ChemPubSoc Europe

DOI: 10.1002/cctc.201402967

CHEMCATCHEM Full Papers

Iron(II) Pincer-Catalyzed Synthesis of Lactones and Lactams through a Versatile Dehydrogenative Domino Sequence

Miguel Peña-López, Helfried Neumann, and Matthias Beller*[a]

The synthesis of lactones and lactams by using iron(II) pincer-catalyzed dehydrogenative methodology was developed. Starting from 1,*n*-diols or 1,*n*-amino alcohols, this domino transformation takes place through initial dehydrogenation of the substrates, subsequent intramolecular cyclization, and final oxidation to afford the desired products in good yields. The ability to access heterocycles of different sizes makes this protocol especially versatile, in which two consecutive oxidation reactions are performed without requiring an external oxidant. In this paper, we report the application of the Fe-MACHO-BH complex [carbonylhydrido(tetrahydroborato)[bis(2-diisopropylphosphinoethyl)amino]iron(II)] in this atom-efficient and environmentally benign process, for which molecular hydrogen is formed as the only stoichiometric side product.

Introduction

Nowadays, one of the most relevant scientific challenges is the development of efficient, low-costing, and environmentally friendly processes.[1] In fact, the discovery of more sustainable methodologies has become even more important than high-yielding synthetic protocols. Towards this end, the designed routes should involve, in terms of green chemistry, a reduced number of steps, the use of renewable resources, high atom economy, and waste minimization.[2] In this context, catalytic reactions performed with the use of nontoxic and easily accessible metallic complexes usually offer versatile and efficient strategies that can satisfy the prior requirements.

Among the numerous chemical transformations developed to date for the synthesis of valuable molecules from cheap and abundant feedstock, metal-catalyzed dehydrogenative coupling methodologies represent a powerful tool box consistent with the principles described above.[3] The well-established hydrogen autotransfer protocol allows the formation of new C–N and C–C bonds from simple alcohols to be performed by using amines or C nucleophiles as reagents.[4,5] For such a reaction, H_2O is formed as the only byproduct, which makes it a benign and highly atom-economic process. In addition, the synthesis of heterocycles by sequential dehydrogenative coupling processes has also been developed.[6] More specifically, several compound classes such as pyrroles, pyridines, and indoles have been prepared, and only molecular hydrogen and water were formed as waste products. On the other hand, it is noteworthy that this methodology can also be applied to the cyclization of diols and amino alcohols to provide the corresponding lactones and lactams, respectively.[7,8] In this case, a dehydrogenative step followed by an intramolecular reaction gives rise to the formation of the mentioned compounds in a sustainable way.

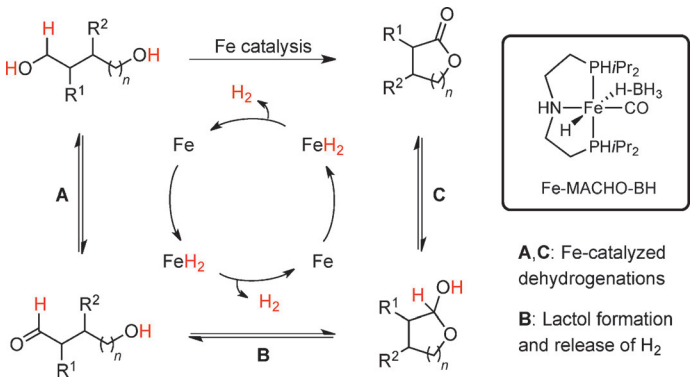
These dehydrogenative coupling protocols are generally catalyzed by transition-metal complexes such as ruthenium, iridium, and palladium. However, the application of nonprecious metals would still provide greater environmental benefits to this methodology.[9] Specifically, the use of iron-based catalysts in such synthetic strategies is of particular interest owing to the low toxicity and bioavailability of iron. On this basis, various iron complexes have already been shown to be active in the dehydrogenation of different alcohols into the corresponding carbonyl compounds,[10] reactivity which might be effectively used in coupling processes.

In function of these precedents and following the experience of our group with iron(II) complexes bearing aliphatic noninnocent PNP pincer ligands,[11] we planned to study their activity in dehydrogenative processes with a focus on the synthesis of heterocycles. In particular, the Fe-MACHO-BH complex [carbonylhydrido(tetrahydroborato)[bis(2-diisopropylphosphinoethyl)amino]iron(II)], see structure in Scheme 1) was successfully applied in the selective hydrogenation of esters and nitriles, as well as in hydrogen production from methanol. After our initial work, other uses of this catalyst were published by different groups,[12] whereas its activity for the acceptorless reversible dehydrogenation–hydrogenation of alcohols and ketones was very recently analyzed.[13] On the basis of these features, we initially considered to develop a general study on the iron pincer-catalyzed lactonization of diols. In agreement with the mechanism proposed for such transformations, the synthesis of lactones would proceed by the following domino sequence (Scheme 1). First, the iron-catalyzed mono-dehydrogenation of the diol would provide the corresponding hydroxy aldehyde. Subsequent intramolecular nucleophilic addition

[a] Dr. M. Peña-López, Dr. H. Neumann, Prof. Dr. M. Beller
Leibniz-Institut für Katalyse e.V. an der Universität Rostock
Albert-Einstein-Strasse 29a, 18059 Rostock (Germany)
Fax: (+49) 381-1281-5000
E-mail: matthias.beller@catalysis.de

Supporting Information for this article is available on the WWW under http://dx.doi.org/10.1002/cctc.201402967.

© 0000 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 1. Iron(II) pincer-catalyzed dehydrogenative lactonization of diols.

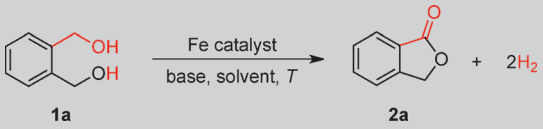
would result in the formation of the intermediate lactol, which after a new oxidation step would afford the desired lactone. Two equivalents of molecular hydrogen would be formed as the only byproduct to regenerate the catalytic species.

