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Synthesis of Hexahydrocyclopenta[*c*]furans by an Intramolecular Iron-Catalyzed Ring Expansion Reaction

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Abstract: The intramolecular iron-catalyzed ring expansion reaction of epoxyalkenes was investigated with a preformed iron(salen) [Fe(Salen)] complex. The formal insertion of the alkene into the epoxide generated hexahydrocyclopenta[*c*]furan derivatives in moderate to good yields and diastereoselectivities depending on other functional groups present in the starting materials. In addition, oxygen-tethered epoxyalkenes were used for the synthesis of lignan isomers. The scope and limitations of the Fe(Salen)-catalyzed process of the reaction are discussed.

Keywords: catalysis; epoxides; iron; ring expansion; salen ligands

Introduction

The synthetic usefulness of iron-catalyzed reactions, particularly in carbon-carbon bond formation processes, is mostly driven by the environmental and economic advantages associated with the use of iron catalysts in organic chemistry. In the last couple of years an increasing number of innovative applications of iron catalysts indicates that some advantageous and intriguing characteristics of iron as a transition metal in organic synthesis compared to the higher homologues and other prominent transition metals justifie a closer look at the organic chemistry of iron.[1] The iron catalysts used either are addressing an alternative substrate spectrum or different chemo- or regioselectivities can be obtained spanning wide fields of useful synthetic organic reactions.[2] Among such transformations we identified some iron catalyst systems that were able to convert epoxides into tetrahydrofurans under formal insertion of an alkene on applying reductive conditions.[3] At the beginning of the investigations the intermolecular reaction was mostly hampered by polymerization side products deriving from the radical mechanism proposed. The electron transfer from the *in situ* generated reduced iron catalyst species to the epoxide initiated the ring opening sequence of the reaction mechanism which could also have led to a radical-based polymerization. An intensive catalyst optimization led to a rather simple catalyst system consisting of a preformed Fe(Salen) complex, NEt_3 and zinc powder in acetonitrile as the solvent of choice at elevated temperatures.[4] Under these conditions the amount of polymerized side products could be minimized. This improved catalyst system was able to increase the yield of the intermolecular ring expansion reaction by 20–45% compared to $Fe(dppe)Cl_2$ or other catalyst systems containing the very prominent class of NHC ligands reported earlier.[5] Also, with the preformed Fe(Salen) catalyst the initial scope of substrates could be considerably enlarged and an increasing number of epoxides (radical donor) could be used in combination with a large number of functionalized alkenes (radical acceptor). An impressive variety of structural modifications and polyfunctionalized products suitable as building blocks for further transformations could be generated. These results prompted us to explore the scope and limitations of the iron-catalyzed ring expansion in intramolecular reactions applying internal epoxyalkene derivatives **1**. Thereby, the synthesis of bicyclic products, mainly hexahydrocyclopenta[*c*]furans **2** ($X = CH_2$) and derivatives was envisaged (Figure 1). The incorporation of heteroatoms in the linker interconnecting the epoxide and the alkene functionality should allow bicyclic systems with a heteroatom in each of the five-membered rings to be addressable, such as the class of tetrahydrofuro[3,4-*c*]furans **2** ($X = O$) and their derivatives. This type of substructure can be found in the vast variety of lignan derivatives and several cyclopentanoids (Figure 1).[6]

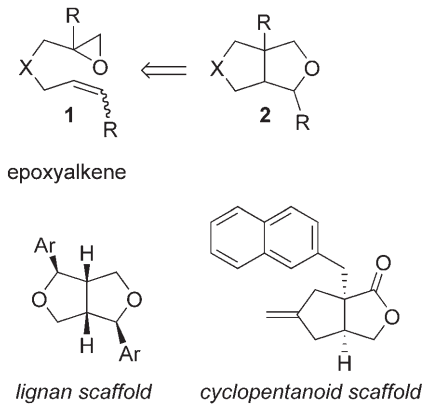


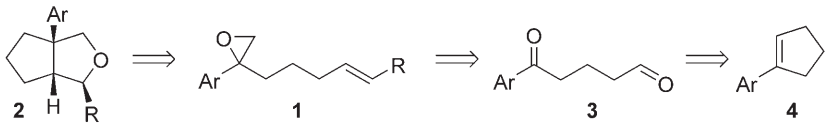
Figure 1. Retrosynthetic approach towards the lignan and cyclopentanoid scaffolds.

