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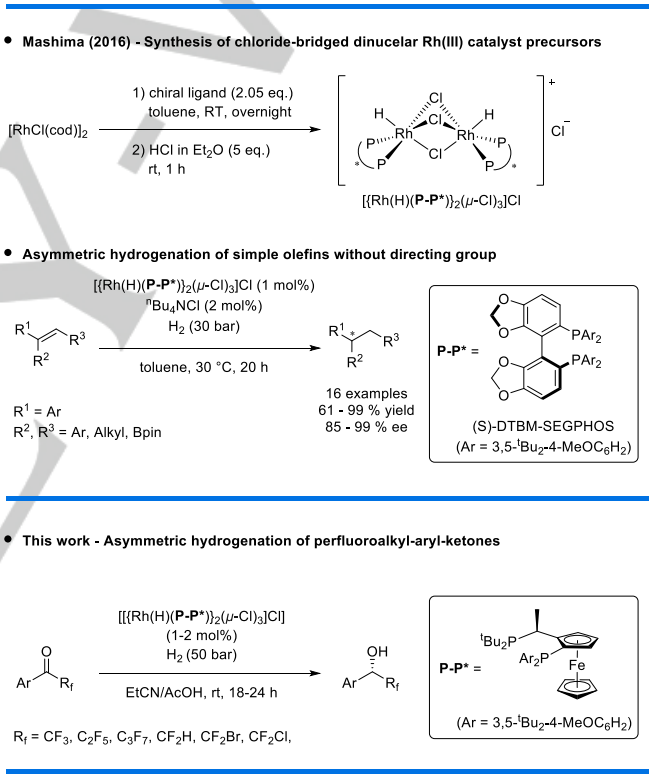
Asymmetric Hydrogenation of Aryl Perfluoroalkyl Ketones Catalyzed by Rhodium(III) Monohydride Complexes Bearing Josiphos Ligands

Fabian Brüning,[a] Haruki Nagae,[b] Daniel Käch,[a] Kazushi Mashima[b] and Antonio Togni*[a]

Abstract: The asymmetric hydrogenation of 2,2,2-trifluoroacetophenones and perfluoroalkyl aryl ketones was developed using a unique, well-defined chloride-bridged dinuclear rhodium(III) complex bearing Josiphos-type diphosphine ligands. These complexes were prepared from $[RhCl(cod)]_2$, Josiphos ligands, and hydrochloric acid. As catalyst precursors they allow for the efficient and enantioselective synthesis (up to 99% ee) of chiral secondary alcohols with perfluoroalkyl groups. This system does not require an activating base for the hydrogenation of 2,2,2-trifluoroacetophenones. Additionally, the enantioselective C=O hydrogenations of 2-phenyl-3-(haloacetyl)-indoles, a class of privileged structures in medicinal chemistry, is reported for the first time.

Chiral secondary alcohols containing a trifluoromethyl group are an important structural motif found in biologically active molecules or as essential intermediates en route to complex molecules.[1–3] Of particular importance is the utilization of 1-aryl-2,2,2-trifluoroethanol derivatives as building blocks in the synthesis of drugs or drug candidates, such as tryptophan hydroxylase inhibitor LX1301.[1,4,5] The rising demand to access such compounds in an enantioselective manner has led to the development of several strategies. For example, contemporary methods include the enantioselective trifluoromethylation of aldehydes,[6] kinetic resolution of racemic 1-aryl-2,2,2-trifluoroethanols[7,8] and enantioselective Hiyama cross-coupling.[9] However, the most efficient and successful method to date is the enantioselective reduction of trifluoromethyl ketones whereby different catalytic methods have been developed. These include chiral oxazoborolidine-catalyzed reductions,[10,11] enzymatic bio-catalysis,[12–14] β-hydrogen transfer with diethylzinc,[15] homogenous transition metal-catalyzed asymmetric hydrogenation (AH) and asymmetric transfer hydrogenation (ATH).[16–19] In contrast to the large number of catalytic methods for the asymmetric (transfer) hydrogenations of non-fluorinated ketones, the hydrogenation of corresponding trifluoromethyl (or perfluoroalkyl) derivatives is largely undeveloped. Indeed, perfluoroalyl ketones are known as low-yielding substrates in classical asymmetric hydrogenation protocols. Not surprisingly, optimized catalytic systems for acetophenones do not proceed efficiently for trifluoroacetophenones and suffer from poor enantioselectivities due to their vastly different stereoelectronic properties.[20–23] In this work, we address this challenge by presenting an efficient protocol for the asymmetric hydrogenation of perfluoroalkyl aryl ketones using rhodium(III) complexes bearing Josiphos-type ligands (Scheme 1).



