An iron-catalysed chemo- and regioselective tetrahydrofuran synthesis†

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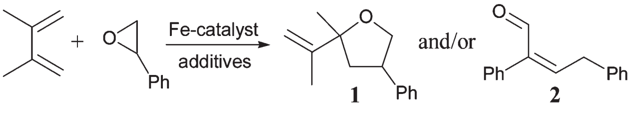
An intermolecular ring expansion reaction of an aryl epoxide with several dienes, acrylates, enynes or styrenes under iron catalysis, generated tetrahydrofuran derivatives in a highly chemo- and regioselective fashion. The process could be used in an unprecedented way for the one step synthesis of racemic calyxolane A and calyxolane B with acceptable diastereoselectivity.

The synthesis of small heterocyclic compounds, and particularly of tetrahydrofuran derivatives, from common starting materials with a high degree of chemo-, regio- and stereoselectivity has been a target of synthetic chemists for a long time. Recent approaches with various reagents or catalyst systems, to achieve an efficient synthesis of polysubstituted THF derivatives, show the urgent need for new synthetic methods.[1]

Herein we report an iron-catalysed ring expansion reaction[2] of epoxides with alkenes to generate polysubstituted tetrahydrofuran derivatives from readily available starting materials under mild reaction conditions. The most reactive and selective catalyst system that was found consisted of a simple iron salt such as iron dichloride, a reducing agent such as zinc powder, triethylamine as a base and a two component ligand system, in acetonitrile as solvent of choice, at 60 °C. We found that mixtures of phosphine and an N-heterocyclic carbene ligand[3] exhibit the most reactive ligand systems and in particular, an equimolar mixture of iron dichloride, triphenylphosphine and an NHC-ligand gave the best results within this study.[4] With this combination of additives we were able to obtain ring expansion products from styrene oxide with several alkenes conjugated with another unsaturated functionality, such as 2,3-dimethyl-1,3-butadiene (Scheme 1).

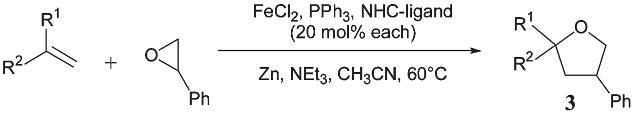
In the absence of the iron catalyst or the zinc powder no, or a negligible amount of the desired product, **1** was formed, while in the absence of the triethylamine, a dimerisation side product **2** was the major product, which is formed upon the rearrangement reaction of the epoxide, under Lewis-acid catalysis (zinc dihalide or iron dihalide), to the aldehyde and subsequent dimerisation *via* aldol condensation.[5] This product was completely suppressed in the presence of triethylamine, indicating that the Lewis-acid's dimerisation activity is efficiently quenched by the triethylamine.



Scheme 1

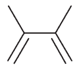
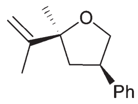
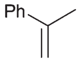
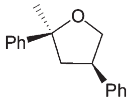
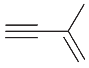
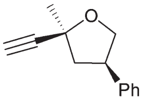
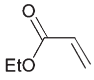
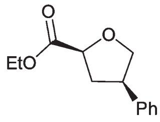
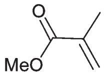
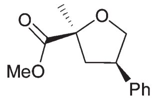
The results of the reactions of unsaturated alkenes with styrene oxide (Scheme 2) under optimised conditions are summarised in Table 1.

The chemo- and regioselectivities of the desired tetrahydrofuran products **3** are excellent and besides the two *cis*- and *trans*-isomers of type **3** no other regioisomer or by-product could be detected by GCMS or TLC.[6] In the predominant products the sterically larger groups were in a 1,3-*cis* relation. When 1,3-cyclohexadiene



Scheme 2

Table 1 Iron-catalyzed ring enlargement reactions of styrene oxide with unsaturated alkenes

Entry	Alkene	(*cis*)-Product[a]	Conditions A[b] (*cis*:*trans*)	Conditions B[c] (*cis*:*trans*)
1			16 h[d] 58% (75:25)	4 h 50% (77:23)
2			15 h[e] 42% (57:43)	4 h 41% (58:42)
3			20 h[e] 24% (50:50)	4 h 37% (53:47)
4			16 h 25% (66:34)	4 h 43% (67:33)
5			15 h 40% (71:29)	4 h 37% (74:26)

[a] Only one enantiomer shown. [b] Conditions A: $FeCl_2(dppe)$ (0.2 mmol), Zn (1.0 mmol), NEt_3 (0.3 mmol), alkene (5 mmol), styrene oxide (1 mmol), CH_3CN (1 ml), 60 °C. [c] Conditions B: $FeCl_2$ (0.2 mmol), PPh_3 (0.1 mmol), NHC-ligand (0.1 mmol), Zn (1.4 mmol), NEt_3 (0.4 mmol), alkene (5 mmol), styrene oxide (1 mmol), CH_3CN (1 ml), 60 °C. [d] $FeBr_2(dppe)$ (0.4 mmol) [e] $FeBr_2(dppe)$ (0.3 mmol).

