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Iron-Salen Complexes as Efficient Catalysts in Ring Expansion Reactions of Epoxyalkenes

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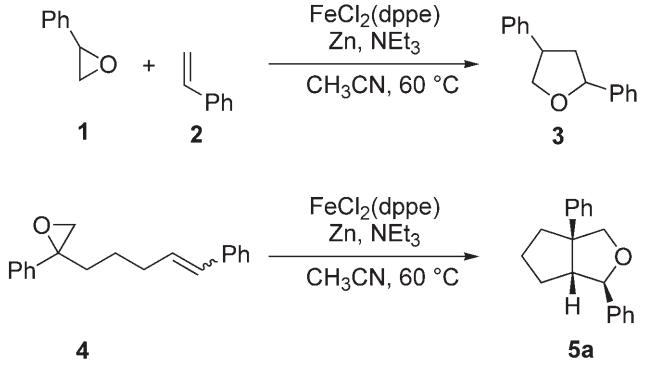
Dedicated to Prof. Ryoji Noyori on the occasion of his 68th birthday.

Abstract: The optimisation of the iron-catalysed ring expansion reaction of epoxyalkenes was considerably improved when the original phosphine ligand system [$FeCl_2$(dppe)] was altered to include nitrogen-containing ligand systems. Especially, the very potent class of salen ligands gave the best results in inter- and intramolecular ring expansion reactions. With a preformed iron(II)-salen complex the yields and diastereoselectivities were greatly enhanced and the scope of the reaction could also be enlarged.

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

Introduction

Iron-catalysed reactions in organic synthesis have been a long-time goal for many organic chemists due to the low toxicity and the abundance of many iron salts and compounds. Among these iron-catalysed reactions are carbon-carbon bond formation processes, cycloadditions, cross-coupling reactions and aldol-type reactions, just to name a few of the most relevant transformations.[1] It can be assumed that in some iron-catalysed reactions lower oxidation states are the active species in the catalytic cycle. Therefore, the active species are often generated *in situ* upon the addition of an appropriate reducing agent. In an attempt to investigate carbon-carbon bond formation processes with low-valent iron species, we found that a ring expansion of epoxides **1** takes place when iron-phosphine complexes are reduced with zinc powder in the presence of triethylamine and an alkene **2**.[2] Thereby, tetrahydrofuran derivatives **3** are generated in an intermolecular approach from readily available starting materials (Scheme 1). However, polymerisation side reactions could only be suppressed when intramolecular reactions were investigated. Under these circumstances the epoxide ring expansion of **4** gives rise to the formation of bicyclic compounds such as **5a.**[3]

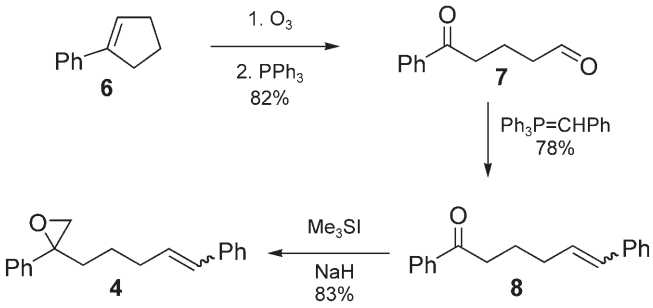


Scheme 1. Inter- and intramolecular iron-catalysed ring expansion reactions.

