Inorganic Chemistry

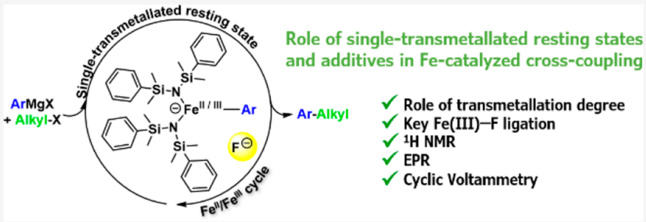
pubs.acs.org/IC Article

Relevance of Single-Transmetalated Resting States in Iron-Mediated Cross-Couplings: Unexpected Role of σ-Donating Additives

Lidie Rousseau, Nadia Touati, Laurent Binet, Pierre Thuéry, and Guillaume Lefèvre*

Cite This: *Inorg. Chem.* 2021, 60, 7991−7997 Read Online

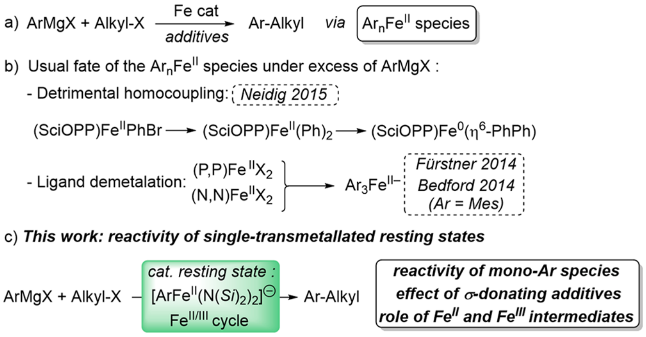
ABSTRACT: Control of the transmetalation degree of organoiron(II) species is a critical parameter in numerous Fe-catalyzed cross-couplings to ensure the success of the process. In this report, we however demonstrate that the selective formation of a monotransmetalated Fe^{II} species during the catalytic regime counterintuitively does not alone ensure an efficient suppression of the nucleophile homocoupling side reaction. It is conversely shown that a fine control of the transmetalation degree of the transient Fe^{III} intermediates obtained after the activation of alkyl electrophiles by a single-electron transfer (SET), achievable using σ-donating additives, accounts for the selectivity of the cross-coupling pathway. This report shows for the first time that both coordination spheres of Fe^{II} resting states and Fe^{III} short-lived intermediates must be efficiently tuned during the catalytic regime to ensure high coupling selectivities.



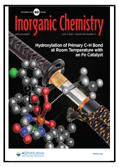
INTRODUCTION

Over the past decades, Fe-catalyzed cross-coupling reactions have been intensely developed, thanks to the pioneer work of Kochi,[1a,b] followed by Cahiez,[1c] Fürstner,[1d,e] Nakamura,[1f,g] and Bedford.[1h,i] Despite the significant ecologic and economic advantages displayed by this metal for its catalytic applications in synthetic chemistry,[2] unveiling the mechanistic facets of the related systems remains a challenging issue, especially due to the short lifetimes of the active species.[3] The Kumada cross-coupling, involving Grignard reagents as nucleophiles, is by far the most developed Fe-catalyzed coupling reaction (see Scheme 1a). The key role of aryliron(II) species in aryl-alkyl cross-coupling has been established for numerous systems, the activation of the electrophile proceeding by a single-electron transfer (SET) between the latter and the aryliron(II), leading to coupling mechanisms based on an Fe^{II}/Fe^{III} sequence.[4] It it not uncommon though that such reactions present undesired byproducts such as a homocoupling of either the Grignard reagent or of the organic electrophile, or even both. This is particularly true when the nucleophile is a sterically unhindered aryl Grignard reagent (ArMgX). It was previously reported that the in situ formation of organoiron(II) species with ratios Ar/Fe > 1 often leads to a homocoupling of the nucleophile or to the formation of *ate*-Fe^{II} species with a decoordination of the ligand (Scheme 1b).[1i,5] Strict control of the transmetalation degree of well-defined Fe^{II} precursors has thus been often presented as a key to minimize the formation of Grignard homocoupling.[5] It is generally admitted that the formation of undertransmetalated Fe^{II} resting states can be achieved by a slow rate addition of the Grignard in the bulk medium[6] or by using suitable coordination frameworks involving σ-donating additives, thus hampering multiple Mg-to-Fe^{II} transmetalations. Classic examples are the aryl−aryl coupling systems developed by Nakamura and Duong, which efficiently suppressed Grignard homocoupling by associating

Scheme 1. (a) Classical Fe-Catalyzed Kumada Reaction Involving an Aryl Grignard Reagent and an Alkyl Electrophile; (b) Usual Fate of Ar_nFe^{II} Species in the Presence of an Excess of ArMgX; (c) Single-Transmetalated Catalytic Resting State Investigated in This Work (*Si* = $SiMe_2Ph$)



Received: February 19, 2021
Published: May 10, 2021



https://doi.org/10.1021/acs.inorgchem.1c00518
Inorg. Chem. 2021, 60, 7991−7997

iron salts with N-heterocycle carbenes (NHCs) and fluoride[7a] or alkoxide salts.[7b]

From a mechanistic standpoint, single-transmetalated species are often elusive in the catalytic process, evolving toward multiple transmetalated intermediates. The latter can also lead to lower oxidation states at various stages of the catalysis (Scheme 1b). On the basis of these reports, it is thus difficult to evaluate the exact effect of the controlled formation of single-transmetalated Fe^{II} intermediates on coupling selectivities.

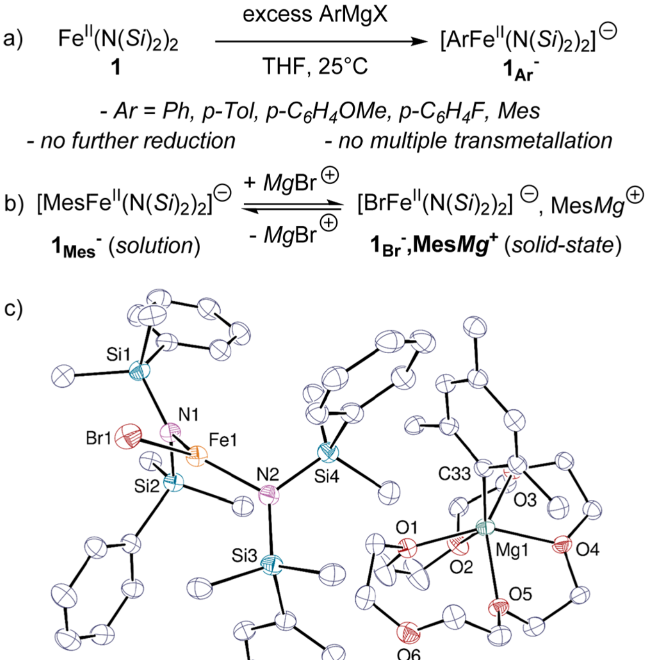
In this work, we report that the *N*-bis-silylamide complex $[Fe^{II}(N(Si)_2)_2]$ (**1**, *Si* = $SiMe_2Ph$) provides a robust framework that undergoes a single transmetalation in the presence of an excess of aryl Grignard reagents, affording monotransmetalated species $[ArFe^{II}(N(Si)_2)_2]^-$ ($\mathbf{1}_{Ar}^-$, Scheme 1c). The latter is able to catalyze Kumada aryl-alkyl cross-coupling with alkyl halides as electrophiles. We demonstrate, on the one hand, that, although $\mathbf{1}_{Ar}^-$ remains the single Fe^{II} resting state during a catalytic regime, this does not ensure a significant suppression of homocoupling side-products, unlike the general mechanistic pattern so far admitted. On the other hand, we bring evidence that σ-donating additives such as fluoride anions allow to limit homocoupling, thanks to a control of the transmetalation degree of transient organoiron(III) intermediates formed at a later stage of the catalytic process. These results are supported by paramagnetic ^1H NMR and cyclic voltammetry as well as electron paramagnetic resonance (EPR) experiments.

