Fe-Catalyzed Olefin Epoxidation with Tridentate NonHeme Ligands and Hydrogen Peroxide as the Oxidant

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The metal-catalyzed epoxidation of alkenes is a very important process in several areas of chemistry including modern organic synthesis and the production of pharmaceutical intermediates and monomers for bulk polymers.[1] For economical and ecological reasons, molecular oxygen and hydrogen peroxide are the preferred oxidants. However, H_2O_2 is easier to handle, and it is cheap and forms water as a byproduct.[2] Currently, the heterogeneous catalysts that make use of such oxidants require harsh reaction conditions. The development of cheap, nontoxic, and selective catalysts that can use hydrogen peroxide as an oxidant is therefore of great interest.[3] In this respect, iron catalysts are very attractive, and in the last decade, excellent results have been achieved.[4] Iron complexes bearing nitrogen donor ligands were reported as efficient catalysts in the epoxidation of olefins.[5–7] The group of Que intensively studied olefin oxidation with hydrogen peroxide in the presence of mononuclear iron catalysts bearing tetra- and pentadentate nitrogen donor ligands.[5] A similar ligand was employed by the groups of Costas and Rybak-Akimova with high efficiency.[8] Furthermore, Beller and co-workers reported an extensive study on in situ generated Fe catalysts containing monodentate imidazole ligands, and optimization of the system resulted in excellent activities and selectivities for a wide range of alkene substrates, including aliphatic olefins.[6] On the basis of these results, these authors proposed a reaction mechanism in which the key intermediate is a solvated iron species coordinated to three imidazole molecules.[6d] In general, tetradentate non-heme ligands constitute the most commonly used ligands in Fe-catalyzed olefin oxidation reactions, and these reactions result in the formation of mixtures of ketones, alcohols, and epoxides.[9] In contrast, the first reports on the use of tridentate non-heme ligands in the Fe-catalyzed epoxidation of olefins appeared very recently.[10] In these reports, ionic ligands were used in both cases. Kozak and co-workers successfully used a series of tridentate amine(bisphenol) ligands in the epoxidation of trans-stilbene.[7c] Niwa and Nakada used carbazole based tridentate ligands as surrogate porphyrins in the asymmetric epoxidation of (E)-alkenes and achieved high levels of enantioselectivity (up to 97%).[10]

Here, we report the use of readily available tridentate nitrogen donor ligands 1–4 for the highly active and selective Fe-catalyzed epoxidation of alkenes.[11–13] The structure of these ligands is described in Figure 1.

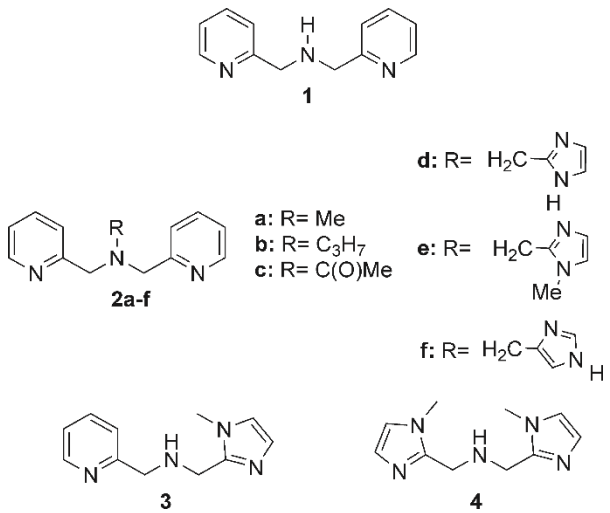
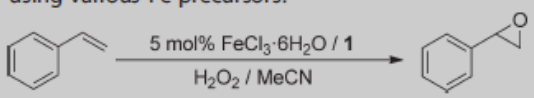


Figure 1. Ligands used in this study.

First, using ligand 1, the mode of addition of H_2O_2 was investigated, as this reagent is known to decompose rapidly in the presence of iron.[14] The optimization was carried out in acetonitrile by using $FeCl_3 \cdot 6H_2O$ as the precursor in the epoxidation of styrene with H_2O_2 (3 equiv.) at room temperature. The dropwise addition of the reagent over the reaction period was the most suitable procedure (see the Supporting Information). Next, the temperature, solvent, and Fe precursor were optimized in the epoxidation of styrene over a 30 min period (Table 1). The reactions were performed by using the catalyst (5 mol%) with H_2O_2 as oxidant at 50, 25, and 08C (Table 1, entries 1–3). Although slightly lower conversion was obtained at 08C, higher selectivity was achieved. Subsequent experiments were carried out at this temperature. The main byproduct detected was phenylacetaldehyde. Upon testing various solvents, large variations in conversion and selectivity were observed (Table 1, entries 3–8).