Results and Discussion

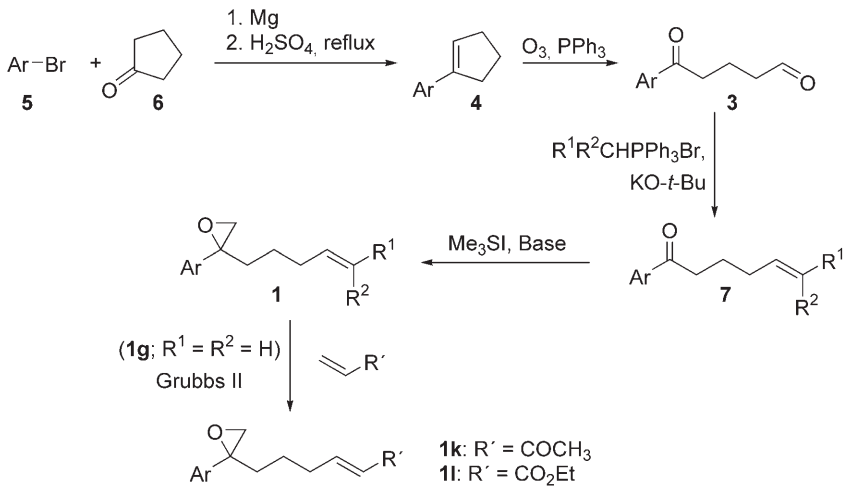
Synthesis of Epoxyalkenes

For the investigation of the key step of the intramolecular iron-catalyzed ring expansion reaction of an epoxyalkene derivative **1** leading to bicyclic products **2**, we choose a retrosynthetic approach outlined in Scheme 1. The epoxyalkene **1** should be generated from a 1,5-dicarbonyl compound **3** which is accessible from a 1-substituted cyclopentene **4**. Based on our preliminary results,[3,4] the substituent on the cyclopentene derivative **4** was chosen to be an aromatic substituent (Ar). This is based on the assumption that, in the proposed radical mechanism for the ring expansion reaction, the intermediately formed benzylic radical is stabilized by this aromatic substituent and favours the ring opening process initiated by an electron transfer from a reduced iron catalyst species to the epoxide subunit.

The synthesis of the desired epoxyalkenes of type **1** was accomplished by a reaction sequence outlined in Scheme 2. Starting from aromatic bromides **5** a Grignard reaction with cyclopentanone **6** and direct dehydration under forcing acidic conditions led to the cyclopentene derivative **4**.[7] An ozonolysis with reductive work-up utilizing triphenylphosphine generated the dicarbonyl compounds of type **3** by applying standard protocols.[7] The chemoselective functionalization of the oxo-aldehyde **3** was accomplished by a Wittig reaction which gave exclusively the oxo-alkene **7** as a mixture of the corresponding *E*- and *Z*-isomers. As could be shown recently,[5] the *E*/*Z*-stereochemistry of the alkene is irrelevant for the diastereoselectivity in an iron-catalyzed intermolecular ring expansion reaction. This indicates that a fast racemization takes place on the step of a radical intermediate. Therefore, very little attention was applied to control the stereochemistry in the olefination reaction. The formation of the epoxide subunit could then be realized by the addition of a simple sulfur ylide[8] affording the desired epoxyalkene **1** in a relatively short reaction sequence and leaving considerable flexibility for

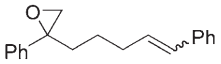
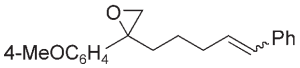
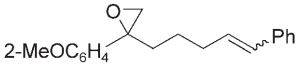
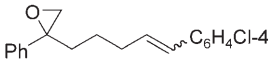
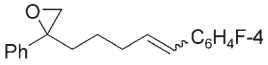
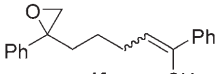
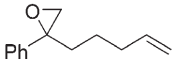
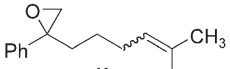
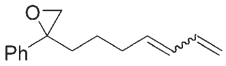


Scheme 1. Retrosynthesis of the cyclopenta[*c*]furans.



Scheme 2. Synthesis of the ring expansion precursors **1**.

Table 1. Compiled results for the synthesis of the precursors **1**.

