COMMUNICATIONS DOI: 10.1002/adsc.202100198 Advanced Synthesis & Catalysis

# Manganese Catalyzed Enantioselective Epoxidation of α,β-Unsaturated Amides with $H_2O_2$

Roman V. Ottenbacher,[a,*] Vladimir I. Kurganskiy,[a] Evgenii P. Talsi,[a] and Konstantin P. Bryliakov[a,*]

[a] Boreskov Institute of Catalysis, Pr. Lavrentieva 5, Novosibirsk 630090, Russian Federation
E-mail: ottenbacher@catalysis.ru; bryliako@catalysis.ru

Manuscript received: February 11, 2021; Revised manuscript received: April 12, 2021;
Version of record online: ■■, ■■

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202100198

**Abstract:** Herewith, we report the enantioselective epoxidation of electron-deficient *cis*- and *trans*-α,β-unsaturated amides with the environmentally benign oxidant $H_2O_2$. The catalysts - manganese complexes with *bis*-amino-*bis*-pyridine and structurally related ligands - exhibit reasonably high efficiency (up to 100 TON) and excellent chemo- and enantioselectivity (up to 100% and 99% *ee*, respectively). Crucially, the *cis*-enamides epoxidation enantioselectivity and yield are dramatically enhanced by the presence of NH-moiety, which effect can be explained by the hydrogen bonding interaction between the *cis*-enamide substrate and the manganese based oxygen transferring species.

**Keywords:** Enantioselective; Epoxidation; Manganese; Enamide; Hydrogen Peroxide

Enantiomerically pure epoxides are ubiquitous intermediates in organic synthesis, serving as useful synthons for accessing functional chiral molecules.[1–3] The epoxides of α,β-unsaturated amides have been involved in manufacturing various biologically active compounds.[4–9] However, effective methods of asymmetric epoxidation of α,β-unsaturated amides have so far been rather limited. Shibasaki and co-workers developed a series of catalyst systems, based on lanthanide metal complexes, employing TBHP as oxidant[10–12] for the asymmetric epoxidation of *trans*-enamides. In recent years, manganese complexes with chiral *bis*-amino-*bis*-pyridine and structurally related ligands have emerged as challenging catalysts for enantioselective epoxidations of various olefins (unfunctionalized alkenes, unsaturated ketones and esters) with environmentally benign oxidant hydrogen peroxide.[13–16]

Recently, Huang and co-workers reported manganese complex bearing chiral $N_4$-donor ligand (Figure 1) and its catalytic activity in the enantioselective epoxidation of *trans*-α,β-unsaturated amides with $H_2O_2$.[17] Costas and co-workers contributed a structurally related manganese catalyst, capable of conducting the enantioselective epoxidation of β,β-disubstituted enamides with $H_2O_2$.[18] Both catalyst systems demonstrated good to excellent enantioselectivities (up to 99% *ee* in a few cases). However, the common drawback of both systems has been the sophisticated multistep syntheses of the chiral ligands; furthermore, the applicability of the above catalysts to the asymmetric epoxidation of *cis*-α,β-unsaturated amides has not been examined. Very recently, Sun and co-workers developed a Mn catalyst bearing *L*-proline-derived $N_4$-ligand and employed it in the epoxidation of *N*,*N*-disubstituted-*trans*-cinnamamides with THBP as oxidant, affording the epoxides in 42–90% yield and 87–99% *ee*.[19] Herein we report the catalytic epoxidation procedure relying on the readily available manganese complexes with *bis*-amino-*bis*-pyridine and structurally related ligands **1**–**4**[20,21] (Figure 1), that exhibit high enantioselectivities both in cases of *trans*- and *cis*-α,β-unsaturated amides. The dramatic effect of the N(Alkyl)-H moiety on the epoxidation enantioselectivity is discussed in terms of hydrogen bonding between the substrate and the metal based oxygen transferring species.

