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Reactivity of mixed organozinc and mixed organocopper reagents: 6. Nickel-catalyzed coupling of methylarylzincs with primary alkyl halides; an atom-economic aryl–alkyl coupling

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ABSTRACT

A nickel-catalyzed process for the cross-coupling of mixed arylzincs and primary alkyl halides has been developed. The reaction of a methylarylzinc with a primary alkyl halide in THF in the presence of NiCl₂/ PPh₃ takes place with selective aryl transfer at room temperature in moderate yields. This protocol provides an atom-economic alternative to aryl-primary alkyl coupling using diarylzincs.

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Organozinc reagents of the type R_2Zn are widely used organometallic reagents due to their high reactivity, ease of preparation, and high tolerance to many functional groups.^{1,2}

However, one drawback of this procedure is that only one of the organic groups can be transferred efficiently to the substrate. In order to achieve atom-economic reactions of diorganozincs, mixed diorganozincs (R^1R^2Zn) in which one of the R groups has a lower rate of transfer than the others have been developed.³ Methyl, ethyl, and *tert*-butyl groups were found to react more slowly than other alkyl, alkenyl, and aryl groups.^{3a-e} Mixed diorganozincs R_RR_TZn composed of one transferable group R_T together with the residual group R_R have recently proved to be synthetically useful.⁴ Trimethylsilylmethyl (Me₃SiCH₂),^{4a} neopentyl (*tert*-BuCH₂), and neophyl (PhMe₂CH₂) groups^{4b} have been reported by Knochel et al. as excellent residual groups.

Diorganozincs are also good reaction partners for Negishi crosscoupling reactions with organic electrophiles in the presence of Pd or Ni catalysis and provide a very popular method for forming new C–C bonds.^{1,5,6} However, coupling with sp³carbon-containing organozinc nucleophiles and/or sp³carbon-containing electrophiles with β -hydrogen atoms still represent a difficult class of coupling partners due to β -hydride elimination in the intermediate alkyl metal complexes leading to alkenes as the main products or side products (Scheme 1). Recently, several Ni and Pd catalyst systems have been reported for the successful coupling of alkyl nucleophiles and/or alkyl electrophiles and they have been summarized in reviews devoted to coupling of organometallics with organic electrophiles⁷ and with alkyl electrophiles,^{8–10} and organozincs¹¹ and alkyl organometallics with organic electrophiles¹² and with alkyl electrophiles.¹³

According to our literature survey during our continuing work on the reactivity and controlling factors of the group selectivity of mixed organozinc reagents,^{14–17} the use of mixed diorganozincs ($R_R R_T Zn$) in the Pd- or Ni-catalyzed coupling reactions with organic electrophiles is quite limited. The reaction of mixed alkylzinc reagents containing Me₃SiCH₂ as the residual group with allylic phosphates under CuCN catalysis^{4j} and with activated alkyl halides in the presence of Ni catalysis has been reported.¹⁸ Mixed isopropylalkenylzincs have been found to react with heteroatom electrophiles such as R_3 SnCl and Ph₂PCl and alkyl halides in the presence of CuCN catalysis as alkenyl selective reagents.^{3f}

Motivated by our early success in using mixed diorganozincs for atom-economic acylation¹⁵ and amination¹⁶ of diorganozincs, we decided to investigate the synthetic applicability of aryl–alkyl Negishi cross-coupling of mixed alkylarylzincs with primary alkyl halides in the presence of nickel catalysis. Palladium catalysis in Negishi cross-coupling reactions is well-developed,^{19–22} however, nickel catalysis has recently become important.¹¹ It is known that aryl nucleophiles are generally less reactive in cross-coupling reactions with alkyl halides, however, they undergo fewer side reactions due to lack of hydrogens.⁹ We postulate that the alkyl nucleophile in the mixed alkylarylzinc reagent does not couple, but may facilitate the coupling reaction. On the other hand, the



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Scheme 1. General mechanism for transition metal catalyzed cross-coupling reactions of organozinc reagents with electrophiles. Catalytic cycle steps: (a) oxidative addition, (b) transmetallation, (c) reductive elimination, (d) and (e) β -hydride elimination in the case of sp³ carbon containing electrophiles and organozinc nucleophiles.

formation of sp²carbon–sp³carbon bonds has been generally performed using alkylzinc reagents and aryl/alkenyl halides.^{9,11,12,20,21} There are a few reports on the alternative coupling using aryl/alkenylzinc reagents and alkyl halides via potential β -hydride elimination.^{8–11} Thus, we aimed to develop suitable reaction conditions for selective aryl transfer in the cross-coupling of mixed arylzincs with primary alkyl halides using Ni catalysts.^{23,24}

Here, we describe our progress toward achieving a simple Ni catalyst system for the atom economic cross-coupling of mixed alkylarylzincs with primary alkyl halides with selective aryl transfer.

