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New Ruthenium Catalysts for Asymmetric Transfer Hydrogenation of Prochiral Ketones

Stephan Enthaler,[a] Bernhard Hagemann,[a] Santosh Bhor,[a] Gopinathan Anilkumar,[a] Man Kin Tse,[a] Bianca Bitterlich,[a] Kathrin Junge,[a] Giulia Erre,[a] and Matthias Beller[a,*]

[a] Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Str. 29a, 18059 Rostock, Germany
Fax: (+49)-381-1281-5000; e-mail: matthias.beller@catalysis.de

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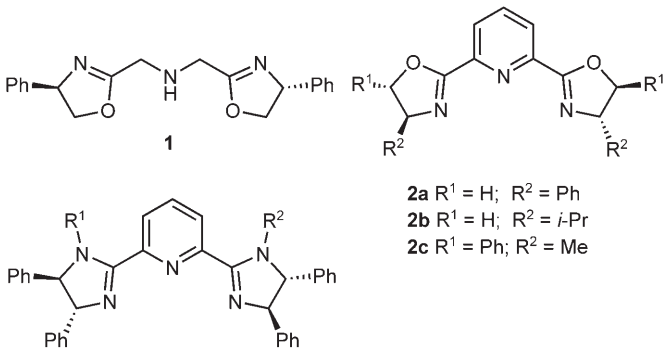
Abstract: Tridentate *N,N,N*-pyridinebisimidazolines have been studied as new ligands for the enantioselective transfer hydrogenation of prochiral ketones. High yields and excellent enantioselectivity up to >99% *ee* have been achieved with an *in situ* generated catalytic system containing dichlorotris(triphenylphosphine)ruthenium and 2,6-bis-([*4R,5R*]-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)-pyridine (**3a**) in the presence of sodium isopropoxide.

Keywords: asymmetric transfer hydrogenation; ketones; phosphines; ruthenium; tridentate nitrogen ligands

Enantiomerically pure alcohols have a wide range of applications, for example, building blocks and synthons for pharmaceuticals, agrochemicals, polymers, syntheses of natural compounds, auxiliaries, ligands and key intermediates in organic syntheses.[1] Within the different molecular transformations to chiral alcohols, transition metal-catalyzed reactions offer efficient and versatile strategies, such as addition of organometallic compounds to aldehydes, hydrosilylation, and hydrogenation of prochiral ketones.[2] From an economic and environmental point of view the asymmetric hydrogenation, in particular the transfer hydrogenation, represents a powerful tool for their synthesis because of its high atom economy and safety advantages.[3] Here, Noyori's ruthenium-based catalysts comprising chiral tosylated diamines constitute state-of-the-art transfer hydrogenation systems.[3d,4] Based on this seminal work an increasing number of ruthenium catalysts with chiral bidentate *N,N*-ligands were developed in the last decade.[3] Significantly fewer systems are known in which transfer of chiral information is promoted by tridentate ligands.[5,6] Up to now only a limited number of auspicious tridentate nitrogen-containing *N,N,N* ligands were established in the field of transfer hydrogenation. For example (*R*)-phenyl-ambox (**1**)[5] and different pyridinebisoxazoline (pybox) ligands (**2**)[6] have been applied for the reduction of acetophenone (Scheme 1).



Scheme 1. *N,N,N*-Tridentate ligands.

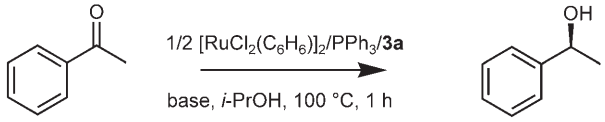
Recently, we reported the synthesis of a new class of chiral tridentate amines.[7] The preparation and tunability of these pyridinebisimidazolines (**3**) (so-called pybim ligands, Scheme 1) are easier and more flexible compared to the popular pyboxes, making the former a suitable ligand tool box for various asymmetric transformations. To date there is no report on the performance of these ligands in hydrogenation reactions. The resemblance between pybim (**3**) and pybox (**2**) stimulated our research to study the potential of this class of ligands in the transfer hydrogenation of aromatic and aliphatic ketones.

