## Room-temperature nickel-catalysed cross-couplings of aryl chlorides with arylzincs<sup>†</sup>

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*Received 5th August 2010, Accepted 9th November 2010* DOI: 10.1039/c0cc03064c

P,N,O-chelate nickel complexes efficiently catalyse the crosscoupling reaction of aryl chlorides with arylzinc reagents in a 1:1 THF-NMP mixture. The reactions proceed at room temperature with low catalyst loading.

Biaryl structures are found in many natural products, pharmaceuticals, agrochemicals, liquid crystals, and advanced materials.<sup>1</sup> Transition-metal-catalysed cross-coupling reactions between aryl halides and arylmetallic reagents are powerful tools for the synthesis of biaryl compounds.<sup>1,2</sup> Among the coupling reactions, the Negishi reaction is one of the most popular approaches to biaryls.<sup>1</sup> Organozinc reagents show much better functional group compatibility compared with Grignard reagents in the Kumada reaction and higher reactivity than organoboron reagents in the Suzuki reaction, organotin reagents in the Stille reaction and organosilicon reagents in the Hiyama reaction.<sup>2</sup> The high reactivity of organozinc reagents makes the coupling reaction proceed under milder reaction conditions. Quite a few coupling reactions of aryl iodides and bromides with arylzinc reagents can be carried out at room temperature or below in the presence of nickel or palladium catalysts.<sup>2,3</sup> However, a Negishi reaction of aryl chlorides often requires an elevated temperature due to the low reactivity of the C-Cl bond.<sup>4</sup> Only a few reports of room temperature Negishi coupling of aryl chlorides have been published, predominantly using activated aryl chlorides.<sup>3e,5</sup> Very recently, Organ and co-workers reported a Pd-catalysed reaction of 2,4,6-Me<sub>3</sub>C<sub>6</sub>H<sub>2</sub>ZnCl with 2-chloro-1,3-dimethylbenzene at 23 °C, giving a cross-coupling product in 90% isolated yield.<sup>5e</sup> On the other hand, the use of aryl chlorides, room temperature reaction conditions and less expensive Ni-based catalysts would economically benefit a number of industrial processes. Herein we report a class of highly efficient nickel catalysts (Ia-IV, Fig. 1) which lead to Negishi crosscoupling of aryl chlorides at room temperature.

Synthetic details of complexes **Ia–IV** are in the ESI.<sup>†</sup> Complex **Ia** was obtained previously as a trace impurity.<sup>6</sup> Now we can prepare it in gram scale for catalytic study. In preliminary studies of the catalytic property, we investigated the reaction of p-ClC<sub>6</sub>H<sub>4</sub>OMe with PhZnCl and found that the reaction proceeded efficiently in the presence of 0.2 mol% **Ia** at



Fig. 1 P,N,O- and P,N,S-chelate nickel complexes.

room temperature using a mixture of THF and NMP (1 : 1) as solvent. Other solvents such as THF, toluene, THF–toluene (1 : 1), THF–DMA (1 : 1) and THF–NMP (5 : 1) were not very effective, leading to a trace to moderate yield of the cross-coupling product (Table 1). Under the same conditions as above using THF–NMP (1 : 1) as solvent, we found that the P,N,O-chelate complexes (I and III) displayed a higher catalytic activity than the P,N,S-chelate complexes (II and IV), and Ib showed almost the same catalytic activity as Ia.

We next tested the reaction using different aryl chlorides and arylzinc reagents in the presence of Ia or III (Table 2). The reactions were carried out in a 1 : 1 mixture of THF and NMP using 1.5 equiv. of ArZnCl prepared *in situ* from ArLi and anhydrous ZnCl<sub>2</sub>. Almost all reactions can be run at room

**Table 1** Evaluation of catalytic activity of complexes Ia-IV in theNegishi reaction<sup>a</sup>

	PhZnCl + MeO	CIMeO	Ph
Entry	Catalyst	Solvent	Yield <sup>b</sup> (%)
1	Ia	THF	31
2	Ia	THF $-$ toluene (1 : 1)	Trace
3	Ia	THF–DMA $(1:1)$	78
4	Ia	THF-NMP $(5:1)$	60
5	Ia	THF-NMP $(1:1)$	98
6	Ib	THF-NMP $(1:1)$	97
7	II	THF-NMP $(1:1)$	67
8	III	THF-NMP $(1:1)$	92
9	IV	THF–NMP $(1 : 1)$	62

