doi:10.2533/chimia.2019.299 Chimia 73 (2019) 299–303

Ruthenium Complexes with PYA Pincer Ligands for Catalytic Transfer Hydrogenation of Challenging Substrates

Philipp Melle[§] and Martin Albrecht*

[§]SCS-DSM Award for best poster presentation in Inorganic & Coordination Chemistry

Abstract: Here we highlight the potential of a series of ruthenium complexes with tridentate *N,N,N* pincer-type ligands featuring two pyridylidene amide (PYA) moieties in the ligand skeleton. They were successfully applied in transfer hydrogenation of ketones and C=C double bonds. Rational ligand design was key for increasing the catalytic performance in the reduction of challenging substrates such as potentially chelating acetylpyridines. The specific reaction profiles indicate catalyst poisoning *via* imine coordination as well as *N,O*-bidentate coordination of the substrate or the product. Approaches to mitigate this inhibition are presented. Furthermore, these PYA pincer ruthenium complexes accomplish the selective reduction of the C=C over C=O bond of α,β-unsaturated ketones such as benzylideneacetone, while other α,β-unsaturated ketones such as *trans*-chalcone predominantly underwent oxidative C=C bond cleavage.

Keywords: Homogenous catalysis · Ligand design · Pyridylidene amides · Transfer hydrogenation

Philipp Melle studied chemistry at the University Hamburg. His bachelor thesis on the development of UV-cross-linkable adhesives was written in cooperation with tesa SE. He went for an Erasmus stay at the University College Dublin to the group of Prof. Albrecht, studying transfer hydrogenation with abnormal dicarbene rhodium(III) complexes. Afterwards he joined the group of Prof. Fröba for his master project about the synthesis and characterization of hierarchically structured aerogels consisting of periodic mesoporous organosilica nanoparticles. In 2016 he moved to Bern for a PhD in the group of Prof. Albrecht, focusing on the synthesis, characterization and catalytic applications of transition metal complexes bearing *N*-mesoionic ligands.

1. Introduction

Pyridylidine amides (PYAs) are a relatively new class of ligands[1] that consist of an alkylated pyridine ring, which is connected to an amide functionality. A wide structural variety of PYAs is accessible taking into account the facile synthetic procedure that normally includes the coupling of aminopyridines with acyl chloride derivates. Depending on the nature of the acyl chloride reagent, different substituents can be introduced to the ligand system, resulting in *e.g.* alkyl-,[2] pyridyl-[3] or phenyl-substituted[4] PYAs. The choice of aminopyridines on the other hand leads to the formation of different pyridine substitution patterns, including *ortho* (2-aminopyridine), *meta* (3-aminopyridine) and *para* (4-aminopyridine) PYAs (Fig. 1). Pyridine alkylation is usually straightforward, *i.e.* using standard methylation reagents such as methyl iodide or methyl trifluorosulfonate, resulting in the corresponding pyridinium salts. Coordination to the metal center occurs *via* the amide nitrogen, which has to be deprotonated with a base either *in situ* or prior to metalation. With varying groups on the amide either monodentate,[5] bidentate (*N,N* and *C,N*)[6] or tridentate[7] *N,N,N* pincer-type bis-PYA ligands have been successfully synthesized.

One of the main features of PYAs is their donor flexibility, derived from limiting resonance structures due to the highly conjugated pyridinium-amide system. The *para* PYA ligand has been shown to adapt to different solvent polarities, toggling between the formally neutral diene-imine resonance structure (L-type coordination mode, weak donor) and the zwitterionic pyridinium-amide resonance structure (X-type coordination mode, strong donor).[8] Also the comparison of *ortho*, *meta* and *para* PYAs showed a strong effect on the electronic properties, with the mesoionic[9] *meta* PYA being the strongest donor.[7,10] Their structural variety and donor flexibility make PYAs a promising class of ligands that may adapt their electronic configuration depending on the requirements of the