First, we investigated the effect of the reaction parameters on the group transfer selectivity of *n*-butylphenylzinc (1ac) in the nickel-catalyzed alkylation with *n*-pentyl bromide and iodide **2** as a model coupling reaction (1).

$$n-\underset{lac}{\operatorname{BuphZn}} + n-\underset{2}{\operatorname{PentX}} \xrightarrow{\operatorname{Ni}}_{\mathsf{THF}} n - \underset{3}{\operatorname{C_9}} H_{20} + Ph-\underset{4}{n-\operatorname{Pent}} X = \operatorname{Br}, I$$
(1)

We carried out the coupling reaction by adding *n*-pentyl iodide (2) to the catalyst system in THF or in THF: cosolvent and then adding *n*-butylphenylzinc (**1ac**). The relative transfer ability of *n*-Bu and Ph groups was determined from the GC yields of coupling products **3** and **4** using authentic samples. We used magnesium based organozinc reagents and prepared the mixed diorganozinc by reacting phenylmagnesium bromide with *n*-butylzinc chloride (Method A_1) and also by reacting *n*-butylmagnesium bromide with phenylzinc chloride (Method A2). However, we found that the group originally attached to Zn (n-Bu or Ph) did not affect the group transfer selectivity. The coupling with *n*-pentyl iodide gave a higher yield than that of *n*-pentyl bromide and we therefore decided to focus our studies on pentyl iodide. The effect of the Ni catalyst, cosolvent and additive (promoter) on the yields and relative transfer ability of the *n*-Bu and Ph groups in the coupling of *n*-BuPhZn with *n*-pentyl iodide in THF are given in Table 1. We also determined the background yields, that is, alkylation yields of *n*- $Bu_2Zn(1a_2)$ and $Ph_2Zn(1c_2)$ under the same conditions.

We carried out the alkylation of *n*-BuPhZn (**1ac**) in THF, (i) using Ni(acac)₂ (acac = acetylacetonate), Ni(PPh₃)₂Cl₂ and NiCl₂ as catalysts, (ii) using a coordinating solvent, such as NMP (*N*-methyl-2-pyrrolidinone), TMEDA (*N*,*N*,*N*',*N*'-tetramethylethylenediamine), and DMPU (*N*,*N*-dimethylpropyleneurea), and (iii) using an additive, that is, 4-fluorostyrene. It has been reported that 4-fluorosty-rene^{10,11,25} and 4-(trifluoromethyl)styrene^{10,11,26} can be used as promoters in the coupling of organozinc reagents with alkyl electrophiles leading to considerable improvements in the coupling.

They are thought to facilitate the reductive elimination from the intermediate oxidative addition product over the potentially competing β -hydride elimination by removing electron density from the metal center. We initiated our experiments by evaluating Ni(a-cac)₂ as the catalyst for the coupling of *n*-BuPhZn (**1ac**) in THF and in THF/NMP (2:1) (entries 1 and 2). The yield was quite low in THF. In THF/NMP (2:1), the yield increased to 48%, and the yields of the individual products **3a** (R¹ = *n*-Bu) and **4** (R² = Ph) were 19% and 29%, respectively. We also observed that reaction at room temperature for about 1 h gave the highest yield although the Negishi reaction is known to take place at lower temperatures.

