

Selective Functionalization of Arenes through the Reaction of Aryne–Zirconocene Complexes and Enol Ethers

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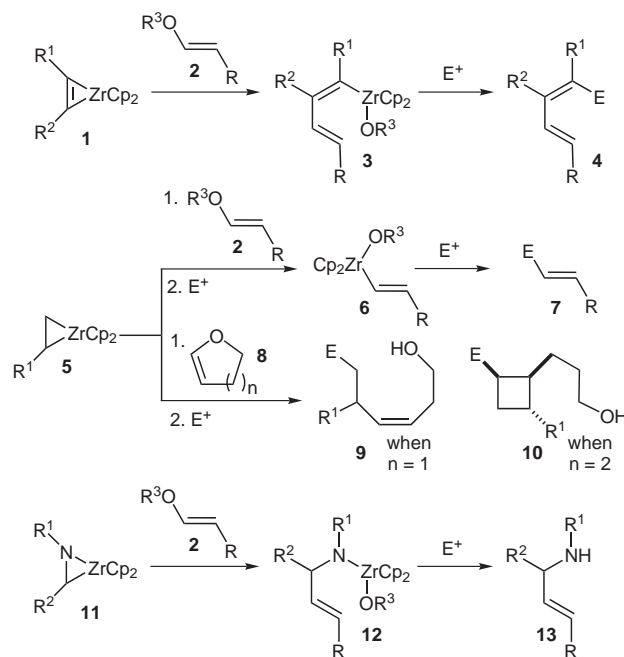
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Abstract: A new method for the selective functionalization of aromatic rings by the zirconium promoted cross coupling reaction of an aryllithium compound and an enol ether is reported. Formation of an aryne–zirconocene complex and its regioselective coupling with an enol ether are the key steps of the process. This methodology allows the synthesis of functionalized styrene or Z-alkenol derivatives from simple and easily available starting materials.

Key words: arynes, cross-coupling, organometallic reagents, regioselectivity, transition metals

Since pioneering investigations by Schwartz¹ and Negishi² in the field of organozirconium chemistry, the use of these complexes in organic and organometallic chemistry has enormously increased.³ Most of the recent investigations are related with the ability of the zirconocene unit (Cp_2Zr) to stabilize unsaturated molecules and to promote the cross-coupling between two of these unsaturated compounds. In this context, we became interested in the reaction of zirconocene complexes and heterosubstituted alkenes.⁴ Particularly, interesting are the reactions with enol ethers. For example, the reaction of alkynezirconocene complexes **1** with enol ethers **2** supposes an easy entry to the dienylzirconocene complexes **3** which can be easily transformed into functionalized 1,3-butadiene derivatives **4** by reaction with electrophiles (Scheme 1).⁵ When the same reaction is performed with alkene–zirconocene complexes **5**, different products can be obtained depending on the nature of the enol ether (Scheme 1). For acyclic enol ethers **2** the reaction leads to the formation of the vinylzirconocene complexes **6**, which can be further transformed into functionalized alkenes **7** by reaction with electrophiles.⁶ On the other hand, when cyclic enol ethers **8** are used, alkenol derivatives **9** or cyclobutanes **10** are obtained.⁷ Finally, the reaction of imine–zirconocene complexes **11** and enol ethers **2** has shown to be an interesting method for the synthesis of allyl amines **13** through intermediate **12** (Scheme 1).⁸

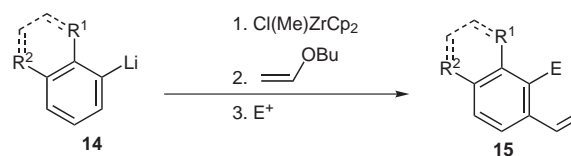
Taking into account all these previous works and in order to complete this systematic study, we decided to investigate the reaction of aryne–zirconocene complexes and enol ethers. Thus, in this paper we describe an easy method for the selective functionalization of aromatic



Scheme 1

rings from starting materials as simple as aryllithium compounds and enol ethers.

