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Iron Catalysis

Iron-Catalyzed Hydrogenation for the In Situ Regeneration of an NAD(P)H Model: Biomimetic Reduction of α-Keto-/α-Iminoesters**

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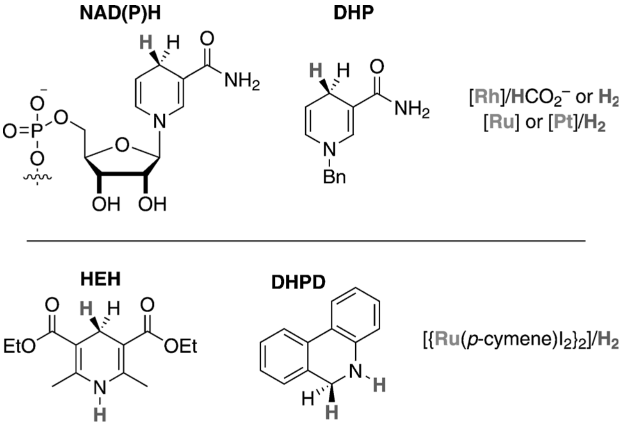
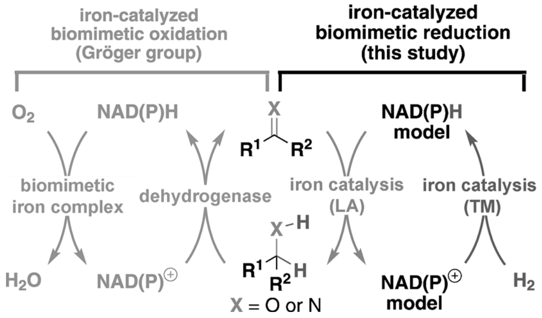
Over millions of years, nature has evolved processes that can inspire chemists to improve the efficiency and sustainability of organic synthesis today.[1] In particular, redox reactions constitute fundamental transformations in biology, and many kinds of redox enzymes catalyze these processes. Among them, enzymes with NAD(P)H and their oxidized form nicotinamide adenine dinucleotide (phosphate) [NAD(P)$^+$] as the cofactors have attracted much interest from the viewpoints of both biomimetic catalysis and large-scale industrial synthesis.[2] For such bioinspired reductions, a key issue is the regeneration of the cofactor NAD(P)H or a model of this cofactor in an efficient and economical way.[2,3] In terms of availability, cost, and the removal of by-products,[4] an in situ regeneration of the cofactor is preferred. When reductive transformations are performed with living cells or isolated enzymes, the cofactor is commonly regenerated in the presence of dehydrogenases, such as formate dehydrogenase, glucose dehydrogenase, or alcohol dehydrogenase, by the use of formic acid, glucose, or alcohols as the hydride source, respectively.[2] However, in comparison with enzymatic methods, the chemical catalytic in situ regeneration of cofactor NAD(P)H and its analogues is still in its infancy (Scheme 1).[3,5] Notably, as early as 1982, Whitesides and Abril[5a] reported a rhodium-complex-catalyzed in situ regeneration of NAD(P)H with hydrogen gas as the most benign hydride source. Since then, interesting developments were disclosed by the research groups of Steckhan,[5b] Bhaduri,[5c] Fish,[5d] Wagenknecht,[5e] and others,[5f,g] who applied other catalyst complexes based on precious metals, such as Rh, Ru, Pt, and Ir. Recently, Zhou and co-workers showed that [{Ru(p-cymene)I$_2$}$_2$] can be used as a highly efficient catalyst for the in situ regeneration of two kinds of NAD(P)H models: the Hantzsch ester (HEH) and dihydrophenanthridine (DHPD) models. This system was applied to the asymmetric biomimetic reduction of a series of azoheterocycles.[5h,i] Nevertheless, in spite of the advances made in recent years, so far all known catalysts are based on noble metals.



Scheme 1. In situ regeneration of NAD(P)H and its models with organometallic complexes. Bn = benzyl.