For comparison, the transfer ability of the *n*-Bu group in *n*-Bu₂Zn ($1a_2$) and in Ph₂Zn ($1c_2$) in THF/NMP (2:1) was 16% (entry 3) and 47% (entry 4), respectively. Thus, using an *N*-donor solvent resulted in the same transfer ability of the *n*-Bu group, but lower transfer of the Ph group in the mixed diorganozinc, *n*-BuPhZn. The coupling in THF/NMP (2:1) was re-examined in the presence of 4-fluorostyrene (20 mol %), however, the coupling was less efficient and gave a lower 23% yield (entry 5), with transfer of only the Ph group, unexpectedly. Increasing the amount of 4-fluorostyrene (1 equiv) did not change the outcome of the coupling (entry 6). The background alkylation yield of Ph₂Zn ($1c_2$) under the same conditions was higher (entry 7). To our delight, the use of Ni(PPh₃)₂Cl₂ as the catalyst for the alkylation of *n*-BuPhZn (1ac) resulted in a 57% yield with only Ph group transfer (entry 8).

Before screening Lewis bases as cosolvents, we determined the coupling yields of n-Bu₂Zn (**1a**₂) and Ph₂Zn (**1c**₂) in the presence of Ni(PPh₃)₂Cl₂ catalysis. Not surprisingly, alkylation of **1a**₂ took place, but with a low 11% yield (entry 9) and alkylation of **1c**₂ gave a somewhat higher 67% yield (entry 10) than that of n-BuPhZn (**1ac**). Coupling was significantly less efficient in THF/NMP (2:1), THF/TMEDA (2:1) and THF/DMPU (2:1) (entries 11–13), possibly due to the presence of PPh₃ as a Lewis base as well as the *N*-donor solvent.

We also used NiCl₂ as the catalyst to determine the effect of PPh₃ as an additive instead of a ligand on the Ni catalyst in the coupling of *n*-BuPhZn (**1ac**). We optimized the catalyst and additive concentration at 10 mol % and coupling gave a 43% yield with the transfer of only Ph group (entry 14). Background coupling yields with *n*-Bu₂Zn (**1a**₂) and Ph₂Zn (**1c**₂) under the same conditions were 8% and 52%, respectively (entries 15 and 16). Coupling of *n*-butylphenylzinc (**1ac**) did not result in a decreased yield compared to the coupling of diphenylzinc with respect to the error limit of GC analysis (10%).

Before investigating the scope of the coupling partner in the NiCl₂/PPh₃ catalyzed aryl–alkyl coupling of *n*-butylarylzinc

Table 1

Organic group transfer ability in the Ni-catalyzed coupling of *n*-butylphenylzinc (1ab) with *n*-pentyl iodide (2) in THF. Effect of the catalyst, solvent and additive^{a,b,c}

$$\begin{array}{c|c} R^{1}R^{2}Zn + n \text{-PentI} & \xrightarrow{\text{Ni catalyst}} R^{1} - n \text{-Pent} + R^{2} - n \text{-Pent} \\ \hline 1 & 2 & \text{THF, rt, 1 h} & 3 & 4 \end{array}$$

n-BuPhZn (1ac), n-Bu₂Zn (1a₂), Ph₂Zn (1c₂)

Entry	1	Catalyst	Solvent	Additive	Total yield (%) ^d	3a:4 ^e
1	1ac	Ni(acac) ₂	THF	_	11	27:73
2	1ac	Ni(acac) ₂	THF:NMP (2:1)	_	48	40:60
3	1a ₂	Ni(acac) ₂	THF:NMP (2:1)	_	16	
4	1c ₂	Ni(acac) ₂	THF:NMP (2:1)	_	47	
5	1ac	Ni(acac) ₂	THF:NMP (2:1)	4-Fluorostyrene (20 mol %)	23	0:100
6	1ac	Ni(acac) ₂	THF:NMP (2:1)	4-Fluorostyrene (1 equiv)	20	0:100
7	1c ₂	Ni(acac) ₂	THF:NMP (2:1)	4-Fluorostyrene (1 equiv)	37	
8	1ac	Ni(PPh ₃) ₂ Cl ₂	THF	_	57	0:100
9	1a ₂	Ni(PPh ₃) ₂ Cl ₂	THF	_	11	
10	1c ₂	Ni(PPh ₃) ₂ Cl ₂	THF	_	67	
11	1ac	Ni(PPh ₃) ₂ Cl ₂	THF:NMP (2:1)	_	43	0:100
12	1ac	Ni(PPh ₃) ₂ Cl ₂	THF:TMEDA (2:1)	_	37	0:100
13	1ac	Ni(PPh ₃) ₂ Cl ₂	THF:DMPU (2:1)	_	45	0:100
14	1ac	NiCl ₂ ^f	THF	PPh ₃ (10 mol %)	43	0:100
15	1a ₂	NiCl ₂ ^f	THF	PPh ₃ (10 mol %)	8	
16	1c ₂	NiCl ₂ ^f	THF	PPh ₃ (10 mol %)	52	

