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Iron-Catalyzed C–H Bond Activation for the *ortho*-Arylation of Aryl Pyridines and Imines with Grignard Reagents

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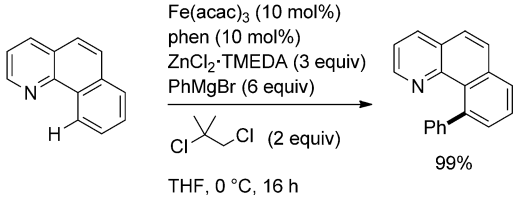
Abstract: Direct arylation of the *ortho*-C–H bond of an aryl pyridine or an aryl imine with an aryl Grignard reagent has been achieved by using an iron-diamine catalyst and a dichloroalkane as an oxidant in a short reaction time (e.g., 5 min) under mild conditions (0 °C). The use of an aromatic cosolvent, such as chlorobenzene and benzene, and slow addition of the Grignard reagent are essential for the high efficiency of the reaction. The present arylation reaction has distinct merits over the previously developed reaction that used an arylzinc reagent, such as its reaction rate and atom economy. Selective C–H bond activation occurs in the presence of a leaving group, such as a tosyloxy, chloro, and bromo group. Studies on a stoichiometric reaction and kinetic isotope effects shed light on the reaction intermediate and the C–H bond-activation step.

Keywords: biaryls · C–H activation · cross-coupling · Grignard reagent · iron

Introduction

Aryl–aryl bond formation is a useful synthetic reaction because of the ubiquity of biaryls in functional molecules.[1] Typically, an aryl–aryl bond has been constructed by a transition-metal-catalyzed cross-coupling reaction of an aryl halide and an arylmetal reagent.[2] More recently, direct conversion of an aryl C–H bond into an aryl–aryl bond is receiving attention[3] because such reactions alleviate the need for the prefunctionalization (halogenation and/or metalation) of the aromatic substrates. However, reactions reported so far typically rely on the use of expensive transition metal catalysts (e.g., Pd, Rh, Ru)[4] and require harsh reaction conditions. These problems can be resolved by the use of iron that is naturally abundant, environmentally benign, and non-toxic.[5–7] We have recently demonstrated the versatility of iron for the oxidative directed arylation reaction of aryl pyridine and imine derivatives [Eq. (1)],[8] which we developed on the basis of our experience of low-valent iron catalysis since the late 1990s.[5e,9] The catalytic system consisting of an iron salt and a diamine ligand (phen or dtbpy) as catalyst precursors and 1,2-dichloro-2-methylpropane as an oxidant allows facile displacement of the *ortho*-C–H bonds of aryl pyridine and imine derivatives with an arylzinc reagent prepared from a zinc salt and the corresponding Grignard reagent under very mild conditions (0 °C). However, the reaction has one unattractive feature, that is, it requires the use of large amounts of the zinc salt (2.5–3 equiv) and the aryl Grignard reagent (5–6 equiv) for the generation of the reactive arylzinc reagent. Our earlier attempts to use solely the Grignard reagent failed because of iron-catalyzed oxidative homocoupling of the Grignard reagent.[10]



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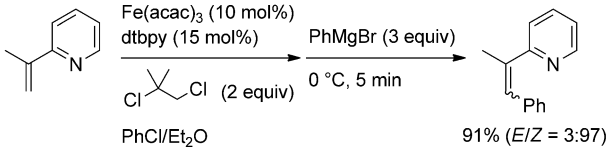
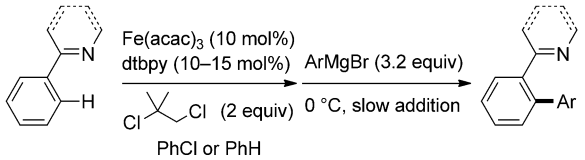
Our recent findings[11] suggested a remedy. Namely, several modifications made on the original catalytic systems allowed us to use an aryl Grignard reagent for stereospecific arylation of an olefinic C–H bond with a stoichiometry closer to the theoretical minimum (i.e., 2 equiv), with a high reaction rate and under mild conditions (0 °C, <5 min, Scheme 1). The key modifications include: 1) the use of an aryl Grignard reagent instead of an arylzinc reagent, 2) slow addition of the reagent over a period of 5 min, and 3) the use of chlorobenzene as a co-solvent. These modifications allowed us to use far less Grignard reagent (2.4–3.2 equiv of PhMgBr) than our original conditions using the zinc reagent, partly because the second modification suppresses oxidative homocoupling of the Grignard reagent. The use of chlorobenzene appears to stabilize an iron intermediate and hence contributes to the enhancement of the overall efficiency of the reaction.



