Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 8095–8099

Biomimetic transfer hydrogenation of ketones with iron porphyrin catalysts

Stephan Enthaler, Giulia Erre, Man Kin Tse, Kathrin Junge and Matthias Beller*

Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Str. 29a, D-18059 Rostock, Germany

Received 17 July 2006; revised 11 September 2006; accepted 12 September 2006
Available online 4 October 2006

Abstract—For the first time in situ generated iron porphyrins have been applied as homogeneous catalysts for the transfer hydrogenation of ketones. Using 2-propanol as hydrogen source various ketones are reduced to the corresponding alcohols in good to excellent yield and selectivity. Under optimized reaction conditions high catalyst turnover frequencies up to 642 h^{-1} are achieved.

Alcohols are key intermediates for the synthesis of pharmaceuticals, agrochemicals, polymers and new materials.[1,2] Starting from carbonyl compounds various catalytic approaches toward the synthesis of alcohols have been developed. Typical examples are the addition of organometallic compounds to aldehydes, hydrosilylation, and hydrogenation of aldehydes or ketones.[2] Among these transformations hydrogenations represent the most atom-efficient and environmentally benign methodology. In particular, transfer hydrogenation is a powerful strategy because of the ease of performance and general applicability.[3] More specifically, a broad scope of alcohols is available by transfer hydrogenation using non-toxic hydrogen donors, for example, 2-propanol or $HCOOH/NEt_3$, under mild reaction conditions in the presence of precious metal catalysts based on Ir, Rh, Ru, or Ni.[4]

With regard to the upcoming catalyst developments a fundamental challenge is the substitution of these expensive and rare transition metals by less toxic, inexpensive and abundantly available metals such as iron.[5] Until now, homogeneous iron catalysts have been most frequently applied for carbon–carbon coupling reactions, such as olefin polymerizations, cross-couplings and cycloadditions as well as reductions of nitro compounds.[6] However, much less attention was directed toward iron-catalyzed (transfer) hydrogenations, although the relevance of such reductions is evident even with respect to industrial applications. To the best of our knowledge only the groups of Noyori,[7] Vancheesan,[8] Bianchini[9] and Gao[10] reported the utilization of iron salts and iron complexes in the reduction of α,β-unsaturated carbonyl compounds and ketones. For tuning the activity and selectivity of these catalysts, oxygen and moisture sensitive tetradentate phosphines[9] or aminophosphines[10] have been predominantly applied as ligands.

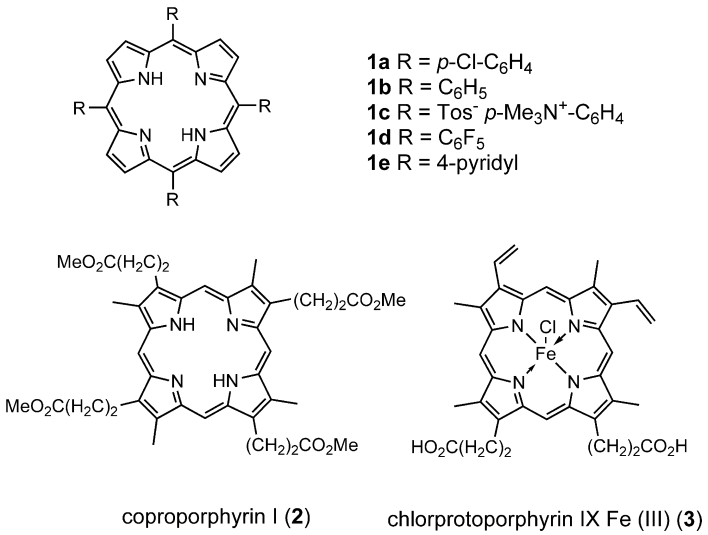
Inspired by nature we thought that multidentate nitrogen ligands should be also suitable ligands for stabilizing iron as metal centre in transfer hydrogenations. In the past biomimetic ligand toolboxes were invented, which are based on natural sources or similar structural motifs, for example, amino alcohols, quinidines, bisoxazolines and porphyrins.[11] Within these potential ligands, porphyrins, which are involved in manifold biological redox processes, seemed of special interest to us due to their strong ability to stabilize the iron centre.[12,13]

Stimulated by our ongoing research in catalytic hydrogenations[15] we became interested in developing new hydrogenation catalysts based on iron. Thus, we report herein for the first time a combination of iron and porphyrins as catalysts for the efficient reduction of various ketones (Scheme 1).

