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Improved synthesis of $Bn_5CpRu(CO)_2Cl$ and its application as racemization catalyst in preparative-scale metalloenzymatic dynamic kinetic resolution of 1-phenylethanol*

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Abstract: An improved gram-scale synthesis of $Bn_5CpRu(CO)_2Cl$ is reported based on heating of pentabenzylcyclopentadiene with $Ru_3(CO)_{12}$ at 160 °C under argon atmosphere in mesitylene followed by addition of chloroform, continued heating, and evaporation of the solvents. Subsequent washing of unreacted ligand precursor with hexane provided pure title compound in 77 % yield. In combination with *Candida antarctica* lipase B (CAL-B) (Novozym 435), this complex forms a highly active racemization catalyst for metalloenzymatic dynamic kinetic resolution (DKR) of secondary alcohols as demonstrated in the present work by converting 100 g of racemic 1-phenylethanol to (*R*)-1-phenylethanol in >99 % ee and 93 % overall yield over two steps using 0.05 mol % loading of the metal catalyst and 1 mass % loading of immobilized enzyme. In addition, the synthesis and crystallographic characterization of the palladium congener $Bn_5CpPd(PPh_3)Cl$ are briefly discussed.

Keywords: chemoenzymatic synthesis; cyclopentadienyl; dynamic kinetic resolution (DKR); Novozym; ruthenium.

INTRODUCTION

Optically active secondary alcohols are important building blocks in organic synthesis [1]. Consequently, a broad variety of methods have been developed for their preparation. The commonly utilized asymmetric hydrogenation is, however, not optimal for aryl-alkyl ketones due to the relatively high price of chiral ligands, low tolerance for reducible functional groups, and the often moderate enantioselectivities [2]. Enzymatic kinetic resolution of *sec*-alcohols by use of lipase-catalyzed enantioselective acylation is in some cases an economically feasible alternative providing products of high enantiopurity [3].

Enzymatic acylation of alcohols (Scheme 1) can be performed with a broad variety of acyl donors [3c]. Conventional esters (such as ethyl acetate) are low-priced but require large excesses in order to shift the equilibrium toward the desired product. Some of the so-called "activated" esters react irre-

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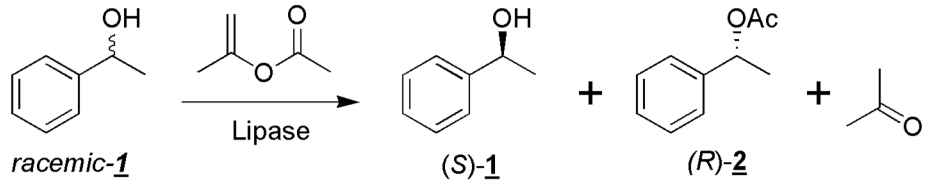
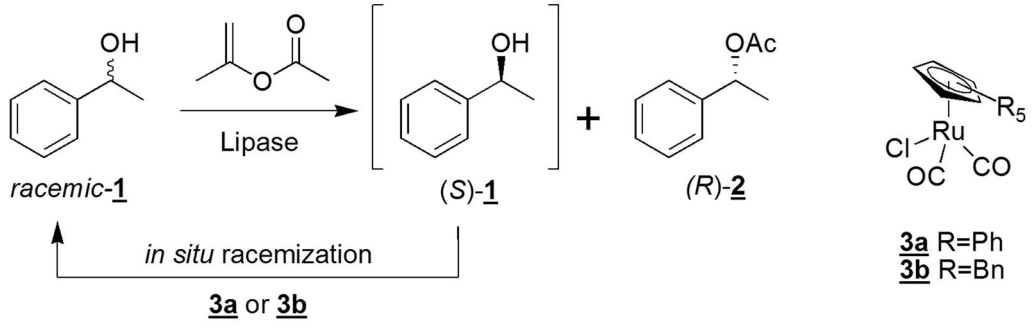


Scheme 1 Enzymatic kinetic resolution of *sec*-alcohols.

versibly. Unsaturated enol acetates (vinyl acetate and isopropenylacetate) are the most utilized among this class of acyl donors. They are readily available and generate carbonyl compounds upon transesterification, which renders the reaction irreversible. Isopropenyl acetate is more preferable since it generates the relatively unreactive acetone as a side product. Of the enzymes most commonly utilized, CAL-B (*Candida antarctica* lipase B) does not require cofactors, can be used in organic solvents, and possesses high activity and enantioselectivity. Novozym 435 is an immobilized form of CAL-B on polyacrylic resin. It is often used in organic synthesis due to its stability and simplicity of operation [4].