In exploratory experiments, isopropyl alcohol-based transfer hydrogenation of acetophenone was examined using a simple *in situ* catalyst system composed of $[RuCl_2(C_6H_6)]_2$, 2,6-bis-([*4R,5R*]-4,5-diphenyl-4,5-

dihydro-1*H*-imidazol-2-yl)-pyridine (**3**) and triphenylphosphine. To ensure complete formation of the active catalyst and avoid an induction period the reaction mixture was heated for 10 min at 100 °C in the presence of base followed by addition of acetophenone. First, studies for optimizing the reaction conditions were carried out with 1 mol% of pre-catalyst and 5 mol% of base. It is well-known that transfer hydrogenations are sensitive to the nature of the base. Thus, the influence of different bases on selectivity and conversion was investigated initially (Table 1). Best results were obtained for sodium isopropoxide and K_2CO_3 with conversions up to 95% and enantiomeric excesses up to 94% (Table 1, entries 1 and 8). Interestingly, NaOH and KOH the most commonly used bases for transfer hydrogenations gave only moderate enantioselectivity (78% and 80%, Table 1, entries 3 and 4). In addition, we tested some organic nitrogen-containing systems such as DBU, DABCO, NEt_3, $N(i\text{-}Pr)_2Et$ and pyridine, but only with $N(i\text{-}Pr)_2Et$ did we obtain significant amounts of product in a reasonable time (Table 1, entry 10). Next, the concentration of sodium isopropoxide was varied at different temperatures. As expected, the increase of the amount of base led to an acceleration of reaction rate; however, this was accompanied by an unacceptable decrease of enantioselectivity (Table 1, entries 13–15). In contrast, improved *ee* is obtained by reducing the amount of base to a ruthenium-to-base ratio of 1 to 0.5 (Table 1, entries 16 and 17). Notably, in the absence of base the transfer of hydrogen did not occur. Based on these results we investigated the behavior of the metal precursor.

Applying different ruthenium sources such as $[RuCl_2(PPh_3)_3]$, $[RuHCl(PPh_3)_3]$,[8] $RuCl_3 \cdot x\,H_2O$, $Ru_3(CO)_{12}$ and Ru(cod)(methylallyl)$_2$, lower conversion and/or poor selectivity were achieved. Nevertheless, $[RuCl_2(PPh_3)_3]$ showed an enantiomeric excess of >99%, which is to our knowledge the highest enantioselectivity in this model reaction for a chiral tridentate ligand (Table 1, entry 17). However, a slight excess of pybim **3a**, 3 equivs. with respect to 1 equiv.

Table 1. Transfer hydrogenation of acetophenone in the presence of pybim ligand **3a** and different bases.[a]



Entry	Base	Base:Metal	Temp. [°C]	Conv. [%][b]	*ee* [%][b]
1	NaO-*i*-Pr	5	100	80	**94 (*S*)**
2	KO-*t*-Bu	5	100	99	9 (*S*)
3	NaOH	5	100	79	78 (*S*)
4	KOH	5	100	85	80 (*S*)
5	LiOH	5	100	72	80 (*S*)
6	K_3PO_4	5	100	65	70 (*S*)
7	K_2HPO_4	5	100	19	96 (*S*)
8	K_2CO_3	5	100	95	93 (*S*)
9	Cs_2CO_3	5	100	45	67 (*S*)
10	$N(i\text{-}Pr)_2Et$	5	100	18	90 (*S*)
11	NaO-*i*-Pr	5	60	93	84 (*S*)[c]
12	NaO-*i*-Pr	5	80	91	83 (*S*)[d]
13	NaO-*i*-Pr	5	90	91	88 (*S*)
14	NaO-*i*-Pr	50	90	98	87 (*S*)
15	NaO-*i*-Pr	250	90	99	44 (*S*)
16	NaO-*i*-Pr	0.5	100	88	95 (*S*)
17	NaO-*i*-Pr	0.5	100	96	**>99 (*S*)**[e]
18	NaO-*i*-Pr	0.5	110	58	84 (*S*)

[a] *Reaction conditions: in situ* catalyst **A** {1.9×10^{-6} mol $[RuCl_2(C_6H_6)]_2$, 3.8×10^{-6} mol ligand **3a**, 3.8×10^{-6} mol PPh_3}; addition of the corresponding base: entries 1–13: 1.9×10^{-5} mol, entry 14: 1.9×10^{-4} mol, entry 15: 9.5×10^{-4} mol and for entries 16–18: 1.9×10^{-6} mol in 2.0 mL isopropyl alcohol, 10 min at corresponding temperature then addition of 3.8×10^{-4} mol acetophenone, 1 h at corresponding temperature.

