

Diastereoselective Synthesis of Highly Substituted Five-Membered-Ring Oxygen Heterocycles by Zirconocene-Mediated C–C Coupling Reactions**

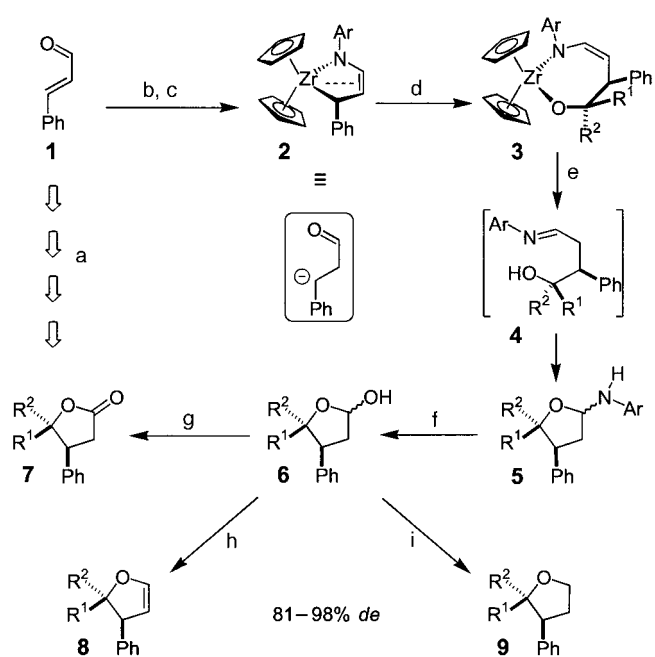
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The synthetic potential of unsaturated compounds has been extended considerably in the last few years by their conversion into the corresponding transition metal complexes.^[1] The use of “Cp₂Zr” (Cp = cyclopentadienyl) as a complexing group has brought forth a number of new synthetic methods during the last ten years,^[2, 3] and the chemistry of zirconocene-imine complexes in particular has led to a series of important innovations in this field.^[4]

In this context we present a new synthesis of highly substituted five-membered-ring oxygen heterocycles, with a high degree of diastereoselectivity. Starting from α,β -unsaturated imines and unsymmetrical ketones highly substituted sterically demanding γ -butyrolactols **6** were synthesized. These could be easily converted into the corresponding γ -butyrolactones **7**, dihydrofurans **8**, and tetrahydrofurans **9**. This new practical route to the heterocycles in the title provides building blocks for the synthesis of natural products and biologically active substances such as alkaloids, macrocyclic antibiotics, lignans, pheromones, and fragrances.^[5]

Inspired by the work of Whitby et al.^[6] and Scholz et al.,^[7] we investigated the use of zirconocene-1-aza-1,3-diene complexes as homoenolate equivalents^[8] in stereoselective synthesis. Scholz et al. had shown that acetophenone inserts into the Zr–C σ bond of 2,2-bis(η^5 -cyclopentadienyl)-1-(2-methylphenyl)-3-phenyl-1-aza-2-zircona-4-cyclopentene (**2**). By extending this principle to other substrates and developing a method for the isolation of the β -substituted carbonyl compounds from the corresponding insertion products (**3**), we were able to use complexes **2** as homoenolate equivalents for the first time (Scheme 1).

In the synthesis of the zirconocene-1-aza-1,3-diene complexes (**2**) we used the *n*BuLi-route introduced by Negishi et al.^[9] and further investigated by Dioumaev and Harrod^[10] in order to generate the zirconocene equivalent. Following this method [Cp₂Zr(*n*Bu)₂] is formed in situ by the reaction of two equivalents of *n*BuLi with [Cp₂ZrCl₂] (–78 °C). By warming up the solution the generated Cp₂Zr fragment can form the desired 1-aza-2-zircona-4-cyclopentene **2** through ligand exchange reactions with the α,β -unsaturated imine added to the reaction mixture.^[11]



Scheme 1. Diastereoselective insertion of unsymmetrical ketones into the Zr–C σ bond of zirconocene-1-aza-1,3-diene complexes (**2**) as a new homoenolate equivalent for the synthesis of trisubstituted five-membered-ring oxygen heterocycles (Ar = 2-methylphenyl or 2-methoxyphenyl): a) 16–78 % over six steps; b) ArNH₂, molecular sieves; c) [Cp₂Zr], “*n*BuLi route”, quantitative over two steps; d) R¹COR², toluene, Δ ; e) C₃H₅NO, H₂O; f) HCl/THF, 51–78 % over four steps; g) Ag₂CO₃, toluene, Δ , 94–100 %; h) pyridinium-*p*-toluenesulfonate (PPTS), toluene, 1 h, >90 %; i) BH₃·Me₂S, THF, 69–94 %.

Scholz et al.^[7] emphasized the high degree of *cis*-stereoselectivity achieved in the insertion reaction of acetophenone into the 1-aza-2-zircona-4-cyclopentene (**2**, Ar = 2-methylphenyl), which was also obtained under drastic experimental conditions. In contrast to this, we were only able to reproduce the stereoselective insertion in ether under reflux conditions (85 % *de*); a lower selectivity was observed in boiling toluene (68 % *de*).

