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Negishi-type coupling of bromoarenes with dimethylzinc

John M. Herbert*

Isotope Chemistry and Metabolite Synthesis Department, Sanofi-Synthélabo, Willowburn Avenue, Alnwick, Northumberland NE66 2JH, UK

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Abstract—Treatment of bromoarenes with dimethylzinc in the presence of a palladium catalyst provides a high-yielding route to methylarenes. The process accommodates a wide range of aromatic substituents and, in the majority of cases, is free of side reactions.

Nucleophilic displacement of an aromatic halogen is an important technique in the construction of polysubstituted aromatic systems with defined regiochemistry. In the course of a route development, aimed at the preparation of a multiply [^{13}C]-labeled drug candidate for human trial purposes, it was necessary to develop a robust method to convert derivatives of 4-bromobenzoic acid, or an ester thereof, into the corresponding 4-toluic acids or esters. Classical methods, involving metal–halogen exchange and exposure of the resulting anion to methyl iodide or dimethyl sulfate, are prone to side reactions where the substrate contains an electrophilic group, as are methods involving the coupling of more reactive organometallics such as Grignard reagents. In addition, the Suzuki–Miyaura coupling using methylboronic acid[1] gave unsatisfactory results with the substrates in question.

The Negishi coupling of organozinc halides with haloarenes or aryl triflates is an effective means for the attachment of a carbon chain to an arene.[2] This procedure normally uses organozinc halides,[3] but the possibility of adapting this methodology to use comparatively cheap dimethylzinc for the conversion of derivatives of 4-bromobenzoic acid into the corresponding *p*-toluic acid derivatives (Scheme 1) appeared attractive. Indeed, when ethyl 4-bromobenzoate was treated with dimethylzinc in the presence of the palladium(II) catalysts 1,1′-bis(diphenylphosphino)ferrocene (dppf) or 1,2-bis(diphenylphosphino)ethane (dppe), conversion into ethyl *p*-toluate proceeded smoothly and without any indication of side reactions. Bis(triphenylphosphine)palladium dibromide promoted the same reaction, but in this case the desired process was accompanied by reductive dehalogenation to give an additional 5% of ethyl benzoate. Bis(triphenylphosphine)palladium dichloride and tetrakis(triphenylphosphine)palladium were ineffective. Nevertheless, in all cases where the reaction proceeded, it was gratifying to note that there was no indication of attack upon the ester group (Table 1).

As shown in Table 2, identical conditions are suitable for the conversion of a range of other bromoarenes **1** into methylarenes **2** (Scheme 2). Isolated yields are generally in excess of 80% and often better than 90%. The process is not adversely affected by the presence of phenolic, amine or ether residues, or of unprotected alcohol groups, and bromophenylacetic acids are converted as effectively as bromobenzoic acids. The isolated yield of *p*-toluidine (**2j**) was modest, although this was improved by carrying out the reaction using the silyl-protected substrate **1k**. The process does, however, appear to be impeded by steric congestion, with the very hindered substrate **1q** undergoing very slow conversion to the methylated product, even in the presence of the slightly more active catalyst, Pd(dppe)Cl_2. Using the slightly less active Pd(dppf)Cl_2 catalyst, complete selectivity was observed for the displacement of bromide over chloride, with 2,4-dichlorotoluene (**2m**) being uncontaminated by chloroxylene, which would have resulted from the displacement of one of the chlorines.

Keywords: Arene alkylation; Palladium; Negishi coupling.

* Tel.: +44-1665-608414; fax: +44-1665-608815; e-mail: john.herbert@sanofi-synthelabo.com

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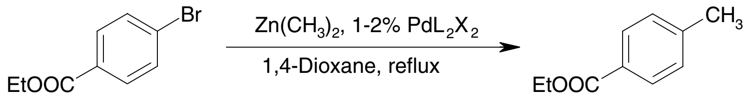


1a **2a**

Scheme 1. Formation of ethyl *p*-toluate from ethyl 4-bromobenzoate.