Table 1. Optimization of the reaction conditions in the epoxidation of styrene by using various Fe precursors.[a]



Entry	Solvent	Fe precursor	T [°C]	Conv.[b] [%]	Sel.[b] [%]
1	MeCN	$FeCl_3 \cdot 6H_2O$	50	82	83
2	MeCN	$FeCl_3 \cdot 6H_2O$	25	76	90
3	MeCN	$FeCl_3 \cdot 6H_2O$	0	73	97
4	*tert*-amyl alcohol	$FeCl_3 \cdot 6H_2O$	0	53	98
5	acetone	$FeCl_3 \cdot 6H_2O$	0	28	–
6	MeOH	$FeCl_3 \cdot 6H_2O$	0	43	55
7	CH_2Cl_2	$FeCl_3 \cdot 6H_2O$	0	–	–
8	THF	$FeCl_3 \cdot 6H_2O$	0	29	7
9	MeCN	$FeCl_2 \cdot 4H_2O$	0	40	85
10	MeCN	$Fe(NO_3)_3 \cdot 9H_2O$	0	16	67
11	MeCN	$Fe_2(SO_4)_3$	0	0	0
12	MeCN	$Fe(SO_4)(NH_4)$	0	0	0
13	MeCN	$Fe(acac)_3$	0	0	0

[a] General conditions: Iron precursor (0.01 mmol), ligand **1** (0.01 mmol), solvent (3 mL), styrene (0.2 mmol), H_2O_2 (0.6 mmol, added dropwise during the reaction), $t = 30$ min. [b] Determined by HPLC by comparing with real samples and by using *m*-xylene as an internal standard.

If tert-amyl alcohol and MeOH were used (Table 1, entries 4 and 6), conversions of about 50% were obtained, which was lower than that in acetonitrile. However, although excellent selectivity was obtained in tert-amyl alcohol (98%), only 55% of the products formed corresponded to the desired epoxide in the case of MeOH. With acetone or THF as the solvent, lower conversions and very low selectivity for the epoxide were obtained (Table 1, entries 5 and 8). In dichloromethane, no conversion was observed (Table 1, entry 7). The polarity of the solvent thus seems to be crucial to obtain high activity of the catalyst under these conditions. Next, several Fe^{III} precursors were used under these conditions and, surprisingly, only $FeCl_3 \cdot 6H_2O$ and $Fe(NO_3)_3$ gave conversion, although the latter gave lower conversion and selectivity (Table 1, entries 3 and 10–13). However, upon using the Fe^{II} precursor $FeCl_2 \cdot 4H_2O$, the conversion was moderate but higher than for $Fe(NO_3)_3$ (Table 1, entry 9).

These results therefore suggest that the nature of the counterion present in the precursor has a greater effect than the oxidation state of the Fe center of this complex, which is in agreement with previous reports.[15]

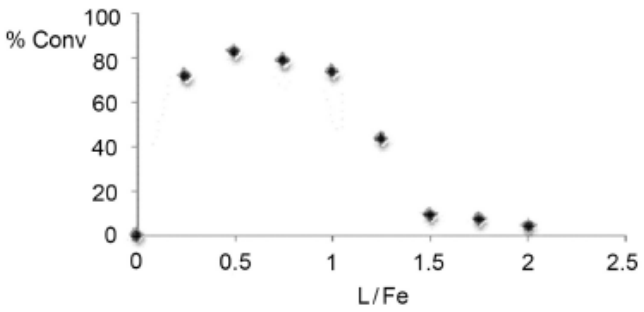


Figure 2. Optimization of the L/Fe ratio in the Fe-catalyzed epoxidation of styrene by using H_2O_2 as the oxidant.

