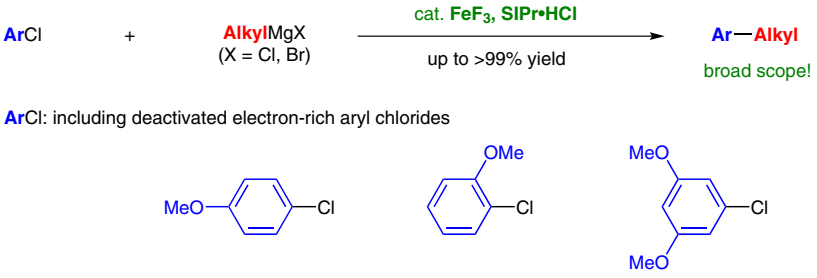
Synthesis R. Agata et al. Paper

Iron Fluoride/N-Heterocyclic Carbene Catalyzed Cross Coupling between Deactivated Aryl Chlorides and Alkyl Grignard Reagents with or without β-Hydrogens

Ryosuke Agata[a,b]
Takahiro Iwamoto[a,b,c]
Naohisa Nakagawa[a,b]
Katsuhiro Isozaki[a,b]
Takuji Hatakeyama[a,d,e]
Hikaru Takaya[a,b]
Masaharu Nakamura*[a,b]

[a] International Research Center for Elements Science, Institute for Chemical Research (ICR), Kyoto University, Uji, Kyoto 611-0011, Japan
masaharu@scl.kyoto-u.ac.jp
[b] Department of Energy and Hydrocarbon Chemistry, Graduate School of Engineering, Kyoto University, Nishikyo-ku, Kyoto 615-8510, Japan
[c] CRESTJapan Science and Technology Agency (JST), 4-1-8 Honcho Kawaguchi, Saitama 332-0012, Japan
[d] Elements Strategy Initiative for Catalysts and Batteries (ESICB), Kyoto University, Nishikyo-ku, Kyoto 615-8520, Japan
[e] Current address: Department of Chemistry, School of Science and Technology, Kwansei Gakuin University, 2-1 Gakuen, Sanda, Hyogo 669-1337, Japan



Received: 08.01.2015
Accepted: 17.02.2015
Published online: 08.04.2015
DOI: 10.1055/s-0034-1380361; Art ID: ss-2015-c0013-st

Abstract High-yielding cross-coupling reactions of various combinations of aryl chlorides and alkyl Grignard reagents have been developed by using an iron(III) fluoride/1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene (SIPr) catalyst composite. The iron(III) fluoride/SIPr-catalyzed aryl–alkyl coupling demonstrates unprecedented scope for both aryl chlorides and alkyl Grignard reagents, thus enabling the first efficient coupling of electron-rich (deactivated) aryl chlorides with alkyl Grignard reagents without β-hydrogens. The present reaction is also effective for diverse alkyl Grignard reagents such as (trimethylsilyl)methyl, primary, and secondary alkyl Grignard reagents.

Key words C–C bond formation, cross coupling, iron fluoride, N-heterocyclic carbene, aryl chloride

Transition-metal-catalyzed cross coupling is one of the most powerful C–C bond forming processes. Specifically, aryl–alkyl coupling reactions are of high importance in the synthesis and mass production of functional aromatic compounds.[1] Such aryl–alkyl coupling reactions have been typically carried out between aryl halides and alkyl Grignard reagents in the presence of nickel, and occasionally, palladium catalysts; this is because of the relatively poor efficiency of palladium when used in conjunction with an alkyl Grignard reagent.[1c,2] Iron catalysts have regained considerable attention in cross-coupling chemistry because of their low toxicity and cost effectiveness.[3] Their use in aryl–alkyl coupling has increased since Fürstner renovated[4] the iron-catalyzed cross coupling of sp^2-carbon (alkenyl) halides with an alkyl Grignard reagent initially developed by Kochi.[5]

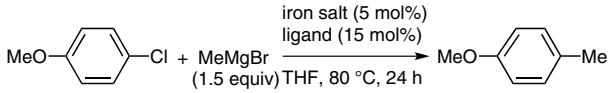
Fürstner thus reported the first iron-catalyzed aryl–alkyl coupling reaction,[6a] where aryl chlorides and alkyl Grignard reagents could be efficiently cross-coupled by using a simple catalyst system of iron(III) acetylacetonate or iron(III) chloride and an excess of 1-methylpyrrolidin-2-one (NMP) as a cosolvent.[6a–c,7] Although this was a clearly promising discovery showing the unprecedented reactivity of the iron catalyst, it had obvious limitations. Because of the limited reactivity of Grignard reagents without β-hydrogens,[6d] which is attributed to their inability to generate low-valent organoiron species,[6e,8] the methyl group[9] could be introduced only into activated aryl and alkenyl electrophiles such as highly electron-deficient heteroaromatics[10a,b] or enol triflates.[10c] In addition, even with reactive Grignard reagents carrying β-hydrogens, aryl chlorides bearing electron-donating alkoxy or alkyl substituents (deactivated aryl chlorides) were reluctant to participate in the aryl–alkyl coupling.[6b]

Considerable research efforts have been made to overcome the aforesaid limitations, and several modifications have been reported, such as the use of aryl carbamates[11a] or sulfamates[11] and sulfonates[6b,11b,c] instead of chlorides, and the use of different iron salts and modifiers.[12,13] Despite the partial solutions derived from these studies, no cross couplings between unreactive alkyl Grignard reagents and deactivated aryl chlorides have been realized, for example, the simple methylation of 1-chloro-4-methoxybenzene with a methyl Grignard reagent. In this paper, we report the effec-

tiveness of a catalyst composite of iron(III) fluoride and 1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene (SIPr) for the cross coupling of various combinations of aryl chlorides and alkyl Grignard reagents, especially for the coupling of deactivated aryl chlorides with the unreactive methyl Grignard reagent.

We began our study by screening catalyst composites of iron salts, specifically, iron fluorides, and N-heterocyclic carbene (NHC) ligands.[14] We envisaged that these composites would work well with the unreactive Grignard reagents, because they were effective even in the cross coupling between aryl chlorides with aryl Grignard reagents.[15] The reaction of 1-chloro-4-methoxybenzene (**1**) with methylmagnesium bromide was examined in the presence of various combinations of iron salts and NHC precursor salts (Table 1, Figure 1).