Table 1. Conversion of **1a** into **2a**, mediated by different palladium catalysts

Catalyst (mol%)	Time (h)	Yield (%)
Pd(dppf)Cl_2 (1.7)	2	81
Pd(dppe)Cl_2 (1.6)	2	95
$Pd(PPh_3)_2Br_2$ (2.2)	2	83
$Pd(PPh_3)_2Cl_2$ (1.6)	2	0
$Pd(PPh_3)_4$ (2.0)	3	0

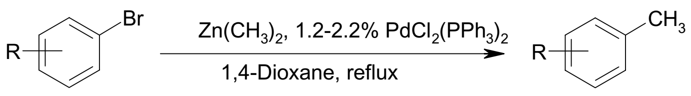
Indeed, the displacement of chlorine catalysed by Pd(dppf)Cl_2 was very much slower than that of bromine, even where the halogen is activated to displacement by the presence of a nitro group or by attachment to a π-deficient heterocycle; 2-nitrochlorobenzene underwent 60% conversion to 2-nitrotoluene after 3 h in the presence of 1.5% Pd(dppf)Cl_2, while 4,7-dichloroquinoline underwent 48% displacement of a single chlorine in 3 h (using 3.4% Pd(dppf)Cl_2) and 2,6-dichloropyridine suffered only 2% monomethylation in 4 h (using 2.6% Pd(dppf)Cl_2). On the other hand, the more activated 2-chloropyrimidine was completely converted into 2-methylpyrimidine within 90 min, in the presence of 1.4% Pd(dppf)Cl_2 (this product was not isolated).

The representative aryl triflate[4] derived from ethyl 4-hydroxybenzoate also undergoes palladium-catalysed methylation, in line with the results obtained using bromoarenes (Scheme 3). However, this substrate appears to be more susceptible to the competing reduction process than is the corresponding bromoarene and, in this instance, the product was accompanied by ethyl benzoate (5%).

One surprise was the observation, in the case of methyl 2-bromobenzoate (**1h**), that the product was accompanied by methyl benzoate, the yield of the latter depending upon the catalyst. This is analogous to the formation of ethyl benzoate in the presence of $Pd(PPh_3)_2Br_2$ mentioned already. In the absence of possibilities for β-hydride elimination, it may be surmised that dimethylzinc acts as a reducing agent, probably by hydride transfer to the palladium centre. This is not exceptional in itself, since formation of the presumed palladium(0) active catalyst would require

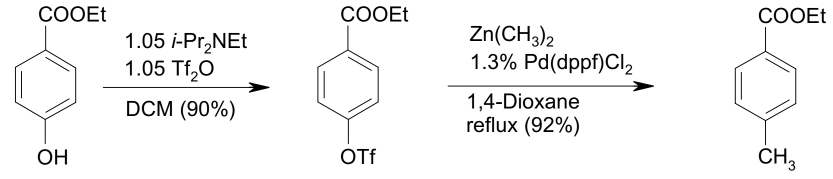
Table 2. Conversion of bromoarenes **1** into methylarenes **2**

