ChemPubSoc Europe

DOI: 10.1002/cctc.201701450

CHEMCATCHEM Full Papers

Hydrogenation and Reductive Amination of Aldehydes using Triphos Ruthenium Catalysts

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An air-stable and readily accessible ruthenium dihydride complex catalyses aldehyde hydrogenation under neutral conditions. A high activity has been shown in a number of examples, and solvent-free conditions are also applicable, which favours industrial-scale applications. The catalyst has also been demonstrated to be active at low catalyst loadings for the reductive amination of aldehydes under mildly acidic conditions. A number of examples of chemoselectivity challenges are also presented in which the catalyst does not reduce carbon–halogen groups, alkene or ketone functionality. The advantage of using the pre-formed complex, Triphos-Ru(CO)H_2 (**1**), over in situ formed catalysts from Triphos and Ru(acac)$_3$ (acac = acetylacetonate) is also shown in terms of both chemoselectivity and activity, in particular this can be seen if low reaction temperatures are used.

Introduction

The reduction of aldehydes to alcohols is an important transformation in chemical synthesis. The application of non-catalytic methods, for example $NaBH_4$, is reliable, well established and effective, although not without drawbacks associated with work-up and waste management.[1] Catalytic methods have advantages in terms of atom efficiency, and if the catalyst cost contributions are acceptable, can become viable alternatives to established hydride-based processes. In addition, homogeneous catalysis used in hydrogenation can find applications in transformations in which alternative heterogeneous catalysts fail to deliver satisfactory chemoselective reductions. Simple phosphine ruthenium complexes were reported to be capable homogeneous catalysts for aldehyde hydrogenation in the late 1970s and early 1980s.[2–6] The well-established phosphine ruthenium diamine catalysts developed by Noyori et al. gave significant improvements in activity for carbonyl reduction under basic reaction conditions, although the requirement of base, in some cases, can also be regarded as a limitation of this technology.[7,8] A number of refinements and advances have been applied to address these limitations, for example, the development of RuH(η^1-BH_4) complexes reported by Noyori et al.[9] and the use of phenylacetylide complexes, H–Ru–(CCPh), reported by Morris et al.[10] More recently, ruthenium carboxylates have been developed by Dupau and co-workers and are employed under neutral or weakly acidic conditions.[11,12] Additionally, an efficient catalytic hydrogenation of aldehydes using a ruthenium glycinate complex has been reported by Zhang and co-workers.[13]

The large-scale industrial use of aldehydes also includes reductive amination reactions. Again, non-catalytic methods are well represented and hydride reagents can give chemoselectivity advantages over heterogeneous catalysis,[14] homogeneous methods have the potential to provide viable alternatives to these existing processes. The reductive amination of aldehydes and ketones using cationic rhodium(I) complexes has been reported by Börner et al.[15] Also with Rh catalysts, the formation of primary amines by the reductive amination of benzaldehyde with ammonia has been described by Beller et al.[16] Ir catalysts were reported by Watanabe et al. and, subsequently, cyclometalated Ir catalysts were reported by Xiao et al. for reductive aminations reactions under transfer hydrogenation conditions.[17–20] More recently, Ru catalysts in transfer hydrogenation have been used for this transformation by Thiel et al. and Zhu.[21,22] Selectivity for primary amines using Ru complexes has also been shown by Meijboom et al.[23]

Herein we describe results from recent studies in which we used catalysts based on Triphos ruthenium complexes. Initial catalytic studies in which a Triphos ruthenium complex was used were performed by Elsevier et al. for the hydrogenation of dimethyl oxalate.[24–26] Around a decade passed before a resurgence of publications in this area was observed, which expanded the applications of Triphos-based catalysts. Generally, earlier studies employed catalysts formed in situ from Triphos and Ru(acac)$_3$ (acac = acetylacetonate) and focused on carbonyl group reductions such as esters,[27] amides[28–30] and acids.[31] Other applications such as N-methylation using CO_2 and the amination of alcohols in the presence of ammonia have also been reported.[32,33] More recently, a Triphos ruthenium precursor complex, [Ru(Triphos)(TMM)] (TMM = trimethylenemethane)