Table 1 Catalyst Screening on Cross Coupling of 1-Chloro-4-methoxybenzene (**1**) with Methylmagnesium Bromide (See Figure 1)[a]



Entry	Iron salt	Ligand	Yield[b] (%)	Recovered **1**[b] (%)
1	FeF_3	SIPr·HCl	92	0
2	FeF_3	SIMes·HCl	33	57
3	FeF_3	IPr·HCl	58	29
4	$FeCl_3$	SIPr·HCl	21	57
5	FeF_3	none	0	94
6	FeF_3	TMEDA[c]	1	94

[a] Reactions were carried out on a 1-mmol scale.
[b] Determined by GC analysis using undecane as an internal standard.
[c] TMEDA (1.5 equiv) was used.

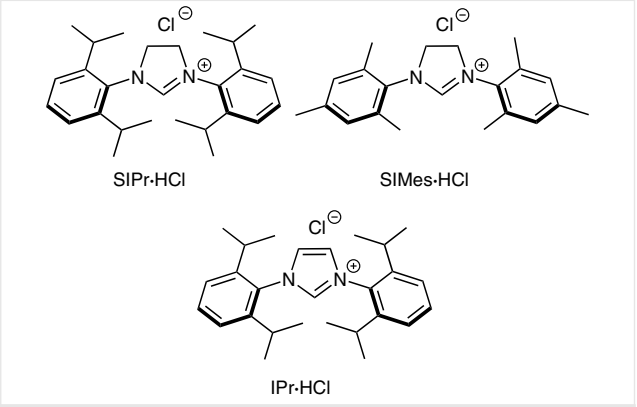


Figure 1

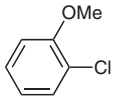
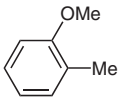
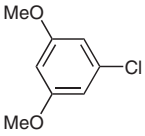
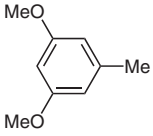
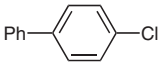
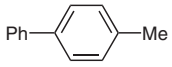
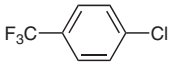
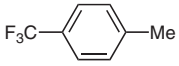
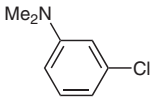
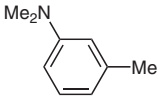
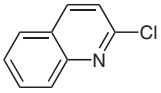
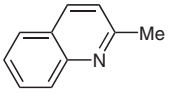
Screening of NHC ligands in the presence of iron(III) fluoride revealed that the 1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene (SIPr) ligand was the best, affording 1-methoxy-4-methylbenzene in 92% yield (entries 1–3). To the best of our knowledge, this is the first example of methylation of deactivated aryl chlorides under iron catalysis.[10a,b] Iron(III) chloride with SIPr could also catalyze the methylation, but the reaction was very sluggish and afforded the desired product in only 21% yield under the same conditions, showing the uniqueness of the fluoride (entry 4). In the absence of a ligand, the reaction did not proceed at all (entry 5). Notably, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) was ineffective in this reaction (entry 6).[12]

Table 2 demonstrates the substrate scope for the aryl chloride in the iron(III) fluoride/SIPr-catalyzed methylation. A more challenging substrate, the electronically and sterically demanding 1-chloro-2-methoxybenzene, participated in the coupling to give the desired product in 93% yield (entry 1). The present protocol is scalable: the reaction of 1-chloro-2-methoxybenzene (20 mmol) with methylmagnesium bromide (30 mmol) provided the corresponding methylation product in quantitative yield (>99% NMR yield). After purification, 1.92 g of 1-methoxy-2-methylbenzene was isolated (79% yield). The reaction with the more electron-rich 1-chloro-3,5-dimethoxybenzene was very slow, providing the desired product in poor yield (entry 3). However, the yield was dramatically improved to 72% by increasing the catalyst loading (15 mol%) (entry 4). Electron-deficient as well as electronically neutral aryl chlorides were effectively converted into the corresponding methylation products (entries 5 and 6).[16] The dimethylamino group did not interfere in the coupling reaction, and the desired product was obtained in 93% yield (entry 7). A heteroaromatic chloride, 2-chloroquinoline, underwent the methylation in moderate yield (entry 8).

Table 3 summarizes the reaction of diverse alkyl Grignard reagents with the electron-rich deactivated 1-chloro-4-methoxybenzene (**1**) and an electronically neutral aryl chloride, 4-chlorobiphenyl (**2**). The reaction with an unreactive Grignard reagent, (trimethylsilyl)methylmagnesium chloride[17] proceeded using similar reaction conditions to those in Tables 1 and 2, although the yield was moderate (entry 1). Among alkylmagnesium reagents possessing β-hydrogens, octyl and cyclohexyl Grignard reagents reacted smoothly with 1-chloro-4-methoxybenzene (**1**) even at 25 °C to give the desired compounds in excellent yields (entries 2[18] and 3). The reaction with isopropylmagnesium chloride proceeded quantitatively, and a 38:62 mixture of branch- and linear-alkylated compounds was obtained (entry 4).[19]

When using 4-chlorobiphenyl (**2**), all the Grignard reagents examined underwent the coupling smoothly to furnish the corresponding alkylated products in excellent yields (entries 5–8). It should be noted that the cross coupling of (trimethylsilyl)methyl magnesium chloride with this electronically neutral aryl chloride **2** proceeded smoothly to give the corresponding coupling product in quantitative yield (entry 5). The reaction with isopropyl-

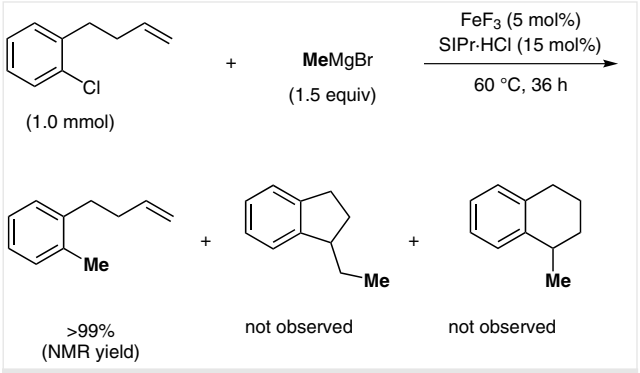
Table 2 Scope of Aryl Chlorides in Iron(III) Fluoride/SIPr-Catalyzed Cross Coupling with Methylmagnesium Bromide[a]