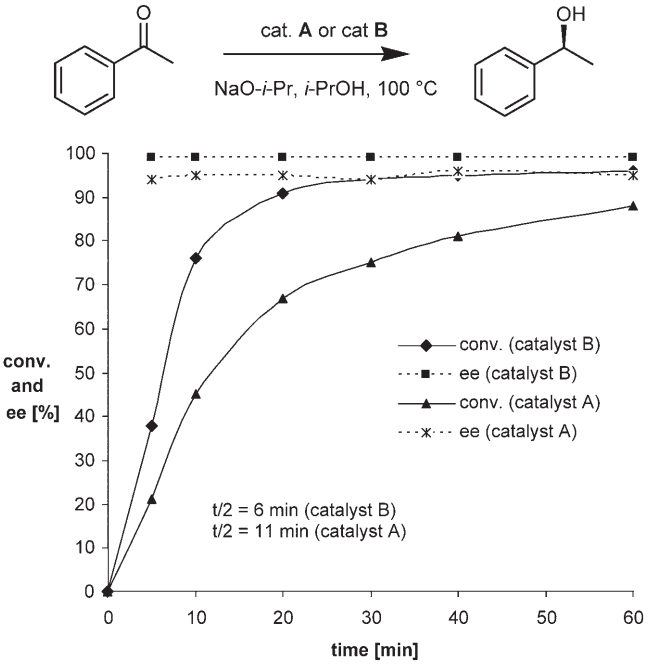
[b] Conversion and *ee* were determined by chiral GC (50 m Lipodex E, 95–200 °C) analysis with diglyme as internal standard.

[c] Reaction time 14 h.

[d] Reaction time 4 h.

[e] *In situ* catalyst **B** {3.8×10^{-6} mol $[RuCl_2(PPh_3)_3]$, 1.14×10^{-5} mol **3a**}. Conversion was determined by GC (30 m HP Agilent Technologies 50–300 °C) with diglyme as internal standard and *ee* was determined by chiral HPLC (Chiralcel OB-H, eluent: *n*-hexane/ethanol, 99:1, flow rate: 2 mL min^{-1}) analysis.

of ruthenium, was necessary to achieve high enantioselectivity. To compare the difference of catalyst system **A** and catalyst system **B**, we investigated the conversion-time and the enantioselectivity-time dependency (Scheme 2). No significant change of enan-



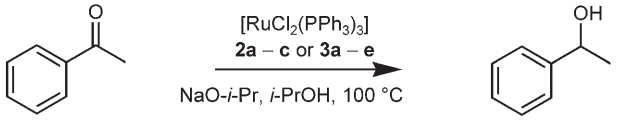
Scheme 2. Conversion-time and enantioselectivity-time behavior of catalyst **A** and catalyst **B**. *Reaction conditions: in situ* catalyst **A** (1.9×10^{-6} mol $[RuCl_2(C_6H_6)]_2$, 3.8×10^{-6} mol ligand **3a**, 3.8×10^{-6} mol PPh_3) or *in situ* catalyst **B** (3.8×10^{-6} mol $[RuCl_2(PPh_3)_3]$, 1.14×10^{-5} mol **3a**); addition of sodium isopropoxide (1.9×10^{-6} mol) in 2.0 mL 2-propanol, 10 min at 100 °C then addition of 3.8×10^{-4} mol acetophenone, reaction temperature: 100 °C. Conversion was determined by GC (30 m HP Agilent Technologies 50–300 °C) with diglyme as internal standard and *ee* was determined by chiral HPLC (Chiralcel OB-H, eluent: *n*-hexane/ethanol, 99:1, flow rate: 2 mL min^{-1}) analysis.

tioselectivity was observed in the shown time frame, while after 24 h full racemization occurred with catalyst **A**. Noteworthy, the analysis of the conversion-time behavior proved a higher catalyst activity for catalyst **B**, while for catalyst **A** a slight deceleration was monitored. We assume a better stabilization of the active species by an excess of **3a** and PPh_3.