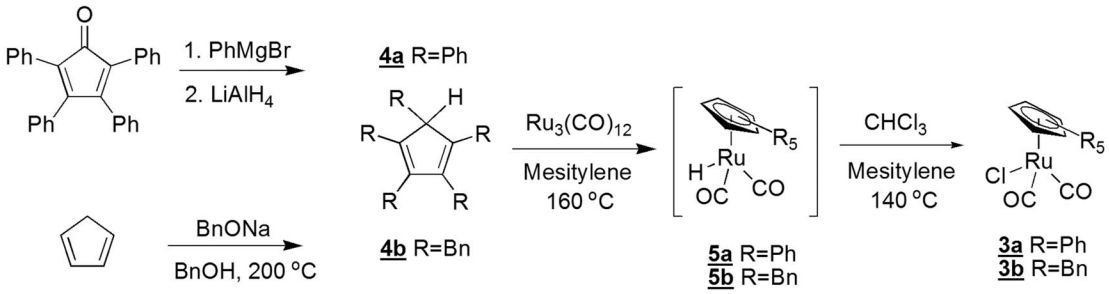
The lipase-catalyzed kinetic resolution of rac-**1** with isopropenyl acetate as the acyl donor proceeds quickly and smoothly, optimally providing a mixture of (*R*)-**2** and unreacted (*S*)-**1**. The proximity of the boiling points of the starting alcohol **1** (204 °C) and the product **2** (213 °C) makes the separation of products by distillation problematic. Furthermore, separation of these compounds by chromatography or, alternatively, by derivatization of the unreacted alcohol is not cost-efficient in large scale.

In metalloenzymatic dynamic kinetic resolution (DKR) (Scheme 2), pioneered by Williams [5], Bäckvall [6], and others, the less reactive enantiomer (*S*)-**1** is racemized in situ with a transition-metal catalyst such as **3a** allowing conversions approaching 100 % [7]. In this case, the sole product (*R*)-**2** formed can be easily separated by distillation. The volatile solvent and acyl donor are likewise removed as a forerun during distillation. The catalyst is nonvolatile, and the immobilized enzyme used can be separated by filtration. Several transition-metal catalysts have been utilized for racemization of *sec*-alcohols [8] with the most prominent examples based on cyclopentadienyl-ligated half-sandwich ruthenium complexes [8,9]. In particular, the (pentaphenylcyclopentadienyl)ruthenium complex **3a** disclosed by Bäckvall and co-workers racemizes alcohols within minutes in the presence of enzymes providing high ee's and yields for a wide variety of *sec*-alcohols and diols [9b]. Phenyl subsitutents on the cyclopentadienyl ligand appear to be essential for high racemization activity. The racemization mechanism is based on reversible transfer of hydride involving catalyst activation by potassium *tert*-butoxide followed by alcohol-alkoxide exchange, ketone formation, hydride transfer, and subsequent release of racemic alcohol, although the exact pathway has not been fully clarified [10].



Scheme 2 DKR of *sec*-alcohols.

In a recent communication, we briefly reported the synthesis of the pentabenzylcyclopentadienyl ruthenium complex **3b** and its preliminary screening in the DKR of 1-phenyl- and 1-(furan-2-yl)ethanols [11] (Scheme 3). In combination with CAL-B, complex **3b** forms a highly active racemization catalyst for chemoenzymatic DKR providing, for both model substrates, yields and ee's comparable to the best ruthenium catalysts reported in the literature [9a,b]. An additional benefit of catalyst **3b** is the simple preparation of its ligand precursor **4b**, conveniently performed in large scale by alkylation of cyclopentadiene with benzyl alcohol under basic conditions facilitated by azeotropic water removal, as originally described by Hirsch and Bailey [12] and later optimized by Rausch and co-workers [13]. This procedure is both simple and cost-efficient in comparison with the preparation of other polyalkylated or arylated cyclopentadienyl ligands [14]. In the present work, we report an improved synthesis of **3b** in gram scale based on purification by simple washing work-up procedure, which provides pure metal complex in 77 % yield, together with the application of this precatalyst in molar-scale metalloenzymatic DKR of 1-phenylethanol at low catalyst loading. In addition, the synthesis and crystallographic characterization of the palladium congener $Bn_5CpPd(PPh_3)Cl$ are briefly discussed.