First of all, we have identified the optimal epoxidation conditions, using *N*,*N*-dimethylcinnamamide **5a** as substrate, in the presence of catalyst **1** (Table 1). The reactions were carried out in acetonitrile at −40 °C. Using acetic acid as catalytic additive resulted in the epoxide formation with good asymmetric induction (85–86% *ee*, Table 1, entries 2–4). Catalyst loading of 1.0 mol% has been found sufficient for achieving quantitative substrate conversion (Table 1, entries 1–4). Replacing acetic acid with the more sterically demanding additives 2-ethylhexanoic acid

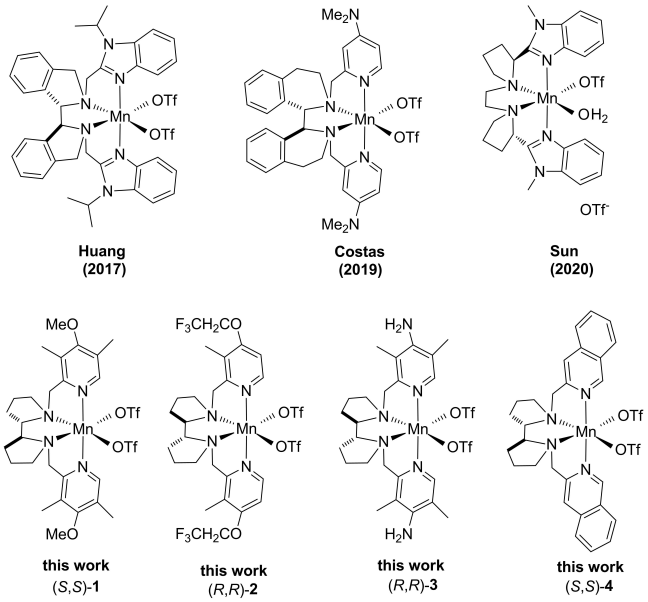



**Figure 1.** Mn(II) bis(amino)bis(pyridine) catalysts.

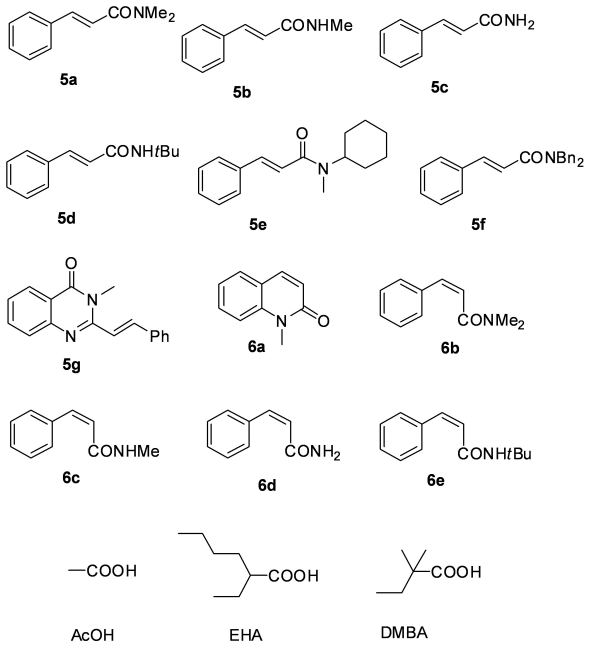
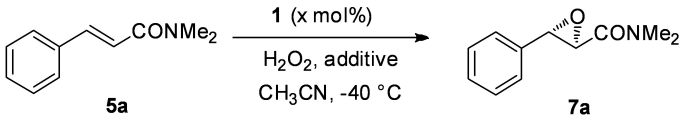



**Figure 2.** Structures of substrates and additives used in this study.

(EHA)[22] and 2,2-dimethylbutyric acid (DMBA)[23] (Figure 2), expectedly, improved the enantioselectivity up to 98–99% *ee* (Table 1, entries 5–6). Using 1 mol% catalyst loading in combination with 8 equiv. of EHA (vs. substrate) ensured the acceptable yield and enantioselectivity (Table 1, entry 12), so these reaction parameters were adopted for subsequent experiments.

