

High Catalytic Efficiency Combined with High Selectivity for the Aldehyde–Water Shift Reaction using (*para*-cymene)Ruthenium Precatalysts

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Supporting Information

ABSTRACT: A family of (*para-cymene*)Ru^{II} complexes are shown to be competent precatalysts for the oxidation of aldehydes to carboxylic acids using water as the oxidant. This reaction, known as the "aldehyde—water shift" (AWS), has been previously demonstrated to be in competition with aldehyde disproportionation. For the few reported mononuclear catalysts for this reaction, either high selectivity for AWS and low conversion or low AWS selectivity and high conversion is observed. A homogeneous precatalyst which is both highly selective for the desired AWS *and* is highly efficient for conversion of the aldehyde to products is reported herein. In addition, catalyst activity is found to be general to a variety of sterically unencumbered aliphatic aldehydes producing the corresponding carboxylic acid and hydrogen gas.



KEYWORDS: aldehyde-water shift, aldehyde oxidation, homogeneous catalysis, dehydrogenation, water

C arboxylic acids are a fundamentally important class of organic compounds with a wide variety of applications. They are one of the monomer units of polyester plastics, and they are frequently used as synthetic precursors to other functional groups such as esters and amides. Oxidative synthesis of carboxylic acids can be effected by many different reagents, such as chromate, permanganate, hydrogen peroxide, and molecular oxygen.¹ An alternative method is through the "aldehyde-water shift" reaction (AWS, Scheme 1),^{2,3} in which water serves as the oxidant and reacts with an aldehyde to produce the carboxylic acid with concomitant release of a valuable coproduct, hydrogen gas.



Murahashi first reported the conversion of aldehydes to carboxylic acids with a ruthenium catalyst, a hydrogen acceptor, and water as the oxidant.⁴ Later, Stanley observed carboxylic acid byproducts in the course of hydroformylation reactions with a rhodium catalyst and suggested the aldehyde–water shift as a potential reaction pathway.² In recent years, work by Milstein,⁵ Grützmacher,⁶ and Prechtl⁷ on the dehydrogenation of alcohols to carboxylic acids proposed the AWS as an intermediate reaction step involving dehydrogenation of a hydrated aldehyde (*geminal*-diol). Computational insight into the Milstein systems further supported the potential to use water as an oxidant for aldehydes.⁸ In closely related work,

Maitlis investigated aqueous aldehyde disproportionation (Scheme 2) in which the substrate itself serves as a hydrogen



acceptor.9,10 Previous work on the AWS in our group investigated π -arene (or cyclopentadienyl) complexes of iridium-, rhodium-, and ruthenium-containing bipyridine ligands as precatalysts in aqueous solution.³ In many cases, competing aldehyde disproportionation (Scheme 2) was observed as the major reaction. Ruthenium-based π -arene precatalysts were the most selective, producing large amounts of carboxylic acid relative to the corresponding alcohol derived from disproportionation. In the first example of a highly selective AWS reaction in the absence of external additives, an acid selectivity of 95% was achieved using [(p-cymene)Ru- $(bpy)OH_2$ [OTf]₂ (bpy =2,2'-bipyridine, OTf = trifluoromethanesulfonate) precatalyst and benzaldehyde as the substrate (Scheme 3). However, this exceptional selectivity came at the expense of conversion, with only 4% of the starting material transformed after 20 h at 105 °C.

Computational studies suggest a mechanism involving a metal hydride species as the key intermediate in the catalytic cycle.¹¹ This hydride is hypothesized to be the source of

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Scheme 3. Previously Reported Highly Selective AWS³



selectivity for AWS versus disproportionation. As illustrated in Scheme 4, a strongly basic hydride will be readily protonated to produce hydrogen gas, whereas a weakly basic hydride can favor disproportionation via nucleophilic attack of the carbonyl.