<sup>*a*</sup> The reactions were carried out at room temperature for 24 h in the presence of 0.2 mol% catalyst, 0.5 mmol p-ClC<sub>6</sub>H<sub>4</sub>OMe and 0.75 mmol PhZnCl were employed. <sup>*b*</sup> Isolated product yields.

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<sup>&</sup>lt;sup>†</sup> Electronic supplementary information (ESI) available: Experimental procedures and characterization details. CCDC 787973. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc03064c

temperature. However, at elevated temperatures the reactions proceeded faster and required less catalyst loading (entries 9 and 10, Table 2). For sterically hindered deactivated aryl chlorides such as o-ClC<sub>6</sub>H<sub>4</sub>OMe an elevated reaction temperature is necessary to drive the reaction to completion (entries 12 and 13, Table 2). While for the sterically hindered chloride substrate with an electron-withdrawing group such as o-ClC<sub>6</sub>H<sub>4</sub>C(O)Ph, the reactions can be completed at room temperature in excellent yields at a catalyst loading of 2 mol% (entries 11 and 19, Table 2). For the reactions of p-MeC<sub>6</sub>H<sub>4</sub>ZnCl with other aryl chlorides except p-ClC<sub>6</sub>H<sub>4</sub>CN, catalyst loading could be as low as 0.05 mol% to 0.2 mol%. Among those substrates, unactivated and activated aryl chlorides exhibited a higher reactivity and deactivated aryl chlorides showed a little lower reactivity. p-ClC<sub>6</sub>H<sub>4</sub>CN displayed different reactivity from other activated aryl chlorides. It required much higher catalyst loading than those

of other activated aryl chlorides such as p-ClC<sub>6</sub>H<sub>4</sub>COOEt, p-ClC<sub>6</sub>H<sub>4</sub>C(O)NEt<sub>2</sub> and p-ClC<sub>6</sub>H<sub>4</sub>CF<sub>3</sub>. For example, reaction between p-ClC<sub>6</sub>H<sub>4</sub>CN and p-MeC<sub>6</sub>H<sub>4</sub>ZnCl requires 2 mol% Ia and gave a cross-coupling product in 87% yield. The same reaction required 1 mol% III and gave 99% yield of the product. This phenomenon has been observed by us and other groups previously and was ascribed to the coordination of the CN group with the nickel centre.<sup>3e,4g</sup> It was also noticed that in those reactions involving p-ClC<sub>6</sub>H<sub>4</sub>CN complex III seems to be a more active catalyst than complex Ia. The electronic and steric properties of the nucleophiles also affect the reactions remarkably. p-Me<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>ZnCl was more reactive than p-MeC<sub>6</sub>H<sub>4</sub>ZnCl due to the electron-donating effect of the NMe<sub>2</sub> group. Reaction of the former with p-ClC<sub>6</sub>H<sub>4</sub>OMe required only 0.1 mol% Ia, affording a cross-coupling product in 96% yield (entry 22, Table 2). o-MeC<sub>6</sub>H<sub>4</sub>ZnCl was less reactive than p-MeC<sub>6</sub>H<sub>4</sub>ZnCl in the coupling reaction. Its

Table 2Cross-coupling of arylzinc chlorides with aryl chlorides catalysed by Ia and  $III^a$ 