Scheme 1. Iron-catalyzed stereospecific arylation of olefinic C–H bond.

With the new finding in hand, we have made possible the use of an aryl Grignard reagent for the direct arylation of aromatic C–H bonds. Herein, we report that the cross-coupling of aryl pyridine and imine derivatives with an aryl Grignard reagent can be achieved (Scheme 2) if the reaction is performed in the presence of an aromatic co-solvent, such as chlorobenzene and benzene, with slow addition of the Grignard reagent (over 5–60 min).[12] Furthermore, the aryl–aryl bond formation takes place very quickly at 0 °C, completing at the end of the addition of the Grignard reagent. This simpler system is more suitable for mechanistic studies, and has allowed us to obtain some information on the nature of the reaction intermediate and the C–H bond-activation step of the catalytic reaction.



Scheme 2. Iron-catalyzed direct arylation of aryl pyridine and imine derivatives with Grignard reagent.

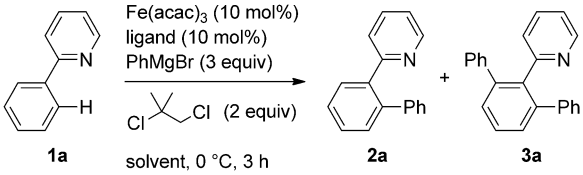
Abstract in Japanese:

鉄触媒とアリールグリニャール試薬によるアリールピリジンおよびアリールイミンのオルト位炭素–水素結合の直接アリール化反応を開発した．触媒前駆体として鉄塩と窒素二座配位子，酸化剤としてジクロロアルカン，THF の共溶媒として芳香族化合物を用い，基質に対して0 ° C でグリニャール試薬をゆっくり滴下することで，直接アリール化反応が極めて速やかに（例えば5分間で）完結した．本反応は，我々が以前報告したアリール亜鉛反応剤を用いた反応に比べ，反応速度および原子効率の面において格段に優れている．量論反応および速度論的同位体効果の検討から，反応中間体および炭素–水素結合活性化段階に関する重要な知見が得られた．

Results and Discussion

Optimization of Reaction Conditions

In the first set of experiments, we examined the phenylation of 2-phenylpyridine (**1a**) with PhMgBr, adding PhMgBr (1.25 M in THF, 3 equiv) to a mixture of **1a**, $Fe(acac)_3$ (10 mol%), ligand (10 mol%), and 1,2-dichloro-2-methylpropane[13] (2 equiv) in tetrahydrofuran or in a mixture of tetrahydrofuran and a co-solvent quickly over approximately 30 seconds [Eq. (2)]



Screening bidentate aromatic amine ligands revealed that dtbpy affords the monophenylated product **2a** in a 45% yield (Table 1, entry 1), whilst other ligands, such as phen, 2,2′-bipyridyl (bpy), and 4,4′-dimethyl-2,2′-bipyridyl (dmbpy), are much less effective, because of the formation of biphenyl by iron-catalyzed oxidative homocoupling

Table 1. Conditions for iron-catalyzed phenylation of 2-phenylpyridine with phenylmagnesium bromide [Eq. (2)].[a]

Entry	Ligand[b]	Solvent	Yield [%][c]		
			2a	**3a**	Ph–Ph
1	dtbpy	THF	45	1	91
2	bpy	THF	19	0	134
3	phen	THF	17	0	142
4	dmbpy	THF	10	0	120
5	dtbpy	benzene/THF	83	4	51
6	dtbpy	toluene/THF	66	2	65
7	dtbpy	Et_2O/THF	39	<1	102
8	dtbpy	*n*-hexane/THF	32	<1	107
9[d]	dtbpy	benzene/THF	70	2	63
10[e]	dtbpy	benzene/THF	87	6	53
11[f]	dtbpy	benzene/THF	88	12	47

[a] Conditions: **1a** (0.4 mmol), $Fe(acac)_3$ (0.04 mmol), ligand (0.04 mmol), PhMgBr (1.25 M in THF, 1.2 mmol), 1,2-dichloro-2-methylpropane (0.8 mmol), solvent (3 mL). PhMgBr was added over ca. 30 s. [b] dtbpy: 4,4′-di-*tert*-butyl-2,2′-bipyridyl; bpy: 2,2′-bipyridyl; phen: 1,10-phenanthroline; dmbpy: 4,4′-dimethyl-2,2′-bipyridyl. [c] Determined by GC using *n*-tridecane as an internal standard. [d] PhMgBr was added over 5 min. [e] PhMgBr was added over 20 min. [f] PhMgBr was added over 1 h.

