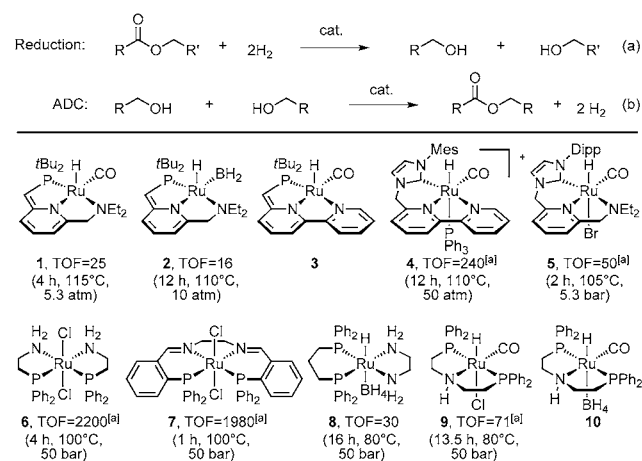


From Esters to Alcohols and Back with Ruthenium and Osmium Catalysts**

Denis Spasyuk, Samantha Smith, and Dmitry G. Gusev*

Hydrogenation is an attractive “green” method for the reduction of esters.^[1–4] The reaction shown in Scheme 1 a is mildly exergonic, for example, formation of ethanol from



Scheme 1. Hydrogenation of esters and dehydrogenation of alcohols. [a] Under basic conditions. Dipp = 2,6-Diisopropylphenyl, Mes = 2,4,6-trimethylphenyl, S/M = molar ratio of substrate to metal, TOF = turnover frequency per hour for hydrogenation of PhCOOR (R = Me, Et).

ethyl acetate is favored by circa -5 kcal mol^{-1} .^[5a] The reverse process of acceptorless dehydrogenative coupling (ADC, Scheme 1 b) is feasible in an open system, because H_2 gas is sparsely soluble and can be efficiently expelled under reflux conditions. Well-defined catalysts for reactions shown in Scheme 1 have been developed in the past five years. Milstein's complex **1**, which was reported in 2005, gives symmetrical esters from primary alcohols upon heating to more than 100°C.^[6] All Milstein-type complexes **1–5**^[1,4a] and Noyori-type catalysts **6–10**^[2,3] are active in ester hydrogenation (Scheme 1). These catalysts employ ligand cooperativity by pyridine aromatization/dearomatization in **1–5** and cleavage/formation of N–H bonds in **6–10**.^[1e,2a,3c]

A meaningful comparison of the efficiency of these catalysts is currently problematic because of significant differences in the employed reaction temperatures and pressures. Available data for hydrogenation of benzoates (PhCOOR, R = Me, Et) serve to highlight the impressive performance of catalysts **6** and **7**, although a major drawback of these systems is the need for 5–10 mol % NaOMe. Hydrogenation of alkyl alkananoates proceeded slower compared to benzoates, for example, a turnover frequency (TOF) of 690 for methyl octanoate versus 2200 for methyl benzoate was reported for catalyst **6**.^[2b,c]

Little is known about selectivity and functional-group tolerance of the existing ester hydrogenation catalysts. Testing of complexes **1**, **2**, **4**, and **5** was restricted to unfunctionalized aliphatic and aromatic esters. Catalyst **3** performed well for hydrogenation of methyl formate (TOF = 534 in 8 h) and dimethyl carbonate (TOF = 314 in 14 h) at 110°C and $p(\text{H}_2) = 50 \text{ bar}$.^[1b] Only complex **7** was studied with alkyl alkenoates and showed an excellent C=O/C=C selectivity, except for substrates with terminal C=C bonds, that is, methyl 10-undecanoate and the α,β -unsaturated methyl cinnamate.^[2] Hydrogenation of *cis* alkenoates (common in plant oils) and their stability with respect to *cis/trans* isomerization under catalytic conditions have not been reported.

