only one data point could be recorded between the start of the reaction and complete conversion (reciprocal rate constant of $\tau < 1$ min), for the Rh/ligand **5b** system (b) the microemulsion provides not only a higher conversion, but also almost one order of magnitude faster reaction rate than dioxane. The data were described by a mono-exponential fit providing the reciprocal rate constant τ (together with the standard deviation) and the maximum yield (Table 3).

Table 3. Reciprocal rate constant and maximum yield of the Rh-catalyzed 1,2-addition of triphenylboroxine **2** to *N*-tosylimine **1** at 60°C in different reaction media and two different Rh/ligand systems (**4a** and **5b**).

Entry	Medium	Ligand	τ [min]	NMR yield [%][a]
1	dioxane	**4a**	< 1.0	>99
2	toluene	**4a**	< 1.0	90
3	ME[b]	**4a**	< 1.0	96
4	dioxane	**5b**	9.1 ± 0.7	76
5	toluene	**5b**	11.9 ± 3.0	4
6	ME[b]	**5b**	< 1.0	93

[a] Mesitylene was used as the internal standard. [b] ME: 0.60 g C_8G_1, 0.89 mL toluene, 0.77 mL H_2O at $\gamma = 0.26$ and $\alpha = 0.54$.

In the next step, the influence of the temperature on the kinetics of the Rh/ligand **4a**-catalyzed 1,2-addition of **2** to tosylimine **1** was studied using dioxane and the microemulsion as reaction media.

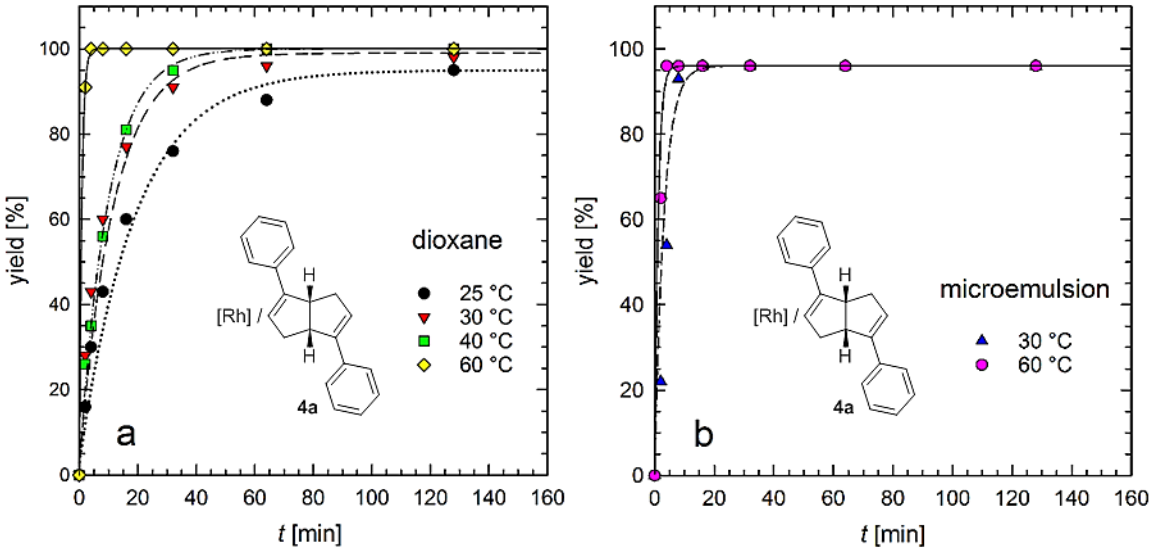


Figure 7. Yield of the 1,2-addition of **2** to *N*-tosylimine **1** in the presence of chiral ligand **4a** as a function of time adjusting different temperatures. (a) In dioxane the reaction proceeded slow at low temperatures. (b) In the microemulsion fast kinetics were also observed at T = 30°C, which were a factor 4 faster than in dioxane at the same temperature. The data were described by a mono-exponential fit providing the reciprocal rate constant τ and the maximum yield (Table 4).