In the past decade, iron catalysis has provoked more and more research interest in homogeneous catalysis, from the development of novel energy technology to green organic synthesis.[6] Owing to the ubiquity of iron in enzymes and its good biotolerance, iron catalysts have also been widely applied in biomimetic oxidation reactions.[7,8] For example, in 2011, Gröger and co-workers[8f] reported the use of a synthetic iron porphyrin for the biomimetic oxidation of alcohols; oxygen was used as the terminal oxidant to regenerate NAD(P)$^+$ with the formation of water as the only by-product (Scheme 2, left). Following our previous studies on biologically inspired iron-catalyzed oxidation reactions,[9] we present herein a reverse biomimetic reduction



Scheme 2. Concept of biomimetic redox reactions under iron catalysis for the in situ regeneration of an NAD(P)$^+$/NAD(P)H model.

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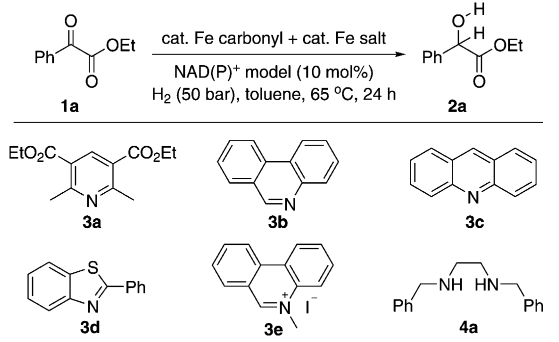
through dual iron catalysis. These iron catalysts are not only responsible for the in situ regeneration of NAD(P)H models with molecular hydrogen (transition-metal (TM) catalysis), but also act as Lewis acids to promote the transfer hydrogenation of carbonyl and imine groups (LA catalysis; Scheme 2, right).

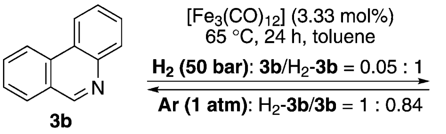
To probe the feasibility of the above proposal, we chose α-ketoesters as substrates because of the significance of the α-hydroxyester products and the reactivity of the substrates. For these reasons, α-ketoesters are used frequently in biomimetic reductions of NAD(P)H and its models.[10] We first tested a series of representative NAD(P)$^+$ models, such as diethyl 2,6-dimethylpyridine-3,5-dicarboxylate (**3a**), phenanthridine (**3b**), acridine (**3c**), 2-phenylbenzo[*d*]thiazole (**3d**), and *N*-methylphenanthridinium iodide (**3e**), with ethyl 2-oxo-2-phenylacetate (**1a**) as the model substrate. Only phenanthridine (**3b**) showed minor catalytic activity in toluene under H_2 (50 bar) at 65 °C in the presence of $[Fe_3(CO)_{12}]$ (3.33 mol %; Table 1, entries 1–5). Although many different iron–carbonyl complexes are known to catalyze the reduction of carbonyl compounds,[11] only $[Fe_3(CO)_{12}]$ promoted the desired reaction of **1a** in the presence of **3b** (Table 1, entries 2 and 6–8), in agreement with its specific reduction of C=N groups.[11d]

Table 1: Iron-catalyzed biomimetic reduction of ethyl phenylglyoxylate in the presence of different NAD(P)$^+$ models.[a]



