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Research Article
doi.org/10.1002/cctc.202301042

Chemistry Europe
European Chemical Societies Publishing

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Manganese-catalyzed Dehydrogenation of Amido Alcohols with Liberation of Hydrogen for the Synthesis of Oxazoles

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Syntheses of important classes of (heterocyclic) compounds, the sustainable generation of hydrogen, and the use of abundantly available metals are highly desirable. We introduce here a catalytic oxazole synthesis. Our reaction is a regio selective, one-pot reaction and starts from esters and amino alcohols. Both are abundantly and diversely available and inexpensive starting materials. Hydrogen is liberated during the reaction and a molecular earth-abundant metal catalyst, a Mn(I) compound, mediates the reaction most effectively - and more efficiently than Ir and Ru catalysts. None of the oxazole derivatives synthesized, except the screening substrate and an active ingredient of a drug (an application), have been reported in literature yet.

Introduction

Reaction discovery is a central focus of chemistry and becomes especially interesting if the existing chemical space can be extended. Catalysis seems a suitable tool in this regard.[1–4] Among the many different important compound classes known, heterocyclic compounds are especially interesting due to their numerous applications as pharmaceuticals, agro chemicals, materials, fine and bulk chemicals.[5] Oxazoles are a prominent example, with their central structural motive seen in pharmaceuticals[6] and in organic materials[7] for example. Consequently, oxazole syntheses have been of great interest for more than a century (Figure 1a).[8–11] The current liveliness of the field is expressed by numerous review articles that have appeared in very recent years.[12] Especially interesting is the cyclization named after Robinson and Gabriel since all carbon substituents can be addressed. Here, the synthesis of the β-ketoamide starting material and its compatibility with the cyclization are the challenges. In addition, a β-ketoamide synthesis from diversely and abundantly available starting materials would be desirable. Established methods (Figure 1b) suffer from challenges to introduce different substituents (Figure 1b, I.),[13] relay on toxic and explosive diazo compounds (Figure 1b, II.),[14] need stoichiometric oxidants (Figure 1b, III.)[15] or a high chemical synthesis effort is required (Figure 1b, IV.)[16]. We have contributed to catalytic dehydrogenation reactions in recent years,[17–20] including *N*-heterocycle synthesis.[21,22] The catalytic pyrrole,[23,24,38] pyridine,[25–27,40] and fertigine or kuenstlerine[28] synthesis is based on a catalytic amino alcohol dehydrogenation step, and we also expected access to oxazoles via dehydrogenation catalysis (Figure 1c). Reactions that permit the generation of hydrogen and catalysts based on abundantly available metals are of general interest too. We report here on a regio selective, two-step, one-pot oxazole synthesis. Our

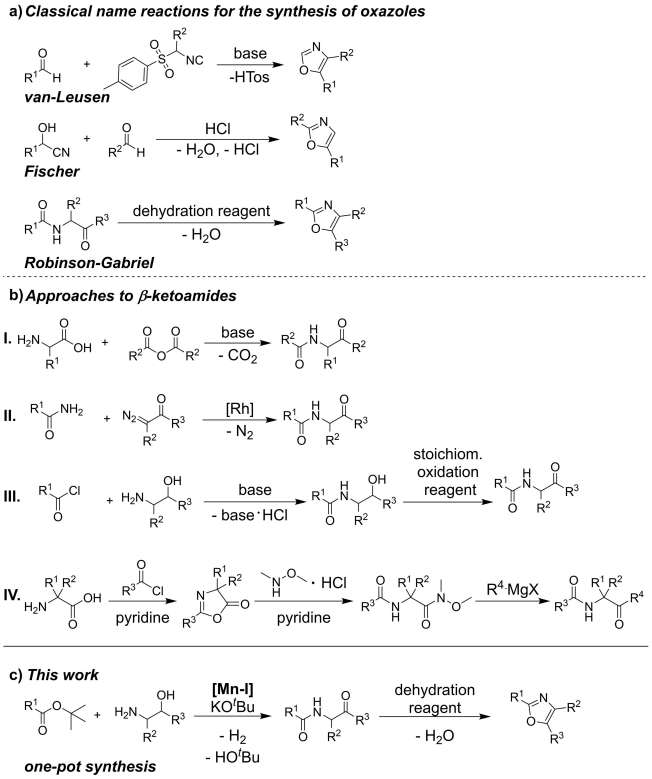

Figure 1. State of the art and work introduced here. a) Classical name reactions for the synthesis of oxazoles. b) Approaches to β-ketoamides. c) One-pot oxazole synthesis introduced here. Synthesis of 44 oxazole derivatives not yet reported. Diversely and abundantly available starting materials. Generation of hydrogen. Earth-abundant metal catalyst – a molecular Mn(I) compound, which is also superior to noble metal catalysts.