This fact together with the use of a nontoxic metal and no need for external stoichiometric oxidants make this atom-efficient strategy environmentally benign. Under these premises, we present herein versatile application of the previously shown iron complex to the dehydrogenative synthesis of lactones and lactams from simple and available substrates such as diols and amino alcohols.

Results and Discussion

Our research started by selecting the best iron-based catalytic system for the model transformation of 1,2-benzenedimethanol (**1a**) into phthalide (**2a**). Initially, we observed that the reaction of **1a** (1 mmol) with 1 mol% of classical iron salts such as $FeBr_3$ and $Fe(acac)_2$ (acac = acetylacetonate) in *tert*-amyl alcohol at 130 °C for 18 h did not provide the expected lactone (Table 1, entries 1 and 2). Nevertheless, the same experiment performed in the presence of the Fe-MACHO-BH complex afforded **2a** in a good 79% yield (Table 1, entry 3), whereas higher temperatures only resulted in a slight change in the yield (82%; Table 1, entry 4). After this first approach, we considered that the addition of a base in a catalytic amount could favor the cyclization step, which would lead to an increase in the efficiency of the process. Thus, the reaction of 1,2-benzenedimethanol with the iron(II) pincer complex in the presence of K_2CO_3 (10 mol%) at 130 °C provided the desired γ-butyrolactone in 85% yield; in this case, a quantitative result for the reaction at 150 °C was observed (Table 1, entries 5 and 6). The solvent showed a high relevance in the transformation, as the use of a less polar, aprotic medium such as toluene resulted in a considerable decrease in the yield (81%; Table 1, entry 7). For further optimization, we decided to analyze other parameters such as the catalyst loading and time. The experiment performed with 0.5 mol% Fe afforded a very good result (96%; Table 1, entry 8), whereas a decrease in the reaction time to 5 h allowed phthalide (**2a**) to be obtained in an excellent 98% yield (Table 1, entry 9). As expected, the same reaction performed in a basic medium in the absence of a catalyst displayed no conversion. Hence, after the screening of the best conditions, we selected the reaction of 1,2-benzenedimethanol (**1a**, 100 mol%) with Fe-MACHO-BH (0.5 mol%) and K_2CO_3 (10 mol%) in *tert*-amyl alcohol at 150 °C for 5 h as the optimal catalytic system. It is important to note the high atom economy of this process, as the diol was completely converted into the product to afford only 2 equivalents of molecular hydrogen as the byproduct. In addition, no external oxidants were required for this transformation, and the only used additive is cheap, safe, and employed in catalytic amounts.

Table 1. Optimization of the reaction conditions for the synthesis of phthalide (**2a**) from 1,2-benzenedimethanol (**1a**).[a]



1a **2a**

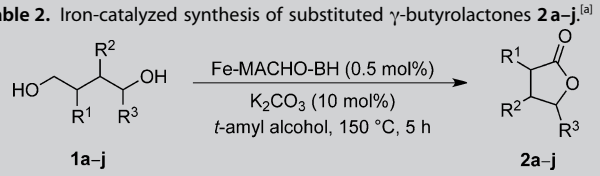
Entry	Catalyst	Base	Solvent	T [°C]	Yield [%][b]
1	$FeBr_3$	–	*t*-amyl alcohol	130	–
2	$Fe(acac)_2$	–	*t*-amyl alcohol	130	–
3	Fe-MACHO-BH	–	*t*-amyl alcohol	130	79
4	Fe-MACHO-BH	–	*t*-amyl alcohol	150	82
5	Fe-MACHO-BH	K_2CO_3	*t*-amyl alcohol	130	85
6	Fe-MACHO-BH	K_2CO_3	*t*-amyl alcohol	150	99
7	Fe-MACHO-BH	K_2CO_3	toluene	150	81
8[c]	Fe-MACHO-BH	K_2CO_3	*t*-amyl alcohol	150	96
9[c,d]	Fe-MACHO-BH	K_2CO_3	*t*-amyl alcohol	150	98
10[c,d]	–	K_2CO_3	*t*-amyl alcohol	150	–

[a] Unless otherwise specified, all reactions were performed with the diol (1 mmol), base (0.1 mmol), and the Fe catalyst (0.01 mmol) in solvent (1 mL) at the indicated temperature for 18 h. [b] GC yields with hexadecane as an internal standard. [c] Catalyst loading: 0.005 mmol. [d] Reaction time: 5 h.

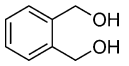
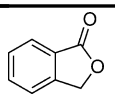
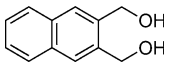
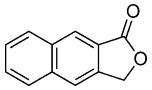
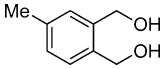
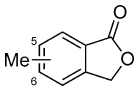
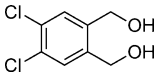
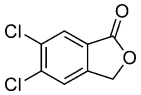
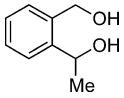
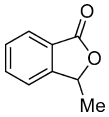
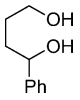
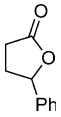
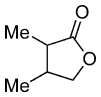
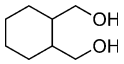
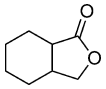
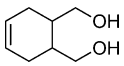
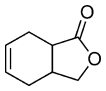
With the aim of expanding the scope of this methodology, the next step consisted in the study of the reactivity of different 1,4-diols that would allow a variety of substituted γ-butyrolactones to be prepared.[14] As shown in Table 2, we observed that aryl substrates such as 1,2-benzenedimethanol (**1a**) and 2,3-naphtalenedimethanol (**1b**) were effectively converted into the corresponding lactones following the previously developed conditions (products **2a** and **2b**, 92 and 84% yield, respectively; Table 2, entries 1 and 2). In the case of 4-methyl-1,2-benzenedimethanol (**1c**), the reaction proceeded quantitatively to afford a 1:1 mixture of regioisomers with the methyl group in the 5,6-positions (**2c**; Table 2, entry 3). This result suggests that this substituent of the aromatic group does not influence the preferential formation of one intermediate hydroxy aldehyde, so the dehydrogenation of the two alcoholic groups takes place at the same rate. Electron-deficient substrates such as 4,5-dichlorobenzene derivative **1d** required an increase in the catalyst loading and an increase in the reaction time to get a good 72% yield (**2d**; Table 2, entry 4). The same experiment under the initially established conditions afforded the desired