Entry	Aryl chloride	Temp (°C), time (h)	Product	Yield (%)
1		80, 24		93[b]
2		80, 15		>99[c,d]
3[e]		80, 48		30[d]
4[e,f]		80, 58		72[b]
5		60, 24		>99[d]
6		60, 48		81[d]
7		80, 36		93[d]
8		60, 26		53[b]

[a] Reactions were carried out on a 1-mmol scale using FeF_3 (5 mol%) and SIPr·HCl (15 mol%) in THF, for the indicated temperature and time.
[b] Determined by GC analysis using undecane as an internal standard.
[c] Reaction was performed on a 20-mmol scale.
[d] Determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane.
[e] MeMgBr (2 equiv) was used.
[f] FeF_3 (15 mol%) and SIPr·HCl (45 mol%) were used.

magnesium chloride again afforded the branch and linear isomers in 1:1 ratio. Isomerization of the isopropyl group indicated the formation of iron hydride species via β-hydrogen elimination from an alkyliron intermediate during the coupling. However, side reactions such as reduction of aryl chlorides were almost negligible (<2%) in all cases.

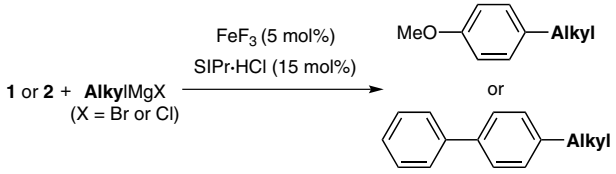
A brief mechanistic study was performed by using a radical probe substrate, 1-(but-3-enyl)-2-chlorobenzene.[20] The cross coupling with methylmagnesium bromide proceeded to give the methylation product in quantitative yield, and no cyclization products were formed (Scheme 1). This result suggests that the present coupling proceeded by a two-electron mechanism[14] rather than the radical mechanism proposed for iron-catalyzed cross coupling of alkyl halides.[5,21]

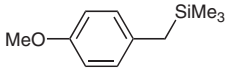
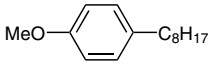
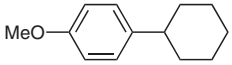
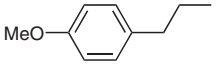
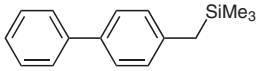
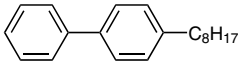
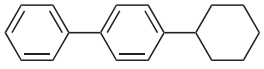
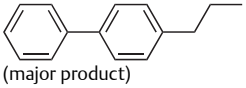


Scheme 1

In summary, we have demonstrated that the iron(III) fluoride/SIPr catalyst composite is effective for the cross coupling between aryl chlorides and alkyl Grignard reagents, with unprecedented substrate/reagent scope as compared to previously reported aryl–alkyl coupling reactions under iron catalysis. The developed reaction is thus applicable to the efficient coupling of electron-rich deactivated aryl chlorides with the methyl Grignard reagent, as well as various alkyl Grignard reagents, offering a practical alternative to conventional nickel- and palladium-catalyzed aryl–alkyl couplings. Further studies to clarify the effect of fluoride ion and the reaction mechanism are underway in our laboratory, and the results will be reported in due course.

Table 3 Scope of Alkyl Grignard Reagents in Iron(III) Fluoride/SIPr-Catalyzed Cross Coupling[a]



Entry	AlkylMgX (equiv)	Temp (°C), time (h)	Product	Yield (%)
1	Me_3SiCH_2MgCl (2.0)	80, 84		60[b,c]
2	$C_8H_{17}MgBr$ (1.5)	25, 24		96[c]
3	CyMgCl (1.5)	25, 14		>99[c]
4[d]	*i*-PrMgCl (2.0)	30, 61	 (major product)	97[c] (38:62)[e]
5	Me_3SiCH_2MgCl (2.0)	80, 36		>99[c]
6	$C_8H_{17}MgBr$ (1.5)	40, 24		>99[c]
7	CyMgCl (1.5)	25, 28		92[f]
8[d]	*i*-PrMgCl (2.0)	30, 48	 (major product)	>99[c] (48:52)[e]

[a] Reactions were carried out on a 1-mmol scale in THF for the indicated temperature and time.
[b] The starting material was recovered in 20% yield. Determined by GC analysis using undecane as an internal standard.
[c] Determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.
[d] FeF_3 (10 mol%) and SIPr·HCl (30 mol%) were used.
[e] Branch/linear ratio was determined by ^1H NMR analysis by using 1,1,2,2-tetrachloroethane as an internal standard.
[f] Isolated yield.

All reactions were carried out in dry vessels under a positive pressure of argon. Preparative recycling gel permeation chromatography (GPC) was performed on a Japan Analytical Industry LC-9204 instrument equipped with JAIGEL-1H-20/JAIGEL-2H-20 columns, using $CHCl_3$ as the eluent. ^1H and ^{13}C NMR spectra were recorded on a JEOL ECS-400NR NMR spectrometer referenced to TMS (δ = 0.00) and $CDCl_3$ (δ = 77.16), respectively. The NMR yields were determined for crude products by ^1H NMR analysis using 1,1,2,2-tetrachloroethane or pyrazine as an internal standard. GC analysis was conducted on a Shimadzu GC-2010 instrument equipped with an FID detector and a capillary column, ZB-1MS (Phenomenex, 10 m × 0.10 mm i.d., 0.10-μm film thickness). HRMS were obtained in fast atom bombardment (FAB) ionization or electron ionization (EI) mode on a JEOL JMS-700 mass spectrometer. IR spectra were recorded on a PerkinElmer Spectrum One FT-IR spectrophotometer. THF was purchased from Wako Pure Chemical Industries, Ltd. (Wako) and distilled from benzophenone ketyl at ambient pressure. Alkylmagnesium bromides and chlorides were prepared from the corresponding aryl halides and magnesium (turnings). MeMgBr was purchased from Tokyo Chemical Industry.

