Accepted Article

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Ru-Catalyzed Transfer Hydrogenation of Nitriles, Aromatics, Olefins, Alkynes, and Esters

Iryna D. Alshakova,[a] Dr.Bulat Gabidullin,[b] and Dr.Georgii I. Nikonov*[a]

Dedicated to Prof. Dr. Yu. A. Ustynyuk on the occasion of his 80th birthday

Abstract: This paper reports the preparation of new ruthenium(II) complexes supported by a pyrazole-phosphine ligand and their application to transfer hydrogenation of various substrates. These Ru complexes were found to be efficient catalysts for the reduction of nitriles and olefins. Heterocyclic compounds undergo transfer hydrogenation with good to moderate yields, affording examples of unusual hydrogenation of all-carbon-rings. Internal alkynes with bulky substituents show selective reduction to olefins with the unusual E–selectivity. Esters with strong electron-withdrawing groups can be reduced to the corresponding alcohols, if ethanol is used as the solvent. Possible mechanisms of hydrogenation and olefin isomerization are suggested on the basis of kinetic studies and labelling experiments.

Introduction

Transfer of a dihydrogen equivalent from an alcohol to an unsaturated moiety, so called transfer hydrogenation (TH), is a useful industrial and laboratory technique that offers the advantage of an easy set up and mild reaction conditions in comparison with direct hydrogenation with hydrogen gas.[1] The usual substrates in TH are ketones and imines,[2] whereas other types of unsaturated compounds received much less attention. In earlier studies, Albrecht et al. and Yamaguchi et al. reported the TH of benzonitrile catalyzed by [(p-cymene)(NHC-olefin)RuCl]+ and RuH2(PPh3)3, respectively.[3] Recently, TH of a large array of nitriles catalyzed by Ru complexes has been reported by our group[4] as well as by the groups of Beller,[5] Kundu,[6] and Hong[7] (Chart 1). The products of these reactions are either primary amines[5a] or imines[4,6,7] obtained as a result of condensation between the amine product and ketone produced from secondary alcohol as a result of TH. With the (Ph3P)3RuCl2 catalyst, Beller et al. also observed secondary TH of the imine products to give secondary amines, affording overall reduction/N-monoalkylation of nitriles.[5b] Whereas the temperatures used in these reactions are usually quite high (110-120°C at 2-10% catalyst load), the application of half-sandwich ruthenium complexes 1[4a] and 2[4b] allowed for much milder reaction conditions (RT at 5% 1 or 60°C at 1% 2).[4a,b]

Transfer hydrogenation of N-heterocycles with Hantzsch esters[8] and formates[4c,9] is well-established whereas the application of alcohols as reducing reagents is less common.[4b,10] Regardless what reducing reagent is used, the usual regioselectivity of transfer hydrogenation is such that the nitrogen containing ring is reduced, leaving the conjugated all-carbon ring (if any) intact.
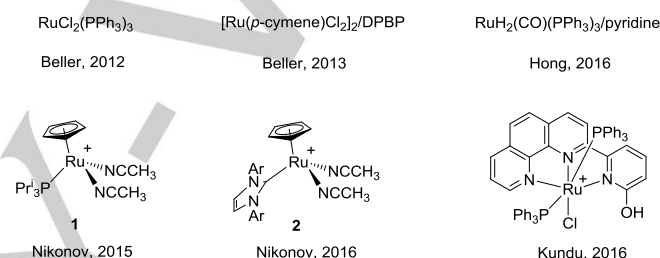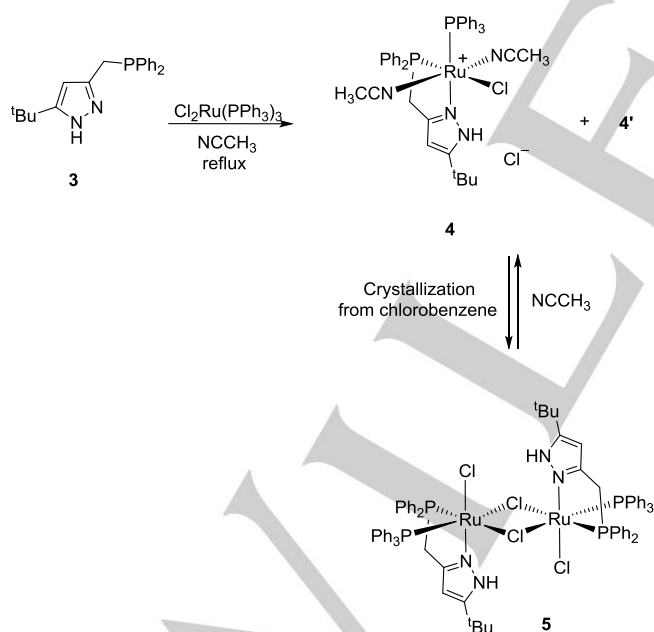
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        Supporting information for this article is given via a link at the end of
        the document.

Chart 1. Ru-based catalyst for the TH of nitriles.

Another class of substrates that has so far received very little attention in the TH are esters. In 2015, we reported the first instance of the TH of esters catalyzed by complex **1**, but the catalyst load was relatively high (5%) and the substrate scope was limited.[4a] Dubey and Khaskin then developed a very efficient TH of esters by ethanol catalyzed by Gusev's (SNS)Ru catalyst.[11] In this process, ethanol was oxidized to ethyl acetate, so that the whole process can be also classified as ester metathesis.

In this paper, we report the preparation of a new pyrazole/phosphine-supported ruthenium complex that shows high activity in the catalytic TH of nitriles, N-heterocycles, and esters, as well as the reduction of olefins and alkynes. The interesting aspect is that we observed rare instances of reduction of all-carbon aromatic cycles and semi-hydrogenation of alkynes with an unusual E-selectivity.

Results and Discussion

Thiel et al. have previously reported the application of pyrazole-based complexes of ruthenium with potential bifunctional activity in the TH of ketones.[12] The Yu group prepared Ru catalysts supported by pyrazole/pyridine ligands and achieved a very high TOF (up to 720000 h⁻¹) in the TH of ketones.[13] We previously reported the application of the Grotjahn's pyrazole/phosphine ligand **3**[14] to the syntheses of ruthenium complexes but only moderate catalytic activity in the TH of carbonyls was achieved.[15] More recently, we have found out that variations of reaction conditions resulted in a new cationic complex that shows increased catalytic activity. Refluxing RuCl2(PPh3)3 and the

