



Negishi cross-coupling with functionalised organozinc compounds prepared by lithium–zinc transmetallation

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Abstract—The reaction of some functionalised organolithium compounds **2** (easily prepared by DTBB-catalysed lithiation of isochroman, phthalan and 2,3-dihydrobenzofuran) with an equimolecular amount of zinc bromide followed by reaction with an aryl or alkenyl bromide in the presence of a catalytic amount of Pd(PPh₃)₄ or Pd(PPh₃)₂(OAc)₂ (5 mol%) under THF reflux overnight gave the expected cross-coupling compounds. These arylation or alkenylation processes, which work also with iodinated substrates, are not possible in the absence of the zinc or palladium compounds under the same reaction conditions. © 2001 Elsevier Science Ltd. All rights reserved.

The use of functionalised organometallic compounds in synthetic organic chemistry makes possible the direct preparation of complex target molecules by reaction with different electrophilic reagents.¹ The stability of the organometallic intermediate depends mainly on the metal present in the molecule: an increase of the ionic nature of the carbon–metal bond increases the reactivity of the organometallic species and provokes less tolerance towards the functional groups present in the molecule. Thus, as expected, functionalised organolithium reagents² are far more reactive than the corresponding organozinc derivatives³ and, consequently, are limited concerning the functionality that they can bear. On the contrary, functionalised organozinc compounds react only with very reactive electrophiles (i.e. allylic or benzylic halides) and frequently they should be activated by transforming them into organocopper compounds or mainly by means of a transition metal catalyst such as nickel or palladium.³ In general, functionalised organozinc reagents are prepared by iodine–zinc or bromine–zinc interchange. Another classical way, consisting of a lithium–zinc transmetallation, is very limited due to the restricted stability of functionalised organolithium compounds,² which in many cases have to be generated and used under Barbier-type reaction conditions.⁴ In the last few years, we have been using an arene-catalysed lithiation^{5–9} under very mild reaction conditions in order to prepare functionalised

organolithium compounds, which by reaction with electrophiles lead to the formation of polyfunctionalised organic molecules. In this paper we describe the transformation of some of these reactive organolithium intermediates into the corresponding organozinc derivatives followed by palladium-catalysed cross coupling with *sp*²-hybridised halogenated materials, the so-called Negishi reaction.^{10,11}

A mixture of a THF filtered solution of the functionalised organolithium intermediate **2a** [2 mmol scale; easily prepared by 4,4'-di-*tert*-butylbiphenyl (DTBB)-catalysed reductive ring opening¹² of isochroman (**1a**)¹³] and dry zinc bromide (1:1 molar ratio) was treated with different aryl bromides in the presence of a palladium catalyst (1:0.05 molar ratio, 5% molar) and refluxed overnight to give, after hydrolysis with hydrochloric acid (see Table 1, footnote f), the expected compounds **3a–h** (Scheme 1, Fig. 1 and Table 1, entries 1–9). As catalyst, either commercially available tetrakis(triphenylphosphine)palladium(0) (method A) or bis(triphenylphosphine)palladium(II) acetate [method B; easily prepared by mixing palladium(II) acetate and triphenylphosphine (1:2 molar ratio)] gave in both cases comparable yields (Table 1, compare entries 1/2 and 14/15). The reaction works nicely with iodobenzene (Table 1, entry 1 and footnote e) but failed for chlorobenzene. In addition, aryl bromides containing electron withdrawing (F, CF₃, MeCO, CN, CO₂Et) or electron donating groups (MeO, Me₂N) (Table 1, entries 3–9) can be used for the coupling reaction as well as naphthalene or heterocyclic derivatives (Fig. 1 and Table 1, entries 10–13).

Keywords: lithium–zinc transmetallation; functionalised organozinc reagents; palladium-catalysed cross-coupling.

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Table 1. Preparation of compounds **3**

Entry	Organolithium intermediate	Brominated derivative	Method ^a	Product No. ^b	Yield (%) ^c
1	2a	PhBr	A	3a	77 (83) ^d
2			B	3a	74
3	2a	4-FC ₆ H ₄ Br	B	3b	69
4	2a	4-CF ₃ C ₆ H ₄ Br	A	3c	67
5	2a	4-MeOC ₆ H ₄ Br	A	3d	63
6	2a	4-Me ₂ NC ₆ H ₄ Br	B	3e	38 ^e
7	2a	4-MeCOC ₆ H ₄ Br	A	3f	33
8	2a	4-NCC ₆ H ₄ Br	B	3g	78 ^e
9	2a	4-EtO ₂ CC ₆ H ₄ Br	B	3h	49 ^e
10	2a	1-Bromonaphthalene	A	3i	56
11	2a	4-Bromopyridine	A	3j	29 ^e
12	2a	2-Bromothiophene	A	3k	59
13	2a	3-Bromofuran	B	3l	30
14	2a	Me ₂ C=CHBr	A	3m	58
15			B	3m	64
16	2b	PhBr	B	3n	43
17	2c	PhBr	B	3o	49