Results and Discussion

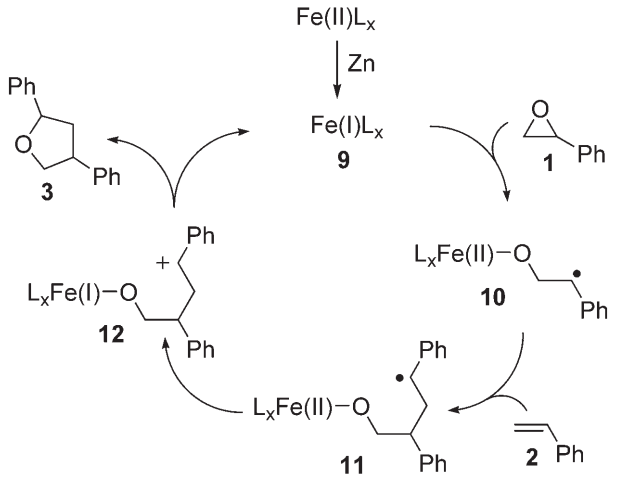
The epoxyalkene **4** (Scheme 1) needed for the intramolecular epoxide ring expansion reaction is prepared from 1-phenylcyclopent-1-ene (**6**) which is converted into **7** in an ozonolysis followed by reductive work-up in 82% yield (Scheme 2).[4] A chemoselective Wittig olefination converts the aldehyde into the alkene **8** in 78% yield as an *E/Z* mixture (1.0:1.5). The following epoxidation of the ketone **8** *via* sulfur ylides produces the desired epoxyalkene **4** (79%) in a straightforward reaction sequence in good overall yield.

The iron-catalysed ring expansion reaction is believed to be initiated by a single electron transfer (SET) from the low-valent iron species **9** to the epoxide **1** which is coordinated to the iron centre.[5] Accordingly, due to the reaction mechanism proposed



Scheme 2. Reaction sequence for the synthesis of the substrate **4**.

for the ring expansion reaction, as outlined in Scheme 3, it can be assumed that the carbon-carbon (reaction from **10** to **11**) and the carbon-oxygen bond formation processes (reaction from **11** to **3**) proceed within the ligand sphere of the iron complex. A back



Scheme 3. Proposed mechanism for the intermolecular iron-catalysed ring expansion reaction.

electron transfer (BET) generates the stabilised carbocation **12** which cyclises to the product **3**. At this stage the diastereoselectivity is controlled by the ligands of the iron catalyst. Therefore, modifications in the ligand sphere are supposed to have a profound influence on the reactivity as well as on the diastereoselectivity of the reaction.

Ligand Screening

For testing the influence on the diastereoselectivity of the iron-catalysed process, the catalysts were generated *in situ* prior to the reduction of the complex with zinc powder in acetonitrile. As a starting point the preliminary results using the $FeCl_2$(dppe) complex yielding **5** in 83% and a 93:7 *cis*:*trans* diastereoselectivity were chosen as comparison for the investigation.[2] Several different ligand types (Figure 1) were tested in the reaction of **4** with respect to the diastereoselectivity for the generation of **5a** and **5b** while the yields were not optimised at this stage (Scheme 4).

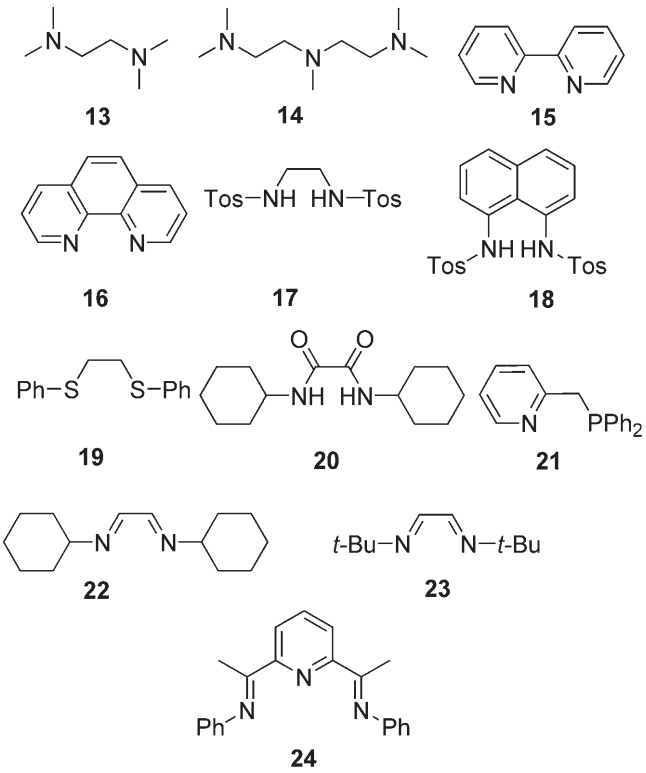
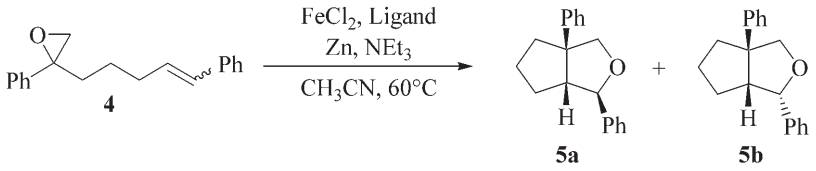


Figure 1. Amine-type ligands applied in the iron-catalysed ring expansion reaction of **4**.