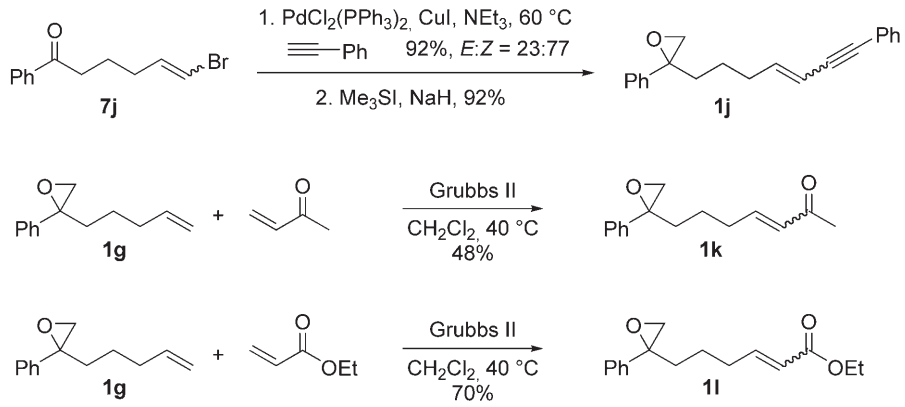
No.	Ar	Yield (**4**)	Yield (**3**)	R^1, R^2	Yield (**7**)	Yield (**1**)	Product (**1**)
1	Ph	52 %	82 %	Ph, H	61 %	94 %	 **1a**
2	4-$MeOC_6H_4$	68 %	38 %	Ph, H	61 %	76 %	 **1b**
3	2-$MeOC_6H_4$	64 %	41 %	Ph, H	43 %	92 %	 **1c**
4	Ph	-	-	4-ClC_6H_4, H	58 %	97 %	 **1d**
5	Ph	-	-	4-FC_6H_4, H	56 %	97 %	 **1e**
6	Ph	-	-	Ph, CH_3	38 %	89 %	 **1f**
7	Ph	-	-	CH_2, H	52 %	90 %	 **1g**
8	Ph	-	-	CH_3, CH_3			 **1h**
9	Ph	-	-	H_2C=CH, H			 **1i**
10	Ph	-	-	CHBr, H	75 %	-	-

the access of differently substituted starting materials. With the terminal alkene functionality (R = H, **1g**) a ruthenium-catalyzed cross-metathesis reaction led to products (**1k, 1l**) not chemoselectively accessible by the regular Wittig olefination route.

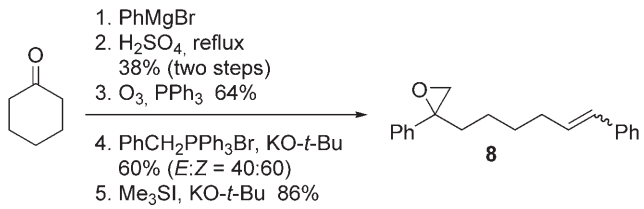
The results for the reaction sequence illustrate the flexible access towards the desired epoxyalkenes **1** by the reaction sequence. Based on the adopted procedures without an extensive optimization the desired products could be obtained in a 5–10-mmol scale within a short period of time. However, some only moderate yields were encountered when electron-rich aromatic substituents were applied in the ozonolysis which is attributed to an oxidative degradation of the aromatic nucleus and the formation of side products. Also, the Wittig olefination to afford **7** gave only moderate yields despite the observation that the chemoselectivity of this transformation was excellent for all cases resulting in the olefination of the aldehyde moiety rather than the ketone functionality. However, no efforts were undertaken to optimize the yields. Nevertheless, the desired precursors **1a–1i** for the intramolecular iron-catalyzed ring expansion reaction could be obtained in reasonable amounts to investigate the key step reaction in detail.

The bromoalkene intermediate of type **7** (Table 1, entry 10) was generated to modify this intermediate in a Sonogashira-type transformation into the enyne **1j** (Scheme 3). On the other hand, the compound **1g** (entry 7) was used to prepare some acceptor-substituted epoxy alkenes such as **1k** and **1l** by means of a ruthenium-catalyzed cross-metathesis reaction with acceptor-substituted alkenes such as methyl vinyl ketone and ethyl acrylate.

The replacement of cyclopentanone with cyclohexanone (Scheme 4) in the reaction sequence led straightforwardly to the chain-elongated higher homologue **8** which could then be tested in a ring expansion reaction leading to the bicyclic 6–5 fused ring system of the octahydroisobenzofuran derivative.



Scheme 3. Sonogashira and Grubbs cross-metathesis reactions for the synthesis of ring expansion precursors **1**.



Scheme 4. Reaction sequence for the synthesis of ring expansion precursors **8**.

Synthesis of Oxygen-Tethered Epoxyalkenes

In a further attempt to broaden the scope of the iron-catalyzed ring expansion reaction, we envisaged the use of derivatives of the epoxyalkene **1** where an oxygen-tether interconnects the epoxy and the alkene subunit either as an ether or as an ester functionality, such as in the epoxyalkenes **1m–1o** (Scheme 5). For the synthesis of **1m** the etherification was undertaken first before the epoxidation was performed in moderate yield. The alternative access was not successful because the etherification of the corresponding epoxide of 2-phenyl-3-propen-1-ol (phenylglycidol) could not be realized to give a clean enough product for further investigations. On the other hand, compound **1n** could be obtained in good yields after esterification and chemoselective epoxidation with mCPBA.