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† Electronic supplementary information (ESI) available: experimental section. See http://www.rsc.org/suppdata/cc/b5/b501100k/
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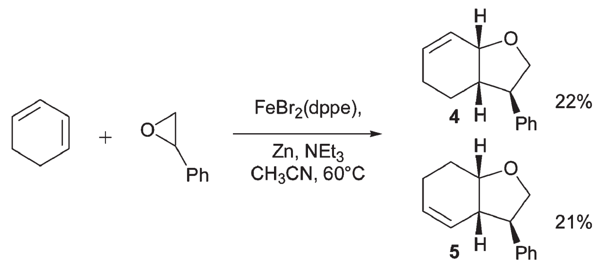


Scheme 3

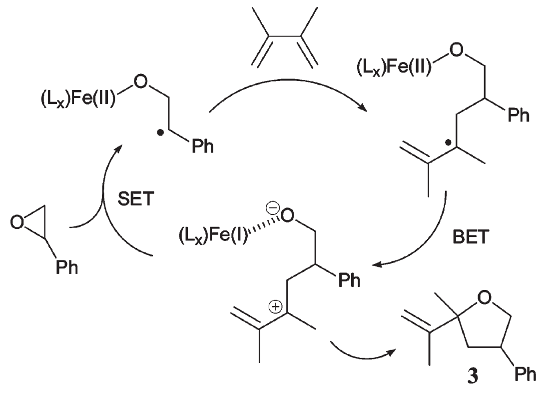
was used in the reaction with styrene oxide (Scheme 3), the bicyclic products **4** and **5** were formed and the relative stereochemistry was determined to be *cis,trans*.[6] Accordingly, as in the case of the monocyclic products of type **3**, the sterically less hindered relative stereochemistry was observed when the bicyclic products **4** and **5** were formed.

Nevertheless, although no other low molecular product was formed and complete conversion of the epoxide was established, the isolated yields for the tetrahydrofurans of type **3** were only moderate. This fact indicates that an alternative reaction pathway exists to yield, most likely, polymerisation side products. These products were isolated and characterised from iron-catalysed reactions involving 2,3-dimethyl-1,3-butadiene (entry 1) and styrene (see below) when less effective ligand systems such as triphenylphosphine were used. Surprisingly, polymers or short oligomers involving styrene oxide as a building block could not be isolated yet.

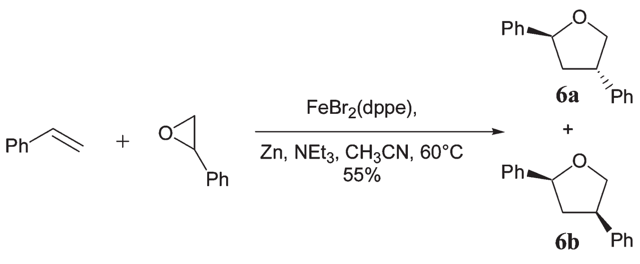
Both observations, the formation of tetrahydrofuran derivatives and the polymerisation activity of the iron catalyst, suggest that the reactive species could be an iron(I) catalyst, generated by reduction of the *in situ*-generated iron(II)-complex by the zinc metal.

A single electron transfer step (SET), from the iron(I) catalyst to the epoxide, initiates the catalytic cycle (Scheme 4) similar to the reaction sequence initiated by titanium catalysts.[7] Addition of the diene to the thereby formed radical generates a stabilised allylic radical. A subsequent back electron transfer step (BET) regenerates the iron(I) catalyst and produces a zwitterionic intermediate prone to cyclisation.