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/cctc.202301042

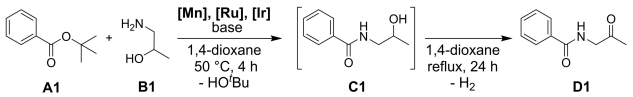
reaction starts from esters and amino alcohols, both of which are abundantly and diversely available starting materials, and hydrogen is liberated in the first step of our reaction (Figure 1c).[29] The reaction has a large scope and none of the examples synthesized, except the screening substrate and an active ingredient of a drug (application), are compounds that have been disclosed in the literature so far. Our reaction has a very good functional group tolerance, including substituents sensitive to hydrogenation, despite the presence of a hydrogenation catalyst and hydrogen.[30] A molecular manganese catalyst mediates the reaction most effectively – and more efficiently than related Ir or Ru catalysts.

Results and Discussion

Firstly, we investigated the reaction between *tert*-butyl benzoate (**A1**) and 1-aminopropan-2-ol (**B1**) to form the *N*-(2-oxopropyl)benzamide intermediate (**D1**). We intended to find optimal conditions for the dehydrogenation step of our oxazole synthesis (Table 1, top). The most efficient base is KO^{t}Bu, 1,4-dioxane seemed the best solvent, and the ester to amino alcohol ratio should be 1:1. Next, $PN_{3\text{-}5}P$-ligand-supported Mn carbonyl complexes were investigated (Table 1, entries 2–10). Precatalyst **[Mn-I]** gives rise to the most active catalyst system (Table 1, entry 2). The metal precursor $[Mn(CO)_5Br]$ showed no catalytic activity in the benchmark dehydrogenation reaction (Table 1, entry 1). An Ir complex (Table 1, entry 11), stabilized by the same ligand as **[Mn-I]**, showed no selective reaction. In addition, a Ru precatalyst was investigated (Table 1, entry 12), but no selective product formation was observed either. We next investigated the cyclodehydration reaction as a one-pot follow-up reaction of our dehydrogenation step. Phosphoryl chloride emerged as the most efficient and selective dehydrating agent (Robinson-Gabriel cyclization). Other reagents, such as phosphorus pentoxide or T3P (T3P = propanephosphonic acid anhydride), were not efficient enough (for details see Supplementary Table 6, entries 1–4). Heating *N*-(2-oxopropyl)benzamide **D1** in 1,4-dioxane for four hours at 85 °C in the presence of phosphoryl chloride and under anaerobic conditions was sufficient to obtain 5-methyl-2-phenyloxazole (**E1**, Supplementary Table 6, entry 4) in a 95% yield. With the suitable reaction conditions for a one-pot oxazole synthesis in hand, we investigated the substrate scope. The products could be isolated in yields up to 97%. A wide range of *tert*-butyl esters and 1,2-amino alcohols can undergo our dehydrogenative oxazole synthesis (Figures 2–4). None of the compounds synthesized, except the product 5-methyl-2-phenyloxazole (**E1**, Supplementary Table 6) of the benchmark reaction and the commercially available oxazole Oxaprozin (**O45**, Figure 4, applications), have been described in the literature previously. The high number of unknown oxazole derivatives synthesized here indicate the degree of novelty of our reaction and the difficulties associated with the synthesis of selectively arylated and alkylated oxazoles.

