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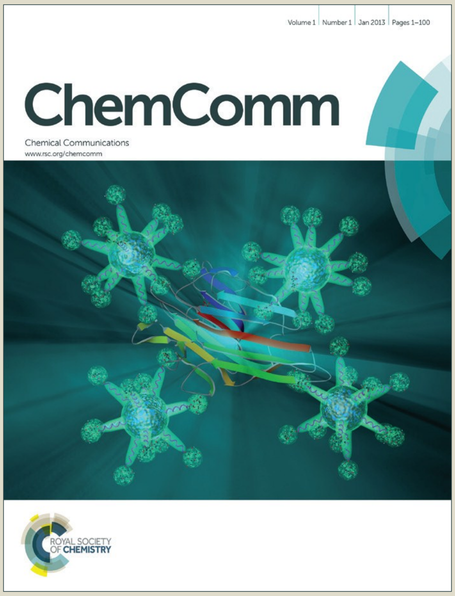

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Iron(II) Triflate/*N*-Heterocyclic Carbene-Catalysed Cross-Coupling of Arylmagnesiums with Aryl Chlorides and Tosylates

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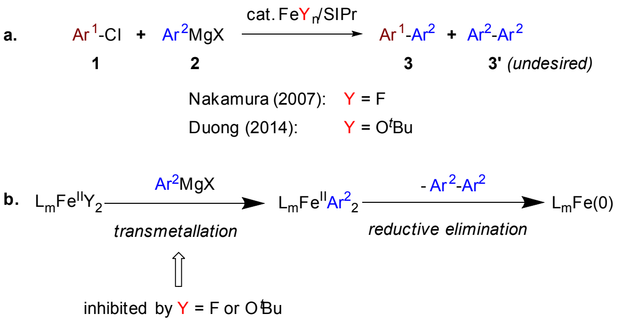
In comparison to iron(II) halides, iron(II) triflate exhibits a greater resistance towards reduction by *p*-tolylmagnesium bromide. This knowledge led to the development of an iron(II) triflate/*N*-heterocyclic carbene-catalysed cross-coupling of aryl Grignard reagents with aryl chlorides and tosylates with a high efficiency, even surpassing that of previously reported catalyst systems employing strongly coordinating counterions in some cases.

Transition metal-catalysed cross-coupling reactions are amongst the most important synthetic technologies at present.[1] Catalysts based on palladium and nickel are predominantly used for this purpose. There have been considerable efforts towards employing iron catalysts as an alternative due to the crustal abundance, inexpensiveness and low toxicity profile of this element.[2] In particular, iron-catalysed Kumada reaction for aryl-aryl coupling is of significant interests since biaryls are ubiquitous in fine chemicals, agrochemicals, pharmaceuticals and materials.[3] However, it is not trivial to control the selectivity of this reaction since arylmagnesiums can undergo self-coupling rather readily in the presence of an iron catalyst.[4]

Significant developments have been achieved with activated substrates such as 2-pyridyl halides or 2-chlorostyrenes.[5] For substrates bearing no activating group, Nakamura et al. showed that a combination of iron fluorides and an *N*-heterocyclic carbene (NHC) ligand can efficiently facilitate cross-coupling of aryl chlorides and arylmagnesiums (Scheme 1a).[6] The high selectivity obtained was attributed to a synergistic modulation of the fluoride counterion and the NHC. Presumably, fluoride strongly coordinates to Fe(II) and stabilises the iron centre against reduction by arylmagnesiums, ultimately suppressing the homocoupling pathway (Scheme 1b). A metalate mechanism via an Fe(II)/Fe(IV) catalytic cycle was proposed.[7,8] We later realized that an iron(III) *tert*-butoxide dimer/NHC catalyst system is also highly effective for the cross-coupling reaction.[9] Cook et al. recently reported an FeF_3/IPr-catalysed coupling of C-O based aryl electrophiles with aryl Grignard reagents.[10]



Scheme 1. (a) Iron/NHC-catalysed cross-coupling of aryl chlorides and arylmagnesiums. (b) A proposed mechanism for the reduction of Fe(II) to Fe(0) by arylmagnesiums.

