Efficient and Practical Transfer Hydrogenation of Ketones Catalyzed by a Simple Bidentate Mn−NHC Complex

van Putten, Robbert; Benschop, Joeri; de Munck, Vincent J.; Weber, Manuela; Müller, Christian; Filonenko, Georgy A.; Pidko, Evgeny A.

DOI
10.1002/cctc.201900882

Publication date
2019

Document Version
Accepted author manuscript

Published in
ChemCatChem

Citation (APA)
van Putten, R., Benschop, J., de Munck, V. J., Weber, M., Müller, C., Filonenko, G. A., & Pidko, E. A. (2019). Efficient and Practical Transfer Hydrogenation of Ketones Catalyzed by a Simple Bidentate Mn−NHC Complex. *ChemCatChem*, *11*(21). https://doi.org/10.1002/cctc.201900882

Efficient and practical transfer hydrogenation of ketones catalyzed by a simple bidentate Mn-NHC complex

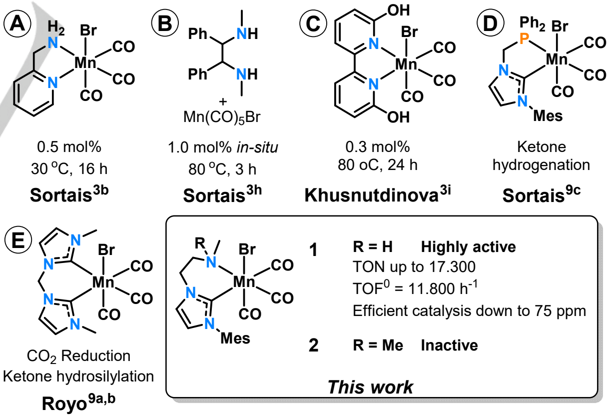
Robbert van Putten[a], Joeri Benschop[a], Vincent J. de Munck[a], Manuela Weber[b], Christian Müller[b], Georgy A. Filonenko[a], and Evgeny A. Pidko[a]*

Abstract: Catalytic reductions of carbonyl-containing compounds are highly important for the safe, sustainable, and economical production of alcohols. Herein, we report on the efficient transfer hydrogenation of ketones catalyzed by a highly potent Mn(I)-NHC complex. Mn-NHC **1** is practical at metal concentrations as low as 75 ppm, thus approaching loadings more conventionally reserved for noble metal based systems. With these low Mn concentrations, catalyst deactivation is found to be highly temperature dependent and becomes especially prominent at increased reaction temperature. Ultimately, understanding of deactivation pathways could help close the activity/stability-gap with Ru and Ir catalysts towards the practical implementation of sustainable earth-abundant Mn-complexes.

The reduction of ketones to their corresponding alcohols is an important transformation for the production of pharmaceuticals, flavors, flagrances, and agrochemicals. Catalytic transfer hydrogenation (TH) protocols offer an attractive and sustainable alternative to well-known stoichiometric approaches.[1] Recently the development of non-noble metal catalysts based on abundant 3d transition metals such as Fe, Co, and Mn has received significant attention.[2] This has led to an impressive expansion of the field and the discovery of novel reactivity patterns of 3d metals versus their noble metal analogues. Remarkably, of the Mn-catalysts currently discussed in the open literature[3], several of the most active systems do not rely on phosphine ligands, but instead are based on simple bidentate N-donors (Scheme 1, **A** - **C**).[3b, 3h, 3i, 4] Sortais and co-workers reported on the use of 2-picolylamine as a ligand for Mn, while also disclosing a series of *in-situ* systems bearing bidentate diamines as ligands.[3b, 3h] Additionally, the group of Khusnutdinova very recently disclosed a Mn-bipyridine-derived complex which showed good activity for the TH of ketones, aldehydes, and imines at 0.3 mol% Mn (3000 ppm Mn; 330 TON).[3i]

However, several challenges remain to be addressed before earth-abundant catalytic systems can be practically utilized in (industrial) organic synthesis. For example, compared to noble metals, reported metal loadings for 3d transition metals (TM) remain up to four orders of magnitude higher at several thousands of ppm (*i.e.*, 0.1 – 1.0 mol%).[1, 5] Although catalyst consumption typically is not a large concern for academic researchers, it likely presents a critical hurdle for any commercial application. Moreover, in order to reduce operational cost it is desirable to replace highly complex, synthetically challenging, and expensive phosphines for simpler and more scalable alternatives.

