Regioselective Zirconium-Mediated Cross Coupling of N-Methyl-N-propargyl Aniline and Alkenes

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Dedicated to Prof. Dr. Dr. h.c. mult. Günther Wilke on the occasion of his 70th birthday

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Regioselective Cross Coupling. Propargylamine-Zirconocene Complex. Zirconacyclopentene

N-(2-bromoallyl)-N-methylaniline 1 is easily converted into the propargylamine-zirconocene complex 3 via loss of methane from 2-[zirconocene(methyl)]allyl amine 2. Regioselective insertion reactions with alkenes and benzophenone afford, after iodinolysis, products 4–10.

Recently the use of zirconium complexes in organic synthesis has been widely recognized [1]. One of the most interesting transformations which has been developed is the formation of unsaturated system-metallocene complexes either by direct complexation between the unsaturated compounds and zirconocene [2] or by a β-hydrogen abstraction process [1b, 3] followed by the insertion of alkyynes, alkenes, carbonyl compounds, or nitriles to generate the corresponding zirconacyclopentanoids. A great limitation of the intermolecular cross-coupling is in most cases the lack of regioselectivity in the coupling reaction when unsymmetrical zirconacyclopropanoids are used [2a, 3b, 3e], and the poor coupling in the case of terminal alkyynes [3e]. On the other hand, 2-lithioallylamines have been prepared by bromine-lithium exchange from 2-bromoallylamines [4]. In the present communication we describe the preparation of η2-propargylamine-zirconocene complexes from 2-bromoallylamines and further coupling with unsaturated compounds followed by iodinolysis.

Results and Discussion

Treatment of N-(2-bromoallyl)-N-methylaniline 1 with tert-butyl lithium at −78 °C followed by reaction with zirconocene methyl chloride at temperatures ranging between −78 and −20 °C affords the zirconocene complex 2, which loses methane rapidly at 20 °C to produce the zirconacyclopropene 3, which can be trapped in situ with ethylene to give, after iodinolysis, exclusively 4. The in situ reaction of 3 with other alkenes has also been examined and the reaction with 1-hexene, cyclopentene, or 4-bromo-1-butene was found to lead, after iodinolysis, exclusively to the products 5, 6, or 7, respectively (Scheme 1).

In contrast with the results reported in the literature [3b], a high regioselectivity has been observed in all cases of insertion of alkenes that we have examined. We assume this to be a result of the zirconocene unit ending up at the carbon nearest to the amino group, presumably from coordination of the nitrogen to the zirconium. In ad-
dition, if unsymmetrically substituted alkenes are used the insertion is also regioselective with respect to the unsaturated substrate, and the regioisomer with the largest substituent furthest from the zirconium is given exclusively.

On the other hand, if benzophenone is used as the unsaturated substrate, the coupling reaction with 3 affords a 4:1 mixture of the regioisomers 8 and 9, probably due to the better coordination of the oxygen to the zirconium than with the nitrogen (Scheme 1).

Finally, insertion of butyl vinyl ether or vinyl bromide into 3 followed by iodinolysis leads to the dienylzirconocene 10. As far as we know, this is the first time that an electron-rich alkene has been used in insertion reactions, and we have observed that the regioselective zirconacyclopentene derivatives 11 undergo a β-elimination process to afford the dienylzirconocenes 12, which after iodinolysis lead to 10 (Scheme 2).

Attempts to isolate intermediate 3 were unsuccessful and the zirconacyclopentene 13 was always obtained. The formation of 13 can be understood by assuming that isobutene, generated in the lithiation step, inserts into 3 (Scheme 3). However, the formation of the zirconocene 13 is inconsequential as it reacts with the same unsaturated systems as intermediate 3, due presumably to the facile cleavage of the Cβ–Cβ' bond [5]. Furthermore, we have observed that the reaction of 13 with benzophenone at 20 °C leads, after iodinolysis, to the formation of a mixture of 8 and 9, but in a 10:1 ratio of regioisomers.

In conclusion, we have developed a convenient method for the formation of a new type of propargylamine-zirconocene complexes, which regioselectively inserts alkenes. In addition, it is the first time that electron-rich olefins have been used as unsaturated substrates in zirconium-mediated coupling reactions. Moreover, we have obtained a zirconacyclopentene, derived from propargylamine and isobutene, which offers a convenient alternative to the propargylamine-zirconocene complexes in coupling reactions. Further studies with protected primary propargylamines are in progress.

**Experimental Section**

A typical reaction was performed as follows. A solution of tert-butyllithium (4 mmol) in pentane was added to a solution of the amine 1 (2 mmol) in diethyl ether (10 ml) at −78 °C under argon and stirred for 1 h at the same temperature. The resulting mixture was added to a solution of zirconocene(methyl)chloride (2.1 mmol) in diethyl ether (20 ml) at −78 °C and in the presence of the unsaturated substrate (2.1 mmol) (electron-rich olefins and benzophenone were added at −20 °C) and stirred for 3 h at temperatures ranging between −78 and 20 °C. To the mixture was added iodine (5 mmol) at 20 °C and stirring was continued for 1 h at the same temperature. The resulting mixture was then hydrolysed with aqueous NH₄Cl, extracted with ethyl acetate, and washed with Na₂S₂O₃ and NaHCO₃. The organic layer was dried (Na₂SO₄), the solvents were removed (15 mmHg), and the residue was purified by flash column chromatography (silica gel, hexane:ethyl acetate)*.

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* The zirconocene 13 was characterized by ¹H and ¹³C NMR spectroscopy.

* The identity and purity of all the products were satisfactorily confirmed by spectroscopic methods (¹H NMR, ¹³C NMR, and mass spectrometry).
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