Whereas previous successes rely on the use of strongly coordinating counterions to attain high selectivity, we discovered that a combination of $Fe(OTf)_2$/NHC can catalyse the cross-coupling reaction in a high efficiency, even surpassing that of the iron fluoride or alkoxide systems in some cases. A broad array of biaryls can be obtained in good to excellent yields from the coupling of arylmagnesiums with aryl chlorides and tosylates under these conditions. We report herein our findings.

During our investigation on the reduction of different iron salts with *p*-tolylmagnesium bromide **2a** in the presence of SIPr as the ligand, we noticed that the reaction of $Fe(OTf)_2$ was rather sluggish compared to iron halides (Table 3). Heating a mixture of $FeCl_2$, SIPr (1 equiv) and **2a** (30 equiv) in THF at 60 °C led to the quantitative formation of **3a’** within 10 min (entry 1) while the reaction of $FeBr_2$ reached full conversion within 1h (entry 2). On the other hand, the reduction of $Fe(OTf)_2$ progressed rather slowly and only produced 24% of **3a** after 1h (entry 3). $Fe(OTf)_3$ was more prone to reduction, giving 83% of **3a’** after 1h (entry 4).

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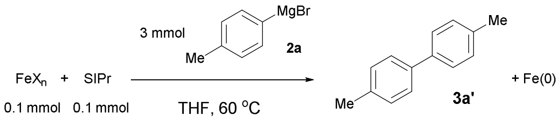
Table 1. Reduction of iron salts with *p*-tolylmagnesium bromide **2a**.

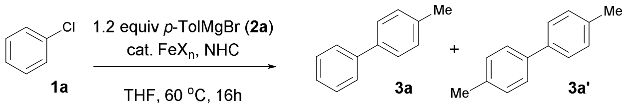


Entry	[FeX$_n$]	t (min)	3a' (mmol)[a]	3a' (%)
1	FeCl$_2$	10	0.10	100
2	FeBr$_2$	10	0.085	85
		60	0.10	100
3	Fe(OTf)$_2$	60	0.024	24
		120	0.039	39
4	Fe(OTf)$_3$	60	0.125	83

[a] Determined by GC using dodecane as an internal standard.

Intrigued by the resistance of Fe(OTf)$_2$ towards the reduction, we investigated the combination of Fe(OTf)$_2$/SIPr as a catalyst for the cross-coupling of chlorobenzene **1a** and **2a**.[11] Remarkably, **3a** was formed in an excellent yield in the presence of 3 mol% Fe(OTf)$_2$ and 9 mol% SIPr with little **3a'** observed (Table 2, entry 1). As expected, iron halides in combination with SIPr only gave low to moderate selectivity (entries 2-5). Further investigations revealed that other NHC's such as IPr and SIMes were not as effective as SIPr (entries 6 and 7). The reaction yield was not affected when the ligand to metal ratio was reduced to 1:1, albeit together with a slight increase in the homocoupling product (entry 8).

Table 2. Fe(OTf)$_2$/SIPr-catalysed cross-coupling of **1a** and **2a**.



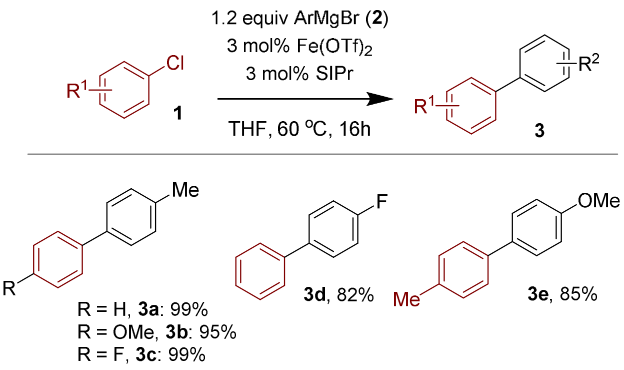
Entry	[FeX$_n$] (mol%)	NHC (mol%)	conv. (%)[a]	3a (%)[a]	3a' (%)[a,b]
1	Fe(OTf)$_2$ (3)	SIPr (9)	100	>99	4
2	FeBr$_2$ (3)	SIPr (9)	85	68	18
3	FeBr$_3$ (3)	SIPr (9)	84	62	22
4	FeCl$_2$ (3)	SIPr (9)	93	81	14
5	FeCl$_3$ (3)	SIPr (9)	73	49	25
6	Fe(OTf)$_2$ (3)	IPr (9)	84	80	8
7	Fe(OTf)$_2$ (3)	SIMes (9)	20	16	13
8	Fe(OTf)$_2$ (3)	SIPr (3)	100	>99	7

[a] Determined by GC using dodecane as an internal standard. [b] Determined based on **2a**.