^a *n*-BuPhZn (**1ac**) was prepared using Method A₁ (see text) at -20 °C

^b Molar ratio of **1:2** was optimized as 2:1. A freshly prepared THF solution of **1** was added to a mixture of **2** and catalyst in solvent at 0 °C and the reaction carried out at room temperature.

^c Catalyst was optimized as 20 mol %.

^d The sum of the GC yields of **3** and **4** determined from the mean value of three or four experiments.

^e The ratio of GC yield of **3** to **4**.

^f Catalyst was optimized at 10 mol %.

reagents, we examined the methyl group as a residual group (Table 2). Methylphenylzinc (1bc) coupled with *n*-pentyl iodide (2) in a much higher yield than that of *n*-butylphenylzinc (**1ac**) in the presence of NiCl₂ (10 mol %) and PPh₃ (10 mol %) (entry 1). Loading a higher amount of catalyst system (entries 2 and 3) did not change the yield. The use of THF/NMP (2:1) as solvent in the catalysis with NiCl₂ (10 mol %)/PPh₃ (1 equiv) (entry 4) or with NiCl₂ (20 mol %)/ PPh₃ (20 mol %) (entry 5) decreased the coupling yield, as expected. Using a lower amount of PPh₃ (entries 6 and 7) led to somewhat decreased yields. Tri-n-butylphosphine as an additive (1 equiv) resulted in an extremely low 2% yield. The reactions were carried out at room temperature for 1 h (optimized conditions) and coupling at -10 °C resulted in a 54% yield after a reaction time of 2-3 h. However, we observed that carrying out the coupling at 40 °C gave an optimized 66% vield in 5 min (entry 8). Thus, 1 equiv of the phenyl group in mixed methylphenylzinc (**1bc**) can lead to aryl-alkyl coupling in the presence of NiCl₂ (10 mol %) and PPh₃

Table 2

Effect of the additive on the phenyl transfer ability in the NiCl₂-catalyzed coupling of methylphenylzinc with *n*-pentyl iodide in THF and THF:NMP $(2:1)^a$

	1000000000000000000000000000000000000	$ntI - \frac{NiCl_2, PPh_3}{THF, rt, 1 h}$	$\rightarrow n-C_6H_{14} + Ph$ 3b	- <i>n</i> -Pent 4
Entry	[NiCl ₂] (mol %)	Solvent	[PPh ₃] (mol %)	Yield of 4 (%) ^b
1	10	THF	10	63
2	20	THF	20	63
3	20	THF	1 equiv	63
4	10	THF:NMP (2:1)	1 equiv	36
5	20	THF:NMP (2:1)	20	37
6	10	THF	15	60
7	10	THF	5	56
8	10	THF	10	66 ^c

^a Molar ratio of **1bc:2** was 2:1. For the preparation of **1bc** and the coupling reaction, see Ref. 27.

^b GC yield.

^c The reaction was carried out at 40 °C for 5 min.

(10 mol %) in 63% yield. This is higher than the 57% yield obtained using *n*-BuPhZn in the presence of Ni(PPh₃)₂Cl₂ (20 mol %). A reduced catalyst loading is used even if the coupling efficiency was almost same within the error limits of GC analysis.

We applied our Ni-catalyzed aryl–primary alkyl coupling conditions using aryl nucleophiles of methylarylzinc reagents (catalyst system: 10 mol % NiCl₂/10 mol % PPh₃ in THF at room temperature) to a series of methyl (substituted phenyl) zinc reagents and *n*-alkyl iodides (Table 3). *n*-Alkyl iodides (C_5 – C_{10}) reacted with aryl nucleophiles of methylarylzincs to give coupled products in moderate yields. As aryl nucleophiles, tolyl, and phenyl nucleophiles containing –I, +M type functional groups (–OMe) were examined. However, we found that these conditions did not tolerate a –I, –M type functional group (–COMe) on the phenyl nucleophile and coupling did not take place. We employed C_5 , C_4 and C_{10} alkyl iodides as primary alkyl electrophiles. Neopentyl iodide gave the coupling product, albeit in a low yield.

