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## Gram-Scale, Cheap, and Eco-Friendly Iron-Catalyzed Cross-Coupling between Alkyl Grignard Reagents and Alkenyl or Aryl Halides

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Supporting Information

ABSTRACT: A new robust methodology for gram-scale iron-catalyzed cross-coupling between alkyl Grignard reagents and alkenyl or aryl halides is developed. This method does not require toxic additives such as NMP or expensive ligands. Its efficiency relies on the use of simple alkoxide magnesium salts as additives. On the basis of these results, a new procedure for one-pot synthesis of substituted benzamides from chloroesters is also proposed.

R<sub>sn3</sub>-MgCl additive: EtOMgCl applicable to alkenyl and (hetero)aryl electrophiles no exogenous ligand required cheap, eco-friendly alkoxide additives

ransition-metal-catalyzed-based methodologies applied to L the formation of C—C bonds by cross-coupling brought an incredible breakthrough in synthetic chemistry.<sup>1</sup> This field is however so far mostly dominated by palladium catalysis. The high cost of palladium coupled with its toxicity<sup>1b</sup> raises the issue of the development of alternative solutions based on the use of non-noble, cheap catalysts with a low toxicity.<sup>2</sup> In this context, iron appears as one of the best candidates since it is cheap, eco-friendly, and abundant.<sup>3</sup> However, the sustainability and the toxicity features of the additives or ligands required by new developed methodologies is also a critical issue. Very representative is the example of the coupling method reported by our group in 1998, demonstrating that the use of Nmethylpyrrolidinone (NMP) as a cosolvent in iron catalysis led to excellent cross-coupling yields between Grignard reagents and alkenyl halides.<sup>4</sup> This methodology requires the use of simple iron salts (e.g.,  $FeCl_3$ ,  $Fe(acac)_3$ ) and thus has the advantage of not requiring any exogenous expensive ligand. This NMP-based strategy has been extensively applied to a large scope of cross-coupling targets ever since.<sup>5</sup> However, a major drawback of this method is the reprotoxicity of NMP, which has been demonstrated a decade ago,<sup>6</sup> and which thus hampers the use of NMP-based procedures at large scales. Numerous powerful methodologies involving well-defined iron complexes with suitable ligands were then reported,<sup>7</sup> and allowed for some of them to circumvent the drawbacks of coligand-free methodologies, such as the homocoupling of the Grignard reagent.<sup>77</sup>

In the course of our investigations on the development of new, eco-friendly, and easily scalable iron-catalyzed crosscoupling methodologies between alkyl Grignard reagents and  $C_{sp2}$  (alkenyl or aryl) organic halides, we observed that the combination of a catalytic charge of FeCl<sub>3</sub> with alkoxide magnesium salts in THF led to a complete conversion of the

reactants and afforded cross-coupling products in good to excellent yields. Importantly, all the reactions reported in this work could be performed at a gram scale (up to 50 mmol for alkyl-alkenyl couplings, up to 10 mmol for alkyl-aryl couplings).

The positive effect of alkoxide salts (RO[M]) on the conversion of the reactants and on the cross-coupling yield was observed using *n*-butylmagnesium chloride and (1,Z)-bromohexene (1a) as coupling partners in the presence of an in situgenerated alkoxide magnesium salt (ROMgCl, Table 1). The latter is prepared by metalation of the corresponding alcohol with *n*BuMgCl prior to addition of the reactants, unless specified otherwise. A first coupling attempt between 1a and *n*BuMgCl in the presence of FeCl<sub>3</sub> (5 mol %) and EtOMgCl (250 mol %) was performed. To our delight, a total conversion of the starting material 1a was observed, and (5,Z)-decene (2a) was obtained with a 85% yield (Table 1, entry 1). In the absence of EtOMgCl, 2a is obtained with a lower 75% yield (Table 1, entry 2). The benefic role of alkoxide salts on the efficiency of this alkyl-alkenyl cross-coupling is similar to what is observed using NMP as additive in Fe-catalyzed methodologies since it also improves cross-coupling product yield.<sup>4</sup> In our case, the use of NMP as a cosolvent in cross-coupling between 1a and nBuMgCl afforded olefin 2a with an excellent 97% yield (Table 1, entry 3). Optimization of the catalyst load and EtOMgCl/Fe ratio (Table 1, entries 4-9) allowed us to obtain 2a with an excellent 93% yield (2.5 mol % FeCl<sub>3</sub>, 100 mol % EtOMgCl – EtOMgCl/Fe = 40, Table 1, entry 6), close to that obtained using 900 mol % NMP. Moreover, this method is highly stereoselective since the stereochemistry of