■ RESULTS AND DISCUSSION

Our first goal was to select a suitable Fe^{II} precursor that (i) selectively undergoes a single transmetalation in the presence of an excess of aryl Grignard reagents and (ii) efficiently achieves aryl-alkyl catalytic cross-couplings with alkyl halides. Several well-defined monoaryliron(II) species have been structurally characterized in the past, involving a variety of σ-donating ligands (e.g., 1,2-diphosphines, 1,2-diamines (Scheme 1b), Bopa-Ph pincers,[5b] β-diketiminates,[8a] NHCs,[8b] tris(pyrazolyl)borates,[8c] *N*-silylamides,[8d] etc.). However, the behavior of those species in the presence of an excess of ArMgX was either not investigated or an evolution toward multiple transmetalations was described (Scheme 1b).

On the one hand, we first investigated the reactivity of Fe^{II} complexes stabilized by sterically crowded *N*-silylamide and *O*-aryloxy ligands ($[Fe^{II}(tmeda)(Cl)(N(SiMe_3)((2\text{-}Ph)C_6H_4))]$ (**2**) and $[Fe^{II}(tmeda)(Cl)(O((2,6\text{-}Ph_2)C_6H_3))]$ (**3**), see Figures S1 and S2 for X-ray diffraction (XRD) characterization), anticipating that those σ-donating frameworks would prevent multiple transmetalations with ArMgBr (Ar = 2,4,6-$C_6H_2Me_3$ (Mes), Ph).[9] However, both complexes underwent a partial or total ligand demetalation upon reaction with an excess of MesMgBr, leading to $[Mes_3Fe^{II}]^-$ (see Figures S3 and S4). On the other hand, iron(II) *N*-bis-silylamide $[Fe^{II}(N(Si)_2)_2]$ (**1**)[10] proved to undergo a single transmetalation upon an addition of an excess of ArMgX (Ar = Ph, *p*-tolyl (*p*-Tol), *p*-$MeOC_6H_4$, *p*-FC_6H_4, Mes), no demetalation being observed. Heteroleptic monoaryliron(II) *ate*-complexes $[ArFe^{II}(N(Si)_2)_2]^-$ ($\mathbf{1}_{Ar}^-$) could thus be characterized in solution by an action of the corresponding Grignard reagent on **1** (Scheme 2a). ^1H NMR data for those high-spin Fe^{II} species are in agreement with less bulky analogues (see Figures S5–S9).[8d,11] Importantly, ^1H NMR speciation showed that **1** underwent almost a quantitative transmetalation with 1 equiv of ArMgBr for Ar = Ph, *p*-Tol, *p*-$MeOC_6H_4$, and *p*-FC_6H_4 to afford $\mathbf{1}_{Ar}^-$. Moreover, the latter species remained intact upon an addition of a large excess of ArMgX (up to 10 equiv, see Figure S10), and underwent neither further transmetalation nor reduction to lower oxidation states. This behavior strongly differs from the other well-defined Fe^{II} precursors used as coupling catalysts (Scheme 1b).[5c,11,12] A selective obtention of single-transmetalated aryliron(II) from **1** mostly originates from two factors. First, the stabilization of the Fe^{II} precursor **1** by two monoanionic ligands leads to the building of an overall formal negative charge at the iron in $\mathbf{1}_{Ar}^-$ upon first transmetalation. For electrostatic reasons, this may discourage the feasibility of a second transmetalation, which would lead to a dianionic species $[Ar_2Fe^{II}(N(Si)_2)_2]^{2-}$, with a formal double negative charge at the iron. A second factor hampering the formation of double-transmetalated species is the high steric pressure brought by the *N*-bis-silylamide moieties around the metal. In this regard, the bulkiness of this ligand even hampers a full transmetalation of bulky aryl Grignard reagents such as MesMgBr with **1**. As a consequence of the steric hindrance, an equilibrium was observed between the species $[MesFe^{II}(N(Si)_2)_2]^-$ ($\mathbf{1}_{Mes}^-$) and free complex **1** upon addition of 1 equiv of MesMgBr onto **1**, leading to a transmetalation ratio of $\mathbf{1}_{Mes}^-/\mathbf{1}$ = 70/30 (Figure S9). This equilibrium was reflected in the solid state, since the halide complex $[BrFe^{II}(N(Si)_2)_2]^-$ ($\mathbf{1}_{Br}^-$) was observed in the solid state associated with the Mes*Mg*$^+$ (*Mg*$^{2+}$ = $Mg(18\text{-}C\text{-}6)^{2+}$) countercation (($\mathbf{1}_{Br}^-$,**Mes*Mg*$^+$**), Scheme 2b,c).

Scheme 2. (a) Selective Formation of $\mathbf{1}_{Ar}^-$ by Transmetallation between 1 and ArMgBr; (b) Equilibrium between $\mathbf{1}_{Mes}^-$ (Solution) and $\mathbf{1}_{Br}^-$,Mes*Mg*$^+$ (Solid State), *Mg*$^{2+}$ = Mg(18-C-6)$^{2+}$; (c) Solid-State Molecular Structure of $\mathbf{1}_{Br}^-$,Mes*Mg*$^+$ with 30% Probability Displacement Ellipsoids Shown; Hydrogen Atoms Are Omitted



Complex **1** provided a single-transmetalated stable species ($\mathbf{1}_{Ar}^-$) in the presence of an excess of aryl Grignard reagents, and its performance as a catalyst for aryl-alkyl cross-coupling was investigated. **1** was able to catalyze cross-coupling between PhMgBr and n-$C_6H_{13}I$ under smooth conditions at long reaction times (43% cross-coupling yield; 24 h at 0 °C were required to reach full n-$C_6H_{13}I$ conversion, Table 1, Entry 1).