Scheme 4. Proposed Origin of AWS Selectivity^{3,11}



New prospective catalysts were, therefore, identified by considering the basicity of the proposed metal-hydride intermediate. From this criterion, the Noyori-type complex¹² (p-cymene)Ru(TsDPEN)(H) $(TsDPEN = (S,S)-TsNCHPhCHPhNH_2⁻)$ was selected. The pK_a of its conjugate acid (16 in MeCN) suggests that this hydride is basic enough to deprotonate water.¹³ The bifunctional TsDPEN ligand, utilized in asymmetric transfer hydrogenation reactions,¹² may also assist in dehydrogenation of a *gem*-diol, likely the key organic intermediate in the AWS reaction.¹⁰

Initial studies with the commercially available precursor, (pcymene)Ru(TsDPEN)Cl (hereafter referred to as Ru-(TsDPEN)), were performed in 10 mL of water and at a precatalyst concentration of 2 mM (0.4 mol % relative to substrate). At room temperature, the precatalyst was sparingly soluble, but the reaction became homogeneous upon heating. Acetaldehyde (5.0 mmol), a water-soluble aldehyde, was used as the initial test substrate. The solution was heated to 105 °C under nitrogen for 20 h in a Teflon-sealed glass reaction vessel.¹⁴ Products and yields were determined via ¹H NMR spectroscopy using phenol as an internal standard. Analysis of the reaction mixture revealed a remarkably high conversion of 79(5)%, significantly higher than that observed previously with other ruthenium precatalysts.³ Moreover, this catalyst also demonstrated high selectivity for acid production, with 85(6)%of the reacted aldehyde being converted to carboxylic acid.¹⁵

Following the promising results using Ru(TsDPEN) as a precatalyst, other diamine ligand frameworks were also explored with ruthenium. Since no chiral centers can be formed in the AWS reaction, the TsDPEN ligand seemed unnecessarily complex. Three simpler diamine ligands were thus tested: PDA (*ortho*-phenylenediamine),¹⁶ TsPDA (*N*-tosyl-*ortho*-phenylenediamine),¹⁷ and TMEDA (*N*,*N*,*N'*,*N'*-tetramethylethylenediamine).¹⁸ The precatalysts are shown in Chart 1. In contrast to the other ligands presented, TMEDA is not expected to function as a bifunctional ligand without dissociation. Notably, the pentamethylcyclopentadienyl rhodium analogue of the PDA complex has been investigated computationally for dehydrogenation reactions and that study

Chart 1. Ruthenium(II) Diamine Precatalysts Tested



suggests that the PDA ligand can operate in a bifunctional manner.¹⁹ For the sake of brevity, catalysts will be referred to only by their diamine ligand for the remainder of this manuscript, as shown in Chart 1.

Precatalysts shown in Chart 1 were examined using our standard test conditions (5.0 mmol acetaldehyde, 10 mL of H_2O , 0.020 mmol precatalyst, 105 °C, 20 h) and the reactions were analyzed by ¹H NMR spectroscopy (Table 1). Reactions

Table 1. Ruthenium Precatalyst Screen^{*a,b*}

catalyst	% conversion	% acid
Ru(TsDPEN)	79(5)	85(6)
Ru(PDA)	92(1)	85(2)
Ru(TsPDA)	33(2)	89(1)
Ru(TMEDA)	71(4)	89(2)
$[(p-cymene)RuCl_2]_2^c$	72(6)	86(2)
RuCl ₃	0	0

^{*a*}Reaction conditions: 5.0 mmol acetaldehyde, 0.020 mmol precatalyst, 10 mL of H₂O, 105 °C, 20 h. ^{*b*}Standard deviation in parentheses. ^{*c*}0.010 mmol precatalyst.

using Ru(TsDPEN) and Ru(PDA) as precatalysts remained homogeneous throughout the reaction. In contrast, the solutions containing Ru(TsPDA) produced an insoluble red solid over the course of the reaction, whereas Ru(TMEDA) produced large quantities of dark heterogeneous material. All precatalysts screened passed the mercury drop test, suggesting that the active catalyst is likely to be a homogeneous species and not metallic ruthenium nanoparticles.²⁰

Surprisingly, while the precatalysts pictured in Chart 1 displayed different conversions, the selectivities of the reactions were all quite consistent at 87 \pm 2%. Following these experiments, a control reaction using the synthetic precursor, $[(p\text{-cymene})\text{RuCl}_2]_2$,²¹ was run to test its catalytic capabilities.²² Remarkably, this parent complex displayed conversion and selectivity on par with the diamine complexes. The ruthenium dimer also produced a coating of heterogeneous material on the inside of the reaction vessel over the course of the reaction, similar to that observed with Ru(TMEDA). In fact, within error, Ru(TMEDA) and $[(p\text{-cymene})\text{RuCl}_2]_2$ function identically (conversion and selectivity), suggesting that the TMEDA ligand may dissociate over the course of the reaction.

