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Enantioselective Hydrogenation of Enones with a Hydroformylation Catalyst

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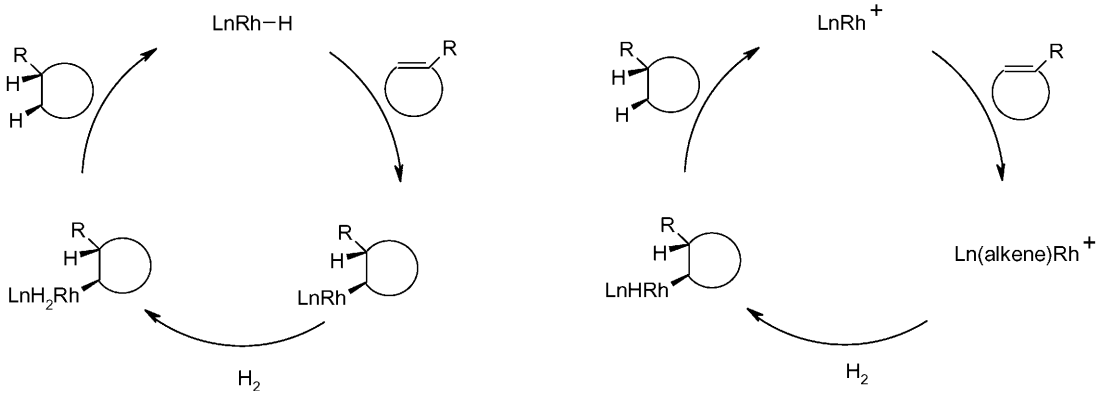
Abstract: Use of a typical rhodium precatalyst for hydroformylation results in the enantioselective hydrogenation of cyclic enones with up to 90% *ee*. Extensive screening of chiral ligands reveals the simple ligand Chiraphos as the best ligand, so far. The hydrogenation shows high chemoselectivity. Exclusive formation of saturated, chiral β-branched ketones is observed. It is proposed that the catalyst follows a frustrated hydroformylation pathway ("monohydride-based mechanism") and differs by that from the classical cationic Schrock–Osborn type rhodium precatalysts ("dihydride-based mechanism") for enantioselective hydrogenation. The catalyst operates under neat conditions and is easily recyclable by simply distilling off the reaction mixture and treatment with syn gas prior to hydrogenation.

Keywords: enantioselectivity; enones; hydroformylation; hydrogenation; isophorone; rhodium

Homogeneous enantioselective hydrogenation has been developed into an efficient tool for the generation of chiral compounds. Chiral rhodium, iridium- and ruthenium-containing catalysts have been especially effective, even for large-scale industrial applications.[1] Historically, achiral rhodium-based hydrogenation catalysts have been divided into two distinct categories, namely catalysts operating *via* either a mechanism in which the hydrogen atoms of the products are delivered from the same hydrogen molecule, or a mechanism in which those hydrogen atoms originate from two different hydrogen molecules. In the literature, those mechanisms have been termed "dihydride-based" mechanism and "monohydride-based" mechanism to account for the observation that the insertion step occurs either at a rhodium dihydride or monohydride intermediate, respectively (Scheme 1).[2]

Remarkably, the two mechanisms also differ from a stereochemical perspective. For the dihydride-based mechanism, detailed experimental evidence demonstrates that the enantioselection typically occurs within a square-planar or octahedral complex geometry with the substrate coordinated in a rigid bidentate



Scheme 1. Monohydride-based *vs.* dihydride-based mechanism.[3]

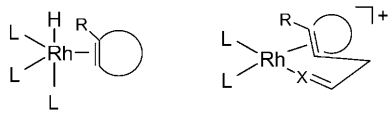


Figure 1. Supposed geometries of Rh-alkene complexes following a mono- or dihydride-based mechanism.

fashion.[4] In contrast to this, it could be expected that enantioselection following a monohydride-based mechanism occurs within a trigonal-bipyramidal geometry, having a single point coordination to the substrate (Figure 1).[2a,5]