Table 3

Ni-catalyzed coupling of methylarylzincs with primary alkyl iodides in THF^a NiCl₂ (10 mol%), PPh₃ (10 mol%)

	$\frac{1}{1} \frac{2}{2}$	THF, rt, 1 h	→ RR 4
Entry	R	R ¹	Yield of 4 (%) ^b
1	Ph	n-C ₅ H ₁₁	63
2	4-MeC ₆ H ₄	$n-C_{5}H_{11}$	69
3	3-MeC ₆ H ₄	$n-C_{5}H_{11}$	66
4	4-MeOC ₆ H ₄	$n-C_{5}H_{11}$	52
5	3-MeOC ₆ H ₄	$n-C_{5}H_{11}$	54
6	4-MeCOC ₆ H ₄	$n-C_5H_{11}$	C
7	3-MeCOC ₆ H ₄	$n-C_5H_{11}$	C
8	Ph	$n-C_4H_9$	58
9	Ph	n-C7H15	50
10	Ph	n-C10H21	59
11	Ph	neo-C ₅ H ₁₁	15

^a For a representative coupling procedure, see reference 29.

^b Yields were determined by GC.

^c No reaction was observed.

In conclusion, we have established a new and simple Ni-catalyzed protocol for the cross-coupling of mixed methylarylzincs with primary alkyl iodides²⁷ leading to an atom-economic alternative to aryl-primary alkyl coupling using diarylzincs. We are working to probe the generality of the mixed arylzinc–alkyl coupling reaction with respect to the coupling of aryl nucleophiles containing a wide range of functional groups and also the coupling of activated alkyl electrophiles such as benzyl, allyl, and α -carbonylalkyl halides.

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- 23. Note. The use of PEPPSI as a Pd catalyst in the coupling of *n*-BuPhZn (**1ac**) with *n*-pentyl iodide **2** did not give selective Ph group transfer. The coupling yield in THF/NMP (2:1) was 67% with a **3:4** molar ratio of 20:80. However, the background coupling yield with Ph₂Zn was 72%.²⁶
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- Typical procedure for the coupling of methylarylzincs with primary alkyl iodides: All reactions were carried out in oven-dried glassware under a positive pressure of nitrogen using standard syringe-septum cap techniques.²⁸ For the preparation of methylarylzinc reagents (aryl: C₆H₅, MeC₆H₄, MeOC₆H₄), arylzinc chlorides were reacted with methylmagnesium chloride. Arylzinc chloride was prepared by addition of arylmagnesium bromide (2 mmol) to ZnCl₂ (2 mmol) in THF (4 ml) at -20 °C and stirring at that temperature for 15 min. To freshly prepared arylzinc chloride (2 mmol), methylmagnesium chloride (2 mmol) was added and the mixture was stirred at -20 °C for another 15 min. For the preparation of methylarylzinc reagents (aryl: 4-MeCOC₆H₄, 3-MeCOC₆H₄), arylmagnesium bromides were reacted with methylzinc chloride.²⁶ Arylmagnesium bromide (2 mmol) was prepared by addition of isopropylmagnesium bromide (2.1 mmol) to a solution of aryl iodide (2 mmol) in THF (4 ml) at -15 °C and stirring at that temperature for 1 hour to complete the Br/Mg exchange.²⁹ AryImagnesium bromide (2 mmol) solution was added to methylagics indigits of the second state o -20 °C and the mixture was stirred at that temperature for 15 min. For the alkyl coupling reaction of methylarylzincs, a mixture of NiCl₂ (10 mol %, 0.013 g), PPh₃ (10 mol %, 0.0263) and primary alkyl iodide in THF (2 ml) was cooled to 0 °C and freshly prepared methylarylzinc (2 mmol) was added slowly. The reaction mixture was stirred at room temperature for 1 h and then hydrolyzed by addition of 1 M HCl and subsequently extracted with Et₂O. The combined ethereal solutions were washed with an NaHCO3 solution, dried and aliquots were analyzed by GC.
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