N-Heterocyclic carbenes (NHCs) in principle meet the main requirements to replace phosphine donors. The steric and electronic properties of NHCs are highly tunable, their synthesis is well established, scalable, and can conveniently be performed in air.[6] Introduction of NHC to noble metals has been very successful, resulting in highly active and (enantio-) selective hydrogenation catalysts for a variety of chemistries.[7] Following these works, several groups have reported the synthesis of Mn(I)-NHCs[8] and their applications in reduction catalysis (Scheme 1, **D** & **E**).[3c, 9] Taking notice of the recent developments in the field of Mn(I)-NHC catalysis, we hypothesized that the combination of a bidentate ligand bearing a strongly donating NHC group and an amine donor function could lead to a highly active and stable catalytic system. At the same time such a complex would maintain attractive ligand simplicity. Based on prior work with NHCs in our group[7d, 7e], we sought to synthesize and test two simple bidentate Mn-NHC complexes **1** and **2** (Scheme 1).



Scheme 1. Mn-complexes for sustainable reduction catalysis.

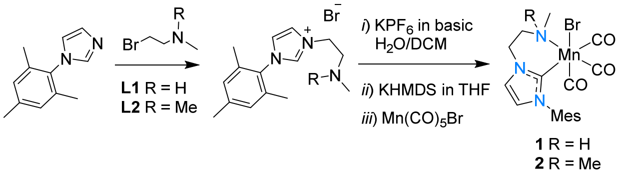
Herein, we report on the catalytic transfer hydrogenation of a broad scope of aromatic and aliphatic ketones with novel Mn(I)-NHC complex **1** (Scheme 1). The catalyst shows unprecedented activity and turnover numbers (TONs) and enables quantitative alcohol yields at Mn concentrations as low as 75 ppm (0.0075 mol%), thereby reducing the activity-gap with noble metal based systems[1, 10] by two orders of magnitude.

---

[a] R. van Putten, J. Benschop, V.J. de Munck, Dr. G.A. Filonenko, Prof. Dr. E.A. Pidko
Inorganic Systems Engineering group, Department of Chemical Engineering, Faculty of Applied Sciences
Delft University of Technology
Van der Maasweg 9, 2629 HZ, Delft, The Netherlands
E-mail: E.A.Pidko@tudelft.nl
[b] M. Weber, Prof. Dr. C. Müller
Institute of Chemistry and Biochemistry
Freie Universität Berlin
Fabeckstraße 34/36, D-14195 Berlin, Germany

Supporting information for this article is given via a link at the end of the document.

Ligands **L1** and **L2** were prepared by reaction of 1-mesityl-1H-imidazole with the corresponding 2-bromoethylamine hydrobromide salt (Scheme 2). We found that the removal of HBr and subsequent ion metathesis to the hexafluorophosphate analogues of **L1**/**L2** was required to obtain the target complexes in their pure form. Compounds **1** and **2** were further obtained by reaction of the *in-situ* generated free carbene with $Mn(CO)_5Br$ in THF. Recrystallization from DCM/Et_2O produced analytically pure **1** and **2** in 67 % and 89 % yield, respectively. The isolated materials were fully characterized with $^1H/^{13}C$ NMR, FTIR, single-crystal X-ray structure determination, and elemental analysis (see Supporting Information).



Scheme 2. Synthetic procedure for Mn(I)-NHCs **1** and **2**.

The FTIR spectra of **1** and **2** each feature three sharp peaks around 2004, 1919, and 1892 cm^{-1}, indicative of an octahedral complex in which the three CO ligands are bound in *cis*-fashion. Single-crystal X-ray analysis confirmed the octahedral geometry and revealed the formation of Mn(I)-NHC bonds with lengths of 2.053 Å in **1**, and 2.055 Å in **2**, respectively (Figure 1). Coordination of the ligand to Mn effectively locks the configuration of the ethylene linker in place. As a consequence, equivalency of the geminal protons within the ethylene linker fragment is lost and they appear as four independent resonances in ^1H NMR (see SI).