Entry	Fe carbonyl	Fe salt	NAD(P)$^+$ model	Yield [%][b]
1	$[Fe_3(CO)_{12}]$	–	**3a**	–
2	$[Fe_3(CO)_{12}]$	–	**3b**	5
3	$[Fe_3(CO)_{12}]$	–	**3c**	–
4	$[Fe_3(CO)_{12}]$	–	**3d**	–
5	$[Fe_3(CO)_{12}]$	–	**3e**	–
6	$[Fe_2(CO)_9]$	–	**3b**	–
7	$[Fe(CO)_5]$	–	**3b**	–
8	$[NEt_3H][HFe_3(CO)_{11}]$	–	**3b**	–
9	$[Fe_3(CO)_{12}]$	$FeCl_3$	**3b**	4
10	$[Fe_3(CO)_{12}]$	$FeCl_2$	**3b**	7
11	$[Fe_3(CO)_{12}]$	$Fe(OTf)_3$	**3b**	4
12	$[Fe_3(CO)_{12}]$	$Fe(OTf)_2$	**3b**	15
13[c]	$[Fe_3(CO)_{12}]$	$Fe(OTf)_2$	**3b**	28
14[c,d]	$[Fe_3(CO)_{12}]$	$Fe(OTf)_2$	**3b**	10
15[d]	$[Fe_3(CO)_{12}]$	$Fe(OTf)_2$	**3b**	30
16[d,e]	$[Fe_3(CO)_{12}]$	$Fe(OTf)_2$	**3b**	93 (89)[f]
17[d,e]	$[Fe_3(CO)_{12}]$	–	**3b**	28
18[d,e]	$[Fe_3(CO)_{12}]$	–	–	–
19[d,e]	–	$Fe(OTf)_2$	**3b**	–
20[d,e]	–	$Fe(OTf)_2$	–	–
21[d,e]	$[Fe_3(CO)_{12}]$	$Fe(OTf)_2$	–	–

[a] Reaction conditions: **1a** (0.25 mmol), iron carbonyl (10 mol %, based on iron), iron salt (3.6 mol %), NAD(P)$^+$ model **3** (10 mol %), toluene (0.5 mL). [b] The yield was determined by GC. [c] Diamine **4a** (3.6 mol %) was added as a ligand. [d] 1,4-Dioxane was used as the solvent. [e] $[Fe_3(CO)_{12}]$ (6.67 mol %), $Fe(OTf)_2$ (7.2 mol %), and **3b** (20 mol %) were used. [f] The yield of the isolated product is given in parentheses.

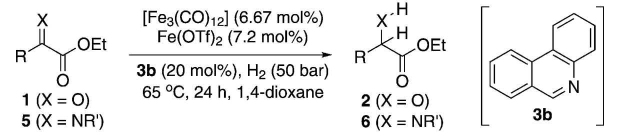


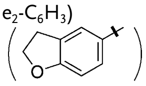
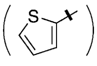
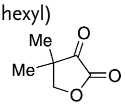
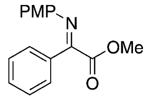
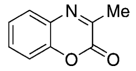
(1)

Next, we conducted stoichiometric reactions of NAD(P)$^+$ model **3b** and its reduced form H_2-**3b** with $[Fe_3(CO)_{12}]$ as the catalyst under H_2 (50 bar) or Ar (50 bar), respectively. The results in Equation (1) imply that NAD(P)H model H_2–**3b** is readily regenerated from its oxidized form **3b** through iron-catalyzed hydrogenation, although the reverse process occurs with the same catalyst in the absence of H_2. We therefore considered that the low yield of the desired α-hydroxyester **2a** might be the result of the low Lewis acidity of the iron–carbonyl complexes. When different higher-valent iron salts were added to the reaction mixture as Lewis acids (Table 1, entries 9–12), the product yield improved slightly, especially with $Fe(OTf)_2$ (Table 1, entry 12, 15 % yield). Moreover, ligand **4a** also had a positive effect on the reactivity in toluene (Table 1, entry 13, 28 % yield). To further improve the reaction efficiency, we tested different solvents and found 1,4-dioxane to be the most suitable (Table 1, entry 15, 30 % yield). However, in contrast to its effect in toluene, ligand **4a** had an adverse influence on the reaction in 1,4-dioxane (Table 1, entry 14, 10 % yield). Finally, the yield was fundamentally improved simply by increasing the catalyst loading (Table 1, entry 16).[12] To verify our concept, we performed several control experiments (Table 1, entries 17–21). We could conclude that: 1) $[Fe_3(CO)_{12}]$ is able to catalytically hydrogenate the NAD(P)$^+$ model **3b** and also possesses some Lewis acidity to promote the transfer hydrogenation of α-ketoester **1a** (Table 1, entry 17). On the other hand, $[Fe_3(CO)_{12}]$ failed to directly hydrogenate substrate **1a** (Table 1, entry 18). 2) NAD(P)$^+$ model **3b** is indispensable for this biomimetic reduction process (Table 1, entry 21). 3) The higher-valent iron salt $Fe(OTf)_2$ is unable to catalyze the hydrogenation of NAD(P)$^+$ model **3b** and α-ketoester **1a** (Table 1, entries 19 and 20).