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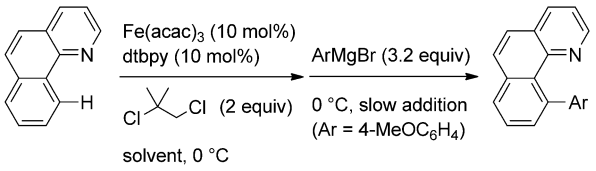
(Table 1, entries 2–4). The use of benzene as a co-solvent dramatically increased the yield of the phenylation products (**2a**, 83%; **3a**, 4%; Table 1, entry 5). Toluene was also effective (Table 1, entry 6), whilst nonaromatic solvents such as diethyl ether and *n*-hexane showed adverse effects (Table 1, entries 7 and 8).

We then found that the yield of the reaction in Table 1, entry 5 tends to fluctuate by ±10%, and that the rate of the addition of PhMgBr causes this problem. Careful control of the rate of addition made the reaction highly reproducible (Table 1, entries 9–11). Slow addition of PhMgBr with a syringe pump over 1 hour afforded quantitative conversion of the starting material into the phenylation products **2a** (88%) and **3a** (12%; Table 1, entry 11). We also noted that vigorous stirring of the reaction mixture is essential to achieving high yield and reproducibility of the reaction (see the Supporting Information). The reaction took place equally efficiently with reagent-grade (>95%) and high-purity (>99.9%) $Fe(acac)_3$ as the iron source.[14] Other iron salts such as $FeCl_3$ or $Fe(acac)_2$ gave slightly lower yields. The reaction proceeded with similar yield when PhMgCl was used as an arylating reagent.

The favorable effects of benzene and toluene as co-solvents for the phenylation reaction prompted us to perform further examination on other aromatic co-solvents. For this study, we chose a lower-yielding reaction of benzo[*h*]quinoline with 4-methoxyphenylmagnesium bromide for the benchmark test (Scheme 3), and screened seven aromatic co-solvents (Table 2, entries 1–7). We found that modestly electron-deficient arenes such as chlorobenzene and fluorobenzene were effective, affording the arylation product in 68% and 62% yields, respectively (Table 2, entries 3 and 4). Whilst benzene and toluene gave modest results (Table 2, entries 1 and 2), highly electron-rich (i.e., mesitylene) or electron-deficient arenes (i.e., *ortho*-dichlorobenzene and trifluoromethylbenzene) exhibited adverse effects (Table 2, entries 5–7). With chlorobenzene as the co-solvent, the use of a slight excess of dtbpy (15 mol%) further improved the product yield to 78% (Table 2, entry 8). In contrast to the conditions employing benzene as the co-solvent (Table 1), the optimum period for the addition of the Grignard reagent was 5 min in this case, with prolonging of the addition time resulting in lower yields (Table 2, entries 9 and 10). The reaction completed at the end of the Grignard addition (i.e., reaction time ≤5 min) and chlorobenzene did not undergo cross-coupling with the Grignard reagent (only a trace amount of 4-methoxybiphenyl was detected by GC analysis).



Scheme 3. Iron-catalyzed *ortho*-arylation of benzo[*h*]quinoline with 4-methoxyphenylmagnesium bromide using arene/THF as a solvent.

Table 2. Effects of aromatic solvents on the reaction of benzo[*h*]quinoline and 4-methoxyphenylmagnesium bromide (Scheme 3).[a]

Entry	Solvent	Addition time [min]	Yield [%][b]
1	benzene/THF	5	50
2	toluene/THF	5	51
3	chlorobenzene/THF	5	68
4	fluorobenzene/THF	5	62
5	mesitylene/THF	5	15
6	*ortho*-dichlorobenzene/THF	5	34
7	trifluoromethylbenzene/THF	5	19
8[c]	chlorobenzene/THF	5	78
9[c]	chlorobenzene/THF	20	66
10[c]	chlorobenzene/THF	60	58