Scheme 3 Preparation of the racemization catalysts.

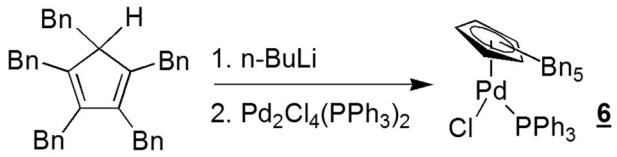
RESULTS AND DISCUSSION

Chlorodicarbonylcyclopentadienyl ruthenium complexes can be prepared by one-pot chlorination of the corresponding hydrides obtained from the reaction of the ligand precursor with ruthenium carbonyl [9b,11]. Such metallation reactions are seldom quantitative and commonly require separation of the unreacted ligand from the metal complex by chromatography or crystallization. Due to the poor solubility of polyarylcyclopentadienyl ligands, the isolation of the corresponding ruthenium complexes is often tedious. Purification by crystallization often results in contamination of the metal complex by small amounts of ligand. Column chromatographic separation on silica in turn requires large amounts of eluent in order to remove the poorly soluble unreacted ligand having R_f value higher than its metal complex. Beneficially, and in contrast to most polyarylated cyclopentadienyl ligand precursors, pentabenzylcyclopentadiene **4b** is highly soluble in common organic solvents. In our earlier report, complex **3b** was initially purified by column chromatography providing the pure ruthenium precatalyst in 53 % yield [11]. In the present work, an improved chromatography-free purification method was sought, which ideally would provide the pure metal complex in multigram scale either by washing of the unreacted and highly soluble ligand precursor with a suitable solvent or, alternatively, by crystallization from a suitable solvent.

Pentabenzylcyclopentadiene **4b** was prepared by reaction of dicyclopentadiene with benzyl alcohol following the improved procedure of Rausch [13b]. Heating of **4b** with $Ru_3(CO)_{12}$ in a sealed tube under argon atmosphere at 160 °C for three days in mesitylene was followed by purging of the CO formed and additional heating for seven days. Subsequent addition of a small amount of chloroform and continued heating for one day provided, after filtration and removal of the solvents, the crude chloro-

dicarbonylruthenium complex. Subsequent washing of the crude material with a small amount hexane gave pure metal complex **3b** as a microcrystalline solid in 77% yield. From this experiment, over 2 g of catalyst was obtained by use of a simple washing procedure. Alternatively, complex **3b** can be purified by crystallization from dichloromethane-heptane mixture. Washing of the crude product with an appropriate organic solvent appears, however, to be the method of choice. The NMR spectroscopic data of **3b** is in agreement with that published by us earlier [11].

In previous reports by other investigators, pentabenzylcyclopentadiene has been complexed with other transition metals including Ti [15], Co [13a], Rh [13a], Mn [16], Re [16], Fe [16,17], Mo [18], and W [18]. In order to further investigate the ligation properties of pentabenzylcyclopentadiene, we now have also prepared the Pd-analogue $Bn_5CpPdCl(PPh_3)$ **6**. The synthesis of **6** was performed by reaction of the pentabenzylcyclopentadienyl **4b** anion lithium salt with dimeric chloro-phosphino-complex $Pd_2Cl_4(PPh_3)_2$ as the Pd source (Scheme 4). Complex **6** was characterized by ^1H, ^{13}C, and ^{31}P NMR and X-ray crystallography. As expected, this complex is not active as a racemization catalyst for *sec*-alcohols under conditions employed for the ruthenium cyclopentadienyl systems [11].



Scheme 4 Synthesis of the (pentabenzylcyclopentadienyl)palladium complex **6**.

Crystal structures

In our earlier communication [11], the crystal structure of **3b** together with its monobenzyltetraphenylcyclopentadienyl analogue was briefly elucidated. A more detailed structural discussion is given here together with the X-ray structure of **6** (Fig. 1), which to our knowledge is the first example of a pentabenzylcyclopentadienyl-ligated Pd-complex. In the asymmetric unit of **6**, there are two similar molecules of which one is presented in Fig. 1.