Catalysts **8** and **10** have been successfully tested with chiral esters of α -amino, α -hydroxy, β -amino, and β -hydroxy acids.^[3] Good conversions and retention of the *ee* values were observed by using 0.1–1 mol % catalyst without base at 80°C and $p(\text{H}_2) = 50 \text{ bar}$. Complex **9** is exceptionally active for hydrogenation of methyl (*R*)-lactate at 27°C when used with 12 mol % of NaOMe.^[3d]

Herein we report new Ru and Os catalysts capable of efficient reduction of esters under neutral conditions. This research is based upon our recent work with $[\text{MH}_2(\text{CO})(\text{HN}(\text{C}_2\text{H}_4\text{PiPr}_2)_2)]$ complexes (M = Ru, Os), which are catalysts for transfer dehydrogenation of ethanol to ethyl acetate at room temperature and for acceptorless dehydrogenation of primary alcohols (Scheme 1 b) at temperatures above 120°C.^[5b] Use of 0.05 mol % $[\text{RuH}_2(\text{CO})(\text{HN}(\text{C}_2\text{H}_4\text{PiPr}_2)_2)]$ gave a turnover frequency of 90 for hydrogenation of methyl benzoate after 18 hours at 100°C with $p(\text{H}_2) = 50 \text{ bar}$. We thought that replacement of the PNHPiPr ligand by a hemilabile NNHPiPr system could facilitate the hydrogenation, by analogy with the Milstein's NNP complex **1**, which is more efficient than its PNP analogue.^[1a]

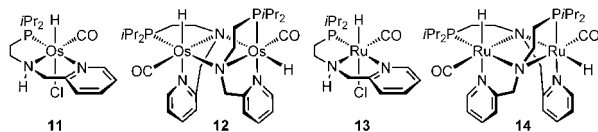
The NNHPiPr = $\text{PyCH}_2\text{NHC}_2\text{H}_4\text{PiPr}_2$ (Py = 2-pyridyl) ligand is easily assembled by condensation of the commercially available picolinaldehyde and 2-(diisopropylphosphino)ethanamine, followed by reduction with DIBAL. The

[*] Dr. D. Spasyuk, S. Smith, Prof. D. G. Gusev
Department of Chemistry, Wilfrid Laurier University
Waterloo, Ontario N2L 3C5 (Canada)
E-mail: dgoussev@wlu.ca
Homepage: http://wlu.ca/homepage.php?grp_id=366

[**] We are grateful to the NSERC of Canada and the SHARCNET facilities (www.sharcnet.ca) for their support of this work.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ange.201108956>.

hydrido carbonyl chlorides $[\text{MHCl}(\text{CO})(\text{NNHPiPr})]$ ($\text{M} = \text{Os}$ (**11**), Ru (**13**); Scheme 2) were prepared from the readily available $[\text{MHCl}(\text{CO})(\text{AsPh}_3)_3]$ precursors by ligand meta-



Scheme 2. Complexes used in this communication.

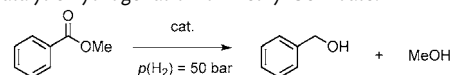
thesis. Treatment of complexes **11** and **13** with *t*BuOK afforded unusual dimers $[\text{MH}(\text{CO})(\text{NNHPiPr})_2]$ ($\text{M} = \text{Os}$ (**12**), Ru (**14**); Scheme 2), presumably via intermediate 16-e amido species $[\text{MH}(\text{CO})(\text{NNHPiPr})]$, which is analogous to the known $[\text{OsH}(\text{CO})(\text{PNHPiPr})]$.^[5b] Characterization of new complexes **11–14** was accomplished by a combination of spectroscopic methods and X-ray crystallography.

Dimers **12** and **14** have similar structures, however, they differ by the arrangements of the NNHPiPr ligands, which are spanning the Ru centers in **14**, but coordinate individual Os centers in **12**. These dimers are lacking symmetry and produce characteristic 1:1 hydride and phosphorus NMR resonances at room temperature. In the temperature range of 40 to 80 °C, a second minor 1:1 pattern appears in the hydride region and in the ³¹P NMR spectra of **12** and **14** because of slow isomerization. No resonances of mononuclear species were seen even at 80 °C, as well as no saturation transfer between the hydrides, thus suggesting significant thermal and kinetic stability of **12** and **14** in solution.