Scheme 1. Development and application of chloride-bridged dinuclear rhodium(III) complexes.

Historically, although the direct asymmetric reduction of trifluoroacetophenone with hydrogen has been challenging, a few noteworthy advances have been reported. In particular, Noyori reported the successful asymmetric hydrogenation of ketones using a ruthenium catalyst with a chiral diamine ligand in addition to the BINAP-type diphosphine, albeit in need of a strong base and a very limited substrate scope.[18] A study by Iseki and co-workers reports the hydrogenation of trifluoromethyl ketones by a rhodium-(amidophosphine-phosphinite) catalyst. While their catalyst demonstrates excellent yields and enantioselectivities for most substrates, trifluoroacetophenones are only hydrogenated

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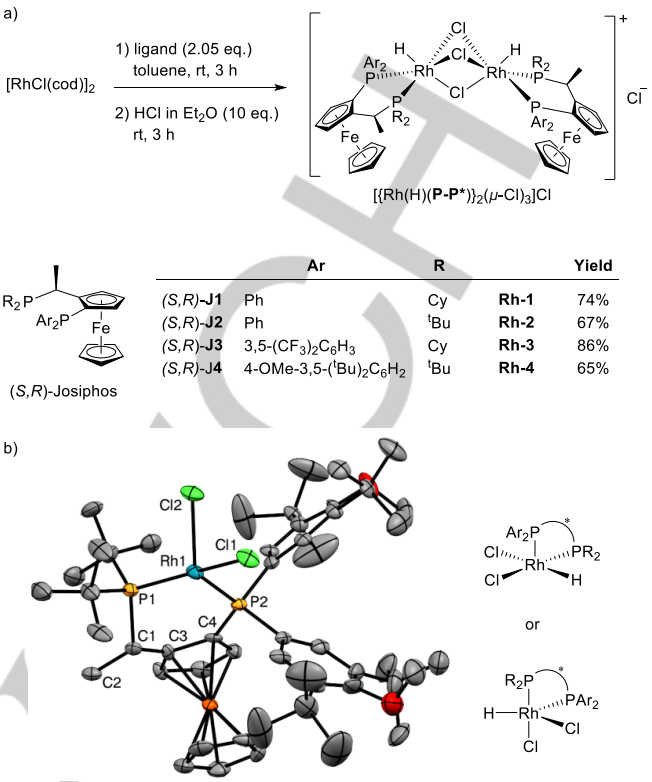
in moderate yields with poor enantioselectivites.[17] Similar results were obtained by Mohar and co-workers who reported the ruthenium-catalysed transfer hydrogenation of fluoroalkyl ketones, yet trifluoroacetophenones could not be hydrogenated with good enantioselectivity.[16]

Recently, the synthesis and application of triply chloride-bridged dinuclear rhodium(III) complexes bearing chiral C_2 symmetric diphosphine ligands such as BINAP and SEGPHOS were reported by Mashima.[24] In analogy to previously developed dinuclear iridium(III) derivatives, these systems display high catalytic activity and enantioselectivity in diverse asymmetric hydrogenation reactions, including that of simple unfunctionalized alkenes.[25–27]