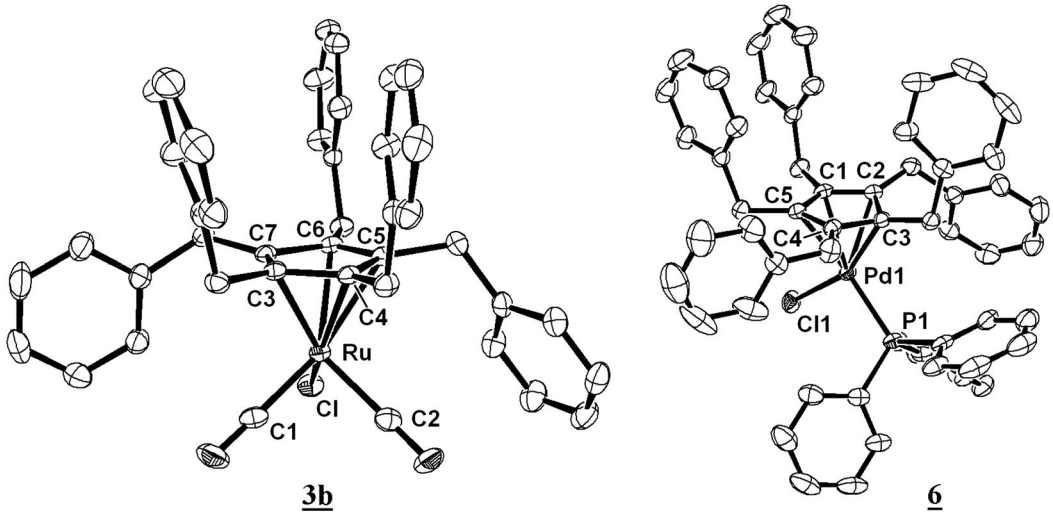


Fig. 1 X-ray structures of **3b** and **6**. Hydrogens are omitted for clarity. Ellipsoids are drawn at 50 % probability level.

The main structural features of complexes **3b** and **6** are summarized in Table 1. In the ruthenium complex **3b**, the bond lengths between the metal atom and carbon atoms of the five-membered ring range from 2.194 to 2.275, being fairly consistent with η^5 coordination mode and also similar to those observed earlier for the pentaphenyl analogue **5a** [9b]. The palladium complex **6**, however, displays a one-short, two-intermediate, two-long bonding pattern with the bond lengths between the metal atom and carbon atoms of the five-membered ring ranging from 2.203 to 2.449 being consistent with tendency towards η^3 (or η^1) bonding mode with three Pd–C bonds much shorter than the other two. Similar splitting of bond lengths has been observed earlier for other sterically encumbered cyclopentadienyl palladium complexes with $Me_5CpPdCl(i\text{-}Pr_3P)$ displaying a one-short, two-intermediate, two-long bonding pattern (2.219–2.403 Å) [19] and $Ph_5CpPd(\eta^3\text{-}CH_2C(CH_2OS(O)Ph)CH_2)$ displaying a four-intermediate, one-long bonding pattern (2.294–2.443 Å) [20]. For both complexes **3b** and **6**, the distances between the metal atoms (M) and Cp centroids are of similar magnitude being 1.875 Å for ruthenium and 1.999, 1.994 Å for palladium. In solution, the benzyl substituents of both complexes rotate freely around the $Cp–CH_2$ bond at ambient temperature displaying only one sharp singlet for the benzylic groups in the ^1H and ^{13}C NMR spectra.

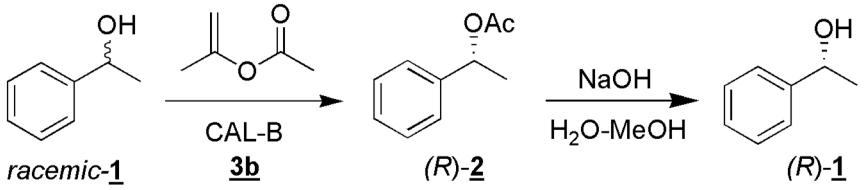
Table 1 Selected bonding parameters for **3b** and **6**.