Table 1. Evolution of Cross-Coupling (cc) Yield between Ar[M] and n-$C_6H_{13}I$ Mediated by 1 in the Absence or the Presence of TBAT as Fluoride Source

$$\text{Ar[M]} + n\text{-}C_6H_{13}I \xrightarrow[y\ \text{TBAT}]{\text{Fe}^{\text{II}}(\text{N}(Si)_2)_2,\ \text{conditions (a,b,c)}} \text{Ar-}C_6H_{13} + \text{Ar-Ar}$$

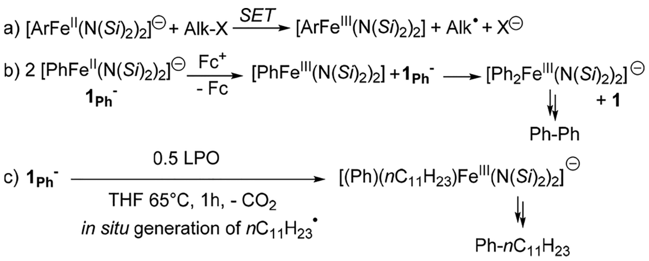
entry	Ar[M]	conditions	$y = 0$ % cc	$y = 0$ r	$y = 5$ % cc	$y = 5$ r	R
1	PhMgBr	*a*	43	1.4	48	1.6	1.1
2	PhMgBr	*b*	59	1.6	62	2.6	1.6
3	p-$C_6H_4MeMgCl$	*b*	47	1.5	37	2.8	1.9
4	m-MeC_6H_4MgBr	*b*	35	1.1	42	2.0	1.8
5	p-$MeOC_6H_4MgBr$	*b*	39	2.2	29	3.2	1.5
6	p-FC_6H_4MgBr	*b*	71	6.4	44	6.3	1.0
7	Ph_2Mn	*c*	20	0.8	35	1.4	1.7
8	$(p$-$C_6H_4Me)_2Mn$	*c*	26	0.6	32	0.9	1.5
9	$(m$-$C_6H_4Me)_2Mn$	*c*	21	0.7	25	1.1	1.6
10	$(p$-$MeOC_6H_4)_2Mn$	*c*	22	0.6	28	1.8	1.2
11	$(p$-$FC_6H_4)_2Mn$	*c*	25	1.6	30	1.4	0.9

[a]Conditions: Fe/ArMgX/n-$C_6H_{13}I$ = 0.05:1:1, 0 °C, 24 h. [b]Fe/ArMgX/n-$C_6H_{13}I$ = 1:1:10, 0 °C, 5 h. [c]Fe/Ar_2Mn/n-$C_6H_{13}I$ = 0.05:0.5:1, 0 °C, 24 h; $r = n(\text{Ar}-C_6H_{13})/n(\text{Ar}-\text{Ar})$; y = n(TBAT)/n(Fe); R = $r(y = 5)/r(y = 0)$; TBAT: n-tetrabutylammonium difluorotriphenylsilicate.

When radical clock 1-bromohexene was used as a coupling partner along with PhMgBr, benzylcyclopentane was formed as a coupling product (18% yield, 25% conversion). The detection of this product, albeit in a small yield, probes a radical activation of the alkyl electrophile, in line with previously reported iron-catalyzed aryl-alkyl coupling systems.[4]

Activation of the alkyl electrophile by $[\text{ArFe}^{\text{II}}(\text{N}(Si)_2)_2]^-$ ($\mathbf{1}_{\text{Ar}}^-$) thus involves a first single-electron transfer (SET) step leading to an alkyl radical and a transient organoiron(III) intermediate (Scheme 3a). ^{1}H NMR monitoring demonstrated that the consumption rate of $\mathbf{1}_{\text{Ph}}^-$ in the presence of an excess of n-$C_6H_{13}I$ is first order in $\mathbf{1}_{\text{Ph}}^-$ (Figure S11), strengthening the hypothesis of a monometallic $\text{Fe}^{\text{II}}/\text{Fe}^{\text{III}}$ activation, by contrast with Hu's system, in which a transmetalation between two monoaryliron(II) species affording an active bis-aryliron(II) is the rate-determining step, leading to an overall second order in iron.[5b] However, although the single-transmetalated species $\mathbf{1}_{\text{Ph}}^-$ is stable in the presence of an excess of PhMgBr, a homocoupling side-reaction significantly occurred. 30% of PhPh was indeed detected in catalytic conditions (Entry 1, conditions a). This prompted us to investigate the reactivity of species $\mathbf{1}_{\text{Ar}}^-$ toward an excess of n-$C_6H_{13}I$, in the absence of additional Grignard reagent (conditions b). Surprisingly, the cross-coupling versus homocoupling ratio r also remained low in those conditions (r ranking between 1.1 and 2.2, Entries 2–5), except when p-C_6H_4FMgBr was used (r = 6.4, Entry 6). The formation of notable quantities of ArAr bisaryl by the reaction of monoaryl species $\mathbf{1}_{\text{Ar}}^-$ and n-$C_6H_{13}I$ demonstrates that, contrary to the widespread idea,[5,6,13] the control of the transmetalation of the iron(II) resting state is not enough to efficiently hamper the formation of bisaryls in Fe-mediated aryl-alkyl couplings.

Scheme 3. Oxidation-Induced Reactivity of $\mathbf{1}_{\text{Ar}}^-$. (a) SET between $\mathbf{1}_{\text{Ar}}^-$ and an Alkyl Halide. (b) Formation of Ph-Ph Induced by 1-Electron Oxidation of $\mathbf{1}_{\text{Ph}}^-$ with Ferrocenium. (c) C–C Bond Formation between In-Situ-Generated Radical n-$C_{11}H_{23}$• and $\mathbf{1}_{\text{Ph}}^-$ (LPO = Lauroyl Peroxide (n-$C_{11}H_{23}C(O)O)_2$)



Inspired by the methodology reported by Nakamura for limiting a homocoupling side reaction in aryl–aryl cross-coupling,[7a] the effect of n-tetrabutylammonium difluorotriphenylsilicate (TBAT) as a fluoride source on cross-coupling between $\mathbf{1}_{\text{Ar}}^-$ and n-$C_6H_{13}I$ was examined. In line with Nakamura's system, the use of TBAT (y = 5 equiv vs Fe, Table 1) could indeed improve the selectivity of $\mathbf{1}_{\text{Ar}}^-$ for the cross-coupling path (Table 1, Entries 2–6, conditions b, y = 5). This led to an R factor higher than 1, with r almost doubling for Ar = p- or m-tolyl when TBAT is used (R = 1.9 and 1.8, Entries 3 and 4). It is of note that the benefic effect of fluorides on the r ratio displays a bell-shaped dependence with respect to the Hammett parameters of the Ar substituents, as shown in Figure 1. This benefic role of fluorides on the r ratio was also observed under catalytic conditions (conditions c) when weak nucleophiles such as $Ar_2[Mn]$ were used (Entries 7–11), a bell-shaped Hammett plot being also observed in that case (Figure 1). No significant effect of TBAT was observed under catalytic conditions with Grignard reagents (conditions a, see Table S2). From a mechanistic standpoint, the absence of an interaction between $[\text{PhFe}^{\text{II}}(\text{N}(Si)_2)_2]^-$ and F^- was ascertained by ^{1}H NMR (see Figure S12), confirming again that the control of the iron(II) resting state coordination sphere alone does not fully govern the occurrence of homocoupling. These results are in stark contrast with the current mechanistic picture rationalizing the competition between Fe-catalyzed