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ligand **3** in acetonitrile afforded a mixture of two isomeric complexes **4/4'** containing one pyrazole/phosphine ligand (Scheme 1). The $^{31}P\{^{1}H\}$ NMR spectrum of the mixture showed two pairs of doublets with resonances at 61.8 and 42.7 ppm and at 57.8 and 43.7 ppm, respectively. The *cis* position of the phosphorous atom of the NP-ligand with respect to triphenylphosphine in both isomers is assumed on the basis of small coupling constants $J_{PP} = 25.6$ Hz and $J_{PP} = 27.4$ Hz, respectively. The poor solubility of this compound in nonpolar solvents and the presence of two nitrile ligands suggest that it has the cationic structure shown in Scheme 1. The major isomer **4** shows a C_s symmetry pattern in the ^{1}H NMR spectrum, indicating the trans arrangement of the nitrile ligands, whereas **4'** is C_1 symmetric. These NMR data for **4'** are consistent with four possible structures **4'a-d** shown in Chart 2. To distinguish between these possibilities, NOE experiments were performed. Excitation of the NCCH$_3$ signal of **4** at 1.86 ppm revealed that this ligand is in proximity to the CH group of the pyrazole ring, which is consistent with the proposed structure. Analogous excitation of the NCCH$_3$ signal in **4'** at 2.01 ppm did not return any NOE, whereas excitation of the second NCCH$_3$ signal at 1.08 ppm showed proximity to the phenyl groups of the NP-ligand but not to the pyrazole ring. Of the four possible structures **4'a-d**, only **4'a** does not have any acetonitrile ligand and the pyrazole ring in the relative orientation similar to that in **4**, and therefore **4'a** is the preferred structure. While we failed to obtain X-ray quality crystals for either **4** or **4'** from acetonitrile, crystallization from chlorobenzene by hexanes layering led to the formation of dimer **5** that does not feature the acetonitrile ligand. In solution, complex **5** retains the *cis* disposition of phosphine ligands evinced by the J_{PP} constant of 37.6 Hz. When two equivalents of acetonitrile are added to a solution of **5** in chlorobenzene, the dimer breaks down with the formation of complexes **4** and **4'**.
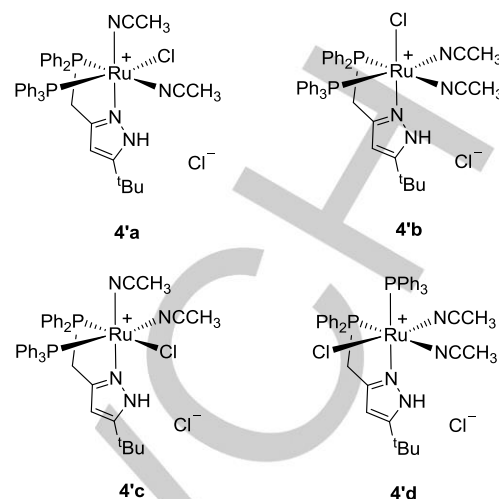

Chart 2. Possible structures of **4'**.

The molecular structure of **5** determined from X-ray analysis is shown in Figure 1. Although the quality of the crystal was rather low and a relatively high R factor was achieved, the quality of the data was sufficient to establish the connectivity of the molecule and discuss key structural parameters. The molecule of **5** is dimeric, with each ruthenium center adopting a distorted octahedral geometry. The phosphine ligands are located *cis* to each other and *trans* to the bridging chloride ligands. Such a sterically unfavorable orientation is likely dictated by an electronic factor, that is the stronger *trans* influence of phosphine relative to chloride. The Ru(1)-P distances are comparable for the NP and PPh$_3$ ligands at 2.249(3) and 2.269(4) Å, respectively, and are close to the Ru-P bond length in the related complex (NP)RuCl$_2$(DMSO)$_2$ (2.299(3) Å), featuring the same pyrazole/phosphine ligand **3**.[15] The Ru(1)-Cl distances to the bridging chlorides are the same, 2.491(3) and 2.494(3) Å, whereas the terminal Ru(1)-Cl(3) distance is shorter
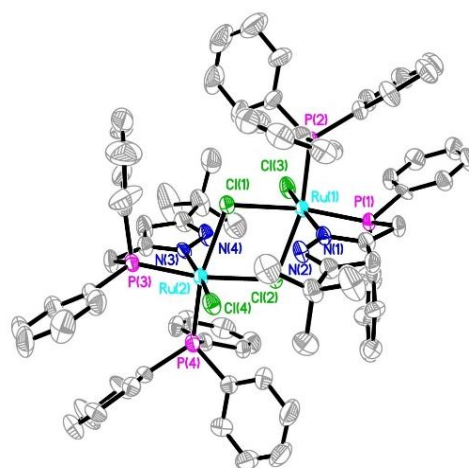

Scheme 1. Preparation of ruthenium catalysts.

Figure 1. Molecular structure of complex **5**. Thermal ellipsoids are shown at 30% probability. Hydrogen atoms are omitted for clarity.

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(2.429(3) Å), as expected. This latter distance is also shorter than the Ru-Cl bond length in (NP)RuCl$_2$(DMSO)$_2$ (2.465(3) Å) which also features the phosphine ligand located *trans* to a chloride. The positions of the bridging chlorides in **5** are symmetrical, with Ru(2)-Cl(1) being 2.497(3) Å and Ru(2)-Cl(2) being 2.498(3) Å. Other metrics associated with the second part of the dimer show trends similar to those observed for the first part.

Catalytic studies. Transfer Hydrogenation of Acetophenone. The catalytic efficiency of complexes **4/4'** and **5** in transfer hydrogenation was first probed in the reduction of acetophenone. The experiments were conducted at 80°C in 2-propanol (solvent) with 1 mol% of catalyst and 1 mol% of base. The addition of a base is considered to be an important factor in the TH after the pioneering work of Bäckvall who showed that the external base mediates conversion of metal halide precursors into metal alkoxides which then undergo β-H elimination with formation of catalytically active hydride complexes.[16,17]

Complexes **4/4'** showed high activity in TH, providing the maximum 90% conversion of acetophenone to 1-phenylethanol within 35 min (Table 1, entry 2).[18] Reducing the catalyst load to 0.5 mol% caused a noticeable decrease in catalytic activity (Table 1, entry 3). The catalyst retains significant efficiency at room temperature too, as 90% conversion was achieved after only 100 min (Table 1, entry 4). Utilizing 2 mol% of KO*t*Bu did not lead to an improvement of the catalytic rate (Table 1, entry 5), so that a low base concentration can be used. The dimer **5** was found to be as active as **4/4'** (Table 1, entry 6), with no induction period observed. For the reasons of easier accessibility, the mixture **4/4'** was applied as a precatalyst in subsequent studies.

Table 1. Transfer hydrogenation of acetophenone catalyzed by ruthenium NP-complexes.

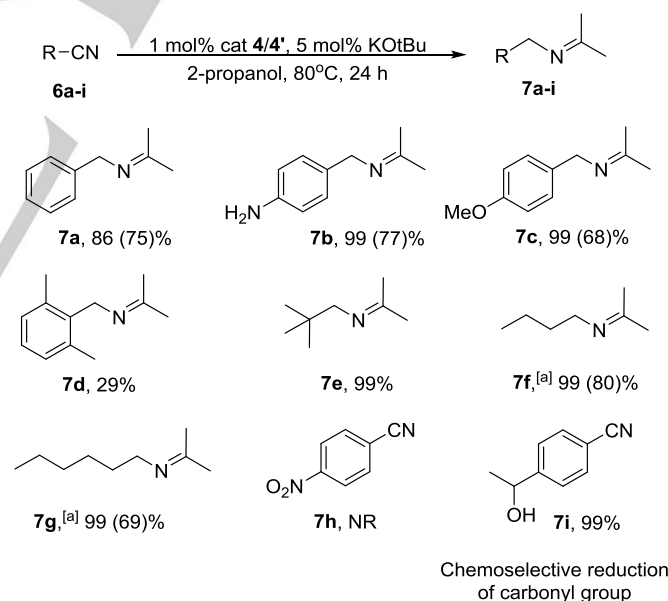| Entry	Complex, mol%	KO^{t}Bu, mol%	Temp.	Time	Conver.[a]
1[b]	-	1	80°C	1 h	NR
2	**4/4', 1**	**1**	**80°C**	**35 min**	**90%**
3	**4/4', 0.5**	0.5	80°C	2 h	52%
4	**4/4', 1**	1	RT	100 min	90%
5	**4/4', 1**	2	RT	100 min	90%
6	**5, 1**	1	80°C	35 min	90%

[a] Conversion was determined by ^{1}H NMR spectroscopy; [b] no complex was added.