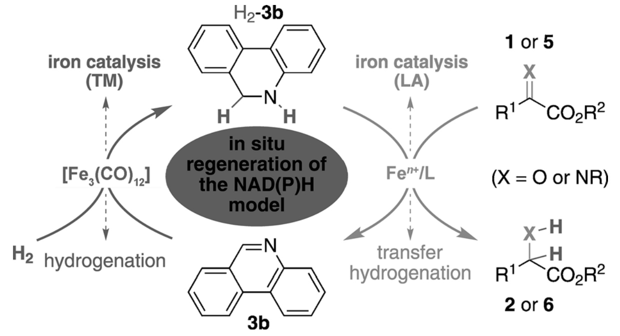
Having optimized the reaction conditions, we examined the scope of the reaction and found that a variety of α-ketoesters are suitable substrates for this biomimetic transformation under dual iron catalysis (Table 2). Comparison of the results with various aryl glyoxylic acid esters showed the electronic effects of different substituents (Table 2, entries 1–12). In general, better yields were observed when electron-deficient substrates were used. In particular, in the case of the highly electron rich substrate **1l**, a prolonged reaction time was needed for good conversion (81 % yield of the isolated product; Table 2, entry 12). Nevertheless, all aromatic substrates tested were reduced to the corresponding α-hydroxyesters in good to excellent yields. Notably, this double iron-

Table 2: Scope of the iron-catalyzed biomimetic reduction.[a]



Entry	Substrate (R)	Product	Yield [%][b]
1	**1a** (Ph)	**2a**	93 (89)
2	**1b** (*p*-MeO-C_6H_4)	**2b**	87 (86)
3	**1c** (*p*-Me-C_6H_4)	**2c**	91 (89)
4	**1d** (*p*-F-C_6H_4)	**2d**	99 (95)
5	**1e** (*p*-Cl-C_6H_4)	**2e**	93 (92)
6	**1f** (*p*-CF_3-C_6H_4)	**2f**	>99 (99)
7	**1g** (*p*-*t*Bu-C_6H_4	**2g**	86 (84)
8	**1h** (*m*-Cl-C_6H_4)	**2h**	>99 (96)
9	**1i** (3,5-F_2-C_6H_3)	**2i**	92 (87)
10	**1j** (3,4-Cl_2-C_6H_3)	**2j**	83 (81)
11	**1k** (3,4-Me_2-C_6H_3)	**2k**	90 (85)
12[c]	**1l** 	**2l**	82 (81)
13	**1m** 	**2m**	92 (88)
14	**1n** (*n*Bu)	**2n**	96
15	**1o** (*i*Pr)	**2o**	98
16	**1p** (cyclohexyl)	**2p**	98
17	**1q**: 	**2q**	98 (91)
18	**5a**: 	**6a**	98 (43)[d]
19	**5b**: 	**6b**	94 (26)[d]

[a] See the Experimental Section for the experimental details. [b] The yield was determined by GC. The yield of the isolated product is given in parentheses. [c] Reaction time: 48 h. [d] The yield determined by GC for the direct hydrogenation of the α-iminoester in the absence of **3b** and Fe(OTf)$_2$ is given in parentheses. PMP = *p*-methoxyphenyl.