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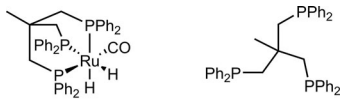
reported by Leitner et al.[34–37] has been used in place of the in situ formed catalyst. The hydrosilylation of aldehydes using a Triphos-Ru(OAc)$_2$ complex has also been reported by Cantat et al.[38] Our own application of Triphos ruthenium complexes to the reduction of aldehyde substrates to some extent appears to bring about a return to more simple phosphine ruthenium catalysts that find application under base-free conditions.

Results and Discussion

Attracted by the concept of using a highly active Ru catalyst under neutral or acidic reaction conditions, the Triphos ruthenium complex Triphos-Ru(CO)H$_2$ (**1**) was selected as a convenient precursor for these studies. The aim was to increase substrate scope to include aldehyde reduction and reductive amination reactions and to demonstrate low catalyst loadings. Complex **1** was first prepared by Bianchini and co-workers[39] and later generated from Ru(acac)$_3$ and Triphos under hydrogenation conditions by the decarbonylation of propanal.[27] Generally, **1** is considered as an inactive catalyst for the reduction of esters, amides and acids,[36] although the removal of the CO ligand under acid conditions with H$_2$ reportedly leads to a catalytically active species, [Ru(Triphos)(solvent)(H)–(H$_2$)]$^+$.[27,36] Complex **1** can be prepared easily from commercially available precursors in good yield. Ru(acac)$_3$ and Triphos are reacted under hydrogenation conditions (30 bar) at 140 °C in the presence of methanol (as the source of the CO ligand). The obtained **1** is reasonably stable at room temperature and does not need protection under inert atmosphere.[40] The structures of **1** and Triphos (**2**) are shown in Figure 1.



Triphos-Ru(CO)H$_2$ **1** Triphos **2**

Figure 1. Structures of **1** and **2**.

Initial tests were conducted using benzaldehyde as the substrate, the catalyst formed in situ from Ru(acac)$_3$ and Triphos was tested using *i*PrOH as solvent and under solvent-free conditions at 90–140 °C. The hydrogenation proceeded with increased reaction rates in the presence of solvent (*i*PrOH, [S] = 5 M, S = substrate). A high reaction temperature resulted in increased reaction rates. The in situ formed catalyst appears to benefit from high reaction temperatures (≥120 °C), presumably to generate the catalytically active species in sufficient quantities. Although high temperatures also improved the reaction rate of pre-formed **1**, a comparison at low temperatures (<120 °C) revealed that **1** retained a good activity for the reduction of aldehydes. Reaction temperatures in the region of 100–140 °C are relatively high compared with typical operating temperatures for Noyori-type catalysts. However, Triphos ruthenium complexes are usually used at even higher temperatures (140–220 °C) for more demanding carboxylic acid derivatives.[36] The ability of the pre-formed complex to operate at low temperatures conveys significant advantages for more challenging aldehyde substrates in which a chemoselective reduction is required.

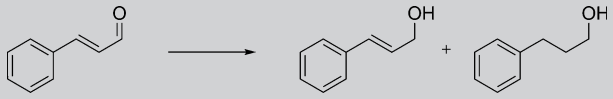
The advantages of the use of **1** for chemoselective aldehyde reduction can be seen if cinnamaldehyde is used as the substrate (Table 1). Catalysts formed in situ and pre-formed **1** were compared at different reaction temperatures. The use of the in situ formed catalyst at 140 °C led to the full conversion to the alcohol products with 83% selectivity for the unsaturated alcohol (entries 1–2). A decrease of the temperature to 120 °C increased the selectivity for the unsaturated alcohol to 93% although at the expense of conversion (78%). Temperatures below 120 °C gave very low conversions (entries 3–4). The requirement of the Triphos ligand to achieve C=O versus C=C chemoselectivity was confirmed if the reduction was attempted using only Ru(acac)$_3$; under these conditions the selectivity for alcohol **4** was very poor (2%), and the major reaction product was hydrocinnamyl alcohol (**5**; entry 5).