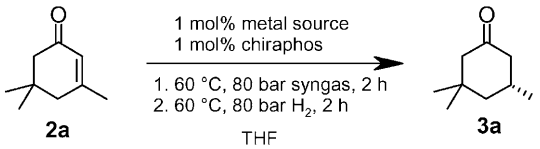
Thus, utilizing the dihydride-based mechanistic manifold, broadly applicable methods for the generation of chiral compounds have been elaborated. Possibilities arising from employing a monohydride-based mechanism for rhodium-catalyzed enantioselective hydrogenations have been exploited to an almost negligible extent.[6,7]

Herein,[8] we report on a first exploitation of a monohydride-based mechanism for the Rh-catalyzed enantioselective hydrogenation.[9,10] We focus on the chemo- and enantioselective hydrogenation of enones to saturated, chiral ketones. This class of substrates is not a preferred class of substrates for Rh-catalyzed enantioselective hydrogenation and the chiral products have since recently[11] only been readily accessible *via* reductions employing high molecular mass hydride donors, such as silanes, borohydrides or dihydropyridines.[12,13]

Initially, we screened various rhodium complexes as suitable precursors for the hydrogenation of isophorone, making use of the readily available chiral ligand Chiraphos (Table 1).[14] The anticipated hydrido-carbonyl species was first generated by a protocol used for the activation of hydroformylation catalysts, i.e., treatment with syn gas.[15] After changing the atmosphere to hydrogen, $[Rh(acac)(CO)_2]$ proved to be the best suited precursor giving the highest conversion and high selectivity. Gratifyingly, the catalyst showed complete chemoselectivity. We were unable to observe any other hydrogenated products such as, for example, allylic alcohols.

Interestingly, no hydrogenation was observed using either high concentrations of carbon monoxide or no carbon monoxide (entries 5 and 6). Thus, we conclude

Table 1. Metal screening.



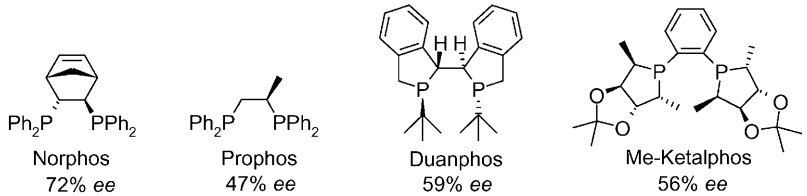
Entry	Metal source[a]	*ee* [%]	Conversion [%]
1	$Rh(CO)(PPh_3)_3H$[b]	(*R*)-90	3
2	[Rh(acac)(cod)]	n.d.[d]	1
3	$Rh_4(CO)_{12}$	(*R*)-77	9
4	$[Rh(acac)(CO)_2]$	(*R*)-88	17
5	$[Rh(acac)(CO)_2]$[b]	–	–
6	$[Rh(acac)(CO)_2]$[c]	n.d.[d]	1
7	$[Rh(cod)_2]BF_4$	–	–
8	$[Ir(acac)(CO)_2]$	–	–

[a] 1 mol% metal, 1 mol% of (*R*,*R*)-Chiraphos, THF, 60 °C, 80 bar syn gas, 2 h. Then 80 bar, 60 °C, H_2, 2 h.
[b] 1 mol% Rh, 1 mol% of (*R*,*R*)-Chiraphos, THF, 60 °C, 80 bar CO/H_2 1:1, 2 h.
[c] 1 mol% Rh, 1 mol% of (*R*,*R*)-Chiraphos, THF, 60 °C, 80 bar H_2, 2 h.
[d] n.d. not determined.

that for the formation of the catalytically active species the presence of CO as a ligand is essential, while an excess of CO inhibits the reaction (*vide infra*). Using a cationic Schrock–Osborn-type precursor or switching the metal to iridium gave no conversion under our reaction conditions.