At first, we synthesized 2,5-substituted oxazoles by using 2-amino-1-propanol and 2-amino-1-butanol as secondary amino alcohols. Variation of the position of the methylene group at the corresponding aromatic ester derivatives had no significant impact on the yield of the oxazoles synthesized (**O15**-**O17**, Figure 2). Using *tert*-butyl 4-(*tert*-butyl)benzoate or 2-naphtoyl *tert*-butyl ester led to the isolation of **O14** in a 71% and **O18** in a 83% yield (Figure 2). In addition, **O2**, **O4**, and **O6**, which were synthesized from sterically demanding esters, could be isolated in yields up to 91% (Figure 2). Using electron-poor aromatic esters resulted in yields of the corresponding oxazoles up to 96% (**O3**, **O10**, **O11**, **O12**, **O13**, Figure 2). The reason for the latter might be a smooth formation of the corresponding β-hydroxyamide intermediate (**C**) due to an increased nucleophilicity at the carbonyl moiety of the ester derivative used. Oxazole **O5**, on the other hand, could be isolated in a 60% yield due to the dehalogenation observed. Moreover, compounds **O1** and **O9**, both containing alkoxy groups at the aromatic system, could be isolated in yields of 83% and 64%, respectively

Table 1. Catalyst identification.[a]



Entry	Precatalyst	Yield of **D1**[b]
1	$[Mn(CO)_5Br]$	0
2	[Mn-I] (R = Ph)	90
3	[Mn-II] (R = Me)	46
4	[Mn-III] (R = NHC_3H_5)	5
5	[Mn-IV] (R = NEt_2)	54
6	[Mn-V] (R = *p*-OMePh)	32
7	[Mn-VI] (R = H)	0
8	[Mn-VII] (R = *p*-CF_3Ph)	55
9	[Mn-VIII]	66
10	[Mn-IX]	6
11	[Ir-I]	33
12	[Ru-I]	31

[a] Reaction conditions: 0.75 mmol **A1**, 0.75 mmol **B1**, 1.125 mmol (1.50 equiv.) KO^{t}Bu, 1.50 mol% precatalyst, 1,4-dioxane (0.10 M, 7.50 mL), reflux conditions: open system under argon atmosphere. [b] Determined by GC with dodecane as an internal standard.

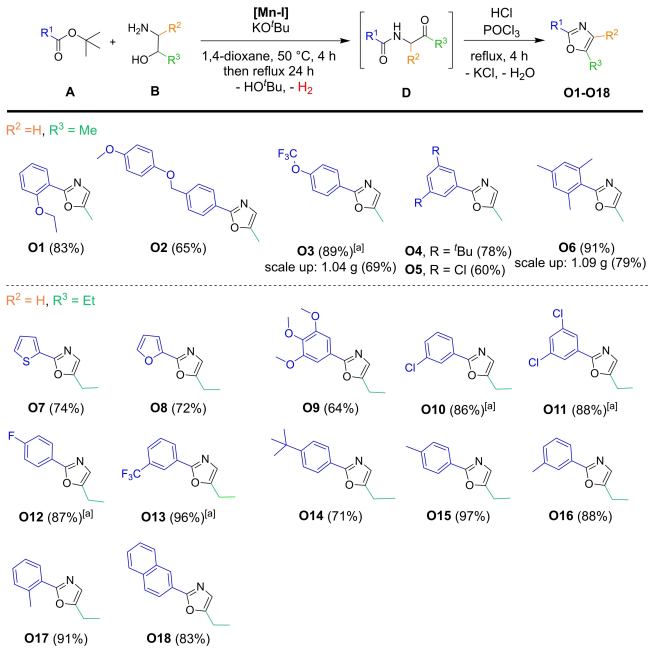


Figure 2. Synthesis of 2,5-substituted oxazoles – variation of R^1 (ester) and R^3 (amino alcohol). Reaction conditions: Step 1: 1.00 equiv. *tert*-butyl ester, 1.00 equiv. 1,2-amino alcohol, 1.50 equiv. KO^{t}Bu, 1.50 mol% **[Mn-I]**, 1,4-dioxane (0.10 M), 50 °C, for 4 h, then reflux for 24 h; reflux conditions: open system under argon atmosphere. Step 2: 1.50 equiv. HCl (4.00 M in 1,4-dioxane), 3.00 equiv. $POCl_3$, 85 °C for 4 h: open system under argon atmosphere. Isolated yields in brackets. [a] Dehydration reaction was carried out at 80 °C for 24 h, open system under argon atmosphere.