© 0000 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Table 2. Iron-catalyzed synthesis of substituted γ-butyrolactones **2a–j**.[a]



1a–j **2a–j**

Entry	Diol		Product		Yield [%][b]
1		**1a**		**2a**	92
2		**1b**		**2b**	84
3		**1c**		**2c**	98[c]
4		**1d**		**2d**	72[d]
5		**1e**		**2e**	93
6		**1f**		**2f**	80[e]
7		**1g**		**2g**	79[f]
8		**1h**		**2h**	65
9		**1i**		**2i**	83
10		**1j**		**2j**	81

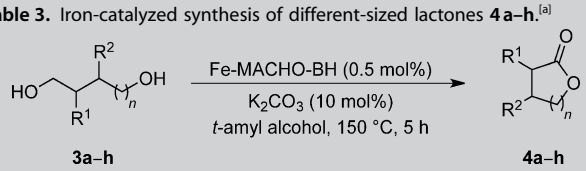
[a] Unless otherwise specified, all reactions were performed with the diol (1 mmol), K_2CO_3 (0.1 mmol), and Fe-MACHO-BH (0.005 mmol) in *tert*-amyl alcohol (1 mL) at 150 °C for 5 h. [b] Yield of isolated product. [c] Mixture of regioisomers: 5-Me/6-Me (1:1). [d] Catalyst loading: 1 mol%; reaction time: 24 h. [e] Yield was determined by NMR spectroscopy by using durene as an internal standard. [f] Catalyst loading: 1 mol%.

product in only 28% yield, and a substantial amount of the unaltered starting material was recovered. Following analysis of the aromatic derivatives, the use of a substrate with primary and secondary hydroxyl moieties allowed access to trisubstituted lactone **2e** in excellent 93% yield (Table 2, entry 5). In this case, oxidation of the primary alcohol to the corresponding conjugated aldehyde and subsequent intramolecular attack of the secondary one to form the intermediate lactol is favored. On the other hand, lactonization of 1,4-butanediol (**1f**) afforded general γ-butyrolactone (**2f**) under the optimized conditions (80% yield, as determined by NMR spectroscopy; Table 2, entry 6), whereas the reaction with 1-phenylbutane-1,4-diol (**1g**) took place to afford the product in 79% yield (Table 2, entry 7). In the latter case, the use of 1 mol% Fe-MACHO-BH was again necessary to achieve a good result, because application of the standard loading led to the desired product in a moderate 42% yield. Other aliphatic linear and cyclic diols were also used for this transformation, and the corresponding lactones were obtained in good yields (products **2h–j**, 65–83% yield; Table 2, entries 8–10). The chemoselectivity of this iron-catalyzed methodology is notable, as the C=C bonds are not reduced under these conditions, although molecular hydrogen is generated as a side product (Table 2, entry 10). This fact contrasts with the well-known ability of ruthenium complexes to promote the isomerization or even the reduction of multiple bonds in such transformations.[15]

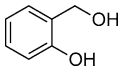
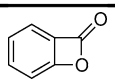
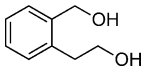
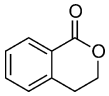
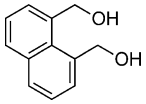
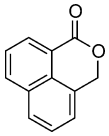
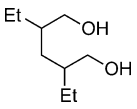
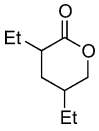
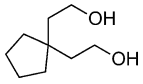
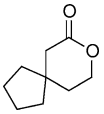
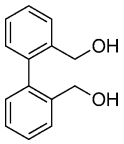
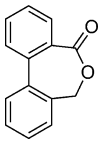
At this point and after the general development of the dehydrogenative synthesis of five-membered lactones from the corresponding 1,4-diols, we proposed to extend this methodology to different sized structures. Using terminal diols of suitable length would allow the versatility of this protocol to be increased. Lactones are present in nature as building blocks in a large variety of relevant compounds, especially five- and six-membered compounds as a result of their high stability.[16] In addition, α- and β-lactones are also found in different molecules,[17] but their synthesis and isolation is more complicated because of their reactivity. On this basis, we initially considered the synthesis of β-propiolactones from 1,3-diols. For this purpose, we chose 2-hydroxybenzyl alcohol (**3a**) as the substrate, but unfortunately, its treatment with the iron(II) pincer complex (0.5 mol%) at 150 °C in the presence of K_2CO_3 did not lead to the desired product (Table 3, entry 1). After this first attempt, we decided to deal with the synthesis of a more stable structure such as six-membered valerolactone. In this case, the reaction of 2-[2-(hydroxymethyl)phenyl]ethanol (**3b**) under the previously optimized conditions afforded isochromanone **4b** in very good yield as a mixture of regioisomers (81% yield, 85:15; Table 3, entry 2). The isochroman-1-one depicted in the table was shown to be the major isomer, because dehydrogenation of the benzyl position is favored as a result of the formation of a conjugated and non-enolizable aldehyde instead of the corresponding aliphatic one. In a similar way, other aromatic derivative such as 1,8-naphthalenedimethanol (**3c**) allowed tricyclic lactone **4c** to be prepared in quantitative yield (98%; Table 3, entry 3). Additionally, this protocol was also assayed for the synthesis of simple δ-valerolactone (**4d**) from 1,5-pentanediol (**3d**). In this case, the application of the standard conditions afforded low yields and a lack of selectivity. However, for the case in which the reaction was catalyzed by Fe-MACHO-BH (1 mol%) in an aprotic solvent such as toluene, the desired compound was obtained in a moderate 55% yield, as determined by NMR spectroscopy (Table 3, entry 4). To demonstrate the versatility of the process, the synthesis of other aliphatic lactones was accomplished. Thus, the transformation of alkyl-substituted 1,5-diols **3e** and **3f** was performed efficiently to give rise to six-membered lactones **4e** and **4f** in yields of 61 and 82%, respectively (Table 3, entries 5 and 6). The next step was to examine the possibility of preparing larger-ring lactones,[18] which sometimes require the use of special methods