As shown in Table 2 we also examined different pybox ligands (**2a–c**), but only unsatisfying results were obtained demonstrating the advantage of **3a** (Table 2, entries 1–3).

Noyori et al. proposed a metal-ligand bifunctional mechanism for the hydride transfer process ("NH effect").[4,13b] Hence, the NH group of the imidazoline rings could be involved in the selectivity transfer and increase the coordination affinity between substrate

Table 2. Transfer hydrogenation of acetophenone in the presence of different pybox and pybim ligands.[a]



Entry	Ligand	Time [h]	Conv. [%][b]	*ee* [%][b]
1	**2a**	1	6	11 (*R*)
2	**2b**	1	10	18 (*S*)
3	**2c**	1	22	8 (*R*)
4	**3a**	1	83	**98 (*S*)**
5	**3b**	2	95	26 (*R*)
6	**3c**	2	74	29 (*S*)
7	**3d**	1	4	7 (*R*)
8	**3e**	1	77	7 (*S*)

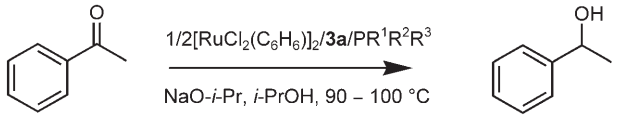
[a] Reaction conditions: 3.8×10^{-6} mol $[RuCl_2(PPh_3)_3]$, 1.14×10^{-5} mol ligand, 3.8×10^{-6} mol PPh_3, 1.9×10^{-6} mol NaO-*i*-Pr, 2.0 mL isopropyl alcohol, 10 min at 100 °C then addition of 3.8×10^{-4} mol acetophenone.

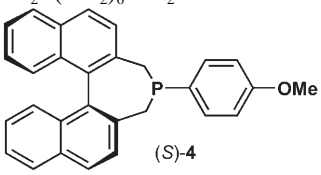
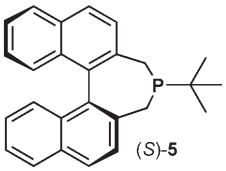
[b] Conversion and *ee* were determined by chiral GC (50 m Lipodex E, 95–200 °C) analysis with diglyme as internal standard.

and catalyst. Due to the formation of a second binding site, a more favorable position for transferring the chiral information is attained.[5,9,13]

In order to understand the role of the free NH functionality for our pybim ligand **3a**, different substitutions at the imidazoline units were carried out. The corresponding monoprotected ligands **3b**, **c** were synthesized by reaction of **3a** with one equivalent of 3,5-di-*tert*-butylbenzoic acid chloride or $Ph_2P(O)Cl$. We presumed that the resulting unsymmetrical complexes would direct the substrate to occupy a specific orientation in the transition state and thereby induce increased selectivity during catalysis. However, 3,5-(*t*-Bu)$_2$C$_6$H$_3$)CO (**3b**) or Ph_2PO substitution (**3c**) decreased the enantioselectivity in the model reaction significantly (Table 2, entries 5 and 6). To confirm the results of the monosubstituted ligands an exchange of both hydrogens with Boc (**3d**) or Bz (**3e**) protecting groups was carried out. A further decrease of enantioselectivity was observed (Table 2, entries 7 and 8). Thus, there is a crucial necessity of both NH functionalities for obtaining high enantioselectivity in the transfer hydrogenation of acetophenone. Interestingly, the NH group is not necessary to achieve significant conversions (Table 2, entry 8), which is in contrast to previous reports by Noyori et al., for example catalysts containing *N*-dimethylamino alcohols are completely inactive compared to their *N*-monomethyl counterparts.[3d,13b] To estimate the influence of the ligands in more detail we varied also the phosphorus ligand part (Table 3). Among the different achiral ligands best results were obtained with PPh_3, (*p*-MeO-C$_6$H$_4$)$_3$P and (*p*-Me-C$_6$H$_4$)$_3$P (Table 3, entries 1, 3 and

Table 3. Influence of different phosphorus ligands on the transfer hydrogenation of acetophenone.[a]