1-Methoxy-4-methylbenzene; Typical Procedure

A 0.94 M soln of MeMgBr in THF (1.59 mL, 1.5 mmol) was added to a mixture of FeF_3 (5.7 mg, 0.050 mmol) and 1,3-bis(2,6-diisopropylphenyl)imidazolinium chloride (64.4 mg, 0.15 mmol) in THF (2.0 mL) at 0 °C; 1-chloro-4-methoxybenzene (143 mg, 1.0 mmol) and undecane were then added at r.t. The mixture was stirred at 80 °C for 24 h. The mixture was cooled to r.t. and an aliquot of the mixture was filtered through a Florisil pad. The product yield was determined by GC analysis (92% yield) using undecane as an internal standard. 1-Methoxy-4-methylbenzene is volatile, hence isolation was performed for the large-scale experiment using starting aryl chloride (5.6 mmol). The

crude product was purified by column chromatography (silica gel, pentane, R_f = 0.06) and subsequent GPC to obtain the title compound (78.7 mg, 11%) as a colorless oil.

^{1}H NMR (392 MHz, $CDCl_3$): δ = 2.29 (s, 3 H, CH_3), 3.78 (s, 3 H, OCH_3), 6.80 (d, J = 8.6 Hz, 2 H, $H2_{Ar}$, $H6_{Ar}$), 7.09 (d, J = 7.8 Hz, 2 H, $H3_{Ar}$, $H5_{Ar}$).

^{13}C NMR (99 MHz, $CDCl_3$): δ = 20.59, 55.43, 113.84 (2 C), 129.98, 130.03 (2 C), 157.61.

HRMS (EI): m/z [M]$^+$ calcd for $C_8H_{10}O$: 122.0732; found: 122.0730.

Anal. Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.81; H, 8.17.

1-Methoxy-2-methylbenzene

The reaction was carried out according to the typical procedure on a 1.0-mmol scale. The large-scale synthesis was also carried out according to the typical procedure on a 20-mmol scale. After the mixture was heated at 80 °C for 15 h, sat. aq sodium potassium tartrate and 1 M aq HCl were added. The aqueous layer was extracted with Et_2O (4 ×). The organic layers were combined, washed with brine, dried (Na_2SO_4), and filtered through a Florisil pad. After solvent removal at 50 °C under ambient pressure, the product yield was determined by ^{1}H NMR analysis (>99% yield) using 1,1,2,2-tetrachloroethane as an internal standard. The crude product was purified by GPC to obtain the title compound (1.92 g, 79%) as a colorless oil.

^{1}H NMR (392 MHz, $CDCl_3$): δ = 2.22 (s, 3 H, CH_3), 3.82 (s, 3 H, OCH_3), 6.82 (d, J = 8.2 Hz, 1 H, $H6_{Ar}$), 6.85 (t, J = 7.5 Hz, 1 H, $H4_{Ar}$), 7.13 (d, J = 7.4 Hz, 1 H, $H3_{Ar}$), 7.16 (t, J = 7.1 Hz, 1 H, $H5_{Ar}$).

^{13}C NMR (99 MHz, $CDCl_3$): δ = 16.35, 55.35, 110.01, 120.38, 126.72, 126.93, 130.74, 157.85.

HRMS (EI): m/z [M]$^+$ calcd for $C_8H_{10}O$: 122.0732; found: 122.0730.

Anal. Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.40; H, 8.25.

1,3-Dimethoxy-5-methylbenzene

The product yield (72%) was determined by GC analysis using undecane as an internal standard. The crude product was purified by GPC to obtain the title compound (32.3 mg, 21%) as a colorless oil.

^{1}H NMR (392 MHz, $CDCl_3$): δ = 2.30 (d, J = 0.6 Hz, 3 H, CH_3), 3.77 (s, 6 H, OCH_3), 6.28 (t, J = 2.1 Hz, 1 H, $H2_{Ar}$), 6.33 (dd, J = 2.3, 0.6 Hz, 2 H, $H4_{Ar}$,$H6_{Ar}$).

^{13}C NMR (99 MHz, $CDCl_3$): δ = 21.96, 55.37 (2 C), 97.66, 107.22 (2 C), 140.36, 160.84 (2 C).

HRMS (EI): m/z [M]$^+$ calcd for $C_9H_{12}O_2$: 152.0837; found: 152.0839.

4-Methylbiphenyl

The product yield (>99%) was determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. The crude product was purified by column chromatography (silica gel, hexane, R_f = 0.23) to obtain the title compound (143 mg, 85%) as a white solid.

^{1}H NMR (392 MHz, $CDCl_3$): δ = 2.40 (s, 3 H, CH_3), 7.25 (d, J = 8.2 Hz, 2 H, $H3_{Ar}$, $H5_{Ar}$), 7.32 (tt, J = 7.4, 1.2 Hz, 1 H, H4′), 7.42 (t, J = 7.8 Hz, 2 H, $H3'_{Ar}$, $H5'_{Ar}$), 7.50 (d, J = 8.2 Hz, 2 H, $H2_{Ar}$, $H6_{Ar}$), 7.57–7.59 (m, 2 H, $H2'_{Ar}$, $H6'_{Ar}$).

^{13}C NMR (99 MHz, $CDCl_3$): δ = 21.24, 127.12 (5 C), 128.85 (2 C), 129.63 (2 C), 137.17, 138.51, 141.31.

HRMS (EI): m/z [M]$^+$ calcd for $C_{13}H_{12}$: 168.0939; found: 168.0934.

1-Methyl-4-(trifluoromethyl)benzene

The product yield (81%) was determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. 1-Methyl-4-(trifluoromethyl)benzene is volatile, hence isolation was performed on a 10-mmol scale. The reaction was carried out at 80 °C, and MeMgBr (20 mmol, 2 equiv). The crude product was purified by distillation at r.t. under reduced pressure (0.133 bars) to obtain the title compound (260 mg, 16%) as a colorless oil.

^{1}H NMR (392 MHz, $CDCl_3$): δ = 2.41 (s, 3 H, CH_3), 7.27 (d, J = 8.2 Hz, 2 H, $H2_{Ar}$, $H6_{Ar}$), 7.50 (d, J = 8.2 Hz, 2 H, $H3_{Ar}$, $H5_{Ar}$).

^{13}C NMR (99 MHz, $CDCl_3$): δ = 21.56, 124.58 (q, $J_{C\text{-}F}$ = 273 Hz, CF_3), 125.27 (q, $J_{C\text{-}F}$ = 3.9 Hz, 2 C), 128.00 (q, $J_{C\text{-}F}$ = 32 Hz), 129.45 (2 C), 142.21.

N,*N*,3-Trimethylaniline

The product yield (93%) was determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. *N*,*N*,3-Trimethylaniline is volatile, hence isolation was performed on a 5.4-mmol scale. The crude product was purified by column chromatography (silica gel, hexane–EtOAc, 10:1, R_f = 0.38), and subsequent GPC, to obtain the title compound (318 mg, 44%) as a brown oil.

^{1}H NMR (392 MHz, $CDCl_3$): δ = 2.32 (s, 3 H, CH_3), 2.93 [s, 6 H, $N(CH_3)_2$,], 6.55–6.58 (m, 3 H, $H2_{Ar}$, $H4_{Ar}$, $H6_{Ar}$), 7.13 (dd, J = 10.6, 7.1 Hz, 1 H, $H5_{Ar}$).

^{13}C NMR (99 MHz, $CDCl_3$): δ = 20.34, 40.82 (2 C), 110.05, 113.58, 117.74, 129.05, 138.83, 150.89.

2-Methylquinoline

The product yield (53%) was determined by GC analysis using undecane as an internal standard. 2-Methylquinoline is volatile, hence isolation was performed on a 5.2-mmol scale. The crude product was purified by column chromatography (silica gel, hexane–EtOAc, 5:1, R_f = 0.19) to obtain the title compound (300 mg, 40%) as a colorless oil.

^{1}H NMR (392 MHz, $CDCl_3$): δ = 2.74 (s, 3 H, CH_3), 7.26 (d, J = 8.6 Hz, 1 H, H3), 7.46 (td, J = 8.2, 1.2 Hz, 1 H, H7), 7.67 (td, J = 8.2, 1.2 Hz, 1 H, H8), 7.75 (d, J = 8.2 Hz, 1 H, H6), 8.01 (d, J = 8.2 Hz, 1 H, H9), 8.03 (d, J = 8.2 Hz, 1 H, H4).

^{13}C NMR (99 MHz, $CDCl_3$): δ = 25.47, 122.06, 125.73, 126.56, 127.72, 128.72, 129.49, 136.22, 147.97, 159.06.

HRMS (FAB): m/z [M + H]$^+$ calcd for $C_{10}H_{10}N$: 144.0813; found: 144.0813.

(4-Methoxybenzyl)trimethylsilane

The product yield (60%) was determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. The crude product was purified by GPC and column chromatography (silica gel, hexane, R_f = 0.14) to obtain the title compound (102 mg, 59%) as a colorless oil.

^{1}H NMR (392 MHz, $CDCl_3$): δ –0.015 [s, 9 H, $Si(CH_3)_3$], 2.01 (s, 2 H, CH_2TMS), 3.78 (s, 3 H, OCH_3), 6.78 (d, J = 9.0 Hz, 2 H, $H3_{Ar}$, $H5_{Ar}$), 6.92 (d, J = 9.0 Hz, 2 H, $H2_{Ar}$, $H6_{Ar}$).

^{13}C NMR (99 MHz, $CDCl_3$): δ = –1.80 (3 C), 25.83, 55.37, 113.77 (2 C), 128.93 (2 C), 132.48, 156.62.

1-Methoxy-4-octylbenzene

The product yield (96%) was determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. The crude product was purified by GPC and column chromatography (silica gel, hexane, R_f = 0.15) to obtain the title compound (216 mg, 93%) as a colorless oil.

^{1}H NMR (392 MHz, $CDCl_3$): δ = 0.88 [t, J = 7.1 Hz, 3 H, $(CH_2)_7CH_3$], 1.26–1.31 [m, 10 H, $(CH_2)_2(CH_2)_5CH_3$], 1.53–1.61 [m, 2 H, $CH_2CH_2(CH_2)_5CH_3$], 2.53 [t, J = 7.4 Hz, 2 H, $CH_2(CH_2)_6CH_3$], 3.78 (s, 3 H, OCH_3), 6.81 (d, J = 8.6 Hz, 2 H, $H2_{Ar}$, $H6_{Ar}$), 7.08 (d, J = 8.6 Hz, 2 H, $H3_{Ar}$, $H5_{Ar}$).

^{13}C NMR (99 MHz, $CDCl_3$): δ = 14.25, 22.83, 29.44 (2 C), 29.65, 31.93, 32.05, 35.20, 55.32, 113.76 (2 C), 129.36 (2 C), 135.17, 157.72.

HRMS (FAB): m/z [M]$^+$ calcd for $C_{15}H_{24}O$: 220.1827; found: 220.1827.

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.53; H, 10.97.

1-Cyclohexyl-4-methoxybenzene

The product yield (>99%) was determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. The crude product was purified by GPC and column chromatography (silica gel, hexane, R_f = 0.23) to obtain the title compound (190 mg, 94%) as a colorless oil.

^{1}H NMR (392 MHz, $CDCl_3$): δ = 1.18–1.29 (m, 1 H, $H4'_{ax}$), 1.32–1.44 (m, 4 H, $H2'_{ax}$, $H3'_{ax}$, $H5'_{ax}$, $H6'_{ax}$), 1.70–1.76 (m, 1 H, $H4'_{eq}$), 1.81–1.89 (m, 4 H, $H2'_{eq}$, $H3'_{eq}$, $H5'_{eq}$, $H6'_{eq}$), 2.44 (tt, $J_{ax–ax}$ = 11.0 Hz, $J_{ax–eq}$ = 3.1 Hz, 1 H, $H1'_{ax}$), 3.78 (s, 3 H, OCH_3), 6.83 (dt, J = 9.0, 2.7 Hz, 2 H, $H3_{Ar}$, $H5_{Ar}$), 7.12 (dt, J = 9.0, 2.4 Hz, 2 H, $H2_{Ar}$, $H6_{Ar}$).

^{13}C NMR (99 MHz, $CDCl_3$): δ = 26.32, 27.10 (2 C), 34.86 (2 C), 44.83, 55.38, 113.78 (2 C), 127.76 (2 C), 140.52, 157.77.

1-Isopropyl-4-methoxybenzene and 1-Methoxy-4-propylbenzene

The product yield (97%) and the ratio of branched to linear (38:62) were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. The crude product was purified by GPC and column chromatography (silica gel, hexane, R_f = 0.16) to obtain a mixture of the title compounds (139 mg, 86%, 37:63) as a colorless oil.