Inspired by the hydrogenation of polar C=N double bonds using Ir(III) monohydride catalysts by Verdaguer and co-workers, we decided to investigate the asymmetric C=O hydrogenation of trifluoroacetophenones using rhodium(III) monohydride systems.[28] We began by expanding the scope of available discrete precatalysts by preparing structurally similar dinuclear rhodium(III) complexes, albeit with Josiphos-type ligands formally replacing BINAP and SEGPHOS (Scheme 2a). The synthesis was carried out by adding ten equivalents of HCl in diethyl ether to a mixture of $[RhCl(cod)]_2$ and 2.05 equivalents of the corresponding chiral ligand in toluene. Rhodium(III) complexes in yields ranging between 65 and 86% could be obtained only in the case of classical Josiphos ligands, i.e. combining a diarylphosphino group directly attached to the ferrocene core with a bulky dialkylphosphino fragment at the stereogenic center. According to both their multinuclear NMR spectroscopic characteristics and NMR diffusion experiments these complexes exist in solution as a single diastereomeric dinuclear monocationic species (see SI for details). However, we were surprised to find by an XRD study that complex $[\{Rh(H)(\mathbf{J4})\}_2(\mu\text{-}Cl)_3]Cl$ exists in the solid state in its dissociated, five-coordinate mononuclear form $[Rh(Cl)_2(H)\mathbf{J4}]$ (Scheme 2b). The position of the hydride ligand could not be determined, hence distorted trigonal bipyramidal or square pyramidal geometries around the rhodium center are in principle possible. Yet, a distorted square pyramidal geometry with the hydride in *trans* position to the slightly elongated Rh-Cl1 bond seems more likely.

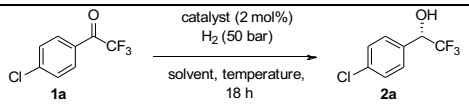
With the catalysts in hand, we began testing their reactivity in the asymmetric hydrogenation of trifluoroacetophenone **1a**. Selected results for the optimization of reaction conditions are shown in Table 1 (for complete tables, see SI). We attempted the reaction with our new catalyst precursors using polar solvents such as DMF and THF at 60 °C, resulting already in quantitative yields but only moderate enantioselectivities of 56% and 35%, respectively (entries 1-2). We were surprised that the reaction proceeded at room temperature in MeCN or EtCN with good enantiomeric excess of 80% and 74%, respectively, albeit in lower yields (entries 3-4). Inspired by the well-studied hydrogenation step in the industrial synthesis of Metolachlor,[29] we anticipated that we could likewise activate the catalysts in AcOH and found that the reaction proceeds smoothly in 72% yield and 44% ee (entry 5). To our surprise, the key to successful enantioselective hydrogenation is the combination of two solvents, an alkyl nitrile and AcOH (entries 6-8).



Scheme 2. Scheme 2. a) Synthesis of chloride-bridged dinuclear Rh(III) complexes and b) molecular structure of the dissociated mononuclear form $[Rh(Cl)_2(H)\mathbf{J4}]$; hydrogen atoms are omitted for clarity. Selected distances (Å) and bond angles (deg): Rh1-P1 2.273(3), Rh1-P2 2.164(3), Rh-Cl1 2.387(3), Rh1-Cl2 2.406(3); P1-Rh1-P2 96.0(1), P1-Rh1-Cl2 97.1(1), Cl2-Rh1-Cl1 88.7(1), Cl2-Rh1-P2 110.5(1), Cl1-Rh1-P1 161.4(1), P2-Rh1-Cl1 98.4(1).

Using these optimized reaction conditions with Rh(III) complexes bearing Josiphos ligands **J1** – **J2**, we obtained only poor enantiomeric excess. Additionally, the reaction did not proceed at all using ligand **J3** (entries 9 - 11).

Table 1. Asymmetric hydrogenation of 4-chloro-trifluoroacteophenone.