The ring expansion reaction did not proceed at all when simple amine-type ligands such as the bidentate ligand **13**, the tridentate amine ligand **14**, bipyridine (**15**) or phenanthroline (**16**) were used (Table 1). To-



Scheme 4. Intramolecular iron-catalysed ring expansion reaction of **4**.

Table 1. The iron-catalysed ring expansion reaction of **4** with ligands **13–24**.

Entry[a]	Ligand	Yield	**5a:5b** (*cis*:*trans*)
1	**13**	0%	-
2	**14**	0%	-
3	**15**	0%	-
4	**16**	0%	-
5	**17**	0%	-
6	**18**	0%	-
7	**19**	0%	-
8	**20**	14%[b,c]	93:7
9	PPh_3 (4 equivs.)	20%[b,c]	80:20
10	**21**	27%[b,c]	91:9
11	**22**	5%[b,c]	94:6
12	**23**	28%[b,c]	94:6
13	**24**	30%	95:5

[a] *Reaction conditions:* iron complex (30 mol %), zinc (2.0 equivs.), NEt_3 (45 mol %), CH_3CN (1.0 mL), **4** (50 mg, 189 μmol), 20 h, 60 °C.
[b] Incomplete conversion.
[c] (Unidentified) side products (>5%) were detected by GC-MS.

sylated amine ligands such as **17** and **18** as well as the disulfide ligand **19** also gave no conversion of the starting material, whereas the oxalyl diamide ligand **20** yielded the desired compound in 14% yield with a good diastereoselectivity of 93:7. With triphenylphosphine (entry 9) or the P,N ligand (**21**) the reactivity of the catalysts was further restored. Compared to the benchmark reaction performed with the dppe ligand (Scheme 1), however, side products were detected by GC-MS while the starting material was not completely consumed. The yields of the mixture of products **5a** and **5b** were considerably lower with 20% (for PPh_3 as ligand) and 27% (for **21** as ligand), respectively. The reactivities of the diimine-type ligands such as **22** and **23** were on similar levels but also side products could be detected while the conversion was not complete after 20 h. However, the desired products were obtained in good diastereoselectivity, **5a**:**5b** = 94:6 (Table 1). The pyridine-diimine ligand **24** gave acceptable yields of 30% and the diastereomers were formed in a good selectivity of 95:5. Although the yields were considerably lower than with the dppe ligand (83%), a noticeable effect on the *cis-trans* diastereoselectivity of the reaction was observed (see Table 1, entries 9 and 12/13) . Accordingly, it must be concluded that the assumption that the bond formation processes take place in the ligand sphere of the iron catalysts was correct and that further investigation regarding other ligands are reasonable.

The salen-type ligands and structurally related ligands (Figure 2) were then tested in the intramolecular iron-catalysed ring expansion reaction of **4**. The