© 0000 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Table 3. Iron-catalyzed synthesis of different-sized lactones **4a–h**.[a]

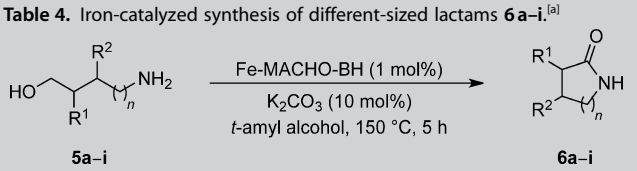


3a–h **4a–h**

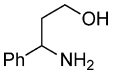
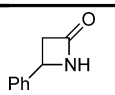
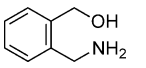
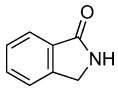
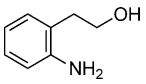
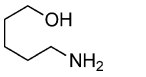
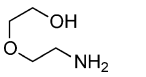
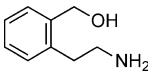
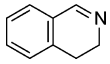
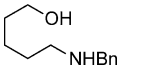
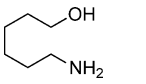
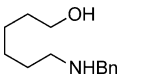
Entry	Diol		Product		Yield [%][b]
1		**3a**		**4a**	n.d.[c]
2		**3b**		**4b**	81[d]
3		**3c**		**4c**	98
4		**3d**		**4d**	55[e,f]
5		**3e**		**4e**	61
6		**3f**		**4f**	82
7		**3g**		**4g**	72
8		**3h**		**4h**	63[e,f]

[a] Unless otherwise specified, all reactions were performed with the diol (1 mmol), K_2CO_3 (0.1 mmol), and Fe-MACHO-BH (0.005 mmol) in *tert*-amyl alcohol (1 mL) at 150 °C for 5 h. [b] Yield of isolated product. [c] n.d.: not detected. [d] Yield of the mixture of isolated regioisomers: isochroman-1-one/isochroman-3-one (85:15). [e] Yield was determined by NMR spectroscopy by using durene as an internal standard. [f] Reaction was performed in toluene with Fe-MACHO-BH (1 mol%).

Table 4. Iron-catalyzed synthesis of different-sized lactams **6a–i**.[a]



5a–i **6a–i**

Entry	Amino alcohol		Product		Yield [%][b]
1		**5a**		**6a**	n.d.[c]
2		**5b**		**6b**	n.d.[c]
3		**5c**		**6c**	86 (83)[d]
4		**5d**		**6d**	75 (64)[d]
5		**5e**		**6e**	49 (91)[e,f]
6		**5f**		**6f**	92[g]
7		**5g**		**6g**	85 (77)[d,e]
8		**5h**		**6h**	82 (74)[d]
9		**5i**		**6i**	41 (95)[e,f]

[a] Unless otherwise specified, all reactions were performed with the amino alcohol (1 mmol), K_2CO_3 (0.1 mmol), and Fe-MACHO-BH (0.01 mmol) in *tert*-amyl alcohol (1 mL) at 150 °C for 5 h. [b] Yield was determined by NMR spectroscopy by using durene as an internal standard. [c] n.d.: not detected. [d] Yield of the isolated product is given in parentheses. [e] Catalyst loading: 2 mol%. [f] Yield based on recovered starting material is given in parentheses. [g] Decomposition observed during isolation by chromatography on silica gel.

for their synthesis. In this direction, we envisaged the conversion of 1,6-diols into the corresponding ε-caprolactones. Aromatic 1,1′-biphenyl-2,2′-dimethanol (**3g**) was transformed into seven-membered compound **4g** in 72% yield (Table 3, entry 7), whereas 1,6-hexanediol (**3h**) needed again the addition of a higher amount of catalyst and toluene as the solvent with the aim of getting good conversion (**4h**, 63% yield, as determined by NMR spectroscopy; Table 3, entry 8). These results show the versatility of this iron-based procedure, which provides access to a variety of lactones simply by selecting appropriately sized diols.

Once having performed the synthesis of lactones from simple diols, we applied this domino sequence to the synthesis of other biologically relevant compounds. The similarity of their structures led us to focus on analogous lactams (Table 4).[19] These cyclic amides can be obtained by using numerous synthetic methods starting from a wide variety of synthons,[20] but there is still a necessity for the development of versatile techniques that allow access to different-sized lactams from simple substrates. Applying the methodology proposed in this article, their synthesis was visualized from the corresponding easily available amino alcohols. In this case, the substrate would be first transformed into the amino aldehyde by iron-catalyzed dehydrogenation, and this would be followed by cyclization through reaction of the amine with the aldehyde moiety to finally generate the lactam after a second oxidation step.

© 0000 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Within this group of compounds, the four-membered β-lactams have special relevance, as they are present in many drugs with antibiotic, anti-inflammatory, and antitumor properties.[21] Owing to this biological significance, we initially proposed their synthesis starting from the corresponding 1,3-amino alcohols. Unfortunately, the reaction of 3-amino-3-pheny-1-propanol (**5a**) with the iron(II) pincer complex (0.5 mol%) in the presence of a catalytic amount of K_2CO_3 at 150 °C in *tert*-amyl alcohol proved to be ineffective in the formation of desired compound **6a** (Table 4, entry 1). Only remaining starting material was observed together with the formation of some decomposition product, whereas the application of other substrates and different reaction conditions did not alter this result. The high ring strain makes these compounds very reactive and susceptible to hydrolysis,[22] whereby specific conditions are sometimes required to perform their synthesis. Later, we focused on the synthesis of the corresponding γ-butyrolactams, but in contrast to the homologous synthesis of the five-membered lactones, the reaction of aromatic substrate **5b** under the standard conditions only showed the presence of the unreacted amino alcohol (Table 4, entry 2). The study of higher catalyst loadings and longer reaction times did not allow the attainment of better outcomes. Interestingly, aniline **5c** displayed good reactivity in the first oxidation and cyclization steps, but then the H_2O elimination was faster than the second dehydrogenation reaction, which gave rise to indole **6c** in excellent yield (Table 4, entry 3).