Further, the epoxidation of other substrates (Figure 2) was examined (Table 2). The epoxidation of *trans*-cinnamic acid amides (Table 2, entries 1–4) yielded the corresponding epoxides in good yields (74–97%) and high enantioselectivity (95–98% *ee*). The presence of bulky alkyl group at the amide moiety did not affect the enantioselectivity: substrate **5d** containing NH*t*Bu group showed nearly the same *ee* as **5b** with the NHMe one (95% *vs.* 96% *ee*). The epoxidation of *cis*-enamides in the presence of **1**

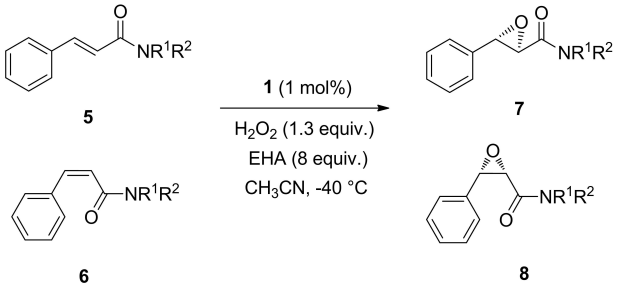
**Table 1.** Optimization of asymmetric epoxidations catalyzed by complex **1**.[a]




| Entry | Catalyst loadings (mol%) | Oxidant (equiv. vs. substrate) | Additive (equiv. vs. substrate) | Conversion [%]/ Yield [%] | *ee* [%] (Config.) |
|---|---|---|---|---|---|
| 1 | 0.1 | 1.3 | AcOH (5.0) | 8/8 | n.d. |
| 2 | 0.2 | 1.3 | AcOH (14.0) | 43/38 | 85 (2*R*,3*S*) |
| 3 | 1.0 | 1.3 | AcOH (5.0) | 100/96 | 86 (2*R*,3*S*) |
| 4 | 0.5 | 1.3 | AcOH (5.0) | 65/63 | 85 (2*R*,3*S*) |
| 5 | 0.5 | 1.3 | EHA (5.0) | 19/18 | 99 (2*R*,3*S*) |
| 6 | 0.5 | 1.3 | DMBA (5.0) | 29/28 | 98.5 (2*R*,3*S*) |
| 7 | 0.5 | 2.0 | DMBA (5.0) | 15/14 | 99 (2*R*,3*S*) |
| 8 | 0.5 | 3.0 | DMBA (5.0) | 28/27 | 98 (2*R*,3*S*) |
| 9 | 1.0 | 1.3 | DMBA (5.0) | 51/49 | 98 (2*R*,3*S*) |
| 10 | 1.0 | 1.3 | EHA (5.0) | 63/59 | 98.5 (2*R*,3*S*) |
| 11 | 1.0 | 1.3 | DMBA (8.0) | 36/34 | 98.5 (2*R*,3*S*) |
| 12 | 1.0 | 1.3 | EHA (8.0) | 100/94 | 98 (2*R*,3*S*) |

[a] Conditions: At −40 °C, [Mn]/[$H_2O_2$]/[substrate]/[additive] = X µmol:130 µmol:100 µmol:Y µmol in $CH_3CN$ (0.4 mL), $H_2O_2$ added by a syringe pump over 30 min. Conversions and yields calculated based on substrate.

**Table 2.** Asymmetric epoxidation of enamides with $H_2O_2$ catalyzed by complex **1**.[a]




| Entry | Substrate | Conversion/Yield **(Isolated Yield)** [%] | *ee* [%] (config.) |
|---|---|---|---|
| 1 | 5a | 100:94 **(92)** | 98 (*2R,3S*) |
| 2 | 5b | 100:83 **(80)** | 96 (*2R,3S*) |
| 3 | 5c | 76:74 **(68)** | 96.5 (*2R,3S*) |
| 4[b] | 5d | 100:97 **(94)** | 95 (*2R,3S*) |
| 5 | 6a | 77:70 **(58)** | 62 |
| 6 | 6b | 100:94 **(90)** | 60 |
| 7 | 6c | 100:98 **(92)** | 86 |
| 8 | 6d | 100:100 **(95)** | 88 |
| 9 | 6e | 100:72 **(62)** | 87 |