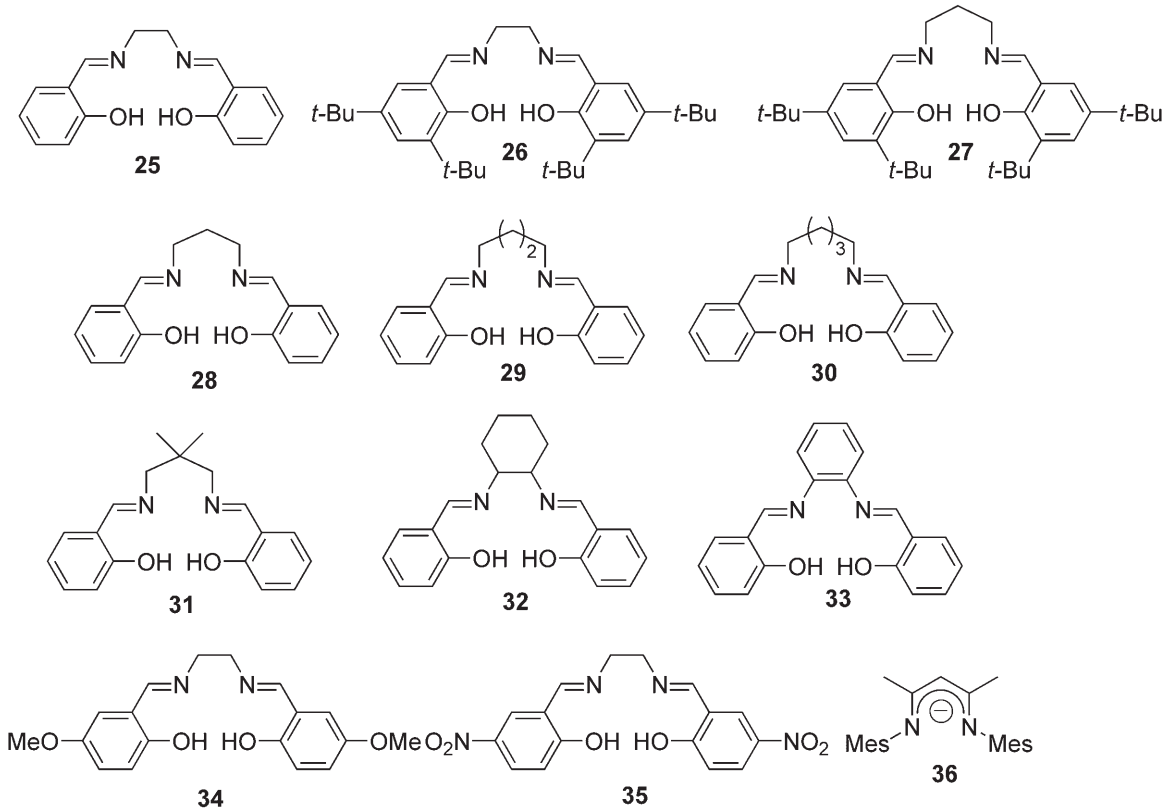


Figure 2. Salen-type ligands applied in the iron-catalysed ring expansion reaction of **4**.

Table 2. The iron-catalysed ring expansion reaction of **4** with ligands **25–36**.

Entry[a]	Ligand	Yield	**5a:5b** (*cis*:*trans*)
1	**25**	65 %	83:17
2	**26**	40 %	96:4
3	**27**	58 %	94:6
4	**28**	61 %	87:13
5	**29**	22 %	91:9
6	**30**	35 %	89:11
7	**31**	40 %	89:11
8	**32**	44 %	87:13
9	**33**	61 %	80:20
10	**34**	61 %	83:17
11	**35**	56 %	83:17
12	**36**	29 %[b]	99:1

[a] *Reaction conditions:* iron complex (30 mol %), zinc (2.0 equivs.), NEt_3 (45 mol %), CH_3CN (1.0 mL), **4** (50 mg, 189 μmol), 20 h, 60 °C.
[b] Incomplete conversion.