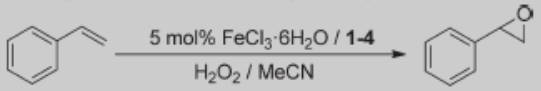
Next, the L/Fe ratio was optimized in the epoxidation of styrene by using values between 0.25 and 2, and the results are summarized in Figure 2. The results show that in the absence of a ligand, the system is inactive and that the conversion increases with the L/Fe ratio until it reaches a maximum at L/ Fe=0.5. At higher ratios of L/Fe, the conversion decreases rapidly. The value of the optimum ratio suggests the potential activity of dimeric species containing one tridentate ligand. Such an observation is in agreement with previous reports in which

dimeric species were isolated, characterized, and used in the Fe-catalyzed epoxidation of several alkenes.[6] In all cases, the selectivity for the epoxide product remained excellent, and this indicates that the amount of ligand present does not influence significantly the selectivity of the reaction.

The identity of the catalyst was investigated by ESI-TOF analysis, and the isolation of dimeric species by using a ligand/Fe ratio of 1:2 was attempted unsuccessfully. Several signals corresponding to high molecular weight compounds were detected by ESI-TOF, but no species could be unambiguously identified.

Ligands 1–4 were tested in the Fe-catalyzed epoxidation of styrene by using a L/Fe ratio of 0.5 with H_2O_2 as the oxidant at 08C over 30 min. The results are described in Table 2. Upon use of ligands 1, 3, and 4, high conversions and selectivities for the epoxide were observed (Table 2, entries 1, 8, and 9).

Table 2. Fe-catalyzed epoxidation of styrene by using ligands 1–4.[a]

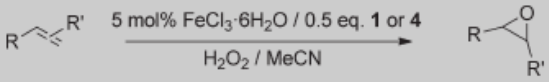


Entry	Ligand	Conv.[b] [%]	Sel.[b] [%]
1	**1**	82	96
2	**2a**	53	94
3	**2b**	55	95
4	**2c**	5	80
5	**2d**	–	–
6	**2e**	–	–
7	**2f**	–	–
8	**3**	69	93
9	**4**	86	98

[a] General conditions: $FeCl_3 \cdot 6H_2O$ (0.01 mmol), ligand (0.005 mmol), acetonitrile (3 mL), styrene (0.2 mmol), H_2O_2 (0.6 mmol, added dropwise during the reaction), $t = 30$ min. [b] Determined by HPLC by using *m*-xylene as an internal standard.

However, upon use of ligands 2a,b containing an N-alkyl group at the central nitrogen atom, lower conversions were obtained, although the selectivity remained high. Upon use of ligands 2c–f containing an amide group or coordinating imidazole substituents, a very low amount or no reaction product was detected. These results clearly indicated that the nature of the substituents at the central N atom of these ligands is crucial to obtain an active catalytic species. Indeed, the highest conversions were obtained if the ligand contained an NH group. The introduction of an alkyl group at the central N atom decreased the activity of the catalysts from about 80% to about 50%. Furthermore, for substituents c–f, the activity of the catalyst was totally inhibited. Notably, the presence of imidazole NH groups in ligands 2d and 2f did not provide catalytic activity to these systems. Beller and co-workers previously observed that slight variations in the substituents of the ligands drastically affect the activity of the catalyst.[6g]

Table 3. Fe-catalyzed epoxidation of various alkenes by using ligands **1** and **4**.



Entry	Substrate	L	Conv.[b] [%]	Sel.[b,c] [%]	Yield [%]
1	4-Me-styrene	1	93	85	70
2	4-Me-styrene	4	94	90	–
3	4-MeO-styrene	1	95	77	65
4	4-MeO-styrene	4	75	80	–
5	4-*t*Bu-styrene	1	93	87	76
6	4-*t*Bu-styrene	4	93	87	–
7	4-Cl-styrene	1	76	87	60
8	4-Cl-styrene	4	81	81	–
9	4-F-styrene	1	55	89	46
10	4-F-styrene	4	70	71	–
11	3-NO_2-styrene	1	10	57	–
12	3-NO_2-styrene	4	13	78	–
13	*trans*-stilbene	1	88	98	72
14	*trans*-stilbene	4	100	97	–
15	*cis*-stilbene	1	39	30[d]	–
16	*cis*-stilbene	4	43	35[d]	–
17	*cis*-cyclooctene	1	68	71	40
18	*cis*-cyclooctene	4	65	68	–
19	1-octene	1	7	75	–
20	1-octene	4	6	66	–

[a] General conditions: $FeCl_3 \cdot 6H_2O$ (0.01 mmol), ligand (0.005 mmol), acetonitrile (3 mL), substrate (0.2 mmol), H_2O_2 (0.6 mmol, added dropwise during the reaction), $t = 30$ min. [b] Determined by HPLC or GC (for non-aromatic olefin) by comparing with real samples and by using *m*-xylene as an internal standard. [c] The only byproduct detected was the corresponding aldehyde, except for the disubstituted olefins *cis*- and *trans*-stilbene and *cis*-cyclooctene, for which the corresponding ketone was formed. [d] The byproducts were the corresponding ketone (≈40 %) and the *trans*-stilbene oxide (≈30 %).