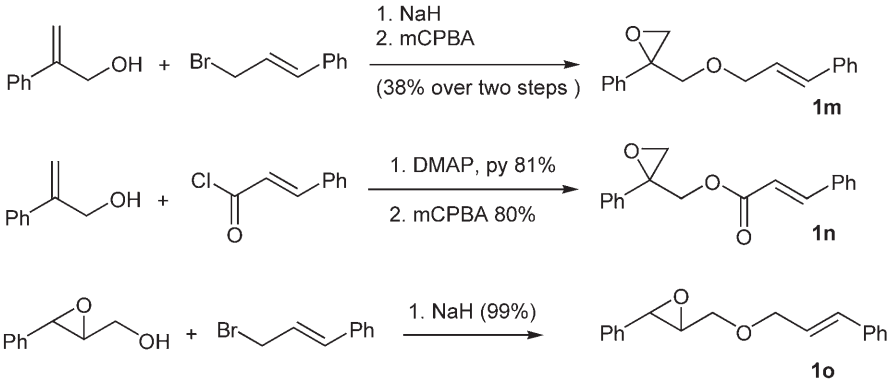
Quite in contrast to the synthesis of **1m**, compound **1o** could be obtained in excellent yields in the etherification of the phenylglycidol with cinnamyl bromide without the formation of side products.

Iron-Catalyzed Ring Expansion Reaction

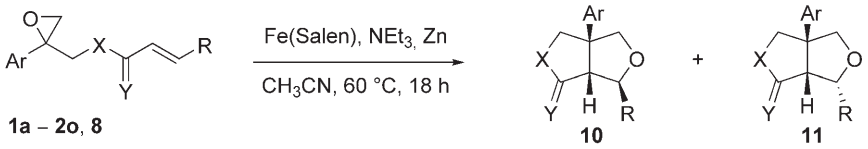
The epoxyalkenes of type **1** and the compound **8** were then applied in iron-catalyzed intramolecular ring expansion reactions utilizing the standard conditions that had proved feasible in such reactions. Therefore, the preformed Fe(Salen) complex (20 mol%), triethylamine (30 mol%), zinc powder (140 mol%) and the starting material (0.5–1.0 mmol) were heated in acetonitrile (0.5 mL) under a nitrogen atmosphere at 60 °C overnight (Scheme 6).

The results for the intramolecular iron-catalyzed ring expansion reaction are summarized in Table 2.

The intramolecular iron-catalyzed ring expansion reaction was performed with a preformed Fe(Salen) complex under identical conditions for all substrates



Scheme 5. Synthesis of heteroatom-tethered ring expansion precursors of type **1**.



Scheme 6. Iron-catalyzed ring expansion reaction.

Table 2. Results for the iron-catalyzed ring expansion reaction.

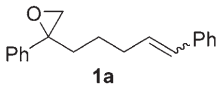
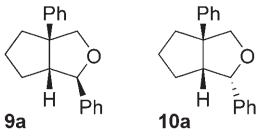
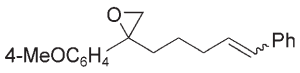
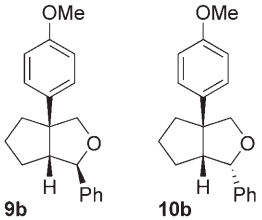
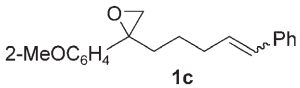
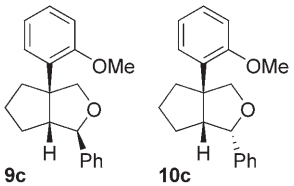
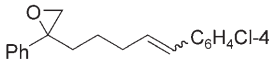
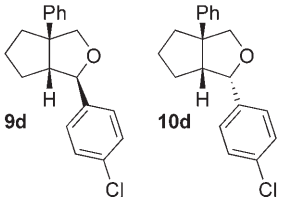
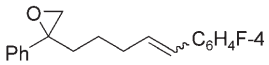
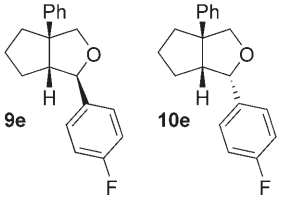
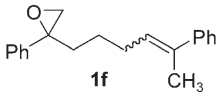
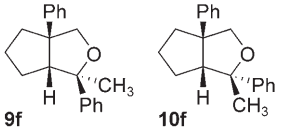
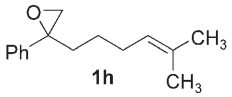
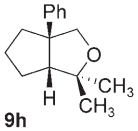
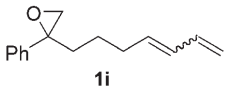
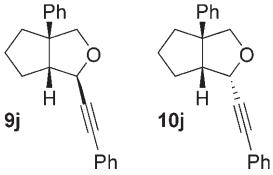
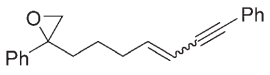
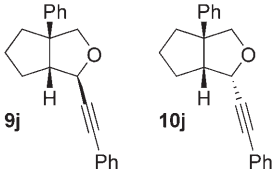
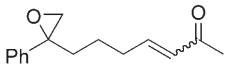
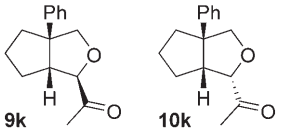
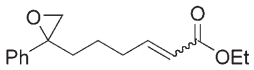
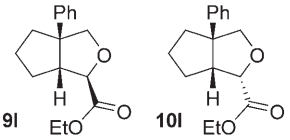
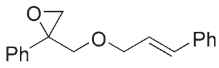
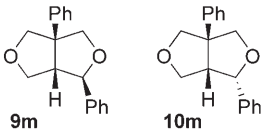
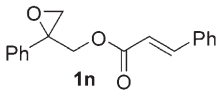
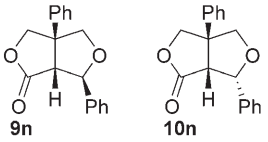
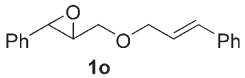
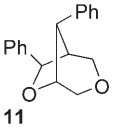
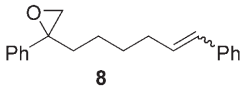
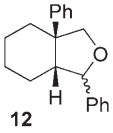
No	Epoxyalkene	Products (**9** + **10**)	Yield (ratio **9**:**10**)
1	 **1a**	 **9a** **10a**	77 % (80:20)
2	 **1b**	 **9b** **10b**	26 %[a] (98:2)
3	 **1c**	 **9c** **10c**	75 % (93:7)
4	 **1d**	 **9d** **10d**	88 % (78:22)
5	 **1e**	 **9e** **10e**	83 % (77:23)
6	 **1f**	 **9f** **10f**	79 % (96:4)
7	 **1h**	 **9h**	12 % -
8	 **1i**	 **9j** **10j**	63 % (66:34)