Entry	P Ligand	Temp. [°C]	Conv. [%][b]	*ee* [%][b]
1	Ph_3P	100	80	**94 (*S*)**
2	without	100	61	7 (*S*)
3	$(p\text{-MeO-}C_6H_4)_3P$	90	91	**87 (*S*)**[c]
4	$(o\text{-Me-}C_6H_4)_3P$	100	20	*rac*
5	$(p\text{-Me-}C_6H_4)_3P$	100	41	**97 (*S*)**
6	$[3,4\text{-}(CF_3)_2\text{-}C_6H_3]_3P$	90	24	66 (S)[c]
7	$(p\text{-F-}C_6H_4)_3P$	100	53	76 (*S*)
8	Cy_3P	90	2	15 (*S*)[c]
9	$t\text{-}Bu_3P$	100	1	12 (*S*)
10	$n\text{-BuPAd}_2$	100	4	5 (*S*)
11	$(i\text{-PrO})_3P$	100	28	75 (*S*)
12	$Ph_2P(CH_2)PPh_2$	100	37	*rac*
13	$Ph_2P(CH_2)_2PPh_2$	100	43	*rac*
14	$Ph_2P(CH_2)_5PPh_2$	100	43	6 (*S*)
15	$Ph_2P(CH_2)_6PPh_2$	100	15	37 (*S*)
16	 (*S*)-**4**	90	90	95 (*S*)[c]
17	 (*S*)-**5**	90	8	24 (*S*)

[a] *Reaction conditions: in situ* catalyst {1.9×10^{-6} mol $[RuCl_2(C_6H_6)]_2$, 3.8×10^{-6} mol **3a**, 3.8×10^{-6} mol of the corresponding P ligand}, 1.9×10^{-5} mol NaO-*i*-Pr, 2.0 mL isopropyl alcohol, 10 min at described temperature then addition of 3.8×10^{-4} mol acetophenone, 1 h at described temperature.

[b] Conversion and *ee* were determined by chiral GC (50 m Lipodex E, 95–200 °C) analysis with diglyme as internal standard.

[c] Experiments also performed at 100 °C, but only low enantioselectivities or conversions were obtained.

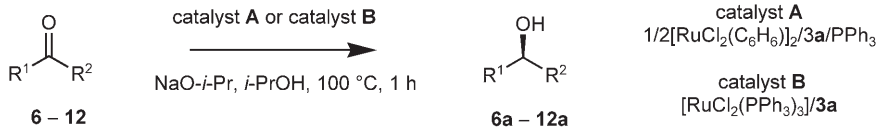
5). Methyl substitution in the *o*-position of arylphosphines decreased the enantioselectivity dramatically compared to that at the *p*-position (from 97% *ee* to *rac*, entries 4 and 5). Moderate conversion and selectivity were obtained for electron-poor substituted arylphosphines (Table 3, entries 6 and 7). Interestingly, also more basic and sterically hindered alkylphosphines such as PCy_3, $P(t\text{-Bu})_3$, and $n\text{-BuPAd}_2$ showed only low activity (Table 3, entries 8–10).

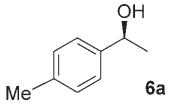
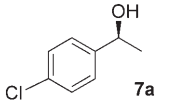
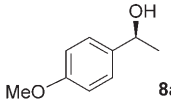
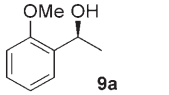
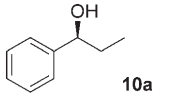
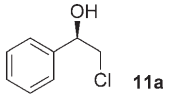
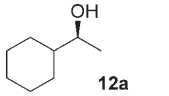
Furthermore, we applied chelating arylphosphine ligands. For bis(diphenylphosphino)methane (DPPM) only disappointing conversion and selectivity were obtained (Table 3, entry 12). By increasing the number of CH_2 groups in the bridge an increase of the enantiomeric excess was detected (Table 3, entries 13–15), probably due to a weaker coordination of the second phosphine group to the ruthenium. In addition, to improve the enantioselectivity and to increase the enantiomeric differentiation in the shape of the catalysts, we investigated the influence of chiral phosphines. Therefore, we tested chiral monodentate ligands (*S*)-**4** and (*S*)-**5** in the transfer hydrogenation of acetophenone in combination with pybim ligand **3a**. Recently, we have demonstrated the successful application of such chiral monodentate 4,5-dihydro-3*H*-dinaphtho-[2,1-*c*;1′,2′-*e*]phosphepines in various asymmetric hydrogenations using molecular hydrogen.[10] Furthermore, Gladiali and co-workers reported previously the application of this ligand class in the rhodium-catalyzed asymmetric hydrogenation of C=C bonds.[21] However, only ligand (*S*)-**4** showed comparable enantioselectivity to PPh_3 of 95% *ee*, while (*S*)-**5** gave poor selectivity and conversion, due to a similar basicity to achiral alkylphosphines (Table 3, entry 16 and 17).