Exposing **12** and **14** to 2-propanol or H_2 (1 atm) failed to produce $[\text{MH}_2(\text{CO})(\text{NNHPiPr})]$. We obtained *trans*- $[\text{OsH}_2(\text{CO})(\text{NNHPiPr})]$ (**15**) by treating **11** with $\text{Li}(\text{Et}_3\text{BH})$ in THF. Characterization of the product in common solvents was hampered by the lack of solubility (in C_6D_6 and $[\text{D}_8]\text{THF}$) or rapid decomposition (in CD_3CN , CD_2Cl_2 , and ethanol). Surprisingly, **15** is soluble and stable in $[\text{D}_6]\text{DMSO}$, in which the ¹H, ¹³C, and ³¹P NMR spectra are fully consistent with the *trans*-dihydride structure analogous to the related *trans*- $[\text{OsH}_2(\text{CO})(\text{PNHPiPr})]$ complex.^[5b] Experimental and computational details for complexes **11–15** are provided in the Supporting Information.

A stoichiometric reaction of dihydride **15** and methyl benzoate in $[\text{D}_8]\text{THF}$ immediately produced methanol, benzyl alcohol, and a mixture of the isomers of **12**. The catalytic activity of complexes **11–14** under $p(\text{H}_2) = 50$ bar was first tested in a series of experiments with methyl benzoate (Table 1). The ultimate performance was observed with ruthenium dimer **14**, which gave 18000 turnovers in 17 hours at 100 °C by using 0.005 mol % (50 ppm) of the catalyst without base. Thus, this complex is one order of magnitude more efficient than $[\text{RuH}_2(\text{CO})(\text{PNHPiPr})]$, which was mentioned above. At 80 °C, complex **14** gave TOF = 1470 (Table 1, entry 11), which is 20 times faster than the hydrogenation rate reported^[3c] for $[\text{RuHCl}(\text{CO})(\text{PNHPPH})]$ with 5 mol % NaOMe (catalyst **9**, Scheme 1). The efficiency of **14** increases markedly from 40 to 100 °C, yet a high conversion was achieved even at 40 °C by using only

Table 1: Catalytic hydrogenation of methyl benzoate.^[a]



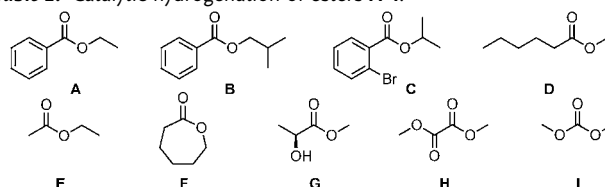
Entry	Cat.	Ester/Metal ^[b]	T [°C]	t [h]	Conv. [%]
1	11 ^[c]	2000	100	1.5	100
2	12	2000	40	22	28
3	12	2000	60	7	82
4	12	2000	80	2.2	76
5	12	2000	100	1.5	99
6	12	3000	100	3	100
7	12	10 000 ^[d]	100	19	80
8	13 ^[c]	2000	100	1.7	100
9	14	2000	40	17	82
10	14	2000	60	2.2	71
11	14	2000	80	1.2	88
12	14	2000	100	1	99
13	14	10 000	100	14	100
14	14	20 000	100	17	90

[a] PhCOOMe (20 mmol) in THF (7 mL) was hydrogenated in a 75 mL Parr pressure vessel. [b] Molar ratio of substrate to metal. [c] With *t*BuOK (1 mol %). [d] With PhCOOMe (120 mmol) in a 300 mL vessel.

0.05 mol % of the catalyst (Table 1, entry 9). Osmium dimer **12** is also an efficient catalyst for hydrogenation of methyl benzoate, however, at a slower rate compared to **14**. The chlorides **11** and **13** are similarly active in the presence of *t*BuOK.