In view of these results, ligands 1 and 4 were used in the Fe-catalyzed epoxidation of several alkene substrates. The results are presented in Table 3. For substituted styrene substrates bearing electron-donating groups, excellent conversions and selectivities were obtained for both catalytic systems (Table 3, entries 1–6). The presence of electron-withdrawing substituents such as chloride, fluoride, and NO_2 resulted in lower values with the formation of the corresponding aldehyde as the byproduct (Table 3, entries 7–12). If trans-stilbene was used, excellent conversions and selectivities were also obtained (Table 3, entries 13 and 14). However, if the cis isomer of stilbene was the substrate, lower conversions were obtained and a strong decrease in selectivity was observed (Table 3, entries 15 and 16). In these cases, 2-phenylacetophenone was detected as a byproduct, and for cis-stilbene as the substrate, about 40% of the trans epoxide was also formed. This observation is in agreement with the results described in the literature.[6d,16] In the case of cis-cyclooctene, somewhat intermediate activities and selectivities were obtained (Table 3, entries 17 and 18). In this case, the corresponding ketone was the byproduct. Interestingly, the use of 1-octene as the substrate gave low conversions but high selectivity (Table 3, entries 19 and 20).

In all cases, very similar results were obtained with both ligands, and this indicates that these ligands possess similar behavior under these conditions. The isolated yields were also determined for most substrates and showed the synthetic utility of this methodology (Table 3, entries 1, 3, 5, 7, 9, 13, and 17).

The catalytic systems bearing tridentate ligands 1 and 4 are therefore highly active and selective for the transformation of aromatic olefins, whereas lower conversions and selectivities were obtained with aliphatic olefin substrates.

In conclusion, we have developed and tested Fe-based catalysts bearing tridentate nitrogen donor ligands 1–4 in the selective epoxidation of olefins by using hydrogen peroxide as the oxidant. The optimum L/Fe ratio was revealed to be 1:2, and this suggests the formation of

dimeric iron species bearing one tridentate ligand. However, further work is required to determine the role of this species in the catalysis system and is currently ongoing in our laboratory. The presence of substituents at the central N atom of the ligands drastically lowers the activity and selectivity of the system. C_2-symmetric ligands 1 and 4 form efficient catalytic systems for the epoxidation of aromatic olefins. Lower conversions and selectivities were obtained for aliphatic olefin substrates.

Experimental Section

Materials and synthesis

All reagents were purchased from commercial suppliers (Sigma–Aldrich, Fluka, Merck) and used without further purification. Ultrapure iron sources were purchased from Aldrich [for example, iron- (III) chloride hexahydrate puriss. p. a., Reag. Ph. Eur., ≥99%; total impurities: ≤0.001%]. Ligand 1 (2,2'-dipicolylamine, DPA) was also purchased from Sigma–Aldrich. Ligands 2–4 were synthesized according to reported procedures and their identities and purities were confirmed by comparison with their published NMR data.[11–13]

Instrumentation

^{1}H NMR and $^{13}C\{^1H\}$ NMR spectra were recorded with a Varian Mercury VX 400 (400 and 100.6 MHz, respectively) or a Varian 400-MR spectrometer in $CDCl_3$ with chemical shifts (δ) referenced to $CDCl_3$ (7.26 ppm for ^{1}H, 77.23 ppm for ^{13}C) or TMS (0.00 ppm). HPLC analyses were performed with an Agilent Technologies series 1200 instrument equipped with a UV detector with a ZORBAX Eclipse XDB-C18 4.6x150 mm, 5 µm column. GC analyses were performed with an Agilent 6850 Series GC with FID detection equipped with a column HP-INNOWAX (30 m lengthx0.25 mm I.D.x0.25 µm film). GC–MS analysis were carried out with a Agilent 7890A with a MS 5975C detector by using a HP5-MS column (30 m, 0.25 mm, 0.25 µm). ESI-TOF analyses were run with an HPLC series 1200, Agilent Technologies coupled with a Time-of-Flight series 6210, Agilent Technologies detector.