With the aim of identifying the best metal/ligand combination, a set of structurally diverse ligands was screened using $[Rh(acac)(CO)_2]$ as the metal source. To our surprise, Chiraphos[16] still showed the highest enantioselectivity and only a few other ligands, sharing the 1,2-diphosphinoethane motif with Chiraphos showed some selectivity (Scheme 2).

Reaction conditions such as hydrogen pressure or choice of solvents often show a marked influence on the selectivity and the rate of rhodium-catalyzed enantioselective hydrogenations. Especially the variation of pressure is known to even, in some cases, invert the chiral induction of rhodium catalysts. Using our system, no dependence of the *ee* on the hydrogen pressure between 20 to 80 bar was observed, while the rate of the reaction steadily increases with in-



Scheme 2. Representative results from ligand screening.

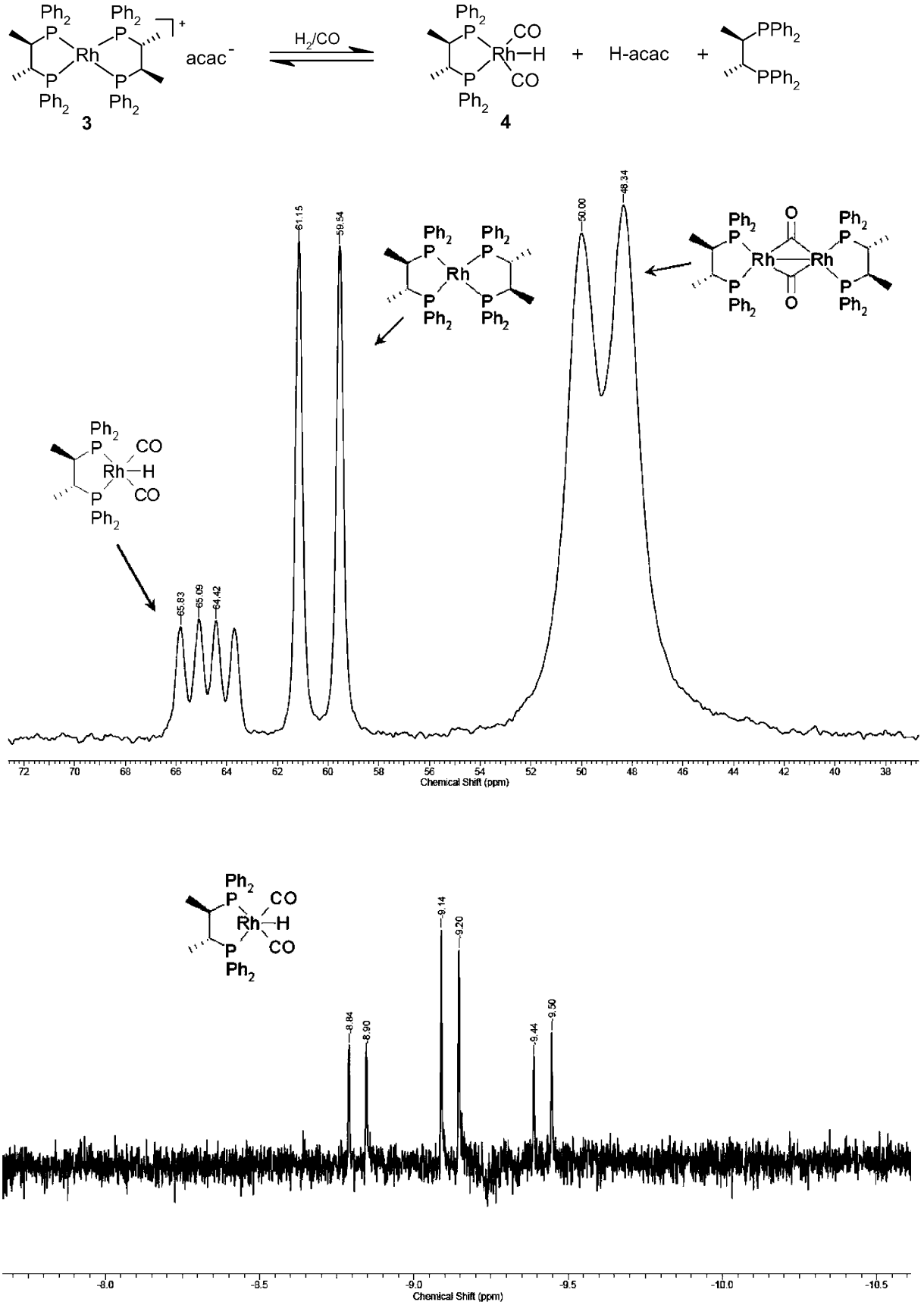


Figure 2. High pressure ^{31}P- and ^{1}H NMR spectra of [Rh(acac)$(CO)_2$] with Chiraphos (10 bar CO/H_2 1:1).

creased pressure.[17] At lower pressures the rate of the reaction prevents the estimation of the enantiomeric excess of the product.

By investigating the solvent dependence of the reaction, we observed almost no effect of the solvent on the selectivity of the reaction. In addition, using THF, we observed over a wide range of concentrations no change in the enantioselectivity of the reaction. Even by performing the reaction without solvent, isophorone is hydrogenated with the same *ee* as in diluted solutions. Interestingly, the rate of the reaction was not accelerated much.

Claver et al. recently reported an *in situ* study on hydroformylation catalysts for the enantioselective hydroformylation of styrene, employing ^{31}P NMR at elevated pressure. There, various rhodium species containing Chiraphos as a ligand have been characterized.[15] We were interested to see whether we could also observe these intermediates under our conditions.