In exploratory experiments, 2-propanol-based transfer hydrogenation of acetophenone was examined using an easy to adopt in situ catalyst system comprising $Fe_3(CO)_{12}$ and porphyrin **1a**. Typically, the active catalyst is prepared by stirring a solution of 1 mol % iron source and 1 mol % **1a** in 2-propanol (1.0 mL) for 16 h

* Corresponding author. Tel.: +49 381 1281 113; fax: +49 381 1281 5000; e-mail: matthias.beller@catalysis.de

0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2006.09.058



Scheme 1. Selection of applied porphyrins.[14]

at 65 °C. After the addition of 50 mol % base the mixture is heated for 5 min at 100 °C and the standard substrate acetophenone **4** is added.[16]

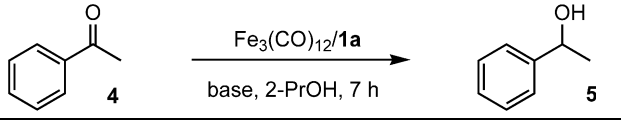
Initially, the influence of temperature and various bases on the reaction rate was investigated. An optimal catalyst activity is obtained at 100 °C (Table 1, entries 1–3). In general, sodium and potassium alkoxides gave an excellent yield of 1-phenylethanol (96–99%, Table 1, entries 4–8). Noteworthy from a practical point of view is that NaOH and K_2CO_3 also led to a high product yield. However, in the presence of organic bases such as NEt_3 and pyridine (Table 1, entries 10 and 11) no significant amount of product is formed in reasonable time. Diminishing the base concentration resulted in a decrease of 1-phenylethanol. In the absence of a base, no transfer of hydrogen was observed.

Interestingly, the transfer hydrogenation proceeds highly chemoselectively (>99%). In no case significant amounts (>1%) of by-products (e.g., aldol condensation products) are obtained.

Next, attempts were made concerning the iron source (Table 2).[17] The best activity was obtained for $Fe_3(CO)_{12}$, $FeBr_2$, $Fe(acac)_3$ and $[Et_3NH][HFe(CO)_4]$.[18]

Surprisingly, no reliable correlation between the oxidation state and reaction rate was observed as high activity was detected for Fe(0)-, Fe(II)- and Fe(III)-salts. Hence, the formation of the active catalyst species is complete for the various pre-catalysts under the applied conditions. However, studying the dependency of conversion versus reaction time in the presence of $Fe_3(CO)_{12}$ revealed an induction period of nearly 2 h.

Table 1. Catalytic transfer hydrogenation of acetophenone **4**

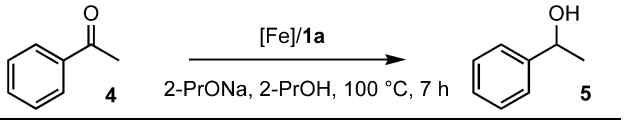


Entry	Iron source	Base	Temperature (°C)	Yield (%)[a]
1	$Fe_3(CO)_{12}$	2-PrONa	80	56
2	$Fe_3(CO)_{12}$	2-PrONa	90	68
3	$Fe_3(CO)_{12}$	2-PrONa	100	96
4	$Fe_3(CO)_{12}$	NaOH	100	98
5	$Fe_3(CO)_{12}$	KOH	100	42
6	$Fe_3(CO)_{12}$	LiOH	100	5
7	$Fe_3(CO)_{12}$	K-*t*-OBu	100	**99**
8	$Fe_3(CO)_{12}$	Na-*t*-OBu	100	97
9	$Fe_3(CO)_{12}$	K_2CO_3	100	89
10	$Fe_3(CO)_{12}$	NEt_3	100	<1
11	$Fe_3(CO)_{12}$	Pyridine	100	<1

Standard reaction conditions: 0.0038 mmol in situ catalyst (0.0013 mmol $Fe_3(CO)_{12}$ and 0.0038 mmol **1a** in 2.0 mL 2-propanol for 16 h at 65 °C), 0.19 mmol base, 5 min at described temperature, then the addition of 0.38 mmol acetophenone **4**, 7 h at described temperature.