Table 2. (Continued)

No	Epoxyalkene	Products (**9** + **10**)	Yield (ratio **9**:**10**)
9	 **1j**	 **9j** **10j**	57 % (50:50)
10	 **1k**	 **9k** **10k**	29 % (99:1)
11	 **1l**	 **9l** **10l**	39 % (99:1)
12	 **1m**	 **9m** **10m**	67 % (93:7)
13	 **1n**	 **9n** **10n**	30 % (99:1)
14	 **1o**	 **11**	26 % (95:5[b])
15	 **8**	 **12**	traces

[a] Rearrangement to a corresponding aldehyde side-product was also observed.
[b] Combined ratio of two additional diastereomers.

listed in Table 2.[9] The ring expansion of **1a** proceeded in good yield to afford the two diastereomers **9a** and **10a** in a 80:20 ratio. The cyclization products of type **9** and **10** were all formed as the *cis*-fused cyclopenta[*c*]furan derivatives and no traces of the corresponding *trans*-fused products were detected or isolated. The introduction of a methoxy group in the benzene ring attached to the epoxide in **1b** and **1c** led to interesting results. While the ring expansion reaction proceeded in good yield with the sterically more demanding 2-methoxy derivative **1c**, the less sterically demanding 4-methoxy derivative **1b** gave only moderate yields. In addition the diastereoselectivities for these two ring expansion reactions are considerably better (up to 98:2) than for the reactions with the unsubstituted phenyl substituent attached to the radical donor epoxide functionality. This behaviour can be rationalized by the stronger electron donating character of the 4-methoxyphenyl functionalized over the 2-methoxyphenyl functionalized starting material due to increasing electron density in the epoxide. Therefore the driving force for an electron transfer from the reduced iron catalyst species to the epoxide is reduced to initiate the ring expansion. This decreased reactivity is associated with a higher selectivity in the bond formation processes to follow. Nevertheless, the electron-donating groups such as in **1b** promoted the Lewis acid-initiated ring opening of the epoxide and the formation of a rearranged aldehyde as a side product.[10] Unfortunately, this side product had an almost identical chromatographical behaviour as the desired products of type **9** and **10** so that extended column chromatography had to be employed to obtain analytically pure samples of the bicyclic prod-

ucts. This also reduced the yield for the ring expansion of the 4-methoxy-functionalized epoxyalkene **1b**. On the other hand, if the radical acceptor functionality was modified with electron-abstracting 4-chlorobenzene and 4-fluorobenzene substituents (**1d** and **1e**) the ring expansion reaction led to very good results in terms of the chemical yields while the diastereoselectivities are comparable to those with the unsubstituted phenyl derivative **1a**. The additional methyl group in **1f** led to a more stabilized radical intermediate and therefore probably increased the yield for the ring expansion reaction to give **9f** and **10f**. The considerably increased chemical yields for the substrates **1i** and **1j** compared to **1h** illustrate that acceptable to good yields are only obtained when the radical acceptor functionality, the alkene, is in conjugation to additional double or triple bond functionalities. The intermediately formed benzyl, allyl or propargyl radical intermediates seem to be essential for the ring closure reaction to occur effectively. While the formation of an allylic radical, starting from **1i** gives the desired products **9i** and **10i** in moderate yield, the ring expansion of **1h** leading to a tertiary radical is less favourable. Consequently, the observation that the unsubstituted epoxyalkene **1g** (Table 1, entry 8) did not undergo the ring expansion reaction can be rationalized. The formation of a propargylic radical for the transformation of **1j** to give **9j** and **10j** in acceptable yields takes place as a 1:1 mixture of diastereomers based on the rod-like substructure of the phenylacetylenic substituent minimizing steric interactions. For the acceptor substituted epoxyalkenes **1k** and **1l** in entries 10 and 11 of Table 2, only moderate yields were obtained, however, the products **9k** and **9l** were isolated essentially as single diastereomeres. The electron-abstracting carbonyl-type substituents in **1k** and **1l** led to a decreased reactivity and a higher selectivity based on the stronger stabilized radical intermediates. The electronic character of the substituents on the radical donor functionality as well as on the radical acceptor functionality seems to be critical for the ring expansion reaction to proceed with good yields and/or good diastereoselectivities.