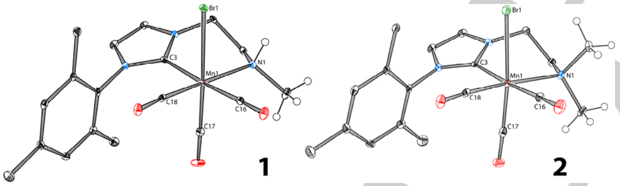
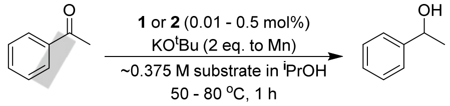


Figure 1. ORTEP diagram of **1** (left) and **2** (right). Thermal ellipsoids are drawn at 30 % probability. Hydrogen atoms (except bound to N and N-Me) and co-crystallized solvent are omitted for clarity.

Complex **1** is a highly active pre-catalyst for TH of ketones with ^{i}PrOH. Fully methylated analogue **2** is inactive under the selected conditions (Table 1, entries 1-2). Initial experiments were performed using acetophenone as a model substrate at 50 °C and 0.5 mol% Mn. Increased reaction temperature allowed a tenfold reduction of catalyst loading down to 0.05 mol% (500 ppm) and resulted in quantitative yields of 1-phenylethanol within 1 h (Table 1, entries 3-5). Further reduction of catalyst concentration led to incomplete reaction progress, while achieving a high turnover number of 4700 at 100 ppm loading (Table 1, entries 6-7). This indicates **1** is catalytically active and remarkably stable over a large number of turnovers and potentially allows for additional optimization. Next, we investigated critical reaction parameters such as base loading, solvent, and the nature of the hydrogen donor to optimize catalysis with **1** (see SI). Presence of 2 eq. KO^{t}Bu to Mn was insufficient to quantitatively activate **1** at this low catalyst concentration of 0.05 mol% Mn (Table S2). We believe this effect is caused by traces impurities in the solvent that react with the base. Generally, highest conversions were observed when hydrogen donors were used as the co-solvent (Table S3). Strongly coordinating solvents such as MeOH and EtOH led to (almost) fully diminished performance, while aliphatic media gave intermediate results. When used neat, secondary alcohol donors 2-propanol, 2-butanol, and 3-methyl-2-butanol all resulted in virtually identical alcohol yields (Table S4). Reaction with the formic acid/NEt_3 mixture or potassium formate as the alternative hydrogen donor unfortunately did not lead to any activity. Thus, all subsequent reactions were performed in neat ^{i}PrOH with 1 mol% KO^{t}Bu as the base relative to the reaction substrate.

Table 1. TH of acetophenone with **1** and **2**.[a]



Entry	Catalyst ([mol% / ppm])	Temp. [°C]	Yield [%]	TON [-]
1	**1** (0.5 / 5000)	50	92	184
2	**2** (0.5 / 5000)	50	1	2
3	**1** (0.5 / 5000)	80	93	186
4	**1** (0.1 / 1000)	80	94	940
5	**1** (0.05 / 500)	80	94	1880
6	**1** (0.02 / 200)	80	85	4250
7	**1** (0.01 / 100)	80	47	4700

[a] Conditions: 1.0 mmol acetophenone, 0.01 – 0.5 mol% **Mn**, 2 eq. KO^{t}Bu to Mn, 2.5 ml ^{i}PrOH, T = 50 – 80 °C, 1 h. Yield determined by GC-FID using n-C_{12} as IS.

Following the discrete optimization, we sought to study the influence of reaction temperature and catalyst concentration. Increased temperature induced pronounced catalyst deactivation, which became particularly noticeable at low metal loadings below ~100 ppm **1** (Figure 2 and SI). At 70 °C and 50 ppm Mn (0.005 mol%), **1** reacts with a high initial TOF^0 of 11.800 h^{-1} and completes 11.100 turnovers in 6 h (56 % yield). Reaction at 60 °C is slower (TOF^0 6100 h^{-1}), but surpasses the integral TON of reaction at 70 °C after approximately 2.5 h (TON = 9600). After 6 h the reaction is 76 % complete, after having undergone 15.100 turnovers. Further reduction of catalyst concentration to 25 ppm expedites the deactivation process and TON-crossover takes place after only 20 min (1800 TON). Under these conditions the reaction progress halts at 8 %. In contrast, at 60 °C **1** achieves a very high TON of 17.300 in 6 h and, importantly, at that time does not show signs of imminent reaction termination. These observations indicate that catalyst deactivation is independent of total catalytic turnover and must be caused by another, as of yet unknown, phenomenon. Ultimately, very good alcohol yield could be obtained in 6 h at 75 ppm **1** and 60 °C (Table S6).