Using sterically demanding aliphatic ketones (such as 3,3-dimethyl-2-butanone, 1-acetyladamantane, etc.) we observed a reaction that differed greatly from that mentioned above. When the zirconocene-1-aza-1,3-diene complexes **2** (Ar = 2-methylphenyl or 2-methoxyphenyl) were mixed with 1.05 equivalents of the ketones in boiling toluene, the corresponding 3-aza-1-oxa-2-zircona-4-cycloheptenes **3a–e** (see Table 1) were formed cleanly within 30 to 60 minutes. In contrast to the situation with the aromatic ketone, very high diastereomeric excesses were reached under these conditions (>80 *de* and in some ones higher than 98%). Additionally NOE experiments and X-ray structural analysis of the resulting products showed that the *trans* insertion products were formed in every aliphatic case (as opposed to *cis* in the aromatic case). This big difference in selectivity can be explained by steric effects for the aliphatic ketones and by attractive π – π interactions for the aromatic ketones. When the symmetric ketones (**g** and **h**) were investigated under these reaction conditions the yields were also nearly quantitative. The zirconocene fragment was removed oxidatively from the insertion products **3** as [Cp₂Zr=O]_{*n*} by the addition of

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pyridinium-*N*-oxide/H₂O. During the course of the reaction an imine–enamine tautomerization took place to yield γ -hydroxyimines (**4**), followed by an intramolecular nucleophilic attack of the hydroxy group on the C=N bond leading to 5,5-disubstituted *N*-aryl(4-phenyltetrahydrofuran-2-yl)-amines (**5**, 1:1 mixture of diastereomers; Figure 1). To obtain

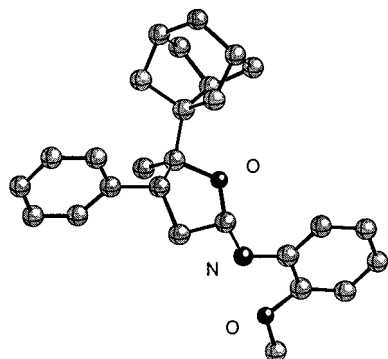


Figure 1. Structure of *N*-(2-methoxyphenyl)(5-methyl-4-phenyl-5-tricyclo[3.3.1.0^{3,7}]non-3-yltetrahydrofuran-2-yl)amine (**5d**).^[14–16]

optimum yields we refrained from the purification of the α -anilinetetrahydrofurans (**5**) as they tended to decompose, even on deactivated silica. Any impurities present had no negative influence on the following steps (cleavage of the aniline unit). If complex **3a** is treated with two equivalents of a freshly prepared ethereal solution of HCl, α -anilinetetrahydrofuran (**5a**) is formed, and the zirconocene fragment is recovered as [Cp₂ZrCl₂]. Nevertheless our less complicated pyridinium-*N*-oxide method was applied in general.

The chemistry of α -anilinetetrahydrofurans **5** is rather unknown apart from their pyrolysis reactions in which the resulting dihydrofurans tend to polymerize.^[12] A method had to be developed, therefore, to cleave the aniline unit from these compounds as efficiently as possible. By reaction with five equivalents of 0.1N HCl we managed to prepare the γ -butyrolactols **6** (Table 1). No spectroscopic evidence for their existence as open-chain γ -hydroxyaldehydes could be found.

The lactols **6** could be quantitatively transformed into lactones **7** by oxidation with Ag₂CO₃^[13] in boiling toluene,

Table 1. Yields and diastereoisomeric excesses of γ -butyrolactols **6**.

6 ^[a]	R ¹	R ²	Yield [%]	<i>de</i> [%] ^[b]
6a	Me	<i>t</i> Bu	64	> 98
6b	Me	cyclohexyl	66	84
6c	Me	1-adamantyl	74	> 96
6d	Me	3-neoadamantyl	72	> 96
6e	Me		78	> 95 ^[c]
6f	Ph	Me	51	> 95 ^[c]
6g	Et	Et	78	–
6h	Ph	Ph	67	–

[a] The data for **6f** and **6h** relate to **2** (Ar = 2-methylphenyl) as the starting material. In all other cases **2** (Ar = 2-methoxyphenyl) was used. Compound **6f** was synthesized according to the procedure of Scholz et al.^[7] [b] The *de* values were determined by ¹H NMR spectroscopy on a Varian Gemini 300 MHz or a Varian Unity 500 MHz spectrometer (**6b**–**f**: 300 MHz; **6a**: 500 MHz). [c] After flash chromatography (SiO₂, diethyl ether/pentane, 1/4).

whereas their reaction with catalytic amounts of pyridinium-*p*-toluenesulfonate (PPTS) under the same conditions gave the dihydrofurans **8** in very good yield. The series of five-membered-ring oxygen heterocycles could finally be completed by the reduction of the γ -butyrolactols **6** with two equivalents of BH₃·Me₂S to form the corresponding tetrahydrofurans **9** (Table 2).