After charging a concentrated sample of [Rh(acac)(CO)$_2$] and Chiraphos with syn gas, the spectrum revealed, besides the expected hydridodicarbonyl compound **4** ($\delta = 64.8$ ppm, dd, $J_{P,Rh} = 113$ Hz, $J_{P,H} = 59$ Hz). also the very stable cation **3** ($\delta =$ 60.3 ppm, d, $J_{P,Rh} = 129$ Hz). In addition, due to the high concentration necessary for the NMR experiment, the carbonyl-bridged dimer could also be observed ($\delta = 49.2$ ppm, d, $J_{P,Rh} = 133$ Hz). The ^{1}H NMR spectrum shows the hydride signal at high field ($\delta =$ -9.17 ppm, dt, $J_{H,Rh} = 12$ Hz, $J_{H,P} = 59$ Hz) (Figure 2). We have not been able to detect a bis-Chiraphos rhodium hydride, as has been reported by Claver et al. This might relate to the use of acetylacetonate as a counter-ion instead of the more basic methoxide as used in Claver's work.[15] This hydride would be an intermediate of the equilibrium shown in Figure 2.

On inspecting the proposed pressure-dependent equilibrium between the rhodium complexes **3** and **4**, we reasoned that if **3** is the dominant species under vacuum and elevated temperature and **4** is readily formed under syn gas, the catalyst should, in principle, be recyclable. This feature is not common for enantioselective hydrogenation catalysts but is certainly highly useful, especially in the context of continuous processing using rather slow catalysts.

To explore this possibility, we simply distilled off the product/solvent mixture after hydrogenation under reduced pressure and submitted the remaining brown-red solid to another activation-hydrogenation cycle. Following this procedure, the catalyst shows identical conversion and selectivity after 3 runs (Table 2).