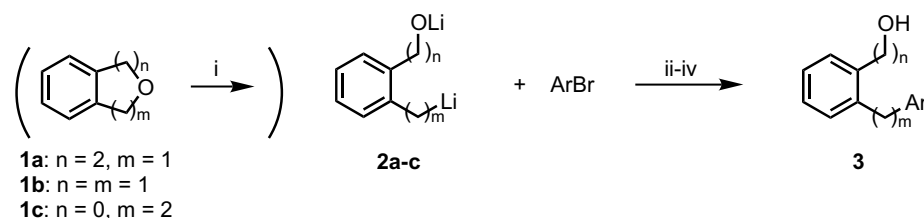
^a Method A: Pd(PPh₃)₄; method B: Pd(PPh₃)₂(OAc)₂.

^b All products **3** were ≥95% pure (300 MHz ¹H NMR and/or GLC) and were fully characterised by spectroscopic means (IR, ¹H and ¹³C NMR, and MS).

^c Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the heterocyclic precursor of intermediates **2a–c** (isochroman, phthalan and 2,3-dihydrobenzofuran, respectively).

^d Iodobenzene was used.

^e Water was used for the final hydrolysis.



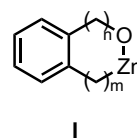
Scheme 1. Reagents and conditions: (i) Li, DTBB cat. (5 mol%), THF, 0 or 20°C, then filter off the excess of lithium; (ii) ZnBr₂, THF, 20°C, 30 min; (iii) Pd(PPh₃)₄ [method A] or Pd(PPh₃)₂(OAc)₂ [method B] cat. (5 mol%), THF, 60°C, overnight; (iv) HCl–H₂O.

The reaction shown in Scheme 1 is also applicable to olefinic derivatives. Thus, for instance the reaction of intermediate **2a** with 1-bromo-2-methylpropene using both methods A and B yielded the expected compound **3m** (Fig. 1 and Table 1, entries 14 and 15).

Finally, and in order to check the cross-coupling reaction with other functionalised organolithium compounds, the reaction of intermediates **2b** and **2c** (easily prepared by DTBB-catalysed lithiation of phthalan¹⁴ and 2,3-dihydrobenzofuran,¹⁵ respectively) with bromobenzene under the same reaction conditions as for intermediate **2a** was studied, yielding compounds **3n** and **3o**, respectively (Scheme 1, Fig. 1 and Table 1, entries 16 and 17).¹⁶

In an attempt to generalise the reaction shown in Scheme 1, we tried the same process with *sp*³- and *sp*-hybridised brominated materials (such as cyclohexyl bromide and 1-bromo-2-phenylacetylene), obtaining only the reduced product, 2-(2-methylphenyl)ethanol (>90%), without any detectable coupling product.

Concerning the mechanism of the reaction, three blank experiments were carried out using the intermediate **2a** and bromobenzene as reagents under the same reaction conditions shown in Scheme 1: (1) in the absence of zinc bromide and the palladium catalyst, bromobenzene (~90%) and 2-(2-methylphenyl)ethanol (>90%), resulting from a lithium–hydrogen exchange, were isolated; (2) in the absence of zinc bromide and with method A, 2-(2-methylphenyl)ethanol (>90%) and biphenyl (91%) were isolated; and (3) in the absence of any palladium catalyst almost quantitative amounts of 2-(2-methylphenyl)ethanol and bromobenzene were obtained. With this information in hand, and considering the **2**/zinc bromide ratio used, an intermediate of type **I** can be initially involved in the process, taking part in the catalytic cycle generally accepted in the Negishi cross-coupling reaction.¹⁰