Scheme 3. Mechanism for the biomimetic reduction of α-keto-/α-iminoesters through dual iron catalysis (L: ligand or solvent).

catalyst system tolerates well carbon–chloride bonds (Table 2, entries 5, 8, and 10) and heteroaryl substrates. For example, when the 2-thiophenyl-substituted substrate **1m** was used, the biomimetic reduction also proceeded smoothly in 88% yield, and was not hampered by the sulfur atom (Table 2, entry 13). Alkyl-substituted α-ketoesters were also tested, and diverse α-hydroxyesters were accessed readily in excellent yield, no matter what acyclic or cyclic substituent was present (Table 2, entries 14–16).[13] Moreover, this biomimetic reduction was also successful in the case of cyclic substrate **1q**, which contains a sterically demanding quaternary carbon center adjacent to the reaction center (Table 2, entry 17, 91% yield).[14]

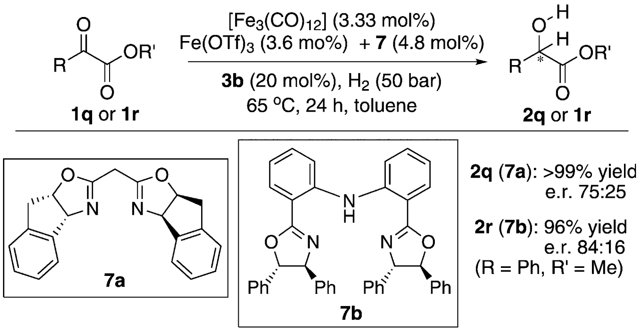
Selective reduction of the C=N group of α-iminoesters is one of the most important methods for the preparation of natural and non-natural α-amino acid esters.[15] Although [Fe$_3$(CO)$_{12}$] itself holds the potential to catalyze the direct hydrogenation of α-iminoesters, the reaction efficiency was improved remarkably when the biomimetic system was applied. Biomimetic reduction of the acyclic α-iminoester **5a** and the cyclic α-iminoester **5b** provided the desired α-amino acid esters in excellent yield (Table 2, entries 18 and 19; **6a**: 98%, **6b**: 94%). Direct hydrogenation of the same substrates gave the desired products in lower yields of 43 and 26%, respectively.

The proposed mechanism of this biomimetic reduction is shown in Scheme 3. In a similar process to the enzymatic regeneration of cofactor NAD(P)H from its oxidized form NAD(P)$^+$, the NAD(P)H model H$_2$-**3b** is generated from **3b** in the presence of a catalytic amount of [Fe$_3$(CO)$_{12}$] and benign hydrogen. H$_2$-**3b** then acts as a direct hydride source to selectively reduce the α-keto C=O or α-imino C=N bond of substrates **1** and **5**.

For the left-hand part of the catalytic cycle, the regeneration of the NAD(P)H model with hydrogen, an inexpensive and readily available iron–carbonyl complex is responsible; the right-hand part of the catalytic cycle, the transfer hydrogenation, is promoted by a Lewis acid catalyst, which decreases the LUMO energy of substrates **1** and **5**. According to our control experiments, we believe that both [Fe$_3$(CO)$_{12}$] or derived species and the dissolved Fe salt may act as Lewis acids.[16]

If the proposed biomimetic reaction sequence is to be used for stereoselective reduction, the inherent Lewis acidity of [Fe$_3$(CO)$_{12}$] has to be inhibited. In this respect, we found that the addition of nitrogen-containing ligands had a pronounced effect on the iron catalysts when toluene was used as the solvent. For example, the addition of diamine **4a** as a ligand had a positive effect on the Lewis acid catalyzed transfer-hydrogenation process and inhibited the catalytic activity of [Fe$_3$(CO)$_{12}$].[17] As a result, a reduced catalyst loading provided the desired α-hydroxyester **2r** in excellent yield when Fe(OTf)$_3$ was used as a Lewis acid in combination with **4a** in toluene. Encouraged by this positive result, we conducted iron-catalyzed biomimetic reductions in the presence of chiral nitrogen-containing ligands. Indeed, when the chiral bisoxazoline ligand **7a** and diphenylamine-tethered bisoxazoline **7b** were used, this asymmetric biomimetic reduction provided the desired chiral α-hydroxyacid esters with moderate enantioselectivity in excellent yield (Scheme 4).