Of particular interest were starting materials where additional heteroatoms or functionalities were involved leading to regioisomeric lignan and lactone derivatives. In this respect the application of the ether derivatives **1m** and **1o** as well as the ester derivative **1n** in the iron-catalyzed ring expansion reaction was investigated. The ring expansion reaction for **1m** could be optimized to give the desired products **9m** and **10m** in acceptable yields and in a good diastereoselectivity of 93:7. The ester substrate **1n** could be transformed into the diastereomerically pure lactone **9n** only in moderate yield. This is most likely based on the conformation of the ester functionality which adopts a *transoid* conformation and all attempts to induce a *cisoid* conformation did not result in a considerably increased yield.[11] The application of the internal epoxide functionality in **1o** was investigated (entry 14) to determine if the iron-induced ring expansion can be used for the formation of bridged bicyclic ring systems. Unexpectedly, the 3,6-dioxabicyclo[3.2.1]octane derivative **11** could be obtained in moderate yield but in good diastereoselectivity. This reaction not only represents the first intramolecular example of an internal epoxide functionality suitable for the iron-catalyzed ring expansion reaction, but also, an unusual strained bicyclic ring system could be obtained from simple starting materials in a short reaction sequence. Beside **11** also two additional diastereomers were detected by GC-MS, however, the low amount of these side product did not allow us to determine their structure or stereochemistry. The main product **11** could be isolated and the connectivity and relative stereochemistry could be verified by X-ray analysis. Also, the regioisomeric lignan derivative **9m** as well as the cyclopenta[*c*]furan derivative **9d** could be obtained in crystalline form suitable for X-ray analysis and their structures are shown in Figure 2.

The rather optimistic approach to verify if, in the iron-catalyzed ring expansion reaction, the main restrictions embedded in the Baldwin rules disfavouring 6-*exo*-trig cyclization for radical reaction pathways can be overcome was investigated in the use of the chain-elongated epoxyalkene **8**. As expected, the desired synthesis of the cyclohexa[*c*]furan derivative **12** (entry 15) could not be realized in more than trace amounts. The iron-catalyzed ring expansion reaction of this substrate is hampered by the disfavoured 6-*exo*-trig cyclizations for the formation of the new carbon-carbon bond. Instead, the epoxide ring opened intermediates led to a number of unidentified side products. Nevertheless, it is noteworthy to point out that the iron-catalyzed ring expansion reaction does not rely on the Thorpe–Ingold (*gem*-dimethyl) effect which is often needed in other reactions to enhance the rate of formation of mono- and bicyclic ring systems. The shown examples represent a range of substrates mostly suitable for the intramolecular iron-catalyzed ring expansion reaction. In combination with the still ongoing investigations concerning other challenging intermolecular iron-catalyzed ring expansion reactions, further improvements in terms of functional group tolerance, scope of substrates and stereochemical aspects can be expected.

Conclusions

In the iron-catalyzed intramolecular ring expansion reaction of epoxyalkenes not only considerable improvements were reported concerning the scope and