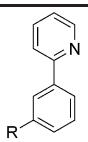
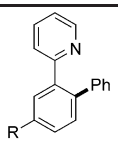
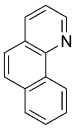
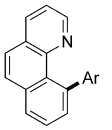
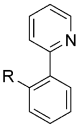
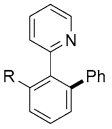
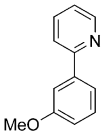
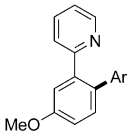
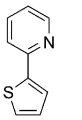
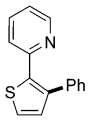
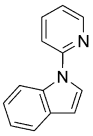
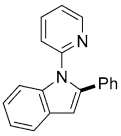
[a] Conditions: benzo[*h*]quinoline (0.4 mmol), $Fe(acac)_3$ (0.04 mmol), ligand (0.04 mmol), $4\text{-}MeOC_6H_4MgBr$ (1.19 M in THF, 1.28 mmol), 1,2-dichloro-2-methylpropane (0.8 mmol), solvent (2.9 mL). [b] Determined by GC using *n*-tridecane as an internal standard. [c] dtbpy (15 mol%) was used. THF = tetrahydrofuran.

Reaction Scope

On the basis of the optimization studies, we used chlorobenzene or benzene as the co-solvent and the slow-addition procedure to explore the scope of the direct arylation reaction (Scheme 2). Table 3 summarizes the results of the arylation of various arylpyridine derivatives. Substrates bearing *meta*-methyl, methoxy, dimethylamino, and chloro substituents **1b**–**1e** underwent exclusive monophenylation at the less-hindered *ortho* position in 82–94% yield (Table 3, entries 1–4). The *meta*-fluoro substrate **1f** afforded the 6-phenylation product **2f** in moderate yield, and only a trace amount of the 2-phenyl regioisomer was detected (Table 3, entry 5). Benzo[*h*]quinoline smoothly reacted with PhMgBr to afford the phenylation product **2g** in 91% yield (Table 3, entry 6). On the other hand, phenyl and methyl substituents on the *ortho* position lowered the yield of the desired products (Table 3, entries 8 and 9), probably for steric reasons. Pyridine-bearing heteroarenes such as thiophene (**1j**) and indole (**1k**) could also be phenylated, albeit in modest yields (Table 3, entries 14 and 15).

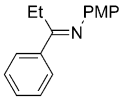
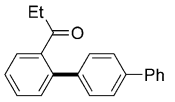
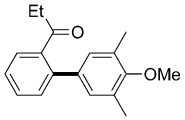
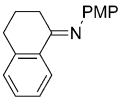
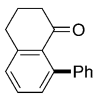
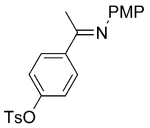
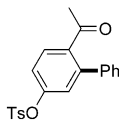
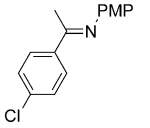
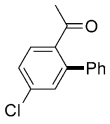
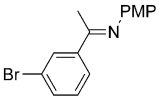
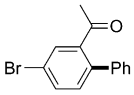
4-Methoxyphenyl, 4-*tert*-butylphenyl, 4-fluorophenyl, and 2-naphthyl Grignard reagents took part in the C–H activation in moderate to good yields (Table 3, entries 7, 10–13), whilst 2-methoxyphenyl and 2-thienyl Grignard reagents did not participate in the arylation reaction at all, and only afforded the corresponding homocoupled products. Methylation of benzo[*h*]quinoline with MeMgBr only took place in 5% yield, and alkylation with *n*-butyl and cyclohexyl Grignard reagents did not take place at all.This catalytic system is also applicable to an aryl imine, derived from the corresponding ketone and *para*-anisidine (Table 4). The phenylation of propiophenone and tetralone imines **1l** and **1m** on a 0.4 mmol scale took place cleanly to give the products **2q** and **2t** in near quantitative yield (Table 4, entries 1 and 4). The latter reaction could be performed on a 4 mmol (ca. 1 g) scale in a good yield of 80%. Other Grignard reagents such as *para*-biphenylmagnesium bromide and 4-methoxy-

Table 3. Direct arylation of 2-arylpyridine derivatives with arylmagnesium bromides.[a]

Entry	Substrate		Product	Yield [%][b]
1		**1b** 	**2b** (R = Me)	94
2		**1c**	**2c** (R = OMe)	90
3		**1d**	**2d** (R = NMe_2)	89
4		**1e**	**2e** (R = Cl)	82
5		**1f**	**2f** (R = F)	58
6		**1g** 	**2g** (Ar = Ph)	91
7			**2h** (Ar = 4-$MeOC_6H_4$)	76
8		**1h** 	**2i** (R = Ph)	56[c]
9		**1i**	**2j** (R = Me)	25[c]
10			**2k** (Ar = 4-$MeOC_6H_4$)	46
11		**1c**	**2l** (Ar = 4-$tBuC_6H_4$)	68
12			**2m** (Ar = 4-FC_6H_4)	58
13			**2n** (Ar = 2-naphthyl)	56
14		**1j** 	**2o**	35[c]
15		**1k** 	**2p**	19

[a] The reaction was carried out on a 0.4 mmol scale using chlorobenzene or benzene as the co-solvent and the slow-addition procedure (for details, see the Supporting Information). [b] Yield of isolated product. [c] Obtained as a mixture with starting material and yields were determined by ^{1}H NMR analysis.