In conclusion, we have demonstrated that an iron-catalyzed hydrogenation can readily be applied to the in situ regeneration of the artificial NAD(P)H cofactor DHPD.



Scheme 4. Demonstration of an asymmetric version of the biomimetic reduction (yields and enantiomeric ratios were determined by GC and GC on a chiral phase).

Thus, a biomimetic reduction of α-ketoesters and related α-iminoesters was developed which makes use of dual iron catalysis. This process provides the desired α-hydroxyesters and amino acid esters in good to excellent yield with benign hydrogen as the reductant and inexpensive iron complexes. Further studies on the scope and optimization of this iron-catalyzed biomimetic reduction are under way.

Experimental Section

General procedure: Under an atmosphere of Ar, an α-ketoester **1** (0.5 mmol) or α-iminoester **5** (0.5 mmol), phenanthridine (**3b**; 18.0 mg, 0.1 mmol), $Fe(OTf)_2$ (15.0 mg, 0.036 mmol, 85 % purity), $[Fe_3(CO)_{12}]$ (16.8 mg, 0.0333 mmol), 1,4-dioxane (1.0 mL), and a magnetic stirrer were placed in a reaction vial, which was then capped with a septum equipped with a syringe needle. The vial was then placed together with an alloy plate in a predried autoclave. Once sealed, the autoclave was purged three times with H_2, then pressurized to 50 bar and heated at 65 °C for 24 h. The autoclave was then cooled to room temperature and depressurized. The reaction mixture was analyzed by GC to determine the yield of the product. Finally, the reaction mixture was concentrated, and the residue was purified by column chromatography on silica gel (eluant: *n*-pentane/ethyl acetate 12:1–8:1) to give the corresponding α-hydroxyacid ester **2** or α-amino acid ester **6**.

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[1] For selected books and reviews about biomimetic chemistry, see: a) *Artificial Enzymes* (Ed.: R. Breslow), Wiley-VCH, Weinheim, **2005**; b) P. A. Frey, A. D. Hegeman, *Enzymatic Reaction Mechanisms*, Oxford University Press, New York, **2007**; for a recent special issue about biocatalysis and biomimetic catalysis, see: c) *ACS Catalysis*, *Vol. 1* (Ed.: H. Zhao), American Chemical Society, New York, **2011**, pp. 989 – 1149.

[2] For selected reviews on the enzymatic in situ regeneration of the cofactor NAD(P)H, see: a) H. K. Chenault, E. S. Simon, G. M. Whitesides, *Biotechnol. Genet. Eng. Rev.* **1988**, *6*, 221 – 270; b) A. Weckbecker, H. Gröger, W. Hummel, *Adv. Biochem. Eng./Biotechnol.* **2010**, *120*, 195 – 242.

[3] For a recent review on chemical catalytic in situ regeneration of the cofactor NAD(P)H and its models, see: W. Du, Z. Yu, *Synlett* **2012**, 1300 – 1304.

[4] For recent reviews on the stoichiometric use of NAD(P)H models, see: a) M. Rueping, J. Dufour, F. R. Schoepke, *Green Chem.* **2011**, *13*, 1084 – 1105; b) C. Zheng, S.-L. You, *Chem. Soc. Rev.* **2012**, *41*, 2498 – 2518.