Our study was initiated with the reaction of organolithium compounds **14** and zirconocene methyl chloride followed by treatment with butyl vinyl ether and an electrophile to obtain the functionalized styrene derivatives **15** as single regioisomers in all cases attempted (Scheme 2 and Table 1).



Scheme 2

Noteworthy, this process supposes an easy functionalization of an aromatic ring by the selective introduction of a vinyl moiety and an electrophile in two adjacent positions of the initial aromatic ring.

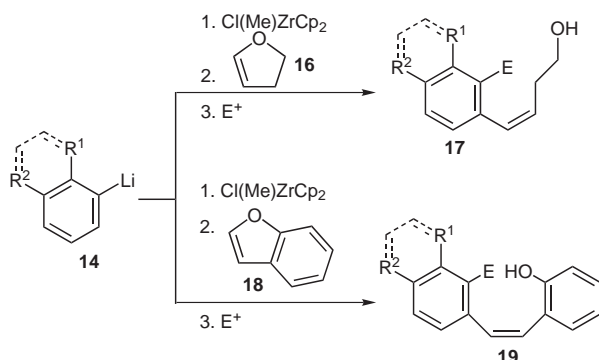
Next, we turned our attention to the reactivity of cyclic enol ethers. Thus, reaction of organolithium compounds **14** with zirconocene methyl chloride followed by

Table 1 Reaction of Organolithium Compounds **14** with Zirconocene Methyl Chloride

Organolithium 14	R ¹	R ²	E ⁺	E	Product 15	Yield (%) ^a
14a	H	H	I ₂	I	15a	79
14a	H	H	Allylchloride, cat. CuCl	Allyl	15b	82
14a	H	H	PhI, ZnCl ₂ , cat. Pd(PPh ₃) ₄	Ph	15c	64
14b	OMe	H	Allylchloride, cat. CuCl	Allyl	15d	78
14c	Ph	H	H ₂ O	H	15e	91
14c	Ph	H	D ₂ O	D	15f	88
14d	-(CH) ₄ -		H ₂ O	H	15g	84
14d	-(CH) ₄ -		D ₂ O	D	15h	77
14d	-(CH) ₄ -		Allylchloride, cat. CuCl	Allyl	15i	86

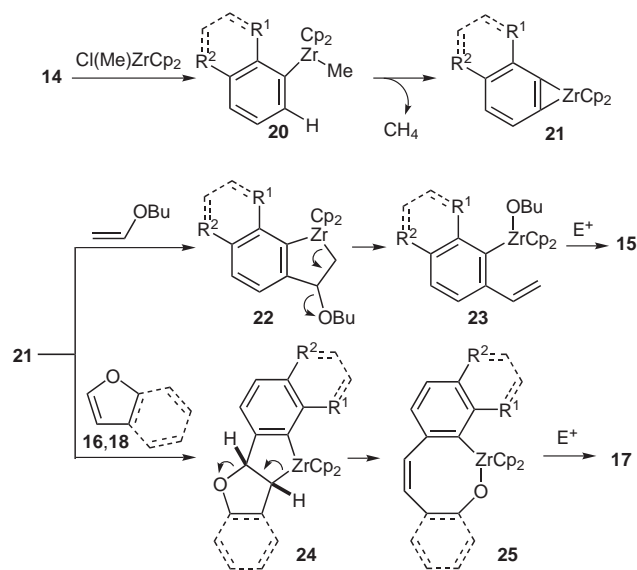
^a Yield based on starting **14**.

treatment with five-membered cyclic enol ethers **16** or **18** led, after addition of an electrophile, to the new alkene derivatives **17** or **19** (Scheme 3 and Table 2). These compounds were obtained as single regioisomers, which contain a *Z*-double bond in their structures. It should be remarked that the final products **17** or **19** are interesting building blocks, not easily available by other methodologies.