 $[(p\text{-cymene})\text{RuCl}_2]_2$ was tested at various temperatures to gain a better understanding of factors that influence catalyst performance and decomposition (Table 2). These experiments demonstrated that a decrease in temperature does not significantly affect the selectivity of the reaction, but does decrease the percent conversion of aldehyde. In addition, reactions run at 91 and 105 °C led to visible heterogeneous decomposition products, whereas reactions run at 80 °C and below appeared to remain homogeneous. The greater amount of heterogeneous material present at 105 °C than at 91 °C may

Table 2. Variable Temperature Reactions using $[(p-cymene)RuCl_2]_2^{a}$

	temperature	% conversion	% acid
	105 °C	72(6)	86(2)
	91 °C	80(2)	86(1)
	80 °C	68(1)	88(4)
	71 °C	63(4)	89(0.3)
	60 °C	34(4)	93(2)
a	_		

^{*a*}Reaction conditions: 5.0 mmol acetaldehyde, 0.010 mmol precatalyst, 10 mL of H_2O , 20 h. Standard deviation in parentheses.

account for the observed decrease in product yield at that temperature.

To confirm H₂ formation from AWS catalysis, a reaction was examined in a 20 mL pressure-relief vial using modified conditions to accommodate the smaller reaction vessel [2.5 mmol acetaldehyde, 5 mL of H₂O, 0.010 mmol Ru(PDA), 105 °C, 20 h]. Hydrogen was detected by GC-TCD, and the pressure buildup in the vial was quantified using a pressure sensor.²⁴

The substrate scope of the AWS reaction with the Ru(PDA) precatalyst was explored with a variety of aliphatic and conjugated aldehydes. Though addition of dioxane as a cosolvent was found to decrease reaction efficiency and selectivity (acetaldehyde as substrate, Ru(PDA) as precatalyst, Table 3), the substrate scope was investigated using a 1:1 (v/v) mixture of water and 1,4-dioxane as solvent to enhance substrate solubility. Full results are shown in Table 4.¹⁴

Table 3	3.	Effect	of	Added	Dioxane ⁴

% acid
85(2)
82(1)
78(1)
72(1)

^{*a*}Reaction conditions: 5.0 mmol acetaldehyde, 0.020 mmol Ru(PDA), 10 mL of total solvent volume, 105 °C, 20 h. Standard deviation in parentheses.

Acetaldehyde was first examined under the chosen conditions (105 °C, 20 h) using both the highly efficient Ru(PDA) precatalyst and the [(p-cymene)RuCl₂]₂ catalyst precursor. For both precatalysts, selectivity for acid production dropped from approximately 85% in pure water to approximately 73% in 1:1 water:dioxane. Interestingly, while precatalyst activity was largely retained with the Ru(PDA) system (92(1)% and 82(3)% conversion, in water and 1:1 water:dioxane, respectively), conversion was found to significantly decrease from 72(6)% to 16(2)% on changing solvent from water to 1:1 water dioxane using $[(p-cymene)RuCl_2]_2$ as precatalyst. Corresponding to the low conversion, heterogeneous black particles were observed within 60 min suggesting rapid catalyst decomposition. In contrast, the Ru(PDA) precatalyst appears to remain in solution for the duration of the reaction.

More complex aliphatic aldehydes, such as propionaldehyde, isobutyraldehyde, heptaldehyde, and phenylacetaldehyde, were all found to react with moderate to high efficiency and high selectivity under the chosen conditions (Table 4). Conversion for phenylacetaldehyde is found to be relatively low, possibly because the substrate is still only partially soluble at 105 °C.