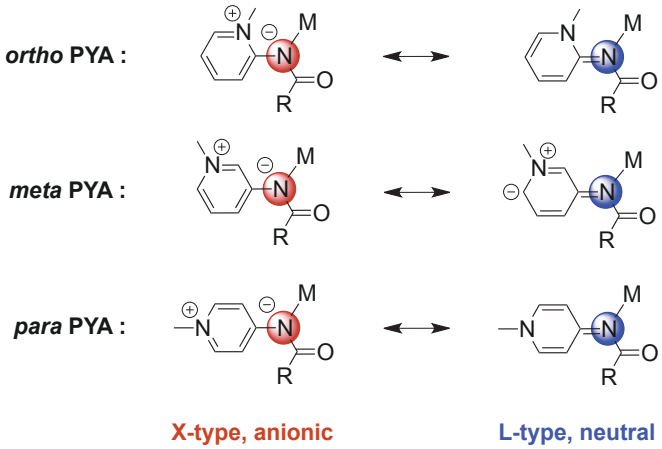


Fig. 1. Limiting resonance structures of *ortho*/*meta*/*para*-PYA ligand systems, featuring the zwitterionic X-type anionic coordination mode on the left and the L-type neutral coordination mode on the right.

*Correspondence: Prof. M. Albrecht
E-mail: martin.albrecht@dcb.unibe.ch
Departement für Chemie und Biochemie, Universität Bern, Freiestrasse 3, CH-3012 Bern

metal center, and therefore these ligands have the potential to stabilize several transition states on a putative catalytic cycle. These properties have led to a number of potent homogeneous catalysts containing rationally designed PYA ligands.[11]

The pincer platform[12] provides robustness of metal bonding (catalyst longevity) and great potential for variability (Fig. 2). They are widely used ligand motifs for numerous potent homogeneous catalysts, with the commercially available Ru-MACHO or Milstein's catalyst as prominent examples.[13] We have therefore incorporated PYA donor sites into a pincer framework based on the well-known pyridine-2,6-dicarboxamide scaffold.[14] Accordingly, the dicationic ligand precursors **1a**,**b** containing two PYA units were prepared and metalated with $[RuCl_2(cym)]_2$ under mildly basic conditions, affording the corresponding *N,N,N* pincer-type bis-PYA ruthenium(II) complexes **2a** and **2b** (Scheme 1). The acetonitrile ligands in complex **2b** were readily replaced with a variety of ancillary ligands, including PPh_3 in complex **3** and 1,2-bis(diphenylphosphino)ethane (dppe) in complex **4** (Scheme 1).

We have shown that the catalytic activity in the hydrogenation of ketones is strongly dependent on a variety of parameters including the PYA moiety, the ancillary ligands, and the reaction conditions (Fig. 3).[7] Here we will highlight their activity towards challenging substrates including heteroaromatic and α,β-unsaturated ketones containing two potential hydrogenation sites.

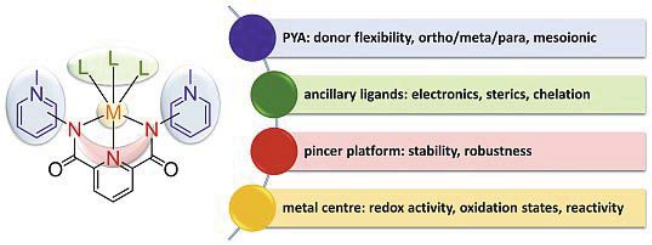
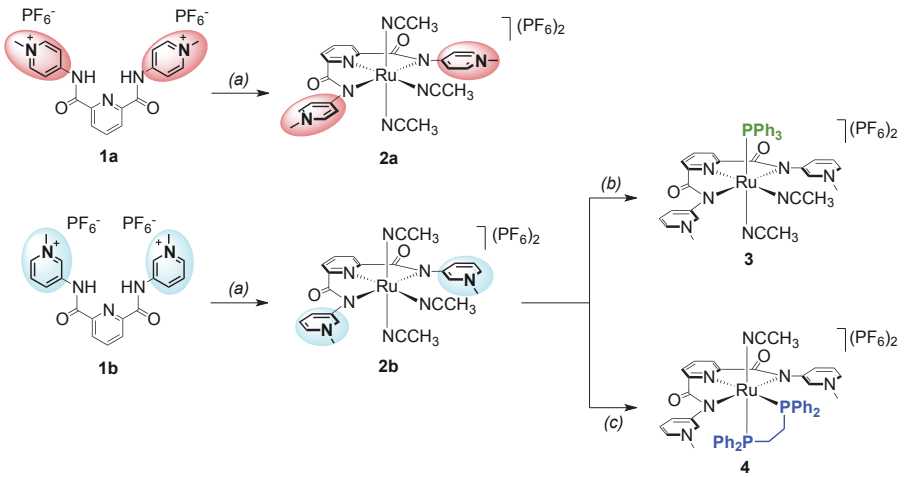


Fig. 2. Complex design: possible modifications of the catalyst for increased activity in transfer hydrogenation.