[5] For previous examples of the use of noble metals as catalysts for the in situ regeneration of cofactor NAD(P)H and its models, see: a) O. Abril, G. M. Whitesides, *J. Am. Chem. Soc.* **1982**, *104*, 1552 – 1554; b) D. Westerhausen, S. Herrmann, W. Hummel, E. Steckhan, *Angew. Chem.* **1992**, *104*, 1496 – 1498; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1529 – 1531; c) S. Bhaduri, P. Mathur, P. Payra, K. Sharma, *J. Am. Chem. Soc.* **1998**, *120*, 12127 – 12128; d) H. C. Lo, R. H. Fish, *Angew. Chem.* **2002**, *114*, 496 – 499; *Angew. Chem. Int. Ed.* **2002**, *41*, 478 – 481; e) P. S. Wagenknecht, J. M. Penney, R. T. Hembre, *Organometallics* **2003**, *22*, 1180 – 1182; f) Hollmann, F. Kleeb, A. Otto, K. A. Schmid, *Tetrahedron: Asymmetry* **2005**, *16*, 3512 – 3519; g) J. Canivet, G. Süss-Fink, P. Štěpnička, *Eur. J. Inorg. Chem.* **2007**, 4736 – 4742; h) Q.-A. Chen, D.-S. Wang, Y.-G. Zhou, Y. Duan, H.-J. Fan, Y. Yang, Z. Zhang, *J. Am. Chem. Soc.* **2011**, *133*, 6126 – 6129; i) Q.-A. Chen, M.-W. Chen, C.-B. Yu, L. Shi, D.-S. Wang, Y. Yang, Y.-G. Zhou, *J. Am. Chem. Soc.* **2011**, *133*, 16432 – 16435.

[6] For selected reviews and books about iron catalysis, see: a) C. Bolm, J. Legros, J. L. Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217 – 6254; b) S. Enthaler, K. Junge, M. Beller, *Angew. Chem.* **2008**, *120*, 3363 – 3367; *Angew. Chem. Int. Ed.* **2008**, *47*, 3317 – 3321; c) *Iron Catalysis in Organic Chemistry* (Eds.: B. Plietker), Wiley-VCH, Weinheim, **2008**; d) “Iron Catalysis”: *Topics in Organometallic Chemistry*, *Vol. 33* (Eds.: B. Plietker), Springer, Heidelberg, **2011**; e) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Rev.* **2011**, *111*, 1293 – 1314; f) M. Darwish, M. Wills, *Catal. Sci. Technol.* **2012**, *2*, 243 – 255.

[7] For selected reviews about iron-catalyzed biomimetic oxidation, see: a) M. Costas, M. P. Mehn, M. P. Jensen, L. Que, Jr., *Chem. Rev.* **2004**, *104*, 939 – 986; b) P. C. A. Bruijnincx, G. van Koten, R. J. M. K. Gebbink, *Chem. Soc. Rev.* **2008**, *37*, 2716 – 2744.

[8] For studies on iron-catalyzed biomimetic oxidation, see: a) J. Bautz, P. Comba, C. L. de Laorden, M. Menzel, G. Rajaraman, *Angew. Chem.* **2007**, *119*, 8213 – 8216; *Angew. Chem. Int. Ed.* **2007**, *46*, 8067 – 8070; b) R. Mas-Ballesté, L. Que, Jr., *J. Am. Chem. Soc.* **2007**, *129*, 15964 – 15972; c) K. Suzuki, P. D. Oldenburg, L. Que, Jr., *Angew. Chem.* **2008**, *120*, 1913 – 1915; *Angew. Chem. Int. Ed.* **2008**, *47*, 1887 – 1889; d) A. Mukherjee, M. Martinho, E. L. Bominaar, E. Münck, L. Que, Jr., *Angew. Chem.* **2009**, *121*, 1812 – 1815; *Angew. Chem. Int. Ed.* **2009**, *48*, 1780 – 1783; e) D. Wang, E. R. Farquhar, A. Stubna, E. Münck, L. Que, Jr., *Nat. Chem.* **2009**, *1*, 145 – 150; f) H. Maid, P. Böhm, S. M. Huber, W. Bauer, W. Hummel, N. Jux, H. Gröger, *Angew. Chem.* **2011**, *123*, 2445 – 2448; *Angew. Chem. Int. Ed.* **2011**, *50*, 2397 – 2400; g) M. A. Bigi, S. A. Reed, M. C. White, *Nat. Chem.* **2011**, *3*, 216 – 220; h) P. Halder, S. Paria, T. K. Paine, *Chem. Eur. J.* **2012**, *18*, 11778 – 11787.