[a] Yield and conversion were determined by GC analysis (50 m Lipodex E, 95–150 °C) with diglyme as an internal standard.

Table 2. Influence of iron sources in the transfer hydrogenation of acetophenone **4**



Entry	Iron source	Yield (%)[a]
1	$Fe_3(CO)_{12}$	96
2	$FeBr_2$	**98**
3	$FeCl_2$	90
4	$FeCl_3$	86
5	$Fe(acac)_2$	74
6	$Fe(acac)_3$	97
7	$CpFe(CO)_2I$	44
8	$FeSO_4$	46
9	$[Et_3NH][HFe(CO)_4]$	97

Standard reaction conditions: 0.0038 mmol in situ catalyst (0.0038 mmol Fe-source or 0.0013 mmol $Fe_3(CO)_{12}$ and 0.0038 mmol **1a** in 2.0 mL 2-propanol for 16 h at 65 °C), 0.19 mmol base, 5 min at 100 °C, then the addition of 0.38 mmol acetophenone **4**, 7 h at 100 °C.

[a] Yield and conversion were determined by GC analysis (50 m Lipodex E, 95–150 °C) with diglyme as an internal standard.

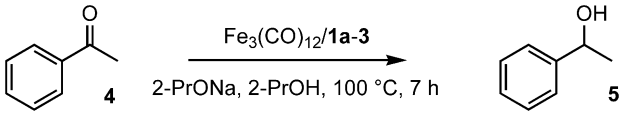
In the case of $Fe(acac)_2$ and $Fe(acac)_3$ a favourable conversion was observed for the Fe(III)-salt. Comparing the results of $FeCl_2$ and $FeBr_2$, a small influence of the corresponding halide was also detected.

Next, we focused our attention on the influence of the metal–ligand ratio. Even without any ligand some catalytic activity is obtained (54% of **5**). The addition of 0.5 or 0.2 equiv of **1a** (with respect to Fe) increased the yield of 1-phenylethanol to 74% and 86%, respectively. The highest yield is obtained at a metal–ligand ratio of 1:1. A further increase of the number of ligand with respect to iron (2:1) resulted in a slight decrease of activity (89% of **5**).

In order to further improve the catalyst system, we applied different porphyrin ligands (**1a**–**3**) in the model reaction in the presence of 0.5 mol % Fe catalyst ($Fe_3(CO)_{12}$, sodium 2-propylate, 100 °C). As shown in Table 3, best yields were achieved with *meso*-substituted porphyrins **1b** and **1e** (Table 3, entries 3 and 6). Substitution in the *meso*-phenylic system of porphyrin **1b** with electron withdrawing groups (**1a**, **1c**, and **1d**) displayed a decrease in activity (Table 3, entries 1, 3 and 4).

In addition, porphyrins substituted in the β-pyrrolenic positions were employed in the reduction of acetophenone. The activity of the symmetric coproporphyrin I **2** was to some extend lower when compared with *meso*-substituted porphyrins. The natural complex chloroprotoporphyrin IX Fe(III) **3** was utilized without catalysts pre-formation as described for all other ligands, and a moderate yield of 1-phenylethanol was detected (Table 3, entry 8). Nevertheless, complex **3** is an interesting catalyst for such reactions due to easier handling and availability.

Table 3. Testing of different porphyrins in the transfer hydrogenation of acetophenone **4**



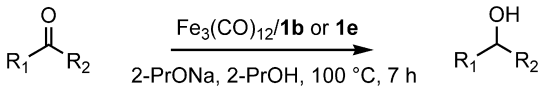
Entry	Porphyrin	Catalyst loading (mol %)	Yield (%)[a]	TOF (h^{-1})[b]
1	**1a**	0.5	90	26
2	**1a**	0.01	45	**642**
3	**1b**	0.5	93	27
4	**1c**	0.5	68	19
5	**1d**	0.5	56	16
6	**1e**	0.5	**94**	27
7	**2**	0.5	45	13
8	**3**	0.5	51	15