2. Results and Discussion

2.1 *Transfer Hydrogenation of Heteroaromatic Substrates*

While precatalyst **3** was successfully applied in transfer hydrogenation of a variety of substrates, including diaryl, aryl-alkyl and dialkyl ketones, the conversion of heteroaromatic substrates bearing nitrogen functionalities remained difficult. In particular pyridyl-containing ketones were only slowly and never fully converted (Fig. 4, Table 1). For example, di(2-pyridyl)ketone was initially a suitable substrate with high catalytic turnovers (entry 1, 40% conversion after 15 min). At later stages, however, the activity drops dramatically and the conversion plateaus at around 60% after 3 h reaction time. This profile is indicative for product inhibition. The substrates 2-, 3- and 4-acetylpyridine (entries 3, 5 & 7) are converted only slowly already at early reaction times, indicative for a substrate-mediated inhibition (Fig. 4).



Scheme 1. Synthesis of ruthenium(II) *N,N,N* pincer-type bis-PYA catalysts. Reaction conditions: (a) 0.5 equiv. of $[RuCl_2(cym)]_2$; 3 equiv. of Na_2CO_3 in MeCN, reflux, 16 h. (b) 1 equiv. of PPh_3 in EtOH, reflux, 16 h. (c) 1 equiv. of dppe in EtOH, reflux, 16 h.

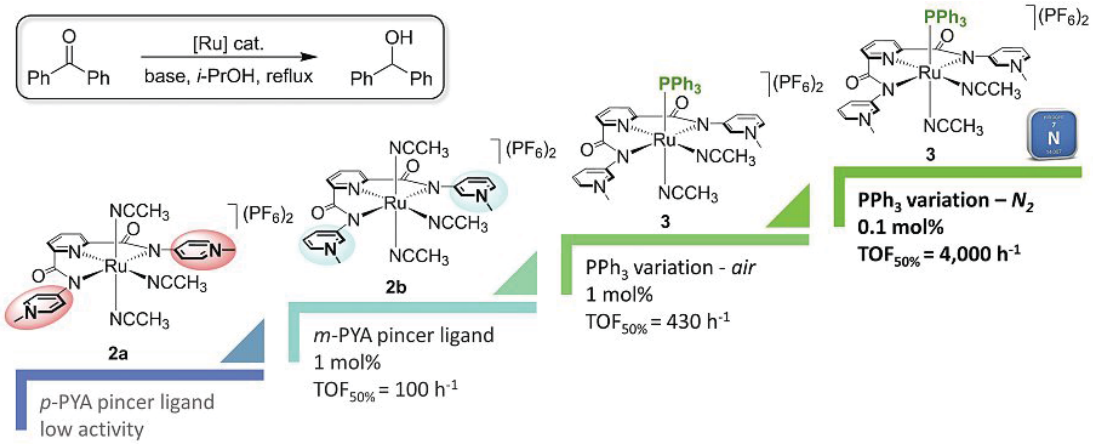


Fig. 3. Evolution of catalytic performance in transfer hydrogenation of benzophenone as the model substrate.

Table 1. Catalytic activity of complexes **3** and **4** in transfer hydrogenation of heteroaromatic substrates.[a]

entry	substrate	catalyst	yield [%][b]			TOF_{ini} [h^{-1}]
			5 min	1 h	6 h	
1		**3**	25	52	63	300
2		**4**	26	> 99	> 99	310
3		**3**	< 2	4	10	< 10
4		**4**	10	> 99	> 99	120
5		**3**	9	22	37	110
6		**4**	4	38	> 99	50
7		**3**	9	17	28	110
8		**4**	4	23	69	50

[a]General reaction conditions: substrate (1 mmol), KOH (0.1 mmol, 10 mol%), [Ru] (0.01 mmol, 1 mol%), *i*PrOH (5 mL), reflux temperature. [b]determined by ^{1}H NMR spectroscopy using hexamethylbenzene as internal standard and averaged over at least two runs, conversions correspond to yields.