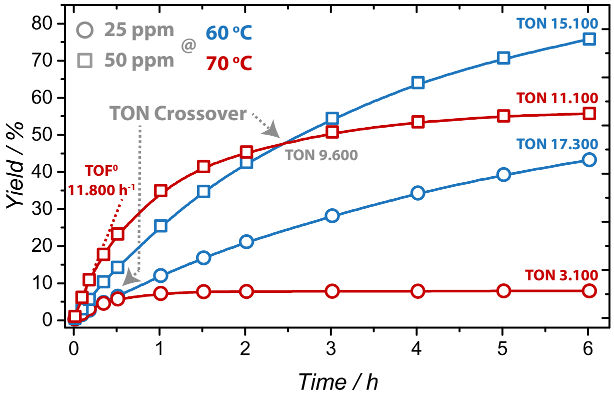
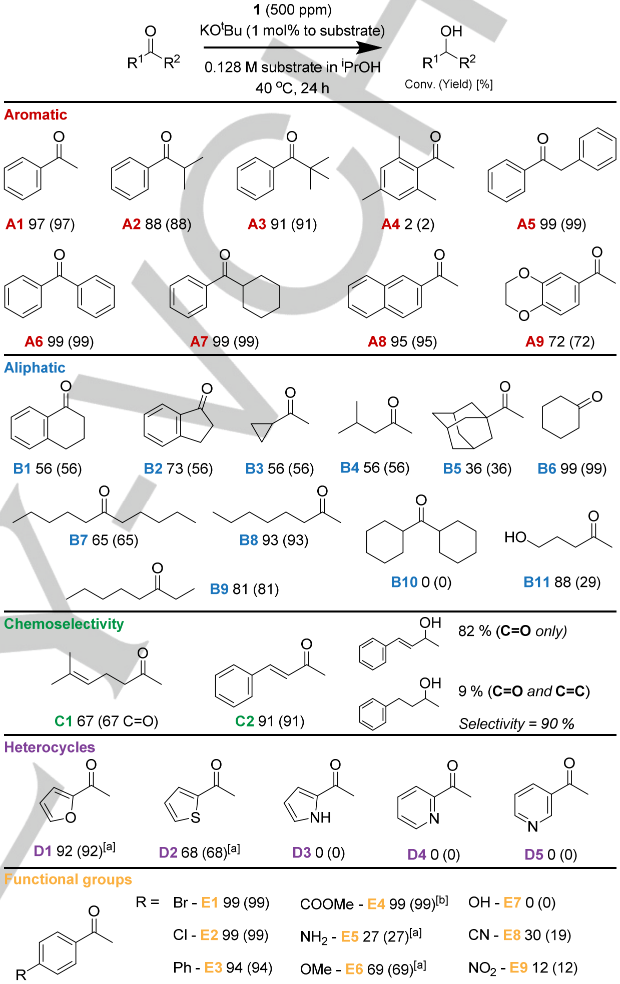


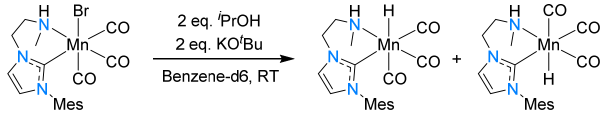
Figure 2. Kinetic traces of acetophenone TH with **1**. Conditions: 0.5 mmol acetophenone, 25 & 50 ppm **1**, 1 mol% KO^{t}Bu to substrate, 3.82 ml ^{i}PrOH, 60 & 70 °C. Yield determined by GC-FID using *n*-C_{12} as the internal standard.