After these failed experiments, we turned our attention to six-membered lactams, which are in principle more stable compounds and for this reason potentially easier to synthesize. Thus, the reaction of 1-amino-5-pentanol (**5d**) catalyzed by Fe-MACHO-BH (0.5 mol%) gave basic δ-valerolactam (**6d**) in a moderate 47% yield, as determined by NMR spectroscopy. As we observed in the reaction with simple and lineal diols (Table 3, entries 4 and 8), a larger amount of catalyst (1 mol%) improved the transformation and delivered a good 75% yield (Table 4, entry 4). Following, we tested a substrate with a heteroatom in its structure such as 2-(2-aminoethoxy)ethanol (**5e**). Curiously, the reactivity changed drastically; a very low conversion was observed, but it was slightly improved by using double the amount of the iron pincer complex with respect to the previous reaction. Lactam **6e** was obtained in a modest 49% yield, as determined by NMR spectroscopy, but considering the amount of recovered starting material, the yield could be set at 91% (Table 4, entry 5). Next, we decided to study the behavior of an aromatic amino alcohol such as [2-(2-aminoethyl)phenyl]methanol (**5f**). As it was shown for the aryl substrate in entry 3 of Table 4, the iron-catalyzed dehydrogenative oxidation and subsequent intramolecular reaction took place effectively, but again the corresponding dehydration provided 3,4-dihydroisoquinoline (**6f**) in 92% yield, as determined by NMR spectroscopy (Table 4, entry 6). On the other hand, the *N*-substituted derivatives have been shown to be useful synthetic intermediates for the preparation of different analogues of lactam-based pharmaceuticals.[23] For this reason, we also assayed this strategy with secondary benzyl amine **5g**, and in this case, respective N-protected lactam **6g** was attained in an excellent yield (85%; Table 4, entry 7). Finally, we proposed to analyze the feasibility of preparing seven-membered lactams. Among this group of cyclic amides, the relevance of ε-caprolactam should be highlighted as a very useful intermediate in the industry for the synthesis of the polyamide nylon 6.[24] Hence, the application of the developed methodology to 1-amino-6-hexanol (**5h**) gave rise to desired product **6h** in a very good 82% yield (Table 4, entry 8). In contrast to the six-membered analogue, the reaction with benzyl derivative **5i** only proceeded moderately, and protected caprolactam **6i** was provided in 41% yield by using the iron(II) pincer complex (2 mol%; 95% yield based on recovered starting material; Table 4, entry 9). Overall, we applied this domino sequence for the first time to the synthesis of six- and seven-membered lactams that generally require higher catalyst loadings than the corresponding cyclic esters previously described.

Conclusion

In conclusion, we developed the synthesis of lactones and lactams by using iron(II) pincer-catalyzed dehydrogenative methodology. This versatile protocol allows a broad scope of heterocyclic compounds to be prepared in good to excellent yields by using simple and easily available substrates such as 1,*n*-diols and 1,*n*-amino alcohols. It is important to remark the high atom economy of this reaction, as molecular hydrogen is the only stoichiometric waste, and the fact that two sequential dehydrogenation reactions can be performed in the absence of external oxidants.

Experimental Section

General methods

Unless otherwise stated, all reactions were conducted under an argon atmosphere with exclusion of moisture from reagents and glassware by using standard techniques for manipulation of air-sensitive compounds. Reaction temperatures refer to external bath temperatures. TLC was effected on silica gel 60 F_{254} (layer thickness 0.2 mm), and components were located by observation under UV light and/or by treating the plates with a phosphomolybdic acid or *p*-anisaldehyde reagent followed by heating. Column chromatography was performed on silica gel (230–400 mesh) by using 30% ethyl acetate/heptane as eluent. NMR spectra were recorded with a Bruker Avance 400 spectrometer by using the residual solvent signal as the internal standard [chloroform: $\delta = 7.26$ ppm (^{1}H), 77.0 ppm (^{13}C)]. All measurements were performed at room temperature unless otherwise stated, and DEPT was used to assign carbon types. Mass spectra were in general recorded with a MAT 95XP or a HP 5973N mass selective detector. Gas chromatography was performed with a HP 6890N chromatograph with a HP5 column. Infrared spectra were taken with a Bruker Alpha with attenuated total reflectance (ATR). Unless otherwise stated, commercial reagents were used as received without purification.

Synthesis of noncommercially available diols

General procedure: In a 100 mL, oven-dried, two-necked flask, the commercially available dicarboxylic acid (1 equiv.) was dissolved in dry THF. $LiAlH_4$ (2 M in THF, 3 equiv.) was added carefully at 0 °C by

© 0000 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

syringe. After this addition, the mixture was stirred at room temperature overnight. After that time, saturated NH_4Cl aqueous solution (20 mL) was added carefully at 0 °C to quench the reaction. The resulting mixture was filtered over Celite, and the solid residue was washed with Et_2O (3×40 mL). The organic phase was later washed with saturated NH_4Cl, and the aqueous layer was extracted with EtOAc (3×20 mL). The combined organic extract was washed with H_2O (2×25 mL) and brine (50 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum to afford the corresponding diol, which was used in the next step without further purification.

Iron-catalyzed dehydrogenative reactions

General procedure: In a glass pressure tube (25 mL) under an argon atmosphere, [Fe-MACHO-BH] (2.1 mg, 0.005 mmol), K_2CO_3 (13.8 mg, 0.10 mmol), and the diol/amino alcohol (1.0 mmol) were dissolved in *t*-amyl alcohol (1 mL). Next, the pressure tube was closed, and the resulting mixture was stirred at 150 °C in an oil bath for 5 h. After cooling to room temperature, the crude material was directly purified by flash chromatography on silica gel to afford, after concentration and high-vacuum drying, the corresponding lactone/lactam.