Table 2. Yields and diastereoisomeric excesses of the resulting five-membered-ring oxygen heterocycles.

7–9	R ¹	R ²	7 yield [%]	8 yield [%]	9 yield [%]	<i>de</i> [%] ^[a]
a	Me	<i>t</i> Bu	64	59	59	> 98
b	Me	cyclohexyl	66 ^[b]	60	57	> 96
c	Me	1-adamantyl	74	69	58	> 96
d	Me	3-neoadamantyl	72	65	68	> 96
e	Me		78	70	54	> 96
f	Ph	Me	51	47 ^[c]	16	> 95
g	Et	Et	78	72	71	–
h	Ph	Ph	67	62	–	–

[a] The *de* values were determined by ¹H NMR spectroscopy with a Varian Gemini 300 MHz spectrometer. [b] 84% *de*. [c] 81% *de*, as the starting material was not enriched.

We have succeeded in using zirconocene-1-aza-1,3-diene complexes **2** as homoenolate equivalents in stereoselective synthesis for the first time. The high degree of flexibility in the range of products as well as the steric demand of the diastereoselectively obtained trisubstituted five-membered-ring oxygen heterocycles must be emphasized. Although they contain quaternary centers adjacent to one another or to tertiary centers, the title compounds could be synthesized in good overall yields and can be broadly used as building blocks for organic synthesis.^[17]

Experimental Section

trans-3a–e and **3g–h**: To a solution of the aza-zirconacyclopentene **2** (Ar = 2-methoxyphenyl; 2-methylphenyl in the case of **3h**) (1.0 mmol) in toluene (20 mL) under an atmosphere of argon was added and the appropriate unsymmetric aliphatic ketone (1.05 equiv), and the mixture heated to reflux. On warming a darkening (red) of the original luminous orange solution took place followed by a further change to yellow. As soon as no further color change was observed the solution was cooled to room temperature (RT) and the solvent evaporated in vacuo. The insertion products were obtained as yellow or orange amorphous solids or oils in greater than 95% purity and were used in this form for the subsequent transformations. A further purification could be achieved by recrystallization from toluene/hexane.

5: Pyridinium-*N*-oxide (0.114 g, 1.2 mmol) was added to solutions of **3** (each 1 mmol) in THF (20 mL). Under vigorous stirring H₂O (1 mL) was added, whereupon an intense clouding caused by the precipitation of [Cp₂Zr=O]_n appeared immediately. After stirring for 8 h at RT the reaction mixture was diluted with ether (40 mL), dried over MgSO₄, and the MgSO₄ filtered off together with the [Cp₂Zr=O]_n. Evaporation of the solvent led to yellow oils or solids that were used in the subsequent manipulations without further purification. Possible impurities do not affect the course of the following steps. In the case of *N*-(2-methoxyphenyl)-*N*-(5-methyl-4-phenyl-5-tricyclo[3.3.1.0^{3,7}]non-3-yltetrahydro-2-furanyl)amine (**5d**) recrystallization (ether/pentane 1/1) resulted in crystals suitable for X-ray structural analysis (see Figure 1).

6: To solutions of the crude α -anilinetetrahydrofurans **5** (1 mmol) in THF (50 mL) was added 0.1N HCl (50 mL) dropwise under vigorous stirring. After completion of the reaction (monitored by TLC, about 6 h) extraction with ether, drying over MgSO_4 , and removal of the solvent in vacuo, the crude product was purified by chromatography (SiO_2 , ether/pentane 1/4). The γ -butyrolactols **6** were obtained as colorless liquids or solids.

8: Lactols **6** were dissolved in toluene (each 20 mL mmol⁻¹) and heated to reflux in the presence of a catalytic amount of pyridinium-*p*-toluenesulfonate (water separator). As soon as no further conversion was detected (as monitored by TLC) the solution was cooled to RT and washed with pH 7 buffer (10 mL). The aqueous phase was extracted with pentane (10 mL), the combined organic layers dried over MgSO_4 , and the solvent evaporated in vacuo. The reddish to orange crude syrups were purified by chromatography (SiO_2 , pentane). Dihydrofurans **9** were obtained as colorless oils.

9: A solution of $\text{BH}_3 \cdot \text{Me}_2\text{S}$ (2N in THF; 1 mL) was added to the appropriate lactol **6** (1 mmol) at 0 °C under an atmosphere of argon. After removal of the cooling bath the mixture was stirred until the evolution of gas ceased and then heated slowly to 60 °C. As soon as no further conversion was detected (monitored by TLC), the solution was cooled to 0 °C. After the addition of methanol (2 mL mmol⁻¹) to hydrolyze any excess borane, the solution was warmed to reflux temperature before removing the volatile components in vacuo. The colorless residue was purified by chromatography (SiO_2 , pentane) to yield the corresponding tetrahydrofurans **9** as colorless liquids or solids.

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