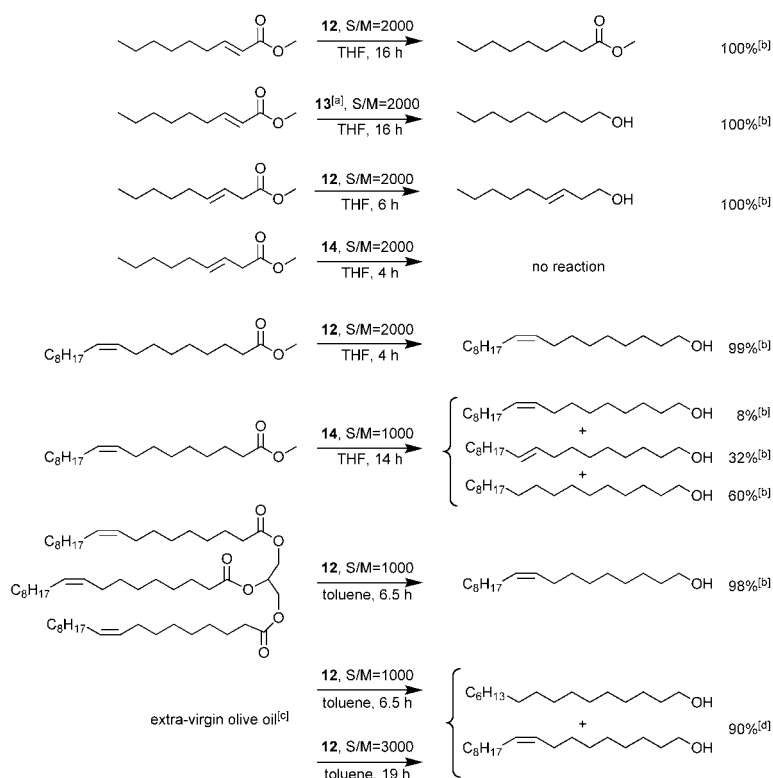
We further investigated hydrogenation of a group of carbonyl compounds (Table 2) and representative alkenoates (Scheme 3) at 100 °C, under $p(\text{H}_2) = 50$ bar. Catalyst **12** is equally active for hydrogenation of ethyl, *iso*-butyl, and methyl benzoates. However, hydrogenation of isopropyl 2-bromobenzoate was unsuccessful, apparently because of

Table 2: Catalytic hydrogenation of esters A–I.



Entry	Ester	Cat.	Ester/Metal ^[b]	t [h]	Conv. [%]
1	A	12	2000	1.6	99
2	B	12	2000	1.5	93
3	C	12	2000	17	0
4	D	12	2000	2	100
5 ^[c]	D	12	3000	2.7	100
6	D	14	2000	1.5	93
7	D	14	10 000	18	71
8	E	12	2000	3	100
9	F	12	2000	1.4	99
10	F	14	2000	5	67
11	G	12	2000	9	72
12	H	12	2000	23	0
13	I	14	2000	5.7	85

[a] Substrate (20 mmol) in THF (7 mL) was hydrogenated in a 75 mL pressure vessel at 100 °C and $p(\text{H}_2) = 50$ bar. [b] Molar ratio of substrate to metal. [c] Substrate (120 mmol) in a 300 mL vessel.



Scheme 3. Hydrogenation of alkenoates at 100 °C and $p(\text{H}_2) = 50$ bar, S/M = molar ratio of alkenoate groups to metal. [a] With $t\text{BuOK}$ (0.5 mol %). [b] Conversion. [c] A mixture of triglycerides of oleic (ca. 85 %), linoleic (ca. 2–3 %), and palmitic acids as the main components in our samples. [d] Total yield of isolated alcohol mixture, containing approximately 85 % of oleyl alcohol.

catalyst deactivation. None of the catalysts shown in Scheme 1 have been tested with halogenated substrates, except **6**, which gave 88 % conversion for methyl 4-chlorobenzoate by using 0.05 mol % catalyst with 10 mol % NaOMe at 100 °C and $p(\text{H}_2) = 50$ bar.^[2b,c]

Complexes **12** and **14** gave 100 % and 93 % reduction for methyl hexanoate in 2 and 1.5 hours, respectively. This compares favourably with the reduction of methyl octanoate with catalyst **6** (by using the same reaction temperature, pressure, and catalyst loading), for which 86 % conversion was reported after 2.5 hours of reaction in the presence of 10 mol % NaOMe.^[2b,c] For ethyl acetate, the reduction with **12** was finished in three hours (Table 2, entry 8). The same reaction under $p(\text{H}_2) = 5$ bar required a 20 times higher catalyst loading to reach 96 % conversion in two hours with **5**^[4a] and 86 % conversion in 12 hours with **1**,^[1a] both at the slightly higher temperatures of 105 and 115 °C, respectively.

