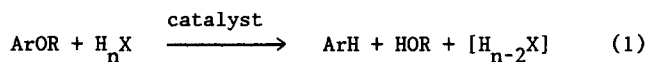# CATALYSED IPSO REPLACEMENT OF PHENOLIC ETHERS BY GRIGNARD REAGENTS

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Summary: Nickel catalysed _ipso_ displacement of phenolic ethers, ArOR, by Grignard reagents, R'MgX, to give arenes, ArR', has been achieved.

The catalytic transfer hydrogenolysis of tetrazolyl and other ethers of phenols, ArOR (R = 5-(1-phenyl)tetrazolyl), has been reported and may be considered as a high-yielding, regiospecific, rapid _ipso_ replacement of phenolic C-O bonds by C-H to give arenes, ArH.[1] The mechanism of this transfer reaction has been elucidated partially and indicates a process in which oxidative addition/reductive elimination on the catalyst surface is controlled by a rate determining separation of a complex of the catalyst and a reaction product.[2] This mechanism suggested that the donor (H_nX) used to supply hydrogen (reaction 1) might be replaced by other

$$\text{ArOR} + H_nX \xrightarrow{\text{catalyst}} \text{ArH} + \text{HOR} + [H_{n-2}X] \qquad (1)$$

kinds of donor molecules to effect _ipso_ replacement as in reaction (2). Initially, reaction

$$\text{ArOR} + R'X \xrightarrow{\text{catalyst}} \text{ArR'} + [XOR] \qquad (2)$$

of tetrazolyl ethers of phenols with alkyl and aryl Grignard reagents was examined. The catalysts effective for reaction (1) were found to be ineffective for reaction (2) but others have been found to promote the latter as a high-yielding, rapid and regiospecific process (R^1 = alkyl or aryl). Similar _ipso_ reaction can be achieved through the use of phenolic trifluoromethylsulphonates, phosphates and methyl ethers.[3] Compared with the present method, these three have serious disadvantages. In particular, with methyl ethers, cross-coupling yields are low even under drastic conditions and only phenyl Grignard reagents can be used.[3a] With the phosphate method,[3b] although yields are quite good, large excesses of Grignard reagent are needed (up to a 5-fold excess) with long reaction times, indicating that the method is not likely to be useful in the presence of a range of other functional groups; the phosphates are described as being only slightly more reactive than the commonly used iodides or bromides. In the third method,[3c] the triflate group is not conducive to giving crystalline derivatives of phenols, reaction times are very long during which a low temperature must be maintained and yields are not as good as those described here. In contrast, tetrazolyl ethers provide highly crystalline, easily purified derivatives and the tetrazole resulting from reaction being acidic is easily recovered. Reaction times are extremely short, often only 5 to 10 minutes, and very

good to excellent yields of cross-coupled products are obtained.   Only a slight excess of Grignard reagent is used, making the process amenable to the presence of other functional groups. Examples of the reaction are shown in the Table.

Table.   **Products and Yields for Reaction of Grignard Reagents with Phenolic Ethers**

Aryl ether, ArOR[a] Ar =	Grignard Reagent,[b] R' =	Catalyst[c]	Yield of Product[d] ArR' (%)
Phenyl	Et	A	50
	Et	B	77
	Et	C	68
	Et	D	47
	n-Pr	C	81
	i-Pr	C	75[e]
	sec-Bu	C	77
2-Naphthyl	Me	A	89
	Ph	A	55
	n-Bu	A	75
4-Methoxyphenyl	Ph	A	49
	n-Bu	B	67

a   In these experiments, R = 5-(1-phenyltetrazolyl) but other ethers have been examined.

b.   Prepared in ether by standard methods from Mg and R'X (X = Cl or Br or I).

c.   Catalysts used : A $\equiv$ $NiCl_2(PPh_3)_2$, B $\equiv$ $Ni(PPh_3)_4$, C $\equiv$ $NiCl_2(Ph_2PCH_2CH_2-PPh_2)$, D $\equiv$ $NiCl_2(Ph_2PCH_2CH_2PPh_2)$; other catalysts have been examined.

d.   An excess of Grignard reagent (2 mole to 1 mole of aryl ether) was used. The excess remaining after reaction was not determined.   Yields are typical of several runs.   Products were identified by gc, gc-ms, ^{1}H-nmr.

e.   In addition, 7.5% of n-propylbenzene was found.

