Transition Metal Catalysed *ipso*-Replacement Reactions of Heteroaromatic Phenolic Ethers by Zinc and Tin Organometallic Compounds

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Highly crystalline tetrazolyl or *pseudo*-saccharyl *O*-ethers of phenols provide good, selective leaving groups for nickel- and palladium-catalysed cross-coupling reactions with organo-zinc and -tin compounds to give a C–C bond in place of the original phenolic C–O bond.

Recently, 3-chloro-1,2-benzisothiazole-1,1-dioxide **1**, easily made from saccharin,[1] was found to provide an inexpensive alternative to 5-chloro-1-phenyltetrazole[2] for *ipso* conversion of phenolic ethers (**3**, **2**, respectively) into arenes (Scheme 1).[3] In both reactions the leaving groups, 1-phenyltetrazolone or saccharin **4**, are water soluble and easily separated from the desired reaction products. Although these are heterogeneous reactions rather than the more usual homogeneous processes found in *ipso* cross-coupling, they appear to involve oxidative addition/reductive elimination[4] similar to the mechanisms advanced for the homogeneous reactions. Owing to apparent similarities in mechanism of transfer reduction[5] and those through which cross-coupling reactions normally occur,[6] the possibility of achieving *ipso*-replacement of a phenolic C–O bond by a C–C bond by using tetrazolyl or pseudo-saccharyl leaving groups was investigated.

Homogeneous methods for *ipso*-replacement of phenolic C–O bonds by C–C to give alkyl-, alkenyl-, aryl-, alkynyl- and acyl-arenes include nickel- or palladium-catalysed cross-coupling of a variety of derivatives[8–13] with tin,[7d,e] zinc,[8] boron and aluminium[7b] organometallics. With these methods, the preparation of the required phenolic derivatives tends to involve hazardous expensive acids or anhydrides and time-consuming chromatographic purification before *ipso* replacement is attempted. In contrast, the crystalline phenolic tetrazolyl or *pseudo*-saccharyl ethers[1,2] are easily synthesised and reaction products are readily separated because of the high solubility of the leaving group in water. Cross-coupling of aryltetrazolyl ethers **2** with alkyl and aryl magnesium (Grignard) reagents [eqn. (1)] in the presence of nickel catalysts has been reported.[9]

$$\text{Aryl ether } \mathbf{2} + \text{RMgX} \rightarrow \text{Ar–R} \qquad (1)$$

In the present work, the efficiency of several nickel and palladium catalysts was tested for cross-coupling of aryl *pseudo*-saccharyl ethers **3** with alkyl magnesium (Grignard) reagents under reaction conditions similar to those used for the cross-coupling with aryl tetrazolyl ethers **3**[9] but they failed to give the desired alkylarene in yields greater than about 10%. However, cross-coupling of ethers **2** and **3** was successfully achieved with zinc and tin organometallic compounds (Table 1). Generally, nickel gave better results than did palladium.

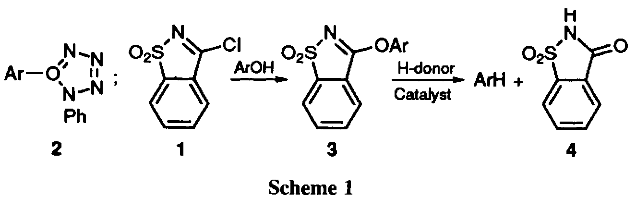
The procedure for cross-coupling of organozinc compounds with aryl heteroaromatic ethers **2** and **3** first requires addition of a small amount of reducing agent (often DIBAL) to prepare the true nickel(0) catalyst *in situ*. Ethers of both 1-phenyltetrazole (**2**, Ar = phenyl or 2-naphthyl) or *pseudo*-saccharin (**3**, Ar = 2-naphthyl) were treated with diethylzinc in the presence of various nickel catalysts and gave the corresponding ethylarenes in good yields (Entries 1–3, Table 1). These results indicated that either of the heteroaromatic ethers **2**, **3** is able to react efficiently with diethylzinc to give the desired cross-coupled product.

As an example, a solution of DIBAL (1 mol dm^{-3} in toluene; 0.07 ml) was added to a stirred mixture of $NiCl_2(dppp)$ (40.5 mg; 0.075 mmol) in dry THF (5 ml). A solution of 3-phenoxy-1,2-benzisothiazole (101.7 mg; 0.39 mmol) and in dry THF (15 ml) was added to the reaction mixture, followed immediately by dropwise addition of a solution of diethylzinc (1 mol dm^{-3} in hexane; 1 ml). The resulting mixture was heated to reflux and examined periodically by TLC. After 4 h, no starting material remained (TLC) and ethylbenzene had been formed in 74% yield (GC with internal standard).