Acknowledgements

We thank the State of Mecklenburg-Vorpommern and the Bundesministerium für Bildung und Forschung (BMBF) for financial support. M.P.L. thanks the European Commission for a Marie Curie Intra-European Fellowship within the 7th Framework Programme (PIEF-GA-2012–328500). We also thank Dr. Christine Fischer, Susann Buchholz, Susanne Schareina, Andreas Koch, and Sandra Leiminger (LIKAT) for analytical and technical support.

Keywords: dehydrogenative oxidation · iron · lactams · lactones · pincer complexes

[1] a) R. Ballini, in *Eco-Friendly Synthesis of Fine Chemicals*, Royal Society of Chemistry, Oxford, **2009**; b) C. A. M. Afonso, J. G. Crespo in *Green Separation Processes: Fundamentals and Applications*, Wiley-VCH, Weinheim, Germany, **2005**; c) M. Eissen, J. O. Metzger, E. Schmidt, U. Schneidewind, *Angew. Chem. Int. Ed.* **2002**, *41*, 414–436; *Angew. Chem.* **2002**, *114*, 402–425.

[2] a) P. T. Anastas, M. M. Kirchhoff, *Acc. Chem. Res.* **2002**, *35*, 686–694; b) P. T. Anastas, M. M. Kirchhoff, T. C. Williamson, *Appl. Catal. A* **2001**, *221*, 3–13; c) P. T. Anastas, J. C. Warner in *Green Chemistry: Theory and Practice*; Oxford University Press, Oxford, **1998**.

[3] a) C. Gunanathan, D. Milstein, *Science* **2013**, *341*, 249–260; b) S. Bähn, S. Imm, L. Neubert, M. Zhang, H. Neumann, M. Beller, *ChemCatChem* **2011**, *3*, 1853–1864; c) G. E. Dobereiner, R. H. Crabtree, *Chem. Rev.* **2010**, *110*, 681–703; d) G. Guillena, D. J. Ramón, M. Yus, *Chem. Rev.* **2010**, *110*, 1611–1641; e) T. D. Nixon, M. K. Whittlesey, J. M. J. Williams, *Dalton Trans.* **2009**, 753–762; f) M. H. S. A. Hamid, P. A. Slatford, J. M. J. Williams, *Adv. Synth. Catal.* **2007**, *349*, 1555–1575.

[4] For references on C–N bond formation using hydrogen autotransfer methodology, see: a) M. Zhang, S. Imm, S. Bähn, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2011**, *50*, 11197–11201; *Angew. Chem.* **2011**, *123*, 11393–11397 ; b) S. Imm, S. Bähn, M. Zhang, L. Neubert, H. Neumann, F. Klasovsky, J. Pfeffer, T. Haas, M. Beller, *Angew. Chem. Int. Ed.* **2011**, *50*, 7599–7603; *Angew. Chem.* **2011**, *123*, 7741–7745; c) S. Imm, S. Bähn, L. Neubert, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2010**, *49*, 8126–8129; *Angew. Chem.* **2010**, *122*, 8303–8306; d) S. Bähn, A. Tillack, S. Imm, K. Mevius, D. Michalik, D. Hollmann, L. Neubert, M. Beller, *ChemSusChem* **2009**, *2*, 551–557; e) D. Hollmann, A. Tillack, D. Michalik, R. Jackstell, M. Beller, *Chem. Asian J.* **2007**, *2*, 403–410.

[5] For references on C–C bond formation using hydrogen autotransfer methodology, see: a) S. J. Pridmore, J. M. J. Williams, *Tetrahedron Lett.* **2008**, *49*, 7413–7415; b) S. Burling, B. M. Paine, D. Nama, V. S. Brown, M. F. Mahon, T. J. Prior, P. S. Pregosin, M. K. Whittlesey, J. M. J. Williams, *J. Am. Chem. Soc.* **2007**, *129*, 1987–1995; c) R. Martínez, D. J. Ramón, M. Yus, *Tetrahedron* **2006**, *62*, 8982–8987; d) P. J. Black, M. G. Edwards, J. M. J. Williams, *Eur. J. Org. Chem.* **2006**, 4367–4378; e) R. Martínez, G. J. Brand, D. J. Ramón, M. Yus, *Tetrahedron Lett.* **2005**, *46*, 3683–3686.

[6] a) M. Peña-López, H. Neumann, M. Beller, *Chem. Eur. J.* **2014**, *20*, 1818–1824; b) A. Monney, M. Peña-López, M. Beller, *Chimia* **2014**, *68*, 231–234; c) S. Michlik, R. Kempe, *Nat. Chem.* **2013**, *5*, 140–144; d) D. Srimani, Y. Ben-David, D. Milstein, *Angew. Chem. Int. Ed.* **2013**, *52*, 4012–4015; *Angew. Chem.* **2013**, *125*, 4104–4107; e) S. Michlik, R. Kempe, *Angew. Chem. Int. Ed.* **2013**, *52*, 6326–6329; *Angew. Chem.* **2013**, *125*, 6450–6454; f) D. Srimani, Y. Ben-David, D. Milstein, *Chem. Commun.* **2013**, *49*, 6632–6634; g) M. Zhang, X. Fang, H. Neumann, M. Beller, *J. Am. Chem. Soc.* **2013**, *135*, 11384–11388; h) M. Zhang, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2013**, *52*, 597–601; *Angew. Chem.* **2013**, *125*, 625–629.

[7] For references on dehydrogenative synthesis of lactones: a) K.-I. Fujita, W. Ito, R. Yamaguchi, *ChemCatChem* **2014**, *6*, 109–112; b) J. Zhang, E. Balaraman, G. Leitus, D. Milstein, *Organometallics* **2011**, *30*, 5716–5724; c) S. Musa, I. Shaposhnikov, S. Cohen, D. Gelman, *Angew. Chem. Int. Ed.* **2011**, *50*, 3533–3537; *Angew. Chem.* **2011**, *123*, 3595–3599; d) M. Ito, A. Osaku, A. Shiibashi, T. Ikariya, *Org. Lett.* **2007**, *9*, 1821–1824; e) J. Zhao, J. F. Hartwig, *Organometallics* **2005**, *24*, 2441–2446.