Table 4. Direct arylation of aryl imines with arylmagnesium bromides.[a]

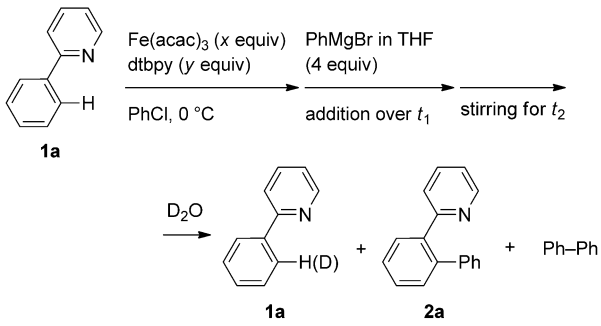
Entry	Substrate[b]		Product	Yield [%][c]
1			**2q**	98
2		**1l** 	**2r**	93
3			**2s**	68
4		**1m** 	**2t**	94 (80)[d]
5		**1n** 	**2u**	88
6		**1o** 	**2v**	70
7		**1p** 	**2w**	19

[a] The reaction was carried out on a 0.4 mmol scale using chlorobenzene or benzene as the co-solvent and the slow-addition procedure, followed by hydrolysis with 3 M aq. HCl (for details, see the Supporting Information). [b] PMP = *p*-methoxyphenyl. [c] Yield of isolated product. [d] The reaction was performed on a 4 mmol scale. Ts = *para*-methylsulfonyl.

3,5-dimethylphenylmagnesium bromide reacted with the propiophenone imine **1l** to give the corresponding arylation products **2r** and **2s** in 93% and 68% yields, respectively (Table 4, entries 2 and 3). The reaction tolerated the presence of electrofugal leaving groups such as tosyloxy and chloro substituents, and yielded the desired products **2u** and **2v** in good yields (Table 4, entries 5 and 6). Even an aromatic C–Br bond was tolerated, whilst its presence lowered the yield of the product **2w**, because the homocoupling reaction of PhMgBr was faster than the desired phenylation reaction, for unknown reasons (Table 4, entry 7). In no case could we observe nucleophilic addition of the Grignard reagent to the C=N bond.

Insight into the Reaction Intermediate and the C–H Bond-Activation Step

The accepted wisdom of directed C–H bond activation calls for the formation of an *ortho*-metalated intermediate where the metal is covalently bonded to the *ortho*-carbon atom and coordinated by the directing group.[3] To probe this putative intermediate, we performed a series of stoichiometric experiments (Scheme 4 and Table 5). First, PhMgBr (4 equiv) was added to a mixture of **1a**, $Fe(acac)_3$ (1 equiv), and dtbpy (2 equiv) in PhCl over a period of 3 minutes. After stirring for 10 seconds, the reaction was immediately quenched with D_2O to afford **1a**, the phenylation product **2a**, and biphenyl in 82%, 6%, and 90% yields, respectively (Table 5, entry 1). A deuterium atom was incorporated into



Scheme 4. Trapping of the *ortho*-metalated intermediate.

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Table 5. Stoichiometric reaction of 2-phenylpyridine with PhMgBr in the presence or absence of iron complex (Scheme 4).[a]