Table 4. Substrate Scope^{*a,b*}

	Substrate	Catalyst	% Conversion	% Acid
S 1	о Н	[(p- cymene)RuCl ₂]2 ^c	16(2)	73(2)
S 1	O ↓ H	Ru(PDA)	82(3)	72(2)
S2	, ⊂ H	Ru(PDA)	56(2)	74(3)
S3	O H	Ru(PDA)	63(2)	67(4)
S4	Р	Ru(PDA)	5(1)	86(3)
S5	⊖ M₅ H	Ru(PDA)	74(1)	71(5)
\$5	⊖ → H	$\operatorname{Ru}(\operatorname{PDA})^d$	91(8) ^e	87(1)
S6	ОН	Ru(PDA)	< 1%	N/A
S 7	O H	Ru(PDA)	30(1)	68(1)
S8	O H	Ru(PDA)	< 1%	N/A

^{*a*}Conditions: 5.0 mmol substrate, 0.020 mmol precatalyst, 5 mL of H_2O , 5 mL dioxane, 105 °C, 20 h. ^{*b*}Standard deviation in parentheses. ^c0.010 mmol precatalyst. ^{*d*}Run in open system. ^{*c*}91(8)% conversion calculated based on the 67(4)% recovered organic material.

Sterically bulky pivaldehyde was not efficiently converted to products, though selectivity for the AWS pathway remained quite high. Conjugated species benzaldehyde and cinnamaldehyde were found to be unreactive; 99% of the recovered material was starting aldehyde.

Heptaldehyde, which boils at a relatively high temperature (153 °C) was also investigated in an open system using Ru(PDA) as the precatalyst in 1:1 (v/v) water:dioxane solvent.¹⁴ In this reaction, a Schlenk flask fitted with a reflux condenser was used as the reaction vessel. A steady stream of N₂ was passed over the reaction mixture for the duration of the 20 h reaction allowing for efficient removal of any hydrogen produced. Since (*p*-cymene)Ru(diamine) complexes are known to be efficient ketone hydrogenation catalysts under low pressures of hydrogen, it was postulated that efficient removal of hydrogen would increase reaction selectivity. Indeed, 91(8)% of the recovered material was found to be products (heptanoic acid and *n*-heptanol) with 87(1)% selectivity for the acid product; a marked improvement in reaction selectivity over reactions run in a closed vessel (71(5)%).²³

In conclusion, a series of (p-cymene)ruthenium(II) diamine complexes have been shown to be competent in catalyzing the aldehyde—water shift reaction. These precatalysts provide an unprecedented combination of reaction efficiency and selectivity for AWS over disproportionation. Interestingly, the synthetic precursor to the diamine complexes, [(p-cymene)- RuCl₂]₂, is also able to catalyze the aldehyde–water shift reaction at similar levels of selectivity and conversion in pure water. In a mixed solvent system, the diamine was found to be essential for catalyst longevity. The best diamine precatalyst, Ru(PDA), was found to be a competent precatalyst for the oxidation of a range of aliphatic aldehydes. This reaction provides a new, mild route for production of carboxylic acids alongside a valuable byproduct, dihydrogen. Ongoing studies are now investigating the reaction mechanism and the exact nature of the active catalytic species for both the diamineligated and $[(p-cymene)RuCl_2]_2$ precatalyst systems.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b02130.

Experimental details (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Smith, M. B.; March, J. March's Advanced Organic Chemistry: Reactions, Mechanisms and Structure, 6th ed.; John Wiley and Sons, Inc: Hoboken, NJ, 2007.

(2) Stanley, G. G.; Aubry, D. A.; Bridges, N.; Barker, B.; Courtney, B. ACS Div. Fuel Chem. Prepr. **2004**, *49*, 712–714.

(3) Brewster, T. P.; Ou, W. C.; Tran, J. C.; Goldberg, K. I.; Hanson, S. K.; Cundari, T. R.; Heinekey, D. M. ACS Catal. 2014, 4, 3034–3038.