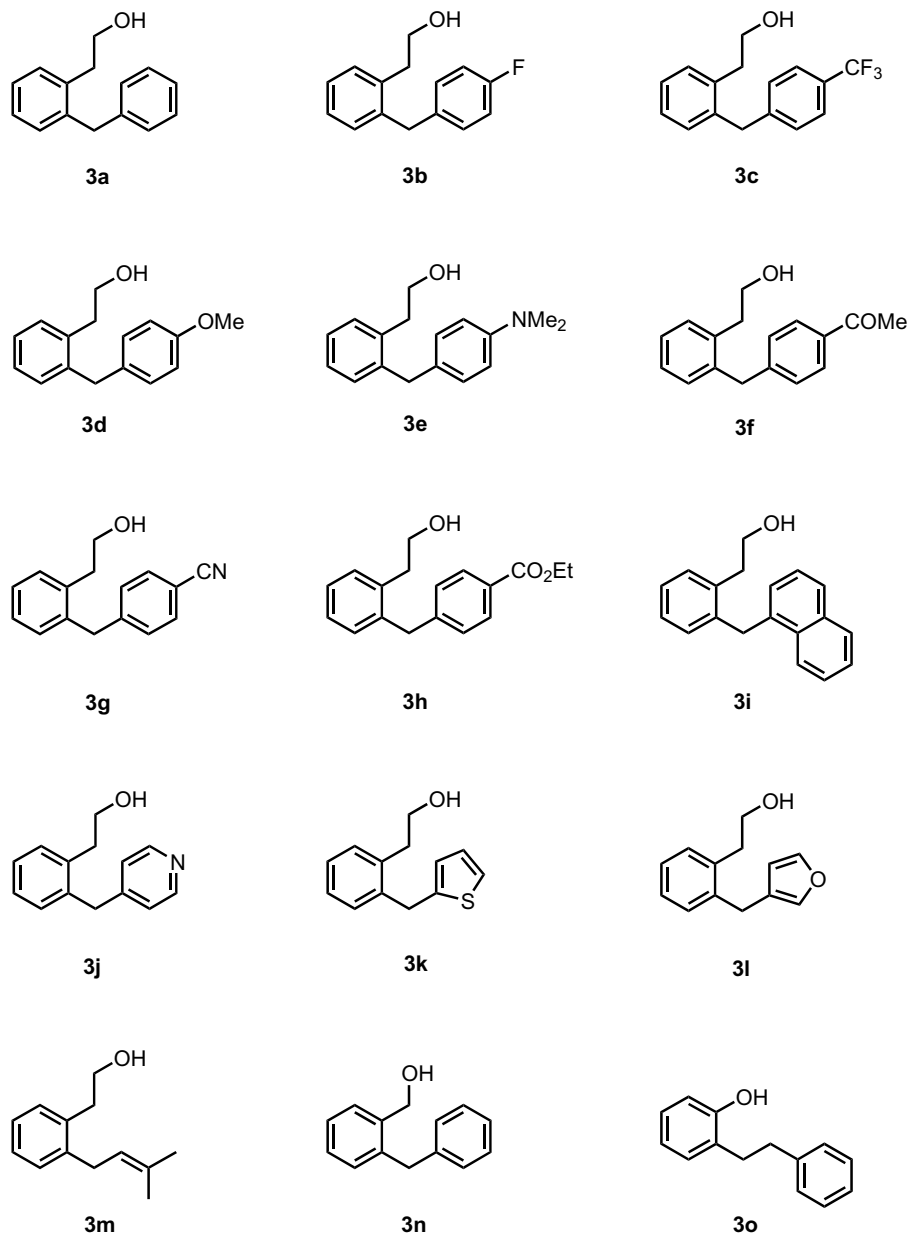


Figure 1. Compounds 3 prepared.

Finally, we can conclude that the palladium-catalysed Negishi cross-coupling reaction can be applied to the in situ generated functionalised organozinc reagents (prepared from the corresponding functionalised organolithium compounds by a lithium–zinc transmetallation process), so in general an arylation reaction takes place at the carbon attached to the metal, the process being not possible with the starting lithiated species.

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16. Typical procedure for compounds **3**: To a stirred green suspension of lithium powder (70 mg, 10 mmol) and DTBB (53 mg, 0.2 mmol) in THF (10 ml) was added dropwise isochroman (**1a**) (0.25 ml, 2 mmol) at room temperature and under an argon atmosphere. After the addition the colour disappeared and after 30 min of stirring the green colour appeared again. Then, the excess of lithium was filtered off under an inert atmosphere and the filtrate was added to a solution of dry zinc bromide (450 mg, 2 mmol) in THF (5 ml). After 30 min of stirring, to the resulting solution was added a solution of the corresponding aryl bromide (2.2 mmol) and the palladium catalyst (0.1 mmol for both methods A and B) in THF (10 ml) and it was refluxed overnight. After cooling to rt, the mixture was successively treated with 3 M hydrochloric acid (4 ml) (see Table 1, footnote f) and water (10 ml), and extracted with ether (3×10 ml). The organic layer was dried (Na_2SO_4) and evaporated (15 torr) to give a residue, which was purified by column chromatography (silica gel, hexane–ethyl acetate) to give pure compounds **3**.