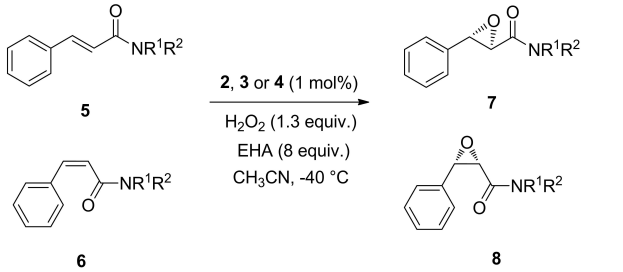
[a] Conditions: At −40 °C, [Mn]/[$H_2O_2$]/[substrate]/[additive] = 4 μmol:520 μmol:400 μmol:3200 μmol in $CH_3CN$ (1.6 mL), $H_2O_2$ added by a syringe pump over 30 min.
[b] At −20 °C.

proceeded with markedly lower enantioselectivities of 62–88% *ee* (Table 2, entries 5–9). Moreover, in the case of *cis*-enamides, the enantioselectivity showed strong dependence on the nature of substituents at the amide functionality. On the one hand, substrates **6c**, **6d** and **6e** containing $NH_2$ or different NHAlk groups were epoxidized with virtually the same *ee* of 86–88% (Table 2, entries 7–9), irrespective of the steric demand of the alkyl substituent. On the other hand, *cis*-olefins **6a** and **6b** without NH-fragments afforded epoxides with significantly lower enantioselectivities of 60–62% *ee* (Table 2, entries 5 and 6).

Manganese complexes **2**, **3** and **4** were also probed as catalysts in the epoxidation of enamides (Table 3), demonstrating good (sometimes quantitative) epoxide yields. Increasing the steric demand of the catalyst, by using complex **4**, did not lead to enantioselectivity improvement either in the case of *trans*- or *cis*-α,β-unsaturated amides (entries 18–23 of Table 3). Interestingly, all catalysts, including **1**, showed rather similar enantioselecitvities with *trans*-enamides (95-99% *ee*, cf. entries 1–4 of Table 2 and entries 1–5, 8–11, 18–20 of Table 3), including the enamide analog **5g** (4-quinazolinone derivative, entry 12 of Table 3).

At the same time, catalysts **2** and **3** exhibited improved enantioselectivity (compared with **1**) in the

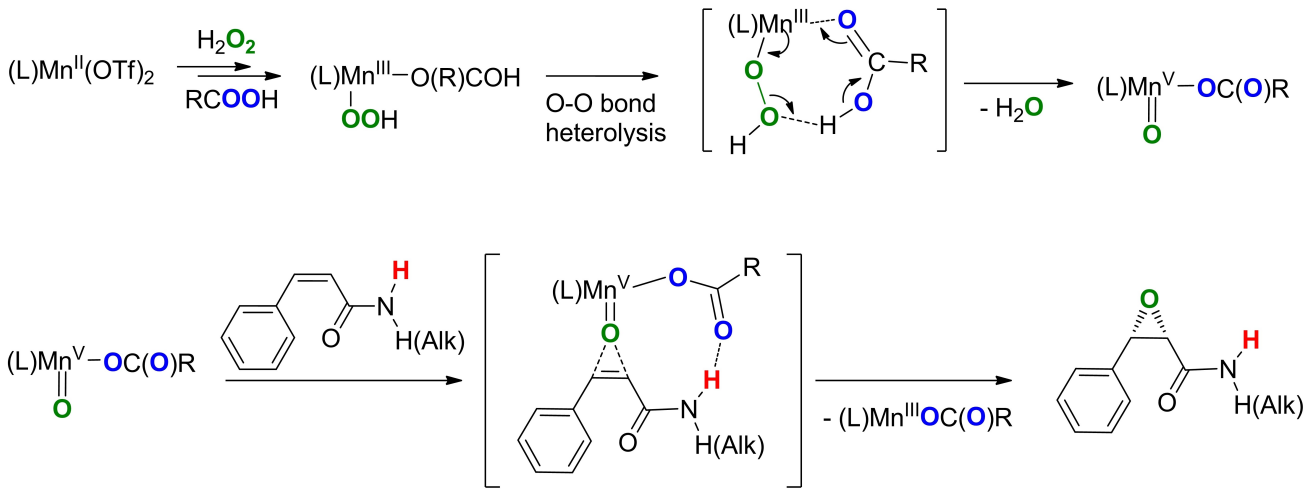
**Table 3.** Asymmetric epoxidation of enamides with $H_2O_2$ catalyzed by complexes **2**, **3** and **4**.[a]