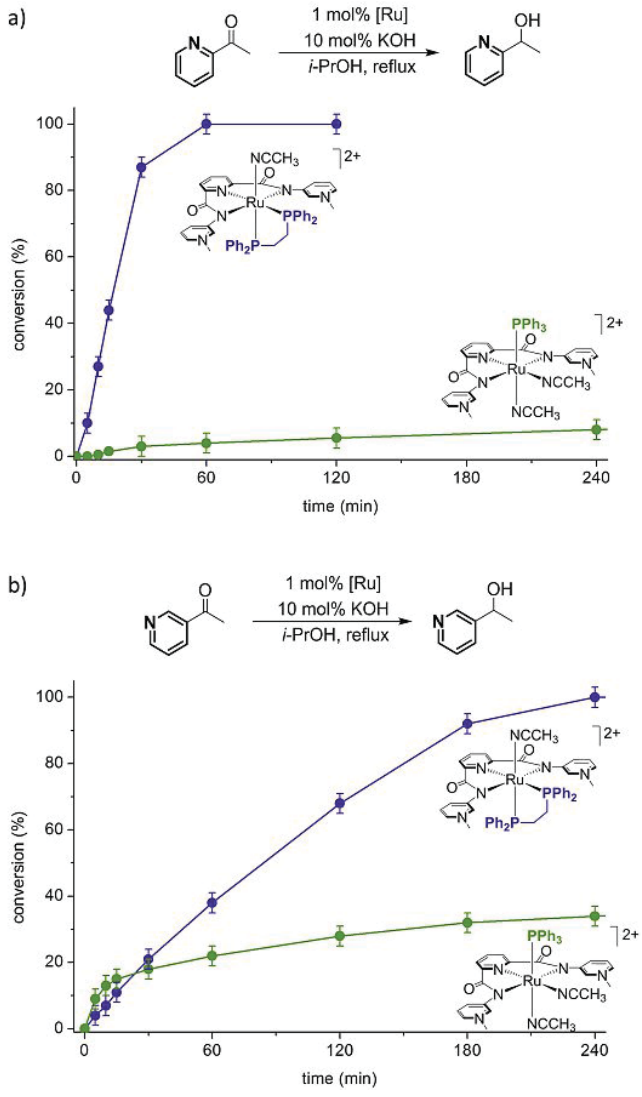
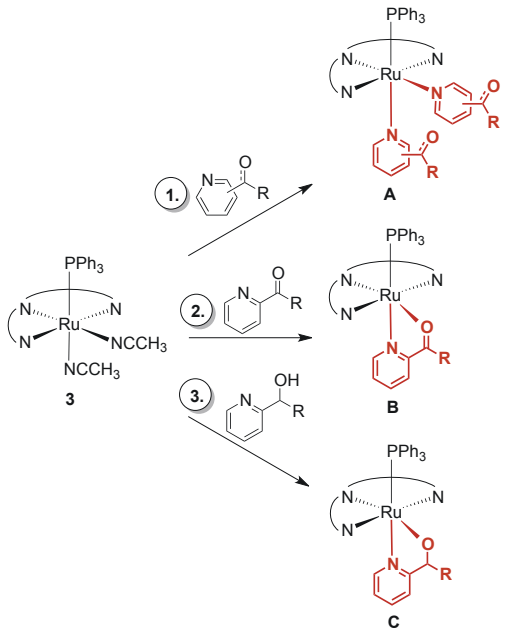


Fig. 4. Time conversion profiles for the transfer hydrogenation of 2-acetylpyridine (a) and 3-acetylpyridine (b) with catalyst **3** (green lines) and catalyst **4** (blue lines) respectively. Reaction conditions: substrate (1 mmol), KOH (0.1 mmol, 10 mol%), [Ru] (0.01 mmol, 1 mol%), iPrOH (5 mL), reflux temperature.

Three potential catalyst inhibition pathways are most conceivable with complex **3** (Scheme 2):

1) Imine *N*-coordination (which should be stronger in the product imine than the starting material due to the electron-withdrawing nature of the carbonyl group in the substrate)
2) *N,O*-bidentate chelation of the substrate *via* the pyridine nitrogen and the carbonyl oxygen
3) *N,O*-bidentate chelation of the deprotonated product alcohol, either after migratory insertion of the ketone into the Ru–H bond or as alkoxide under basic conditions



Scheme 2. Possible inhibition pathways of catalyst **3** with heteroaromatic substrates, including imine *N*-coordination (1.), *N,O*-bidentate chelation of substrate (2.) or *N,O*-bidentate chelation of the product alcohol (3.).