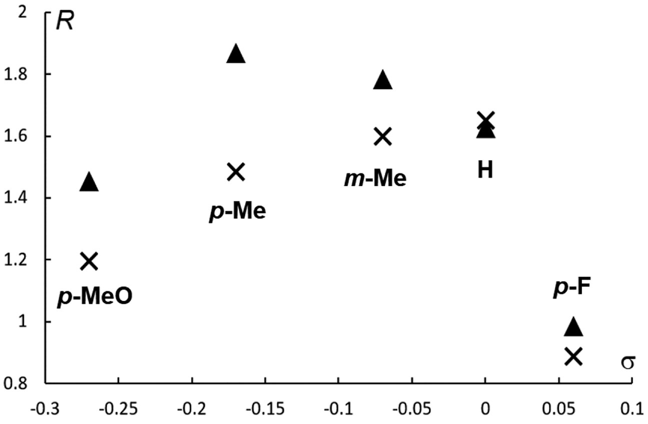


Figure 1. Evolution of the R ratio as a function of the Hammett σ constant for cross-coupling between n-hexyl iodide and ArMgX (▲, conditions b) or $Ar_2[Mn]$ (×, conditions c).

aryl-alkyl cross-coupling and nucleophile homocoupling. The commonly reported hypothesis is indeed that fluoride anions actually bound to the organoiron(II) resting states to avoid multiple transmetalations and thus suppressed the homocoupling process.[13] Consequently, the homocoupling of the Grignard reagent is not mediated by a bielectronic Fe^{II}/Fe^{0} sequence, which suggests that this side process involves later-stage intermediates, formed after the electron transfer between $\mathbf{1_{Ph}}^-$ and the electrophile.

In order to reproduce the one-electron oxidation of $\mathbf{1_{Ph}}^-$ by the organic halide, the former was subjected to reaction with a ferrocenium salt ($[Cp_2Fe][PF_6]$, Scheme 3b). When $\mathbf{1_{Ph}}^-$ was treated by an excess (5.6 equiv) of $[Cp_2Fe][PF_6]$, only 7% of biphenyl PhPh was detected, whereas 25% of PhPh was obtained by treating $\mathbf{1_{Ph}}^-$ with 0.5 equiv of $[Cp_2Fe][PF_6]$. This suggests that, in the latter case, a half quantity of $\mathbf{1_{Ph}}^-$ is oxidized into $[PhFe^{III}(N(Si)_2)_2]$, which reacts with the remaining $\mathbf{1_{Ph}}^-$ to afford the bis-arylated species $[Ph_2Fe^{III}(N(Si)_2)_2]^-$ after an Fe^{II}-to-Fe^{III} aryl transmetalation. Biphenyl is then formed from $[Ph_2Fe^{III}(N(Si)_2)_2]^-$ in a two-electron reductive elimination process (Scheme 3b).[14] However, $[Fe^{I}(N(Si)_2)_2]^-$ ($\mathbf{4}^-$) obtained after a reductive elimination could not be observed by ^1H NMR. ^1H NMR monitoring showed the disappearance of $\mathbf{4}^-$ upon treatment by PhMgBr, suggesting that the former might undergo a ligand demetalation in the presence of PhMgBr followed by a decomposition (see Figure S14). The reactivity of the Fe^{III} species obtained after the SET between $\mathbf{1_{Ph}}^-$ and organic electrophiles (Scheme 3a) was then investigated by cyclic voltammetry, mimicking the redox processes during electrophile activation. $\mathbf{1_{Ph}}^-$ displayed a reversible Fe^{II}/Fe^{III} oxidation signal at $E_{p,O1} = -0.32$ V versus $Fc^{0/+}$, associated with the reduction peak $E_{p,R1} = -0.52$ V versus $Fc^{0/+}$, observed on the reverse scan (Figure 2a).[15] The quasi-reversibility observed for this system ($i_{p,R1}/i_{p,O1} \approx 0.7$ at 0.1 $V \cdot s^{-1}$) suggests that $[PhFe^{III}(N(Si)_2)_2]$, formed after a one-electron oxidation of $\mathbf{1_{Ph}}^-$, is stable at the time scale of the cyclic voltammetry. This species is reduced in the diffusion layer of the electrode on the reverse scan at R_1, leading back to complex $\mathbf{1_{Ph}}^-$ (Figure 2c). $\mathbf{1_{Ph}}^-$ is less easily oxidized than similar species described by Deng ($[(IPr_2Me_2)_2Fe^{II}Ph_2]$, $E_{ox} = -0.93$ V vs $Fc^{0/+}$)[16a] or Tonzetich ($[(IPr)Fe^{II}(CH_2Ph)_2]$, $E_{ox} = -0.86$ V vs $Fc^{0/+}$),[16b] themselves used as cross-coupling catalysts, explaining the long reaction times required to reach full *n*-hexyl iodide conversions using catalyst **1** (Table 1).

When $\mathbf{1_{Ph}}^-$ was subjected to an addition of 1.2 equiv of TBAT, its oxidation potential remained unchanged (Figure 2b). This confirms the absence of reaction of $\mathbf{1_{Ph}}^-$ with fluoride salts, excluding the formation of any new Fe^{II} species featuring a $F{-}Fe^{II}$ ligation. However, the oxidation peak O_1 became irreversible, and the reduction peak R_1 fully disappeared, while a new reduction peak developed at potential R_2 ($E_{p,R2} = -1.15$ V vs $Fc^{0/+}$, Figure 2b). In other words, $[PhFe^{III}(N(Si)_2)_2]$, generated at the O_1 potential, reacts with the fluoride source to afford a new complex, reduced at the more negative R_2 potential. This strongly suggests that $[PhFe^{III}(N(Si)_2)_2]$ reacts with F^- to afford a new species featuring a $F{-}Fe^{III}$ ligation, less easily reduced than $[PhFe^{III}(N(Si)_2)_2]$ (Figure 2c). This stabilization of the Fe^{III} oxidation state in the presence of fluorides is mirrored by an EPR analysis of the catalytic medium, which shows an increase of the high-spin Fe^{III} intermediates concentration by ca. 5 (Figure 2d, $g = 4.27$).