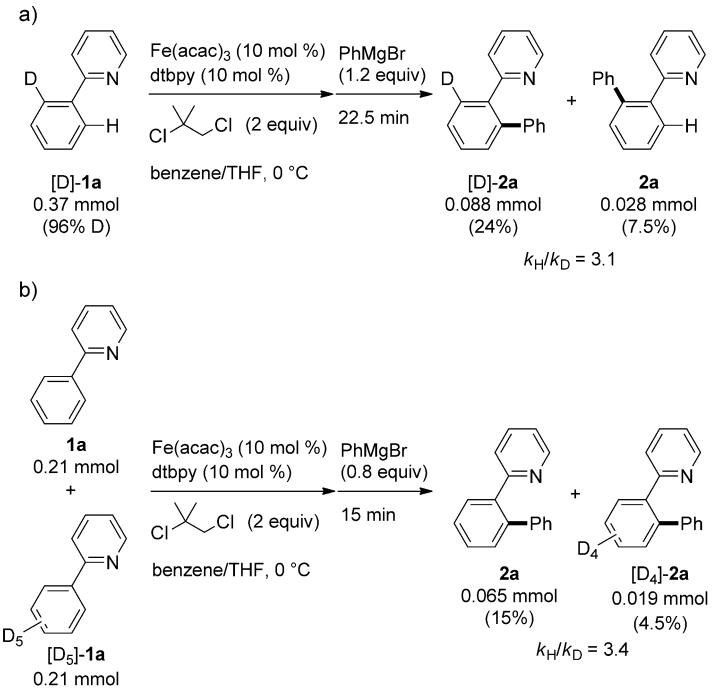
Entry	x	y	t_1	t_2	Yield [%][b]		
					1a [%D][c]	**2a**	Ph–Ph
1	1	2	3 min	10 s	82 (59)	6	90
2	1	2	3 min	1 h	80 (86)	6	92
3	1	2	3 min	40 s[d]	27 (20)	59	114
4	1	0	5 min	30 s	86 (0)	0	138
5	0	0	5 min	30 s	>95 (0)	0	0

[a] The reaction was performed on a 0.2 mmol scale. [b] Determined by GC using *n*-tridecane as an internal standard. [c] Determined by ^{1}H NMR analysis. [d] Stirring for 10 s, addition of 1,2-dichloro-2-methylpropane, and additional stirring for 30 s were followed by the addition of D_2O.

the *ortho* position of **1a** in 59%. When the same reaction was stirred for 1 hour before quenching, the proportion of the deuterium atom increased to 86%, while the yields of the products did not change (Table 5, entry 2). When 1,2-dichloro-2-methylpropane was added before quenching with D_2O, the recovery of **1a** decreased to 27% whilst the yield of **2a** increased to 59% (Table 5, entry 3). In the absence of dtbpy, oxidative dimerization (biphenyl formation) took place, and neither phenylation nor deuterium incorporation occurred (Table 5, entry 4). Not unexpectedly, the reaction of **1a** with PhMgBr without any catalyst resulted in quantitative recovery of **1a** without deuterium incorporation (Table 5, entry 5).

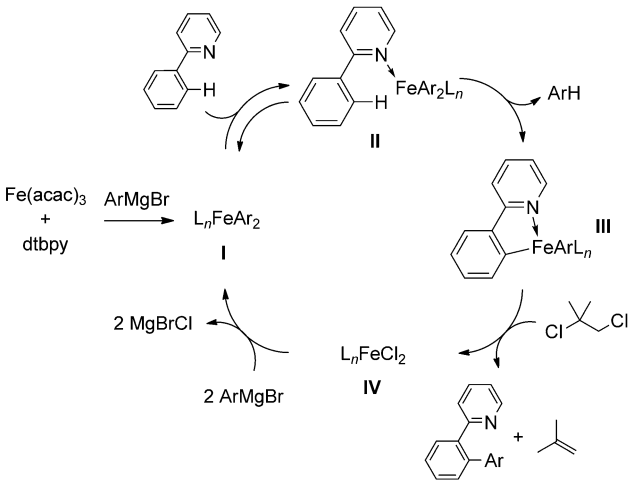
Several mechanistic implications can be inferred from the above stoichiometric experiments, which indicate the presence of a stable intermediate that bears an *ortho* C–metal bond and decomposes into the *ortho*-phenylation product under oxidative conditions. First, the deuterium incorporation into the *ortho* position of **1a** (Table 5, entries 1 and 2) supports the formation of an *ortho*-metalated intermediate. The intermediate forms only when the iron salt and the dtbpy ligand are present, as shown by the control experiments (Table 5, entries 4 and 5). The deuterium incorporation of 59%, achieved when the reaction time was 3 minutes (Table 5, entry 1), is consistent with the high reaction rate of the arylation reaction. Furthermore, the higher level of the deuterium incorporation for the 1 hour reaction (Table 5, entry 2) indicates that the *ortho*-metalated intermediate is stable enough at 0°C. This intermediate quickly decomposes to give the *ortho*-phenylation product **2a** upon addition of 1,2-dichloro-2-methylpropane (Table 5, entry 3). Putting the above considerations together, the intermediate appears to be an iron complex bearing 2-(2-pyridyl)phenyl and phenyl ligands, which undergoes aryl–aryl bond-forming reductive elimination upon interaction with the dichloroalkane (see below).