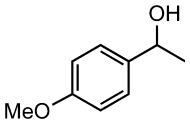
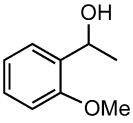
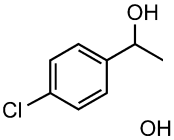
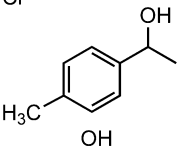
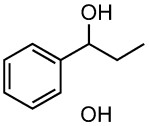
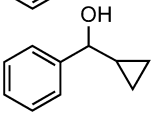
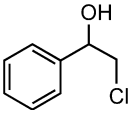
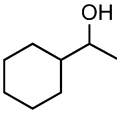
Standard reaction conditions: 0.0038 mmol or 0.000038 mmol in situ catalyst (0.0013 mmol or 0.000013 mmol $Fe_3(CO)_{12}$ and 0.0038 mmol or 0.000038 mmol porphyrin in 2.0 mL 2-propanol for 16 h at 65 °C), 0.19 mmol or 0.0019 mmol sodium 2-propylate, 5 min at 100 °C, then the addition of 0.76 mmol acetophenone **4**, 7 h at 100 °C.

[a] Conversion was determined by GC analysis (50 m Lipodex E, 95–150 °C) with diglyme as an internal standard.

[b] Turnover frequencies were determined after 7 h.

Table 4. Fe-catalyzed reduction of various ketones in the presence of porphyrins **1b** and **1e**



Entry	Product	**1b** Yield (%)[a]	**1e** Yield (%)[a]
1		46	72
2		>99	>99
3		93	95
4		50	68
5		92	87
6		21	22
7		<1	<1
8		26 [71][b]	89
9		11 [55][b]	90

Standard reaction conditions: 0.0038 mmol in situ catalyst (0.0013 mmol $Fe_3(CO)_{12}$ and 0.0038 mmol porphyrin in 2.0 mL 2-propanol for 16 h at 65 °C), 0.19 mmol sodium 2-propylate, 5 min at 100 °C, then addition of the corresponding ketone (0.76 mmol), 7 h at 100 °C.

[a] Conversion was determined by GC analysis (entry 1 (25 m Lipodex E, 80–180 °C), entries 2, 6, 8 and 9 (30 m, HP Agilent Technologies, 50–300 °C), entry 3 (25 m Lipodex E, 100 °C), entry 4 (50 m Lipodex E, 90–105 °C), entry 5 (25 m Lipodex E, 90–180 °C), entry 7 (50 m Lipodex E, 90–180 °C)) with diglyme as internal standard.

[b] In brackets the results after 24 h reaction time.

In order to demonstrate the utility of our concept, we selected ligand **1b** and **1e** and used the corresponding Fe pre-catalysts in the reduction of nine aliphatic and aromatic ketones (Table 4). When using 0.5 mol % pre-catalyst in the presence of 50 mol % sodium 2-propylate, most substrates were hydrogenated in a good yield. Only disappointing activities were obtained for ketones substituted adjacent to the carbonyl group by a chloromethyl or a cyclopropyl group (Table 4, entries

6 and 7). Comparing different substitutions on the phenyl ring no reliable relationship between electron donating and electron withdrawing substituents and activity was observed (Table 4, entries 1–4). Similar to the model reaction, in all cases conversion and yield were nearly identical.

In agreement with previous findings the highest yield is obtained with 2-methoxyacetophenone due to the presence of a second coordination site.[19]

In addition to aryl alkyl ketones, we also examined more challenging dialkyl ketones in this iron-catalyzed transfer hydrogenation. Good conversion and yield (89–90%) were observed for both substrates applying an iron catalyst containing **1e** as ligand. In general, ligand **1e** gave better results compared to **1b**. This effect is especially pronounced for the dialkyl substrates (Table 4, entries 8 and 9).

In conclusion, we have demonstrated for the first time the successful application of in situ prepared iron porphyrin catalysts in the transfer hydrogenation of ketones. The catalyst system is easily prepared and mimics biologically occurring Fe complexes. Under optimized conditions turnover frequencies up to 642 h^{-1} were achieved. The scope and limitation of the catalyst were demonstrated on the reduction of nine different ketones with good to excellent yields.

Acknowledgements

This work has been financed by the State of Mecklenburg-Western Pomerania, the Bundesministerium für Bildung und Forschung (BMBF) and the Deutsche Forschungsgemeinschaft (Leibniz-award). We thank Mr. B. Hagemann, Mrs. C. Mewes, Mrs. M. Heyken, Mrs. S. Buchholz, and Dr. C. Fischer (all Leibniz-Institut für Katalyse e.V. an der Universität Rostock) for their excellent technical and analytical support.