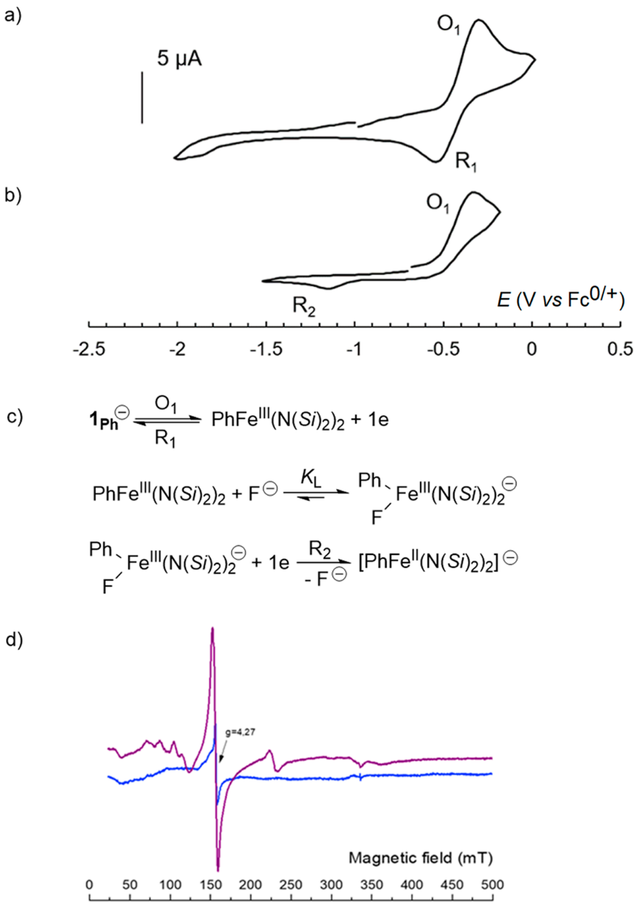
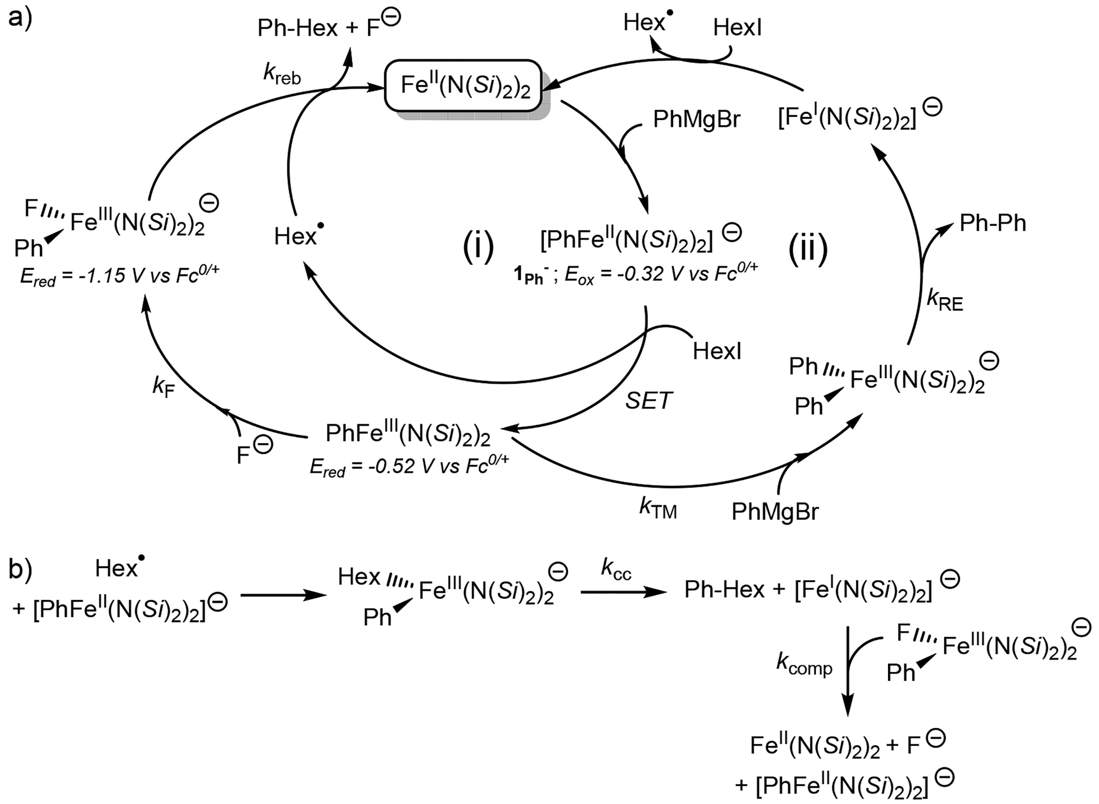


Figure 2. Cyclic voltammetry performed in tetrahydrofuran (THF) at 22 °C at a gold disk electrode (d = 2 mm) in the presence of nBu_4N^+,BPh_4^- (0.05 M) as a supporting electrolyte (scan rate = 0.1 $V \cdot s^{-1}$) of a solution of (a) $\mathbf{1_{Ph}}^-$,$\mathbf{MgBr}^+$ (6.5 mM); (b) same as (a) after addition of 1.2 equiv of TBAT; (c) related redox events; (d) cw-EPR spectrum (0.02:1 2-MeTHF/THF glass, T = 10 K) of a solution of **1** treated by 10 equiv of PhMgBr and 10 equiv of $n\text{-}C_6H_{13}I$ in the absence (blue) or the presence (purple) of 5 equiv of TBAT, frozen after 5 min at 20 °C.

Taken together, these results demonstrate that σ-donating additives such as fluoride anions actually act in this system as ancillary ligands to the Fe^{III} intermediate $[ArFe^{III}(N(Si)_2)_2]$, obtained after the SET step between the alkyl iodide and the organoiron(II) resting state $\mathbf{1_{Ar}}^-$ and not as Fe^{II} ligands. This $F{-}Fe^{III}$ ligation allows the blocking of an Fe^{III} coordination site and hampers a second transmetalation between the latter and an aryl nucleophile Ar[M]. Formation of a bisaryliron(III) intermediate $[Ar_2Fe^{III}(N(Si)_2)_2]^-$ is thus prevented, which limits the amount of bisaryl formed by a reductive elimination.

The monoaryliron(III) intermediate $[ArFe^{III}F(N(Si)_2)_2]^-$ is then involved in the last step of the coupling process, that is, the formation of the C−C bond. The first scenario that can occur is a classic radical rebound of the alkyl radical Alk· with the Fe^{III}-ligated Ar group (Scheme 4a, cycle (i)), affording the coupling product and regenerating complex **1**, as described by Tonzetich for similar NHC-ligated systems.[16b] A second scenario is the radical addition of Alk· onto $\mathbf{1_{Ar}}^-$, leading to the cross-coupling after an $Fe^{II}/Fe^{III}/Fe^{I}$ sequence. This hypothesis is sustained by the formation of 35% of the coupling product $Ph\text{-}nC_{11}H_{23}$ when $\mathbf{1_{Ph}}^-$ is treated by an

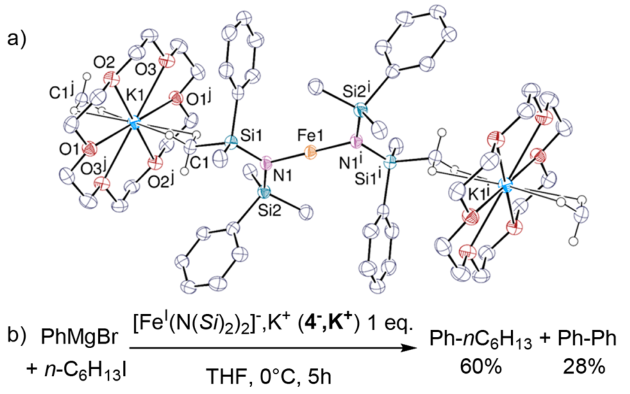
Scheme 4. (a) Mechanisms of the Formation of (i) Ph-Hex by Cross-Coupling between PhMgBr and n-$C_6H_{13}I$ Involving the Classical Radical Rebound as Final Step and (ii) Ph-Ph by Homocoupling, in the Presence of a Fluoride Source and with $\mathbf{1}_{\mathbf{Ph}}^-$ as Resting State; (b) Alternative Coupling Mechanism Featuring a $Fe^{II}/Fe^{III}/Fe^{I}$ Sequence, Followed by an Fe^{I}/Fe^{III} Comproportionation



excess of lauroyl peroxide (LPO) under thermal conditions, allowing generation of free radical n-$C_{11}H_{23}\cdot$ (Scheme 3c; 16% of Ph-$n$$C_{11}H_{23}$ is also detected in the absence of a thermal activation, in a coupling process initiated by oxidation of $\mathbf{1}_{\mathbf{Ph}}^-$ by LPO). This suggests that the in-situ-generated radical n-$C_{11}H_{23}\cdot$ is able to react with $\mathbf{1}_{\mathbf{Ph}}^-$ to afford the heteroleptic species $[(Ph)(nC_{11}H_{23})Fe^{III}(N(Si)_2)_2]^-$, which leads after reductive elimination to Ph-$n$$C_{11}H_{23}$ and $[Fe^{I}(N(Si)_2)_2]^-$ ($\mathbf{4}^-$). A comproportionation reaction between $\mathbf{4}^-$ and $[ArFe^{III}F(N(Si)_2)_2]^-$ can then occur, leading to $\mathbf{1}$ and $\mathbf{1}_{\mathbf{Ar}}^-$, which both re-enter the catalytic cycle as summarized in Scheme 4b.[17]

The role of fluoride additives is thus to enhance the stability of the intermediate $[ArFe^{III}(N(Si)_2)_2]$ and to prevent the transmetalation leading to $[Ar_2Fe^{III}(N(Si)_2)_2]^-$. Because they hamper the homocoupling process (Scheme 4a, cycle (ii)), they allow an efficient closure of the cross-coupling cycle through the rebound (Scheme 4a, cycle (i)) and Fe^{I}/Fe^{III} comproportionation (Scheme 4b) steps. This also explains the bell-shaped dependence of the role of fluoride anions on the cross-coupling ratio (R, Figure 1) with the Hammett parameters of the nucleophile substituents (Ar[M], Table 1). Nucleophiles bearing electron-rich aryl groups easily afford the double-transmetalated symmetric species $[Ar_2Fe^{III}(N(Si)_2)_2]^-$ regardless of the presence of F^-, quickly entering cycle (ii). After a fast reductive elimination, bisaryl ArAr is obtained (k_{TM} and $k_{RE} \gg k_F$). On the one hand, this behavior is similar to the reductive elimination of electron-rich bisaryls in symmetric $[(P,P)Pt^{II}Ar_2]$, faster than that of electron-poor analogues.[18] On the other hand, nucleophiles involving electron-poor aryl groups do not easily provide $[Ar_2Fe^{III}(N(Si)_2)_2]^-$, reductive elimination of the corresponding bisaryl also being a slow process. In that case, a single transmetalated Ar—Fe^{III} species quickly completes the cross-coupling process, following either the rebound (Scheme 4a, cycle (i)) or the comproportionation (Scheme 4b) path (k_{TM} and $k_{RE} \ll k_F$, k_{reb} and k_{comp}), regardless of the presence of fluorides. A low influence of fluoride additives on the r ratio is thus observed for both electron-rich and -poor Ar groups, leading to R values close to 1 (Figure 1). However, fluoride anions efficiently block the transmetalation of aryl groups with intermediate electronic effects onto $[ArFe^{III}(N(Si)_2)_2]$, leading to an improvement of the cross-coupling selectivity (R values greater than 1, Figure 1).[19] The formation of bisaryls by cycle (ii) nevertheless allows to re-enter the main cross-coupling cycle (i). Two-electron reductive elimination from $[Ar_2Fe^{III}(N(Si)_2)_2]^-$ indeed affords $[Fe^{I}(N(Si)_2)_2]^-$ ($\mathbf{4}^-$), which was synthesized, characterized by X-ray diffraction (associated to the K(18-C-6)$^+$ countercation), and proved to be an efficient cross-coupling promotor (Scheme 5, stoichiometric experiment). An Evans speciation moreover showed that $\mathbf{4}^-$ displays a high-spin Fe^{I} center (S = 3/2; μ_{eff} = 5.02 μ_B, $\mu_{s.o.}$ = 3.87 μ_B), akin to the recently reported analogue $[Fe^{I}(N(SiMe_3)_2)_2]^-$ (μ_{eff} = 5.12 μ_B).[20] As suggested by a recent report by Werncke et al., an SET step between $\mathbf{4}^-$ and n-$C_6H_{13}I$ should quickly occur, allowing the formation of $\mathbf{1}$, which can re-enter the cross-coupling process (Scheme 4, last step of cycle (ii)).[8d]

Scheme 5. (a) Solid-State Molecular Structure of 4^-,(18-C-6)K^+ Obtained by Reduction of 1 with 1 equiv of KC_8. Displacement Ellipsoids Shown at 50% Probability, Hydrogen Atoms Omitted. (b) Cross-Coupling between PhMgBr and n-$C_6H_{13}I$ Mediated by 4^-,K^+



CONCLUSION

We demonstrated that bulky N-bis-silylamides used as Fe^{II} ligands provide robust frameworks that selectively afford single-transmetalated aryliron(II) species as resting states in Fe-catalyzed aryl-alkyl cross-couplings. Unlike the currently admitted mechanistic picture, we proved that access to single-transmetalated Fe^{II} resting states is a nonsufficient condition to impede the usual bisaryl side-product formations. Bisaryls are indeed also significantly formed by a reductive elimination from transient bis-aryliron(III) intermediates obtained after the activation of the alkyl halide. Hampering multiple transmetalations at the Fe^{III} stage can be performed using σ-donating additives such as fluoride anions, limiting the formation of bisaryls. A fine control of the Fe^{III} coordination sphere therefore proves to be a critical parameter to access a good cross-coupling selectivity, in addition to a control of the Fe^{II} resting states coordination sphere (multiple transmetalations at the Fe^{II} stage being also controlled by either the coordination sphere of the latter or also by the use of suitable σ-donating additives). In a general way, this shows that the design of the coordination sphere of transient oxidized iron intermediates in those couplings is as essential as the design of the resting state itself.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.inorgchem.1c00518.