Entry[a]	Solvent	Catalyst	T [°C]	Yield [%][b]	ee [%][c]
1	THF	**Rh-4**	60	>99	56
2	DMF	**Rh-4**	60	>99	35
3	MeCN	**Rh-4**	RT	12	80
4	EtCN	**Rh-4**	RT	25	74
5	AcOH	**Rh-4**	RT	72	44
6	MeCN/AcOH (1:1)	**Rh-4**	RT	>99	85
7	EtCN/AcOH (1:1)	**Rh-4**	RT	>99	88
8[d]	^{i}PrCN/AcOH(1:1)	**Rh-4**	RT	77	84
9[d]	EtCN/AcOH (1:1)	**Rh-1**	RT	31	3
10[d]	EtCN/AcOH (1:1)	**Rh-2**	RT	>99	5
11[d]	EtCN/AcOH (1:1)	**Rh-3**	RT	0	n.d.

[a]Reaction conditions: 0.1 mmol of ketone and 0.02 mmol catalyst in 1.0 mL solvent. [b]Determined by ^{19}F-NMR spectroscopy using α,α,α-trifluorotoluene as internal standard. [c]Determined by chiral GC-analysis. [d]1 mol-% catalyst used.

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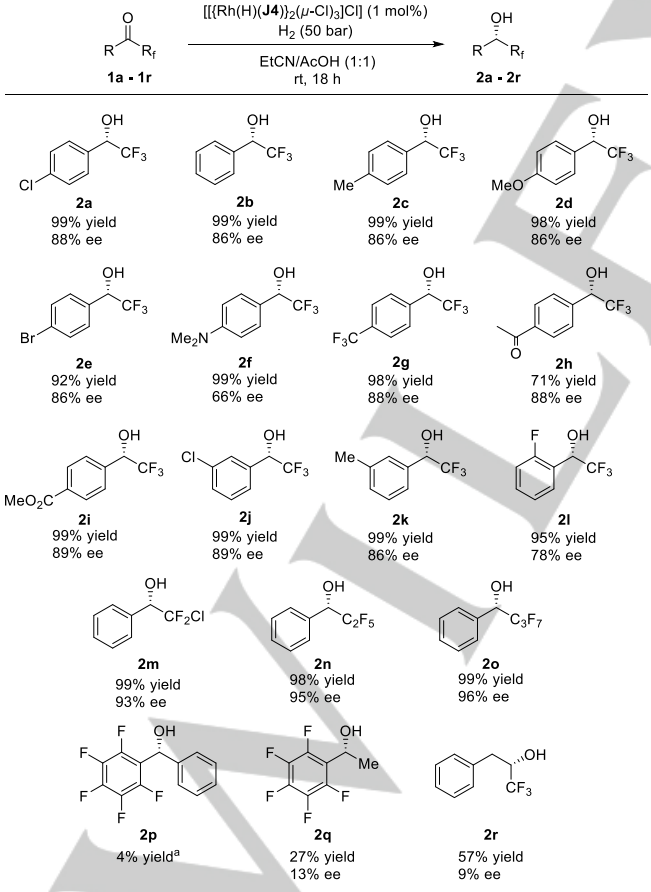
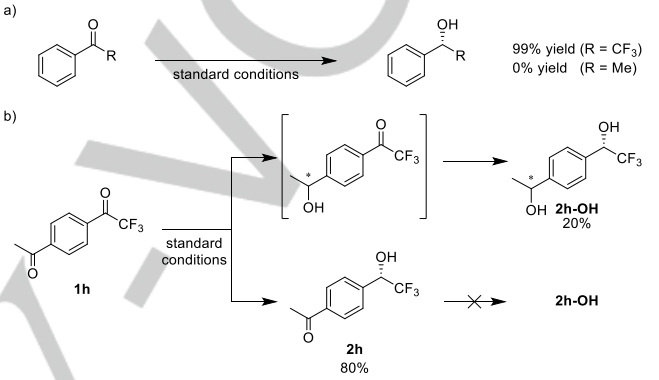
Using the catalyst with ligand **J4,** we next addressed the asymmetric hydrogenation of several trifluoroacetophenones and the results are summarized in Table 2. Simple trifluoroacetophenone and methyl-, methoxy- and bromo *para*-substituted derivatives were efficiently hydrogenated to the corresponding alcohols **2b** – **2e** in excellent yields of 92 - 99% and enantioselectivities of 86% for all substrates. Even a dimethylamino group was tolerated under the reaction conditions and product **2f** was obtained in quantitative yield, albeit only with 66% enantiomeric excess. Trifluoromethyl and acetyl substitution in *para*-position are well tolerated with yields of 98% and 71%, respectively, and 88% ee for both substrates **2g** and **2h**. In addition, a methyl ester was also well tolerated and gave alcohol **2i** in 99% yield and 89% ee. Substrates with *ortho*- and *meta*-substitutions can also be efficiently hydrogenated with good enantioselectivities, as demonstrated by compounds **2j** – **2l**. We then turned our attention to other fluorinated ketones bearing a CF_2Cl, C_2F_5 and a C_3F_7 moiety. Surprisingly, we found that the increased steric demand results in higher enantioselectivities of 93%, 95%, and 96% for substrates **2m**, **2n** and **2o**, respectively. Finally, we attempted to hydrogenate perfluorophenyl ketones, but these afforded the alcohols **2p** and **2q** in 4% and 27% yields only. Similarly, alcohol **2r** was only obtained in 57% yield and 9% ee.