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Table 1. Optimization of Nature of RO[M] Additive and of ROM/FeCl<sub>3</sub> Ratio

	nBu Br	+ aBuMaCl	FeCl <sub>3</sub> x mol% RO[M] y mol%	n Du
	<b>1a</b> (1 equiv.)	(1.2 equiv.)	THF, 0 °C, 5 min	<b>2a</b> , Z > 99%
entry	FeCl <sub>3</sub> (mol %)	RO[N	M] (mol %)	% conversion $(GC yield)^a$
1	5	EtOMgCl	(250)	100 (85)
2	5			100 (75)
3	5	0 (900 mol % NMP)		100 (97)
4	5	EtOMgCl (200)		100 (92)
5	5	EtOMgCl (100)		100 (83)
6	2.5	EtOMgCl	(100)	100 (93)
7	1	EtOMgCl	(40)	100 (83)
8	2.5	EtOMgCl	(90)	100 (83)
9	2.5	EtOMgCl	(80)	100 (80)
10	2.5	MeOMgCl	(100)	100 (82)
11	2.5	nOctOMg	Cl (100)	100 (81)
12	2.5	iPrOMgCl	(100)	100 (67)
13	2.5	tBuOMgCl	(100)	$100~(67^{b})$
14	2.5	ClMgOCH (50)	I <sub>2</sub> CH <sub>2</sub> OMgCl	100 (76)
15	2.5	PhOMgCl	(100)	100 (80)
16	2.5	CF <sub>3</sub> CH <sub>2</sub> OI	MgCl (100)	100 (67)
17	2.5	AcOMgCl	(100)	100 (77)
18	2.5	Et <sub>2</sub> NMgCl	(100)	100 (70)
19	2.5	EtOLi (10	0) <sup>c</sup>	100 (95)
20	2.5	EtONa (10	$(00)^{d}$	100 (72)
21	2.5	EtOK (100	$))^d$	80 (56)
22	2.5	EtOMgOE	t $(100)^d$	100 (70)
<i>а</i> тт.	1 1	· / 1	$(1 1 b_{37} 1)$	6 1 1

<sup>*a*</sup>Using dodecane as internal standard. <sup>*b*</sup>Yield after 1 h reaction. <sup>*c*</sup>Prepared by metalation of EtOH with *n*BuLi. <sup>*d*</sup>Commercial salt.

the starting alkenyl halide is conserved in all cases (obtention of **2a** with a stereoisomeric purity Z > 99%).

Encouraged by these results, we investigated the effect of different alkoxide salts on the cross-coupling of 1a and nBuMgCl. Various in situ-generated magnesium alkoxide chloride salts were used in the optimized conditions (2.5 mol %  $FeCl_{3}$ , and RO[M]/Fe = 40). The use of MeOMgCl and n-octylOMgCl, respectively, afforded 82 and 81% of 2a (Table 1, entries 10–11), whereas the use of *i*PrOMgCl and of the bulkier tBuOMgCl led to yields lower than in the absence of alkoxide additives (67% and 67%, entries 12-13). Interestingly, the use of bidentate glycoxide salts such as ClMgOCH<sub>2</sub>CH<sub>2</sub>OMgCl did not have a significant effect on the global yield (76%, entry 14). Alkoxide salts with a lower Brønsted basicity led to yields similar to that obtained in the absence of additive (entries 15-16). The effect of alkali salts (entries 19-21) was also investigated. Use of EtOLi (entry 19) allowed the formation of 2a with an excellent 95% yield. The use of the magnesium diethoxide salt only led to 70% of crosscoupling product (entry 22), probably due to the poor solubility of this salt in THF. In all examples displayed in Table 1, the steroisomeric purity was excellent since the Z isomer of **2a** was selectively obtained (Z:E > 99:1).

The scope of this methodology was determined using EtOMgCl as additive associated to  $FeCl_3$  (2.5 mol %  $FeCl_3$ , EtOMgCl/FeCl\_3 = 40) since the magnesium salt is more convenient to prepare *in situ* compared to its lithium analogue. Moreover, this scope has been investigated using *i*PrMgCl as a metalation reagent for the preparation of the alkoxide

magnesium salt (Table 2). This choice has been made to demonstrate the versatility of this method and show that the Grignard reagent used for the magnesiation step can differ from the cross-coupling partner introduced in the coupling step. Supplanting *n*BuMgCl by *i*PrMgCl did not have a significant impact on the cross-coupling yield determined earlier between 1a and *n*BuMgCl (Table 1, entry 6) since 2a

Table	e 2. Cross-Coup	ling Scope	of Alkyl	Grignard	Reagents
with	Various Alkenyl	Halides <sup>a</sup>			