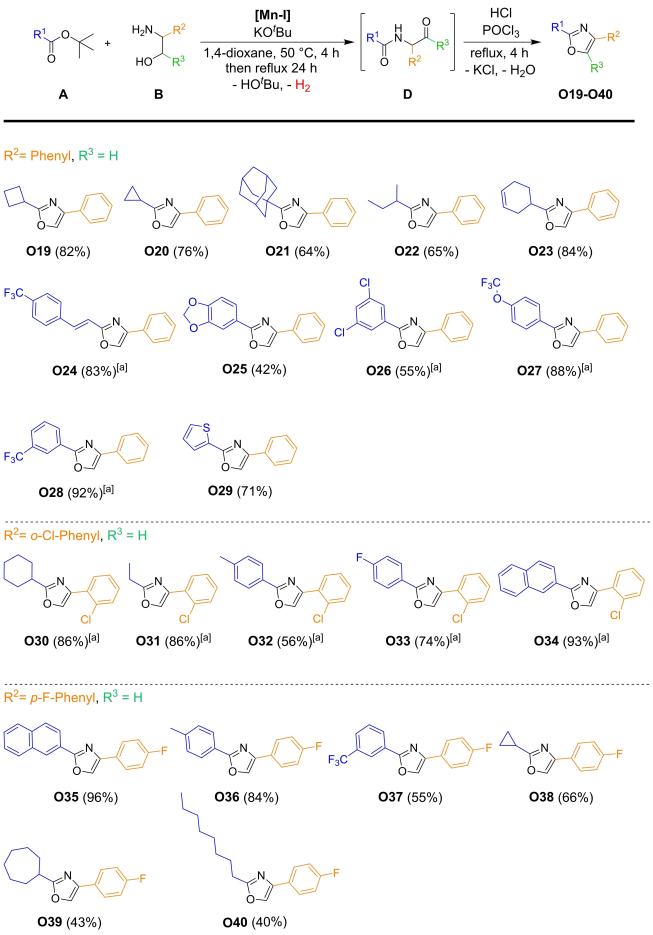


Figure 3. Synthesis of 2,5-substituted oxazoles – variation of R^1 (ester) and R^2 (amino alcohol). Reaction conditions: Step 1: 1.00 equiv. *tert*-butyl ester, 1.00 equiv. 1,2-amino alcohol, 1.50 equiv. KO^{t}Bu, 1.50 mol% **[Mn-I]**, 1,4-dioxane (0.10 M), 50 °C, for 4 h, then reflux for 24 h; reflux conditions: open system under argon atmosphere. Step 2: 1.50 equiv. HCl (4.00 M in 1,4-dioxane), 3.00 equiv. $POCl_3$, 85 °C for 4 h: open system under argon atmosphere. Isolated yields in brackets. [a] Dehydration reaction was carried out at 80 °C for 24 h, open system under argon atmosphere.