Table 2. Rh-catalyzed asymmetric hydrogenation of perfluoroalkyl aryl ketones.



[a] ^{19}F-NMR yield, ee could not be determined.

The functional group tolerance for the acetyl moiety in substrate **2h** sparked our interest to investigate the selectivity difference between acetophenone and trifluoroacetophenone (Scheme 3). In contrast to trifluoroacetophenone providing the corresponding alcohol **2b** in quantitative yield, we did not observe any reactivity with the non-fluorinated analogue (Scheme 3a). Closer investigation of the hydrogenation towards alcohol **2h**, however, revealed the formation of diol **2h-OH** in up to 20% yield. As alcohol **2h** cannot be further hydrogenated to **2h-OH** under our reaction conditions (Scheme 3b), the formation of the diol must proceed via the corresponding 1-(4-trifluoroacetylphenyl)-ethanol, the formation of which can be attributed to the strongly electron withdrawing trifluoroacetyl group in *para* position.



Scheme 3. a) Reactivity comparison of trifluoroacetophenone and acetophenone. b) Selectivity in the hydrogenation of 4-acetyl-trifluoroacetophenone. Standard conditions: 1 mol-% [{Rh(H)(**J4**)}$_2$(μ-Cl)$_3$]Cl, AcOH/EtCN (1:1), H_2 (50 bar), rt, 18 h. Yields were determined by ^{19}F NMR spectroscopy.

Following the asymmetric hydrogenation of various fluorinated acetophenones, we turned our attention to indoles, a particularly important class of heteroarenes. 3-Substituted-2-phenylindoles have been recognized as privileged structures in medicinal chemistry with a broad biological activity profile for G protein-coupled receptor modulation.[30,31] The available synthetic methods for the installation of the stereogenic, (trifluoromethyl)hydroxymethyl group at position 3 of indoles are presently limited to a radical cross-dehydrogenative coupling[32] and an enantioselective Friedel-Crafts reaction of indoles with trifluoroacetaldehyde, catalyzed by cinchona alkaloids.[33] The latter approach, however, provides only very low enantioselectivities. Hence, we decided to start our investigation with the asymmetric hydrogenation of 3-trifluoroacetyl-2-phenylindole **3a**, as there are no reported enantioselective procedures for the synthesis of the corresponding model alcohol **4a**. We obtained **4a** in excellent yield of 98% and 88% enantiomeric excess using 2 mol-% catalyst in EtCN (Table 3) while the previous reaction conditions using EtCN and AcOH as solvents gave unsatisfactory results (see SI for full optimization data). We further examined the influence of substitution at position 2 of the indole and found decreased yields and enantioselectivities of only 62% and 73% for indoles **4b** and **4c** bearing no substituent or only a methyl group, whereas for 2-naphthyl and ^{t}Bu groups the corresponding products **4d** and **4e** were both obtained in good ee of 87% and 86%. Remarkably, *N*-