Having established critical performance parameters, we performed a substrate scope to investigate the effect of several functional groups and varied electronic and steric configurations on catalysis with **1** (Scheme 3). Reactions were performed at 40 °C and 500 ppm Mn (0.05 mol%) to minimize potential detrimental effects caused by irreversible catalyst deactivation. These conditions were estimated to provide a reasonable trade-off between reaction rate, catalyst consumption, and the temperature-influenced rate of deactivation. Aromatic ketones **A1** to **A9** were all reduced in good to quantitative yield, except for sterically demanding 2,4,6-trimethylacetophenone **A4**. Aliphatic ketones were significantly less reactive towards reduction. The corresponding alcohols from ketones **B1** – **B4** were all obtained in fair yield of 56 %. Bulky 1-adamantyl methyl ketone **B5** was only partially reduced under the selected conditions. Evidently, steric accessibility is an important factor for catalysis with **1**. Long-chain aliphatic alcohols from **B7** – **B9** were obtained in good to excellent yield, depending on the exact location of the functional group. Dicyclohexyl methyl ketone **B10** was not reduced, while reaction with **B11** was not selective and resulted in extensive (cyclic) side product formation. Chemoselectivity for carbonyl versus alkene reduction was probed with aliphatic and aromatic examples **C1** and **C2**. 6-Methyl-5-hepten-2-one **C1** was selectively reduced to the corresponding unsaturated alcohol in 67 % yield. Aromatic benzylideneacetone **C2** showed good chemoselectivity and enabled production of the unsaturated alcohol in 82 % yield (90 % selectivity C=O *vs.* C=C; 9 % fully reduced product was observed). GC-MS suggests TH of heterocyclic compounds **D1** and **D2** was quantitatively followed by dehydration to 2-vinylfuran (92 % yield) and 2-vinylthiophene (68 % yield). Unfortunately, introduction of nitrogen to the heterocyclic ring led to complete loss of catalytic activity (**D3** – **D5**). Conclusively, functional group tolerance was studied using *para*-substituted acetophenones **E1** to **E9**. Incorporation of halides or a phenyl moiety had no effect on performance (**E1** – **E3**), nor did presence of an ester (**E4**). Similar to the products of **D1** and **D2**, 4-acetylaniline **E5** and 4-acetylanisole **E6** were reduced to the corresponding vinylic products. Catalytic performance was severely decreased for substrates containing a hydroxyl (**E7**), cyano (**E8**), or nitro-group (**E9**). Thus, our results show that **1** is a potent catalyst for a broad scope of substrates. Strongly coordinating substrates are a limitation in the scope and lead to complete loss of catalytic activity.



Scheme 3. Substrate scope with **1**. Conditions: 0.5 mmol substrate, 0.05 mol% **1** (500 ppm), 1 mol% KO^{t}Bu to substrate, 3.82 ml ^{i}PrOH, 40 °C, 24 h. Yields determined by GC-FID using *n*-C_{12} as internal standard. [a] Corresponding vinyl (ID by GC-MS). [b] Corresponding isopropyl ester (ID by GC-MS).

To gain mechanistic insight into catalysis with **1**, we investigated the pre-catalyst activation in a series of ^{1}H NMR stoichiometric reactivity experiments (Scheme 4). Addition of 2 eq. ^{i}PrOH in presence of 2 eq. KO^{t}Bu in benzene-d_6 led to the formation of two new resonances at δ = -4.09 ppm and δ = -3.59 ppm. We attribute these peaks to the two expected *cis* and *trans* Mn(I)-H species (relative to N-*H*), which are formed in an approximate 5:1 ratio. Under these conditions Mn-NHC **1** is quantitatively converted into the corresponding Mn-Hs upon dehydrogenation of ^{i}PrOH. No hydrides were be observed in absence of base and ^{i}PrOH. In contrast, only ~2 % hydride signal was observed with **2**, suggesting that loss of the reactive N-*H* functionality in **2** prevents metal-ligand cooperativity and formation of the active hydride species from ^{i}PrOH. These findings, combined with the practical inactivity of **2**, indicate catalysis with **1** likely operates via the well-established bifunctional protonation/deprotonation mechanism.[5b, 11]



1 85 % 15 %

Scheme 4. Stoichiometric ^{1}H NMR studies into pre-catalyst activation.

In conclusion, we have prepared the novel Mn(I)-NHC complex **1** and reported on its remarkable catalytic activity for transfer hydrogenation of ketones with ^{i}PrOH. Catalysis with **1** proceeds with very high maximum TON of at least 17.000. The complex is useful at unprecedented catalyst loadings and enables quantitative alcohol yields at only 75 ppm Mn. Such loadings approach those more conventionally utilized for Ru and Ir catalysts, thus highlighting the high potential of **1** and other 3d TM-catalyzed processes for sustainable catalysis. Significant catalyst deactivation was observed at elevated temperatures, which inhibited further reduction of metal content. Therefore, we believe thorough understanding of the deactivation processes will ultimately enable a leap forward in rational catalyst design towards improved catalytic systems.