References and notes

1. (a) Lennon, I. C.; Ramsden, J. A. *Org. Process Res. Dev.* **2005**, *9*, 110–112; (b) Hawkins, J. M.; Watson, T. J. N. *Angew. Chem.* **2004**, *116*, 3286–3290; (c) Noyori, R.; Ohkuma, T. *Angew. Chem.* **2001**, *113*, 40–75; (d) Miyagi, M.; Takehara, J.; Collet, S.; Okano, K. *Org. Process Res. Dev.* **2000**, *4*, 346–348.
2. (a) *Transition Metals for Organic Synthesis*, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004; (b) Cornils, B.; Herrmann, W. A. *Applied Homogeneous Catalysis with Organometallic Compounds*; Wiley-VCH: Weinheim, 1996; (c) Kitamura, M.; Noyori, R. In *Ruthenium in Organic Synthesis*; Murahashi, S.-I., Ed.; Wiley-VCH: Weinheim, 2004; (d) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; (e) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.
3. (a) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *51*, 1051–1069; (b) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97–102; (c) Gladiali, S.; Mestroni, G. In *Transition Metals for Organic Synthesis*, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004; pp 145–166; (d) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103–151; (e) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226–236; (f) Samec, J. S. M.; Bäckvall, J.-E.; Andersson, P. G.; Brandt, P. *Chem. Soc. Rev.* **2006**, *35*, 237–248.
4. Selected recent examples of transfer hydrogenations: (a) Schlatter, A.; Kundu, M. K.; Woggon, W.-D. *Angew. Chem., Int. Ed.* **2004**, *43*, 6731–6734; (b) Xue, D.; Chen, Y.-C.; Cui, X.; Wang, Q.-W.; Zhu, J.; Deng, J.-G. *J. Org. Chem.* **2005**, *70*, 3584–3591; (c) Wu, X.; Li, X.; King, F.; Xiao, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3407–3411; (d) Hayes, A. M.; Morris, D. J.; Clarkson, G. J.; Wills, M. *J. Am. Chem. Soc.* **2005**, *127*, 7318–7319; (e) Baratta, W.; Chelucci, G.; Gladiali, S.; Siega, K.; Toniutti, M.; Zanette, M.; Zangrando, E.; Rigo, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 6214–6219.
5. Due to the widespread abundance of iron in earth's crust and the easy accessibility the current price of iron is relatively low (approximately 300 US-dollar/t) compared to rhodium, iridium or ruthenium. Furthermore, iron is an essential trace element (daily dose for humans 5–28 mg) and is involved in an extensive number of biological processes.
6. Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217–6254.
7. Noyori, R.; Umeda, I.; Ishigami, T. *J. Org. Chem.* **1972**, *37*, 1542–1545.
8. (a) Jothimony, K.; Vancheesan, S. *J. Mol. Catal.* **1989**, *52*, 301–304; (b) Jothimony, K.; Vancheesan, S.; Kuriacose, J. C. *J. Mol. Catal.* **1985**, *32*, 11–16.
9. Bianchini, C.; Farnetti, E.; Graziani, M.; Peruzzini, M.; Polo, A. *Organometallics* **1993**, *12*, 3753–3761.
10. Chen, J.-S.; Chen, L.-L.; Xing, Y.; Chen, G.; Shen, W.-Y.; Dong, Z.-R.; Li, Y.-Y.; Gao, J.-X. *Huaxue Xuebao* **2004**, *62*, 1745–1750.
11. (a) Jacqueline, H.-P. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley and Sons: New York, 1995; (b) Larrow, J. F.; Jacobsen, E. N. *Topics Organomet. Chem.* **2004**, *6*, 123–152.
12. (a) *Porphyrins and Metalloporphyrins*; Smith, K. M., Ed.; Elsevier: Netherlands, 1975; (b) *The Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1978; (c) Che, C.-M.; Huang, J.-S. *Coord. Chem. Rev.* **2002**, *231*, 151–164; (d) Simonneaux, G.; Le Maux, P. *Coord. Chem. Rev.* **2002**, *228*, 43–60; (e) Rose, E.; Andrioletti, B.; Zrig, S.; Quelquejeu-Etheve, M. *Chem. Soc. Rev.* **2005**, *34*, 573–583.
13. (a) Munire, B. *Chem. Rev.* **1992**, *92*, 1411–1456; (b) Mansuy, D. *Coor. Chem. Rev.* **1993**, *125*, 129–141; (c) *Metalloporphyrins in Catalytic Oxidations*; Sheldon, R. A., Ed.; M. Dekker Inc.: New York, 1994; (d) Che, C.-M.; Yu, W.-Y. *Pure Appl. Chem.* **1999**, *71*, 281–288; (e) Vinhado, F. S.; Martins, P. R.; Iamamoto, Y. *Curr. Topics. Catal.* **2002**, *3*, 199–213; (f) Rose, E.; Andrioletti, B.; Zrig, S.; Quelquejeu-Etheve, M. *Chem. Soc. Rev.* **2005**, *34*, 573–583; (g) Shitama, H.; Katsuki, T. *Tetrahedron Lett.* **2006**, *47*, 3203–3207; (h) Zhou, C. Y.; Chan, P. W. H.; Che, C. M. *Org. Lett.* **2006**, *8*, 325–328; (i) Berkessel, A. *Pure Appl. Chem.* **2005**, *77*, 1277–1284.
14. All porphyrins are commercial available by Strem or Aldrich except porphyrin **1d**, which was synthesized according to a literature protocol: (a) Lindsey, J. S.; Hsu, H. C.; Schreiman, I. C. *Tetrahedron Lett.* **1986**, *27*, 4969–4970; (b) Lindsey, J. S.; Schreiman, I. C.; Hsu, H. C.; Kearney, P. C.; Marguerettaz, A. M. *J. Org. Chem.* **1987**, *52*, 827–836.
15. (a) Junge, K.; Oehme, G.; Monsees, A.; Riermeier, T.; Dingerdissen, U.; Beller, M. *Tetrahedron Lett.* **2002**, *43*,