| Entry | Catalyst | Substrate | Conversion/Yield (Isolated Yield) [%] | *ee* [%] (config.) |
|---|---|---|---|---|
| 1 | 2 | 5a | 98/97 **(95)** | 96 (*2S,3R*) |
| 2 | | 5b | 100/98 **(97)** | 95 (*2S,3R*) |
| 3 | | 5c | 100/100 **(96)** | 95 (*2S,3R*) |
| 4 | | 5e | 70/69 **(63)** | 98.5 (*2S,3R*) |
| 5[b] | | 5f | 88/88 **(80)** | 99.5 (*2S,3R*) |
| 6 | | 6d | 100/100 **(95)** | 95 |
| 7 | | 6e | 100/75 **(61)** | 92 |
| 8 | 3 | 5a | 100/100 **(95)** | 97 (*2S,3R*) |
| 9 | | 5b | 74/74 **(69)** | 97.5 (*2S,3R*) |
| 10 | | 5c | 61/61 **(55)** | 98 (*2S,3R*) |
| 11[b] | | 5f | 100/99 **(93)** | 99.1 (*2S,3R*) |
| 12[c] | | 5 g | 98/98 **(93)** | 96 |
| 13 | | 6a | 78/73 **(62)** | 88 |
| 14 | | 6b | 86/82 **(79)** | 82 |
| 15 | | 6c | 98/96 **(94)** | 95.5 |
| 16 | | 6d | 100/94 **(91)** | 96 |
| 17 | | 6e | 100/90 **(75)** | 97 |
| 18 | 4 | 5a | 51/51 **(46)** | 95.5 (*2R,3S*) |
| 19 | | 5b | 92/90 **(88)** | 94.5 (*2R,3S*) |
| 20 | | 5c | 100/99 **(95)** | 97 (*2R,3S*) |
| 21 | | 6b | 84/77 **(74)** | 76 |
| 22 | | 6c | 100/76 **(70)** | 77 |
| 23 | | 6d | 100/75 **(71)** | 83 |

[a] Conditions: At −40 °C, [Mn]/[$H_2O_2$]/[substrate]/[additive] = 4 μmol:520 μmol:400 μmol:3200 μmol in $CH_3CN$ (1.6 mL), $H_2O_2$ added by a syringe pump over 30 min.
[b] Additional solvent ($CH_2Cl_2$, 1.6 mL) was added.
[c] Additional solvent (TFE, 4 mL) was added.

epoxidation of *cis*-enamides (entries 6, 7, 13–17 of Table 3 *vs.* entries 5–9 of Table 2). Complex **3** displayed the best enantioselectivity in the series (95–

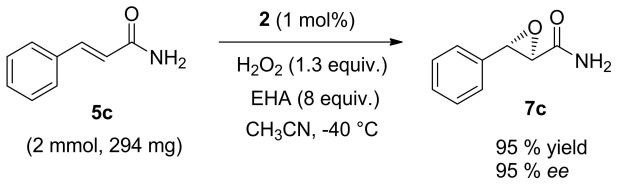



**Scheme 1.** Preparative-scale epoxidation of cinnamamide **5c**.

97% *ee*) in the oxidation of *cis*-enamides with NH groups. This can be ascribed to the effect of strong electron-donating amino groups at the pyridine moieties of the ligand, which reduces the catalyst electrophilicity and reactivity, thus resulting in the more product-like transition state and hence leading to enantioselectivity enhancement.[20] Predictably, *cis*-enamides **6a** and **6b** lacking N–H moieties were epoxidized with lower enantioselection (82-88% *ee*, entries 13 and 14 of Table 3), still much higher than in case of catalyst **1** (60-62% *ee*, entries 5 and 6 of Table 2). The epoxidation of *cis*-enamides in the presence of catalysts **1**–**4** was found to occur stereospecifically. This is not surprising, given that even the epoxidation of the very epimerization-prone *cis*-stilbene, catalyzed by **1**, was highly stereoretentive (*cis*/*trans* = 12).[24] The scalability of the catalyst system was demonstrated on a preparative-scale epoxidation of cinnamamide **5c** (Scheme 1). The corresponding epoxide was obtained in 95% isolated yield and 95% *ee*.