ArZnCl + Ar'Cl Ar-Ar' THF-NMP (1:1)								
Entry	Ar	Ar <sup>1</sup> Cl	Catalyst (mol%)	Time/h	$\operatorname{Yield}^{f}(\%)$			
1	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	PhCl	Ia (0.05)	24	99			
2	p-MeC <sub>6</sub> H <sub>4</sub>	p-PhC(O)C <sub>6</sub> H <sub>4</sub> Cl	Ia (0.1)	24	98			
3	p-MeC <sub>6</sub> H <sub>4</sub>	p-NCC <sub>6</sub> H <sub>4</sub> Cl	Ia (2)	24	87			
4	p-MeC <sub>6</sub> H <sub>4</sub>	$p-CF_3C_6H_4Cl$	Ia (0.05)	24	95			
5	p-MeC <sub>6</sub> H <sub>4</sub>	$2-ClC_5H_4N$	<b>Ia</b> (0.1)	24	99			
6	p-MeC <sub>6</sub> H <sub>4</sub>	$p-Et_2NC(O)C_6H_4Cl$	Ia (0.05)	12	99			
7	p-MeC <sub>6</sub> H <sub>4</sub>	p-EtOC(O)C <sub>6</sub> H <sub>4</sub> Cl	Ia (0.05)	12	99			
8	$p-MeC_6H_4$	$p-MeOC_6H_4Cl$	Ia (0.15)	24	96			
$9^b$	p-MeC <sub>6</sub> H <sub>4</sub>	p-EtOC(O)C <sub>6</sub> H <sub>4</sub> Cl	Ia(0.03)	6	98			
$10^{b}$	$p-MeC_6H_4$	p-MeOC <sub>6</sub> H <sub>4</sub> Cl	Ia (0.02)	12	99			
11	$p-\text{MeC}_6H_4$	o-PhC(O)C <sub>6</sub> H <sub>4</sub> Cl	Ia (2)	24	97			
12	p-MeC <sub>6</sub> H <sub>4</sub>	o-MeOC <sub>6</sub> H <sub>4</sub> Cl	Ia(2.5)	24	74			
13 <sup>c</sup>	p-MeC <sub>6</sub> H <sub>4</sub>	o-MeOC <sub>6</sub> H <sub>4</sub> Cl	Ia(2.5)	12	98			
14	p-MeC <sub>6</sub> H <sub>4</sub>	5-Cl-2-MeOC <sub>6</sub> H <sub>3</sub> COOMe	Ia(2)	24	93			
15	p-MeC <sub>6</sub> H <sub>4</sub>	p-Et <sub>2</sub> NC(O)C <sub>6</sub> H <sub>4</sub> Cl	<b>III</b> (0.05)	24	94			
16	p-MeC <sub>6</sub> H <sub>4</sub>	p-NCC <sub>6</sub> H <sub>4</sub> Cl	$\mathbf{III}(1)$	24	99			
17	p-MeC <sub>6</sub> H <sub>4</sub>	PhCl	$\mathbf{III}(0,1)$	24	98			
18	p-MeC <sub>6</sub> H <sub>4</sub>	p-MeOC <sub>6</sub> H <sub>4</sub> Cl	III(0.2)	24	91			
19	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	$\rho$ -PhC(O)C <sub>6</sub> H <sub>4</sub> Cl	$\mathbf{III}(2)$	24	98			
20	$p-MeC_6H_4$	p-EtOC(O)C <sub>6</sub> H <sub>4</sub> Cl	III(0.1)	24	99			
21	p-Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	PhCl	Ia (0.05)	12	99			
22	$p-Me_2NC_6H_4$	p-MeOC <sub>6</sub> H <sub>4</sub> Cl	<b>Ia</b> (0.1)	12	96			
23	o-MeC <sub>6</sub> H <sub>4</sub>	p-PhC(O)C <sub>6</sub> H <sub>4</sub> Cl	Ia(0.5)	24	97			
24	o-MeC <sub>6</sub> H <sub>4</sub>	p-EtOC(O)C <sub>6</sub> H <sub>4</sub> Cl	Ia (0.15)	24	99			
25	o-MeC <sub>6</sub> H <sub>4</sub>	p-Et <sub>2</sub> NC(O)C <sub>6</sub> H <sub>4</sub> Cl	<b>Ia</b> (0.1)	24	96			
26	o-MeC <sub>4</sub> H <sub>4</sub>	<i>p</i> -MeOC <sub>c</sub> H <sub>4</sub> Cl	$\mathbf{Ia}(1)$	24	82			
27	$\rho$ -MeC <sub>6</sub> H <sub>4</sub>	p-Et <sub>2</sub> NC(O)C <sub>6</sub> H <sub>4</sub> Cl	$\mathbf{III}(0.15)$	24	99			
28	o-MeC <sub>6</sub> H <sub>4</sub>	p-EtOC(O)C <sub>6</sub> H <sub>4</sub> Cl	III(0.2)	24	98			
29	o-MeC <sub>6</sub> H <sub>4</sub>	p-NCC <sub>6</sub> H <sub>4</sub> Cl	$\mathbf{III}$ (3)	24	86			
30	o-MeC <sub>6</sub> H <sub>4</sub>	p-MeOC <sub>6</sub> H <sub>4</sub> Cl	$\mathbf{\overline{H}}(\mathbf{I})$	24	76			
31	2-Furvl	p-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> Cl	Ia (1.5)	24	94			
32	2-Furvl	p-EtOC(O)C <sub>6</sub> H <sub>4</sub> Cl	Ia (0.75)	24	99			
33	2-Furvl	p-NCC <sub>c</sub> H <sub>4</sub> Cl	Ia (2.5)	24	79			
34	2-Furvl	p-NCC <sub>c</sub> H <sub>4</sub> Cl	$\mathbf{III}(2)$	24	99			
35	2-Furvl	p-EtOC(O)C <sub>4</sub> H <sub>4</sub> Cl	$\mathbf{\overline{III}}$	24	99			
$36^d$	p-EtO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>	p-NCC <sub>4</sub> H <sub>4</sub> Cl	$\mathbf{Ia}$ (5)	12	69			
$37^d$	p-EtO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>	p-PhC(O)C <sub>6</sub> H <sub>4</sub> Cl	III (5)	12	75			
38 <sup>b,e</sup>	p-EtO <sub>2</sub> CC <sub>4</sub> H	<i>p</i> -NCC <sub>2</sub> H <sub>4</sub> Cl	Ia(5)	12	65			
39 <sup>b,e</sup>	$p = EtO_2 C C_6 H_4$	p-PhC(O)C <sub>4</sub> H <sub>4</sub> Cl	$\mathbf{III}$ (5)	12	67			
$40^e$	p-MeC <sub>4</sub> H <sub>4</sub>	p-EtOC(O)C <sub>4</sub> H <sub>4</sub> Cl	Ia(2)	12	30			