1	R	Catalyst (mol%)	Time (h)	2	Yield (%)	Side products
1a	4-COOEt	Pd(dppf)Cl_2 (1.7)	2	**2a**	81	
1b	4-COOH	Pd(dppf)Cl_2 (1.3)	2	**2b**	100	
1c	4-$COCH_3$	Pd(dppf)Cl_2 (1.7)	1	**2c**	100	
1d	4-CH_2CH_2OH	Pd(dppf)Cl_2 (1.0)	1	**2d**	100	
1e	4-COOH, 3-NO_2	Pd(dppf)Cl_2 (3.0)	2	**2e**	100	
1f	3-$COCH_3$	Pd(dppf)Cl_2 (2.2)	2	**2f**	84	
1f	3-$COCH_3$	Pd(dppe)Cl_2 (3.3)	2	**2f**	79	
1g	3-CH_2COOH	Pd(dppf)Cl_2 (1.8)	1	**2g**	92	
1h	2-$COOCH_3$	Pd(dppf)Cl_2 (2.0)	2	**2h**	61	PhCOOMe (39%)
1h	2-$COOCH_3$	Pd(dppe)Cl_2 (4.4)	1.5	**2h**	88	PhCOOMe (11%)
1i	2-$COCH_3$	Pd(dppe)Cl_2 (1.2)	1.5	**2i**	100	
1j	4-NH_2	Pd(dppf)Cl_2 (1.8)	1.5	**2j**	55	
1k	4-$N(TMS)_2$	Pd(dppf)Cl_2 (1.5)	1.5	**2j**	81	
1m	2,4-Cl_2	Pd(dppf)Cl_2 (2.2)	2	**2m**	91	
1m	2,4-Cl_2	Pd(dppe)Cl_2 (4.0)	1.5	**2m**	73	Chloroxylene (2%)
1n	7-Hydroxy-3,4-benzo-	Pd(dppf)Cl_2 (2.0)	1	**2n**	84	
1o	2-NO_2, 4-OMe	Pd(dppf)Cl_2 (2.0)	1	**2o**	93	
1p	2,3-Benzo	Pd(dppf)Cl_2 (1.5)	2	**2p**	100	
1q	2,4,6-Triisopropyl	Pd(dppe)Cl_2 (3.5)	2.5	**2q**	12.5	
1r	2-Indolyl	Pd(dppf)Cl_2 (2.0)	1.5	**2r**	61	



1 **2**

Scheme 2. General conversion of bromoarenes into methylarenes.



2a

Scheme 3.

reduction by dimethylzinc. However, where bidentate palladium catalysts (Pd(dppf)Cl$_2$ or Pd(dppe)Cl$_2$) are used, this side reaction is observed only in the presence of an *ortho*-ester substituent. It is therefore possible that a cyclometalated species is formed, with the ester coordinated to the metal centre, and that the cyclometalated species is more susceptible to reductive dehalogenation than are intermediates in the principal catalytic cycle.

A few instances of palladium-catalysed ethylation, using diethylzinc in hexane were examined also, in an effort to test the limits of the process. Compound **1a** undergoes ethylation in the presence of Pd(dppe)Cl$_2$ (1.5%) to give ethyl 4-ethylbenzoate (89%), while bromine is displaced selectively from 2,6-dichlorobromobenzene in the same manner as above (81% conversion after 2 h with 2% Pd(dppf)Cl$_2$). Bearing in mind that with diethylzinc, β-hydride elimination from any ethylpalladium species might be expected, there was no indication of reductive dehalogenation in either of these cases. Moreover, methyl 2-bromobenzoate behaved in much the same way towards diethylzinc as to dimethylzinc, with the formation of methyl *o*-toluate (74%) and methyl benzoate (26%) in a ratio comparable to those noted above (reaction time 2 h, with 1.9% Pd(dppf)Cl$_2$).

In conclusion, the results presented demonstrate that treatment of bromoarenes with dialkylzinc reagents (and particularly with dimethylzinc) in the presence of a catalytic quantity of a bidentate phosphine-containing palladium catalyst constitutes an efficient means for their conversion to methylarenes. Of the catalysts examined, Pd(dppf)Cl$_2$ is slightly less active than Pd(dppe)Cl$_2$, and the former is therefore better suited to carry out displacement of bromine in the presence of chlorine.

A general procedure is as follows: Dimethylzinc (2 M in toluene; 2 M equiv) is added under nitrogen to bromoarene and bis(triphenylphosphine)palladium dichloride (1.2–3.0 mol%) in dioxane (2–3 mL/mmol) and the resulting pale yellow solution is heated at reflux for 1–2 h. Upon cooling, the mixture is quenched by the addition of methanol (0.2 mL/mmol), and then diluted with *tert*-butyl methyl ether, washed with 1 M hydrochloric acid and water and dried. The mixture may be filtered through a short pad of silica gel to remove coloured impurities. Solvent evaporation leaves the product, which is generally suitable for use without further purification. All compounds prepared are known, and were characterised by NMR and mass spectrometric methods.

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