General procedures, ^1H NMR spectra, kinetics plots (PDF)

Accession Codes

CCDC 2045621−2045624 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

Guillaume Lefèvre − *Chimie ParisTech, PSL University, CNRS, Institute of Chemistry for Life and Health Sciences, CSB2D, 75005 Paris, France;* orcid.org/0000-0001-9409-5861; Email: guillaume.lefevre@chimieparistech.psl.eu

Authors

Lidie Rousseau − *Chimie ParisTech, PSL University, CNRS, Institute of Chemistry for Life and Health Sciences, CSB2D, 75005 Paris, France; Université Paris-Saclay, CEA, CNRS, NIMBE, 91191 Gif-sur-Yvette cedex, France*

Nadia Touati − *ChimieParisTech, Université PSL, CNRS, Institut de Recherche de Chimie-Paris, PCMTH, 75005 Paris, France*

Laurent Binet − *ChimieParisTech, Université PSL, CNRS, Institut de Recherche de Chimie-Paris, PCMTH, 75005 Paris, France*

Pierre Thuéry − *Université Paris-Saclay, CEA, CNRS, NIMBE, 91191 Gif-sur-Yvette cedex, France;* orcid.org/0000-0003-1683-570X

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.inorgchem.1c00518

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Funding

G.L. thanks the ANR (Project JCJC SIROCCO), the ERC (Project DoReMI StG, 852640), and the CNRS (Project IrMaCAR) for their financial support. Dr A. Simonneau (LCC, Toulouse, France) is thanked for his technical assistance.

Notes

The authors declare no competing financial interest.

REFERENCES

(1) (a) Tamura, M.; Kochi, J. K. Vinylation of Grignard reagents. Catalysis by iron. *J. Am. Chem. Soc.* **1971**, *93*, 1487−1489. (b) Neumann, S. M.; Kochi, J. K. Synthesis of olefins. Cross-coupling of alkenyl halides and Grignard reagents catalyzed by iron complexes. *J. Org. Chem.* **1975**, *40*, 599−606. (c) Cahiez, G.; Avedissian, H. Highly Stereo- and Chemoselective Iron-Catalyzed Alkenylation of Organomagnesium Compounds. *Synthesis* **1998**, *1998*, 1199−1205. (d) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. Iron-Catalyzed Cross-Coupling Reactions. *J. Am. Chem. Soc.* **2002**, *124*, 13856−13863. (e) Martin, R.; Fürstner, A. Cross-Coupling of Alkyl Halides with Aryl Grignard Reagents Catalyzed by a Low-Valent Iron Complex. *Angew. Chem., Int. Ed.* **2004**, *43*, 3955−3957. (f) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. Iron-Catalyzed Cross-Coupling of Primary and Secondary Alkyl Halides with Aryl Grignard Reagents. *J. Am. Chem. Soc.* **2004**, *126*, 3686−3687. (g) Hatakeyama, T.; Hashimoto, T.; Kondo, Y.; Fujiwara, Y.; Seike, H.; Takaya, H.; Tamada, Y.; Ono, T.; Nakamura, M. Iron-Catalyzed Suzuki−Miyaura Coupling of Alkyl Halides. *J. Am. Chem. Soc.* **2010**, *132*, 10674−10676. (h) Bedford, R. B.; Huwe, M.; Wilkinson, M. C. Iron-catalysed Negishi coupling of benzylhalides and phosphates. *Chem. Commun.* **2009**, *0*, 600−602. (i) Bedford, R. B.; Brenner, P. B.; Carter, E.; Cogswell, P. M.; Haddow, M. F.; Harvey, J. N.; Murphy, D. M.; Nunn, J.; Woodall, C. H. TMEDA in Iron-Catalyzed Kumada Coupling: Amine Adduct versus Homoleptic "ate" Complex Formation. *Angew. Chem., Int. Ed.* **2014**, *53*, 1804−1808.

(2) (a) Bauer, I.; Knölker, H.-J. Iron Catalysis in Organic Synthesis. *Chem. Rev.* **2015**, *115*, 3170−3387. (b) Bedford, R. B.; Brenner, P. B. *The development of iron catalysts for cross-coupling reactions. Iron Catalysis II*; Bauer, E., Ed.; Springer International, 2015.

(3) (a) Carpenter, S. H.; Neidig, M. L. A Physical-Inorganic Approach for the Elucidation of Active Iron Species and Mechanism

in Iron-Catalyzed Cross-Coupling. *Isr. J. Chem.* **2017**, *57*, 1106−1116. (b) Sears, J. D.; Neate, P. G. N.; Neidig, M. L. Intermediates and Mechanism in Iron-Catalyzed Cross-Coupling. *J. Am. Chem. Soc.* **2018**, *140*, 11872−11883. (c) Neidig, M. L.; Carpenter, S. H.; Curran, D. J.; DeMuth, J. C.; Fleischauer, V. E.; Iannuzzi, T. E.; Neate, P. G. N.; Sears, J. D.; Wolford, N. J. Development and Evolution of Mechanistic Understanding in Iron-Catalyzed Cross-Coupling. *Acc. Chem. Res.* **2019**, *52*, 140−150.

(4) For a recent review on Fe-catalyzed couplings involving radical key steps, see Kyne, S. H.; Lefèvre, G.; Ollivier, C.; Petit, M.; Ramis Cladera, V.-A.; Fensterbank, L. Iron and cobalt catalysis: new perspectives in synthetic radical chemistry. *Chem. Soc. Rev.* **2020**, *49*, 8501−8542.

(5) (a) Sun, C. L.; Krause, H.; Fürstner, A. A Practical Procedure for Iron Catalyzed Cross Coupling Reactions of Sterically Hindered Aryl-Grignard Reagents with Primary Alkyl Halides. *Adv. Synth. Catal.* **2014**, *356*, 1281−1291. (b) Bauer, G.; Wodrich, M. D.; Scopelliti, R.; Hu, X. Iron Pincer Complexes as Catalysts and Intermediates in Alkyl−Aryl Kumada Coupling Reactions. *Organometallics* **2015**, *34*, 289−298. (c) Daifuku, S. L.; Kneebone, J. L.; Snyder, B. E. R.; Neidig, M. L. Iron(II) Active Species in Iron−Bisphosphine Catalyzed Kumada and Suzuki−Miyaura Cross-Couplings of Phenyl Nucleophiles and Secondary Alkyl Halides. *J. Am. Chem. Soc.* **2015**, *137*, 11432−11444.

(6) Cahiez, G.; Habiak, V.; Duplais, C.; Moyeux, A. Iron-Catalyzed Alkylations of Aromatic Grignard Reagents. *Angew. Chem., Int. Ed.* **2007**, *46*, 4364−4366.