(Figure 2). Furthermore, we were interested to see whether potentially catalyst-inhibiting heteroaromatic *tert*-butyl esters could be applied. Therefore, *tert*-butyl thiophen-2-carboxylate and *tert*-butyl furan-2-carboxylate were used and the corresponding oxazoles (**O7**, **O8**, Figure 2) were isolated in yields of 74% and 72%, respectively. Finally, two scale-up experiments were carried out. The resulting products, **O3** and **O6**, could be isolated in a 69% (1.04 g, 4.29 mmol, Figure 2) and 79% yield (1.09 g, 5.38 mmol, Figure 2), respectively. We next investigated the synthesis of a range of 2,4-substituted oxazoles by using 2-amino-2-phenylethan-1-ol, 2-amino-2-(2-chlorophenyl)ethan-1-ol, and 2-amino-2-(4-fluorophenyl)ethan-1-ol as amino alcohol starting materials. Various aliphatic *tert*-butyl esters were readily converted into the corresponding oxazoles and isolated in yields of up to 86% (**O19**-**O22**, **O30**, **O31**, **O38**-**O40**, Figure 3). The reaction of 2-naphtoyl *tert*-butyl ester with 2-amino-2-(2-chlorophenyl)ethan-1-ol or 2-amino-2-(4-fluorophenyl)ethan-1-ol led to the isolation of oxazoles **O34** and **O35** in yields of 93% and 96%, respectively (Figure 3). Having an electron-withdrawing group in the para position at the aromatic amino alcohol had a positive impact on the yield, combining *tert*-butyl 4-methylbenzoate with 2-amino-2-(2-chlorophenyl)ethan-1-ol or 2-amino-2-(4-fluorophenyl)ethan-1-ol. **O32** and **O36** could be isolated in yields of 56% and 84%, respectively (Figure 3). The use of aromatic *tert*-butyl esters with electron-withdrawing groups led to the isolation of the corresponding compounds in yields up to 92% (**O26**-**O28**,**O33**,**O37**, Figure 3). Once again, it was possible to demonstrate that a potentially catalyst-inhibiting heteroaromatic *tert*-butyl ester could be applied in this protocol. *tert*-Butyl thiophen-2-carboxylate and 2-amino-2-phenylethan-1-ol could converted readily into **O29** in a 71% yield (Figure 3). Interestingly, hydrogenation-sensitive functional groups, such as olefins or Michael systems, can be tolerated despite the presence of hydrogen and a (de)hydrogenation catalyst (**O23**, **O24**, Figure 3). In addition, an acetal group could be tolerated under the basic conditions. Thus, compound **O25** could be isolated in a 42% yield (Figure 3). Using cyclic 1,2-amino alcohols led to the isolation of the corresponding oxazoles **O41**, **O42** and **O43** in yields from 71 to 88% (Figure 4). Furthermore, the active component of the drug Oxaprozin could be synthesized using adjusted conditions for the dehydration reaction (**O45**, Figure 4). These reactions indicate that oxazole derivatives, where all carbon atoms are substituted, can be obtained by applying our reaction. In addition, Gemfibrozil, a commercially available lipid-lowering agent was converted in its corresponding 4-phenyl oxazole derivative in a 59% yield (**O44**, Figure 4). Finally, we became interested in the

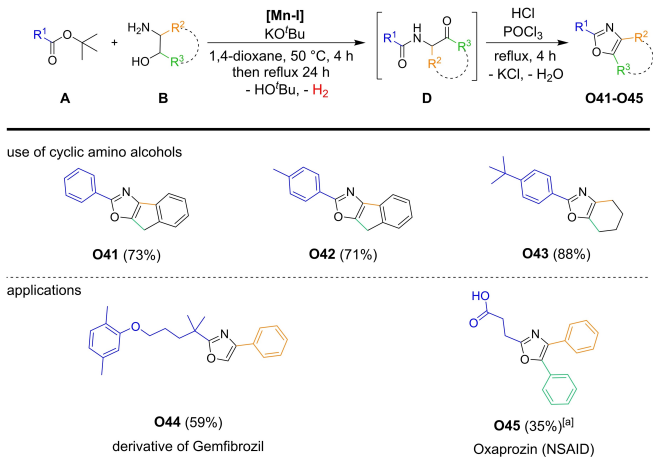


Figure 4. Synthesis of oxazoles – use of cyclic amino alcohols and applications. Reaction conditions: Step 1: 1.00 equiv. *tert*-butyl ester, 1.00 equiv. 1,2-amino alcohol, 1.50 equiv. KO^{t}Bu, 1.50 mol% **[Mn-I]**, 1,4-dioxane (0.10 M), 50 °C, for 4 h, then reflux for 24 h, open system (anaerobic conditions). Step 2: 1.50 equiv. HCl (4.00 M in 1,4-dioxane), 3.00 equiv. $POCl_3$, 85 °C for 4 h: open system under argon atmosphere. Isolated yields in brackets. [a] The catalytic dehydration was carried out with 5.00 mol% **[Mn-I]**, 3.50 equiv. KO^{t}Bu for 3 days: open system under argon atmosphere.