We further investigated hydrogenation of ϵ -caprolactone, a substrate that is known to undergo ring opening polymerization (ROP) in the presence of $t\text{BuOK}$ and similar bases.^[7] Indeed, polymeric material was formed in an attempted reduction of ϵ -caprolactone with **13** in the presence of $t\text{BuOK}$. When catalyzed by **14** without base, the hydrogenation proceeded without polymerization, but stopped at 67 % conversion as if the catalyst was deactivated at that time. Rapid reduction of ϵ -caprolactone was achieved with osmium dimer **12** (Table 2, entry 9).

Substrates **G** and **I** are difficult to hydrogenate and require longer reaction times. The TOF of 160 for **G** (Table 2, entry 11) and 298 for **I** (entry 13) compare well with the best reported values under neutral conditions with catalysts **10** (TOF = 62 in 16 h at 80 °C)^[3c] and **3** (TOF = 314 in 14 h at 110 °C).^[1b] No hydrogenation of methyl oxalate (**H**) was observed with **12**; this substrate has not been studied with catalysts **1–10**.^[8]

Activity and selectivity of complexes **12–14** were tested with substrates containing C=C bonds. The results show significant differences for ruthenium and osmium catalysts (Scheme 3). Hydrogenation of α,β -unsaturated methyl 2-nonenate was not selective with **13** and afforded nonanol, which is not surprising with regard to the poor selectivity of **7** with methyl cinnamate.^[2a] Unexpectedly, reduction of methyl 2-nonenate with **12** quantitatively afforded methyl nonanoate. Such unusual selectivity and the lack of further conversion to nonanol in this case are puzzling. Osmium dimer **12** successfully catalyzed reduction of methyl 3-nonenoate to 3-nonanol, whereas ruthenium dimer **14** proved inactive in this reaction. Methyl oleate was hydrogenated with **12** with retention of the C=C bond to give (*Z*)-octadec-9-enol. The same reaction was very sluggish and required more catalyst with **12**; the reaction also lacked selectivity and afforded a mixture of octadecanol and (*E*)- and (*Z*)-octadec-9-enols.

We further tested osmium dimer **12** for reduction of glyceryl trioleate and a sample of domestic olive oil, which is a natural mixture of triglycerides of oleic (ca. 85 %), linoleic (ca. 2–3 %), and palmitic acids (main components). Hydrogenation of the trioleate quantitatively afforded neat (*Z*)-octadec-9-enol (oleyl alcohol) after aqueous washing, based on comparison of the ¹H and ¹³C NMR spectra of the product with those of an authentic sample of the alcohol. A similar product containing mostly oleyl (85 %) and palmityl alcohols was obtained after hydrogenation of olive oil followed by aqueous washing. The reduction appeared close to quantitative, although we noted that the ¹H NMR spectra of the product were missing the characteristic C11-CH₂ resonance of linoleyl alcohol (expected at 2.77 ppm in CDCl₃). Hydrogenation of esters of polyunsaturated acids will need to be studied further.

We finally tested the activity of the NNHPiPr catalysts for dehydrogenative coupling of alcohols. Two complexes were selected for this study, the ruthenium hydrido chloride **13** and osmium dimer **12** (Table 3). We found the catalytic activity of **12** particularly impressive in ethanol and propanol at 78 ° and 96 °C respectively, as conversions of these alcohols to ethyl acetate and propyl propionate with high yields have never been observed below 100 °C. The previously reported best ADC catalyst **1** was inactive for ethanol and propanol and required heating to more than 100 °C to produce esters from butanol and higher-boiling alcohols. The exceptional activity of **12** for ester synthesis naturally correlates with the excellent