[8] For references on dehydrogenative synthesis of lactams: a) D. Pingen, D. Vogt, *Catal. Sci. Technol.* **2014**, *4*, 47–52; b) J. H. Dam, G. Osztrovszky, L. U. Nordstrøm, R. Madsen, *Chem. Eur. J.* **2010**, *16*, 6820–6827; c) A. Nova, D. Balcells, N. D. Schley, G. E. Dobereiner, R. H. Crabtree, O. Einsenstein, *Organometallics* **2010**, *29*, 6548–6558; d) L. U. Nordstrøm, H. Vogt, R. Madsen, *J. Am. Chem. Soc.* **2008**, *130*, 17672–17673.

[9] a) B. Plietker in *Iron Catalysis: Fundamentals and Applications, Topics in Organometallic Chemistry*, Springer, Berlin, **2011**; b) R. M. Bullock in *Catalysis without Precious Metals*, Wiley-VCH, Weinheim, **2010**; c) C. Bolm, J. Legros, J. Le Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217–6254.

[10] a) H. Song, B. Kang, S. H. Hong, *ACS Catal.* **2014**, *4*, 2889–2895; b) M. Kamitani, M. Ito, M. Itazaki, H. Nakazawa, *Chem. Commun.* **2014**, *50*, 7941–7944; c) M. G. Coleman, A. N. Brown, B. A. Bolton, H. Guan, *Adv. Synth. Catal.* **2010**, *352*, 967–970.

[11] a) S. Werkmeister, K. Junge, B. Wendt, E. Alberico, H. Jiao, W. Baumann, H. Junge, F. Gallou, M. Beller, *Angew. Chem. Int. Ed.* **2014**, *53*, 8722–8726; *Angew. Chem.* **2014**, *126*, 8867–8871; b) E. Alberico, P. Sponholz, C. Cordes, M. Nielsen, H.-J. Drexler, W. Baumann, H. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2013**, *52*, 14162–14166; *Angew. Chem.* **2013**, *125*, 14412–14416; c) C. Bornschein, S. Werkmeister, B. Wendt, H. Jiao, E. Alberico, W. Baumann, H. Junge, K. Junge, M. Beller, *Nat. Commun.* **2014**, *5*, 4111.

[12] a) S. Chakraborty, W. W. Brennessel, W. D. Jones, *J. Am. Chem. Soc.* **2014**, *136*, 8564–8567; b) S. Chakraborty, H. Dai, P. Bhattacharya, N. T. Fairweather, M. S. Gibson, J. A. Krause, H. Guan, *J. Am. Chem. Soc.* **2014**, *136*, 7869–7872; c) I. Koehne, T. J. Schmeier, E. A. Bielinski, C. J. Pan, P. O. Lagaditis, W. H. Bernskoetter, M. K. Takase, C. Würtele, N. Hazari, S. Schneider, *Inorg. Chem.* **2014**, *53*, 2133–2143; d) S. Qu, H. Dai, Y. Dang, C. Song, Z.-X. Wang, H. Guan, *ACS Catal.* **2014**, *4*, 4377–4388.

[13] S. Chakraborty, P. O. Lagaditis, M. Förster, E. A. Bielinski, N. Hazari, M. C. Holthausen, W. D. Jones, S. Schneider, *ACS Catal.* **2014**, *4*, 3994–4003.

[14] For references on biological relevance of γ-butyrolactones, see: a) F. Cateni, J. Zilic, M. Zacchigna, P. Bonivento, F. Frausin, V. Scarcia, *Eur. J. Med. Chem.* **2006**, *41*, 192–203; b) M. Seitz, O. Reiser, *Curr. Opin. Chem. Biol.* **2005**, *9*, 285–292; c) R. Bandichhor, B. Nosse, O. Reiser, *Top. Curr. Chem.* **2005**, *243*, 43–72; d) M. A. Hughes, J. M. McFadden, C. A. Townsend, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3857–3859; e) S. S. Canan Koch, A. R. Chamberlin, *Stud. Nat. Prod. Chem.* **1995**, *16*, 687–725.

[15] a) S. Muthaiah, S. H. Hong, *Adv. Synth. Catal.* **2012**, *354*, 3045–3053; b) S. Shahane, C. Fischmeister, C. Bruneau, *Catal. Sci. Technol.* **2012**, *2*, 1425–1428; c) T. J. Donohoe, T. J. O'Riordan, C. P. Rosa, *Angew. Chem. Int. Ed.* **2009**, *48*, 1014–1017; *Angew. Chem.* **2009**, *121*, 1032–1035.

© 0000 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

[16] For references on biological relevance of δ-valerolactones, see: a) V. Boucard, G. Broustal, J. M. Campagne, *Eur. J. Org. Chem.* **2007**, 225–236; b) P. A. Amaral, A. M. Bergold, V. L. Eifler-Lima, *J. Pharm. Pharm. Sci.* **2005**, *8*, 69–75; c) L. Bialy, H. Waldmann, *Chem. Commun.* **2003**, 1872–1873; d) M. Kalesse, M. Christmann, U. Bhatt, M. Quitschalle, E. Claus, A. Saeed, A. Burzlaff, C. Kasper, L. O. Haustedt, E. Hofer, T. Scheper, W. Beil, *ChemBioChem* **2001**, *2*, 709–714.

[17] a) N. J. Lajkiewicz, A. B. Cognetta, M. J. Niphakis, B. F. Cravatt, J. A. Porco, *J. Am. Chem. Soc.* **2014**, *136*, 2659–2664; b) T. Böttcher, S. A. Sieber, *Med. Chem. Commun.* **2012**, *3*, 408–417; c) S. J. Kridel, F. Axelrod, N. Rosenkrantz, J. W. Smith, *Cancer Res.* **2004**, *64*, 2070–2075; d) J. G. Buchanan, M. H. Charlton, M. F. Mahon, J. J. Robinson, G. D. Ruggiero, I. H. Williams, *J. Phys. Org. Chem.* **2002**, *15*, 642–646; e) G. Ruggiero, I. H. Williams, *J. Chem. Soc. Perkin Trans. 2* **2001**, 733–737; f) H. W. Yang, D. Romo, *Tetrahedron* **1999**, *55*, 6403–6434.