	$R^2 R^3$	FeCl <sub>3</sub> 2.5 mol% EtOMgCl 100 mol <sup>0</sup>	$R^2 R^3$
	R <sup>1</sup> X (1.3 equiv	.) THF, 0 °C, 5 min	R <sup>1</sup> R 2
Entry	RMgCl	1	<b>2</b> (% isolated yield)
1	nBuMgCl	nBu Br 1a	<b>2a</b> (82) (GC yield: 91%) Z/E > 99:1
2	$nC_{1C}H_{21}MgCl$	<i>n</i> Bu Br	<b>2b</b> (68)
3	iPrMgCl	la nBu Br la	Z/E > 99:1 <b>2c</b> (65) Z/E > 99:1
4	C <sub>6</sub> H <sub>11</sub> MgCl	nBu Br	<b>2d</b> (81) Z/E > 99:1
5	nC <sub>10</sub> H <sub>21</sub> MgCl	کر Br 1b	<b>2e</b> (74) <i>Z/E</i> = 45:55
6	nBuMgCl	Z/E = 40:60 Ph Br 1c	<b>2f</b> (94) <i>Z:E</i> > 15:85
7	nBuMgCl	Z/E = 15:85 nBu nBu X	
8	nC1CH21MgCl	1d (X = Br) $1e (X = Cl)$ $X$ $1f (X = Br)$	<b>2g</b> (37) <b>2g</b> (20) <b>2h</b> (66)
9	$nC_{10}H_{21}MgCl$	$\frac{\operatorname{Ig}\left(X=\operatorname{Cl}\right)}{\operatorname{Br}}$	<b>2h</b> (31) <b>2i</b> (81)
10	nC <sub>10</sub> H <sub>21</sub> MgCl	1h <sup>ک</sup> ر Br	<b>2j</b> (63) Z/E = 45:55
11	$nC_{1C}H_{21}MgCl$	1i (Z/E = 43:57) $Cl Cl$ $Ij$	<b>2k</b> $(31)^{b}$ <i>Z</i> : <i>E</i> > 99:1
12	nBuMgCl		<b>2l</b> (87)

<sup>&</sup>lt;sup>*a*</sup>EtOMgCl was preliminary prepared by metalation of EtOH with *i*PrMgCl (0.95 equiv) in THF. <sup>*b*</sup>Only traces of coupling products are detected by GC–MS when *E*-dichloroethene is used as starting material.

could also be obtained with an excellent 91% GC yield upon use of *i*PrMgCl as a metalation reagent (Table 2, entry 1). Olefin **2a** was then isolated by distillation under reduced pressure with a good 82% yield. Reaction of **1a** with various alkyl Grignard reagents afforded the corresponding olefins with good yields (Table 2, entries 2–4), ranking between 65% (use of *i*PrMgCl, entry 3) and 81% (use of C<sub>6</sub>H<sub>11</sub>MgCl, entry 4). Alkenyl bromides MeCH=CHBr (**1b**) and PhCH=CHBr (**1c**), respectively, afforded cross-coupling products **2e** (reaction with  $nC_{10}H_{21}MgCl$ ) and **2f** (reaction with *n*BuMgCl) with good (74%) and excellent (94%) yields (entries 5–6).

Unfortunately, bulky disubstituted vicinal alkenyl halides were poorly converted to the corresponding cross-coupling products:  $nBu_2C=CHX$  (1d, X = Br; 1e, X = Cl) reacted with nBuMgCl to afford  $nBu_2C=CHnBu$  (2g) with a low 37% (X = Br) or 20% (X = Cl) yield (Table 2, entry 7). Less hindered Me<sub>2</sub>C=CHX (1f, X = Br; 1g, X = Cl) could however react with  $nC_{10}H_{21}MgCl$  to afford Me<sub>2</sub>C=CHnBu (2h) with a moderate 66% (X = Br) yield (Table 2, entry 8). Similarly, alkenyl bromides 1h and 1i reacted with  $nC_{10}H_{21}MgCl$  to afford 2i and 2j in, respectively, 81% and 63% yield (entries 9–10). Again, the stereoselectivity of this method was excellent since we observed a retention of the C=C bond configuration in all cases.  $\alpha,\beta$ -Unsaturated ketones were moreover tolerated since substrate 1k could efficiently react with nBuMgCl to afford 2l with an excellent 87% yield (entry 12).

