Iridium Ferrocenyl Diphosphine Catalyzed Enantioselective Reductive Alkylation of a Hindered Aniline

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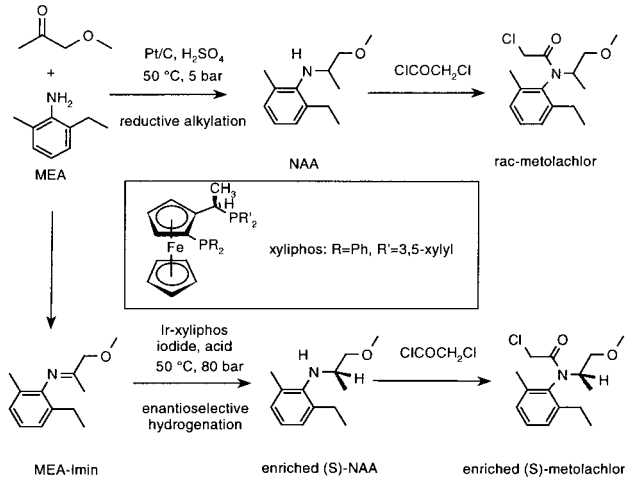
Abstract: The enantioselective reductive alkylation of 2-methyl-5-ethyl-aniline (MEA) with methoxyacetone - using a catalyst generated *in situ* from $[Ir(cod)Cl]_2$ and (*R*)-(*S*)-PPF-P(3,5-xyl)$_2$ - to give enriched (*S*)-*N*-(2-ethyl-6-methylphenyl)-*N*-(1'-methoxymethyl)-ethyl-amine is described. At 80 bar and 50 °C in the presence of iodide and methane sulfonic acid and with cyclohexane as solvent, complete conversion is reached within 14 h with a substrate to catalyst ratio of 10'000 and an ee of 76-78 %. The effect of solvent and acid type were found to be important. To our knowledge, this is the first enantioselective reductive alkylation ever reported.

Key words: enantioselective reductive alkylation, hindered N-alkyl aniline, Ir-ferrocenyl diphosphine, acid catalysis, (S)-metolachlor

Metolachlor is the active ingredient of Dual®, one of the most important grass herbicides for use in maize and a number of other crops. It is an N-chloroacetylated, N-alkoxyalkylated *ortho* disubstituted aniline. The commercial product was introduced to the market in 1976 as a mixture of four stereoisomers and is produced via a Pt catalyzed reductive alkylation of 2-methyl-5-ethyl-aniline (MEA) with aqueous methoxyacetone in the presence of traces of sulfuric acid followed by chloroacetylation[1] (see upper part of the Scheme). Already in 1982 it was found that about 95% of the herbicidal activity of metolachlor lies in the two (1'*S*)-diastereomers[2]. In 1997, after years of intensive research[3], Dual Magnum® with a content of approximately 90% (1'*S*)-diastereomers and with the same biological effect at about 65% of the use rate was introduced in the USA. To make this 'chiral switch' possible, a new technical process had to be found that allowed the economical production of the enantiomerically enriched precursor of metolachlor. Key step of this new synthesis is the enantioselective hydrogenation of *N*-(2-ethyl-6-methylphenyl)-*N*-(1'-methoxymethyl)-ethylidene-amine (see lower part of the Scheme). The optimized process operates at 80 bar hydrogen and 50 °C with a catalyst generated *in situ* from $[Ir(cod)Cl]_2$ and the ferrocenyldiphosphine ligand xyliphos at a substrate to catalyst ratio (s/c) of >1'000'000. Complete conversion is reached within 3-4 h, the initial tof exceeds 1'800'000 h^{-1} and enantioselectivity is approximately 80%.

It would be a further improvement to combine the advantages of both production processes and to use the chiral homogeneous catalyst for carrying out a reductive alkylation without isolating and purifying the imine. This paper describes the investigation of the reductive alkylation of MEA with methoxyacetone using the Ir-xyliphos catalyst in presence of iodide ions and acid.



Scheme

Table 1 Reaction of MEA with methoxyacetone in presence of Ir-xyliphos, acetic acid, and iodide ions: Effect of solvents on reaction time, conversion and ee.