These pathways take into account that both MeCN ligands are very labile and dissociate under catalytic conditions. *N,O*-chelation is much more favored for di(pyridyl)ketone and 2-acetylpyridine substrates, since the spatial arrangement of the pyridine nitrogen and the oxygen atom is preset for bidentate coordination and formation of a stable 5-membered metallacycle. Moreover, di(pyridyl)ketone is known to act also as a *N,N*-bidentate coordinating ligand.[15] With 3- and 4-acetylpyridine as substrate, on the other hand chelation is not possible and inhibition pathways 2 and 3 are of minor relevance.

The initial rates of di(pyridyl)ketone and 2-acetylpyridine, the two potential chelators, are substantially different, which may be due to their specific electronic properties. 2-acetylpyridine shows a strong affinity for *N,O*-bidentate bonding *via* pathways 2 and 3, *i.e.* binding as *N,O*-chelate with the ketone oxygen directly or as alkoxide after migratory insertion. Taking into account the +I effect of the methyl group, which increases the electron density on the carbonyl group, the oxygen lone pair is much more available for metal bonding. The di(pyridyl)ketone on the contrary features two electron-withdrawing pyridyl substituents on the carbonyl group which leads to substantially lower electron density on the oxygen atom and prevents direct chelation of the substrate *via* ketone bonding. The base-mediated alkoxide formation of product inhibition pathway 3 however is expected to be more pronounced for alcohols with electron-deficient substituents. The higher acidity of the OH-group in di(pyridyl)methanol facilitates *N,O*-chelation after formation of a substantial amount of the hy-

drogenated product as seen in the conversion plateau after *ca.* 30 minutes reaction time. Hence, the reaction with di(pyridyl)ketone is product-inhibited, while the conversion of 2-acetylpyridine is substrate-inhibited.

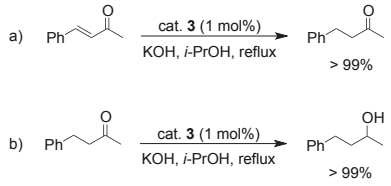
Inhibition pathway 1, *viz.* the formation of a Ru–N bond to the pyridine nitrogen, is much more favored for sterically unshielded pyridine substrates. In this model the substrate mediated catalyst inhibition will increase in the following order: di(pyridyl)ketone ≈ 2-acetylpyridine < 3-acetylpyridine < 4-acetylpyridine, which explains the higher conversion of 3-acetylpyridine (37% after 6 h) compared to 4-acetylpyridine (28% after 6 h).

Catalyst inhibition *via N,O*-bidentate chelation of the substrate or the product to the ruthenium center may be prevented when substituting the monophosphine ligand in complex **3** with a diphosphine ligand, which reduces the number of substitution-labile MeCN ligands from two to only one. Thus, reaction of complex **2b** with dppe affords complex **4** featuring only one potential coordination site for substrate coordination (*cf* Scheme 1).

Complex **4** indeed transfer hydrogenates 2-acetylpyridine and di(pyridyl)ketone quantitatively and with appreciable reaction rates (Fig. 4, Table 1), demonstrating the potential of rational catalyst design and also supporting chelation as the major catalyst inhibition pathway with these two substrates. A closer look at the time-conversion profiles shows that the potentially chelating substrates are converted >20 times faster (2-acetylpyridine, entries 3, 4) and to completion without any detectable product inhibition (di(pyridyl)ketone, entries 1, 2). However, the turnover frequency increased less dramatically for the pyridyl derivatives with the acyl group in more remote position (entries 5–8). The less substantial enhancement of catalytic activity is in agreement with monodentate imine coordination to the metal center, which is not prevented by the bidentate phosphine. Imine coordination is much less favored for 2-acetylpyridine due to the steric shielding of the acyl group in *ortho* positon. The increased activity of complex **4** towards the transfer hydrogenation of these substrates as compared to complex **3** is rationalized by the fact that imine coordination is less competitive with complex **4** because of the high *trans* effect of the phosphine, whereas in complex **3**, imine coordination may occur *trans* to the central pyridyl site of the PYA pincer ligand and hence be kinetically much less labile and more inhibiting. Indeed, ^{1}H NMR spectroscopic investigations on the lability of the two MeCN ligands in complex **3** revealed that the MeCN ligand *trans* to the pyridyl unit is exchanged more than 2 orders of magnitude slower ($t_{1/2}$ = 8 h) than the ligand *trans* to the phosphine ($t_{1/2}$ < 2 min). Hence, imine coordination *trans* to pyridyl in complex **3** is much more effective than *trans* to the phosphine in complex **4** and thus decelerates the catalytic activity of complex **3** towards the conversion of heteroaromatic substrates that are otherwise little shielded.