Transfer Hydrogenation of Nitriles. Encouraged by these preliminary results, we applied complexes **4/4'** in the TH of nitriles. However, the reduction of benzonitrile under the conditions optimized for acetophenone did not lead to the formation of an appreciable amount of the product even after 24 hours. Nevertheless, further optimization of the reaction conditions showed that increased concentration of base causes a noticeable acceleration of the reaction while still maintaing a low load of the ruthenium catalyst (Table S1). Thus, up to 58% conversion can be observed with 5 mol% KO*t*Bu after 3 hours and 75% after 24 hours. Further increase in the base concentration did not lead to any significant improvement of the catalytic activity. The effect of the

alkali metal cation was investigated, but using LiO*t*Bu or NaO*t*Bu instead of KO*t*Bu did not result in any change in the activity of the catalyst. The use of base alone, without any Ru complex, did not result in any reduction.

As it was previously observed for catalysts **1** and **2**, the initially formed amine product, reacts further with acetone, the by-product of the TH in 2-propanol, to yield ketimine as the final product. No further reduction of the ketimine to a secondary amine, which was observed by Beller et al. for the (Ph$_3$P)$_3$RuCl$_2$ catalyst, takes place under these conditions. We attribute the difference between our observations and the Beller results to the increased steric hindrance of catalysts **4/4'**, so that the ketimine becomes too bulky to get access to the catalytic site. The treatment of the imine products with HCl affords the corresponding primary ammonium salts.

Further substrate screening showed that aromatic nitriles with electron donating groups, such as amino and alkoxy, are reduced easier than benzonitrile, with full conversion in 24 hours, i.e. **6b** and **6c** in Scheme 2. Full conversions were also observed for aliphatic nitriles, although the TH of butyronitrile and valeronitrile requires more time than the TH of pivalonitrile (**6f,g** vs **6e**). The TH of sterically hindered 2,6-dimethylbenzonitrile afforded a low yield of the imine product **6d** (29% after 24 hours). No reaction was observed in the TH of 3-nitrobenzonitrile likely because of poisoning of the catalyst by the nitro group of the substrate. *p*-Acetylbenzonitrile, featuring both the keto and nitrile functionalities, was selectively reduced at the keto group (**7i** in Scheme 2).

$$R-CN \xrightarrow[\text{2-propanol, 80°C, 24 h}]{\text{1 mol\% cat 4/4', 5 mol\% KOtBu}} R \diagup N \diagdown$$

6a-i → **7a-i**

7a, 86 (75)%

7b, 99 (77)%

7c, 99 (68)%

7d, 29%

7e, 99%

7f,[a] 99 (80)%

7g,[a] 99 (69)%

7h, NR

7i, 99%

Chemoselective reduction of carbonyl group

Scheme 2. Transfer hydrogenation of nitriles. Reaction conditions: 1 mol% **4/4'**, 5 mol% KO*t*Bu in 2 ml of 2-propanol at 80°C. Conversions were determined by ^{1}H NMR spectroscopy, isolated yields of the corresponding ammonium salts are shown in parentheses. [a] Heating for 36 h.

Transfer Hydrogenation of Heterocyclic Compounds. The TH of heterocycles was investigated next. As for nitriles, the dependence of the reaction rate on the base loading was also noticed (Table S2). Thus, it was found that the TH of quinoline accelerates when the amount of

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KOtBu increases up to 10 mol%. Further increase of the base loading does not lead to any improvement. Thus, a 84% conversion of quinoline can be reached in 24 hours.

The scope of *N*-heterocyclic substrates reduced by this catalytic system is shown in Scheme 3. Using the conditions optimized for quinoline, 1,5-naphthyridine **8b** and quinoxaline **8c** can be hydrogenated in good yields. Unexpectedly, reduction of isoquinoline **8d** and quinaldine **8e** resulted in hydrogenation of the all-carbon rings, although the conversion in the latter case was low. The exact reason for this unusual regioselectivity is unknown, although we can speculate that in the case of quinaldine the reduction of the N=C bond is not possible for steric reasons (see the discussion above why ketimines are not reduced).For isoquinoline, however, we believe that an electronic factor can be responsible. In the case of phenanthridine **8f**, the C-N double bond was hydrogenated with moderate conversion after 24 hours. Interestingly, the yield did not increase upon addition of a larger amount of the catalyst, suggesting that an equilibrium was reached. We attribute this observation to the propensity of 5,6-dihydrophenanthridine to serve as hydrogen source.[19]
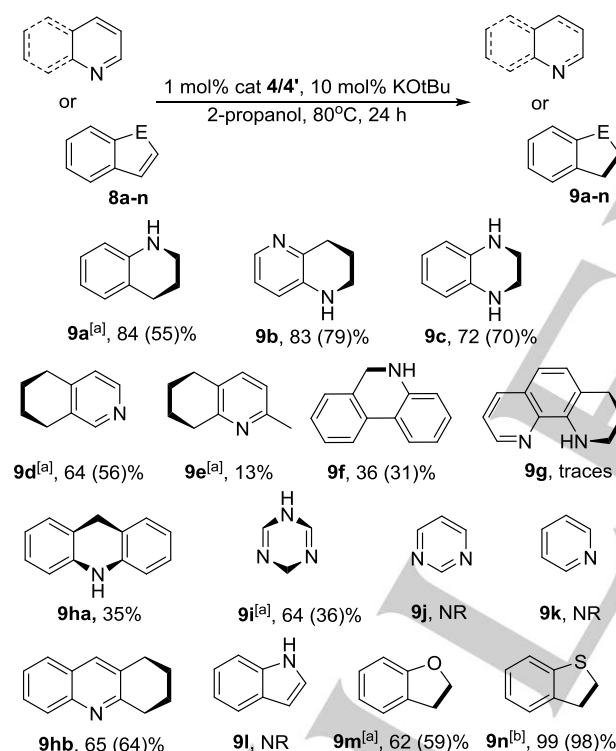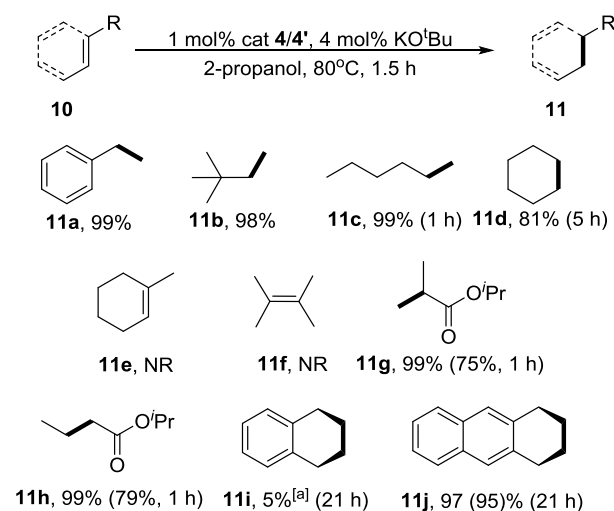

Scheme 3. Transfer hydrogenation of heterocyclic compounds. Reduced bonds are highlighted in bold. Reaction conditions: 1 mol% **4/4'**, 10 mol% KOtBu in 3 ml of 2-propanol at 80°C. Conversions were determined by ^{1}H NMR spectroscopy, isolated yields of selected products are shown in brackets. [a] 5 mol% **4/4'**, 50 mol% KOtBu. [b] 5h.