3b		**6**		
Ru-C3	2.210(2)	Pd1-C1	2.323(2)	2.295(2)[a]
Ru-C4	2.194(2)	Pd1-C2	2.314(2)	2.297(2)[a]
Ru-C5	2.275(2)	Pd1-C3	2.203(2)	2.203(2)[a]
Ru-C6	2.274(2)	Pd1-C4	2.418(2)	2.435(2)[a]
Ru-C7	2.234(2)	Pd1-C5	2.443(2)	2.449(2)[a]
Ru-C1	1.890(2)	Pd1-P1	2.2538(6)	2.2523(6)[a]
Ru-C2	1.906(2)	Pd1-Cl1	2.3552(6)	2.3594(6)[a]
Ru-Cl	2.4162(5)	Pd-centroid	1.999	1.994[a]
Ru-centroid	1.875			

[a]Corresponding bond lengths and angles of the second molecule in the asymmetric unit.

Large-scale DKR

In order to demonstrate the practicability of catalyst **3b**, a molar-scale DKR of 1-Ph-ethanol was performed (Scheme 5). In designing this experiment, we particularly set out to investigate the limits of catalyst loading while aiming at high conversion and enantiomeric excess at ambient temperature at the expense of reaction time. As established earlier [21], the racemization reaction proceeds much faster in the absence of enzyme as compared to the racemization of the less reactive enantiomer in DKR. A possible explanation is the deactivation of catalyst by acetic acid formed during enzymatic hydrolysis of the acyl donor due to trace water impurities. Another explanation for catalyst deactivation could be a competing Meerwein–Ponndorf–Verley–Oppenauer (MPVO)-type reaction between the acetone formed from the acyl donor in the enzymatic reaction and phenylethanol. In such a case, a significant amount of acetophenone should be visible in gas chromatography (GC). In the present reaction, however, detectable formation of acetophenone was not observed. In order to overcome this limitation, an excess of catalyst is typically utilized in small-scale model reactions (commonly 4 mol % of catalyst for 1 mmol loading) [6b]. It is well known that large-scale organometallic reactions are less sensitive toward oxygen and moisture traces in solvents, reagents, glassware and environment. In this regard, chemoenzymatic DKR is not an exception. As demonstated earlier by Bäckvall and co-workers [21], using 122 g of 1-phenylethanol, a 0.05 mol % loading of the pentaphenyl catalyst **3a** with 0.5 mass %



Scheme 5 Large-scale DKR of 1-Ph-ethanol.

of immobilized CAL-B (Novozym 435) is sufficient to provide (*R*)-**2** in >99 % ee and 97 % yield over 20 h at 70 °C.

In the present work, 0.05 mol % (0.3 mass %) loading of catalyst **3b** and 1 mass % loading of immobilized enzyme was sufficient to obtain full conversion in 17 days at *ambient temperature* [22]. High conversion (98 %) and excellent optical purity of the product (*R*)-**2** (ee > 99 %) were observed after 10 days already. For preparing optically pure (*R*)-**1**, however, conversions close to 100 % are required in the DKR. Stopping of the reaction at lower conversion would retain the (*S*)-enriched alcohol as an impurity, which after hydrolysis of (*R*)-**2** into (*R*)-**1** significantly decreases the enantiomeric excess. To exemplify, work-up of the rection at 98 % conversion would provide a mixture of (*R*)-**2** and (*S*)-enriched alcohol **1** in 49:1 ratio. Furthermore, quantitative separation of alcohol **1** (b.p. 204 °C) and acetate **2** (b.p. 213 °C) by distillation is difficult due to proximity of their boiling points and by subsequent alkaline hydrolysis at 98 % conversion (*R*)-**1** would be obtained in 96 % ee only. By extending the reaction time in order to reach >99 % conversion of the starting material, the final product (*R*)-**1** was, however, obtained in high yield and enantiopurity. Here, the DKR product (*R*)-**2** was isolated by vacuum distillation followed by subsequent alkaline hydrolysis without significant decrease in optical purity. By this procedure, over 100 g of the final alcohol product (*R*)-**1** was isolated after vacuum distillation in >99 % ee and 93 % overall yield over steps.

CONCLUSIONS

A new chromatography-free protocol for multigram-scale preparation of a highly efficient racemization catalyst for metalloenzymatic DKR of *sec*-alcohols has been developed. The main benefit of the pentabenzyl-substituted catalyst **3b** when compared with its pentaphenyl-substituted analogue **3a**, often considered as the leading (cyclopentadienyl)ruthenium-based racemization catalyst candidate for chemoenzymatic DKR, is its simple and cost-efficient preparation, while the catalysts otherwise show very similar behavior. Applicability of this catalyst for a molar-scale DKR reaction of 1-phenylethanol was demonstrated. (*R*)-Phenylethanol of excellent optical purity was obtained from racemic 1-phenylethanol in two steps with overall yield 93 % without the use of chromatography.