The observed enantioselectivity pattern in case of *cis*-substrates with N–H moieties may indicate the presence of some specific interaction between the *cis*-enamides featuring at least one N–H moiety, and the putative [(L)(RCOO)Mn$^{V}$=O] active species.[16,21,22,25] We would expect that such substrate-catalyst interaction could occur via weak hydrogen bonding (Scheme 2), which additional stabilization ensures tighter stereocontrol of asymmetric epoxidation.[26] Such molecular mechanism of stereoselectivity enhancement well fits within the concept of "biomimetic control of chemical selectivity", archetypical for biochemical reactions involving enzymes, which bind and orient the reactant(s).[27]

Overall, *bis*-amino-*bis*-pyridine chiral manganese complexes **1**–**4** (Figure 1) have been demonstrated to




**Scheme 2.** Proposed formation of Mn based oxygen transferring active species (top), and hydrogen bonding interaction between Mn active species[21] and *cis*-enamide (bottom).

efficiently catalyze the enantioselective epoxidations of *trans*- and *cis*-substituted enamides with $H_2O_2$ as oxidant, using 2-ethylhexanoic acid as additive. The corresponding epoxides are formed in good yields (up to 100%) and high enantioselectivities (up to 99% *ee*). Crucially, in the case of *cis*-enamide substrates, the presence of at least one N–H moiety significantly improves the enantioselectivity of epoxidation (from 60 up to 97% *ee*). Such effect can be explained in terms of hydrogen bonding interaction between the *cis*-enamide substrate and the manganese based oxygen transferring species. Interestingly, such specific interaction, in the case of *cis*-enamides with N–H moiety, is also crucial for attaining quantitative substrate conversion, otherwise unachievable under the conditions.

## Experimental Section

**General procedure for the catalytic epoxidation of *α,β*-unsaturated amides with $H_2O_2$.** In a typical experiment, substrate (400 μmol) and carboxylic acid (3200 μmol) were added to the solution of the manganese catalyst (4.0 μmol) in $CH_3CN$ (1.6 mL), and the mixture was thermostated at the desired temperature. Then, 400 μL of $H_2O_2$ solution in $CH_3CN$ (520 μmol of $H_2O_2$) was injected by a syringe pump over

30 min upon stirring (300 rpm). The resulting mixture was stirred for 1.5 h at required temperature. The reaction was quenched with saturated aqueous solution of $Na_2CO_3$ and the products were extracted with $Et_2O$ (3 × 12 mL). The solvent was evaporated and the residue was analyzed by $^1H$ NMR spectroscopy to determine conversions and yields and by HPLC on chiral stationary phases to measure enantiomeric excess values of the chiral epoxides as previously described.[20b] The absolute configuration was assigned by comparison of HPLC chromatogram peaks with that reported by Huang and co-workers.[17] The isolated yields were calculated based on substrate after purification of the crude material on silicagel column (hexane/acetone).

## Acknowledgements

*This work was supported by the Ministry of Science and Higher Education of the Russian Federation, project for the Boreskov Institute of Catalysis (project AAAA-A21-121011390008-4).*

