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Received 21st April 2014, Accepted 6th June 2014 Selective Kumada biaryl cross-coupling reaction enabled by an iron(III) alkoxide-N-heterocyclic carbene catalyst system[†]

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A catalyst system comprising $Fe_2(O^tBu)_6$ and an N-heterocyclic carbene ligand enables efficient syntheses of (hetero)biaryls from the reactions of aryl Grignard reagents with a diverse spectrum of (hetero)aryl chlorides. Amongst the alkoxide and amide counterions investigated, *tert*-butoxide was the most effective in inhibiting the homocoupling of arylmagnesiums.

Biaryls are ubiquitous in fine chemicals, agrochemicals, pharmaceuticals and materials.¹ A common method to prepare biaryls is *via* the palladium- or nickel-catalyzed cross-coupling reactions.² There are, however, some major economic and ecological disadvantages associated with the use of these metals. Palladium is a precious metal whose supply fluctuates while nickel has high toxicity, which taints its use in consumer goods and healthcare products. The search for alternative catalysts based on cheap and environmentally benign metals is thus an increasingly important task. Iron, being the most abundant metal in the earth's crust (4.7% by weight) with low toxicity, is an excellent candidate for these purposes.

A major challenge in the development of iron-catalysed Kumada reaction for biaryl cross-coupling is the propensity of aryl Grignard reagents to undergo homocoupling reaction.³ A number of efficient catalyst systems have been developed for the cross-coupling of aryl-magnesiums with aryl halides bearing an activating group. Examples include coupling of π -electron deficient *N*-heteroaryl (pseudo)-halides at the α -carbon (*i.e.* 2-pyridyl),⁴ and of chlorostyrenes utilizing olefin as an activating substituent (Scheme 1a).⁵ To date, the only catalyst system facilitating selective cross-coupling of non-activated aryl halides and aryl Grignard reagents was that reported by Nakamura *et al.* A combination of iron(m) fluoride and an N-heterocyclic carbene (NHC) ligand was found to suppress the homocoupling reaction (Scheme 1b).^{6,7} It was proposed that

fluoride strongly coordinates to the iron centre and inhibits the formation of a ferrate complex that is responsible for the homocoupling pathway.

We hypothesized that, similar to fluoride, alkoxide and amide ancillary ligands may induce cross-coupling selectivity in the ironcatalysed reaction. Alkoxides, for example, are known to form strong bonds with the early and middle first-row transition metals through ionic bonding, which is reinforced by π -donation.⁸ In fact, these ligands have permitted the isolation of a wide range of metal complexes,⁸ including those of iron.⁹ We envisioned that, in contrast to fluoride, the properties of alkoxides and amides could be altered for fine tuning of the iron centre. In this report, we disclose an iron alkoxide/NHC catalyst system that promotes the selective biaryl cross-coupling (Scheme 1b). The scope of the reaction encompasses a diverse spectrum of (hetero)aryl chlorides, leading to the synthesis of a broad array of valuable (hetero)biaryls.

We set out to explore the influence of strongly basic counterions on the catalytic activity of an iron catalyst in the crosscoupling reaction of chlorobenzene **1a** and *p*-tolylmagnesium bromide **2a** (Table 1). A combination of 3 mol% FeBr₃, 9 mol%



Scheme 1 Selective Kumada biaryl cross-coupling under iron catalysis.

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Table 1
Effects of counterions and ligands on the iron-catalysed Kumada

biaryl cross-coupling^a
Image: Coupling Coup

,	,	5				
CI		1.2 equiv <i>p</i> -To 3 mol% Fe 9 mol% L, 18 r		Me		
1a		THF, 80 %		3a		
Entry	Fe source	Ligand	Base	$\operatorname{Conv.}^{b}(\%)$	3a ^{b,c}	3a' ^{b,d}
1^e	FeBr ₃	SIPr·HCl	NaO ^t Bu	90	77	22
2	FeBr ₃	SIPr ·HCl	NaO ^t Bu	100	100	13
3^f	FeBr ₃	SIPr ·HCl	NaO ^t Bu	100	87	16
4	FeBr ₃	SIPr ·HCl	NaOMe	61	58	7
5	FeBr ₃	SIPr ·HCl	NaHMDS	93	83	21
6	FeBr ₃	SIPr ·HCl	KO ^t Bu	100	86	19
7	FeBr ₂	SIPr ·HCl	NaO ^t Bu	100	90	19
8	FeCl ₃	SIPr ·HCl	NaO ^t Bu	97	88	13
9	Fe(OTf) ₃	SIPr ·HCl	NaO ^t Bu	52	47	16
10^g	$Fe_2(O^tBu)_6$	SIPr ·HCl	NaO ^t Bu	100	100	4
11^h	$Fe_2(O^tBu)_6$	SIPr ·HCl	NaO ^t Bu	26	24	9
12^i	$Fe_2(O^tBu)_6$	SIPr ·HCl	NaO ^t Bu	76	76	6
13^g	$Fe_2(O^tBu)_6$	SIPr ·HCl	None	97	97	4
14^g	$Fe(OEt)_3$	SIPr ·HCl	NaOEt	56	56	7
15^g	$Fe_2(O^tBu)_6$	IPr·HCl	NaO ^t Bu	39	32	10
16^g	$Fe_2(O^tBu)_6$	SIMes·HCl	NaO ^t Bu	14	8	6
17 ^g	$Fe_2(O^tBu)_6$	None	NaO ^t Bu	<1	Trace	9