1-Isopropyl-4-methoxybenzene

^{1}H NMR (392 MHz, $CDCl_3$): δ = 1.22 [d, J = 7.1 Hz, 6 H, $CH(CH_3)_2$], 2.86 [sept, J = 7.1 Hz, 1 H, $CH(CH_3)_2$], 6.84 (d, J = 9.4 Hz, 2 H, $H3_{Ar}$, $H5_{Ar}$), 7.14 (d, J = 8.6 Hz, 2 H, $H2_{Ar}$, $H6_{Ar}$).

1-Methoxy-4-propylbenzene

^{1}H NMR (392 MHz, $CDCl_3$): δ = 0.92 [t, J = 7.4 Hz, 3 H, $(CH_2)_2CH_3$], 1.60 (sext, J = 8.2 Hz, 2 H, $CH_2CH_2CH_3$), 2.52 (t, J = 7.8 Hz, 2 H, $CH_2CH_2CH_3$), 6.82 (d, J = 8.6 Hz, 2 H, $H2_{Ar}$, $H6_{Ar}$), 7.08 (d, J = 8.2 Hz, 2 H, $H3_{Ar}$, $H5_{Ar}$).

1-Isopropyl-4-methoxybenzene and 1-Methoxy-4-propylbenzene

^{13}C NMR (99 MHz, $CDCl_3$): δ = 13.92, 24.35, 24.93, 33.40, 37.28, 55.38, 113.76, 113.81, 127.38, 129.44, 134.95, 141.19, 157.76.

(Biphenyl-4-ylmethyl)trimethylsilane

The product yield (>99%) was determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. The crude product was purified by GPC and column chromatography (silica gel, hexane, R_f = 0.22) to obtain the title compound (231 mg, 96%) as a white solid.

^{1}H NMR (392 MHz, $CDCl_3$): δ = 0.02 [s, 9 H, $Si(CH_3)_3$], 2.12 (s, 2 H, CH_2TMS), 7.07 (d, J = 7.8 Hz, 2 H, $H3_{Ar}$, $H5_{Ar}$), 7.31 (td, J = 7.3, 1.7 Hz, 1 H, $H4'_{Ar}$), 7.40–7.47 (m, 4 H, $H2_{Ar}$, $H6_{Ar}$, $H3'_{Ar}$, $H5'_{Ar}$), 7.58 (dt, J = 7.1, 1.6 Hz, 2 H, $H2'_{Ar}$, $H6'_{Ar}$).

^{13}C NMR (99 MHz, $CDCl_3$): δ = –1.72 (3 C), 26.90, 126.88, 126.93 (2 C), 126.96 (2 C), 128.58 (2 C), 128.81 (2 C), 136.87, 139.90, 141.35.

HRMS (FAB): m/z [M]$^+$ calcd for $C_{16}H_{20}Si$: 240.1334; found: 240.1336.

Anal. Calcd for $C_{16}H_{20}Si$: C, 79.93; H, 8.39. Found: C, 79.98; H, 8.11.

4-Octylbiphenyl

The product yield (>99%) was determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. The crude product was purified by GPC and column chromatography (silica gel, hexane, R_f = 0.46) to obtain the title compound (257 mg, 97%) as a white solid.

^{1}H NMR (392 MHz, $CDCl_3$): δ = 0.88 [t, J = 6.7 Hz, 3 H, $(CH_2)_7CH_3$], 1.28–1.38 [m, 10 H, $(CH_2)_2(CH_2)_5CH_3$], 1.65 [quint, J = 7.4 Hz, 2 H, $CH_2CH_2(CH_2)_5CH_3$], 2.64 [t, J = 7.8 Hz, 2 H, $CH_2CH_2(CH_2)_5CH_3$], 7.25 (d, J = 7.8 Hz, 2 H, $H3_{Ar}$, $H5_{Ar}$), 7.32 (tt, J = 7.1, 1.2 Hz, 1 H, $H4'_{Ar}$), 7.42 (tt, J = 8.2, 2.0 Hz, 2 H, $H3'_{Ar}$, $H5'_{Ar}$), 7.50 (dt, J = 8.2, 2.0 Hz, 2 H, $H2_{Ar}$, $H6_{Ar}$), 7.57–7.60 (m, 2 H, $H2'_{Ar}$, $H6'_{Ar}$).

^{13}C NMR (99 MHz, $CDCl_3$): δ = 14.26, 22.83, 29.43, 29.54, 29.64, 31.67, 32.05, 35.77, 127.09, 127.13, (4 C), 128.83 (2 C), 128.96 (2 C), 138.67, 141.34, 142.27.

4-Cyclohexylbiphenyl

The reaction was carried out according to the typical procedure on a 1.0-mmol scale. The crude product was purified by column chromatography (silica gel, hexane, R_f = 0.18) to obtain the title compound (216 mg, 92%) as a white solid.

^{1}H NMR (392 MHz, $CDCl_3$): δ = 1.23–1.33 (m, 1 H, $H4''_{ax}$), 1.36–1.51 (m, 4 H, $H2''_{ax}$, $H3''_{ax}$, $H5''_{ax}$, $H6''_{ax}$), 1.74–1.80 (m, 1 H, $H4''_{eq}$), 1.84–1.94 (m, 4 H, $H2''_{eq}$, $H3''_{eq}$, $H5''_{eq}$, $H6''_{eq}$), 2.55 (tt, J_{ax-ax} = 11.8 Hz, J_{ax-eq} = 3.1 Hz, 1 H, $H1''_{ax}$), 7.29 (d, J = 8.2 Hz, 2 H, $H3_{Ar}$, $H5_{Ar}$), 7.32 (tt, J = 7.4, 1.6 Hz, 1 H, $H4'_{Ar}$), 7.42 (t, J = 8.2 Hz, 2 H, $H3'_{Ar}$, $H5'_{Ar}$), 7.52 (d, J = 8.2 Hz, 2 H, $H2_{Ar}$, $H6_{Ar}$), 7.57–7.59 (m, 2 H, $H2'_{Ar}$, $H6'_{Ar}$).

^{13}C NMR (99 MHz, $CDCl_3$): δ = 26.33, 27.07 (2 C), 34.62 (2 C), 44.39, 127.08, 127.17 (4 C), 127.38 (2 C), 128.82 (2 C), 138.87, 141.34, 147.38.