results summarised in Table 2 show that the salen-type ligands are better suited for the reaction than the previously discussed ligands. While the product mixtures of **5a** and **5b** are generated in acceptable yields of up to 65 % (entry 1) acceptable to very good *cis*:*trans* selectivities of up to 96:4 (entry 2) can be observed without optimisation at this stage. Interestingly, the amounts of side products detectable by GC-MS or TLC were considerably reduced and the starting materials were completely consumed. Nevertheless, the mass balance suggests that some polymerisation side products could have been formed. On the other hand, small losses during the work-up on the small scale applied (189 μmol) easily result in > 10 % loss of material and yield. When the carbon backbone of the salen ligand was stepwise elongated by one carbon at a time (**25**, **28**, **29** and **30**) it could be seen that the reactivities for the ligands **25** and **28** are comparable to the benchmark dppe ligand and drop when longer carbon backbones are involved. On the other hand, the selectivity is slightly enhanced and reaches 91:9 for **29**. The introduction of bulky substituents on either the phenyl substituent of the salen-type ligands (**26**, **27**) or in the backbone of the salen-type ligands (**31**, **32** and **33**) has an effect both on the diastereoselectivities as well as on the yields of the reaction. While in the case of the modifications on the phenyl ring (**26** and **27**), inspired by the work of Jacobsen,[6] the introduction of *tert*-butyl substituents increased the diastereoselectivity to excellent levels while the yield was somewhat diminished for **26**. On the other hand, electronic modifications of the salen-type ligands on the phenyl rings (**34** and **35**) gave almost identical results with around 60 % yields and identical diastereoselectivities of 83:17. However, substituents in the backbone (**31**, **32**, **33**) decreased the *cis*:*trans* ratio while the yields of the desired product were again in an acceptable range. Almost exclusive diastereoselectivities (99:1) were obtained with ligand **36**. Unfortunately, the yields were rather low and the conversion was incomplete after 20 h reaction time. Accordingly, the ligand design would favour sterically bulky substituents on the phenyl ring for a better diastereoselectivity and a possible chiral modification in the carbon backbone as realised in the Jacobsen ligand for possible enantioselective versions of the reaction which have not been the subject of this investigation so far.

Even though good candidates in the salen-type ligand series have already been identified for the iron-catalysed ring expansion reaction. Nevertheless, also the salicylenimine-type ligands shown in Figure 3

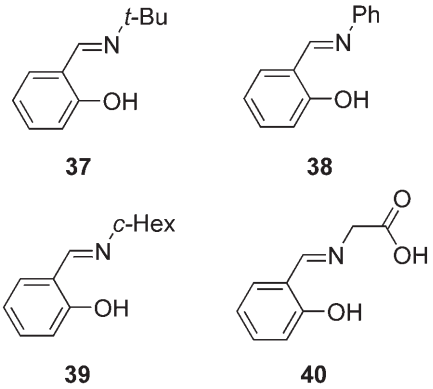


Figure 3. Salicylenimine-type ligands applied in the iron-catalysed ring expansion reaction of **4**.

were investigated in the iron-catalysed reaction. Although the iron to ligand ratio was altered (1.0 and 2.0 equivs. of ligands were used) almost identical yields and diastereoselectivities were observed for the salicylenimine-type ligands **37**, **38** and **39** (Table 3, en-

Table 3. The iron catalysed ring expansion reaction of **4** with ligands **37–40**.

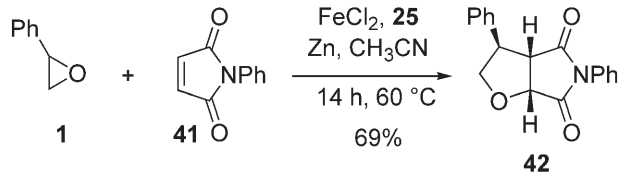
Entry[a]	Ligand	Yield	**5a:5b** (*cis*:*trans*)
1	**37**	16 %[b,c]	90:10
2	**37** (2 equivs.)	20 %[b,c]	86:14
3	**38**	22 %[b,c]	90:10
4	**38** (2 equivs.)	20 %[b,c]	89:11
5	**39**	20 %[b,c]	95:5
6	**39** (2 equivs.)	18 %[b,c]	95:5
7	**40**	44 %[b,c]	90:10

[a] *Reaction conditions:* iron complex (30 mol %), zinc (2.0 equivs.), NEt_3 (45 mol %), CH_3CN (1.0 mL), **4** (50 mg, 189 μmol), 20 h, 60 °C.
[b] Incomplete conversion.
[c] (Unidentified) side products (> 5 %) were detected by GC-MS.

tries 1–6). Furthermore, an interesting ligand motif derived from an α-amino acid was tested (**40**), which would allow a simple access to chiral iron complexes. However, in all cases the conversion was not complete and varying amounts of side products were detected. Therefore, the salen-type ligands, which can easily be accessed and sterically as well as electronically modified, seem to be the most promising candidates for further investigations.