[18] a) W. Zhao, Z. Li, J. Sun, *J. Am. Chem. Soc.* **2013**, *135*, 4680–4683; b) W. Zhao, Z. Wang, J. Sun, *Angew. Chem. Int. Ed.* **2012**, *51*, 6209–6213; *Angew. Chem.* **2012**, *124*, 6313–6317; c) I. Shiina, *Chem. Rev.* **2007**, *107*, 239–273.

[19] For some references on biological relevance of lactams-based compounds, see: a) T. Janecki in *Natural Lactones and Lactams*, Wiley-VCH, Weinheim, **2014**, pp. 101–188; b) G. Veinberg, I. Potorocina, M. Vorona, *Curr. Med. Chem.* **2014**, *21*, 393–416; c) G. Liu, Y.-M. Ma, W.-Y. Tai, C.-M. Xie, Y.-L. Li, J. Li, F.-J. Nan, *ChemMedChem* **2008**, *3*, 74–78; d) Y. Wang, S. V. O'Neil, J. A. Wos, K. A. Oppong, M. C. Laufersweiler, D. L. Soper, C. D. Ellis, M. W. Baize, A. N. Fancher, W. Lu, M. K. Suchanek, R. L. Wang, W. P. Schwecke, C. A. Cruze, M. Buchalova, M. Belkin, B. De, T. P. Demuth, *Bioorg. Med. Chem.* **2007**, *15*, 1311–1322.

[20] For some references on synthesis of lactams-based compounds, see: a) L.-W. Ye, C. Shu, F. Gagosz, *Org. Biomol. Chem.* **2014**, *12*, 1833–1845; b) J. Qi, C. Sun, Y. Tian, X. Wang, G. Li, Q. Xiao, D. Yin, *Org. Lett.* **2014**, *16*, 190–192; c) C. Shu, M.-Q. Liu, S.-S. Wang, L. Li, L.-W. Ye, *J. Org. Chem.* **2013**, *78*, 3292–3299; d) D. Chaturvedi, A. K. Chaturvedi, N. Mishra, V. Mishra, *Synlett* **2012**, *23*, 2627–2630; e) P. S. Baran, *Chem. Soc. Rev.* **2011**, *40*, 1976–1991; f) H. M. A. Hassan, *Chem. Commun.* **2010**, *46*, 9100–9106; g) R. Shintani, S. Park, F. Shirozu, M. Murakami, T. Hayashi, *J. Am. Chem. Soc.* **2008**, *130*, 16174–16175.

[21] For references on biological relevance of β-lactams, see: a) B. K. Banik in *β -Lactams: Unique Structures of Distinction for Novel Molecules*, Springer, Heidelberg, **2013**; b) A. Kamath, I. Ojima, *Tetrahedron* **2012**, *68*, 10640–10664; c) P. Galletti, D. Giacomini, *Curr. Med. Chem.* **2011**, *18*, 4265–4283; d) G. S. Singh, *Mini-Rev. Med. Chem.* **2004**, *4*, 69–93; e) A. Fleming, *Br. J. Exp. Pathol.* **1929**, *10*, 226–236.

[22] a) P. Imming, B. Klar, D. Dix, *J. Med. Chem.* **2000**, *43*, 4328–4331; b) J. Frau, M. Coll, J. Donoso, F. Muñoz, B. Vilanova, F. García-Blanco, *Electron. J. Theor. Chem.* **1997**, *2*, 56–65.

[23] a) K. Thai, L. Wang, T. Dudding, F. Bilodeau, M. Gravel, *Org. Lett.* **2010**, *12*, 5708–5711; b) C. H. Yoon, A. Nagle, C. Chen, D. Gandhi, K. W. Jung, *Org. Lett.* **2003**, *5*, 2259–2262; c) A. Lei, J. Waldkirch, M. He, X. Zhang, *Angew. Chem. Int. Ed.* **2002**, *41*, 4526–4529; *Angew. Chem.* **2002**, *114*, 4708–4711; d) C. H. Yoon, M. J. Zaworotko, B. Moulton, K. W. Jung, *Org. Lett.* **2001**, *3*, 3539–3542.

[24] a) F. Zhang, L. Zhou, Y. Yaochi, X. Weijian, X. Yuaquin, *J. Appl. Polym. Sci.* **2008**, *108*, 2365–2372; b) K. Ueda, K. Yamada, M. Nakai, T. Matsuda, M. Hosoda, K. Tai, *Polym. J.* **1996**, *28*, 446–451; c) L. J. Mathias, R. A. Vaidya, J. B. Canterberry, *J. Chem. Educ.* **1984**, *61*, 805–807; d) P. Schlack, German Patent 748,253 (, **1938**), U. S. Patent 2,241,321 (**1941**).

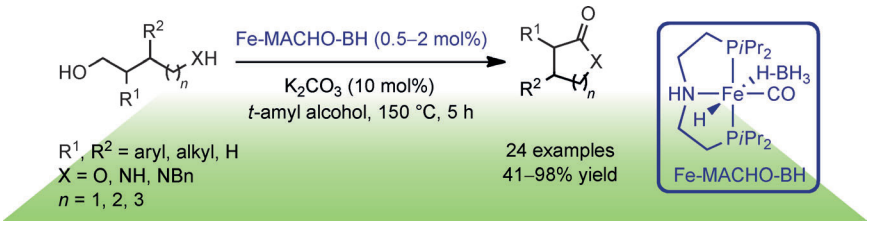
Received: December 1, 2014
Published online on ■■ ▮▮, 0000

© 0000 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

*M. Peña-López, H. Neumann, M. Beller**

■■ – ■■

Iron(II) Pincer-Catalyzed Synthesis of Lactones and Lactams through a Versatile Dehydrogenative Domino Sequence



Just a little pinch: The iron(II) pincer-catalyzed synthesis of lactones and lactams from easily available 1,*n*-diols and 1,*n*-amino alcohols is explored. The use of a nontoxic metal as well as the generation of molecular hydrogen as the only stoichiometric byproduct makes this method a highly atom-efficient and environmentally benign process.

© 0000 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim