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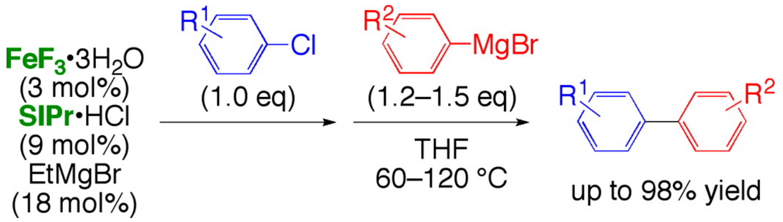

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Iron-Catalyzed Selective Biaryl Coupling: Remarkable Suppression of Homocoupling by the Fluoride Anion

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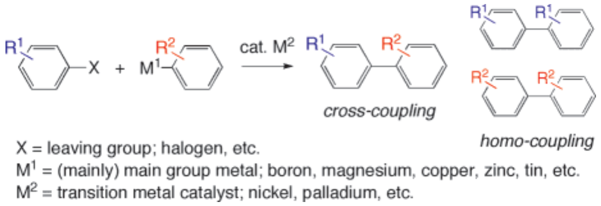
Biaryls constitute core structural units for a wide range of functional molecules[1] and are synthesized primarily using transition metal-catalyzed aryl−aryl cross-coupling reactions.[2] Palladium and nickel catalysts have been the dominant choice for such a purpose and are widely used in academia as well as in industry. Whereas iron, a practically ideal transition metal, has been actively investigated as a catalyst in the field of cross-coupling reactions,[3,4] iron-catalyzed aryl−aryl cross-coupling has remained a challenge because of competition from the homocoupling reaction caused by oxidation with organic halides or iron-catalyzed halogen−metal exchange.[5] Knochel reported a partial remedy, which utilizes aryl copper reagents and reactive aryl iodides to suppress the homocoupling reaction and selectively yield the biaryl products.[4h] Herein, we report a simple and highly selective biaryl synthesis based on iron(III) fluoride-catalyzed cross-coupling of aryl chlorides with aryl Grignard reagents (Scheme 1, X = chlorine, M^1 = magnesium, M^2 = iron).

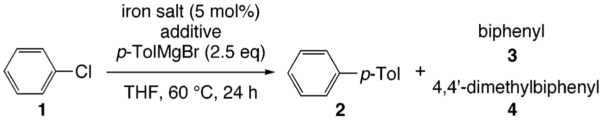
Scheme 1. Transition Metal-Catalyzed Biaryl Coupling Reaction



The key finding for the selective biaryl cross-coupling was a novel combination of iron fluoride salts with an *N*-heterocyclic carbene (NHC) ligand,[6] which specifically suppressed homocoupling reactions. Table 1 summarizes the results of catalyst screening for the reaction between chlorobenzene and *p*-tolylmagnesium bromide (*p*-TolMgBr, 2.5 equiv) at 60 °C for 24 h. The optimum yield (98%) of 4-methylbiphenyl **2** was achieved with 5 mol % of $FeF_3{\cdot}3H_2O$ and 15 mol % of SIPr·HCl[7] (entry 1). The undesired homocoupling reaction occurred only at the very first stage of the reaction and gave a negligible amount of biphenyl **3** and a small amount of 4,4′-dimethylbiphenyl **4** (0.018 mmol, 4% yield based on the amount of *p*-TolMgBr). This can be accounted for by the initial reduction of iron(III) fluoride.

The reaction was sluggish without the NHC precursors (entry 2). Ferrous fluoride ($FeF_2{\cdot}4H_2O$) showed comparable catalytic activity, indicating that the in situ reduction of $FeF_2{\cdot}4H_2O$ or $FeF_3{\cdot}3H_2O$ probably gives the same catalytically active iron species (entry 3). Entries 4 and 5 show that the anhydrous iron salts, FeF_3 and FeF_2, were ineffective, probably because of their low solubility in THF. The addition of water did not affect much the product yield (entry 6). The homocoupling reaction was predominant with $FeCl_3$ in the presence or absence of SIPr·HCl (entry 7).[8] Pretreatment of $FeCl_3$ with KF also gave catalytically active species to suppress the homocoupling (entry 8). These results clearly indicate that the fluoride anion plays a key role in suppressing the undesired homocoupling reaction.

Table 1. Iron-Catalyzed Cross-Coupling of Chlorobenzene and *p*-Tolylmagnesium Bromide



entry[a]	iron salt	additive (mol %)	yield[b] (%)			
			2	3	1	4[c]
1	$FeF_3{\cdot}3H_2O$	SIPr·HCl (15)	98	<1	0	4
2	$FeF_3{\cdot}3H_2O$	none	6	trace	93	4
3	$FeF_2{\cdot}4H_2O$	SIPr·HCl (15)	96	<1	2	4
4	FeF_3	SIPr·HCl (15)	29	trace	69	2
5	FeF_2	SIPr·HCl (15)	18	trace	81	1
6[d]	FeF_3	H_2O (15), SIPr·HCl (15)	40	trace	57	1
7	$FeCl_3$	SIPr·HCl (15)	32	2	10	32
8[e]	$FeCl_3$	KF (20), SIPr·HCl (15)	92	1	0	8

[a] Reactions were carried out on a 0.4−1.0 mmol scale. [b] Yield was determined by GC analysis using undecane as an internal standard. [c] Yield based on the amount of *p*-TolMgBr. [d] Iron salt and additives were mixed in THF for 10 min at room temperature prior to the reaction. [e] $FeCl_3$ was treated with KF in MeOH/THF, which were then removed in vacuo.

