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Palladium-Catalyzed Cross-Coupling Reaction of Organostannoates with Aryl Halides in Aqueous Medium

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Abstract: Water-soluble hydroxocomplexes **2**, easily formed from organotin trihalides **1** in aqueous alkaline solution, react readily with aryl halides in the same medium in the presence of palladium complexes to give cross-coupled products **3** in high yields.

Palladium-catalyzed cross-coupling of organotin reagents with organic halides offers the method of C-C bond formation remarkable for its efficiency and selectivity.[1] Commonly used tetraorganotins $RSnAlk_3$ contain, however, three inert anchoring groups. To overcome this disadvantage it seems promising to employ organotin trihalides **1**, notable also for their low toxicity and availability via economic direct synthesis from tin (II) compounds.[2] Unfortunately, these substances are poorly reactive towards electrophiles (e. g., in transmetallation) and unstable in most donor solvents.

We wish to report here that catalytic cross-coupling of halides **1** with aryl halides may be accomplished *via* the intermediate anionic hydroxocomplexes **2**,[3] produced *in situ* when the reaction is carried out in aqueous alkaline solution. This result is in good agreement with the well-known activation of organotin reagents with nucleophilic catalysts [4] and more recent experiments showing water to be highly effective medium for palladium-catalyzed reactions.[5,6]

The reaction was carried out with organotin reagents **1a-c** and aryl halides bearing various functionalities, the catalyst precursor being palladium dichloride or its complexes with the water-soluble phosphine ligand *m*-$NaO_3SC_6H_4PPh_2$ (dpm).[6] In most cases reaction in ca. 1 M aqueous KOH at 100° C was complete in 3 h giving excellent yields of cross-coupled products (see Table).

$$\underset{\mathbf{1}}{RSnHal_3} \xrightarrow[H_2O]{KOH} \underset{\mathbf{2}}{K_n[RSn(OH)_{3+n}]} \xrightarrow[PdCl_2 \text{ or } Pd(dpm)_2Cl_2]{ArI} \underset{\mathbf{3}}{Ar\text{-}R}$$

a R=Ph, Hal=Cl; **b** R=Me, Hal=Br; **c** R= $-CH_2CH_2CO_2H$, Hal=Cl; n=1,2

The most reactive of the organotin reagents studied has proved to be **1a**, reaction of which with potassium *m*-iodobenzoate was complete in 2 h at ambient temperature with the catalyst precursor as simple

as $PdCl_2$ (entry 1). Even strongly deactivated potassium *p*-iodophenolate gave a high yield of the phenylated product, although accompanied in this case by the symmetric dimer (p-$HOC_6H_4)_2$ (entry 2). For insoluble halides to react smoothly the water-soluble phosphine ligand dpm had to be employed, otherwise the catalyst decomposed rapidly and palladium black formed (entry 3,5 and 4,6,7). Moderately electron-withdrawing (entry 4) as well as donating (entry 6,7) substituents, even *o*-amino, were tolerated. Some aryl bromides may also be phenylated with this reagent (entry 8), though strong donor groups are not allowed (entry 9, compare with 2).

Methyl group transfer from the compound **1b** was also successful and, despite longer reaction times, quantitative isolated yields were achieved with soluble substrates (entry 10, 11).

Reagent **1c**, prepared from $SnCl_2$, HCl and acrylic acid,[2c] was chosen as an example of a functionalized organotin. Unfortunately, a significant role was played in its reactions by side processes leading to symmetric biaryls, probably due to β-H elimination (entry 12, 14). This problem was partly overcome by increasing the P : Pd ratio (entry 13, 16), although the use of chelating phosphine ligands might be preferable. With *o*-iodoaniline the isolated product was that of intramolecular cyclization: 3,4-dihydro-2(1H)-quinolone (hydrocarbostyril, entry 16).

One can conclude that if hard nucleophilic catalysis is applied one single organic radical of organotin reagent may be efficiently utilized in catalytic cross-coupling reaction with aryl halides. The present method combines the easy accessibility of starting materials with well-known advantages of using water as a reaction medium. Further study is under way in our group.