With the aim to improve the reaction selectivity, the use of pre-formed **1** at lower reaction temperatures was investigated. At temperatures in the range of 80–120 °C at catalyst loadings of substrate/catalyst (S/C) = 5000:1, **1** performed significantly better than the in situ formed catalyst (entries 6–10). These results show clearly that in the case of cinnamaldehyde, there is a distinct advantage of the use of the pre-formed complex, as higher reactivity and selectivity are observed under mild reaction conditions.

Low catalyst loadings of S/C = 10000:1, a selection of solvents and solvent-free conditions were tested. Full conversion was observed in most cases and, pleasingly, improved selectivity was observed, up to 98:2 in favour of cinnamyl alcohol (entries 11–17). The low catalyst loading and high selectivity for the allylic alcohol compare favourably with the best homogenous catalysts under hydrogenation conditions, for example: (Ir) S/C = 500:1,[41] (Ru) S/C = 500:1,[8] (Ru) S/C = 200:1,[42] (Ru) S/C = 200:1,[43] (Ru) SC = 500:1,[44] (Ru) S/C = 1000:1,[45] (Fe) S/C = 200:1,[46] (Fe) S/C = 500:1,[47] (Fe) S/C = 20000:1,[48] (Ru) S/C = 10000:1.[49]

The substrate scope was then investigated using **1** (Table 2). In most cases a loading of S/C = 10000:1 was achievable without the need for the significant optimisation of the reaction conditions. Temperatures in the range of 100–140 °C were used, and solvents such as *i*PrOH, dioxane, heptane and toluene and solvent-free conditions are compatible in many cases. The conversion of aldehyde to alcohol was measured by using GC (peak area using flame ionisation detection; FID) and confirmed by using ^{1}H NMR spectroscopy of the crude reaction mixtures. Hydrogenation reactions were performed by using Biotage Endeavor parallel screening equipment on a small scale (16–50 mmol) or on a larger scale (100–150 mmol) by using 50 mL Parr vessels (entries 1–5, 14–15 and 17). Benzaldehyde could be reduced with low catalyst loadings (S/C = 100000:1) under solvent-free conditions to give the alcohol product in a high yield and purity (entry 1). Lower catalyst loadings are also possible (S/C = 200000:1) to give a full conversion within a reasonable reaction time (20 h; entry 3). A catalyst loading of S/C = 500000:1 also led to a full conversion

Table 1. Reduction of cinnamaldehyde.[a]



3 **4** **5**

Entry	Catalyst	S/C	Solvent	Concentration [M]	*T* [°C]	Conversion [%][b]	Selectivity **4**/**5** [%][b]
1	$Ru(acac)_3$ & **2**	5000	*i*PrOH	5	140	99	83/17
2	$Ru(acac)_3$ & **2**	5000	*i*PrOH	5	120	78	93/7
3	$Ru(acac)_3$ & **2**	5000	*i*PrOH	5	100	9	100/0
4	$Ru(acac)_3$ & **2**	5000	*i*PrOH	5	90	5	100/0
5	$Ru(acac)_3$	5000	*i*PrOH	5	140	100	2/98
6	**1**	5000	*i*PrOH	5	120	98	88/12[c]
7	**1**	5000	*i*PrOH	5	100	98	93/7[c]
8	**1**	5000	*i*PrOH	5	100	98	95/5
9	**1**	5000	*i*PrOH	5	90	98	96/4
10	**1**	5000	*i*PrOH	5	80	98	97/3
11	**1**	10000	*i*PrOH	4	100	99	96/4
12	**1**	10000	*i*PrOH	3	100	72	97/3
13	**1**	10000	–	–	100	98	97/3
14	**1**	10000	heptane	4	100	99	97/3
15	**1**	10000	heptane	3	100	99	98/2
16	**1**	10000	toluene	4	100	99	98/2
17	**1**	10000	toluene	3	100	90	99/1