The oxidation state of the iron precursor did not have a large effect on the reaction of **4**. When iron(II) chloride was used as precursor for the *in situ* generated salen complex with ligand **25**, a 65% yield and a diastereoselectivity of 83:17 were found. Similar results were found when iron(III) chloride was used as iron source with ligand **25** (59% yield, 80:20). Therefore, we assume that the reducing agent (zinc powder) converts the two complexes to identical low-valent iron species.

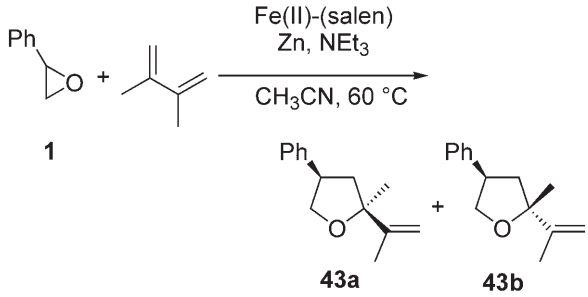
The good results for the iron-salen complex (ligand **28**) were then further optimised on a larger scale and in these reactions (1.0 mmol) easily up to 88% yields of the isolated bicyclic product **5** were achieved.[7] A further application and a considerable enlargement of the substrate scope were realised in the iron-salen-catalysed intermolecular reaction of styrene oxide (**1**) with **41** (Scheme 5).



Scheme 5. Intermolecular iron-catalysed ring expansion reaction with an internal double bond.

In this reaction, for the first time, an internal acceptor-substituted double bond was brought to reaction and the yield of 69% is excellent compared to earlier results in intermolecular reactions.[2] Furthermore, the product **42** was isolated as a single diastereomer with a *trans* correlation of the phenyl substituent and the imide moiety as was concluded from the coupling constants of the corresponding protons of 7.4 and 3.0 Hz, nOe experiments and an X-ray structure of **42**.

Another most considerable improvement in the iron-catalysed ring expansion reaction was achieved when the preformed Fe(II)-(salen) complex was used in the intermolecular reaction of styrene oxide (**1**) with 2,3-dimethyl-1,3-butadiene to yield the tetrahydrofuran derivatives **43a** and **b** (Scheme 6). In this reaction with the preformed iron-salen complex the regio- and diastereoselectivities are also very good but the yield of these quite polymerisation-sensitive



Scheme 6. Intermolecular iron catalysed ring expansion reaction with the 2,3-dimethyl-1,3-diene.

starting materials is enhanced considerably, **43** was obtained in 83% as a 4.2:1.0 mixture of **43a**:**43b** as single regioisomers.

Therefore, the preformed iron-salen complexes seem to be a very useful catalyst motif for further inter- and intramolecular epoxide ring expansion reactions for the synthesis of regiochemically, diastereo- and (hopefully) enantiomerically pure tetrahydrofuran and bicyclic heterocyclic ring systems.

Conclusions

In the iron-catalysed ring expansion reaction of epoxyalkenes considerable improvements are realised when the original phosphine ligand system [$FeCl_2$(dppe)] is altered to include nitrogen-containing ligand systems. Thereby, the very potent class of salen ligands (**26**, **27**) gave the best results concerning the yields and the diastereoselectivity in an intramolecular test reaction. When the reaction was performed with a preformed iron-salen complex the yields of intra- and intermolecular epoxide ring expansion reactions were greatly enhanced. Also, for the first time, internal alkenes could be used as substrates in intermolecular ring expansion reactions so that the scope of the iron-catalysed process was enlarged during this study.