The combination of 3 mol% Fe(OTf)$_2$ and 3 mol% SIPr indeed catalysed the reactions of aryl Grignard reagents with aryl chlorides bearing electron-donating and electron-withdrawing groups in good to excellent yields (Table 3).

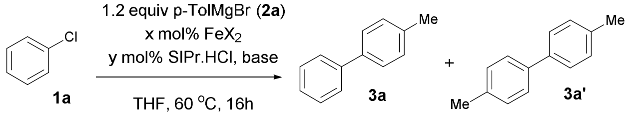
We further investigated the generation of SIPr in situ from the air-stable precursor SIPr.HCl (Table 4). While the reaction yield dropped significantly in the absence of an added base (entry 1), strong bases such as NaH, NaO^{t}Bu or KO^{t}Bu was found to efficiently promote catalyst generation (entries 2-4). An excellent yield of **2a** can be obtained using 3 mol% Fe(OTf)$_2$, 3 mol% SIPr.HCl and 3 mol% base (entry 5). Notably, the reaction could be run at as low as 0.5 mol% Fe(OTf)$_2$ (entry 6) without compromising the reaction yields. Attempts to lower the reaction temperature to rt resulted in low conversions (entry 7). Iron halides displayed only moderate activity (entries 8-9). Notably, reaction with *p*-tolylmagnesium chloride led to only 55% yield of **3a** (entry 10).

Table 3. Biaryl cross-coupling using Fe(OTf)$_2$/SIPr.[a]



[a] Conditions: 1.2 equiv ArMgBr, 3 mol% Fe(OTf)$_2$, 3 mol% SIPr, THF (0.3-0.4 M).

Table 4. Generation of SIPr in situ from a combination of SIPr.HCl and a base.



Entry	X	x	y	Base (mol%)	conv. (%)[a]	3a (%)[a]	3a' (%)[a]
1	OTf	3	9	None	76	33	31
2	OTf	3	9	NaH (9)	100	>99	3
3	OTf	3	9	NaO^{t}Bu (9)	100	>99	5
4	OTf	3	9	KO^{t}Bu (9)	100	>99	4
5	OTf	3	3	NaO^{t}Bu (3)	100	>99	7
6	OTf	0.5	1.5	NaO^{t}Bu (1.5)	100	98	4
7[b]	OTf	3	9	NaO^{t}Bu (9)	30	29	13
8	Cl	3	3	NaO^{t}Bu (3)	67	55	16
9	Br	3	3	NaO^{t}Bu (3)	79	70	15
10[c]	OTf	3	3	NaO^{t}Bu (3)	68	55	13

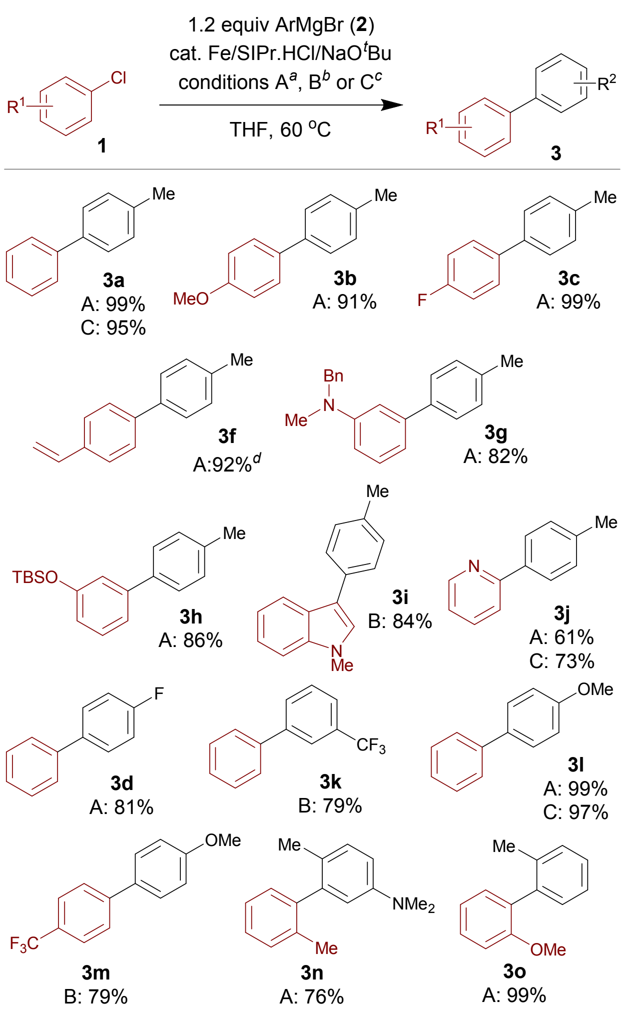
[a] Determined by GC using dodecane as an internal standard. [b] Reaction was run at rt. [c] *p*-tolylmagnesium chloride was used instead of **2a**.