2.2 *Selectivity in Transfer Hydrogenation of α,β-Unsaturated Ketones*

Michael systems, *i.e.* α,β-unsaturated ketones, constitute another class of challenging substrates for (transfer) hydrogenation as both the C=C and C=O double bonds may undergo reduction. Depending on the substrate, complex **3** induces different reactivity patterns. Transfer hydrogenation of benzylideneacetone under aerobic conditions produced selectively the saturated ketone as the exclusive product (Scheme 3a). Complex **3** achieves full conversion in just about 30 min (1 mol% catalyst loading) and even upon prolonged reaction times, no hydrogenation of the C=O bond was observed, thus featuring one of the rare homogeneous catalytic systems that selectively reduces the C=C bond in α,β-unsaturated ketones. Other catalysts typically show selectivity for hydrogenation of the carbonyl bond[16] or produce the fully hydrogenated product.[17] Of note, benzylacetone is a natural product found in wild tobacco or cocoa beans to attract melon flies[18] and



Scheme 3. Selective transfer hydrogenation of benzylideneacetone catalyzed with **3** gives exclusively benzylacetone, even though benzylacetone is converted to the fully saturated product in independent runs.

widely used in the fragrance industry as a perfume ingredient.[19] The main industrial production processes rely on heterogeneously catalyzed hydrogenation reactions.[20]

This selectivity pattern is particularly remarkable when considering that the benzylacetone is readily transfer hydrogenated when used as a substrate (Scheme 3b). In a separate catalytic run under the exact same conditions benzylacetone is quantitatively hydrogenated within one hour, giving 4-phenyl-2-butanol as the only product. Based on these results we assume deactivation of the catalytically active species after C=C bond hydrogenation, which prevents further reduction. Catalyst deactivation is supported by the results obtained from reduction of benzylideneacetone, followed by addition of acetophenone after 30 min to the reaction mixture. Negligible hydrogenation of acetophenone was noted after 6 h, although this substrate was fully converted after 30 min when applied on its own.

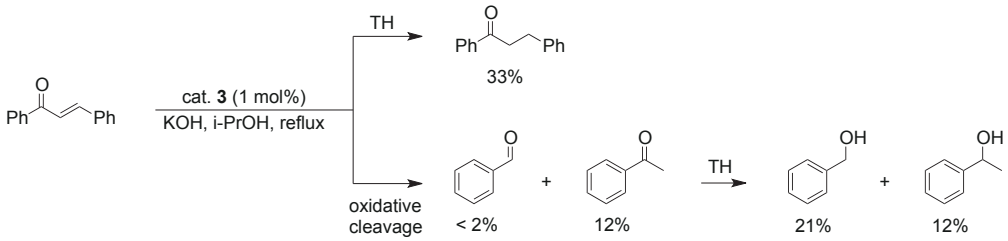
A different reactivity pattern was observed when using *trans*-chalcone as substrate, which afforded a mixture of products consisting of the saturated ketone, acetophenone, benzaldehyde, and their hydrogenated products (Scheme 4). The selective formation of the 1,3-diphenyl-1-propanone without further reduction of the carbonyl group parallels the selectivity pattern observed for benzylideneacetone (see above). The formation of the other products is more intriguing and suggests an oxidative cleavage of the C=C bond to yield benzaldehyde and acetophenone, which themselves are substrates for transfer hydrogenation and afford benzyl alcohol and 1-phenylethanol. Monitoring the reaction progress using ^{1}H NMR spectroscopy allows for time-dependent quantification of the various products (Fig. 5). Accordingly, benzaldehyde and acetophenone are formed simultaneously at the early stages and at much faster rates (TOF_{ini} = 130 h^{-1}) than transfer hydrogenation of the substrate takes place (TOF_{ini} = 50 h^{-1}). These initial observations imply that ruthenium-catalyzed oxidative C=C bond cleavage is substantially faster than the hydrogenation of this bond. Moreover, time-dependent monitoring clearly indicates that aldehydes are converted much faster than ketones (*cf* the rapid consumption of benzaldehyde compared to the slow hydrogenation of acetophenone). Notably, the very slow formation of 1-phenylethanol and benzylalcohol may probably be related to the same catalyst deactivation as observed in the selective hydrogenation of benzylideneacetone.