HRMS (FAB): m/z [M]$^+$ calcd for $C_{18}H_{20}$: 236.1565; found: 236.1564.

4-Isopropylbiphenyl and 4-Propylbiphenyl

The product yield (>99%) and the ratio of branched to linear (48:52) were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. After purification by GPC and column chromatography (silica gel, hexane, R_f = 0.34), a mixture of the title compounds was obtained (184 mg, 94%, 49:51) as a colorless oil.

4-Isopropylbiphenyl

^{1}H NMR (392 MHz, $CDCl_3$): δ = 1.29 [d, J = 7.5 Hz, 6 H, $CH(CH_3)_2$], 2.95 [sept, J = 7.1 Hz, 1 H, $CH(CH_3)_2$], 7.22–7.59 (m, 9 H).

4-Propylbiphenyl

^{1}H NMR (392 MHz, $CDCl_3$): δ = 0.97 [t, J = 7.1 Hz, 3 H, $(CH_2)_2CH_3$], 1.68 (sext, J = 7.4 Hz, 2 H, $CH_2CH_2CH_3$), 2.62 (t, J = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 7.22–7.59 (m, 9 H).

4-Isopropylbiphenyl and 4-Propylbiphenyl

^{13}C NMR (99 MHz, $CDCl_3$): δ = 14.04, 24.15 (2 C), 24.70, 33.94, 37.84, 126.98, 127.10, 127.13, 127.16, 127.20, 128.82, 129.02, 138.72, 138.88, 141.32, 141.98, 148.13.

1-(But-3-enyl)-2-methylbenzene

The product yield (>99%) was determined by ^{1}H NMR analysis using pyrazine as an internal standard. The crude product was purified by GPC to obtain the title compound (47.9 mg, 34%) as a colorless oil.

IR (neat): 3076, 3017, 2977, 2932, 2367, 1892, 1829, 1641, 1605, 1493, 1459, 1379, 995, 911, 752 cm^{-1}.

^{1}H NMR (392 MHz, $CDCl_3$): δ = 2.31 (s, 3 H, CH_3), 2.30–2.36 (m, 2 H, $CH_2CH_2C_2H_3$), 2.67–2.72 (m, 2 H, $CH_2CH_2C_2H_3$), 4.99 (d, *J* = 10.2 Hz, 1 H, $CH{=}CH_{trans}H_{cis}$), 5.06 (d, 1 H, *J* = 17.0 Hz, $CH{=}CH_{trans}H_{cis}$), 5.90 (ddt, 1 H, *J* = 17.0, 10.2, 6.7 Hz, $CH_2CH_2CH{=}CH_2$), 7.08–7.15 (m, 4 H, H_{Ar}).

^{13}C NMR (99 MHz, $CDCl_3$): δ = 19.46, 32.87, 34.45, 114.95, 126.04, 126.10, 128.92, 130.27, 136.04, 138.43, 140.19.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{14}$: 146.1096; found: 146.1094.

Anal. Calcd for $C_{11}H_{14}$: C, 90.35; H, 9.65. Found: C, 90.10; H, 9.77.

Acknowledgment

This work was supported by the Japan Society for the Promotion of Science (JSPS) through the 'Funding Program for Next-Generation World-Leading Researchers (NEXT Program),' initiated by the Council for Science and Technology Policy (CSTP) and supported in part by the Japan Science and Technology Agency (JST), the Core Research for Evolutional Science and Technology (CREST 1102545) Program, and MEXT program 'Elements Strategy Initiative to Form Core Research Center.' T.I. and K.I. also thank RIKEN for the provision of beam time in SPring-8 (BL14B2: 2014B1907 and 2014B1654).

Supporting Information

^{1}H and ^{13}C NMR spectra of the coupling products. This material is available online at http://dx.doi.org/10.1055/s-0034-1380361.

References

(1) (a) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 4544. (b) Banno, T.; Hayakawa, Y.; Umeno, M. *J. Organomet. Chem.* **2002**, *653*, 288. (c) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442. (d) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417.

(2) (a) Tamao, K. In *Comprehensive Organic Synthesis*; Vol. 3; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, **1991**, Chap. 2, 435. (b) Hegedus, L. S.; Söderberg, B. C. G. *Transition Metals in the Synthesis of Complex Organic Molecules*; University Science Books: Sausalito, **2010**, 3rd ed. (c) *Metal-Catalyzed Cross-Coupling Reactions and More*; de Meijere, A.; Bräse, S.; Oestreich, M., Eds.; Wiley-VCH: Weinheim, **2014**, 995–1066.

(3) (a) Czaplik, W. M.; Mayer, M.; Cvengroš, J.; von Wangelin, A. J. *ChemSusChem* **2009**, *2*, 396. (b) Nakamura, E.; Stao, K. *Nat. Mater.* **2011**, *10*, 158. (c) Nakamura, E.; Hatakeyama, T.; Ito, S.; Ishizuka, K.; Ilies, L.; Nakamura, M. *Org. React.* **2014**, *83*, 1.

(4) Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500; and see also ref. 6a.

(5) (a) Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1487. (b) Neumann, S. M.; Kochi, J. K. *J. Org. Chem.* **1975**, *40*, 599.

(6) (a) Fürstner, A.; Leitner, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 609. (b) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856. (c) Fürstner, A.; Leitner, A.; Seidel, G. *Org. Synth.* **2005**, *81*, 33. (d) Fürstner, A.; Krause, H.; Lehmann, C. W. *Angew. Chem. Int. Ed.* **2006**, *45*, 440. (e) Fürstner, A.; Martin, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 8773.

(7) The iron–NMP catalyst system was originally developed by Cahiez for cross coupling of alkenyl halides with alkyl Grignard reagents: (a) Cahiez, G.; Marquais, S. *Pure Appl. Chem.* **1996**, *68*, 53. (b) Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199.

(8) (a) Aleandri, L. E.; Bogdanović, B.; Bons, P.; Dürr, C.; Gaidies, A.; Hartwig, T.; Huckett, S. C.; Lagarden, M.; Wilczok, U.; Brand, R. A. *Chem. Mater.* **1995**, *7*, 1153. (b) Siedlaczek, G.; Schwickardi, M.; Kolb, U.; Bogdanović, B.; Blackmond, D. G. *Catal. Lett.* **1998**, *55*, 67. (c) Bogdanović, B.; Schwickardi, M. *Angew. Chem. Int. Ed.* **2000**, *39*, 4610.

(9) For recent review showing the importance of introduction of methyl group in medicinal compounds, see: (a) Barreiro, E. J.; Kümmerle, A. E.; Fraga, C. A. M. *Chem. Rev.* **2011**, *111*, 5215. (b) Schonherr, H.; Cernak, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 12256.

(10) (a) Hocek, M.; Dvoráková, H. *J. Org. Chem.* **2003**, *68*, 5773. (b) Malhotra, S.; Seng, P. S.; Koenig, S. G.; Deese, A. J.; Ford, K. A. *Org. Lett.* **2013**, *15*, 3698. (c) Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3943.

(11) (a) Silberstein, A. L.; Ramgren, S. D.; Garg, N. K. *Org. Lett.* **2012**, *14*, 3796. (b) Agrawal, T.; Cook, S. P. *Org. Lett.* **2013**, *15*, 96. One example of cross-coupling of biphenyl sulfamate with methyl Grignard reagent in the presence of catalytic $FeF_3{\cdot}3H_2O$/IPr was reported, see: (c) Agrawal, T.; Cook, S. P. *Org. Lett.* **2014**, *16*, 5080.

(12) *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine acted as a good modifier in the iron-catalyzed aryl–alkyl coupling reaction, albeit being limited to electron-deficient aryl chlorides with a primary alkyl Grignard reagent, see: Rushworth, P. J.; Hulcoop, D. G.; Fox, D. J. *J. Org. Chem.* **2013**, *78*, 9517.

(13) The $FeCl_2{\cdot}4H_2O$/SIPr composite was reported to catalyze the cross-coupling of deactivated aryl chlorides, such as *p*-tolyl and *p*-anisyl chlorides, with primary and secondary alkyl Grignard reagents possessing β-hydrogens: Perry, M. C.; Gillet, A. N.; Law, T. C. *Tetrahedron Lett.* **2012**, *53*, 4436.

(14) Recent reviews: (a) Riener, K.; Haslinger, S.; Raba, A.; Högerl, M. P.; Cokoja, M.; Herrmann, W. A.; Kühn, F. E. *Chem. Rev.* **2014**, *114*, 5215. (b) Bézier, D.; Sortais, J.-B.; Darcel, C. *Adv. Synth. Catal.* **2013**, *355*, 19. (c) Ingleson, M. J.; Layfield, R. A. *Chem. Commun.* **2012**, *48*, 3579. The favorable effect of NHC ligands on iron-catalyzed cross-coupling was first reported by Bedford, see: (d) Bedford, R. B.; Betham, M.; Bruce, D. W.; Danopoulos, A. A.; Frost, R. M.; Hird, M. *J. Org. Chem.* **2006**, *71*, 1104.

(15) For the synergistic effect of fluoride ion and NHC ligand in iron catalysis, see: (a) Hatakeyama, T.; Nakamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 9844. (b) Hatakeyama, T.; Hashimoto, S.; Ishizuka, K.; Nakamura, M. *J. Am. Chem. Soc.* **2009**, *131*, 11949. These reactions are considered to proceed via a high-valent organoiron(IV) species, without the need for the generation of low-valent organoiron species, which cause aryl–alkyl coupling.[6e] The iron fluoride/NHC catalyst system was applied to the coupling of aryl sulfonates and sulfamates.[11b,c] Iron–NHC catalyst also shows high activity toward the cross-coupling of nonactivated alkyl chlorides with aryl Grignard reagents, see: (c) Ghorai, S. K.; Jin, M.; Hatakeyama, T.; Nakamura, M. *Org. Lett.* **2012**, *14*, 1066.

(16) The reaction of 4-chlorobiphenyl was also catalyzed by $FeCl_3$, to afford the product in excellent yield (96%). The details will be reported elsewhere in due course.

(17) (Trimethylsilyl)methyl group acts as a nontransferable or unreactive dummy ligand in the iron-catalyzed Negishi coupling reaction, see: (a) Nakamura, M.; Ito, S.; Matsuo, K.; Nakamura, E. *Synlett* **2005**, 1794. (b) Bedford, R. B.; Huwe, M.; Wilkinson, M. C. *Chem. Commun.* **2009**, 600.

(18) Trace amounts of alkene and the dimeric alkane byproducts (octenes and hexadecane) were detected on GLC analysis. The formation of a significant amount of hexane, which is derived

from the hydrolysis of octylmagnesium bromide, was also observed.

(19) The use of $FeCl_3$ instead of FeF_3 provided the linear product in 93% yield with 98% selectivity. Similar switching of linear/branch selectivity was also observed in the iron-catalyzed alkyl coupling of aryl sulfamates and tosylates when using FeF_3 and $FeCl_3$ as the precursor salts.[10b]

(20) Yamamoto, E.; Izumi, K.; Horita, Y.; Ito, H. *J. Am. Chem. Soc.* **2012**, *134*, 19997.

(21) For a recent mechanistic study on iron-catalyzed cross-coupling of alkyl halides, see: (a) Daifuku, S. L.; Al-Afyouni, M. H.; Snyder, B. E. R.; Kneebone, J. L.; Neidig, M. L. *J. Am. Chem. Soc.* **2014**, *136*, 9132; and references cited therein. See also selected papers from our group: (b) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686. (c) Hatakeyama, T.; Hashimoto, T.; Kondo, Y.; Fujiwara, Y.; Seike, H.; Takaya, H.; Tamada, Y.; Ono, T.; Nakamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 10674. (d) Hatakeyama, T.; Fujiwara, Y.; Okada, Y.; Itoh, T.; Hashimoto, T.; Kawamura, S.; Ogata, K.; Takaya, H.; Nakamura, M. *Chem. Lett.* **2011**, *40*, 1030. (e) Kawamura, S.; Kawabata, T.; Ishizuka, K.; Nakamura, M. *Chem. Commun.* **2012**, *48*, 9376. (f) Takaya, H.; Nakajima, S.; Nakagawa, N.; Isozaki, K.; Iwamoto, T.; Imayoshi, R.; Gower, N. J.; Adak, L.; Hatakeyama, T.; Honma, T.; Takagaki, M.; Sunada, Y.; Nagashima, H.; Hashizume, D.; Takahashi, O.; Nakamura, M. *Bull. Chem. Soc. Jpn.* **2015**, *88*, 410.