Entry	Solvent	Time (h)	Conv. (%)	ee (%)	Remarks
1	MEA imine	1.3	100	77.2	reference[(a)]
2	H_2O (3 ml)	24	47	76	2 phases
3	none	22	87	76	2 phases
4	EtOH (10 ml)	18	24	15	1 phase
5	cyclohexane (10 ml)	21	92	77	2 phases

Reaction conditions[4]: 0.1 mol MEA; 0.12 mol MOA (dry); 2.5 ml AcOH; 20 mg TBAI; 80 bar H_2; 50 °C. [(a)] s/c 8000, 50 bar.

Even though metal catalyzed reductive alkylation is a method with a large preparative potential, no literature reports on a successful enantioselective version could be found. Therefore, in a first attempt, MEA and aqueous methoxyacetone were used as in the racemic process and reaction conditions close to the optimized enantioselective process with an s/c ratio of 10'000. In presence of acetic acid and TBAI (tetrabutyl ammonium iodide), the desired reaction indeed took place with a remarkably high

ee of 76% (Table 1, entry 2) but compared to the reference reaction with the isolated imine (Table 1, entry 1), the catalyst activity was quite low. When dry methoxyacetone was used, conversion increased significantly (Table 1, entry 3). Since it was noticed that in both cases two liquid phases were formed, the effect of ethanol addition was investigated. However, the resulting activity in a one-phase situation was even lower and the ee dropped to 15% (Table 1, entry 4). As a consequence, cyclohexane was added to the reaction mixture and the expected increase in conversion and also a slightly better enantioselectivity was observed (Table 1, entry 5).

From these results it was concluded that best effects would be obtained when as little water and MEA as possible were present in the organic phase. Since acetic acid can also act as solvent mediator and is used in large amounts, it was replaced by stronger acids that are effective at much lower concentrations. Thus, as shown in Table 2, the catalyst activity was further improved. Best results were achieved with small amounts of trifluoroacetic acid or of methane sulfonic acid while sulfuric acid was not effective probably due to its low solubility .

Table 2 Reaction of MEA with methoxyacetone in presence of cyclohexane, Ir-xyliphos, acetic acid, and iodide ions: Effect of acid type on reaction time, conversion and ee.

acid	time (h)	conv. (%)	ee (%)
AcOH (2.5 ml)	21	92	77
CF_3COOH (0.1 ml)	16	99	78
H_2SO_4 (0.2 ml)	19	42	72
CH_3SO_3H (0.2 ml)	14	99	76

Reaction conditions[4]: 0.1 mol MEA; 0.12 mol MOA (dry); 10 ml cyclohexane; 20 mg TBAI; 80 bar H_2; 50 °C.

These results are quite remarkable because this is the first enantioselective reductive alkylation of an aniline with a ketone and the ee values and especially the s/c ratio of 10'000 are respectable. However, we clearly missed our objective to find a more economical process for the production of the (1'*S*)-diastereomers of metolachlor because the catalyst productivity is far too low compared to the imine hydrogenation process. It seems that even in presence of cyclohexane there is still too much MEA and water present that are known to deactivate the Ir ferrocenyldiphosphine catalyst. The reason for this behavior could either be a strong complexation, thereby blocking the access of the imine, or a slow dimerization of the Ir xyliphos complex to give an inactive species as observed for other Ir catalysts[5].

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References and Notes

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(4) *General hydrogenation procedure*. The appropriate amounts of 2-methyl-5-ethyl aniline and methoxyacetone were placed in a 50 ml autoclave. Then, $[Ir(cod)Cl]_2$, xyliphos, tetrabutylammonium iodide, and (if stated) the solvent and/or acid were added. The autoclave was sealed, first set under argon and then under the required pressure of hydrogen. The reaction mixture was intensively stirred with a magnetic stirring bar (1200 rpm) for the time given at the specified temperature. After removal of the solvent, the conversion was determined by glc (column: DB 17/30W, 15 m (JCW Scientific Inc.), temperature program: 60 °C/1 min. to 220 °C, ΔT: 10°/min), and the ee was measured by HPLC on Chiralcel-OD-H (hexane/2-propanol: 99.7:0.3; flow rate 1ml/min; α=1.11).
Xyliphos. The ligand was prepared according to the procedure described by Togni et al.[6]
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