The same reactivity and selectivity patterns were observed when 1-phenyl-2-buten-1-one was used as α,β-unsaturated ketone substrate. However, the presence of a methyl rather than a phenyl group at the ene terminus increased the propensity for Michael aldol condensation reactions and produced a mixture of products from C–C bond formation in addition to selective C=C hydrogenation and oxidative C=C bond cleavage products.

3. Conclusions

Here we introduced two electronically flexible PYA moieties into the well-known pincer coordination motif and demonstrated that the corresponding Ru(II) complexes are excellent catalyst precursors for transfer hydrogenation. Catalyst tailoring by introducing ancillary phosphine ligands induces a substantial enhancement of the catalytic performance and allows for the efficient

Scheme 4. Product distribution after 6 h reaction time for the substrate trans-chalcone (TH = transfer hydrogenation).



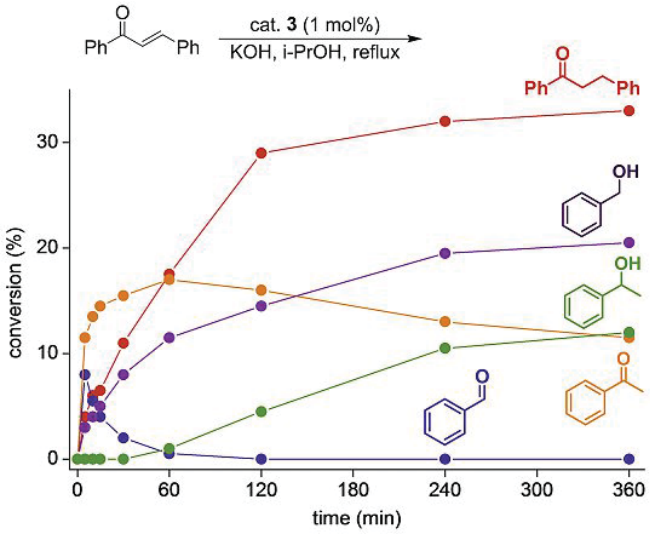


Fig. 5. Time-conversion profile of the catalytic transfer hydrogenation of *trans*-chalcone showing the relative product distribution.

reduction of challenging substrates such as potentially chelating pyridyl ketones and α,β-unsaturated ketones. Understanding the catalyst inhibition pathways allows for a rational design of second-generation catalysts, underpinning the advantages of molecularly well-defined homogeneous catalysts. Potentially chelating PYA ligands as implemented here in pincer-type complexes constitute a synthetically versatile platform for further catalyst design for reduction and oxidation catalysis and provide exciting perspectives also for the coordination and catalytic application of other transition metals.

Acknowledgements

We are grateful for generous financial support from the Swiss National Science Foundation (Project 2000021_162868, and R'equip projects) as well as the European Research Council (CoG 615653).