In a second time, we sought to investigate the extensibility of our methodology to alkyl–aryl cross-coupling systems. The reaction conditions (catalyst load and alkoxide/iron ratio) were thus reoptimized using *n*BuMgCl and ethyl 4chlorobenzoate (**3a**) as coupling partners (see Supporting Information) since the latter is known to easily react under iron-catalyzed coupling conditions with Grignard reagents.<sup>5</sup> To our delight, 4-*n*BuC<sub>6</sub>H<sub>4</sub>COOEt (**4a**) could be quantitatively obtained using a low 1 mol % catalyst load, and 15 mol % EtOMgCl (EtOMgCl/Fe ratio = 15, Table 3, entry 1). It is

## Table 3. Effect of Leaving Group in Alkyl-Aryl Cross-Coupling

×_/=\_	E	FeCl <sub>3</sub> 1 mol% tOMgCl 15 mol%			
3	(1.2 equiv.)	THF, 0 °C, 1 h	- //Bu4a	JUUEI	
entry	leaving group	(X) ·	<b>4a</b> (% isolated yiel	d)	
1	Cl (3a)		99		
2	$CF_3SO_3$ (3a)	ia)	70		
3	PhSO <sub>3</sub> (3ab	)	57 <sup>a</sup>		
4	Br (3ac)		$22^{a,b}$		
5	I (3ad)		17 <sup><i>a</i>,<i>b</i></sup>		
6	F (3ae)		0 <sup><i>a,c</i></sup>		

<sup>*a*</sup>GC yield. <sup>*b*</sup>Reduction product  $C_6H_5COOEt$  was obtained as a major product. <sup>*c*</sup>Addition product 4-FC<sub>6</sub>H<sub>4</sub>C(*n*Bu)<sub>2</sub>(OH) was obtained as a major product.

noticeable that these conditions require both a lower catalyst load and a lower EtOMgCl/Fe ratio than the alkyl–alkenyl coupling conditions reported above. Moreover, we also investigated the effect of the leaving group, and chloroarenes proved to be the most reactive. In cross-coupling reaction with *n*BuMgCl, triflate 4-TfOC<sub>6</sub>H<sub>4</sub>COOEt (**3aa**) led to 70% of the cross-coupling product **4a**; benzenesulfonate 4-PhSO<sub>3</sub>– $C_6H_4COOEt$  (**3ab**) led to a modest 57% yield. Ethyl 4-

bromobenzoate (**3ac**) and ethyl 4-iodobenzoate (**3ad**), respectively, gave poor 22% and 17% yields (**Table 3**, entries 4–5), along with a significant amount (ca. 40% in each case) of the arene reduction product  $C_6H_5$ COOEt. This side reaction explains why the efficiency of the cross-coupling pathway is hampered for these substrates. Ethyl 4-fluorobenzoate (**3ae**) did not lead to the expected coupling product, and side addition of *n*BuMgCl onto the ester was observed (entry 6).

The excellent alkyl-aryl cross-coupling yield displayed thereabove using activated aryl chloroesters prompted us to investigate the scope of the (hetero)aryl electrophiles, which can be efficiently converted thanks to this methodology. Methyl 4-chlorobenzoate (3b) and menthyl 4-chlorobenzoate (3c) could be quantitatively converted into the cross-coupling products 4b and 4c by reaction with  $nC_6H_{13}MgCl$  and nBuMgCl (Table 4, entries 2–3). Moreover, it is of note that quantitative formation of esters 4b and 4c demonstrates that no transesterification occurs between the ethoxide additive and the starting material.  $\alpha$  and  $\beta$ -Chloronaphtalene mixtures also reacted with *n*BuMgCl to afford the mixture 4d in a good 85% yield (entry 4). Unfortunately, this methodology was inefficient for electrophiles substituted in ortho and nonactivated meta positions since ethyl 2-chlorobenzoate (3e) and its meta isomer (3f) poorly reacted with nBuMgCl (entries 5-6). Similarly, no reaction was observed using nonactivated substrates such as chlorobenzene (3g, entry 7).

As outlined above, the reaction is compatible with the presence of esters (Table 4, entries 1–3) and also tolerated nitriles (entry 10). Chloroaryl ketones are however not tolerated (Table 4, entry 11). Heteroaryl chlorides such as 2-chloroquinoline (31) and 2-chloropyrimidine (3m) were also successfully used as cross-coupling partners with *n*BuMgCl in, respectively, 97% and 88% yield (4k and 4l, Table 3, entries 12–13). Interestingly, when aryl dihalide 4-ClC<sub>6</sub>H<sub>4</sub>Br (3n) is used, the chloride atom acts more like an activating electron-withdrawing group than a leaving group since the cross-coupling occurs on the brominated carbon with no displacement of the chloride. The coupling product 4m is however obtained in a low 17% yield (Table 4, entry 14), along with reduction product of the C—Br into C—H bond.

