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Iridium-catalyzed alternative of the Meinwald rearrangement

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Abstract—A novel and easy to handle procedure for the regioselective rearrangement of epoxides has been developed, based on an iridium catalyst.

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Epoxides are very important and versatile intermediates in organic synthesis since they can be readily transformed into a variety of functional groups.¹ One of the useful synthetic routes to aldehydes and ketones from epoxides is the Meinwald rearrangement.² This reaction could be performed in the presence of various Lewis acids. The nature of the obtained product depends on the migratory aptitude of the substituents on the epoxide group but also on the nature of the Lewis acid and the solvent (Scheme 1).^{3–6}

The Meinwald rearrangement is usually carried out with methylaluminium bis(4-bromo-2,6-di-*tert*-butyl-phenoxide) (MABR),³ BF₃·Et₂O,⁴ MgBr₂,⁴ lithium salts⁵ or indium chloride⁶ in stoichiometric amounts or even in excess. As some of these reactants are air-sensitive, corrosive or toxic, anhydrous conditions and inert atmosphere are generally needed.



Scheme 1. Meinwald rearrangement.

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Some examples of catalytic Meinwald rearrangements have been reported in the last decade. Kulasegaram and Kulawiec⁷ reported the isomerization of epoxides to carbonyl compounds with catalytic amounts of palladium species (5% mol) formed in situ from Pd(OAc)₂ and a phosphine ligand. Recently, Mohan et al.⁸ employed a bismuth-based catalyst^{8b} for the rearrangement of epoxides with good regioselectivities. We report in this paper the first use of an iridium species as regiospecific catalyst for the Meinwald rearrangement of epoxides under mild reaction conditions.

Iridium trichloride was used in 1% molar ratio relative to the epoxide (THF, 50°C; Table 1). Rearrangement of styrene oxide gave pure phenylacetaldehyde (entry 1). *trans*- β -Methylstyrene oxide and α -methylstyrene oxide (entries 2-3) rearranged selectively and quantitatively into phenylacetone and 2-arylpropanal, respectively. For trans and cis-stilbene (entries 4-5), diphenylacetaldehyde was the only formed product. In this later case, iridium lead to the aldehyde, while $Pd(OAc)_2$, combined to PPh₃, gave^{7a} the ketone, deoxybenzoin. The only case in which $IrCl_3 xH_2O$ lead to some traces of a secondary product was the reaction with dihydronaphtalene oxide (entry 6). Only 4% of cyclohexene oxide rearranges into cyclopentane carboxaldehyde (entry 7). Several tests were realized in order to improve this result by increasing the temperature to 100°C in toluene or DMF, without success. It was reported that LiBr-HMPA allowed more than 90% yield of cyclopentane carboxaldehyde in benzene at 80°C.^{5a}

The optically active α -arylpropanoic acid derivatives are effective nonsteroidal analgesics⁹ and synthetic routes to the corresponding enantiopure aldehydes are thus of high interest. As 2-arylpropanal was easily

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Table 1. Rearrangement of epoxides with IrCl₃·xH₂O catalyst (1% mol)^a

Entry	Epoxide	Time	Product	Conversion ^b (%)
1		2h	C H	100
2		2h		100
3		15 min	H FO	100
4		2h	H-CO	100
5		2h	H-O C	100
6 [°]		2h		100
7	⊂ °	24h	99.6 0.4	4

^a in THF at 50°C

^b No other product detected either by CPV or by ¹H NMR

^c in CH_2Cl_2 at room temperature

prepared by a Meinwald rearrangement (Table 1, entry 2) we focused on the chiral version. We first prepared the (R)- α -methylstyrene oxide in 60% ee with Jacobsen catalyst¹⁰ at -78°C. The rearrangement of this epoxide,

was carried out with iridium trichloride in THF at 50°C but almost racemic aldehyde was obtained (Scheme 2). When the epoxide bears on the same carbon atom a methyl and a bulkier group, such as phenyl or



Scheme 2. Rearrangement of chiral α -methylstyrene oxide.

adamantly, distinct migratory aptitudes of the two hydrogen atoms have been observed by Yamamoto et al. with monodeuteriated epoxides.³ Nevertheless, the use of a bulky and chiral Lewis acid, or of a chiral iridium catalyst, may lead to a stereoselective control for this reaction.

In summary, this work presents a new effective and regioselective alternative for the Meinwald rearrangement of epoxides catalyzed by iridium(III) species. The hydrated iridium complex used is very stable and the reaction can be run under mild conditions (no inert atmosphere or high temperature are required). This alternative of the Meinwald rearrangement is also interesting since many chiral complexes of iridium are already described in the literature, and we are now focusing on the enantioselective isomerization of epoxides to carbonyl groups.

Representative procedure for the isomerization of epoxides: The epoxide (40 µl, 0.335 mmol for styrene epoxide) was added to a solution of $IrCl_3 \cdot x H_2O$ (1 mg, 3.35×10^{-3} mmol) in THF (1 mL) and the reaction mixture stirred at room temperature. The reaction time was determined by GC analysis. After 2 h at 50°C, the solvent was removed and phenylacetaldehyde was recovered. Its purity (>99%) was determined by GC, ^{13}C and ¹H NMR. Conversions and ee values were determined by GC on a chiral column (β -dex-225 column, 30 m). All the final products were isolated in almost quantitative yields and characterized by comparison of their ¹³C and ¹H NMR spectra with already reported data.

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