cat.

<sup>*a*</sup> The reactions were carried out on a 0.5 mmol scale and run at 25 °C unless otherwise specified, 1.5 equiv. of ArZnCl were used. <sup>*b*</sup> The reaction was run at 70 °C. <sup>*c*</sup> The reaction was run at 100 °C. <sup>*d*</sup> *p*-EtO<sub>2</sub>CC<sub>6</sub>H<sub>4</sub>ZnBr was employed. <sup>*e*</sup> *p*-RC<sub>6</sub>H<sub>4</sub>ZnI (R = COOEt or Me) was employed. <sup>*f*</sup> Isolated product yields.

reaction with various chloride substrates required 0.1-3 mol% of Ia or III (entries 23-30, Table 2). This is ascribed to its steric hindrance. 2-Furylzinc chloride behaved a little unusually. It is less reactive than both p-MeC<sub>6</sub>H<sub>4</sub>ZnCl and o-MeC<sub>6</sub>H<sub>4</sub>ZnCl as we observed previously although it seems to be an electronrich nucleophile.<sup>4g</sup> It can only react with activated aryl chlorides at room temperature with a relatively high catalyst loading. This is probably because the coordination of the oxygen atom of the furyl ring to a metal ion (for example  $Zn^{2+}$ ) reduces the nucleophilic activity of the 2-furyl anion. The reaction of less nucleophilic p-EtO<sub>2</sub>CC<sub>6</sub>H<sub>4</sub>ZnBr with either p-NCC<sub>6</sub>H<sub>4</sub>Cl or p-PhC(O)C<sub>6</sub>H<sub>4</sub>Cl at room temperature catalysed by Ia and III, respectively, gave a relatively low product yield (entries 36 and 37, Table 2), while with p-MeC<sub>6</sub>H<sub>4</sub>Cl afforded trace cross-coupling product. If p-EtO<sub>2</sub>CC<sub>6</sub>H<sub>4</sub>ZnI was employed as a nucleophile, the reaction with p-NCC<sub>6</sub>H<sub>4</sub>Cl or p-PhC(O)C<sub>6</sub>H<sub>4</sub>Cl required an elevated reaction temperature (entries 38 and 39, Table 2), and at room temperature resulted in no product formation. Reaction of p-MeC<sub>6</sub>H<sub>4</sub>ZnI with p-EtO<sub>2</sub>CC<sub>6</sub>H<sub>4</sub>Cl catalysed by 2 mol% Ia gave a coupling product in 30% yield. This may be due to the iodide-counterion of the zinc reagent leading to a different reaction mechanism compared to chlorides and bromides. In addition, the catalysts are incompatible with NO2 and CHO groups. No cross-coupling product was obtained from the reaction of p-ClC<sub>6</sub>H<sub>4</sub>NO<sub>2</sub> with arylzinc chlorides catalysed by either Ia or III. A similar catalytic reaction between p-ClC<sub>6</sub>H<sub>4</sub>CHO and p-MeC<sub>6</sub>H<sub>4</sub>ZnCl gave a complicated mixture.