[9] For our previous studies on iron-catalyzed biomimetic oxidation reactions, see: a) F. G. Gelalcha, G. Anilkumar, M. K. Tse, M. Beller, *Chem. Eur. J.* **2008**, *14*, 7687 – 7698; b) K. Schröder, S. Enthaler, B. Bitterlich, T. Schulz, A. Spannenberg, M. K. Tse, K. Junge, M. Beller, *Chem. Eur. J.* **2009**, *15*, 5471 – 5481; c) K. Schröder, K. Junge, A. Spannenberg, M. Beller, *Catal. Today* **2010**, *157*, 364 – 370; d) K. Schröder, B. Join, A. J. Amali, K. Junge, X. Ribas, M. Costas, M. Beller, *Angew. Chem.* **2011**, *123*, 1461 – 1465; *Angew. Chem. Int. Ed.* **2011**, *50*, 1425 – 1429.

[10] For a review on the significance and synthesis of α-hydroxyesters, see: a) *α-Hydroxy Acids in Enantioselective Synthesis* (Eds.: G. M. Coppola, H. F. Schuster), Wiley-VCH, Weinheim, **1997**; for selected examples of the synthesis of α-hydroxyesters

through hydrogenation and biomimetic reduction, see: b) Y. Sun, X. Wan, J. Wang, Q. Meng, H. Zhang, L. Jiang, Z. Zhang, *Org. Lett.* **2005**, *7*, 5425–5427; c) J. W. Yang, B. List, *Org. Lett.* **2006**, *8*, 5653–5655; d) N. Erathodiyil, H. Gu, H. Shao, J. Jiang, J. Y. Ying, *Green Chem.* **2011**, *13*, 3070–3074, and references therein.

[11] a) S. Zhou, K. Junge, D. Addis, S. Das, M. Beller, *Angew. Chem.* **2009**, *121*, 9671–9674; *Angew. Chem. Int. Ed.* **2009**, *48*, 9507–9510; b) S. Zhou, S. Fleischer, K. Junge, S. Das, M. D. Addis, M. Beller, *Angew. Chem.* **2010**, *122*, 8298–8302; *Angew. Chem. Int. Ed.* **2010**, *49*, 8121–8125; c) S. Zhou, S. Fleischer, K. Junge, M. Beller, *Angew. Chem.* **2011**, *123*, 5226–5230; *Angew. Chem. Int. Ed.* **2011**, *50*, 5120–5124; d) S. Fleischer, S. Zhou, K. Junge, M. Beller, *Chem. Asian J.* **2011**, *6*, 2240–2245.

[12] See the Supporting Information for details of the optimization of the reaction conditions.

[13] α-Hydroxyesters substituted with alkyl groups were found to be volatile under reduced pressure, so only the yields determined by GC are provided.

[14] For the reaction of **1q**, the loading of catalyst **3b** could be reduced to 10 mol% with the same efficiency (98% yield). See the Supporting Information for more details of our investigation into the amount of **3b** required for the reaction.

[15] For selected examples of the synthesis of α-amino acid esters through hydrogenation and transfer hydrogenation, see: a) G. Shang, Q. Yang, X. Zhang, *Angew. Chem.* **2006**, *118*, 6508–6510; *Angew. Chem. Int. Ed.* **2006**, *45*, 6360–6362; b) G. Li, Y. Liang, J. C. Antilla, *J. Am. Chem. Soc.* **2007**, *129*, 5830–5831; c) C. Zhu, T. Akiyama, *Adv. Synth. Catal.* **2010**, *352*, 1846–1850, and references therein.

[16] When H_2-**3b** (1.0 equiv) was used in the absence of $[Fe_3(CO)_{12}]$ and the Fe salt under Ar (1 atm) in toluene, only a trace amount of product **2r** (1.7% yield) was found by GC analysis. When $[Fe_3(CO)_{12}]$ (3.33 mol%) or $Fe(OTf)_3$ (3.6 mol%) was added under otherwise identical conditions, the yield of **2r** increased to 33 and 66%, respectively.

[17] In toluene, $Fe(OTf)_3$ gave better results than $Fe(OTf)_2$ in the presence of ligand **4a**. The ligand is believed to improve the solubility of the Fe salt in toluene. See the Supporting Information for details of our investigation of ligand effects.