## References

[1] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021; *Angew. Chem.* **2001**, *113*, 2056–2075.
[2] K. P. Bryliakov, *Environmentally Sustainable Catalytic asymmetric Oxidations*, CRC Press: Boca Raton, **2014**.
[3] K. Matsumoto, T. Katsuki, *Asymmetric Oxidations and Related Reactions in Catalytic Asymmetric Synthesis, 3rd ed.* (Ed.: I. Ojima), John Wiley & Sons: Hoboken, NJ, **2010**.
[4] J. M. Concellón, E. Bardales, C. Gómez, *Tetrahedron Lett.* **2003**, *44*, 5323–5326.
[5] V. K. Aggarwal, G. Hynd, W. Picoul, J.-L. Vasse, *J. Am. Chem. Soc.* **2002**, *124*, 9964–9965.
[6] L. Yang, D.-X. Wang, J. Pan, Q.-Y. Zheng, Z.-T. Huang, M.-X. Wang, *Org. Biomol. Chem.* **2009**, *7*, 2628–2634.
[7] R. Csuk, A. Barthel, R. Kluge, D. Ströhl, H. Kommera, R. Paschke, *Bioorg. Med. Chem.* **2010**, *18*, 1344–1355.
[8] Y.-N. Xuan, H.-S. Lin, M. Yan, *Org. Biomol. Chem.* **2013**, *11*, 1815–1817.
[9] M.-X. Wang, *Chem. Commun.* **2015**, *51*, 6039–6049.
[10] T. Nemoto, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 9474–9475.
[11] T. Nemoto, H. Kakei, V. Gnanadesikan, S.-Y. Tosaki, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2002**, *124*, 14544–14545.
[12] S.-Y. Tosaki, R. Tsuji, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 2147–2155.
[13] a) K. P. Bryliakov, *Chem. Rev.* **2017**, *117*, 11406–11459; b) R. M. Philip, S. Radhika, C. M. A. Abdulla, G. Anilkumar, *Adv. Synth. Catal.* **2021**, *363*, 1272–1289.
[14] R. V. Ottenbacher, E. P. Talsi, K. P. Bryliakov, *Chem. Rec.* **2018**, *18*, 78–90.
[15] R. V. Ottenbacher, *Recent Advances in Bioinspired Asymmetric Epoxidations with Hydrogen Peroxide, in Frontiers of Green Catalytic Selective Oxidations*; (Ed.: K. P. Bryliakov), Springer: Singapore, **2019**, 199–221.
[16] W. Sun, Q. Sun, *Acc. Chem. Res.* **2019**, *52*, 2370–2381.
[17] X. Chen, B. Gao, Y. Su, H. Huang, *Adv. Synth. Catal.* **2017**, *359*, 2535–2541.
[18] C. Claraso, L. Vicens, A. Polo, M. Costas, *Org. Lett.* **2019**, *21*, 2430–2435.
[19] D. Xu, Q. Sun, J. Lin, W. Sun, *Chem. Commun.* **2020**, *56*, 13101–13104.
[20] a) O. Cussó, I. Garcia-Bosch, D. Font, X. Ribas, J. Lloret-Fillol, M. Costas, *Org. Lett.* **2013**, *15*, 6158–6161; b) R. V. Ottenbacher, D. G. Samsonenko, E. P. Talsi, K. P. Bryliakov, *ACS Catal.* **2014**, *4*, 1599–1606.
[21] Manganese complex **1** was previously used by Costas and co-workers for the epoxidation of styrenes, unsaturated ketones, esters and N-alkoxyl amides (Weinreb enamides).[20].
[22] O. Yu. Lyakin, R. V. Ottenbacher, K. P. Bryliakov, E. P. Talsi, *ACS Catal.* **2012**, *2*, 1196–1202.
[23] D. Shen, B. Qiu, D. Xu, C. Miao, C. Xia, W. Sun, *Org. Lett.* **2016**, *18*, 372–375.
[24] R. V. Ottenbacher, D. G. Samsonenko, K. P. Bryliakov, E. P. Talsi, *ACS Catal.* **2016**, *6*, 979–988.
[25] J. Du, C. Miao, C. Xia, Y.-M. Lee, W. Nam, W. Sun, *ACS Catal.* **2018**, *8*, 4528–4538.
[26] Previously, Costas and co-workers documented comparable enantioselectivities (97% *ee* and 96% *ee*, respectively)[20] in the epoxidation of *trans*- and *cis*-isomers of one Weinreb enamide, containing no N–H moieties. The reason of the close enantioselectivities was not scrutinized.
[27] R. Breslow, *Acc. Chem. Res.* **1980**, *13*, 170–177.

## COMMUNICATIONS

Manganese Catalyzed Enantioselective Epoxidation of *α,β*-Unsaturated Amides with $H_2O_2$

*Adv. Synth. Catal.* **2021**, *363*, 1 – 6

R. V. Ottenbacher*, V. I. Kurganskiy, E. P. Talsi, K. P. Bryliakov*