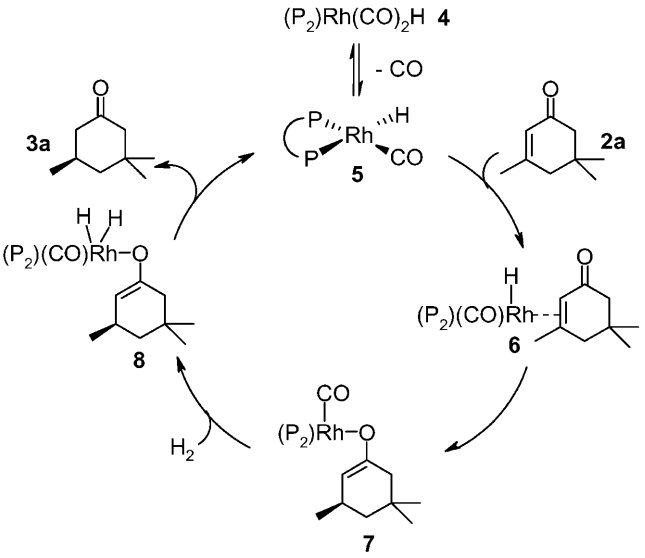
Based on the available data so far, we propose the following catalytic cycle (Scheme 3).[18]

Dissociation of one CO molecule from the 18-electron resting state **4** and coordination of the substrate

Table 2. Recycling experiments of catalyst **1** with isophorone.

Run	*ee*[a] [%]	Conversion [%]
1	(*R*)-89	24
2	(*R*)-89	17
3	(*R*)-89	24

[a] 1 mol% [Rh(acac)(CO)$_2$], THF, 60 °C, 80 bar syn gas, 2 h. Then 80 bar H_2, 60 °C, 2 h.



Scheme 3. Proposed catalytic cycle.

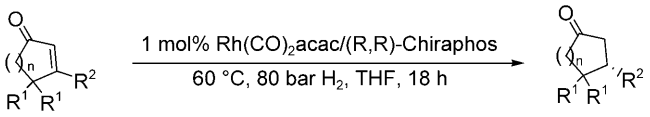
via the double bond of the enone results in a hydridoalkene complex **6**, which, after subsequent insertion of the enone into the Rh–H bond, forms a rhodium enolate **7**.[5,19,20] Rate-limiting hydrogenolysis regenerates the monohydride **5.**

We have further investigated the utility of this catalyst by testing its scope towards other α,β-unsaturated ketones (Table 3).

Isophorone gives the highest enantiomeric excess (Table 3, entry 1). Removing the methyl groups in the 5-position reduces the enantiomeric excess to 79%. Alkyl groups larger than Me as substituents at the 3-position showed lower selectivities, while aryl substituents, e.g., Ph or *p*-Tol, in the 3-position lead to a significant decrease in the observed *ee*. The ring size of the α,β-unsaturated ketones also had an effect on conversion and *ee* of the resulting saturated ketone. In general, using cyclopentenones slightly higher conversion and *ee* could be achieved.

In conclusion, the results of this study reveal a new mechanistic alternative for exploitation in enantioselective rhodium-catalyzed hydrogenations. We have utilized this in a first useful application for the enantioselective hydrogenation of β-substituted cyclic enones, substrates not suitable for two-point coordination. The catalytic system shows high chemo- and

Table 3. Hydrogenation of α,β-unsaturated cyclohexenones and cyclopentenones using $Rh(CO)_2H(R,R)$-Chiraphos.



2a – 2j **3a – 3j**

Entry	Educt	Product	n	R^1	$R^{2[a]}$	*ee*[c] [%]	Conversion [%]
1	**2a**	**3a**	2	Me	Me[b]	(*R*)-90	100
2	**2b**	**3b**	2	H	Me	(*R*)-79	78
3	**2c**	**3c**	2	H	Et	(*R*)-55	100
4	**2d**	**3d**	2	H	*n*-Bu	(*R*)-60	10
5	**2e**	**3e**	2	H	*i*-Bu	(*S*)-75	18
6	**2f**	**3f**	2	H	Ph	(*S*)-49	11
7	**2g**	**3g**	2	H	*p*-Tol[b]	(*S*)-41	85
8	**2h**	**3h**	1	H	Me	(*R*)-86	79
9	**2i**	**3i**	1	H	*n*-Bu	(*R*)-73	52
10	**2j**	**3j**	1	H	Ph	(*S*)-41	100

[a] 1 mol% $[Rh(acac)(CO)_2]$, 1 mol% of (*R*,*R*)-Chiraphos, THF, 80 bar syn gas, 60 °C, 2 h. Then 80 bar H_2, 60 °C, 18 h.