The aforementioned procedure requires a large excess of aryl magnesium bromide because of the insufficient reactivity of the Grignard reagent toward $FeF_3{\cdot}3H_2O$ and SIPr·HCl as a base.[9] After extensive screening of various bases, EtMgBr was found to react the catalyst precursors to produce active iron species: A THF solution of EtMgBr (18 mol %) was added to $FeF_3{\cdot}3H_2O$ (3 mol %) and SIPr·HCl (9 mol %) at 0 °C. After stirring for 4 h at room temperature, chlorobenzene **1** (1.0 equiv) and *p*-TolMgBr (1.2 equiv) were added. The coupling reaction completed in 24 h at 60 °C to give the desired product **2** in 98% yield (eq 1). It is noteworthy that the treatment of *anhydrous* FeF_3 (3 mol %) and SIPr·HCl (9 mol %) with EtMgBr (9 mol %) gave a similarly active iron catalyst to give **2** in 98% yield (Table 2, entry 2 and see SI for details). With these optimized procedures, yields of the homocoupling byproducts were almost negligible.

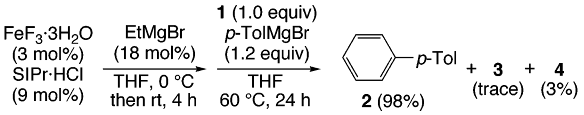
 (1)

Table 2 summarizes the scope of the present iron-catalyzed cross-coupling reaction. As shown in entries 1−5, the cross-coupling depends critically on the nature of the leaving group: chlorobenzene gave the desired cross-coupling product **2** selectively (98%), while bromo- and iodobenzene gave more homocoupling **4** (36 and 38%) than **2** (28 and 23%). Phenyl triflate showed lower reactivity to give 27% of **2** and 6% of **4**. The C−F bond was entirely inert under the reaction conditions.

A variety of aryl chlorides and aryl magnesium bromides are coupled selectively and efficiently (entries 6−17). Electron-rich 4-chloroanisole reacted with *p*-TolMgBr to give the desired product

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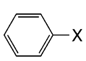
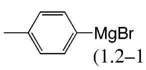
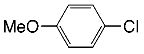
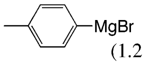
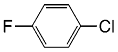
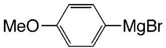
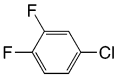
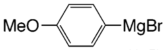
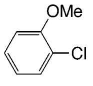
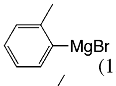
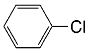
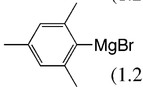
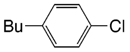
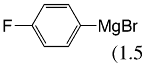
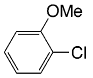
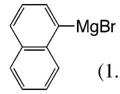
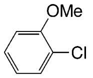
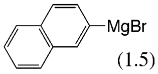
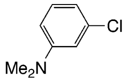
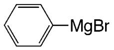
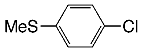
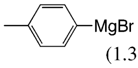
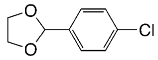
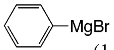
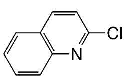
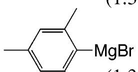
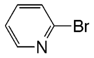
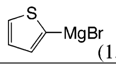
Table 2. Iron-Catalyzed Selective Biaryl Coupling Reactions

entry[a]	Ar^1–X	Ar^2MgBr (equiv)	yield[b] of Ar^1–Ar^2(%) (conditions)
1		 (1.2–1.5)	**0**[c] (X = F)
2			**98**[d] (X = Cl)
3			**28**[c] (X = Br)
4			**23**[c] (X = I)
5			**27**[c] (X = OTf) (60 °C, 24 h)
6		 (1.2)	**92** (60 °C, 24 h)
7		 (1.2)	**91** (60 °C, 24 h)
8[e]		 (1.5)	**81** (60 °C, 24 h 80 °C, 12 h)
9		 (1.2)	**90** (80 °C, 24 h)
10		 (1.2)	**93**[c] (120 °C, 24 h)[f]
11[g]		 (1.5)	**87** (60 °C, 24 h)
12[e]		 (1.2)	**92** (70 °C, 48 h)
13		 (1.5)	**96** (60 °C, 24 h)
14		 (1.2)	**94** (60 °C, 24 h)
15[h]		 (1.35)	**80** (60 °C, 24 h)
16		 (1.35)	**88** (60 °C, 24 h 80 °C, 12 h)
17		 (1.35)	**82** (100 °C, 8 h)[f]
18[h]		 (1.5)	**74** (80 °C, 24 h)