4977–4980; (b) Junge, K.; Oehme, G.; Monsees, A.; Riermeier, T.; Dingerdissen, U.; Beller, M. *J. Organomet. Chem.* **2003**, *675*, 91–96; (c) Junge, K.; Hagemann, B.; Enthaler, S.; Spannenberg, A.; Michalik, M.; Oehme, G.; Monsees, A.; Riermeier, T.; Beller, M. *Tetrahedron: Asymmetry* **2004**, *15*, 2621–2631; (d) Junge, K.; Hagemann, B.; Enthaler, S.; Oehme, G.; Michalik, M.; Monsees, A.; Riermeier, T.; Dingerdissen, U.; Beller, M. *Angew. Chem.* **2004**, *116*, 5176–5179; *Angew. Chem., Int. Ed.* **2004**, *43*, 5066–5069; (e) Hagemann, B.; Junge, K.; Enthaler, S.; Michalik, M.; Riermeier, T.; Monsees, A.; Beller, M. *Adv. Synth. Catal.* **2005**, *347*, 1978–1986; (f) Enthaler, S.; Hagemann, B.; Junge, K.; Erre, G.; Beller, M. *Eur. J. Org. Chem.* **2006**, 2912–2917.

16. All experiments were carried out under an inert gas atmosphere (argon) with exclusion of air. For the standard reaction procedure $Fe_3(CO)_{12}$ (0.0013 mmol) and porphyrin **1a** (0.0038 mmol) is dissolved in 1.0 mL 2-propanol and stirred for 16 h at 65 °C. Then a solution of sodium 2-propylate (0.19 mmol) in 0.5 mL 2-propanol is added. The solution is stirred for 5 min at 100 °C followed by the addition of 0.38 mmol acetophenone **4**. After 7 h at 100 °C, the mixture is cooled to rt and filtered over a plug of silica gel. The conversion and yield were determined by GC without further purification. All synthesized alcohols are known compounds. Their characterization is done by a comparison with authentic samples.
17. Sodium 2-propylate was chosen due to easier handling.
18. Dahl, L. F.; Blount, J. F. *Inorg. Chem.* **1965**, *4*, 1373–1375.
19. Enthaler, S.; Hagemann, B.; Erre, G.; Junge, K.; Beller, M. *Chem. Asian J.* **2006**, *1*, in press.