Attempted TH of 1,10-phenanthroline **8g** returned only a very small amount of the product, with one of the external heterocycles being reduced, although the loading of the catalyst was increased to 5 mol%. The reason for the low yield is likely the ability of 1,10-phenanthroline to act as a bidentate ligand and thus poison the catalyst. Acridine **8h** was

hydrogenated with excellent yield in 21 hours to give a mixture of 9,10-dihydroacridine **9ha** and 1,2,3,4-tetrahydroacridine **9hb**, the latter species being the major product and having the all-carbon ring hydrogenated. In the case of triazine **8i**, only one of the C=N bonds can be reduced in moderate yield. Pyrimidine **8j** gave only 9% conversion , whereas the strongly aromatically stabilized pyridine **8k** cannot be hydrogenated under these conditions; neither is the five-membered heterocycle in indole **8l**. In contrast, benzofuran **8m** was found to be more active in the TH under these conditions, so that 66% conversion can be achieved. Likewise, benzothiophene **8n** was fully converted to 2,3-dihydrothiophene with 1 mol% catalyst loading within 5 hours. The difference between the nitrogen-containing five-membered cycles on one side, and oxygen- and sulfur-containing cycles on the other, can be attributed to the presence of the NH bond in indole which may lead to an interaction with the catalyst and inhibition.

Transfer Hydrogenation of C=C Bonds. Intrigued by the observation of carbon ring reduction, we decided to extend the use of complexes **4/4'** to the reduction of alkenes and conjugated arenes. Treatment of 3,3-dimethylbutene-1 with 1 mol% of **4/4'** and 1 mol% of KOtBu in 2-propanol did not even give traces of the reduced product after 1.5 hours at 80°C. However, an increase of base loading to 2 mol% resulted in dramatic enhancement of the catalytic activity, so that 90% conversion was achieved after 1.5 h. (Table S3). Experiments with 3 and 4 mol% KOtBu showed only slight improvement of the catalyst performance. Control experiment without ruthenium complexes did not lead to any reduction of the double bond.

With this catalytic system in hand, the substrate scope was screened (Scheme 4). Mono- and disubstituted alkenes were easily reduced. Moreover, no isomerization was observed in the TH of terminal hexene **10c**, but more sterically encumbered tri- and tetra-substituted alkenes did not enter this reaction. Conjugated α,β-unsaturated esters, such as ethyl methacrylate **10g** and ethyl crotonate **10h**, were reduced to the corresponding saturated esters in high yield. Naphthalene underwent only marginal reduction but the less aromatically stabilized anthracene **10j** was hydrogenated at one of the lateral rings to 1,2,3,4-tetrahydroanthracene in excellent yield within 21 hours.
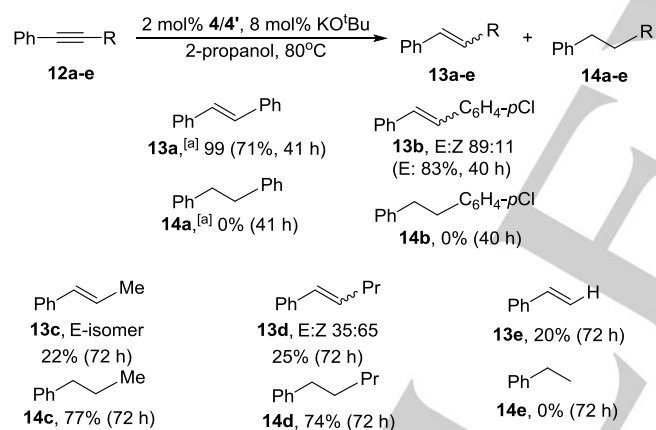

Scheme 4. Transfer hydrogenation of unsaturated hydrocarbons. Reduced bonds are highlighted in bold. Reaction conditions: 1 mol% **4/4'**, 4 mol% KOtBu in 2 ml of 2-

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propanol at 80°C. Conversions were determined by ^{1}H NMR spectroscopy, isolated yields of selected products are shown in brackets. [a] 3 mol% **4/4'**, 12 mol% KO*t*Bu.

Transfer Hydrogenation of Alkynes. Semi-hydrogenation of alkynes is of significant current interest as it provides a route to valuable olefin products,[20,21,2223] but very little is known about the application of TH in this reaction.[24] We therefore decided to test this Ru catalytic system in the reduction of alkynes, although the catalyst load was increased to 2 mol% (Scheme 5). Rewardingly, diphenylacetylene **12a** was selectively reduced to diphenylethylene **13a** with the unexpected *E*-selectivity evinced from the observation of the olefinic CH peak at 7.16 ppm in the ^{1}H NMR spectrum in CDCl3 and by comparison to literature data.[21f] This fact is of significance because previous studies on the semi-transfer hydrogenation of alkynes showed *Z*-selectivity.[24] Semi-hydrogenation was also observed for 1-chloro-4-(phenylethynyl)benzene **12b** with the preferential formation of *E*-isomer (*E:Z* = 89:11). However, alkynes with less bulky substituents, such as methylphenylacetylene **12c** and 1-phenyl-1-pentyne **12d**, were first reduced to mixtures of *Z* and *E* alkenes (see Supporting Information) and then further hydrogenated to the corresponding aliphatics, propylbenzene **14b** and pentylbenzene **14d**, respectively. Attempted reduction of a terminal alkyne, phenylacetylene **12e**, resulted in a very low conversion. We attribute this behavior to the ability of monosubstituted alkynes to poison the catalyst by formation of stable π-alkyne metal complexes or by C-H bond activation.
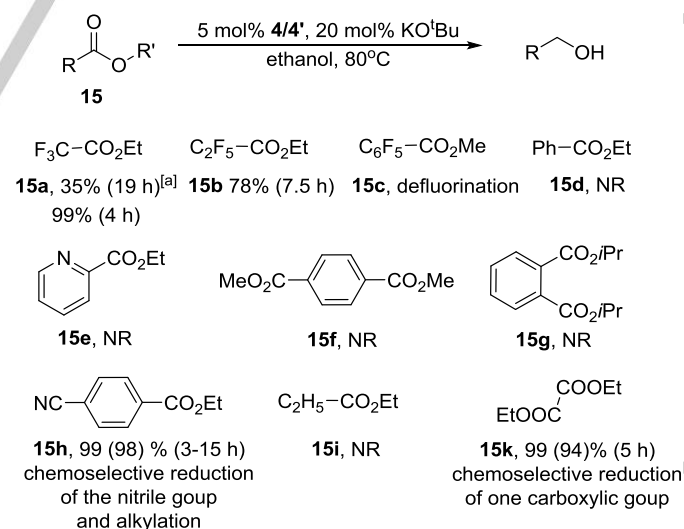

Scheme 5. Transfer hydrogenation of alkynes. Reaction conditions: 2 mol% **4/4'**, 2 mol% KO*t*Bu in 2 ml of 2-propanol at 80°C. Conversions were determined by ^{1}H NMR spectroscopy, isolated yields of selected products are shown in brackets. [a] 1 mol% **4/4'**, 4 mol% KO*t*Bu.