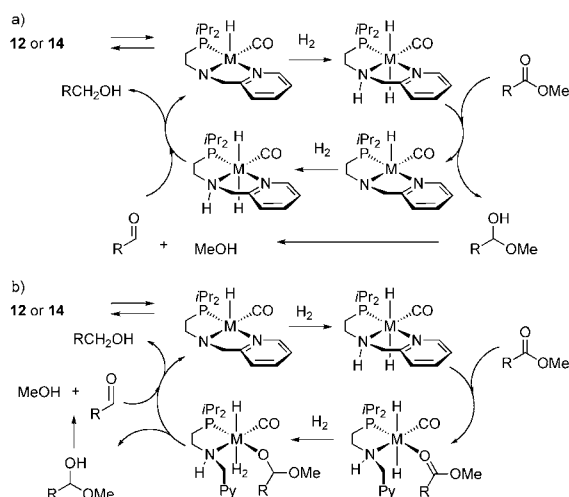
Table 3: Catalytic acceptorless dehydrogenation of alcohols.

$2 \text{ R-CH}_2\text{OH} \xrightarrow[\text{reflux}]{\text{cat.}} \text{R-CO-O-CH}_2\text{R} + 2 \text{ H}_2$						
Entry	R ^[a]	T [°C]	Cat.	ROH/Metal ^[b]	t [h]	Conv. [%]
1	Me	78	12	1000	24	7
2	Me	78	12 ^[c]	1000	8	61
3	Me	78	12 ^[c,d]	1000	8	96
4	Me	78	13 ^[d]	1000	7.5	30
5	Et	96	12	1000	8.5	86
6	Et	96	13 ^[d]	1000	8	73
7	Pr	118	12	1000	3	93
8	Pr	118	13 ^[d]	1000	3	78
9	<i>i</i> -Amyl	131	12	1000	3	86
10	<i>i</i> -Amyl	131	13 ^[d]	1000	2.5	92
11	Hexyl	158	12	1000	1.3	97
12	Hexyl	158	12	4000	1.3	71
13	Hexyl	158	13 ^[d]	1000	1	86

[a] Neat substrate (52 mmol). [b] Molar ratio of substrate to metal. [c] In toluene (3 mL). [d] With *t*BuOK (0.5 mol%).

activity of this catalyst for the reverse reaction, the reduction of esters under hydrogen pressure.

Both the Noyori-type outer-sphere and the classical inner-sphere hydrogenation mechanisms are possible with the NNHPiPr complexes (Scheme 4). The superior activity of **12**



Scheme 4. Outer-sphere (a) and inner-sphere (b) hydrogenation. Py = pyridine.

versus $[\text{RuH}_2(\text{CO})(\text{PNHPiPr})]$ for hydrogenation of methylbenzoate suggests an important role of hemilability of the NNHPiPr-coordinated catalysts. Continuing work in our group with XNHP ligands that are modified in order to disfavor dimerization and to enhance lability of the X group of the product complexes may shed more light on the mechanistic details of the reactions catalyzed by complexes **11–14**.

In conclusion, this communication presents outstanding versatile catalysts for reduction of esters and for dehydrogenative coupling of alcohols. Ruthenium dimer **14** has shown an unmatched efficiency under neutral conditions by giving

18000 turnovers in 17 hours for methyl benzoate and 7100 turnovers in 18 hours for methyl hexanoate. Osmium dimer **12** has proved to be a particularly useful catalyst for hydrogenation of esters with C=C bonds. To the best of our knowledge, complex **12** is the first homogenous catalyst efficient for hydrogenation of triglycerides, allowing production of fatty alcohols directly from olive oil. Complex **12** is also uniquely distinguished by effecting conversion of alcohols to esters, for example, ethanol into ethyl acetate, at temperatures below 100 °C.