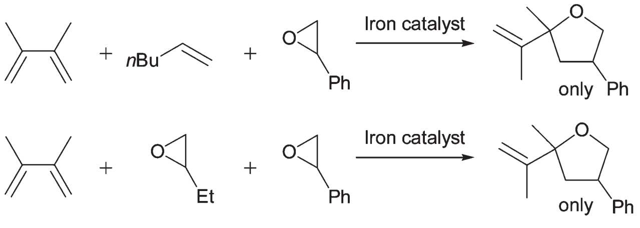
Although the reactivity and the yields should be further optimised in the future, an interesting application of such an iron-catalysed reaction could be realised in the one step synthesis of the natural products calyxolane A (*trans*-isomer) **6a** and calyxolane B (*cis*-isomer) **6b** (Scheme 5) by using simple and very cheap starting materials such as styrene and styrene oxide.‡[7]



Scheme 4



Scheme 5



Scheme 6

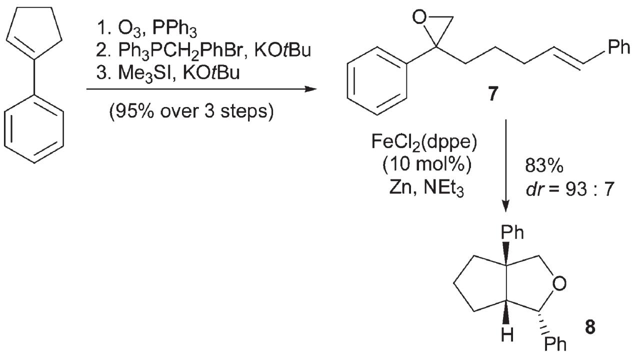
In this process the highest yields of regiochemically pure **6a**,**b** (55%) and a moderate diastereoselectivity (*cis*:*trans* = 63:37) were obtained with the dppe ligand. Better selectivities (71:29) for the synthesis of **6a**,**b** were found with a simple salene ligand[7] accompanied with a lower yield (27%). The diastereoselectivity of the 2,3-dimethyl-1,3-butadiene adduct (Table 1, entry 1) was increased by the salene ligand[9] to 82:18 (42% yield). These results indicate that the ring expansion process, and especially the ring closure step, takes place in the iron ligand sphere so that further optimisations of the ligand system could increase both reactivity and selectivity.

The high degree of chemoselectivity was visualised by the conduction of competition experiments. In these experiments an alkene and a 1,3-diene were mixed in the presence of styrene oxide and a 1,3-diene was mixed with an aliphatic epoxide and styrene oxide (Scheme 6). In both cases the only detected and isolated product was the tetrahydrofuran derivative formed by the reaction of 1,3-diene with styrene oxide.

With the current catalyst system, the intermolecular ring enlargement can be performed with good regioselectivity and good chemoselectivity in moderate yields as shown above. Side reactions such as the polymerisation of the starting materials, however, could not be completely suppressed. Therefore, the application of the iron catalyst system in intramolecular reactions should diminish these alternative reaction pathways. The intramolecular ring expansion process was tested on the easily accessible starting material **7** (Scheme 7).

The conversion with the iron catalyst system led to the bicyclic compound **8** in a good yield of 83%. This product was obtained as a single regioisomer consisting of a mixture of diastereomers in a 93:7 ratio in favour of the isomer with the phenyl substituents in a *trans*-relation.[6] This result indicates that for intramolecular reactions the polymerisation process is diminished and excellent results can be obtained.

In summary we have shown that, starting from very simple adducts such as an aromatic epoxide and a conjugated alkene,



Scheme 7

under iron catalysis, polysubstituted and functionalised tetrahydrofuran derivatives can be obtained with a high degree of regio- and chemoselectivity.

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Notes and references

‡ **Representative procedure** for the synthesis of **6a**,**b**: in a Schlenk tube under nitrogen $FeCl_2$ (25 mg, 0.2 mmol), PPh_3 (26 mg, 0.1 mmol), NHC-ligand (34 mg, 0.1 mmol) [or the preformed $FeCl_2$(dppe) complex] and zinc dust (91 mg, 1.4 mmol) were suspended in CH_3CN (1 ml) and heated until boiling. After 5 min stirring, styrene (0.5 ml, 4.4 mmol) and styrene oxide (115 μl, 1 mmol) were added and the mixture stirred for 4 h at 60 °C. Then the reaction mixture was filtered through a pad of silica, using Et_2O (150 ml) as eluent. The solvents were evaporated under reduced pressure and the crude product was purified by flash column chromatography (silica, CH_2Cl_2:pentane 1:1). The analytical data are in accordance with the literature (ref. 8).

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9 As salene ligand, *N*,*N′*-ethylenebis(salicylidenimine) was used.