Similar to the iron fluoride and alkoxide catalyst systems, a broad range of biaryls can be accessed in high yields in the presence of 3 mol% Fe(OTf)$_2$, 3 mol% SIPr.HCl and 3 mol% NaO^{t}Bu at 60 °C (Table 5, condition A). In comparison to previous systems that normally require 3 mol% of iron salt and 9 mol% of the carbene precursor, the significantly lower loadings of the expensive carbene ligand employed in the current system is rather attractive. In the case of highly electron-rich chloroindole (**3i**) or deactivated Grignard reagent (**3k**), a 3:1 ligand to metal ratio helped improve the reaction yields significantly (condition B). Similarly, for highly activated *p*-(trifluoromethyl)chlorobenzene (**3m**), less decomposition was observed with more added ligand. For chlorobenzene and chloropyridine, high yields of the cross-coupled products (**3a**,

3j and, **3l)** could be obtained at 0.5 mol% $Fe(OTf)_2$, 1.5 mol% SIPr.HCl and 1.5 mol% NaO^tBu (condition C).

Overall, the reaction tolerated electron-rich and electron-deficient substituents on both coupling partners. In particular, even highly deactivated 3-(trifluoromethyl)phenylmagnesium bromide (**3k**) can be coupled with chlorobenzene in 79% yield. Challenging π-electron rich aromatic systems such as 4-chlorostyrene **3f** or 3-chloroindole **3i** were arylated in very good yields.[9] The sterically hindered *ortho*, *ortho'*-disubstituted biphenyls **3n** and **3o** were formed under our conditions in 77% and 99% yields, respectively.

Table 5. Cross-coupling of aryl chlorides and arylmagnesiums using $Fe(OTf)_2$/SIPr.HCl/NaO^tBu.