**Scheme 3**

A plausible mechanism for these reactions is shown in Scheme 4. Thus, the transmetalation reaction of the organolithium compounds **14** and the zirconocene methyl chloride leads to the formation of the new aryl-zirconocene complex **20**. These complexes are known to evolve through a β -abstraction of a hydrogen atom to furnish the aryne-zirconocene complex **21** and a molecule of methane.⁹ An insertion reaction of the corresponding enol ether generates intermediate **22** or **24**. This process is doubly regioselective: insertion occurs at the zirconium-carbon bond of **21** which is far away from the R¹ group. Also, the double bond of the enol ether is oriented during the insertion step so that the oxygen atom is far away from the zirconocene moiety. Elimination of the alkoxy group from **22** or **24** results in the formation of intermediates **23** or **25**.

We believe that the *Z* stereochemistry observed in products **17** is fixed by the *cis* geometry of the cyclic derivative **25**. Finally, the reaction of intermediates **23** or **25** with the corresponding electrophile leads, after the hydrolysis step, to the final products **15** or **17** (Scheme 4).

**Scheme 4**

In summary, we have developed a new method for the selective functionalization of aromatic rings by the zirconium promoted cross-coupling reaction of an aryllithium compound and an enol ether. Interesting building blocks from very simple starting materials are obtained following this methodology. The key steps of the process are the formation of an aryne-zirconocene complex and a doubly regioselective insertion of an enol ether. The work completes previously published investigations on the coupling reactions of zirconocene complexes and heterosubstituted alkenes.

Table 2 Reaction of Organolithium Compounds **14** with Zirconocene Methyl Chloride

Organolithium 14	R ¹	R ²	Enol ether 16 or 18	E ⁺	E	Product 17 or 19	Yield (%) ^a
14a	H	H	16	H ₂ O	H	17a	71
14a	H	H	16	Allylchloride, cat. CuCl	Allyl	17b	60
14a	H	H	18	H ₂ O	H	19a	55
14b	OMe	H	16	D ₂ O	D	17c	64
14b	OMe	H	16	Allylchloride, cat. CuCl	Allyl	17d	70
14b	OMe	H	18	H ₂ O	H	19b	72
14d	-(CH) ₄ -		16	H ₂ O	H	17e	88
14d	-(CH) ₄ -		16	I ₂	I	17f	54
14d	-(CH) ₄ -		16	Allylchloride, cat. CuCl	Allyl	17g	76
14d	-(CH) ₄ -		18	H ₂ O	H	19c	82
14d	-(CH) ₄ -		18	Allylchloride, cat. CuCl	Allyl	19d	80

^a Yield based on starting **14**.

Zirconium-Mediated Couplings of Organolithium Compounds **14** and Butyl Vinyl Ether to give Compounds **15**. Typical Procedure.

The corresponding aryllithium compound **14** (2 mmol) was added dropwise to a -78 °C stirred solution of zirconocene methyl chloride (2 mmol) and butyl vinyl ether (3 mmol) in dry THF (10 mL) in a sealed tube. After 30 min at this temperature, the solution was allowed to warm to r.t. and then heated to 80 °C for 3 h. The reaction was cooled to r.t. and the corresponding electrophile was added (excess of water, deuterium oxide, or 2 mmol of iodine). After 1 h, the reaction was worked up by addition of H₂O (20 mL) or a sat. solution of Na₂S₂O₃ (20 mL, when iodine was used as electrophile) and extracted with Et₂O (3 × 10 mL). When allyl chloride is used as electrophile: allyl chloride (3 mmol), and CuCl (5 mol%) were added and the reaction mixture stirred for 1 h at 25 °C and then heated at 80 °C for 20 min. After cooling to r.t., the reaction was worked up by addition of H₂O (20 mL) and extracted with Et₂O (3 × 10 mL). When iodobenzene is used as electrophile: zinc dichloride (2.4 mmol), Pd(PPh₃)₄ (5 mol%), and iodobenzene (3 mmol) were added and the reaction mixture stirred for 6 h at 25 °C. After cooling to r.t., the reaction was worked up by addition of H₂O (20 mL) and extracted with Et₂O (3 × 10 mL). The combined organic layers were dried over anhyd Na₂S₂O₃, concentrated and the residue purified by column chromatography to give compounds **15**.

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