Figure 7a shows that in dioxane the kinetics of the addition exhibits a strong temperature dependence. The reciprocal rate constant τ was found to decrease from τ ≈ 11.9 min at 30°C (the maximum yield of 98% was reached only after 128 min) to τ < 1 min at 60°C, i.e. showing that the reaction proceeds slowly at low temperatures. On the other hand, the reaction profiles shown in Figure 7b demonstrate that the Rh-catalyzed addition reaction in the microemulsion proceeds fast also at T = 30°C, i.e. a complete conversion was detected at t = 16 min. The reciprocal rate constant τ and the maximum yield of the reaction profiles are compiled in Table 4.

Table 4. Reciprocal rate constants and maximum yield of the Rh/**4a**-catalyzed addition of **2** to *N*-tosylimine **1** at different temperatures in dioxane and the microemulsion.

Entry	Medium	*T* [°C]	τ [min]	NMR yield [%][a]
1	dioxane	25	19.2 ± 1.3	95
2	dioxane	30	11.8 ± 1.4	>99
3	dioxane	40	9.8 ± 0.3	>99
4	dioxane	60	< 1.0	>99
5	ME[b]	30	3.1 ± 0.6	96
6	ME[b]	60	< 1.0	96

[a] Mesitylene was used as the internal standard. [b] ME: 0.60 g C_8G_1, 0.89 mL toluene, 0.77 mL H_2O at $\gamma = 0.26$ and $\alpha = 0.54$.

Conclusion

In order to study the influence of the reaction media, i.e. homogeneous versus nanostructured, on asymmetric Rh-catalyzed nucleophilic additions of triphenylboroxine **2** to *N*-tosylimine **1** we developed synthetic routes towards two series of novel chiral diene ligands based on C_2-symmetrical enantiomerically pure 1,4-diarylbicyclo[3.3.0]octadienes **4a**–**e** and diastereomerically enriched and enantiomerically pure norbornadiene oxazolidinone ligands **5a**–**d**, **6a**–**d** carrying either the Evans auxiliary (**5a**–**d**) or the SuperQuat auxiliary (**6a**–**d**). The diene ligands **4**–**6** differed in their polarity and ligands **5**, **6** possessed an additional binding site for Rh, which led for **5b** to the formation of a mononuclear complex [RhCl(**5b**)]. While toluene and dioxane were the homogeneous reaction media, a microemulsion was used as reaction medium providing not only liquid confinement but also mediated the miscibility between polar and nonpolar reactants. The aqueous domains of the microemulsion are a good solvent for KOH, needed to activate catalyst/ligand system. The hydrophobic reactants *N*-tosylimine **1** and triphenylboroxine **2** dissolve well in the toluene domains, while the catalyst/ligand system, possessing both polar and apolar parts, can reside in/at the amphiphilic surfactant film. Assuming that the bicontinuous

structure allows for the easiest access of the catalyst/ligand system with respect to both KOH and the reactants, we aimed for a microemulsion containing equal amounts of water and oil (i.e. hydrophobic phase). Starting from the well-known microemulsion system of the type H_2O–cyclohexane–pentaethylene glycol monohexyl ether (C_6E_5), cyclohexane was replaced with the more polar toluene. In order to compensate for the shift of the phase boundaries to lower temperature, the surfactant C_6E_5 was partially replaced by the hydrophilic surfactant *n*-octyl β-D-glucopyranoside C_8G_1.

The influence of KOH, catalyst and ligands as well as reactants on the phase behaviour was examined to find the optimal toluene-microemulsion as reaction medium. While the presence of the Rh diene catalysts as well as KOH (low concentration) of had almost no influence on the phase boundaries, *N*-tosylimine **1** and particularly triphenylboroxine **2** showed a strong influence. Using the pendant drop technique, we found that the addition of **2** decreased the water/toluene interfacial tension from 36 mNm^{-1} to 12 mNm^{-1}. This somewhat unexpected effect points to the formation of hydrolysis products as e.g. boronic acid, which rather act as hydrophobic co-surfactants and thus not only decrease the water/toluene interfacial tension but also change the curvature of the amphiphilic film and thus the phase behaviour of the microemulsion system. This effect was compensated replacing the remaining surfactant C_6E_5 with the hydrophilic C_8G_1 to give the reaction microemulsion H_2O/KOH–toluene/*N*-tosylimine **1**/triphenylboroxine **2**–C_8G_1. The length scale of the liquid confinement was determined via SAXS, showing a domain size of the aqueous and toluene/*N*-tosylimine **1**/triphenylboroxine **2** compartments of 55 Å. Considering that the concentration of the catalyst/ligand complex with respect to reactant **1** is 2.5 mol%, on average every second toluene domain contains a catalyst/ligand complex.