mechanism of our reaction. The mechanism proposed is shown in Figure 5. All steps shown in Figure 5 are observable by spectroscopic methods, such as nuclear magnetic resonance. The formation of the β-hydroxyamide intermediate is the first step and runs base-mediated. The complete formation of the corresponding β-hydroxyamide for the benchmark substrate was accomplished after four hours at 50 °C. The catalytic active species **[Mn-Ia]** is formed by treatment of the precatalyst **[Mn-I]** with two equiv. of KO^{t}Bu.[31,32] **[Mn-Ia]** abstracts hydrogen atoms from the β-hydroxyamide and forms the β-ketoamide, the doubly metallated hydride **[Mn-Ib]**, and butanol in the presence of KO^{t}Bu. The complete formation of the corresponding β-ketoamide for the benchmark substrate was accomplished after 24 hours with 1.50 mol% catalyst loading at about 100 °C. **[Mn-Ib]** is able to liberate hydrogen if butanol is present. The hydrogen can be collected (obtained: 3.72 mL, calculated: 3.95 mL, Supplementary Figure 21). In addition, nuclear magnetic resonance experiments have shown that the hydroxyamide formed *in situ* is responsible for the protonation of the guanidine pocket of the ligand backbone and, therefore, stoichiometric amounts of base are necessary to keep the metalated Mn-catalysts alive (Supplementary Figure 20).

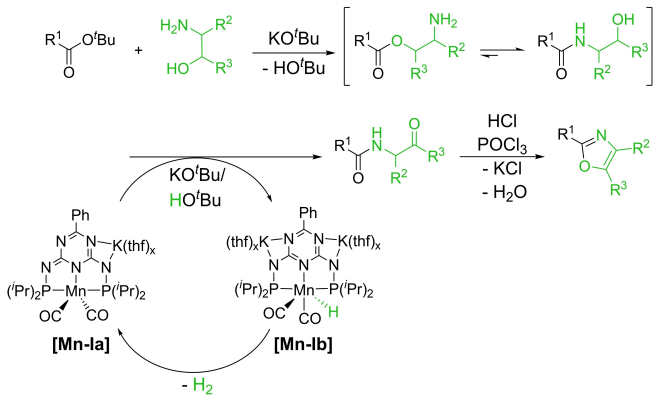


Figure 5. Mechanism proposed. All steps can be followed by spectroscopic methods.

Conclusions

In conclusion, we introduced a catalytic oxazole synthesis. The number of compounds synthesized, which have not yet been disclosed in the literature (**O1**-**O44**), indicate the degree of novelty of our synthesis and the challenges associated with the synthesis of selectively arylated and/or alkylated oxazoles. The educts, esters, and amino alcohols used are abundantly and diversely available, inexpensive, and partially accessible from renewable resources. An earth-abundant metal catalyst, namely a molecular Mn(I) compound, mediates our reaction most efficiently, also in comparison to noble metal catalysts, and hydrogen is liberated and collectable in the first part of our two-step one-pot reaction.

Experimental Section

***General reaction conditions for the synthesis of substituted oxazole derivatives*:** In a Schlenk tube the corresponding ester **A** (1.00 equiv.), the 1,2-amino alcohol **B** (1.00 equiv.), KO^{t}Bu (1.50 equiv.) and **[Mn-I]** (1.50 mol%) are dissolved in 1,4-dioxane (0.10 M). The solution is stirred at 50 °C for 4 h and then for 24 h at reflux conditions under anaerobic conditions in an open system. In case of halogenated substrates, the reaction mixture is stirred at 80 °C under identical conditions. The reaction mixture is cooled to 0 °C. HCl (4.00 M in 1,4-dioxane, 1.50 equiv.) is added. The reaction mixture is stirred at 0 °C for 5 min before $POCl_3$ (3.00 equiv.) is slowly added. The mixture is heated to 85 °C and stirred for another 4 h under anaerobic conditions in an open system. The reaction is quenched by adding ice. After adding Et_2O, the organic phase is washed with brine : water : NH_4Cl (1 : 1 : 1). The aqueous phase is extracted with Et_2O several times and then dried over $MgSO_4$. Removing the solvents under reduced pressure leads to the crude product. Column chromatography finally gives the desired product.

Supporting Information

The authors have cited additional references within the Supporting Information.[33–41]

Acknowledgements

We thank the University of Bayreuth and Deutsche Forschungsgemeinschaft (KE-756/31-2) for financial support and Dr. Ulrike Lacher for the measurements of the HRMS spectra. Open Access funding enabled and organized by Projekt DEAL.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: amino alcohols · dehydrogenation · esters · manganese · oxazoles

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Manuscript received: September 4, 2023
Revised manuscript received: September 7, 2023
Accepted manuscript online: September 8, 2023
Version of record online: October 23, 2023