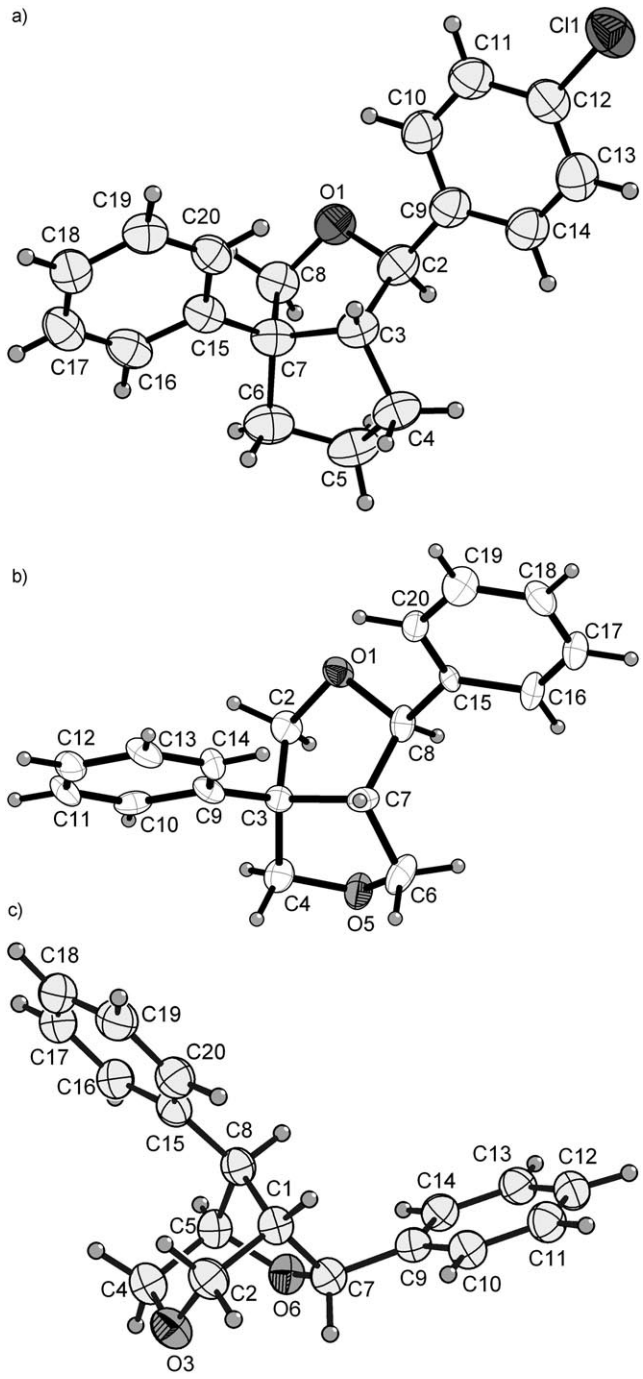


Figure 2. X-Ray structures of **9d** (*top*), **9m** (*middle*) and **11** (*bottom*).

limitations of the reaction but most importantly an insight into the electronic demands responsible for high yield or good to excellent diastereoselectivities were obtained. Generally, the radical donor epoxide functionality will lead to good results in terms of reactivity and selectivity when moderately electron-enriched arene substituents are attached to the epoxide. On the other hand, the stabilization of an intermediately formed radical in the radical acceptor functionality can most efficiently be realized when hyperconjugation effects are combined with mesomeric stabilization of these radicals in allylic, benzylic or propargylic positions. Also, excellent diastereoselectivities were observed with ketone- or ester-functionalized double bonds as radical acceptors. The application of an internal epoxide was realized in combination with the formation of a rather unusual dioxobicyclic ring system (**11**). These results illustrate that the application of iron catalysts in organic chemistry can generate rather complex bicyclic systems in mostly good diastereoselectivities and moderate to good yields in a short reaction sequence. Further investigations based on these results will lead to new and innovative approaches towards cyclopenta[*c*]furans and other derivatives.

Experimental Section

General Remarks

NMR-spectra were recorded on a Bruker Avance 300 or DRX 500 (^{1}H: 300 MHz or 500 MHz, ^{13}C: 75 MHz or 125 MHz) spectrometer using TMS as internal standard ($\delta = 0$) unless otherwise noted. MS and GC/MS were measured on a Hewlett Packard 6890 GC-System including a Hewlett Packard 5973 Mass Selective Detector. For (high resolution) mass spectra a Finnigan MAT 95S and a Finnigan LTQ (ESI, HRMS) spectrometer were used. Analytical thin layer chromatography was performed on Merck silica gel 60 F254. For column chromatography Merck silica gel 60 (230–400 mesh ASTM) was used. All reactions were carried out under an inert atmosphere (nitrogen or argon) using standard Schlenk techniques. Dichloromethane and acetonitrile were dried over phosphorus pentoxide, tetrahydrofuran and diethyl ether over sodium.

The Grignard Reaction and the following dehydration for the synthesis of the cyclopentene derivatives **4**, the ozonolysis under reductive work-up for the generation of the keto aldehydes **3** and the Wittig olefination reaction to obtain the keto alkenes **7** were performed following known or adopting similar literature procedures.

Epoxidation

Sodium hydride (60% in mineral oil, 4.0 equivs.) was suspended in dimethyl sulfoxide. The suspension was carefully heated until a gas evolution started. Then the solution was stirred for 20 min, the four-fold amount of tetrahydrofuran (DMSO:THF = 1:4) was added and cooled to 0 °C. After the addition of trimethylsulfonium iodide (4.0 equivs.) the solution was stirred for 1 h at 0 °C and then the ketone was added. After stirring for 24 h at room temperature the solution was diluted with water and methyl *tert*.-butyl ether was added. The phases were separated and the water phase was extracted with methyl *tert*.-butyl ether three times. The combined organic phases were washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography

and 3% triethylamine was added to the eluent to avoid the rearrangement of the epoxide.