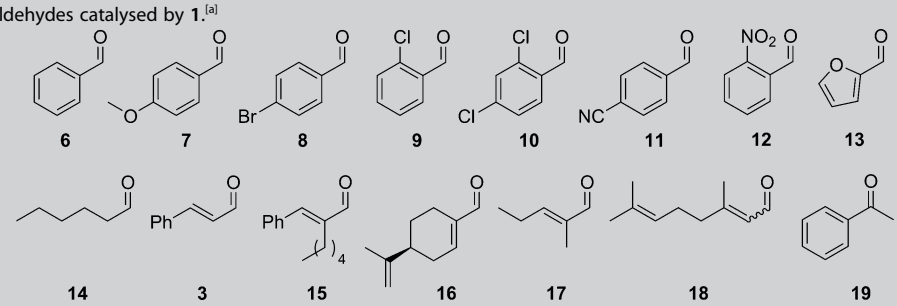
[a] Conditions: 16–20 mmol scale, 30 bar H_2, 16 h. [b] Calculated from the GC–FID peak areas. [c] A catalyst batch of lower purity, ≈50% by using ^{31}P NMR spectroscopy, was used; for all other entries in which **1** was used the catalyst batch was of higher purity, >90% by using ^{31}P NMR spectroscopy.

after extended reaction times (144 h), which demonstrates the high catalyst stability under the reaction conditions (entry 4).[50,51] A low catalyst loading (S/C = 100000:1) was also demonstrated on *p*-anisaldehyde if heptane was used as the solvent (entry 5). Various substitution patterns and functionalities were tolerated on the aromatic group (entries 6–9). However, some functional groups led to problems with reactivity, for example, 4-cyanobenzaldehyde showed an incomplete conversion and low product purity (entry 10), whereas 2-nitrobenzaldehyde led to improved results if a higher catalyst loading and lower reaction temperature were used (entries 11 and 12). The efficient hydrogenation of furfural was observed under solvent-free conditions and a high-purity product was obtained with a catalyst loading of S/C = 50000:1 (entry 13). The use of a Parr vessel on a larger scale (150 mmol) gave a high product yield but required a longer reaction time, possibly because less efficient mixing and causes a slightly lower purity (entry 14). Aliphatic aldehydes such as hexanal were also reduced efficiently. A catalyst loading of S/C = 100000:1 was demonstrated with an improved product purity if *i*PrOH was used as the solvent (entries 15–16). A selection of α,β-unsaturated aldehydes was also tested to establish the substrate scope for the chemoselective C=O reduction. Loadings of S/C = 5000:1 were used, and high conversions and good to excellent selectivity for the α,β-unsaturated alcohols were obtained (entries 17–21). For a comparison of activity towards ketones, acetophenone was tested under typical reaction conditions and a low conversion was observed, which indicates the potential to discriminate between the ketone and aldehyde functionality (entry 22).

As the reactivity for aldehydes versus ketones appeared to be very different we were interested in the evaluation of imines as potential substrates and we expected the reactivity to be more in line with that of aldehydes on steric grounds. Therefore, we turned our attention to reductive amination reactions (Table 3). The use of acid additives such as acetic acid was explored to promote the reaction.[16] Again, the in situ formed catalyst and pre-formed **1** were compared. The use of $Ru(acac)_3$ in the absence of the Triphos ligand gave only trace amounts of reduction products, and the major reaction component was identified as imine **22**, which results from aldehyde and amine condensation (entry 1). The use of the bidentate ligand, 1,3-bis(diphenylphosphino)propane (DPPP), also showed no reactivity (entry 2). In contrast, the in situ formed catalyst that incorporates the Triphos ligand gave a full conversion and good selectivity for the secondary amine product (entry 3). A decrease of the catalyst loading highlights the limitation of the use of the in situ system; at S/C = 2000:1 the conversion was reduced slightly, whereas the decrease in the reactivity was significant at S/C = 5000:1 (entries 4 and 5). In contrast, pre-formed **1** retained a high activity under these conditions. A loading of S/C = 5000:1 gave a full conversion within a reasonably short time of approximately 5 h based on hydrogen consumption data (entry 7). Once again these results demonstrate a clear advantage of the pre-formed system for the reductive amination reaction of benzaldehyde and benzylamine. The presence of acetic acid (1 equivalent) had a positive effect on the selectivity for reductive amination over the competing aldehyde reduction. In the presence of the acid additive, 77% product was obtained compared to 69% without acid along with increased amounts of benzyl alcohol (11%; entries 8 and 9).

The substrate scope was extended to include 2-chlorobenzaldehyde and additional primary and secondary amines (Table 4). 2-Chlorobenzyldimethylamine is an intermediate in

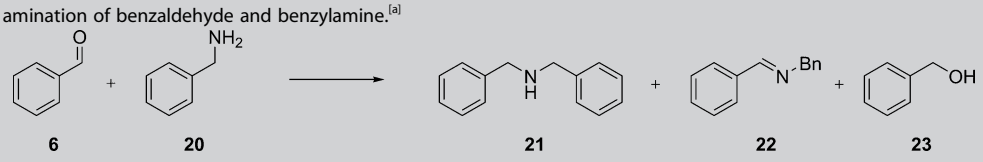
Table 2. Reduction of aldehydes catalysed by **1**.[a]



Entry	Substrate	S/C	Solvent	Concentration [M]	T [°C]	H_2 uptake [h][b]	Conversion [%][c]	Purity [%][c]
1	**6**	100 000	–	–	140	11	99.7 (98)[d]	99.6
2	**6**	100 000	*i*PrOH	3	140	7[e]	99.7[d]	97.6
3	**6**	200 000	*i*PrOH	3	140	20	99.7[c,f]	98.9
4	**6**	500 000	*i*PrOH	3	140	n/d	96.9[d,g]	95.5
5	**7**	100 000	*n*-heptane	4	140	n/d	99.3 (98)[d]	97.6
6	**8**	10 000	*n*-heptane	3	100	5	100	99.6
7	**8**	10 000	*i*PrOH	4	140	2	100	98.9
8	**9**	10 000	*i*PrOH	4	140	4	100	99.6
9	**10**	10 000	1,4-dioxane	4	140	4	100	99.0
10	**11**	10 000	*n*-heptane	5	100	>16	76.0	51.1
11	**12**	10 000	*i*PrOH	4	140	6	82.3	78.0
12	**12**	5000	*i*PrOH	1	100	10	100	95.3
13	**13**	50 000	–	–	120	9	99.9[h]	98.1
14	**13**	50 000	–	–	120	42	99.8 (96)[e,i]	95.5
15	**14**	100 000	–	–	140	6	100 (92)[d]	90.7
16	**14**	100 000	*i*PrOH	4	140	n/d	100	97.6
17	**3**	10 000	–	–	100	12	96.5 (98)[d]	92.5
18	**15**	5000	–	–	100	16	98.0	91.8[j]
19	**16**	5000	–	–	100	>16	96.0	91.0[j]
20	**17**	5000	–	–	100	>16	78.2	75.4
21	**18**	5000	–	–	100	40[f]	>95[k]	91.8[l]
22	**19**	10 000	*i*PrOH	4	100	–	3	–

[a] Conditions: (16–150 mmol), 30 bar H_2, 16 h. [b] Approximate time for completion according to the hydrogen consumption data. [c] Calculated from GC–FID peak areas, isolated yield given in parenthesis. [d] 100 mmol scale in Parr vessel. [e] With the use of the in situ formed catalyst, full conversion to benzyl alcohol at S/C = 100 000:1 was achieved for which the consumption of hydrogen ended after ≈15 h. [f] Reaction run for 40 h. [g] Reaction run for 144 h. [h] 50 mmol scale by using a Biotage Endeavor. [i] 150 mmol scale by using a Parr vessel. [j] Unsaturated product confirmed by using ^{1}H NMR spectroscopy. [k] Determined by using ^{1}H NMR spectroscopy. [l] Mixture of alkene isomers.

Table 3. Reductive amination of benzaldehyde and benzylamine.[a]

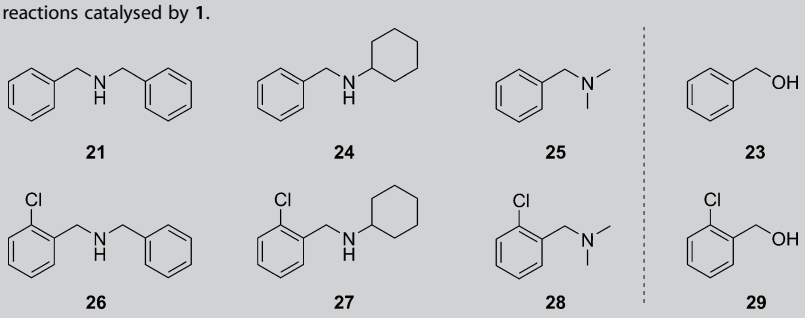


Entry	Catalyst	S/C	H_2 uptake [h][b]	$HN(Bn)_2$ **21** [%][c]	H_2NBn **20** [%][c]	PhCH=NBn **22** [%][c]	BnOH **23** [%][c]	BzH **6** [%][c]
1	$Ru(acac)_3$	1000	no uptake	1	4	85	0	4
2	$Ru(acac)_3$ & DPPP	1000	no uptake	1	4	85	0	4
3	$Ru(acac)_3$& **2**	1000	12	88	3	2	1	0
4	$Ru(acac)_3$ & **2**	2000	16	80	4	11	1	0
5	$Ru(acac)_3$ & **2**	5000	no uptake	4	5	85	0	3
6	**1**	2000	4	87	4	1	3	0
7	**1**	5000	5	88	3	1	2	0
8	**1**	10 000	>40[d]	69	11	9	11	0
9	**1**	10 000	5	77	0	0	2	0

[a] Conditions: (5 mmol scale), AcOH additive (1 equiv.), *i*PrOH [S] = 1 M, 30 bar H_2, 100 °C, 16 h. [b] Approximate time for completion according to hydrogen consumption data. [c] Calculated from GC–FID peak areas. [d] No acetic acid added, reaction run for 40 h.

the production of active agrochemical compounds and microbicides of the methoximinophenylglyoxylic ester series.[52] Further assessment of the reaction parameters was made in an effort to improve selectivity for amine products (Supporting In-

Table 4. Reductive amination reactions catalysed by **1**.



Entry	Catalyst	Aldehyde	Amine	Product	H_2 uptake [h][b]	Product [%][c]	Alcohol **23**/**29** [%][c]
1	**1**	**6**	$BnNH_2$	**21**	6	93 (89)	0
2	**1**	**6**	$CyNH_2$	**24**	2	94 (94)	0
3	**1**	**6**	$HNMe_2$[d]	**25**	2	99 (63)	0
4	**1**	**9**	$CyNH_2$	**27**	7	88 (94)	2
5	**1**	**9**	$BnNH_2$	**26**	12	78 (95)	3
6	**1**	**9**	$HNMe_2$[d]	**28**	2	99 (85)	0
7	**1**	BnOH	$BnNH_2$	**21**	no uptake	0	58[e]

[a] Conditions: complex **1**, S/C = 10 000:1, in MeOH [S] = 1 M, AcOH 1 equiv., 30 bar H_2, 16 h. [b] Approximate time for completion according to hydrogen consumption data. [c] Calculated from GC–FID peak areas, yield given in parenthesis (as acetic acid salt after the removal of volatile components). [d] Added as a 2 M solution in MeOH. [e] 42% amine **20** from the GC–FID peak area.

formation). A switch of the solvent to methanol gave a high selectivity for the reductive amination products and in general fast reaction rates, with all reactions except one complete within 7 h according to hydrogen consumption data (entries 1–6). To probe whether the reaction proceeds by reductive amination as opposed to aldehyde reduction followed by an alkylation/hydrogen-borrowing-type process,[30] benzyl alcohol was subjected to the reaction conditions; no evidence of a higher amine product was observed, which supports a reductive amination-type process (entry 7). The attempted reductive amination of acetophenone with benzylamine also showed no evidence of ketone reactivity, which was assessed by using GC and seen from the lack of hydrogen uptake. Overall, reductive amination with primary and secondary amines gave very encouraging results. Unfortunately, reductive amination to give primary amines has not yet been optimised, and brief testing indicated that selectivity for the primary amine was low but could be improved with the addition of ammonia, although the secondary amine persisted as the major reductive amination product (Supporting Information).

Conclusions

We have applied a readily available ruthenium Triphos complex to aldehyde hydrogenation under neutral conditions. The catalyst is active at low or very low catalyst loadings. A number of examples of chemoselectivity challenges are presented in which the catalyst does not reduce carbon–halogen groups, ketone or alkene functionality. The extension to reductive amination reactions demonstrates the versatility of this complex. In this case the use of an acidic additive, acetic acid, was found to give significant benefits. The advantage of the pre-formed complex over an in situ formed catalyst has been demonstrated clearly, in terms of both selectivity and activity, and the pre-formed complex gave higher-purity products at lower catalyst loadings.

Experimental Section

General

All reagents were purchased from catalogue companies and used as supplied without further purification. Triphos was purchased from Sigma–Aldrich. $Ru(acac)_3$ was obtained from Johnson Matthey. The aldehydes **3** (99%), **6** (≥99%), **7** (98%), **8** (99%), **9** (99%), **10** (99%), **11** (95%), **12** (≥99.0%), **14** (98%), **15** (97%), **16** (92%), **17** (97%) and **18** (95%) were purchased from Sigma–Aldrich; aldehyde **13** (≥98%) was purchased from Alfa Aesar. Benzylamine (99%) and cyclohexylamine (≥99.9%) were purchased from Sigma–Aldrich. Dimethylamine (2 M solution in THF) was purchased from Fisher. Dimethylamine, (2 M in MeOH) was purchased from Alfa Aesar. Acetic acid (≥99.7%) was purchased from Sigma–Aldrich. All solvents used were of anhydrous grade and purchased from Sigma–Aldrich. NMR spectra were recorded by using a Bruker Avance III 400 (400 MHz) spectrometer. GC analyses were performed by using a Varian 3900 gas chromatograph system with an Agilent J&W HP-1 column of 50 m of length, internal diameter of 0.20 mm, flow rate of 2 mL min^{-1}, He as carrier gas and a FID. The injector and detector temperature was 270 °C. Program used: initial T = 100 °C ramped to 280 °C at 15 °C min^{-1} and then held at 280 °C for 2 min. The hydrogenation experiments were performed by using a Biotage® Endeavor and a Parr autoclave.

Preparation of 1

A 50 mL Parr autoclave was charged with $Ru(acac)_3$ (900 mg, 2.2 mmol) and Triphos (1.6 g, 2.6 mmol). The vessel was sealed and purged with nitrogen by pressurising to 3 bar then releasing pressure and repeating five times. To the vessel was then added *i*PrOH (10 mL) followed by methanol (10 mL, 0.25 mol). Another further five nitrogen-purge cycles at 3 bar were performed. The mixture

was stirred at 1500 rpm and the system was again purged five times with nitrogen. Following this, five hydrogen purges at 20 bar were performed before stirring for 20 h under hydrogen at 30 bar and 140 °C. After cooling to RT, the reaction mixture was purged with nitrogen for five cycles. The pale yellow precipitate was collected by filtration and washed with acetone (2×4 mL). Complex **1** was obtained (1.4 g, yield 84%) and its ^{1}H and ^{31}P NMR spectra were consistent with literature values.[27]

Hydrogenation of aldehydes, general procedure (up to 50 mmol scale)

Catalyst **1** or that formed in situ from $Ru(acac)_3$ and Triphos are weighed into each vial of a Biotage Endeavor. To the vial was then added solvent (if applicable) and the aldehyde. The vials were loaded into a Biotage Endeavor and purged with nitrogen by pressurising to 3 bar and releasing the pressure (five cycles). The mixtures were stirred at 250 rpm, and the purge procedure was repeated. Subsequently, the system was purged with hydrogen by pressurising to 20 bar and releasing the pressure (five cycles). The vials were stirred at the relevant temperatures under hydrogen at 30 bar for 16 h. After the reactions had cooled to RT, a final series of nitrogen purges were performed. The reactions were then sampled (≈20 μL, diluted to 1 mL with *i*PrOH) and analysed by using GC. The crude reaction mixture was also analysed by using ^{1}H NMR spectroscopy to support product identification and purity assessment. Product yields were calculated after the removal of solvent under reduced pressure and without further purification.

Hydrogenation of aldehydes, general procedure (50–150 mmol scale)

Catalyst **1** was weighed into either a 25 or 50 mL Parr autoclave (added either as a solid or solution in dichloromethane 1 mg mL^{-1} followed by solvent removal under a flow of nitrogen). The vessel was sealed and purged with nitrogen by pressurising to 3 bar and releasing the pressure (five cycles). To the reactor was added solvent (6–12 mL) followed by the substrate (50–150 mmol). The vessel was purged with nitrogen by pressurising to 3 bar and releasing the pressure (five cycles). The mixture was stirred at 1500 rpm, and this purge procedure was repeated. The system was subsequently purged with hydrogen by pressurising to 20–30 bar and releasing the pressure (five cycles) with stirring at 1500 rpm. The reaction heated to 140 °C under hydrogen at 30 bar for 16–144 h. After the reactions had cooled to RT, a final series of nitrogen purges was performed. The reactions were then sampled (≈20 μL, diluted to 1 mL with *i*PrOH) and analysed by using GC. The crude reaction mixture was also analysed by using ^{1}H NMR spectroscopy to support product identification and purity assessment. Product yields were calculated following the removal of solvent under reduced pressure and without further purification.

Reductive amination of aldehydes, general procedure

Catalyst **1** or that formed in situ from $Ru(acac)_3$ and Triphos was weighed into each vial of a Biotage Endeavor. This was followed by the addition aldehyde (5 mmol), the appropriate volume of solvent, amine (5 mmol) and acetic acid (0.3 mL, 5 mmol). The vials were loaded into a Biotage Endeavor and purged with nitrogen by pressurising to 3 bar and releasing the pressure (five cycles). The mixtures were stirred at 250 rpm, and this purge procedure was repeated. The system was subsequently purged with hydrogen by pressurising to 20 bar and releasing the pressure (five cycles). The vials were stirred under hydrogen at 30 bar at 600 rpm and the stated temperatures for 16 h. After the reactions had cooled to RT, a final series of nitrogen purges was performed. The reactions were then sampled and analysed by using GC (≈20 μL, diluted to 1 mL with *i*PrOH). Product yields were calculated following removal of solvent under reduced pressure and are given for un-purified acetic acid salts. The crude reaction mixture was also analysed by using ^{1}H NMR spectroscopy following aqueous work-up with CH_2Cl_2 and 10% $NH_4OH_{(aq)}$ to support product identification.

Conflict of interest

The authors declare no conflict of interest.

Keywords: aldehydes · amination · homogeneous catalysis · hydrogenation · ruthenium

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Manuscript received: September 5, 2017
Revised manuscript received: October 5, 2017
Version of record online: ■■ ■■, 0000

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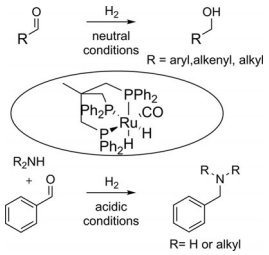
Hydrogenation and Reductive Amination of Aldehydes using Triphos Ruthenium Catalysts



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