[b] 1 mol% $[Rh(acac)(CO)_2]$, 1 mol% of (*R*,*R*)-Chiraphos, THF, 60 °C, 80 bar syn gas, 60 °C, 2 h. Then 80 bar H_2, 72 h.

[c] Absolute configuration established for **3a** (see Supporting Information); other absolute configurations tentatively assigned according to **3a**.

quite useful enantioselectivities, while activity still needs improvement. The here described precatalyst shows two remarkable features, which differentiate it from established chiral cationic Rh catalysts. First, the enantioselectivity is insensitive to solvents and the catalyst operates even under neat conditions. Second, it forms a stable complex after pressure release which is easily activated again for subsequent hydrogenations. Thus, the precatalyst is easily recyclable. We believe that these features are derived from inherent properties of the monohydride-based mechanism for Rh-catalyzed hydrogenations, complementing the traditionally employed dihydride based mechanism.

Future work will focus on improving reactivity and selectivity of the catalytic system, as well as broadening the scope of the reaction towards alternative substrates.

Experimental Section

Preparation of the Active Precatalyst $RhH(CO)_2$[(*R*,*R*)-Chiraphos]

$[Rh(acac)(CO)_2]$ (148 mg, 5.7 mmol) and (*R*,*R*)-Chiraphos (320 mg, 7.41 mmol) were dissolved in THF (20 mL) in an autoclave under argon. The mixture was then stirred under syn gas (CO/H_2 1:1) at 60 °C for 2 h. After release of pressure, the solution can be used directly for hydrogenations. ^{31}P NMR (THF, 81 MHz): $\delta = 64.8$ (q, $J_{P,Rh} = 113$ Hz, $J_{P,H} = 59$ Hz, **4**), 60.3 (d, $J_{P,Rh} = 129$ Hz, **3**), 49.2 (d, $J_{P,Rh} = 133$ Hz, carbonyl-bridged dimer); ^1H NMR (THF, 200 MHz): $\delta = -9.17$ (dt, $J_{H,Rh} = 12$ Hz, $J_{H,P} = 59$ Hz).

General Procedure for the Enantioselective Homogeneous Hydrogenation

In the glove-box the precatalyst solution (0.142 mmol in 5 mL of THF) was added to a solution of the substrate (14.2 mmol) dissolved in anhydrous THF (20 mL), this mixture was then filled into an autoclave and sealed under an inert atmosphere. The autoclave was then transferred to the autoclave station, the system was flushed with hydrogen 3 times, charging to 80 bar each time. The system was finally sealed under 80 bar pressure of H_2 and heated at 60 °C for 18 h unless otherwise stated. The GC samples were prepared by using 8 drops of the resulting solutions which were then filtered through a pipette containing neutral alumina which was washed with HPLC grade toluene.

(*R*)-3,5,5-Trimethylcyclohexanone

The precatalyst mixture and isophorone were heated under hydrogen gas (80 bar) at 60 °C for 72 h to provide the title compound (100% conversion, 90% *ee*). The physical data were identical to those of the commercially available 3,5,5-trimethylcyclohexanone. The enantiomeric ratio was determined by chiral GC using a 174-BGB (50 m × 0.25 mm) column (130 °C isotherm) $T_R = 5.332$ min (minor), 5.426 min (major). $[\alpha]_{578}^{20.0}$: −19.7° (*c* 1.170, $CHCl_3$).

Supporting Information

Detailed results from the ligand screening, kinetic data, details of the recycling procedure and characterization data for compounds **3b**–**3j** are available in the Supporting Information.

Acknowledgements

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