Received: December 19, 2011

Published online: February 8, 2012

Keywords: dehydrogenation · ester reduction · hydrogenation · osmium · ruthenium

- [1] a) J. Zhang, G. Leitus, Y. Ben-David, D. Milstein, *Angew. Chem.* **2006**, *118*, 1131–1133; *Angew. Chem. Int. Ed.* **2006**, *45*, 1113–1115; b) E. Balaraman, C. Gunanathan, J. Zhang, L. J. W. Shimon, D. Milstein, *Nat. Chem.* **2011**, *3*, 609–614; c) E. Fogler, E. Balaraman, Y. Ben-David, G. Leitus, L. J. W. Shimon, D. Milstein, *Organometallics* **2011**, *30*, 3826–3833; d) J. Zhang, E. Balaraman, G. Leitus, D. Milstein, *Organometallics* **2011**, *30*, 5716–5724; e) C. Gunanathan, D. Milstein, *Acc. Chem. Res.* **2011**, *44*, 588–602.
- [2] a) L. A. Saudan, C. M. Saudan, C. Debieux, P. Wyss, *Angew. Chem.* **2007**, *119*, 7617–7620; *Angew. Chem. Int. Ed.* **2007**, *46*, 7473–7476; b) L. Saudan, P. Dupau, J.-J. Riedhauser, P. Wyss (Firmenich SA), WO 2006106483, **2006**; c) L. Saudan, P. Dupau, J.-J. Riedhauser, P. Wyss (Firmenich SA), US 2010280273, **2010**.
- [3] a) W. Kuriyama, Y. Ino, O. Ogata, N. Sayo, T. Saito, *Adv. Synth. Catal.* **2010**, *352*, 92–96; b) Y. Ino, W. Kuriyama, O. Ogata, T. Matsumoto, *Top. Catal.* **2010**, *53*, 1019–1024; c) W. Kuriyama, T. Matsumoto, Y. Ino, O. Ogata, N. Saeki (Takasago Int. Co.), WO 2011048727, **2011**; d) W. Kuriyama, T. Matsumoto, O. Ogata, Y. Ino, K. Aoki, S. Tanaka, K. Ishida, T. Kobayashi, N. Sayo, T. Saito, *Org. Process Res. Dev.* **2012**, *16*, 166–171.
- [4] a) Y. Sun, C. Koehler, R. Tan, V. T. Annibale, D. Song, *Chem. Commun.* **2011**, *47*, 8349–8351; b) F. Stempfle, D. Quinzler, I. Heckler, S. Mecking, *Macromolecules* **2011**, *44*, 4159–4166; c) M. J. Hanton, S. Tin, B. J. Boardman, P. Miller, *J. Mol. Catal. A* **2011**, *346*, 70–78; d) W. W. N. O, A. J. Lough, R. H. Morris, *Chem. Commun.* **2010**, *46*, 8240–8242; e) T. Touge, T. Hakamata, H. Nara, T. Kobayashi, N. Sayo, T. Saito, Y. Kayaki, T. Ikariya, *J. Am. Chem. Soc.* **2011**, *133*, 14960–14963; f) M. Ito, T. Ootsuka, R. Watari, A. Shiibashi, A. Himizu, T. Ikariya, *J. Am. Chem. Soc.* **2011**, *133*, 4240–4242; g) S. Takebayashi, S. H. Bergens, *Organometallics* **2009**, *28*, 2349–2351; h) M. C. van Engelen, H. T. Teunissen, J. G. de Vries, C. J. Elsevier, *J. Mol. Catal. A* **2003**, *206*, 185–192; i) H. Teunissen, C. J. Elsevier, *J. Chem. Soc. Chem. Commun.* **1988**, 1367–1368; j) H. T. Teunissen, C. J. Elsevier, *Chem. Commun.* **1997**, 667–668.
- [5] a) M. Bertoli, A. Choualeb, D. G. Gusev, A. J. Lough, Q. Major, B. Moore, *Dalton Trans.* **2011**, *40*, 8941–8949; b) M. Bertoli, A. Choualeb, A. J. Lough, B. Moore, D. Spasyuk, D. G. Gusev, *Organometallics* **2011**, *30*, 3479–3482.
- [6] J. Zhang, G. Leitus, Y. Ben-David, D. Milstein, *J. Am. Chem. Soc.* **2005**, *127*, 10840–10841.
- [7] M. Labet, W. Thielemans, *Chem. Soc. Rev.* **2009**, *38*, 3484–3504.
- [8] Reduction of dimethyl oxalate to ethylene glycol was reported by using 0.2 mol% of a catalyst prepared from $[\text{Ru}(\text{acac})_3]$ and $\text{MeC}(\text{CH}_2\text{PPh}_2)_3$. It took 16 hours at 120 °C and $p(\text{H}_2) = 80$ bar to achieve full conversion.^[4b,j]