Next, we explored the influence of the concentration of PPh_3. The results indicated a necessity of 1 equiv. of PPh_3 relating to 1 equiv. of ruthenium, while the reaction with more than 1 equiv. of PPh_3 or in the absence of PPh_3 resulted in a decrease of enantioselectivity (Table 3, entries 1 and 2). Noteworthy, the use of an excess of PPh_3 has no disordered effect on selectivity while a negative influence was reported for other catalytic systems when PPh_3 was not removed.[5,6] In analogy to Gimeno et al.[6,11] and Yu et al.[12] we assume a *cis*-coordination of the phosphine with respect to the *N*-*N*-*N* plane, which forms after removal of the *cis*-coordinated chlorides (with respect to each other) a highly selective vacancy for substrate coordination and chirality transfer.

To demonstrate the usefulness of the novel catalysts we employed system **A** ($[RuCl_2(C_6H_6)]_2$/pybim/PPh_3) and **B** ($[RuCl_2(PPh_3)_3]$/pybim) in the asymmetric transfer hydrogenation of six aromatic and one aliphatic ketones (Table 4). In general, catalyst system **A** gave some higher enantioselectivities compared to catalyst **B**. Substituted acetophenones and propiophenone gave enantioselectivities up to 98% *ee* (Table 4, entries 1–5). In the case of methoxy-substitution the position of the substituent plays an important role, because *ortho*-substitution was favored (Table 4, entries 3 and 4). A chloro substituent in the α-position to the carbonyl group proved to be problematic and deactivated both catalysts (Table 4, entry 6). Compared to aromatic ketones, aliphatic ketones are more challenging substrates. Nevertheless, 1-cyclohexylethanone was reduced by catalyst **A** in good yield and enantioselectivity (Table 4, entry 7).

Table 4. Transfer hydrogenation of prochiral ketones.[a]



Entry	Alcohol	Catalyst **A**[b,c,d]		Catalyst **B**[b,c,d]	
		Conv. [%]	*ee* [%]	Conv. [%]	*ee* [%]
1	 **6a**	89	89 (*S*)	>99	85 (*S*)
2	 **7a**	84	94 (*S*)	>99	89 (*S*)
3	 **8a**	86[e]	72 (*S*)	68[f]	74 (*S*)
4	 **9a**	>99	98 (−)	99 [g]	70 (−)
5	 **10a**	>99	97 (*S*)	98[e]	87 (*S*)
6	 **11a**	12[g]	70 (*R*)	<2[f]	12 (*R*)
7	 **12a**	91	82 (*S*)	96[f]	72 (*S*)

[a] *Reaction conditions: in situ* catalyst **A** {1.9×10^{-6} mol $[RuCl_2(C_6H_6)]_2$, 3.8×10^{-6} mol **3a**, 3.8×10^{-6} mol PPh_3), 1.9×10^{-5} mol NaO-*i*-Pr, 2.0 mL isopropyl alcohol, 10 min at 100 °C then addition of 3.8×10^{-4} mol substrate, 1 h at 100 °C.

[b] Conversion and *ee* were determined by chiral GC (entry 1: 25 m Lipodex E, 80–180 °C; entry 2: 25 m Lipodex E, 100 °C; entry 3: 50 m Lipodex E, 90–105 °C; entry 4: 50 m Lipodex E, 90–180 °C; entry 5: 25 m Lipodex E, 90–180 °C; entry 6: 50 m Lipodex E, 95–180 °C; entry 7: 25 m Lipodex E, 100 °C) analysis with diglyme as internal standard.