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. Mass and GC-mass spectra 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 inert atmosphere (nitrogen or argon) using standard Schlenk techniques. Dichloromethane and acetonitrile were dried over phosphorus pentoxide, tetrahydrofuran and diethyl ether over sodium. 5-Oxo-5-phenylpentanal (**7**) was synthesised according to the literature method of Hsu.[3] The ligands were prepared according to or by adapting literature methods.[8] For the larger scale reaction the Fe(II)-(salen) complex was synthesised by an adapted method.[9]

1,6-Diphenylhex-5-en-1-one (8)

Potassium *tert*-butoxide (15.0 mmol, 1.68 g) was suspended in 70 mL of dichloromethane and cooled to 0 °C. Benzyltriphenylphosphonium bromide was added and the solution turned red. After stirring for 10 min, the solution was cooled to −78 °C and **7** (12.5 mmol, 2.21 g) dissolved in 20 mL of dichloromethane was slowly added by syringe. The solution was kept at −78 °C for 1 h and stirred at room temperature for 20 h. After addition of water (100 mL) the phases were separated and the water phase was extracted with dichloromethane (3 × 30 mL). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate/pentane, 1:10) to afford **8** as a colourless oil as a mixture of diastereomers (*E*:*Z* = 1.0:1.4); yield: 2.47 g (9.8 mmol, 78 %). ^{1}H NMR (300 MHz, $CDCl_3$; main diastereomer, *Z*-isomer): δ = 7.99–7.91 (m, 2H). 7.60–7.16 (m, 8H), 6.47 (d, 1H, *J* = 11.8 Hz), 5.69 (dt, 1H, *J* = 11.6, 7.2 Hz), 2.99 (t, 2H, *J* = 7.3 Hz), 2.44 (qd 2H, *J* = 7.5, 1.8 Hz), 1.89–1.86 (m, 2H). Further resolved signals of the minor diastereomer (*E*-isomer): δ = 6.42 (d, 1H, *J* = 16.0 Hz), 6.23 (dt, 1H, *J* = 15.8, 6.8 Hz), 3.03 (t, 2H, *J* = 7.3 Hz), 2.33 (q, 2H, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$; main diastereomer, *Z*-isomer): δ = 199.9, 137.4, 136.8, 132.8, 131.8, 129.5, 128.6, 128.4, 128.0, 127.8, 126.4, 37.8, 27.9, 24.2. Further resolved signals of the minor diastereomer (*E*-isomer): δ = 200.0, 137.5, 136.9, 130.5, 129.8, 128.3, 126.8, 125.8, 37.6, 32.3, 23.6. MS (EI): *m/z* (%) = 250 (M^+, 3), 130 (100), 115 (12), 105 (10), 91 (3), 77 (16), 51 (2); HM-RS (EI): *m/z* = 250.1353, calcd. for $C_{18}H_{18}O$: 250.1358.

2-Phenyl-2-(5-phenyl-pent-4-en-1-yl)oxirane (4)

Sodium hydride (162 mg, 60 % in mineral oil, 6.6 mmol) was suspended in 5 mL of dimethyl sulfoxide. The suspension was carefully heated until gas evolution started. Then the solution was stirred for 20 min, 40 mL of tetrahydrofuran were added and the mixture was cooled to 0 °C. After the addition of trimethylsulfonium iodide (1.10 g, 6.0 mmol) the solution was stirred for 1 h at 0 °C, compound **8** (500 mg, 2.0 mmol) was added by syringe and the mixture stirred for 24 h at room temperature. Then the solution was diluted with water (50 mL) and methyl *tert*-butyl ether (50 mL) was added. The phases were separated and the water phase was extracted with methyl *tert*-butyl ether (3 × 50 mL). The combined organic phases were washed with water (50 mL), brine (50 mL), dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (triethylamine:ethyl acetate:pentane = 1:5:100) to yield **4** as a colourless oil as a mixture of diastereomers (*E*:*Z* = 1.0:1.5); yield: 420 mg (1.6 mmol, 80 %). ^{1}H NMR (300 MHz, $CDCl_3$; main diastereomer, *Z*-isomer): δ = 7.66–7.44 (m, 10H), 6.67 (d, 1H, *J* = 11.6 Hz), 5.85 (dt, 1H, *J* = 11.7, 7.0 Hz), 3.19 (d, 1H, *J* = 5.3 Hz), 2.97 (d, 1H, *J* = 5.3 Hz), 2.66–2.57 (m, 2H), 2.06–1.90 (m, 2H), 1.90–1.69 (m, 2H). Further resolved signals of the minor diastereomer (*E*-isomer): δ = 6.41 (dt, 1H, *J* = 15.9, 6.9 Hz), 3.22 (d, 1H, *J* = 5.3 Hz), 2.53–2.43 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$; main diastereomer, *Z*-isomer): δ = 139.8, 137.5, 132.2, 129.1, 128.6, 128.3, 128.2, 128.0, 127.3, 126.4, 125.8, 55.4, 34.9, 28.3, 25.1. Further resolved signals of the minor diastereomer (*E*-isomer): δ = 139.9, 137.6, 130.2, 130.1, 128.8, 128.3, 60.1, 34.8, 32.7, 24.5. MS (EI): *m/z* (%) = 264 (M^+, 1), 250 (3), 144 (3), 130 (100), 115 (27), 105 (16), 91 (21), 77 (27), 65 (4), 51 (7). HM-RS (EI): *m/z* = 264.1519, calcd. for $C_{19}H_{20}O$: 264.1514.