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Table. Product Yields in Reactions of ArX (1 mmol) with $RSnX_3$ in the Presence of $PdCl_2$ (0.01 mmol) in Aqueous Alkaline Medium.[7]

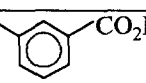
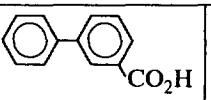
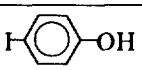
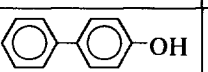
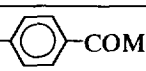
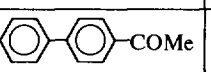
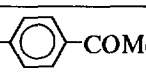
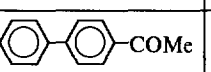
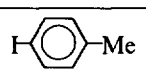
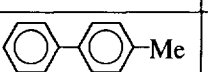
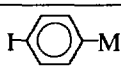
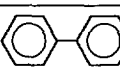
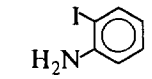
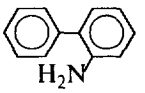
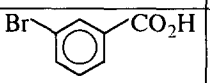
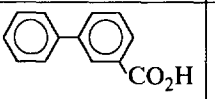
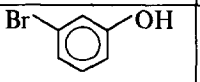
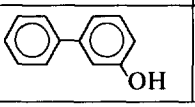
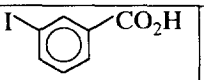
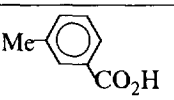
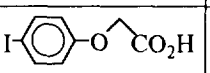
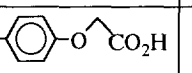
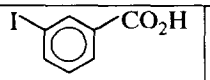
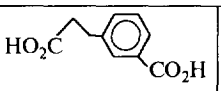
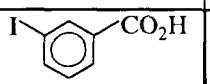
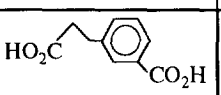
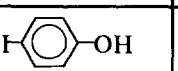
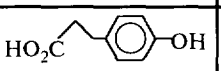
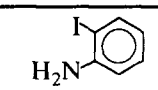
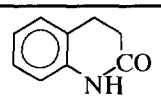
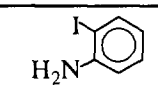
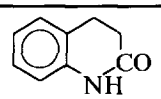
Entry	ArX	Product	T, °C	Time, h	Yield, % [a]
	+ **1a** $PhSnCl_3$ (1.2 mmol)				
1			25	2	83
2			100	3	87
3			100	3	(65)
4 [b]			100	3	80
5			100	3	(trace)

Table (Continued)

6[b]			100	3	86
7[b]			100	3	88
8			100	3	88
9			100	6	13
+ **1b** $MeSnBr_3$ (1.5 mmol)					
10			100	6	98
11			100	6	98
+ **1c** $HO_2CCH_2CH_2SnCl_3$ (1.2 mmol)					
12			25-40	24	<10
13[c,d]			100	3	71
14[c,d]			100	3	<10
15[b]			100	4	45
16[c]			100	3	57

a) Isolated yield based on starting ArX; GLC yield in parentheses

b) [dpm] : [Pd] = 2 : 1

c) [dpm] : [Pd] = 4 : 1

d) 0.002 mmol $PdCl_2$

References and Notes

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7. In a typical experiment the solution of **1a** (1.2 mmol, 0.19 ml) in water (2 ml) was treated with 3 M aq. KOH (3 ml, 9 mmol) and stirred for several minutes. The phosphine ligand (0.008 g, 0.02 mmol), *p*-iodoacetophenone (0.250 g, 1.0 mmol) and 0.1 M aq. $PdCl_2$ (0.1 ml, 0.01 mmol) were then added and the mixture was stirred for 3 h at 100° C under argon. The product was extracted with ether and recrystallized from aq. acetone to give an analytically pure sample of 4-acetylbiphenyl.

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