[c] *In situ* catalyst **B** {3.8×10^{-6} mol $[RuCl_2(PPh_3)_3]$, 1.14×10^{-5} mol **3a**}.

[d] The absolute configurations were determined by comparing the sign of specific rotation with reported data.

[e] 4 h.

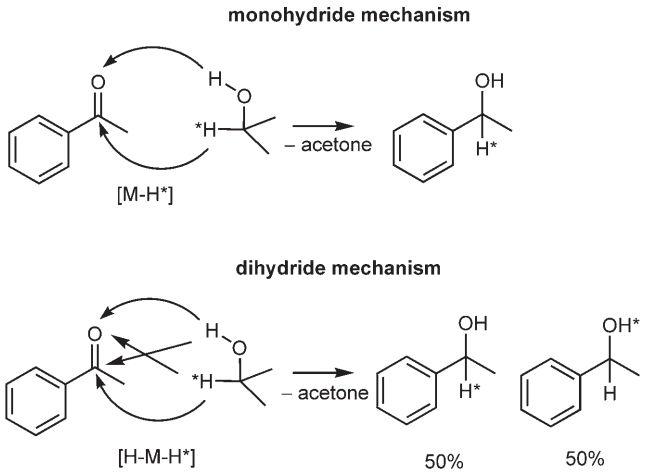
[f] 8 h.

[g] 24 h.

Various methods (^{1}H, ^{13}C, ^{31}P and ^{15}N NMR, COSY NMR, HMQC NMR and MS) were used for characterization of the pre-catalyst, but unfortunately no precise structure has been proven. The ^{31}P NMR spectrum of the pre-catalyst in $CDCl_3$ indicated a single compound, because a singlet appeared at 30 ppm (free PPh_3: −6 ppm and O=PPh_3: 27 ppm). Furthermore, the composition of the pre-catalyst was confirmed by HR-MS as $[RuCl_2(PPh_3)$(**3a**)] (calculated mass: 953.17549, detected mass: 953.17572). However, the coordination abilities of ligand **3a** are so far unclear, because a rapid exchange of NH protons was detected, which causes a broad signal in the ^{1}H NMR spectrum for the four protons adjacent to the nitrogen atoms and furthermore one signal for the corresponding carbons in the ^{13}C NMR spectrum.

Next, we focused our attention on a deeper comprehension of the reaction mechanism. For metal-catalyzed transfer hydrogenation two general mechanisms are accepted, designated as direct hydrogen transfer *via* formation of a six-membered cyclic transition state composed of metal, hydrogen donor and acceptor, and the hydridic route, which is subdivided into two pathways, the monohydride and dihydride mechanism (Scheme 3). More specifically, the formation of monohydride-metal complexes promotes an

exclusive hydride transfer from carbon (donor) to carbonyl carbon (acceptor) (Scheme 3), whereas a hydride transfer *via* dihydride-metal complexes leads to



Scheme 3. Monohydride and dihydride mechanisms for transfer hydrogenations.

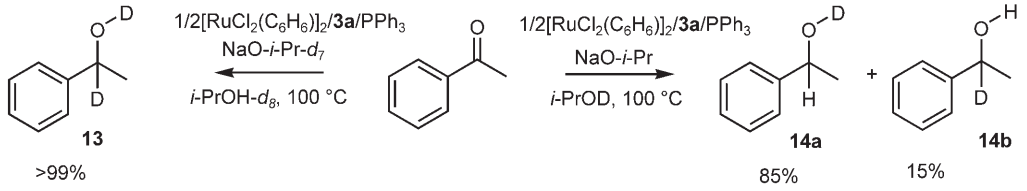
no accurate prediction of hydride resting state, because the former hydride was transferred to the carbonyl carbon (acceptor) as well as to the carbonyl oxygen (acceptor) (Scheme 3). Indications for both pathways (hydridic route) have been established by various research groups, when following the hydride transfer catalyzed by metal complexes, e.g., Ru, Rh or Ir.[13]

Reaction of cyclopropyl phenyl ketone ("radical clock"-substrate) with isopropyl alcohol in the presence of 1 mol% catalyst **A** gave exclusively the corresponding cyclopropylphenyl alcohol (>99% by ^{1}H NMR). Apparently there is no radical reduction induced by the transition metal or by sodium alkoxides.[14] The second assumption is also confirmed by performing the reduction of acetophenone in the presence of base and in the absence of the ruthenium catalyst. Here, no product at all was detected.