Intra- and intermolecular kinetic isotope effects (KIEs) on the arylation reaction shed light on the iron-mediated C–H bond-activation step as well as on the preceding coordination of the pyridyl group to the iron catalyst (Scheme 5).[15,16] The reaction of [D]-**1a** (0.37 mmol) with 1.2 equivalents of PhMgBr in a benzene/tetrahydrofuran mixture afforded a mixture of the phenylation products [D]-**2a** (0.088 mmol) and **2a** (0.028 mmol), the ratio of which indicated an intramolecular KIE value of 3.1 (Scheme 5a). The intermolecular competitive reaction of **1a** and [D_5]-**1a** was performed under similar conditions to give a KIE value of 3.4 (Scheme 5b). The similarly large magnitude of the intramolecular and intermolecular KIE values indicates that coordination of the pyridyl group to the iron catalyst takes place in a reversible manner, and that the following C–H bond-cleavage step is the first irreversible step of the catalytic cycle,[17] where the C–H bond is significantly elongated.



Scheme 5. Intramolecular and intermolecular kinetic isotope effects.

On the basis of the above mechanistic experiments as well as the previous study on the *ortho*-arylation reaction with an arylzinc reagent,[8a] we suggest a possible catalytic cycle, as shown in Scheme 6. Reversible coordination of the pyridyl group of the substrate to the iron center of an aryliron species (**I**, **II**) is followed by irreversible metalation of the *ortho* position with concomitant elimination of an arene molecule.[18–20] The *ortho*-ferrated intermediate **III** undergoes reductive elimination upon interaction with 1,2-dichloro-2-methylpropane to afford the *ortho*-arylation product, isobutene, and dichloroiron species **IV**. Transmetalation of **IV** and the Grignard reagent regenerates the active species **I**. The undesirable oxidative homocoupling of the Grignard reagent occurs if the species **I** directly reacts with the dichloroalkane. The relevance between the reaction mechanism and the key reaction conditions (the aromatic solvent and the slow addition) need further clarification. At this time, we speculate that the aromatic solvent serves as a ligand that stabilizes a low-valent iron species,[21] and that the slow addition is necessary for controlled formation of the reactive iron species.[9c,18]



Scheme 6. Possible catalytic cycle.

Conclusions

In summary, an iron-catalyzed cross-coupling reaction of aryl pyridines and imines with aryl Grignard reagents has been developed, and the new conditions revealed herein have significant assets over the same transformation achieved by the use of organozinc reagents. The key elements of the development are the use of an aromatic co-solvent, such as chlorobenzene and benzene, and the slow addition of the Grignard reagent. Under the optimized catalytic conditions, the aryl–aryl bond formation with the Grignard reagent takes place faster than that with the zinc reagent, and immensely faster than those catalyzed by precious metals at elevated temperatures. The stoichiometric experiments suggested the formation of an iron complex bearing an *ortho* C–Fe bond as a stable reaction intermediate, which undergoes C–C bond formation upon oxidation. The C–H bond-activation step is the first irreversible step of the catalytic cycle and shows substantial kinetic isotope effects as examined in both the intramolecular and intermolecular competitive reactions. The proposed catalytic cycle is consistent with the mechanistic information gained thus far, whilst further studies are necessary to elucidate the nature of the reactive intermediates and the detail of the bond cleavage and formation processes.

Experimental Section

*General Procedure for Iron-Catalyzed Direct Arylation with Aryl Grignard Reagent in PhH/THF: 2-(4-Methylbiphenyl-2-yl)pyridine (**2b**)*

In a Schlenk flask were placed 4,4′-di-*tert*-butyl-2,2′-bipyridyl (10.7 mg, 0.04 mmol), 2-(3-methylphenyl)pyridine (68.2 mg, 0.40 mmol), benzene (2.0 mL), and a 0.125 M solution of $Fe(acac)_3$ in THF (0.32 mL, 0.04 mmol). The resulting mixture was cooled to 0 °C, followed by addition of 1,2-dichloro-2-methylpropane (93 μL, 0.80 mmol). PhMgBr (0.76 M in THF, 1.68 mL, 1.28 mmol) was added to the vigorously stirred solution with a syringe pump over 1 h. The reaction mixture was diluted with Et_2O and quenched by the addition of saturated aqueous solution of $NaHCO_3$. After extraction with ethyl acetate and Et_2O, the organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (toluene as an eluent) to afford the title compound as a colorless oil (93.3 mg, 94%). The spectral data were in accordance with those reported in the literature.[22]