These results are comparable with other NMP-free methodologies reported by some of us using  $Fe(S-2-naphthyl)_2$  as catalyst,<sup>7b</sup> or by Fox, who used a catalytic amount of  $Fe(acac)_3$ associated with *N*,*N*-tetramethylethylenediamine as a stoichiometric additive.<sup>7f</sup> In both cases, excellent yields were also obtained using activated *para*-substituted aryl chloroesters. The methodology reported herein demonstrates that very simple and cheap alkoxide salts can efficiently supplant such additives. These salts can moreover be used at catalytically loads for alkyl–aryl couplings.

We then transposed these results to the one-pot synthesis of alkylbenzamides starting from 4-chloroester 3a, amide salts and *n*BuMgCl (Table 5). In a first step, amidification of 3a is performed by addition of an amide magnesium salt, generating *in situ* one equivalent of EtOMgCl. In a second time, the cross-coupling step is performed by successive additions of FeCl<sub>3</sub> and *n*BuMgCl. Alkyl benzamides 5a-d could be obtained in excellent yields (90–99%, Table 5). It is noteworthy to state that this method could be applied to both alkyl (entries 1–3) and aryl (entry 4) amide salts.

In summary, we developed a new efficient iron-catalyzed alkyl-alkenyl and alkyl-aryl coupling methodology between

	(Het)ArCl <b>3</b>	FeCl <sub>3</sub> 1 mol% + RMgCl (1.2 equiv.) THF, 0 °C, 1 h	► (Het)ArR 4
Entry	RMgCl	3	4 (isolated yield)
1	<i>n</i> BuMgCl	CI-COOEt	<b>4a</b> (99)
2	nC₀H₁₃Mg	Cl CI-COOMe	<b>4b</b> (99)
3ª	<i>n</i> BuMgCl		<b>4c</b> (99)
4	<i>n</i> BuMgCl	3c	<b>4d</b> (85) <sup>b</sup>
5	<i>n</i> BuMgCl	3d <sup>b</sup>	<b>4e</b> (13) <sup>c</sup>
6	<i>n</i> BuMgCl		<b>4f</b> (6) <sup>c</sup>
7	<i>n</i> BuMgCl		no reaction
8	<i>n</i> BuMgCl		<b>4g</b> (traces)
9	<i>n</i> BuMgCl		<b>4h</b> (20) <sup>c</sup>
10 <sup>d</sup>	<i>n</i> BuMgCl		<b>4i</b> (80)
11	<i>n</i> BuMgCl		<b>4j</b> (traces)
12	nBuMgCl		<b>4k</b> (97)
13	<i>n</i> BuMgCl		<b>4l</b> (88)
14	<i>n</i> BuMgCl	3m Cl-	$CI \longrightarrow nBu$

# Table 4. Cross-Coupling Scope of Alkyl Grignard Reagents with Various (Hetero)aryl Halides

Grignard reagents and organic halides. This method involves alkoxide magnesium salts as additives, which circumvent the



Table 5. One-Pot Alkylbenzamide (5) Synthesis from

toxicity problems of NMP-based strategies. Moreover, this method proceeds without the need of expensive functionalized ligands. The performances of this system are comparable to the current procedures for similar Fe-mediated cross-coupling between Grignard reagents and organic halides. An intriguing point is the lack of reactivity of bromo- and iodoarenes in this cross-coupling procedures, which undergo preferentially oneelectron reduction of the C-halide bond, echoing previous mechanistic studies that were performed on similar Fe(acac)<sub>3</sub>catalyzed Kumada cross-coupling systems.<sup>8a</sup> From a mechanistic standpoint, the nature of the catalytically active iron species is so far unknown. For similar systems using NMP as additive, the group of Neidig recently demonstrated that tricoordinated ate iron(II) species could react with sp2 electrophiles at catalytically relevant rates and that NMP actually acted as a ligand to the magnesium and not to the iron.<sup>8b</sup> On the other hand, some of us also demonstrated that in situ-generated iron(0) species could efficiently promote the activation of sp2 electron-poor organic halides.<sup>8c</sup> The exact role of the alkoxide salts in the overall catalytic process as well as the nature of the catalytically active oxidation state and the redox elementary steps governing this cross-coupling system are currently investigated, and results will be reported in due course.

## ASSOCIATED CONTENT

## **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.9b00665.

Standard experimental procedures and spectral data for all compounds (PDF)

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#### Notes

The authors declare no competing financial interest.

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#### DEDICATION

This work is dedicated to the memory of Prof. Gérard Cahiez.

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