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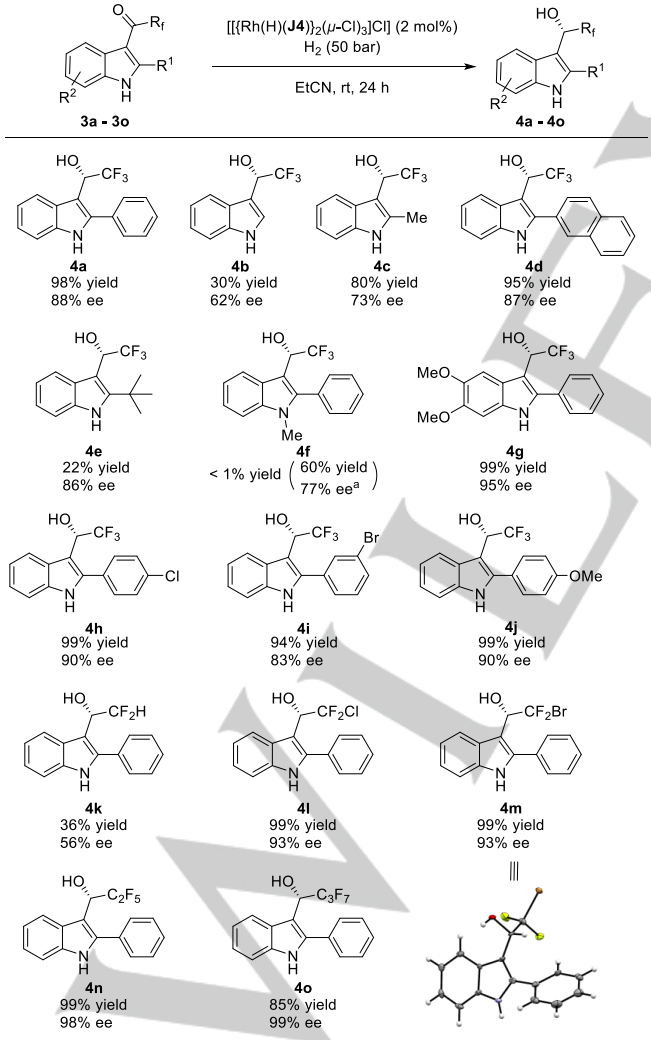
methyl protected indole **4f** could not be obtained under our reaction conditions but was formed in 60% yield and 77% ee upon addition of AcOH. Dimethoxy substituted indole **4g** was obtained in an excellent 99% yield and 95% ee. In addition, halogen- or methoxy substitution on the phenyl ring, as for substrates **4h** – **4j** was well tolerated giving excellent yields. Next, we addressed different fluoroalkyl ketones using the 2-phenylindole scaffold including 3-difluoroacetyl-2-phenylindole that was obtained in 36% yield and 56% ee. Increasing the size of the fluoroalkyl group to -CF_2Cl or -CF_2Br, led to quantitative yields and an increase in enantiomeric excess to 93% for both substrates. Even higher enantiomeric excesses of 98% and 99% were obtained for indoles **4n** and **4o** bearing sterically more demanding -C_2F_5 and -C_3F_7 fragments. The increase in enantiomeric excess seemingly correlates with the size of the fluoroalkyl group on the ketone, as we had similarly observed for acetophenone-type substrates. The absolute configuration of all indoles was determined to be *S* when utilizing catalysts with (*S,R*)-Josiphos ligands, as determined by single crystal analysis of substrate **4m** and comparison of the optical rotation with literature data for indole **4b.**[33]

Table 3. Asymmetric hydrogenation of 3-(trifluoroacetyl)-2-arylindoles and related substrates.