Reactions of multichlorobenzenes with arylzinc chlorides at room temperature catalysed by complex **Ia** were also studied. Treatment of 1,4-dichlorobenzene with 3 equiv. of p-MeC<sub>6</sub>H<sub>4</sub>ZnCl or p-Me<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>ZnCl in the presence of 0.2 mol% **Ia** at room temperature afforded 1,4-bis(p-tolyl)benzene and 1,4-bis(p-dimethylaminophenyl)benzene, respectively, in 91% yields (entries 1 and 2, Table 3). A similar reaction using p-MeC<sub>6</sub>H<sub>4</sub>ZnCl required 1 mol% of **Ia** and gave a coupling product in 87% yield (entry 3, Table 3). Reaction of 1,2-dichlorobenzene with 3 equiv. of p-MeC<sub>6</sub>H<sub>4</sub>ZnCl or p-Me<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>ZnCl in the presence of 0.75 mol% **Ia** at room temperature generated the corresponding cross-coupling products in 88% and 86% yields,

**Table 3**Reaction of arylzinc reagents with dichlorobenzene catalysedby  $\mathbf{Ia}^a$ 



Entry	Ar	Aryl polychloride	Amount of cat. (mol%)	Yield <sup>b</sup> (%)
1	p-MeC <sub>6</sub> H <sub>4</sub>	1,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	0.2	91
2	p-Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	$1,4-Cl_2C_6H_4$	0.2	91
3	o-MeC <sub>6</sub> H <sub>4</sub>	$1,4-Cl_2C_6H_4$	1	87
4	p-MeC <sub>6</sub> H <sub>4</sub>	$1,2-Cl_2C_6H_4$	0.75	88
5	p-Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	$1,2$ - $Cl_2C_6H_4$	0.75	86

<sup>*a*</sup> The reactions were carried out on a 0.5 mmol scale according to the conditions indicated by the above equation, 3 equiv. of ArZnCl were employed. <sup>*b*</sup> Isolated product yields.

respectively (entries 4 and 5, Table 3). It seems that the reaction of 1,2-dichlorobenzene was affected little by the steric hindrance of the *ortho*-substituent. 1,3,5-Trichlorobenzene also reacted smoothly with 4.5 equiv. of p-MeC<sub>6</sub>H<sub>4</sub>ZnCl at room temperature in the presence of 1 mol% Ia, giving 1,3,5-tri(p-tolyl)benzene in 81% yield (eqn (1)).



In summary, we have developed new nickel catalysts for the Negishi reaction of aryl chlorides. The nickel complexes are highly active and able to catalyse cross-coupling of unactivated and deactivated aryl chlorides efficiently with arylzinc reagents at room temperature. The reaction showed good functional group tolerance and required low catalyst loading.

This work was supported by National Basic Research Program of China (2009CB825300), the National Natural Science Foundation of China (20772119) and Research Fund for the Doctoral Program of Higher Education of China (20070358031).

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