General procedure for the epoxidation of olefins

In a test tube, $FeCl3{\cdot}6H_2O$ (13.5 mg, 0.05 mmol) and the appropriate ligand (0.025 mmol) were dissolved in MeCN (15 mL). After 10 min of stirring at room temperature, the reaction mixture was cooled to 0 °C and the olefin (1 mmol) was added. To the stirred mixture, a 5% solution of hydrogen peroxide in acetonitrile (diluted from 30% aqueous, 2.05 mL) was added dropwise over a period of 30 min. After addition of the oxidant, a saturated solution of $NaHCO_3$ (20 mL) was added. The organic layer was separated in a separating funnel, and the aqueous fraction was extracted with dichloromethane (3x5 mL). The combined organic layer was washed with 10% $NaHCO_3$ solution and brine. The washed organic layer was dried with $MgSO_4$, filtered, and concentrated. The oxidation product obtained was purified by chromatography over silica gel (hexane/ethyl acetate/triethylamine=94:1:5). The products were analyzed by ^{1}H NMR and GC–MS, and their identities were confirmed by comparison with reported results.

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Keywords: epoxidation · alkenes · iron · tridentate ligands · N ligands

[1] J. E. Backvall, Modern Oxidation Methods, Wiley-VCH, Weinheim, 2004.

[2] G. Grigoropoulou, J. H. Clark, J. A. Elings, Green Chem. 2003, 5, 1–7.

[3] a) B. S. Lane, K. Burgess, Chem. Rev. 2003, 103, 2457–2474; b) R. Noyori, M. Aoki, K. Saito, Chem. Commun. 2003, 1977–1986.

[4] For reviews on iron-based catalysts see: a) K. Schrçder, K. Junge, B. Bitterlich, M. Beller, Top. Organomet. Chem. 2011, 33, 83–109; b) E. B. Bauer, Curr. Org. Chem. 2008, 12, 1341–1369; c) C. Bolm, J. Legros, J. Le Paih, L. Zani, Chem. Rev. 2004, 104, 6217–6254.

[5] a) K. Chen, M. Costas, J. Kim, A. K. Tipton, L. Que, Jr., J. Am. Chem. Soc. 2002, 124, 3026–3035; b) Y. Feng, J. England, L. Que, Jr., ACS Catal. 2011, 1, 1035–1042; c) P. D. Oldenburg, Y. Feng, I. Pryjomska-Ray, D. Ness, L. Que, Jr., J. Am. Chem. Soc. 2010, 132, 17713–17723.

[6] a) K. Schrçder, S. Enthaler, B. Join, K. Junge, M. Beller, Adv. Synth. Catal. 2010, 352, 1771–1778; b) S. Enthaler, K. Schrçder, S. Inuoe, B. Eckhardt, K. Junge, M. Beller, M. Drieß, Eur. J. Org. Chem. 2010, 4893–4901; c) K. Schrçder, K. Junge, A. Spannenberg, M. Beller, Catal. Today 2010, 157, 364–370; d) K. Schrçder, S. Enthaler, B. Bitterlich, T. Schulz, A. Spannenberg, M. K. Tse, K. Junge, M. Beller, Chem. Eur. J. 2009, 15, 5471–5481; e) B. Bitterlich, K. Schrçder, M. K. Tse, M. Beller, Eur. J. Org. Chem. 2008, 4867–4870; f) B. Bitterlich, G. Anilkumar, F. G. Gelalcha, B. Spilker, A. Grotevendt, R. Jackstell, M. K. Tse, M. Beller, Chem. Asian J. 2007, 2, 521–529; g) K. Schrçder, X. Tong, B. Bitterlich, M. K. Tse, F. G. Gelalcha, A. Brìckner, M. Beller, Tetrahedron Lett. 2007, 48, 6339–6342; h) F. G. Gelalcha, B. Bitterlich, G. Anilkumar, M. K. Tse, M. Beller, Angew. Chem. 2007, 119, 7431–7435; Angew. Chem. Int. Ed. 2007, 46, 7293–7296; i) K. Schrçder, 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; j) F. Shi, M. K. Tse, Z. Li, M. Beller, Chem. Eur. J. 2008, 14, 8793–8797; G. Anilkumar, B. Bitterlich, F. G. Gelalcha, M. K. Tse, M. Beller, Chem. Commun. 2007, 289–291.