EXPERIMENTAL

General

All glassware was oven-dried at 150 °C overnight and cooled down in a desiccator over phosphorus pentoxide. Solvents were dried according to standard procedures. Potassium *tert*-butoxide was sublimated in vacuum. Isopropenylacetate was redistilled over calcium hydride under argon atmosphere. 1-Phenylethanol was refluxed and redistilled over calcium hydride under reduced pressure. Sodium carbonate was dried at 180 °C in vacuum. CAL-B in the form of Novozym-435 was obtained from Novozymes A/S (Denmark). Pentabenzylcyclopentadiene **4b** [13b] and $Pd_2Cl_4(PPh_3)_2$ [23] were prepared according to literature procedures. NMR spectra were recorded using a Bruker Avance 600 MHz spectrometer. Conversion and enantiomeric excess were measured with an Agilent GC equipped with a

chiral column Varian CP7502. HRMS were recorded using a Bruker Micro Q-TOF with ESI (electrospray ionization) operated in positive mode.

Catalyst 3b

$Ru_3(CO)_{12}$ (0.96 g, 1.5 mmol), Bn_5CpH **4b** (2.35 g, 4.5 mmol) and dry mesitylene (30 ml) was placed in a 40-ml Ace pressure tube equipped with a magnetic stirring bar. The tube was purged with argon, sealed, and the mixture was heated in an oil bath at 160 °C for 3 d. Next, the tube was cooled down, opened, and argon was bubbled through the reaction mixture with a Pasteur pipette for a few minutes in order to remove carbon monoxide formed. The tube was sealed again and heating was continued for 7 d at the same temperature. The reaction mixture was then cooled down, 3 ml of chloroform was added, the tube was closed, and heating continued at 140 °C overnight. The mixture was cooled down to room temperature and filtered through a cotton wool to remove a small amount of insoluble material. The solvents were removed under reduced pressure and the residual semi-crystalline mass was washed twice with hexane with the aid of ultrasonic bath leaving 2.45 g (77 %) of complex **3b** as a yellow microcrystalline powder. The absence of unreacted ruthenium carbonyl in the product was confirmed by quantitative ^{13}C NMR analysis. ^1H NMR (600 MHz, $CDCl_3$): δ 7.14–7.10 (m, 15H), 6.90–6.86 (m, 10H), 3.57 (s, 10H). Quantitative ^{13}C NMR (150 MHz, $CDCl_3$): δ 197.13 (2C), 137.94 (5C), 128.58 (10C), 128.49 (10C), 126.74 (5C), 105.27 (5C), 30.73 (5C).

Complex 6

To a stirred solution of 278 mg (0.54 mmol) of Bn_5CpH in 20 ml of THF at –78 °C was added 0.25 ml (0.62 mol) of 2.5 M solution of *n*-BuLi in hexanes. The reaction mixture was stirred for 1 h, then 158 mg (0.18 mmol) of $Pd_2Cl_4(PPh_3)_2$ was added. The mixture was stirred 30 min at –78 °C and then 2 h at room temperature. The solvents were evaporated and the residue was purified by chromatography (hexane-dichloromethane) providing 60 mg (18 %) of **6** as a dark-green solid. Single crystals for X-ray structure determination were obtained by slow recrystallization from dichloromethane/heptane at 4 °C. ^1H NMR (600 MHz, $CDCl_3$): δ 7.57 (m, 6H), 7.48 (t, 3H, J = 7.8 Hz), 7.41 (t, 6H, J = 7.8 Hz), 6.97 (t, 5H, J = 7.5 Hz), 6.93 (t, 10H, J = 7.5 Hz), 6.87 (d, 10H, J = 7.5 Hz), 3.17 (s, 10H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 138.91, 134.58 (d, J = 12.1 Hz), 132.30 (d, J = 45.0 Hz), 130.37, 128.68, 128.39 (d, J = 11.0 Hz), 127.96, 125.71, 117.15, 30.72. ^{31}P NMR (243 MHz, $CDCl_3$): δ 30.48. MS (ESI+): exact mass calcd. for $C_{58}H_{50}{}^{106}PdPCl$ (–Cl) 883.2685, found 883.2692.