^{*a*} Conditions: a mixture of an iron catalyst (3 mol%), L (9 mol%) and base (18 mol%) in THF was stirred at rt for 1 h. After addition of **1a** and **2a** (1.2 equiv.), the mixture was heated at 80 °C for 16 h. ^{*b*} Determined by GC using dodecane as an internal standard. ^{*c*} The yield of **3a** was calculated based on **1a**. ^{*d*} **3a**': 4,4-dimethylbiphenyl, the yield of **3a'** was calculated based on **2a**. ^{*e*} 9 mol% base was used. ^{*f*} 27 mol% base was used. ^{*f*} 1.5 mol% iron catalyst, 9 mol% L and 9 mol% base were used. ^{*h*} 1 mol% iron catalyst, 6 mol% L and 6 mol% base were used. ^{*i*} 1.5 mol% iron catalyst, 6 mol% L and 6 mol% base were used.

SIPr·HCl and 9 mol% NaO⁶Bu resulted in 77% yield of **3a** together with a significant amount of the homocoupling product 4,4'-dimethylbiphenyl **3a**' (Table 1, entry 1). Complete conversions of **1a** could be achieved at a higher loading of NaO⁶Bu (entries 2 and 3) with the optimal selectivity attained at 18 mol% of the base (entry 2). Other base additives including NaOMe (entry 4), NaHMDS (entry 5) and KO⁶Bu (entry 6) were all less effective towards promoting the selective formation of **3a**.



Amongst the iron precursors studied (entries 7–10), $Fe_2(O^tBu)_6^{10}$ (1.5 mol%) gave the best result. An excellent yield of **3a** was obtained with little homocoupling (entry 10). Lowering the catalyst loading to 1 mol% (entry 11), decreasing the amount of SIPr relative to iron to 2:1 (entry 12), or running the reaction in the absence of NaO^tBu (entry 13) resulted in an incomplete conversion of **1a**. A combination of "Fe(OEt)₃"¹¹ and NaOEt was detrimental to the conversion and selectivity (entry 14). The presence of SIPr proved to be critical to the successful heterocoupling as other NHC ligands such as IPr and SIMes resulted in low yields of **3** (entries 15–17). Notably, the activity of the iron catalyst system was sensitive to the steric properties of both alkoxide and NHC ligands. This is in agreement with previous

Table 2	: Sc	ope	of	aryl	Grignard	reagents	in	the	iron-catalysed	Kumada
biaryl c	ross-	cou	plir	ng ^a						



^{*a*} Reaction conditions: 1.5 mol% Fe₂(O'Bu)₆, 9 mol% SIPr·HCl and 9 mol% NaO'Bu, 1.2 equiv. of ArMgBr. ^{*b*} 2.5 mol% Fe₂(O'Bu)₆, 15 mol% SIPr·HCl and 15 mol% NaO'Bu were used. ^{*c*} Yield in brackets is determined by GC.

reports that bulky alkoxides disrupt the formation of multimetallic species, which is formed through alkoxo bridges between two or three metals,^{8b} and could lead to highly reactive low coordinate metal centers.^{9a,b}

Similar to fluoride,^{6b} tert-butoxide was found to significantly hinder the reduction of Fe(m) to Fe(0) by aryl Grignard reagents, which may explain its ability to suppress the homocoupling reaction. While a complete reduction of $FeBr_3$ to Fe(0) was observed when a mixture of $FeBr_3$ (1 equiv.), SIPr (3 equiv.) and

Table 3	Scope of aryl	chlorides in the	iron-catalyzed	Kumada biaryl	cross-coupling ^a
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	R ¹	1.2 equiv <i>p</i> -TolM 2.5 mol% Fe ₂ (0 Cl 15 mol% SIPr 15 mol% NaC	MgBr 2a D [/] Bu) ₃ ∷HCl D [/] Bu R ^{1[}	Me	
Entry	Aryl chloride	1 THF, 80 °C, Biaryl, yield (%)	16h Entry	3 Aryl chloride	Biaryl, yield (%)
1 ^b	CI	3a , 99	11	S CI 1k	3q , (trace) ^c
2	Me Me Me Me 1b	3h , 94	12		3r , (23) ^c
3	MeO CI	3 i , 82	13	MeO NeO Ne Me 1m	3s , 85
4	F Id	3 j , 92	14	F N Me 1n	3t , 92
5	Me Cl	3k , 98	15	CI Ne 10	3u , 80
6	TBSO CI	31 , 85	16	N CI 1p	3v , 62
7	BnMeN Cl	3m , 81	17	Ph N 1q	3w , 80
8	Cl Cl	3n , 89	18	Ph N 1r	3x , 65
9	CI 1i	30 , 79	19	N CI 1s	3y , 63
10^b	Me CI	3 p , 90	20^d	N Ph 1t	3z , 53