Received: January 25, 2019

[1] a) B. Brzezinski, G. Zundel, *J. Phys. Chem.* **1979**, *83*, 1787; b) D. Rais, I. R. Gould, R. Vilar, A. J. P. White, D. J. Williams, *Eur. J. Inorg. Chem.* **2004**, *9*, 1866; c) C. H. Chien, M. K. Leung, J. K. Su, G. H. Li, Y. H. Liu, Y. Wang, *J. Org. Chem.* **2004**, *69*, 1866; d) M. E. Doster, S. A. Johnson, *Angew. Chem. Int. Ed.* **2009**, *48*, 2185; e) M. E. Doster, J. A. Hatnean, T. Jeftic, S. Modi, S. A. Johnson, *J. Am. Chem. Soc.* **2010**, *132*, 11923; f) R. J. Thatcher, D. G. Johnson, J. M. Slattery, R. E. Douthwaite, *Chem. Eur. J.* **2012**, *18*, 4329.
[2] M. E. Doster, S. A. Johnson, *Organometallics* **2013**, *32*, 4174.
[3] M. Navarro, V. Rosar, T. Montini, B. Milani, M. Albrecht, *Organometallics* **2018**, *37*, 3619.
[4] P. D. W. Boyd, L. J. Wright, M. N. Zafar, *Inorg. Chem.* **2011**, *50*, 10522.
[5] Q. Shi, R. J. Thatcher, J. Slattery, P. S. Sauari, A. C. Whitwood, P. C. McGowan, R. E. Douthwaite, *Chem. Eur. J.* **2009**, *15*, 11346.
[6] M. Navarro, C. A. Smith, M. Albrecht, *Inorg. Chem.* **2017**, *56*, 11688.
[7] P. Melle, Y. Manoharan, M. Albrecht, *Inorg. Chem.* **2018**, *57*, 11761.
[8] V. Leigh, D. J. Carleton, J. Olguin, H. Mueller-Bunz, L. J. Wright, M. Albrecht, *Inorg. Chem.* **2014**, *53*, 8054.
[9] Mesoionic compounds are defined by IUPAC as "dipolar five- (possibly six-) membered heterocyclic compounds in which both the negative and the positive charge are delocalized, for which a totally covalent structure cannot be written, and which cannot be represented satisfactorily by any one polar structure. The formal positive charge is associated with the ring atoms, and the formal negative charge is associated with ring atoms or an exocyclic nitrogen or chalcogen atom." IUPAC. 'Compendium of Chemical Terminology', 2nd edn. Gold Book Compiled by A. D. McNaught and A. Wilkinson, Blackwell Scientific Publications, Oxford, **1997**. XML on-line corrected version: *http://goldbook.iupac.org* (**2006**) created by M. Nic, J. Jirat, B. Kosata, updates compiled by A. Jenkins. ISBN 0- 9678550-9-8.
[10] M. Navarro, C. A. Smith, L. Mo, S. Bernhard, M. Albrecht, *Chem. Eur. J.* **2018**, *24*, 6386.
[11] M. Navarro, M. Li, H. Mueller-Bunz, M. Albrecht, *Chem. Eur. J.* **2016**, *22*, 6740.
[12] a) 'Organometallic Pincer Chemistry', Eds. G. van Koten, D. Milstein, Springer Berlin, Germany, **2013**; b) 'Pincer and Pincer-Type Complexes: Applications in Organic Synthesis and Catalysis' Eds. K. J. Szabó, O. F. Wendt, Wiley-VCH Weinheim, Germany, **2014**; c) 'The Privileged Pincer-Metal Platform: Coordination Chemistry & Applications', Eds. G. van Koten, R. A. Gossage, Springer Berlin, Germany, **2016**; d) 'Pincer Compounds: Chemistry and Applications', Eds. D. Morales-Morales, Elsevier Amsterdam, NL, **2018**; e) M. Albrecht, G. van Koten, *Angew. Chem. Int. Ed.* **2001**, *40*, 3750.
[13] M. E. Van Der Boom, D. Milstein, *Chem. Rev.* **2003**, *103*, 1759.
[14] P. Kumar, R. Gupta, *Dalton Trans.* **2016**, *45*, 18769.
[15] A. C. Deveson, S. L. Heath, C. J. Harding, A. K. Powell, *Dalton Trans.* **1996**, 3173.
[16] R. Noyori, R. T. Ohkuma, *Angew. Chem. Int. Ed.* **2001**, *40*, 40.
[17] S. Horn, C. Gandolfi, M. Albrecht, *Eur. J. Inorg. Chem.* **2011**, 2863.
[18] D. Kessler, T. Baldwin, *The Plant Journal* **2006**, *49*, 840.
[19] H. Surburg, J. Panten, 'Common Fragrance and Flavor Materials: Preparation, Properties and Uses', Wiley-VCH Weinheim, Germany, **2006**.
[20] W. Kuhn, H.-U. Funk, G. Senft, 'Process for the preparation of benzylacetone', U.S. Patent US644124B1, issued August 27, **2002**.