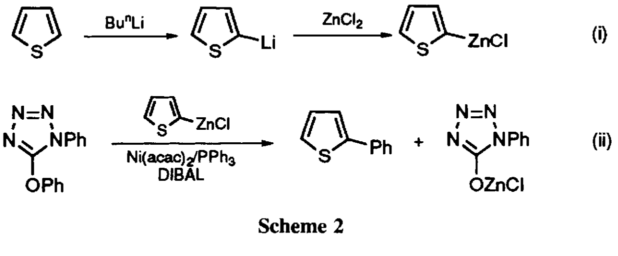
Table 1 Cross-coupling of aryl tetrazolyl **2** and aryl *pseudo*-saccharyl **3** ethers with organometallic compounds (R′–M) in the presence of transition metal catalysts

Ar–O–R (2 or 3)[a]					Yield[b]
Ar	Ether	R′–M	Catalyst	*t*/h	(%)
1[d] Phenyl	**3**	Et_2Zn	$NiCl_2(dppp)$ DIBAL	4.0	74
2[d] Phenyl	**2**	Et_2Zn	$NiCl_2(dppp)$ DIBAL	2.0	70
3[d] 2-Naphthyl	**2**	Et_2Zn	$NiCl_2(dppp)$ DIBAL	1.2	74[c]
4[e] 2-Naphthyl	**3**	Et_2Zn	$Ni(acac)_2$ PPh_3/DIBAL	3.0	59[c]
5[d] 2-Naphthyl	**2**	PhLi $ZnCl_2$	$Ni(acac)_2$ PPh_3/n-BuLi	8.0	76[c]
6[d] Phenyl	**2**	Thiophene--2-Li $ZnCl_2$	$Ni(acac)_2$ PPh_3/DIBAL	4.3	48[c]
7[e] 4-Acetylphenyl	**2**	PhLi $ZnCl_2$	$Ni(acac)_2$ PPh_3/DIBAL	4.0	61
8[e] 2-Naphthyl	**3**	Me_4Sn	$Pd(PPh_3)_4$ LiCl	23.0	48
9[e] 1-Naphthyl	**3**	Me_4Sn	$Pd(PPh_3)_4$ LiCl	6.5	63
10[d] 1-Naphthyl	**3**	Me_4Sn	$Ni(acac)_2$ PPh_3/DIBAL	3.3	80
11[d] 2-Naphthyl	**2**	Me_4Sn	$Ni(acac)_2$ PPh_3/DIBAL	4.0	24

[a] The synthesis of ethers **2**[1] and **3**[3,15] has been reported previously. [b] Yield of Ar–R′ were determined by GC (tridecane as internal standard) unless otherwise stated. [c] Isolated yield. [d] THF solvent. [e] Dioxane solvent.



Scheme 1



Scheme 2

In the absence of an external reducing agent (generally DIBAL), no formation of cross-coupled product was observed. Further, in agreement with previous findings,[14] replacement of DIBAL by n-butyllithium proved to be beneficial for the preparation of the active Ni^0 catalyst. For example, the yield of 2-phenylnaphthalene increased from 54% using DIBAL to 76% with n-butyllithium (Table 1).

Cross-coupling of tetrazolyl ethers was also attempted with aryl and heteroaryl zinc organometallics. In these cases, the necessary organozinc reagents were prepared *in situ* and were immediately treated with the heteroaromatic ether (Scheme 2). Heteroaromatic zinc derivatives can be used in this type of reaction (Entry 6, Table 1) and, importantly, it is selective enough to be used with an unprotected carbonyl group (Entry 7).

The possibility of using organotin reagents in cross-coupling with heteroaromatic ethers **2** and **3** was also investigated (Entries 8 to 11; Table 1). The results indicate that *pseudo*-saccharyl ethers (**3**, Entry 10) are more reactive than the corresponding tetrazolyl ones (**2**, Entry 11). In these reactions, nickel catalysts act better than palladium. Reaction yields were not optimised.

Interesting switches in activity are observed. Thus, although it was found previously that aryl tetrazolyl ethers **2** reacted well with Grignard reagents in the presence of nickel catalysts,[9] *pseudo*-saccharyl ethers **3** do not. Both types of ether react equally well with organozinc reagents in the presence of nickel or palladium catalysts and, with tetramethyltin, *pseudo*-saccharyl ethers **3** were more reactive than the corresponding tetrazolyl ones **2**. Thus, as the cross-coupling reagent changes from magnesium to zinc to tin, the nickel and palladium-catalysed response of the pseudo-saccharyl ethers improves remarkably and the response of the tetrazolyl ethers falls. These opposing effects give rise to the possibility of using the two heterocycles in the same molecule to attain selectivity towards different organometallic reagents.

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