Large-scale DKR

Catalyst **3b** (353 mg, 0.5 mmol), Novozym-435 (1 g), sodium carbonate (10.6 g, 0.1 mol) and magnetic stirring bar were placed into a 1000-ml one-necked round bottom flask. The flask was introduced into a nitrogen-filled glovebox (oxygen and water content below 1 ppm). Next, 450 ml of toluene was added followed by 2 ml (0.5 mmol) of 0.25 M solution of potassium *tert*-butoxide in THF. The reaction mixture was stirred for 30 min. Then 121 ml (1 mol) of rac-**1** was added during 20 min, followed by 132 ml (1.2 mol) of isopropenylacetate. The mixture was stirred at room temperature for 17 days (92 % conversion was achieved in 6 days, 98 % in 10 days). Analysis of the reaction mixture was performed by quenching of 10 μL sample with 50 μL of propionic anhydride and 20 μL of 1 % DMAP solution in pyridine. The derivatized mixture was kept at room temperature for 20 min to ensure full derivatization of unreacted alcohol and filtered through silica using ethylacetate as an eluent in order to prevent contamination of GC with ruthenium. The prepared sample was analyzed by chiral GC. After >99 % conversion had been reached, the reaction mixture was taken out from the glovebox and filtered. The residue on the filter was distributed between water and ethylacetate, organic phase was separated and combined with the filtrate. The solvent was distilled off at atmospheric pressure and (*R*)-1-phenyl-ethyl-

acetate was redistilled at reduced pressure providing 160 g (97 %) of (*R*)-**2** as a colorless oil. ee > 99 % (by chiral GC). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37–7.33 (m, 4H), 7.31–7.27 (m, 1H), 5.88 (q, ^3J = 6.4 Hz, 1H), 2.07 (s, 3H), 1.54 (d, ^3J = 6.4 Hz, 3H).

(*R*)-1-phenyl-ethanol (*R*)-1

160 g (0.97 mol) of (*R*)-**2** were added dropwise to an ice-cooled solution of 120 g (3 mol) of sodium hydroxide in 2000 ml of methanol-water (3:1) mixture. The reaction mixture was stirred for 60 h at room temperature. Conversion >99 % was confirmed by GC analysis. Methanol was removed under reduced pressure, the residue was diluted with water and extracted three times with diethyl ether. The organic phases were combined, washed with brine and dried over sodium sulfate. Diethyl ether was removed under reduced pressure and (*R*)-**1** was isolated by vacuum distillation to yield 113.5 g (0.93 mol, 96 %) of product as a colorless oil. ee > 99 % (by chiral GC). [α]D +45° (5 % in MeOH, 20 °C, lit. +45°, 5.1 % in MeOH, 20 °C [24]). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40–7.33 (m, 4H), 7.27 (t, ^3J = 7.2 Hz, 1H), 4.90 (q, ^3J = 6.4 Hz, 1H), 1.87 (br. s, 1H), 1.50 (d, ^3J = 6.4 Hz, 3H).

X-ray crystallography

The crystallographic data were collected at 173 K on an Enraf Nonius Kappa CCD area-detector diffractometer using graphite monochromatised MoK_α radiation (λ = 0.71073 Å). Data collection was performed using φ and ω scans and the data were processed using DENZO-SMN v0.93.0 [25]. SADABS [26] absorption correction was applied to the data of all compounds. The structures were solved by direct methods using the SHELXS-97 program and full-matrix least-squares refinements on F^2 were performed using the SHELXL-97 program [27]. Structure figures were drawn using Ortep-3 for Windows [28].

Crystal data for 6

$C_{58}H_{50}ClPPd$, M_r = 919.80, triclinic, space group P –1 (no. 2), a = 10.6766(2), b = 18.0890(3), c = 25.9289(4) Å, α = 67.280(1), β = 83.116(1), γ = 90.907(1)°, V = 4575.19(13) Å^3, T = 173 K, Z = 4, μ(Mo-K) = 0.537 mm^{-1}, 19959 unique reflections (R_{int} = 0.035) which were used in calculations. The final $wR(F^2)$ was 0.0877 (all data) and $R[F^2 > 2\,(F^2)]$ = 0.0395.

The deposition number CCDC-798985 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge at <www.ccdc.cam.ac.uk/conts/retrieving.html> [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

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