Examination of the Table shows that the nature of the catalyst is important.   Further, with any one catalyst, lower yields of product, ArR', were obtained if the Grignard reagent was added all at once rather than dropwise.   For example, rapid addition of ethyl magnesium bromide to 5-phenoxy-1-phenyltetrazole, PhOR (R = 5-1-phenyltetrazolyl), gave ethylbenzene in only 51% yield but this rose to 83% on slow dropwise addition.   Solvent was also important in the reaction.   Best yields of product, ArR', were obtained in diethyl ether.   In a non-polar solvent such as benzene, only low yields of the cross-coupled (ipso) product could be isolated. Similar results were found for strongly coordinating solvents such as tetrahydrofuran.   In these cases, extensive displacement of the group, R', was observed with consequent isolation of the original phenol, ArOH.

Although the impetus for this work came from the Pd(O) catalysed replacement of a tetrazolyloxy group by hydrogen,[2] palladium complexes of various kinds were uniformly inactive for the ipso displacement of the heterocyclic group by alkyl or aryl.   Similarly, whilst ipso replacement by hydrogen can be effected with other heterocyclic ethers such as 5,6-diphenyl-1,2,4-triazinyl in place of 1-phenyltetrazolyl,[2] only the latter derivative was found to give

uniformly high yields in *ipso* replacement by alkyl or aryl. This marked specificity in both metal catalyst and leaving group indicates that the catalytic cycle is delicately balanced. A further pointer to this fine balance appears in the effect of solvent. The reaction is successful in diethyl ether, a weakly coordinating polar solvent but not in tetrahydrofuran, a strongly coordinating polar solvent; conversely, in a non-coordinating non-polar solvent such as benzene, no reaction was observed.
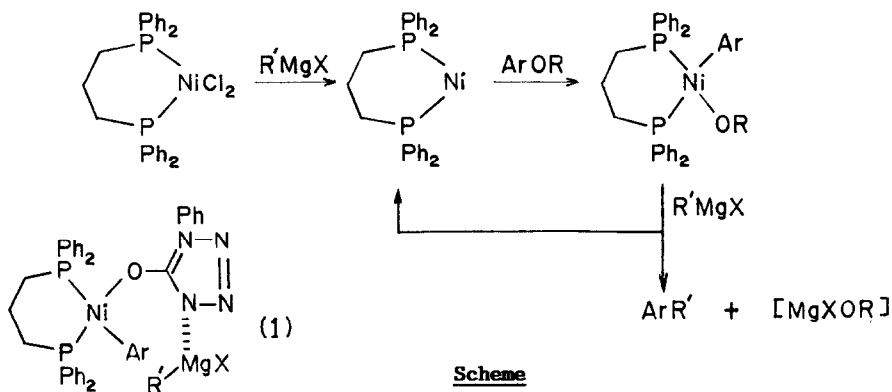
Scheme

A probable mechanism for the *ipso* displacement or cross-coupling is shown in the Scheme which is based on other work on the reaction of Grignard reagents with aryl iodides and nickel catalysts.[4] Reaction of $NiCl_2$.dppp with Grignard reagent generates the true catalyst, a Ni(O) species, which oxidatively adds the tetrazolyl ether, ArOR; decomposition of this complex by Grignard reagent leads to regeneration of the catalyst and elimination of the cross-coupled product, ArOR'. Strongly coordinating solvents such as tetrahydrofuran could interfere with this catalytic cycle by bonding strongly to the Ni(O) species. A non-polar solvent like benzene might be expected to destabilise the catalyst or prevent the Grignard reagent from attacking the catalyst complex. The specific role of the tetrazolyl ether may lie in its ability to coordinate to magnesium through one of the nitrogen atoms (Scheme, structure 1). It is known that tetrazoles form good complexes with a variety of metals[5] and an X-ray structure determination of a Pd(II) complex with a phenyl tetrazolyl ether has been published.[5] There seems little uniformity in the point of attachment of metals to the tetrazole ring.[6] Palladium chloride forms a complex in which the metal is co-ordinated to the N3 atom in 1-phenyl-5-phenoxytetrazole[5] whereas as, with zinc chloride, the metal is co-ordinated to N4 in 1-methyltetrazole. This variation in the site of co-ordination may explain, at least partly, why other heterocyclic groups found to be effective for hydrogenolysis of the C-O bond were not effective in this *ipso* replacement. Further work on this reaction is proceeding.

In a typical reaction, the tetrazolyl ether of phenol (equation 2; R = 5-(1-phenyl)tetrazolyl; 1.0 mmole) was mixed with dichloro-1,3-bisdiphenylphosphinopropane nickel ($NiCl_2$dppp; 0.029 mmole) in diethyl ether (10 ml) under nitrogen and was reacted dropwise, under reflux, with sec-butyl magnesium chloride (1.2 mmole). The mixture was stirred under reflux for ten minutes to yield sec-butylbenzene (77%, pure by gc and [1]H- nmr) after hydrolysis with dilute HCl and extraction with aqueous NaOH to remove 5- hydroxy-1-phenyltetrazole. No evidence for

self-coupling of the aryl ether was observed.

References

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