[a] Reactions were carried out on a 1.0 or 30.0 mmol scale following the procedure in eq 1 unless otherwise noted. [b] Isolated yield. [c] GC yield. [d] Treatment of anhydrous FeF_3 (3 mol %) and SIPr·HCl (9 mol %) with EtMgBr (9 mol %) also gave the active catalyst. [e] 5 mol % of iron catalyst was used. [f] Reaction was carried out in toluene. [g] 4 mol % of iron catalyst was used. [h] 6 mol % of iron catalyst was used.

in 92% yield (entry 6). Fluorine-substituted biaryls, the representative mesogen structure of liquid crystal molecules, can be synthesized with 4-fluoro-1-chlorobenzene and 3,4-difluoro-1-chlorobenzene in good yields (entries 7 and 8). While the reactions of *o*-tolyl- and mesitylmagnesium bromide were rather slow because of their steric hindrance, an elevated reaction temperature (80 and 120 °C) gave the corresponding products in 90 and 93% yields, respectively (entries 9 and 10). Electron-deficient 4-fluorophenylmagnesium bromide gave the desired product in 87% yield (entry 11). 1- and 2-naphthylmagnesium bromide took part in the reaction (92 and 96% yields, entries 12 and 13). The dimethylamino and methylthio groups did not interfere in the cross-coupling (entries 14 and 15). Note that a small amount of 4,4″-dimethyl-[1,1′;4′,1″]terphenyl (4%) formed via cleavage of the C−S bond, which is often a problem in the nickel-catalyzed coupling reactions.[10] An acetal remained intact under the conditions used here (entry 16). 2-Chloroquinoline reacted with mesitylmagnesium bromide at 100 °C to give the desired product in 82% yield (entry 17). The reaction of 2-thienylmagnesium bromide with 2-chloropyridine did not take place, but with 2-bromopyridine it smoothly gave 4-thiophen-2-yl pyridine in 74% yield (entry 18).

Mechanistically, we assume that the fluoride anion coordinating to the iron center would suppress the formation of a ferrate complex[11] possessing excess aryl groups (such as $Ar^1Ar^2_2Fe$ and $Ar^1Ar^2_3Fe$) and the consequent nonselective reductive elimination (formation of $Ar^1{-}Ar^2$ and $Ar^2{-}Ar^2$). The fluoride effect is also observed in cobalt- and nickel-catalyzed cross-coupling reactions to suppress the homocouplings.[12]

In summary, we have demonstrated an iron-catalyzed selective cross-coupling reaction of aryl chlorides with aryl Grignard reagents. The addition of NHC ligand and fluoride counteranion proved critical to achieving high yield and selectivity. This method has several synthetically attractive features: operational simplicity, rare-metal free, phosphine free, and minimal byproducts. "Fluoride-tuned" metal-catalyzed cross-coupling reactions are now being actively investigated in our laboratory and will be reported in due course.

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Supporting Information Available: Details of the experimental procedure, characterization, and physical data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) Heteroaromatic compounds undergo cross-coupling: see ref 4a,b.

(6) Favorable effects of NHC ligands in iron-catalyzed cross-couplings of haloalkanes were reported. (a) Bica, K.; Gaertner, P. *Org. Lett.* **2006**, *8*, 733. (b) Bedford, R. B.; Betham, M.; Bruce, D. W.; Danopoulos, A. A.; Frost, R. M.; Hird, M. *J. Org. Chem.* **2006**, *71*, 1104.

(7) Other NHC or phosphine ligands are not effective. See Supporting Information for details.

(8) $Fe(acac)_3$ also gave the homocoupling product **4** as a major product.

(9) In situ generation of NHC ligand, see: Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290 and references cited therein.

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(11) $[Ar_4Fe^{III}][Li(THF)_3]$: (a) Alonso, P. J.; Arauzo, A. B.; Forniés, J.; Garcia-Monforte, M. A.; Martin, A.; Martinez, J. I.; Menjón, B.; Rillo, C.; Sáiz-Garitaonandia, J. J. *Angew. Chem., Int. Ed.* **2006**, *44*, 6707. $[Me_4Fe^{II}][Li(OEt_2)]_2$: (b) Fürstner, A.; Krause, H.; Lehmann, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 440. Fe−F complex: (c) Vela, J.; Smith, J. M.; Yu, Y.; Ketterer, N. A.; Flaschenriem, C. J.; Lachicotte, R. J.; Holland, P. L. *J. Am. Chem. Soc.* **2005**, *127*, 7857.

(12) The reactions with $CoF_2{\cdot}4H_2O$ and $NiF_2{\cdot}4H_2O$ were carried out according to the procedure in Table 1: the cobalt and nickel catalysts gave cross-coupling product **2** in 91 and 93% yields, respectively. Some other catalyst precursors ($Co(acac)_3$, $Ni(acac)_2$, etc.) produced significant amounts of homocoupling products **3** and **4** (6−30% yields) and reduced the cross-coupling product yield.

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