^{*a*} Reaction conditions: 2.5 mol% $Fe_2(O^tBu)_{6}$, 15 mol% SIPr·HCl and 15 mol% NaO^tBu, 1.2 equiv. of **2a**. ^{*b*} 1.5 mol% $Fe_2(O^tBu)_{6}$, 9 mol% SIPr·HCl and 9 mol% NaO^tBu were used. ^{*c*} Yield in brackets was determined by GC analysis. ^{*d*} 4-Anisylmagnesium bromide was used instead of *p*-tolylmagnesium bromide.

2a (10 equiv.) was heated at 80 $^\circ C$ for 1 h, only 13% of 3a' was obtained from the reaction of $Fe_2(O'Bu)_6$ under similar conditions.^{12}

Under the optimized conditions, high yielding syntheses of biaryls were achieved with a number of arylmagnesiums differing in electronic and steric properties (Table 2). In most cases except **2f** (entry 6), complete conversion of the aryl chlorides was obtained with 1.5 mol% of the iron catalyst. In the case of the acetal 3g (entry 7), the yield was determined to be 91% by GC analysis. After purification manipulations involving column chromatography and recrystallization, 3g was isolated in 76% yield.

A range of (hetero)aryl chlorides was evaluated in the reaction with *p*-tolylmagnesium bromide (Table 3). In general, 2.5 mol%

of $Fe_2(O^tBu)_6$ was needed to ensure the complete conversion of 1. Aryl chlorides featuring either electron-donating or electronwithdrawing substituents were efficiently converted to the corresponding biaryl compounds (entries 1-8). The reaction tolerated ortho-, meta- and para-substituted aryl chlorides.

Chlorostyrenes constitute a valuable class of substrate for the Kumada reaction since the alkene moiety offers various opportunities for further functionalization. Yet, their π -electron rich nature renders them deactivated in cross-coupling reactions. In addition, their potential to undergo side reactions such as carbometallation and dimerization could further complicate the problem.¹³ Recently, Jacobi von Wangelin et al. successfully developed an iron catalyst system to couple a range of chlorostyrenes with aryl Grignard reagents.5 In the presence of the current iron alkoxide catalyst system, biaryls resulting from the reaction of chlorostyrenes such as 1i and 1j could be obtained in very good yields (entries 9 and 10). Notably, the reaction of 1i was unproductive under the conditions developed by Jacobi von Wangelin et al.⁵

Encouraged by the success with chlorostyrenes, we further evaluated π -electron rich heterocyclic substrates (Table 3, entries 11-15). While 2-chlorothiophene 1k failed to convert to any appreciable extent as indicated by GC analysis (entry 11), reaction of 2-chlorobenzofuran 1l resulted in mainly decomposition (entry 12). Interestingly, chloroindoles could be reacted with organomagnesiums at either the pyrrole ring (entries 13 and 14) or the benzenoid (entry 15) to give arylated indoles in very good yields.

A number of important developments in the iron-catalyzed cross-coupling of any Grignard reagents with π -electron deficient N-heteroaryl halides have been reported.⁴ However, the scope of these reactions thus far is exclusive to coupling at the activated α -carbon (e.g. 2-pyridyl). The ability to access other substituted products is highly desirable considering the importance of pyridines and quinolines in biologically active compounds.¹⁴ In the presence of the alkoxide-based iron catalyst, α -, β -, or γ -arylated pyridines can all be prepared in moderate to good yields (Table 2, entries 16-18). In addition, the reaction of 2-chloroquinoline 1s led to the isolation of 3y in 63% yield. 4-Chloroquinoline 1t, which was previously a challenging substrate for iron catalysis,^{4g,h,15} could be cross-coupled with 4-anisylmagnesium bromide to give 3z in 53% yield.

Overall, the iron-catalysed reaction tolerated a number of functional groups, including fluoro (Table 2, entry 4; Table 3, entries 4 and 14), silyl-protected phenol (Table 3, entry 6), tertiary amines (Table 2, entry 5 and Table 3, entry 7), and acetal (Table 2, entry 7).

In conclusion, a new iron alkoxide catalyst system has been developed for the Kumada biaryl cross-coupling reaction. Amongst the alkoxide and amide counterions investigated, tert-butoxide was the most effective in inhibiting the homocoupling of arylmagnesiums, and enabled efficient synthesis of a broad array of (hetero)biaryls. Further studies to gain insights into the origin of the observed selectivity, and to apply the current findings in developing new iron-catalysed reactions are now underway in our laboratory.

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