*General Procedure for Iron-Catalyzed Direct Arylation with an Aryl Grignard reagent in PhCl/THF: 8-Phenyl-3,4-dihydronaphthalen-1(2H)-one (**2t**)*

In a Schlenk flask were placed 4,4′-di-*tert*-butyl-2,2′-bipyridyl (16.1 mg, 0.06 mmol), (*E*)-*N*-(3,4-dihydro-1(2*H*)-naphthalenylidene)-4-methoxybenzenamine (100 mg, 0.40 mmol), chlorobenzene (3.2 mL), and $Fe(acac)_3$ (14.1 mg, 0.04 mmol). The resulting mixture was cooled to 0 °C, followed by addition of 1,2-dichloro-2-methylpropane (93 μL, 0.80 mmol). PhMgBr (1.53 M in THF, 0.84 mL, 1.28 mmol) was added to the vigorously stirred solution with a syringe pump over 5 min. The reaction mixture was directly subjected to acidic hydrolysis with 3 M hydrochloric acid, and then extracted with ethyl acetate and Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (*n*-hexane/AcOEt = 49:1 to 19:1) to afford the title compound as a colorless solid (83.6 mg, 94%). The spectral data were in accordance with those reported in the literature.[16a]

Trapping of ortho-Metalated Intermediate with D_2O (Table 5)

A THF solution of PhMgBr (0.76 M, 1.05 mL, 0.8 mmol) was added to a solution of 2-phenylpyridine (31.0 mg, 0.2 mmol), $Fe(acac)_3$ (70.5 mg, 0.2 mmol), and 4,4′-di-*tert*-butyl-2–2′-bipyridyl (107 mg, 0.4 mmol) in PhCl (3.0 mL) over 3 min at 0 °C. After a certain period of time (10 s or 1 h), the reaction was quenched with D_2O followed by the addition of saturated aqueous solution of potassium sodium tartrate and water. The organic layer was collected and analyzed by GC using *n*-tridecane as an internal standard to determine the yield, and by ^1H NMR to determine the deuterium incorporation into the recovered substrate.

Intramolecular Kinetic Isotope Effect (Scheme 5a)

In a Schlenk flask were placed 4,4′-di-*tert*-butyl-2,2′-bipyridyl (11.1 mg, 0.04 mmol), 2-(2-deuteriophenyl)pyridine (58.5 mg, 0.37 mmol), benzene (2.0 mL), THF (0.3 mL), and $Fe(acac)_3$ (14.3 mg, 0.04 mmol). The resulting mixture was cooled to 0 °C, and 1,2-dichloro-2-methylpropane (93 μL, 0.80 mmol) was added. A solution of PhMgBr in THF (0.76 M, 0.63 mL, 0.48 mmol) was added to the vigorously stirred solution with a syringe pump over 22.5 min. The reaction mixture was diluted with diethyl ether and quenched by the addition of saturated aqueous solution of $NaHCO_3$. After extraction with ethyl acetate and Et_2O, the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (*n*-hexane/AcOEt = 19:1 to 4:1) to afford a mixture of the monophenylated products and dtbpy as a colorless solid (27.9 mg). ^1H NMR analysis indicated $k_H/k_D = 3.1$.

Intermolecular Kinetic Isotope Effect (Scheme 5b)

In a Schlenk flask were placed 4,4′-di-*tert*-butyl-2,2′-bipyridyl (10.8 mg, 0.04 mmol), 2-phenylpyridine (32.6 mg, 0.21 mmol), 2-(2,3,4,5,6-pentadeuteriophenyl)pyridine (33.9 mg, 0.21 mmol), benzene (2.0 mL), THF (0.3 mL), and $Fe(acac)_3$ (14.3 mg, 0.04 mmol). The resulting mixture was cooled to 0 °C, and 1,2-dichloro-2-methylpropane (93 μL, 0.80 mmol) was added. A solution of PhMgBr in THF (0.76 M, 0.42 mL, 0.32 mmol) was added to the vigorously stirred solution with a syringe pump over 15 min. The reaction mixture was diluted with Et_2O and quenched by the addition of saturated aqueous solution of $NaHCO_3$. After extraction with ethyl acetate and Et_2O, the combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/AcOEt = 9:1) to afford a mixture of the monophenylated products and dtbpy as a colorless solid (20.0 mg). ^1H NMR analysis indicated $k_H/k_D = 3.4$.

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