Experimental Section

Supporting information contains all available data for synthesis, characterization, and catalysis for this work.

Acknowledgements

This work has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (grant agreement #725686). M.W. and C.M. gratefully acknowledge the Deutsche Forschungsgemeinschaft (DFG) for financial support.

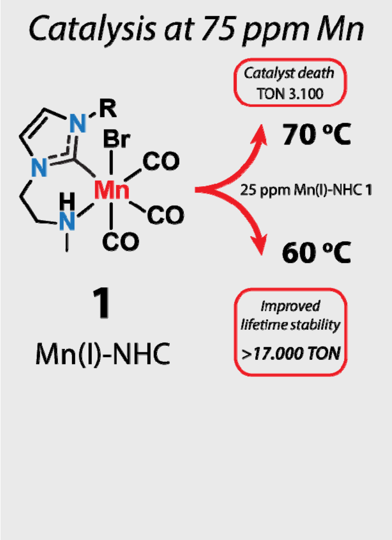
Keywords: Manganese • N-Heterocyclic Carbene • Transfer Hydrogenation • Ketones • Alcohols

[1] D. Wang, D. Astruc, *Chem. Rev.* **2015**, *115*, 6621-6686.
[2] a) G. A. Filonenko, R. van Putten, E. J. M. Hensen, E. A. Pidko, *Chem. Soc. Rev.* **2018**, *47*, 1459-1483; b) F. Kallmeier, R. Kempe, *Angew. Chem. Int. Ed.* **2018**, *57*, 46-60; c) N. Gorgas, K. Kirchner, *Acc. Chem. Res.* **2018**, *51*, 1558-1569; d) B. G. Reed-Berendt, K. Polidano, L. C. Morrill, *Org. Biomol. Chem.* **2018**, *17*, 1595-1607; e) M. Garbe, K. Junge, M. Beller, *Eur. J. Org. Chem.* **2017**, *2017*, 4344-4362.
[3] a) M. Perez, S. Elangovan, A. Spannenberg, K. Junge, M. Beller, *ChemSusChem* **2017**, *10*, 83-86; b) A. Bruneau-Voisine, D. Wang, V. Dorcet, T. Roisnel, C. Darcel, J.-B. Sortais, *Org. Lett.* **2017**, *19*, 3656-3659; c) O. Martínez-Ferraté, C. Werlé, G. Franciò, W. Leitner, *ChemCatChem* **2018**, *10*, 4514-4518; d) N. V. Shvydkiy, O. Vyhivskyi, Y. Nelyubina, D. Perekalin, *ChemCatChem* **2019**, *11*, 1602-1605; e) A. Zirakzadeh, S. R. M. M. de Aguiar, B. Stöger, M. Widhalm, K. Kirchner, *ChemCatChem* **2017**, *9*, 1744-1748; f) J. Schneekönig, K. Junge, M. Beller, *Synlett* **2019**, *30*, 503-507; g) K. Z. Demmans, M. E. Olson, R. H. Morris, *Organometallics* **2018**, *37*, 4608-4618; h) D. Wang, A. Bruneau-Voisine, J.-B. Sortais, *Catal. Commun.* **2018**, *105*, 31-36; i) A. Dubey, S. M. W. Rahaman, R. R. Fayzullin, J. Khusnutdinova, *ChemCatChem* **2019**, DOI: 10.1002/cctc.201900358.
[4] K. Ganguli, S. Shee, D. Panja, S. Kundu, *Dalton Trans.* **2019**, *48*, 7358-7366.
[5] a) R. Noyori, M. Kitamura, T. Ohkuma, *PNAS* **2004**, *101*, 5356-5362; b) P. A. Dub, J. C. Gordon, *Nat. Rev. Chem.* **2018**, *2*, 396-408.
[6] a) E. Peris, *Chem. Rev.* **2018**, *118*, 9988-10031; b) H. V. Huynh, *Chem. Rev.* **2018**, *118*, 9457-9492; c) R. E. Andrew, L. González-Sebastián, A. B. Chaplin, *Dalton Trans.* **2016**, *45*, 1299-1305; d) D. J. Nelson, S. P. Nolan, *Chem. Soc. Rev.* **2013**, *42*, 6723-6753.