Grubbs Cross-Metathesis

The Grubbs II catalyst (5 mol%) was suspended in dichloromethane and then the alkene (2.0 equivs.) and the epoxyalkene (1.0 equiv.) were added. The solution was stirred at 40°C overnight, filtered over a small pad of silica (eluent: Et_2O) and concentrated. The residue was purified by column chromatography and 3% triethylamine was added to the eluent to avoid the rearrangement of the epoxide.

Sonogashira Cross-Coupling Reaction

To a solution of phenylacetylene (2.1 equivs.) in triethylamine the bromoalkene (1.0 equiv.) copper(I) iodide (5 mol%) and bis(triphenylphosphino)palladium(II) chloride (5 mol%) were added. After the solution had been stirred at 60°C overnight the mixture was concentrated under reduced pressure and filtered over a small pad of silica (eluent: Et_2O). The solution was concentrated and the residue was purified by column chromatography.

Intramolecular Fe(II)Salen-Catalyzed Ring Expansion Reaction

Fe(II)Salen (20 mol%) and zinc (140 mol%) were suspended in 0.5 mL of acetonitrile and triethylamine (30 mol%) was added. Then the solution was heated until boiling. Afterwards, the epoxyalkene (0.5–1.0 mmol) was added by syringe and the solution was stirred at 60°C for 15–20 h. Then the mixture was filtered over a pad of silica (eluent: diethyl ether) and concentrated under reduced pressure. The residue was purified by column chromatography.

References

[1] Recent review for the application of iron-catalysts and reagents in organic synthesis: C. Bolm, J. Legros, J. Le Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217; A. Fürstner, R. Martin, *Chem. Lett.* **2005**, *34*, 624; D. D. Diaz, P. O. Miranda, J. L. Padron V. S. Martin, *Curr. Org. Chem.* **2006**, *10*, 457.

[2] For some selected recent applications see: M. Seitz, W. Milius, H. G. Alt, *J. Mol. Catal. A: Chemical* **2007**, *261*, 246; G. Anilkumar, B. Bitterlich, F. G. Gelalcha, M. K. Tse, M. Beller, *Chem. Commun.* **2007**, 289; B. Plietker, *Angew. Chem.* **2006**, *118*, 1497; *Angew. Chem. Int. Ed.* **2006**, *45*, 1469; S. Enthaler, B. Hagemann, G. Erre, K. Junge, M. Beller, *Chem. Asian J.* **2006**, *1*, 598; M. W. Bouwkamp, A. C. Bowman, E. Lobkovsky, P. J. Chirik, *J. Am. Chem. Soc.* **2006**, *128*, 13340 I. Sapountzis, W. Lin, C. C. Kofink, C. Despotopoulou, P. Knochel, *Angew. Chem.* **2005**, *117*, 1682; *Angew. Chem. Int. Ed.* **2005**, *44*, 1654; A. Fürstner, R. Martín, K. Majima, *J. Am. Chem. Soc.* **2005**, *127*, 12236.

[3] G. Hilt, P. Bolze, I. Kieltsch, *Chem. Commun.* **2005**, 1996.

[4] G. Hilt, C. Walter, P. Bolze, *Adv. Synth. Catal.* **2006**, *348*, 1241.

[5] G. Hilt, P. Bolze, K. Harms, *Chem. Eur. J.* **2007**, *13*, in press.

[6] I. J. S. Fairlamb, S. Grant, G. Grogan, D. A. Maddrell, J. C. Nichols, *Org. Biomol. Chem.* **2004**, *2*, 1831; H. Lavreysen, S. N. Pereira, J. E. Leysen, X. Langlois, A. S. J. Lesage, *Neuropharmacology* **2004**, *46*, 609.

[7] J.-L. Hsu, J.-M. Fang, *J. Org. Chem.* **2001**, *66*, 8573.

[8] J. A. Ciaccio, A. L. Drahus, R. M. Meis, C. T. Tingle, M. Smrtka, R. Geneste, *Synth. Commun.* **2003**, *33*, 2135; C. H. Heathcock, E. P. Lodge, *J. Am. Chem. Soc.* **1987**, *109*, 3353.

[9] Neither the use of polar solvents such as NMP nor diluted reaction conditions led to enhanced yields.

[10] C. Lemini, M. Ordonez, J. Perez-Flores, R. Cruz-Almanza, *Synth. Commun.* **1995**, *25*, 2695.

[11] Neither the addition of Lewis acids leading to a *cisoid* conformation of the ester functionality in **1n** nor the addition of orthoesters leading to the formation of orthoesters of **1n** did result in enhanced yields.