Transfer Hydrogenation of Esters. The very first application of alcohols in the TH was accomplished by Meerwein[25] with the application of ethanol as the reaction media.[26] However, ethanol and other primary alcohols were later replaced by 2-propanol because secondary alcohol oxidation to ketone is more thermodynamically favorable than the oxidation of primary alcohol to aldehyde and to avoid complications arising from condensation reactions of the acetaldehyde product (in the case of ethanol) with the usual ketone and imine substrates.[27] However, recently ethanol received renewed attention as a green, renewable reagent in the TH.[28] As mentioned in the introduction, the TH of esters

is a very recently discovered phenomenon, likely because in this case the equilibrium of reduction by alcohols is usually shifted toward the side of starting compounds. However, it is here where the application of ethanol may be very beneficial because acetaldehyde produced in the first step of the TH can under basic conditions undergo the Tishchenko reaction[29] with the formation of ethyl acetate, resulting in the formal ester metathesis, i.e. a thermodynamically neutral process.

With this idea in mind, we opted to study the TH of esters in ethanol. Given the generally lower activity of esters in reduction processes, we started our investigation with electrophilically activated substrates. Gratifyingly, with 5 mol% load of the catalyst **4/4'**, full conversion of trifluoroacetate **15a** to 1,2,3-trifluoroethanol was accomplished in 4 hours (Scheme 6). As expected, ethyl acetate was ideantified as the co-product. Pentafluoropropionate (**15b**) can be reduced in good yield, although a longer reaction time is required. In the case of pentafluorobenzoate (**15c**), there was no reduction of the ester group. However, several products were observed, which on the basis of a ^{19}F{^{1}H} NMR spectrum may be attributed to the products of defluorination;[30] but more research is required to delineate their nature. Other aromatic substrates, having both electron-neutral (**15d**) and electron-poor rings (**15e-g**), were also unreactive. 4-Cyanobenzoate **15h**, however, reacted at the cyano group affording an amine, which further underwent coupling with acetaldehyde to form an imine. Unlike the ketimines formed in the TH of nitriles in 2-propanol, this aldimine is more sterically accessible and can be further hydrogenated under the catalytic conditions to give a secondary amine (see Supporting Information). Likewise, α,β-unsaturated ester **11h** (Scheme 4) was chemoselectively hydrogenated at the C-C double bond. However, the oxalate **15k** was chemoselectively reduced at one ester group in excellent yield after only 5 hours. The product of the latter reaction is hydroxyacetate, which is not sufficiently activated for the subsequent reduction of the remaining ester group.

Scheme 6. Transfer hydrogenation of esters. Reaction conditions: 5 mol% **2/2'**, 20 mol% KO*t*Bu in 3 ml of ethanol at 80°C. Conversions were determined by ^{1}H NMR spectroscopy. [a] 1 mol% **4/4'**, 4 mol% KO*t*Bu.

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Kinetic Studies of Catalytic Transfer Hydrogenation of Alkenes.

To shed light on the possible mechanism of catalytic TH, kinetic studies were performed for the TH of cyclohexene as a model substrate. Cyclohexene was chosen because of the relatively low rate of its hydrogenation in comparison with external alkenes. The fact that more than two equivalents of a base are required for the TH of alkenes may indicate that the true catalyst is a dihydrido-ruthenium complex.[16] However, no hydrido complexes could be detected by NMR monitoring of the reaction mixture, likely because of their labile nature. Neither were we able to observe any ruthenium hydrides while attempting reactions of **4/4'** with sodium *tert*-butoxide, lithium triethylborohydride or L-selectride in isopropanol. A mercury drop test was performed to determine the heterogeneity of the catalytic system. Neither inhibition nor deceleration of the reaction, as compared to a reference reaction with the same catalyst and substrate under identical conditions, was observed, indicating the homogenic nature of the reaction mixture.

Reduction of cyclohexene was studied under pseudo first order conditions by using neat 2-propanol. The progress of the reaction (Figure 2) was monitored by ^1H NMR spectroscopy. The kinetic analysis was done with the help of Dynamics Center 2.4.5. The data were truncated at about 20% conversion (the initial rate analysis), to minimize the effect of possible catalyst deactivation. Linearization of the data in coordinates $-Ln(x/x_0)$ vs time revealed the first order in the substrate. A series of experiments were then performed by varying the amount of complexes **4/4'** and the base (1, 2, 3, 4, 5 mol% of **4/4'** and 4, 8, 12, 16, 20 mol% of KO*t*Bu, respectively). The effective rate constants obtained for each catalyst load were plotted against the amount of the catalyst, which revealed a linear dependence on the catalyst (Figure 3).
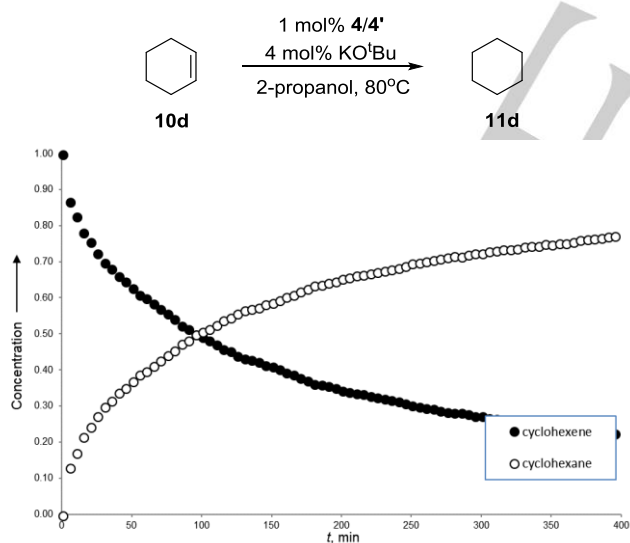
Figure 2. Kineric profile for the TH of cyclohexene catalyzed by **4/4'** under the pseudo first order conditions. Points were created with Dynamics Center 2.4.5.
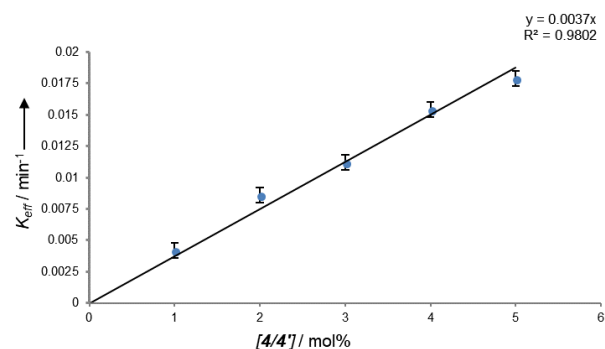
Figure 3. The dependence of the effective rate constant K on the catalyst loading under the pseudo first order conditions. K^{eff} values were derived from Dynamics Center 2.4.5.

The reaction rate does not change when an O-labelled alcohol, $(CH_3)_2CH$-OD, was used as the solvent (Table 2). However, when the reaction was performed in the fully deuterated 2-propanol-d_8, a kinetic isotope effect of 3.2 was observed. This significant KIE is consistent with the cleavage of the C-H bond in the rate determining step. Moreover, we observed scrambling of deuterium over all positions in the product, as well as over the yet unreacted substrate, which indicates the reversibility of hydride transfer and intermediacy of a Ru-cyclohexyl complex.

Table 2. Determination of kinetic isotope effect.

Entry	Solvent	K, min^{-1}	KIE
1	$(CH_3)_2$-CH-OH	0.00419	—
2	$(CH_3)_2$-CH-OD	0.00408	1.0
3	$(CD_3)_2$-CD-OD	0.00131	3.2

The proposed mechanism of the TH of olefins catalyzed by **4/4'** is presented on Figure 4. This is a conventional dihydride mechanism.[17,31] A reaction of complexes **4/4'** with alcohol under the presence of an external base produces the putative dihydride complex **16**. Replacement of the labile nitrile ligand by substrate would give the adduct **17**. Alkene insertion into the Ru-H bond results in the alkyl complex **18**. This step should be reversible, which accounts for the observed D-scrambling. Subsequent coordination of alcohol to the created vacant site, followed by reductive elimination, releases the cyclohexane product. Proton shift would generate the alkoxide **19**, which after β-H shift would afford the dihydride complex **20** with a π-coordinated ketone. Substitution of the latter by alkene closes the catalytic cycle.
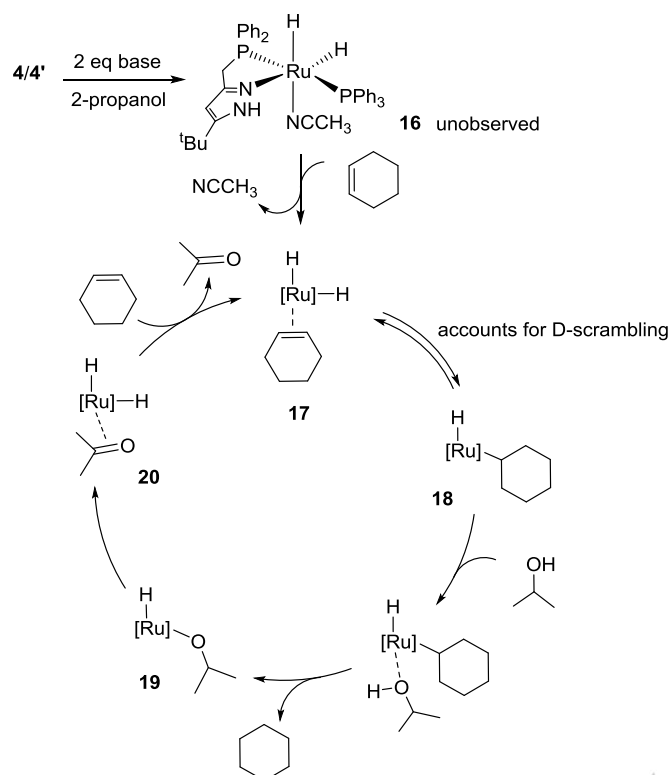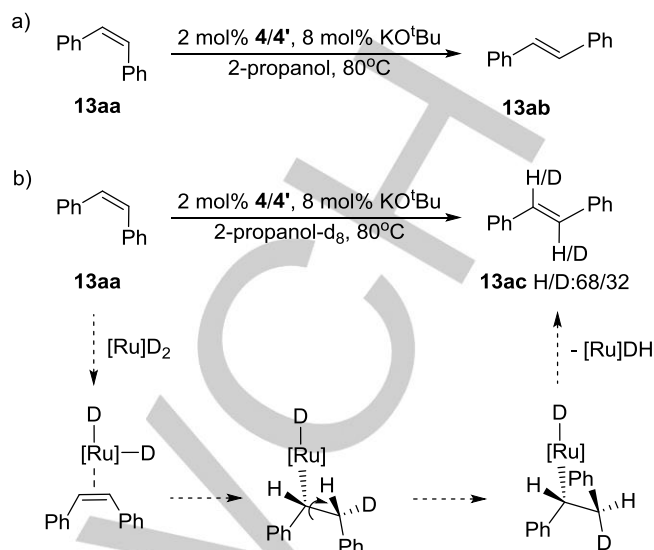
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Figure 4. Proposed catalytic cycle for the TH of olefins with **4/4'**.

Scheme 7. a) Isomerization of *cis*-stilbene under the catalytic conditions. b) the mechanism of H/D scrambling and the stilbene isomerization

Conclusions

A new ruthenium(II) complex bearing a pyrazole-based NP-ligand was synthesized as a mixture of two isomers **4** and **4'** and applied to the transfer hydrogenation of nitriles, heterocyclic compounds, olefins, alkynes, and esters. Aromatic and aliphatic nitriles, except sterically hindered, can be reduced to primary amines with excellent yields. Different compounds containing unsaturated heterocycles can be reduced with moderate to good yields. In some cases, such as acridine, isoquinoline, and quinaldine, we observed unusual hydrogenation of the conjugated benzene ring, instead of the usually observed reduction of the heterocycle. Mono- and disubstituted alkenes can be efficiently reduced with excellent yields, whereas sterically encumbered alkenes were unreactive. Diphenylacetylene and 1-chloro-4-(phenylethynyl)benzene also undergo TH under the proposed conditions to give alkenes with the unusual *E*-selectivity. Some electrophilically activated esters were shown to be reduced if ethanol is used as solvent and hydrogen source instead of 2-propanol. Based on kinetic and labelling studies, a mechanism of the TH of alkenes and isomerization of *Z* to *E* alkenes was proposed.

When applied to alkyne reduction, this mechanism predicts the formation of *Z*-alkenes, i.e. the products of *cis*-hydrogenation. However, our experiments revealed the preferential formation of the more thermodynamically stable *E*-alkenes. Fout et al. have recently shown by the application of para-hydrogen that Co-catalyzed hydrogenation of alkynes proceeds by the expected *cis*-addition followed by isomerization.[21g] We believe that a similar process occurs under our catalytic conditions. To test the possibility of a Ru-mediated *Z-E* isomerization, we heated *cis*-stilbene **13aa**, the possible product of initial *cis*-hydrogenation of tolane, under our catalytic conditions (Scheme 7a). Full conversion to the *trans*-stilbene **13ab** was observed after 3 hours.

The way how *Z-E* isomerization takes place is also of interest. For the related Ru-catalyzed hydrogenation of alkynes to *E*-olefins, Fürstner suggested a mechanism based on the formation of alkylidene complexes.[32] To understand better the isomerization process in the **4/4'** mediated catalysis, a labelling experiment was conducted. Thus, *cis*-stilbene was heated in 2-propanol-d$_8$ to yield the deuterated *trans*-stilbene **13ac** (Scheme 7b). The possible rationalization of this transformation is that *Z-E* isomerization occurs as a result of interrupted hydrogenation of olefin. Namely, insertion of alkene into the Ru-H bond affords an alkyl intermediate, which is a reversible process (e.g. see **17** → **18**, Figure 4) and should lead to D-scrambling if the C-H elimination step is much slower. Therefore, we believe that *Z-E* isomerisation may proceed via a sequence of migratory insertion, rotation around the C-C bond, and β-hydrogen elimination (Scheme 7b).

Experimental Section

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Synthesis of 4/4'. RuCl$_2$(PPh$_3$)$_3$ (0.800 g, 0.836 mmol) was dissolved in acetonitrile. 3-tert-butyl-5-[(diphenylphosphanyl)methyl]-1H-pyrazole (**3**) (0.270 g, 0.836 mmol) was added. The mixture was refluxed under the nitrogen atmosphere for 2 hours. After that acetonitrile was removed under reduced pressure, the yellow residue was recrystallized by slow diffusion of hexane into a saturated chloroform solution at -30°C. A yellow powder was obtained. Yield: 0.380 g, 57%. ^{1}H NMR (CDCl$_3$; 400 MHz) for a mixture of two isomers **4** (minor) and **4'** (major): δ = 12.12 (s, NH, minor), 11.84 (s, 1 H, NH, major), 7.72-7.79 (m, 6H, Ph-H, major), 7.58-7.65 (m, 2H, Ph-H, major), 7.43-7.57 (m, 27H, Ph-H, major), 7.31-7.39 (m, 27H, Ph-H, major), 7.22-7.30 (m, 16H, Ph-H, major), 7.01-7.17 (m, 27H, Ph-H, major), 6.39 (s, 1H, CH, major), 6.18 (s, 1H, CH, minor), 3.56 (d, J_{HH} = 9.98 Hz, 2H, CH$_2$, major), 3.43-3.61 (m, CH$_2$ - minor), 2.01 (s, CH$_3$CN, minor), 1.86 (s, 6H, CH$_3$CN, major), 1.44 (s, 9H, C(CH$_3$)$_3$, major), 1.36 (s, C(CH$_3$)$_3$, minor), 1.08 (s, CH$_3$CN, minor); ^{13}C NMR (CDCl$_3$; 400 Hz) for a mixture of two isomers: δ = 172.8 (minor), 157.3, 155.3 (minor), 152.0 (d, J_{PC} = 4.5 Hz, major), 150.8 (d, J_{PC} = 4.5 Hz, minor), 136.0 (d, J_{PC} = 43.0 Hz, major), 134.6 (d, J_{PC} = 10.1 Hz, minor), 134.0 (d, J_{PC} = 9.0 Hz, major), 133.9 (minor), 133.7 (d, J_{PC} = 41.5 Hz, major), 132.1 (d, J_{PC} = 9.0 Hz, major), 131.6 (d, J_{PC} = 9.0 Hz, major), 131.2 (d, J_{PC} = 2.2 Hz, major), 130.1 (d, J_{PC} = 9.0 Hz, major), 129.3 (d, J_{PC} = 2.2 Hz, minor), 128.9 (d, J_{PC} = 10.1 Hz, major), 128.7 (d, J_{PC} = 2.2 Hz, minor), 128.1 (d, J_{PC} = 9.6 Hz, major), 127.8 (d, J_{PC} = 9.2 Hz, major), 127.2 (d, J_{PC} = 9.2 Hz, minor), 127.5 (NCCH$_3$, major), 119.94 (NCCH$_3$, minor), 101.3 (d, J_{PC} = 9.2 Hz, major), 100.0 (d, J_{PC} = 9.8 Hz, minor), 34.9 (d, J $_{PC}$ = 28.2 Hz, minor), 34.8 (d, J_{PC} = 28.9 Hz, major), 32.0, 31.7 (minor), 31.2 (minor), 30.0, 22.6 (CH$_3$CN, minor), 4.3 (CH$_3$CN), 3.11 (CH$_3$CN, minor); ^{31}P {1H} NMR (CDCl$_3$; 400 MHz): δ = 62.9 (d, J_{PP} = 24.9 Hz, 1 P, NP-ligand, major), 58.9 (d, J_{PP} = 29.8 Hz, NP-ligand, minor), 44.1 (d, J_{PP} = 29.8 Hz, PPh$_3$, minor), 42.6 (d, J_{PP} = 29.8 Hz, 1 P, PPh$_3$, major) ppm. ESI-MS (positive mode): m/z 803.2 C$_{42}$H$_{44}$ClN$_4$P$_2$Ru], 762.2 [C$_{40}$H$_{41}$ClN$_2$P$_2$Ru]. FTIR (KBr): $\tilde{v}$ = 529.85 (S), 722.15 (s), 746.48 (m), 999.23 (w), 1028.05 (w), 1090.98 (m), 11.87.06 (w), 1288.42 (w), 1315.43 (w), 1367.15 (w), 1435.11 (s), 1483.36 (m), 1622.13 (m), 1668.45 (m), 22.53.71 (m), 2274.62 (m), 2973.90 (m), 3055.33 (m), 3399.98 (m, br) cm^{-1}. El. Anal. for C$_{42}$H$_{44}$Cl$_2$N$_4$P$_2$Ru: calcd. C 60.14, H 5.29, N 6.68; found. C 60.25, H 5.04, N 7.03.

Synthesis of 5. Mixture of isomers **4/4'** was dissolved in chlorobenzene. Orange crystals were obtained by slow diffusion of hexanes at -30°C. ^{1}H NMR (C$_6$D$_5$Br; 400 MHz): δ = 13.37 (s, 1 H, NH), 8.03-8.13 (m, 2H, Ph-H), 7.54-7.65 (m, 6H, Ph-H), 7.40-7.50 (m, overlapped with C$_6$H$_5$Br), 7.00-7.26 (m, overlapped with C$_6$H$_5$Br), 6.86-6.94 (m, 6H, Ph-H), 6.10 (d, J = 1.49 Hz, CH), 3.54-3.73 (m, 1H, CH$_2$), 2.98 (dd, J = 5.64, 15.84, 1H, CH$_2$), 1.67 (s, 9H, C(CH$_3$)$_3$); ^{13}C NMR (C$_6$D$_5$Br; 400 MHz): δ = 157.1, 151.5, 136.1 (d, J_{CP} = 43.7 Hz), 134.5 (d, J_{CP} = 9.0 Hz), 125.99-131.99 (overlapped with C$_6$D$_5$Br), 100.9 (d, J_{CP} = 14.5 Hz), 32.0, 30.3, 30.6 (d, J_{CP} = 8.4 Hz); ^{31}P {1H} NMR (C$_6$D$_5$Br; 400 MHz): δ = 59.8 (d, J_{PP} = 34.8 Hz, 1P, NP-ligand), 53.9 (d, J_{PP} = 37.6 Hz, 1P, PPh$_3$) ppm. ESI-MS (positive mode): m/z 1479.3 [C$_{76}$H$_{76}$Cl$_3$N$_4$P$_4$Ru$_2$], 721.2 [C$_{38}$H$_{38}$ClN$_2$P$_2$Ru]. FTIR (KBr): $\tilde{v}$ = 518.85 (s), 696.30 (s), 746.45 (m), 999.13 (w), 1028.06 (w), 1091. 71 (m), 1159.22 (w), 1188.15 (w), 1288.45 (w), 1315.45 (w), 1367.53 (m), 1435.04 (s), 1483.26 (m), 1573.91 (w), 1622.13 (m), 1668.43 (m), 2960.73 (m), 3055.24 (m), 3396.64 (m, br) cm^{-1}. El. Anal. for C$_{76}$H$_{76}$Cl$_4$N$_4$P$_4$Ru$_2$: calcd. C 60.32, H 5.06, N 3.70; found C 60.58, H 5.20, N 4.38.

General Procedure for the TH of Nitriles. A Schlenk flask was charged with nitrile (0.50 mmol), a stock solution of **4/4'** in 2-propanol (0.42 mL), a stock solution of KO*t*Bu in 2-propanol (0.28 mL), and 2-propanol (1.3 mL) under nitrogen atmosphere. The flask was heated at 80°C. The progress of the reaction was monitored by NMR spectroscopy. To isolate the product as an ammonium salt, the reaction mixture was treated with aqueous HCl (1M, 1.5 mL), and stirred for 1 hour at r.t. The solvent was removed under the vacuum and water (5 mL) was added to the residual solid to dissolve the ammonium salt. It was crystallized then by hexane (1 mL) layering. The ammonium salts were obtained as yellowish or cream-colored solids.

General Procedure for the TH of Heterocyclic Compounds. A Schlenk flask was charged with a heterocyclic compound (0.50 mmol), a stock solution of **4/4'**

in 2-propanol (0.42 mL), a stock solution of KO*t*Bu in 2-propanol (0.56 mL), and 2-propanol (1.3 mL) under N$_2$ atmosphere. The flask was heated at 80°C. The progress of the reaction was monitored by NMR spectroscopy. When the highest possible conversion of the substrate to the corresponding hydrogenated product was achieved, the solvent was removed under vacuum. Hexane was added to the residual solid to isolate the product. It was further purified on a chromatographic column with silica gel, eluted with a mixture of hexane and ethyl acetate (4:1).

General Procedure for the TH of Olefins and Alkynes. A Schlenk flask was charged with a substrate (0.50 mmol), a stock solution of **4/4'** in 2-propanol (0.42 mL), a stock solution of KO*t*Bu in 2-propanol (0.22 mL) and 2-propanol (1.3 mL) under N$_2$ atmosphere. The flask was heated at 80°C. The progress of the reaction was monitored by NMR spectroscopy. When the highest possible conversion of the substrates to the corresponding hydrogenated product was achieved, the reaction mixture was treated with diethyl ether (6 mL) and water (4 mL). The aqueous phase was separated and washed with diethyl ether (2×1 mL). Combined organic fractions were dried under MgSO$_4$.

General Procedure for the TH of Esters. A Schlenk flask was charged with a substrate (0.5 mmol), a stock solution of **4/4'** in ethanol (2.1 mL), and a stock solution of KO*t*Bu in ethanol (1.1 mL) under N$_2$ atmosphere. The flask was heated at 80°C. The progress of the reaction was monitored by NMR spectroscopy.

X-ray diffraction analyses. Single crystal of complexes **5**, suitable for X-ray diffraction analysis, was grown from at -30°C from chlorobenzene layered with hexanes. The crystal was coated in a film of perfluoropolyether oil and mounted on a glass fibre and transferred to a diffractometer. Intensity data were collected on a transferred to a diffractometer. Prior to data collection crystals were cooled to 120 K. Data were collected on a Bruker APEX II single crystal diffractometer equipped with a sealed Mo tube source (wavelength 0.71073 Å) and APEX II CCD detector. Raw data collection and processing were performed with APEX II software package from BRUKER AXS.[34] Diffraction data for all four samples were collected with a sequence of 0.5° ω scans at 0, 120, and 240° in φ. Initial unit cell parameters were determined from 36 data frames with 0.5° ω scan each, collected at the different sections of the Ewald sphere. Semi-empirical absorption corrections based on equivalent reflections were applied.[35] The structural model was refined with full set of anisotropic thermal displacement coefficient for all non-hydrogen atoms. All hydrogen atom positions were calculated based on the geometry of related non-hydrogen atoms. All hydrogen atoms were treated as idealized contributions during the refinement. All scattering factors are contained in several versions of the SHELXTL program library, with the latest version used being v.6.12.[36] The guest molecule - probably solvent - was heavily disordered and could not be modelled properly. The SQUEEZE routine of PLATON was applied to remove its contribution to the scattering. It indicated four solvent regions per unit cell, 163 Å^3 each and containing approximately 42 electrons each.

Table 3. Data collection and refinement data for **5**.

Parameter	**5**
Empirical formula	C$_{76}$H$_{76}$Cl$_4$N$_4$P$_4$Ru$_2$
Formula weight	1513.22
Temperature, K	200(2) K
Color, habit	orange, plate
Wavelength, Å	0.71073
Crystal system	Monoclinic
Space group	P 21/n
a, Å	22.2100(8)
b, Å	12.7915(5)
c, Å	27.9520(11)
α, °	90
β, °	113.185(2)°
γ, °	90
Volume, Å^3	7299.8(5)

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Z	4
Density (calcd), Mg/m^3	1.377
Absorption coefficient, mm^{-1}	0.692
F(000)	3104
Crystal size, mm^3	0.960 x 0.790 x 0.190
Theta range for data collection (°)	1.778 to 25.249
Index ranges	-26<=h<=26, -15<=k<=13, -32<=l<=33
Reflections collected	60653
Independent reflections	13172 [R(int) = 0.0730]
Completeness to θ	99.7
Absorption correction	SADABS, Bruker (2003)
Max. and min. transmission	0.5994 and 0.5994
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	13172 / 597 / 812

Goodness-of-fit on F^2	1.153
Final R indices [I>2sigma(I)]	R$_1$ = 0.0979, wR$_2$ = 0.2105
R indices (all data)	R$_1$ = 0.1381, wR$_2$ = 0.2354

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New ruthenium(II) complexes supported by a pyrazole-phosphine ligand were applied to catalytic transfer hydrogenation of nitriles, olefins, and heterocyclic compounds, affording examples of unusual hydrogenation of all-carbon-rings. Application of these complexes to the reduction of internal alkynes with bulky substituents resulted in selective hydrogenation to olefins with the uncommon *E*–selectivity. Switching the solvent from 2-propanol to ethanol, allowed for the reduction of activated esters to the corresponding alcohols.

Iryna D. Alshakova, Bulat Gabidullin, and Georgii I. Nikonov

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Ru-Catalyzed Transfer Hydrogenation of Nitriles, Aromatics, Olefins, Alkynes, and Esters