[7] a) S. N. Sluijter, T. J. Korstanje, J. I. van der Vlugt, C. J. Elsevier, *J. Organomet. Chem.* **2017**, *845*, 30-37; b) W. W. N. O, R. H. Morris, *ACS Catal.* **2013**, *3*, 32-40; c) D. Zhao, B. Beiring, F. Glorius, *Angew. Chem. Int. Ed.* **2013**, *52*, 8454-8458; d) G. A. Filonenko, M. J. B. Aguila, E. N. Schulpen, R. van Putten, J. Wiecko, C. Müller, L. Lefort, E. J. M. Hensen, E. A. Pidko, *J. Am. Chem. Soc.* **2015**, *137*, 7620-7623; e) G. A. Filonenko, E. Cosimi, L. Lefort, M. P. Conley, C. Copéret, M. Lutz, E. J. M. Hensen, E. A. Pidko, *ACS Catal.* **2014**, *4*, 2667-2671.
[8] a) J. Ruiz, Á. Berros, B. F. Perandones, M. Vivanco, *Dalton Trans.* **2009**, 6999-7007; b) J. Ruiz, B. F. Perandones, G. García, M. E. G. Mosquera, *Organometallics* **2007**, *26*, 5687-5695.
[9] a) F. Franco, M. F. Pinto, B. Royo, J. Lloret-Fillol, *Angew. Chem. Int. Ed.* **2018**, *57*, 4603-4606; b) M. Pinto, S. Friães, F. Franco, J. Lloret-Fillol, B. Royo, *ChemCatChem* **2018**, *10*, 2734-2740; c) R. Buhaibeh, O. A. Filippov, A. Bruneau-Voisine, J. Willot, C. Duhayon, D. A. Valyaev, N. Lugan, Y. Canac, J.-B. Sortais, *Angew. Chem. Int. Ed.* **2019**, *58*, 6727-6731.
[10] a) F. Foubelo, C. Nájera, M. Yus, *Tetrahedron: Asymmetry* **2015**, *26*, 769-790; b) T. Ikariya, A. J. Blacker, *Acc. Chem. Res.* **2007**, *40*, 1300-1308; c) K. Murata, T. Ikariya, R. Noyori, *J. Org. Chem.* **1999**, *64*, 2186-2187; d) R. Malacea, R. Poli, E. Manoury, *Coord. Chem. Rev.* **2010**, *254*, 729-752; e) N. Pannetier, J.-B. Sortais, J.-T. Issenhuth, L. Barloy, C. Sirlin, A. Holuigue, L. Lefort, L. Panella, J. G. de Vries, M. Pfeffer, *Adv. Synth. Catal.* **2011**, *353*, 2844-2852.
[11] a) S. E. Clapham, A. Hadzovic, R. H. Morris, *Coord. Chem. Rev.* **2004**, *248*, 2201-2237; b) A. A. Mikhailine, M. I. Maishan, A. J. Lough, R. H. Morris, *J. Am. Chem. Soc.* **2012**, *134*, 12266-12280; c) P. A. Dub, N. J. Henson, R. L. Martin, J. C. Gordon, *J. Am. Chem. Soc.* **2014**, *136*, 3505-3521; d) P. A. Dub, J. C. Gordon, *ACS Catal.* **2017**, *7*, 6635-6655; e) P. A. Dub, B. L. Scott, J. C. Gordon, *J. Am. Chem. Soc.* **2017**, *139*, 1245-1260.

Entry for the Table of Contents

COMMUNICATION

Mn(I)-NHC complex **1** is a highly active and robust catalyst for the transfer hydrogenation of ketones. Catalysis with **1** proceeds efficiently at unprecedented catalyst loadings as low as 75 ppm, thus approaching levels more conventionally reserved for privileged Ru-based catalysts.



*Robbert van Putten, Joeri Benschop, Vincent J. de Munck, Manuela Weber, Christian Müller, Georgy A. Filonenko, Evgeny A. Pidko**

Page No. – Page No.

Efficient and practical transfer hydrogenation of ketones catalysed by a simple bidentate Mn-NHC complex