[7] a) G. Dubois, A. Murphy, T. D. P. Stack, Org. Lett. 2003, 5, 2469–2472; b) G. J. P. Britovsek, J. England, S. K. Spitzmesser, A. J. P. White, D. J. Williams, Dalton Trans. 2005, 945–955; c) K. Hasan, N. Brown, C. M. Kozak, Green Chem. 2011, 13, 1230–1237; d) M. C. White, A. G. Doyle, E. N. Jacobsen, J. Am. Chem. Soc. 2001, 123, 7194–7195.

[8] a) A. Company, L. Gûmez, X. Fontrodona, X. Rivas, M. Costas, Chem. Eur. J. 2008, 14, 5727–5731; b) E. A. Mikhalyova, O. V. Makhlynets, T. D. Pallucio, A. S. Filatov, E. V. Rybak-Akimova, Chem. Commun. 2012, 48, 687– 689.

[9] a) R. Mas-Balleste, M. Fujita, C. Hemmila, L. Que, Jr., J. Mol. Catal. AChem. 2006, 251, 49–53; b) M. Wu, C.-X. Miao, S. Wang, X. Hu, C. Xia, F. E. Kìhn, W. Sun, Adv. Synth. Catal. 2011, 353, 3014–3022; c) A. Bassan, M. R. A. Blomberg, P. E. M. Siegbahn, L. Que, Jr., Angew. Chem. 2005, 117, 2999–3001; Angew. Chem. Int. Ed. 2005, 44, 2939–2941; d) J. Bautz, P. Comba, C. L. de Laorden, M. Mentzel, G. Rajaraman, Angew. Chem. 2007, 119, 8213–8216; Angew. Chem. Int. Ed. 2007, 46, 8067–8070; e) G. Bilis, K. C. Christoforidis, Y. Deligiannakis, M. Louloudi, Catal. Today 2010, 157, 101–106; f) B. Wang, S. Wang, C. Xia, W. Sun, Chem. Eur. J. 2012, 18, 7332–7335; g) E. P. Talsi, K. P. Bryliakov, Coord. Chem. Rev. 2012, 256, 1418–1434.

[10] T. Niwa, M. Nakada, J. Am. Chem. Soc. 2012, 134, 13538–13541.

[11] a) C. Hemmert, M. Verelst, J. P. Tuchagues, Chem. Commun. 1996, 617– 618; b) M. Pascaly, M. Duda, A. Rompel, B. H. Sift, W. Meyer-Klaucke, B. Krebs, Inorg. Chim. Acta 1999, 291, 289–299; c) H. Ohtsu, Y. Shimazaki, A. Odani, O. Yamauchi, W. Mori, S. Itoh, S. Fukuzumi, J. Am. Chem. Soc. 2000, 122, 5733–5741; d) B.

de Bruin, J. A. W. Verhagen, C. H. J. Schouten, A. W. Gal, D. Feichtinger, D. A. Plattner, Chem. Eur. J. 2001, 7, 416– 422; e) M. Livieri, F. Mancin, G. Saielli, J. Chin, U. Tonellato, Chem. Eur. J. 2007, 13, 2246–2256; f) M. C. Rodriguez, I. Morgenstern-Badarau, Inorg. Chem. 1996, 35, 7804–7810.

[12] A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff, R. D. Shah, J. Org. Chem. 1996, 61, 3849–3862.

[13] A. Temperini, R. Terlizzi, L. Testaferri, M. Tiecco, Synth. Commun. 2009, 40, 295–302.

[14] W. Nam, R. Ho, J. S. Valentine, J. Am. Chem. Soc. 1991, 113, 7052–7054.

[15] R. K. Afshar, A. A. Eroy-Reveles, M. M. Olmstead, P. K. Mascharak, Inorg. Chem. 2006, 45, 10347–10354.

[16] a) J. F. Kinneary, J. S. Albert, C. J. Burrows, J. Am. Chem. Soc. 1988, 110, 6124–6129; b) N. Murugesan, S. M. Hecht, J. Am. Chem. Soc. 1985, 107, 493–500.