The catalyses were strongly dependent on both ligand type and reaction medium. For 1,4-diarylbicyclo[3.3.0]octadienes **4** good yields (up to 87%) and enantioselectivities (>95% *ee*) of

the addition products **3** were obtained irrespective of the polarity of ligand **4** and reaction medium (microemulsion vs dioxane or toluene). The exception were alkyne-terminated ligands **4c**,**d**, which provided moderate yields (≤ 61%), but high enantioselectivities (up to 93% *ee*) of **3** and considerable amounts (up to 30%) of racemic secondary alcohol **13** in dioxane, whereas the microemulsion led to preferred formation of the alcohol **13** (up to 74%) at the expense of amines **3** (up to 32%).

When employing norbornadiene oxazolidinones **5**, **6** catalytic reactions were more sluggishly in dioxane and almost ceased in toluene. Yields and *ee* values showed considerable variations depending on the substitution pattern of the ligands **5**, **6**. In contrast, when the reactions were performed in microemulsions, yields (up to 97%) and enantioselectivities (up to 96% *ee*) increased in most cases. The most pronounced effect of the microemulsions was observed for diastereomerically pure ligands **5d**, **5d'**, which led to improved yields and *matched/mismatched* selectivities. While the preferred configurations of the *matched* cases were similar for microemulsions and dioxane (92% *ee* (*R*) and 94% *ee* (*R*) for **5d**), the *mismatched* cases gave opposite configurations in microemulsions and dioxane (12% *ee* (*R*) and 56% *ee* (*S*) for **5d'**).

The observed rate enhancement of the catalytic reaction by the microemulsion, in particular for ligand **5b** which is less active in dioxane solution as compared to ligands **4** could also be clearly confirmed by kinetic studies, which showed that at T = 60°C the reaction rate in the microemulsion is almost one order of magnitude faster than in dioxane and more than one order of magnitude faster than in toluene, where a yield of only 4% was obtained. Furthermore, performing the 1,2-addition with Rh/ligand **4a** catalyst at T = 30°C, the reaction in microemulsion was 4 times faster than in dioxane.

In conclusion, we have shown for the nucleophilic addition of phenylboroxine **2** to *N*-tosylimine **1** catalyzed by chiral Rh-diene complexes that the liquid confinement provided by micro-

emulsions can improve both reaction rate and enantioselectivity. These experiments will extend the practical use of microemulsions as organized reaction media for other asymmetric catalyses.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis • C–C coupling • diene ligands • kinetics • sugar surfactants

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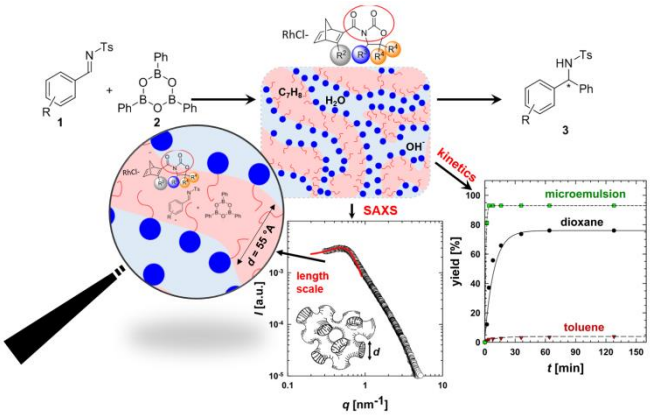
Graphical Abstract



Improved reaction rate and enantioselectivity was realized when microemulsions stabilized by the hydrophilic sugar surfactant *n*-octyl β-D-glucopyranoside (C_8G_1) containing a Rh chiral diene complex and equal amounts of H_2O/KOH and toluene/reactants replaced conventional solutions in asymmetric 1,2-additions of phenylboroxine **2** to *N*-tosylimine **1**. The norbornadiene ligands differ in the substitution pattern and oxazolidinone unit.