[a]Previous conditions - EtCN/AcOH and 1 mol% catalyst used.

Conventionally, asymmetric hydrogenations of polar C=O double bonds are associated with Ru catalysts, whereas Rh catalysts play a pivotal role in the AH of C=C double bonds with a directing group.[34] Noteworthy, these reactions involve a rhodium(I) complex and proceed via their corresponding *in-situ* generated rhodium(III) dihydride species. However, the behaviour of the dinuclear rhodium(III) monohydride species reported herein is significantly different from that of the well-established rhodium(I) catalysts. By monitoring the yield as a function of time, we found a rather long induction period of the reaction of about five hours. (see SI). This induction period is not observed, when the catalyst is stirred in the solvent under an argon atmosphere overnight before applying hydrogen pressure. Based on the previously reported mechanisms for the dinuclear iridium(III)-catalyzed asymmetric C=N hydrogenations[35–37] and investigations of alkene insertion into the Rh-H bond,[38] we propose that a plausible mechanism could involve a similar catalytic cycle. Accordingly, the dinuclear rhodium species slowly dissociates to form mononuclear species possibly stabilized by the nitrile solvent. The ketone coordinates to the catalytically active mononuclear complex (see Scheme 2b) followed by insertion into the Rh-H bond. The resulting intermediate alcoholato complex reacts with H_2 by heterolytic hydrogen activation to generate the product and the Rh(III) catalyst. Considering the dependency of the enantiomeric excess on the nitrile ranging from zero to 88%, it is reasonable to assume that a nitrile molecule acts as a ligand during the reaction, whereas a chloride ligand dissociates. This is consistent with the observation that a chloride additive such as tetrabutylammonium chloride reduces the activity of the catalyst. Furthermore, the Rh(III) complex with ligand **J3** bearing electron withdrawing substituents on one phosphine demonstrated no reactivity in comparison with the strongly electron donating substituents on **J4**, favourable for a cationic Rh(III) intermediate. As this mechanistic hypothesis is still speculative, further detailed mechanistic investigations are currently underway in our laboratory.

In conclusion, we have developed a series of chloride-bridged dinuclear rhodium(III) complexes bearing Josiphos-type ligands. The complexes were used as catalyst precursors for the asymmetric hydrogenations of trifluoroacetophenones and similar perfluoroalkyl aryl ketones with excellent yields, chemoselectivity, and enantioselectivities under mild reaction conditions. The optimized Rh-catalyst was applied to the asymmetric hydrogenation of 3-(haloacetyl)-2-arylindoles, providing the first efficient enantioselective protocol for the synthesis of the corresponding alcohols. By extending alkene hydrogenation to the C=O bond of acetyls, we underscore the versatility of bridged dinuclear rhodium(III) compounds in catalytic asymmetric hydrogenations.

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Keywords: Asymmetric Catalysis • Hydrogenation • Rhodium • Trifluoroacetophenone • Josiphos

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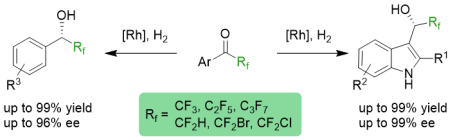

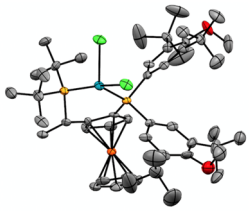

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Asymmetric Hydrogenation of Aryl Perfluoroalkyl Ketones Catalyzed by Rhodium(III) Monohydride Complexes Bearing Josiphos Ligands

Dinuclear Rh(III) monohydride complexes bearing Josiphos-type ligands have been developed. These complexes serve as catalyst precursors for the efficient enantioselective carbonyl hydrogenation of trifluoroacetophenones. Related perfluoroalkyl aryl ketones and 3-(haloacetyl)-2-arylindoles are viable substrates, affording the corresponding secondary alcohols in high yield and enantiomeric excess.