(7) (a) Hatakeyama, T.; Nakamura, M. Iron-Catalyzed Selective Biaryl Coupling: Remarkable Suppression of Homocoupling by the Fluoride Anion. *J. Am. Chem. Soc.* **2007**, *129*, 9844−9845. (b) Chua, Y.-Y.; Duong, H. A. Selective Kumada biaryl cross-coupling reaction enabled by an iron(iii) alkoxide−N-heterocyclic carbene catalyst system. *Chem. Commun.* **2014**, *50*, 8424−8427.

(8) (a) Yu, Y.; Brennessel, W. W.; Holland, P. L. Borane B−C Bond Cleavage by a Low-Coordinate Iron Hydride Complex and N−N Bond Cleavage by the Hydridoborate Product. *Organometallics* **2007**, *26*, 3217−3226. (b) Ohki, Y.; Hatanaka, T.; Tatsumi, K. C−H Bond Activation of Heteroarenes Mediated by a Half-Sandwich Iron Complex of N-Heterocyclic Carbene. *J. Am. Chem. Soc.* **2008**, *130*, 17174−17186. (c) Jové, F. A.; Pariya, C.; Scoblete, M.; Yap, G. P. A.; Theopold, K. H. A Family of Four-Coordinate Iron(II) Complexes Bearing the Sterically Hindered Tris(pyrazolyl)borato Ligand Tp^{tBu,Me}. *Chem. - Eur. J.* **2011**, *17*, 1310−1318. (d) Werncke, C. G.; Pfeiffer, J.; Müller, I.; Vendier, L.; Sabo-Etienne, S.; Bontemps, S. C-Halide bond cleavage by a two-coordinate iron(i) complex. *Dalton Trans.* **2019**, *48*, 1757−1765.

(9) The syntheses of **2** and **3** were adapted from Stokes, S. L.; Davis, W. M.; Odom, A. L.; Cummins, C. C. Low-Coordinate Iron Complexes Stabilized by N-(tert-Hydrocarbyl)anilide Ligation: Adduct Formation, Chemical Oxidation, and Nitric Oxide Complexation. *Organometallics* **1996**, *15*, 4521−4530.

(10) Chen, H.; Bartlett, R. A.; Dias, H. V. R.; Olmstead, M. M.; Power, P. P. The use of very crowded silylamide ligands -N(SiMenPh3-n)2(n = 0, 1, or 2) to synthesize crystalline, two-coordinate, derivatives to manganese(II), iron(II), and cobalt(II) and the free ion [Ph3SiNSiPh3]-. *J. Am. Chem. Soc.* **1989**, *111*, 4338−4345.

(11) Rousseau, L.; Herrero, C.; Clémancey, M.; Imberdis, A.; Blondin, G.; Lefèvre, G. Evolution of Ate-Organoiron(II) Species towards Lower Oxidation States: Role of the Steric and Electronic Factors. *Chem. - Eur. J.* **2020**, *26*, 2417−2428.

(12) Clémancey, M.; Cantat, T.; Blondin, G.; Latour, J.-M.; Dorlet, P.; Lefèvre, G. Structural Insights into the Nature of Fe0 and FeI Low-Valent Species Obtained upon the Reduction of Iron Salts by Aryl Grignard Reagents. *Inorg. Chem.* **2017**, *56*, 3834−3848.

(13) Hatakeyama, T.; Hashimoto, S.; Ishizuka, K.; Nakamura, M. Highly Selective Biaryl Cross-Coupling Reactions between Aryl Halides and Aryl Grignard Reagents: A New Catalyst Combination of N-Heterocyclic Carbenes and Iron, Cobalt, and Nickel Fluorides. *J. Am. Chem. Soc.* **2009**, *131*, 11949−11963.

(14) The homocoupling from bis-aryliron(III) generated in situ by a one-electron oxidation of Fe^{II} precursors was also reported by Deng: Liu, Y.; Xiao, J.; Wang, L.; Song, Y.; Deng, L. Carbon−Carbon Bond Formation Reactivity of a Four-Coordinate NHC-Supported Iron(II) Phenyl Compound. *Organometallics* **2015**, *34*, 599−605.

(15) The oxidation of [Fe^{II}(N(SiMe$_3$)$_2$)$_3$)]$^-$ occurred in the same range, at −0.45 V versus Fc$^{0/+}$: Margraf, G.; Schödel, F.; Sänger, I.; Bolte, M.; Wagner, M.; Lerner, H.-W. Eine elektrochemische und strukturelle Studie an den Eisensilylamiden Fe[N(SiMe$_3$)$_2$]$_2$ und Fe[N(SiMe$_3$)$_2$]$_3$. *Z. Naturforsch., B: J. Chem. Sci.* **2012**, *67b*, 549−556.

(16) (a) See citation of Deng reference in note 14. (b) Przyojski, J. A.; Veggeberg, K. P.; Arman, H. D.; Tonzetich, Z. J. Mechanistic Studies of Catalytic Carbon−Carbon Cross-Coupling by Well-Defined Iron NHC Complexes. *ACS Catal.* **2015**, *5*, 5938−5946.

(17) Because of the very low concentration of the Fe^{I} and Fe^{III} species involved in the comproportionation step, it cannot be excluded that the Fe^{I} reacts with the alkyl halide to afford an alkyl radical and the complex **1**, which can re-enter a catalytic cycle. In that case, the most likely evolution pathway for the species [Ar-Fe^{III}F(N(Si)$_2$)$_2$]$^-$ is to undergo a one-electron reduction of the Fe^{III} to the Fe^{II} stage, thus generating an aryl radical Ar· in an off-cycle, noncatalytic pathway. In this regard, it cannot be excluded that bisaryls Ar−Ar are generated from this pathway, for example, from an in-cage recombination of Ar· or formation of transient dinuclear {Ar−[Fe^{III}]}$_2$ species leading to a one-electron bimetallic reductive elimination.

(18) Shekhar, S.; Hartwig, J. F. Distinct Electronic Effects on Reductive Eliminations of Symmetrical and Unsymmetrical Bis-Aryl Platinum Complexes. *J. Am. Chem. Soc.* **2004**, *126*, 13016−13027.

(19) This also explains why the beneficial effect of fluoride on the selectivity for cross-coupling is more important in stoichiometric studies (Table 1, conditions b) or in catalytic cross-couplings involving soft nucleophiles (conditions c) than in catalytic conditions with Grignard partners, the high nucleophilicity of the latter inhibiting the Fe(III) ligation by fluorides.

(20) Werncke, C. G.; Bunting, P. C.; Duhayon, C.; Long, J. R.; Bontemps, S.; Sabo-Etienne, S. Two-Coordinate Iron(I) Complex [Fe{N(SiMe3)2}2]−: Synthesis, Properties, and Redox Activity. *Angew. Chem., Int. Ed.* **2015**, *54*, 245−248.