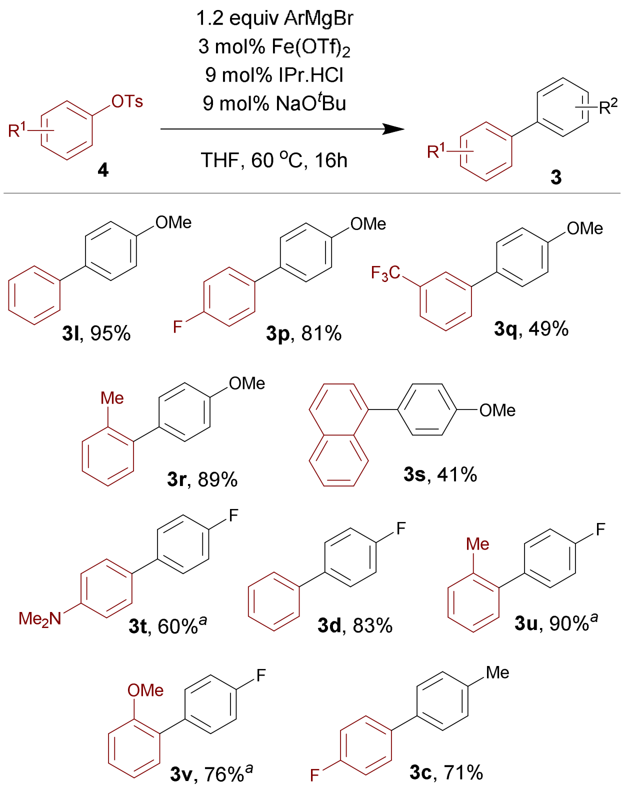


[a] Condition A: 3 mol% $Fe(OTf)_2$, 3 mol% SIPr.HCl, 3 mol% NaO^tBu, THF (0.3-0.4 M), 60 °C. [b] Condition B: 3 mol% $Fe(OTf)_2$, 9 mol% SIPr.HCl, 9 mol% NaO^tBu, THF (0.3-0.4 M), 60 °C. [c] Condition C: 0.5 mol% $Fe(OTf)_2$, 1.5 mol% SIPr.HCl, 1.5 mol% NaO^tBu, THF (0.6-0.7 M), 60 °C. [d] Reaction was run at 0.08 M.

The reaction is compatible with a range of functional groups including ether, alkene, tertiary amines and silyl-protected phenol. Attempts to couple aryl chlorides incorporating a methyl ester or a pivalate group have thus far only resulted in decomposition of the starting materials.

We then turned our attention to aryl tosylates, a highly attractive class of compounds for cross-coupling due to their ease of access from broadly abundant and inexpensive phenols. Cook et al. recently reported the first iron-catalysed cross-coupling of C-O based aryl electrophiles with aryl Grignard reagents employing 10 mol% FeF_3 and 20 mol% IPr.HCl.[10] A large excess of the organomagnesiums (ca. 3-4 equiv relative to aryl tosylates) was, however, required to obtain high conversions. We found that a combination of 3 mol% $Fe(OTf)_2$, 9 mol% IPr.HCl and 9 mol% NaO^tBu could enable efficient coupling of aryl tosylates and arylmagnesiums (Table 6). A variety of biaryls featuring electron-donating or electron-withdrawing substituents were successfully prepared in good yields employing only 1.2 equiv of the Grignard reagent. Running the reaction at diluted conditions (0.06 M) helped improve the yields of the desired products. In the case of highly electron-rich 4-chloro-*N*,*N*-dimethylaniline (**3t**) and sterically hindered *ortho*-substituted aryl chlorides (**3u** and **3v**), 5 mol% of the iron catalyst was needed to achieve good conversions. A significant amount of phenol was observed in the reactions of highly electron-deficient 3-(trifluoromethyl)phenyl tosylate (**3q**) and 1-naphthyl tosylate (**3s**), resulting in only moderate yields of the cross-coupled products.

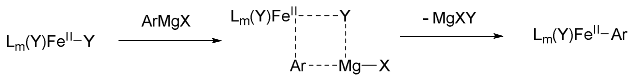
Table 6. Cross-coupling of aryl tosylates and arylmagnesiums.



[a] Conditions: 5 mol% $Fe(OTf)_2$, 15 mol% SIPr.HCl, 15 mol% NaO^tBu, THF (0.06 M), 60 °C.

To probe the relative reactivity of aryl chlorides and tosylates, we performed a competitive iron-catalysed reaction between *p*-chlorotoluene **1e** (1 equiv) and phenyl tosylate **4a** (1 equiv) with *p*-anisylmagnesium bromide (1 equiv). A poor selectivity was obtained (see supporting information for more details).

The high efficiency of $Fe(OTf)_2$/NHC is rather remarkable in comparison to previous catalyst systems employing strongly coordinating counterions.[6,9,10,12] It is in particular interesting to note the ability of $Fe(OTf)_2$ to resist reduction the by Grignard reagents.[13] Presumably, a mechanism for the transmetallation of arylmagnesiums with iron(II) halides could involve initial coordination of the main group element to the halogen, which facilitates removal of the halogen from the iron centre and the transfer of the carbon nucleophile (Scheme 2).[14] Possibly, this assistance is diminished in the case of a non-coordinating counterion such as triflate, rendering the reduction of $Fe(OTf)_2$ by **2a** less facile. Further studies are needed to evaluate this possibility and to better understand the effect observed.



Scheme 2. A possible mechanism for the transmetallation of iron(II) halides and aryl Grignard reagents.

Conclusions

In conclusion, the non-coordinating triflate counterion was found to significantly slow down the reduction of the iron centre by arylmagnesiums. In comparison to previously reported iron catalyst systems, $Fe(OTf)_2$/NHC exhibited comparable or better catalytic efficiency in the cross-coupling of aryl Grignard reagents with aryl chlorides and tosylates.

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