(4) Murahashi, S.; Naota, T.; Ito, K.; Maeda, Y.; Taki, H. J. Org. Chem. 1987, 52, 4319-4327.

(5) (a) Balaraman, E.; Khaskin, E.; Leitus, G.; Milstein, D. Nat. Chem. 2013, 5, 122–125. (b) Khusnutdinova, J. R.; Ben-David, Y.; Milstein, D. J. Am. Chem. Soc. 2014, 136, 2998–3001. (c) Gellrich, U.; Khusnutdinova, J. R.; Leitus, G. M.; Milstein, D. J. Am. Chem. Soc. 2015, 137, 4851–4859. (d) Hu, P.; Ben-David, Y.; Milstein, D. J. Am. Chem. Soc. 2016, 138, 6143–6146. (e) Hu, P.; Diskin-Posner, Y.; Ben-David, Y.; Milstein, D. ACS Catal. 2014, 4, 2649–2652.

(6) (a) Rodriguez-Lugo, R. E.; Trincado, M.; Vogt, M.; Tewes, F.; Santiso-Quinones, G.; Grützmacher, H. *Nat. Chem.* 2013, *5*, 342–347.
(b) Zweifel, T.; Naubron, J.-V.; Grützmacher, H. *Angew. Chem., Int. Ed.* 2009, *48*, 559–563. (7) Choi, J.-H.; Heim, L. E.; Ahrens, M.; Prechtl, M. H. G. Dalton Trans. 2014, 43, 17248–17254.

(8) Li, H.; Hall, M. B. J. Am. Chem. Soc. 2014, 136, 383-395.

(9) Cook, J.; Hamlin, J. E.; Nutton, A.; Maitlis, P. M. J. Chem. Soc., Chem. Commun. 1980, 144–145.

(10) Cook, J.; Hamlin, J. E.; Nutton, A.; Maitlis, P. M. J. Chem. Soc., Dalton Trans. 1981, 2342–2352.

(11) Ou, W. C.; Cundari, T. R. ACS Catal. 2015, 5, 225-232.

(12) Ohkuma, T.; Utsumi, N.; Tsutsumi, K.; Murata, K.; Sandoval,

- C.; Noyori, R. J. Am. Chem. Soc. 2006, 128, 8724-8725.
- (13) Morris, R. H. J. Am. Chem. Soc. 2014, 136, 1948-1959.

(14) For full details, see Supporting Information.

(15) Two products were observed in all reactions: the desired carboxylic acid and the corresponding alcohol. % acid indicates the percent of converted product observed as the carboxylic acid. The remaining product, in all cases, is the alcohol. For example, 85(6)% acid indicates 15(6)% alcohol.

(16) Garcia, G.; Solano, I.; Sanchez, G.; Santana, M. D.; Lopez, G.; Casabo, J.; Molins, E.; Miravitlles, C. J. Organomet. Chem. **1994**, 467, 119–126.

(17) Bierenstiel, M.; Dymarska, M.; de Jong, E.; Schlaf, M. J. Mol. Catal. A: Chem. 2008, 290, 1–14.

(18) Zuccaccia, D.; Macchioni, A. Organometallics 2005, 24, 3476–3486.

(19) Nova, A.; Taylor, D. J.; Blacker, A. J.; Duckett, S. B.; Perutz, R. N.; Eisenstein, O. *Organometallics* **2014**, *33*, 3433–3442.

(20) Crabtree, R. H. Chem. Rev. 2015, 115, 127-150.

(21) Bennett, M. A.; Huang, T.-N.; Matheson, T. W.; Smith, A. K.; Ittel, S.; Nickerson, W. *Inorg. Synth.* **1982**, *21*, 74–78.

(22) This precursor was previously investigated for aldehyde disproportionation activity at decreased temperature in references 9 and 10.

(23) Only 67(4)% of the substrate/products was recovered in this reaction so a meaningful comparison of percent conversion is not possible.

(24) Approximately 50% of the expected H_2 pressure was detected by this method (see Supporting Information). Some gas was noticeably lost upon puncturing the pressure-relief vial with the pressure sensor and this would account for the underdetection of pressure.