Next, we followed the incorporation of hydrogen from the donor molecule (isopropyl alcohol) into the product by applying a deuterated donor.[15] The precatalyst (1 mol%) is generated by stirring a solution of isopropyl alcohol-d_8, 0.5 equivs. of $[RuCl_2(C_6H_6)]_2$, ligand **3a** and PPh_3 for 16 h at 65 °C. Then, sodium isopropoxide-d_7 was added and the solution was stirred for 10 min at 100 °C. The reaction mixture was charged with acetophenone and after 1 h compound **13** was observed as main product (>99%) by ^{1}H NMR (Scheme 4).[16] The result proved an exclusive transfer of the deuterium into the carbonyl group, therefore a C–H activation of the substrate/product under the described conditions did not occur. Furthermore, this result rules out an enol formation in the catalytic cycle.[17]

To specify the position and the nature of the transferred hydride, the reaction was performed with isopropyl alcohol-d_1 (hydroxy group deuterated) as solvent/donor and sodium isopropoxide as base under identical reaction conditions. In the transfer hydrogenation of acetophenone we obtained a mixture of two deuterated 1-phenylethanols (Scheme 4, **14a** and **14b**).The ratio between **14a** and **14b** (85:15) indicated a specific migration of the hydride, albeit some scrambling was detected.[18] This was probably caused by rearrangement of the hydride complex, starting from HN–Ru–D *via* N=Ru(HD) to DN–Ru–H and subsequent transfer process into acetophenone yielding **14b**. In conclusion the incorporation is in agreement with the monohydride mechanism, implying the formation of a metal hydride species in the catalytic cycle (Scheme 3). Furthermore, this indication is confirmed by the above-mentioned influence of the NH groups. In conclusion, the transfer of hydrogen, in the case of catalyst **A**, is subdivided into the hydride transfer by the metal and the proton transfer by the NH group in analogy to the metal-ligand bifunctional catalysis.[13r]

We demonstrated for the first time the successful application of chiral tridentate pyridinebisimidazoline ligands in the asymmetric ruthenium-catalyzed transfer hydrogenation of aliphatic and aromatic ketones. Enantioselectivities up to >99% *ee* were obtained under optimized reaction conditions. Comparison experiments of **3a** with monoprotected pybims and pybox ligands displayed the crucial influence of the free NH functionality. Mechanistic experiments indicated the transfer of hydrogen from the donor molecule into the substrate *via* a metal-ligand bifunctional mechanism.



Scheme 4. Deuterium incorporation into acetophenone catalyzed by catalyst system **A**.

Experimental Section

General Remarks

All manipulations were performed under an argon atmosphere using standard Schlenk techniques. Isopropyl alcohol was used without further purification (purchased from Fluka, dried over molecular sieves). Sodium isopropoxide was prepared by reacting sodium with isopropyl alcohol under an argon atmosphere (stock solution). All ketones were dried over CaH_2, distilled in vacuum and stored under argon, except 4′-methoxyacetophenone and phenacyl chloride, which were used without further purification. $BuP(Ad)_2$[19] and *N*-phenyl-2-(di-*tert*-butylphosphino)-pyrrole[20] were synthesized according to literature protocols.

General Procedure for the Transfer Hydrogenation of Ketones

In a 10-mL Schlenk tube, the *in situ* catalyst was prepared by stirring a solution of $[RuCl_2(C_6H_5)]_2$ (1.9×10^{-6} mmol), ligand **3a** (3.8×10^{-6} mmol) and PPh_3 (3.8×10^{-6} mmol) in 1.0 mL isopropyl alcohol for 16 h at 65 °C. To this mixture sodium isopropoxide (1.9×10^{-5} mmol in 0.5 mL isopropyl alcohol (stock solution)) was added and the solution stirred at 100 °C for 10 min. After addition of the corresponding ketone (0.38 mmol in 0.5 mL isopropyl alcohol (stock solution)) the reaction mixture was stirred for 1 h at 100 °C. The solution was cooled to room temperature and filtered over a plug of silica. The conversion and *ee* were measured by GC without further manipulations.

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