General Procedure for Iron-Catalysed Intramolecular Ring Expansion of Epoxides (Ligand Screening)

Iron dichloride (7 mg, 57 μmol), the ligand (57 μmol or 114 μmol when 2.0 equivs. of ligand were applied) and zinc (25 mg, 378 μmol) were suspended in 1.0 mL of acetonitrile and triethylamine (9 mg, 85 μmol, 10 μL) was added. Then the solution was heated until boiling. Afterwards, the epoxyalkene **4** (50 mg, 189 μmol) was added by syringe and the solution was stirred at 60 °C for 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 (ethyl acetate:pentane, 1:50)

1,3a-Diphenylcyclopenta[*c*]tetrahydrofuran (5a)

According to the general procedure the product **5** was obtained as a colourless oil. Yields and diastereoselectivities, see Tables 1–3. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.08 (m, 10H), 4.45 (d, 1H, *J* = 7.6 Hz), 4.20 (d, 1H, *J* = 9.0 Hz), 3.75 (d, 1H, *J* = 9.0 Hz), 2.79–2.68 (m, 1H), 2.09–1.73 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): *d* = 148.8, 142.0, 128.4, 128.3, 127.3, 125.9, 125.8, 125.7, 88.8, 80.8, 60.7, 60.2, 37.7, 30.9, 25.0; MS (EI): *m/z* (%) = 264 (M^+, 25), 234 (37), 191 (17), 173 (17), 158 (100), 143 (80), 129 (72), 115 (67), 105 (35), 91 (95), 77 (41), 67 (18), 51 (15); HR-MS (EI): *m/z* = 264.1508, calcd. for $C_{19}H_{20}O$: 264.1514.

3,5-Diphenyltetrahydrofuro[2,3-*c*]pyrrole-4,6-dione (42)

Fe(II)-(salen) (64 mg, 0.20 mmol) and zinc powder (91 mg, 1.40 mmol) were suspended in 1.0 mL of acetonitrile and triethylamine (30 mg, 0.30 mmol, 42 μL) was added. Then the mixture was heated until boiling. After 5 min, *N*-phenyl-

maleimide (173 mg, 1.00 mmol) and styrene oxide (360 mg, 3.00 mmol, 0.34 mL) were added. After stirring for 14 h at 60 °C the mixture was filtered through a pad of silica (eluent: diethyl ether) and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate:pentane, 1:4) to furnish the diastereomerically pure product 42 as a white solid; yield: 202 mg (0.69 mmol, 69 %); mp 166–168 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.53$–7.48 (m, 2H). 7.42–7.29 (m, 8H), 5.08 (d, 1H, $J = 7.4$ Hz), 4.23–4.18 (m, 2H), 3.88–3.84 (m, 1H), 3.60 (dd, 1H, $J = 7.4$, 3.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 175.0, 173.1, 140.9, 131.3, 129.2, 129.1, 128.9, 127.5, 126.8, 126.2, 77.9, 74.5, 53.2, 49.0; MS (ESI): *m/z* (%) = 316 (M^+ + Na, 100), 294 (10), 277 (45), 198 (5); HRMS (ESI): *m/z* = 316.0944, calcd. for $C_{18}H_{15}NNaO_3$: 316.0950.

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